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DOTTORATO DI RICERCA TOSCANO IN NEUROSCIENZE

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Active training promotes visual cortex plasticity and recovery from amblyopia in adult rats

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INTRODUCTION

1. NEURAL PLASTICITY AND BRAIN DEVELOPMENT

1.1 Neural plasticity

Neural plasticity, also known as neuroplasticity, can be defined as the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections.

A fundamental property of neurons is their ability to modify the strength and efficacy of synaptic transmission through a different number of mechanisms, typically referred as synaptic plasticity. The brain is able to reshape neuronal functionality at different levels by modulating the expression of ions channels and membrane receptors and modifying the efficacy of already existing synapses, building new synaptic contacts or removing the existing ones.

Studies focusing on neural plasticity have not only been a milestone in basic neuroscience research but they are considered a driving force in the well-being of our societies, since this phenomenon is involved in learning and memory, brain development and homeostasis, sensorial training, and recovery from brain lesions.

1.2 Environment-gene interaction and critical periods

Genes and environment work together during brain development and for building the adult brain structure.

During maturation, neurons and synapses are continuously replaced to allow the birth of stable connections: plastic changes are mostly confined to early specific time windows, known as critical periods (CPs). During these specific periods, different for distinct developing functions, a tight cooperation between genetic patterns and experience-dependent plastic changes finally lead to the

accomplishment of an adaptive individual nervous system (Lewis and Maurer, 2009; Weliky, 2000). Critical periods are present in all species studied so far, from Drosophila (Barth et al., 1997) to mammals, with a time extension that is closely correlated with the average life expectancy (Berardi et al., 2000).

The existence of CPs has been proved for different sensory systems (visual, auditory and somatosensory systems), but also for other several complex functions such as social behavior in monkeys, song in birds and language in humans (Harlow H et al., 1965; Doupe and Kuhl, 1999; Werker and Hensch, 2015). At the end of CPs, neural plasticity decays, leading to a final stabilization and maturation of the complex neural network, a fundamental property for maintenance of sensory functions.

As CPs are characterized by a remarkable sensitivity of neural connections to modifications of environmental stimuli, alterations in experience-dependent activity occurring during these time windows could generate deficits in the brain developmental processes, resulting in moderate to severe damages of cerebral neural systems (Antonini et al., 1999; Takao K Hensch, 2005; Knudsen and Knudsen, 1990).

Focusing on the paradigmatic model of visual system, the total absence of sensory inputs and experience leads to a marked delay in the functional and anatomical maturation of the visual cortex, which remains immature far beyond the end of the CP. A classical model is to raise animals in dark rearing (DR) from birth: in these conditions, visual stimulation is completely absent, while spontaneous electrical activity along the visual pathways is preserved. Dark rearing lead to profound changes in basic physiological functions, including reduced orientation and direction tuning, lower cell responsiveness and increased latency, larger receptive field sizes, altered spontaneous activity, rapid habituation to repeated stimulus presentation, immature ocular dominance (OD) distribution and lower visual acuity (Fregnac and Imbert, 1978; Timney et al., 1978; Benevento et al., 1992; Fagiolini et al., 1994; Pizzorusso et al., 1997).

Moreover, interesting observations showed that animals reared since birth in complete darkness express a delayed CP time course with plasticity persisting into adulthood (Fagiolini et al., 1994; Iwai et al., 2003; Mower, 1991).

1.3 Manipulating brain plasticity

As stated before, the visual system emerges as a paradigmatic model for neural plasticity studies. First studies on visual system plasticity came in the 1960s, thanks to the pioneering work of Nobel Prize winners Torsten Wiesel and David Hubel.

These authors demonstrated that occluding one eye in kittens, a manipulation usually referred to as monocular deprivation (MD), strongly affects the binocularity properties of cortical neurons: this is reflected by a considerable loss of neurons driven by the deprived eye and an almost simultaneous gain of neurons driven by the open eye. In normal binocular conditions, even if a large number of neuronal cells in the visual cortex receive input from both eyes, they show different degrees of preference for one of them, a property defined ocular dominance (OD).

Loss of sensory experience in one eye results in a marked shift of OD in favor of the non-deprived one. In parallel, the deprived eye shows a strongly reduced visual acuity and its contrast sensitivity is blunted, i.e. the deprived eye becomes amblyopic (Wiesel and Hubel, 1963; Hubel and Wiesel, 1970; Olson and Freeman, 1975; Movshon and Dürsteler, 1977; Olson and Freeman, 1980).

It is widely known that the deprived retina remains completely unaffected, suggesting that modifications in amblyopia pathology occur at cortical level (Hubel and Wiesel, 1963; Sherman and Stone, 1973; Kratz et al., 1979; Baro et al, 1990).

Anatomically, early MD causes a decline of areas in the cortical layer IV guided by the deprived eye and innervated by lateral geniculate nucleus (LGN) with a subsequent expansion of those driven by the open eye (Katz and Shatz, 1996). The sensitivity of ocular dominance to the effects of MD finely depends on age: OD plasticity is reversible only when MD is performed during

the CP; after CP closure, the effects of MD become irreversible (Wiesel and Hubel, 1965; Movshon, 1976; Sluyters, 1978; Blakemore et al., 1981; Antonini et al., 1998; Berardi et al., 2000).

1.4 Mechanisms underlying OD plasticity

1.4.1 Neurotrophins

The neurotrophins are a family of closely related proteins, characterized by their capability to promote neural survival and growth during development (Barde et al., 1982; Hohn et al., 1990; Levi-Montalcini and Cohen, 1956). Over time, these important neuronal factors have been associated with cellular differentiation (Ghosh and Greenberg, 1995), synapse formation (Wang et al., 1995) and different forms of synaptic plasticity (Bonhoeffer, 1996; Thoenen, 1995). Neurotrophins' production and release are developmentally regulated and rely on electrical activity (Bozzi et al., 1995; Castrén et al., 1992; McAllister et al., 1999). Once released, these important proteins can modulate synaptic transmission and electrical activity at both presynaptic and postsynaptic levels (Carmignoto et al., 1997; Berardi and Maffei, 1999; Poo, 2001).

Several observations have suggested that neurotrophins, in particular BDNF (Brain-derived Neurotrophic Factor), control visual cortical plasticity during CP (Berardi et al., 1994; Cabelli et al., 1997; Domenici et al., 1994, 1991; Lodovichi et al., 2000; Pizzorusso et al., 1999; Rossi et al., 1999; Sansevero et al., 2019). It has been proposed that connections receiving inputs from the two eyes compete, in the visual cortex, for limited amounts of activity-dependent neurotrophins: in this model, the deprived eye is thought to receive reduced amounts of neurotrophins in respect to the non-deprived eye (Rossi et al, 1999).

An alternative view describes a more direct role of neurotrophins on synaptic efficacy, rather than on thalamo-cortical afferents. It has been demonstrated that NGF (Nerve Growth Factor) can act directly on cholinergic afferents from the basal forebrain and on a population of glutamatergic cortical neurons. BDNF instead, aims principally at cortical glutamatergic pyramidal neurons and inhibitory

cells while another factor, NT4, strikes glutamatergic thalamic afferents and inhibitory interneurons (Berardi and Maffei, 1999).

The link between neurotrophins and inhibitory processes development has been examined carefully, using a model of BDNF overexpression in transgenic mice: this condition accelerates the maturation of intracortical GABA-mediated inhibition and leads to an early development of visual acuity with respect to wild type animals; consequently, the CP time window have a shorter extent (Huang et al., 1999).

1.4.2 The insulin growth factor 1 (IGF-1)

Another essential neuronal factor, capable to controlling brain development, cell proliferation, gliogenesis, neurogenesis, neuron survival, differentiation, synaptogenesis and myelination, is the Insulin Growth Factor 1 (IGF-1) (Aberg et al., 2006; D'Ercole et al., 1996, 2002; Fernandez and Torres-Alemán, 2012).

During MD, IGF-1 binding protein increases its expression and affects several genes within the IGF-1 signaling pathway. Exogenous application of IGF-1 prevents the physiological effect of MD on OD plasticity examined in vivo (Tropea et al., 2006), suggesting that this peptide is involved in visual cortex experience-dependent plasticity. The vast majority of cerebral IGF-1 derives from the periphery (Carro et al., 2000; Fernandez and Torres-Alemán, 2009 and 2012; Sale et al., 2007). Serum IGF-1 enters the brain regions through brain vessels by an activity-dependent mechanism (Nishijima et al., 2010).

Cerebral IGF-1 and the inhibitory system are tightly correlated with each other: disruption of IGF-1 gene, indeed, results in a loss of PV+ cells, one of the most representing GABAergic interneurons (Beck et al., 1995). Moreover, intracerebral IGF-1 injections decrease the ratio between NKCC1/KCC2 transporters, leading the membrane potential towards more negative values and

thereby promoting the developmental switch of GABA polarity from excitation to inhibition (Baroncelli et al., 2017).

Moreover, the exogenous supply of IGF-1 accelerates PV+ neurons development and, consequently, allows GABAergic circuitry maturation (Baroncelli et al., 2017). Thus, IGF-1 has a key role in setting the rhythm of visual development and acts, together with inhibitory system, as a "master mediator" in controlling the CP time course. In addition, in the past few years several studies investigated the molecular mechanisms of visual cortex plasticity using genetic screens, and they opened the door to new families of molecules in plasticity (e.g. proteins related to IGF-I pathway or immune/inflammation system signals).

1.4.3 Neuromodulators

The distribution of different neuromodulators and their receptors is developmentally regulated (Foote and Morrison, 1984) and depends on cortical input (Prusky et al., 1988). Different molecules acting on adrenergic, cholinergic or serotoninergic systems critically operate on OD plasticity (Bear and Singer, 1986; Gu, 2003; Gu and Singer, 1995; Kasamatsu and Pettigrew, 1976): for example, chronic administration of fluoxetine, a selective serotonin re-uptake inhibitor, is able to reduce the inhibitory tone in adult amblyopic animals (Vetencourt et al., 2008).

The role of serotoninergic system has been widely studied in OD plasticity: for example, a depletion in serotonin concentration prevents the OD shift in MD kittens (Gu and Singer, 1995). Serotoninergic neurons are directly connected with GABAergic interneurons (Paspalas and Papadopoulos, 2001), and can strongly influence intracortical inhibition in the primary visual cortex (Edagawa et al., 2000; Roerig and Katz, 1997; Xiang et al., 1998).

Also the role of cholinergic system has been investigated in kittens, through experiments on the basal forebrain. Cholinergic fibers arising from the basal forebrain reach all cortical layers early after the first postnatal week, until they reach a complete maturation during the third postnatal week

(Origlia et al., 2008). The importance of the cholinergic system for OD plasticity has been investigated through pharmacological experiments and lesion-based manipulations in the cat visual cortex (Bear and Singer, 1986): a chronically blockade of cholinergic receptors (muscarinic but not nicotinic receptors) showed their remarkable role in the OD shift of monocularly deprived kittens. In particular, chronic blockade of muscarinic M1, but not M2 receptor subtypes, totally prevents the OD shift (Gu and Singer, 1989; Gu and Singer, 1993).

The endogenous prototoxin Lynx1 shares structural characteristics with the snake venom toxin α-bungarotoxin and likewise, binding to nicotinic receptors, inhibits the acetylcholine signaling transduction (Miwa et al., 1999). Lynx1 expression increases after the CP in adult brain, both at protein and mRNA level, and is expressed in the cortex and in the dLGN. It has been suggested that Lynx1 accumulation in the mature visual cortex could act as a limiting brake for plasticity, since in mice lacking this gene, OD preference is no different from that of non-deprived mice (Morishita et al., 2010; Sadahiro et al., 2016). Lynx1 transgenic mice have also a doubled spine turnover (Bukhari et al., 2015), which is known to physiologically decline towards adulthood (Holtmaat et al., 2005). Besides acting on cholinergic system, this prototoxin could induce structural changes in the visual cortex probably hampering the tissue plasminogen activator (tPA), an extracellular matrix component (Bukhari et al., 2015).

1.5 Intracellular signaling of cortical plasticity

The use of genetic technologies, as transgenic mice and/or pharmacological manipulations, allowed to identify three key protein kinases that can modulate synaptic strength and are critical for inducing OD plasticity: the extracellular signal-regulated kinase 1,2 (ERK-1,2), the cAMP-dependent protein kinase (PKA), and the calcium/calmodulin-dependent protein kinase II alpha (CaMKIIα) (Cristo, 2001; Taha et al., 2002; Taha and Stryker, 2005). These three kinases phosphorylate molecules directly involved in plasticity (such as glutamate or GABA receptors) or cytoplasmic substrates,

crucial for synaptic transmission, neuronal excitability and morphological stabilization (e.g. synapsin I, potassium channels, MAP2), promoting OD plasticity. They may also signal to the nucleus to mediate changes in gene transcription. These kinases activate many signaling pathways at the intracellular level, some able to increase cAMP-responsive element binding protein (CREB) level, which in turn controls CRE-mediated gene expression of a series of synaptic signaling molecules (Cancedda et al., 2003; Suzuki et al. 2004).

Manipulations of visual experience, like MD, induce activation of CREB (Pham et al., 1999). While PKA and ERK inhibition affect CRE-mediated gene expression, the effects of PKA are dependent on ERK phosphorylation (Cancedda et al., 2003): based on these results, ERK has been pointed out as a molecular sensor for visually driven activity.

Interestingly, while ERK activation and CRE-gene expression appear to be strongly correlated, ERK activation and CREB phosphorylation do not always overlap (Suzuki et al., 2004), suggesting the involvement of other co-activators of CREB, important transducers of synaptic activity.

1.6 The extracellular environment

The extracellular environment, and in particular the extracellular matrix (ECM), is an important player in controlling spine dynamics and visual cortical plasticity.

Different studies have shown a key role both in OD plasticity and in CP closure for the major components of brain ECM, the chondroitin-sulfate proteoglycans (CSPGs) (Fawcett et al., 2019; Pizzorusso et al, 2002; Berardi et al, 2004). During development, CSPGs condense at high concentration in lattice-like structures, called perineuronal nets (PNNs), which completely envelop visual cortical neurons, in particular PV+ interneurons. The time course of PNNs condensation in the visual cortex is tightly correlated to the CP due to the effects of MD (Hartig et al., 1992; Köppe et al., 1997; Brückner et al., 2000; Pizzorusso et al., 2002). Moreover, as it was for DR, the CSPGs'

development is regulated by visual activity, as the process of PNNs condensation is prolonged when visual experience is completely prevented (Hockfield et al., 1990).

When CSPGs are degraded by artificial enzymatic digestion, OD plasticity can be reinstated in adult monocularly deprived animals. This suggests that the mature ECM exerts a powerful inhibitory control on OD plasticity (Pizzorusso et al., 2002).

The proper maturation of PNNs and their maintenance in adulthood is regulated by the diffusible protein OTX2 (Sugiyama et al., 2009): during brain development, OTX2 is produced in the retina and transported across visual pathway towards the cortex, where it binds to PNNs (Sugiyama et al., 2008). OTX2 then, enters the cells, promoting the maturation of PV+ interneurons and PNNs (Beurdeley et al., 2012). It has been shown that pharmacological inhibition of the endogenous enzyme tissue plasminogen activator (tPA) hampers visual cortical plasticity (Mataga et al., 1996; Muller and Griesinger, 1998) and that MD is ineffective in mice with a deletion of the tPA gene, both at functional and structural level. Plasticity can be rescued in tPA knockout mice by the exogenous administration of tPA during a period of MD. The correlation between tPA and experience-dependent plasticity is strengthened by the observation that, in wild type animals, MD elicits a fast and transient increase of tPA activity during the CP but not in adult age (Mataga et al., 2002, 2004). The released tPA increases extracellular proteolysis directly or through plasmin enzyme activation. Converging data point to an important role for tPA in "freeing up" the extracellular matrix to promote the structural reorganization of connections during deprivation (Mataga et al., 2004; Oray et al., 2004).

Another extracellular factor involved in OD plasticity regulation comes from oligodendrocytes, in particular from their ability to produce myelin. Myelin, indeed, emerges as an essential candidate thanks to its interaction with the Nogo receptor (NgR). A complete absence of either Nogo or NgR prevents the closure of CP (McGee et al., 2005).

1.7 Epigenetic pathway

The term epigenetics (from the Greek "ἐπί" -above and "γεννητικός" -relating to the family inheritance) was introduced by Conrad Hal Waddington to describe those processes in which the same genetic code can give birth to different phenotypes through the action of undiscovered molecular factors (Baedke, 2013). Nowadays, many of the molecular processes underlying this effect have been elucidated; among these, particularly relevant are structural and functional chromatin modifications regulating the transcriptional process, non-coding RNAs that affect gene expression through mRNAs degradation or translational repression, and modifications of the DNA bases such as methylation or de-acetylation (Allis and Jenuwein, 2016).

Epigenetic modifications can translate external information into activity-dependent modulation of molecular pathways controlling gene expression and, consequently, experience-dependent plasticity. A downregulation of experience-dependent regulation of histone H3 and H4 acetylation during development, for instance, is involved in the CP closure (Putignano et al., 2007). Treatments with trichostatin or valproic acid, two histone deacetylases inhibitors, can consistently enhance visual plasticity in adult animals (Putignano et al., 2007; Silingardi et al., 2010). These experiments were performed in animals raised in darkness and then quickly exposed to light, or in adult animals, past the end of CP (Baroncelli et al., 2016). These epigenetic modifications are also developmentally modulated in the visual cortex of animals reared in normal light conditions, and they are causally linked, under physiological conditions, to the closure of the CP.

Epigenetic mechanisms controlling histone post-translational modifications in visual cortex regulate the expression of specific microRNAs (miRNAs). For example, upregulation of miR-132/212 family during visual cortex development is a requisite for both binocular matching of orientation preference and depth perception maturation (Mazziotti et al., 2017). Other types of studies demonstrate that DR can delay the upregulation of CREB-induced miR-132, normally activated immediately after eye opening (Mellios et al., 2011; Tognini et al., 2011). In MD animals, miR-132

is subjected to a silencing due to the histone methylation of a CRE locus important for its transcription (Tognini et al., 2011). Fortunately, RG108, a DNA methyl-transferase inhibitor, can partially revert the transcriptional program induced by visual deprivation, attenuating, among other factors, the MD-related miR-132 reduction (Tognini et al., 2015).

1.8 Amblyopia

Amblyopia (from Greek, "*amblyos"*-blunt and "*ops"*-vision), also called "lazy eye", is a neurodevelopmental disorder occurring early in life, arising from conditions of physiological alteration in visual cortex (Ciuffreda et al., 1991; Holmes and Clarke, 2006). In humans, this pathology occurs in approximately 1-5% of the population, and the presence of amblyopia is generally associated with an abnormal visual experience: binocular mis-registration (i.e. strabismus), image degradation (high refractive errors, astigmatism and anisometropia) or congenital cataract, ptosis, or an impairment in the orientation tuning of cortical neurons (binocular matching) (Holmes and Clarke, 2006; Levi et al., 2015; Simmers et al., 2003; Wang et al., 2013).

Amblyopia is typically unilateral: the visual acuity of one eye, the deprived one, breaks down with respect to that of the non-pathological eye. Amblyopia finally leads to reduced visual acuity, poor stereoscopic depth perception, low contrast sensitivity and reduced motion sensitivity, thus resulting in a broad range of neural, perceptual and clinical abnormalities (Barrett et al., 2004; Kiorpes, 2006; Levi, 2006). Although the retina was once believed to be one of the main site of amblyopia symptomatology (Hess, 2001), human electrophysiological investigations and animal studies have shown that the retina does not exhibit sign of physiological alterations. The general consensus is that amblyopia originates from dysfunctions at the primary visual cortex level, although functional and structural reorganizations may also occur, according to recent evidence, in the dorsolateral geniculate nucleus of the thalamus (dLGN) (Jaepel et al., 2017; Sommeijer et al., 2017).

In humans, evaluations with fMRI have shown that the striate cortex area responding to the amblyopic eye display reduced neural activity (Barnes et al., 2001).

As already seen, amblyopia occurs at an early stage of life and does not develop after 6-8 years of age (Worth, 1903; von Noorden, 1981), suggesting that there is a "sensitive period" for the pathology development.

1.8.1 Within the pathology

Much of our knowledge about amblyopia derives from studies on animal models. Amblyopia can be easily reproduced in several species of mammals, keeping one eye deprived of any visual stimuli through a long-term monocular deprivation, started during the CP (i.e. at first weeks of birth) and maintained until adulthood (Blakemore et al., 1978; Emerson et al., 1982; Fagiolini et al., 1994; Horton and Hocking, 1997; Hubel et al., 1977; Issa et al., 1999; Le Vay et al., 1980; Van Sluyters and Stewart, 1974). Long-term MD lastly leads to amblyopia: the visual acuity of deprived eye is heavily decreased, and its contrast sensitivity blunted (Hubel and Wiesel, 1970; Movshon and Dursteler, 1977; Olson and Freeman, 1980, 1975; Wiesel and Hubel, 1963). With MD, connections emerging from the non-deprived eye increase their strength at the expense of those from the deprived one.

At least in the mouse, the OD shift in response to MD is first due to a rapid weakening of deprived-eye response, followed by a strengthening of open-eye responses (Frenkel and Bear, 2004). While binocularity in primary visual cortex is affected in all cortical layers, it is more pronounced in the extra-granular layers than in layer IV, with the greatest shift in infra-granular cells (layer V/VI) (Gordon and Stryker, 1996). Anatomical changes accompany functional plasticity in the mouse developing visual cortex, as they do in higher mammals (Antonini et al., 1999). Using two-photon microscopy, Oray et al. (2004) showed that sensory deprivation starts a rapid sequence of events which allows to increase structural dynamics at individual spines level: spine motility in the binocular

region of V1, contralateral to the deprived eye, becomes 35% higher than motility in control, non-deprived animals. A loss of a great amount of spines is correlated to the rapid reduction in the deprived-eye drive (Mataga et al., 2004).

1.9 The heterosynaptic model

David Hubel and Torsten Wiesel proposed a mechanism in which OD plasticity operates through a competitive interaction between inputs from the two eyes for the control of cortical neurons, based on the activity state of postsynaptic neurons. Normally, in binocular mammals, primary visual cortex receives information from both eyes. Exploiting radioactive tracers (Le Vay et al., 1980; Wiesel et al., 1974), Hubel and Wiesel discovered that, in the cortex, these inputs are precisely organized in alternating stripes of eye-specific domains that they called ocular dominance (OD) columns. Using single-cell recordings, these authors classified the primary visual cortical neurons in seven OD groups, based on their response to either contralateral and ipsilateral eye stimulation. Neurons were clustered in group 1 if they were preferentially activated by contralateral eye stimulation, whereas cells exclusively excited by the ipsilateral eye stimulation were clustered in group 7. Neurons responding evenly to either eyes were instead assigned to the intermediate groups (from 2 to 6) (Hubel and Wiesel, 1962). The number of cells belonging to each OD group is strictly dependent on visual experience.

Electrical activity in the primary visual cortex of deprived animals is robustly shifted toward the inputs deriving from the non-deprived eye. Hubel and Wiesel explained this phenomenon proposing a mechanism in which OD plasticity operates through an Hebbian interaction between the inputs emerging from the two eyes that compete for cortical neurons control. This hypothesis was validated by several experimental findings, which show that binocular lid suture is not effective in shifting OD in mammals (Antonini et al., 1998; Gordon and Stryker, 1996; Wiesel and Hubel, 1965). The normal OD columns' organization, as well as the alterations consequent to MD, are therefore the

result of a competition between the fibers that represent homologous regions of the visual field. In addition, a reversible blockade in the discharge activities of cortical neurons by intracortical infusion of tetrodotoxin (TTX) or muscimol completely prevents the OD shift in response to MD, or even causes a paradoxical shift in favor of the deprived eye (Reiter et al., 1986; Reiter and Stryker, 1988; Hata and Stryker, 1994; Hata et al., 1999).

The mechanisms underlying binocular competition remain elusive. The classic competition-based model is related to heterosynaptic mechanisms, with open eye inputs driving down the synaptic efficacy of the deprived ones (Miller et al., 1989; Harris et al., 1997). A series of studies have implicated an activity-dependent uptake of neurotrophins, as mediators of binocular competition (Maffei et al., 1992; Cabelli et al., 1995). Subsequent experiments showed that neurotrophins actually have cell specific effects, such as the regulation of inhibitory circuitry development (Berardi and Maffei, 1999; Huang et al., 1999).

1.10 The homosynaptic model

In contrast to the assumptions of the heterosynaptic model, it has been shown that loss or gain of visual activity in V1 during the critical period in response to MD can be the result of homosynaptic long-term depression (LTD) or potentiation (LTP) of excitatory connections (Mitzdorf and Singer, 1980; Shatz and Stryker, 1978; Tsumoto and Suda, 1978). MD, indeed, induces two different modifications: long-term potentiation (LTP) of non-deprived eye synapses and long-term depression (LTD) of deprived eye synaptic connections (Smith et al., 2009; Frenkel and Bear, 2004; Heynen et al., 2003; Kirkwood et al., 1996).

On the one hand, several works have described the existence of LTP in visual cortex (Bear et al., 1987; Heynen and Bear, 2001; Singer, 1995); accordingly, many manipulations, known to disrupt LTP, cause disruption of OD plasticity as well (Frenkel et al., 2006; Gordon et al., 1996; Sawtell et al., 2003; Taha et al., 2002).

On the other hand, its' widely accepted that LTD-like mechanisms influence depression of deprived-eye responses (Crozier et al., 2007; Heynen et al., 2003; Kirkwood and Bear, 1994a; Yoon et al., 2009). Cooke and Bear (2014) experimentally showed that LTD can mimic the response caused by visual deprivation measuring visual evoked potentials (VEPs) after LTD induction via low frequency stimulation provided in dLGN.

1.11 A key role for GABAergic circuitries

Synaptic inhibition matures later than excitatory transmission in the neocortex (Blue and Parnavelas, 1983; Luhmann and Prince, 1991; Benevento et al., 1992; Guo et al., 1997; Micheva and Beaulieu, 1997; Gao et al., 2000; Mower and Guo, 2001; Murphy et al., 2005). By controlling excitation, GABAergic circuits are ideally posed to control the engagement of activity-dependent synaptic modification. Thus, the mismatch in the excitatory/inhibitory (E/I) systems maturation may define a window of opportunity for activity-dependent plasticity to occur.

Along maturation, there is a progressive increase in the inhibitory tone: during early neonatal period, the γ-aminobutyric acid (GABA) provides most of the excitatory drive, whereas in adult brain it acts as the main inhibitory transmitter (Ben-Ari, 2002). This shift of GABA actions is caused by an early higher intracellular chloride concentration, which lead to depolarization instead of hyperpolarization. This is due to the relative activity of two chloride cotransporters: NKCC1 and KCC2, respectively importing and exporting chloride. In the adult but not in developing central nervous system (CNS), KCC2 prevails whereas NKCC1 is less active, leading to a lower intracellular chloride concentration in the former and not in the latter (Ben-Ari et al., 2012).

How the inhibitory circuit influences CP was mostly clarified by Takao Hensch and Michela Fagiolini: the GABA neurotransmitter is synthesized by the glutamic acid decarboxylase (GAD) enzyme, which is coded by two different genes, GAD65 and GAD67 (Erlander et al., 1991). GAD65 is mainly localized in axon terminals, while GAD67 is present throughout the cytosol (Esclapez et

al., 1994; Kaufman et al., 1991). GAD65 knockout juvenile mice show no induction of OD plasticity, but normal OD plasticity can be rescued with the infusion of diazepam, a drug that boosts up the inhibitory transmission (Hensch et al., 1998a); Mice with GAD65 disruption show no shift in their responsiveness in favor of the open eye, and cortical neurons don't change their response to contralateral eye input. Enhancement of inhibition obtained by local delivering of diazepam produces a complete OD shift in the infused mutant visual cortex (Fagiolini and Hensch, 2000). However, similar effects cannot be induced by diazepam in adult animals, once the CP has passed. Furthermore, increase levels of excitation, obtained by preventing the natural developmental switch of NMDA receptor subunit composition, also weakens the response to MD. Similarly, in NR2A knockout mice, the absence of the 2A subunit prolongs the synaptic response of NMDA receptors, yielding an increased charge transfer (Fagiolini et al. 2003). An acute infusion of benzodiazepines concomitant with MD restores full plasticity in NR2A knockout mice, proving a decisive role of the excitatory-inhibitory balance (Fagiolini et al. 2003).

The inhibitory inputs that one neuron receives usually originate from a variety of inhibitory neurons, which in turn receive highly diverse inputs. GABAergic cells are extremely heterogeneous and classified in different functional subclasses based on their electrophysiological, morphological and molecular features. Considering the expression of molecular markers, cortical interneurons are divided in three major groups: Parvalbumin, Somatostatin and Serotonin-receptor positive cells.

The parvalbumin positive (PV+) interneurons are the major subtype of the total GABAergic population (about 40%). PV+ interneurons are divided in two subclasses: the chandelier cells, whose function is still poorly understood, and the basket cells, that exert a dominant inhibitory control on excitatory neuronal cells, which are mostly represented by pyramidal neurons. Their cell bodies are found in all cortical layers, with the exception of layer I, and are most present within layers IV and V. Most of basket cells project locally, but in some cases, their axons can cross different layers. Optogenetic approaches have shown that PV+ basket cells act on cortical excitatory neurons by both thresholding and scaling their responses, thus keeping the system within its optimal balance (Atallah

et al., 2012; Runyan et al., 2010). PV+ basket cells are also believed to arrange oscillatory activity in the gamma range (30–80 Hz), through their extensive interconnectivity and gap junctions (Cardin et al., 2009; Galarreta and Hestrin, 2002; Sohal et al., 2009; Tamas et al., 2000). According to several studies PV+ interneurons display, together with pyramidal neurons, an OD shift in response to MD (Gandhi et al., 2008; Kameyama et al., 2010; Yazaki-Sugiyama et al., 2009).

The somatostatin positive cells (SOM+), instead, account for 30% of all cortical interneurons and are classified as Martinotti or non-Martinotti cells based on their morphological appearance. The soma of these cells are most abundant in layers II/III and V, and, as almost the totality of neurons, absent in layer I (Markram et al., 2001; Kawaguchi and Kubota, 1998; Gonchar et al., 2007; Wang et al., 2004). SOM+ interneurons receive excitatory input from local pyramidal cells and form most of their inhibitory synapses on dendritic arbor. Their distal dendrites receive connections from other pyramidal neurons within primary visual cortex, while the dendritic tufts receive associative and feedback connections from many different cortical areas and thalamic nuclei.

The third main group (the remaining 30% of all interneurons) expresses functional serotonin (5HT3a) and nicotinic receptors. These interneurons are enriched in supra-granular layers, where they represent the largest inhibitory group, and they are further divided in vasoactive intestinal peptide positive (VIP+) and non-VIP cells. Most of VIP+ interneurons are bipolar shaped and are specialized in inhibiting other interneuron subtypes, especially SOM+ interneurons and, to a lesser extent, PV+ basket cells (Tremblay et al., 2016; van Versendaal and Levelt, 2016, Sansevero et al, 2020). In addition, VIP+ tufted cells have been identified, which also inhibit pyramidal neurons (Jiang et al., 2015). All VIP+ interneurons are activated by cholinergic and serotonergic inputs (Paspalas and Papadopoulos, 2001; Kawaguchi, 2007), but they also receive long-range intercortical and thalamic inputs.

2. TOWARDS POSSIBLE STRATEGIES FOR THE TREATMENT OF AMBLYOPIA IN ADULTHOOD

2.1 A preface

A classic view considers the adult brain a change-resistant structure. The transition to adulthood, indeed, is accompanied by the maturation of several plasticity-limiting factors, commonly referred to as 'brakes', like the GABAergic system (Fagiolini and Hensch, 2000).

While amblyopia can be reversed when treated early during the CP (Wu and Hunter, 2006), this is not generally possible in adults, due to the dramatic reduction of plasticity. The mainstay treatment for amblyopia is early occlusion therapy (temporary exclusion of the better eye from visual activity by means of an eye patch) (Loudon and Simonsz, 2005). This treatment can completely reverse amblyopia only when performed during CP; later on, it shows much lower efficiency (Fronius et al., 2014).

In recent years, several studies have shed new light on the mechanisms that limit plasticity to early life, indicating that adult brain is not "hardwired" with fixed and immutable neural circuits; on the contrary, following specific treatments, it can reacquire a certain degree of plasticity even well after the end of CP. Thus, treatments for amblyopia in adulthood are focused on reactivating plasticity processes, acting on those factors that have an active role in cortical plasticity, with either an inactivating or permissive action on plasticity. Several pharmacological attempts have been done to enhance adult visual cortical plasticity, acting on the factors which are thought to contribute to its time course and which have been previously described (Fagiolini and Hensch, 2000; Harauzov et al., 2010; Morishita et al., 2010; Pizzorusso et al., 2002). Given the key role of E/I circuit balance in controlling plasticity, a reduction of GABAergic transmission could be a crucial step in restoring plasticity processes in adulthood (Hensch, 2005; Baroncelli et al., 2011). In agreement with this, a 2010 study showed that a pharmacological reduction of intracortical inhibition obtained through the

infusion of either MPA (an inhibitor of GABA synthesis) or picrotoxin (a GABA antagonist) directly into the visual cortex reactivates OD plasticity in response to MD in adult rats (Harauzov et al., 2010).

Even if a direct pharmacological manipulation in humans is theoretically appealing, the indiscriminate modulation of plasticity throughout the brain may cause more harm than good (Pascual-Leone et al., 2005). Therefore, the development of non-invasive but targeted manipulations, able to endogenously increase residual plasticity in adult brain, can avoid the potential side effects of direct pharmacological treatments. In this regard, environmental enrichment emerges as a promising procedure.

2.2 Environmental enrichment

One of the most effective approach capable to enhance brain plasticity is the environmental enrichment (EE). Introduced in the early 1960s by Rosenzweig and colleagues, EE is the most direct approach to manipulate the environment in order to enhance neural plasticity (Diamond et al., 1966; Rosenzweig et al., 1967; Rosenzweig et al., 1962). EE refers to an alteration of standard laboratory rearing conditions, that modifies the quality and intensity of environmental stimulation, positively influencing brain and behavior (Rosenzweig and Bennett, 1996; Diamond, 2001; van Praag et al., 2000). Indeed, EE is classically defined as "a combination of complex inanimate and social stimulation" (Rosenzweig et al., 1978). "Enriched" animals are reared in large groups (6-10 per cage is the common practice) in wide cages, where a variety of objects that stimulate attention and memory are frequently changed (e.g. running wheels, platforms, boxes, toys, tunnels, shelters, stairs and nesting material, all replaced at least once a week). Thus, the fundamental purpose of EE is to improve animals' life quality by providing them with the opportunity to receive high levels of multi-sensory stimulation, encouraging their cognitive activity and natural social interaction, increasing voluntary physical activity and enhancing their explorative behavior.

The definition of EE is based on a comparison of enriched conditions with either standard environmental conditions (SCs), in which 2-5 individuals are reared in laboratory standard cages without any particular object other than food, water and litter, or impoverished environmental conditions (ICs), that consists in housing the animals individually in cages identical to those used for SC, or even smaller (Berardi et al., 2015). It has been widely reported that the thickness of cerebral cortex in EE animals is significantly higher compared to littermates housed in ICs or SCs (Rosenzweig et al., 1964; Beaulieu et al., 1987; Bennet et al., 1967; Bennet et al., 1964; Diamond et al., 1964, 1966, 1972). Furthermore, an exposure to EE leads, in different cortical layers, to an increment in the size of neurons' soma and nucleus (Altman and Das, 1964), dendritic branching and length (Holloway, 1966; Kozorovitskiy et al., 2005; Volkmar et al., 1972; Greenough and Volkmar, 1973; Green et al., 1983), number of dendritic spines (Globus et al., 1973), synaptic size and density (Mollgaard et al., 1973; Diamond et al., 1975; Turner and Greenough, 1985; Beaulieu and Colonnier, 1987), postsynaptic thickening (Diamond et al., 1964), gliogenesis (Diamond et al., 1966) and angiogenesis (Ekstrand et al., 2008). The anatomical changes are not limited to cortical regions: indeed, similar effects have been found for striatum (Comery et al., 1995), amygdala (Ichikawa et al., 1993), cerebellum (Floeter and Greenough, 1979; Kleim et al., 1997) and hippocampus (Ekstrand et al., 2008; Diamond et al., 1976; Rosenzweig et al., 1996; Rampon and Tsien, 2000). Moreover, EE increases hippocampal neurogenesis and integration of newly born cells into functional circuits (Kempermann, 1997; Nilsson et al., 1999). Moreover, EE also affects neuronal cell death (Young et al., 1999).

The beneficial effects of EE are detectable at functional and morphological level, in different brain areas, at all ages analyzed so far (Sale, 2018; Sale et al., 2014; van Praag et al., 2000), in animal models of various nervous system disorders, including neurodegenerative diseases (Fischer et al., 2007; Nithianantharajah and Hannan, 2006; Berardi et al., 2007) and different types of brain injury (Comeau et al., 2008; Koopmans et al., 2006; Johansson, 1996).

Focusing on amblyopia, Sale and colleagues showed that EE promotes a full recovery of visual acuity and OD in adult amblyopic animals, an effect due to a marked reduction of GABA levels in the visual cortex (Sale et al., 2007). A decreased cortical inhibition was also demonstrated at synaptic level using in vitro LTP recordings of layer II–III field potentials induced by theta-burst stimulation from white matter (WM–LTP). The WM–LTP is normally not present in adults, as a result of inhibitory circuits maturation (Huang al., 1999; Kirkwood and Bear, 1994b), but it can be restored if GABA-mediated inhibition is reduced (Artola and Singer, 1987; Kirkwood and Bear, 1994b). Notably, WM–LTP was fully restored in the visual cortex of EE adult rats (Sale et al., 2007). This effect was accompanied by an increased expression of BDNF and a lower density of PNNs in the visual cortex contralateral to the previously amblyopic eye (Sale et al., 2007).

Since it has been proposed that beneficial effects of EE might be of reduced interest in terms of their applicability to clinic area, as humans are generally considered already "enriched" in their living conditions (Stryker and Löwel, 2018), it is important to underscore that a significant amount of visual acuity recovery can be also achieved in animals exposed to only one EE component, like animals attaining high levels of voluntary physical exercise or actively engaged in a visual perceptual learning task (Baroncelli et al., 2012). These active training procedures, akin to EE, act through a reduction of I/E balance in the visual cortex. Given their totally non-invasive nature and immediate applicability to human subjects, physical exercise and visual perceptual learning can have a great potential for application to amblyopic patients (Levi and Li, 2009; Lunghi et al., 2018; Lunghi and Sale, 2015).

2.3 Voluntary physical exercise

Besides its widely recognized beneficial effects on total body physiology (Agarwal, 2012; Brown et al., 2012; Colberg et al., 2010; Nystoriak and Bhatnagar, 2018; Segal et al., 2017), physical exercise (PE) promotes brain plasticity, improving memory functions and preventing physiological and

pathological age-related cognitive decline. Aerobic exercise improves cognition (Hillman et al., 2008; Suominen-Troyer et al., 1986; Winter et al., 2007), counteracts age-related memory decline (Kramer et al., 1999; Laurin et al., 2001; Van Praag et al., 2005), delays onset of neurodegenerative diseases (Adlard et al., 2005; Buchman et al., 2012; Larson et al., 2006; Tillerson et al., 2003) and promotes recovery from brain injuries (Archer, 2012; Bohannon, 1993; Morris et al., 2016) and depression (Blumenthal et al., 2007; Lawlor and Hopker, 2001; Murri et al., 2019). Several studies indicate that running is able to induce adult neurogenesis in the dentate gyrus of the hippocampus (Voss et al., 2019, Van Praag et al., 1999), a crucial brain area for learning and memory (Jarrard, 1995). In humans, PE increases hippocampal volume and vascularization (Maass et al., 2015; McAuley et al., 2011; Pereira et al., 2007) and improves hippocampus-dependent episodic memory, probably by increasing hippocampal-neocortical functional connectivity (Suwabe et al., 2018). Similar running-induced changes have been also found in the rodent hippocampus (Patten et al., 2016; van Praag, 2008).

At molecular level, PE modifies the function of several neurotransmitter systems, including glutamatergic system (with a genetic upregulation of the NMDAR, $NMDAR_{2A}$ and $NMDAR_{2B}$ units), GABAergic system (with a downregulation of GABA A receptor and GAD65 expressing genes, (Molteni et al., 2002)), and serotonergic system (Heijnen et al., 2016).

The beneficial effects of PE are tightly linked to the activation of peripheral factors, such as IGF-1 (Carro et al., 2000; Fernandez and Torres-Alemán, 2012), via an activity-dependent mechanism (Nishijima et al., 2010). Moreover, a molecule that has been receiving a lot of attention is irisin (Boström et al., 2012). In the muscles PE activates, through the 5' AMP-activated protein kinase (AMPK), the peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), that controls the expression of the fibronectin type III domain-containing protein 5 (FNDC5), a transmembrane protein from which irisin is cleaved and released in circulation. When released in large quantities, this hormone has antidepressant-like effects, as seen in animal models (Siteneski et al., 2018; Wang and Pan, 2016), and confers neuroprotection against Alzheimer's like neurodegeneration (Lourenco et al., 2019; Noda et al., 2018; Xia et al., 2017).

In addition to irisin, other factors are released from muscles during PE, as the myokine cathepsin B. The concentration of cathepsin B is increased during exercise in the plasma of adult mice and, similarly, in the blood of Rhesus monkeys and humans experiencing treadmill exercise (Moon et al., 2016). Cathepsin B plays a fundamental role in promoting PE-induced brain benefits: it has anti-amyloidogenic and neuroprotective functions (Mueller-Steiner et al., 2006) and its expression is required for spatial memory, adult neurogenesis and for proper mood-related behavior (Moon et al., 2016). Not only the muscle, but also the liver is known to be a main source for key circulating factors in response to PE, such as β-hydroxybutyrate (Sleiman et al., 2016). Interestingly, these factors converge, at the brain level, in the activation of BDNF expression (Landi et al., 2009; Lourenco et al., 2019; Moon et al., 2016; Sleiman et al., 2016; Sleiman and Chao, 2016).

The precise mechanisms leading to the final increase of BDNF may probably involve epigenetic changes on BDNF gene promoters (Gomez-Pinilla et al., 2011; Sleiman et al., 2016). An artificial administration of histone deacetylase (HDAC) inhibitors increases BDNF expression, mimicking the beneficial effects of PE (Calfa et al., 2012; Koppel and Timmusk, 2013; Nan et al., 1998). PE-induced β-hydroxybutyrate, produced within the liver, can endogenously inactivate HDACs triggering increased hippocampal BDNF expression (Sleiman et al., 2016).

The cellular and molecular mechanisms mediating the effects of PE on visual cortex plasticity are becoming to be elucidated. One key molecule in this respect is exercise-induced IGF-1. This molecule is indeed responsible for a faster maturation of both the retina and cortex (Ciucci et al., 2007; Landi et al., 2009; Maya-Vetencourt et al., 2012; Sale et al., 2007). (Ciucci et al., 2007; Landi et al., 2009). Surprisingly, the action of IGF-1 extends also to prenatal phases of brain development, with PE in pregnant dams resulting in increased levels of IGF-1 in the embryos, accelerating intrauterine retinal maturation (Sale et al., 2007). Maya-Vetencourt et al. (2012) proved that exogenous administration of IGF-1 in the adult visual cortex restores OD plasticity and promotes recovery of visual functions in amblyopic animals.

Physical activity has a striking capability to promote recovery from amblyopia in adult subjects. Adult amblyopic rats subjected to voluntary physical exercise completely recover visual functions, an effect totally absent in sedentary control animals (Baroncelli et al., 2012).

A series of elegant experiments performed by Stryker and co-workers provided a deep elucidation of the mechanisms underlying this process. Fu et al. (2014) characterized the responses of different types of visual cortical inhibitory neurons in awake animals free to run on a spherical treadmill. The authors performed calcium imaging of genetically labelled VIP+ cells in freely running mice, exposed to either visual stimulation combined to running or to only running without any visual stimulation. Neural activity of VIP+ neurons (but not of other inhibitory cell types) turned out to be significantly increased during locomotion bouts, with visual stimulation not further increasing the activation of VIP+ cells during the episodes of physical activity. Using the same approach, SOM+ neurons were instead found to be inhibited by locomotion, in a complex circuit in which VIP+ cells establish their synapses on neighboring SOM+ cells, triggering their inhibition (Fu et al., 2015). Thus, during locomotion, activation of VIP+ neurons releases excitatory pyramidal cells from the inhibition exerted by SOM+ neurons, leading to an increased gain of cortical responsiveness (Fu et al., 2015).

Optogenetic activation of VIP+ neurons in non-moving mice consistently mimicked the effect of locomotion, increasing the visual responses of cortical neurons; on the contrary, focal damage to these neurons blocked the gain in responsiveness (Fu et al., 2014). Moreover, local pharmacological blockade of nicotinic receptors, but not of glutamatergic input, greatly reduced the response of VIP+ neurons, suggesting acetylcholine, and not glutamate, is the principal mediator of the PE effects in visual cortex (Fu et al., 2014). Further analysis revealed that upper layer VIP+ cells receive direct input from nucleus of the diagonal band of Broca (NDB), a cholinergic center in the basal forebrain (Fu et al., 2014).

The starting area of this PE driven cholinergic-cortical network seems to be the mesencephalic locomotor region (MLR). The MLR is a midbrain region associated with the ascending reticular activating system described by Moruzzi and Magoun (1949), whose activation is sufficient to induce

locomotion: Lee et al. (2014) found that MLR, when optogenetically stimulated, in awake and head-fixed mice induced locomotion and increased gain of visual cortical responses. Optogenetic activation of the MLR was shown to be sufficient to increase visual responses even in the absence of movement (subthreshold stimulation). This complex disinhibitory circuit activation underlies PE-induced beneficial effects on adult visual cortical plasticity, as proved by artificial silencing of VIP+ synaptic transmission in binocular visual cortex. This genetic interference, indeed, completely prevents the recovery of amblyopic eye cortical responses induced by PE (Fu et al., 2015). Moreover, the same group also showed that locomotion is able to boost adult plasticity also when in response to brief MD periods.

Four/five days of MD are normally insufficient to significantly shift OD in adult mice; however, OD shift in response to MD becomes possible when MD is coupled with locomotion. Also in this case, a genetic silencing of VIP+ neurons in running mice makes MD ineffective in shifting OD of cortical neurons; on the contrary, their optogenetic activation in sedentary mice reproduces the effects of locomotion (Fu et al., 2015).

2.4 Visual perceptual learning

"Perceptual Learning" (PL) refers to long-lasting changes in perception that result from practice or experience, based on a variety of simple sensory tasks (Gibson, 1963). In visual perceptual learning (vPL) such tasks consist in the identification of differences in simple visual attributes, such as position, orientation, texture or shape. PL can remarkably improve visual functions through the use of a wide range of tasks: discrimination of orientation (Holmes and Clarke, 2006; Karni and Sagi, 1991; Matthews et al., 1999; Matthews and Welch, 1997; Schoups et al., 1995; Shiu and Pashler, 1992; Vogels and Orban, 1985), motion direction (Ball and Sekuler, 1987, 1982; Matthews and Welch, 1997), texture (Ahissar and Hochstein, 1996; Karni and Sagi, 1993, 1991) waveforms differences between two sinusoidal stimuli (Berardi and Fiorentini, 1987; Fiorentini and Berardi,

1981, 1980), detection of visual gratings (De Valois, 1977; Mayer, 1983), changes in spatial frequency within simple or complex plaid pattern (Fine and Jacobs, 2000), the ability to detect small depth differences between two targets (Fendick and Westheimer, 1983; Westheimer and Truong, 1988) or to perceive depth in random-dot stereograms (Ramachandran and Braddick, 1973), and object (Furmanski and Engel, 2000) and face recognition (Gold et al., 1999). The vPL time course is specific for each individual task: for some tasks, the effects of learning take place within one or two hours of training (Fahle et al., 1995; Fiorentini and Berardi, 1981, 1980; Liu and Vaina, 1998; Shiu and Pashler, 1992), whereas for others, they are completed after few hundreds of trials (Fiorentini and Berardi, 1981, 1980), showing fast saturation. In other cases, there is an initial fast saturating phase of learning, followed by a slow phase during which the performance continues to improve from one daily session to the next one, until reaching a stable optimal level (Karni and Sagi, 1991).

A usual characteristic of vPL is that it is highly specific and dependent on the stimulus used in the learning task: many studies reported that the visual performance is typically improved on test trials that use the same stimuli as those used during training, and that the performance achieved during training decrease almost totally when the stimuli deviate even slightly from that used at first. This specificity of learning can be found for different stimuli, such as orientation of lines and gratings (Fahle and Edelman, 1993; Fiorentini and Berardi, 1981, 1980; Karni and Sagi, 1991; McKee and Westheimer, 1978; Ramachandran and Braddick, 1973; Schoups et al., 1995), direction of motion (Ball and Sekuler, 1987, 1982) and retinal location of the stimuli (Ball and Sekuler, 1987; Fiorentini and Berardi, 1981; Karni and Sagi, 1991; Schoups et al., 1995; Shiu and Pashler, 1992). Moreover, practice improves discrimination between complex gratings, but the achieved improvement does not transfer to stimuli rotated by 90° (Fiorentini and Berardi, 1980).

The vPL selectivity for the basic features of stimuli suggests the involvement of early stages in cortical processing, where neurons have relatively small receptive fields and are selective for stimulus features, as orientation or size. In general terms, learning specificity is likely mediated by mechanisms present at early stages of visual pathways, where a more accurate representation of

stimulus attributes is present. Many studies have proved this hypothesis in humans (Furmanski et al., 2004; Kourtzi et al., 2005; Pourtois et al., 2008; Skrandies and Fahle, 1994; Yotsumoto et al., 2009), and even in non-human subjects (Chung et al., 2008; Crist et al., 2001; Schoups et al., 2001). However, vPL does not only occur in early stages of visual system, but also in higher levels of visual processing (Chowdhury and DeAngelis, 2008; Law and Gold, 2008; Yang and Maunsell, 2004).

The exact knowledge of areas involved in vPL and the underlying mechanisms of the phenomenon remain largely unknown. One possibility is that specific neuronal changes in brain areas coding for the practiced task, eventually lead to long-lasting modifications in synaptic efficacy. Although the notion that synaptic plasticity underlies learning is widely accepted for declarative memory processes mediated by temporal lobe areas or for some implicit forms of memory such as classical conditioning (Kandel, 2009), the specific role of synaptic plasticity in PL, a form of implicit memory, remains unclear. The most widely accepted view is that the number of neurons representing the learned stimulus increases after training; this mechanism has been found mainly in the auditory (Recanzone et al., 1993) and somatosensory cortex (Recanzone et al., 1992).

In the visual system, vPL seems to be driven, more than by large-scale changes in the entire cortical network, by changes at response level and tuning strength of individual neurons. Schoups and colleagues, in 2001, founded that changes in the orientation tuning of visual cortical neurons lead to an improved performance in the discrimination capacity within primary visual cortex of adult monkeys: this was accompanied, at the trained orientation, by an increase in the slope of the tuning curve, occurring only for neurons with a preferred orientations lying between 12° and 20° of the trained one. This finding led the authors to suggest that learning is correlated with changes in the tuning curves of specific groups of neurons that are most sensitive to small changes near the trained orientation (Schoups et al., 2001). On the other hand, Ghose et al. (2002) found that vPL caused only a small reduction in response amplitude, suggesting that the psychophysical change is mediated by top-down influence for the trained task, and not by an improved neural representation of orientation in early visual areas.

To date, there are only few studies concerning vPL in rodents: some of these describe that OD plasticity can be triggered, in visually stimulated adult mice, by displaying moving square wave gratings during a period of MD, even within two days (Matthies et al., 2013). Moreover, a form of experience-dependent response enhancement (Stimulus-selective Response Potentiation SRP) was described in the visual cortex of awake mice (Frenkel et al., 2006), in which repeated presentations of grating stimuli of a single orientation result in a persistent enhancement of responses evoked by test stimulus. Response potentiation, specific to the orientation of test stimulus, developed gradually over the course of several training sessions, and occurred in both juvenile and adult mice (Frenkel et al., 2006). Being a passive viewing of stimulus presentation, SRP lacks the active component of perceptual learning, albeit the observed effects are consistent with a cortical change induced by vPL. vPL can be dependent on LTP-like phenomena at intra-cortical synaptic responses level in adult visual cortex (Sale et al., 2011).

In the Sale et al. (2011) work, adult rats were required to distinguish between two vertical gratings differing only for their spatial frequency; then, the two stimuli were made progressively more similar to each other, until the animal performance reached a constant value of discrimination (plateau). At the same time, a group of control animals were subjected to an associative version of the same test, in which the animals were to discriminate between a grating and a homogeneous gray panel. Measuring LTP from layer II-III of cortical slices within 1h from the last trial, synaptic potentiation appeared to be occluded in trained animals compared to controls, both in vertical (stimulating electrode placed in layer IV) and horizontal configuration (stimulating electrode placed in layer II/III). Moreover, a significant leftward shift was found in the input/output curves of trained animals compared to controls. All these effects were not detected in primary somatosensory cortex (Sale et al., 2011). Thus, the data fulfilled criteria of occlusion, mimicry, and specificity, three of the most commonly accepted principle connecting LTP with learning. Moreover, the results suggest that improvements in visual discrimination abilities induced by vPL can be explained in terms of long-term increments of synaptic efficacy in primary visual cortex (Sale et al., 2011).

VPL is increasingly considered a very promising strategy for amblyopia treatment in adulthood (Bonaccorsi et al., 2014). In amblyopic subjects, vPL can remarkably enhance visual functions on a wide range of tasks, including Vernier acuity (Levi and Polat, 1996; Levi et al., 1997), positional acuity (Li and Levi, 2004; Li et al., 2005, 2007), contrast sensitivity (Polat et al., 2004; Zhou et al., 2006; Huang et al., 2008), first-order letter identification (Levi, 2005; Chung et al., 2008), and second-order letter identification (Chung et al., 2006). Practicing vPL tasks with the amblyopic eye shows little or no transfer to attributes of visual stimuli other than those used during training (Levi and Polat, 1996; Levi et al., 1997; Li and Levi, 2004).

Since vPL is specific to the trained stimulus, its therapeutic value for treating amblyopia can be uncertain. However, in many vPL tasks (Vernier acuity, position discrimination and contrast sensitivity), a partial transfer to improvements in visual acuity has been reported (Levi and Polat, 1996; Levi et al., 1997; Li and Levi, 2004; Polat et al. 2004; Zhou et al. 2006; Huang et al. 2008). Besides visual acuity, other visual functions can also beneficially be affected by vPL, such as stereo-acuity and visual counting (Li and Levi 2004; Li et al. 2007). Li et al. (2004) showed that the improvement in visual acuity in the amblyopic eye resulting from position discrimination training persisted for quite a long time period (from three to twelve months). Polat et al. (2004) also reported a very high level of retention of improved visual acuity following the end of learning, and Zhou et al. (2006) reported that, in few cases tested, the improvement in visual acuity showed a learning maintenance of approximately 90% for at least one year.

PL might be effective in amblyopia therapy for several reasons. First, some of the improvements obtained with PL can reflect the effects of conventional patching: in fact, the preferred eye of amblyopic observers is patched while they perform the perceptual task. Second, and probably most importantly, PL is a form of "active" treatment, during which the amblyopic eye is forced closer to the limit of its performance. Third, through constant practice, perceptual learning is able to retune the previously amblyopic visual system towards a correct visual perception (Li et al., 2008). Thus, practicing position discrimination can reduce spatial distortion (internal positional noise) and enhance

sampling efficiency (the ability to extract stimulus information) in amblyopic vision (Li and Levi, 2004; Li et al., 2007, 2008). In a similar way, practicing identification of low contrast letters in noise (Levi, 2005) improves the contrast threshold for letter recognition primarily through increased efficiency.

In animals' models, adult amblyopic subjects subjected to vPL display a marked recovery of visual functions compared to control groups subjected to two different associative versions of the same task, i.e. animals trained to discriminate between a grating and a homogeneous gray panel or trained only to discriminate between two panels whose spatial frequencies area always maintained fixed (Baroncelli et al., 2012).

AIMS OF THE THESIS

Non-invasive strategies based on enhanced voluntary physical exercise and vPL appear as very promising tools to treat amblyopia in adult subjects. Despite the increasing evidence showing beneficial effects elicited by these non-invasive active training procedures, many open issues remain.

Can active training promote recovery of visual functions when performed under binocular sigh conditions? Are active training procedures effective enough to induce recovery of visual depth perception? How long can visual recovery last? Which are the mechanisms underlying the reduced GABAergic tone associated with plasticity enhancement after active training?

As stated before, a considerable amount of experimental work has shown the possibility to exploit behavioral approaches to enhance visual plasticity in V1: this step is essential for visual function recovery from amblyopia. The recovery paradigms tested so far were based either on a reverse suture approach (Baroncelli et al, 2012), not easily applicable to adult human subjects, or involved episodes of physical activity in head-fixed animals exposed to specific visual stimuli (Kaneko and Stryker, 2014), leaving completely unexplored the possibility to rescue visual functions in adult amblyopic subjects exposed to totally free moving paradigms and conserving binocular sight conditions. Furthermore, since is known that early sensory deprivation also affects stereoscopic abilities, and many experiments have already tested the effectiveness of non-invasive treatments such as EE on visual depth perception (Baroncelli et al, 2013), it is crucial to test whether active training is able to elicit similar effects.

To date, indeed, the effects of voluntary physical exercise or visual perceptual learning on stereopsis have not been clarify yet. Furthermore, the long-term maintenance of visual function recovery past the end of treatment, an essential requirement for clinical application, has not been investigated.

Moreover, little is known about the molecular and physiological mechanisms underlying the recovery process. A well-established role emerges for the GABAergic system and a modulation of the E/I balance in specific cortical circuits, with recent papers reported the key role of a disinhibitory circuit where GABAergic interneurons interact with each other to control brain plasticity enhancement (Fu et al, 2014 and 2015; Sansevero et al, 2020).

With the aim of providing an answer to all these still unsolved issues, in the present PhD Thesis I investigated whether specific active training procedures, namely voluntary physical exercise and visual perceptual learning, are able to reactivate cortical plasticity and restore visual functions in adult amblyopic rats.

MATERIAL AND METHODS

1. Animal housing

All experiments were conducted, in accordance with the approved guidelines and regulations of Italian Ministry of Public Health, on Long-Evans black hooded rats (Charles River, Massachusetts, USA) of both genders and at 2-3 months of age. Animals were housed in a room with a temperature of 21°C and a 12- h light–dark cycle, with food and water available *ad libitum*. All efforts were made to minimize animal suffering, to reduce the number of animals used, and to utilize alternatives to in vivo techniques, if available.

2. Surgical procedures

Rats were anesthetized with zolazepam + tiletamine (Zoletil, 1 mg/kg) and monocular deprivation (MD) was performed through eyelid suture at postnatal day (P) 21 (He et al., 2007; Pizzorusso et al., 2006; Silingardi et al., 2010; Vetencourt et al., 2008). Lid margins were trimmed and sutured with 6-0 silk. Animals were allowed to completely recover from anesthesia and then rehoused to their cages. A post-operative health check control was performed daily both until complete cicatrization and until critical period closure (P45); subjects with even minimal spontaneous re-opening were excluded from succeeding experiments.

At adult age the long-term deprived eye was reopened under anesthesia using thin scissors. Again, if eye anomalies were detected animals were completely excluded. Animals were allowed to recover from anesthesia for few days before starting the treatment. Then, they were subjected to one of the two active training procedures with restored binocular sight conditions.

3. Voluntary physical exercise

Adult deprived rats (P70) were subjected to deprived eye reopening and divided in three groups according to the experimental protocol: naïve (not deprived), sedentary and running animals. Sedentary and naïve animals were individually maintained in standard housing conditions, consisting of 40 x 25 x 20 cm cages.

Running rats were placed in cages endowed with a running wheel connected to an automatic device recording the number of wheel turns. The wheel rounds were then converted in covered meters. The numbers of rounds were recorded weekly and the turning device was offset to zero.

Training experiment was carried on for three weeks under binocular sight conditions. Animals were constantly inspected to prevent the closure of the reopened eye leads. Food and water were provided *ad libitum*.

4. In vivo electrophysiological recording

Running and sedentary rats were anesthetized with an intraperitoneal injection of 20% urethane (0.7 ml/hg of body weight) and mounted in a stereotaxic apparatus. Additional doses of urethane were used to keep the anesthesia stable throughout the experiment. Both eyes were restrained in a fixed position through adjustable metal rings surrounding the external portion of the eye bulb. Body temperature was continuously monitored and maintained at 37°C with a thermostatic electric blanket during the experiment. Respiration was facilitated through an oxygen mask.

A portion of the skull overlying the OcB1 was carefully drilled and the dura mater was removed. An electrode (2×2-tet-3 mm-150-150-121-A16-15, Neuronexus Technologies) was inserted into the cortex perpendicularly to the stereotaxic plane, 5 mm lateral to lambda (intersection between sagittal- and lambdoid-sutures). The electrode was made by two symmetrical tips of 3 mm, 150 μm distant one from another, bearing each a pair of four microwire electrodes (tetrode; 121 μm2 each electrode) separated by 150 μm.

Visual evoked potentials (VEPs) were recorded from the binocular portion of the visual cortex (Oc1B). The visual stimuli were sinusoidal gratings of different spatial frequencies (SFs) presented on the face of a monitor. The display was placed 20 cm in front of the animal. Electrical signals were amplified, digitized and averaged (at least 50 events) in synchrony with the stimulus contrast reversal.

Binocularity was evaluated by calculating the contralateral to ipsilateral VEP ratio (C/I ratio), i.e. the ratio of VEP amplitudes recorded by stimulating the eye contralateral and ipsilateral, respectively, to the visual cortex where the recording is performed.

During recording through one eye, the other was covered by a mechanical-driven automatized slit. To prevent sampling bias for each animal, at least three well-spaced penetrations were performed. Care was taken to equally sample VEPs across the cortical depths so that all layers contributed to the analysis.

VA of each eye was obtained by extrapolation to zero amplitude of the linear regression through the data points in a curve where VEP amplitude is plotted against log SF.

5. Behavioural procedures

5.1 Visual acuity assessment: The Prusky water maze

A group of deprived animals were subjected to a behavioural task for visual acuity assessment.

To measure visual acuity, we used the visual water maze task (Prusky et al., 2000; Sale et al., 2007): visual acuity was measured, first, on the open eye (not deprived), then, after reverse suture (RS, i.e. the reopening of deprived eye and the closure of the other one) we measured the visual acuity of the amblyopic eye. This last procedure was repeated four times, i.e. immediately at the end of treatment, and then at 30, 90 and 180 days after the end of treatment (Follow up procedures, FUP).

The basic apparatus used for visual acuity task consists of a trapezoidal-shaped pool with two computer-controlled monitors placed side-by side at one end. The pool is made of 6 mm clear Plexiglas and comprises a rectangular floor (140 cm long x 80 cm wide) and 55 cm (high) walls. The

pool is wider at one end (80 cm) than the other (25 cm) and the two long walls and narrow end are finished on the inside with flat black paint to reduce reflections. A midline divider (50 cm long) extends from the end wall between the monitors into the pool, bisecting it along its long axis. The divider is painted black on both sides to make it opaque and reduce reflections within the pool. The length of the divider sets the choice point and effective SF: it is the closest an animal can get to the monitors without entering one of the two arms. The pool is filled with tepid (22°C) opaque water to a depth of 15 cm. Screen reflections on the surface of the water render the platform invisible from water level.

Animals start to swim from the center at the end of the pool, opposite to panels. A portable escape platform is placed below one of the monitors. The position of the grating and the platform was alternated in a pseudorandom sequence over training trials while the rats were shaped to swim towards the grating in one of the maze arms.

A trial was recorded as incorrect if an animal entered the arm without the platform. Animals were removed from the pool when they found the platform.

Rats were first trained to distinguish a low (0.1 cycles deg–1) SF vertical grating from grey. Once 80% accuracy was achieved in 10 trials made in three subsequent sessions distributed in two consecutive days, the limit of the discrimination was estimated by increasing the SF of the grating.

Visual acuity was calculated as the SF corresponding to 70% of correct choices on the sigmoidal function fitting the psychometric function in which the percentage of corrected choices was plotted against SF.

5.2 Visual perceptual learning task

A modified version of Prusky visual water maze was used to perform a visual perceptual learning task. After establishing binocular sight conditions through fellow eye reopening, the perceptual learning group of animals (PL rats) was first required (training phase) to distinguish a 0.116 cycles

per degree (c/deg) SF grating (reference grating) from a 0.592 c/deg SF grating (test grating). The two gratings had the same luminance (40.06 cd/m2) and the same contrast (100%).

A custom-made software presented the two stimuli on the monitors, alternating the position of the test and the reference grating in a pseudorandom schedule. The submerged platform was always positioned in correspondence of the reference grating.

After the animals achieved at least 80% of accuracy in three subsequent sessions of 10 trials each, distributed in two consecutive days, the PL protocol was started. The test consisted in three sessions per day of 15 trials each, separated by 60 minutes. The SF of the test grating was gradually reduced from 0.592 c/deg to 0.122 c/deg. If the animal made a correct choice, the SF of the test grating was decreased by one step and another trial was executed. This procedure continued until an error was made.

After trials covering approximately half of the task were completed, the minimum number of trials in a block was increased to four. For the last SFs of the test grating, the required performance to decrease the SF was increased to 7/10 correct choices. Three correct responses in a block of four trials or seven in a block of ten trials were required to decrease the SF by one step. Instead, if more than 1/4 or 3/10 errors were made, the SF was increased by one step and another block of trials was run.

The PL task ended when the animal performance reached a plateau (performance at a given SF of the test grating oscillating around 70% of correct choices for three consecutive days).

A group of control animals (1^{st} step rats) were allowed to only discriminate the reference grating from a test grating whose SF was keep fixed at the starting value of 0.592 c/deg. Also for this group of animals, the test consisted in three sessions per day of 15 trials each, separated by 60 minutes.

5.3 Visual Cliff Task for depth perception abilities assessment

All the procedures used for this task were previously described by Baroncelli et al. (2013). The apparatus consisted of a rectangular arena (100 x 40 cm) constructed in poly (vinyl chloride) with black walls and bordered by black shutters preventing animals to escape. A patterned floor consisting of 3 cm black-and-white checked paper covered the surface of the platform below a Plexiglas plate. Lamps placed below the patterned floor illuminated the deep surfaces to equate the brightness of the two sides. A camera hanging on the apparatus was connected to a computer allowing the experimenter to observe and record the rat behaviour.

The arena was divided into a shallow and a deep side: on the shallow side the patterned floor was positioned immediately below the plate, whereas on the deep side it was moved below the plate.

Each animal was placed on the shallow side, and the total time spent exploring each side of the arena was recorded. The trial ended after 5 min. The arena was then cleaned between trials with alcohol solution. A discrimination index (indicating the time spent on the shallow side of the arena) was calculated as follows: (Ts-Td)/Ttot, where Ts and Td are, respectively, the time spent exploring the shallow and the deep side of the arena and Ttot means instead the total time of the test.

The visual cliff test was performed five times, before treatment, immediately after treatment and then 30, 90 and 180 days after the end of treatment. A separate group of animals accomplished the same test 1, 30, 90 and 180 days after physical exercise (follow up procedure, FUP).

6. Transcardial perfusion and brain collection

After the end of experimental procedures, rats were subjected to eyelid suture of the fellow eye, placed in a dark light-proof room for two days and then re-exposed to light for 2 hours.

Animals were anesthetized with an overdose of chloral hydrate (10% in saline; Sigma Aldrich) and perfused transcardially with Phosphate Buffered Saline (10 mM; PBS) followed by fixative (4% Paraformaldehyde, 0.1 M Sodium Phosphate, pH 7.4).

Brain was then removed and post-fixed for 3 hours in the same fixative (4%) at room temperature (RT), before being washed three times with PBS and immersed in a sucrose solution (30% in sodium phosphate pH 7.4) until complete precipitation.

7. Immunohistochemical staining

Brain slices of 50 µm thickness were cut with a sliding microtome (Leitz, Germany). All the reactions were performed on free-floating sections.

After a blocking step in 10% NGS (Normal Goat Serum) and 0,4% Triton X-100 in PBS (1 hour at RT) a double staining for C-Fos and GABAergic inhibitory interneurons markers was done used a primary antibodies' solution with 2% NGS, 0,2% Triton X-100, 1:1000 guinea pig anti C-Fos polyclonal antibody (Synaptic System, Gottingen, Germany) and either 1:2000 mouse anti-Parvalbumin, 1:2000 (Sigma Aldrich) or rabbit anti-Somatostatin (DBA Italia s.r.l., Italy), or 1:500 rabbit anti-Vasoactive Intestinal Peptide (DBA Italia s.r.l., Italy), in PBS (overnight at 4°C).

Antigen-antibody binding was revealed with a solution composed by 1% NGS, 0,1% Triton X-100, 1:500 goat Alexa Fluor 448 anti-guinea pig, 1:500 goat Alexa Fluor 568 anti-mouse and 1:500 goat Alexa Fluor 568 anti-rabbit (2 hours covered at RT).

Slices were mounted on glass slides and covered with VectaShield mounting medium (Vector Labs, USA). Images from the binocular primary visual cortex were acquired at 20x magnification. For each animal, 5 to 7 slices were acquired and, for each section, labeled cells were counted in three different sample windows, corresponding to layers 2/3, layer 4 and layers 5/6, in the V1 area. Sections were acquired using a high resolution fluorescent microscope empowered with an Apotome 2.0 slit (Zeiss, Germany) to analyze the number of active GABAergic-positive interneurons.

Double stained cells were counted manually using a blind procedure, and their density was calculated using Fiji ImageJ software. The obtained values, expressed as positive cells/mm2, were used for statistical analysis.

8. Statistical analysis

Statistical analysis was done using SigmaStat Software. Differences between two independent groups were assessed with a two-tailed t-test; differences between two dependent groups (e.g. visual acuity of the deprived and fellow eyes in the same animals) were assessed with a two-tailed paired t-test. One-way ANOVA, Two-way ANOVA and Two-way RM ANOVA, followed by Holm–Sidak multiple comparison procedure, were used to compare data belonging to more groups. Level of significance was $p < 0.05$, unless otherwise specified.

RESULTS

1. Experimental design

To investigate the effects of active training on visual functions recovery in adult amblyopic animals, monocular deprivation (MD) was performed through eyelid suture at postnatal day (p) 21. Adult animals (p60) were subjected to two different treatments, either voluntary physical exercise or visual perceptual learning, both performed under binocular sight conditions. Visual acuity and visual depth perception abilities were measured at different time points in all animals behaviorally, using the visual water box task and a "visual cliff" apparatus, respectively. At the end of treatment, the animals were transferred to darkness for 48h, re-exposed to light and sacrificed. The brain was collected for Immunohistochemical and anatomical analysis aimed at evaluating the activation of distinct subclasses of GABAergic interneurons. To evaluate whether visual function recovery was also detectable at the level of primary visual cortical circuits, a separate group of animals was assigned for electrophysiological analysis, where visual acuity and ocular dominance were measured using electrophysiological recordings of visual evoked potentials (VEPs) from V1. Ocular dominance was determinate measuring the contralateral to ipsilateral (C/I) VEP ratio in response to a low spatial frequency grating (0.1 c/deg).

Since they are still ongoing, the electrophysiological and Immunohistochemical experiments for the vPL are not reported in this Thesis.

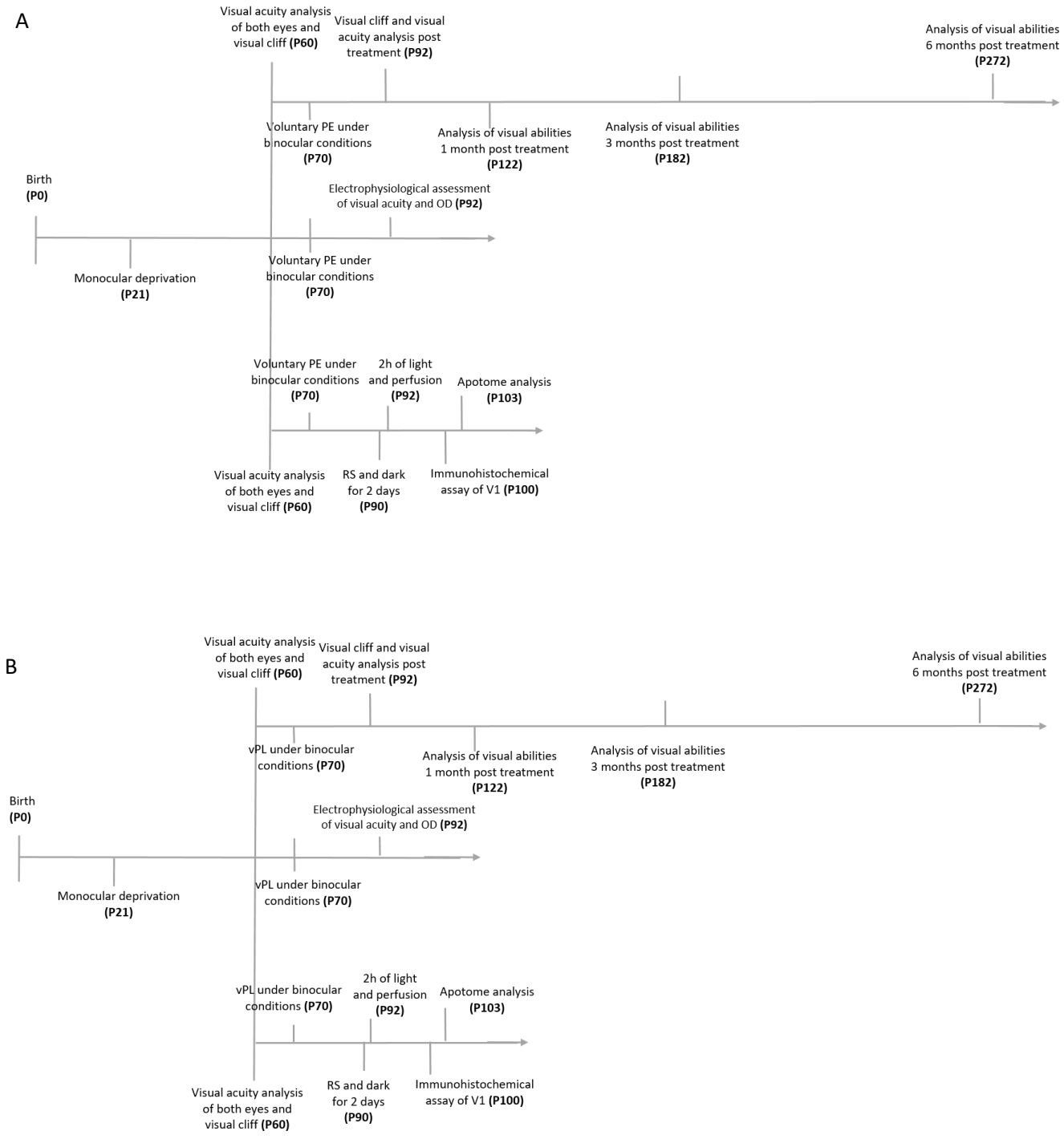

Figure 1. Schematic diagram of the physical activity experimental protocol (A) and of the vPL protocol (B).

2. *Voluntary physical exercise promotes long lasting recovery of visual acuity*

To investigate the effects of voluntary physical activity on visual function recovery in adult amblyopic rats, we compared visual abilities in a group of adult long-term deprived rats subjected to three weeks of free running (in cages supplied with a running wheel), with those reared in conventional standard conditions (sedentary animals), and with those of non-deprived rats (naïve rats). Past the end of the monocular deprivation period (P21-P60) visual acuity (VA) was first measured through the non-amblyopic (fellow) eye. Rats were then subjected to reverse suture (RS), and VA was measured through the amblyopic (deprived) eye. Then, animals underwent active training under binocular sight conditions and, immediately after that, VA of the amblyopic eye was re-evaluated, keeping surgically closed the non-amblyopic eye. VA was then re-evaluated at three additional follow-ups (1, 3, and 6 months past the end of the treatment). VA assessment was performed using a modified version of the Prusky visual water maze (Fig. 2) (Prusky et al., 2000; Sale et al., 2007).

After three weeks of voluntary running, a robust recovery of visual acuity was evident in running animals (n = 6) (amblyopic eye: 0.86 ± 0.02 c deg–1; fellow eye: 0.89 ± 0.02 c deg–1) (Fig. 3); on the contrary, visual acuity recovery was totally absent in control sedentary rats (n = 5; amblyopic eye: 0.64 ± 0.01 c deg–1; fellow eye: 0.99 ± 0.02 c deg–1) (Two-Way RM ANOVA, treatment x time $F = 39.078$, Holm-Sidak method, $p = 0.403$ for running rats, $p < 0.001$ for sedentary rats) (Fig. 3). Visual acuity recovery in running rats was maintained at all follow-ups after the end of the exercise training (Two-Way RM ANOVA, Holm-Sidak method, post-treatment vs. 1 month after treatment, $p = 0.760$; post-treatment vs. 3 months, $p = 0.178$; post treatment vs. 6 months, $p = 0.996$) (Fig. 3). Importantly, the formerly amblyopic eye in running animals had a visual acuity value not significantly different from that of naïve animals; both groups had a visual acuity significantly higher than that of control sedentary rats, at the same time points (naïve, 0.87 ± 0.03 c deg–1; One Way ANOVA, $F = 25.319$, Holm-Sidak method, $p = 0.838$, $p < 0.001$, $p < 0.001$, respectively) (Fig. 3).

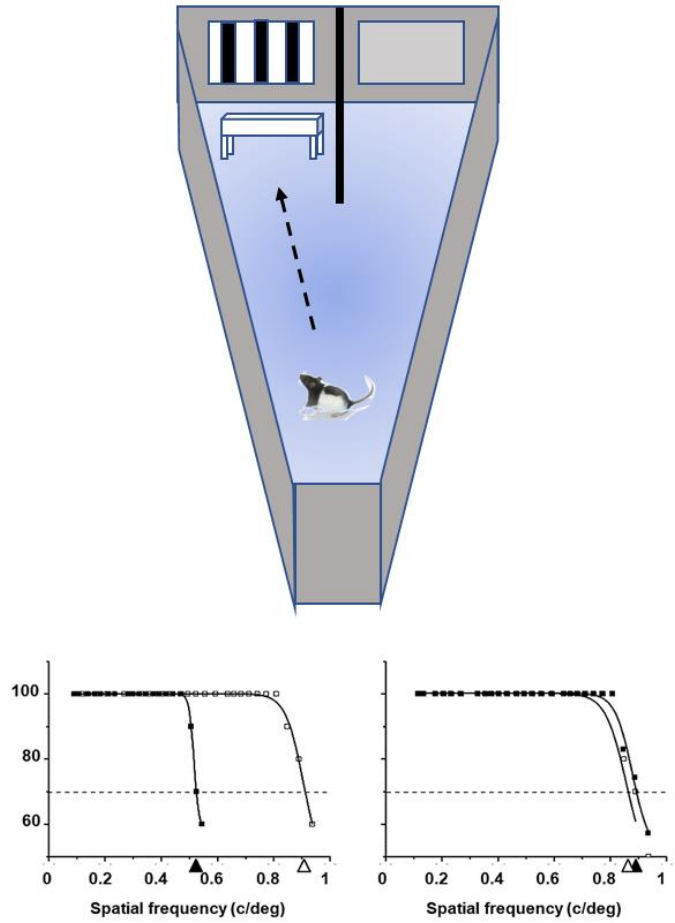

Figure 2: The visual water box task. In the top-panel, a representation of the Prusky visual water maze. Small incremental changes in the SF of the stimulus are made between successive blocks of trials until the ability of animals to distinguish a grating from grey falls to chance. In the bottom-panel, VA has been taken as the SF corresponding to 70% of correct choices (dashed line) on the sigmoidal function fitting the psychometric function. After active training, the VA measured through the amblyopic eye (filled triangle) remained different from that measured through the non-deprived eye (empty triangle) in control animals (graph on the left), but not in treated animals (graph on the right).

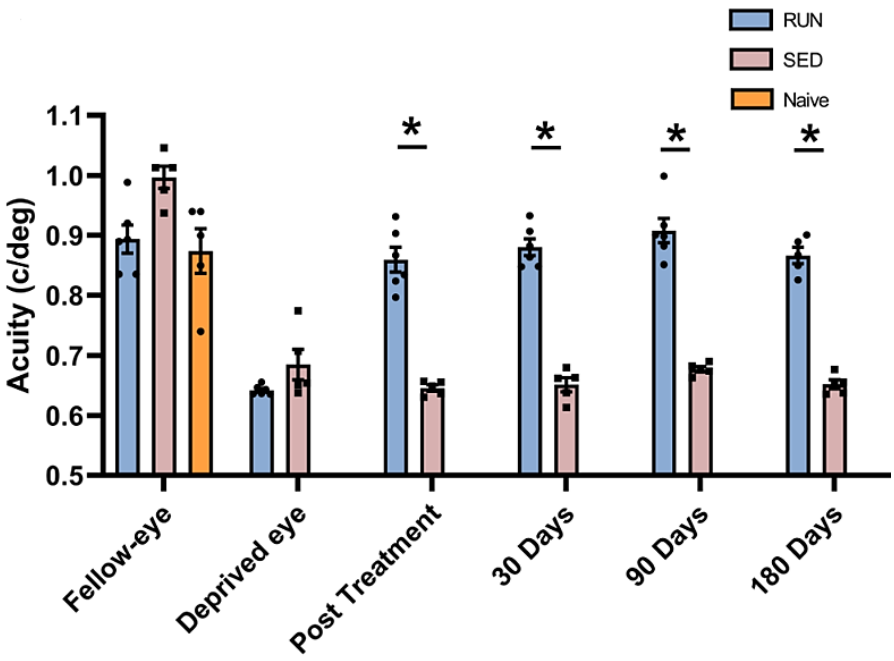

Figure 3: **Behavioral assessment of visual acuity.** Visual acuity measurement using the visual Prusky water maze. At the end of the physical activity period, the previously amblyopic eye was different from that of the fellow eye in sedentary animals (Two-Way RM ANOVA, $p<0.001$) but not in running animals ($p=0.403$). Two-Way RM ANOVA revealed that, in running animals, the visual acuity of the previously deprived eye, measured immediately after the end of treatment, was significantly increased with respect to that measured before treatment ($p<0.001$). Moreover, it remained unaltered 30, 90 and 180 days after the end of the treatment ($p=0.760$; $p=0.178$; $p=0.996$). In contrast, the visual acuity of the deprived eye did not change in sedentary rats (Two-Way RM ANOVA, Holm-Sidak method, pre-treatment vs. post-treatment $p=0.403$; pre-treatment vs. 1 month after treatment $p=0.575$; pre-treatment vs. 3 months $p=0.992$; pre-treatment vs. 6 months $p=0.566$).

3. Voluntary physical exercise rescues visual depth perception abilities

Then, I investigate, through the visual cliff task (Gibson and Walk, 1960; Booher and Walk, 1968; Bauer,1973; Baroncelli et al, 2013), the effects of physical activity on visual depth perception abilities. The visual cliff task exploits the spontaneous tendency of rodents to avoid the deep side of a visual cliff arena.

While I found no preference for the shallow side of the arena in sedentary rats (n = 8; exploration index = 0.16 ± 0.06), exercised rats (n = 7) displayed a clear preference for the shallow side of the arena, with an exploration index (0.51 ± 0.08) much higher than that found in control rats and equal to that of naïve rats with normal binocular vision (n = 6; 0.520 ± 0.03) (One-way ANOVA, between groups $F = 9.717$, Holm-Sidak method, $p < 0.05$, $p = 0.977$, respectively) (Fig. 4). In agreement with the results of visual acuity, recovery of visual depth perception abilities in running rats was long lasting, persisting for the entire 6-months follow-up period (Fig. 4).

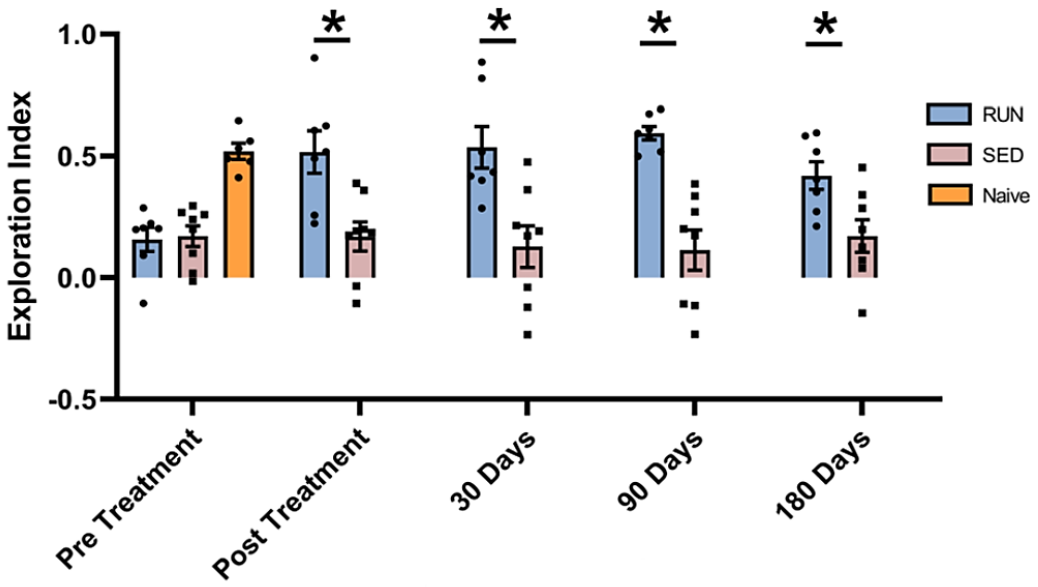

Figure 4. Results of visual depth perception abilities assessment obtained using the visual cliff task. Visual depth perception ability was assessed using the visual cliff task, as the exploration preference for the shallow and the depth side of the arena. One-way ANOVA showed a significant preference for the shallow side in running animals, which exhibited an exploration index statistically higher, respectively, than that founded in sedentary rats (Holm-Sidak method, $p<0.05$). All animals were tested under binocular sight conditions.

4. Electrophysiological assessment of visual function recovery in long-term deprived adult animals

To evaluate whether visual function recovery was also detectable at the level of primary visual cortical circuits, visual acuity and ocular dominance were measured using electrophysiological recordings of visual evoked potentials (VEPs) from V1 (Fig. 5).

Recordings were made immediately at the end of the physical activity period. In sedentary control rats (n = 5), visual acuity of the deprived eye remained significantly lower (0.62 ± 0.02 c deg–1) than that of the fellow eye (0.86 ± 0.03 c deg–1) (Two-Way RM ANOVA, Holm-Sidak method, F = 25.601, p < 0.001) (Fig. 5). On the contrary, there was no difference between the visual acuity values of the two eyes either in running rats (n = 5, contralateral visual acuity: 0.93 ± 0.04 c deg–1; ipsilateral visual acuity: 0.88 ± 0.04 c deg–1; p = 0.101), or in naïve animals (n = 4, contralateral visual acuity: 1.01 ± 0.06 c deg–1; ipsilateral visual acuity: 0.97 ± 0.04; p = 0.200) (Fig. 5).

In full agreement with the behavioral analysis, visual acuity in the formerly amblyopic eye of running animals did not significantly differ from that of naïve rats; in both groups of animals, visual acuity was higher than that of sedentary rats (p = 0.127 and p < 0.001, respectively).

To determine ocular dominance (OD), I measured the contralateral to ipsilateral (C/I) VEP ratio in response to a low spatial frequency grating (0.1 c/deg). C/I VEP ratio is calculated as the ratio of average VEP amplitudes recorded by stimulating the eye contralateral and ipsilateral, respectively, to the visual cortex where the recording is performed. In sedentary rats (n = 9), there was no recovery of OD in the primary visual cortex contralateral to the formerly deprived eye, which remained significantly lower than in naïve rats (n = 9) (Fig. 6) (C/I VEP ratio in sedentary animals: = 0.92 ± 0.09, in naïve rats 2.76 ± 0.26, One-Way ANOVA on ranks, Tukey test, $p < 0.05$) (Fig. 5). In contrast, running rats (n = 9) showed a marked rescue of OD, with a C/I VEP ratio of 2.69 ± 0.36 (Fig. 6). The C/I VEP ratio in running animals was significantly higher than in sedentary rats (One-way ANOVA,

on ranks, Tukey test, $p < 0.05$), while it was not different from that of naïve rats (n = 9; C\I VEP ratio = 2.76 ± 0.26; $p > 0.05$) (Fig. 6).

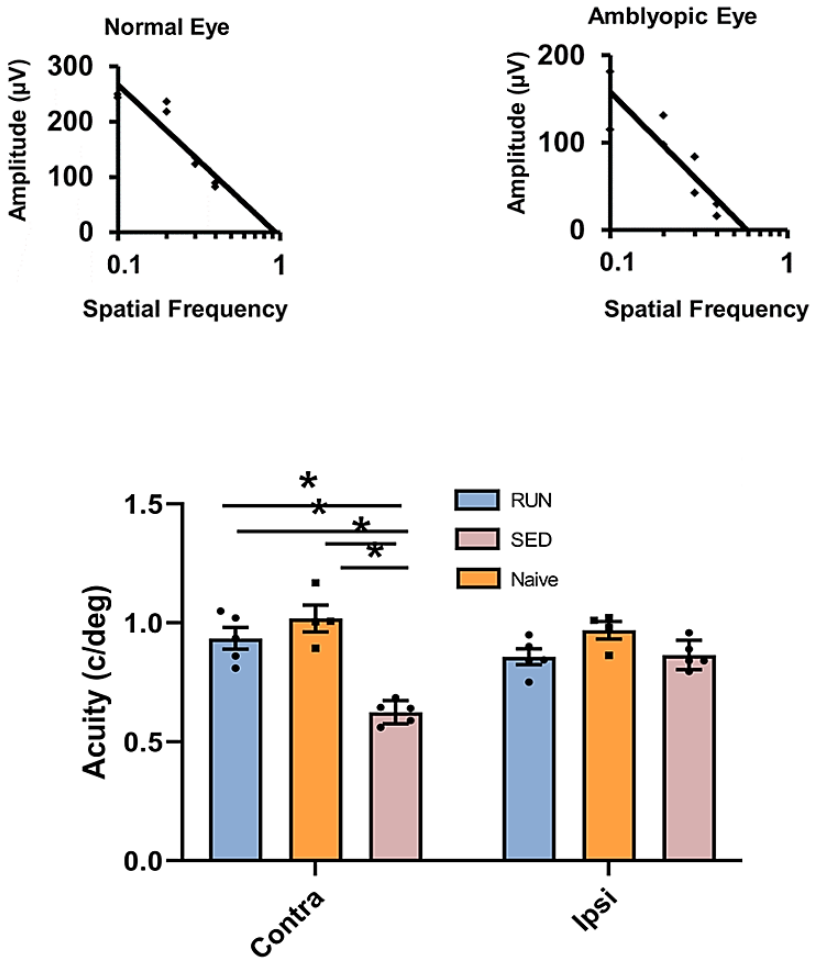

Figure 5: Electrophysiological recording of Visual Evoked Potentials (VEPs) from V1. VEPs were recorded in the visual cortex contralateral to the long-term deprived eye. Sedentary animals displayed a significantly lower visual acuity value in the deprived eye with respect to the fellow eye (Two-Way RM ANOVA, Holm-Sidak method, $p<0.001$). Running animals showed a significant recovery of visual acuity in the deprived eye (running animals: deprived eye vs. fellow eye, $p= 0.101$). Running and naïve animals showed no significant difference in visual acuity (running rats vs. naive animals deprived eye, $p= 0.127$).

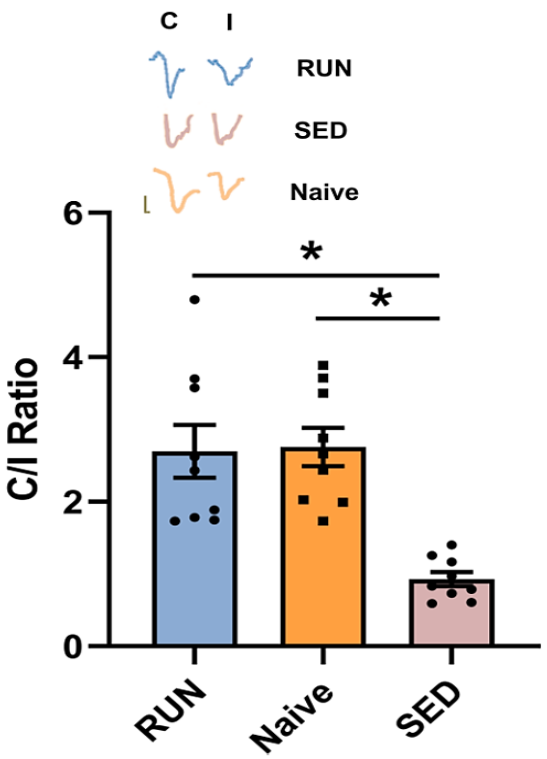

Figure 6: Assessment of ocular dominance (OD) in V1. OD was measured through the C/I VEP ratio in response to a low spatial frequency grating. The C/I VEP ratio was significantly higher in running animals (approximately 2,5) with respect to sedentary animals, which had a ratio value that remains around 0,5 (One-Way ANOVA on ranks, Tukey test $p<0.05$). Furthermore, running animals C/I VEP ratio did no differ from naive animals ratio value ($p>0.05$). Error bars indicate s.e.m; * indicates statistical significance.

5. Phenotypical dissection of active GABAergic connections in amblyopia recovery induced by voluntary physical activity

Seminal papers by Stryker's group have suggested that physical activity in tethered mice modulates a gain of visual cortical responses acting on visual cortical inhibitory interneurons, acting via a synaptic disinhibition involving two specific subpopulations of cortical GABAergic interneurons, i.e. somatostatin-positive and vasoactive-positive interneurons (Stryker, 2014; Fu et al, 2014; Fu et al, 2015). Thus, I addressed the impact of long-term deprivation and exposure to enhanced physical activity on selective activation of different inhibitory neuronal sub-populations.

To target specific cortical interneurons, I used immunohistochemistry for the activity-dependent marker c-Fos, in association with markers selective for three distinct GABAergic subclasses of cells: intestinal peptide positive (VIP+), somatostatin positive (SOM+) and parvalbumin positive (PV+) interneurons. The analysis was performed in the V1 of naïve (n = 6), running (n = 5) and sedentary rats (n = 6). To estimate the number of neurons activated by the deprived eye, animals were put in total darkness for 2 days at P81, which, in running and sedentary animals, corresponds to the end of binocular experience with or without physical exercise; shortly before transferring the animals in darkness, their fellow eye was closed, so that, upon light re-exposure, only the previously long-term deprived eye was open. At the same manner, also in naïve animals one eye was closed during the 2 days of dark exposure. All groups of animals were then re-exposed to 2h of normal light condition. In this way, it was possible to evaluate the activation of specific GABAergic interneurons in response to a selective stimulation through the long-term deprived eye. All the animals were then sacrificed and an evaluation of the number of active GABAergic inhibitory cells was performed in V1.

Significant changes in interneuron activation were only detectable in the V1 layer 2/3. In sedentary animals (n = 6), a marked increase in the number of active SOM+ interneurons was found compared to naïve animals (sedentary rats: 7.200 ± 2.15; naïve rats: 0.257 ± 0.16) (One-way ANOVA

on ranks, Dunn's Method, q = 2.687, $p < 0.05$) (Fig. 7). This effect was completely reversed in running animals (n = 5), in which the number of active SOM+ interneurons did not differ from that of naïve rats (running rats: 0.259 ± 0.23; naïve rats: 0.257 ± 0.16) (One-way ANOVA on ranks, Dunn's Method, q = 0.109, $p < 0.01$) (Fig. 7). A similar trend was found in the V1 layer 5/6 for which, however, differences did not reach statistical significance (sedentary rats: 3.064 ± 1.14; running rats: 0.137 ± 0.12; naïve: 0.367 ± 0.24) (One-way ANOVA on ranks, Dunns' Method, $p < 0.05$ for difference among the three groups; $p = 0.09$ sedentary animals vs. naïve; $p > 0.1$ running rats vs. naïve) (Fig. 7).

In running animals, I also observed an increment in the number of active VIP+ interneurons in comparison with sedentary rats in layers 2/3 (running rats: 7.149 ± 2.56; sedentary animals: 0.852 ± 0.31; naïve: 1.375 ± 0.60) (One-way ANOVA on ranks, Dunns' Method, q = 2.453, $p < 0.05$). No difference was found in the number of VIP+ active interneurons among naïve, running and sedentary animals in layers 5/6 (One-way ANOVA on ranks, Dunns' Method, $p = 0.948$) (sedentary animals: 0.080 ± 0.08; running animals: 0.313 ± 0.28; naïve: 0.162 ± 0.16) (Fig. 7).

No difference was found in the number of active PV+ interneurons among naïve, running and sedentary animals (One-way ANOVA on ranks, q = 0.587), in agreement with previous results (Fig. 7).

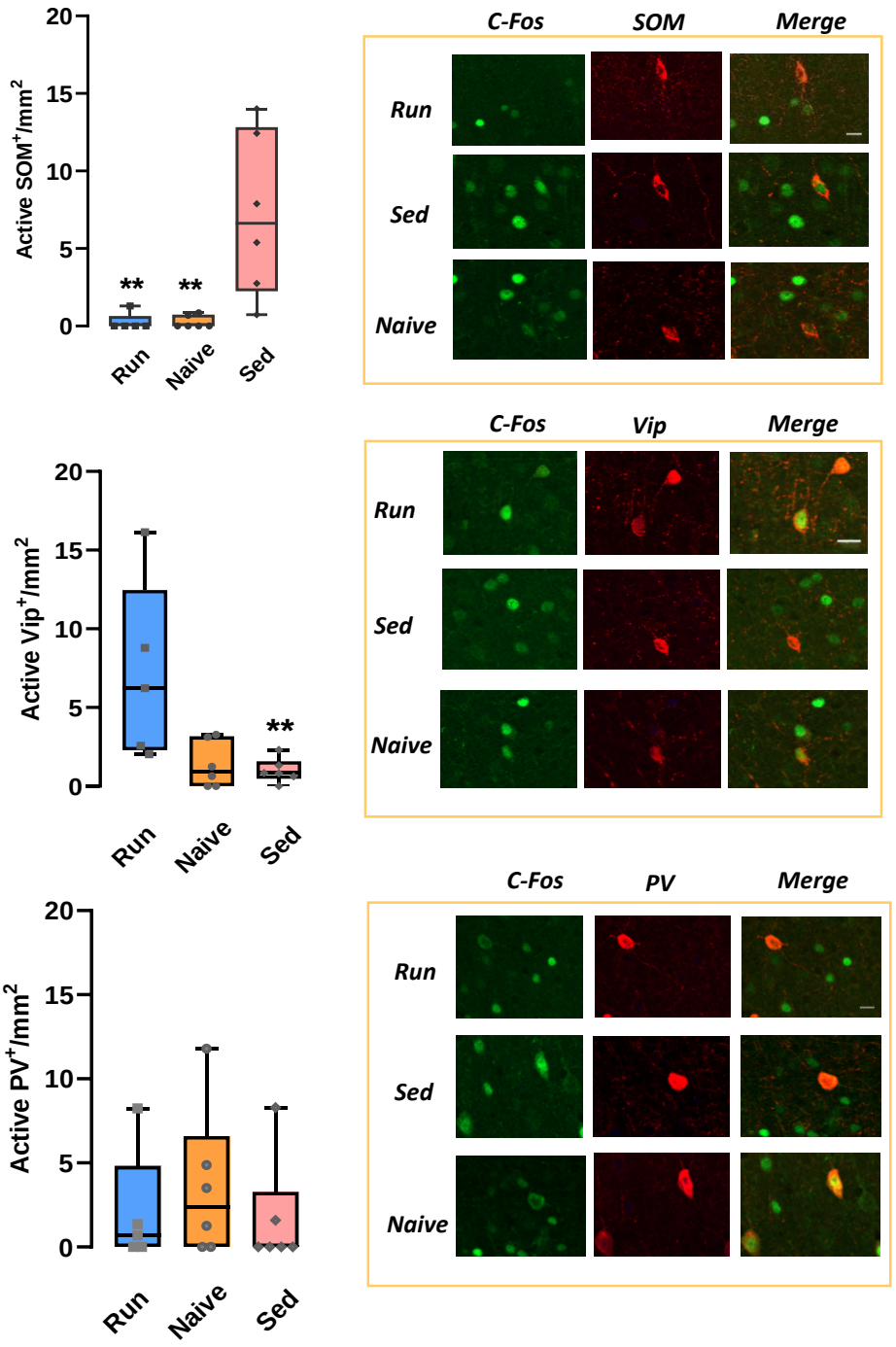

Figure 7: Phenotypical dissection of active GABAergic interneurons in amblyopia recovery induced by voluntary physical activity. Representative images of double immunostaining of somatostatin positive (SOM+)/cFos, VIP positive (VIP+)/cFos and parvalbumin positive (PV+)/cFos interneurons in the primary visual cortex of sedentary, running and naïve animals. The number of SOM+ increased in sedentary animals with respect to naïve rats, but it returned to normal levels in running rats (One-Way ANOVA on ranks, Dunn's method, q= 2.687 and q= 0.109, respectively). On the contrary, the numbers of VIP+ cells was significantly increased in running animals and naïve animals with respect to sedentary rats (One-Way ANOVA on ranks, Dunn's method, q= 2.453, $p<0.05$). No changes was found on the number of PV+ interneurons in all three groups of animals (One-Way ANOVA on ranks, q= 0.587). Error bars indicates s.e.m, * indicates statistical significance. Scale-bar: 12 µm.

6. vPL promotes long-lasting recovery of visual acuity

A separate group of long-term deprived rats was subjected to vPL training; as control, a group of amblyopic animals were trained to distinguish only a fixed combination of the two visual gratings (0.116 c deg-1 vs. 0.592 c deg-1), without any further incremental training (1st step rats).

In both groups, I first measured VA through the fellow eye and then through the amblyopic eye, at P60. Then, all rats were subjected to the visual training protocol with both eyes open. After the end of the active training procedure, VA of the amblyopic eye was re-evaluated four times, i.e. immediately at the end of visual training and at three additional follow-ups (1, 3, and 6 months from the end of treatment).

A marked recovery of visual acuity was evident in PL animals (n = 7) (amblyopic eye: 1.036 ± 0.062 c deg–1; fellow eye: 1.008 ± 0.054 c deg–1), which had visual acuity values not significantly different from those of naïve rats (PL rats amblyopic eye: 1.036 ± 0.062 c deg–1; naïve fellow eye: 0.874 ± 0.037 c deg–1) (Fig. 8); instead, visual acuity recovery was totally absent in 1st step rats (n = 5; amblyopic eye: 0.662 ± 0.014 c deg–1; fellow eye: 0.994 ± 0.023 c deg–1) (t-test analysis, Mann-Whitney rank sum, $p < 0.001$ trained animals deprived eye vs. 1st step rats deprived eye) (Fig. 8).

Strikingly, visual acuity recovery in PL rats was maintained at all follow-ups (trained animals, n = 7; amblyopic eye 30 days after treatment: 1.045 ± 0.060 c deg–1; amblyopic eye 90 days after treatment: 1.135 ± 0.058 c deg–1; amblyopic eye 180 days after treatment: 1.025 ± 0.038 c deg–1) (Fig. 8). In PL rats, visual acuity of the previously amblyopic eye did not differ among the various follow-ups (Two-Way RM ANOVA, Holm-Sidak method, post-treatment vs. 1 month after treatment, trained animals: $p = 0.832$; post-treatment vs. 3 months, trained animals: $p = 0.098$; post treatment vs. 6 months, trained animals: $p = 0.805$) (Fig. 8). At the same time, in 1st step rats did never change during the course of the entire study, either at the end of the treatment or at the different follow-ups (paired t-test, pre-treatment vs. post treatment, 1st step animals: $p=0.086$) (Two-Way RM ANOVA, Holm-Sidak method, pre-treatment vs. 1 month after treatment, 1st step animals: $p = 0.876$;

pre-treatment vs. 3 months, 1st step animals: p = 0.915; pre-treatment vs. 6 months, 1st step animals: p = 0.680) (Fig. 8).

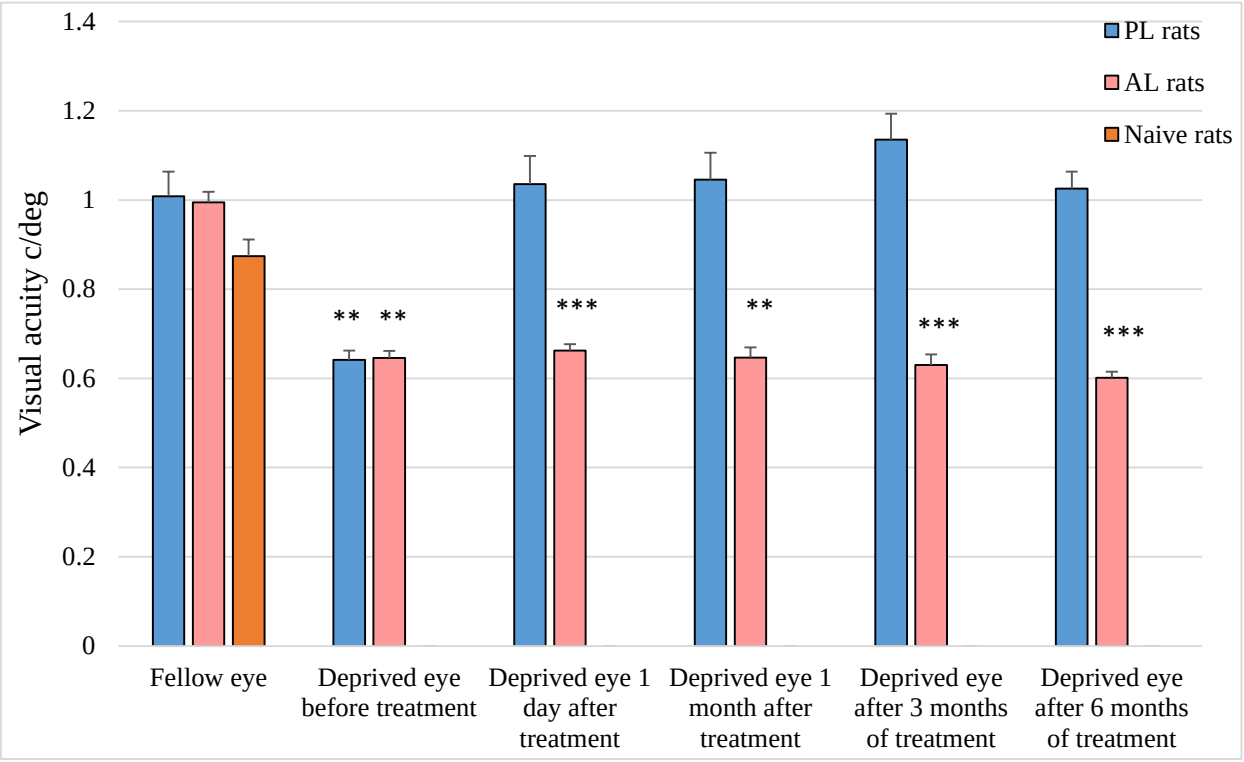

Figure 8: **Behavioral assessment of visual acuity.** Visual acuity was measured using the visual Prusky water maze. A paired t-test analysis revealed that, in treated animals, the visual acuity value of the previously deprived eye, measured immediately after the end of treatment, was significantly increased with respect to that measured before treatment ($p<0.01$). Moreover, it remained unaltered 30, 90 and 180 days after the end of treatment (Two-Way RM ANOVA, post-treatment vs. 1 month $p=0.832$; post-treatment vs. 3 months $p=0.098$; post-treatment vs. 6 months $p=0.805$). In contrast, the visual acuity value of deprived eye did not change in 1st step rats (paired t-test, pre-treatment vs. post-treatment $p=0.086$; One-Way RM ANOVA, pre-treatment vs. 1 month after treatment $p=0.876$; pre-treatment vs. 3 months $p=0.915$; pre-treatment vs. 6 months $p=0.680$).

7. vPL rescues visual depth perception abilities

In a separate group of experimental animals, I investigated, using the visual cliff task, whether visual perceptual learning could also induce a recovery of visual depth perception abilities.

No preference for the shallow side of the arena was found in 1st step rats (n = 4; exploration index = 0.16 ± 0.06) (Fig. 9); on the contrary, PL rats (n = 4) displayed a clear preference for the arena shallow side, with an exploration index (0.51 ± 0.08) much higher than that found in control animals (t-test, PL rats vs. 1st step rats' exploration index, post-treatment $p < 0.05$), and very similar to that found in naïve rats (n = 5; exploration index = 0.5199 ± 0.032) (t-test, naïve rats vs. PL rats, $p = 0.258$; naïve rats vs. 1st step rats, $p < 0.05$) (Fig. 9). Recovery of visual depth perception abilities in PL rats was long-lasting, persisting at least for 1 month past the end of the treatment (Two-way RM ANOVA, Holm-Sidak method, post-treatment vs. 1 month after treatment, $p = 0.388$) (Fig. 9).

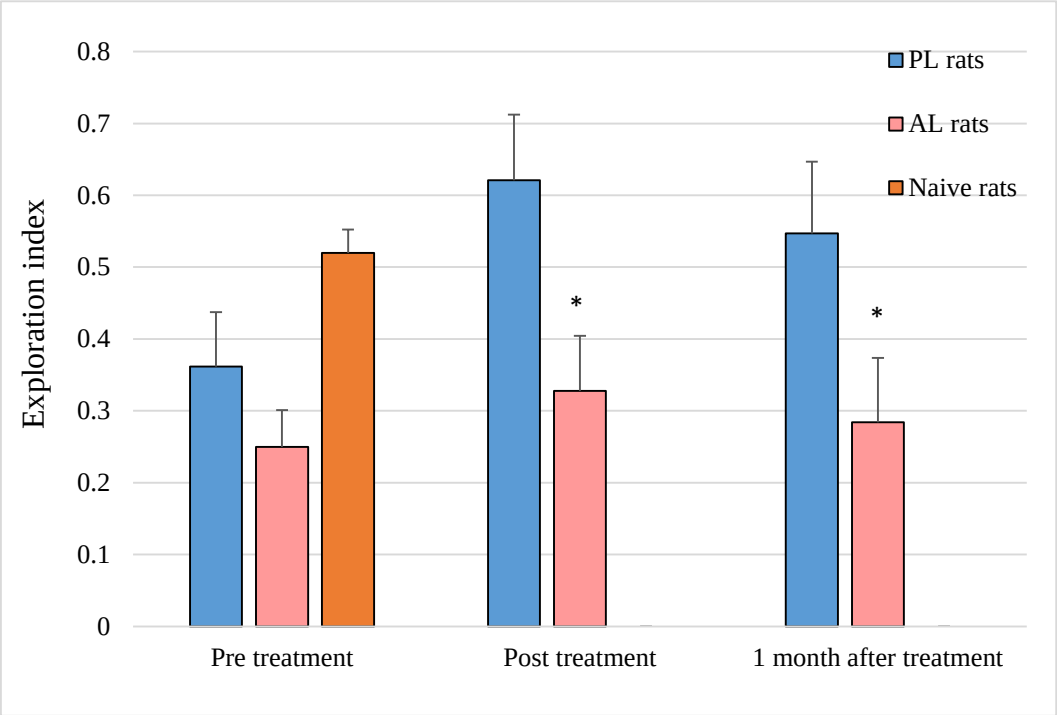

Figure 9. Visual depth perception abilities in amblyopic animals trained in a vPL task. Visual depth perception ability was assessed using the visual cliff task, as the exploration preference for the shallow and the depth side of the arena. T-test analysis showed a significant preference for the shallow side in treated animals, which exhibited an exploration index statistically higher, respectively, than that founded in 1st step rats (t-test analysis, $p<0.05$). All animals were tested under binocular sight conditions.

DISCUSSION

The findings reported in the first part of this Thesis show that voluntary physical activity performed under binocular conditions in the usual visual environment promotes a marked and long lasting recovery of visual functions in adult amblyopic rats. Both visual acuity and depth perception recovered, reaching the same levels of rats with typical development, and the recovery remained stable for at least 6 months. This is a rather long period of recovery stability in terms of rat life span, which, translated in terms of humans, would correspond to several years.

Most papers in the large literature on amblyopia recovery in animal models have employed reverse-occluded animals (Sale et al, 2007; Pizzorusso et al, 2006; Vetencourt et al, 2008; Spolidoro et al, 2011). Rescue of visual functions was here achieved in rats attaining physical activity under conditions of normal binocular sight. This is central in terms of possible translational applications to human patients, in which protocols of reverse eye occlusion are of very limited interest due to potentially relevant and intrinsic risks (Levi et al, 2015; Hess et al, 2015). While running coupled with short-term occlusion of the amblyopic eye has been reported to elicit substantial visual function recovery in adult anisometropic amblyopes (Lunghi et al., 2019), the present study suggests the possibility of a rescue of visual functions in amblyopic rats even in the absence of eye patching. Actually, in the Lunghi et al. work (Lunghi et al., 2019), subjects spent the vast majority of their time with unrestricted binocular vision, similarly to the condition we tested in amblyopic rats, and short-term eye patching was used only during the periods of physical activity. In this condition, short-term eye patching is suggested to evoke a form of homeostatic plasticity in the adult visual cortex, with time-restricted physical exercise acting as a specific boost for it, and the subsequent binocular vision driving recovery of both visual acuity and stereopsis. In the present study, unrestricted physical activity is suggested to act as a general boost for visual cortical plasticity and activity, with concomitant binocular vision driving recovery of visual acuity and stereopsis. We do not know, at

present, whether physical exercise per se, not coupled with amblyopic eye patching, might promote some recovery of vision also in amblyopic humans.

Increasing the potential exploitability of physical exercise in human amblyopia recovery are the data showing that physically exercised rats displayed a remarkable recovery of visual depth perception abilities. Deficits of stereopsis are widely considered the most disturbing impediment in normal everyday life for amblyopic subjects (Webber and Wood, 2005; Levi et al., 2015), calling for procedures able to counteract them, independently on visual acuity (Baroncelli et al, 2013; Mitchell et al, 2016). It has been previously shown that 3 weeks of exposure to environmentally enriched conditions under binocular conditions rescue the ocular dominance and the binocular matching deficits caused by an early visual deprivation during the CP in mice (Levine et al, 2017), and a recovery of deprived eye responses was also reported in head-fixed animals in which binocular visual stimulation with specific visual stimuli was paired with running on a treadmill (Kaneko and Stryker, 2014). Here, rescue of the OD deficit in exercising animals was for the first time linked to recovery not only of visual acuity (see also Baroncelli et al, 2012), but also of visual depth perception abilities, directly assessed at the behavioural level. The Levine et al (2017) paper also offers an interesting answer to the criticism, sometimes moved to rodent models of human amblyopia, that monocular deprivation in rats, given that it reduces the strong contralateral bias present in rodents, increases the number of binocular neurons in the primary visual cortex contralateral to the deprived eye, and this is not easily reconciled with a reduced binocular vision (depth perception). The Levine paper strongly suggests that the sheer number of binocular neurons in V1 is not sufficient to sustain a good binocular vision: it is a necessary, but not a sufficient factor. In monocularly deprived mice the binocular matching process is completely disrupted, resulting in binocular visual cortical neurons displaying different optimal orientations in response to the left or the right eye, with foreseeable consequences for binocular vision. Environmental enrichment, which rescues both ocular dominance and binocular matching (Baroncelli et al, 2012; Levine et al, 2017), also rescues depth perception (Baroncelli et al, 2013). In the Kaneko and Stryker paper (2014), physical exercise in head fixed animals exposed to

specific visual stimuli for 4 h per day led to recovery of normal levels of response to the deprived eye for excitatory neurons, while narrow-spiking (inhibitory) neurons remained less active. We found that ocular dominance recovered both for excitatory and inhibitory neurons in physically exercised rats (data not shown in this Thesis, see Sansevero et al., 2020). This may be due to the different manner of physical exercise (free running vs head fixed) and to the ecological, varied, prolonged visual stimulation animals experience while running on the wheel in their cage.

It is interesting to notice that, in our model, animals were allowed to exert voluntary physical exercise at any moment of the day. When running is performed during the light phase of the day, animals receive natural visual stimulation from the surroundings, coupled with strong visual stimulation arising from the running wheel; this is likely to generate a condition of much more sensory richness than that associated with the condition of specific visual stimuli coupled with the exercise bouts reported in the paper of Kaneko et al, 2014. On the other hand, it has been demonstrated that running in the absence of any visual stimulation can also strongly activate the disinhibitory VIP-SOM-Pyr network in the visual cortex (Dipoppa et al, 2018); thus, activation of this neural circuit may have been elicited, in our paradigm, also when rats performed physical exercise during the dark phase of the day.

The water maze task we used to assess behavioural visual acuity did not per se result in any amount of visual function recovery in the control group of sedentary rats. This is in line with previous work showing that visual acuity assessment in this task does not ameliorate visual discrimination performance, even when it is repeated several times (Sansevero et al, 2019), possibly as result of the stressful component of forced physical exercised intrinsic to the task (Bonaccorsi et al, 2014). Conversely, a modified version of the same task can lead to marked visual function recovery in adult amblyopic rats when used to perform visual perceptual learning, a strong and highly targeted visual training that is able to robustly enhance visual discrimination performances (Eaton et al, 2016; Levi et al, 2009). We previously showed that while this form of visual perceptual learning is linked to

LTP-like changes in visual cortex circuitries, this effect is not seen in control animals lacking the incremental component of the visual training task (Sale et al, 2011).

When focusing on GABAergic connections, c-Fos immunohistochemistry revealed a differential regulation in the activity of distinct sub-populations of interneurons. Specifically, amblyopia resulted in increased numbers of active SOM+ interneurons, without any detectable effect on either VIP+ or PV+ cells. In contrast, physical exercise was associated with both a specific increase of active VIP+ cells, and a restoration to basal numbers of active SOM+ interneurons. These results fit well with the framework of a recent model put forward by Stryker and coll. (2014). In this model, running in restrained animals enhances visual cortical activity in non-deprived mice, and favour recovery from amblyopia in deprived subjects, via a disynaptic disinhibitory circuit whereby activation of VIP+ interneurons increase inhibition of SOM+ cells in the visual cortex, thus disinhibiting pyramidal neurons. Activation of this circuit was previously reported only in head-fixed mice during individual bouts of high locomotor activity, and was never associated with direct assessment of visual recovery in amblyopia animals, with a functional analysis in line with clinical analysis in human patients. Our data show for the first time that the same disinhibiting circuit is also active in rats in which a fully spontaneous running behaviour takes place, and that this activation persists well past the end of the individual bouts of physical activity. Indeed, c-Fos immunohistochemistry was performed following a 48 h protocol of dark and light exposure in the absence of any running wheel, at the end of the physical exercise three-week regimen.

No effect was instead found at the level of global activation of PV+ cells, which displayed a low responsiveness to the effects of long-term MD deprivation, in agreement with previous work (Mainardi et al, 2009). However, spike sorting indicated that the specific change of ocular preference in response to MD was similar for both narrow spiking, putative inhibitory PV+ neurons, and for broad spiking, putative excitatory neurons, as also previously reported in juvenile rats during the CP (Iurilli et al, 2013). Thus, the balance between excitation and inhibition in the visual cortex appeared to be preserved after long-term MD and after recovery from amblyopia induced by physical activity.

This might be essential to ensure a proper encoding of visual information, independently on the OD shift.

Running in head-fixed mice was previously reported to depend on activation of V1 cholinergic afferents from the midbrain locomotor region (Lee et al, 2014). In addition to this link between physical activity and V1 recovery, physical activity might also have elicited a rescue of visual functions acting on peripheral factors capable to promote brain epigenetic changes, finally controlling the action of specific genes involved in V1 plasticity, like the *bdnf* gene (Baroncelli et al, 2016; Medini and Pizzorusso, 2008; Silingardi et al, 2010). Indeed, physical activity enhances the expression of BDNF through the action of the ketone body β-hydroxybutyrate, and BDNF was recently shown to play a remarkable and specific action in eliciting recovery from amblyopia in adult amblyopic rats (Sansevero et al, 2019).

A point that was not addressed in the present study was whether the changes in visual perception (visual acuity and depth perception), and those at the level of OD and activity of GABAergic interneurons elicited by motor activity were correlated among each other's. Since behavioural, electrophysiological and immunohistochemistry were performed on different cohorts of animals, it was not possible to perform this type of analysis. Future research may specifically focus on this issue.

In the second part of the Thesis, I started to investigate whether a recovery of visual functions can also be found in amblyopic animals subjected to a visual perceptual learning protocol under binocular conditions. I found that adult amblyopic rats subjected to vPL showed a marked recovery of visual functions, both at visual acuity and depth perception level. No recovery was found in control rats that only learned to discriminate the reference spatial frequency grating from a spatial frequency grating always maintained at its initial value (1^{st} step perceptual learning group), suggesting that the component of incremental training is essential for the capability of visual learning to promote plasticity and visual function recovery.

On the other hand, the lack of recovery in the 1st step perceptual learning group might seem controversial: in fact, although this group did not perform an incremental visual training protocol, it was subjected to a considerable amount of physical activity, that might in principle be expected to elicit robust brain plasticity. Indeed, a great number of studies reported positive effects of motor activity on brain plasticity enhancement: physical activity increases BDNF levels (Neeper et al., 1995; Farmer et al., 2004), promotes angiogenesis (Swain et al., 2003) and hippocampal neurogenesis (van Praag, 2000), and induces the generation of new microglia in the cortex (Ehninger et al., 2003). The structural changes associated with exercise are also reflected in improvements in synaptic plasticity: LTP is enhanced in hippocampal slices in the dentate gyrus of running versus sedentary mice (van Praag et al., 1999) and, in vivo, in rats that had been housed with a running wheel (Farmer et al., 2004). The lack of recovery in the 1st step perceptual learning group might be due to the purely forced nature of the exercise imposed during visual perceptual learning. The kind of exercise (i.e. voluntary vs. forced) may be particularly important, since several lines of evidence suggest that forced exercise and voluntary exercise exert different effects on the brain and behaviour: forced and voluntary exercise, for example, differentially affect monoamine neurotransmitters (Dishman, 1997), hippocampal parvalbumin expression (Arida et al., 2004), hippocampal BDNF and synapsin-1 expression (Ploughman et al., 2005), longevity and body composition (Narath et al., 2001), taste aversion learning (Masaki and Nakajima, 2006) and open-field behaviour (Burghardt et al., 2004).

In order to use perceptual learning as a strategy to treat amblyopia, one important point which needs to be considered is the persistence of the recovery effect. I measured visual acuity and visual depth perception at the behavioural level (using the visual water box test and visual cliff task) and I found that the recovery outlasted the end of the treatment, persisting for at least 6 months for visual acuity recovery and at least 3 months for recovery of visual depth perception. Since it has been estimated that a day of a rat's life is equivalent to approximately 35 human days (Sengupta, 2013), the reported results show that active training, performed under binocular sight conditions, appear particularly promising for clinical application to human patients.

Previous results have shown that the visual perceptual learning protocol used in the present thesis leads to reduced intracortical inhibition in the visual cortex (see Baroncelli et al., 2012). Moreover, it has been shown that visual stimulation is essential for the recovery from amblyopia also in animals exposed to environmental enrichment conditions (Baroncelli et al., 2012). Ongoing research will characterise this effect, investigating the possible involvement of differential activation in different subtypes of GABAergic interneurons, as reported to rats subjected to enhanced physical exercise.

In conclusion, the results reported in the present thesis show that non-invasive procedures of active training (i.e. voluntary physical exercise and visual perceptual learning) may emerge as a highly effective strategy to increase plasticity in adult brain, eliciting recovery from amblyopia well beyond the closure of the critical period. These results could have a direct impact on human health, opening new treatment possibilities for amblyopia and other still cureless neurodevelopmental disorders (John et al., 2004; Karaminis et al., 2017; LeBlanc et al., 2015).

REFERENCES

Åberg, N. D., Brywe, K. G., & Isgaard, J. (2006). Aspects of growth hormone and insulin-like growth Factor-I related to neuroprotection, regeneration, and functional plasticity in the adult brain. In *TheScientificWorldJournal*. https://doi.org/10.1100/tsw.2006.22

Adlard, P. A., Perreau, V. M., & Cotman, C. W. (2005). The exercise-induced expression of BDNF within the hippocampus varies across life-span. *Neurobiology of Aging*, *26*(4), 511–520. https://doi.org/10.1016/j.neurobiolaging.2004.05.006

Agarwal, S. K. (2012). Cardiovascular benefits of exercise. In *International Journal of General Medicine* (Vol. 5, pp. 541–545). Dove Medical Press Ltd. https://doi.org/10.2147/IJGM.S30113

Ahissar, M., & Hochstein, S. (1996). Learning pop-out detection: Specificities to stimulus characteristics. *Vision Research*, *36*(21), 3487–3500. https://doi.org/10.1016/0042-6989(96)00036-3

Aleman, A., & Torres-Alemán, I. (2009). Circulating insulin-like growth factor I and cognitive function: Neuromodulation throughout the lifespan. In *Progress in Neurobiology*. https://doi.org/10.1016/j.pneurobio.2009.07.008

Allis, C. D., & Jenuwein, T. (2016). The molecular hallmarks of epigenetic control. In *Nature Reviews Genetics*. https://doi.org/10.1038/nrg.2016.59

Altman, J., & Das, G. D. (1964). Autoradiographic examination of the effects of enriched environment on the rate of glial multiplication in the adult rat brain. *Nature*, *204*(4964), 1161–1163. https://doi.org/10.1038/2041161a0

Antonini, A., Fagiolini, M., & Stryker, M. P. (1999). Anatomical correlates of functional plasticity in mouse visual cortex. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.19-11-04388.1999

Antonini, A., Gillespie, D. C., Crair, M. C., & Stryker, M. P. (1998). Morphology of single geniculocortical afferents and functional recovery of the visual cortex after reverse monocular deprivation in the kitten. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.18-23-09896.1998

Archer, T. (2012). Influence of physical exercise on traumatic brain injury deficits: Scaffolding effect. In *Neurotoxicity Research* (Vol. 21, Issue 4, pp. 418–434). Neurotox Res. https://doi.org/10.1007/s12640-011-9297-0

Arida, R. M., Scorza, C. A., Da Silva, A. V., Scorza, F. A., & Cavalheiro, E. A. (2004). Differential effects of spontaneous versus forced exercise in rats on the staining of parvalbumin-positive neurons in the hippocampal formation. *Neuroscience Letters*, *364*(3), 135–138. https://doi.org/10.1016/j.neulet.2004.03.086

Artola, A., & Singer, W. (1990). The Involvement of N-Methyl-D-Aspartate Receptors in Induction and Maintenance of Long-Term Potentiation in Rat Visual Cortex. *European Journal of Neuroscience*, *2*(3), 254–269. https://doi.org/10.1111/j.1460-9568.1990.tb00417.x

Artola, A., & Singer, W. (1987). Long-term potentiation and NMDA receptors in rat visual cortex. *Nature*, *330*(6149), 649–652. https://doi.org/10.1038/330649a0

Atallah, B. V., Bruns, W., Carandini, M., & Scanziani, M. (2012). Parvalbumin-Expressing Interneurons Linearly Transform Cortical Responses to Visual Stimuli. *Neuron*, *73*(1), 159–170. https://doi.org/10.1016/j.neuron.2011.12.013

Baedke, J. (2013). The epigenetic landscape in the course of time: Conrad Hal Waddington's methodological impact on the life sciences. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*. https://doi.org/10.1016/j.shpsc.2013.06.001

Ball, K., & Sekuler, R. (1982). A specific and enduring improvement in visual motion discrimination. *Science*. https://doi.org/10.1126/science.7134968

Ball, K., & Sekuler, R. (1987). Direction-specific improvement in motion discrimination. *Vision Research*, *27*(6), 953–965. https://doi.org/10.1016/0042-6989(87)90011-3

Barde, Y. A., Edgar, D., & Thoenen, H. (1982). Purification of a new neurotrophic factor from mammalian brain. *The EMBO Journal*. https://doi.org/10.1002/j.1460-2075.1982.tb01207.x

Barnes, G. R., Hess, R. F., Dumoulin, S. O., Achtman, R. L., & Pike, G. B. (2001). The cortical deficit in humans with strabismic amblyopia. *Journal of Physiology*. https://doi.org/10.1111/j.1469-7793.2001.0281b.x

Baro, J. A., Lehmkuhle, S., & Kratz, K. E. (1990). Electroretinograms and visual evoked potentials in long-term monocularly deprived cats. *Investigative Ophthalmology and Visual Science*

Baroncelli, L., Bonaccorsi, J., Milanese, M., Bonifacino, T., Giribaldi, F., Manno, I., Cenni, M. C., Berardi, N., Bonanno, G., Maffei, L., & Sale, A. (2012). Enriched experience and recovery from amblyopia in adult rats: impact of motor, social and sensory components. *Neuropharmacology*, *62*(7), 2388–2397

Baroncelli, L., Braschi, C., Spolidoro, M., Begenisic, T., Maffei, L., & Sale, A. (2011). Brain plasticity and disease: A matter of inhibition. In *Neural Plasticity* (Vol. 2011). Hindawi Publishing Corporation. https://doi.org/10.1155/2011/286073

Baroncelli, L., Cenni, M. C., Melani, R., Deidda, G., Landi, S., Narducci, R., Cancedda, L., Maffei, L., & Berardi, N. (2017). Early IGF-1 primes visual cortex maturation and accelerates developmental switch between NKCC1 and KCC2 chloride transporters in enriched animals. *Neuropharmacology*. https://doi.org/10.1016/j.neuropharm.2016.02.034

Baroncelli, L., Maffei, L., & Sale, A. (2011). New perspectives in amblyopia therapy on adults: A critical role for the excitatory/inhibitory balance. In *Frontiers in Cellular Neuroscience*. https://doi.org/10.3389/fncel.2011.00025

Baroncelli, L., Scali, M., Sansevero, G., Olimpico, F., Manno, I., Costa, M., & Sale, A. (2016). Experience affects critical period plasticity in the visual cortex through an epigenetic regulation of histone post-translational modifications. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.1787-15.2016

Barrett, B. T., Bradley, A., & McGraw, P. V. (2004). Understanding the Neural Basis of Amblyopia. In *Neuroscientist*. https://doi.org/10.1177/1073858403262153

Barth, M., Hirsch, H. V, Meinertzhagen, I. A., & Heisenberg, M. (1997). Experience-dependent developmental plasticity in the optic lobe of Drosophila melanogaster. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *17*(4), 1493–1504

Bear, M. F., Cooper, L. N., & Ebner, F. F. (1987). A physiological basis for a theory of synapse modification. *Science (New York, N.Y.)*, *237*(4810), 42–48. https://doi.org/10.1126/science.3037696

Bear, M. F., & Singer, W. (1986). Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature*. https://doi.org/10.1038/320172a0

Beaulieu, C., & Colonnier, M. (1987). Effect of the richness of the environment on the cat visual cortex. *Journal of Comparative Neurology*, *266*(4), 478–494. https://doi.org/10.1002/cne.902660404

Beck, K. D., Powell-Braxtont, L., Widmer, H. R., Valverde, J., & Hefti, F. (1995). Igf1 gene disruption results in reduced brain size, CNS hypomyelination, and loss of hippocampal granule and striatal parvalbumin-containing neurons. *Neuron*. https://doi.org/10.1016/0896-6273(95)90216-3

Ben-Ari, Y. (2002). Excitatory actions of GABA during development: The nature of the nurture. In *Nature Reviews Neuroscience* (Vol. 3, Issue 9, pp. 728–739). Nat Rev Neurosci. https://doi.org/10.1038/nrn920

Ben-Ari, Y., Khalilov, I., Kahle, K. T., & Cherubini, E. (2012). The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. In *Neuroscientist* (Vol. 18, Issue 5, pp. 467–486). Neuroscientist. https://doi.org/10.1177/1073858412438697

Benevento, L. A., Bakkum, B. W., Port, J. D., & Cohen, R. S. (1992). The effects of dark-rearing on the electrophysiology of the rat visual cortex. *Brain Research*, *572*(1–2), 198–207. https://doi.org/10.1016/0006-8993(92)90470-T

Bennett, E. L., Diamond, M. C., Krech, D., & Rosenzweig, M. R. (1964). Chemical and anatomical plasticity of brain. *Science*. https://doi.org/10.1126/science.146.3644.610

Bennett, E. L., Rosenzweig, M. R., & Diamond, M. C. (1969). Rat brain: Effects of environmental enrichment on wet and dry weights. *Science*. https://doi.org/10.1126/science.163.3869.825

Berardi, N., Cellerino, A., Domenici, L., Fagiolini, M., Pizzorusso, T., Cattaneo, A., & Maffei, L. (1994). Monoclonal antibodies to nerve growth factor affect the postnatal development of the visual system. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.91.2.684

Berardi, N., & Fiorentini, A. (1987). Interhemispheric transfer of visual information in humans: spatial characteristics. *The Journal of Physiology*. https://doi.org/10.1113/jphysiol.1987.sp016474

Berardi, N., Braschi, C., Capsoni, S., Cattaneo, A., & Maffei, L. (2007). Environmental enrichment delays the onset of memory deficits and reduces neuropathological hallmarks in a mouse model of Alzheimer-like neurodegeneration. *Journal of Alzheimer's Disease*, *11*(3), 359–370. https://doi.org/10.3233/JAD-2007-11312

Berardi, N., & Maffei, L. (1999). From visual experience to visual function: Roles of neurotrophins. *Journal of Neurobiology*. https://doi.org/10.1002/(SICI)1097-4695(199910)41:1<119: AID-NEU15>3.0.CO;2-N

Berardi, N., Pizzorusso, T., & Maffei, L. (2004). Extracellular matrix and visual cortical plasticity: Freeing the synapse. In *Neuron*. https://doi.org/10.1016/j.neuron.2004.12.008

Berardi, N., Pizzorusso, T., & Maffei, L. (2000). Critical periods during sensory development. In *Current Opinion in Neurobiology* (Vol. 10, Issue 1, pp. 138–145). Current Biology Ltd. https://doi.org/10.1016/S0959-4388(99)00047-1

Berardi, N., Sale, A., & Maffei, L. (2015). Brain structural and functional development: Genetics and experience. *Developmental Medicine and Child Neurology*, *57*(s2), 4–9. https://doi.org/10.1111/dmcn.12691

Beurdeley, M., Spatazza, J., Lee, H. H. C., Sugiyama, S., Bernard, C., Di Nardo, A. A., Hensch, T. K., & Prochiantz, A. (2012). Otx2 binding to perineuronal nets persistently regulates plasticity in the mature visual cortex. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.0394-12.2012

Blakemore, C., Movshon, J. A., & Van Sluyters, R. C. (1978). Modification of the kitten's visual cortex by exposure to spatially periodic patterns. *Experimental Brain Research*. https://doi.org/10.1007/BF00239812

Blakemore, C., Vital-Durand, F., & Garey, L. J. (1981). Recovery from monocular deprivation in the monkey. I. Reversal of physiological effects in the visual cortex. *Proceedings of the Royal Society of London - Biological Sciences*. https://doi.org/10.1098/rspb.1981.0072

Blakemore, C., Garey, L. J., & Vital-Durand, F. (1978). The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex. *The Journal of Physiology*, *283*, 223–262. https://doi.org/10.1113/jphysiol.1978.sp012498

Blue, M. E., & Parnavelas, J. G. (1983). The formation and maturation of synapses in the visual cortex of the rat. II. Quantitative analysis. *Journal of Neurocytology*, *12*(4), 697–712. https://doi.org/10.1007/BF01181531

Blumenthal, J. A., Babyak, M. A., Doraiswamy, P. M., Watkins, L., Hoffman, B. M., Barbour, K. A., Herman, S., Craighead, W. E., Brosse, A. L., Waugh, R., Hinderliter, A., & Sherwood, A. (2007). Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosomatic Medicine*, *69*(7), 587–596. https://doi.org/10.1097/PSY.0b013e318148c19a

Bohannon, R. W. (1993). Physical rehabilitation in neurologic diseases. In *Current Opinion in Neurology* (Vol. 6, Issue 5, pp. 765–772). Curr Opin Neurol. https://doi.org/10.1097/00019052-199310000-00015

Bonaccorsi, J., Berardi, N., & Sale, A. (2014). Treatment of amblyopia in the adult: Insights from a new rodent model of visual perceptual learning. In *Frontiers in Neural Circuits* (Vol. 8, Issue JULY). Frontiers Research Foundation. https://doi.org/10.3389/fncir.2014.00082

Bonhoeffer, T. (1996). Neurotrophins and activity-dependent development of the neocortex. *Current Opinion in Neurobiology*. https://doi.org/10.1016/S0959-4388(96)80017-1

Boström, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., Rasbach, K. A., Boström, E. A., Choi, J. H., Long, J. Z., Kajimura, S., Zingaretti, M. C., Vind, B. F., Tu, H., Cinti, S., Højlund, K., Gygi, S. P., & Spiegelman, B. M. (2012). A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*, *481*(7382), 463–468. https://doi.org/10.1038/nature10777

Bozzi, Y., Pizzorusso, T., Cremisi, F., Rossi, F. M., Barsacchi, G., & Maffei, L. (1995). Monocular deprivation decreases the expression of messenger RNA for brain-derived neurotrophic factor in the rat visual cortex. *Neuroscience*. https://doi.org/10.1016/0306-4522(95)00321-9

Brown, J. C., Huedo-Medina, T. B., Pescatello, L. S., Ryan, S. M., Pescatello, S. M., Moker, E., LaCroix, J. M., Ferrer, R. A., & Johnson, B. T. (2012). The efficacy of exercise in reducing depressive symptoms among cancer survivors: A meta-analysis. *PLoS ONE*, *7*(1). https://doi.org/10.1371/journal.pone.0030955

Brown, J. C., Winters-Stone, K., Lee, A., & Schmitz, K. H. (2012). Cancer, Physical Activity, and Exercise. In *Comprehensive Physiology*. John Wiley & Sons, Inc. https://doi.org/10.1002/cphy.c120005

Brückner, G., Grosche, J., Schmidt, S., Härtig, W., Margolis, R. U., Delpech, B., Seidenbecher, C. I., Czaniera, R., & Schachner, M. (2000). Postnatal development of perineuronal nets in wild-type mice and in a mutant deficient in Tenascin-R. *Journal of Comparative Neurology*. https://doi.org/10.1002/1096-9861(20001225)428:4<616: AID-CNE3>3.0.CO;2-K

Buchman, A. S., Boyle, P. A., Yu, L., Shah, R. C., Wilson, R. S., & Bennett, D. A. (2012). Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology*, *78*(17), 1323–1329. https://doi.org/10.1212/WNL.0b013e3182535d35

Bukhari, N., Burman, P. N., Hussein, A., Demars, M. P., Sadahiro, M., Brady, D. M., Tsirka, S. E., Russo, S. J., & Morishita, H. (2015). Unmasking proteolytic activity for adult visual cortex plasticity by the removal of Lynx1. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.4315-14.2015

Burghardt, P. R., Fulk, L. J., Hand, G. A., & Wilson, M. A. (2004). The effects of chronic treadmill and wheel running on behavior in rats. *Brain Research*, *1019*(1–2), 84–96. https://doi.org/10.1016/j.brainres.2004.05.086

Cabelli, R. J., Hohn, A., & Shatz, C. J. (1995). Inhibition of ocular dominance column formation by infusion of NT-4/5 or BDNF. *Science*. https://doi.org/10.1126/science.7886458

Cabelli, R. J., Shelton, D. L., Segal, R. A., & Shatz, C. J. (1997). Blockade of endogenous ligands of TrkB inhibits formation of ocular dominance columns. *Neuron*. https://doi.org/10.1016/S0896-6273(00)80348-7

Calfa, G., Chapleau, C. A., Campbell, S., Inoue, T., Morse, S. J., Lubin, F. D., & Pozzo-Miller, L. (2012). HDAC activity is required for BDNF to increase quantal neurotransmitter release and dendritic spine density in CA1 pyramidal neurons. *Hippocampus*, *22*(7), 1493–1500. https://doi.org/10.1002/hipo.20990

Cancedda, L., Putignano, E., Impey, S., Maffei, L., Ratto, G. M., & Pizzorusso, T. (2003). Patterned vision causes CRE-mediated gene expression in the visual cortex through PKA and ERK. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.23-18-07012.2003

Cardin, J. A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., Tsai, L. H., & Moore, C. I. (2009). Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature*, *459*(7247), 663–667. https://doi.org/10.1038/nature08002

Carmignoto, G., Pizzorusso, T., Tia, S., & Vicini, S. (1997). Brain-derived neurotrophic factor and nerve growth factor potentiate excitatory synaptic transmission in the rat visual cortex. *Journal of Physiology*. https://doi.org/10.1113/jphysiol.1997.sp021848

Carro, E., Nuñez, A., Busiguina, S., & Torres-Aleman, I. (2000). Circulating insulin-like growth factor I mediates effects of exercise on the brain. *Journal of Neuroscience*, *20*(8), 2926–2933. https://doi.org/10.1523/jneurosci.20-08-02926.2000

Castren, E., Zafra, F., Thoenen, H., & Lindholm, D. (1992). Light regulates expression of brain-derived neurotrophic factor mRNA in rat visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.89.20.9444

Chowdhury, S. A., & DeAngelis, G. C. (2008). Fine Discrimination Training Alters the Causal Contribution of Macaque Area MT to Depth Perception. *Neuron*, *60*(2), 367–377. https://doi.org/10.1016/j.neuron.2008.08.023

Chung, S. T. L., Li, R. W., & Levi, D. M. (2006). Identification of contrast-defined letters benefits from perceptual learning in adults with amblyopia. *Vision Research*, *46*(22), 3853–3861. https://doi.org/10.1016/j.visres.2006.06.014

Chung, S. T. L., Li, R. W., & Levi, D. M. (2008). Learning to identify near-threshold luminance-defined and contrast-defined letters in observers with amblyopia. *Vision Research*, *48*(27), 2739–2750. https://doi.org/10.1016/j.visres.2008.09.009

Ciucci, F., Putignano, E., Baroncelli, L., Landi, S., Berardi, N., & Maffei, L. (2007). Insulin-like growth factor 1 (IGF-1) mediates the effects of enriched environment (EE) on visual cortical development. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0000475

Ciuffreda, K. J., Rosenfield, M., & Stark, L. (1991). The Role of Binocular Disparity Vergence Eye Movements in Disambiguating Superimposed Retinal Images. In *Presbyopia Research*. https://doi.org/10.1007/978-1-4757-2131-7_21

Colberg, S. R., Sigal, R. J., Fernhall, B., Regensteiner, J. G., Blissmer, B. J., Rubin, R. R., Chasan-Taber, L., Albright, A. L., & Braun, B. (2010). Exercise and type 2 diabetes: The American

College of Sports Medicine and the American Diabetes Association: Joint position statement. In *Diabetes Care* (Vol. 33, Issue 12). Diabetes Care. https://doi.org/10.2337/dc10-9990

Comeau, W., Gibb, R., Hastings, E., Cioe, J., & Kolb, B. (2008). Therapeutic effects of complex rearing or bFGF after perinatal frontal lesions. *Developmental Psychobiology*, *50*(2), 134–146. https://doi.org/10.1002/dev.20253

Comery, T. A., Shah, R., & Greenough, W. T. (1995). Differential rearing alters spine density on medium-sized spiny neurons in the rat corpus striatum: Evidence for association of morphological plasticity with early response gene expression. *Neurobiology of Learning and Memory*, *63*(3), 217–219. https://doi.org/10.1006/nlme.1995.1025

Cooke, S. F., & Bear, M. F. (2014). How the mechanisms of long-term synaptic potentiation and depression serve experience-dependent plasticity in primary visual cortex. In *Philosophical Transactions of the Royal Society B: Biological Sciences* (Vol. 369, Issue 1633). Royal Society. https://doi.org/10.1098/rstb.2013.0284

Crist, R. E., Li, W., & Gilbert, C. D. (2001). Learning to see: Experience and attention in primary visual cortex. *Nature Neuroscience*, *4*(5), 519–525. https://doi.org/10.1038/87470

Crozier, R. A., Wang, Y., Liu, C. H., & Bear, M. F. (2007). Deprivation-induced synaptic depression by distinct mechanisms in different layers of mouse visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(4), 1383–1388. https://doi.org/10.1073/pnas.0609596104

De Valois, K. K. (1977). Spatial frequency adaptation can enhance contrast sensitivity. *Vision Research*, *17*(9), 1057–1065. https://doi.org/10.1016/0042-6989(77)90010-4

D'Ercole, A. J., Ye, P., Calikoglu, A. S., & Gutierrez-Ospina, G. (1996). The role of the insulin-like growth factors in the central nervous system. *Molecular Neurobiology*. https://doi.org/10.1007/BF02740625

D'Ercole, J. A., Ye, P., & O'Kusky, J. R. (2002). Mutant mouse models of insulin-like growth factor actions in the central nervous system. *Neuropeptides*. https://doi.org/10.1054/npep.2002.0893

Diamond, M. C. (2001). Response of the brain to enrichment. *Anais Da Academia Brasileira de Ciencias*, *73*(2), 210–220. https://doi.org/10.1590/s0001-37652001000200006

Diamond, M. C., Ingham, C. A., Johnson, R. E., Bennett, E. L., & Rosenzweig, M. R. (1976). Effects of environment on morphology of rat cerebral cortex and hippocampus. *Journal of Neurobiology*, *7*(1), 75–85. https://doi.org/10.1002/neu.480070108

Diamond, M. C., Johnson, R. E., & Ingham, C. A. (1975). Morphological changes in the young, adult and aging rat cerebral cortex, hippocampus, and diencephalon. *Behavioral Biology*, *14*(2), 163–174. https://doi.org/10.1016/S0091-6773(75)90161-3

Diamond, M. C., Johnson, R. E., Ingham, C., Rosenzweig, M. R., & Bennett, E. L. (1975). Effects of differential experience on neuronal nuclear and perikarya dimensions in the rat cerebral cortex. *Behavioral Biology*, *15*(1), 107–111. https://doi.org/10.1016/S0091-6773(75)92144-6

Diamond, M. C., Krech, D., & Rosenzweig, M. R. (1964). The effects of an enriched environment on the histology of the rat cerebral cortex. *Journal of Comparative Neurology*, *123*(1), 111–119. https://doi.org/10.1002/cne.901230110

Diamond, M. C., Law, F., Rhodes, H., Lindner, B., Rosenzweig, M. R., Krech, D., & Bennett, E. L. (1966). Increases in cortical depth and glia numbers in rats subjected to enriched environment. *Journal of Comparative Neurology*, *128*(1), 117–125. https://doi.org/10.1002/cne.901280110

Diamond, M. C., Lindner, B., Johnson, R., Bennett, E. L., & Rosenzweig, M. R. (1975). Difference in occipital cortical synapses from environmentally enriched, impoverished, and standard colony rats. *Journal of Neuroscience Research*, *1*(2), 109–119. https://doi.org/10.1002/jnr.490010203

Diamond, M. C., Rosenzweig, M. R., Bennett, E. L., Lindner, B., & Lyon, L. (1972). Effects of environmental enrichment and impoverishment on rat cerebral cortex. *Journal of Neurobiology*, *3*(1), 47–64. https://doi.org/10.1002/neu.480030105

Dishman, R. K. (1997). Brain monoamines, exercise, and behavioral stress: Animal models. *Medicine and Science in Sports and Exercise*, *29*(1), 63–74. https://doi.org/10.1097/00005768-199701000-00010

Domenici, L., Berardi, N., Carmignoto, G., Vantini, G., & Maffei, L. (1991). Nerve growth factor prevents the amblyopic effects of monocular deprivation. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.88.19.8811

Domenici, L., Cellerino, A., Berardi, N., Cattaneo, A., & Maffei, L. (1994). Antibodies to nerve growth factor (NGF) prolong the sensitive period for monocular deprivation in the rat. *NeuroReport*. https://doi.org/10.1097/00001756-199410270-00013

Doupe, A. J., & Kuhl, P. K. (1999). Birdsong and human speech: common themes and mechanisms. *Annual Review of Neuroscience*, *22*, 567–631. https://doi.org/10.1146/annurev.neuro.22.1.567

Edagawa, Y., Saito, H., & Abe, K. (2000). The serotonin 5-HT2 receptor-phospholipase C system inhibits the induction of long-term potentiation in the rat visual cortex. *European Journal of Neuroscience*. https://doi.org/10.1046/j.1460-9568.2000.00007.x

Ekstrand, J., Hellsten, J., & Tingström, A. (2008). Environmental enrichment, exercise and corticosterone affect endothelial cell proliferation in adult rat hippocampus and prefrontal cortex. *Neuroscience Letters*, *442*(3), 203–207. https://doi.org/10.1016/j.neulet.2008.06.085

Ekstrand, J., Hellsten, J., Wennström, M., & Tingström, A. (2008). Differential inhibition of neurogenesis and angiogenesis by corticosterone in rats stimulated with electroconvulsive seizures. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(6), 1466–1472. https://doi.org/10.1016/j.pnpbp.2008.05.012

Emerson, V. F., Chalupa, L. M., Thompson, I. D., & Talbot, R. J. (1982). Behavioural, physiological, and anatomical consequences of monocular deprivation in the golden hamster (Mesocricetus auratus). *Experimental Brain Research*. https://doi.org/10.1007/BF00235776

Erlander, M. G., Tillakaratne, N. J. K., Feldblum, S., Patel, N., & Tobin, A. J. (1991). Two genes encode distinct glutamate decarboxylases. *Neuron*, *7*(1), 91–100. https://doi.org/10.1016/0896-6273(91)90077-D

Esclapez, M., Tillakaratne, N. J. K., Kaufman, D. L., Tobin, A. J., & Houser, C. R. (1994). Comparative localization of two forms of glutamic acid decarboxylase and their mRNAs in rat brain supports the concept of functional differences between the forms. *Journal of Neuroscience*, *14*(3 II), 1834–1855. https://doi.org/10.1523/jneurosci.14-03-01834.1994

Fagiolini, M., Pizzorusso, T., Berardi, N., Domenici, L., & Maffei, L. (1994). Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. *Vision Research*, *34*(6), 709–720. https://doi.org/10.1016/0042-6989(94)90210-0

Fagiolini, M., & Hensch, T. K. (2000). Inhibitory threshold for critical-period activation in primary visual cortex. *Nature*. https://doi.org/10.1038/35004582

Fagiolini, M., Katagiri, H., Miyamoto, H., Mori, H., Grant, S. G. N., Mishina, M., & Hensch, T. K. (2003). Separable features of visual cortical plasticity revealed by N-Methyl-D-aspartate receptor 2A signaling. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(5), 2854–2859. https://doi.org/10.1073/pnas.0536089100

Fahle, M., Edelman, S., & Poggio, T. (1995). Fast perceptual learning in hyperacuity. *Vision Research*, *35*(21), 3003–3013. https://doi.org/10.1016/0042-6989(95)00044-Z

Fahle, M., & Edelman, S. (1993). Long-term learning in vernier acuity: Effects of stimulus orientation, range and of feedback. *Vision Research*, *33*(3), 397–412. https://doi.org/10.1016/0042-6989(93)90094-D

Fawcett, J. W., Oohashi, T., & Pizzorusso, T. (2019). The roles of perineuronal nets and the perinodal extracellular matrix in neuronal function. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/s41583-019-0196-3

Fendick, M., & Westheimer, G. (1983). Effects of practice and the separation of test targets on foveal and peripheral stereoacuity. *Vision Research*, *23*(2), 145–150. https://doi.org/10.1016/0042-6989(83)90137-2

Fernandez, A. M., & Torres-Alemán, I. (2012). The many faces of insulin-like peptide signalling in the brain. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3209

Fine, I., & Jacobs, R. A. (2000). Perceptual learning for a pattern discrimination task. *Vision Research*. https://doi.org/10.1016/S0042-6989(00)00163-2

Fiorentini, A., & Berardi, N. (1980). Perceptual learning specific for orientation and spatial frequency. *Nature*, *287*(5777), 43–44. https://doi.org/10.1038/287043a0

Fischer, A., Sananbenesi, F., Wang, X., Dobbin, M., & Tsai, L. H. (2007). Recovery of learning and memory is associated with chromatin remodelling. *Nature*, *447*(7141), 178–182. https://doi.org/10.1038/nature05772

Floeter, M. K., & Greenough, W. T. (1979). Cerebellar plasticity: Modification of Purkinje cell structure by differential rearing in monkeys. *Science*, *206*(4415), 227–229. https://doi.org/10.1126/science.113873

Foote, S. L., & Morrison, J. H. (1984). Postnatal development of laminar innervation patterns by monoaminergic fibers in monkey (Macaca fascicularis) primary visual cortex. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.04-11-02667.1984

Frégnac, Y., & Imbert, M. (1978). Early development of visual cortical cells in normal and dark-reared kittens: relationship between orientation selectivity and ocular dominance. *The Journal of Physiology*. https://doi.org/10.1113/jphysiol.1978.sp012290

Frenkel, M. Y., & Bear, M. F. (2004). How monocular deprivation shifts ocular dominance in visual cortex of young mice. *Neuron*. https://doi.org/10.1016/j.neuron.2004.12.003

Frenkel, M. Y., Sawtell, N. B., Diogo, A. C. M., Yoon, B., Neve, R. L., & Bear, M. F. (2006). Instructive Effect of Visual Experience in Mouse Visual Cortex. *Neuron*. https://doi.org/10.1016/j.neuron.2006.06.026

Fronius, M., Cirina, L., Ackermann, H., Kohnen, T., & Diehl, C. M. (2014). Efficiency of electronically monitored amblyopia treatment between 5 and 16years of age: New insight into declining susceptibility of the visual system. *Vision Research*, *103*(1), 11–19. https://doi.org/10.1016/j.visres.2014.07.018

Fu, Y., Kaneko, M., Tang, Y., Alvarez-Buylla, A., & Stryker, M. P. (2015). A cortical disinhibitory circuit for enhancing adult plasticity. *ELife*, *2015*(4). https://doi.org/10.7554/eLife.05558

Fu, Y., Tucciarone, J. M., Espinosa, J. S., Sheng, N., Darcy, D. P., Nicoll, R. A., Huang, Z. J., & Stryker, M. P. (2014). A cortical circuit for gain control by behavioral state. *Cell*, *156*(6), 1139–1152. https://doi.org/10.1016/j.cell.2014.01.050

Furmanski, C. S., & Engel, S. A. (2000). Perceptual learning in object recognition: Object specificity and size invariance. *Vision Research*, *40*(5), 473–484. https://doi.org/10.1016/S0042-6989(99)00134-0

Furmanski, C. S., Schluppeck, D., & Engel, S. A. (2004). Learning strengthens the response of primary visual cortex to simple patterns. *Current Biology*, *14*(7), 573–578. https://doi.org/10.1016/j.cub.2004.03.032

Galarreta, M., & Hestrin, S. (2002). Electrical and chemical synapses among parvalbumin fast-spiking GABAergic interneurons in adult mouse neocortex. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(19), 12438–12443. https://doi.org/10.1073/pnas.192159599

Gandhi, S. P., Yanagawa, Y., & Stryker, M. P. (2008). Delayed plasticity of inhibitory neurons in developing visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(43), 16797–16802. https://doi.org/10.1073/pnas.0806159105

Gao, W. J., Wormington, A. B., Newman, D. E., & Pallas, S. L. (2000). Development of inhibitory circuitry in visual and auditory cortex of postnatal ferrets: Immunocytochemical localization of calbindin- and parvalbumin-containing neurons. *Journal of Comparative Neurology*, *422*(1), 140–157. https://doi.org/10.1002/(SICI)1096-9861(20000619)422:1<140: AID-CNE9>3.0.CO;2-0

Ghose, G. M., Yang, T., & Maunsell, J. H. R. (2002). Physiological correlates of perceptual learning in monkey V1 and V2. *Journal of Neurophysiology*, *87*(4), 1867–1888. https://doi.org/10.1152/jn.00690.2001

Ghosh, A., & Greenberg, M. E. (1995). Distinct roles for bFGF and NT-3 in the regulation of cortical neurogenesis. *Neuron*. https://doi.org/10.1016/0896-6273(95)90067-5

Gibson, E. J. (1963). Perceptual learning. *Annual Review of Psychology*, *14*, 29–56. https://doi.org/10.1146/annurev.ps.14.020163.000333

Globus, A., Rosenzweig, M. R., Bennett, E. L., & Diamond, M. C. (1973). Effects of differential experience on dendritic spine counts in rat cerebral cortex. *Journal of Comparative and Physiological Psychology*, *82*(2), 175–181. https://doi.org/10.1037/h0033910

Gold, J., Bennett, P. J., & Sekuler, A. B. (1999). Signal but not noise changes with perceptual learning. *Nature*, *402*(6758), 176–178. https://doi.org/10.1038/46027

Gomez-Pinilla, F., Zhuang, Y., Feng, J., Ying, Z., & Fan, G. (2011). Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. *European Journal of Neuroscience*, *33*(3), 383–390. https://doi.org/10.1111/j.1460-9568.2010.07508.x

Gonchar, Y., Wang, Q., & Burkhalter, A. (2008). Multiple distinct subtypes of GABAergic neurons in mouse visual cortex identified by triple immunostaining. *Frontiers in Neuroanatomy*, *1*(MAR). https://doi.org/10.3389/neuro.05.003.2007

Gordon, J. A., Cioffi, D., Silva, A. J., & Stryker, M. P. (1996). Deficient plasticity in the primary visual cortex of α- calcium/calmodulin-dependent protein kinase II mutant mice. *Neuron*, *17*(3), 491–499. https://doi.org/10.1016/S0896-6273(00)80181-6

Gordon, J. A., & Stryker, M. P. (1996). Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.16-10-03274.1996

Green, E. J., Greenough, W. T., & Schlumpf, B. E. (1983). Effects of complex or isolated environments on cortical dendrites of middle-aged rats. *Brain Research*, *264*(2), 233–240. https://doi.org/10.1016/0006-8993(83)90821-1

Greenough, W. T., Volkmar, F. R., & Juraska, J. M. (1973). Effects of rearing complexity on dendritic branching in frontolateral and temporal cortex of the rat. *Experimental Neurology*. https://doi.org/10.1016/0014-4886(73)90278-1

Gu, Q., & Singer, W. (1989). The role of muscarinic acetylcholine receptors in ocular dominance plasticity. *EXS*. https://doi.org/10.1007/978-3-0348-9138-7_30

Gu, Q. (2003). Contribution of acetylcholine to visual cortex plasticity. *Neurobiology of Learning and Memory*. https://doi.org/10.1016/S1074-7427(03)00073-X

Gu, Q., & Singer, W. (1993). Effects of Intracortical Infusion of Anticholinergic Drugs on Neuronal Plasticity in Kitten Striate Cortex. *European Journal of Neuroscience*. https://doi.org/10.1111/j.1460-9568.1993.tb00514.x

Gu, Q., & Singer, W. (1995). Involvement of Serotonin in Developmental Plasticity of Kitten Visual Cortex. *European Journal of Neuroscience*. https://doi.org/10.1111/j.1460-9568.1995.tb01104.x

Harauzov, A., Spolidoro, M., DiCristo, G., De Pasquale, R., Cancedda, L., Pizzorusso, T., Viegi, A., Berardi, N., & Maffei, L. (2010). Reducing intracortical inhibition in the adult visual cortex promotes ocular dominance plasticity. *Journal of Neuroscience*, *30*(1), 361–371. https://doi.org/10.1523/JNEUROSCI.2233-09.2010

Harlow, H. F., Dodsworth, R. O., & Harlow, M. K. (1965). Total social isolation in monkeys. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.54.1.90

Härtig, W., Brauer, K., & Brückner, G. (1992). Wisteria floribunda agglutinin-labelled nets surround parvalbumin-containing neurons. *NeuroReport*. https://doi.org/10.1097/00001756-199210000-00012

Hata, Y., & Stryker, M. P. (1994). Control of thalamocortical afferent rearrangement by postsynaptic activity in developing visual cortex. *Science*. https://doi.org/10.1126/science.8085163

Hata, Y., Tsumoto, T., & Stryker, M. P. (1999). Selective pruning of more active afferents when cat visual cortex is pharmacologically inhibited. *Neuron*. https://doi.org/10.1016/S0896-6273(00)81097-1

He, H.-Y., Ray, B., Dennis, K., & Quinlan, E. M. (2007). Experience-dependent recovery of vision following chronic deprivation amblyopia. *Nature Neuroscience*, *10*(9), 1134–1136. https://doi.org/10.1038/nn1965

Heijnen, S., Hommel, B., Kibele, A., & Colzato, L. S. (2016). Neuromodulation of aerobic exercise-A review. In *Frontiers in Psychology* (Vol. 6, Issue JAN). Frontiers Research Foundation. https://doi.org/10.3389/fpsyg.2015.01890

Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1787

Hensch, T. K., Fagiolini, M., Mataga, N., Stryker, M. P., Baekkeskov, S., & Kash, S. F. (1998). Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science*, *282*(5393), 1504–1508. https://doi.org/10.1126/science.282.5393.1504

Hess, R. F. (2001). Amblyopia: Site unseen. In *Clinical and Experimental Optometry*. https://doi.org/10.1111/j.1444-0938.2001.tb06604.x

Heynen, A. J., & Bear, M. F. (2001). Long-term potentiation of thalamocortical transmission in the adult visual cortex in vivo. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *21*(24), 9801–9813.

Heynen, A. J., Yoon, B. J., Liu, C. H., Chung, H. J., Huganir, R. L., & Bear, M. F. (2003). Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. *Nature Neuroscience*. https://doi.org/10.1038/nn1100

Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: Exercise effects on brain and cognition. In *Nature Reviews Neuroscience* (Vol. 9, Issue 1, pp. 58–65). Nat Rev Neurosci. https://doi.org/10.1038/nrn2298

Hockfield, S., Kalb, R. G., Zaremba, S., & Fryer, H. (1990). Expression of neural proteoglycans correlates with the acquisition of mature neuronal properties in the mammalian brain. *Cold Spring Harbor Symposia on Quantitative Biology*. https://doi.org/10.1101/sqb.1990.055.01.049

Hohn, A., Leibrock, J., Bailey, K., & Barde, Y. A. (1990). Identification and characterization of a novel member of the nerve growth factor/brain-derived neurotrophic factor family. *Nature*. https://doi.org/10.1038/344339a0

Holloway, R. L. (1966). Dendritic branching: some preliminary results of training and complexity in rat visual cortex. *Brain Research*, *2*(4), 393–396. https://doi.org/10.1016/0006-8993(66)90009-6

Holmes, J. M., & Clarke, M. P. (2006). Amblyopia. In *Lancet*. https://doi.org/10.1016/S0140-6736(06)68581-4

Holtmaat, A. J. G. D., Trachtenberg, J. T., Wilbrecht, L., Shepherd, G. M., Zhang, X., Knott, G. W., & Svoboda, K. (2005). Transient and persistent dendritic spines in the neocortex in vivo. *Neuron*. https://doi.org/10.1016/j.neuron.2005.01.003

Horton, J. C., & Hocking, D. R. (1997). Timing of the critical period for plasticity of ocular dominance columns in macaque striate cortex. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.17-10-03684.1997

Huang, C. B., Zhou, Y., & Lu, Z. L. (2008). Broad bandwidth of perceptual learning in the visual system of adults with anisometropic amblyopia. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(10), 4068–4073. https://doi.org/10.1073/pnas.0800824105

Huang, Z. J., Kirkwood, A., Pizzorusso, T., Porciatti, V., Morales, B., Bear, M. F., Maffei, L., & Tonegawa, S. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell*. https://doi.org/10.1016/S0092-8674(00)81509-3

Hubel, D. H., & Wiesel, T. N. (1963). Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. *Journal of Neurophysiology*.

Hubel, D. H., & Wiesel, T. N. (1965). Receptive fields and functional architecture in two nonstriate visual areas (18 and 19) of the cat. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.1965.28.2.229

Hubel, D. H., & Wiesel, T. N. (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *The Journal of Physiology*. https://doi.org/10.1113/jphysiol.1970.sp009022

Hubel, D. H., Wiesel, T. N., & Stryker, M. P. (1977). Orientation columns in macaque monkey visual cortex demonstrated by the 2-deoxyglucose autoradiographic technique. *Nature*. https://doi.org/10.1038/269328a0

Ichikawa, M., Muramoto, K., Kobayashi, K., Kawahara, M., & Kuroda, Y. (1993). Formation and maturation of synapses in primary cultures of rat cerebral cortical cells: an electron microscopic study. *Neuroscience Research*, *16*(2), 95–103. https://doi.org/10.1016/0168-0102(93)90076-3

Issa, N. P., Trachtenberg, J. T., Chapman, B., Zahs, K. R., & Stryker, M. P. (1999). The Critical Period for Ocular Dominance Plasticity in the Ferret's Visual Cortex. *The Journal of Neuroscience*, *19*(16), 6965–6978. https://doi.org/10.1523/JNEUROSCI.19-16-06965.1999

Iwai, Y., Fagiolini, M., Obata, K., & Hensch, T. K. (2003). Rapid critical period induction by tonic inhibition in visual cortex. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.23-17-06695.2003

Jaepel, J., Hübener, M., Bonhoeffer, T., & Rose, T. (2017). Lateral geniculate neurons projecting to primary visual cortex show ocular dominance plasticity in adult mice. *Nature Neuroscience*. https://doi.org/10.1038/s41593-017-0021-0

Jarrard, L. E. (1995). What does the hippocampus really do? *Behavioural Brain Research*, *71*(1–2), 1–10. https://doi.org/10.1016/0166-4328(95)00034-8

Johansson, B. B., & Ohlsson, A. L. (1996). Environment, social interaction, and physical activity as determinants of functional outcome after cerebral infarction in the rat. *Experimental Neurology*, *139*(2), 322–327. https://doi.org/10.1006/exnr.1996.0106

Kameyama, K., Sohya, K., Ebina, T., Fukuda, A., Yanagawa, Y., & Tsumoto, T. (2010). Difference in binocularity and ocular dominance plasticity between GABAergic and excitatory cortical neurons. *Journal of Neuroscience*, *30*(4), 1551–1559. https://doi.org/10.1523/JNEUROSCI.5025-09.2010

Kandel, E. R. (2009). The biology of memory: A forty-year perspective. In *Journal of Neuroscience* (Vol. 29, Issue 41, pp. 12748–12756). J Neurosci. https://doi.org/10.1523/JNEUROSCI.3958-09.2009

Karni, A., & Sagi, D. (1993). The time course of learning a visual skill. *Nature*, *365*(6443), 250–252. https://doi.org/10.1038/365250a0

Karni, A., & Sagi, D. (1991). Where practice makes perfect in texture discrimination: Evidence for primary visual cortex plasticity. *Proceedings of the National Academy of Sciences of the United States of America*, *88*(11), 4966–4970. https://doi.org/10.1073/pnas.88.11.4966

Kasamatsu, T., & Pettigrew, J. D. (1976). Depletion of brain catecholamines: Failure of ocular dominance shift after monocular occlusion in kittens. *Science*. https://doi.org/10.1126/science.959850

Katz, L. C., & Shatz, C. J. (1996). Synaptic activity and the construction of cortical circuits. In *Science*. https://doi.org/10.1126/science.274.5290.1133

Kaufman, D. L., Houser, C. R., & Tobin, A. J. (1991). Two Forms of the γ-Aminobutyric Acid Synthetic Enzyme Glutamate Decarboxylase Have Distinct Intraneuronal Distributions and Cofactor Interactions. *Journal of Neurochemistry*, *56*(2), 720–723. https://doi.org/10.1111/j.1471-4159.1991.tb08211.x

Kawaguchi, Y., & Kubota, Y. (1998). Neurochemical features and synaptic connections of large physiologically-identified GABAergic cells in the rat frontal cortex. *Neuroscience*, *85*(3), 677–701. https://doi.org/10.1016/S0306-4522(97)00685-4

Kiorpes, L. (2006). Visual processing in amblyopia: Animal studies. *Strabismus*. https://doi.org/10.1080/09273970500536193

Kirkwood, A., Rioult, M. G., & Bear, M. F. (1996). Experience-dependent modification of synaptic plasticity in visual cortex. *Nature*. https://doi.org/10.1038/381526a0

Kirkwood, A., & Bear, M. F. (1994). Hebbian synapses in visual cortex. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.14-03-01634.1994

Kirkwood, A., & Bear, M. F. (1994). Homosynaptic long-term depression in the visual cortex. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.14-05-03404.1994

Kleim, J. A., Vij, K., Ballard, D. H., & Greenough, W. T. (1997). Learning-dependent synaptic modifications in the cerebellar cortex of the adult rat persist for at least four weeks. *Journal of Neuroscience*, *17*(2), 717–721. https://doi.org/10.1523/jneurosci.17-02-00717.1997

Knudsen, E. I., & Knudsen, P. F. (1990). Sensitive and critical periods for visual calibration of sound localization by Barn owls. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.10-01-00222.1990

Koopmans, G. C., Brans, M., Gómez-Pinilla, F., Duis, S., Gispen, W. H., Torres-Aleman, I., Joosten, E. A. J., & Hamers, F. P. T. (2006). Circulating insulin-like growth factor I and functional recovery from spinal cord injury under enriched housing conditions. *European Journal of Neuroscience*, *23*(4), 1035–1046. https://doi.org/10.1111/j.1460-9568.2006.04627.x

Köppe, G., Brückner, G., Brauer, K., Härtig, W., & Bigl, V. (1997). Developmental patterns of proteoglycan-containing extracellular matrix in perineuronal nets and neuropil of the postnatal rat brain. *Cell and Tissue Research*. https://doi.org/10.1007/s004410050790

Koppel, I., & Timmusk, T. (2013). Differential regulation of Bdnf expression in cortical neurons by class-selective histone deacetylase inhibitors. *Neuropharmacology*, *75*, 106–115. https://doi.org/10.1016/j.neuropharm.2013.07.015

Kourtzi, Z., Betts, L. R., Sarkheil, P., & Welchman, A. E. (2005). Distributed neural plasticity for shape learning in the human visual cortex. *PLoS Biology*, *3*(7), 1317–1327. https://doi.org/10.1371/journal.pbio.0030204

Kozorovitskiy, Y., Gross, C. G., Kopil, C., Battaglia, L., McBreen, M., Stranahan, A. M., & Gould, E. (2005). Experience induces structural and biochemical changes in the adult primate brain. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(48), 17478–17482. https://doi.org/10.1073/pnas.0508817102

Kramer, A. F., Hahn, S., Cohen, N. J., Banich, M. T., McAuley, E., Harrison, C. R., Chason, J., Vakil, E., Bardell, L., Boileau, R. A., & Colcombe, A. (1999). Ageing, fitness and neurocognitive function [7]. In *Nature* (Vol. 400, Issue 6743, pp. 418–419). Nature. https://doi.org/10.1038/22682

Kratz, K. E., Sherman, S. M., & Kalil, R. (1979). Lateral geniculate nucleus in dark-reared cats: Loss of Y cells without changes in cell size. *Science*. https://doi.org/10.1126/science.424758

Landi, S., Ciucci, F., Maffei, L., Berardi, N., & Cenni, M. C. (2009). Setting the pace for retinal development: Environmental enrichment acts through insulin-like growth factor 1 and brain-derived neurotrophic factor. *Journal of Neuroscience*, *29*(35), 10809–10819. https://doi.org/10.1523/JNEUROSCI.1857-09.2009

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., & Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine*, *144*(2), 73–81. https://doi.org/10.7326/0003-4819-144-2-200601170-00004

Laurin, D., Verreault, R., Lindsay, J., MacPherson, K., & Rockwood, K. (2001). Physical activity and risk of cognitive impairment and dementia in elderly persons. *Archives of Neurology*, *58*(3), 498–504. https://doi.org/10.1001/archneur.58.3.498

Law, C. T., & Gold, J. I. (2008). Neural correlates of perceptual learning in a sensory-motor, but not a sensory, cortical area. *Nature Neuroscience*, *11*(4), 505–513. https://doi.org/10.1038/nn2070

Lawlor, D. A., & Hopker, S. W. (2001). The effectiveness of exercise as an intervention in the management of depression: Systematic review and meta-regression analysis of randomised controlled trials. *British Medical Journal*, *322*(7289), 763–767. https://doi.org/10.1136/bmj.322.7289.763

Le Vay, S., Wiesel, T. N., & Hubel, D. H. (1980). The development of ocular dominance columns in normal and visually deprived monkeys. *Journal of Comparative Neurology*. https://doi.org/10.1002/cne.901910102

Le Vay, S., Wiesel, T. N., & Hubel, D. H. (1980). The development of ocular dominance columns in normal and visually deprived monkeys. *Journal of Comparative Neurology*, *191*(1), 1–51. https://doi.org/10.1002/cne.901910102

Lee, A. M., Hoy, J. L., Bonci, A., Wilbrecht, L., Stryker, M. P., & Niell, C. M. (2014). Identification of a brainstem circuit regulating visual cortical state in parallel with locomotion. *Neuron*, *83*(2), 455–466. https://doi.org/10.1016/j.neuron.2014.06.031

Levi, D. (2006). Visual processing in amblyopia: Human studies. *Strabismus*. https://doi.org/10.1080/09273970500536243

Levi, D. M. (2005). Perceptual learning in adults with amblyopia: A reevaluation of critical periods in human vision. In *Developmental Psychobiology* (Vol. 46, Issue 3, pp. 222–232). Dev Psychobiol. https://doi.org/10.1002/dev.20050

Levi, D. M., Knill, D. C., & Bavelier, D. (2015). Stereopsis and amblyopia: A mini-review. In *Vision Research*. https://doi.org/10.1016/j.visres.2015.01.002

Levi, D. M., & Li, R. W. (2009). Improving the performance of the amblyopic visual system. In *Philosophical Transactions of the Royal Society B: Biological Sciences* (Vol. 364, Issue 1515, pp. 399–407). Royal Society. https://doi.org/10.1098/rstb.2008.0203

Levi, D. M., & Li, R. W. (2009). Perceptual learning as a potential treatment for amblyopia: A mini-review. *Vision Research*, *49*(21), 2535–2549. https://doi.org/10.1016/j.visres.2009.02.010

Levi, D. M., & Polat, U. (1996). Neural plasticity in adults with amblyopia. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(13), 6830–6834. https://doi.org/10.1073/pnas.93.13.6830

Levi, D. M., Polat, U., & Hu, Y. S. (1997). Improvement in Vernier acuity in adults with amblyopia: Practice makes better. *Investigative Ophthalmology and Visual Science*, *38*(8), 1493–1510.

Levi-Montalcini, R., & Cohen, S. (1956). In vitro and in vivo effects of a nerve growth-stimulating agent isolated from snake venom. *Proceedings of the National Academy of Sciences*. https://doi.org/10.1073/pnas.42.9.695

Lewis, T. L., & Maurer, D. (2009). Effects of early pattern deprivation on visual development. In *Optometry and Vision Science*. https://doi.org/10.1097/OPX.0b013e3181a7296b

Li, R. W., Klein, S. A., & Levi, D. M. (2008). Prolonged perceptual learning of positional acuity in adult amblyopia: Perceptual template retuning dynamics. *Journal of Neuroscience*, *28*(52), 14223–14229. https://doi.org/10.1523/JNEUROSCI.4271-08.2008

Li, R. W., & Levi, D. M. (2004). Characterizing the mechanisms of improvement for position discrimination in adult amblyopia. *Journal of Vision*. https://doi.org/10.1167/4.6.7

Li, R. W., Provost, A., & Levi, D. M. (2007). Extended perceptual learning results in substantial recovery of positional acuity and visual acuity in juvenile amblyopia. *Investigative Ophthalmology and Visual Science*, *48*(11), 5046–5051. https://doi.org/10.1167/iovs.07-0324

Li, R. W., Young, K. G., Hoenig, P., & Levi, D. M. (2005). Perceptual learning improves visual performance in juvenile amblyopia. *Investigative Ophthalmology and Visual Science*, *46*(9), 3161–3168. https://doi.org/10.1167/iovs.05-0286

Liu, Z., & Vaina, L. M. (1998). Simultaneous learning of motion discrimination in two directions. *Cognitive Brain Research*, *6*(4), 347–349. https://doi.org/10.1016/S0926-6410(98)00008-1

Loudon, S. E., & Simonsz, H. J. (2005). The history of the treatment of amblyopia. In *Strabismus* (Vol. 13, Issue 2, pp. 93–106). Strabismus. https://doi.org/10.1080/09273970590949818

Lourenco, M. V., Frozza, R. L., de Freitas, G. B., Zhang, H., Kincheski, G. C., Ribeiro, F. C., Gonçalves, R. A., Clarke, J. R., Beckman, D., Staniszewski, A., Berman, H., Guerra, L. A., Forny-Germano, L., Meier, S., Wilcock, D. M., de Souza, J. M., Alves-Leon, S., Prado, V. F., Prado, M. A. M., … De Felice, F. G. (2019). Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nature Medicine*, *25*(1), 165–175. https://doi.org/10.1038/s41591-018-0275-4

Luhmann, H. J., & Prince, D. A. (1991). Postnatal maturation of the GABAergic system in rat neocortex. *Journal of Neurophysiology*, *65*(2), 247–263. https://doi.org/10.1152/jn.1991.65.2.247

Lunghi, C., & Sale, A. (2015). A cycling lane for brain rewiring. In *Current Biology* (Vol. 25, Issue 23, pp. R1122–R1123). Cell Press. https://doi.org/10.1016/j.cub.2015.10.026

Lunghi, C., Sframeli, A. T., Lepri, A., Lepri, M., Lisi, D., Sale, A., & Morrone, M. C. (2019). A new counterintuitive training for adult amblyopia. *Annals of Clinical and Translational Neurology*, *6*(2), 274–284. https://doi.org/10.1002/acn3.698

Lunghi, C., Sframeli, A. T., Lepri, A., Lepri, M., Lisi, D., Sale, A., & Morrone, M. C. (2018). A new counter-intuitive therapy for adult amblyopia. *BioRxiv*, 360420. https://doi.org/10.1101/360420

Maass, A., Düzel, S., Brigadski, T., Goerke, M., Becke, A., Sobieray, U., Neumann, K., Lövdén, M., Lindenberger, U., Bäckman, L., Braun-Dullaeus, R., Ahrens, D., Heinze, H. J., Müller, N. G., Lessmann, V., Sendtner, M., & Düzel, E. (2016). Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults. *NeuroImage*, *131*, 142–154. https://doi.org/10.1016/j.neuroimage.2015.10.084

Maffei, L., Berardi, N., Domenici, L., Parisi, V., & Pizzorusso, T. (1992). Nerve growth factor (NGF) prevents the shift in ocular dominance distribution of visual cortical neurons in monocularly deprived rats. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.12-12-04651.1992

Masaki, T., & Nakajima, S. (2006). Taste aversion in rats induced by forced swimming, voluntary running, forced running, and lithium chloride injection treatments. *Physiology and Behavior*, *88*(4–5), 411–416. https://doi.org/10.1016/j.physbeh.2006.04.013

Mataga, N., Imamura, K., Shiomitsu, T., Yoshimura, Y., Fukamauchi, F., & Watanabe, Y. (1996). Enhancement of mRNA expression of tissue-type plasminogen activator by L-threo-3,4-dihydroxyphenylserine in association with ocular dominance plasticity. *Neuroscience Letters*. https://doi.org/10.1016/S0304-3940(96)13139-6

Mataga, N., Mizuguchi, Y., & Hensch, T. K. (2004). Experience-dependent pruning of dendritic spines in visual cortex by tissue plasminogen activator. *Neuron*. https://doi.org/10.1016/j.neuron.2004.11.028

Mataga, N., Nagai, N., & Hensch, T. K. (2002). Permissive proteolytic activity for visual cortical plasticity. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.102088899

Matthews, N., Liu, Z., Geesaman, B. J., & Qian, N. (1999). Perceptual learning on orientation and direction discrimination. *Vision Research*, *39*(22), 3692–3701. https://doi.org/10.1016/S0042-6989(99)00069-3

Matthews, N., & Welch, L. (1997). Velocity-dependent improvements in single-dot direction discrimination. *Perception and Psychophysics*, *59*(1), 60–72. https://doi.org/10.3758/BF03206848

Matthies, U., Balog, J., & Lehmann, K. (2013). Temporally coherent visual stimuli boost ocular dominance plasticity. *Journal of Neuroscience*, *33*(29), 11774–11778. https://doi.org/10.1523/JNEUROSCI.4262-12.2013

Maya-Vetencourt, J. F., Baroncelli, L., Viegi, A., Tiraboschi, E., Castren, E., Cattaneo, A., & Maffei, L. (2012). IGF-1 restores visual cortex plasticity in adult life by reducing local GABA levels. *Neural Plasticity*, *2012*. https://doi.org/10.1155/2012/250421

Mayer, M. J. (1983). Practice improves adults' sensitivity to diagonals. *Vision Research*, *23*(5), 547–550. https://doi.org/10.1016/0042-6989(83)90130-X

Mazziotti, R., Baroncelli, L., Ceglia, N., Chelini, G., Sala, G. Della, Magnan, C., Napoli, D., Putignano, E., Silingardi, D., Tola, J., Tognini, P., Arthur, J. S. C., Baldi, P., & Pizzorusso, T. (2017). Mir-132/212 is required for maturation of binocular matching of orientation preference and depth perception. *Nature Communications*. https://doi.org/10.1038/ncomms15488

McAllister, A. K., Katz, L. C., & Lo, D. C. (1999). Neurotrophins and synaptic plasticity. In *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev.neuro.22.1.295

McAuley, E., Szabo, A. N., Mailey, E. L., Erickson, K. I., Voss, M., White, S. M., Wójcicki, T. R., Gothe, N., Olson, E. A., Mullen, S. P., & Kramer, A. F. (2011). Non-exercise estimated cardiorespiratory fitness: Associations with brain structure, cognition, and memory complaints in older adults. *Mental Health and Physical Activity*, *4*(1), 5–11. https://doi.org/10.1016/j.mhpa.2011.01.001

McGee, A. W., Yang, Y., Fischer, Q. S., Daw, N. W., & Strittmatter, S. H. (2005). Neuroscience: Experience-driven plasticity of visual cortex limited by myelin and nogo receptor. *Science*. https://doi.org/10.1126/science.1114362

Mckee, S. P., & Westhe, G. (1978). Improvement in vernier acuity with practice. *Perception & Psychophysics*, *24*(3), 258–262. https://doi.org/10.3758/BF03206097

Mellios, N., Sugihara, H., Castro, J., Banerjee, A., Le, C., Kumar, A., Crawford, B., Strathmann, J., Tropea, D., Levine, S. S., Edbauer, D., & Sur, M. (2011). MiR-132, an experience-dependent microRNA, is essential for visual cortex plasticity. *Nature Neuroscience*. https://doi.org/10.1038/nn.2909

Micheva, K. D., & Beaulieu, C. (1997). Development and plasticity of the inhibitory neocortical circuitry with an emphasis on the rodent barrel field cortex: A review. *Canadian Journal of Physiology and Pharmacology*, *75*(5), 470–478. https://doi.org/10.1139/y97-032

Miller, K. D., Keller, J. B., & Stryker, M. P. (1989). Ocular dominance column development: Analysis and simulation. In *Science*. https://doi.org/10.1126/science.2762813

Mitzdorf, U., & Singer, W. (1980). Monocular activation of visual cortex in normal and monocularly deprived cats: an analysis of evoked potentials. *The Journal of Physiology*. https://doi.org/10.1113/jphysiol.1980.sp013320

Miwa, J. M., Ibañez-Tallon, I., Crabtree, G. W., Sánchez, R., Šali, A., Role, L. W., & Heintz, N. (1999). lynx1, an endogenous toxin-like modulator of nicotinic acetylcholine receptors in the mammalian CNS. *Neuron*. https://doi.org/10.1016/S0896-6273(00)80757-6

Møllgaard, K., Diamond, M. C., Bennett, E. L., Rosenzweig, M. R., & Lindner, B. (1971). Quantitative synaptic changes with differential experience in rat brain. *International Journal of Neuroscience*, *2*(3), 113–127. https://doi.org/10.3109/00207457109148764

Molteni, R., Barnard, R. J., Ying, Z., Roberts, C. K., & Gómez-Pinilla, F. (2002). A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience*, *112*(4), 803–814. https://doi.org/10.1016/S0306-4522(02)00123-9

Moon, H. Y., Becke, A., Berron, D., Becker, B., Sah, N., Benoni, G., Janke, E., Lubejko, S. T., Greig, N. H., Mattison, J. A., Duzel, E., & van Praag, H. (2016). Running-Induced Systemic Cathepsin B Secretion Is Associated with Memory Function. *Cell Metabolism*, *24*(2), 332–340. https://doi.org/10.1016/j.cmet.2016.05.025

Morishita, H., Miwa, J. M., Heintz, N., & Hensch, T. K. (2010). Lynx1, a cholinergic brake, limits plasticity in adult visual cortex. *Science*, *330*(6008), 1238–1240. https://doi.org/10.1126/science.1195320

Morris, T., Osman, J. G., Muñoz, J. M. T., Costa-Miserachs, D., & Leone, A. P. (2016). The role of physical exercise in cognitive recovery after traumatic brain injury: A systematic review. In *Restorative Neurology and Neuroscience* (Vol. 34, Issue 6, pp. 977–988). IOS Press. https://doi.org/10.3233/RNN-160687

Moruzzi, G., & Magoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology*, *1*(1–4), 455–473. https://doi.org/10.1016/0013-4694(49)90219-9

Movshon, J. A. (1976). Reversal of the physiological effects of monocular deprivation in the kitten's visual cortex. *The Journal of Physiology*. https://doi.org/10.1113/jphysiol.1976.sp011551

Movshon, J. A., & Dursteler, M. R. (1977). Effects of brief periods of unilateral eye closure on the kitten's visual system. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.1977.40.6.1255

Mower, G. D., & Guo, Y. (2001). Comparison of the expression of two forms of glutamic acid decarboxylase (GAD67 and GAD65) in the visual cortex of normal and dark-reared cats. *Developmental Brain Research*, *126*(1), 65–74. https://doi.org/10.1016/S0165-3806(00)00139-5

Mower, G. D. (1991). The effect of dark rearing on the time course of the critical period in cat visual cortex. *Developmental Brain Research*, *58*(2), 151–158. https://doi.org/10.1016/0165-3806(91)90001-Y

Mueller-Steiner, S., Zhou, Y., Arai, H., Roberson, E. D., Sun, B., Chen, J., Wang, X., Yu, G., Esposito, L., Mucke, L., & Gan, L. (2006). Antiamyloidogenic and Neuroprotective Functions of Cathepsin B: Implications for Alzheimer's Disease. *Neuron*, *51*(6), 703–714. https://doi.org/10.1016/j.neuron.2006.07.027

Müller, C. M., & Griesinger, C. B. (1998). Tissue plasminogen activator mediates reverse occlusion plasticity in visual cortex. *Nature Neuroscience*. https://doi.org/10.1038/248

Murphy, G. J., Darcy, D. P., & Isaacson, J. S. (2005). Intraglomerular inhibition: Signaling mechanisms of an olfactory microcircuit. *Nature Neuroscience*, *8*(3), 354–364. https://doi.org/10.1038/nn1403

Murri, M. B., Ekkekakis, P., Magagnoli, M., Zampogna, D., Cattedra, S., Capobianco, L., Serafini, G., Calcagno, P., Zanetidou, S., & Amore, M. (2019). Physical exercise in major depression: Reducing the mortality gap while improving clinical outcomes. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00762

Nan, X., Ng, H. H., Johnson, C. A., Laherty, C. D., Turner, B. M., Eisenman, R. N., & Bird, A. (1998). Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. *Nature*, *393*(6683), 386–389. https://doi.org/10.1038/30764

Narath, E., Skalicky, M., & Viidik, A. (2001). Voluntary and forced exercise influence the survival and body composition of ageing male rats differently. *Experimental Gerontology*, *36*(10), 1699–1711. https://doi.org/10.1016/S0531-5565(01)00145-0

Nilsson, D. E., & Warrant, E. J. (1999). Visual discrimination: Seeing the third quality of light. In *Current Biology* (Vol. 9, Issue 14). Current Biology Ltd. https://doi.org/10.1016/S0960-9822(99)80330-3

Nishijima, T., Piriz, J., Duflot, S., Fernandez, A. M., Gaitan, G., Gomez-Pinedo, U., Verdugo, J. M. G., Leroy, F., Soya, H., Nuñez, A., & Torres-Aleman, I. (2010). Neuronal Activity Drives Localized Blood-Brain-Barrier Transport of Serum Insulin-like Growth Factor-I into the CNS. *Neuron*. https://doi.org/10.1016/j.neuron.2010.08.007

Nithianantharajah, J., & Hannan, A. J. (2006). Enriched environments, experience-dependent plasticity and disorders of the nervous system. In *Nature Reviews Neuroscience* (Vol. 7, Issue 9, pp. 697–709). Nat Rev Neurosci. https://doi.org/10.1038/nrn1970

Noda, Y., Kuzuya, A., Tanigawa, K., Araki, M., Kawai, R., Ma, B., Sasakura, Y., Maesako, M., Tashiro, Y., Miyamoto, M., Uemura, K., Okuno, Y., & Kinoshita, A. (2018). Fibronectin type III domain-containing protein 5 interacts with APP and decreases amyloid β production in Alzheimer's disease 11 Medical and Health Sciences 1109 Neurosciences Tim Bliss. *Molecular Brain*, *11*(1). https://doi.org/10.1186/s13041-018-0401-8

Nystoriak, M. A., & Bhatnagar, A. (2018). Cardiovascular Effects and Benefits of Exercise. In *Frontiers in Cardiovascular Medicine* (Vol. 5). Frontiers Media S.A. https://doi.org/10.3389/fcvm.2018.00135

Olson, C. R., & Freeman, R. D. (1980). Profile of the sensitive period for monocular deprivation in kittens. *Experimental Brain Research*. https://doi.org/10.1007/BF00237065

Olson, C. R., & Freeman, R. D. (1975). Progressive changes in kitten striate cortex during monocular vision. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.1975.38.1.26

Oray, S., Majewska, A., & Sur, M. (2004). Dendritic spine dynamics are regulated by monocular deprivation and extracellular matrix degradation. *Neuron*. https://doi.org/10.1016/j.neuron.2004.12.001

Origlia, N., Righi, M., Capsoni, S., Cattaneo, A., Fang, F., Stern, D. M., Chen, J. X., Schmidt, A. M., Arancio, O., Shi, D. Y., & Domenici, L. (2008). Receptor for advanced glycation end product-dependent activation of p38 mitogen-activated protein kinase contributes to amyloid-β-mediated cortical synaptic dysfunction. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.0204-08.2008

Pascual-Leone, A., Amedi, A., Fregni, F., & Merabet, L. B. (2005). The plastic human brain cortex. In *Annual Review of Neuroscience* (Vol. 28, pp. 377–401). Annu Rev Neurosci. https://doi.org/10.1146/annurev.neuro.27.070203.144216

Paspalas, C. D., & Papadopoulos, G. C. (2001). Serotoninergic afferents preferentially innervate distinct subclasses of peptidergic interneurons in the rat visual cortex. *Brain Research*. https://doi.org/10.1016/S0006-8993(00)03193-0

Patten, A. R., Yau, S. Y., Fontaine, C. J., Meconi, A., Wortman, R. C., & Christie, B. R. (2016). The Benefits of Exercise on Structural and Functional Plasticity in the Rodent Hippocampus of Different Disease Models. *Brain Plasticity, 1*(1), 97–127. https://doi.org/10.3233/bpl-150016

Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., Sloan, R., Gage, F. H., Brown, T. R., & Small, S. A. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(13), 5638–5643. https://doi.org/10.1073/pnas.0611721104

Pham, T. A., Impey, S., Storm, D. R., & Stryker, M. P. (1999). Cre-mediated gene transcription in neocortical neuronal plasticity during the developmental critical period. *Neuron*. https://doi.org/10.1016/S0896-6273(00)80679-0

Pizzorusso, T., Medini, P., Landi, S., Baldini, S., Berardi, N., & Maffei, L. (2006). Structural and functional recovery from early monocular deprivation in adult rats. *Proceedings of the National Academy of Sciences*, *103*(22), 8517–8522. https://doi.org/10.1073/pnas.0602657103

Pizzorusso, T. (1999). TrkA activation in the rat visual cortex by antirat trkA IgG prevents the effect of monocular deprivation. *European Journal of Neuroscience*. https://doi.org/10.1046/j.1460-9568.1999.00417.x

Pizzorusso, T., Fagiolini, M., Porciatti, V., & Maffei, L. (1997). Temporal aspects of contrast visual evoked potentials in the pigmented rat: Effect of dark rearing. *Vision Research*. https://doi.org/10.1016/S0042-6989(96)00172-1

Pizzorusso, T., Medini, P., Berardi, N., Chierzi, S., Fawcett, J. W., & Maffei, L. (2002). Reactivation of ocular dominance plasticity in the adult visual cortex. *Science*. https://doi.org/10.1126/science.1072699

Ploughman, M., Granter-Button, S., Chernenko, G., Tucker, B. A., Mearow, K. M., & Corbett, D. (2005). Endurance exercise regimens induce differential effects on brain-derived neurotrophic factor, synapsin-I and insulin-like growth factor I after focal ischemia. *Neuroscience*, *136*(4), 991–1001. https://doi.org/10.1016/j.neuroscience.2005.08.037

Poo, M. ming. (2001). Neurotrophins as synaptic modulators. *Nature Reviews Neuroscience*. https://doi.org/10.1038/35049004

Pourtois, G., Rauss, K. S., Vuilleumier, P., & Schwartz, S. (2008). Effects of perceptual learning on primary visual cortex activity in humans. *Vision Research*, *48*(1), 55–62. https://doi.org/10.1016/j.visres.2007.10.027

Prusky, G. T., Arbuckle, J. M., & Cynader, M. S. (1988). Transient concordant distributions of nicotinic receptors and acetylcholinesterase activity in infant rat visual cortex. *Developmental Brain Research*. https://doi.org/10.1016/0165-3806(88)90078-8

Putignano, E., Lonetti, G., Cancedda, L., Ratto, G., Costa, M., Maffei, L., & Pizzorusso, T. (2007). Developmental Downregulation of Histone Posttranslational Modifications Regulates Visual Cortical Plasticity. *Neuron*. https://doi.org/10.1016/j.neuron.2007.02.007

R, S., C, Z., E, G., JR, T., A, L., & T, P. (2017). Exercise for people with cancer: a systematic review. *Current Oncology (Toronto, Ont.)*, *24*(4). https://doi.org/10.3747/CO.24.3619

Ramachandran, V. S., & Braddick, O. (1973). Orientation specific learning in stereopsis. *Perception*, *2*(3), 371–376. https://doi.org/10.1068/p020371

Rampon, C., & Tsien, J. Z. (2000). Genetic analysis of learning behavior-induced structural plasticity. *Hippocampus*, *10*(5), 605–609. https://doi.org/10.1002/1098-1063(2000)10:5<605: AID-HIPO11>3.0.CO;2-3

Recanzone, G. H., Merzenich, M. M., Jenkins, W. M., Grajski, K. A., & Dinse, H. R. (1992). Topographic reorganization of the hand representation in cortical area 3b of owl monkeys trained in a frequency-discrimination task. *Journal of Neurophysiology*, *67*(5), 1031–1056. https://doi.org/10.1152/jn.1992.67.5.1031

Recanzone, G. H., Schreiner, C. E., & Merzenich, M. M. (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *Journal of Neuroscience*, *13*(1), 87–103. https://doi.org/10.1523/jneurosci.13-01-00087.1993

Reiter, H. O., & Stryker, M. P. (1988). Neural plasticity without postsynaptic action potentials: Less-active inputs become dominant when kitten visual cortical cells are pharmacologically inhibited. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.85.10.3623

Reiter, H. O., Waitzman, D. M., & Stryker, M. P. (1986). Cortical activity blockade prevents ocular dominance plasticity in the kitten visual cortex. *Experimental Brain Research*. https://doi.org/10.1007/BF00243841

Roerig, B., & Katz, L. C. (1997). Modulation of intrinsic circuits by serotonin 5-HT3 receptors in developing ferret visual cortex. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.17-21-08324.1997

Rosenzweig, M. R., Bennett, E. L., & Diamond, M. C. (1967). Effects of differential environments on brain anatomy and brain chemistry. *Proceedings of the Annual Meeting of the American Psychopathological Association*, *56*, 45–56.

Rosenzweig, M. R., Krech, D., Bennett, E. L., & Zolman, J. F. (1962). Variation in environmental complexity and brain measures. *Journal of Comparative and Physiological Psychology*, *55*, 1092–1095.

Rosenzweig, M. R., & Bennett, E. L. (1996). Psychobiology of plasticity: Effects of training and experience on brain and behavior. *Behavioural Brain Research*, *78*(1), 57–65. https://doi.org/10.1016/0166-4328(95)00216-2

Rosenzweig, M. R., Bennett, E. L., Hebert, M., & Morimoto, H. (1978). Social grouping cannot account for cerebral effects of enriched environments. *Brain Research*, *153*(3), 563–576. https://doi.org/10.1016/0006-8993(78)90340-2

Rosenzweig, M. R., Bennett, E. L., & Krech, D. (1964). Cerebral effects of environmental complexity and training among adult rats. *Journal of Comparative and Physiological Psychology*, *57*(3), 438–439. https://doi.org/10.1037/h0046387

Rosenzweig, M. R., Krech, D., Bennett, E. L., & Diamond, M. C. (1962). Effects of environmental complexity and training on brain chemistry and anatomy: A replication and extension. *Journal of Comparative and Physiological Psychology*, *55*(4), 429–437. https://doi.org/10.1037/h0041137

Rossi, F. M., Bozzi, Y., Pizzorusso, T., & Maffei, L. (1999). Monocular deprivation decreases brain-derived neurotrophic factor immunoreactivity in the rat visual cortex. *Neuroscience*. https://doi.org/10.1016/S0306-4522(98)00463-1

Runyan, C. A., Schummers, J., Van Wart, A., Kuhlman, S. J., Wilson, N. R., Huang, Z. J., & Sur, M. (2010). Response Features of Parvalbumin-Expressing Interneurons Suggest Precise Roles for Subtypes of Inhibition in Visual Cortex. *Neuron*, *67*(5), 847–857. https://doi.org/10.1016/j.neuron.2010.08.006

Sadahiro, M., Sajo, M., & Morishita, H. (2016). Nicotinic regulation of experience-dependent plasticity in visual cortex. In *Journal of Physiology Paris*. https://doi.org/10.1016/j.jphysparis.2016.11.003

Sale, A., De Pasquale, R., Bonaccorsi, J., Pietra, G., Olivieri, D., Berardi, N., & Maffei, L. (2011). Visual perceptual learning induces long-term potentiation in the visual cortex. *Neuroscience*, *172*, 219–225. https://doi.org/10.1016/j.neuroscience.2010.10.078

Sale, A., Berardi, N., & Maffei, L. (2014). Environment and Brain Plasticity: Towards an Endogenous Pharmacotherapy. *Physiological Reviews*, *94*(1), 189–234. https://doi.org/10.1152/physrev.00036.2012

Sale, A. (2018). A Systematic Look at Environmental Modulation and Its Impact in Brain Development. *Trends in Neurosciences*, *41*(1), 4–17. https://doi.org/10.1016/j.tins.2017.10.004

Sale, A., Maya Vetencourt, J. F., Medini, P., Cenni, M. C., Baroncelli, L., De Pasquale, R., & Maffei, L. (2007). Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nature Neuroscience*. https://doi.org/10.1038/nn1899

Sansevero, G., Baroncelli, L., Scali, M., & Sale, A. (2019). Intranasal BDNF administration promotes visual function recovery in adult amblyopic rats. *Neuropharmacology*. https://doi.org/10.1016/j.neuropharm.2018.02.006

Sawtell, N. B., Frenkel, M. Y., Philpot, B. D., Nakazawa, K., Tonegawa, S., & Bear, M. F. (2003). NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. *Neuron*, *38*(6), 977–985. https://doi.org/10.1016/S0896-6273(03)00323-4

Schoups, A. A., Vogels, R., & Orban, G. A. (1995). Human perceptual learning in identifying the oblique orientation: retinotopy, orientation specificity and monocularity. *The Journal of Physiology*. https://doi.org/10.1113/jphysiol.1995.sp020623

Schoups, A., Vogels, R., Qian, N., & Orban, G. (2001). Practising orientation identification improves orientation coding in V1 neurons. *Nature*, *412*(6846), 549–553. https://doi.org/10.1038/35087601

Segal, R., Zwaal, C., Green, E., Tomasone, J. R., Loblaw, A., & Petrella, T. (2017). Exercise for people with cancer: A clinical practice guideline. *Current Oncology*, *24*(1), 40–46. https://doi.org/10.3747/co.24.3376

Senn, W., Markram, H., & Tsodyks, M. (2001). An algorithm for modifying neurotransmitter release probability based on pre- and postsynaptic spike timing. *Neural Computation*, *13*(1), 35–67. https://doi.org/10.1162/089976601300014628

Shatz, C. J., & Stryker, M. P. (1978). Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation. *The Journal of Physiology*. https://doi.org/10.1113/jphysiol.1978.sp012421

Sherman, S. M., & Stone, J. (1973). Physiological normality of the retina in visually deprived cats. *Brain Research*. https://doi.org/10.1016/0006-8993(73)90861-5

Shiu, L. P., & Pashler, H. (1992). Improvement in line orientation discrimination is retinally local but dependent on cognitive set. *Perception & Psychophysics*, *52*(5), 582–588. https://doi.org/10.3758/BF03206720

Silingardi, D., Scali, M., Belluomini, G., & Pizzorusso, T. (2010). Epigenetic treatments of adult rats promote recovery from visual acuity deficits induced by long-term monocular deprivation. *European Journal of Neuroscience*. https://doi.org/10.1111/j.1460-9568.2010.07261.x

Simmers, A. J., Ledgeway, T., Hess, R. F., & McGraw, P. V. (2003). Deficits to global motion processing in human amblyopia. *Vision Research*. https://doi.org/10.1016/S0042-6989(02)00684-3

Singer, W. (1995). Development and plasticity of cortical processing architectures. *Science (New York, N.Y.)*, *270*(5237), 758–764. https://doi.org/10.1126/science.270.5237.758

Siteneski, A., Cunha, M. P., Lieberknecht, V., Pazini, F. L., Gruhn, K., Brocardo, P. S., & Rodrigues, A. L. S. (2018). Central irisin administration affords antidepressant-like effect and modulates neuroplasticity-related genes in the hippocampus and prefrontal cortex of mice. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *84*(Pt A), 294–303. https://doi.org/10.1016/j.pnpbp.2018.03.004

Skrandies, W., & Fahle, M. (1994). Neurophysiological correlates of perceptual learning in the human brain. *Brain Topography*, *7*(2), 163–168. https://doi.org/10.1007/BF01186774

Sleiman, S. F., & Chao, M. V. (2016). Downstream Consequences of Exercise Through the Action of BDNF. *Brain Plasticity*, *1*(1), 143–148. https://doi.org/10.3233/bpl-150017

Sleiman, S. F., Henry, J., Al-Haddad, R., El Hayek, L., Haidar, E. A., Stringer, T., Ulja, D., Karuppagounder, S. S., Holson, E. B., Ratan, R. R., Ninan, I., & Chao, M. V. (2016). Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β- hydroxybutyrate. *ELife*, *5*(JUN2016). https://doi.org/10.7554/eLife.15092

Smith, G. B., Heynen, A. J., & Bear, M. F. (2009). Bidirectional synaptic mechanisms of ocular dominance plasticity in visual cortex. In *Philosophical Transactions of the Royal Society B: Biological Sciences*. https://doi.org/10.1098/rstb.2008.0198

Sohal, V. S., Zhang, F., Yizhar, O., & Deisseroth, K. (2009). Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature*, *459*(7247), 698–702. https://doi.org/10.1038/nature07991

Sommeijer, J. P., Ahmadlou, M., Saiepour, M. H., Seignette, K., Min, R., Heimel, J. A., & Levelt, C. N. (2017). Thalamic inhibition regulates critical-period plasticity in visual cortex and thalamus. *Nature Neuroscience*. https://doi.org/10.1038/s41593-017-0002-3

Stryker, M. P., & Löwel, S. (2018). Amblyopia: New molecular/pharmacological and environmental approaches. In *Visual neuroscience* (Vol. 35, p. E018). Vis Neurosci. https://doi.org/10.1017/S0952523817000256

Stryker, M. P. (2014). A neural circuit that controls cortical state, plasticity, and the gain of sensory responses in mouse. *Cold Spring Harbor Symposia on Quantitative Biology*. https://doi.org/10.1101/sqb.2014.79.024927

Sugiyama, S., Di Nardo, A. A., Aizawa, S., Matsuo, I., Volovitch, M., Prochiantz, A., & Hensch, T. K. (2008). Experience-Dependent Transfer of Otx2 Homeoprotein into the Visual Cortex Activates Postnatal Plasticity. *Cell*. https://doi.org/10.1016/j.cell.2008.05.054

Sugiyama, S., Prochiantz, A., & Hensch, T. K. (2009). From brain formation to plasticity: Insights on Otx2 homeoprotein. In *Development Growth and Differentiation*. https://doi.org/10.1111/j.1440-169X.2009.01093.x

Suominen-Troyer, S., Davis, K. J., Ismail, A. H., & Salvendy, G. (1986). Impact of physical fitness on strategy development in decision-making tasks. *Perceptual and Motor Skills*, *62*(1), 71–77. https://doi.org/10.2466/pms.1986.62.1.71

Suwabe, K., Byun, K., Hyodo, K., Reagh, Z. M., Roberts, J. M., Matsushita, A., Saotome, K., Ochi, G., Suzuki, K., Sankai, Y., Yassa, M. A., Soyaa, H., & Fukuie, T. (2018). Rapid stimulation of human dentate gyrus function with acute mild exercise. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(41), 10487–10492. https://doi.org/10.1073/pnas.1805668115

Suzuki, S., Al-Noori, S., Butt, S. A., & Pham, T. A. (2004). Regulation of the CREB signaling cascade in the visual cortex by visual experience and neuronal activity. *Journal of Comparative Neurology*. https://doi.org/10.1002/cne.20310

Taha, S. A., & Stryker, M. P. (2005). Ocular dominance plasticity is stably maintained in the absence of α calcium calmodulin kinase II (αCaMKII) autophosphorylation. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0508185102

Taha, S., Hanover, J. L., Silva, A. J., & Stryker, M. P. (2002). Autophosphorylation of αCaMKII Is required for ocular dominance plasticity. *Neuron*. https://doi.org/10.1016/S0896-6273(02)00966-2

Tamás, G., Buhl, E. H., Lörincz, A., & Somogyi, P. (2000). Proximally targeted GABAergic synapses and gap junctions synchronize cortical interneurons. *Nature Neuroscience*, *3*(4), 366–371. https://doi.org/10.1038/73936

Thoenen, H. (1995). Neurotrophins and neuronal plasticity. *Science*. https://doi.org/10.1126/science.270.5236.593

Tillerson, J. L., Caudle, W. M., Reverón, M. E., & Miller, G. W. (2003). Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease. *Neuroscience*, *119*(3), 899–911. https://doi.org/10.1016/S0306-4522(03)00096-4

Timney, B., Mitchell, D. E., & Giffin, F. (1978). The development of vision in cats after extended periods of dark-rearing. *Experimental Brain Research*. https://doi.org/10.1007/BF00239811

Tognini, P., Napoli, D., Tola, J., Silingardi, D., Della Ragione, F., D'esposito, M., & Pizzorusso, T. (2015). Experience-dependent DNA methylation regulates plasticity in the developing visual cortex. *Nature Neuroscience*. https://doi.org/10.1038/nn.4026

Tognini, P., Putignano, E., Coatti, A., & Pizzorusso, T. (2011). Experience-dependent expression of miR-132 regulates ocular dominance plasticity. *Nature Neuroscience*. https://doi.org/10.1038/nn.2920

Tremblay, R., Lee, S., & Rudy, B. (2016). GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. In *Neuron* (Vol. 91, Issue 2, pp. 260–292). Cell Press. https://doi.org/10.1016/j.neuron.2016.06.033

Tropea, D., Kreiman, G., Lyckman, A., Mukherjee, S., Yu, H., Horng, S., & Sur, M. (2006). Gene expression changes and molecular pathways mediating activity-dependent plasticity in visual cortex. *Nature Neuroscience*. https://doi.org/10.1038/nn1689

Tsumoto, T., & Suda, K. (1978). Evidence for excitatory connections from the deprived eye to the visual cortex in monocularly deprived kittens. *Brain Research*. https://doi.org/10.1016/0006-8993(78)91137-X

Turner, A. M., & Greenough, W. T. (1985). Differential rearing effects on rat visual cortex synapses. I. Synaptic and neuronal density and synapses per neuron. *Brain Research*, *329*(1–2), 195–203. https://doi.org/10.1016/0006-8993(85)90525-6

Van Praag, H. (2008). Neurogenesis and exercise: Past and future directions. In *NeuroMolecular Medicine* (Vol. 10, Issue 2, pp. 128–140). Neuromolecular Med. https://doi.org/10.1007/s12017-008-8028-z

Van Praag, H., Kempermann, G., & Gage, F. H. (2000). Neural consequences of enviromental enrichment. *Nature Reviews Neuroscience*, *1*(3), 191–198. https://doi.org/10.1038/35044558

Van Praag, H., Kempermann, G., & Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience*, *2*(3), 266–270. https://doi.org/10.1038/6368

Van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *Journal of Neuroscience*, *25*(38), 8680–8685. https://doi.org/10.1523/JNEUROSCI.1731-05.2005

Van Sluyters, R. C., & Stewart, D. L. (1974). Binocular neurons of the rabbit's visual cortex: effects of monocular sensory deprivation. *Experimental Brain Research*, *19*(2), 196–204. https://doi.org/10.1007/bf00238534

Van Sluyters, R. C., & Stewaet, D. L. (1974). Binocular neurons of the rabbit's visual cortex: Effects of monocular sensory deprivation. *Experimental Brain Research*. https://doi.org/10.1007/BF00238534

Van Versendaal, D., & Levelt, C. N. (2016). Inhibitory interneurons in visual cortical plasticity. In *Cellular and Molecular Life Sciences*. https://doi.org/10.1007/s00018-016-2264-4

Vetencourt, J. F. M., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, O. F., Castrén, E., & Maffei, L. (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science*. https://doi.org/10.1126/science.1150516

Vogels, R., & Orban, G. A. (1985). The effect of practice on the oblique effect in line orientation judgments. *Vision Research*, *25*(11), 1679–1687. https://doi.org/10.1016/0042-6989(85)90140-3

Volkmar, F. R., & Greenough, W. T. (1972). Rearing complexity affects branching of dendrites in the visual cortex of the rat. *Science*. https://doi.org/10.1126/science.176.4042.1445

Von Noorden, G. K. (1981). New clinical aspects of stimulus deprivation amblyopia gunter. *American Journal of Ophthalmology*. https://doi.org/10.1016/0002-9394(81)90534-1

Voss, M. W., Soto, C., Yoo, S., Sodoma, M., Vivar, C., & van Praag, H. (2019). Exercise and Hippocampal Memory Systems. In *Trends in Cognitive Sciences* (Vol. 23, Issue 4, pp. 318–333). Elsevier Ltd. https://doi.org/10.1016/j.tics.2019.01.006

Wang, B. S., Feng, L., Liu, M., Liu, X., & Cang, J. (2013). Environmental Enrichment Rescues Binocular Matching of Orientation Preference in Mice that Have a Precocious Critical Period. *Neuron*. https://doi.org/10.1016/j.neuron.2013.07.023

Wang, Q., Rowan, M. J., & Anwyl, R. (2004). β-amyloid-mediated inhibition of NMDA receptor-dependent long-term potentiation induction involves activation of microglia and stimulation of inducible nitric oxide synthase and superoxide. *Journal of Neuroscience*, *24*(27), 6049–6056. https://doi.org/10.1523/JNEUROSCI.0233-04.2004

Wang, S., & Pan, J. (2016). Irisin ameliorates depressive-like behaviors in rats by regulating energy metabolism. *Biochemical and Biophysical Research Communications*, *474*(1), 22–28. https://doi.org/10.1016/j.bbrc.2016.04.047

Wang, T., Xie, K., & Lu, B. (1995). Neurotrophins promote maturation of developing neuromuscular synapses. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.15-07-04796.1995

Weliky, M. (2000). Correlated neuronal activity and visual cortical development. In *Neuron*. https://doi.org/10.1016/S0896-6273(00)00053-2

Werker, J. F., & Hensch, T. K. (2015). Critical periods in speech perception: New directions. *Annual Review of Psychology*. https://doi.org/10.1146/annurev-psych-010814-015104

Westheimer, G., & Truong, T. T. (1988). Target crowding in foveal and peripheral stereoacuity. *Optometry and Vision Science*, *65*(5), 395–399. https://doi.org/10.1097/00006324-198805000-00015

Wiesel, T. N., & Hubel, D. H. (1965). Extent of recovery from the effects of visual deprivation in kittens. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.1965.28.6.1060

Wiesel, T. N., & Hubel, D. H. (1963). Single-cell responses in striate cortex of kittens deprived of vision in one eye. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.1963.26.6.1003

Wiesel, T. N., & Hubel, D. H. (1963). Responses in Striate Deprived of Vision Cortex of One Eye1. *Journal of Neurophysiology*, *26*, 1003–1017.

Winter, B., Breitenstein, C., Mooren, F. C., Voelker, K., Fobker, M., Lechtermann, A., Krueger, K., Fromme, A., Korsukewitz, C., Floel, A., & Knecht, S. (2007). High impact running improves learning. *Neurobiology of Learning and Memory*, *87*(4), 597–609. https://doi.org/10.1016/j.nlm.2006.11.003

Wu, C., & Hunter, D. G. (2006). Amblyopia: Diagnostic and therapeutic options. *American Journal of Ophthalmology*, *141*(1). https://doi.org/10.1016/j.ajo.2005.07.060

Xia, D. Y., Huang, X., Bi, C. F., Mao, L. L., Peng, L. J., & Qian, H. R. (2017). PGC-1α or FNDC5 is involved in modulating the effects of Aβ1-42 oligomers on suppressing the expression of BDNF, a beneficial factor for inhibiting neuronal apoptosis, Aβ deposition and cognitive decline of APP/PS1 Tg mice. *Frontiers in Aging Neuroscience*, *9*(MAR). https://doi.org/10.3389/fnagi.2017.00065

Xiang, Z., Huguenard, J. R., & Prince, D. A. (1998). Cholinergic switching within neocortical inhibitory networks. *Science*. https://doi.org/10.1126/science.281.5379.985

Yang, T., & Maunsell, J. H. R. (2004). The Effect of Perceptual Learning on Neuronal Responses in Monkey Visual Area V4. *Journal of Neuroscience*, *24*(7), 1617–1626. https://doi.org/10.1523/JNEUROSCI.4442-03.2004

Yazaki-Sugiyama, Y., Kang, S., Cteau, H., Fukai, T., & Hensch, T. K. (2009). Bidirectional plasticity in fast-spiking GABA circuits by visual experience. *Nature*, *462*(7270), 218–221. https://doi.org/10.1038/nature08485

Yoon, B. J., Smith, G. B., Heynen, A. J., Neve, R. L., & Bear, M. F. (2009). Essential role for a long-term depression mechanism in ocular dominance plasticity. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0901305106

Yotsumoto, Y., Sasaki, Y., Chan, P., Vasios, C. E., Bonmassar, G., Ito, N., Náñez, J. E., Shimojo, S., & Watanabe, T. (2009). Location-Specific Cortical Activation Changes during Sleep after Training for Perceptual Learning. *Current Biology*, *19*(15), 1278–1282. https://doi.org/10.1016/j.cub.2009.06.011

Zhou, Y., Huang, C., Xu, P., Tao, L., Qiu, Z., Li, X., & Lu, Z. L. (2006). Perceptual learning improves contrast sensitivity and visual acuity in adults with anisometropic amblyopia. *Vision Research*, *46*(5), 739–750. https://doi.org/10.1016/j.visres.2005.07.031