Neuroplasticity refers to the ability psychology essay

Attempts to improve visual acuity and quality of vision have included advances in visual outcomes evaluation, optical imaging and surgical techniques. However, even if we had the perfect method to correct the optics of the eye, our vision would still be determined by the retina-brain interaction. Vision is also a perception and not only an optically perfect image. Neuroplasticity refers to the ability of the brain to reorganize the structure and function of its connections in response to the changing environment.[1] There is growing evidence that visual plasticity occurs not only during childhood, as traditionally considered, but also during all stages of life in response to changes in stimuli.[1] An emerging view is that the brain is plastic and neural networks are initially shaped by experience during the sensitive period and subsequently stabilized during normal development.[2] Functional magnetic resonance imaging (fMRI) has opened an unprecedented opportunity for studying brain activity in vivo and thus to better understand plasticity in the visual cortex.[3] This can have major implications in the treatment of ocular and cerebral diseases and in the evaluation of materials and surgical techniques (including refractive surgery, cataract surgery and presbyopia correction). Furthermore, in rodent models plasticity can be elicited by reducing intracortical inhibition through pharmacologic treatment with antidepressants, which opens new perspectives in developing therapeutic strategies that harness plasticity for better medical and surgical outcomes.

This review focuses on four major questions concerning visual plasticity in an ophthalmological perspective: 1. Does visual plasticity occur in adults? 2. What forms of visual plasticity exist in the human visual cortex? 3. What is

the biological background of visual plasticity? and 4. What is the relevance of visual plasticity for ophthalmology?

Does visual plasticity occur in adults?

Neuroplasticity can be thought as the subtle but orchestred dance between the brain and the environment.[1] It is the ability of the brain to be shaped by experience and, in turn, for this newly remolded brain to facilitate the embrace of new experiences.[1] Although plastic changes in the brain can occur at any time point in the life cycle, they occur with varying degrees of success.[4] It is known that an abnormal visual experience early in life, usually caused by strabismus, anisometropia or congenital cataracts, causes amblyopia, an unilateral reduction of best corrected visual acuity that persists during the patient´s life.[4] The explanation for these findings is that there are transient connections that go through a process of Hebbian competition in which stronger input signals are favoured and unused connections are pruned permanently.[5] In other words, Hebbian competition works during normal early development to tune the connections to visual cortical neurons, eliminating non-visual inputs and balancing the input from the two eyes.[5] FMRI has shown that visual dysfunctions in amblyopia occur both within and beyond primary visual cortex (V1) including extrastriate and later specialized cortical areas (V4+/ V8, lateral occipital complex).[4] The connectivity of geniculate-striate and striate-extrastriate networks is reduced and both feedforward and feedback interactions are affected equally.[6] This is in agreement with the traditional view in which the visual system is assumed to be hard-wired long before adolescence. However, recent studies indicate that some cortical connections are inhibited rather than pruned and

that, for some visual functions, there is visual plasticity in adolescence and adulthood.[1] These functionally dormant connections appear to provide the substrate for rapid readaptation in adulthood.[7] In addition, there are reports of improved vision in an adult´s amblyopic eye after vision in the fellow good eye was lost, with changes occurring so rapidly in some cases that new connections are unlikely to have formed.[5]

Plastic changes have been seen in the adult human cortex in association not only with frank lesions but also in healthy individuals as a function of experience and training.[8] There is evidence of a relation in old age between regional cortical shrinkage and increased task related activation in neuroimaging, suggesting that losses in regional brain integrity drive functional reorganization that compensate/ mask cognitive losses from the atrophy.[8]

In conclusion, the majority of studies point to the existence of plasticity in adult human visual cortex in response to retinal disorders and severe visual loss in one or both eyes and there is also a role for visual cortex plasticity in healthy adult humans.

Does our brain change in response to a modification in input stimuli? To answer this question it is necessary to define the different forms of visual plasticity.

Question 2. What manifestations of visual plasticity exist in the human visual cortex?

Several fMRI studies have shown that perceptual learning and voluntary attention can bias visual selection and modulate neuronal response in

human adult visual cortex.[9] Adaptation is a form of rapid plasticity and shows strong perceptual effects. By enhancing the visual processing of relevant information and reducing processing of ignored stimuli, learning, attention and adaptation shape the landscape of our present and future visual experiences.[9]

Perceptual learning

A behavioural manifestation of plasticity in humans is perceptual learning, a process in which practicing a challenging task repeatedly leads to significant and persistent improvements in visual performance over time.[7] The effects of perceptual learning have been well documented beyond the critical period of development in visually normal adults.[4] It has been reported that perceptual learning elicits plastic changes in the visual system, as shown by changes in V1 activation during fMRI.[4] To evaluate this form of plasticity, neural activity has been measured after participants were intensively trained in a visual task, such as texture discrimination and detecting stimuli orientation.[10] Retinotopic increase in blood oxygenation level-dependent signal (BOLD) response after learning provides empirical support that learning favours activity in the visual cortex in order to increase the discrimination of trained targets from background flankers.[11] The improvement has occurred in adults as well as in juveniles, is specific to the trained eye and develops only across multiple days of training.[7] Training can improve the discrimination of small differences in the offset of two lines (Vernier acuity), discriminate orientation, segregate elements of the visual scene and detect small differences in the depth of two targets.[12] The recruitment of larger assemblies of interconnected neurons after learning

produces a higher total neural response to the trained stimuli associated with increased regionally-specific BOLD response. Perceptual learning in the visual system appears to be mediated primarily by changes in the response strength or tuning of individual neurons, rather than large-scale spatial reorganization of the cortical network as found in the auditory and somatosensory systems.[7] Perceptual experience may trigger long lasting functional reorganization within the early visual cortex of adult humans.[7] The fact that all areas of the adult cerebral cortex have the capacity for plasticity, changing functional properties and architecture in an experience-dependent fashion is now abundantly evident in perceptual learning experiments.[12] More recently, in line with the benefits of perceptual learning, video games have been shown to improve perception, visuo-motor coordination, spatial cognition and attention, illustrating how action game play can reshape the adult brain.[2, 13] These plastic changes have been shown to be long lasting, remaining even 2 years after the end of intervention.[13] Action game play primarily targets top-down, attentional systems, possibly altering the excitatory/inhibition balance to allow heightened plasticity.[13] Perceptual learning shows strong interaction with attention, indicating that it is under top-down control. Top-down projections from the frontal eye field to visual area V4 can enhance stimulus-related activity,[14] but attention is necessary for consolidation of memory.[12]

Attention

When processing a visual scene, mechanisms are needed for selecting relevant and filtering out irrelevant information.[15] This function is accomplished by the attentional system. Two basic sources are assumed to

determine attentional processing: attention driven by the salience of a signal (bottom-up) and, second, intentions of the observer that guide focus of attention (top-down).[15] Although these top-down influences originate in the frontal lobe, they primarily modulate neural activation in striate and extrastriate visual areas.[15] fMRI studies have shown that attention can enhance the fMRI signal at early cortical stages of visual processing, including the primary visual cortex.[16] Spatial attention seems not only to enhance processing at attended locations but may also selectively suppress processing at non-attended locations.[17] Experiments performed in which more attentional capacity is allocated at central fixation show that cortical activation for task irrelevant peripheral stimulation is reduced.[18] The attentional effect increases from V1 to V4, along the hierarchy of visual areas.[19] Top-down signals related to spatially directed attention may be generated by a network of areas in frontal and parietal cortex.[20] Sensory activity in the brain is modulated by attention, memory and even by the intention to act.[21] As an example, in experiences with monkeys, the baseline firing rate of neurons in lateral intraparietal area increases when the animal is working in a task in which it expects a relevant stimulus will appear.[21] Likewise, imaging studies have shown that attention modulates visual responsivity in the human brain.[21] The visual system modifies the retinal image so as to maximize its usefulness to the subject, often originating nonveridical percepts.[22] The visual system does not provide a copy of the external visual world, in contrast, it optimizes processing resources. Attention is an example of this perceptual optimization.[23] Visual attentional load also influences plasticity in the human motor cortex, suggesting that the top-down influence of attention on plasticity is a general

feature of the adult human brain.[24] In sum, attention acts upon sensory signals at many levels to construct a selective representation of visual space. [21]

Adaptation

Looking at a pattern for a short time typically decreases sensitivity to that pattern and results in a bias in the appearance of other patterns. [25] Visual adaptation is considered to occur with brief exposures and aftereffects. [26] However, the visual system has a large variety of adjustments and it is difficult to safely define adaptation in a way that it can be clearly distinguished from other forms of plasticity.[25] In addition, adaptation to luminance has been observed not only in the retina and lateral geniculate nucleus but also in primary visual cortex.[27] The relationship between adaptation and learning is not entirely clear. Perceptual learning usually produces improvements in discrimination whereas adaptation is characterized as a more immediate loss in sensitivity when exposed to a stimulus.[28-30] Learning can be distinguished from adaptation because it mainly reflects changes in performance rather than in appearance and facilitation instead of suppression. It has a longer time course and changes how the visual system interprets neural signs and not the strength of those signals.[30] However, like adaptation, learning can also change the appearance of patterns and, like learning, adaptation can facilitate some discriminations.[25] Morover, some artifacts described as adaptation show remarkably long persistence. There is increasing evidence for sensitivity adjustments that occur during much longer times, from hours to weeks or even years.[25] For example, when the senescent crystalline lens is removed

in cataract surgery, the changes in colour appearance follow a very long time course and are not entirely normal even months after surgery.[31] Long term adaptation has also been detected for stimuli orientation and contrast sensitivity.[32, 33] In fact, the process of adaptation itself might contain forms of learning.[34] Adaptation has also been shown to occur in natural visual environment, to stimuli that reflect the type of images that observers encounter in everyday viewing.[25] Many aspects of natural vision are routinely regulated by adaptation. Thus, the way we perceive colours, faces and scenes is strongly dependent on the specific environments we are adapted to.[25] Adaptation also occurs when there are changes in the observer, rather than in the environment, because of eye injury, cataract surgery or simply a new pair of glasses. For example, adaptation to long term defocus (myopia and hyperopia) leads to improvements in visual acuity.[35] Both short and long term adaptation can occur from the blur resulting from the optics of the eye, including low and high order aberrations.[36] In addition, compensatory adjustments of adaptation tend to mask sensitivity losses that appear with disease, so that observers may not be aware of developing visual impairment.[25] Similarly, compensation for age related losses implies that the process of adaptation remains largely functional in the senescent visual system.[37, 38] Thus, adaptation may be important for matching vision to the optical quality of the eye throughout life.

Question 3. What is the biological background of neuroplasticity?

Two types of neuroplasticity can be distinguished: structural plasticity and synaptic or functional plasticity. Synaptic plasticity refers to changes in synaptic activity, leading to changes in synaptic efficacy and in behaviour.[39] Structural plasticity refers to changes in neuronal morphology (axons, dendrites and dendritic spines), suppression and creation of synapses, genesis of new neurons and neuritis.

Repetitive electrical stimulation of animal nerve fibers can induce an immediate and prolonged increase in synaptic transmission. This effect is called long-term potentiation (LTP).[40, 41] In contrast, low-frequency stimulation typically induces long-term depression (LTD). These synaptic mechanisms play a role in many forms of learning and memory as well as neuronal development and circuit reorganization.[41]

Physiological mechanisms that regulate developmental plasticity in the visual system

The experience-dependent maturation of GABA-mediated inhibition during development establishes the beginning of the critical period for plasticity in the visual system.[42] After monocular deprivation during early life in transgenic animals lacking one isoform of GABA, no variation of visual cortex responsiveness was observed.[43] Therefore, a reduction of inhibitory transmission in early life halts the onset of the critical period for visual cortex plasticity.[42] The limited plasticity in the adult visual cortex can be enhanced by previous visual deprivation, which is associated with a loss of

GABA receptors, and reduced by GABAergic modulators.[44] It has been shown that a brief reduction of GABAergic inhibition in the brains of rats is able to reopen a window of plasticity in the visual system a long time after the normal closure of the critical periods.[4]

The effects caused by early sensory experience in the remodeling of visual cortical circuitries are actively preserved throughout life by the late appearance of molecular factors in the extracellular milieu that restrict plasticity.[45] The establishment of neuronal connectivity may be, at least in part, under control of structural factors such as myelin-associated proteins (NgR, PirB) and chondroitin sulphate proteoglycans (CSPGs), which all are inhibitory for axonal sprouting.[46] Other important players are the major modulatory systems in the brain, i. e., adrenaline, noradrenaline, dopamine, acetylcholine and serotonin. The adrenergic system has a significant impact on plasticity.[41] Similarly, a single dose of the serotonin reuptake inhibitor citalopram enhances and prolongs plasticity.[41] Calcium channel blockade by nimodipine and dopamine receptor blockade by sulpiride or haloperidol diminish a form of plasticity.[41] Likewise, in the face of compromised cholinergic input to the visual cortex of rats, the ability to perform fine discriminations is impaired, whereas the ability to perform previously learned discrimination remains unaffected, which suggests that acetylcholine facilitates plastic changes in the sensory cortices.[47, 48] Functionally, acetylcholine contributes to plasticity in V1 and is involved in the alteration of tuning properties and map organization in other areas of cortex.[48] Global dopaminergic activation has heterogeneous effects on plasticity. A certain amount of activity of the dopaminergic system is necessary for the

induction of plasticity. But higher dopaminergic activity results in non-linear effects on plasticity, depending on the dosage, the plasticity induction protocol and the balance of D1 versus D2 receptor activation.[41] These mediators regulate complex functions of the central nervous system such as different forms of brain plasticity, cognitive processes and behaviour.[46]

Functional plasticity in the visual cortex

Epigenetic mechanisms of plasticity, short noncoding mRNAs and the regulation of plasticity

Long-term functional modifications of neural circuitries are mediated by a complex interplay between cellular and molecular mechanisms that activate intracellular signal transduction pathways regulating gene expression.[49]

Experience-dependent brain plasticity is consolidated by sleep, likely thorough the phosphorylation of protein synthesis regulators and the translation of key plasticity related mRNAs.[50] Sleep promotes cortical mRNA translation and interruption of this process prevents the consolidation of a form of cortical plasticity in vivo.[50] This way, although experience is required for the transcription of key plasticity-related mRNAs, their translation into protein requires sleep, which may represent a sleep-dependent mechanism that converts labile plastic changes into more permanent forms.[50]

Another mechanism involves CREB (a transcription factor) activity. CREB activity is induced following monocular deprivation in juveniles and declines with maturation of the visual cortex.[51]

Growing experimental evidence indicates that chromatin structure is highly dynamic within the nervous system and that it is recruited as a target of plasticity-associated signal transduction pathways.[52, 53] These mechanisms seem to be important also in the mature system, as increasing acetylation of histones by treatment with histone deacetylase inhibitors effectively reactivates plasticity in the adult visual system.[54, 55]

In addition to the function of transcription factors and modifications of chromatin structure, growing experimental evidence supports a critical role for short noncoding RNAs (microRNAs) which interact with and control translation of mRNA targets, in the regulation of gene expression patterns at the basis of plastic phenomena in the mammalian nervous system.[56]

Mitochondrial organization-movement-activity and synaptic activity

The brain can perceive, detect, discriminate and recognize consciously just those pieces of external information which reach a critical intrinsic energetic level, guaranteed by neuronal mitochondrial activity.[57] Representation of various sensory information can become conscious in our mind only if it reaches a threshold level of energy and duration.[57] Neurotransmitters dopamine and serotonin (which regulate different forms of brain plasticity, as explained previously) can reversibly control mitochondrial motility and distribution. Dopamine displays a net inhibitory effect on mitochondrial movement, but serotonin has a stimulatory effect.[57]

There is a direct coupling between mitochondrial organization-movement-activity and synaptic activity.[58] The spatiotemporal dynamic patterns of mitochondrial distribution can work as a “ mitochondrial memory code” that

dictates the potentiation of specific synapses and the plasticity of the neuronal network.[59]

Structural plasticity in the visual cortex

Experience-dependent plasticity in the human visual cortex includes macrostructural changes and microstructural changes.[60]

Animals under environmental enrichment (cages containing toys that are frequently changed) develop an increase in brain weight and cortical thickness, including the occipital cortex. Similarly, grey matter macrostructure changes have been reported in humans after juggling training, aerobic exercise and intense language studies.[60] Volume and thickness changes are specific to those brain regions that are functionally relevant for the task at hand.[61]

Microstructural changes consisting on an increase in N-acetylaspartate (available almost only in neurons) measured with magnetic ressonance imaging were detected in adult men after a period of navigation training.[60] Functional modifications in the visual system are accompanied by a structural remodeling of synaptic connectivity, in terms of growth and loss of dendritic spines. Dendritic spines in pyramidal neurons are markedly sensitive to experience during early life.[62] Despite the absence of large-scale structural remodeling later in life, the reorganization of cortical connections in terms of growth and loss of dendritic spines may be the structural substrate for experience-dependent plasticity.[46] Lastly, although plasticity is usually seen as a mechanism of optimizing resources, it also underlies addiction related processes, such as drug sensitization, drug

seeking and hypofrontality. Psychostimulant drugs such as amphetamine and cocaine are prototypic drugs inducing neuroplasticity changes.[39]

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Figure 1. Plasticity in the adult visual cortex. In the presence of specific stimuli, such as performing a perceptual task, playing action video games or pharmacological treatment, several functional alterations take place. These include a decrease in inhibition/excitation ratio, epigenetic remodeling of chromatin structure, mitochondrial redistribution, activation of transcription factors and protein synthesis, leading to synaptic and structural plasticity. Structural plasticity includes modifications in neuronal morphology (axons, dendrites and dendritic spines), suppression and creation of synapses, genesis of new neurons and neuritis. The interplay of these mechanisms leads to adult neuronal plasticity, as revealed by the increased perception of a trained stimulus, improvement of visual function in amblyopia and long term adaptation to changes in the subject (such as cataract surgery) or in the environment. Plasticity is under the top-down influence of attention, as attention acts upon sensory signals at many levels to construct a selective representation of visual space.

Question 4. What is the relevance of visual plasticity for ophthalmology?

Plasticity in the context of retinal disorders

Retinitis Pigmentosa (RP) consists in a progressive degeneration of photoreceptors, starting at the mid-peripheral and advancing towards the central retina. The age of onset varies from infancy to adulthood, although

the typical manifestations start at adolescence.[63] A recent fMRI study found visual cortical activation on the lesion projection zone during a task, in contrast with a passive viewing stimulation, in RP. Authors suggested the unmasking of cortical extrastriate feedback that is normally present but is blocked from entering V1 by lateral geniculate nucleus gating signals, which are missing in RP.[64] Another study showed cross-modal activity in visual cortex for tactile tasks, and a relationship between the amount of activation and the degree of visual field loss in RP.[65]

Macular Degeneration (MD), in contrast with RP, mainly affects the macula of the retina causing a progressive central vision loss. MD can affect elderly individuals – age-related macular degeneration – or younger patients – juvenile macular degeneration. Patients usually adopt a peripheral retinal region for fixation – preferred retinal locus – and some studies claim that this process results from visual cortex reorganization.[66] Activation of lesion projection zone was found in stimuli presented at the preferred retinal locus or an isoeccentric non- preferred retinal locus location, suggesting that reorganization is not driven by use-dependent mechanisms,[67] but the preferred retinal locus seems to be represented more extensively in visual cortex.[68] Some fMRI studies did not find evidences of large-scale reorganization on visual cortex in MD, in contrast to congenital retinal lesions such as rod monochromatism.[69-72] However, other studies showed that visual stimulus falling on the peripheral retina activated the foveal projection zone,[73] even when there was no residual foveal function. Apparently, reorganization was not dependent on the age of onset or on the type of MD.[74] Other authors found activation in the lesion projection zone in juvenile

macular degeneration patients during a stimulus-related task, but not on a passive viewing or a stimulus-unrelated task, possible due to the unmasking of the task-dependent cortico-cortical signals in the absence of geniculo-cortical signals.[75] Liu and colleagues demonstrated an incomplete functional reorganization when the extent of the silence zone was smaller in active than in passive tasks. This effect was more prominent in juvenile macular degeneration patients, suggesting a possible role for age of onset and disease etiology.[68]

Animal studies in monkeys and cats with induced central scotomas showed a rapid expansion of receptive fields of neurons near the border of the lesion projection zone, possible caused by reweighting or unmasking of existing neural connections. Evidences for axonal and dendritic sprouting have also been found in animal studies.[66]

In conclusion, the degree of adult visual cortical plasticity due to retinal diseases remains questionable. It is known that feedback signals into primary visual cortex (V1) arise from higher order visual areas, frontal and parietal cortices and are involved in attention, visual imagery, and task-related visual processing.[64, 74, 75] The major limitations of studies concerning this issue are the reduced number of subjects, the heterogeneity among patients, and the variations in methodologies.[64] [74, 76] Several hypotheses have been established to explain visual cortical reorganization: 1) development of new synapses to create new lateral connections; 2) large increase of synaptic signals that carry feedback and lateral connections; 3) unmasking of existing feedback caused by the deletion of feedforward signals; 4) increase of receptive field sizes or shift of receptive fields into the

lesion projection zone and 5) modifications at precortical stages of visual system, although neurophysiological analyses suggest an absence of reorganization at precortical stages or in their projections to cortex.[64, 68, 74, 75].

Plasticity in the context of refractive surgery

Anisometropia, a difference between the two eyes refractive errors generally exceeding 3 diopters, is an important cause of amblyopia. However, contrary to the expected permanency of visual deficiencies, refractive surgery is able to improve visual acuity in amblyopic patients.[77-79] A study comparing fMRI activation patterns between preoperative and 12 month postoperative cortical maps found a decrease in the number of active voxels in the anisometropic fovea.[80] The rationale for this finding is that before surgery a large network of neurons is activated for each visual stimulus. After surgery, however, only a subgroup of neurons is activated because stimuli processing has become more efficient.[80] This study thus provides evidence for plastic changes taking place in the primary visual cortex of adult anisometropic patients after refractive surgery.

Neuroadaptation to presbyopia correcting intraocular lenses

Presbyopia is the natural decline in near vision that occurs in human healthy aging. Surgical interventions to correct presbyopia are widely used, such as multifocal intraocular lenses, but rely on the simultaneous presentation of distance and near images to the retina.[81] These lenses are associated with unwanted side effects, such as glare, halos and loss of contrast sensitivity, that tend to improve over time in some patients, but not in others.[82, 83]

These symptoms are usually more severe under low light (mesopic) conditions.[84] It is thought that the brain adapts to those unwanted stimulus, but it is unknown if it is an adaptive process or a form of perceptual learning. Multifocal intraocular lens may target different forms of plasticity, comprising 1) adaptation, triggered to decrease sensitivity to “ background noise” images and glare, 2) perceptual learning, for better discrimination of low contrast targets and 3) attention, to selectively see the image of interest despite the presence of two images (distance and near) in focus. Either way, it is clear that the brain plays a major role in visual performance with these more complex intraocular lenses.[85, 86]

Amblyopia treatment and the reinstatement of plasticity in the adult visual system

Amblyopia can be considered the result of a lack of plasticity. Knowledge of neuroplasticity and the factors that control the opening and closure of critical periods will lead to new therapeutic strategies which may allow for greater recovery of visual functions in both children and adults with amblyopia.[4] As previously described, the developmental maturation of intracortical inhibitory circuitries causes the end of plasticity in the visual system. In keeping with this notion, it is possible to restore plasticity in adult life by reducing levels of inhibition.[4] A direct demonstration that GABAergic signaling is a crucial brake limiting visual cortex plasticity derives from the observation that a pharmacological decrease of inhibitory transmission effectively restores ocular dominance plasticity in adulthood.[46] Indeed, intracortical inhibitory circuitry has now emerged as a key factor in defining the limits of cortical plasticity.[4] It has thus been hypothesized that a critical

factor in restoring plasticity and inducting recovery from amblyopia is to increase the ratio between excitation (glutamate receptors) and inhibition (GABA receptors) by reducing intracortical inhibition. In rodent models, plasticity can be elicited by reducing intracortical inhibition through pharmacologic treatment with administration of antidepressants.[4, 54] In humans, memantine, a glutamate receptor antagonist, abolishes a form of long term potentiation plasticity. The GABAergic drugs diazepam, tiagabine and baclofen also reduce this form of plasticity.[41]

In conclusion, there are several forms of plasticity that remain largely functional in the adult visual system. Several biological systems are implicated in different forms of plasticity. Both changes in the environment and in the observer are likely to involve different forms of plasticity that act together for perceptual optimization. Understanding how these mechanisms interplay could open new forms of diagnosis and treatment of cerebral and ophthalmic disorders.