Plasticity of the visual cortex and treatment of amblyopia

Over the last 50 years, research into the developmental plasticity of the visual cortex has led to a growing understanding of first the causes and then of the underlying cellular mechanisms of amblyopia or 'lazy eye', the commonest childhood disorder of vision. While it is widely believed that amblyopia cannot be treated successfully after the age of about 7, recent animal studies have demonstrated that visual cortex plasticity can be restored or enhanced later in life, paving the way for new strategies for the treatment of amblyopia that attempt to remove molecular brakes on plasticity. On the other hand, both animal and human work has established that amblyopia is not simply a monocular deficit, and therefore the most promising new non-invasive approaches force the two eyes to cooperate as opposed to conventional procedures that severely penalise the good eye.

Since the pioneering work by Hubel and Wiesel in the 1960s, the visual system has become a key paradigm for studies of neural plasticity, and added clinical interest stems from efforts to find better treatments for amblyopia ('lazy eye'), a common developmental disorder of vision affecting 2-4% of the population. Amblyopia is defined clinically as reduced visual acuity despite optimal refraction, in the absence of a persisting ocular pathology. It is due to disruption of normal visual development in childhood and is accompanied by one or more known amblyogenic factors, such as strabismus (crossed eyes), anisometropia (different refractive errors in the two eyes) and cataract. Amblyogenic factors interfere with normal development of the visual pathways during a critical period of maturation [1]. It is thought that amblyopia is caused by a mismatch between the images seen by the two eyes, resulting in vision in one eye being suppressed [2]. Because amblyopia is the result of maldevelopment of structure and function of the visual cortex, it is important

1

to understand normal cortical development and plasticity in order to make progress in its treatment.

Why is plasticity important? The visual system adapts on a second-by-second level to characteristics of the visual environment such as luminance, contrast, colour and speed of motion but it also undergoes lifelong changes e.g. in response to degradation of input through one eye. Every individual needs to adapt to their environment in a way that is far too complex to be encoded in a set of genes. This process is especially important during ontogeny; once an individual has reached puberty it is usually complete. The critical period is the time during early postnatal life when the development and maturation of brain functions such as sensory processing or language is particularly dependent on and shaped by experience or environmental influences. In the absence of appropriate stimulation during this period, the affected function(s) may not develop at all, or not develop properly. The focus of studies of the neurobiological basis of visual cortex plasticity as well as of its application to clinically relevant conditions such as amblyopia is ocular dominance (OD) plasticity, a shift in the relative strength of neuronal responses to left and right eye stimulation. It is typically probed by monocular deprivation (MD), the patching or suturing of the lids of one eye. OD plasticity on a short timescale (of hours) involves primarily functional, synaptic changes which may be reversible while long-term plasticity involves structural modifications that tend to be more persistent.

Functional plasticity. Work by Bear and colleagues established that the NMDA receptor as a 'coincidence detector' plays a key role in mediating at least some aspects of functional plasticity, since blocking NMDA receptor function abolished the OD shift towards the open eye normally observed following MD during the critical period [3]. Moreover, NMDA receptor mediated plasticity is bidirectional, such that the changes to synaptic

transmission caused by one form of visual experience (e.g. complete darkness) can be reversed by exposure to a different form of experience (e.g. a normal day-night cycle)[4].

More recently, the key role of GABAergic intracortical inhibition in controlling the time course of the critical period has been revealed. Work by Hensch and colleagues showed that a threshold level of synaptic GABA is required to open the critical period since mice lacking the GABA synthesising enzyme glutamic acid decarboxylase (GAD) 65 never exhibit OD plasticity [5]. Infusion into the visual cortex of the GABA agonist diazepam restores OD plasticity on GAD65 knock-out mice at any age. Conversely, attaining a threshold level of intracortical inhibition precipitates closure of the critical period such that GAD65 knock-out mice whose GABAergic transmission has been enhanced early in life become insensitive to monocular deprivation as adults [6]. Subsequent work has shown that it is the balance of excitation and inhibition (E/I) which controls the time course of the critical period. Interventions that enhance or accelerate the maturation of inhibition, such as brain-derived neurotrophic factor (BDNF) overexpression or benzodiazepines, bring it forward while interventions that delay or decrease inhibition, such as dark-rearing or GAD65 knock-out, shift the critical period back [7].

Structural plasticity. Synaptic modifications need to be consolidated in order to leave a lasting experience-dependent 'trace'. It has been known for some time that monocular deprivation leads to rapid remodelling of geniculocortical afferents, in particular a retraction of those representing the deprived eye [8]. More recent research has focused on postsynaptic changes, consisting of an increase in spine motility and spine turn-over, the addition of new and elimination of existing spines [9]. The extracellular protease tissue plasminogen activator (tPA) plays a key role in spine motility; mice in which its gene has been deleted lack OD plasticity, but this can be restored by the exogenous administration of

tPA [10]. Moreover, the spine loss normally observed after three days of MD during the critical period is reduced [11]. Important structural changes occurring in the extracellular matrix towards the end of the critical period are thought at least in part to be responsible for the decline in experience dependent plasticity. Key among these is the increase in cross-linked chondroitin sulphate proteoglycans (CSPGs) such as aggrecan which contribute to the gradual elaboration of an insoluble matrix in the maturing brain. Aggrecan expression has been shown to be activity (and therefore experience) dependent [12]. Furthermore, CSPGs form dense perineuronal nets in particular around GABAergic parvalbumin-positive cells, thus inhibiting axonal growth.. A second brake on structural plasticity is Nogo-66 receptor (NgR) signalling mediated through the low-affinity neurotrophin receptor p75, with which NgR forms a complex and through which it activates the Rho pathway, again inhibiting neurite growth [13]. Although the absolute abundance of the NgR ligand Nogo-A in the visual cortex does not change much over the time course of the critical period, abundance in layer 4 (which receives the retinal inputs) increases significantly [14].

How can understanding plasticity help with the treatment of disorders of vision?

Until quite recently eye care professionals insisted on treating amblyopia by full-time patching of the fellow, non-amblyopic eye: "The value of the time proven constant occlusion treatment of the sound eye remains unchallenged even though minor modifications have become necessary to prevent occlusion amblyopia in infants and young children. Part-time occlusion and penalization are of ancillary value but cannot be considered equal in effectiveness to constant occlusion" [15]. The rationale behind patching is that depriving the fellow eye of vision eliminates suppression of vision in the amblyopic eye and allows visual experience to promote recovery of visual acuity in that eye; however this approach has significant shortcomings in that it treats amblyopia largely as a monocular disease [1].

Recent research has not only led to a revision of conventional patching treatment but suggests a number of alternative treatment avenues that opened up the possibility of improved visual outcomes in teenage and early adulthood.

In conceptual terms the emphasis has moved from one of binocular competition to one of binocular cooperation. The first experimental evidence for this revised view came from a study which investigated recovery from amblyopia in cats by restoring binocular vision after a period of MD during the critical period [16]. Cats recovered close to normal visual acuity and visual cortex responses through the deprived eye if the two eyes' visual axes were aligned during the period of binocular vision but not if the animals were strabismic. With respect to patching treatment, research involving both animals and humans has proven that the best outcomes, i.e. the maximal improvement of visual acuity in the amblyopic eye without compromising vision in the fellow eye, is achieved by part-time occlusion (Fig. 1). Only if reverse occlusion is carried out for 50% of daylight hours every day vision in the initially deprived (amblyopic) eye will recover without acuity of the fellow eye being compromised (Fig.1A) [17]. Conversely, if kittens are part-time monocularly deprived by wearing an eye patch on a daily basis then this has no detrimental effect on visual cortex responses or acuity as long as about 30% or 2 h of daily binocular visual experience are provided (Fig. 1B) [18, 19]. Children wearing an eye patch that objectively monitors the time the patch is worn similarly show near-maximal improvement of acuity in the amblyopic eye if the fellow eye is occluded for just 4-5 h a day, meaning that there is little benefit from patching 12 hours a day (Fig. 1C) [20, 21]. The Pediatric Eye Disease Investigator Group similarly failed to find significant additional benefits when comparing acuity outcomes for prescribed patching doses of 6 h and 12 h/day [1].

What are the prospects for treating amblyopia in teenagers and adults? Any

treatment has to be preceded by correction of the underlying ocular deficits, such as a

combination of optical measures, surgery on the extra-ocular muscles, or orthoptic training

in case of strabismic amblyopia, or optimal refraction in case of anisometropic amblyopia.

Patching treatment is generally only effective when started before the age of 8, and even

then amblyopia recurs in 27% of cases, with the rate of recurrence being higher in younger

children [22]. No drug treatment of amblyopia is currently available, but a number of

avenues are being explored based on present knowledge of critical period control (for a

review see [23]. These either aim at altering the E/I balance in a way that favours increased

plasticity or at removing structural obstacles to plasticity. For example, pharmacological

reduction of GABAergic inhibition in adult rat visual cortex by infusing either picrotoxin or 3-

mercaptopropionic acid for 1 week facilitates OD plasticity [24]. While this approach is

obviously not immediately suitable for clinical use, the ability of the antidepressant

fluoxetine to reactivate cortical plasticity is much more promising. Fluoxetine is a selective

serotonin reuptake inhibitor whose chronic administration not only results in increased

expression of BDNF and reduced levels of extracellular GABA but also re-instates LTP in

response to theta burst stimulation in adult rat visual cortex [25]. Fluoxetine-treated adult

rats exhibit both an OD shift in response to MD and recovery of vision in a previously

deprived eye [25]. The Finnish pharmaceutical company Hermo Pharma Ltd. (which was co-

founded by one of the authors of the study by Maya Vetencourt and colleagues [25]) has

completed a Phase II clinical trial of HER-801 for treatment of amblyopia in adults, the active

component of which is fluoxetine (http://www.hermopharma.com/pipeline).

Another pharmacological intervention that is currently undergoing a clinical trial is

supplementation of occlusion with carbidopa and levodopa (Jaeb Center for Health

Research, USA; http://clinicaltrials.gov/ct2/show/NCT01190813). This approach has been reported to result in greater improvement of vision over patching alone, especially in older children, in some studies [26] but not in others [27]. Compared with fluoxetine, the biological underpinnings of the supposed enhancement of cortical plasticity by increasing dopamine levels are less clear although depletion of catecholamines has been reported to disrupt OD plasticity [28] and local infusion of noradrenalin has been reported to restore it [29].

Other promising targets for drug development are aimed at overcoming structural barriers to plasticity. Pioneering work in the field of spinal cord injury suggests some leads for the treatment of amblyopia. For example, cleavage of CSPGs such as aggrecan by the bacterial enzyme chondroitinase, injected into the visual cortex of adult rats, can restore ocular dominance plasticity [30] and even promote recovery from long-term monocular deprivation [31]. However, similar treatment was less successful in cats [32], underlining the need for caution when extrapolating from rodents (who have both a lower level of juvenile plasticity and a greater degree of 'adult' plasticity beyond the end of the classical critical period) to higher mammals. Another approach is to remove the blockade to neurite outgrowth in the CNS caused by myelin, specifically Nogo-A. Function-blocking Nogo-A antibodies are undergoing clinical trials for the treatment of spinal cord injury, having been shown to promote regenerative and compensatory sprouting of fibres and formation of new connections in the spinal cord and functional recovery in animal models of spinal cord injury [33]. Mice lacking either Nogo-A or its receptor NgR display OD plasticity well into adulthood [14], but whether Nogo-A antibodies can restore visual cortex plasticity in adult wild type animals has not been tested yet.

Non-invasive treatment of amblyopia. Both animal and human studies indicate that amblyopia may be treatable using appropriate sensory stimulation alone. In animal studies two very different strategies have proven successful; in one, so-called environmental enrichment maximises sensory (including, but not limited to, visual) stimulation to increase cortical plasticity through a reduction of intracortical inhibition, and this promotes recovery from MD in adult rats [34]. One caveat for the application of this finding to treating human amblyopia is the fact that humans live in a less 'impoverished' environment than laboratory rats and therefore effective enrichment may be harder to provide. It should also be pointed out that the effects of monocular deprivation on rodent vision are much less severe to begin with than those in higher mammals and humans. At the other extreme, a period of time spent in total darkness can restore cortical plasticity and lead to partial recovery of visual acuity in adult rats [35] while it enables a fast and complete recovery from amblyopia in cats (Fig. 2) [36]. These results are remarkable but at this point it is unknown whether they can be translated into treatment for humans given that prolonged periods in total darkness are unlikely to be attractive to patients, unless it can be established that a less extreme form of visual deprivation can also be effective.

Another very different strategy aimed at reducing intracortical inhibition or altering the E/I balance involves repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) applied to the visual cortex. Both techniques can transiently improve contrast sensitivity of adult amblyopes [37], [38], and theta-burst rTMS has recently been reported to improve contrast sensitivity for up to 78 days later [39].

The most successful non-invasive treatments of human amblyopia are all based on 'training' vision through the amblyopic eye. Several studies have employed perceptual learning paradigms to improve various aspects of vision in the amblyopic eye (for a review

see [40]. A major drawback of most perceptual learning paradigms is that the improvements are specific to the trained task and do not transfer readily to other tasks. However, some exceptions have been reported [41]. Moreover, perceptual learning that reduces crowding in central vision of amblyopes has been shown to also improve standard measures of visual acuity [42]. An alternative approach is the use of video games for training. In the case of action video games, vision is thought to be improved by engaging attentional mechanisms [43, 44]. A different approach is embodied in video games that require both eyes to cooperate. Eastgate and colleagues developed a virtual reality display system on which interactive games are played via stereo display, with different elements of the 'scene' visible to the two eyes (at the same contrast) [45]. An uncontrolled pilot study recently found a clinically significant improvement in acuity in 6 out of 9 amblyopic patients [46]. In contrast, Hess and colleagues start from the premise that lack of recovery from amblyopia is caused by interocular suppression which is stronger going from the fellow to the amblyopic eye than vice versa [47]. By using dichoptic stimulation, with the contrast of the stimuli presented to the good eye reduced to match the appearance of the same stimuli when shown to the amblyopic eye, suppression can be alleviated, allowing greater plasticity than when the good eye is simply occluded. Improvements in vision in the amblyopic eye are therefore seen as a consequence of the reduction in suppression. Hess and colleagues developed a version of the video game Tetris that can be played on an iPod and is viewed dichoptically, with blocks visible to the good eye displayed at a lower contrast than those visible to the amblyopic eye such that they appeared the same to the two eyes (Fig. 3) [48]. After playing the game for 1 hour each day for 2 weeks subjects exhibited significantly greater improvement in visual acuity and stereopsis when training had been dichoptic rather than using just the amblyopic eye [49].

Conclusion. Given the number of treatment strategies that have been advanced in recent years, including several that have reached the clinical trial stage there is hope that applying our knowledge of visual cortex plasticity will lead to a breakthrough in treating amblyopia in childhood and beyond in the not too distant future.

Figure legends

Figure 1: Daily binocular vision required to reverse or prevent amblyopia. (**A**) Visual acuity of the amblyopic eye of kittens that had been monocularly deprived for 6 weeks and then part-time reverse occluded for 6 weeks. During the latter period the animals had 7 hours of daily light exposure during which they wore a patch in front of the non-deprived eye for the time indicated on the abscissa. Fitted line represents the best fit of a cubic polynomial (R^2 = 0.832). Note that the deprived eye recovers the greatest acuity when both eyes are open for about half of the time. Data replotted from [17]. (**B**) Cortical territory dominated by the part-time deprived eye of kittens that wore an eye patch for a certain amount of time every day while having binocular exposure (plotted on the abscissa) for the remaining hours of light (total daily light exposure was either 7 h or 3.5 h). Fitted line represents the best fit of a logarithmic function (R^2 = 0.589). Data replotted from [18]. (**C**) Relation between objectively measured mean daily patching of the fellow eye and proportion of deficit corrected in the amblyopic eye. Red line and symbols, children aged <4 years, blue line and symbols, children aged 4-6 years, fitted lines represent LOWESS (locally weighted smoothed) lines of best fit. Data replotted from [21].

Figure 2: Dark exposure promotes recovery from amblyopia. Amblyopia was induced by monocular lid suture in kittens aged 30 days. After re-opening the eye seven days later,

visual acuity was assessed daily for both eyes in an orientation discrimination task. Acuity in the non-deprived eye (dotted curve) increased steadily to reach adult levels by 90 days of age. The animal was initially blind in the deprived eye (solid line); vision improved gradually but reached a plateau by 90 days of age at roughly half of normal acuity. After 10 days in a dark-room, acuity in the amblyopic eye suddenly increased within a few days to that of the fellow eye. Figure adapted from [50].

Figure 3: Binocular treatment of amblyopia using a video game. Amblyopic subjects dichoptically view a version of Tetris in which the contrast of the blocks visible to the fellow eye has been reduced in order to match the subjective appearance of the blocks visible to the amblyopic eye. In one variant (shown here), the blocks on the bottom are seen by both eyes. The falling piece is divided so that its whole shape is only seen if both eyes combine the information together, with one of its four blocks visible to the amblyopic eye, one block to the fellow eye, and the remaining two blocks to both eyes. In the second variant, the lower layer of the blocks is visible to both eyes, high contrast in the amblyopic eye and low contrast in the fellow eye; the upper layer of blocks, in low contrast, are presented only to the fixing (non-amblyopic) eye. Figure after [48].

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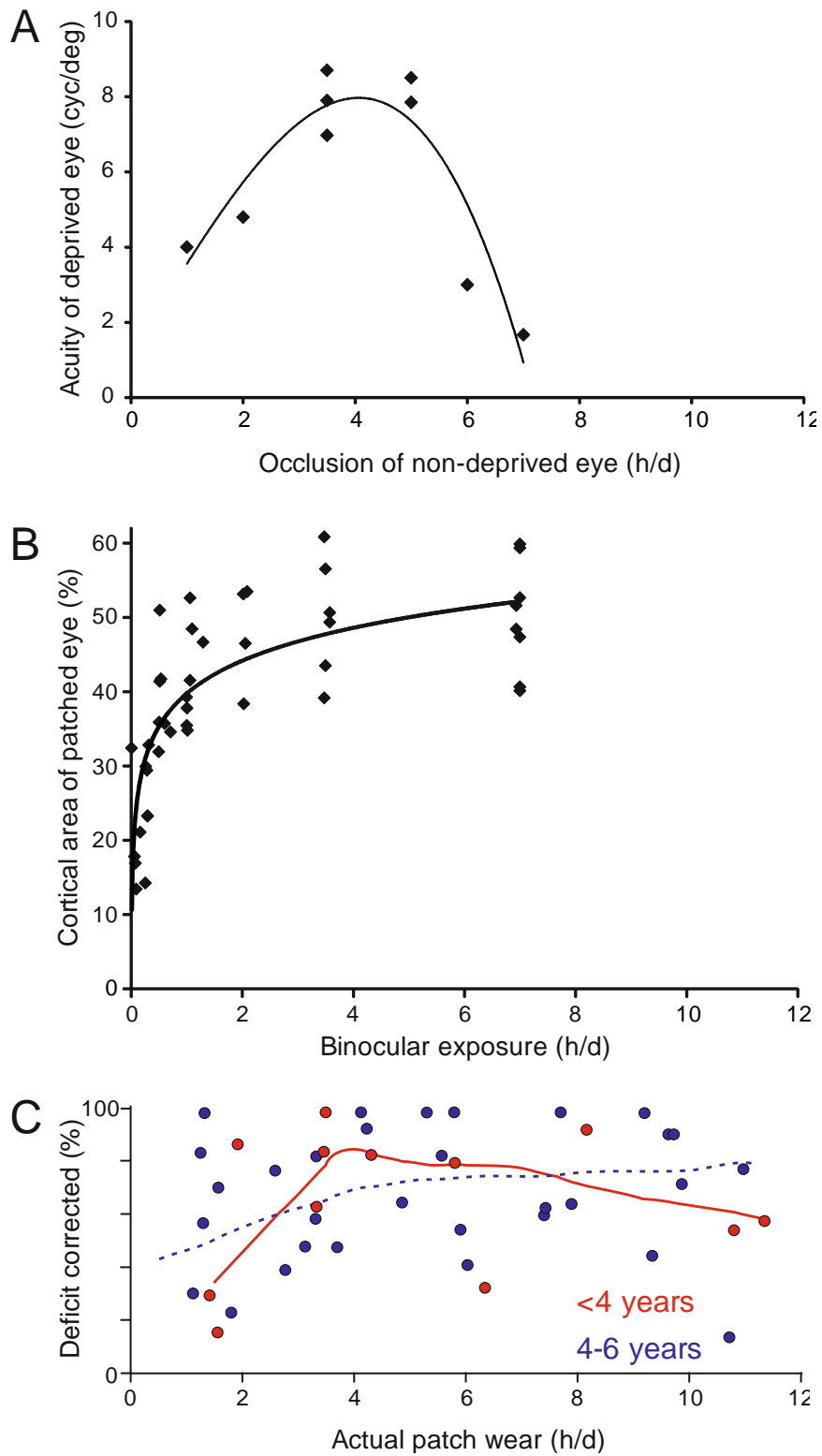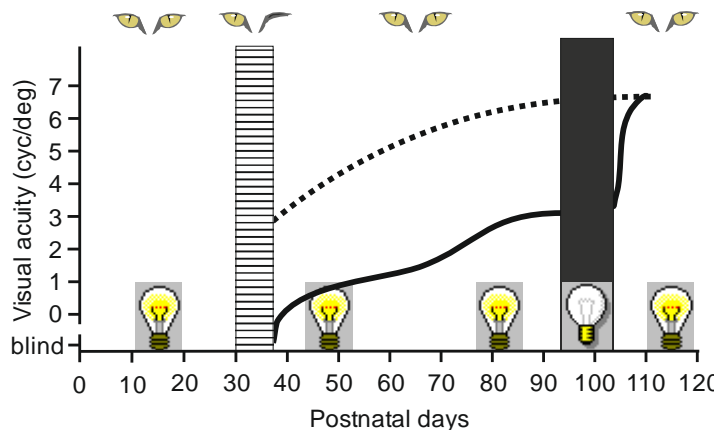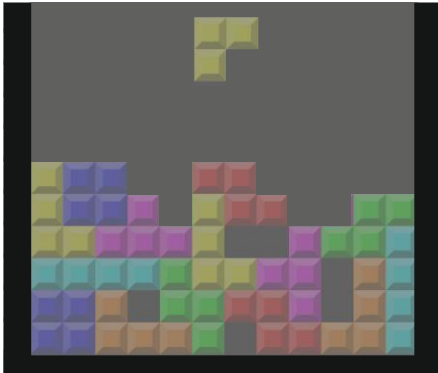
Figure 1

Figure 2

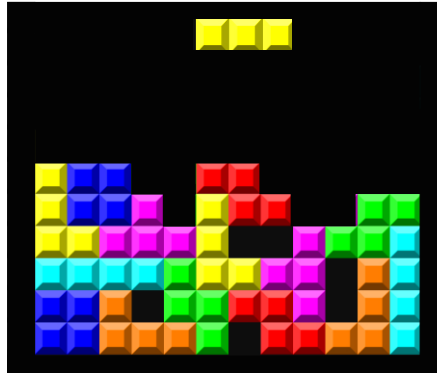Fixing eye view   Amblyopic eye view

Figure 3