New concepts concerning the neural mechanisms of amblyopia and their clinical implications

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ABSTRACT • RÉSUMÉ

Amblyopia is a visual impairment secondary to abnormal visual experience (e.g., strabismus, anisometropia, form deprivation) during early childhood that cannot be corrected immediately by glasses alone. It is the most common cause of monocular blindness globally. Patching remains the mainstay of treatment, but it is not always successful and there are also compliance and recurrence issues. Because amblyopia is a neural disorder that results from abnormal stimulation of the brain during the critical periods of visual development, it is essential to understand the neural mechanisms of amblyopia in order to devise better treatment strategies. In this review, I examine our current understanding of the neural mechanisms that underlie the characteristic deficits associated with amblyopia. I then examine modern neuroimaging findings that show how amblyopia affects various brain regions and how it disrupts the interactions among these brain regions. Following this, I review current concepts of brain plasticity and their implications for novel therapeutic strategies, including perceptual learning and binocular therapy, that may be beneficial for both children and adults with amblyopia.

L’amblyopie est une déficience visuelle résultant d’une expérience visuelle anormale (par exemple, le strabisme, l’anisométropie, la privation de vision des formes) dans la première enfance, qui ne peut être corrigée immédiatement par des lunettes seulement. C’est la cause la plus commune de cécité monoculaire à l’échelle planétaire. L’occlusion demeure la base du traitement, mais il ne réussit pas toujours et il y a des problèmes d’observance et de récurrence. Comme l’amblyopie est un trouble résultant d’une stimulation anormale du cerveau pendant la période critique du développement de la vue, il est essentiel d’en comprendre les mécanismes neuraux pour mettre au point de meilleures stratégies de traitement. La présente revue examine notre compréhension actuelle des mécanismes neuraux qui sous-tendent les déficiences caractéristiques associées à l’amblyopie. Nous examinons ensuite les données modernes de la neuroimagerie, qui montrent comment l’amblyopie affecte les différentes régions du cerveau et comment elles perturbent les interactions entre ces régions. Par la suite, nous revoyons les notions courantes concernant la plasticité du cerveau et leurs implications dans les nouvelles stratégies thérapeutiques, y compris l’apprentissage perceptuel et la thérapie binoculaire, qui peuvent être bénéfiques pour les enfants et les adultes atteints d’amblyopie.

INTRODUCTION

Amblyopia is a unilateral (or less commonly, bilateral) reduction of best-corrected visual acuity that cannot be attributed only and directly to the effect of a structural abnormality of the eye.1 It is caused by abnormal visual experience early in life and cannot be remedied immediately by spectacle glasses alone.1 It is defined clinically as a 2-line difference in best-corrected acuity between the eyes.1 Amblyopia is the most common cause of monocular blindness, affecting about 3% to 5% of the population worldwide.2,8 Because of its prevalence, amblyopia has a huge financial impact. It has been estimated that untreated amblyopia is associated with a loss of US$7.4 billion in gross domestic product and an additional cost of US$341 million for its prevention and treatment annually in the United States alone.8 In addition to the financial cost, the personal cost of amblyopia is also considerable. People with amblyopia (including those treated successfully and those whose treatment has failed) often have restricted career options and reduced quality of life,10 including decreased social contact, cosmetic issues when amblyopia is associated with strabismus, distance and depth estimation deficits, visual disorientation, and anxiety about losing vision in the fellow eye.11 Amblyopia is associated most commonly with early childhood strabismus, anisometropia, or both (mixed-mechanism) and, more rarely, with visual deprivation, including congenital cataract or ptosis. A large study of 427 adults has shown that these subtypes of amblyopia are associated with distinctive patterns of loss of acuity and contrast sensitivity.12 This study used a variety of tests for acuity (Vernier, grating, and Snellen), for contrast sensitivity (Pelli-Robson and edge test), and for binocular function (motion integration and stereo-optical circles). It was found that strabismic amblyopia is associated with moderate acuity loss and better-than-normal contrast sensitivity at low spatial frequencies.12 Anisometropic amblyopia is associated with moderate acuity loss and worse-than-normal contrast sensitivity.12 Mixed-mechanism amblyopia is associated with very poor acuity and normal or subnormal contrast sensitivity.12 The status of residual binocular function is also a major determinant of the pattern of visual deficits. People with no residual binocular function tend to have poorer acuity but better contrast sensitivity, whereas...
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those with residual binocular function tend to have better acuity but poorer contrast sensitivity.12

The mainstay of treatment for amblyopia has been occlusion therapy (patching or pharmacologic penalization), with the rationale that the visual acuity in the amblyopic eye will improve when vision in the fellow eye is blocked. Depending on how treatment success is defined,13 the success rate of patching ranges from 60% to 80%,14-16 and it is critically dependent on patients’ compliance.15 Recurrence may occur after treatment is discontinued,17 requiring continued monitoring of visual acuity and initiation of further treatment if necessary. Furthermore, because occlusion therapy does not promote binocular cooperation, many patients with histories of amblyopia continue to have abnormal binocular vision despite improved acuity. A better therapeutic approach is thus needed.

Although amblyopia has been treated traditionally by eye care professionals, it is a neural disorder that results from abnormal stimulation of the brain during the critical periods of visual development. In order to devise a more effective treatment strategy, it is crucial to understand the neural underpinnings of amblyopia. In this review, I examine our current understanding of the neural mechanisms that underlie the deficits typically seen in amblyopia, based on existing neuroanatomic, neurophysiologic, electrophysiologic, and psychophysical evidence. I then examine modern neuroimaging findings that shed light on the level of neural dysfunctions in amblyopia. Following this, I review the concept of brain plasticity and its implications for new therapeutic strategies, including perceptual learning and binocular therapy.

**NEURAL MECHANISMS OF AMBLYOPIA**

In the past few decades, significant inroads have been made into our understanding of the neural mechanisms of amblyopia. Extensive studies have shown no significant anatomic or physiologic abnormalities in the retina.18-30 Similarly, no significant abnormality has been found in the response properties of cells in the lateral geniculate nucleus (LGN).31-37 There is evidence, however, of changes in cell morphology in the LGN but these changes are not sufficient to explain the behavioural changes in animals and humans with amblyopia (see also the latest functional magnetic resonance imaging [fMRI] findings discussed below). It is generally agreed that the earliest functional and anatomic abnormalities that contribute significantly to the functional and anatomic abnormalities that contribute significantly to the functional and anatomic abnormalities that contribute significantly to the behavioural losses in amblyopia occur in cortical area V1.36,48-61 The pioneering work of Wiesel and Hubel18,49 and a large body of subsequent work18,50-64 have demonstrated that abnormal visual experience results in alterations in functional properties and anatomic architecture in V1, and more profound changes are seen in animals with early visual deprivation than in those with anisometric or strabismic amblyopia. It has been shown that amblyopia leads to a neuronal acuity (spatial resolution) deficit for mid- to high-stimulus spatial frequencies in V1.36,58,60,61

In addition, amblyopia is associated with a reduction in binocularly driven neurons in V1, a reduction of V1 neurons driven by the amblyopic eye, and increased binocular suppression.36,48,49,58,65-67 Furthermore, recent work using dichoptic visual evoked potential (VEP) has shown that suppression likely originates from V1.68

The first locus of dysfunction in amblyopia appears to occur in V1, but a number of studies suggest that there are also abnormalities in downstream extrastriate and later specialized cortical areas. For example, neurophysiologic studies in amblyopic monkeys have shown that the neuronal acuity loss in V1 is not sufficient to account for the behaviourally measured acuity loss.58 In addition, no reliable difference in neuronal contrast sensitivity is detected between the amblyopic and the fellow eye, despite a substantial difference in contrast sensitivity as measured behaviourally.58 Furthermore, it was found that a very brief period (3 days) of prism-induced strabismus in monkeys during the critical period increases the prevalence of V1 neurons that exhibit binocular suppression without altering their neuronal acuity.66 Recently, Bi et al.69 demonstrated that robust binocular suppression can be found in both V1 and V2, further indicating that cortical development is affected beyond V1.

Rigorous psychophysical and electrophysiologic studies in humans provide further support that abnormalities are also evident in extrastriate areas and beyond. Numerous deficits in higher level visual processing that are not solely related to the basic losses in spatial resolution and contrast sensitivity in V1 have been demonstrated. For example, during amblyopic eye viewing, people with amblyopia exhibit higher order perceptual deficits that involve abnormal processing of spatial information in the ventral “what” pathway,70 including global form perception,71-75 global contour processing,76-80 crowding,76,80 and Vernier acuity plus positional certainty,77,81,82 even after acuity and contrast sensitivity deficits have been taken into account. They also exhibit higher order deficits that involve abnormal processing of spatiotemporal information in the dorsal “motion” pathway70 during amblyopic eye viewing, including global motion integration,83-86 second-order motion detection,87-90 complex motion detection,81 and motion-defined form.91 Deficits in higher cognitive functions, including perception of real-world scenes,92 tasks that involve higher order attentional components,93-95 number processing,96 and reading97 are also evident. It is interesting that deficits have also been found during fellow-eye98-100 and binocular viewing.92-97,101

In addition to sensory deficits, amblyopia also affects motor functions,102-106 including the initiation and execution of saccadic eye movements,107 planning and execution of reaching movements,108 the temporal coordination of combined eye-hand movements,109 and online control of reach movements in 3 dimensions.110 The common elements in many of these sensory and motor tasks are that they are not acuity limited; rather, they require both
local and global processing, as well as integration over relatively large regions of space, time, or both, and they involve extracting and segregating a signal from background noise, clearly implicating higher order processing.

**Neuroimaging in Amblyopia**

A number of neuroimaging studies have investigated the loci and extent of cortical deficits in humans with amblyopia using such techniques as positron emission tomography, anatomic and fMRI, and magnetoencephalography. Some neuroimaging studies have suggested that V1 may be normal, in contrast to many other neuroimaging studies and the large body of neurophysiologic work that have pointed to V1 as the first locus of dysfunction. The discrepancy among these studies may result from differences in techniques or stimuli used, as well as from differences in patient characteristics (e.g., amblyopia subtypes). Although the stimuli used in most of these studies adequately stimulated striate and early extrastriate areas, they were not optimized to activate fully the later specialized cortical regions. In addition, functional brain imaging techniques measure gross neural activity and the pattern of responses recorded from visual areas is critically dependent on both the type of visual stimuli presented during scanning and the baseline conditions used to isolate visual activity. It is now generally agreed that visual dysfunctions occur both within V1 and beyond V1 to include extrastriate and later specialized cortical areas. In this regard, several studies that investigated later specialized cortical areas deserve special attention. Lerner et al. asked their subjects to identify, during fMRI, famous faces or buildings as well as the facial expression or building category. They found a selective abnormality in the fusiform gyrus, which is important for face perception, but they found that the parahippocampal area, which is important for scene recognition, is normal in amblyopia. Using grating stimuli of different spatial frequencies, Muckli et al. showed a progressive reduction in activity in the V4+/V8 and lateral occipital complex, a brain area that is important for object recognition, during ambylopic eye stimulation. Most recently, Secen et al. compared attentive tracking of 1, 2, or 4 moving targets during passive viewing with baseline fixation in an ambylopic group and an age-matched control group. They found that the activity in areas involved in motion processing—including the middle temporal complex (MT+), frontal eye fields, and anterior intraparietal sulcus—are reduced during ambylopic eye viewing in humans. Their results are consistent with a recent neurophysiologic study that showed, for the first time, abnormal neuronal responses in area MT/V5 in ambylopic monkeys with motion sensitivity deficits that are typically associated with amblyopia.

This locus of dysfunction view, however, is inherently simplistic. The function of a given brain area depends not only on the cooperative activity of neuronal populations within the same area, it also depends strongly on the interactions of this brain area with other areas, locally and over considerable extents across both space and time. Thus, a more complete understanding of amblyopia requires investigations into whether amblyopia is associated with abnormal interactions among various visual areas and, if so, whether feedforward and feedback interactions are affected differentially. For example, although evidence from animal neurophysiologic and human fMRI studies have suggested reduced activation in both the LGN and V1, is the reduced activity in the LGN due to a primary deficit in the LGN itself (i.e., reduced feedforward to V1, plausibly from changes in LGN cell size) or in V1 (i.e., abnormal feedback from V1)? Given that no significant functional abnormalities have been found in the LGN that could explain the behavioural loss in amblyopia, does the reduced fMRI activity in LGN indicate abnormal feedback from V1? Similarly, because visual processing are affected in both striate and extrastriate areas, are these effects due to feedback mechanisms predominately, or is feedback interactions also involved? Recently, advanced analytic techniques, such as effective connectivity and functional connectivity, have been used to investigate the interactions among various brain regions in a host of neurologic diseases. To date, only one study has applied this technique in combination with fMRI to examine amblyopia. They found that the effective connectivity of geniculate-striate and striate-extrastriate networks was reduced during ambylopic eye viewing and that feedforward and feedback interactions were affected equally. In an important finding, they reported that the effective connectivity loss did not correlate to the regional activity loss demonstrated by fMRI, but it did correlate with the depth of amblyopia. They also found that reduced LGN activity may not be determined solely by feedback mechanisms from the cortex.

**Plasticity and Its Clinical Implications**

Although modern neuroimaging has opened an unprecedented window for us to investigate brain activity in humans in vivo in health and disease, tremendous scientific advances have also been made in our understanding of brain development, in particular, the fundamental concept of brain plasticity. The term plasticity refers to the dynamic ability of the brain to reorganize its connections functionally and structurally in response to changes in the environment. The existence of critical periods in early postnatal life during which neuronal circuits display a heightened plasticity in response to external stimuli is well established. After the end of the critical periods, plasticity
declines dramatically. Much effort has been made in the past decades to elucidate the mechanisms underlying the activation and regulation of critical periods in the brain. Although earlier studies in cats and humans suggested some plasticity, the prevailing consensus was that because of the lack of sufficient plasticity within the brain, amblyopia therapy is effective only early in life, before the critical periods end. Recent studies using rodent (mouse and rat) models as well as humans, however, have challenged this notion. 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 well after the normal closure of the critical periods. Indeed, intracortical inhibitory circuitry has now emerged as a key factor in defining the limits of cortical plasticity. Pharmacologic and epigenetic manipulations of cellular and molecular “brakes” that normally confine plasticity to the critical periods (e.g., Lynx1 and histone acetylation) have been shown to reopen the critical period and restore normal visual functions in adult amblyopic mice, again underscoring intracortical inhibition as a main obstacle. It has thus been hypothesized that a critical factor in restoring plasticity and inducing recovery from amblyopia is to increase the ratio between excitation and inhibition by reducing intracortical inhibition.

For example, in rodent models, plasticity can be elicited by reducing intracortical inhibition through pharmacologic treatment with chronic antidepressants (e.g., fluoxetine, a selective serotonin reuptake inhibitor), anticonvulsants (e.g., valproic acid), or chondroitinase ABC. Intracortical inhibition could also be reduced by exposure to environmental enrichment, prolonged dark exposure, or caloric restriction. In agreement with this hypothesis, it has been shown that vision in the amblyopic eye in adult humans can be improved after only a 10- to 15-minute application of repetitive transcranial magnetic stimulation (rTMS) to the visual cortex. This visual improvement is likely through adjusting the balance between excitation and inhibition, similar to a reduction of intracortical inhibition in the motor cortex after rTMS.

It is interesting to note that both fluoxetine and valproic acid are FDA-approved drugs that are widely prescribed for depression (fluoxetine) and seizure disorders (valproic acid) and have well-described beneficial and side effects, and thus may hold promise for treatment of amblyopia. Although these findings in rodent models are very interesting, they are still a long way from being clinically useful as alternative approaches to the treatment of amblyopia.

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. The effects of perceptual learning have been well documented beyond the critical period of development in visually normal adults, with improvements in visual performance in a wide range of tasks, but these improvements are usually task specific. It is interesting that visual improvements after perceptual learning in individuals with amblyopia are not task specific and generalize to untrained tasks and novel stimuli, which makes perceptual learning attractive as a potential therapy. Indeed, some improvements in visual acuity (30%; 1.5 letter lines), positional acuity (16%), and stereopsis (54%) have been reported, in a small nonrandomized pilot trial, in adults with amblyopia after a period of playing an action-based video game using the amblyopic eye. In addition, the effects of perceptual learning on amblyopic visual acuity are often long-lasting.

Although the neural mechanisms of perceptual learning are not known for certain, they are generally believed to operate through a reduction of internal noise in the visual system or via improved efficiency in extracting stimulus information by changing the relative weighting of the information. It has been reported that perceptual learning elicits plastic changes in the visual system, as shown by changes in V1 activation during fMRI in humans. At present, whether perceptual learning occurs at a lower level (e.g., V1) or at a higher “decision stage” of visual processing, or both (e.g., via feedback, or improved lateral interaction), remains an open question.

Given that perceptual learning generalizes to tasks for which people have not been trained and results in enduring visual improvements—a property essential for amblyopia treatment—it holds promise as a primary intervention or as an adjunct to supplement occlusion or penalization therapy for amblyopia. In this regard, it is important to clarify the difference between perceptual learning and the Cambridge Stimulator treatment (CAM) that was first described in the 1970s. CAM treatment might be considered to be the first application of perceptual learning. It consisted of having patients passively view slowly rotating stripes during monocular viewing with the amblyopic eye. Its effectiveness, however, has been challenged by a number of negative studies over the past few decades. CAM treatment also differs in important ways from the perceptual learning studies conducted in the past 15 years in that it relies on very brief and passive exposures, whereas perceptual learning requires prolonged active participation and attention. Many studies have shown that perceptual learning improves amblyopic visual function, but to date, only 3 small studies with control groups have investigated the effectiveness of perceptual learning as a therapeutic option. Polat et al. found that patients (n = 63) who underwent perceptual learning showed substantial improvement over a patching-only group (n = 10), with a twofold improvement in contrast sensitivity and in letter-recognition tasks. In another study, Chen et al. found that patching was superior to perceptual learning, with a mean improvement of 0.34 logMAR in the patching group (n = 27) and 0.25 logMAR in the
perceptual learning group (n = 26). However, the 2 groups of patients differed in baseline characteristics, including age and “dosage” of treatment. In a third study, Liu et al.232 demonstrated that perceptual learning had a small but significant therapeutic impact on children who had never had (n = 13) or who were no longer responsive to (n = 10) occlusion therapy with improvement of single E acuity by 0.9 to 1.5 lines and crowded E acuity by 0.7 to 1.2 lines. Compared with patching, it is important to point out that the visual experience of the amblyopic eye during perceptual learning differs substantially from that during routine patching. Perceptual learning involves an intensive, active, supervised visual experience with feedback, and thus its effects might be more efficacious than simply relying on everyday experiences during patching. Clearly, randomized, controlled clinical trials that directly compare patching alone with patching plus perceptual learning are needed to address the effectiveness of perceptual learning as a potential therapy for amblyopia.

**INTEROCULAR SUPPRESSION AND ITS CLINICAL IMPLICATIONS**

In addition to perceptual learning, reducing interocular suppression has also received considerable attention as a therapeutic strategy for amblyopia. Classic studies of visual deprivation using animal models have shown a loss of binocularly driven neurons and those driven by the amblyopic eye in V1.36,48,49,58 Newer emerging evidence (primarily from humans233-239 and also from a feline model240), however, suggests that binocularly driven neurons are actually present in strabismic amblyopia, but suppressive mechanisms render the visual cortex functionally monocular during binocular viewing. For example, it has been demonstrated that the loss of binocular responsiveness by V1 neurons is reversible when interocular suppression is removed by ionophoretic applications of bicuculline (a selective blocker of GABA receptors that blocks GABAergic inhibition) in cats.240 This finding indicates that the loss of binocular summation is a result of active suppression rather than a decrease in binocularly driven neurons.241

The importance of interocular suppression is further supported by new psychophysical findings in humans with amblyopia.233-237 Baker et al.238 showed that normal binocular contrast summation is possible when the signal attenuation by the ambylopic eye was accounted for by varying the signal strength to the fellow eye, suggesting that the apparent lack of binocular summation is due to an imbalance in the monocular signals. In addition, a reduction in suppression has been shown to lead to improved binocular function in patients with amblyopia.239 Furthermore, by using fMRI, Farivar et al.242 demonstrated that during amblyopic eye stimulation, the early cortical response was more attenuated and delayed when the fellow eye was open than when the fellow eye was closed, further indicating the important role of interocular suppression in amblyopia.

Based on these findings, it has been argued that amblyopia is intrinsically a binocular problem, not a monocular problem on which occlusion treatment is predicated, which may explain why improvement in binocular function does not always occur despite monocular vision improvement.238 Accordingly, binocular treatment in the form of refractive adaptation (spectacle correction) has been used for some time in the treatment of amblyopia.243 In addition, it has been suggested that the binocular problem involving suppression should be addressed first, if good binocular outcome is to be achieved, as opposed to hoping that binocular vision will return after monocular acuity improvement as the result of occlusion therapy. Based on this suggestion, a new binocular treatment has been proposed. It is based on strengthening binocular combination through a gradual reduction in suppression.244 Using this binocular approach, Hess et al.244-246 demonstrated that individuals with strabismic amblyopia could combine information normally between their eyes when suppression was reduced by presenting stimuli of different contrasts to each eye via dichoptic viewing. By gradually increasing the contrast presented to the fellow eye, they showed that this approach led to improvement in binocular vision and, eventually, binocular combination occurred when the eyes viewed objects of the same physical contrast. In addition, concomitant improvement in stereopsis and monocular acuity of the amblyopic eye also occurred. Based on these initially promising results, a working prototype of a portable gaming device (Apple iPod Touch, Cupertino, Calif.) has been developed and implemented.244,247 However, it should be noted that the sample sizes in these studies were small.244-246 In addition, many of the subjects in these studies244-246 had small-angle strabismus that was detected later in childhood, a situation that differs substantially from the typical population commonly encountered in clinical settings. These factors may have increased the probability of residual binocular function and may raise questions about the general applicability of the results. Furthermore, intractable diplopia is a potentially debilitating complication, especially in patients with strabismic amblyopia. Larger studies are needed to further investigate its therapeutic values and potential side effects. It should also be emphasized that due to test-retest variability, a real improvement requires a change in visual acuity of at least 0.2 logMAR (or 2 Snellen lines)240 or a change in stereoacuity of at least 2 octaves for most stereoacuity tests.249

**CONCLUSIONS**

Although amblyopia has traditionally been treated by eye care professionals, it is a neural disorder that results from abnormal stimulation of the brain during critical periods of development. At first glance, amblyopia appears to result in subtle neural dysfunction, which upon closer examination produces far-reaching consequences. Although
tremendous resources are spent on preventing or treating amblyopia, many patients with amblyopia continue to have abnormal vision throughout their lives. To devise effective therapeutic strategies for the prevention and treatment of this disorder, we must first understand how early anomalous visual experience disturbs brain development. Based on available neuroanatomic, neurophysiologic, electrophysiologic, psychophysical, and neuroimaging evidence, it is now clear that the neural deficits in amblyopia have several key characteristics: (i) abnormal spatial and temporal processing; (ii) deficits in both ventral and dorsal processing streams; (iii) abnormal activities in V1, extrastriate and later specialized cortical areas; (iv) deficits in local and global processing; (v) abnormal integration of visual information over space and time; (vi) abnormal segregation of signals from noise; and (vii) abnormal interocular suppression. In addition, it is now known that higher brain functions rely upon a fine balance between local specialization and global integration of brain processes. Viewing the brain as a complex network of interacting subsystems has led to a shift from searching for locally activated regions toward identifying task-related functional networks. New neuroimaging and analytic techniques will allow us better understanding of how amblyopia affects the spatiotemporal coordination across the entire cortical visual network. Furthermore, our knowledge of brain plasticity and the factors that control the opening and closure of critical periods has increased dramatically in the past decades. New insights gained from this knowledge have led to new therapeutic strategies that harness plasticity (e.g., perceptual learning and binocular therapy), which may allow for greater recovery of visual functions in both children and adults with amblyopia well beyond the critical period.

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