Amblyopia: neural basis and therapeutic approaches

Ambliopia: bases neurais e intervenções terapêuticas

Caio César Peixoto Bretas[1], Renato Nery Soriano[2]

ABSTRACT

Abnormalities in visual processing caused by visual deprivation or abnormal binocular interaction may induce amblyopia, which is characterized by reduced visual acuity. Occlusion therapy, the conventional treatment, requires special attention as occlusion of the fellow normal eye may reduce its visual acuity and impair binocular vision. Besides recovering visual acuity, some researchers have recommended restoration of stereoacuity and motor fusion and reverse suppression in order to prevent diplopia. Recent studies have documented that the amblyopic visual cortex has a normal complement of cells but reduced spatial resolution and a disordered topographical map. Changes occurring in the late sensitive period selectively impact the parvocellular pathway. Distinct morphophysiologic and psychophysical deficits may demand individualization of therapy, which might provide greater and longer-lasting residual plasticity in some children.

Keywords: Amblyopia; Visual acuity; Neural plasticity; Visual cortex

RESUMO

Anormalidades nos processamentos visuais causadas por privação visual ou interação binocular anormal podem gerar ambliopia, caracterizada por redução da acuidade visual. A terapia de oclusão (tratamento convencional) necessita de cuidados especiais, pois a oclusão do olho normal (não-amblíope) pode reduzir a acuidade visual do mesmo e prejudicar a visão binocular. Além de recuperar a acuidade visual, alguns pesquisadores alertam para a necessidade em potencial de se restaurar a estereoacuidade e a fusão motora, bem como reverter a supressão a fim de impedir diplopia. Estudos recentes revelam que nos córtices visuais de amblíopes há uma quantidade normal de células, mas com resolução espacial reduzida e mapa topográfico desorganizado. Alterações ocorridas durante o período crítico tardio do desenvolvimento visual humano impactam seletivamente a via parvocelular. Déficits morfofisiológicos e psicofísicos distintos podem exigir programas de tratamento potencialmente seletivos e poderiam explicar a plasticidade residual maior e mais duradoura em algumas crianças.

Descritores: *Ambliopia; Acuidade visual; Plasticidade neuronal; Córtex visual*

INTRODUCTION

Visual processing occurs as neural coding is transmitted from cells of the lateral geniculate nucleus of the thalamus to the primary visual cortex (V1, the striate cortex). This is located in the occipital lobe calcarine sulcus (Broadmann area 17), where inhibitory and excitatory binocular convergence occurs[1]. Cortical synaptic connections integrate a fragmented representation of a scene or object, creating a recognizable visual perception[2]. Color and form are perceived through the ventral pathway (parvocellular cells) in the temporal lobe, while localization and motion are processed through the dorsal pathway (magnocellular cells) in the parietal lobe[3].

Morphophysiologic changes associated with abnormalities of visual processing may generate amblyopia, characterized by reduced visual acuity and contrast sensitivity either uni- or bilaterally. Patients with amblyopia also present with deficits in binocular vision, color, and form perception (parvocellular pathway), motion perception (magnocellular pathway), and contour integration. There may be abnormal function of the fellow normal eye as well. Overall, there is diminished capacity to generate a tridimensional representation of the world adequate to coordinate manipulation (eye-hand coordination), reading, and visual decision making[4-8].

Amblyopia has no detectable organic cause[9] but occurs as a result of visual deprivation (congenital cataracts; ametropia) and/or abnormal binocular interaction (strabismus; anisometropia)[10]. Amblyopia is the main source of preventable child blindness[11] and of monocular vision in 20- to 70-year-old patients[9]. The incidence is 1% to 5% in children[12], and it accounts for about 60% of vision disorders in preschool and school-age children[13].

Despite the high incidence of amblyopia in children and the fact that it affects their cognitive development, school performance, social integration, and future profession[13,14], its neural basis is relatively poorly understood. Investigations have produced apparently conflicting results[1,9,15,16]. Studies in the last two years have suggested that it is essential to discover when the visual deficit took place, that is, in the early sensitive period *versus* late sensitive period[17] to prescribe proper treatment.

Based on the most recent advances in understanding the neural basis of amblyopia, the present article reviews clinical and neurophysiologic aspects related to its causes, symptoms, and therapeutic approaches.

Causes

Ametropia, anisometropia, and strabismus[18] during childhood are the most common causes of amblyopia. They result in an abnormal visual experience that impairs visual development and processing. Development of the visual system is completely dependent on visual stimuli[16] that induce elaboration of neural circuits[19]. Maturation of neural circuits begins at birth, with an early sensitive period at 4 to 18 months[17] and a late sensitive period to about 7 years of age[15,17]. After that, there is a significant reduction in neuroplasticity. Until the end of

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[1] Faculdade de Medicina, Universidade Federal de Juiz de Fora (UFJF), Governador Valadares, MG, Brazil.
[2] Núcleo de Fisiologia e Biofísica, Departamento de Ciências Básicas da Vida, Universidade Federal de Juiz de Fora (UFJF), Governador Valadares, MG, Brazil.

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Corresponding author: Renato Nery Soriano. Setor de Fisiologia e Biofísica. Departamento de Ciências Básicas da Vida. Universidade Federal de Juiz de Fora, Governador Valadares, MG - 35010-177 - Brazil - E-mail: renato.soriano@ufjf.edu.br

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the late sensitive period[17] (Table 1), there is macular maturation, optic nerve myelination, fusion of images for binocular vision[20], formation of the ocular dominance columns in V1 by competition, and maturation of binocular connections by cooperation among afferents from both eyes[21]. Once past this period, even if the cause of the deficit is corrected, an 8- to 10-year-old child is likely to have persistent reduction in visual acuity and contrast sensitivity[22].

Ametropia

The most common ametropias are hyperopia, myopia, and astigmatism. Hyperopia is characterized by a refractive error produced by a shorter than normal ocular axial length. There is an imbalance between refractive capacity and the anteroposterior length of the eye[22,23]. In a study performed on 37 children 5 to 8 years of age with bilateral hyperopia and esotropic amblyopia, it was found that hyperopia in the amblyopic eyes was more severe than that of the fellow eye[24]. In contrast to hyperopia, myopia is a refractive error occurring when the anteroposterior ocular axial lenght is longer than normal[22]. Astigmatism, on the other hand, is detected when the vertical diopter value differs from the horizontal value[22]. Astigmatism is the most common refractive error associated with amblyopia[12] as it substantially affects visual system development[25]. The term meridional amblyopia is commonly used to refer to amblyopia caused by astigmatism. Ametropias, therefore, reduce visual acuity[26], generating a mild visual deprivation that affects development of the visual system in childhood[26]. The reported incidence of ametropia as a cause of amblyopia is quite high at 62.7%, with 9.4% due to myopia, 21.8% to hyperopia, and 31.3% to astigmatism[12,22].

Anisometropia

Anisometropia is an ophthalmic disorder in which optical measurements differ between the eyes, which have myopia or hyperopia of different degrees and which impairs binocular fusion[22]. Variations greater than 1.0 diopter (D) in hypermetropic anisometropia or 2.0 D in myopic anisometropia are associated with an increased incidence of amblyopia[27]. Frequent coexistence of anisometropia and amblyopia in the first clinical test in the child and the persistence of reduced visual acuity after refractive correction strengthen the evidence that anisometropia is a cause of amblyopia[28].

Strabismus

Strabismus, one of the principal ocular deficits in low-income children[29,30], is characterized by dysfunction of the extraocular muscles, generating binocular misalignment. The strabismic eye may fail to receive visual stimuli onto the macular area[31], thus affecting various developmental stages of cortical processing[16]. Identification of factors that cause strabismus may be important for diagnosis and treatment of amblyopia[25].

Congenital cataracts

Congenital cataracts cause significant visual deficiency and generate visual deprivation. If cataracts are not surgically treated, they can lead to amblyopia[32]. This, however, is a less frequent cause[18].

Congenital ptosis

Congenital ptosis (blepharoptosis) refers to an upper eyelid positioned lower than normal, narrowing the vertical dimension of the palpebral cleft[33]. Visual deprivation and consequently amblyopia may occur if the pupil is covered by the upper eyelid. Studies have shown that 6% of patients with congenital ptosis develop amblyopia[34,35], called stimulus deprivation amblyopia.

Diagnosis

The diagnosis of amblyopia is challenging since there is no specific test to detect it, and it depends on the child's ability to cooperate, potentially compromising the diagnostic process[35]. The Snellen chart for visual acuity, together with its successors are the main instruments used to evaluate visual acuity, that is, high contrast, black-and-white recognition acuity.

Possibility of amblyopia should be considered when in the first stage of investigation a child presents with visual acuity less than 20/30 or when the light reflexes in the two eyes are not symmetrical and a visual difference between eyes is maintained after correcting refractive defects and organic visual defects. Suspicion for amblyopia increases if, even after cycloplegic refraction, there is astigmatism greater than 2.5 D in both eyes or a ≥1.5 D difference between eyes, myopia greater than 5.0 D in both eyes or a ≥3.0 D difference between eyes, as well as hyperopia greater than 4.5 D in both eyes or a ≥+1.5 D difference between eyes[36].

In addition to using the Snellen chart, it is always important to perform a cover test to evaluate ocular alignment. During the clinical interview, noting whether the patient had congenital ptosis or cataracts and/or refractive defects during childhood is useful to aid in the diagnosis of amblyopia.

Strabismic amblyopia is most easily detected by parents. Teachers' contribution is also important to detect amblyopia as early as possible[37]. In Israel and Sweden, screening to detect amblyopia is performed for school-age children. Ethical concerns have been raised regarding this screening, however, as the results may subject children to bullying, with an adverse impact on their mental health[38].

Researchers emphasize the importance of trying to discover the age of onset of abnormal visual experience, as this information is believed to be essential for choosing specific treatment, at least during each of the two sensitive periods of human visual development[17] (Table 1).

Table 1. Differences in characteristics of amblyopia and response to treatment by time of onset

	Early sensitive period	Late sensitive period
Duration	4 to 18 months of age[a(17)]	18 months to 7 years of age[a(17)]
Predominant mechanism in binocular connections	Competition[b(21)]	Cooperation[b(21)]
Ocular dominance columns	Under development[b(46,68)]	Already developed[b(46,68)]
Occlusion	Hypertrophy of LGN[c] cells of the non-occluded eye; shrinkage of LGN cells of the occluded eye[b(69-71)]	Selective shrinkage of cells in the parvocellular pathway in both non-occluded and occluded eyes[b]. Normal size of the magnocellular cells[b(69-71)]
Functional impairment	Parvocellular-related function is more diminished in both the amblyopic and fellow eyes of early and late onset[d(72)]	Parvocellular-related function is more diminished in the amblyopic eye of late-onset subjects[d(72)]

[a]= the age ratio of 1:4 has been considered to compare the relative timing in monkey and man, so that 1 week in the monkey is approximately equivalent to 4 weeks in man; [b]= outcomes from studies in monkeys; [c]= LGN, lateral geniculate nucleus of the thalamus; [d]= outcomes from human studies.

Main treatments

Conventional treatment of amblyopia consists of occlusion of the fellow eye. This tends to augment visual acuity of the amblyopic eye and to improve binocular function, as long as it is correctly performed[39]. Treatment schedules vary from months to years[40] but last 3 years on average[39]. American and British guidelines both advise daily occlusion for 2 h for moderate and 6 h for severe amblyopia. However, 10 or more hours have also been reported[40]. Occlusion therapy (also called patching) should be monitored frequently as to its results[41]. It can be used in association with other therapeutic modalities[19,40,42]. Parents' participation is essential for successful treatment; therefore, they should be aware of the necessity, urgency, and potential effectiveness of the therapeutic program[43].

Despite having been used for many years, occlusion therapy still needs to be investigated as to the neural events responsible for reversal of the symptoms[39]. Clarification is needed as to what is involved in the consolidation of visual neurophysiologic development driven by the effects of visual processing using the amblyopic eye. It is believed that the neural basis of the treatment is associated with the phenomenon of neuroplasticity, an intrinsic capacity to adapt to diverse conditions to which the nervous system is submitted. Visual cortex plasticity occurs in response to changes in neuronal activity and is generated mainly by the action of neuromodulators that promote long-term synaptic changes[44]. Patching of the fellow eye and visual stimuli to the amblyopic eye appear to remodel cortical functions[45]. Besides functional alterations, patching also induces morphologic changes (indicating that there is morphologic plasticity) in cells of the retina, lateral geniculate nucleus, and visual cortex (Table 1)[9,46]. In experimental studies in monkeys, it has been shown that eye occlusion by lids suturing at birth and then removal of the sutures at the third week of age caused a re-expansion of the ocular dominance columns in layer IVcβ of V1, where the afferents to parvocellular cells of the lateral geniculate nucleus synapse, and, conversely, a reduction of the adjacent columns of magnocellular cells in layer IVcα[46]. Hence, there is a dissociation between the magno- and parvocellular pathways, which may have some effect on visual function. Interestingly, such an effect was found only if deprivation and reversal were performed at a specific period of visual development[46]. These findings raise the following question: Would this dissociation between the magno- and parvocellular pathways explain why patching is not successful in some children with amblyopia?

As mentioned, plasticity in the visual pathways is substantially diminished as children develop, yet the finding that treatment may be partially effective in older subjects with late-onset amblyopia indicates that a certain residual plasticity is present that can reverse or attenuate the symptoms of amblyopia after the late sensitive period[17,40,47]. As the period of greater plasticity varies in different parts of the brain and with distinct sensory functions, the period in which it is possible to reverse the symptoms caused by visual deprivation may vary as well[40].

Outcomes of treatment vary because of a number of factors. Even though there is not yet a consensus on the influence of age on treatment[48], studies indicate that treatment initiated after 6 to 8 years of age has the lowest success rate[11,19,39,46]. Thus, it has been recommended to initiate treatment as early as possible[48,49], even though 8- to 12-year-old children may sometimes satisfactorily respond to therapy[39]. The severity of amblyopia also significantly affects treatment outcome, with the greatest rate of success found for mild amblyopia[47]. Response to treatment is a function of initial visual acuity and treatment adherence[39,50]. For example, success in patients with mild amblyopia and good adherence to treatment is higher than 80%, whereas it is only about 15% in subjects with severe amblyopia and poor adherence[47].

It is worth pointing out that occlusion treatment requires special attention since occlusion of the fellow eye may reduce its visual acuity and impair binocular vision. Beyond the visual effects, this may result in disturbance of the child's self-esteem[49] and disruption of the family routine. Hence, these factors should be evaluated in each case before treatment is prescribed[51].

Another crucial aspect that deserves attention is that recovering visual acuity is only one of the goals of an amblyopia therapy program. Other aims are to restore stereoacuity and motor fusion and possibly to reverse suppression. Some researchers have warned that if suppression is reversed but sensory and motor fusion are not restored, there will be a risk of intractable diplopia.

Pharmacological and behavioral forms of treatment in association with occlusion therapy tend to reinforce neuroplasticity and ease vision recovery (Table 2). Patching combined with perceptual learning achieves outcomes better than those with occlusion only[40]. This association improves visual performance, mainly in binocular[52] and timing[49] function and reduces or corrects spatial distortion of images[9]. An intrinsic difficulty of this treatment is that children must cooperate and remain attentive. It is, however, a promising approach for patients who have not responded to occlusion alone[52].

The following drugs have been used in association with occlusion: gamma aminobutyric acid (GABA) synthesis inhibitors, citicoline, and levodopa (Table 2). It has been shown in animal studies that a GABA synthesis inhibitor potentiates cortical plasticity[19]. Citicoline, an intermediate in acetylcholine and phospholipids biosynthesis, appears to ameliorate visual acuity by favoring action potential conduction, but its long-term effects need to be evaluated[48]. Levodopa, a dopamine precursor used in treating Parkinson disease, ameliorates visual function of patients with irreversible amblyopia. It is believed that levodopa is capable of restoring visual neuroplasticity, although it is remains to be verified if this is a long-lasting effect[53].

As a form of treatment independent of occlusion, some studies have reported the use of atropine (Table 2), a parasympatholytic muscarinic antagonist. Atropine may help in treating moderate amblyopia[29], as it interferes with visual accommodation of the fellow normal eye, thus indirectly forcing use of the amblyopic one[19]. However, atropine treatment is not always effective[48]. Less conventional treatments such as refractive therapy, acupuncture, and others have also been described[54]. Randomized, controlled trials of treatment modalities for amblyopia are necessary.

According to some authors, experimental evidence reveals that abnormal visual experience can both extend[55,56] and reduce[57] plasticity. This may be a significant observation for amblyopia treatment because such children had abnormal visual experiences before being treated. This may account for the variability and unpredictability of the response to occlusion[58], positive response in some children[59], relatively low incidence of amblyopic children with non-treated, early-onset strabismus[60] in comparison to those with congenital cataracts.

Neural basis

Significant advances in understanding the neural basis of amblyopia are plausibly associated with development of more effective therapeutic approaches. As of the middle of the last year (2015), gaps in science-based knowledge about the neural basis of amblyopia still existed, and some aspects remained controversial and were a matter of debate.

Although it is not expected that the classical psychophysical deficits in amblyopia, such as loss of contrast sensitivity at high spatial frequencies, spatial distortion, mislocalization, and reduced sensitivity for form and motion, may be understood from a single model or explanation, some recent findings shed new light on the neural basis of amblyopia.

An important aspect for understanding the cortical deficits in patients with amblyopia is the possible reduction in the number of cortical neurons stimulated by foveal projections, which would induce loss of contrast sensitivity and mislocalization. It is believed that the visual impairment could therefore be explained at least partially by a reduced complement of cortical cells excited by the amblyopic projections[61] or because cortical magnification would be reduced[62] (Table 3).

Some intriguing questions have been raised in the literature: Would V1 dysfunction be a consequence of loss of binocularity of cortical cells,

Table 2. Main treatments for amblyopia: neurophysiologic effects and disadvantages

Treatment	Neurophysiologic effects	Disadvantages
Occlusion	Stimulates amblyopic eye, improving its visual acuity by plasticity[40]	Reduces binocular function[32], changes family routine[49], may induce psychological problems[32]. Adherence varies[26,31]
Occlusion + perceptual learning	Improves binocular, spatial, and timing functions[32]	Requires the child's attentiveness and cooperation[50]
Occlusion + levodopa	Increases cortical plasticity[33]	Long-term outcomes need to be monitored[33]
Occlusion + citicoline	Improves action potential conduction[33]	Long-term outcomes need to be monitored[33]
Atropine	Prevents fellow normal eye accommodation, stimulating the amblyopic one[45]	Occlusion outcomes are faster[45]

Table 3. Cortical deficits in amblyopia*

	Striate cortex (V1)	Extrastriate cortex (V2 and V3)
Complement of cells	Normal	Normal
Spatial resolution	Reduced	Reduced
Cortical magnification factor	Normal	Normal
Topographical map	Disordered	Very disordered
Population receptive field size	Enlarged	Very enlarged

*= results from population receptive field functional magnetic resonance imaging analysis[4].

or would impairment of excitation-inhibition balance exist in binocular cells? Some researchers have speculated that cellular interactions in amblyopia are reduced in intensity, whereas others think that sensitivity and spatial resolution are both reduced in cortical neurons stimulated by foveal projections[63]. Furthermore, it has been speculated that the cortical deficits would not necessarily occur in V1[64]; perhaps the problem might lie only in V2 and V3, with normal processing in V1[65]. The following hypothesis has also been proposed in the literature: The amblyopic projections are disordered, and there is a significant reduction (or loss) of spatial resolution of cortical neurons stimulated by projections from the fovea, which is thicker in subjects with amblyopia when evaluated by optical coherence tomography[1]. It remains to be investigated whether thickening of the fovea directly influences visual acuity, whether it is associated with worse visual prognosis, and whether intensive early intervention is capable of controlling or preventing such thickening.

Guided by simulations of how different types of cellular disturbances (e.g., loss of cells' spatial resolution, increased cellular disarray, and reduced cellular sampling) would affect the neuronal population receptive field, researchers have used functional magnetic resonance imaging to analyze population receptive fields in V1 (striate cortex), V2 and V3 (extrastriate cortex) of humans with moderate-to-severe amblyopia[4]. The model regularly samples responses at the voxel level from a dense array of receptive fields. Hence, it forecast the effects of the size of the population receptive field versus eccentricity and also the effects of eccentricity versus cortical distance, which reflects cortical magnification[4].

Substantial evidence now supports the contention that the deficits in visual processing are also found in V2 and V3, and that these are not a consequence of abnormal processing occurred in V1[4] (Table 3). It is conceivable that patients with amblyopia possess an immature visual system with a normal complement of cells, i.e., the quality of global cortical topographical representation of information from the amblyopic eye is preserved and, therefore, there is no reduction in the number of cells excited[61]. Moreover, cortical magnification is not reduced as believed[62] but is normal[4] (Table 3). Although this last conclusion may be contested by those who propose that the amblyopic eye would activate fewer neurons, hence generating a reduced sample, the counterargument is supported by data revealing that a reduced cortical sample alone would not induce changes in the size of population receptive fields[4] and thus cannot be the only explanation.

Interestingly, although subjects with amblyopia have a normal complement of cells, population receptive fields are enlarged in V1 and even more so in V2 and V3. Enlarged population receptive field might be consequence of unstable movement of the amblyopic eye[66], but such a possibility can be discarded due to the methodological criteria adopted[4]. Another possibility is that an enlarged population receptive field may be a result of a reduced contribution of smaller population receptive fields for the amblyopic eye projections. Even though this last proposal sounds plausible, another relevant finding explains that enlarged population receptive fields is the disordered topographical map[4] derived from increased positional disarray of cells (Table 3).

There are important questions that have not yet been addressed. Is spatial resolution reduced in amblyopic cortical cells? Do subjects with amblyopia experience spatial distortions and reduced positional accuracy as a function of reduced or lost spatial resolution? The response to this question seems to be indicated by findings that show greater positional variability is found in amblyopic population receptive fields[4,67].

Taken together, the recent advances in understanding the neural basis of amblyopia reveal that patients with amblyopia exhibit a normal complement of cells whose spatial resolution is reduced and topographical map is disordered (Table 3).

Final remarks

Visual abnormalities vary with different types of abnormal visual experience and the age of onset. Children with amblyopia having similar visual acuity may exhibit very distinct morphophysiologic variations and distinct visual functions. These anatomical and psychophysical differences, besides accounting for greater and longer-lasting plasticity in some children, may require special treatment programs in order to improve therapeutic effectiveness. Therefore, combining subjects with early- and late-onset amblyopia in research studies is not recommended.

Given that binocular function may affect plasticity, it is very important in the diagnosis and treatment of amblyopia to detect the presence or absence of binocularity. It should be investigated whether the loss of binocular function was subsequently followed by a reduction of visual acuity or if abnormal monocular afferent signals first reduced visual acuity with a subsequent loss of binocularity. In many children, amblyopia develops at an age in which the ocular dominance columns of V1[46,68] are no longer affected, i.e., after the early sensitive period (Table 1). It has been documented that morphologic changes occurring during the late sensitive period selectively affect cells of the parvocellular pathway[17,21,69-71]. It seems reasonable to recommend that treatment for amblyopia should be individualized, as some children with amblyopia may not respond to occlusion because of morphophysiologic dissociation between the magno- and parvocellular pathways[72].

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