

# Amblyopia: neural basis and therapeutic approaches

## *Ambliopia: bases neurais e intervenções terapêuticas*

CAIO CÉSAR PEIXOTO BRETAS<sup>1</sup>, RENATO NERY SORIANO<sup>2</sup>

### 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 morphophysiological 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-ambliope) 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 estereoauidade e a fusão motora, bem como reverter a supressão a fim de impedir diplopia. Estudos recentes revelam que nos córtices visuais de ambliopes 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 (Brodmann area 17), where inhibitory and excitatory binocular convergence occurs<sup>(1)</sup>. Cortical synaptic connections integrate a fragmented representation of a scene or object, creating a recognizable visual perception<sup>(2)</sup>. 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<sup>(3)</sup>.

Morphophysiological 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<sup>(4-8)</sup>.

Amblyopia has no detectable organic cause<sup>(9)</sup> but occurs as a result of visual deprivation (congenital cataracts; ametropia) and/or abnormal binocular interaction (strabismus; anisometropia)<sup>(10)</sup>. Amblyopia is the main source of preventable child blindness<sup>(11)</sup> and of monocular

vision in 20- to 70-year-old patients<sup>(9)</sup>. The incidence is 1% to 5% in children<sup>(12)</sup>, and it accounts for about 60% of vision disorders in preschool and school-age children<sup>(13)</sup>.

Despite the high incidence of amblyopia in children and the fact that it affects their cognitive development, school performance, social integration, and future profession<sup>(13,14)</sup>, its neural basis is relatively poorly understood. Investigations have produced apparently conflicting results<sup>(1,9,15,16)</sup>. 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<sup>(17)</sup> 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<sup>(18)</sup> 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<sup>(16)</sup> that induce elaboration of neural circuits<sup>(19)</sup>. Maturation of neural circuits begins at birth, with an early sensitive period at 4 to 18 months<sup>(17)</sup> and a late sensitive period to about 7 years of age<sup>(15,17)</sup>. After that, there is a significant reduction in neuroplasticity. Until the end of

Submitted for publication: July 11, 2016  
Accepted for publication: August 28, 2016

<sup>1</sup> Faculdade de Medicina, Universidade Federal de Juiz de Fora (UFJF), Governador Valadares, MG, Brazil.

<sup>2</sup> Núcleo de Fisiologia e Biofísica, Departamento de Ciências Básicas da Vida, Universidade Federal de Juiz de Fora (UFJF), Governador Valadares, MG, Brazil.

**Funding:** No specific financial support was available for this study.

**Disclosure of potential conflicts of interest:** None of the authors have any potential conflict of interest to disclose.

**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

the late sensitive period<sup>(17)</sup> (Table 1), there is macular maturation, optic nerve myelination, fusion of images for binocular vision<sup>(20)</sup>, formation of the ocular dominance columns in V1 by competition, and maturation of binocular connections by cooperation among afferents from both eyes<sup>(21)</sup>. 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<sup>(22)</sup>.

### 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<sup>(22,23)</sup>. 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<sup>(24)</sup>. In contrast to hyperopia, myopia is a refractive error occurring when the anteroposterior ocular axial length is longer than normal<sup>(22)</sup>. Astigmatism, on the other hand, is detected when the vertical diopter value differs from the horizontal value<sup>(22)</sup>. Astigmatism is the most common refractive error associated with amblyopia<sup>(12)</sup> as it substantially affects visual system development<sup>(25)</sup>. The term meridional amblyopia is commonly used to refer to amblyopia caused by astigmatism. Ametropias, therefore, reduce visual acuity<sup>(26)</sup>, generating a mild visual deprivation that affects development of the visual system in childhood<sup>(26)</sup>. 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<sup>(12,22)</sup>.

### 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<sup>(22)</sup>. 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<sup>(27)</sup>. 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<sup>(28)</sup>.

### Strabismus

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

### Congenital cataracts

Congenital cataracts cause significant visual deficiency and generate visual deprivation. If cataracts are not surgically treated, they can lead to amblyopia<sup>(32)</sup>. This, however, is a less frequent cause<sup>(18)</sup>.

### Congenital ptosis

Congenital ptosis (blepharoptosis) refers to an upper eyelid positioned lower than normal, narrowing the vertical dimension of the palpebral cleft<sup>(33)</sup>. 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<sup>(34,35)</sup>, 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<sup>(35)</sup>. 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  $\geq 1.5$  D difference between eyes, myopia greater than 5.0 D in both eyes or a  $\geq 3.0$  D difference between eyes, as well as hyperopia greater than 4.5 D in both eyes or a  $\geq +1.5$  D difference between eyes<sup>(36)</sup>.

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<sup>(37)</sup>. 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<sup>(38)</sup>.

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

<sup>a</sup>= 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; <sup>b</sup>= outcomes from studies in monkeys; <sup>c</sup>= LGN, lateral geniculate nucleus of the thalamus; <sup>d</sup>= 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<sup>(39)</sup>. Treatment schedules vary from months to years<sup>(40)</sup> but last 3 years on average<sup>(39)</sup>. 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<sup>(40)</sup>. Occlusion therapy (also called patching) should be monitored frequently as to its results<sup>(41)</sup>. It can be used in association with other therapeutic modalities<sup>(19,40,42)</sup>. Parents' participation is essential for successful treatment; therefore, they should be aware of the necessity, urgency, and potential effectiveness of the therapeutic program<sup>(43)</sup>.

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<sup>(39)</sup>. 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<sup>(44)</sup>. Patching of the fellow eye and visual stimuli to the amblyopic eye appear to remodel cortical functions<sup>(45)</sup>. 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)<sup>(9,46)</sup>. 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 IVc $\beta$  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 IVc $\alpha$ <sup>(46)</sup>. 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<sup>(46)</sup>. 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<sup>(17,40,47)</sup>. 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<sup>(40)</sup>.

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<sup>(48)</sup>, studies indicate that treatment initiated after 6 to 8 years of age has the lowest success rate<sup>(11,19,39,46)</sup>. Thus, it has been recommended to initiate treatment as early as possible<sup>(48,49)</sup>, even though 8- to 12-year-old children may sometimes satisfactorily respond to therapy<sup>(39)</sup>. The severity of amblyopia also significantly affects treatment outcome, with the greatest rate of success found for mild amblyopia<sup>(47)</sup>. Response to treatment is a function of initial visual acuity and treatment adherence<sup>(39,50)</sup>. 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<sup>(47)</sup>.

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<sup>(49)</sup> and disruption of the family routine. Hence, these factors should be evaluated in each case before treatment is prescribed<sup>(51)</sup>.

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<sup>(40)</sup>. This association improves visual performance, mainly in binocular<sup>(52)</sup> and timing<sup>(49)</sup> function and reduces or corrects spatial distortion of images<sup>(9)</sup>. 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<sup>(52)</sup>.

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<sup>(19)</sup>. 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<sup>(48)</sup>. 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<sup>(53)</sup>.

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<sup>(29)</sup>, as it interferes with visual accommodation of the fellow normal eye, thus indirectly forcing use of the amblyopic one<sup>(19)</sup>. However, atropine treatment is not always effective<sup>(48)</sup>. Less conventional treatments such as refractive therapy, acupuncture, and others have also been described<sup>(54)</sup>. Randomized, controlled trials of treatment modalities for amblyopia are necessary.

According to some authors, experimental evidence reveals that abnormal visual experience can both extend<sup>(55,56)</sup> and reduce<sup>(57)</sup> 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<sup>(58)</sup>, positive response in some children<sup>(59)</sup>, relatively low incidence of amblyopic children with non-treated, early-onset strabismus<sup>(60)</sup> 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<sup>(61)</sup> or because cortical magnification would be reduced<sup>(62)</sup> (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 <sup>(40)</sup>	Reduces binocular function <sup>(32)</sup> , changes family routine <sup>(49)</sup> , may induce psychological problems <sup>(32)</sup> . Adherence varies <sup>(26,31)</sup>
Occlusion + perceptual learning	Improves binocular, spatial, and timing functions <sup>(32)</sup>	Requires the child's attentiveness and cooperation <sup>(50)</sup>
Occlusion + levodopa	Increases cortical plasticity <sup>(33)</sup>	Long-term outcomes need to be monitored <sup>(33)</sup>
Occlusion + citicoline	Improves action potential conduction <sup>(33)</sup>	Long-term outcomes need to be monitored <sup>(33)</sup>
Atropine	Prevents fellow normal eye accommodation, stimulating the amblyopic one <sup>(45)</sup>	Occlusion outcomes are faster <sup>(45)</sup>

**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<sup>(4)</sup>.

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<sup>(63)</sup>. Furthermore, it has been speculated that the cortical deficits would not necessarily occur in V1<sup>(64)</sup>; perhaps the problem might lie only in V2 and V3, with normal processing in V1<sup>(65)</sup>. 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<sup>(1)</sup>. 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<sup>(4)</sup>. 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<sup>(4)</sup>.

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<sup>(4)</sup> (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<sup>(61)</sup>. Moreover, cortical magnification is not reduced as believed<sup>(62)</sup> but is normal<sup>(4)</sup> (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<sup>(4)</sup> 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<sup>(66)</sup>, but such a possibility can be discarded due to the methodological criteria adopted<sup>(4)</sup>. 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<sup>(4)</sup> 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<sup>(4,67)</sup>.

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 morphophysiological 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<sup>(46,68)</sup> 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<sup>(17,21,69-71)</sup>. It seems reasonable to recommend that treatment for amblyopia should be individualized, as some children with amblyopia may not respond to occlusion because of morphophysiological dissociation between the magno- and parvocellular pathways<sup>(72)</sup>.

## REFERENCES

- Ribeiro L, Saraiva E, Oliveira M, Varandas R, Agrelos L. Avaliação da espessura macular e da camada das fibras nervosas da retina na ambliopia por tomografia de coerência óptica. *Oftalmologia*. 2012;36:51-6.
- Brincat SL, Connor CE. Underlying principles of visual shape selectivity in posterior inferotemporal cortex. *Nat Neurosci*. 2004;7(8):880-6.
- Albright TD, Stoner GR. Contextual influences on visual processing. *Annu Rev Neurosci*. 2002;25:339-79.
- Clavagnier S, Dumoulin SO, Hess RF. Is the cortical deficit in amblyopia due to reduced cortical magnification, loss of neural resolution, or neural disorganization? *J Neurosci*. 2015;35(44):14740-55.
- Suttle C, Melmoth D, Finlay A, Sloper JJ, Grant S. Eye-hand coordination skills in children with and without amblyopia. *Invest Ophthalmol Vis Sci*. 2011;52(3):1851-64.
- Grant S, Suttle C, Melmoth DR, Conway ML, Sloper JJ. Age- and stereo dependent eye-hand deficits in children with amblyopia and abnormal binocularity. *Invest Ophthalmol Vis Sci*. 2014;55(9):5687-701.
- Kanonidou E, Proudlock F, Gottlob I. Reading strategies in mild to moderate strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 2010;51(7):3502-8.
- Farzin F, Norcia A. Impaired visual decision-making in individuals with amblyopia. *J Vis*. 2011;11(14):pii 6.
- Roper-Hall G. Current concepts of amblyopia: a neuro-ophthalmology perspective. *Am Orthoptic J*. 2007;57:2-12.
- Couto Junior AS, Jardim JL, Oliveira DA, Gobetti TC, Portes AJF, Neurauder R. Alterações oculares em crianças pré-escolares e escolares no município de Duque de Caxias, Rio de Janeiro, Brasil. *Rev Bras Oftalmol*. 2010;69(1):7-11.
- Procianny E, Fuchs FD, Procianny F, Procianny L. Uso de levodopa em pacientes com ambliopia. *Arq Bras Oftalmol*. 2000;63(5):399-402.
- Couto Junior AS, Pinto GR, Oliveira DA, Holzmeister D, Portes ALF, Neurauder R, et al. Prevalência das ametropias e oftalmopatias em crianças pré-escolares e escolares em favelas do Alto da Boa Vista, Rio de Janeiro, Brasil. *Rev Bras Oftalmol*. 2007;66(5):304-8.
- Beer SMC, Scarpi MJ, Minello AA. Achados oculares em crianças de zero a seis anos de idade, residentes na cidade de São Caetano do Sul, SP. *Arq Bras Oftalmol*. 2003;66(6):839-45.
- Rocha MN, De Ávila MP, Isaac DL, Mendonça LS, Nakanishi L, Auad LJ. Prevalência de doenças oculares e causas de comprometimento visual em crianças atendidas em um Centro de Referência em Oftalmologia do centro-oeste do Brasil. *Rev Bras Oftalmol*. 2014;63(4):225-9.
- Vasconcelos GC, Da Costa MF. Tratamento atual da ambliopia: onde estamos? *Arq Bras Oftalmol*. 2013;76(4):5-6.
- Hou C, Pettet MW, Norcia AM. Acuity-independent effects of visual deprivation on human visual cortex. *Proc Natl Acad Sci U S A*. 2014;111(30):3120-8.
- Davis AR, Sloper JJ, Neveu MM, Hogg CR, Morgan MJ, Holder GE. Electrophysiological and psychophysical differences between early- and late-onset strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 2003;44(2):610-7.
- Lucena AR, Cantanhede TMI, Trigueiro SA, Tavares S, Ventura LO. Frequência e causas da ambliopia em pacientes assistidos na Fundação Altino Ventura, Recife-PE. *Rev Bras Oftalmol*. 2001;60(1):50-4.
- Bonaccorci J, Berardi N, Sale A. Treatment of amblyopia in the adult: insights from a new rodent model of perceptual learning. *frontiers in neural circuits*. *Front Neural Circuits*. 2014;8:82. doi: 10.3389/fncir.2014.00082.
- Graziano RM, Leone CR. Problemas oftalmológicos mais frequentes e desenvolvimento visual do pré-termo extremo. *J Pediatr*. 2005;81(1):95-100.
- Sloper JJ. Edridge-Green Lecture: Competition and cooperation in visual development. *Eye (Lond)*. 1993;7(Pt 3):319-31.
- Bicas HEA. Ametropias e presbiopia. *Medicina(Ribeirão Preto)*. 1997;30(1):20-6.
- Goedert ME, Rohr JT, Pinto LD. Associação entre hiperopia e outros erros refrativos e visuais em crianças. *Rev Bras Oftalmol*. 2016;75(1):50-4.
- Debert I, de Alencar LM, Polati M, Souza MB, Alves MR. Oculometric parameters of hyperopia in children with esotropic amblyopia. *Ophthalmic Physiol Opt*. 2011;31(4):389-97.
- Read SA, Vincent SJ, Collins MJ. The visual and functional impacts of astigmatism and its clinical management. *Ophthalm Physiol Opt*. 2005;34(3):267-94.
- Simons K. Amblyopia characterization, treatment, and prophylaxis. *Surv Ophthalmol*. 2005;50(2):123-66.
- Rocha MN, Sanches A, Pessoa FF, Braz GS, Rego LP, Auad LJ, et al. Forma clínica e fatores de risco associados ao estrabismo na binocularidade visual. *Rev Bras Oftalmol*. 2016;75(1):34-9.
- Weakley DR Jr. The association between nonstrabismic anisometropia, amblyopia, and subnormal binocularity. *Ophthalmology*. 2001;108(1):163-71. Comment in: *Ophthalmology*. 2002;109(1):3-4.
- Barrett BT, Bradley A, Candy TR. The relationship between anisometropia and amblyopia. *Progr Retin Eye Res*. 2013;36:120-58.
- Gonçalves F, Schellini SA, Heimbeck FG, Furuya MT, Padovani CR. Causas de ambliopia e resultados do tratamento. *Rev Bras Oftalmol*. 2006;65(2):104-8.
- Albuquerque RC, Alves, JG. Afecções oculares prevalentes em crianças de baixa renda atendidas em um serviço oftalmológico na cidade do Recife - PE, Brasil. *Arq Bras Oftalmol*. 2003;66(6):831-4.
- Sperandio AM. Promoção da saúde ocular e prevenção precoce de problemas visuais nos serviços de saúde pública. *Rev Saúde Públ*. 1999;33(5):513-20.
- Rezende MS, Souza SB, Dib O, Branzoni E, Ribeiro LE. Abordagem da catarata congênita: análise de série de casos. *Rev Bras Oftalmol*. 2008;67(1):32-8.
- Saito FL, Gemperli R, Hiraki PY, Ferreira CM. Cirurgia da ptose palpebral: análise de dois tipos de procedimentos cirúrgicos. *Rev Bras Cir Plast*. 2010;25(1):11-7.
- Lucci LM, Portellinha W, Sant'Anna AE. Ptose palpebral: estudo de 390 casos/Blepharoptosis: study of 390 cases. *Arq Bras Oftalmol*. 1997;60(5):455-7.
- Ojaghi H, Moghaddar R, Ahari SS, Bahadoram M, Amani F. Amblyopia prevention screening program in Northwest Iran (Ardabil). *Int J Prev Med*. 2016;7:45. doi: 10.4103/2008-7802.177887.
- Sousa RL, Funayama BS, Catâneo L, Padovanni CR, Schellini SA. Comparação entre acuidade visual e photoscreening como métodos de triagem visual para crianças em idade escolar. *Rev Bras Oftalmol*. 2012;71(6):358-63.
- Bechara SJ, Kara-Jose N. Detecção e tratamento de pacientes ambliopes na cidade de São Paulo, SP (Brasil). *Rev Saúde Públ*. 1987;21(4):326-30.
- Schmucker C, Grossefinger R, Riemsma R, Antes G, Lange S, Lagrèze W, et al. Effectiveness of screening preschool children for amblyopia: a systematic review. *BMC Ophthalmol*. 2009;9:3. doi: 10.1186/1471-2415-9-3.
- Arakaki MR, Schellini SA, Heimbeck FG, Padovanni CR. Adesão ao tratamento da ambliopia. *Arq Bras Oftalmol*. 2004;67(2):201-5.
- Levi DM, Li RW. Improving the performance of the amblyopic visual system. *Philos Trans R Soc Lond B Biol Sci*. 2009;364(1515):399-407.
- Fielder AR, Irwin M, Auld R, Coker KD, Jones HS, Moseley MJ. Compliance in amblyopia therapy: objective monitoring of occlusion. *Br J Ophthalmol*. 1995;79(6):585-9.
- Costa DS, Klein RC, Leite CA, Ginguerra MA, Polati M. Ambliopia por estrabismo: estudo retrospectivo de pacientes em hospital universitário. *Arq Bras Oftalmol*. 2006;69(2):181-5.
- Astle AT, McGraw PV, Webb BS. Can human amblyopia be treated in adulthood? *Strabismus*. 2011;19(3):99-109.
- McCoy PA, Huang H, Philpot BD. Advances in understanding visual cortex plasticity. *Curr Opin Neurobiol*. 2009;19(3):298-304.
- LeVay S, Wiesel TN, Hubel DH. The development of ocular dominance columns in normal and visually deprived monkeys. *J Comp Neurol*. 1980;191(1):1-51.
- Astle AT, Webb BS, McGraw PV. The pattern of learned visual improvements in adult amblyopia. *Invest Ophthalmol Vis Sci*. 2011;52(10):7195-204.
- Arnoldi KA. Current recommendations for amblyopia treatment. *Am Orthoptic J*. 2007;57(1):60-7.
- Mendonça RH, Ferreira EL. Visual evoked potentials (VEP) and visual acuity improvement after cytidine 52-diphosphocholine (CDP-Choline) therapy in amblyopic patient. *Rev Bras Oftalmol*. 2012;71(5):328-30.
- Levi DM, Li RD. Perceptual learning as a potential treatment for amblyopia: A mini-review. *Vision Res*. 2009;49(21):2535-49.
- Hussein MA, Coats DK, Muthialu A, Cohen E, Paysse EA. Risk factors for treatment failure of anisometropic amblyopia. *J AAPOS*. 2004;8(5):429-34.
- Webber AL, Wood, J. Amblyopia: prevalence, natural history, functional effects and treatment. *Clin Exp Optom*. 2005;88(6):365-75.
- Polati U, Ma-Naim T, Spierer A. Treatment of children with amblyopia by perceptual learning. *Vision Res*. 2009;49(21):2500-603.
- Maconachie GD, Gottlob I. The challenges of amblyopia treatment. *Biomed J*. 2015;38(6):510-6.
- Cynader M. Prolonged sensitivity to monocular deprivation in dark-reared cats: effects of age and visual exposure. *Brain Res*. 1983;284(2-3):155-64.
- Timney B, Mitchell D, Giffin F. The development of vision in cats after extended periods of dark-rearing. *Exp Brain Res*. 1983;31(4):547-59.
- Smith EL 3rd, Harwerth R, Siderov J, Wingard M, Crawford ML, Von Noorden GK. Prior binocular dissociation reduces monocular form deprivation amblyopia in monkeys. *Invest Ophthalmol Vis Sci*. 1992;33(5):1804-10.
- Stewart CE, Moseley MJ, Stephens D, Fielder AR. Treatment dose-response in amblyopia therapy: the monitored occlusion treatment of amblyopia study. *Invest Ophthalmol Vis Sci*. 2004;45(9):3048-54.
- Scheiman MM, Hertle RW, Beck RW, Edwards AR, Birch E, Cotter SA, Crouch ER Jr, Cruz OA, Davitt BV, Donahue S, Holmes JM, Lyon DW, Repka MX, Sala NA, Silbert DI, Suh DW, Tamkins SM; Pediatric Eye Disease Investigator Group. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch Ophthalmol*. 2005;123(4):437-47.
- Calcutt C, Murray A. Untreated essential infantile esotropia: factors affecting the development of amblyopia. *Eye (Lond)*. 1998;12(Pt 12):167-72. Comment in: *Eye (Lond)*. 1998;12(Pt 2):165-6.
- Levi DM. Spatial vision in amblyopia. In: Regan D, editor. *Vision and visual dysfunction*. London: MacMillan; 1991. p.212-38.
- Hussain Z, Svensson C, Besle J, Webb B, Barrett B, McGraw P. Estimation of cortical magnification from positional error in normally sighted and amblyopic subjects. *J Vis*. 2015;15(2):pii:25.
- Kiropes L, Kiper DC, O'Keefe LP, Cavanaugh JR, Movshon JA. Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *J Neurosci*. 1998;18(16):6411-24.
- Sincich LC, Jocson CM, Horton JC. Neuronal projections from V1 to V2 in amblyopia. *J Neurosci*. 2012;32(8):2648-56.

65. Sireteanu R, Tonhausen N, Mickli L, Zanella FE, Singer W. Cortical site of amblyopic deficit in strabismic and anisometropic subjects. *Invest Ophthalmol Vis Sci.* 1998;39:5909.
66. Levin N, Dumoulin SO, Winawer J, Dougherty RF, Wandell BA. Cortical maps and white matter tracts following long period of visual deprivation and retinal image restoration. *Neuron.* 2010;65(1):21-31.
67. Li X, Dumoulin SO, Mansouri B, Hess RF. The fidelity of the cortical retinotopic map in human amblyopia. *Eur J Neurosci.* 2007;25(5):1265-77.
68. Hubel DH, Wiesel TN, LeVay S. Plasticity of ocular dominance columns in monkey striate cortex. *Philos Trans R Soc Lond B Biol Sci.* 1977;278(961):377-409.
69. Headon MP, Sloper JJ, Hiorns RW, Powell TP. Effects of monocular closure at different ages on deprived and undeprived cells in the primate lateral geniculate nucleus. *Brain Res.* 1985;350(1-2):57-78.
70. Headon M, Sloper JJ, Hiorns RW, Powell TP. Sizes of neurons in the primate lateral geniculate nucleus during normal development. *Brain Res.* 1985;350(1-2):51-6.
71. O'Kusky J, Colonnier M. Postnatal changes in the number of neurons and synapses in the visual cortex (area 17) of the macaque monkey: a stereological analysis in normal and monocularly deprived animals. *J Comp Neurol.* 1982;210(3):291-306.
72. Davis AR, Sloper JJ, Neveu MM, Hogg CR, Morgan MJ, Holder GE. Differential changes of magnocellular and parvocellular visual function in early- and late-onset strabismic amblyopia. *Invest Ophthalmol Vis Sci.* 2006;47(11):4836-41.

## 40º Simpósio Internacional Moacyr Álvaro - SIMAsp

16 a 18 de fevereiro 2017

Macksoud Plaza Hotel

São Paulo - SP

### Informações:

Tel.: (11) 5084-4246 / 5081-7028

E-mail: [info@fernandapresteseventos.com.br](mailto:info@fernandapresteseventos.com.br)