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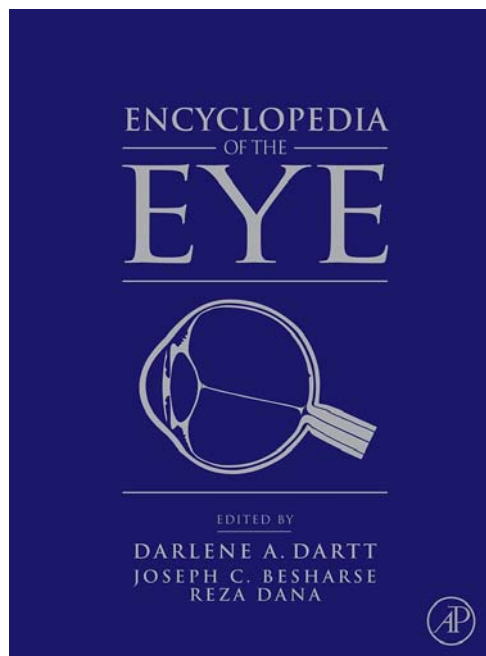
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## Amblyopia

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### Glossary

**Anisometropia** – A condition in which the two eyes have unequal refractive power so that the two eyes are in different states of myopia.

**Astigmatism** – An optical defect causing blurred images due to failure to focus a point object into a sharp image on the retina.

**Sensitive period** – An early developmental period that is particularly sensitive to development of amblyopia.

**Snellen acuity** – Clarity of vision as measured by eye care professionals using a chart called the Snellen chart.

**Strabismus** – Misregistration or misalignment of the images from the two eyes preventing the development of binocular vision.

### What Is Amblyopia?

Amblyopia (from the Greek, *amblyos* – blunt; *opia* – vision) is a developmental abnormality that results from physiological alterations in the visual cortex and impairs form vision. Amblyopia is clinically important because, aside from refractive error, it is the most frequent cause of vision loss in infants and young children, occurring naturally in about 2–4% of the population; and it is of basic interest because it reflects the neural impairment which can occur when normal visual development is disrupted. The damage produced by amblyopia is generally expressed in the clinical setting as a loss of visual acuity in an apparently healthy eye, despite appropriate optical correction; however, there is a great deal of evidence showing that amblyopia results in a broad range of neural, perceptual, and clinical abnormalities. Currently, there is no positive diagnostic test for amblyopia. Instead, amblyopia is diagnosed by exclusion: in patients with conditions such as strabismus and anisometropia, a diagnosis of amblyopia is made through the exclusion of uncorrected refractive error and underlying ocular pathology. Amblyopic patients (especially those with strabismic amblyopia) often exhibit crowding problems, meaning they have better visual acuity when letters are presented in isolation than when they are presented in a line or a full chart.

Clinically, crowding may be a useful sign to aid in the diagnosis of amblyopia.

### Amblyopia Is a Significant Public Health Problem

Amblyopia can easily be reversed or eliminated when diagnosed and treated early in life. Thus, there is a premium on early detection of amblyopia and its risk factors. It has been estimated that perhaps as many as three-quarters of a million preschoolers are at risk for amblyopia in the United States, and roughly half of those may not be detected before school age. Moreover, detection is likely to be more delayed in low socioeconomic areas. Improved vision screening and access to treatment could, in principle, eliminate amblyopia as a public health issue.

### Types of Amblyopia

Amblyopia comes in different sizes (degree of loss) and flavors (types). The presence of amblyopia is almost always associated with an early history of abnormal visual experience: binocular misregistration (i.e., strabismus – a turned eye), image degradation (high refractive error and astigmatism, anisometropia), or, less commonly, form deprivation (congenital cataract, ptosis). The severity of the amblyopia appears to be associated with the degree of imbalance between the two eyes (e.g., dense unilateral cataract results in severe loss), and to the age at which the amblyogenic factor occurred. Precisely how these factors interact is as yet unknown, but it is evident that different early visual experiences result in different functional losses in amblyopia, and a significant factor that distinguishes performance among amblyopes is the presence or absence of binocular function. Binocular function is much more likely to be damaged when amblyopia results from binocular misregistration (strabismus) than from image blur (anisometropia).

### The Site(s) of Amblyopia

A longstanding question is the site of damage in amblyopia. Current opinion places the earliest functional physiological abnormalities in cortical area V1. Exhaustive anatomical and physiological experiments failed to find retinal alterations in monkeys reared with experimentally induced amblyopia. These same animals had marked

abnormalities in V1. Moreover, although human electroretinogram (ERG) studies are equivocal, after optimizing optical focus, fixation alignment, and fixation stability, Robert Hess and colleagues found no pattern ERG deficit in deep amblyopes, in a spatial frequency range where there were obvious psychophysical deficits for the same stimuli. Although it is possible that retrograde degeneration may affect the lateral geniculate nucleus (where there is some shrinkage of the cells in the parvocellular layers) and retina, it seems unlikely that these effects contribute significantly to the behavioral losses. In contrast, amblyopia results in profound alterations in V1 both in cats and monkeys. In monkeys, visual deprivation (via lid suture) leads to a massive loss of neurons in V1 that can be driven by the deprived eye. Experimentally induced blur during development leads to a selective loss of V1 neurons tuned to high spatial frequencies and the spatial tuning of neurons may be markedly different when tested through the two eyes. Experimentally induced strabismus disrupts the binocular connections of cortical neurons. It is difficult to draw distinctions based on the type of rearing from the physiology, because the effects of abnormal visual experience are complicated by the onset, duration, and depth of deprivation; however, there is evidence that the physiological deficits in amblyopia do not fully explain the behavioral losses (in the same monkeys), suggesting that there may be deficits downstream from V1.

The most dramatic changes in V1 involve alterations in binocularity. Specifically, neurons that appeared to be monocular often demonstrate clear binocular interactions during dichoptic stimulation. In strabismic (prism-reared) monkeys, there is marked binocular suppression during dichoptic stimulation suggesting that inhibitory connections are less susceptible to the effects of strabismus than excitatory connections. Interestingly, even very brief periods (just 3 days) of prism-induced strabismus at the height of the critical period (4 weeks in monkeys, which translates to about 4 months in humans) increased the prevalence of V1 neurons that exhibited binocular suppression without altering their sensitivity to interocular spatial phase disparity. This result suggests that the earliest change in V1 is increased binocular suppression and, importantly, that the suppression originates at a site downstream from where information from the two eyes is first combined.

Very much less is known about the physiological effects of amblyopia on visual areas downstream from V1. Brain-imaging studies using positron emission tomography and functional magnetic resonance imaging show a clear deficit in V1, and several studies have also found deficits in other areas (e.g., V2). However, it is difficult to discern whether these downstream losses are simply a pass-through effect from V1 or whether the V1 losses are amplified downstream. However, several imaging and psychophysical

studies are consistent with the idea that the abnormalities in V1 are amplified in V2 and possibly beyond. These studies show losses in second-order detection global form and motion integration, symmetry detection, and counting.

### **Sensitive Periods for the Development of Amblyopia**

Clinicians are well aware that amblyopia does not develop after 6–8 years of age, suggesting that there is a sensitive period for the development of amblyopia; however, in humans with naturally occurring amblyopia, the age of onset of the amblyogenic condition(s) is difficult to ascertain, and the effects of intervention combine to make it difficult to obtain a clear picture of the natural history of amblyopia development. Thus, much of our current understanding of the development of amblyopia accrues from animal studies, and from retrospective studies of clinical records. Technological improvements in infant testing have also provided more direct data on the development of naturally occurring amblyopia in humans and monkeys. All of these studies provide strong evidence for amblyopia induced by early deprivation.

While the upper limit for susceptibility of binocular interactions (binocular summation and stereopsis) is not yet certain, it appears to be later than that for acuity or contrast sensitivity in monkeys, and may extend to at least 7 or 8 years (and possibly more) in humans. Psychophysical studies of interocular transfer in humans with a history of strabismus provide an indirect estimate of the period of susceptibility of binocular connections. The results of both studies suggest that binocular connections are highly vulnerable during the first 18 months of life, and remain susceptible to the effects of strabismus until at least age 7 years.

### **Traditional Treatment of Amblyopia**

For centuries, the primary treatment for amblyopia has consisted of patching or penalizing the fellow preferred eye, thus forcing the brain to use the weaker amblyopic eye. Typically, patients with mild to moderate amblyopia are prescribed complete occlusion for 2–6 waking hours per day, over several months to more than a year. Patients with moderate to severe amblyopia are often prescribed 6–10 h or more a day, and some clinicians recommend more aggressive full-time occlusion for severe amblyopia. As reported in a recent large-scale clinical study of children (3–8 years of age), the dose–response rate for occlusion is approximately 0.1 log unit (1 chart line) per 120 h of occlusion, and the treatment efficacy is 3–4 logMAR lines. The dose–response curve appears to plateau only after 100–400 h. The treatment outcome is dependent on

occlusion dose, the depth of amblyopia, binocular status, fixation pattern, the age at presentation, and patient compliance. Recent clinical studies suggest that atropine penalization may be just as effective as patching.

The notion that there is a sensitive period (or periods) for the development of amblyopia has often been taken to indicate that there is also a critical period for the treatment of amblyopia. This concept grew out of the work of Claude Worth in 1903. Worth suggested that the presence of a sensory obstacle (e.g., unilateral strabismus) arrested the development of visual acuity (amblyopia of arrest), so that the patient's acuity remained at the level achieved at the time of onset of strabismus. In this view, the depth of amblyopia is a direct function of the age of onset of the sensory obstacle. Worth further suggested that, if amblyopia of arrest were allowed to persist, amblyopia of extinction could occur as a result of binocular inhibition. In Worth's view, only this extra loss of sensory function (i.e., the amblyopia of extinction) could be recovered by treatment. Although this latter notion is open to question in the light of present knowledge, the ideas of Worth have had a powerful influence upon both clinicians and basic scientists. Many of our currently held concepts of amblyopia, such as plasticity, sensitive periods, and abnormal binocular interaction, were already described more than a century ago, and gained currency with the work of Hubel and Wiesel in 1970 and the many anatomical and physiological studies that followed. Consequently, while amblyopia can often be reversed when treated early, treatment is generally not undertaken in older children and adults. Below we consider both experimental and clinical evidence for plasticity in the adult visual system that calls into question the notion of a sensitive period for treatment.

### Clinical Studies

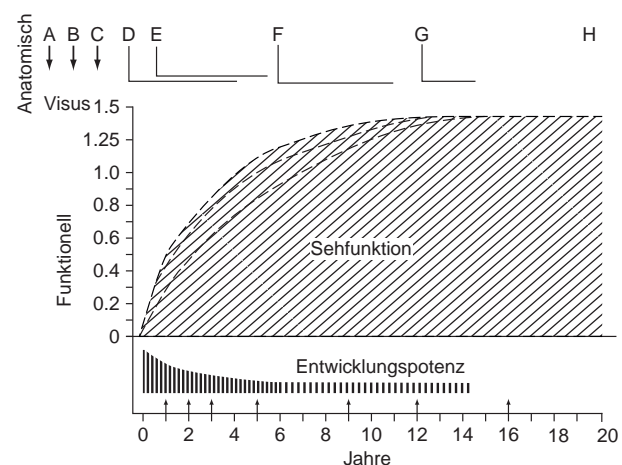
It is often stated that humans with amblyopia cannot be treated beyond a certain age; however, a review of the literature suggests otherwise. Recent clinical trials suggest that in children, 2 h of patching per day may be just as effective as 6 h per day. Moreover, treatment may be just as effective in older (13–17 years) patients who have not been previously treated as in younger (7–12 years) children.

Plasticity in adults with amblyopia is also dramatically evident in the report of amblyopic patients whose visual acuity spontaneously improved in the wake of visual loss due to macular degeneration in the fellow eye. There are also reports suggesting that some adult amblyopes recover vision in their amblyopic eye following loss of vision in their fellow (nonamblyopic) eye. These studies are consistent with the notion that the connections from the amblyopic eye may be suppressed rather than destroyed. Loss of the fellow eye would allow these existing connections to be unmasked, as occurs in adult cats with retinal lesions (Figure 1).

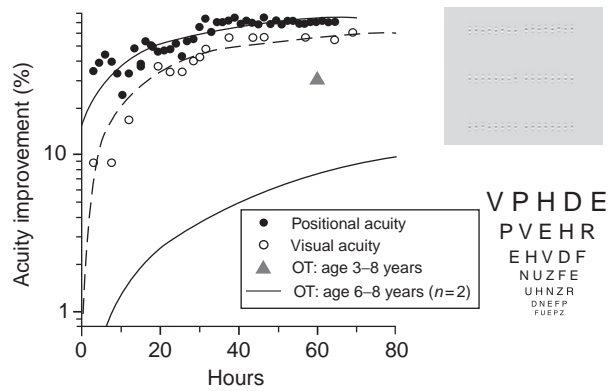
### Experimental Treatment of Amblyopia Beyond the Sensitive Period

Adults are capable of improving performance on sensory tasks through repeated practice or perceptual learning ('yes, you can teach old dogs new tricks!'), and this learning is considered to be a form of neural plasticity that also has consequences in the cortex. Specifically, in adults with normal vision, practice can improve performance on a variety of visual tasks, and this learning can be quite specific (to the trained task, orientation, eye, etc.). Interestingly, similar neural plasticity exists in the visual system of adults with naturally occurring amblyopia due to anisometropia and/or strabismus, suggesting that perceptual learning may be a useful approach for amblyopia treatment. Perceptual learning can improve visual functions in amblyopia on a wide range of tasks, including: Vernier acuity, positional acuity, contrast sensitivity, and letter identification. Practicing each of these tasks results in improved performance on the practiced task.

The specificity of perceptual learning noted above poses some interesting difficulties. If the improvement following practice was solely limited to the trained stimulus, condition and task, then the type of plasticity documented here would have very limited (if any) therapeutic value for amblyopia, since amblyopia is defined primarily on the basis of reduced Snellen acuity. Importantly, perceptual learning of many tasks (e.g., Vernier acuity, position discrimination, contrast sensitivity) appears to transfer, at least in part, to improvements in Snellen acuity, as does practicing contrast detection. In addition to visual acuity improvement, other degraded visual functions such as stereoacuity and visual counting improve as well.



**Figure 1** The postnatal development of visual function. Cartoon illustrating visual functions (*sehfunktion*) developing at somewhat different rates, while the developmental potential (*entwicklungspotenz*, in the lower panel) dissipates over the years (*Jahre*). Reproduced from Teller, D. Y. and Movshon, J. A. (1986) Visual Development. *Vision Research* 26: 1483–1506.



**Figure 2** Improvement in positional acuity (solid circles) and Snellen acuity (open circles) of a severe juvenile amblyope (observer AL, 8.8 years old, with unilateral strabismus). The triangle shows the improvement based on occlusion alone. The gray line shows the improvement based on occlusion alone (OT: occlusion therapy) in 2 amblyopes (aged 6–8) with acuities similar to that of AL. Replotted from Li et al., 2007; Stewart et al., 2004, 2005, 2007.

## Perceptual Learning as a Clinical Tool for Treating Amblyopia

Occlusion therapy is the gold standard method for treating amblyopia. In all previous perceptual learning studies, the subjects are occluded while performing the visual task, so it is reasonable to ask whether active perceptual learning actually provides an added benefit over occlusion alone. Recent work suggests that occlusion plus perceptual learning may be more effective than occlusion alone (Figure 2). Combining occlusion with perceptual learning may be a useful method for obtaining the optimal treatment outcome in the shortest possible time. Eliminating or reducing the need to wear an eye patch in public would eliminate, or at the very least reduce, the emotional stress that often accompanies occlusion therapy.

Over the centuries, there have been numerous attempts to increase the effectiveness of treatment. These attempts have a long and chequered history, ranging from the sublime to the ridiculous, and include: subcutaneous injection of strychnine, electrical stimulation of the retina and optic nerve, flashing lights, red filters and rotating gratings, administration of Levodopa/Carbidopa and shocks to the brain via transcranial magnetic stimulation. Few were subjected to rigorous scrutiny, and those that were often failed to stand up to it. Thus, any promising new method should be examined critically and there is a clear need for careful controlled studies.

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See also: Astigmatism; Binocular Vergence Eye Movements and the Near Response; Fundamentals of Stereopsis.

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