Critical Periods and Amblyopia

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During the past 20 years, basic science has shown that there are different critical periods for different visual functions during the development of the visual system. Visual functions processed at higher anatomical levels within the system have a later critical period than functions processed at lower levels. This general principle suggests that treatments for amblyopia should be followed in a logical sequence, with treatment for each visual function to be started before its critical period is over. However, critical periods for some visual functions, such as stereopsis, are not yet fully determined, and the optimal treatment is, therefore, unknown. This article summarizes the current extent of our knowledge and points to the gaps that need to be filled.

Amblyopia comes from the Greek word meaning dull sight or blunt sight. It results from a variety of sensory and motor abnormalities, which have multiple causes and multiple effects. The conditions leading to functional amblyopia are well known and include strabismus, anisometropia, astigmatism, myopia, cataract, and other forms of stimulus deprivation. In some of these conditions, amblyopia is not the only result. There may also be changes in binocular summation and suppression, some loss of binocular function, and loss of stereopsis. Amblyopia is not a simple phenomenon. As well as loss of Snellen and grating acuity, there may be loss of vernier acuity, loss of sensitivity to the contrast in a stimulus, distortions in the shape of a stimulus, some uncertainty about the position of a stimulus, motion deficits, and an increase in the magnitude of the crowding effect or separation difficulty. This review considers some generalizations about the development of these various phenomena, leading to some conclusions and also some unknowns about related treatments.

PERIODS OF DEVELOPMENT

There are 3 periods in the development of visual acuity and in the development of ocular dominance. Evidence about acuity comes primarily from studies with humans. During the first 3 to 5 years of life, acuity develops from less than 20/200 to near 20/20, as measured by tests that exclude any crowding effects. During these years, acuity can be reduced by the various forms of deprivation listed previously, leading to amblyopia. However, amblyopia is not confined to the first 3 to 5 years of life, but can result from strabismus or anisometropia at any age, from several months to 7 or 8 years of age. Recovery of acuity lost to amblyopia can occur in even older individuals. Eye care professionals have obtained positive results after sustained treatment of teenagers, and in a few cases adults who are affected by amblyopia. Thus, one can talk about 3 periods for acuity: the period of development of visual acuity (birth to 3-5 years of age), the period during which deprivation is effective in causing amblyopia (a few months to 7 or 8 years of age), and the period during which recovery from amblyopia can be obtained (time of deprivation to the teenaged years or even into the adult years). A similar distinction of pe-
periods is found in the study of ocular dominance in animals. The nerve fibers from the lateral geniculate, that terminate in layer IV of the visual cortex, segregate into left and right eye stripes between birth and 6 weeks of age in the macaque monkey, but this pattern of stripes can be altered by monocular deprivation until 10 weeks of age.

**CRITICAL PERIOD**

The term critical period became widely used in all visual system literature after Wiesel and Hubel presented their experiments on monocular deprivation. They talked about the critical period for changes in the ocular dominance of cells in the primary visual cortex of the cat, which occurs between eye opening and several months of age as a result of monocular deprivation. Thus, the critical period corresponds to the period during which deprivation is effective, rather than the initial period of development or the period during which recovery can be obtained. Generally speaking, the critical period starts some time after the onset of development of a visual property. For example, anisometropia does not have much effect on acuity unless it is persistent for 3 years; i.e., a short period of anisometropia after birth does not lead to acuity deficits.

The critical period depends on the anatomical level of the system being studied. The retina projects to the lateral geniculate nucleus, which projects on to the primary visual cortex, then other areas within the occipital cortex, and finally to the visual areas within the parietal and temporal cortex (Figure). Cells at higher levels of the system have a critical period that lasts for a longer time. For example, the ocular dominance of cells in layers II, III, V, and VI of the primary visual cortex can be changed by monocular deprivation after the ocular dominance of cells in layer IV has been established.

The critical period also depends on the visual function being studied. Many cells in the visual cortex respond to movement in a particular direction—a property known as direction selectivity. The direction selectivity of cells in the visual cortex can be changed by rearing an animal in an environment continually moving in 1 direction. However, the critical period for changes in direction selectivity ends earlier than the critical period for ocular dominance changes, according to studies of both properties in primary visual cortex. Many cells also respond to the orientation of a bar or edge of light, and it seems likely that the critical period for changes in orientation selectivity also ends earlier than the critical period for ocular dominance changes.

Furthermore, the critical period depends on the previous visual history of the animal. For example, rearing an animal in the dark postpones both the start and the end of the critical period for ocular dominance changes. Thus, one cannot talk simply about the critical period, rather, one has to talk about the critical period for a particular visual property in a particular part of the visual system in a particular species, after a specified form of visual deprivation in an animal with a specified visual history.
tivity ends earlier than the critical period for ocular dominance, since direction selectivity is determined largely in the input layer of primary visual cortex in the cat, while binocularity is more developed in the output layers.20 There are not many studies of critical periods for areas higher than primary visual cortex, but it is known that visual areas of temporal cortex in the macaque monkey have a critical period lasting longer than that in the primary visual cortex.27 Monocular deprivation affects a variety of visual functions with critical periods that end earlier for functions dealt with at lower levels of the system. As an example, monocular deprivation in the macaque monkey affects absolute sensitivity to light before 3 months of age, sensitivity to wavelength and increments of light before 6 months of age, sensitivity to contrast at high frequencies before 18 months of age, and binocular summation before 24 months of age.28

How does all this information affect clinical practice? It is easy to state the general principles, but not always easy to apply them, partly because of overriding clinical considerations, and partly because some of the basic science experiments required have not been performed. One general principle is that, if possible, visual functions with an early critical period should be treated before visual functions with a later critical period. As a practical consideration, many strabismologists believe that acuity in the amblyopic eye needs to be improved by patching or other means before the eyes are aligned, otherwise, the patient will not maintain straight eyes after they are aligned. After this treatment there are many other visual functions that can be treated by a variety of orthoptic techniques. These functions include single-letter acuity, contrast sensitivity, binocular function, depth perception, stereopsis, perception of location, vernier acuity, the crowding phenomenon (acuity for letters close to each other in a line), and so on. Information on how the critical periods for these various visual functions differ from each other is limited. There is some evidence that vernier acuity continues to develop after grating acuity reaches adult levels,20 and vernier acuity can be improved by the treatment of adults who are affected by amblyopia.30 There is also evidence that crowding effects continue to decrease after basic acuity has matured. In other words, Snellen acuity continues to improve after grating and single-letter acuity have matured.31 Thus, deficits in the crowding phenomenon, which affect reading, may remain after single-letter acuity has been corrected and the critical period for this is over. In any case, a good rehabilitative program should treat all of these visual properties in a logical sequence.

AMBLIOPIA AND STEREOPSIS

In the management of amblyopia, clinical intervention should take place as soon after the deficit that all visual functions that the physician and the patient want to treat can be treated. This point arises most clearly in relation to stereopsis. Stereopsis will never be obtained unless amblyopia is treated, the eyes are aligned, and binocular fusion and function are achieved before the critical period for stereopsis ends. Clinical data suggest that this occurs before 24 months of age.1,32,33 but we do not know exactly when it occurs, because crucial pieces of basic science information are missing.

We do know when stereopsis develops. Stereoscopic acuity reaches 60 minutes of arc between 2 and 5 months of age, then increases very rapidly over the next month.34 There is a slower increase between 6 months and 3 years of age.35,36 Going back to general principles, one would expect to be able to destroy stereopsis during a period lasting longer than the first 3 years of life, and to recover it during an even longer period. But, does the general principle arising out of data on acuity and ocular dominance also apply to stereopsis? Is stereopsis, because of its dependence on acuity and binocularity, different from these other functions? Hopefully, basic science experiments performed during the next few years will tell us the answers to these questions. Only then will the clinician have a better idea as to what degree stereopsis can be developed after surgery at various times between 4 and 24 months of age.

In the absence of definite information, the optimum forms of treatment have yet to be elucidated. Experience suggests that perfect stereopsis has never been achieved in cases of congenital or infantile esotropia.37 However, more aggressive practitioners claim that early intervention can produce improved results. In an extreme case of unilateral cataract, intervention on the day after birth, a thoughtfully designed long-term program of patching, produced in the patient at 8 years of age a visual acuity of 20/25 in the treated eye, and stereoaucuity of 50 seconds of arc.38 The philosophy that one should intervene around 4 months of age in congenital esotropia may have a good rationale, since this is the age at which stereopsis is developing rapidly. Two of 7 patients treated at this age had stereoaucuity better than 60 seconds of arc at 5 to 8 years of age.40 Maybe one could leave surgery until later than this, if the period of recovery from stereoscopic deficits was known to last longer than the period for the development of stereopsis.

Of all the evidence that has been produced during the last 40 years, there are still some important missing pieces of information. What are the critical periods for higher visual functions, and what is the critical period for stereopsis? More specifically, when the crowding phenomenon, a higher visual property, is degraded more than acuity, does this justify a different course of therapy?31 Does the critical period for stereopsis end concurrently with the period of development of stereopsis, or does it extend beyond? Perhaps scientists will produce evidence to suggest new sequences of therapy after surgery has been performed. Perhaps the results of scientists’ studies will also support the value of early and aggressive treatment of strabismus, just as scientific evidence now supports the early treatment of unilateral cataract,39,40 in cases that would have been regarded as intractable 20 or 30 years ago.

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