The Critical Period for Susceptibility of Human Stereopsis

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Purpose. To define the critical period for susceptibility of human stereopsis to an anomalous binocular visual experience.

Methods. Random dot stereocuity was measured in 152 children with a history of onset of either infantile or accommodative strabismus before 5 years of age. In each of these populations and in the combined population, the critical periods for susceptibility of stereopsis are described using four-parameter developmental weighting functions.

Results. In children with infantile strabismus, the critical period for susceptibility of stereopsis begins at 2.4 months and peaks at 4.3 months. In children with accommodative esotropia, the critical period for susceptibility of stereopsis begins at 10.8 months and peaks at 20 months. When the data are combined across the two populations, the critical period begins soon after birth and peaks sharply at 3.5 months but shows continued susceptibility to at least 4.6 years.

Conclusions. An anomalous binocular visual experience during early infancy severely disrupts stereopsis, yet the critical period for susceptibility of stereopsis extends through late infancy and early childhood and continues to at least 4.6 years of age.

Research over the past four decades supports separate and distinct critical periods for the development and susceptibility of binocular vision. The critical period for development of stereopsis in humans is well defined. After an abrupt onset at approximately 3 months of age,1–5 there is a rapid period of maturation until 8 to 18 months of age,6 followed by a continued gradual improvement until at least 3 years of age.7,8 Early physiological studies have investigated the critical period for susceptibility of the binocular visual system in cats and monkeys. Many of these studies have examined the period during which an anomalous binocular visual experience is effective in producing anatomic and electrophysiological changes in the underlying neurophysiological functional correlates. Classic monocular deprivation studies suggest that the critical period for susceptibility of stereopsis overlaps the critical period for development.9–11 Clinical studies in humans have also helped to define the critical period for susceptibility of stereopsis. Both retrospective medical chart reviews12–15 and prospective clinical studies16–19 of stereocuity outcomes after surgical eye realignment for infantile esotropia (ET) indicate that the critical period for susceptibility of stereopsis overlaps the critical period for development. Eye misalignment during infancy is associated with severe deficits in stereopsis, whereas eye misalignment after age 2 years typically is associated with better stereocuity outcomes.16–18 Yet, there is ample evidence that the critical period for susceptibility of stereopsis does not end during infancy, since there appears to be continued susceptibility of stereocuity up to at least age 5 years.20–23 In many children with late-onset accommodative ET, monofixation syndrome develops, causing deficiencies in both high-grade stereopsis and foveal fusion after as few as 3 months of constant eye misalignment after normal maturation of binocular vision.24 Twenty-eight years ago, Banks et al. (1975) reported intracocular transfer (IOT) of the tilt aftereffect in 24 patients with strabismus and provided the first evidence of a critical period for susceptibility of binocular vision in humans.24 There is no simple relationship between IOT and stereocuity. Although there is an overall tendency for less IOT when deficits in stereocuity are present, stereoblind subjects always show some IOT, and some patients with normal stereocuity show reduced or no IOT.25 Defining the critical period for susceptibility of human stereopsis is fundamental to understanding normal maturation and susceptibility of the maturing binocular visual system.

The purpose of the present study was to develop a quantitative model of the critical period for susceptibility of stereocuity by using data from a large clinical population with a diversity of stereocuity outcomes. The approach was to examine how the effect of an anomalous binocular visual experience on long-term stereocuity outcome varies as a function of onset and duration of constant eye misalignment. This approach to defining the critical period for susceptibility, of course, depends on the assumption that the underlying physiology for stereocuity was normal at birth and that the observed random dot stereocuity deficits resulted directly from an anomalous binocular visual experience. That this is a reasonable assumption is supported by the finding that the same percentage of infants with normal eye alignment1–5 and with infantile ET20,27 exhibit stereocuity near the age of onset of strabismus, with their angle of strabismus corrected with prisms. Furthermore, most patients with accommodative ET have an onset of strabismus after the peak of the critical period for development of stereocuity between 2 and 4 years of age.20

Methods

Participants

To ensure a diversity of age of onset and duration of anomalous binocular visual experience, participants included 152 consecutive children with infantile ET (n = 92) and accommodative ET (n = 60). Patients with these two diagnoses were included in the study because patients with a diversity of ages of onset of eye misalignment and eye realignment are necessary to probe sufficiently the critical periods for disruption of stereocuity. Participants received diagnoses from and were referred for sensory evaluation by local pediatric ophthalmologists and were enrolled in prospective clinical research studies with their parents’ written consent. At the time of testing, participants

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Research over the past four decades supports separate and distinct critical periods for the development and susceptibility of binocular vision. The critical period for development of stereopsis in humans is well defined. After an abrupt onset at approximately 3 months of age,1–5 there is a rapid period of maturation until 8 to 18 months of age,6 followed by a continued gradual improvement until at least 3 years of age.7,8 Early physiological studies have investigated the critical period for susceptibility of the binocular visual system in cats and monkeys. Many of these studies have examined the period during which an anomalous binocular visual experience is effective in producing anatomic and electrophysiological changes in the underlying neurophysiological functional correlates. Classic monocular deprivation studies suggest that the critical period for susceptibility of stereopsis overlaps the critical period for development.9–11 Clinical studies in humans have also helped to define the critical period for susceptibility of stereopsis. Both retrospective medical chart reviews12–15 and prospective clinical studies16–19 of stereocuity outcomes after surgical eye realignment for infantile esotropia (ET) indicate that the critical period for susceptibility of stereopsis overlaps the critical period for development. Eye misalignment during infancy is associated with severe deficits in stereopsis, whereas eye misalignment after age 2 years typically is associated with better stereocuity outcomes.16–18 Yet, there is ample evidence that the critical period for susceptibility of stereopsis does not end during infancy, since there appears to be continued susceptibility of stereocuity up to at least age 5 years.20–23 In many children with late-onset accommodative ET, monofixation syndrome develops, causing deficiencies in both high-grade stereopsis and foveal fusion after as few as 3 months of constant eye misalignment after normal maturation of binocular vision.24 Twenty-eight years ago, Banks et al. (1975) reported intracocular transfer (IOT) of the tilt aftereffect in 24 patients with strabismus and provided the first evidence of a critical period for susceptibility of binocular vision in humans.24 There is no simple relationship between IOT and stereocuity. Although there is an overall tendency for less IOT when deficits in stereocuity are present, stereoblind subjects always show some IOT, and some patients with normal stereocuity show reduced or no IOT.25 Defining the critical period for susceptibility of human stereopsis is fundamental to understanding normal maturation and susceptibility of the maturing binocular visual system.

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ranged in age from 3 to 13 years (mean, 4.75) and were orthotropic (<8 PD), with their best corrections at distance and at near. Age of onset and age at eye alignment ranged from 2 to 48 months and 6 to 72 months, respectively. Patients with infantile ET had eye muscle surgery, and patients with accommodative ET had either spectacle correction alone or a combination of spectacle correction and eye muscle surgery. Exclusion criteria included anisometropia ≥1.5 D, amblyopia ≥2 Snellen lines, and neurologic or other coexisting disease. Only patients who experienced a single period of constant eye misalignment and who experienced <24 months duration of eye misalignment participated. Children with solely intermittent ET were excluded, as it was not possible to define a period of abnormal binocular experience. The procedures of the experiment were approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and were performed according to the guidelines of the Declaration of Helsinki.

Measure of Stereopsis

Random dot stereacuity was measured in all participants with a battery of random dot stereacuity tests including the Randot Preschool Stereacuity test, the Randot (ver 2) Shapes Test, the Lang I, and the Randot Butterfly (Stereo Optical, Inc., Chicago, IL). When random dot stereacuity was not present, the Titmus Fly (Oculus, Wetzlar, Germany) was used to measure gross stereacuity. Because the Titmus and Randot circles tasks are frequently difficult to administer to young children and because they contain monocular cues that make the tests possible to pass to the initial two to four levels without stereacuity,29–33 they were not used to quantify stereoacuity. The Randot Preschool Stereacuity Test is a quick and simple-to-administer random dot test with a range of measurable disparities from 800 to 40 seconds of arc. Its unique test design incorporates a set of 11 shapes recognized by >95% of 3-year-old children, making this test easy to administer to young children.8 Its random dot shapes are also detectable only with the use of binocular form cues, eliminating the detection of monocular cue information.

Developmental Weighting Function

Age of onset of constant ET was calculated to the nearest month, according to the average of the parents’ and/or pediatricians’ reports of onset and the age at initial visit to the referring pediatric ophthalmologist, minus the average delay between referral and scheduling an office visit (2 weeks). Fewer than 6% of participants had an estimated onset age <2 months; in these cases an onset age of 2 months was assigned, to be consistent with the literature that strongly suggest that infantile strabismus is rarely present in the neonate.34,35 Age of onset of participants with infantile ET ranged between 2 and 48 months and 6 to 72 months, respectively. Patients with infantile ET had eye muscle surgery. Exclusion criteria included anisometropia ≥1.5 D, amblyopia ≥2 Snellen lines, and neurologic or other coexisting disease. Only patients who experienced a single period of constant eye misalignment and who experienced <24 months duration of eye misalignment participated. Children with solely intermittent ET were excluded, as it was not possible to define a period of abnormal binocular experience. The procedures of the experiment were approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and were performed according to the guidelines of the Declaration of Helsinki.

FIGURE 1. The four-parameter developmental weighting function.

For each participant, we calculated the NBE and then computed the correlation between NBE and stereoacuity in the entire cohort. For the purpose of deriving a developmental weighting function, all participants required an assigned number to represent their measurable stereoacuity. Patients with no measurable stereoacuity were assigned 6000 seconds of arc (3.8 log seconds of arc), because it is 1 octave above 3000 seconds of arc (3.5 log seconds of arc; the limit of measurable stereoacuity in this study). Choice of other default values for no measurable stereoacuity (ranging from 3,001 to 10,000 seconds of arc) made little difference in the shape of the best-fitting developmental weighting function.

The shape of the developmental weighting function was systematically varied with a computer program (MatLab; The Math Works, Natick, MA) to derive the best fit between the amount of NBE and the stereoacuity by determining the values for \( r_1 \), \( r_2 \), \( k \), and \( d \) that led to the highest correlation \( r \) between the NBE index and the stereoacuity outcome. The criterion for \( r \) was set at \( P < 0.001 \). The equation is not normalized, but when we plotted the curve, the best-fitting function was normalized relative to the peak. Parameters evaluated included the onset of the weighting function, the peak of the developmental weighting function, and the correlation between NBE and final stereoacuity.

After deriving the developmental weighting functions, we examined the relationship between stereoacuity outcome and NBE, by using the optimized parameters of the best-fitting developmental weighting functions by calculating the Spearman correlation coefficients \( r_s \) between the stereoacuity scores and NBE.

RESULTS

Infantile Esotropia

Age of onset of participants with infantile ET ranged between 2 and 6 months (median, 3.65). Age at eye realignment ranged between 3.5 and 22 months (median, 11). Random dot stereoacuity of patients with infantile ET ranged from between 40 seconds of arc and nil (median, nil). Of the 92 participants with infantile ET, 51 (55%) exhibited no measurable stereoacuity.

The range of parameters that meet the criterion \( P < 0.001 \) is \( r = 0.535–0.540 \); peak = 0.25–0.36; \( r_1 = 0.25–0.42 \); \( r_2 = 0.08–0.17 \); and \( d = 0.00–0.20 \). The best-fitting developmental weighting function derived from consideration of the group of patients with infantile ET only is shown in Figure 2. The onset and peak of the developmental weighting function are 0.20 years (2.4 months) and 0.36 years (4.3 months), respectively.

Stereocuity outcome and NBE among patients with infantile ET correlated significantly \( r_s = -0.509; P < 0.001 \). Generally, patients with a higher NBE had better stereocuity (Fig. 3).

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Accommodative Esotropia

Age of onset in participants with accommodative ET ranged between 4 and 58 months (median, 23.5). Age at eye realignment ranged between 7 and 78 months (median, 39.5). Random dot stereoacuity of patients with accommodative ET ranged between 40 seconds of arc and nil (median, nil). Of the 60 participants with accommodative ET, 31 (52%) exhibited no measurable stereopsis.

The range of parameters that met the criterion $P < 0.001$ is $r = 0.640 - 0.643$, peak $= 1.55 - 1.75$, $\tau_1 = 0.75 - 1.00$, $\tau_2 = 0.50 - 0.75$, and $d = 0.80 - 1.00$. The best-fitting developmental weighting function derived from consideration of the group of patients with accommodative ET only is shown in Figure 4. The onset and peak of the developmental weighting function are 0.90 years (10.8 months) and 1.67 years (20 months), respectively.

Stereoacuity outcome and NBE among patients with accommodative ET correlated significantly ($r_s = -0.781; P < 0.001$; Fig. 5).

Combined Patients

The range of parameters that met the criterion $P < 0.001$ is $r = 0.485 - 0.490$, peak $= 0.25 - 0.35$, $\tau_1 = 1.35 - 1.75$, $\tau_2 = 0.1$, and $d = 0.00 - 0.10$. The best-fitting function derived by combining the two populations is shown in Figure 6. The onset and peak of susceptibility in the combined group occurred at 0 years (0 months) and at 0.29 years (3.5 months), respectively. The range of onset and peak in the combined best-fitting function are virtually identical with the range of onset and peak in the best-fitting function from the patients with infantile ET. The end of the critical period for susceptibility of stereopsis is 4.6 years (55.2 months), based on 95% of the area under the developmental weighting function.

Stereoacuity outcome and NBE in the combined population correlated significantly ($r_s = -0.562; P < 0.001$; Fig. 7).

DISCUSSION

The parameters of the critical period for susceptibility of human binocular vision were first investigated in a classic modeling study by Banks et al. In a small cohort of patients with infantile and late-onset strabismus, the percentage of individual patients' IOT of the tilt aftereffect correlated with their estimated NBE. Similar to the present study, a four-parameter best-fitting developmental weighting function was used to determine the age of greatest susceptibility to anomalous binocular visual experience. The onset of the critical period for...
susceptibility of human binocular vision was between 3.6 and 6 months of age, and the peak was between 12 and 20.4 months.24 The findings of Banks et al., however, are limited by both the patient inclusion criteria and the measure of binocularity used in the study. Because patients with amblyopia and/or residual postoperative strabismus <10 PD were included, the period of anomalous binocular vision in some patients continued through to the test age. Apparent binocular sensory deficits by patients in Banks et al. may have been the result of manifest strabismus and/or monocular acuity deficits (amblyopia) at the time of testing, rather than the result of binocular sensory impairment. In the present study, patients with an acuity difference ≥2 lines or with residual strabismus ≥8 PD were excluded. This inclusion criterion was chosen because there is a body of evidence showing that it is sufficient to support stereopsis.36 Finally, although the extent of IOT of the tilt aftereffect correlates with stereoacuity in normal observers,37 stereoblind observers always show some IOT of the tilt aftereffect, and some patients with normal stereoacuity show reduced or absent IOT.25

In the present study, we defined the critical period for susceptibility of stereopsis separately for each of the patient groups, as well as for the combined groups. In patients with infantile ET, the critical period for susceptibility of stereopsis is defined as having an onset at 2.4 months of age and a peak at 4.3 months of age. The best-fitting function derived for this group demonstrates the importance of early detection and intervention. The high degree of susceptibility to abnormal binocular visual experience during early infancy suggests that early infancy represents an activity-dependent stage of binocular maturation. Because infantile ET interferes with binocular sensory maturation during this stage, it is likely that only prompt eye realignment can support the development of stereopsis.

We also defined the critical period for susceptibility of stereopsis in patients with accommodative ET, who in our study may have had an onset as early as 4 months or as late as 48 months of age. In this group of patients, the onset of the critical period for susceptibility of stereopsis began at 10.8 months and peaked at 20 months. Although the range of onset of anomalous binocular visual experience by patients with accommodative ET was broader and was frequently later than that by patients with infantile ET, an equivalent percentage of patients within the two groups had an absence of measurable stereopsis. Together with this observation, the peak of susceptibility at nearly 2 years of age in this population supports the need to treat binocular vision disorders aggressively, even when the onset occurs after stereoacuity maturation is nearly complete.

Combining all participants in this study into a single developmental weighting function derives a critical period for susceptibility of stereopsis representative of adverse binocular visual experiences that may occur anytime from birth through early childhood, with various durations, ages of onset, and ages at successful treatment. The combined data set derives a critical period for susceptibility of stereopsis as beginning at or soon after birth and peaking between 3 and 4 months of age, with continuing susceptibility through early childhood (i.e., the time course is similar to that of the critical period for development). For this combined data set of children who have an onset of binocular visual disruption before the age of 4 years, we offer a definition of the end of the critical period as 4.6 years, based on 95% of the area under the developmental weighting function.

The two best-fitting functions derived by the individual groups with distinct times of onset and eye realignment capture different parts of the critical period. The infantile ET (early-onset) group captures the peak and the onset of the critical period and the accommodative ET (late-onset) group captures the tail, or the end, of the critical period. The peak and the onset of the critical period for susceptibility of stereopsis are comparable between the best-fitting functions for the infantile ET group and the combined group. The ranges of the peak (0.25–0.36 and 0.25–0.35) and the ranges of the onset (0.00–0.20 and 0.00–0.10) of the critical period in these two groups are virtually identical. Similarly, the tail of the overall critical period is comparable to the tail of the best fit function for the accommodative ET (late onset) group. These observations suggest that neither best-fitting function alone sufficiently represents the critical period, by the very nature of the ages of onset and eye realignment of the patients included in each of the analyses alone. The infantile ET group was limited to patients with an early onset of eye misalignment (before 6 months of age). This group was also limited in the size of the critical period that can be explored, as correction of eye misalignment by 24 months of age limits the critical period to 2 years. Conversely, most patients with accommodative ET had a later onset (18–48 months of age).

In each of the patient groups and in the combined population, stereoacuity outcome correlated significantly with NBE. Children with higher NBE values (more NBE) had better stereoacuity. Previous studies indicate that stereoacuity outcome also depends on other factors that are not reflected by this

![Figure 6](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932931/ on 04/02/2017)

**Figure 6.** The developmental weighting function for all patients that yielded the highest correlation between stereoacuity and amount of NBE.

![Figure 7](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932931/ on 04/02/2017)

**Figure 7.** Scatterplot of stereoacuity as a function of NBE, for the combined group of 152 patients.
model, including the age of onset of abnormal binocular experience. The NBE model does not take into account the actual time point when NBE is interrupted.

Finally, it is important to acknowledge that binocular vision disturbances can have an onset after the end of the critical period as defined herein. Whether permanent binocular vision deficiencies can occur after this age may depend on the cause and duration of the binocular vision disruption. There is evidence to support continued susceptibility of stereopsis throughout life. Adults with strabismus acquired after the critical period for development may have a permanent deficiency of fine stereoacuity, despite successful surgical eye realignment, particularly when the treatment is delayed.46

References