



## **Sensitive Period for the Development of Human Binocular Vision**

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remove cellular debris, followed by ultracentrifugation at 105,000g.

Analysis of these supernatants by radioimmunoassay indicated that neither the malignant throat cells nor the malignant cervical epithelial cells in any hormonal milieu used were capable of detectable  $\alpha$ -LA synthesis. MCF-7 cells, however, synthesized readily measurable quantities of  $\alpha$ -LA. The amount of  $\alpha$ -LA synthesized by MCF-7 cells in insulin-containing media corresponded to 200 ng per milligram of soluble cell protein in  $20 \times 10^6$  cells. This quantity did not increase significantly when either cortisol or prolactin was added to the medium for periods up to 16 days (Table 1). The results of other experiments in which  $\alpha$ -LA synthesis was measured both as a function of prolactin concentration and duration of prolactin exposure also indicated no stimulation of  $\alpha$ -LA synthesis in the presence of prolactin. The fact that calf serum was used to supplement the growth media, which could contain sufficient endogenous prolactin to stimulate  $\alpha$ -LA synthesis, prevents rigorous exclusion of a prolactin effect. Experimentation in which prolactin was added to serum-free chemically defined medium (15) has not resulted in increased  $\alpha$ -LA synthesis.

The immunochemical data in our study provided further evidence that the MCF-7 cell line is mammary and epithelial and that the capacity to synthesize  $\alpha$ -LA was not lost as a function of malignant transformation. An alternative to that interpretation is that MCF-7 cells are not breast epithelial, but only acquired  $\alpha$ -LA synthesizing ability ectopically in culture. However, MCF-7 cells exhibit other markers of breast epithelium (12, 13) and the probability of coordinate synthesis of breast receptor proteins and  $\alpha$ -LA in non-breast cells is considered remote. Should  $\alpha$ -LA synthesis be present in a significant number of other cultured breast carcinomas, the assay would then serve as an additional marker to identify neoplastic cell lines of questionable phenotype as breast epithelium.

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Breast Cancer Detection Center of the Michigan Cancer Foundation, Detroit.

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## Sensitive Period for the Development of Human Binocular Vision

**Abstract.** *Twenty-four subjects with abnormal binocular experience, due to a condition of convergent strabismus that existed during different periods of their lives, were tested. Interocular transfer of the tilt-aftereffect was used to assess binocularity. Individuals between 1 and 3 years of age are most susceptible to abnormal binocular experience.*

The structure and function of the mammalian visual system are greatly affected by abnormal visual experience, provided that the abnormal experience occurs during a specific period of development. Several properties of visual cortical neurons are affected by abnormal experience during this critical or sensitive period (1, 2). Kittens deprived of visual input in one eye fail to develop a significant number of binocular cortical neurons if the monocular deprivation occurs during the period beginning at age 4 weeks and ending at age 12

weeks (2). Experimentally induced strabismus (misalignment of the visual axes) also results in a failure to develop cortical binocularity if the strabismus occurs during that 4- to 12-week period (3). Thus, adult cortical binocularity in the cat is dependent on concordant binocular visual experience during the sensitive period.

The development of the human visual system is also affected by early visual experience (4), but the period of greatest susceptibility to abnormal experience has not been determined. We have demonstrated the existence and estimated the time parameters of a sensitive period for the development of binocularity.

We tested 24 human subjects who have

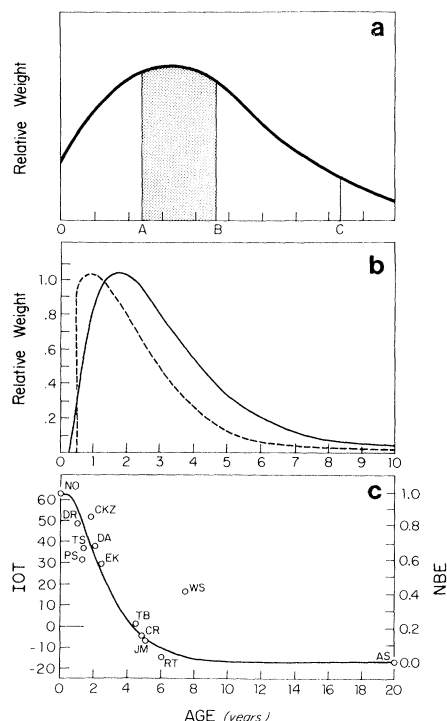


Fig. 1. (a) Method for describing the sensitive period for the development of binocularity. The curve represents one form of the arbitrary four-parameter function (10). For subjects with a history of esotropia, the area under the curve from the age of onset of esotropia (A) to the age at surgical correction (B) was subtracted from the area under the curve from birth 0 to the age at which we tested them (C). The resultant value for each subject is an estimate of the amount of normal binocular experience (NBE) which that subject encountered. (b) Developmental weighting functions which yielded the highest correlations between interocular transfer (IOT) and NBE. The solid line represents the best-fitting function for 12 congenital esotropes, and the broken line, that for 12 late-onset esotropes. These functions indicate the relative importance of abnormal binocular experience from birth to age 10. (c) Point plot of the IOT values as a function of the age at corrective surgery, for each of the 12 congenital esotropes. The solid line represents NBE for congenital esotropia [derived from the function in (b)] as a function of age at surgery (13).

had abnormal binocular experience due to a condition of convergent strabismus or esotropia during different periods of their lives. These subjects were selected from a population of 300 persons who have had corrective surgery for esotropia. Three normal subjects had never had strabismus.

Interocular transfer (IOT) of the tilt aftereffect was used to assess the binocularity of our subjects (5). This measure is highly correlated with stereopsis, a common clinical index of binocular function. Furthermore, persons with a history of esotropia exhibit poor stereopsis and low interocular transfer of the tilt aftereffect (6).

Our subjects were selected according to the following criteria: (i) concomitant esotropia during some period of life with no evidence of paralytic or accommodative components (7), (ii) preoperative esotropic deviation greater than 20 diopters (approximately 10°), (iii) postoperative deviation less than 10 diopters (approximately 5°), and corrected acuity better than 20/60 in the less acute eye, and (iv) a reasonably well-defined age at which the strabismic deviation began and a well-defined age at which it was surgically corrected. Table 1 shows the ages between which each subject exhibited esotropia.

The apparatus used to measure IOT

contained two fields, each 3° in diameter (8). The adapting field was a high-contrast square-wave grating (7.5 cycles per degree) rotated 10° clockwise from vertical. The test field was a lower-contrast grating of the same spatial frequency, which the subject could adjust in tilt by turning a dial. Two vertical reference lines, 5° to either side of the test field, were also provided. Polaroid filters controlled the eye to which the adapting and test gratings were presented.

Each subject initially adjusted the test grating from a random starting position to perceived vertical. The adapting grating was then presented to either the right or the left eye for 3 minutes. Subjects then made vertical adjustments of the test field, which was alternately presented to the adapted and to the unadapted eye (stable adaptation was maintained by intermittent presentations of the adapting grating). After a rest period, the other eye was adapted in the same manner, and the adapted and unadapted eyes were tested again.

The magnitude of the tilt aftereffect for each combination of adapting and test stimuli was obtained by subtracting the postadaptation mean of vertical adjustments from the mean of vertical adjustments made before adaptation. The

amount of IOT was the mean tilt aftereffect of the two interocular combinations divided by the mean aftereffect of the two same-eye combinations.

The subjects were divided into three groups: those with congenital esotropia (9), those with late-onset esotropia, and those who have never had strabismus (Table 1). To describe the sensitive period for the development of binocularity, we chose an arbitrary four-parameter function to represent the relative importance of different periods of development for the attainment of normal binocularity (10). This developmental weighting function is simply descriptive and is not based on any presumed physiological or psychological processes. It can take on various forms depending on the values of the four parameters. From the weighting function, estimates of the amount of normal binocular experience (NBE) were calculated for each subject (the estimates varied depending on the particular values of the four parameters) (10). These estimates were obtained by calculating the integral of the weighting function (Fig. 1a). The integral of the weighting function from the age of strabismus onset to the age of strabismus termination is represented by the shaded area. This integral was subtracted from the integral evaluated from birth to the age of testing. The resulting value is an estimate of the total NBE a given subject had encountered up to his age at testing. The shape of the weighting function was varied until the function yielding the NBE values most highly correlated with the observed IOT values was obtained.

Among the congenital esotropes, the onset of the weighting function occurs at 0.3 year and the peak at 1.7 years (Fig. 1b) (11). The Pearson correlation coefficient between the calculated NBE and observed IOT values is .92. For the late-onset esotropes, the function begins at 0.5 year and peaks at 1.0 year. The correlation between NBE and IOT is .62 ( $P < .01$ ) for this group. The two developmental weighting functions are similar in general form to a recent representation of the sensitive period for cortical binocularity in the cat (12), although the peak of susceptibility in the cat occurs at approximately 5 weeks of age.

Higher IOT values among the congenital esotropes are associated with early surgery (Fig. 1c). The predicted NBE function accurately describes the IOT data (13). This representation of the data shows that congenital esotropes who have had early corrective surgery tend to develop greater cortical binocularity than those who have had later surgery. This contradicts the suggestion that congenital

Table 1. Period of development during which each subject had esotropia, measured interocular transfer (IOT), and predicted normal binocular experience (NBE).

Subject	Age (years : months)			IOT	NBE
	Onset	Surgery	Testing		
<i>Congenital</i>					
DR	0:2	1:2	5:4	48	.74
PS	0:4	1:3	7:9	31	.82
TS	0:4	1:4	7:2	37	.79
CKZ	0:3	1:10	9:0	52	.68
DA	0:0	2:1	10:6	38	.63
EK	0:3	2:6	14:3	29	.53
TB	0:0	4:6	17:4	1	.20
CR	0:0	4:10	13:2	-5	.17
JM	0:0	5:2	15:2	-7	.14
RT	0:0	6:0	11:6	-16	.08
WS	0:0	7:6	14:8	16	.04
AS	0:0	19:10	33:0	-18	.00
<i>Late-onset</i>					
GMK	0:6	1:11	14:10	19	.50
JT	0:9	24:9	29:0	33	.09
GSK	1:0	2:4	14:10	27	.57
BK	1:0	4:5	15:6	2	.28
CKT	1:3	16:0	28:0	26	.28
DW	1:6	2:9	16:9	46	.66
PJ	2:6	4:6	10:6	33	.74
SJ	2:6	5:7	12:4	21	.69
KM	2:6	5:11	18:6	36	.68
MM	5:6	7:4	14:6	21	.97
SS	7:0	8:1	13:0	107	.99
CT	12:9	13:10	15:8	68	.99
<i>Normal</i>					
RA				64	1.00
LP				66	1.00
JS				60	1.00
Mean of normal subjects				63	1.00

esotropia is uncorrectable, at least in terms of the development of cortical binocularity (14).

Our primary conclusion is that the sensitive period for the development of binocularity begins several months after birth, and peaks between 1 and 3 years of age. In cases of congenital esotropia, early corrective surgery appears to be indicated for the development of cortical binocularity, which is presumably a prerequisite for fusion and stereopsis. Our data are consistent with several clinical reports that success in managing esotropia is more likely if surgery is performed early (15). In contrast, our findings suggest that immediate corrective surgery is not necessary to maintain cortical binocularity when the esotropia is of late onset (approximately 4 years and over).

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5. The tilt aftereffect may be defined in the following way. After prolonged adaptation to a high-contrast grating tilted slightly from vertical, a vertical test grating appears to be rotated slightly in the opposite direction. If the adapting grating is viewed with one eye and the test grating with the other, interocular transfer is defined as the amount of transfer of the aftereffect from the adapted eye to the unadapted eye.
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7. Concomitant esotropia refers to a convergent deviation that is essentially equal for all directions of gaze. Esotropia with an accommodative component is one in which the angle of deviation varies with the accommodative state of the crystalline lens.
8. The apparatus and procedure are described more fully in M. S. Banks, R. N. Aslin, R. D. Letson, in preparation.
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10. The function used to describe the relative importance of different periods for the development of binocularity was:

$$f(t) = e^{-(t-d)/\tau_1} - ke^{-(t-d)/\tau_2}$$

where  $t$  represents age, and  $\tau_1$ ,  $\tau_2$ ,  $k$ , and  $d$  are constants. The integral of this function is used to estimate the cumulative normal binocular experi-

ence encountered by a subject. For a subject with a history of esotropia from age  $A$  to age  $B$  the estimate of NBE is given by

$$\text{NBE} = \frac{\int_0^C [e^{-(t-d)/\tau_1} - ke^{-(t-d)/\tau_2}] dt}{\tau_1 - k\tau_2} \\ - \frac{\int_A^B [e^{-(t-d)/\tau_1} - ke^{-(t-d)/\tau_2}] dt}{\tau_1 - k\tau_2}$$

where  $A$  is the subject's age at the onset of esotropia;  $B$ , the age at the end of esotropia; and  $C$ , the age when we tested the subject. With a computer program, we systematically varied  $\tau_1$ ,  $\tau_2$ ,  $k$ , and  $d$  to find the values which yielded the highest correlation between NBE and interocular transfer. The optimum values were  $\tau_1 = 1.6$ ,  $\tau_2 = 1.2$ ,  $k = 1.0$ ,  $d = 0.3$  for the congenital esotropes.

11. It can be argued that the reported onset of esotropia is an inaccurate index of when the strabismic deviation first began, especially in view of the difficulty of reliably diagnosing esotropia during the first 6 months of life [F. D. Costenbader, *Trans. Am. Ophthalmol. Soc.* **59**, 397 (1961)]. To test whether such an inaccuracy affected our findings, we performed the data analysis with all onsets less than 6 months set to age zero. The resultant best-

fitting function was nearly identical to the function obtained when reported onsets were used. Thus, the use of reported onsets did not appear to lead to artifactual findings.

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13. The NBE values were obtained by setting age at testing to a large value and by setting age at strabismic onset to zero such that NBE is equal to

$$1 - \frac{\int_0^B [e^{-(t-d)/\tau_1} - ke^{-(t-d)/\tau_2}] dt}{\tau_1 - k\tau_2}$$

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## Apnea During Sleep in Infants: Possible Relationship with Sudden Infant Death Syndrome

**Abstract.** Several types of apnea are described in premature infants and in infants who have survived breathing-stoppage episodes which may be related to the sudden infant death syndrome. Upper airway apnea appears to induce the greatest changes: oxygen desaturation is more pronounced than in a central apnea of similar duration, and secondary cardiac changes are observed earlier and are more severe.

It has been hypothesized that sleep apnea is involved in certain cases of sudden infant death syndrome (SIDS) (1, 2). There is also evidence that premature infants with prolonged apneas and "near-miss" infants—infants that survived episodes of prolonged cessation of breathing like those leading to crib death—have a much higher risk of subsequently dying of SIDS (3). In order to better understand the relationship between apneic episodes and sleep and the possible involvement of the two in cases of SIDS, we conducted polygraphic recordings during sleep and wakefulness in a population at risk, that is, near-miss infants and premature infants who presented long apneic episodes after birth.

Fifteen premature infants were studied. Group A included 11 premature infants continuously recorded for 6 to 8 hours, at 3 to 9 weeks of age. All weighed less than 2000 g at the time of study (range, 1000 to 1900 g; mean, 1650 g). Group B included four premature infants continuously recorded for approximately 20 hours, at 6 to 14 weeks of age. These infants weighed between 2400 and 3500 g.

Eight full-term babies who had been taken to the emergency room or to their pediatricians for "stop-breathing" episodes were also studied. These episodes reportedly occurred during sleep and required stimulation to terminate; stimulation ranged from shaking to mouth-to-

mouth resuscitation. When found, the babies were described by the parents as cyanotic or white, unconscious, and not breathing. Complete pediatric examination failed to explain the sudden loss of consciousness during sleep in these infants. However, upper airway infections were present in five infants when hospitalized. A complete work-up, including cultures, was systematically performed to identify possible infections. All these infants were seen between October and March. Those in group C were three males (patients A to C), mean age 45 days, who were recorded for 6 to 8 hours. Infants in group D (patients D to H), mean age 108 days, were recorded continuously for a minimum of 18 hours. Several follow-up recordings were also made on near-miss infants. Three low-risk (control) infants were also monitored (group E).

The family histories of patients B and H indicated a similar problem in a sibling. Patient B's half-brother (same mother), who is now 6 years old and apparently healthy, was hospitalized for two stop-breathing episodes at 13 and 14 weeks of age. Patient H's brother was found dead during a daytime nap 3 days after developing symptoms suggestive of a mild upper respiratory infection. Final diagnosis in this case was SIDS.

Patients were studied during sleep and wakefulness. Electroencephalograms ( $C_3/A_2$ - $C_4/A_1$  and usually  $O_2/O_1$ ), elec-