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THE DEVELOPMENT OF SPATIAL RESOLUTION AND CONTRAST SENSITIVITY IN NATURALLY STRABISMIC MONKEYS*

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Summary—1. The development of spatial vision was studied in seven naturally strabismic monkeys. Six monkeys were esotropic; one was exotropic. Spatial resolution and contrast sensitivity were measured monocularly as a function of age.

2. The development of spatial vision was considerably slower in the naturally strabismic monkeys than in normal monkeys. Spatial resolution appeared to be normal near birth, but followed a developmental time course that included at least the first two postnatal years; in normal monkeys, this process is complete within the first year after birth.

3. Initially, resolution was similar for the two eyes in each animal. Thereafter, most animals developed interocular differences in spatial resolution and contrast sensitivity. In some cases these differences persisted throughout the period of study. In other cases, the deficits became smaller over time.

4. An analysis of the contrast data revealed that the functions from all monkeys were of similar shape regardless of the age or degree of amblyopia. The major feature of development in the second year was attributable to improvement of the nonpreferred eyes.

5. The form of the visual deficits found in the naturally strabismic monkeys resembled those seen in strabismic humans. These data lend further support to the suggestion that macaque monkeys provide a good model for visual function in human strabismus. The data also suggest that it may not be appropriate to equate the length of the "sensitive period" with the time period for normal visual development.

Key words—Visual development; strabismus; macaque monkey; acuity; contrast sensitivity.

INTRODUCTION

Strabismus is characterized by a misalignment of the visual axes of the eyes. This condition appears in a variety of forms, and occurs with a frequency of 2–5% in human infants and children (Fledelius, 1976; Simons and Reinecke, 1978). When strabismus has an onset during infancy and early childhood, it is often associated with the development of ambylopia. Amblyopia is commonly characterized by a deficit in visual resolution of the nonpreferred eye relative to the preferred eye, which is not due to any obvious organic cause and cannot be corrected optically.

The causes of strabismus are not well understood, in part because of the diverse nature of strabismus. The more common forms of strabismus, esotropia (inward deviation of the visual axes) and exotropia (outward deviation of the visual axes), can appear as either constant or intermittent deviations and can be paralytic or nonparalytic in nature (see von Noorden, 1980). Identified causes of strabismus range from accommodative and oculomotor disorders to sensory deprivation, such as that which results from the presence of cataracts. It is also generally believed that strabismus is familial, although the mechanism of heritability is unclear (Schlossman and Priestley, 1952; Mash *et al.*, 1975). This diversity makes the nature of strabismus difficult to characterize and study clinically.

There is very little information available on the development of visual function in strabismic infants or the influence of accompanying visual problems, such as high refractive errors, on this developmental process. A few studies of human infants with congenital or infantile esotropia (esotropia that has an onset during the first 6–12

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postnatal months) have been conducted. The results suggest that amblyopia can develop as early as 5–6 months of age (Thomas *et al.*, 1979; Jacobson *et al.*, 1981; Birch and Stager, 1985). However, the earlier postnatal months seem to constitute a period during which visual acuity appears to develop normally in spite of the presence of discordant input from the two eyes.

It is impossible to follow the natural course for the development of vision in strabismic human infants and children since some form of therapy is usually begun as soon as a visual deficit becomes apparent. An animal model would be extremely valuable in this regard; strabismic animals can be studied extensively without complications from intervention. In addition, the same animals can later be studied physiologically and anatomically so that the mechanisms underlying the development of visual deficits can be investigated. Several animal models of human strabismus have been studied previously (see Mitchell, 1988). The macaque monkey has been a particularly useful animal model for many human visual disorders (see Boothe *et al.*, 1985a; for review; Smith *et al.*, 1985; Kiorpes *et al.*, 1987).

Constant strabismus has been modelled previously in macaque monkeys by surgical creation of ocular deviations (von Noorden and Dowling, 1970; Kiorpes and Boothe, 1980; Harwerth *et al.*, 1983). This procedure usually results in a large-angle paralytic strabismus, which may not be especially representative of the human condition because nonparalytic, comitant strabismus is more common than paralytic strabismus in human infants (Jampolsky, 1978). Another procedure that has been used recently is injection of one of the horizontal rectus muscles with *Botulinum A* neurotoxin (Scott *et al.*, 1973), which causes a short-term paralysis but allows the eventual return of relatively normal ocular motility. Longitudinal studies of monkeys with experimental strabismus suggest that, like human infants, there is a period during the early postnatal weeks within which visual acuity appears to continue developing normally in spite of the presence of strabismus (Kiorpes and Boothe, 1980; Kiorpes *et al.*, 1984; Kiorpes *et al.*, 1989). However, 60–70% of those experimentally strabismic monkeys eventually developed amblyopia (Kiorpes *et al.*, 1985b; Kiorpes *et al.*, 1989).

The present report describes the results of a longitudinal study of the development of spatial vision in monkeys with a naturally occurring strabismus. Macaque monkeys naturally develop a variety of forms of strabismus, which are similar in nature to types of strabismus seen clinically (Kiorpes and Boothe, 1981a; Kiorpes *et al.*, 1985a). In the present study, contrast sensitivity and spatial resolution were assessed during development in seven naturally strabismic monkeys. Some of these animals demonstrated visual deficits that were characteristic of the type of strabismus present and accompanying ocular or refractive problems. Moreover, most of these monkeys showed a longer period of development than normal monkeys. In some cases, the extent of the visual deficits became smaller during the extended developmental period. Some of these data have been presented briefly elsewhere (Kiorpes and Boothe, 1981a,b; Kiorpes, 1982; Kiorpes *et al.*, 1985a).

METHODS

Subjects

Subjects in this study were seven pigtailed macaque monkeys (*Macaca nemestrina*) that were screened from the Washington Regional Primate Center breeding colony. These monkeys were selected for the presence of either a constant strabismus or strabismus with an accommodative component. The screening and evaluation procedures have been described in detail previously (Kiorpes *et al.*, 1985a). Most of the subjects were raised from infancy in the Infant Primate Research Laboratory at the University of Washington. Care of the animals conformed to the guidelines established by the Washington Regional Primate Center, in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Clinical methods

For each monkey, refractive error, angle of deviation and fixation pattern were evaluated soon after the strabismus was first noted. Clinical evaluations were performed by a pediatric ophthalmologist. Refractive errors were measured by retinoscopy with cycloplegia; cyclopegia was induced with a combination of 1% cyclopentolate and 10% phenylephrine. Except at the youngest ages, the animals were lightly sedated with ketamine hydrochloride for the period of the ophthalmic examination. Fundi were examined during the same sessions and were in each case found to be normal. The angle of deviation and pattern of fixation were evaluated from photographs of the corneal reflexes

Table 1. Summary of clinical data on the eight naturally strabismic monkeys. Tabulated for each subject are: the age that strabismus was first noted, refractive error as measured closest to the age that most of the behavioral data were collected (diopters), the type and extent (prism diopters) of the deviation (ET = esotropia, XT = exotropia, A = alternating, Int = intermittent)

Subject	Age noted (weeks)	Refractive error OD	Refractive error OS	Type and extent of deviation
T79139-KY	15	$+4.00+0.50\times 90$	$+5.00$S	25-30$^{\Delta}$ Int. RET
M79434-UN	5	$0.00+0.75\times 180$	$-0.25+0.50\times 180$	30-35$^{\Delta}$ AET
T81008-KF	12	$+4.00$S	$+4.25\times 0.50\times 80$	25-30$^{\Delta}$ Int. LET
T81345-VP	4	$+3.00+1.50\times 150$	$+2.00+1.00\times 30$	40-50$^{\Delta}$ AET
T82250-JF	1	$+1.00$S	$+1.25$S	15-20$^{\Delta}$ AXT
T82327-LM	12	$+4.00+1.00\times 90$	$+5.00+1.50\times 90$	40-50$^{\Delta}$ AET
F82366-MS	5	$+6.00$S	-1.00S	20-25$^{\Delta}$ LET, Cataracts

and from cover testing. All cover test sessions were video-taped for later confirmation of the observed fixation pattern. In some cases, the Krimsky prism reflex test or the prism-and-cover test were used to measure the angle of deviation. In these cases, comparison between the clinical measures of deviation angle and the photographic measures showed close agreement between methods. Refractive errors and other clinical data for all subjects are presented in Table 1; these data are those obtained nearest the beginning of behavioral testing. All of the naturally strabismic monkeys tested were esotropic except JF, who was exotropic. The characteristics of the strabismus shown by some of these monkeys were similar to common types of human strabismus. The esotropia demonstrated by UN and VP was similar to that of human infantile esotropes. The deviations were of a constant, large angle that was similar in all directions of gaze and developed during the early postnatal weeks. They held fixation well with either eye, but occasionally showed a preference for one eye or the other. VP showed a strong preference for the left eye, whereas UN showed no consistent eye preference. On the other hand, KY and KF exhibited a strabismus that was similar in nature to that of human accommodative esotropes. Their esotropia was of later onset (12–16 weeks), and the angle of deviation was greater for near fixation (0.5 m or less) than for distant fixation (1 m or more). They each showed a clear eye preference. Also, they showed a high degree of hyperopia throughout the period of the study. Although monkey LM also exhibited a high degree of hyperopia, she was not observed prior to 12 weeks of age when her strabismus was first noted. Therefore, the status of her eye alignment during the early postnatal weeks is unknown and the nature of her strabismus is difficult to establish. She could hold fixation with either eye and showed no clear eye preference. Finally, monkey MS had early diffuse occlusion which may have led to the development of his strabismus. He had bilateral anterior chamber hemorrhage that was noted near birth and cleared by 10 days postnatal; eye alignment was normal at that time. Intermittent strabismus was first noted at 5 weeks; it became constant by 12 weeks, at which time cataracts were noted. The lenses cleared by 14 months, at which time a substantial anisometropia was noted. Although both the hemorrhage and the cataracts were bilateral, the left eye was in each case more severely affected than the right eye. For additional information on these animals, see Kiorpes *et al.* (1985a) and Kiorpes and Boothe (1981a,b). (Monkeys KY and UN are referred to as KAY and ANU, respectively, in Kiorpes and Boothe, 1981.)

Psychophysical methods

Visual development was assessed in most of these monkeys starting near the time that they were first identified as strabismic. Testing was continued for as long as the animals were available, in some cases up to 3 years of age. Monocular spatial resolution and/or contrast sensitivity was measured as a function of age in each monkey. Two techniques were used to assess spatial vision: forced-choice preferential looking (Teller, 1979) and an operant two-alternative forced-choice discrimination task (Williams *et al.*, 1981). These techniques are described briefly below.

Grating acuity was assessed in monkeys younger than 20 weeks using the forced-choice preferential looking procedure. For this procedure, a human observer held the monkey in front of a grey screen containing two circular apertures; one aperture contained a high contrast square wave grating and the other contained a homogeneous field which was matched in space-average luminance to the grating and the screen. The holder observed the animal's face via a video camera and monitor (an earlier version of the apparatus provided a periscope for viewing). On the basis of the animal's looking behavior, the observer made a forced-choice judgement as to whether the grating stimulus was on the right or left side of the display on each trial. The observer was blind as to the position and identity of the grating stimulus, both of which were randomized from trial to trial. Feedback was provided as to whether each judgement was correct or wrong. The grey screen was viewed by the monkey from a distance of 36 cm. At this distance, each aperture subtended 14 deg of visual angle, with a center-to-center separation of 58 deg. The luminance of the display was 30 cd/m^2; testing was conducted in an otherwise darkened room. During testing, the monkey subject wore an adhesive eye patch over one eye and was wrapped snugly in a cloth diaper.

The method of constant stimuli was used to define resolution threshold. Four grating sizes (spatial frequencies) were chosen to span the performance range from chance to near perfection. Thirty trials were collected for each spatial frequency, presented in a randomized order. Threshold (acuity) was taken to be the spatial frequency at which the observer's performance was 75% correct. The threshold values and standard errors of estimate were obtained by probit analysis (Finney, 1971). Estimates of acuity for each eye at each age were obtained in counterbalanced order over a period of seven days or less.

Monkeys older than 20 weeks were trained to perform a spatial two-alternative forced-choice discrimination task. On each trial the monkey was required to discriminate a sinusoidal grating stimulus from a homogeneous field of equal space-average luminance. The monkey was trained to pull one of two grab bars to indicate which of two adjacent displays contained the grating stimulus. Correct responses were rewarded with apple juice; incorrect responses resulted in a short time out period that was signalled by a tone.

During the testing sessions the monkey roamed freely in a specially designed testing cage that had a mask, which was moulded to the shape of a monkey's face, mounted on one wall (Sackett *et al.*, 1971). To initiate a trial, the monkey placed its face in the mask; photocells imbedded in the mask sensed the presence of the face. This procedure served to control viewing distance without restraining the monkey. In addition, the mask restricted head position so that monocular testing could be achieved by blocking one eye's view of the displays. Correcting lenses were mounted in front of the test eye when necessary. Photographic measurements of pupil size during testing revealed that pupil size remained relatively constant at around 6 mm.

The animals were tested at viewing distances ranging from 0.5 to 1.2 m depending on their spatial resolution. The displays (Tektronix 602 CRT display units with P31 phosphor) had a space-average luminance of 27 cd/m^2 and were surrounded by electroluminescent panels of approximately matching mean luminance and color. The stimuli were generated using the method of Campbell and Green (1965). All aspects of stimulus presentation and data collection were controlled by a PDP11 computer. Further details of stimulus generation and calibration can be found in Williams *et al.* (1981).

In order to define the contrast sensitivity function, threshold percent contrast was measured for each of a number of spatial frequencies within the resolution limit of the monkey. For each spatial frequency, five contrast levels were chosen to span the range of the psychometric function. Generally, 40 trials were collected for each contrast condition, with the order of presentation of the various conditions randomized. Threshold contrast was again taken to be the 75% correct level. To define the contrast sensitivity function, the reciprocal of threshold contrast (contrast sensitivity) and the standard error of estimate at each spatial frequency are plotted as a function of spatial frequency on log–log coordinates. A double-exponential function, defined as follows, is fit to the data:

$$S = v(\omega f)^a e^{-b\omega f};$$

where S is contrast sensitivity and ω is spatial frequency. The four free parameters affect primarily the steepness of the low (a) and high frequency (b) portions of the curve, lateral shifts along the frequency axis (f), and vertical shifts along the sensitivity axis (v). This curve is similar to that suggested by Wilson (1978) for human adult CSF's. It was chosen because it produces reasonable fits to data collected from both normal and amblyopic monkeys (Williams *et al.*, 1981; Boothe *et al.*, 1982; 1988; Kiorpes *et al.*, 1987). The spatial frequency at the point

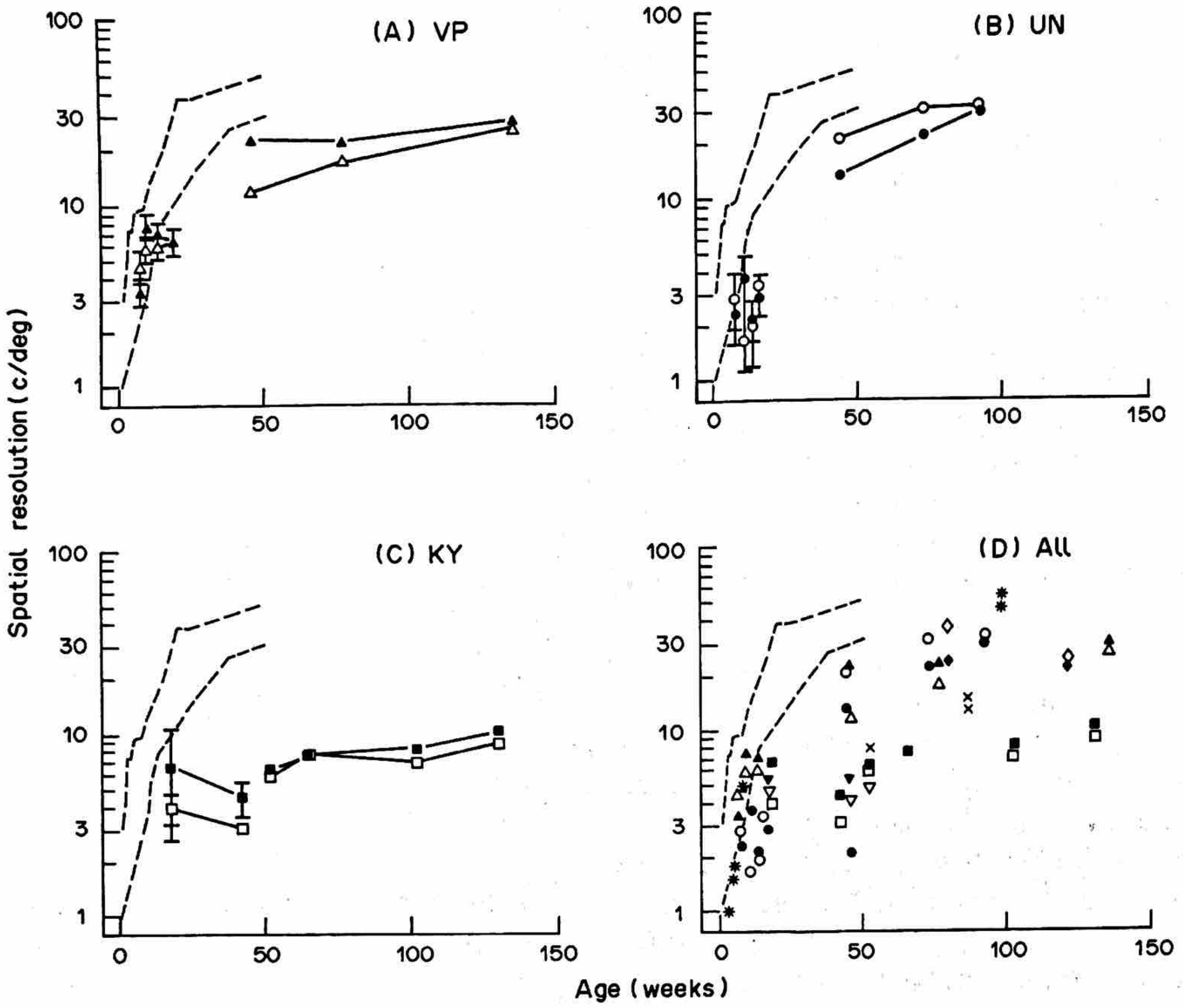

Fig. 1. The developmental time course for spatial resolution in naturally strabismic monkeys. Spatial resolution is plotted as a function of age in weeks for each eye of each monkey; open symbols represent right eye data and solid symbols represent left eye data. Developmental time courses are presented for three individual animals: VP (A), UN (B), and KY (C); data for all animals tested are plotted in D. Different symbols in D represent different animals and are consistent in subsequent figures. The dashed lines represent the range of visual resolution data obtained from 38 normal animals tested cross-sectionally in the same lab during the same time period. On the age axis, 0 weeks represents birth. Error bars around grating acuity estimates represent ± 1 SEM. Resolution estimates without error bars in A–C are extrapolated cutoffs of contrast sensitivity functions (see Methods). To get a sense of the average SEM for operant data from these monkeys, see Figs 2–7; the SEM is generally comparable to or slightly greater than the extent of the symbol. Error bars have been removed in D for clarity.

of maximum sensitivity for the fitted curve is taken to be the *peak frequency*; the contrast sensitivity at the peak frequency is taken to be *peak sensitivity*. Extrapolation of the curve to a sensitivity of 1 (contrast of 100%) yields an estimate of *spatial resolution*, which represents a measure of acuity.

RESULTS

Spatial resolution

The time course for the development of spatial vision in the naturally strabismic monkeys was in general slower than that for normal monkeys. This slowed development was evident in spatial resolution as well as in contrast sensitivity. Figure 1 (A, B, C) shows the developmental time course for grating acuity in three individual monkeys for which data were obtained over at least the first two postnatal years. In these plots, the open and filled symbols represent right and left eye data, respectively; the dashed lines delimit the range of grating acuity values for normal monkeys tested with the same apparatus. Figure 1A shows data for monkey VP, whose strabismus was apparent in the early postnatal weeks. At the earliest test ages, her grating acuity was within the range of normal monkeys, however, between 8 and 10 weeks development appeared to arrest temporarily so that no further improvement was seen between 10 and 15 weeks. In the 25 weeks between the last preferential looking test and the first operant test (break in curves), spatial resolution of both eyes improved. During this period, resolution improved to a greater degree for the left eye than for the right eye, resulting in a difference between the eyes of more than a factor of two. Over the course of the next two years, there was little further improvement in resolution of the left eye while the right eye's resolution improved by nearly a factor of two.

A similar pattern of development was shown by monkey UN (Fig. 1B). Although at the earliest test age (8 weeks) UN's resolution was close to the normal range, resolution appeared to remain at the 8 week level through at least 15 weeks. Between 15 and 44 weeks, spatial resolution improved for both eyes. However the extent of the increase in resolution was greater for the right eye than for the left eye. Over the course of the subsequent year, the development of spatial resolution continued for both eyes, although the extent of the improvement in resolution during this time period was greatest for the left eye. By 92 weeks, spatial resolution was similar for each eye. The data from these monkeys suggest that spatial resolution may be normal, or nearly so, during the early postnatal weeks in naturally strabismic monkeys but that at some point development slows overall. Thereafter, development seems to proceed at different rates for the two eyes. The most extreme case that exemplifies the slowed development is shown Fig. 1C. Monkey KY showed little development of spatial resolution over the entire 3 years that she was tested, hence, her visual performance never approached adult levels. Since she was tested for the first time at 18 weeks it is unknown whether or not her vision was normal near birth.

The overall time course for the development of spatial resolution in naturally strabismic monkeys is shown in Fig. 1D, where resolution data from all the naturally strabismic monkeys tested are plotted along with the range of spatial resolution values shown by normal monkeys. Individual animals are identified by the different symbols. It is clear that at the earliest test ages the resolution data from the naturally strabismic monkeys appear to be near the normal range, but beyond 10–15 postnatal weeks their spatial resolution is poor relative to normal. The development of spatial resolution then continues over at least the first *two* postnatal years in the naturally strabismic monkeys, whereas in normal monkeys, the development process is essentially complete by the end of the first postnatal year (Teller and Boothe, 1979; Boothe, 1981).

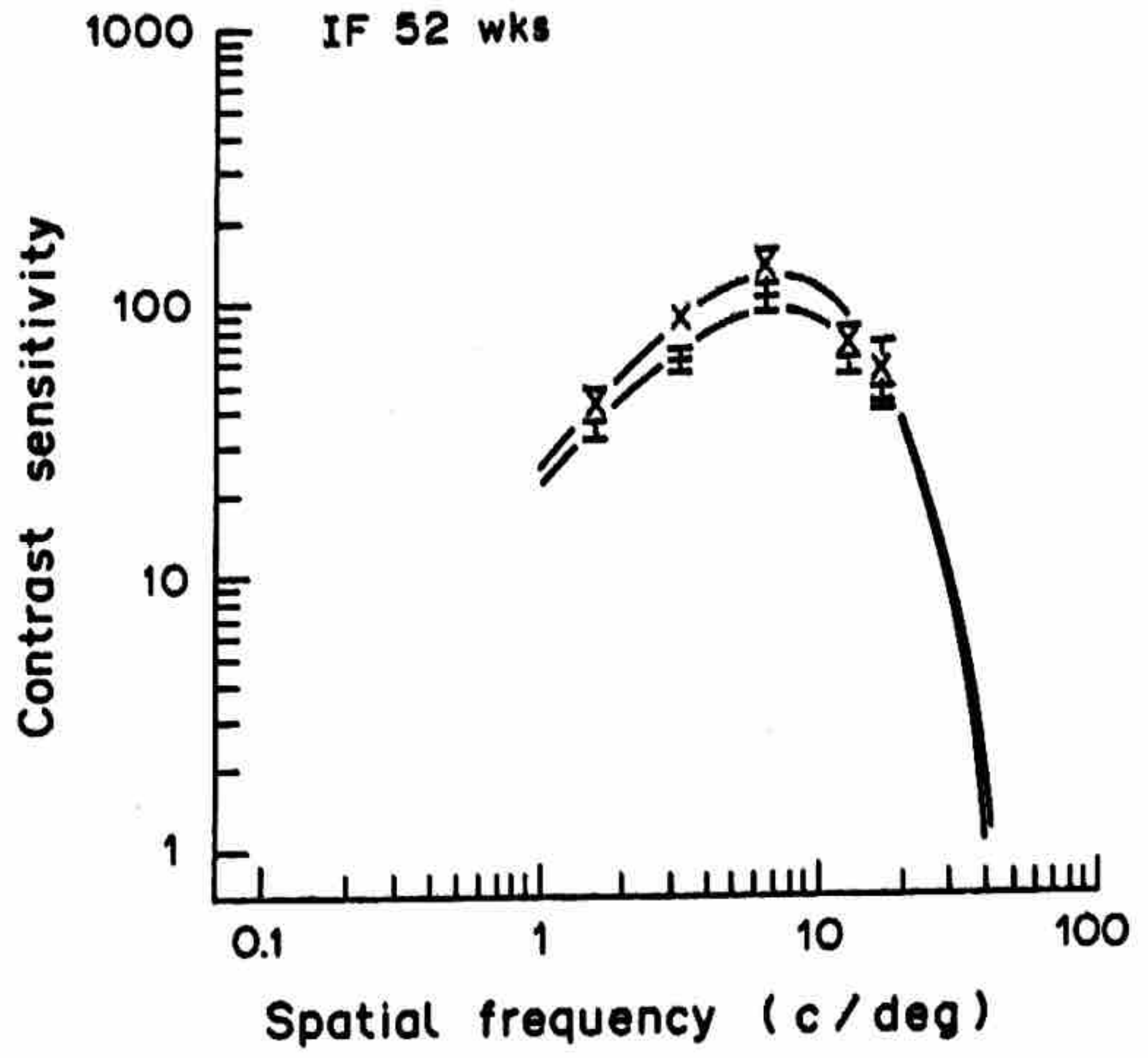

Fig. 2. Contrast sensitivity functions for each eye of a normal 1-year-old monkey. The ×'s represent right eye data and the +'s represent left eye data. The curves fits are generated by computer using the function described in the Methods section.

Contrast sensitivity

The spatial resolution measure corresponds to the upper spatial frequency limit for visual sensitivity, and as such describes only one point on the spatial contrast sensitivity function. In order to characterize spatial vision throughout the range of resolvable spatial frequencies, we measured contrast sensitivity at several spatial frequencies below the resolution limit for each eye of each monkey. Monocular contrast sensitivity data from a normal (nonstrabismic) monkey obtained near the age of one year are presented in Fig. 2. As is generally true for normal animals, this monkey has similar contrast sensitivity for each eye at all spatial frequencies tested. Peak spatial frequency and peak sensitivity of these functions are within the normal range for adult monkeys of this species (Williams *et al.*, 1981). The development period for contrast sensitivity and spatial resolution in normal monkeys has been demonstrated to extend over the first postnatal year, but is essentially complete by the end of the first year (Boothe *et al.*, 1988). Like spatial resolution, the time course for the development of contrast sensitivity in the naturally strabismic monkeys was delayed with respect to that of normal monkeys. The naturally strabismic monkeys showed continuing development of contrast sensitivity during the second postnatal year.

Monocular contrast sensitivity functions from three naturally strabismic monkeys are presented in Figs 3–5. For each monkey, data obtained for each eye at two or more ages are presented. The open and solid symbols in all

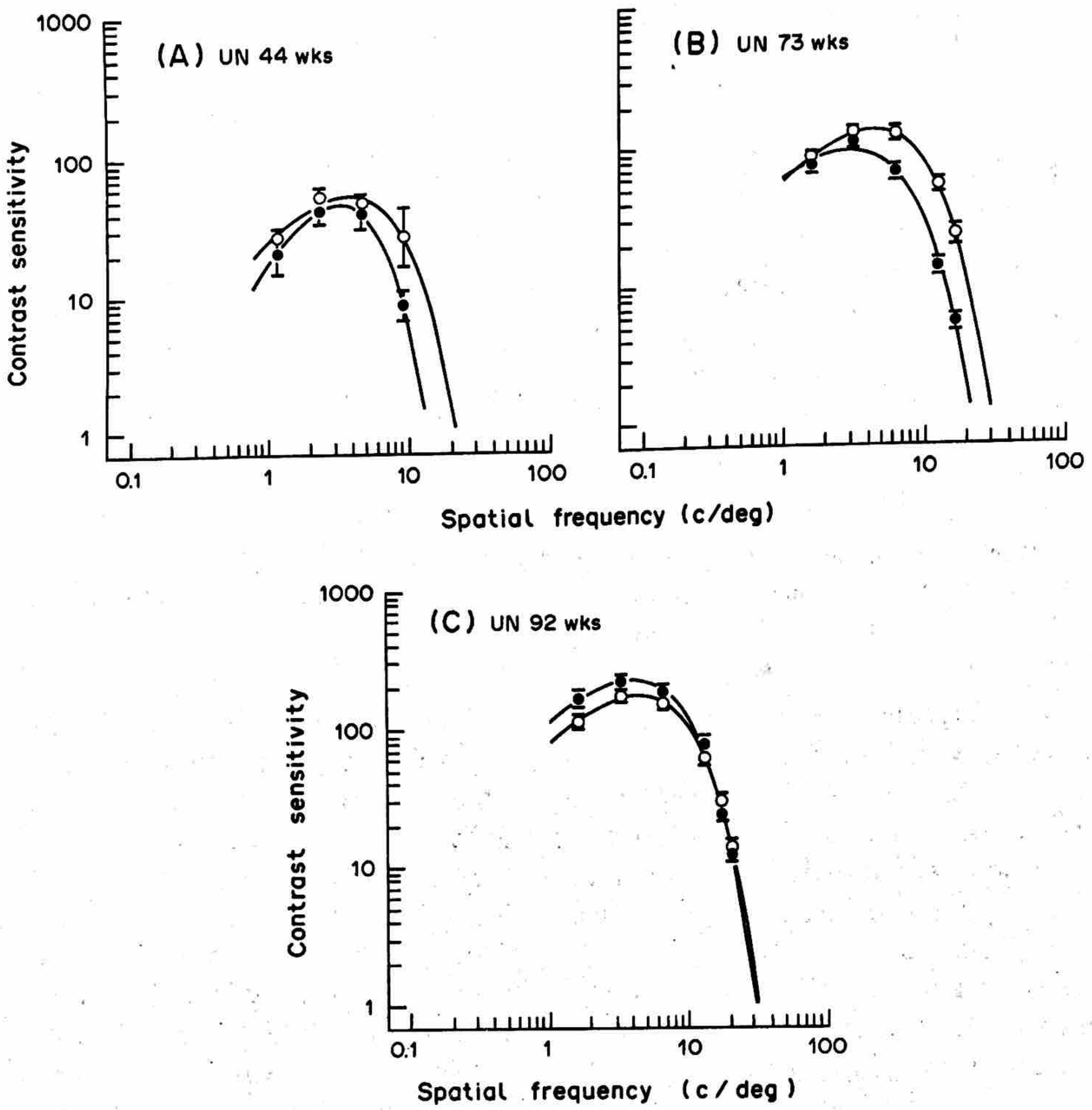

Fig. 3. Monocular contrast sensitivity data for monkey UN at one early (A), one middle (B) and one late (C) age. Open symbols represent right eye data; solid symbols represent left eye data. Error bars indicate ±1 SEM.

figures represent right and left eye data, respectively. The earliest contrast sensitivity data from these monkeys were obtained near the age of 1 year (Figs 3A, 4A and 5A). In this age range, four of the five naturally strabismic monkeys tested showed substantial differences in contrast sensitivity between the eyes. Two examples are shown: UN and VP (Figs 3A and 4A, respectively). In both of these cases, the interocular differences in contrast sensitivity were largest at

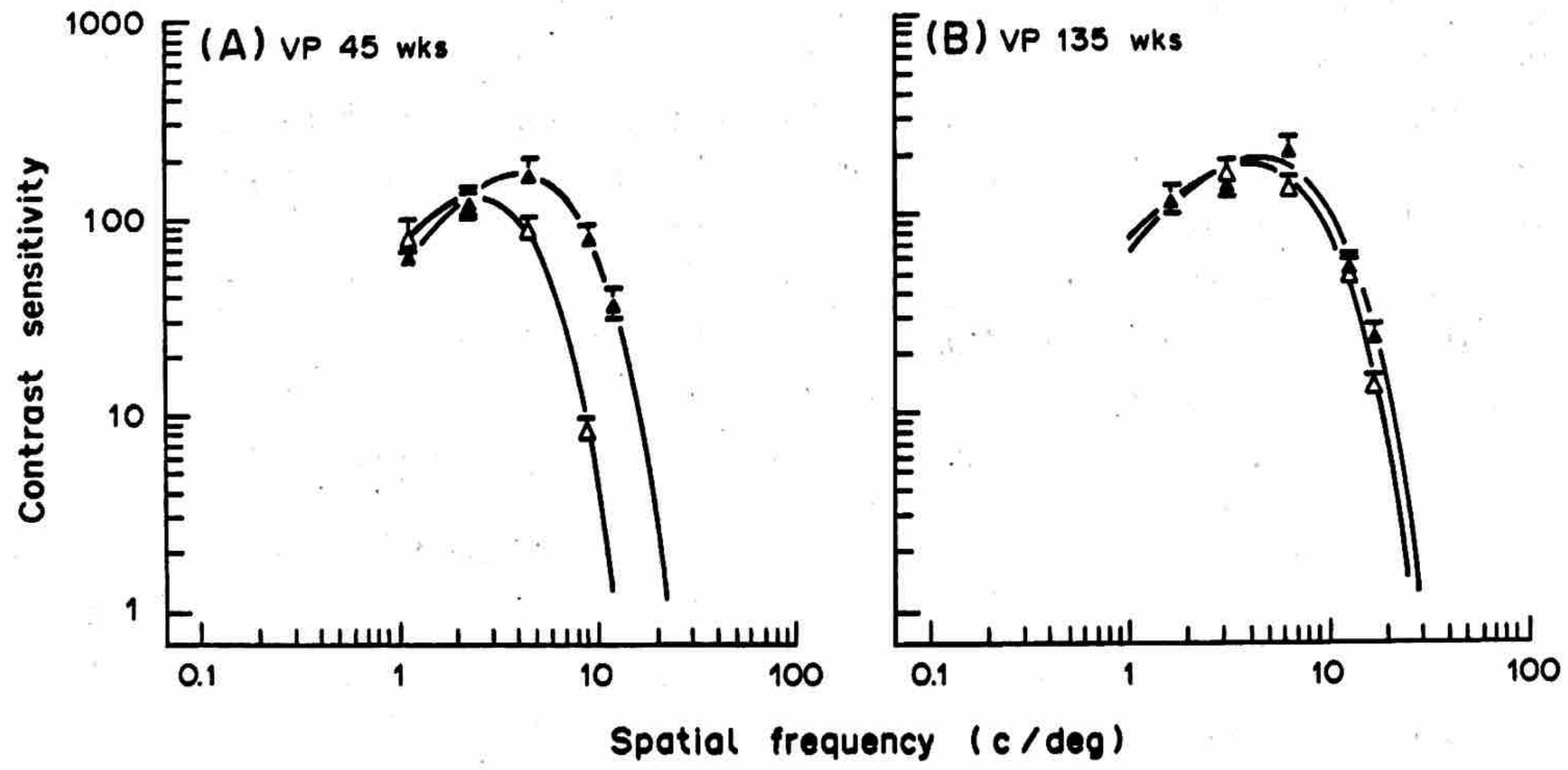

Fig. 4. Monocular contrast sensitivity data for monkey VP at one early (A) and one late (B) age. Symbols are the same as for Fig. 3.

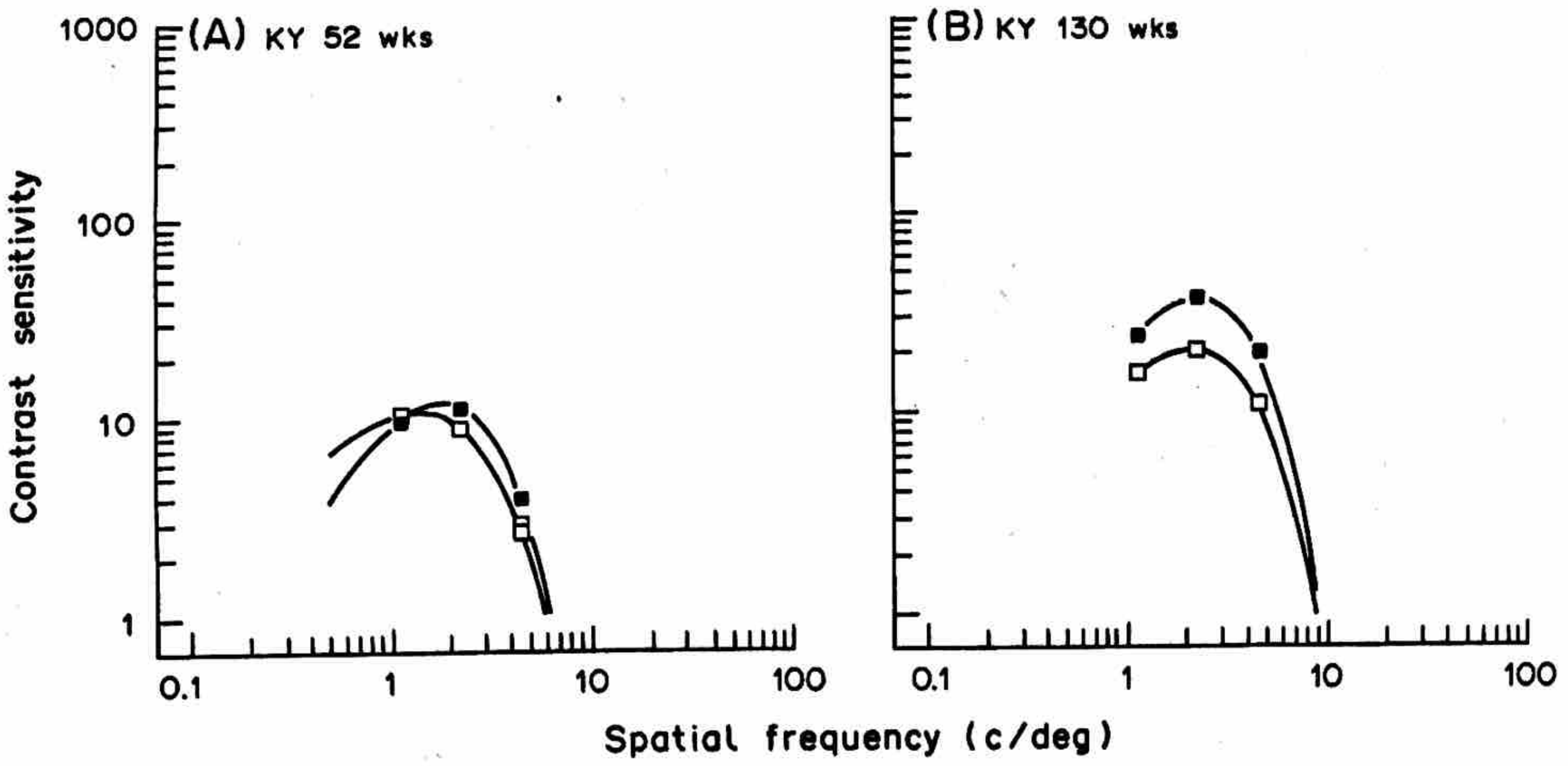

Fig. 5. Monocular contrast sensitivity data for monkey KY at one early (A) and one late (B) age. Symbols are the same as for Fig. 3. Note that the error bars for these data are equal to or smaller than the extent of the symbol, and are therefore obscured.

the highest spatial frequencies; the same pattern of contrast sensitivity loss was present in two other monkeys, LM and KF, when first tested. This pattern of interocular difference in contrast sensitivity is also characteristic of many human strabismic amblyopes (e.g. Hess and Howell, 1977; Levi and Harwerth, 1977).

The data shown in Fig. 5 are from the one monkey tested near 1 year of age who showed little contrast sensitivity difference between the eyes. There is some suggestion of superior sensitivity of the left eye at the highest frequency tested, although the difference in sensitivity is small. It is important to notice, though, that overall contrast sensitivity and spatial resolution were extremely poor relative to normal for *both* eyes of this monkey.

Contrast sensitivity functions obtained at older test ages from the three naturally stabismic monkeys described above are shown in Figs 3B and C, 4B and 5B. Each of these monkeys showed changes in contrast sensitivity for each eye relative to that seen at first test. UN (Fig. 3) showed the most dramatic changes of all the subjects. At 44 weeks, overall contrast sensitivity was low for both eyes relative to normal, and he showed a deficit in contrast sensitivity for the left eye relative to the right at the highest frequency tested. By 73 weeks, the sensitivity difference between the eyes was considerable for all frequencies above 3 c/deg. Thereafter, contrast sensitivity of both eyes improved, but the left eye improved to a greater extent than the right. By 92 weeks, contrast sensitivity was similar for the two eyes at all frequencies tested. The changes in relative sensitivity between the eyes were gradual over the intervening weeks.

The pattern of development shown by monkey VP (Fig. 4) is characteristic of most of the other subjects: the extent of the interocular difference in contrast sensitivity reduced over time but was still present at the oldest test age. She showed a large deficit in contrast sensitivity for her right eye at 45 weeks. At 135 weeks, the contrast sensitivity functions for the two eyes were more similar than at previous test ages, however there was still a deficit at highest frequencies. The improvement of the right eye relative to the left was in this case also a gradual rather than an abrupt change.

One of the naturally strabismic monkeys showed a pattern of development that was different from those described above. Monkey KY (Fig. 5) showed a small, gradual improvement in contrast sensitivity for both eyes during the course of the second postnatal year, however, the slight superiority of her left eye over her right eye became more pronounced over time. At 130 weeks, the sensitivity of the left eye was higher at all spatial frequencies tested (Fig. 5B). The abnormally low sensitivity for both eyes, that was evident at 52 weeks, was still apparent at 130 weeks.

Among the group of naturally strabismic monkeys tested, only one was exotropic—monkey JF. He showed no interocular difference in acuity or contrast sensitivity at any test age (see Fig. 1D, stars). Contrast sensitivity data obtained from JF at 2 years of age are shown in Fig. 6. The contrast sensitivity was similar for each eye at all frequencies tested.

The one monkey who had early diffuse binocular occlusion, MS, developed a substantial deficit in contrast sensitivity for the left eye. It

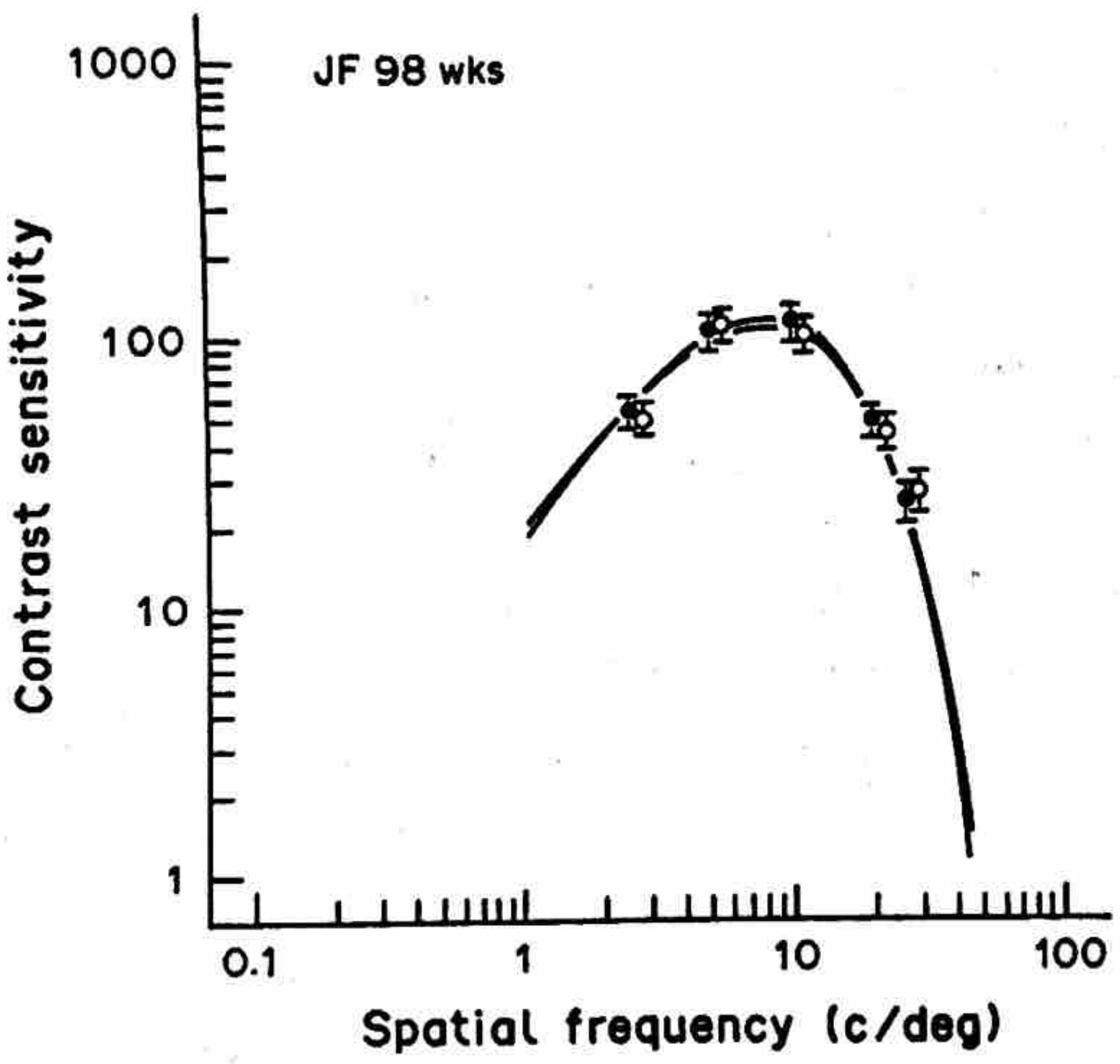

Fig. 6. Monocular contrast sensitivity data for exotropic monkey JF at 98 weeks. Open and filled circles represent right and left eye data, respectively; this animal's data are represented in other figures as stars. Right eye data are shifted slightly for clarity.

is interesting to note, though, that the left eye had a smaller refractive error than the right eye (see Table 1). It might be expected, based on the anisometropia, that the right eye would become amblyopic. Indeed, if the anisometropia was left uncorrected the contrast sensitivity data reflected the optical difference between the eyes (Fig. 7A). However, once the anisometropia was corrected it became clear that the visual deficit was not tied to the optical difference between the eyes. Figure 7B shows contrast sensitivity data collected with the optimal optical correction as measured behaviorally (Kiorpes and Boothe, 1984). The contrast sensitivity of the left eye was in fact considerably poorer than that of the right. It is likely that the visual deficit in this monkey was linked to the early diffuse occlusion and not to the refractive error. The left eye was more severely affected by the opacities than was the right eye (see Clinical Methods); it was also the deviating eye.

Optical correction was unnecessary in most of the other cases; the animals accommodated well to the visual displays without optical correction. This was demonstrated by testing contrast sensitivity for each eye at a single mid-range spatial frequency as a function of lens power (see Kiorpes and Boothe, 1984; Kiorpes *et al.*, 1987). Lens power was systematically varied over a 5–10 D range (in 0.5 D steps), which always included the best correction as determined by retinoscopy. The best correction determined in this way was generally close to but not identical to that suggested by retinoscopy with cycloplegia. The addition of correcting lenses improved contrast sensitivity only for MS and LM.

Analysis of CSF form

Clearly, there are dramatic changes in contrast sensitivity taking place during the second postnatal year in these monkeys. These changes are for the most part not simple improvements in overall sensitivity, that is, they are not simple upward shifts in the contrast sensitivity function. Instead, the changes seen in most monkeys include both upward and rightward shifts in the position of the contrast sensitivity function to

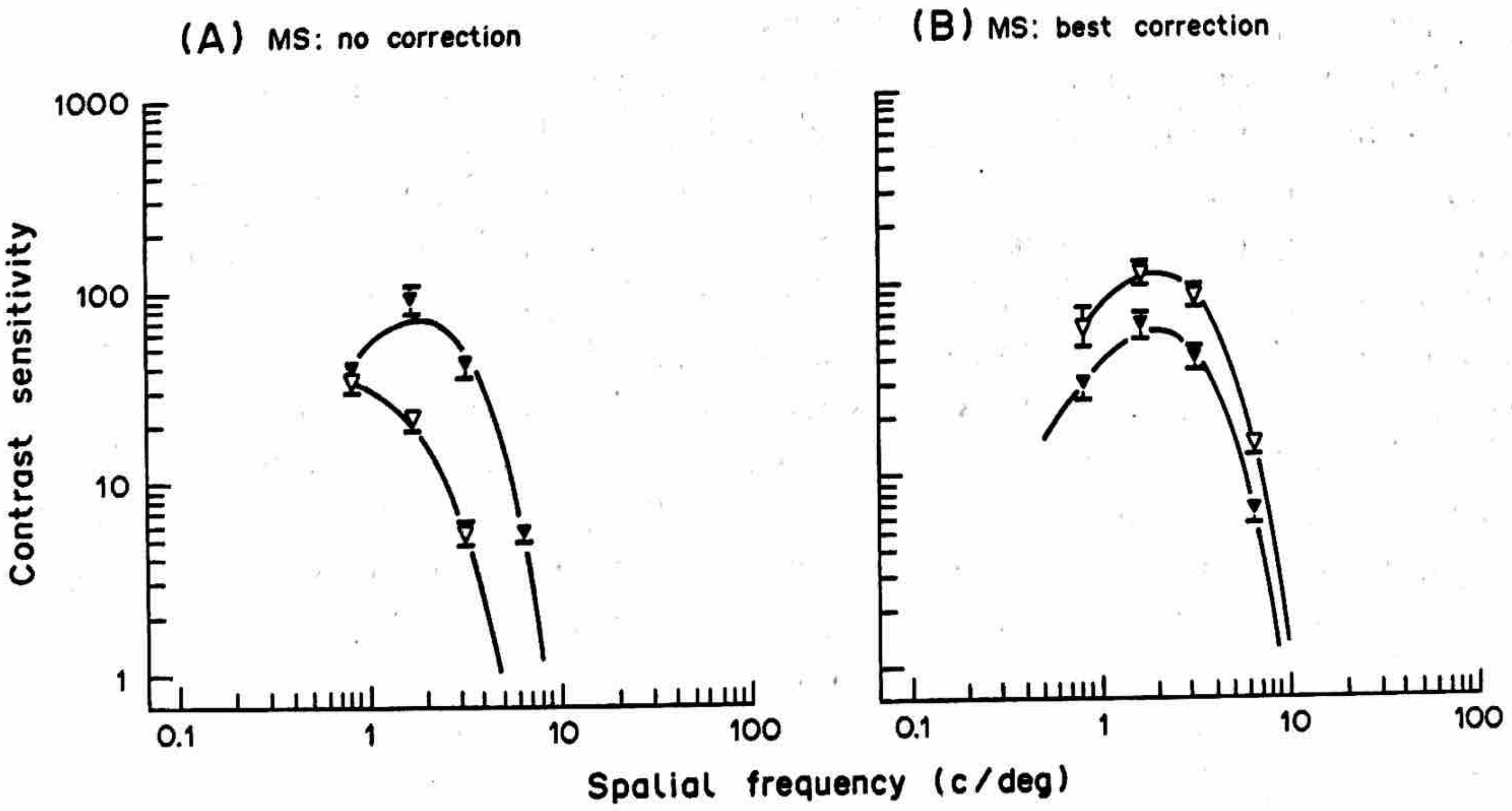

Fig. 7. Monocular contrast sensitivity data for monkey MS (A) without and (B) with optical correction. The lens values used for optical correction were +5.0 D for the right eye and −2.0 D for the left eye; the viewing distance was 60 cm. The data were collected between 52 and 64 weeks of age. Symbols are the same as for earlier figures. Note that the apparently reduced sensitivity of the left eye after correction is probably due to fluctuation in measured sensitivity at the peak spatial frequency (1.6 c/deg); sensitivity at higher frequencies are similar under both test conditions.

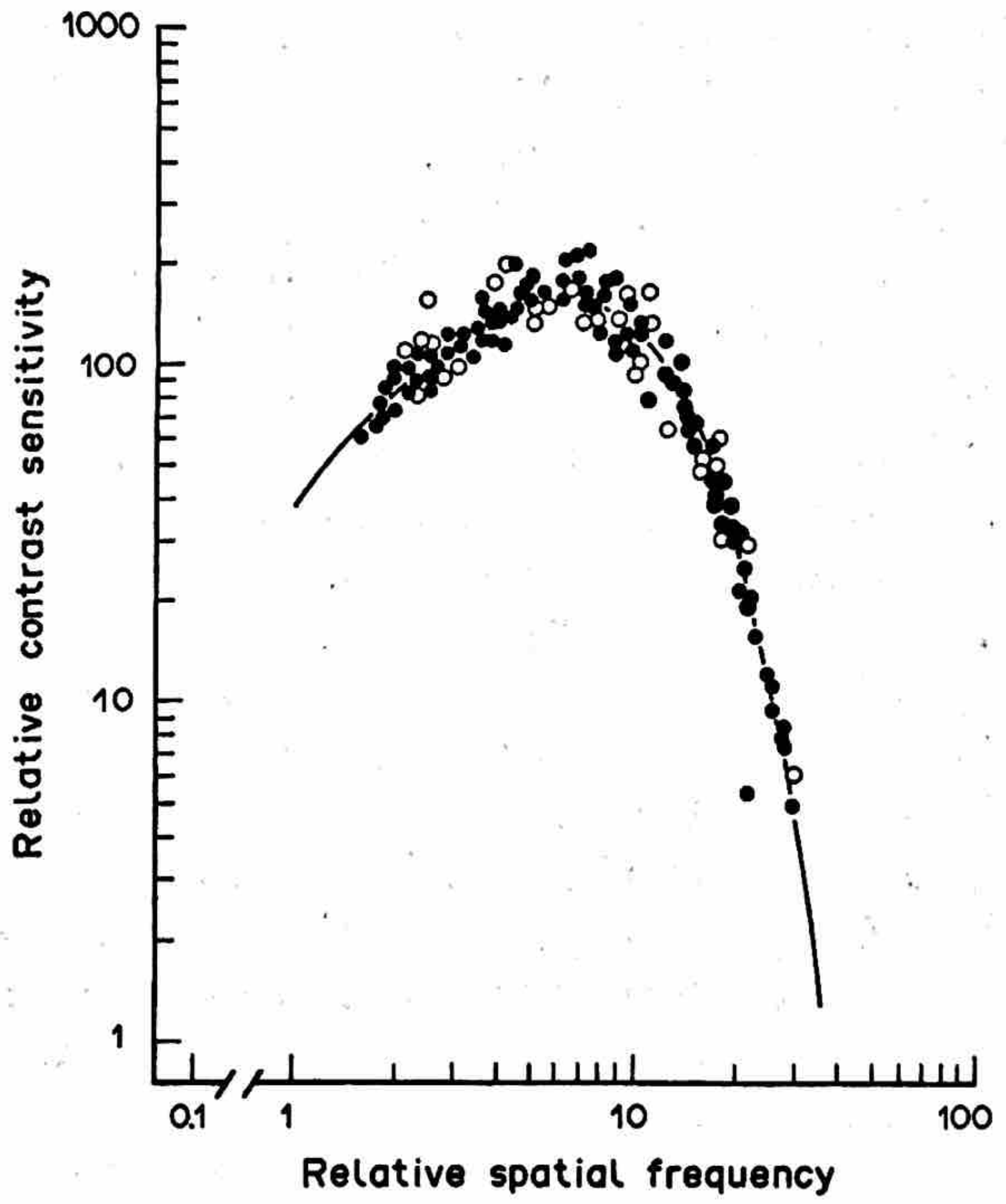

Fig. 8. The template contrast sensitivity curve for the naturally strabismic monkeys. The data from each monkey are plotted about the template curve. The curve was calculated using the same double-exponential function used for individual curve fits (see Methods); in this case the parameters for the curve fit were calculated based on all of the data from each eye of each monkey (except MS) at all ages. The data points from each individual data set and the template curve are normalized to a peak sensitivity of 150 and a peak spatial frequency of 6 c/deg.

higher levels of sensitivity and higher spatial frequencies. These shifts could be achieved by changes in the shape of the function or by changes in the position of a characteristic function that is not changing in shape. In order to clarify the nature of the changes in the contrast sensitivity function, an analysis of the shape of the contrast sensitivity function across monkeys and test ages was done.

The analysis involved calculating the parameters for a unified curve fit for all of the data from the naturally strabismic monkeys using the same double-exponential function as was used for the individual curve fits (see Methods; see also, Movshon and Kiorpes, 1988, for details). The computation optimized the shape parameters of a "template" contrast sensitivity function by shifting all the data sets into common register and estimating the curve shape that best fit the combined data. The resultant template curve is shown in Fig. 8, with all of the data plotted together (data from MS were omitted from the analysis because of his history of diffuse occlusion). Each data set is normalized to the peak of the template curve, which is arbitrarily placed at a spatial frequency of 6 c/deg and a sensitivity of 150. Since there are no systematic deviations of the data points from the template curve, the curve provides a reasonable representation of the *form* of the underlying function. This point is illustrated further in Fig. 9, where data from individual monkeys are plotted about the template curve. Figure 9A and B show the data each eye of monkey VP, across test ages, scattered about the template curve. Figure 9C and D are similar plots for monkey KY. Notice that the data conform well to the shape of the curve regardless of the presence of a deficit in contrast sensitivity (VP, right eye, Fig. 9B; also, refer to Fig. 4) or the overall poor sensitivity of both eyes of monkey KY (Fig. 9C and D; also, refer to Fig. 5).

On the basis of the above analysis, it can be asserted that the shape of the underlying function is the same across this population of monkeys, regardless of age or visual deficit. The change in the position of this curve as a function of age can then be defined for individual monkeys by plotting the change in the location of the peak. Figure 10 shows the change in peak contrast sensitivity (vertical position; top panel) and peak spatial frequency (horizontal position; bottom panel) for each monkey (solid symbols connected with solid lines). Data for the preferred and nonpreferred eyes are shown in Fig. 10A and B, respectively. For animals that did not show an obvious eye preference, the eye showing the best sensitivity at the beginning of behavioral testing was taken to be the preferred eye. Similar data for normal monkeys, obtained from a separate analysis using the same procedure as that described above, are delimited by the dashed lines in each panel of Fig. 10. The normative data on which the analysis was based are from Boothe *et al.* (1988).

The progession of the peak, in sensitivity and spatial frequency, with age for the preferred eyes of the naturally strabismic monkeys can be seen by following the pattern for each symbol in Fig. 10A (symbols for individual animals are consistent with those in previous figures). The figure shows that the position of the peak for the preferred eyes changes to some degree during the second postnatal year. Most animals showed small gradual changes; one, UN (circles), showed relatively large changes. Although there is little overlap in the range of test ages for the normal monkeys and the naturally strabismic monkeys, where they do overlap the preferred eyes of the strabismic animals are usually lower

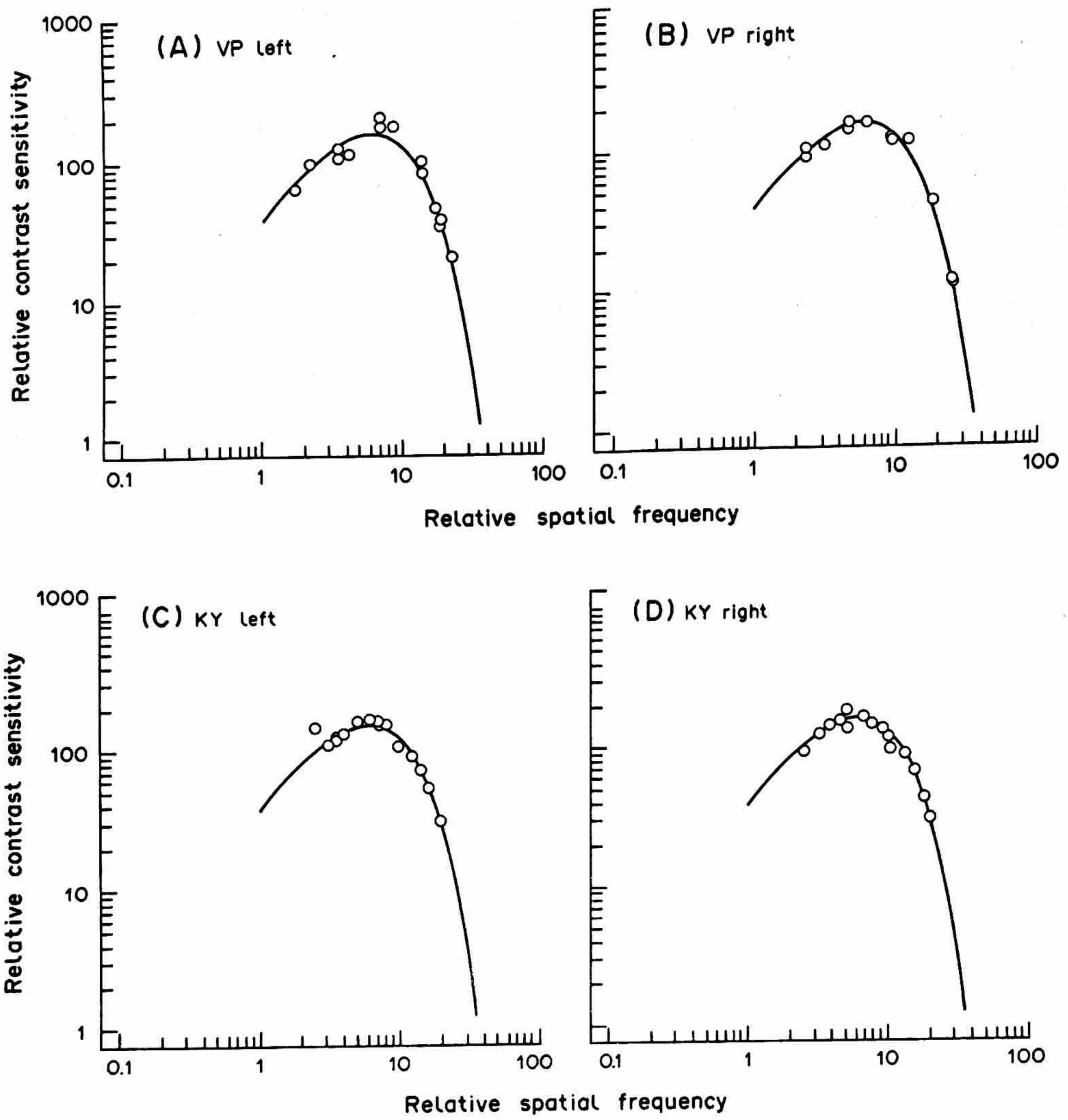

Fig. 9. The template curve is shown with all data from each eye of two individual monkeys, VP (A,B) and KY (C,D). The figure shows that the template curve provided a good representation of the form of the common underlying function in spite of large individual differences in sensitivity and resolution.

in peak sensitivity and spatial frequency than the normal animals. However, some of the strabismic animals eventually reached normal levels of peak sensitivity and spatial frequency. It is worth noting that the position of the peak had stabilized by 40–50 weeks in the population of normal monkeys. Figure 10B shows the progression of the peak with age for the nonpreferred eyes of the naturally strabismic monkeys. There is a greater amount of change in the position of the peak for the nonpreferred eyes than for either the preferred eyes of the strabismic monkeys or eyes of normal monkeys beyond 30 weeks of age. Overall, the comparison shows that the developmental time courses are different for the preferred and nonpreferred eyes, and that the peak is lower in both spatial frequency and contrast sensitivity for the nonpreferred eyes than for the preferred eyes.

DISCUSSION

The purpose of this study was to document the natural course for the development of spatial vision in naturally strabismic monkeys. The results show that the time course for visual development in the naturally strabismic monkeys is at least twice as long as that for normal monkeys. The naturally strabismic monkeys showed substantial changes in spatial resolution and contrast sensitivity throughout the first two postnatal years, whereas the development of these visual functions is essentially complete by the end of the first year in normal monkeys. Monocular assessment of spatial vision in the naturally strabismic monkeys also revealed that interocular differences in resolution and contrast sensitivity appeared with some delay after the strabismus was first noted.

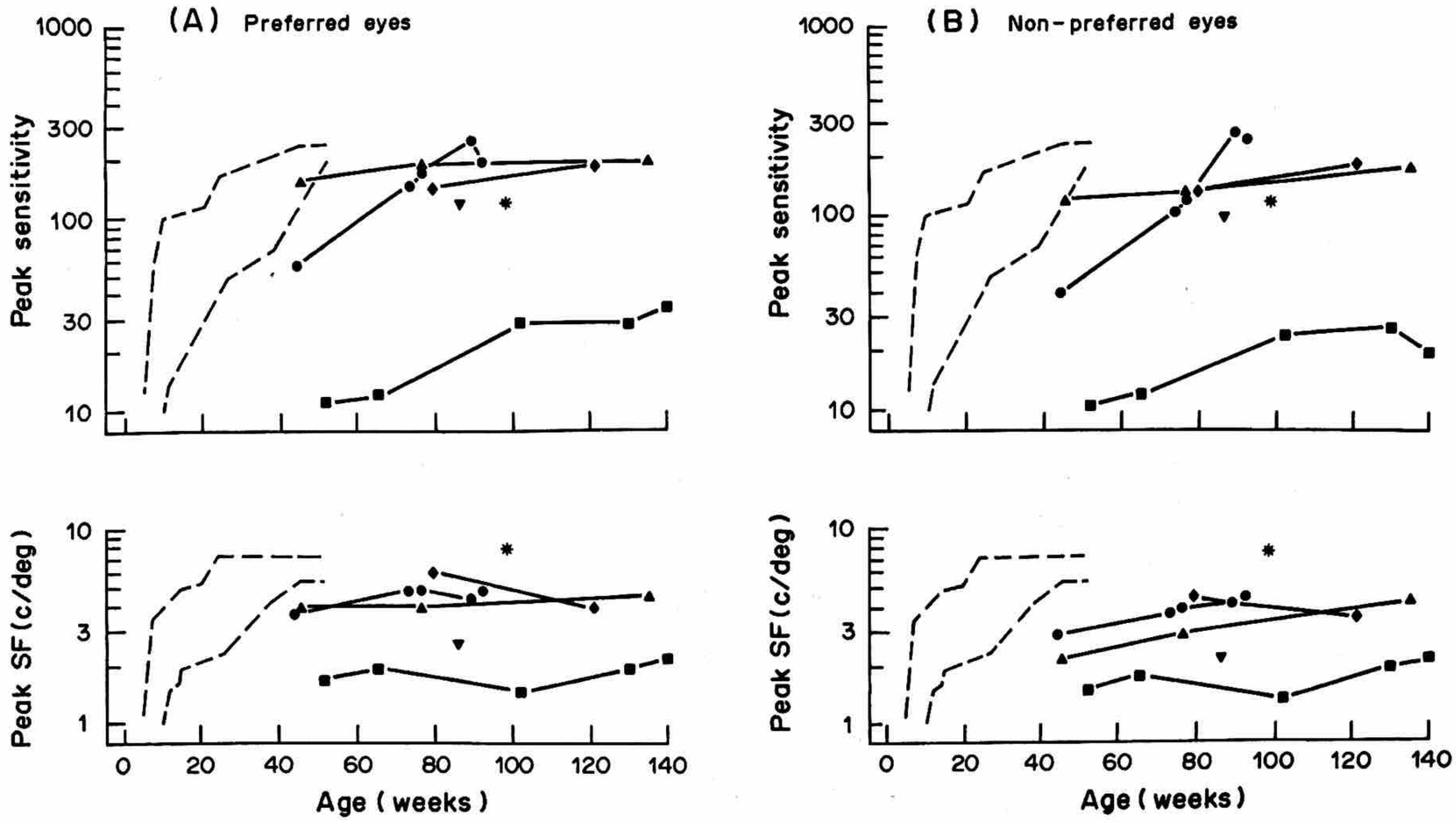

Fig. 10. The location of the peak of the contrast sensitivity function for each eye of each monkey at each test age, as compared with the pattern of normal development. Peak contrast sensitivity and peak spatial frequency are shown in the top and bottom panels, respectively. Data for the preferred eyes (or the eye showing the best sensitivity at the beginning of contrast sensitivity testing for each monkey) appear in A and the data for the non-preferred eyes appear in B. One monkey, JF, had no eye preference by either criterion; his right and left eye data are represented in 10A and 10B, respectively. The dashed lines represent the limits of peak sensitivity and spatial frequency for normal animals during development. The pattern of normal development was determined by a similar analysis of development data from normal monkeys; the normal data used for this analysis were from Boothe *et al.* (1988). Other symbols are consistent with earlier figures (solid lines connect data for individual animals).

These changes in spatial resolution and contrast sensitivity appear to reflect a slower, more extended period of development relative to normal, rather than abnormally poor visual function at birth. As can be seen in Fig. 1D, most monkeys that were tested during the early postnatal weeks showed normal or nearly normal spatial resolution at that time. However, thereafter development appeared to lag behind the rate seen in normal monkeys. At the end of the first postnatal year, when normal monkeys have reached adult levels of spatial resolution and contrast sensitivity, the naturally strabismic monkeys showed subnormal performance on both measures of spatial vision. Over the course of the following 1–2 years, spatial vision gradually improved; some monkeys eventually reached normal levels of spatial resolution and contrast sensitivity. It is important to note that the naturally strabismic monkeys were not generally slow developmentally. These monkeys were included in an unrelated, ongoing study on general physical, motor and social development in macaques at the Infant Primate Research Laboratory. Their growth and development, when assessed according to these nonvisual measures, was unremarkable relative to their peers.

The pattern of changes in the contrast sensitivity function with age shown by the naturally strabismic monkeys was reminiscent of the pattern of normal development. Boothe *et al.* (1988) found that the normal pattern of development of the contrast sensitivity function could be described as a concurrent upward and rightward shift in the position of the curve to higher spatial frequencies and higher contrast sensitivity. A similar trend is apparent in the data from the naturally strabismic monkeys, although the pattern is more obvious for the nonpreferred eyes than for the preferred eyes (refer to Fig. 10). The normal developmental pattern is also characterized by lower spatial frequencies reaching asymptotic levels of sensitivity earlier than higher frequencies. This pattern was evident in the data from the naturally strabismic monkeys as well (see, for example, Fig. 4A and B).

The monkeys that were evaluated during the early postnatal weeks initially had similar spatial resolution with each eye. Thereafter, most monkeys developed interocular differences in spatial resolution and contrast sensitivity. The time course for this change (the development of interocular differences in performance) is reminiscent of that seen in experimentally strabismic monkeys. Kiorpes *et al.* (1984, 1989) reported that most monkeys with surgically-induced esotropia exhibited a delay between the onset of the esotropia and the development of interocular differences in grating acuity. However, the delay was on the order of 3–10 weeks in the experimentally strabismic monkeys whereas the delay was greater than 10 weeks in the naturally strabismic monkeys studied from early infancy. This difference could be due to the unrestricted ocular motility of the naturally strabismic monkeys compared to the experimentally strabismic monkeys, and the tendency of the naturally strabismic monkeys to use either eye for fixation. Experimentally strabismic monkeys that alternated fixation tended to have smaller interocular acuity differences and longer delays between the onset of esotropia and the development of interocular acuity differences than monkeys that did not alternate fixation (Kiorpes *et al.*, 1985b; Kiorpes *et al.*, 1989).

The development of interocular differences in spatial resolution and contrast sensitivity in the naturally strabismic monkeys was subsequently followed by a reduction in the extent of the interocular differences. It is possible that this gradual reduction in the size of the interocular differences over time was the result of practice or "therapy" for the nonpreferred eyes provided by the extensive psychophysical testing. Although this possibility cannot be ruled out, it seems somewhat less likely in view of the fact that in most cases both eyes were subnormal in spatial resolution and contrast sensitivity at the time the interocular deficit was first seen. Since both eyes were tested equally one would expect practice to affect each eye to a similar extent over a similar period of time. In our animals, the improvements in spatial vision followed different time courses for the preferred and nonpreferred eyes. Also, it is worth noting, that monkeys KY and UN were both tested extensively throughout the period of study. While UN showed considerable improvements in contrast sensitivity and spatial resolution, KY showed little improvement on either measure.

It is difficult to describe the visual deficits demonstrated by the naturally strabismic monkeys as being amblyopia. This is primarily because the type of test used for the monkeys is quite different from that used for human clinical patients. Human clinical patients are most often evaluated with an eye chart and the resultant measure is Snellen letter acuity. Psychophysical studies of human strabismic amblyopes have demonstrated that grating acuity, as was measured in this study, is generally superior to letter acuity as measured with an eye chart, and that visual deficits in amblyopes are smaller when measured by grating acuity than with Snellen letters (e.g. Levi and Klein, 1982). In any case, the generally accepted criterion for defining amblyopia on the basis of acuity is a difference of one octave (factor of two) between the eyes. Interocular differences in spatial resolution of one octave or more were present in two monkeys, VP and UN (Fig. 1A and B), when tested near 40 weeks but these differences were not maintained long-term. Beyond the above mentioned criteria for defining amblyopia, human strabismic amblyopes exhibit characteristic deficits in contrast sensitivity with the amblyopic eye. Human amblyopes show deficits in contrast sensitivity that tend to be greater in extent at high spatial frequencies than at low spatial frequencies; in some cases there is no deficit in sensitivity at the low spatial frequencies (e.g. Hess and Howell, 1977; Levi and Harwerth, 1977). Inspection of the pattern of interocular differences in contrast sensitivity exhibited by most of the naturally strabismic monkeys reveals patterns that are reminiscent of those seen in human amblyopes. Thus, although the extent of the differences in spatial resolution tended to be smaller than one octave at the oldest test ages, the form of the deficits in contrast sensitivity resembled that of human amblyopes.

The naturally strabismic monkeys seem to provide reasonable animal models for vision in humans with strabismus. They are of particular value for investigating the nature of the strabismus and its effects on the development of the visual system. Among the small group of naturally strabismic monkeys studied, at least two kinds of esotropia were apparent, as was exotropia, and strabismus subsequent to diffuse occlusion. The visual deficits found in these animals in general reflected the fixation patterns of the individual animals. The delay between the development of strabismus and the appearance of interocular differences in resolution that was found in these monkeys has been reported to occur in human infants as well (Thomas *et al.*, 1979; Jacobson *et al.*, 1981; Birch and Stager, 1985). There is also some suggestion that, like the strabismic monkeys, vision develops more slowly in strabismic human infants (Day *et al.*, 1988). Day *et al.* (1988) showed that infants with infantile esotropia (in this case, esotropia that had an onset prior to 6 months after birth) had significantly poorer acuity than normal infants, as measured with the frequency sweep VEP technique. Interestingly, those infants tested prior to about 20 weeks showed acuity within the normal range. Also, Sebris and Dobson (1987), in a prospective behavioral study of infants with infantile esotropia, showed that acuity at 3 years of age was lower for the esotropes than for normal 3 year-olds. In both of these studies, there were no significant interocular differences in acuity. However, one study of grating acuity in 3–14 month-old infantile esotropes found no difference on average between either eye of alternating esotropes and normal eyes (Birch and Stager, 1985). No individual data were included for normal or esotropic infants though.

The finding that spatial vision develops more slowly, over a longer period of time in strabismic than in normal animals is particularly important when considering the sensitive period for visual development. It has often been suggested that the sensitive period, the period during which visual function can be improved or disrupted, correlates with the period of maturation, or visual development (e.g. Freeman and Marg, 1975; von Noorden, 1978; but see also, Birnbaum *et al.*, 1977; and von Noorden and Crawford, 1979, for discussion). This time period would be about the first 5 years in humans (Mayer and Dobson, 1982; Birch *et al.*, 1983), and the first year in monkeys (Teller and Boothe, 1979; Boothe, 1981; Boothe *et al.*, 1988). However, there have been many reports that vision can be improved or disrupted beyond these time periods for both humans and monkeys (e.g. monkeys, Wiesel, 1982; Harwerth *et al.*, 1986; humans, see Birnbaum *et al.*, 1977; Vaegan and Taylor, 1979). While it is clear that plasticity remains for some time beyond the period of normal maturation, it may also be the case that abnormal visual experience, such as results from strabismus, effectively slows the developmental time course. A similarly slowed developmental time course has been reported for grating acuity (Kiorpes *et al.*, 1989) and vernier acuity (Kiorpes and Movshon, 1988) in experimentally strabismic monkeys.

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