

Differential development of two visual functions in primates

(visual development/grating acuity/vernier acuity/strabismus)

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ABSTRACT Psychophysical data suggest that spatial resolution and spatial position sensitivity may be limited by different neural mechanisms. We investigated this hypothesis from a developmental perspective by studying the development of these two kinds of visual performance in two groups of infant macaque monkeys (*Macaca nemestrina*), one normal and one given an experimental strabismus. The results show that these two visual functions develop at different rates in normal monkeys and are disrupted differentially by abnormal early visual experience. However the relationship between the two measures is the same in strabismic and normally reared monkeys; the performance of strabismic monkeys resembles that of younger normal monkeys.

There are many ways to measure the spatial performance of the visual system. *Spatial resolution* can be measured by determining the finest grating pattern that can be distinguished from a homogeneous field. *Positional discrimination* can be measured by determining the smallest positional offset that can be detected in an otherwise collinear pattern. Psychophysical studies suggest that performance on positional discrimination tasks may be limited by different neural mechanisms than those limiting simple visual resolution (1, 2). The spatial resolution of the adult visual system is comparable to the diameter of a single foveal cone, whereas spatial position discrimination is considerably finer. Positional discrimination, as measured by *vernier acuity*, falls off rapidly as test targets are moved away from the fovea and into the periphery, while visual resolution, as measured by *grating acuity*, falls off more slowly. Strabismus (a misalignment of the visual axes) in infancy or early childhood often leads to the development of amblyopia, a deficit in visual function that reflects abnormalities in central visual processing. Strabismic amblyopes are reported to show a greater deficit in positional discrimination than in spatial resolution (3, 4). Taken together, these studies suggest that different neural factors may limit these two kinds of visual performance. This led us to ask whether their developmental time courses differ and how their development is affected by abnormal early visual experience.

The development of spatial vision has commonly been characterized by measuring spatial resolution as a function of age. In human infants, spatial resolution, as measured behaviorally, is poor at birth, 0.5–1 cycle (c)/degree of arc (deg), and develops to adult levels over the first 5 postnatal years (5–8); a similar sequence occurs in monkey infants during the first year after birth (9–11). Recent studies of human infants suggest that spatial position sensitivity exceeds resolution sensitivity by 4 months of age (12, 13). One study of human infants, during the early postnatal weeks, found that spatial position sensitivity developed with a different time course than spatial resolution (14). We studied the development of spatial resolution and positional sensitivity in

two groups of pigtailed macaque monkeys (*Macaca nemestrina*), one raised normally and one raised with experimentally induced strabismus. We show that these two visual functions develop with different time courses and are differentially disrupted by strabismus.

MATERIALS AND METHODS

We assessed visual development longitudinally in seven normal monkeys and five monkeys with experimentally induced strabismus. Esotropia (inward deviation of one eye) was induced by injection of *Clostridium botulinum* A neurotoxin into the left lateral rectus muscle of infant monkeys anesthetized with ketamine hydrochloride (15). Injections were guided by a combination of electromyogram recording through the injection needle and direct visualization of the muscle; the dose was 0.05 ml of 7–10 units of *C. botulinum* A toxin per muscle. The monkeys were between 3 and 8 weeks of age at the time of injection. Further details on this procedure and the resulting strabismus can be found in an earlier report (16). Animal care was provided in accordance with the National Institutes of Health guidelines for laboratory animal welfare and approved university protocols.

To assess visual function, we used a combination of preferential looking and operant methods (16–18). We used grating acuity as a measure of spatial resolution and vernier acuity as a measure of spatial position sensitivity, using high-contrast grating stimuli like those shown as insets in Fig. 1A. To measure grating acuity, we established the finest grating supporting discrimination between the grating and a blank field (*Inset*, Fig. 1A Lower). The spatial frequency of this grating is our measure of spatial resolution. To measure vernier acuity, we established the smallest offset supporting discrimination between two clearly visible gratings (*Inset*, Fig. 1A Upper). The inverse of this offset is our measure of position sensitivity. The spatial frequency of the carrier grating for the vernier task ranged from 0.25 c/deg for preferential looking to 4 c/deg for operant testing; the carrier frequency was typically 1–2 c/deg for operant testing of amblyopic animals. The luminance of the displays was 30 cd/m². Preferential looking methods (16, 17) were used from birth to 12 weeks; thereafter, operant methods (16, 18) were used. For each measure, a human observer's performance based on the animal's visual preference (preferential looking) or the animal's performance on a two-alternative forced-choice discrimination task (operant) was determined on 25–50 trials at each of four or five stimulus values spanning the range around threshold. The resulting psychometric functions were analyzed by probit analysis (19) to obtain estimates of the highest spatial frequency (grating acuity) or smallest spatial offset (vernier acuity) that supported 75% correct performance. We did not systematically monitor the monkeys' fixation during testing, although observation of the monkeys during testing suggested that they were fixating centrally. Thus, any undetected error in fixation would be small. Moreover, we know of no reports of eccentric fixation in experimentally strabismic monkeys.

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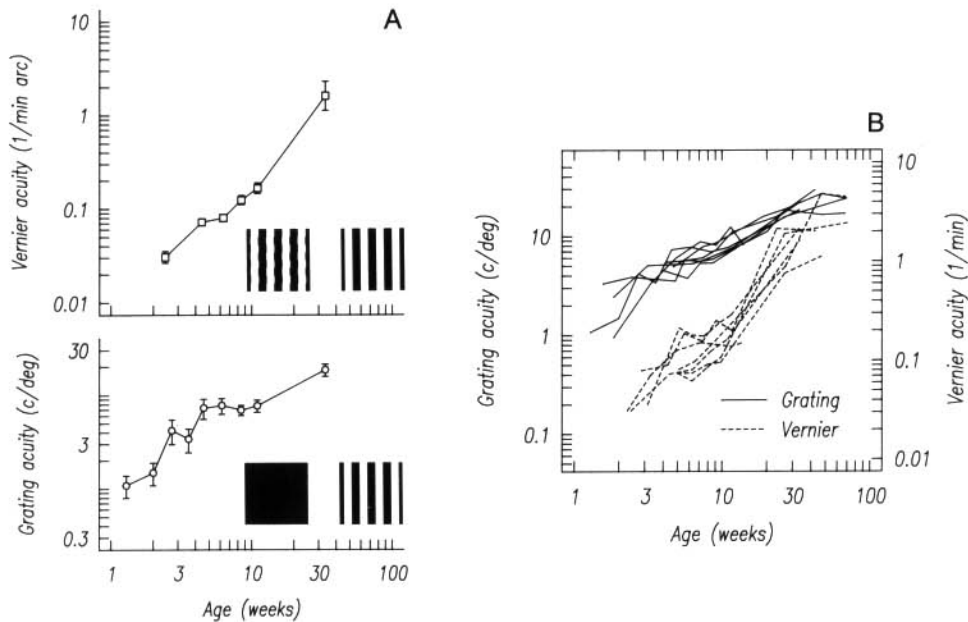


FIG. 1. (A) Development of grating acuity (Lower) and vernier acuity (Upper) for a single normally reared infant monkey. Grating acuity is expressed in cycles per degree of arc and vernier acuity is expressed as the inverse of the threshold offset in minutes of arc. Error bars indicate the standard error of the estimate of threshold. (Insets) Schematic illustrations of the stimuli used in these experiments. The inset in Lower shows the square-wave grating and blank field that were used to measure grating acuity. The spatial frequency of the grating was increased until performance fell to chance. The inset in Upper shows the square-wave grating with and without vernier offset used to measure vernier acuity. The size of the offset was reduced until performance fell to chance. Note that the offset was static in our display rather than dynamic as was used in the experiments with human infants (12–14). (B) Development of grating acuity (solid lines) and vernier acuity (broken lines) for seven normally reared monkeys. The two sets of curves are plotted together, and the two scales are shifted so that they align at adult values for a single representative normal monkey (vernier acuity: 12.6 arc sec, or 4.76/min; grating acuity: 26.7 c/deg). Individual data points and standard errors are omitted for clarity.

RESULTS

Data from a normal infant monkey appear in Fig. 1A, where grating acuity and vernier acuity are plotted as a function of age. Both visual functions develop to near adult levels over the first 30–40 postnatal weeks. However, over the measurement period, grating acuity improved 15-fold whereas vernier acuity improved 60-fold. Therefore, the two functions developed at different rates. Developmental functions for all seven normal monkeys are shown in Fig. 1B. To make the comparison easier, we have aligned the data to the adult performance level of a representative individual; this representation of the data presents each acuity measure relative to adult levels. Fig. 1B reinforces the impression that vernier acuity is relatively poorer than grating acuity in very young monkeys but develops at a faster rate.

Strabismus disrupted the development of both vernier acuity and grating acuity. Fig. 2A shows the pattern of development for each eye of a monkey made strabismic at the age of 32 days. While vision in the nondeviated eye developed relatively normally (open symbols), the deviated eye showed abnormally poor development by both measures (filled symbols). Moreover, the deficit in vernier acuity was greater than the deficit in grating acuity. This difference was a regular feature of the data from the strabismic monkeys. Fig. 2B compares the extent of the deficit in vernier acuity to that for grating acuity for each strabismic monkey. For four of the five strabismic monkeys, the vernier acuity deficit was larger than the grating acuity deficit; the fifth monkey adopted an alternating pattern of fixation and showed no deficit on either measure of visual function. This result is consistent with those reported for human strabismic amblyopes (3, 4).

Because vernier acuity and grating acuity each develop monotonically and at different rates (Fig. 1), the relationship between vernier acuity and grating acuity changes with age. Fig. 3A shows this relationship for normal monkeys over the

course of development. We refer to the region containing the data as the *normal sequence*; the sequence defines the expected vernier acuity for a particular value of grating acuity, regardless of the age of the animal. The normal sequence does not lie along a line with a slope of 1, reflecting the changing relationship seen during normal development. Interestingly, the data of Shimojo and Held (14) comparing grating and vernier acuity data for human infants fall near the normal sequence for our monkeys, suggesting that the relative development of these two functions is similar in monkeys and humans.

Because the development of both visual functions is disrupted by strabismus, it is of interest to know if the relationship between them is different in strabismic animals. Fig. 3B shows the relationship between vernier acuity and grating acuity during development for each eye of the strabismic monkeys; the stippled background represents the data for the normal monkeys from Fig. 3A. All of the data for the strabismic monkeys fall near or within the normal sequence defined by the data from normal monkeys. For the nondeviated eyes (open symbols), development proceeds roughly as it does in normal animals. For the deviated eyes (closed symbols), both the absolute levels of performance and the relationship between the two measures are similar to those defined for younger normal monkeys. In other words, the relationship between vernier acuity and grating acuity for the strabismic eyes is abnormal for a particular chronological age, but it resembles the relationship expected of a younger visual system. This suggests that the disproportionate deficit in vernier acuity in strabismic amblyopes may reflect a disruption of the developmental time course rather than a particular disorder of vernier acuity.

DISCUSSION

Because our results show different developmental time courses for spatial resolution and spatial position sensitivity,

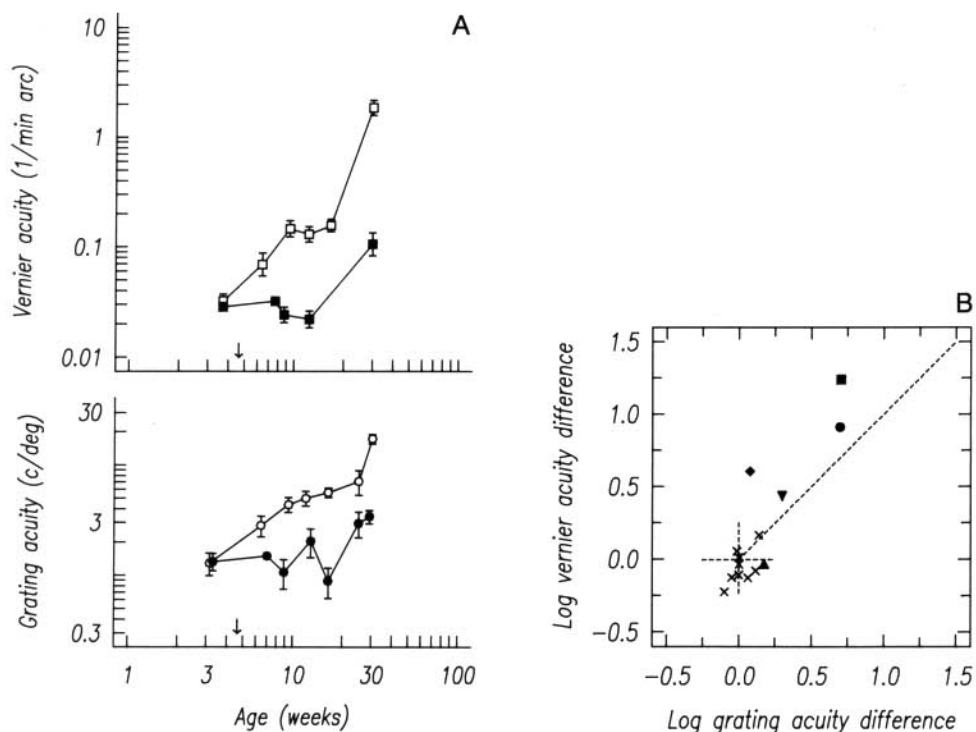


FIG. 2. (A) Development of grating acuity and vernier acuity for each eye of a monkey made strabismic at the age of 32 days (arrow). Data from the treated eye are represented with open symbols, and those from the untreated eye are shown with filled symbols. Conventions otherwise are as for Fig. 1A. (B) Comparison of interocular differences in grating and vernier acuity for normal and strabismic monkeys. For each monkey, the ratio of acuities for the two eyes, expressed in logarithmic units, was calculated from the values obtained in the final testing session. The large plus marks the 0 log difference expected (and observed) for normally reared animals (×). The broken diagonal marks a slope of 1, where values indicate equivalent interocular difference in vernier and grating acuity. For strabismic monkeys, the ratios were calculated with the treated eye in the denominator, so that positive values reflect a superiority of performance in the untreated eye. For normal animals, the eyes were randomly assigned to the numerator and denominator.

and differential disruption by abnormal early visual experience, they support the hypothesis that these functions are limited by different neural mechanisms. However, because the relationship between these functions remains the same, it

is also possible that a single developmental factor acts with a different effect on the mechanisms subserving different visual tasks. Such a single limiting process has recently been proposed by Banks and Bennett (20), for example. Using an

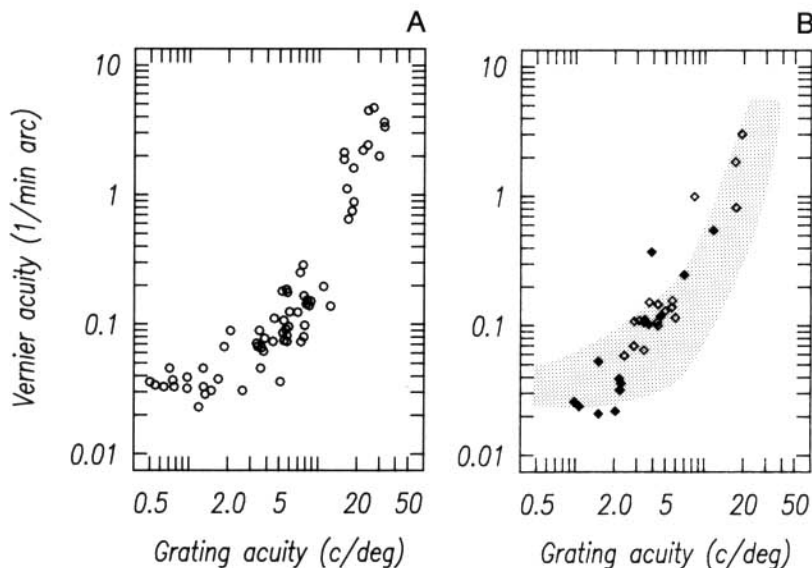


FIG. 3. (A) Relationship between vernier acuity and grating acuity for normally reared monkeys; included are data from Fig. 1B, for the seven animals studied longitudinally, as well as data from six normally reared animals tested cross-sectionally. The two measures are plotted against one another, collapsing the data across age, to reveal the characteristic normal sequence within which most data fall, even though individual animals may develop at different rates. (B) Relationship between vernier acuity and grating acuity for five strabismic monkeys; open symbols represent untreated eye data and filled symbols represent treated eye data. As in A, the two measures are plotted against one another, and the data are collapsed across age. The stippled region is transferred from A and represents the normal sequence for data obtained from normally reared monkeys.

ideal observer analysis, they suggest that known changes in photoreceptor efficiency could result in differing developmental slopes for vernier and grating acuity. Whether or not the effect is due to a single factor, if the effect of strabismus is to slow the development of all visual neural mechanisms equally, as has been suggested on the basis of previous studies of visual development in strabismic monkeys (16, 21), one would expect to find the greater disruption of vernier acuity relative to grating acuity that we and others (3, 4) have observed in strabismic amblyopes. The end of the sensitive period would find the neural machinery devoted to the strabismic eye in an immature state, and it would thus be fixed in that immature state for the remainder of life.

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