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Contour integration in amblyopic monkeys

PETRA KOZMA[1] AND LYNNE KIORPES[2]
[1]Retina Foundation of the Southwest, Dallas
[2]Center for Neural Science, New York University, New York

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Abstract

Amblyopia is characterized by losses in a variety of aspects of spatial vision, such as acuity and contrast sensitivity. Our goal was to learn whether those basic spatial deficits lead to impaired global perceptual processing in strabismic and anisometropic amblyopia. This question is unresolved by the current human psychophysical literature. We studied contour integration and contrast sensitivity in amblyopic monkeys. We found deficient contour integration in anisometropic as well as strabismic amblyopic monkeys. Some animals showed poor contour integration in the fellow eye as well as in the amblyopic eye. Orientation jitter of the elements in the contour systematically decreased contour-detection ability for control and fellow eyes, but had less effect on amblyopic eyes. The deficits were not clearly related to basic losses in contrast sensitivity and acuity for either type of amblyopia. We conclude that abnormal contour integration in amblyopes reflects disruption of mechanisms that are different from those that determine acuity and contrast sensitivity, and are likely to be central to V1.

Keywords: Contour integration, Amblyopia, Nonhuman primate

Introduction

Amblyopia is typically thought of as a developmental acuity deficit associated with conditions such as strabismus or anisometropia. However, a number of additional deficits in spatial vision have been identified in amblyopes that extend the amblyopic deficit well beyond simple acuity (see Levi & Carkeet, 1993, and Daw, 1995, for an overview). The most dramatic and intensely studied of the spatial visual losses in amblyopia fall into the general category of spatial imprecision, including vernier acuity deficits (e.g. Levi & Klein, 1983), spatial distortions (e.g. Hess et al., 1978), and spatial localization errors (e.g. Flom & Bedell, 1985; Sireteanu & Fronius, 1989). Many psychophysical studies in human amblyopes have identified performance differences between strabismic and nonstrabismic amblyopes in the degree of spatial imprecision. While anisometropic amblyopes typically show impairment that is predictable from the acuity deficit, strabismic amblyopes often have a disproportionately large loss on vernier acuity and other tasks requiring fine spatial precision (Levi & Klein, 1985; Hess et al., 1990; Hess & Holliday, 1992). However, a large-scale survey of carefully classified human amblyopes has shown a much greater range of overlap among anisometropic and strabismic amblyopes than the smaller-scale psychophysical studies report (McKee et al., 2003). McKee has further provided evidence that the existence of binocular integration is an important underlying distinguishing factor, more so than etiology (McKee et al., 2003).

On the other hand, Levi and coworkers have identified "second-order" orientation-dependent discrimination tasks on which amblyopes perform normally despite substantial losses in acuity and contrast sensitivity (Levi et al., 1994; Levi & Sharma, 1998; Mussap & Levi, 1999). For example, Mussap and Levi (1999) measured texture segmentation based on local orientation differences between target and background regions. Their strabismic amblyopic subjects showed no deficits in amblyopic eye performance. Demanins et al. (1999) investigated the effect of spatial frequency and orientation bandwidth on orientation discrimination, also in strabismic amblyopes. They found that the amblyopic deficit in most of their subjects was reduced or absent at large stimulus bandwidths.

An important question has emerged from the many studies on the nature of amblyopia, which is, to what extent do the basic spatial visual deficits lead to impairment in global visual processing? Several recent investigations of spatial integration have shown evidence of perceptual-level deficits in amblyopes that are apparently *independent* of the simple acuity and contrast-sensitivity losses. Contour integration and other tasks that require spatial integration are impaired in strabismic amblyopia (Hess et al., 1997; Kovács et al., 2000; Mussap & Levi, 2000). However, Hess and Demanins (1998) reported that most anisometropic amblyopes do not show interocular differences for contour integration. This finding has been questioned by Chandna et al. (2001), who studied contour integration in untreated anisometropic amblyopes and found that most of their subjects did have significant interocular differences on their task. Finally, "high-level" abilities such as the

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Address correspondence and reprint requests to: Petra Kozma, Retina Foundation of the Southwest, 9900 N. Central Expressway, Suite 400, Dallas, TX 75231, USA. E-mail: petra@retinafoundation.org
*E-mail: lynne@cns.nyu.edu

perception of illusions (Popple & Levi, 2000) and individuation of features within an image (Sharma et al., 2000) are reportedly abnormal in amblyopes. Collectively, these results suggest that global perceptual organization is affected in amblyopia. However, it remains unclear from the human studies what are the important characteristics of global perceptual tasks compromised in amblyopia and the extent to which anisometropic amblyopes differ from strabismic amblyopes. Here we address these questions in nonhuman primate amblyopes.

We have extensively studied a nonhuman primate model of amblyopia to gain an understanding of the underlying neural correlates (Kiorpes & Movshon, 1996; Kiorpes et al., 1998; Kiorpes & McKee, 1999; Kiorpes, 2001). Macaque monkeys raised with experimentally created anisometropia or strabismus develop amblyopia, as do human infants and children with the naturally occurring conditions. The characteristics of amblyopia in monkeys, in terms of grating acuity (Kiorpes et al., 1989), contrast sensitivity (Harwerth et al., 1983; Smith et al., 1985; Kiorpes et al., 1993), vernier acuity (Kiorpes, 1992; Kiorpes et al., 1993), spatial phase discrimination (Kiper, 1994), and suprathreshold contrast discrimination (Kiper & Kiorpes, 1994), closely mirror those of human amblyopia. The animal model allows us to study subjects with known etiology and visual history, and to explore the neural correlates directly in future studies. Unlike humans in most previous studies, our amblyopes are not treated, which gives us the opportunity to study amblyopia in its pure form.

In the present study, our aim was to characterize the contour integration performance of strabismic and anisometropic nonhuman primate amblyopes in comparison to contrast sensitivity losses. That is, do both types of amblyopes show losses on contour integration tasks and if so are these losses related to or predictable from their contrast sensitivity losses? We report data showing obvious abnormalities in global visual processing in anisometropic as well as strabismic amblyopes using the contour integration task. These deficits are not clearly related to the contrast sensitivity deficits. Our task was similar to some previously used to study contour integration in humans. We measured the ability of amblyopic observers to extract a feature (circular contour) from background noise. Detection of the feature requires perceptual linking of the elements in the contour over space. Such large-scale spatial integration is considered to be a global task, as the perceptual problem cannot be solved on the basis of detection of the local features of the display alone. Some of the behavioral data reported here have been presented previously (Kozma et al., 2000).

Materials and methods

Subjects

Thirteen *Macaca nemestrina* monkeys were subjects in this study. Five monkeys were visually normal and eight were experimentally amblyopic. All animals were born at the Washington National Primate Research Center, and were hand-reared in the Visual Neuroscience Laboratory at New York University. Their visual environment was a normal laboratory, which was enriched with a wide variety of appropriate visual and tactile stimuli. The animals were also given daily opportunities for interaction with other monkeys and humans. All animal care conformed to guidelines approved by the New York University IACUC and the NIH Guide for Care and Use of Laboratory Animals. All of the amblyopic animals were adults (2.5 years or older) at the time of testing for this study; the normal controls were 1.2 years or older.

Experimental amblyopia

Amblyopia developed following either early-induced strabismus or simulated anisometropia. Experimental strabismus was induced in four monkeys 25–31 days after birth (see Kiorpes et al., 1989, 1993; Kiorpes & Wallman, 1995). Esotropia (inward deviation of the eye) of the left eye was created by transection of the left lateral rectus muscle; the left medial rectus muscle was resected and advanced to the limbus and the conjunctiva was reattached to the globe. Surgery was carried out under ketamine hydrochloride sedation using sterile surgical techniques. The resulting esotropia was moderate, ranging from 10 prism diopters to 25 prism diopters. The angle of deviation was estimated by the Hirschberg method from photographs; these estimations are accurate to about 5 prism diopters (see Kiorpes et al., 1989, for details). One of the strabismic animals developed an alternating fixation pattern (WW; see Table 1); the others used the nondeviated eye preferentially.

Anisometropia was simulated in four monkeys by inserting a −10 D extended-wear soft contact lens in the right eye and a

Table 1. *Procedural and clinical data for the experimental subjects*[a]

					Refractive error	
Monkey	Condition	Onset age (days)	Age at test (years)	Amblyopia Index	Fellow eye	Amblyopic eye
TX	Strab	26	4.2	0.78	+2.00–0.50 × 180	+6.00**
WW	Strab*	31	4.75	0.39	+0.25	+0.25
HF	Strab	25	2.8	0.623	plano–0.50 × 180	plano
HN	Strab	27	2.7	0.667	−0.50	+4.50–1.00 × 90**
CY	Lens	25	4.5	0.80	+1.25–0.25 × 180	+8.50–0.75 × 165***
CM	Lens	20	4.5	0.75	−0.25	+8.50–0.50 × 180***
HK	Lens	24	3.5	0.60	+1.25–1.00 × 15	+5.50***
IR	Lens	24	3.25	0.60	+0.75	+5.75–0.25 × 90

[a] For each monkey, we list the rearing condition (Condition), the age at which the rearing condition was imposed (Onset age), the age at the time of testing for this study, a measure of the depth of amblyopia (Amblyopia Index; see Methods for details), and refractive error of each eye near the time of testing. Note: * indicates alternating fixation pattern; Strab = esotropic strabismus; Lens = lens reared; ** indicates greater than 2 D anisometropia was detected during first 9 months after birth; *** indicates greater than 2 D anisometropia was detected during lens rearing.

zero-power lens in the left (Kiorpes et al., 1993) 20–25 days after birth. The monkeys wore the lenses continuously for a period of 7–8 months. The status and condition of the lenses were checked frequently throughout each day; missing lenses were infrequent, but when noticed were replaced immediately. The lenses were changed and cleaned weekly. Regular ophthalmic examinations were performed to insure the health of the eyes. Eye alignment was evaluated by inspection daily and by the Hirschberg method once during rearing. No strabismus was obvious during the rearing period or thereafter in any of the lens-reared animals, however, we would not have detected a tropia or phoria of less than 5 prism diopters.

Additional data from the animals in this study have been published elsewhere (Kiorpes et al., 1999).

Clinical evaluation

Refractive errors were evaluated during rearing in all subjects. For refraction, both eyes were dilated with 1–3 drops of 2.5% phenylephrine hydrochloride and 3 drops of 0.5% or 1% cyclopentolate. Each strabismic monkey was refracted at least twice within the first postnatal year; the lens-reared monkeys were refracted every 1–2 months. All refractions were performed by the same pediatric ophthalmologist. All monkeys had essentially equal refractive errors in the two eyes at the beginning of rearing. Two strabismic monkeys (TX, HN) developed natural anisometropia of greater than 2 diopters during the first postnatal year and thus may be considered compound amblyopes. All four of the lens-reared monkeys developed natural hyperopic anisometropia of greater than 2 diopters. Most became anisometropic during the lens-rearing period; one monkey (IR) developed anisometropia after the lenses were removed. Rearing histories and refractive errors measured closest to the age at test are presented in Table 1. Note that none of these animals showed a significant amount of astigmatism at the age of test ($>$1.5 D; Mitchell et al., 1973), nor did any subject maintain high astigmatism during rearing.

Contour integration

The methods are described in detail in the companion paper (Kiorpes & Bassin, 2003). Briefly, the stimulus was a ring of co-circular Gabor patches presented in a field of randomly arrayed and randomly oriented Gabor patches (Kovács, 1996; Pettet et al., 1998). The stimulus field subtended 22 × 16.8 deg. Gabor patches were made by multiplying a 3 cycles/deg sinusoid by a Gaussian with a 0.1-deg standard deviation. The contour (the ring of Gabors) comprised 14 patches with 1.6-deg center-to-center spacing; the ring diameter was 7 deg. The noise (the background Gabors) varied in density from 0.39 patches/deg^2 to 2.51 patches/deg^2. Stimulus contrast was 98% except where stated otherwise.

Behavioral methods

The behavioral methods in this paper were similar to those used by Kiorpes and Bassin (2003). On each trial, the contour was presented on either the left or right side of the display monitor with added uncertainty as to its precise location. A spatial two-alternative forced-choice task was used. The monkeys had to indicate, by pulling one of a pair of grab bars located on the front of the cage, on which side of the display the contour had appeared. Each stimulus was presented for 1 s, after which time the monkeys were given 3 s to respond. Correct responses were rewarded with apple juice; errors were signaled by a tone. Noise tolerance, the background noise density at which performance fell to 75% correct, was established using the method of constant stimuli. Each tolerance estimate was based on at least 375 trials; we collected 75–150 trials at each of 3–5 noise densities chosen to span the performance range from 50% to 100% correct. Noise-tolerance estimates and standard errors were calculated using Probit analysis (Finney, 1971) of the log-transformed data sets. Note that a minimum of 80% correct performance at the lowest density was required for the data to meet our criterion for acceptability. Further details of the training and testing procedures can be found in earlier reports (Kiorpes et al., 1993; Kiorpes & Movshon, 1998).

We initially measured noise tolerance with co-circular contour patches. We also measured tolerance for orientation jitter of the contour patches. Orientation jitter ranged from 0 deg–60 deg. Sample stimuli are shown in Kiorpes and Bassin (2003). The orientation of each contour element was assigned independently within the specified jitter range. Data collection was counterbalanced across level of orientation jitter.

Each eye of the amblyopic monkeys was tested separately, with optical correction provided as needed (see Kiorpes & Boothe, 1984). The dominant eye was tested first. Control subjects were tested binocularly, since they were participants in a developmental study (Kiorpes & Bassin, 2003). We compared monocular and binocular performance for two control monkeys and found no substantial difference in noise density tolerance in either case.

Contrast sensitivity

We measured contrast sensitivity in two ways: (1) contrast sensitivity as a function of spatial frequency for traditional grating stimuli, and (2) contrast detection threshold for the individual Gabor elements that were used in the contour integration stimuli.

Full contrast sensitivity functions for each eye of amblyopic subjects were collected immediately before or at the conclusion of contour integration testing; control subjects were tested binocularly. To measure spatial contrast sensitivity, sinusoidal gratings were generated under computer control with the same video display system as was used for contour integration. Grating patches were vignetted by a two-dimensional spatial Gaussian ($\sigma = 0.75$ deg, except for very low spatial frequencies for which σ was increased to ensure visibility of at least three grating cycles). Spatial frequencies ranged from 0.3 cycle/deg to 16 cycles/deg; viewing distance ranged from 0.5 m to 2 m. The monkey's task was to detect the presence of the grating patch on either the right or left side of an otherwise homogenous gray field that matched the grating in space-average luminance. Contrast threshold, the contrast at which performance fell to 75% correct, was established using the method of constant stimuli. Each contrast threshold was based on at least 40 trials for each of 3–5 contrast levels per spatial frequency; at least four spatial frequencies were tested for each function. Threshold values and standard errors of estimate were obtained by Probit analysis of the log-transformed data sets (Finney, 1971) using a maximum-likelihood technique.

Our monkey contrast sensitivity data are well described by the double exponential function:

$$S_\omega = a\omega^b e^{-c\omega},$$

where ω is spatial frequency, S_ω is contrast sensitivity, and a, b, and c are fitted parameters. Since the contrast sensitivity loss in amblyopes varies with spatial frequency, the depth of amblyopia cannot be captured by looking at a single point on the curve, for example the peak or the cutoff. A more inclusive measure is needed that takes into account which spatial frequencies the subject is sensitive to. Therefore, to characterize the depth of amblyopia of each subject, we calculated a dimensionless *amblyopia index*. The area between the fitted contrast sensitivity functions for the amblyopic and fellow eye was divided by the area under the function for the fellow eye. This index ranges from 0 (no deficit) to 1 (no measurable sensitivity in the amblyopic eye). While the index does not capture the detailed form of the loss, it captures quite completely losses in both contrast sensitivity and spatial resolution. The amblyopia index for each monkey is listed in Table 1.

We also measured the detectability of the individual Gabor elements that were used to construct the contour integration displays. We established contrast threshold for a single Gabor patch, using the methods described above for contrast sensitivity functions. In this case we specified only one contour element and set the amplitude of the noise patches to zero. The task was to detect the location of the single patch as a function of contrast. These contrast thresholds were used to establish the effective contrast of the display elements. Finally, to investigate the dependence of contour integration ability on contrast, we established the lowest contrast at which the task could still be performed and measured noise density tolerance at that contrast level. In some cases, we also measured tolerance for orientation jitter with the elements in the display at contrast threshold.

Results

Contour integration was compromised in all amblyopic eyes. Surprisingly, contour integration was impaired in some fellow eyes as well in comparison with controls. Fig. 1 shows noise tolerance for co-circular contour elements (no orientation jitter) for all subjects, visually normal as well as amblyopic. The open symbols represent data from controls and fellow eyes, whereas filled symbols represent amblyopic eyes. It is important to note that most of the amblyopes showed compromised contour integration with their fellow eyes as well as with their amblyopic eyes. The range of interocular differences in contour integration among the amblyopes was quite broad. The alternating esotrope (WW) had a very small interocular difference on contour integration; however, this is because she showed deficient performance with the fellow eye as well. One strabismic (HN) and one anisometropic (CY) amblyope were unable to perform reliably on this task with the amblyopic eye (filled arrows). Increased element size, reduced carrier spatial frequency, and an increased number of elements in the contour (e.g. reduced spacing) failed to improve performance for these amblyopes. We confirmed in each case that they could reliably detect the individual elements of the display by measuring contrast threshold for a single Gabor patch (see Methods). We also confirmed that they could locate the contour at 100% accuracy in the absence of noise. Only an added contrast cue (where the contour elements were higher in contrast than the noise elements) enabled them to perform reliably above 80% correct with noise density matched to the spacing of the contour elements. CY required a 20% and HN a 30% contrast difference between the contour and the noise to meet criterion performance.

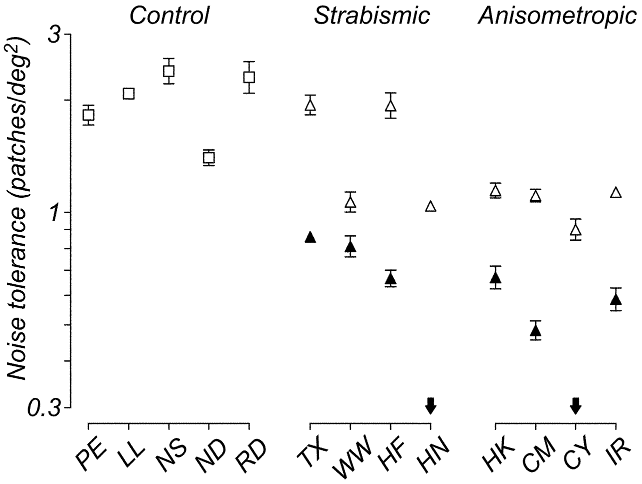

Fig. 1. Noise tolerance in the collinear condition is plotted for each subject. Open squares represent control subject data (collected with binocular viewing). Open and filled triangles represent fellow and amblyopic eyes of the amblyopic monkeys. The arrows pointing to the abscissa above HN and CY indicate that the monkey could not reliably detect the contour with his amblyopic eye. Error bars are ± 1 SEM; SE is smaller than the data points for measurements that do not appear to have error bars.

We next evaluated the effect of jittering relative orientation of the contour patches on noise density tolerance. The effect of orientation jitter on contour integration performance is shown in Fig. 2. Fig. 2A shows representative data from a control animal. Noise tolerance decreased steadily with increasing orientation jitter; the monkey was unable to reliably detect the contour beyond a 60-deg range of jitter. Note that this monkey had an exceptionally large range of sensitivity on this task; the range of orientation jitter tolerance for most normally sighted animals was usually 40 deg (Kiorpes & Bassin, 2003). Figs. 2B–2D show data from each eye of three amblyopes. In all figures of this form, amblyopic eye performance is represented by filled symbols; fellow eyes and control data are represented by open symbols. In each case, the fellow eye shows the same pattern as the normal controls, with noise density tolerance decreasing as orientation jitter increases. The maximum tolerance range for orientation jitter for fellow eyes was typically 40 deg. The amblyopic eyes show comparatively little variation in performance with increasing orientation jitter. While TX's, amblyopic eye performance declines similarly to the fellow eye with increasing orientation jitter, the functions for HK and HF are relatively flat. For four of the eight amblyopes, we collected data over a range of orientation jitter levels for amblyopic as well as fellow eyes. We fit Gaussian functions to the orientation jitter tolerance data to obtain a measure of relative curvature (these are the smooth fits to the data in Fig. 2) (see also, Kiorpes & Bassin, 2003). Three of the four animals have flatter fits for the amblyopic eye than for the fellow eye (WW, HF, & HK). Only TX (Fig. 2D) has similar fit values for the two eyes. Also, in general, the tolerance range for orientation jitter is lower for amblyopic eyes, thus the functions for the amblyopic eyes do not extend to as high jitter values as the fellow eye functions. Strabismic monkey TX showed the greatest change in noise tolerance with orientation jitter and the greatest range of jitter tolerance of any of the monkeys' amblyopic eyes.

We tested our amblyopes at reduced contrast levels to determine whether the deficits were strictly contrast dependent in either group of amblyopes. Data from two animals are shown in Fig. 3; they represent the range of effects we observed. Fig. 3 shows noise

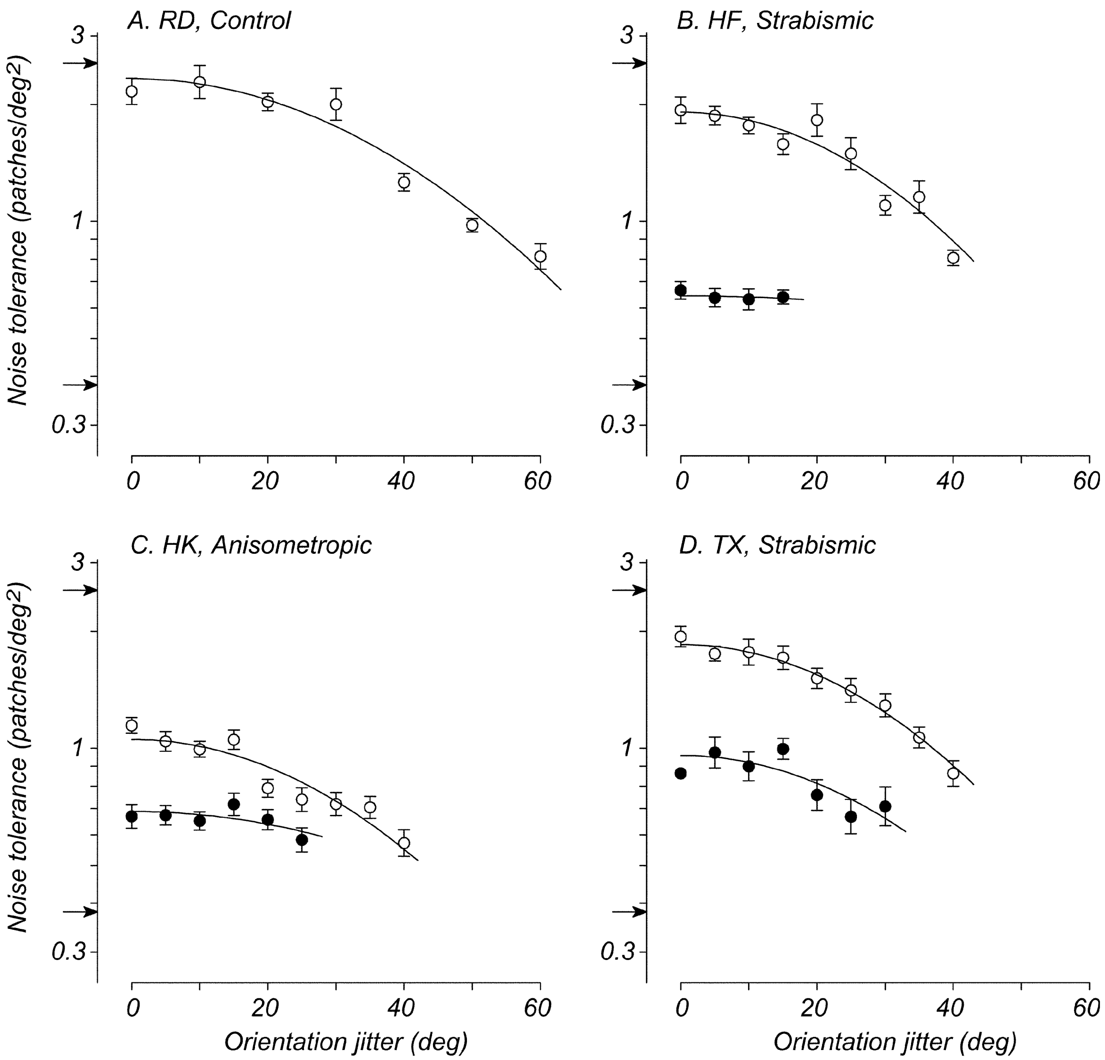

Fig. 2. The effect of orientation jitter of the contour elements on noise tolerance. The orientation jitter values along the abscissa specify the range of jitter in each direction, so 40 deg on the axis indicates ± 40 deg. The arrows pointing to the ordinate indicate the limits of the noise density range we used. The open and filled symbols represent fellow and amblyopic eye data, respectively (means ± 1 SEM). The curves fit to the data are simple Gaussians (we plot $\frac{1}{2}$ of the function for each data set). Data are shown for four monkeys: a control monkey (A), two strabismic monkeys (B, D), and an anisometropic monkey (C).

tolerance as a function of orientation jitter for maximum contrast stimuli (open and filled circles; the same data as shown in Fig. 2) and for threshold level stimuli (open and filled triangles; the lowest contrast at which the task could still be performed successfully). TX, a strabismic amblyope, showed the largest effect of contrast among the amblyopes. Noise tolerance was reduced across all orientation jitter values for the fellow eye, but the range of jitter tolerance was the same at low and high contrast. HK, an anisometropic amblyope, showed a small effect of contrast for the fellow eye with small amounts of orientation jitter. His performance was similar at high contrast and at contrast threshold with large amounts of jitter. While we found a range of contrast effects for the fellow eyes, none of the amblyopic eyes tested showed a further reduction in noise density tolerance at low contrast. For this reason, we did not add orientation jitter in the low contrast condition for the amblyopic eyes.

Since most animals performed similarly at low and high contrast, our task is not likely to be contrast dependent. However, it is possible that our high-contrast displays were low in *effective* contrast for amblyopic subjects. Effective contrast was established by measuring contrast threshold for a single Gabor element or by measuring the lowest contrast at which the task could be performed (see Methods). These two measures were comparable and so are used interchangeably ($r = 0.81$, $P = 0.027$). The range of effective contrast is illustrated in Fig. 4A for controls as well as amblyopes, and tabulated individually for amblyopes in Table 2. The stimuli are 7–10 times threshold in normal controls. In most cases, the stimuli for the amblyopes were typically a factor of 2–4 above contrast threshold. To show the relationship between contrast threshold for the Gabor patches and contour integration performance, we plot the ratio of noise tolerance at high and threshold-level contrast as a function of the effective contrast of the stimuli for control, fellow, and amblyopic eyes (Fig. 4A). Clearly the effect of contrast is minimal for most animals, control as well as amblyopic. The largest reduction in noise tolerance for low-contrast stimuli is a factor of 2; most cases show essentially no

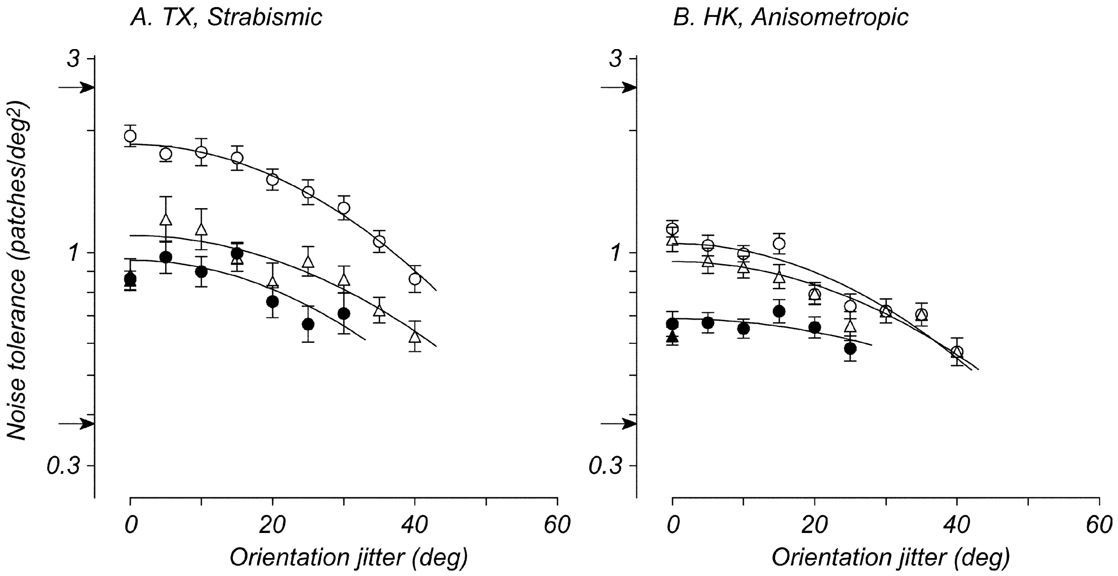

Fig. 3. The effect of contrast on noise tolerance as a function of orientation jitter. Two representative data sets from Fig. 2 are replotted here with the addition of noise-tolerance data collected at contrast threshold for the task. The low-contrast data sets are shown as open triangles for the fellow eyes. The amblyopic eye low-contrast data are single filled triangles (TX's amblyopic eye datum is obscured by his high-contrast point).

effect (data cluster near a ratio of 1; $r = 0.33$; $P = 0.22$). This analysis suggests that there is no relationship between the level of effective contrast of the stimuli and the extent of the deficit, and further supports the notion that contrast is not an important limiting factor for either strabismic or anisometropic amblyopes.

However, to directly assess the relationship between the extent of the contrast sensitivity and contour integration deficits in amblyopes, we plotted the comparison in Fig. 4B. We assess this relationship by plotting the noise tolerance ratio of the fellow eye alone at high contrast and threshold contrast levels as a function of the interocular noise tolerance ratio (the ratio of fellow eye performance to amblyopic eye performance, for the collinear condition). If the deficits in contour integration were due to reduced contrast sensitivity for the stimuli, the data would fall a long the diagonal. Data are plotted for five animals [the ratios could not be calculated for HN and CY since they were unable to do the task with their amblyopic eye; a third animal did not complete the low-contrast conditions (CM)]. Only two of the five cases fall close to the diagonal, strabismic monkeys TX and WW. The simple correlation was $r = 0.56$, which was not statistically significant ($P = 0.32$). Thus, there is no compelling support for the notion that the contour integration deficits are related to a task-based contrast limitation.

Table 2. *Effective contrast of the Gabor stimuli for the amblyopic subjects*[a]

Monkey	Fellow	Amblyopic
TX	4.6	2.7
WW	4.2	4.4
HF	5.4	4.4
HN	3.2	2.3
CY	10.9	2.9
CM	—	—
HK	2.7	1.3
IR	3.8	4.0

[a] Effective contrast, expressed as multiples of contrast threshold, is determined by measurement of contrast threshold for a single Gabor patch or the threshold for performance of the task. Note that these two measures are essentially equivalent meaning that once the individual stimuli are above threshold, the task can be performed. CM did not complete testing on the low-contrast conditions hence her data are unavailable.

Finally, it is important to determine whether the degree of impairment on contour integration tasks can be predicted from the basic spatial contrast sensitivity deficit in amblyopia. We measured full contrast sensitivity functions for each eye of the amblyopes. Functions for each anisometropic amblyope are shown in Fig. 5; data for each strabismic amblyope are shown in Fig. 6. A range of deficits were found in both groups of animals. For amblyopic eyes, both peak contrast sensitivity (the maximum height of the function) and spatial scale (position on the abscissa) were usually reduced with respect to the fellow eye. However, two strabismic amblyopes (TX & WW) had similar peak contrast sensitivity for each eye and therefore no overall sensitivity loss was detected. They each showed losses at higher spatial frequencies, while the data from TX suggest an additional overall shift in spatial scale for the amblyopic eye. The amblyopia index (see Methods), our measure of the depth of amblyopia which takes into account differences in both sensitivity and scale, for each monkey appears at the bottom left of each panel in Figs. 5 and 6. The depth of amblyopia in this group of animals ranged from quite mild, for example, WW with only high spatial-frequency losses (Fig. 6D), to severe, for example, CY with large losses at all spatial frequencies above 1 cycle/deg (Fig. 5B).

To test the predictive power of spatial contrast sensitivity losses, we plotted the interocular noise tolerance ratio as a function of the amblyopia index in Fig. 7. Data are shown for six monkeys

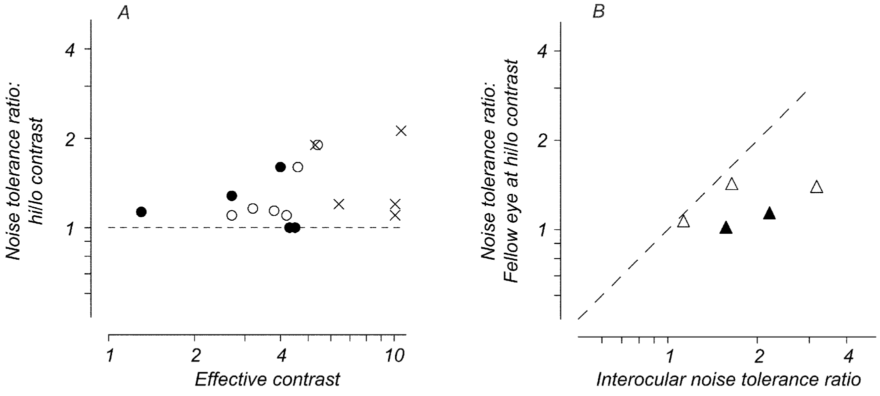

Fig. 4. The relationship between contrast threshold for the Gabor stimuli and contour integration deficits. (A) The ratio of noise tolerance at high contrast to that at threshold contrast, for the collinear condition, for all eyes plotted as a function of effective contrast of the stimulus (note that amblyopic eye data are not represented for HN and CY as they could not perform the contour integration task with that eye). Effective contrast is the contrast of the standard stimulus in units of contrast threshold (see Table 2 for tabulation of effective contrast for each amblyope). The horizontal dashed line represents equal contour integration performance for each eye. There is no consistent variation in task performance with contrast threshold. (B) The relationship between the extent of the contour integration deficits and task contrast sensitivity. The interocular ratio of noise tolerance for the collinear condition (fellow eye/amblyopic eye) is plotted against the noise tolerance ratio for the fellow eye in the collinear condition at high and low contrast (as in A). Strabismic monkey data are represented by open triangles and anisometropic monkey data are represented by filled triangles. If the performance of the fellow eye at contrast threshold is similar to the performance of the amblyopic eye at high contrast, then the amblyopic deficit can be accounted for by a loss of contrast sensitivity and the data will fall along the diagonal. The data mostly fall well below the line indicating the failure of this prediction.

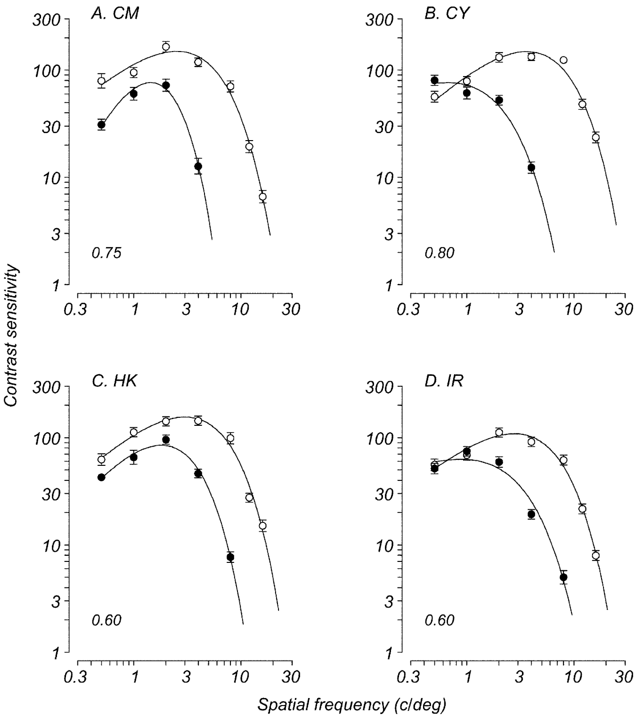

Fig. 5. Contrast-sensitivity functions for each eye of each anisometropic amblyopic subject. Contrast sensitivity is plotted as a function of spatial frequency for fellow eyes (open symbols) and amblyopic eyes (filled symbols). The amblyopia index appears in the lower left corner of each plot.

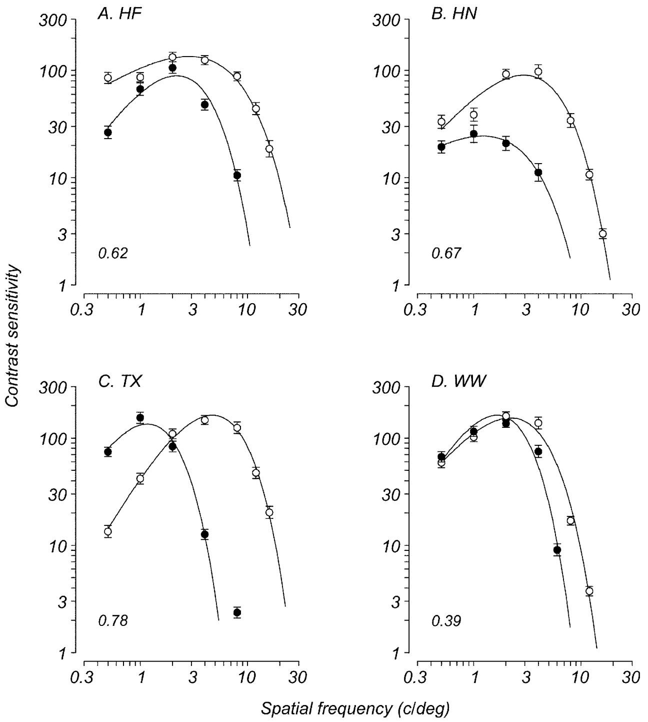

Fig. 6. Contrast-sensitivity functions for each eye of each strabismic amblyopic subject. Axes and symbols are the same as in Fig. 5.

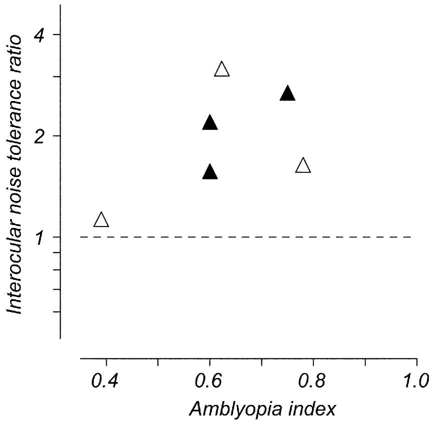

Fig. 7. The relationship between the extent of the contour integration deficits and the depth of amblyopia. Interocular noise tolerance ratio for the collinear condition is plotted against the amblyopia index, which represents the depth of amblyopia, for each monkey. Strabismic monkey data are represented by open triangles and anisometropic monkey data are represented by filled triangles. The horizontal dashed line represents equal contour integration performance for each eye. Depth of amblyopia does not predict contour integration losses.

(these are the same animals as in Fig. 4B, with the addition of anisometrope CM). There is clearly no consistent relationship between the depth of amblyopia and contour integration performance ($r = 0.54$, $P = 0.27$) for this group of animals. Furthermore, neither grating acuity nor peak contrast sensitivity alone, which are traditional gauges of amblyopia, were predictive of the contour integration loss (acuity: $r = 0.38$, $P = 0.46$; peak sensitivity: $r = 0.65$, $P = 0.16$).

Discussion

The results we have presented show deficient contour integration in *both* strabismic and anisometropic amblyopes. In many cases, contour integration was also poor in *fellow* eyes compared to control eyes. Contour integration deficits are not strongly related to the basic losses in acuity and contrast sensitivity. We found no systematic effect of contrast on the contour detection ability of amblyopes, strabismic or anisometropic, and losses in contrast sensitivity were not predictive of losses in contour integration. Orientation jitter of the elements in the contour had a systematic effect on performance in control and fellow eyes, however, it had relatively less effect on amblyopic eye performance.

Our finding that both strabismic and anisometropic amblyopes are impaired on contour integration is contradictory to some human studies. While all studies of strabismic amblyopes report deficiencies in contour integration (Hess et al., 1997; Kovács et al., 2000; Chandna et al., 2001), Hess and Demanins (1998) reported no interocular difference in contour integration for anisometropic amblyopes provided that the stimuli were equally visible for each eye. In practice, the stimuli were simply high contrast (90%) rather than explicitly matched for effective contrast. Our stimuli were high in contrast throughout, except when directly testing the effect of contrast on the amblyopic and fellow eye. We found no consistent effect of contrast on contour integration generally (Fig. 4A), and reducing stimulus contrast to the level of the amblyopic eye threshold had a normalizing effect on the fellow eye only in two strabismic amblyopes (WW & TX). No anisometropic amblyopes showed this normalization. Thus it is unlikely that stimulus contrast was a factor.

Is this a difference between the monkey model and the natural human case? We think not. None of our monkeys had significant astigmatism (Table 1), so it is unlikely that performance was degraded by meridional amblyopia or uncorrected astigmatism (Verghese & Levi, 2003). Our anisometropic amblyopes are in general deeper amblyopes than the typical human anisometropic amblyope. It is interesting to note that out of the three similarly deep anisometropes tested by Hess and Demanins (1998) only the deepest amblyope showed an interocular difference in contour detection. Also, Chandna et al. (2001) reported a significant correlation between acuity losses and contour integration. Although depth of amblyopia was shown to not correlate with deficits in contour integration in our population (Fig. 7), it is possible that a stronger relationship may be found with a larger group or a broader range of amblyopia. The lens-rearing model imposes defocus rather early in development while anisometropic amblyopia is thought to develop relatively late in humans (see Levi & Carkeet, 1993). Classically, earlier abnormal input disrupts the development of a given visual function more severely than later abnormality (see, e.g. Harwerth et al., 1986; Kiorpes et al., 1989; Daw, 1995). However, we and others have found relatively late development of contour integration (Pennefather et al., 1999; Kovács, 1999; Kiorpes & Bassin, 2003), so the age of onset of significant anisometropia, independently of depth of amblyopia, is unlikely to be a determining factor for this task. In any case, our data are consistent with Chandna et al. (2001), who found deficits in contour integration in the majority of their human anisometropic amblyopes independently from the degree of anisometropia. They argued that treatment history can influence performance on spatial integration tasks, as their subjects were all relatively young, untreated amblyopes. Our monkeys are also untreated amblyopes, thus treatment may be an important factor for the outcome in anisometropic amblyopia.

It is important to note that there is a major task difference between that used by Hess and colleagues and that used in the present study. Hess and Demanins (1998) and Hess et al. (1997) asked their subjects to detect a collinear chain of Gabors in a fixed density of background Gabors (around 1.7 patches/deg^2 for the viewing conditions that most closely approximated ours). Performance (percent correct) was measured as a function of path angle (offset from collinearity of successive elements in the chain). Thus, Hess and colleagues measure is one of tolerance for misalignment at a single noise density. Although thresholds were not actually measured, it is clear from their psychometric data that strabismic amblyopes perform more poorly with their amblyopic eye than with their fellow eye on path detection; in many cases performance is poor even for collinear paths (path angle 0).

In our study, and that of Kovács et al. (2000) and Chandna et al. (2001), detection of a contour was measured as a function of background noise density. This task is a signal-detection-in-noise problem and shows that amblyopes have low noise tolerance. This result is consistent with an earlier study, which showed elevated intrinsic noise in strabismic and anisometropic amblyopes, some of which were also participants in the current study (Kiorpes et al., 1999; see below). As is clear from Figs. 2 and 3, the extent of the deficit varies with relative orientation jitter of the contour elements, but does not vary with contrast (Fig. 4). Furthermore, Kovács et al. (2000) noted that contour element spacing as well as noise density affect the extent of the amblyopic interocular deficit.

Therefore, the particular stimulus conditions used may determine whether or not a deficit is identified; a range of conditions must be sampled to document the nature and the degree of loss.

Orientation jitter substantially degraded contour integration performance in normally sighted control monkeys and in the fellow eyes of amblyopes. Interestingly, orientation jitter had relatively little effect on amblyopic eye noise tolerance. For cases in which we tested a range of orientation jitter values, the functions for the amblyopic eyes were relatively flat. When orientation jitter became large, noise tolerance did not decrease systematically as it did for the fellow eyes. Instead, performance dropped to chance even for the lowest noise density. Also, the range of jitter tolerance was truncated for amblyopic compared to fellow eyes (average range 33 deg for fellow eyes and 18 deg for amblyopic eyes). Previous human studies have not tested amblyopic subjects over a range of orientation jitters at different noise densities so we cannot say if this is a general feature of amblyopic contour integration. Hess et al. (1997) measured percent correct path detection (for a fixed noise density) as a function of element orientation jitter in some strabismic amblyopes. The performance of their amblyopic eyes fell to chance at lower levels of orientation jitter than the fellow eyes, which is consistent with our finding of reduced jitter tolerance.

The range of orientation jitter over which our animals were able to perform the task accurately may seem large. However, it is important to realize that the designated jitter level is the maximum allowable for any given element in the contour and each element's orientation offset is assigned independently (see Kiorpes & Bassin, 2003). Since the patterns are generated anew on every trial, the absolute level of jitter of any given contour element will vary within the specified range, say 60 deg, from trial-to-trial. The probability that any given element will be 30 deg off from perfect alignment is the same as the probability that it will be 5 deg off. Normally sighted human observers tested on the same task (with identical stimuli) show maximum ranges of orientation jitter tolerance between 30 deg and 50 deg; the range for our normally sighted monkey control subjects was 35–60 deg. It is likely that the maximum jitter tolerance will depend on the nature of the task and the manner in which the jitter is generated.

We found compelling evidence for impaired contour integration in many fellow eyes for our subjects compared to controls (Fig. 1). Kovács et al. (2000) also noted poor contour integration performance by some amblyopes with their fellow eyes. Levi and colleagues reported compromised performance for both eyes of amblyopes on a different test of global pattern discrimination (Levi & Sharma, 1998) and on tolerance for positional disorder (Levi et al., 2000). These results suggest that there may be binocular effects on global spatial integration tasks in amblyopia. In addition, there have been a number of reports in the literature of fellow eye deficits on other form discrimination (Giaschi et al., 1992) and local discrimination tasks (e.g. Rentschler & Hilz (1979), Kandel et al., 1980; Leguire et al., 1990; Kozma et al., 2001). Thus, it is important to determine whether or not the fellow eye is "normal" in addition to assessing the relationship between the fellow and amblyopic eye to establish whether or not amblyopes have performance losses.

Oddly, two of our animals were unable to perform the contour integration task to our criterion using their amblyopic eye. We established that each animal could detect the individual Gabor elements. In HN's case, we reduced the spatial frequency of the patches to 2 cycles/deg and doubled their size. For CY, spatial frequency was the standard, 3 cycles/deg, but patch size was increased by 50%. We were able to measure detection thresholds for the individual patches and establish that they could locate the ring with better than 90% accuracy as long as there was a contrast cue, that is, a difference in contrast between signal and noise, or no noise present. HN has been tested on numerous spatial tasks and shows a pattern of elevated thresholds and performance failures on tasks requiring spatial precision (Kiorpes, unpublished data). For example, his amblyopic eye vernier acuity is quite elevated, 5.1 min of arc, on a vernier detection task. Moreover, he was unable to perform a vernier offset discrimination task that required him to indicate the direction of offset (left or right) of the central line segment in a 3-line vernier task. He was also unable detect the structure in static Glass patterns (Glass, 1969), although he could discriminate dynamic Glass patterns from dynamic noise (Kiorpes, 2003). CY also has extremely elevated acuity on vernier detection tasks using his amblyopic eye: 6.9 min of arc. Fellow eye vernier acuity for both monkeys was only slightly elevated compared to normal: 0.68 and 0.75 min of arc for HN and CY, respectively. Normally reared monkeys have vernier acuity in the range of 0.17–0.5 min of arc (Kiorpes, 1992; Kiorpes et al., 1993). This pattern suggests that these animals have severely compromised spatial localization abilities in general. Thus, the perceived location of each element would have a high degree of uncertainty for them and linking the elements of the contour would be impossible in the presence of distractors (i.e. noise patches). The type of amblyopia is clearly not responsible for these animals' failure on the task as one was strabismic and the other anisometropic. HN can be considered a compound amblyope: his esotropia was induced at 4 weeks and he became anisometropic before age 11 weeks. However, TX was also a compound amblyope and he performed relatively well on contour integration. CY has no detectable strabismus, and is therefore a purely anisometropic amblyope.

It is unclear what mechanism accounts for the pattern of our results. To avoid stimulus limitations for the amblyopes, we used relatively low spatial frequency Gabor patches and relatively long presentation times (1 s). We also established that the subjects could detect the individual patches, as well as the overall contour, with each eye. By measuring contrast threshold for the individual Gabor elements, we established that reduced effective contrast did not explain the amblyopic deficit for either type of amblyopia. Therefore, there does not appear to be a low-level explanation based on abnormal encoding of basic stimulus properties. Hess et al. (1997) concluded that the poor performance of their strabismic amblyopes could be modeled by increased positional uncertainty (see also, Hess & Field, 1994). While we did not measure positional uncertainty on this task, we studied the range of tolerance for positional jitter in an earlier (unpublished) study with a different group of amblyopes (Kiorpes & Movshon, 1995). The monkeys were asked to perform a 3-line vernier discrimination task in which the lines were composed of discrete dots, each of which had a positional offset within a specified range of Gaussian distributed jitter. We measured equivalent intrinsic jitter (see Watt & Hess, 1987; Levi et al., 2000) for fellow and amblyopic eyes of anisometropic and strabismic amblyopes, as well as normal controls. Equivalent intrinsic jitter was elevated by a consistent factor of about 3.5 for amblyopic eyes (avg. normal, fellow 0.53 min; avg. amblyopic 1.9 min). However, this elevated intrinsic jitter is unlikely to have influenced our results because the elements in the ring had a larger, inherent positional jitter (25%; see Methods), which encompassed a range of up to 12 min. The vernier acuity deficit in high jitter, beyond the equivalent intrinsic jitter level, can be thought of as a jitter signal/noise ratio. Jitter signal/noise was also elevated but to a smaller degree: a factor of about 1.5 (avg. normal, fellow ratio 0.52.; avg. amblyopic ratio 0.75). Elevated signal/noise ratio, which could result from greater positional uncertainty, could in principle reflect a central "noise floor" which stimuli must exceed to be detected. The range of deficits found in the present study largely exceed a factor of 1.5 (interocular ratios in Figs. 4B & 7; range 1.3–3.2) but one can imagine the process of linking contour elements, as well as simply locating them, as amplifying a basic positional uncertainty.

The foregoing analysis does not exclude the possibility of a primary increase in positional uncertainty in amblyopia, however, positional uncertainty is but one of many types of "noise" that could be affecting vision in amblyopes. In an earlier study, which included all of the amblyopes in the present study, we examined the more general idea that amblyopes suffer from heightened internal noise (see Kiorpes et al., 1999). We measured equivalent intrinsic noise and central signal/noise ratio using a noise masking paradigm (cf. Pelli, 1990). The monkeys were asked to detect a grating pattern as a function of contrast over a range of added random spatiotemporal broadband noise. All of the amblyopes in the present study showed elevated equivalent intrinsic noise which did not completely account for their poor performance. All but one, WW, also showed compromised signal-to-noise processing meaning that there were persistent interocular deficits in high noise. Since the same animals were tested across studies, we evaluated the idea that contour integration deficits were predictable from the elevated signal/noise ratio. In fact, we found that this was the case ($r = 0.89$, $P = 0.017$). This analysis supports the idea that elevated intrinsic noise generally can account for the contour integration deficits in our amblyopes. Several recent studies in human amblyopes have also concluded that elevated central noise is a likely substrate for amblyopic deficits (Wang et al., 1998; Sharma et al., 2000; Levi & Klein, 2003).

The remaining challenge is to identify the neural "noise" mechanism. Physiological investigation of neuronal response properties in striate cortex (V1) of behaviorally verified amblyopic monkeys failed to find evidence of abnormality in basic neuronal selectivity (Kiorpes et al., 1998). Orientation tuning and bandwidth as well as spatial and temporal bandwidths were similar for amblyopic and fellow eye neurons. This suggests that local organization of the primary V1 filters is not abnormal. The primary deficit among the cells driven by the amblyopic eye in monkeys with strabismic or anisometropic amblyopia was a reduction in acuity, similar to the behavioral acuity deficit but smaller in extent (Movshon et al., 1987; Kiorpes et al., 1998). Reduced contrast sensitivity has also been reported in populations of amblyopic V1 cells (Movshon et al., 1987; see also, Kiorpes & Movshon, 2003).

Anatomical evidence for cortical abnormalities in amblyopia is elusive. The pattern of long-range horizontal connections in V1, which is presumed to be an important mechanism underlying contour integration (see Kiorpes & Bassin, 2003, for discussion), has been studied in strabismic monkeys, some of which had documented amblyopia (Tychsen & Burkhalter, 1992, 1995; Tychsen et al., 1996). While "between-eye" connections were abnormal or absent, connections made to "same-eye" columns appeared normal and were presumed to link neurons with similar preferred orientations as they do in nonstrabismic cortex. Furthermore, Lowel and Engelmann (2002) used a combination of optical imaging and neuroanatomical tracing techniques to investigate the anatomy of long-range connectivity in V1 of strabismic amblyopic cats. They confirmed the monkey data showing a monocular pattern of connectivity. It is important to note though that these connections are typically monocular in normal cortex as well (Malach et al., 1993), so it is not clear that long-range connectivity is particularly abnormal in amblyopia. The overall pattern of binocular organization is disrupted in amblyopic monkeys (Hendrickson et al., 1987; Movshon et al., 1987; Smith et al., 1997; Kiorpes et al., 1998), although there is no evidence of abnormal periodicity of ocular-dominance organization (Horton et al., 1997; Tychsen & Burkhalter, 1997; Murphy et al., 1998). It is possible that the monocular connections are imprecise locally, so that they link cells of matching eye dominance but of nonmatching orientation. However, this is unlikely given that Lowel and Englemann (2002) showed similar connection patterns *within* domains for each eye as indexed by patterns of orientation preference and selectivity following stimulation of either eye. Lowel and Singer (1992) have argued that the formation and/or maintenance of precise local connections is dependent on correlated activity. Therefore the reduced correlation, or synchrony, of neurons driven by the amblyopic eye reported in strabismic amblyopic cats (Roelfsema et al., 1994; Lowel & Englemann, 2002) could reflect local imprecision or imbalance of subsequent connectivity. But at the moment it is unclear whether reduced synchrony is due to weak inputs, disrupted connectivity, a temporal abnormality of feedback signaling, or any of a number of other possibilities.

It is also possible that the amblyopic deficit in contour integration depends on processes beyond V1. Numerous physiological studies in monkey and human (using brain imaging) have evaluated the idea that contour integration depends on processing downstream from V1 and/or within the feedback circuits between V1 and higher visual cortical areas (see Kiorpes & Bassin, 2003, for discussion). There is currently considerable disagreement among authors on the "site" of contour integration. There is also considerable disagreement as to the "site" of amblyopia. The physiological and anatomical abnormalities that have been noted in amblyopic V1 (reviewed above) are comparatively mild considering the dramatic deficits identified psychophysically in humans and in nonhuman primate models. fMRI studies of amblyopia are inconsistent at best. Most studies report some activation decrease in V1 with amblyopic eye viewing compared to fellow eye viewing (e.g. Goodyear et al., 2000, 2002; Barnes et al., 2001; Algaze et al., 2002), while others report activation reductions beyond V1 (Imamura et al., 1997; Barnes et al., 2001). Our psychophysical data suggest that primary spatial filters are not responsible for the contour integration deficits.

We and others have identified elevated central noise as an important potential substrate for amblyopia. It is interesting then to ask what constitutes "central" in this context. In the Pelli scheme (Pelli, 1990; also Barlow, 1977), equivalent intrinsic noise reflects a "peripheral" visual system limitation while the signal/noise ratio represents a central limitation. We have used the noise-masking method described above to study the level of equivalent intrinsic noise in infant lateral geniculate nucleus (LGN) neurons (Movshon et al., 1994; Kiorpes & Movshon, 2003). We found that equivalent intrinsic noise limitations lie downstream of the LGN. Therefore, peripheral in this case is at best at the level of V1, and central is even later in the system. The fact that we and others have identified substantial deficits in fellow eye performance on contour integration and context-based tasks also points to a higher level mechanism where information from the two eyes is pooled in relatively large receptive fields.

In summary, the contour integration deficits we report are found in anisometropic as well as strabismic amblyopes, and in some fellow eyes as well as amblyopic eyes. The deficits are not simply a reflection of primary losses in acuity or contrast sensitivity. We show that this disorder of global processing in amblyopia may be due to elevated central noise in amblyopes. We suggest that the mechanisms responsible for global visual integration in general, and contour integration in particular, lie either beyond V1 or in the pattern of projections between V1 and extrastriate visual areas, and that these higher order mechanisms are affected in amblyopia.

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