



Abnormal Long-range Spatial Interactions in Amblyopia

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Neural interactions between widely separated stimuli were explored with psychophysical and visual evoked potential (VEP) measures in normal and amblyopic observers. Contrast detection thresholds were measured psychophysically for small foveally viewed Gabor patches presented in isolation and in the presence of similar, but laterally displaced flanks. The amplitude and phase of VEPs elicited by similar targets were also measured. The presence of neural interaction between the target and flank responses was assessed by comparing the unflanked threshold to the flanked threshold in the psychophysical experiments and by comparing the response predicted by the algebraic sum of test and flank responses to that measured when test and flanks were presented simultaneously. In normal observers simultaneous presentation of test and flank targets produces a VEP response that is up to a factor of two larger than the linear prediction (facilitation). Psychophysical threshold is also facilitated by a comparable factor. Facilitation was found mainly for configurations in which local (carrier) and global (patch) orientations resulted in collinearity, independent of global orientation (meridian). Amblyopic observers showed several deviations from the normal pattern. The facilitation for the collinear configurations was either markedly lower than normal or was replaced by inhibition. The normal pattern of spatial interaction may facilitate the grouping of collinear line segments into smooth curves. In contrast, abnormal long-range spatial interactions may underlie the grouping disorders and perceptual distortions found in amblyopia.

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Amblyopia Long-range-interaction Detection Grouping Evoked potentials

INTRODUCTION

Amblyopia is a disorder of spatial vision that is due to abnormal binocular interaction during a developmental critical period. Amblyopia is defined clinically as reduced visual acuity that occurs in the absence of ocular structure abnormalities. In addition to acuity loss for optotypes and gratings, amblyopia causes reduced contrast sensitivity (Bradley & Freeman, 1981; Hess & Howell, 1977; Gstalder & Green, 1971; Levi & Harwerth, 1977), vernier acuity (Bradley & Freeman, 1981; Levi & Klein, 1982a, b), crowding (Levi & Klein, 1985) and spatial distortion (Bedell & Flom, 1981, 1983; Hess *et al.*, 1978; Lagrèze & Sireteanu, 1991; Sireteanu *et al.*, 1993). Current theoretical explanations of the amblyopic deficit (Hess *et al.*, 1990; Levi, 1991; Morgan, 1991; Wilson, 1991; Wilson *et al.*, 1990) are based on perturbations of the responses of arrays of localized, orientation selective spatial channels.

Recently, long-range *excitatory* and *inhibitory* inter-

actions have been found psychophysically (Polat & Sagi, 1993a, 1994a,b, 1995) and neurophysiologically (Polat & Norcia, 1996). The visibility of a small foveally viewed Gabor patch can either be enhanced or suppressed by laterally placed Gabor patches of similar orientation and spatial frequency. The sign of the effect, enhancement or suppression, depends on target and flank separation and on the relative orientation of the target and its flanks. Maximal facilitation occurs for co-oriented, collinear targets that are separated by several wavelengths of the spatial frequency of the Gabor patches. This facilitation is independent of the target and mask orientations and locations (meridian). These interactions suggest that spatial filtering is more complex and less local than is typically assumed in computational models of normal and amblyopic vision.

The pattern of results observed by Polat & Sagi (1993a, 1994a,b) and Polat & Norcia (1996) indicates that lateral interaction occurs over considerable distances and depends not only on separation, but on relative orientation of test elements and their contrast. Since abnormal spatial interactions are the defining feature of the amblyopic crowding effect, we felt that studying lateral interaction with techniques that can probe both facilitatory as well as inhibitory interactions might lead to a better understanding of spatial interaction in amblyopia.

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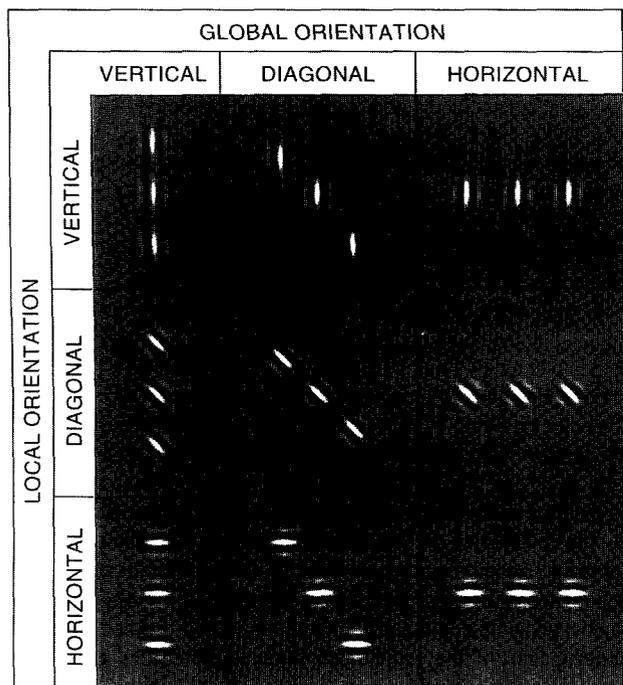


FIGURE 1. Experimental stimuli—psychophysical experiments. Three Gabor signals were positioned along the vertical, diagonal and horizontal meridians (global orientation). For each global orientation, each combination of three local orientations (vertical, horizontal and oblique) were presented. In all the experiments the central Gabor target coincided with the fixation point. The Gaussian envelope size ($\sigma = \lambda = 0.15$ deg) was selected so that at least one cycle would be within a range of $\pm \sigma$ from the Gaussian center. The carrier spatial frequency of the Gabor signals was 6.6 cpd ($\lambda = 0.15$ deg). Mask contrast was 0.4.

To anticipate, we have found that the pattern of long-range lateral interaction in amblyopic eyes differs not only quantitatively from that of normals, but also qualitatively. Parts of these experiments have been reported in abstract form (Polat & Sagi, 1993b; Polat & Norcia, 1995a,b).

METHODS

Observers

Two groups of amblyopic observers (three in the psychophysical and six in the VEP experiments) were compared to two groups of normal observers (three in psychophysical and six in the VEP experiments). All observers were fully corrected for the viewing distances used in the experiments. The optotype acuities of the amblyopic eyes ranged between 6/12 and 6/30. Strabismic, anisometropic and patients with both strabismus and anisometropia were tested. Since the sample sizes in the two experiments were small, we have made no effort to separately analyze the data as a function of clinical classification or severity.

Psychophysics

Stimuli consisted of three Gabor patches arranged in

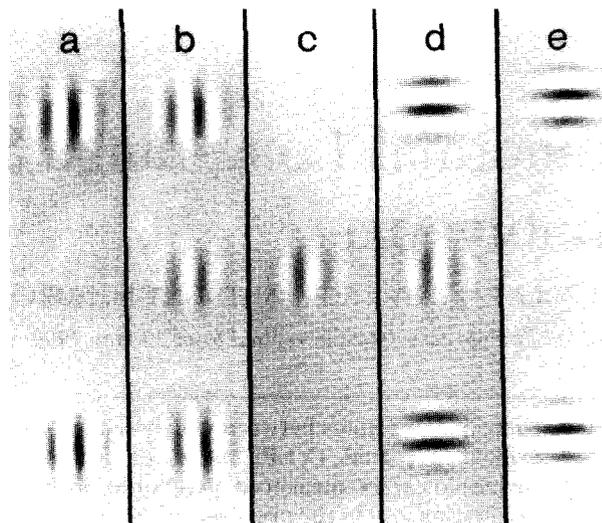


FIGURE 2. Experimental stimuli—VEP experiments. Gabor patches (0.3 deg standard deviation, 3 c/deg carrier) were temporally modulated at 4.1 Hz in On/Off mode at contrasts of 4, 8, 16 and 32% with no change in space average luminance (160 cd/m^2). The series of foveal Gabors were either presented alone (c) or in the presence of two flanking Gabor patches (b, d) of the same spatial frequency but of fixed contrast (50% contrast). The flanks, also modulated at 4.1 Hz, were placed 2 deg above and below the foveal Gabor and were oriented either vertically [collinear, (a)] or horizontally [non-collinear (e)]. The flank response was also measured separately. The Gabor patches were presented in the middle of a 13.8 by 10.40 field set to the mean luminance of the patches.

the spatial configurations depicted in Fig. 1. All combinations of three local (vertical, diagonal and horizontal) and three global orientations (vertical, diagonal and horizontal) were presented in separate threshold runs (one condition is not illustrated in the figure). The observers fixated the central Gabor patch monocularly from a distance of 180 cm. Contrast threshold for the central (fovea) Gabor patch was measured with and without the flanking masks. The carrier spatial frequency of both the target and masks was 6.6 cpd ($\lambda = 0.15$ deg). Mask contrast was 40% and test-mask distance was 3λ . Three to four threshold estimates for a given configuration were averaged for each observer. Thresholds were estimated by a two alternative, forced-choice staircase procedure. Further details are provided in Polat & Sagi (1993a).

Visual evoked potentials

To elicit time-locked evoked activity, the Gabor patches (0.3 deg standard deviation, 3 c/deg carrier spatial frequency) were temporally modulated at 4.1 Hz in On/Off mode at contrasts of 8, 16 and 32% with no change in space average luminance (160 cd/m^2). The series of foveal Gabors were either presented alone [Fig. 2(c)] or in the presence of two flanking Gabors [Fig. 2(b, d) of the same spatial frequency but of fixed contrast (50%). The flanks, also modulated at 4.1 Hz, were placed 2 deg (6λ) above and below the foveal Gabor and were oriented either vertically [collinear, Fig. 2(b)] or

horizontally [non-collinear, Fig. 2(d)]. The amplitude and phase of the VEP at the first four harmonics of the stimulus frequency were determined by a Recursive Least Squares adaptive filter (Tang & Norcia, 1994). The EEG was digitized at 397 Hz over an amplifier passband of 1–100 Hz (6 dB). The recording montage comprised five electrodes arranged in a cross array over O_z each referenced to C_z (3 cm inter-electrode spacing). The first harmonic component (F_1) was the largest and most consistent component across observers. All the data reported below were based on measurements at F_1 selected from the recording channel with the lowest statistical error, as assessed by the T^2_{circ} statistic (Victor & Mast, 1991). The flank responses from stimuli shown in Fig. 2(a) and Fig. 2(e) were also measured. Test-alone and flank-alone VEPs were summed vectorially and compared to the measured response to test plus flank together. Further details are provided in Polat & Norcia (1996).

RESULTS

Psychophysical thresholds

The psychophysical data are presented as the log of the ratio of the masked and unmasked contrast thresholds. Values greater than zero indicate that the flanks produced a threshold reduction (facilitation) and values less than zero indicate that masking produced a threshold elevation. This normalization allows us to examine effects due to different global configurations, regardless of the local carrier orientations which may have different thresholds due to orientational anisotropies. The test–mask distance was 2–3 wavelengths (λ) of the carrier spatial frequency. Stimulus separations were set in terms of λ units rather than absolute distances, because threshold facilitation curves as a function of test-to-mask distance scale with λ (Polat & Sagi, 1993a).

Figure 3(a) presents the results of three normal observers redrawn from Polat & Sagi (1994a). Each bar represents the mean facilitation index for an individual observer pooled across the three collinear configurations (0 offset between local and global orientations), the three 45 deg offset configurations and the three 90 deg offset configurations. Maximal threshold facilitation was found when the triplet conjoined the same local and global orientations (collinear configuration, zero offset). A 45 deg offset yielded the smallest degree of facilitation and 90 deg offsets yielded facilitation over the unmasked threshold varying from 0 to 50% (cf. Polat & Sagi, 1994a). In the normal observers, the masking effect was consistent across global orientations, with the same offsets as indicated by the relatively small degree of variance shown by each observer in each set of conditions.

Figure 3(b) presents the results of three amblyopic observers, using the same format as in Fig. 3(a). In contrast to the normal observers, one of the amblyopic observers (EG) showed a highly variable pattern of interaction within each of the offset conditions. For

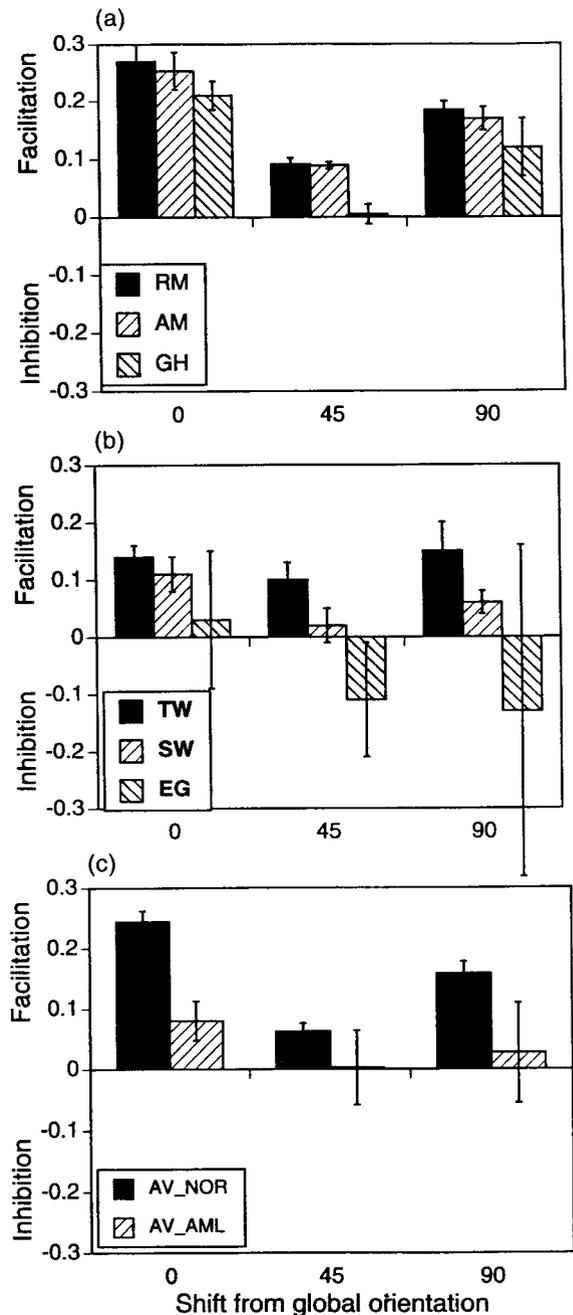


FIGURE 3. Psychophysical data presented as the log ratio of the masked and unmasked contrast thresholds. (a) Presents the results of three normal observers. Each bar represents the mean facilitation index for an individual observer pooled across the three collinear configurations (0 offset between local and global orientations), the three 45 deg offset configurations and the three 90 deg offset configurations. Facilitation is maximal for collinear configurations, followed by 90 and 45 deg offset configurations. (b) Presents the results of three amblyopic observers, using the same format as in (a). Overall facilitation is lower, with high variability within a configuration. (c) Group data from the amblyopic and normal observers for each set of offset configurations (normals, dark bars; amblyopes, hatched bars). Amblyopic observers have less facilitation, especially for the collinear configurations (0 offset) where the normal observers showed about a factor of 3 more facilitation.

example, inhibition was found for all 45 deg offset configurations and even in the collinear configuration for the vertical global orientation. Another observer (TW) showed the same small amount of facilitation for all

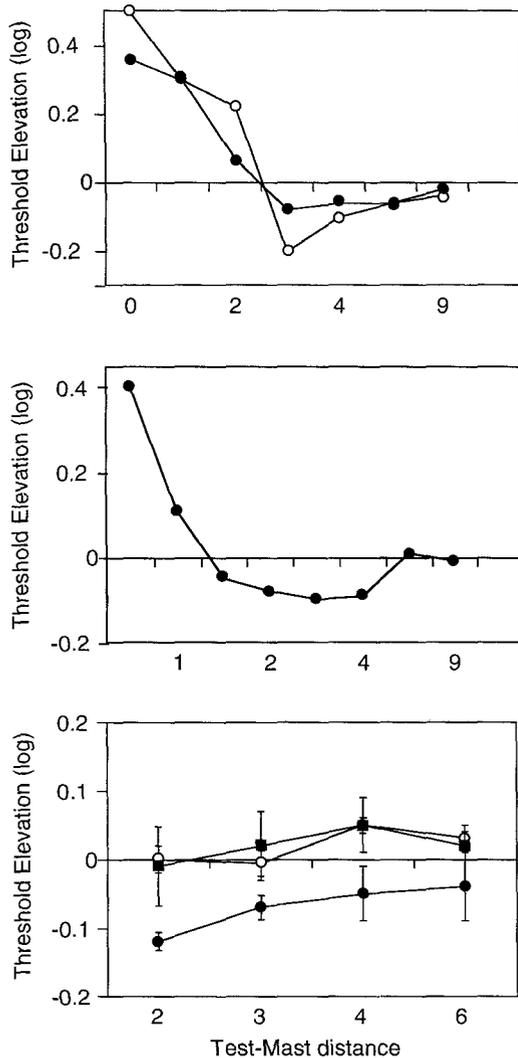


FIGURE 4. Psychophysical threshold facilitation and suppression as a function of target-mask separation: amblyopic observers. The top panel plots data for the amblyopic (solid circles) and fellow eye (open circles) of observer SW. Fellow-eye interaction shows a pattern that is quantitatively and qualitatively similar to that of normals. The amblyopic eye shows reduced suppression at small separations and reduced facilitation over the 2–4 λ range. The middle panel plots data from observer TW's amblyopic eye. Facilitation occurs over the range of 2–4 λ , as it does in normals, but the magnitude of facilitation is reduced. The bottom panel plots data from observer TW's amblyopic eye for the three configurations shown in the first column of Fig. 1. The solid circles are from the collinear configuration. Facilitation is present, but at a lower level than is seen in normals. The two other iso-orientation conditions do not show facilitation (see text for details).

configurations and another (SW) showed the same pattern as normals, however, maximal facilitation was only 0.1 log units. This observer was the most highly experienced of the three amblyopic observers.

Group data from the amblyopic and normal observers are presented in Fig. 3(c), for each set of offset configurations (normals, dark bars; amblyopes, hatched bars). The facilitation effect for the collinear configurations (0 offset) was lower than that of the normal observers by about a factor of 3. Facilitation was reduced in the other two offset configurations.

Effect of spatial separation

In two of the amblyopic observers (SW and TW) we obtained complete threshold facilitation functions over a range of test-mask separations. These results are presented in Fig. 4. Observer SW provided data for both her amblyopic [open symbols, Fig. 4(a)] and fellow eyes [solid symbols, Fig. 4(a)]. The threshold function for the fellow eye is similar to that seen in normal observers (Polat & Sagi, 1993a, 1994a) in the magnitude of the facilitation and suppression effects and the separations at which they are maximum. The amblyopic eye shows less suppression at small separations and less facilitation at 2–4 λ . The shape of the functions is not appreciably different from that of normals. Similarly, for observer TW, maximal facilitation is reduced from that seen in normals, but it occurs at the same range of separations [Fig. 4(b)].

Figure 4(c) presents additional data from observer TW, taken several months after the data of Fig. 4(c) were collected. In each data set, the global orientation was vertical and the local orientations were either vertical (collinear), oblique or horizontal (first column of Fig. 1). For each configuration, a portion of the threshold facilitation function for the collinear targets shown in Fig. 4(b) was tested. The data from the collinear configuration (solid circles) are very similar to those obtained in the earlier sessions. Facilitation was not seen for either of the other configurations.

VEP interactions

VEP data from six normal and six amblyopic observers are presented in Fig. 5. The amblyopic eye response was compared to the dominant eye of normal observers. The data are presented as the log ratio of the flanked response relative to that of the algebraic sum of the isolated test and flank responses (Polat & Norcia, 1996). This response normalization procedure allows us to examine effects regardless of the test response amplitude which may be different due to amblyopia or orientational anisotropies. In normal observers, the interaction index is significantly above the linear prediction for the collinear configuration at 8% contrast, indicating facilitation. At 16 and 32% contrast facilitation has declined and is no longer significantly higher than the prediction. In the amblyopic observers, significant inhibition was found at 16% contrast. The measured response was not significantly different than the prediction at 8 and 32% contrast. For the orthogonal configuration, suppression was observed at 16 and 32% contrast in normal observers. For the amblyopic observers, there is no significant interaction at any contrast, although there is a trend for facilitation to occur at 32% contrast. At 32% contrast, individual amblyopic observers exhibited facilitation of their response—a pattern never seen in normals for the orthogonal configuration.

DISCUSSION

Normal eyes show psychophysical threshold facilitation in all configurations, with maximal facilitation

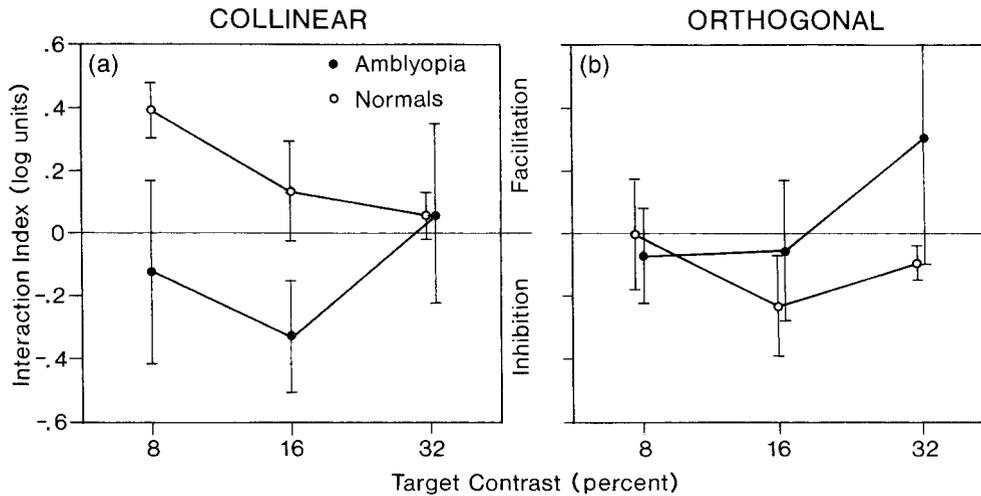


FIGURE 5. VEP interaction indices for six normal and six amblyopic observers. The amblyopic eye response (solid circles) is compared to the dominant eye of normal observers (open circles). Positive values of the interaction index indicate response facilitation and negative ones indicate suppression. Normal observers show significant facilitation for collinear configurations at 8% test contrast. By contrast, amblyopic observers showed suppression (at 16% test contrast). For the orthogonal configuration (b) suppression was observed at 16 and 32% contrast in normal observers. For the amblyopic observers, there was no significant interaction at any contrast, but individual observers showed facilitation at 32% contrast.

occurring in the collinear configurations (Polat & Sagi, 1994a). Individual differences across stimulus conditions, within a given set of configurations were small. By contrast, the amblyopic observers showed considerable individual differences. The degree of test mask interaction could vary considerably, even within a given set of stimulus configurations that had the same offset between local and global orientations. Moreover, two of the three amblyopic observers showed suppressive interactions for at least one stimulus configuration, a pattern never seen in normal observers. When the data from the amblyopic eyes were pooled across observers, they showed reductions of psychophysical threshold facilitation in all three offset conditions.

The amblyopic abnormality in our task appears to involve primarily changes in the magnitude or sign of the interaction between test and mask, rather than a wholesale rescaling of the interaction zone. That is, facilitation did not occur at a larger or smaller separation than it does in normals (Fig. 3). Our data on this point are limited, and further investigation is needed, especially since Flom *et al.* (1963) have found that the range of contour interaction in letter recognition scales with the resolution of the amblyopic eye.

In the VEP experiment, a vertical collinear configuration leads to a nonlinear facilitative interaction over a range of low suprathreshold contrasts in the dominant eye of normal observers. This pattern of results is similar to that seen binocularly by Polat & Norcia (1996) and in single units of cat striate cortex (Mizobe *et al.*, 1996). The effect has been modeled by Stemmler *et al.* (1995) as being due to a higher threshold for long-range inhibitory interactions. As in the psychophysical experiments, some amblyopic observers showed a suppressive interaction between test and mask in the collinear configuration. The VEP experiments also examined interaction for stimuli

that contained orthogonal local orientations of test and mask. Under these conditions, normal observers showed suppression at 16 and 32% contrast, similar to what was found binocularly by Polat & Norcia (1996). At the lowest contrast, no interaction was found in agreement with Polat & Sagi (1993a), who showed no interaction at psychophysical threshold with the same configuration. Amblyopic observers, by contrast showed no significant interaction for all contrasts when considered as a group. Individual amblyopic observers, however, showed significant facilitation in the orthogonal configuration, a pattern never seen in normal observers.

Before concluding that the pattern of results observed in the amblyopic eyes is due to abnormal neural interaction, we will consider possible extraneous variables that may have affected the performance of the amblyopic eyes. Amblyopes may have inaccurate or unsteady fixation and or accommodation (Ciuffreda *et al.*, 1980). Any of these variables could reduce contrast sensitivity or VEP amplitude for the test or mask or the combination. However, it is unlikely that global oculomotor instabilities would vary significantly across stimulus configuration. By normalizing the test plus mask data to the unflanked test results, we should have eliminated these effects from the measures of interaction. Moreover, inaccurate fixation would be expected to affect performance most for vertical stimuli, since drift in amblyopic eyes is primarily horizontal and would, therefore, smear vertical contours. However, we found that the strongest effect psychophysically is not in the vertical meridian, but rather in the oblique and horizontal meridians. Unstable accommodation of the amblyopic eye should affect all the configurations similarly, but we find differential effects that are configuration-dependent both within and across observers. In the VEP experiments, unsteady fixation and accommodation should

have the same effect on the predicted and the measured responses since the targets were the same in each case. However, the pattern of non-linear interaction is clearly different in the amblyopic eyes. Again, oculomotor instabilities should not affect the collinear configuration more than the orthogonal one.

Models of amblyopia

Several psychophysical models have been proposed to explain the abnormalities of spatial vision seen in amblyopia (Hess *et al.*, 1990; Levi, 1991; Morgan, 1991; Wilson *et al.*, 1990; Wilson, 1991). These models have considered how the response of a set of independent spatial filter mechanisms is degraded in amblyopia by reduction in filter number, filter sensitivity and scrambling of filter location labels. The abnormal spatial interactions we have found in amblyopia are unlikely to be due to lowered contrast sensitivity *per se*. Maximal facilitation magnitude in normal observers is independent of the isolated target sensitivity (Polat & Sagi, 1994a). The facilitation values obtained for the different local orientations within the collinear configurations are about the same, although local target thresholds differ. Thus, the parameter affecting enhancement of target detection is the difference between global and local orientations (pattern configuration) and not the observer's local target sensitivity. Neither undersampling or positional uncertainty predicts differential effects of the specific configuration (collinear, 45 deg offset, 90 deg offset). More importantly, models with independent filters have a difficult time predicting any sort of configurational effects, especially for widely separated targets such as we have used (Wilson, 1991).

Rather than positing that the visual image is decomposed by a bank of independent linear spatial filters of different scales, we argue that local sensitivity (as measured by the test threshold or isolated test VEP) is modulated by contextual information pooled in specific patterns over a large area. In normal observers, pooling is done preferentially along the orientation axis, as has been shown psychophysically (Kapadia *et al.*, 1995; Field *et al.*, 1993; Kovács & Julesz, 1993; Mussap & Levi, 1995; Polat & Sagi, 1994a,b) and electrophysiologically (Bosking & Fitzpatrick, 1995; Kapadia *et al.*, 1995; Mizobe *et al.*, 1996; Polat & Norcia, 1996; Polat *et al.*, 1996). Collinear facilitation is likely to be at least partially responsible for the enhancement of contrast sensitivity for extended contours seen in the psychophysical tasks of Kovács & Julesz (1993) and Field *et al.* (1993). In those studies, detection of a path consisting of a series of widely separated, non-randomly oriented Gabor patches embedded in a background of randomly oriented Gabor patches depends on the smoothness of the gradient produced by the local orientations comprising the path and on contour closure. Collinear facilitatory interactions may increase the saliency of smooth contours, but they are unlikely to explain the additional effects of contour closure (cf. Kovács & Julesz, 1993).

Orientation-specific facilitative interactions may sub-

serve a binding function by which targets with similar stimulus properties and configurational continuity are linked together (Kapadia *et al.*, 1995; Kovács & Julesz, 1993; Polat *et al.*, 1996; Polat & Sagi, 1994b). Amblyopes fail dramatically in the Kovács & Julesz (1993) binding task (Kovács *et al.*, 1996). In Kovács *et al.* (1996), we could not mimic the amblyopic deficit in normals by blurring or undersampling the image or by spatial jitter.

A reduction of the efficacy of long-range pooling mechanisms may contribute to lowered contrast sensitivity for extended targets in the amblyopic eye. That is, a loss of long-range connectivity could lower the visibility of extended contours such as those present in gratings. However, our present results point to the possibility of deeper abnormalities of spatial integration in amblyopic eyes. Some observers showed patterns of interaction that are simply not seen in normal observers. In particular, EG showed a suppressive interaction for the collinear configuration rather than a facilitative one. Such inappropriate patterns of interaction may affect the processing of stimuli that are placed in complex contexts. Abnormal patterns of interaction elicited by spatially separated, oriented stimulus elements may contribute to the well known crowding effect, whereby acuity is degraded by the presence of nearby contours.

Physiological basis of long-range interactions

The long-range lateral interactions we have observed may have as their basis the long-range horizontal intrinsic connections that have been observed in visual cortex (Blasdel *et al.*, 1985; Callaway & Katz, 1990; Gilbert & Wiesel, 1983, 1989; Malach *et al.*, 1993). These connections run over long distances in cortex (Gilbert & Wiesel, 1989; Luhmann *et al.*, 1986) and are thought to interconnect cells with similar stimulus preferences (Gilbert & Wiesel, 1989; Luhmann *et al.*, 1986; Malach *et al.*, 1993; Ts'o *et al.*, 1986; Das & Gilbert, 1995). These connections are refined post-natally in an experience-dependent fashion (Callaway & Katz, 1990; Löwel & Singer, 1992) and they have a later critical period than do local intrinsic connections (Burkhalter *et al.*, 1993).

Long-range intrinsic connections are believed to underlie the non-classical surrounds of cortical receptive fields (Hirsch & Gilbert, 1991). Using the same paradigm we have used in the VEP experiments, we (Mizobe *et al.*, 1996; Polat *et al.*, 1996) have found that flanks placed outside of the classical receptive field modulate the discharges of isolated single units in cat striate cortex. Response modulation from the non-classical surround was orientation specific—collinear flanks facilitated the center response over a range of low contrasts and orthogonal masks inhibited the center response. Similar results have been found for monkey V1 using line segments (Kapadia *et al.*, 1995). The amblyopic deficit may thus be due, at least in part, to abnormalities in the interaction between the classical receptive field and its non-classical surround.

It has been suggested (König *et al.*, 1993; Singer &

Gray, 1995; Roelfsema *et al.*, 1994) that abnormal synchronization of oscillatory activity may underlie the amblyopic deficit. Synchronized oscillatory interactions between horizontally separated cells are also thought to depend on long-range intrinsic connections. Oscillatory synchronization tends to be largest when the cells have the same orientation preference (Eckhorn *et al.*, 1988; Gray *et al.*, 1989). Oscillatory coupling between co-oriented collinear receptive fields has been observed over distances of at least 7 mm in cat cortex (Gray *et al.*, 1989) and it has been suggested that synchronization serves to bind disparate but related parts of the visual image that have the same temporal phase (see Singer and Gray, 1995). Synchronized activity among cells connected to the amblyopic eye is much less robust than that observed among cells responsive to the normal eye (Roelfsema *et al.*, 1994). Moreover, in strabismic cats, response synchronization does not occur between cell groups connected to different eyes, but it appears to be normal between cell groups connected to the same eye (König *et al.*, 1993).

What relationship exists between our findings of abnormal long-range interaction in amblyopia and failures of response synchronization in experimental models of amblyopia is unclear at present. Synchronization of the oscillatory component of cell responsiveness is a form of long-range, non-linear interaction as is the interaction observed in our test/mask paradigm. However, unlike our responses, the oscillatory components of cell responses, while being stimulus related are not stimulus locked (see Singer and Gray, 1995). Our results indicate that non-linear interactions also occur between the stimulus-locked responses themselves, and that these long-ranging lateral interactions are abnormal in amblyopia.

In summary, failure to develop a normal pattern of long-range connections may contribute to the distortions of spatial vision that are characteristic of amblyopia, not only through a loss of synchronized oscillations, but through a fundamental reorganization of the pattern of functional interaction between the stimulus-evoked activity of orientation and configuration-selective mechanisms. Loss of appropriate configuration-specific interactions may also contribute to a loss of contrast sensitivity for extended patterns.

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