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NOVARTIS FOUNDATION MEETING REVIEW

Visual Processing in Amblyopia: Animal Studies

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ABSTRACT In the past five years, substantial progress has been made in our knowledge of the neural basis of amblyopia. Recent advances based on animal models are described, along with new psychophysical data showing perceptual deficits in amblyopic animals that are not explained by simple losses in contrast sensitivity. Studies of contour integration and integration of motion and form signals in the presence of noise show that 1) there are fundamental losses in temporal as well as spatial vision, 2) the losses extend to the fellow eye in many cases, 3) amblyopic animals are especially impaired in the presence of background noise, and 4) these losses must depend on a process downstream from area V1 in the extrastriate cortex.

KEYWORDS Amblyopia pathogenesis; visual processing; visual cortex; contrast sensitivity; perceptual deficit; contour integration; cats; macaque monkeys

INTRODUCTION

Substantial progress has been made over the past five years in our understanding of the development of and neural mechanisms underlying amblyopia. Much of this progress is the result of work with animal models. The dominant model species for research in amblyopia are cat and macaque monkey. Led by the early work of Wiesel and Hubel, showing disruption of the binocular organization of the visual cortex following deprivation of vision through one eye in developing animals (Hubel et al., 1977; Wiesel, 1982; Wiesel & Hubel, 1963, 1965), there was an expectation that the site of the primary neural loss in amblyopia would be the primary visual cortex, area V1. While animal studies have identified deficiencies in the neural properties of area V1 in amblyopia, these losses are not sufficient to account for the identified losses of spatial vision as measured by behavior (Kiorpes, 2002; Kiorpes & McKee, 1999; Kiorpes et al., 1998). Thus, the data suggest that neuronal abnormalities in area V1 represent the first site of amblyopia in the visual pathways, but point to important neural processing deficiencies further along the visual pathway in extrastriate visual areas. In this paper, I will briefly summarize findings on the nature of area V1 organization in amblyopia and describe recent behavioral and neurophysiological data that support the idea of amblyopia as a disorder involving far more perceptual disruption

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than was previously believed, and one that depends on losses beyond area V1.

REVIEW AND DISCUSSION

Amblyopia at its most basic level is a loss of visual acuity in one eye that is not due to an obvious organic defect and is not correctable by spectacle lenses. Several recent reviews have described the relationship between the acuity loss in amblyopic monkeys and the spatial properties of neurons in area V1 (Kiorpes, 2002; Kiorpes & MeKee, 1999; Kiorpes & Movshon, 2003). There is no evidence of abnormality in receptive field properties of neurons earlier in the visual pathway (Blakemore & Vital-Durand, 1986; Levitt et al., 2001; Movshon et al., 1987). The studies show that there is a shift of neuronal "acuity" to lower spatial frequencies, consistent with a behavioral acuity deficit, although this shift is small in comparison to the actual acuity loss measured behaviorally (Kiorpes et al., 1998). Schmidt et al. (2004), using optical imaging, found a weakening of cortical activation for mid to high spatial frequency stimuli in amblyopic cats that correlated well with losses in visual function as measured by another electrophysiological assay, the VEP. Similarly, Crewther and Crewther (1990) found a close relationship between VEP acuity in strabismic cats and neuronal acuity in area V1. Some studies report a reduction in neuronal contrast sensitivity that reflects the behavioral loss noted in many amblyopes (Movshon et al., 1987), but this is an inconsistent feature of the data across studies (Kiorpes & Movshon, 2003). Other properties of area V1 neurons, such as orientation and direction specificity, appear to be normal (Chino et al., 1991; Crewther & Crewther, 1990; Kiorpes et al., 1998; Movshon et al., 1987).

Optical imaging has been used to evaluate the quality of orientation and ocular dominance organization in the amblyopic area V1. These highly characteristic cortical maps (Bartfeld & Grinvald, 1992; Blasdel, 1992a, 1992b; Ts'o et al., 1990) are found not to be different from normal. The spacing of ocular dominance domains is largely normal (Horton et al., 1997; Murphy et al., 1998; Schmidt et al., 2004; Tychsen & Brukhalter, 1997), although note the findings of Crawford and Harwerth (2004) and Löwell (1994), and the normal features and scale of orientation maps are present (Schmidt et al., 2004). One consistent abnormality in cortical organization is in the pattern of long-range horizontal connections that link domain-similar zones in area V1 (Malach et al., 1993; Yoshioka et al., 1996). These connections are disrupted such that, in amblyopes, they link domains influenced exclusively by either the amblyopic or fellow eye (Löwell & Engelmann, 2002; Löwell & Singer, 1992; Tychsen et al., 2004), which is consistent with historical and recent findings of disruption of the binocular organization of the visual cortex in amblyopia (Kiorpes & Movshon, 2003; Kumagami et al., 2000; Mori et al., 2002; Smith et al., 1997; Wiesel, 1982). However, some caution is warranted as one study has shown that there is a predominance of monocular eye-specific connectivity in area V1 of visually normal primates (Malach et al., 1993). Within these domains, the connection patterns appear to be normal (Löwell & Engelmann, 2002; Schmidt et al., 2004). Finally, there have been reports of reductions in correlated firing of amblyopic eye neurons in strabismic cats (Löwell & Engelmann, 2002; Roelfsema et al., 1994). While there is no known anatomical substrate for this effect, the expression of activity-dependent NMDAR1 is reduced in the central visual field of amblyopic cats (Murphy et al., 2004; Yin et al., 1996), perhaps reflecting less efficient synaptic transmission in amblyopic neurons.

Taken together, these findings show that area V1 is the first site along the visual pathways that reflects abnormalities consistent with those found behaviorally in amblyopes. The primary deficits are reduced spatial scale of neurons driven by the amblyopic eye and physiological and anatomical disruption of binocular organization, which correlate well with common characteristics of amblyopia such as poor acuity, suppression, and poor or absent stereopsis. The disruption of binocular organization in area V1 may be a particularly important neural mechanism given that presence or absence of binocular function has recently been shown to discriminate different constellations of amblyopic loss and also functional subtypes of amblyopia in humans (Levi, 2006; McKee et al., 2003).

A dearth of binocular neurons in area V1 is a ubiquitous finding in amblyopic and visually deprived animals, but a loss of neurons dominated by the amblyopic eye is not clearly related to depth of amblyopia, except in cases of severe amblyopia (Kiorpes, 2002; Kiorpes et al., 1998; Kiorpes & Movshon, 2003; Movshon et al., 1987). While there are now many studies exploring residual binocular interactions in are VI neurons of animals reared with abnormal binocular vision (Crawford et al., 1996; Kumagami et al., 2000; Mori et al., 2002;

Sengpiel & Blakemore, 1996; Smith et al., 1997; Zhang et al., 2003), the relationship of these findings to amblyopia is unclear. Behavioral studies in some of the same animals have shown that the abnormal binocular interactions are present independently of amblyopia (Smith et al., 1997; Wensveen et al., 2003). Wong et al. (2005) reported suppression of metabolic activity in ocular dominance domains related to the amblyopic eye of strabismic amblyopic monkeys, which is not apparent in non-amblyopic strabismics. Physiological studies have also identified enhanced suppressive interactions in amblyopic neurons (Crewther & Crewther, 1993; Sengpiel & Blakemore, 1996; Smith et al., 1997),which are somewhat more predominant in strabismic than anisometropic amblyopia (Smith et al., 1997). Clearly, an important avenue for future animal studies to pursue is therefore the particular nature of the binocular processing abnormality in amblyopia with a focus on any differences that exist between subtypes.

In terms of spatial vision, the deficits in neuronal acuity and contrast sensitivity in area V1 in amblyopic monkeys are not sufficient to account for the behaviorally measured losses (Kiorpes et al., 1998; Kiorpes & Movshon, 2003). Furthermore, research in humans and animals over the past 10 years has identified numerous deficits in visual sensitivity and global perception that are not obviously related to the basic losses in spatial resolution and contrast sensitivity (Constantinescu et al., 2005; Gingras et al., 2005; Kiorpes et al., 2006; Kozma & Kiorpes, 2003; Levi, 2006; Simmers et al., 2005; Tang et al., 1998). The common factors in those abilities that are most severely compromised in amblyopia are that they are not acuity-limited tasks, they require integration of information over relatively large regions of space and/or time, and they involve extracting a signal from noise. We have measured the performance of amblyopic monkeys, anisometropic and strabismic, on three such tasks: contour integration, motion discrimination, and form detection; the studies are described in brief below. The data show that 1) there are primary losses in temporal as well as spatial vision, 2) vision through the fellow eye is often compromised along with the amblyopic eye, and 3) compromised integration of visual information over space and time is a consistent finding, pointing to a noise-limited neural mechanism.

Contour integration depends on the ability to link features across space to extract a coherent figure from background noise. This ability was tested in amblyopic macaque monkeys by asking the animals to locate a co-circular ring of Gabor patches in a field of randomly arrayed and oriented noise Gabors (Kozma & Kiorpes, 2003) (see Fig. 1, inset). Performance, termed noise tolerance, was measured by determining the density of background noise at which the location of the feature could be identified with 75% accuracy. Strabismic and anisometropic animals were tested along with visually normal controls; the data are shown in Fig. 1.

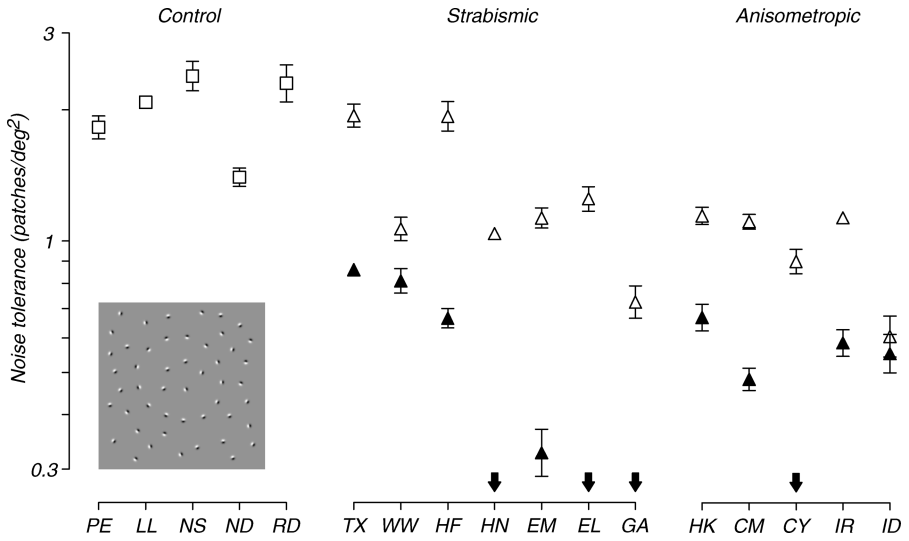

FIGURE 1 **Contour integration. Noise tolerance is plotted for control adults and for each eye of 12 amblyopes. A schematic rendition of the stimulus is inset in the lower left portion of the figure. The open symbols represent control or fellow eye data; filled triangles represent amblyopic eye data. The arrows pointing down toward the abscissa indicate cases for which performance was poorer than 0.3 patches per square degree, the usual spacing of the feature elements in the ring. The data show deficits in amblyopic eye performance for all subjects, as well as compromised fellow eye performance for many subjects. After Fig. 1 in Kozma and Kiorpes (2003).**

Noise tolerance is plotted for control adults and for each eye of the amblyopic monkeys. All amblyopic monkeys were impaired on this task with their amblyopic eye, and many showed deficits with their fellow eye as well. It is important to note that two amblyopic animals showed little interocular difference in performance (WW, ID) but this is due to relatively poor performance with the fellow eye rather than normal performance with the amblyopic eye. One strabismic monkey adopted an alternating fixation pattern and did not develop amblyopia (data not shown); he performed within the range of the controls with each eye. To evaluate whether the degree of impairment on contour integration depends on the loss in basic spatial vision, we computed a dimensionless "amblyopia index" (Kiorpes et al., 1998; Kozma & Kiorpes, 2003), which takes account of losses in contrast sensitivity at all spatial scales. The relationship between the deficit in contour integration and that in basic spatial vision is shown in Fig. 2.

While there is little impairment in contour integration for very mild amblyopic animals, there is no apparent correlation with depth of amblyopia across those with moderate to severe amblyopia. The results from this study show that amblyopic monkeys are impaired on tasks requiring perceptual organization, the impairment is unrelated to the basic loss in contrast sensitivity,

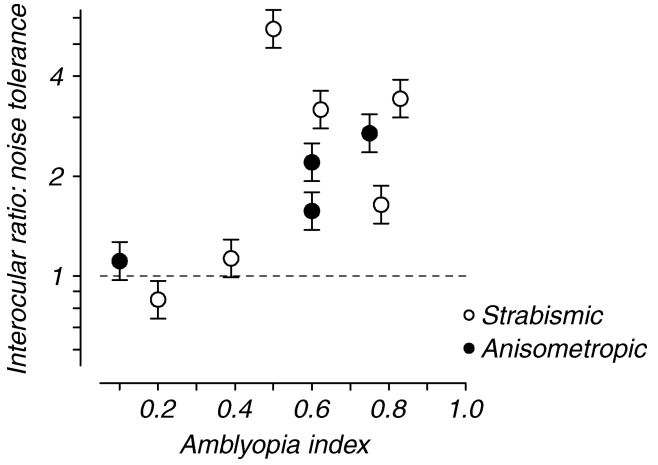

FIGURE 2 **Comparison of deficits in contour integration and contrast sensitivity. The interocular ratio of noise tolerance is plotted against a dimensionless amblyopia index, which reflects the severity of the contrast sensitivity deficit (Kiorpes et al., 1998) for each subject for which both measures could be computed. The dashed horizontal line denotes equal noise tolerance for the two eyes of an individual. Open and filled symbols represent strabismic and anisometropic amblyopes, respectively. The data show that there is no orderly relationship between the depth of amblyopia and the deficit in contour integration. After Fig. 7 in Kozma and Kiorpes (2003).**

and this ability is severely compromised in the presence of noise.

Motion integration depends on the ability to integrate information over space and time to detect and discriminate direction of motion. To test this ability, macaque monkeys were asked to indicate the direction of motion of a random-dot kinematogram (Kiorpes & Movshon, 2004). Our measure of performance in this case was sensitivity to coherence (proportion of dots that carry the motion signal) of the dot pattern, which we tested across a range of spatial scales of motion (Kiorpes et al., 2006; Tang et al., 1998). Large displacements per unit time produce fast speeds of apparent motion whereas small displacements produce slow speeds. Typical data for two amblyopic monkeys are shown in Fig. 3.

Motion sensitivity, the inverse of the percent coherence required for discrimination of direction at threshold (75% correct), is shown as a function of dot displacement in minutes (the relationship of dot displacement to dot speed is indicated on the abscissa at the top of each panel). The data from these two animals show several important features of the results. First, sensitivity to the motion signal varies substantially with the underlying scale of displacement, much as contrast sensitivity varies with the underlying spatial scale of the stimulus. Second, the motion sensitivity functions are of similar shape for the two eyes of the amblyopic animals but the function for the amblyopic eye (filled symbols) is shifted toward larger displacements compared to the fellow eye (open symbols). This results in a zone, at very large displacements–and fast speeds–where sensitivity is *better* for the amblyopic eye. At smaller displacements–and slow speeds–amblyopic eye performance is severely compromised. Third, most animals showed an overall reduction in best motion sensitivity (left panel) but in some cases the reduction was small (right panel). There was no apparent relationship between a loss of overall sensitivity to motion and type or depth of amblyopia. Interestingly, some amblyopic monkeys also showed reduced motion sensitivity with their fellow eyes compared to visually normal monkeys. This was particularly apparent for strabismic animals at slow speeds. The pattern of results from this study suggests that there is not only a limitation of spatial vision in amblyopia, but also a fundamental deficiency in temporal processing.

Form detection in a Glass pattern display is conceptually similar to motion integration but is based on static displays. Glass (1969) showed that a percept of global

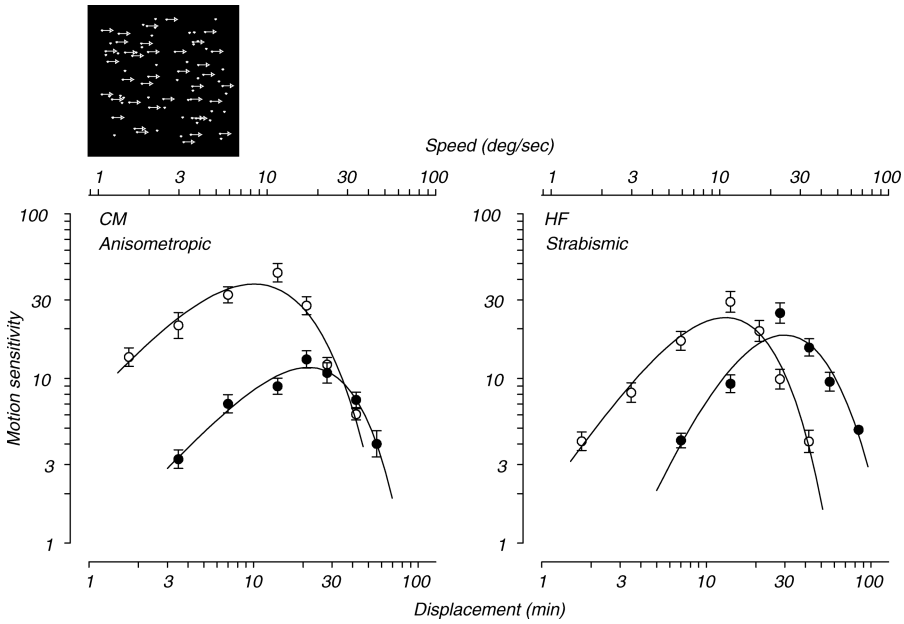

FIGURE 3 **Motion discrimination. Motion sensitivity is plotted as a function of the spatial scale of dot displacement for each eye of two amblyopic monkeys. Displacement refers to the distance a dot moved from frame to frame in the random dot kinematogram. The schematic rendition of the stimulus in the upper left of the figure indicates a sample dot displacement (distance from the head to the tail of the arrows) underlying a rightward motion percept; lone dots indicate "noise" dots that do not reappear in a subsequent stimulus frame. The relationship between dot displacement and dot speed can be grasped by comparing the top and bottom abscissae. Motion sensitivity is the inverse of the coherence level needed for discrimination of the direction of motion in the display at threshold. Sensitivity is reduced for the amblyopic eye of most subjects. In all cases, the motion sensitivity function was shifted to larger displacement ranges for amblyopic eyes.**

form can be extracted from a pattern generated from a set of random dots combined with a copy of that dot set displaced according to a particular geometric rule, such as a horizontal shift of each dot by a fixed amount. Figure 4 (inset) illustrates such a pattern. Glass patterns have been used in many human psychophysical studies to probe the nature of neural mechanisms that analyze form information (e.g., Dakin, 1997; Wilson & Wilkinson, 1998). To appreciate the global structure in Glass patterns it is necessary to integrate over space

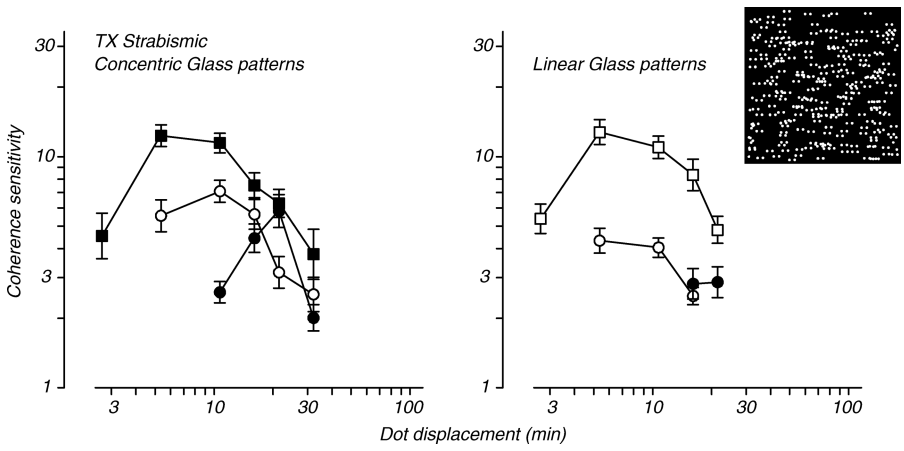

FIGURE 4 **Form detection in Glass patterns. Coherence sensitivity is plotted as a function of the spatial scale of the displacement between paired dots in the stimulus. The inset image on the upper right represents a linear Glass pattern with a sample horizontal displacement between members of a dot pair. Coherence sensitivity is the inverse of the coherence level needed to discriminate a structured pattern from a random dipole at threshold. The squares are data from an adult control. The circles represent data from an individual strabismic amblyope with concentric (left) or linear (right) Glass patterns; open circles are fellow eye data and filled circles are amblyopic eye data. Note that data for all displacements at which the animal could perform above 75% correct are plotted. The data show substantial losses of sensitivity with each eye for both pattern types, although performance was more impaired with linear Glass patterns than with concentric ones. A shift in scale of performance is evident for this spatial integration task, similarly to motion discrimination.**

the orientation information conveyed by the pairs of dots.

We used two types of Glass patterns, linear and concentric, to probe the form integration capabilities of amblyopic monkeys (Kiorpes, 2003; Kiorpes et al., 2005). The task was to detect which of a pair of patterns contained global structure; each pair consisted of a Glass pattern and a pattern of random dipoles. Again, our measure of performance was the coherence necessary for 75% correct discrimination of the pattern structure, but in this case coherence was the proportion of dot pairs that conformed to the geometric rule defining the Glass pattern. Data from an individual strabismic animal are shown in Figure 4 for the two pattern types; data from a visually normal adult animal are shown for comparison.

A number of features of the results are illustrated in this example data set. First, as with the motion integration task, performance on this task varies with the underlying spatial scale of dot displacement. Best performance for control animals was typically found with relatively fine scale displacement regardless of pattern type. The best performance for fellow and amblyopic eyes of the amblyopic monkeys was shifted toward larger displacement generally, with the amblyopic eye functions shifted to a greater extent than fellow eyes. Thus, as with motion integration, we found that the range of spatial scale underlying performance was larger than normal in amblyopic animals and that over some displacement ranges, performance with the amblyopic eye was better than with the fellow eye. Second, most amblyopic animals showed an overall reduction in coherence sensitivity with the fellow eye as well as the amblyopic eye compared to visually normal animals. Third, amblyopic animals generally performed more poorly with linear Glass patterns than with concentric ones (compare the left and right panels of Fig. 4). What may not be apparent from this figure is the profound difficulty that the animals had with this task. In fact, of 12 animals tested, seven (two anisometropic and five strabismic) were unable to perform the discrimination at any coherence level below 100% coherence with the amblyopic eye. The results from this study confirm our earlier finding, with contour integration, that amblyopic monkeys are profoundly deficient in their ability to organize information into a coherent global form percept. These perceptual losses are apparent when viewing with the fellow eye as well as with the amblyopic eye. The relatively greater difficulty with linear compared to concentric Glass patterns was not expected and presents an interesting puzzle.

As summarized above, these studies show that there are significant perceptual level deficits in amblyopia. These findings from the non-human primate model are consistent with those in human amblyopes showing deficits in second-order (not luminance based), integrative, global form and motion processing (Levi, 2006). The types of tasks on which amblyopes are most impaired suggest a site beyond the primary spatial filters in area V1. Psychophysical and physiological studies indicate that global motion and form perception depend on extrastriate processing (Britten et al., 1992; Celebrini & Newsome, 1995; Hegde & Van Essen, 2003; Newsome & Pare, 1988; Smith et al., 2002; Wilson & Wilkinson, 1998). The nature of the integrative process and the appearance of fellow eye deficits suggest large binocular receptive fields as a substrate, as would be found in extrastriate cortical areas. The particular difficulty that amblyopes have with extracting a coherent signal from noise, as shown by these studies, can also be explained most easily assuming an extrastriate locus. Several studies have shown reduced efficiency of amblyopic vision and abnormal processing of even simple grating stimuli and letters in noise (Kersten et al., 1988; Kiorpes et al., 1999; Nordmann et al., 1992; Pelli et al., 2004); this reduced efficiency is likely to depend on areas downstream from area V1 (Kiorpes et al., 1999). Also, a number of recent studies have shown abnormal suppressive spatial interactions in amblyopia (Crewther & Crewther, 1993; Ellemberg et al., 2002; Levi et al., 2002; Polat et al., 1997; Sengpiel & Blakemore, 1996; Smith et al., 1997). Assuming that large receptive fields pool over extended regions of space, and that pooling in amblyopes extends over larger regions of space than in normals (at least in the fovea) (Hariharan et al., 2005; Levi et al., 2002), the opportunity exists for failures of segmentation of figure from background, as in contour integration, due to increased pooling of noise and increased suppressive interactions across space. If, in addition, there is reduced precision of feedforward projections to extrastriate areas from the predominantly low spatial frequency filters representing the amblyopic eye in area V1 (Smith et al., 1997), then the opportunity exists for reduced efficiency of integration of information over space, as revealed by the tasks described above. Two studies have shown effects of amblyopia on binocularity in extrastriate areas (Movshon et al., 1987; Schroder et al., 2002). Investigation of the organization

and precision of receptive fields in extrastriate visual areas will be an important next step in understanding the neural mechanisms underlying amblyopia.

CONCLUSIONS

Recent studies using animal models have provided a greater understanding of the nature of the neural mechanisms underlying amblyopia. While the structure of the primary visual cortex is largely normal, amblyopic animals show deficits in neural processing, particularly at mid to high spatial frequencies, revealing a neuronal "acuity" deficit at this early stage of processing. In addition, there is substantial disruption of the binocular organization of receptive fields and abnormal binocular interactions within individual neurons. These identified deficiencies are similar for anisometropic and strabismic amblyopes, leaving open the question of which binocular mechanisms account for the different constellation of deficits seen in binocular and non-binocular human amblyopes. Perceptual level visual disorders have been identified that are not accounted for by basic losses in acuity and contrast sensitivity. These disorders are characterized by difficulty in extracting a coherent signal from background noise, difficulty with integrating visual information over space and time, and compromises to the vision of the fellow eye as well as the amblyopic eye. These findings strongly suggest that, while the first evidence of amblyopia is apparent at the level of area V1, there are significant downstream deficiencies in neural processing.

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