

Neural mechanisms underlying amblyopia

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The nature of the neural basis of amblyopia is a matter of some debate. Recent neurophysiological data show correlates of amblyopia in the spatial properties of neurons in primary visual cortex. These neuronal deficits are probably the initial manifestation of the visual loss, but there are almost certainly additional deficits at higher levels of the visual pathways.

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Abbreviations

LGN lateral geniculate nucleus
V1 primary visual cortex

Introduction

Amblyopia is a loss of vision that is associated with abnormal visual experience during infancy and early childhood, and is not of optical or organic origin. Children who develop anisometropia (i.e. unequal refractive error in the two eyes) or strabismus (a misalignment of the visual axes), or other conditions that create an obstacle to clear, equal binocular vision are at risk for developing amblyopia. Amblyopia is commonly identified by a difference in acuity between the eyes of at least a factor of 2 (comparable to a two-line difference on an eye chart). On average, 40–60% of children with anisometropia and/or strabismus in childhood develop amblyopia; estimates of the incidence of amblyopia in the general population range from 2–4% [1]. Amblyopia is a disorder of development as the same visual conditions that cause amblyopia in childhood have no lasting effect on vision when they occur in adulthood. The critical period for the development of amblyopia is correlated with the time period for normal visual development [2*,3–5].

The neural basis of amblyopia has been a matter of interest and speculation for many decades. Of necessity, animal models are used to study the mechanisms underlying amblyopia. Studies using primate models have shown a direct causal link between early abnormal visual experience and permanent deficits in visual function that are qualitatively and quantitatively similar to human amblyopia [5–9]. Figure 1a, c illustrates the range of basic spatial visual deficits in amblyopic monkeys, as measured psychophysically; amblyopic humans have a similar range of deficits. The spatial deficits are the hallmarks of amblyopia, but they are not the only manifestation of amblyopia; deficits in binocular vision may play a role in the development of amblyopia ([10,11]; see also

[12]): stereopsis may be severely degraded and other aspects of form perception may be compromised.

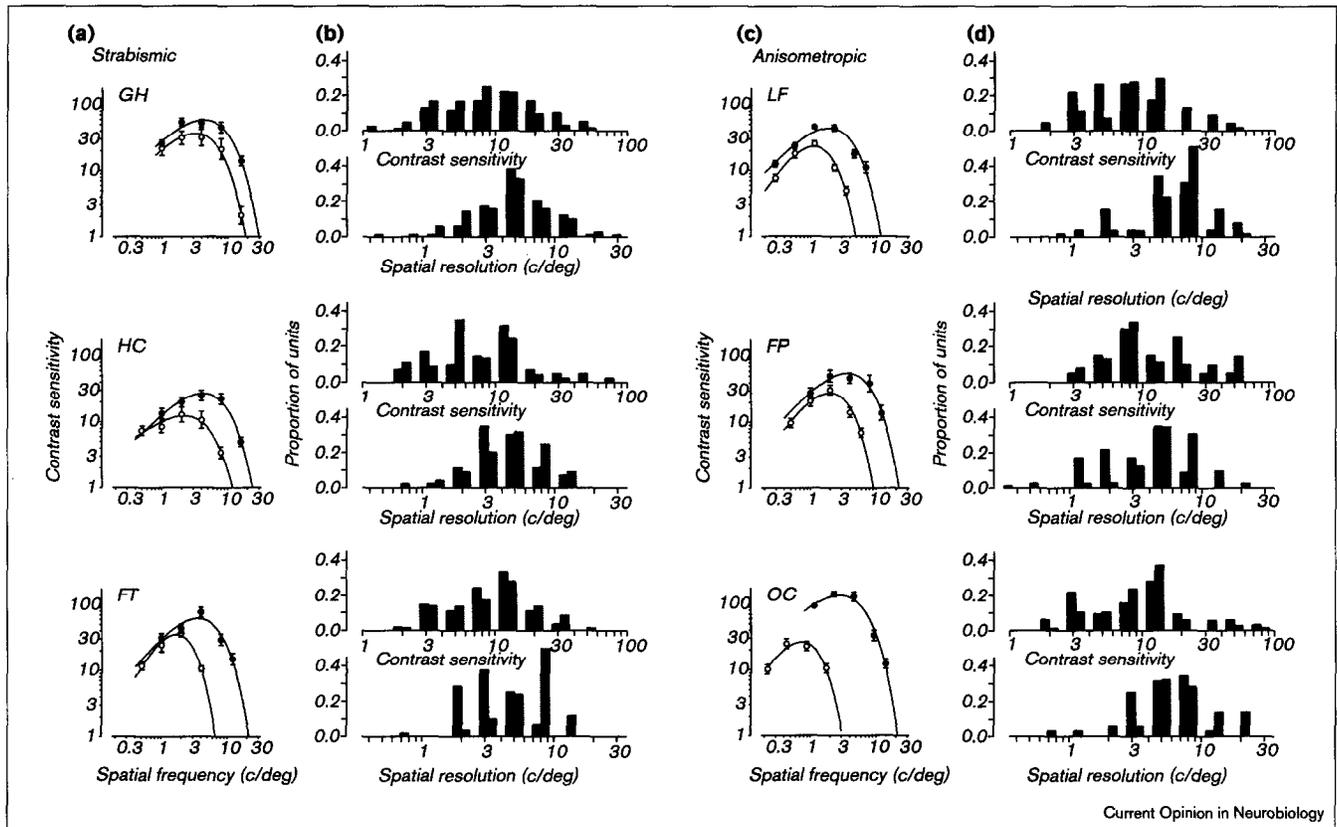
In this review, we primarily discuss work that concentrates on strabismus or anisometropia, conditions that are most commonly associated with amblyopia in humans. We focus on primate studies because data from cat models of amblyopia are inconsistent (and it is not clear that cats develop amblyopia in a manner similar to humans). We discuss four proposed neural bases of amblyopia: abnormal neuronal response properties, poor synchronization of neuronal responses, abnormal topographic representation of receptive fields, and undersampling of visual space. The first two were proposed on the basis of neurophysiological data from animals; the second two are based on human psychophysics. Some degree of controversy surrounds each notion. We conclude that there are both primary and secondary neural deficits involved in amblyopia; the first evidence of neural deficits appears at the level of the primary visual cortex (V1).

Early work on amblyopia

The earliest investigations into the neural basis of amblyopia were directed towards the binocular properties of neurons in V1 [13]. These studies followed on the pioneering work of Hubel and Wiesel (see [14]), who sutured the eyelids of young animals, resulting in nearly complete deprivation of form vision (this is a reasonable model, only, for the less common, very deep amblyopia resulting from congenital cataracts). Following lid-suture, binocularity is obliterated and neurons in V1 shift their allegiance away from the deprived eye. Some investigators, therefore, suggested that amblyopia resulted from a reduced representation of the deprived eye in V1; however, this effect is not a consistent correlate of more common forms of amblyopia.

Because amblyopia is primarily a disorder of spatial vision, other investigators looked at the spatial properties of neurons early in the visual pathways. Data from amblyopic monkeys suggest that no functional abnormalities exist earlier than V1. Most studies of the retina in amblyopes conclude that there is no change at this level [15,16]. However, an intriguing recent report suggests optic disc abnormalities, observable at birth, predict later development of amblyopia [17]. Spatial and temporal response properties of neurons in the lateral geniculate nucleus (LGN), in which afferents from the two eyes remain segregated, are largely normal in amblyopic monkeys [18], even following more devastating, lid-suture deprivation [19–21]. There are reports of anatomical deficits in the LGN of deprived monkeys, in the form of shrunken or cell-sparse deprived eye layers, but they seem to have no apparent correlate in neural signalling [13,15,22].

Figure 1



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Behavioral and physiological data for six amblyopic monkeys.

(a,c) Spatial contrast sensitivity functions through the amblyopic (open circles) and fellow (filled circles) eye. The smooth curves were used to estimate the peak contrast sensitivity (height of curve), optimal spatial frequency (spatial frequency at the peak), and spatial resolution (i.e. the spatial frequency at which the curve falls to 1). The interocular difference on each of these parameters is used to capture the depth of

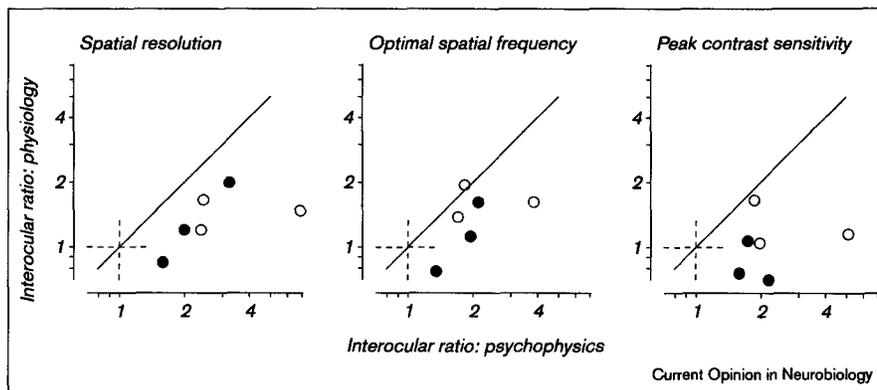
amblyopia in Figure 2. (b,d) Distributions of contrast sensitivity and spatial resolution for neurons tested through each eye. The black bars represent amblyopic eye cells and the grey bars represent fellow eye cells. The physiological data for each monkey are placed adjacent to their behavioral data; within each amblyopia group, the data are shown in order of increasingly severe amblyopia (top to bottom). Data from [25**].

Neurophysiological approaches

In amblyopic monkeys, correlates of abnormal early visual experience have consistently been found in V1, which is where information from the two eyes is first combined. Many studies support the notion that amblyopia reflects the abnormal receptive field properties of the neurons linked to the amblyopic eye [18,23,24,25**]. Two comprehensive investigations of V1 neurons in monkeys with behaviorally documented amblyopia have been conducted [18,25**]; these studies are particularly important because they carefully documented visual function in the same animals from which the physiological data were drawn. Assessment of the full contrast sensitivity function was used to classify the depth of amblyopia in monkeys raised with either experimental anisometropia or strabismus (Figure 1). Spatial, temporal, orientation, and contrast response properties, as well as binocular organization, were assessed for neurons driven by each eye in the foveal representation of V1. There is a wide range of cell sensitivities on all response dimensions tested, as is

characteristic of normal monkeys; however, there are clear interocular differences in the distributions for all but the mildest amblyopes. Figure 1b,d shows spatial resolution and contrast sensitivity data from three strabismic and three anisometric amblyopes [25**]. For each monkey, the range of overlap of the resolution and sensitivity data for neurons driven by each eye is substantial but the neural deficit, as captured by the geometric mean of each distribution, is clear in most animals (see [25**] for details). The effect is particularly clear for spatial resolution. The extent of the neural deficit is related to the animal's depth of amblyopia (Figure 2). Interestingly, some neurons driven by the amblyopic eye have spatial resolution finer than the behavioral acuity of the amblyopic eye. Amblyopic animals do not appear to be able to use the responses of just a few cells to make a psychophysical judgement. This result suggests that it is important to look at the whole neuronal sample rather than only at the responses of the very best cells (i.e. the cells with the highest spatial resolution).

Figure 2



A quantitative comparison of behavioral and physiological deficits on spatial resolution, optimal spatial frequency, and contrast sensitivity in amblyopic monkeys. The interocular ratios (fellow eye/amblyopic eye, for each parameter) for psychophysical performance are taken from the curves in Figure 1a,c; the interocular ratios for physiological sensitivity are taken from the geometric means of neuronal distributions (Figure 1b,d; [25**]). If the behavioral and physiological deficits were commensurate, the data would cluster along the diagonal in each panel; the data largely fall below the diagonal, indicating a larger behavioral than physiological deficit. Data from [25**].

Although loss of binocular activation in V1 neurons is a consistent finding in amblyopic animals, recent studies have demonstrated residual binocular interactions in neurons that do not appear to be binocular by conventional evaluation [12,26]. The data show deficient excitatory interactions with binocular stimulation but a relative sparing of inhibitory, suppressive interactions, particularly in strabismic. The relationship between these residual binocular interactions and amblyopia is not clear. However, the data are important because they suggest a shift in the balance of interocular excitatory and inhibitory connections among binocular neurons in animals raised with conditions that can cause amblyopia. They also are puzzling because several studies have reported significant anatomical disruption of interocular long-range connections following strabismus [27,28]. If these connections are absent, one wonders what the substrate might be for the physiologically identified interactions.

In addition to a reduction in binocular connectivity, strabismus reportedly affects the strength of interactions among neurons driven by the same eye. Roelfsema *et al.* [29] have reported a reduction in synchronization strength among amblyopic eye neurons in V1 of strabismic cats. They recorded responses from multiple neurons simultaneously and used a cross-correlation analysis in an attempt to assess synchrony of firing among neurons with similar properties (see review by Bair, in this issue, pp 447–453). The strength of correlated firing among amblyopic eye neurons was in some cases reduced compared to fellow eye neurons. Even though the reduced correlation was found in only a subset of the cats, Roelfsema *et al.* [29] proposed that a lack of synchronous firing was the neural basis for amblyopia. A number of factors call this interpretation into question. First, the reported behavioral acuities for both eyes of most of the cats were substantially poorer than normal; the cats may have been bilateral amblyopes, if amblyopes at all [30]. Chino *et al.* [31] showed cortical neuronal abnormalities, including reduced spatial resolution and contrast sensitivity, in cells driven by each eye of strabismic cats; some of the abnormalities were more dramatic

for cells driven by the deviated eye than for cells driven by the fellow eye. Several of the cats were behaviorally identified as bilateral amblyopes. It is therefore likely that there were neural abnormalities in addition to reduced synchrony in the Roelfsema *et al.* [29] study. Also, the interpretation of cross-correlograms is complex and may be compromised by slow neural changes that can yield a misleading impression of fast synchrony [32]. Finally, the phenomenon has been reported only in strabismic cats, and may again be secondary to strabismus, or idiosyncratic to cats, rather than a correlate of amblyopia generally.

Psychophysical approaches

The most extensively investigated proposals for the neural basis of amblyopia come from human psychophysics. For more than a decade, these studies have concentrated on understanding the substantial loss of positional acuity in the amblyopic fovea. Positional acuity refers to the precision in judging the relative location of two features (e.g. Vernier acuity; see Figure 3c), which in normal fovea is typically 5–10 arcsec. Positional acuity is much poorer than normal in all amblyopes. But for most anisometric amblyopes, the loss can be predicted from their loss in grating acuity and is readily accounted for by a shift in spatial processing from high spatial frequency filters (small cortical receptive fields) to mid-range filters (larger receptive fields; see Figure 4a,b). In strabismic amblyopes, the positional acuity deficit is often much larger than would be predicted from their grating acuity. Two explanations have been proposed to account for this extra loss in strabismic positional acuity: first, undersampling of the post-receptoral filtering array [33–35], or second, spatial disarray in the locations of the filters [36,37,38**] (see Figure 4c–f).

The undersampling hypothesis proposes that there are too few filters at the scale corresponding to the strabismic amblyope's grating acuity to tile the central visual field optimally. The disarray hypothesis proposes that the number of cortical filters is normal, but topographical information is incorrect or 'jittered'. Topographical jitter could theoretically arise either

Figure 3

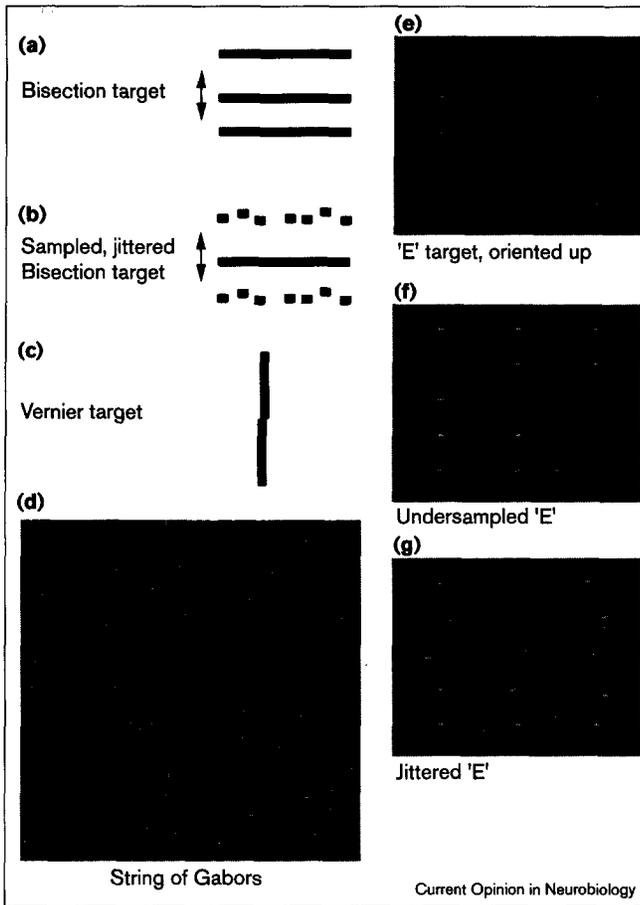
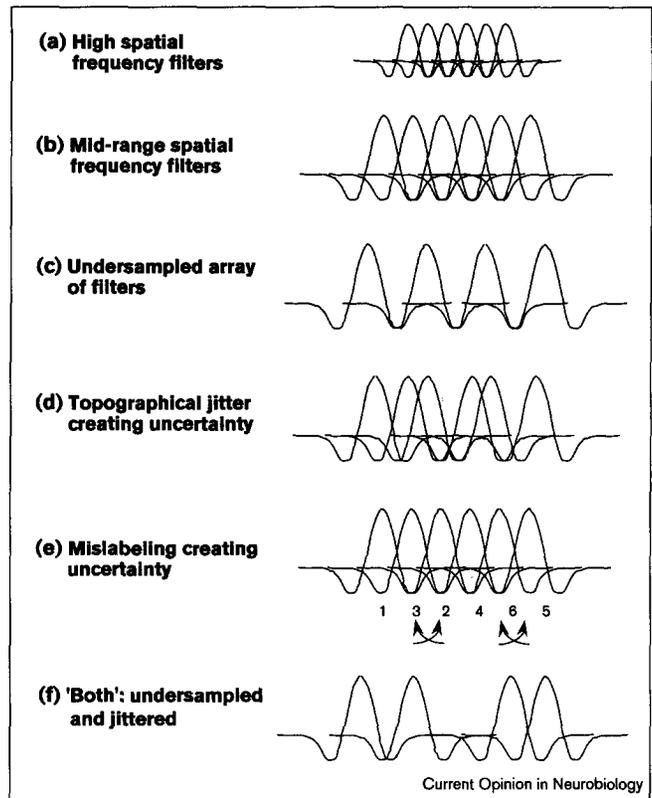


Illustration of targets used for psychophysical studies of amblyopia. Bisection target (a) without and (b) with added noise jitter [42]; the subject discriminates the relative location of the central bar. (c) A classical Vernier target; the subject discriminates the relative positions of the top and bottom bar. (d) A typical contour integration stimulus; the subject determines the location of a string of aligned Gabor elements in a field of randomly oriented Gabor elements [47,48*,49]. 'E' target used by Wang *et al.* [43*], composed of Gabor elements, (e) as a complete figure, (f) with undersampling, and (g) with positional jitter.

because of uncalibrated irregularity in the local filter array [38**,39] or because the local filters are mislabeled, so that the representation of spatial sequence is disordered [40]. Systematic mislabeling over large extents ought to be corrected by experience [41]. However, small random irregularities in the sampling matrix would be confounded with random fluctuations in the filter responses making compensation difficult for a biological system. Both undersampling and topographical jitter effectively leave 'holes' in the representation of visual space at the finest scales, such that small differences in location are less well encoded than in the normal fovea; both ideas predict the extra loss in strabismic positional acuity.

Attempts to provide support for these hypotheses have taxed the experimental ingenuity of their proponents.

Figure 4



Cartoon representation of psychophysical explanations for amblyopia. Anisotropic amblyopes suffer (a) loss of high spatial frequency filters, which (b) shifts their acuity to mid-range filters. In addition to the loss of high spatial frequency filters, strabismics may also suffer from (c) too few filters near their acuity limit or from (d,e) topographical disarray, or possibly (f) from both.

Several investigators have used an equivalent noise paradigm to estimate the postulated internal jitter in normal and amblyopic observers [42,43*,44**,45]. Wang *et al.* [43*] used a bisection acuity task and added random noise to the reference components of the stimuli (Figure 3a,b). The standard deviation of the added noise was varied to estimate equivalent internal jitter. Estimated internal jitter in both strabismic and anisotropic amblyopes was much higher than in normals and showed a strong dependence on stimulus visibility in all observers except one strabismic. Wang *et al.* [43*] concluded that amblyopic tolerance for increased external jitter was attributable to blurring associated with dependence on larger spatial filters. They also parametrically varied the number of dots in the stimuli to estimate efficiency of the amblyopic observers. They found a striking difference between anisotropic and strabismic amblyopes; anisotropic and normal observers were equally efficient in using the information in each additional dot, but strabismic amblyopes were woefully inefficient, needing many more samples to improve performance. While the latter observation supports the undersampling hypothesis, some amount of random jitter in the filter array is not ruled out.

Recent studies have turned toward more global perceptual consequences of positional deficits in amblyopes. Hess *et al.* [38**] compared the ability of normals and strabismic amblyopes to detect deformations in a large circle, formed of a narrow band of spatial frequencies. Strabismic amblyopes had difficulty detecting these global deformations, even for targets composed of spatial frequencies well within their acuity range. The authors showed that both undersampling and topographical jitter could account for their results. However, in this case, undersampling would need to extend over a wide range of spatial scales, not just those near the acuity limit, so they concluded that the jitter explanation was more reasonable. Levi *et al.* [44**] took a direct approach to the question, using a task that required observers to integrate information over fairly substantial distances. They perturbed the position of the elements within an 'E' pattern and measured thresholds for discrimination of 'E' orientation (Figure 3e–g). Tolerance for positional jitter was identical for normal and strabismic amblyopes over a wide range of contrast levels. Levi *et al.* [44**] also assessed sampling efficiency for this task by determining how many elements of the pattern were needed for threshold identification. Strabismic amblyopes were much less efficient than normals, needing more elements in the pattern to perform the task, especially at fine spatial scales. These results suggest that, for strabistics, some of the pattern elements are not available for use in pattern integration, providing further support for the undersampling hypothesis.

Several investigators have suggested that contour integration is disrupted in amblyopes [46,47,48*]. The phenomenon of contour integration is exemplified by the ability to detect a string of oriented Gabor patches aligned to form a common contour, when the string is embedded in a background of randomly oriented patches [49] (Figure 3d). Two careful studies from the Hess laboratory [48*,50*] have shown that contour integration is in fact abnormal in some strabismic, but not in anisometropic, amblyopes. Strabistics, using their amblyopic eye, are much more sensitive to perturbations in the orientation and position of patches forming the contour, and they need more patches in the string to equal the performance of fellow eye [48*]. In anisometropes, amblyopic eye performance is essentially identical to the normal eye, provided that the contrast and spatial frequency of the patches are chosen to guarantee equal visibility in the two eyes [50*,51]. The contour integration results in strabistics are consistent with the hypothesis of Roelfsema ([52*]; see also [29]), which predicts that strabismic amblyopes should have difficulty with feature detection tasks that may depend on 'binding' together elements of the feature through synchronous neural activity. However, Hess' data [48*,50*] generally argue against the notion that reduced neuronal synchrony, *per se*, is the neural basis of amblyopia, because anisometropic amblyopes do not have deficient performance on these feature-binding tasks.

Conclusions

On balance, psychophysical data from humans and monkeys (see [7]) suggest that the basic deficit in amblyopia is one of simple visual sensitivity, that is, reduced contrast sensitivity and spatial resolution. There is wide agreement that the extraordinary positional acuity deficits can be accounted for by equating stimulus visibility between the two eyes of an anisometropic amblyope, and also for some proportion of strabismic amblyopes. Strabismic and anisometropic monkeys show a similar pattern of behavioral deficits, which typically follows the pattern of human anisometropes. However, it is important to note that a large-scale evaluation of human amblyopes shows greater similarity between anisometropes and strabistics than was previously believed [53]. The neurophysiological data of Kiorpes *et al.* [25**] and Movshon *et al.* [18] qualitatively account well for these basic deficits; amblyopic eye contrast sensitivity and acuity is reflected in reduced contrast response and spatial resolution of the neuronal population driven by that eye. Quantitatively, the neural deficit is smaller than the behavioral deficit, and the effect on neural contrast sensitivity is somewhat inconsistent. There is a reasonable neural substrate for undersampling in that fewer cells are driven by the amblyopic eye at fine spatial scales (near the acuity limit), and the neurons that are driven by the amblyopic eye tend to have larger receptive fields (i.e. respond to lower spatial frequencies). The physiological recordings did not reveal evidence for topographic disarray in the form of mislabelled receptive field locations, but they did not allow precise enough localization of the receptive fields to detect subtle disorder. If topographic disarray is conceptualized as simply random, uncalibrated disarray, in place of a regular array of receptive fields, then it is really no different from undersampling. The sparse representation of amblyopic eye neurons in foveal V1, found in a subset of animals [18,25**], could be a substrate for undersampling, as postulated for a subset of human strabismic amblyopes.

It is likely that the identified neurophysiological correlates of amblyopia are the basis of the perceptual deficits, but that they are amplified and extended at subsequent levels of the visual system. So the possibility remains that topographic disarray, while not apparent in V1, exists at another level of the system, perhaps in the interareal feedforward or feedback projections or perhaps in extrastriate visual areas. Future research should be directed to higher levels of the visual system to see how the basic neural deficiencies are propagated beyond V1. Imaging studies of human amblyopes are likely to be instrumental in establishing the loci of higher level deficits [54].

Acknowledgements

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Strabismic amblyopes were more impaired on this shape discrimination task compared to normals. Modeling of the results showed that both neural disarray and undersampling could account for the results. The authors favored the disarray hypothesis because the undersampling would need to be scale invariant to completely capture the strabismic deficit.

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