

Haphazard neural connections underlie the visual deficits of cats with strabismic or deprivation amblyopia

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Keywords: acuity, alignment accuracy, contrast discrimination, development, ocular dominance, visual cortex

Abstract

Identification of the neural basis of the visual deficits experienced by humans with amblyopia, particularly when associated with strabismus (strabismic amblyopia), has proved to be difficult in part because of the inability to observe directly the neural changes at various levels of the human visual pathway. Much of our knowledge has necessarily been obtained on the basis of sophisticated psychophysical studies as well as from electrophysiological explorations on the visual pathways in animal models of amblyopia. This study combines these two approaches to the problem by employing similar psychophysical probes of performance on animal models of two forms of amblyopia (deprivation and strabismic) to those employed earlier on human amblyopes (Hess & Field, 1994, *Vis. Res.*, **34**, 13397–13406). The tests explore two competing explanations for the visual deficits, namely an evenly distributed loss of neural connections (undersampling) with the amblyopic eye as opposed to disordered connections with this eye (neural disarray). Unexpectedly, the results in animal models of deprivation amblyopia were not in accord with expectations based upon an even distribution of lost connections with the amblyopic eye. However, the results were similar to those observed in a strabismic amblyopic animal and to strabismic amblyopic humans. We suggest that deprivation amblyopia may be accompanied by an uneven loss of connections that results in effective neural disarray. By contrast, amblyopia associated with strabismus might arise from neural disarray of a different origin such as an alteration of intrinsic cortical connections.

Introduction

Amblyopia is a developmental visual disorder, characterized by poor spatial vision in one or both eyes, that is thought to be caused by some peripheral obstruction to concordant binocular visual input in early life (Daw, 1995). Because of the complex nature of the visual spatial deficits in amblyopia, the nature of the visual loss has proved difficult to model and especially so for strabismic amblyopia (see Hess, 2002; Barrett *et al.*, 2004 as well as Hess & Malin, 2003). Attempts to identify the neural basis of the visual loss in amblyopia have benefited from study of animal models (Kiorpes & McKee, 1999). Three of the major forms of human amblyopia namely, strabismic-, anisometric- and deprivation amblyopia, have been modelled successfully in both cats and monkeys by depriving them selectively in appropriate ways of concordant binocular visual input in early life. Although studies of animal models have allowed identification of neural deficits that exist at the single cell level in early visual cortical areas (for reviews see Kiorpes & McKee, 1999; Daw, 1995), little is known of the neural deficits involving cellular network interactions in area 17 (but see Schmidt *et al.*, 2004) and there is only sparse knowledge of the single or multicellular deficits in higher cortical areas of these animals (e.g. Chino *et al.*, 1988; Sireteanu & Best, 1992; Schröder *et al.*, 2002). Attempts to identify the neural basis of the different forms of human amblyopia on the basis of psychophysical studies have had some

success, but have failed to achieve a consensus as to the neural deficit in strabismic amblyopia. The visual deficits in anisometric amblyopia appear to follow as a direct consequence of their loss of contrast sensitivity and hence the reduced visibility of the stimuli, but the deficits in strabismic amblyopia defy such a simple explanation (Hess & Holliday, 1992). Such deficits as the perceptual distortions (Hess *et al.*, 1978; Bedell & Flom, 1981; Fronius & Sireteanu, 1989), anomalous global shape perception (Hess *et al.*, 1999) and the inaccurate position coding (Levi & Klein, 1985; Levi *et al.*, 1987; Hess & Holliday, 1992) can be explained only on the basis of at least one additional source of noise.

Two potential sources of noise have received considerable attention, namely an evenly distributed loss of neural connections (undersampling) with the amblyopic eye as opposed to disordered connections with this eye (neural disarray). On the basis of psychophysical tests, Hess & Field (1994) concluded that the positional deficits (inaccuracy and distortion) in strabismic amblyopia were consistent with a disordered neural map as opposed to an undersampled representation (see also Hess *et al.*, 1999 and Demanins *et al.*, 1999 for similar arguments). Conceivably, animal models of amblyopia could provide an additional potential source of data relevant to the debate over the nature of the underlying deficit in amblyopia because of the potential ability to examine directly both the physiological and behavioural deficits. This paper describes an application of similar psychophysical tests of visual function to those employed by Hess & Field (1994) to three cats that were visually deprived in early life so as to produce animal models of either deprivation or strabismic amblyopia.

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Received 2 February 2005, revised 25 April 2005, accepted 6 May 2005

Materials and methods

Strategy

According to Hess & Field (1994), the hypothesis of neural undersampling (i.e. an even loss of connections) predicts that interocular measures of positional accuracy should be associated with interocular errors of perceived contrast of similar magnitude (see Hess & Field, 1993 for a detailed explanation but also see Levi & Klein, 1996 and Hess & Field, 1996). Hess & Field (1994) tested this hypothesis by comparing the ability of amblyopes to detect a misalignment between three Gabor patches with their ability to discriminate a difference in contrast between one of the patches and its neighbours. However, in violation of this prediction, human strabismic amblyopes exhibited much smaller deficits on the latter discrimination in comparison to the severe positional deficits. On the basis of this finding as well as those from a second test of the ability to detect image distortion, Hess & Field (1994) concluded that the data were more compatible with the hypothesis of neural disarray than undersampling. In an effort to explore this issue further, we used a variant of the first test employed by Hess & Field (1994) on two monocularly deprived cats for which a substantial loss of connections with the deprived eye would be expected in area 17, as well as on a cat on which a strabismus was induced in the third week of postnatal life.

Animals and experimental procedures

The studies reported here were conducted on three cats that were born and raised in a closed laboratory colony at Dalhousie University and employed in a prior study of alignment accuracy (Gingras *et al.*, 2005). The procedures followed the 'Principles of laboratory animal care' (NIH publication no. 86-23, revised 1985) and animal protocols approved by Dalhousie University that were prepared in accordance with standards and regulations established by the Canadian Council on Animal Care. A detailed description of the rearing history of the animals is available from the earlier paper (Gingras *et al.*, 2005). The surgical procedures for both experimental manipulations were performed under gaseous halothane anaesthesia following partial induction with Xylazine (2 mg/kg i.m.). Two of the cats were monocularly deprived by eyelid suture at 11 days of age until either 60 (LMD2) or 82 (LMD3) days old. The procedure for eyelid suture (Gingras *et al.*, 2005) was slightly different from those used in this laboratory in the 1970s; the most significant departure from the old practice was to suture the freed palpebral conjunctivae together to form an additional

occlusion layer to that provided by the eyelids themselves. Although electrophysiological recordings were not made from these animals, the rearing history of one of the animals (LMD2) was identical to that of an animal (60B) from which such recordings were made in an earlier study from this laboratory (Mitchell, Cynader & Movshon, 1977). The ocular dominance histogram recorded from this animal is reproduced in Fig. 2 in order to provide an indication of the magnitude of the loss of connections with the deprived eye that might be expected to be present in the visual cortex (area 17) of LMD2 and LMD3. The third cat (S1) was reared with a strabismus (esotropia) induced by partial myectomy of the lateral rectus muscle of the left eye at 17 days of age by use of standard procedures described in detail in a previous publication (Mitchell *et al.*, 1984). The esotropia was evident immediately and remains obvious to this day (see Gingras *et al.*, 2005, their figure 11).

Partly because of slight differences in the method of eye occlusion and also to allow comparison with data from animals with similar deprivation histories reared in earlier studies (Giffin & Mitchell, 1978), longitudinal measurements were made of speed and the extent of the recovery of the grating acuity of the deprived eye. Measurements of the visual acuity for square-wave gratings were made on a jumping stand (Mitchell *et al.*, 1977) by use of procedures that differed in only one respect from those described in detail previously (Murphy & Mitchell, 1987; Mitchell, 1991), namely the use of a discrimination rather than a detection task where the kitten was required to jump toward a vertical grating (the positive stimulus) as opposed to an adjacent horizontal grating of the same spatial frequency. A more complete description of the procedure and stimuli employed for these measurements is provided in the earlier paper (Gingras *et al.*, 2005) that describes the spatial localization deficits of these and other animals. Tests of the vision of the deprived (or deviating) eye were made with an opaque hard contact lens placed on the other eye following administration of a drop of local ophthalmic anaesthetic (proparacaine hydrochloride 0.5%) into the conjunctival sac to eliminate any potential physical discomfort. The acuity of the nondeprived eye was usually assessed on the basis of measures of acuity made with both eyes open, as comparison measurements indicated that these measures were identical to values obtained with the deprived eye occluded. A practical disadvantage of the latter measures was the need to wait 24 h before measures of the vision of the deprived eye were possible because of the potential for distortion of the corneal curvature of this eye due to the use of the contact lens occluder (Dzioba *et al.*, 1986).

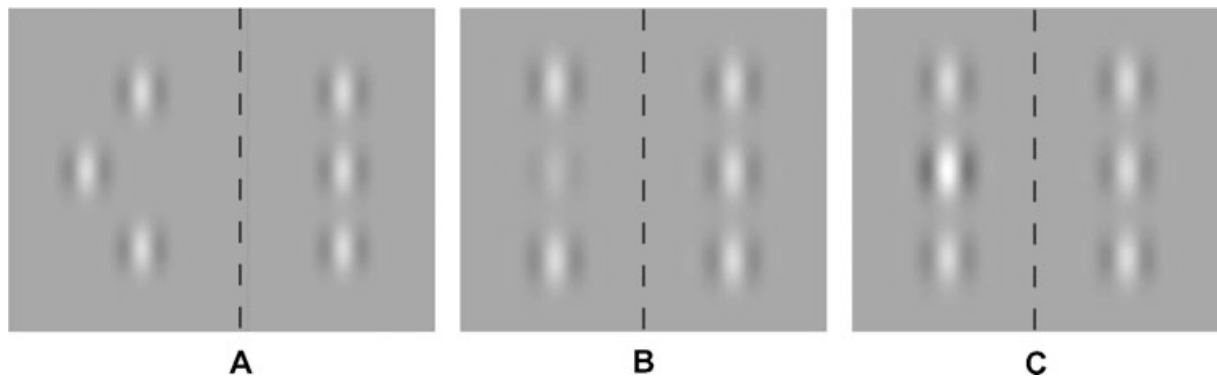


FIG. 1. Illustration of the stimulus displays for the tests of alignment accuracy (A) and for detection of contrast decrements (B) and increments (C). In each case the animal was rewarded for jumps to the odd stimulus of each pair, in these cases the stimuli on the left.

Measurement of alignment accuracy and contrast discrimination

Contrast discrimination and alignment accuracy data were collected when the animals were approximately 4.5 years old. Based on earlier observations (Cynader *et al.*, 1980; Giffin & Mitchell, 1978) it is highly unlikely that any changes would have occurred in the visual acuity of either eye during the years that elapsed before the measurements of contrast discrimination and alignment accuracy were commenced. Similar stimuli to those employed by Hess & Field (1994) were used for these two tasks, namely two sets of three Gabor patches were presented on a display screen of a computer monitor. For the tests of alignment accuracy, the 3 Gabor patches of one set were in vertical alignment, while in the other set the middle patch was displaced horizontally from a hypothetical line that joined the centres of the two vertically aligned outer patches (see Fig. 1A). The latter misaligned set was the positive stimulus to which the cat was trained to jump. For the tests of contrast discrimination both sets of Gabor patches were in vertical alignment but for one, the central patch was of either lower (Fig. 1B) or higher (Fig. 1C) contrast than either of the two flanking Gabors or the contrast of all three patches of the adjacent set that represented the negative stimulus. Thus, for both tasks the positive stimulus was the set of three Gabors for which the central patch was either misaligned or else of different contrast than its neighbours. The measurements were made with Gabor patches of a size (for which the standard deviation of the Gaussian envelope was 22.9 min) that allowed alignment thresholds to be made on both eyes of all three animals. The spatial frequency of the vertical carrier grating of each Gabor was 0.63 cycles/deg and the Gabor patches of each set were separated by five standard deviations from their nearest neighbour. The observation distance of the cats on the jumping stand was 60 cm. The stimuli were displayed on a Mitsubishi Diamond Scan monitor controlled by an Apple iMac computer. Calibration of the monitor was enabled by use of a United Detector Technology Model 161 Optometer. The mean luminance and Michelson contrast of the fixed Gabor stimuli were, respectively, 40 cd/m² and 0.5.

Training on both tasks began with the positive stimulus having the largest magnitude possible with our displays, namely a misalignment of 40 mm for alignment accuracy, or a contrast of 1.0 vs. 0.5 for the contrast discrimination. The cats reached criterion performance with these stimuli (20 consecutively correct responses) within two sessions of 40 trials. Training was continued with progressively smaller offsets or contrast differences for 5 sessions after which formal measurements of thresholds were begun. For the measurements of alignment accuracy, the offset of the middle Gabor patch of the positive stimulus set was reduced in small steps that were equated on a logarithmic scale (8–10 steps to the octave) beginning from a value that was substantially suprathreshold until the cat failed to achieve criterion performance (defined as at least seven correct out of a maximum of 10 trials for any given offset). Because previous measurements (Gingras *et al.*, 2005) revealed no difference between displacements to the left or to the right, all the data was obtained with the middle Gabor displaced to the left. The measurements of contrast discrimination thresholds were made separately for incremental and decremental contrast of the central Gabor with respect to that of the flanking patches (0.5). As with the measurements of alignment accuracy, the animals were confronted first with large suprathreshold contrast differences after which the contrast of the central Gabor was altered in small steps to a value where the cat failed to achieve criterion performance. For all animals the measurements of alignment accuracy followed immediately the conclusion of the measurements of contrast discrimination thresholds. The performance of the nondeprived eye on both measures was assessed on the basis of binocular measurements as

the performance on the latter was shown in control experiments to be identical to the monocular performance of the nondeprived eye. Moreover, because binocular measurements could be made without the use of a contact lens occluder, they could be followed immediately by measurements of the alignment accuracy or the contrast discrimination accuracy of the deprived eye made with the fellow eye occluded thereby permitting comparison of the performance of the two eyes in a single daily session. The thresholds reported for each stimulus condition represent the mean of at least six measurements. In the vast majority of cases these thresholds were identical or very close so that the standard errors were extremely small.

Results

Recovery of grating acuity

The results of longitudinal measurements of the recovery of grating acuity of the two monocularly deprived animals, LMD2 and LMD3, are displayed, respectively, in Fig. 2A and C. Equivalent data for an animal (60B) from an earlier study (Mitchell, Cynader & Movshon, 1977) that was monocularly deprived to the same age as LMD2 is shown in Fig. 2B. For 15 days after visual input was restored to the deprived eye of LMD2, this animal was classified as blind on the jumping stand when using this eye as it was unable to find an open from a closed door by visual cues alone (indicated by the black bar in Fig. 2). On the next day and for a further 4 days it recovered sufficient rudimentary vision to allow it to make this discrimination but was unable to pass a formal test of form vision (discrimination of a horizontal from a vertical grating of 32 mm period from 15 cm). Form vision was first regained three weeks after vision was restored to the deprived eye after which the vision of this eye improved gradually for the next 6 weeks before reaching asymptotic levels. The pattern of recovery observed in LMD2 was similar to that observed earlier for 60B; the small differences that were apparent did not fit a pattern consistent with a different degree of deprivation. Thus, whereas the period of blindness for LMD2 was somewhat longer than that for 60B (10 days), the final acuity attained by the deprived eye of LMD2 (5.03 cycles/deg) was slightly better than that of 60B (4.45 cycles/deg.). Consistent with the longer period of deprivation, the vision recovered by the deprived eye of LMD3 was less than that of LMD2 and occurred at a slower rate.

Although the effects of the period of monocular deprivation on the ocular dominance of cells in the visual cortex of LMD2 and LMD3 were not investigated, the results of such a physiological assay made in area 17 of 60B (shown in Fig. 2D) immediately after the behavioural data displayed in Fig. 2B were collected, provides an indication of what might be expected.

Comparison of deficits of spatial localization and contrast discrimination

As demonstrated earlier using Gaussian blobs (Gingras *et al.*, 2005), the deficits of alignment accuracy for the deprived or deviating eye measured with Gabors were very large. Moreover, the thresholds for the two eyes measured with Gabors were very similar to values obtained in the earlier study with Gaussians having the same envelope size (Gingras *et al.*, 2005) despite the fact that they were made more than 3 years apart. This point is emphasized in Table 1, which displays the alignment accuracy thresholds for both eyes as well as the interocular ratio of the thresholds for the two stimuli. The close similarity of the data measured with Gaussian and Gabor stimuli is consistent with the observations made on humans (Hess & Holliday,

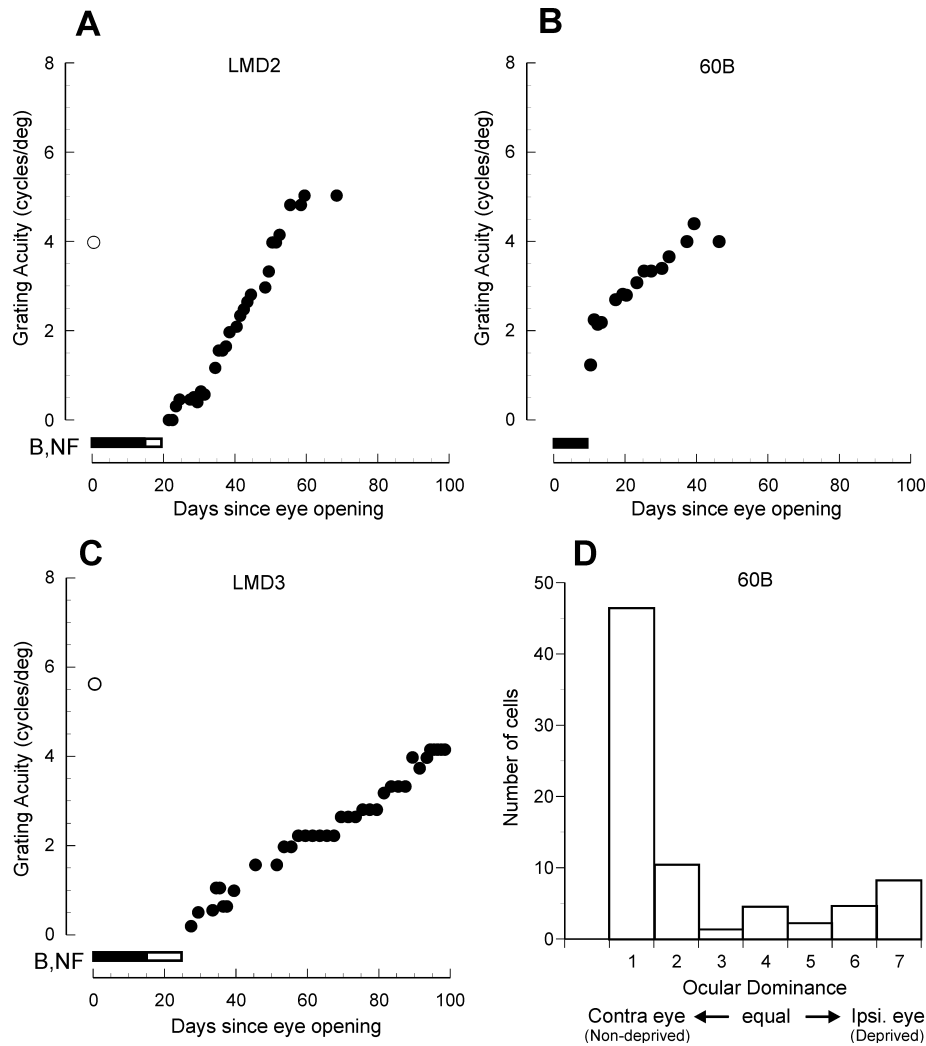


FIG. 2. Longitudinal changes in the grating acuity of the deprived eye (filled symbols) of LMD 2 (A) and LMD3 (C) following the end of the period of monocular deprivation at either 60 days (LMD2) or at 82 (LMD3) days of age. During the period indicated by the filled bar, the animals appeared blind (indicated as B on the ordinate) on formal tests and during the period indicated by the open bar, they were able to discriminate only an open from a closed door on the jumping stand suggesting that at best they were capable only of making luminance discriminations (NFV, no form vision). Equivalent data from an animal, 60B, reared in an identical manner to LMD2 for a previous study (Mitchell, Cynader & Movshon, 1977), is shown in B. (D) The ocular dominance distribution of a sample of cells recorded in area 17 of 60B at the conclusion of the behavioural testing.

1992) that alignment accuracy measured with Gabor patches is determined by the size of the Gaussian envelope of the stimuli rather than the spatial frequency of the carrier grating.

In contrast to alignment accuracy, the contrast discrimination deficits for the deprived or deviating eye were comparatively small. For all animals the ratios measured with contrast decrements were slightly greater than for contrast increments. For LMD2, LMD3 and S1 the ratios calculated for contrast decrements were, respectively, 1.66, 1.68 and 2.11 while the corresponding ratios for contrast increments were, respectively, 1.51, 1.58 and 1.68. However, because of the close similarity of the two ratios measured for contrast decrements and increments on each animal, the mean of the two ratios calculated for each animal was used for the comparison of the interocular alignment accuracy and contrast discrimination ratios for the three animals displayed in Fig. 3. Whereas the interocular alignment accuracy ratios among the three animals were all high (from 11.5 to 34.6), the corresponding interocular contrast discrimination ratios were all less than a factor of 2. As a consequence, the data all fall well below the line with a slope of 1.0 that represents the situation

where the deficits for alignment accuracy and contrast discrimination were the same. Although the discrepancy between the two ratios was greatest for the strabismic animal (S1), the differences for the two monocularly deprived animals were also very large.

TABLE 1. Alignment accuracy thresholds measured with Gaussian and Gabor patches for the nondeprived and deprived eye in three experimental animals

	Alignment accuracy threshold (min)				Interocular Ratio (Non-deprived/ Deprived)	
	Gaussians		Gabors			
	Non-deprived eye	Deprived eye	Non-deprived eye	Deprived eye	Gaussians	Gabors
Cat						
LMD2	4.0	40.1	3.6	41.7	10.0	11.5
LMD3	7.0	86.0	7.3	85.0	12.3	11.7
S1	7.5	240	7.6	263	32	34.6

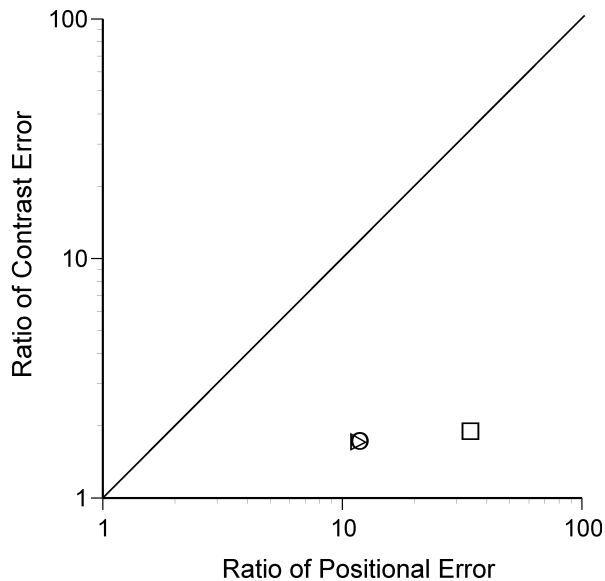


FIG. 3. A comparison of the ratios of the positional errors between the deprived (deviating) and nondeprived eyes of the three animals with the equivalent contrast discrimination ratios. The reference line has a slope of unity. LMD2 (triangle); LMD3 (circle); S1 (square).

Discussion

The finding from the strabismic cat, S1, of substantially larger deficits of alignment accuracy than of contrast discrimination, is in excellent agreement with the results obtained by application of the same tests on human strabismic amblyopes by Hess & Field (1994). However, the results obtained on the two monocularly deprived animals were unexpected as this form of deprivation when imposed from near birth for 2–3 months can be expected to lead to long-term loss of connections from the deprived eye in the visual cortex. Indeed, electrophysiological data obtained earlier (Mitchell, Cynader & Movshon, 1977) from an animal (60B, see Fig. 1D) with an identical rearing history to that of LMD2 revealed that substantial shifts of ocular dominance toward the nondeprived eye remained after the end of behavioural recovery. On this basis, LMD3, that was deprived for nearly 3 months would be expected to have suffered at least as severe a shift of ocular dominance and hence loss of connections of the deprived eye in area 17. As a consequence of the anticipated loss of connections from the deprived eye to the visual cortex, it might have been expected that both LMD2 and LMD3 would have exhibited similar contrast discrimination deficits to those of alignment accuracy. The fact that the deficits of alignment accuracy and of contrast discrimination in the two monocularly deprived animals were far from equivalent was not consistent with the predictions of a model based on undersampling (i.e. an evenly distributed loss of connections).

Although the results from the two monocularly deprived animals were not consistent with a simple model based solely on undersampling, the findings are not incompatible with the predictions based on an additional source of noise, namely a disordered neural map. Such a disorder might be introduced if the loss of cells during the period of deprivation occurred in an uneven fashion, or if the limited number of connections that were re-established after the period of deprivation occurred in a nonordered manner. A similar suggestion was made by Jeffrey *et al.* (2004) on the basis of global shape deficits in humans with deprivation amblyopia.

The earliest studies of the physiological deficits in area 17 associated with surgically induced strabismus (for a review see Mitchell & Timney, 1984) painted a very different picture to the observations made following monocular deprivation. Whereas the latter deprivation was universally found to result in a loss of cells dominated by the deprived eye, with exotropia there was no such loss of responsiveness to the deviated eye but instead a substantial reduction in the proportion of cells that could be excited through either eye. In contrast to exotropia, surgically induced esotropia is usually accompanied by severe amblyopia (Mitchell, 1988; Gingras *et al.*, 2005). The neural correlates of the amblyopia in area 17 can be quite subtle with inconsistent observations reported in different studies. While the loss of binocularly excitable cells observed in exotropia has been confirmed in esotropia as well, there is disagreement concerning the extent of any bias of ocular dominance in favour of the nonamblyopic eye. Some investigators (Berman & Murphy, 1982; Freeman & Tsumoto, 1983; Sireteanu & Best, 1992) report a slight bias but others (Mower *et al.*, 1982; Chino *et al.*, 1983; Kalil *et al.*, 1984; Crewther & Crewther, 1990; Roelfsema *et al.*, 1994) observed no inequality between the number of cells dominated by the two eyes. On the other hand, various studies have reported lower spatial resolution of cells in area 17 driven by the amblyopic eye (Chino *et al.*, 1983; Crewther & Crewther, 1990; Schmidt *et al.*, 2004). However, in addition to differences between the number or spatial resolution of cells driven by the two eyes in V1 of strabismic cats, other deficits have been reported in V1 such as stimulus-independent interocular suppression (Sengpiel *et al.*, 1994) and a loss of synchronization of neural activity that is selective for gratings of high spatial frequency (Roelfsema *et al.*, 1994), any or all of which could underlie the amblyopic deficit. By contrast, the suggestion has been made that the neural substrate for strabismic amblyopia must be sought in cortical areas beyond area 17 in both cats and monkeys (Kiorpes *et al.*, 1998). This suggestion receives support from observations of larger deficits in the postero-medial lateral suprasylvian area (PMLS) and area 21a (e.g. Sireteanu & Best, 1992; Schröder *et al.*, 2002) of cats.

Whereas early monocular deprivation results in profound physiological changes in area 17 including a major decoupling of the influence of the deprived eye upon cortical cells, the similarity in the behavioural results for form-deprivation and strabismus suggests that the loss of connectivity from the deprived eye in area 17 which only consistently occurs in the former may not be the key factor in determining positional sensitivity. In addition to dominant features of a form-deprived visual system that include a loss of connections with the deprived eye and changes in the properties of single cells dominated by this eye, we suggest that there may be a loss or rewiring of connections with this eye that is unevenly distributed across the retinotopic maps in area 17 and beyond. We further suggest that the neural disarray that represents the dominant feature of a strabismic visual system, may be of a different nature to that observed in form deprivation such as a selective loss of excitatory connections between opposite-eye domains in V1 (Lowel & Singer, 1992; Burkhalter & Tychsen, 1993).

Acknowledgements

This work was supported by an NSERC Discovery grant to DEM and CIHR grants (MT108-18 and MOP-53346) to RFH. GG was supported by a scholarship (Centre de développement de la formation et de la main-d'oeuvre Huron-Wendat). We wish to thank Debbie Fice, Nicki MacGillivray and Marc Jones for their care of the animals and help with data collection and Jane Anne Horne for programming the visual displays.

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