SPATIAL LOCALIZATION DEFICITS IN AMBLYOPIC CATS

by

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Abstract

Amblyopia is a neuro-developmental disorder of the visual system that is defined as a loss of visual acuity that cannot be corrected with lenses nor attributed to a disease. Although amblyopia is defined as a loss of visual acuity, the condition is further characterized by other visual anomalies, including large deficits of spatial localization. Because the latter aspect of amblyopic vision has not been addressed by animal models of amblyopia, the spatial localization abilities of visually deprived kittens were investigated using the same spatially bandpass stimuli as those employed for the assessment of human amblyopes. The tests were conducted on 2 normal kittens, 2 animals reared with a strabismus and 6 other kittens following different periods of early monocular deprivation. Measurements were made of the accuracy with which the animals could detect a misalignment between three Gaussian blobs of high contrast. Alignment accuracy for both normal and the non-deprived eye of the visually deprived kittens increased in a proportional manner to the spatial scale of the stimuli, a result comparable to that observed in normal humans. As with human amblyopes, the deficits in alignment accuracy were scaled in proportion to blob size but were in general larger than those reported in human amblyopes. Moreover, the alignment deficits were considerably larger than those of grating acuity. Tests with stimuli of various contrasts revealed that the deficits in the deprived eyes could not be explained in terms of the contrast sensitivity loss in this eye. Comparisons of the ratios of alignment accuracy between the amblyopic and the non-amblyopic eyes of the visually deprived animals with the corresponding ratios for contrast discrimination revealed that the former were much larger than the latter, a result that conflicts with simple versions of models of the spatial localization deficits based on neural undersampling. The close similarities between the spatial localization deficits found in amblyopic cats and those found in human amblyopes provide strong support for the use of this particular animal model for study of the neural basis of human amblyopia.

List of Abbreviations and Symbols Used

°	Degrees
c/deg	Cycles/degree
dB	Decibel
LGN	Lateral geniculate nucleus
LMD	Long-term monocularly deprived animals
min	Minutes of arc
N	Normal animals
NDE/DE	Non-deprived eye/deprived eye
S	Strabismic animals
SD	Standard deviation
SMD	Short-term monocularly deprived animals

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Chapter 1. GENERAL INTRODUCTION

The landmark studies of Hubel and Wiesel that began over 40 years ago inspired an avalanche of work on the functional organization of the visual cortex pathways as well as investigations that explored the time course and underlying rules of their development. The latter studies revealed that the development of the visual pathways continues postnatally and that this development is affected by the nature of the visual inputs during certain critical periods. Although most of the development of the basic organization of the visual pathways occurs prenatally (for example, the lamination and segregation of the lateral geniculate nucleus into eye-specific layers, as well as the retinotopic organization of many visual neural structures), other organizational features continue to develop after birth. The latter development, unlike that which occurs prenatally, can be influenced by the animal's early visual input. The extent of this influence as well as the time over which it can exert an effect have been documented through extensive studies of animals that have been visually deprived in specific ways for known periods of time. Many excellent reviews of the extensive literature on this topic exist (e.g. Blake, 1979; Movshon and van Sluyters, 1981; Sherman and Spear, 1982; Wiesel, 1982; Mitchell and Timney, 1984; Daw, 1995; Boothe, Dobson and Teller, 1985; Hubel and Wiesel, 1998; Kiorpes and Movshon, 2003; Mitchell, 2003), so only the main points relevant to this study will be summarized here.

The majority of the studies of visual system development have been conducted on the domestic cat, which, like primates, has eyes that are frontal and whose visual fields show substantial overlap. Like primates, cats possess stereoscopic vision (Fox and Blake, 1971; Ptito, Lepore and Guillemot, 1991). The additional benefit of their comparatively small body size, more rapid maturation, and lower cost make cats the species of choice over monkeys for the study of the experience-dependent nature of the development of the visual cortex. Most of the major concepts that guide research on the experience-dependent nature of the development of the central visual pathways have emerged from studies of cats subjected to one particular form of visual deprivation (or selective visual exposure), namely monocular deprivation. Another motive for studying the effects of this particular form of early visual deprivation was the early realization

(Wiesel and Hubel, 1963b) of the insight these manipulations on the visual system provided into the origin of the human developmental visual disorder, amblyopia.

Human amblyopia

Amblyopia is a neuro-developmental disorder affecting the visual system. The incidence of amblyopia in the general population has been estimated at between 2 to 2.5 % and is the most common cause of decreased vision in childhood (Von Noorden, 1996; Wright, 2003). Keech and Kutschke (1995) found that children up to seven years old are susceptible to develop this disorder, and amblyopia remains the number one cause of monocular vision in people (von Noorden, 1996). Amblyopia (from the Greek, amblyos, dull; -opia, vision) was originally defined as poor vision, or blunt sight. Clinically, amblyopia is defined as a unilateral, or less frequently, bilateral loss of visual acuity, caused by form vision deprivation and/or abnormal binocular interaction for which no organic causes can be detected on physical examination of the eye and which, in appropriate cases, is reversible by therapeutic measures (von Noorden, 1996). The visual deficit most commonly associated with amblyopia is a loss of visual acuity, but the deficit is much more complicated than that. Hess (1982) even suggested replacing amblyopia by tarachopia (from the Greek, taraché, which means confusion or a jumble), while Asper, Crewther and Crewther (2000a) described amblyopia as a "syndrome of visual cacophony". Amblyopia is much more than a loss of visual acuity. Many other visual deficits are present, including deficits in shape discrimination/ detection (Pointer and Watt, 1987; Hess, Wang, Demanins, Wilkinson and Wilson, 1999), orientation discrimination (Skottun, Bradley and Freeman, 1986; Demanins, Hess, Williams and Keeble, 1999a; Simmers and Bex, 2004), contour integration/interaction (Hess, McIlhagga and Field, 1997; Kovács, Polat, Pennefather, Chandna, Norcia, 2000; Chandna, Pennefather, Kovács and Norcia, 2001; Hess, Dakin, Tewfik and Brown, 2001), binocular integration (Harrad and Hess, 1992), motion sensitivity/detection (Hess and Anderson, 1993; Simmers, Ledgeway, Hess and McGraw, 2003), undercounting features (Sharma, Levi and Klein, 2000), perception of illusion (Popple and Levi, 2000), distortions (described below) and many other deficits (for review: Asper et al., 2000a; McKee, Levi and Movshon, 2003). But the spatial deficits are the hallmark of human

amblyopia, and the main deficits are manifest on tests of spatial resolution and localization of image features.

Classification of amblyopia

There are four major types of amblyopia (von Noorden, 1967, 1996; Wright, 2003) that receive their names from an associated condition that is assumed to be the predisposing cause. These are deprivation amblyopia, anisometropic amblyopia, strabismic amblyopia or a combination of anisometropic and strabismic amblyopia. Deprivation amblyopia is associated with unilateral cataracts or other opacities of the optical media that cause a diffuse image on the retina. Anisometropic amblyopia is characterized by a difference in the refractive state of the two eyes. Strabismic amblyopia is associated with a misalignment of the eyes that creates a mismatch of the visual information from the two retinae. Finally, mixed amblyopia represents a combination of anisometropic and strabismic amblyopia. Most of the human amblyopes are classified as either anisometropic, strabismic or both (approximately 30% for each category), while deprivation amblyopia is extremely rare (< 1%).

Because of their association with specific forms of amblyopia, considerable attention has been placed on the consequences of rearing animals with the monocular form deprivation, experimentally-induced strabismus, or anisometropia.

Monocular deprivation in animals

Hubel and Wiesel (1959, 1962) were the first researchers to demonstrate that many cells in the adult cat's visual cortex could be excited by visual stimulation of either eye. They described a gradation of ocular dominance for striate cortical neurons, and established a system of categorization based upon the relative extent to which a given neuron could be excited by visual stimuli through the two eyes. Some of the cells (approximately 20%) were strictly monocular, meaning that these cells could only be excited by visual stimulation of one eye, while the remaining cells were binocular, meaning that either eye could excite these cells. Although either eye could excite these cells, one eye's influence was greater than that of the other eye. The cells could be classified into one of seven groups. Neurons classified as belonging to Group 1 were exclusively responsive to stimulation of the contralateral eye, while Group 7 neurons were strictly responsive to the ipsilateral eye. Cells that were equally responsive through

either eye were classified as belonging to Group 4. Finally, Groups 2, 3, 5 and 6 neurons represented intermediate levels of influence from the two eyes. Shortly afterwards, they described the changes in the distribution of ocular dominance among neurons in the visual cortex of kittens deprived of patterned visual input through one eye for periods of 1-4 months from birth (Wiesel and Hubel, 1963b, 1965a). Since then, this particular form of early deprivation, referred to as "monocular deprivation", has become by far the most-often used rearing procedure for studies directed at the understanding of the experience-dependent nature of development at all levels of analysis (molecular, anatomical, physiological and behavioural). In brief, the eyelids of one eye are sutured closed for a period of time, resulting in light but not pattern perception through this eye (Wiesel and Hubel, 1963a; Crawford and Marc, 1976; Loop and Sherman, 1977). For a month or so, some form information can pass through the eyelids of kittens to the extent that orientation-specific receptive fields can be plotted through the closed eyelids (Spear, Tong and Langsetmo, 1978). As the eyelids thicken and the hair grows and darkens, the amount of patterned light that passes through them declines.

Possibly the most important information to emerge from this work on monocularly deprived cats was the documentation of sensitive or critical periods during which this form of deprivation produced lasting changes in the central visual pathways. To date, the critical periods have been documented with greatest precision for area 17: in the cat, shifts of ocular dominance are observed first at 2 weeks of age, peak in magnitude at 4-5 weeks, after which the size of the shifts gradually decline to zero at 10 months of age (Olson and Freeman, 1980; Jones, Spear and Tong, 1984; Daw, Fox, Sato and Czepita, 1992).

Although a number of studies have reported anatomical changes in the retina of monocularly deprived animals (Leventhal and Hirsch, 1983; Hsiao and Sherman, 1986), it seems likely that visual deprivation in these animals has no important functional effect on the development of retinal function. In contrast to the studies mentioned above, Wiesel and Hubel (1963b), Sherman and Stone (1973) and Spear and Hou (1990) found that the retinae of deprived animals were functionally normal. This was confirmed by studies that reported that the retinal ganglion cells of monocularly deprived animals were

quantitatively normal in their responsiveness and organization (Cleland, Mitchell, Gillard-Crewther and Crewther, 1980).

Unlike the robust neurophysiological effects of monocular deprivation observed in the visual cortex, there is little agreement on the nature and size of the effects in the lateral geniculate nucleus. Originally, Wiesel and Hubel (1963a) found that the physiological properties of the cat lateral geniculate nucleus cells driven by the deprived eye were essentially normal, a conclusion that was confirmed by Derrington and Hawken (1981). In opposition, Sherman, Hoffmann and Stone (1972) found that there was a marked reduction of Y cells encountered in the LGN of monocularly deprived cats. Moreover, it was shown that the X cells of the cat LGN had a reduction in spatial resolution (Lehmkuhle, Kratz, Mangel and Sherman, 1978, 1980). Further evidence for functional disturbance of cells in the cat LGN was demonstrated using visual evoked potentials (Mitzdorf and Neumann, 1980). In monkeys, von Noorden and Crawford (1978) also found that only cells from the non-deprived eye could be recorded, but more recently, Levitt, Schumer, Sherman, Spear and Movshon (2001) found few differences between the response properties of magnocellular and parvocellular cells driven by either eye. In view of the contradictory reports from both the cat and the monkey literature, it can be concluded that the effects of monocular deprivation on LGN functional cell properties are, at most, subtle.

The initial major functional effects of early monocular deprivation are observed in the striate cortex (area 17), the first level of the visual pathway where individual cells in normal animals can be influenced through either eye. As first described by Wiesel and Hubel (1963b), the major physiological consequence of monocular deprivation is a shift of ocular dominance of cells in the visual cortex. Their initial finding was that if a kitten was monocularly deprived during the first three months of life, the animal appeared blind when forced to use its deprived eye and that cells in the striate cortex only responded to stimulation through the non-deprived eye. Later, they confirmed these results in monkeys (Hubel, Wiesel and Levay, 1977; LeVay, Wiesel and Hubel, 1980). The limited data that exist suggest that in monkeys, the neurophysiological effect of monocular deprivation persists until 2 years of age. Even short periods of monocular deprivation imposed in infancy result in a shift of ocular dominance if the procedure is performed in

kittens at the peak of the critical period, at around 4-5 weeks of age (Hubel and Wiesel, 1970; Olson and Freeman, 1975, 1978, 1980; Movshon and Dürsteller, 1977; van Sluyters, 1978; Freeman, 1979; Malach, Ebert and van Sluyters, 1984; Mioche and Singer, 1989). Freeman (1979) showed that the ocular dominance shifts were observed after only 8 hours of monocular deprivation on postnatal day 29. The results showed that even with such a short period of monocular deprivation, there was a reduction of binocular cells (only 36% of the cells were binocular) and the non-deprived eye controlled 70% of the cells. More recently, the shifts of ocular dominance columns in monocularly deprived kittens have been confirmed in optical imaging studies (Kim and Bonhoeffer, 1994; Crair, Ruthazer, Gillespie and Stryker, 1997; Trachtenberg, Trepel and Stryker, 2000; Kind, Mitchell, Ahmed, Blakemore, Bonhoeffer and Sengpiel, 2002).

The shift of ocular dominance columns in monocularly deprived animals was also illustrated anatomically in layer IV of the visual cortex. In normal adult monkeys, the geniculocortical afferents from the two eyes are segregated into alternating bands at their terminals in layer IVc of the visual cortex. These segregated bands are the anatomical basis of the neurophysiological ocular dominance columns found in the extragranular layers of the visual cortex of animals. This orderly pattern is dramatically altered in monocularly deprived monkeys (Hubel et al., 1977; LeVay et al., 1980). In these animals, the bands that receive input from the deprived eye are significantly shrunken, while those receiving visual inputs from the non-deprived eye are expanded. In other words, the bands receiving visual inputs from the normal eye are proportionally increased compared to the bands receiving visual input from the deprived eye. A similar pattern was described in layer IV of the visual cortex of monocularly deprived cats (Shatz and Stryker, 1978). Even short-periods (4-7 days) of monocular deprivation in kittens results in shrinkage of geniculocortical afferents of the deprived eye to that observed after a month of deprivation (Antonini and Stryker, 1993, 1996). The branch length of the axonal arbors for the deprived eye were shorter and were reduced in numbers compared to those of normal animals, indicating that brief periods of monocular deprivation not only interfere with growth, but also induce rapid elimination of axonal branches. Interestingly, in postmortem anatomical analysis of human brains, no shrinkage of the ocular dominance columns was found in a patient with anisometropic amblyopia (Horton

and Stryker, 1993) nor in another patient with amblyopia associated with accommodative esotropia (Horton and Hocking, 1996). This suggests that if shrinkage of ocular dominance columns occurs in humans, it does so only after severe forms of pattern deprivation in one eye.

Although early studies reported that the physiological effects of prolonged periods of monocular deprivation on the kitten visual cortex were permanent (Wiesel and Hubel, 1965b; Hoffman and Cynader, 1977), substantial recovery is possible if visual input to the deprived eye is restored sufficiently early in life. Physiological experiments have shown that following extended periods of binocular vision (i.e. the situation where both eyes are open during the recovery period), monocularly deprived kittens show significant cortical recovery (Olson and Freeman, 1978; Mitchell, Cynader and Movshon, 1977a; Blasdel and Pettigrew, 1978). These physiological changes are even more accentuated when the non-deprived eye is occluded at the same time that normal visual input is provided to the deprived eye, a procedure referred to as "reverse occlusion" (Blakemore and van Sluyters, 1974; Movshon and Blakemore, 1974; Movshon, 1976a; Mitchell et al., 1977a; van Sluyters, 1978). When initiated at 4 weeks of age, complete shifts of ocular dominance toward the originally deprived eye can be achieved after 9-10 days of reverse occlusion (Movshon, 1976a; Antonini, Gillespie, Crair and Stryker, 1998). In monocularly deprived monkeys, similar physiological recovery has been found following reverse occlusion (Blakemore, Garey and Vital-Durand, 1978; LeVay et al., 1980; Blakemore, Vital-Durand and Garey, 1981). However, unlike cats, little or no recovery occurs in monkeys when both eyes receive visual input after a period of monocular deprivation. Thus, reverse occlusion seems to be required for monocularly deprived monkeys to show any physiological recovery at all (LeVay et al., 1980; Blakemore et al., 1981). It is noteworthy that recovery from monocular deprivation in monkeys has also been shown anatomically (Swindale, Vital-Durand and Blakemore, 1981).

Behavioural studies of monocular deprivation

Because of the severity of the deficits, the majority of studies have investigated the spatial visual abilities of monocularly deprived cats, with particular emphasis placed on visual acuity. Besides conventional visual acuity, vision through the deprived eye of monocularly deprived cats is impaired in several respects, including spatial gap detection (Dews and Wiesel, 1970), pattern discrimination (Ganz, Hirsch and Tieman, 1972; Ganz and Haffner, 1974), visuomotor behaviour (Ganz and Fitch, 1968; van Hof-van Duin, 1976), spatial and temporal contrast sensitivities (Lehmkuhle, Kratz and Sherman, 1982) and Vernier acuity (Murphy and Mitchell, 1991). Vernier acuity of monocularly deprived cats (deprived from birth and up to 17 weeks of age) has been reported to be 16-70 times worse than that of normal cats as compared to at most 10-fold differences in grating acuity (Murphy and Mitchell, 1991). Incidentally, the Vernier acuity of normal cats was found to be six times better than grating acuity, a ratio comparable to that observed in humans (Levi and Klein, 1982b).

Behavioural measurements of visual acuity in normal cats have been obtained using a variety of methodologies (for a review see Hall and Mitchell, 1991). Depending on the methodology used, values for the visual acuity of normal cats range from 2 c/deg (Loop, Smyly, Millican and Greifer, 1981) to 9.5 c/deg (Mitchell, Giffin and Timney, 1977b). The jumping stand is the methodology of choice to study the visual acuity of monocularly deprived kittens. Not only does this technique allow an accurate and rapid assessment of the immediate effects of various regimens of deprivation on the visual resolution through the deprived eye, but it also allows study of the time course and the extent of any recovery of vision of the deprived eye following restoration of normal visual input.

Similar to the physiological effects of monocular deprivation, the behavioural effects of monocular deprivation in kittens are severe and profound, but are not necessarily permanent. Immediately after the opening of the deprived eye, the animal appears to be blind (Wiesel and Hubel, 1963b; Chow and Stewart, 1972; Movshon, 1976b; Mitchell et al., 1977a; Giffin and Mitchell, 1978; Mitchell, Murphy and Kaye, 1984a, 1984b; Mitchell, 1988; Mitchell and Gingras, 1998; Mitchell, Gingras and Kind, 2001). However, considerable and rapid improvement of vision of the deprived eye can

occur if normal visual input is provided to this eye sufficiently early in life (Mitchell et al., 1977a; Giffin and Mitchell, 1978; Mitchell, 1988). Mitchell (1988) provided the most systematic study of the recovery of vision in the deprived eye of kittens monocularly deprived from birth and with increasing periods of deprivation. The speed and extent of the recovery depends on the timing of the deprivation such that following short periods of deprivation that terminate early in life, kittens recover more rapidly and to a greater extent than with longer periods of deprivation. Mitchell (1988) noted that first, it took progressively longer for kittens to exhibit signs of vision in their deprived eye with increased period of deprivation. Second, as the period of the deprivation increased, the recovery of vision in the deprived eye declined. Whereas kittens deprived to 4-6 weeks displayed signs of form vision with their deprived eye after only a few days, for animals deprived for longer periods, it took weeks or even months before they showed signs of pattern vision and the acuity that was eventually attained was progressively lower as the period of deprivation increased in length. For example, Mitchell (1988, Figure 1) displays data for kittens deprived to 42, 94 and 302 days of age. The kitten that was deprived for 42 days was blind for 5 days before it regained pattern vision. In contrast, the kitten that was deprived for 3 months (94 days) was blind for 17 days, while the third kitten deprived for 10 months (302 days) was blind for two months and for the next two months was only able to make luminance discriminations. Thereafter, the vision in its deprived eye gradually improved to eventually attain a visual acuity of only 1.35 c/deg. Kittens deprived to 12 months only regained rudimentary light perception. A final point needs to be made concerning the recovery of vision of monocularly deprived kittens. Even with long periods of deprivation to 3-4 months (but excluding those that extend through the sensitive period to 10 months of age), the deficits in visual acuity measured with sine-wave gratings are only about 1-1.5 octaves (where an octave is a factor of two) in relation to the visual acuity of the non-deprived eye. In other words, the visual acuity measured for the deprived eye is only about 2-3 times lower than that for the non-deprived eye. However, deficits in contrast sensitivity are much larger (Mitchell, 1988) as are the deficits in Vernier acuity (Murphy and Mitchell, 1991)

Similar to cats, visual deficits of great severity are also observed in monocularly deprived monkeys. Contrast sensitivity (Harwerth, Crawford, Smith and Boltz, 1981; Harwerth, Smith, Boltz, Crawford and von Noorden, 1983; Kiorpes, Kiper and Movshon, 1993), Vernier acuity (Kiorpes, Kiper and Movshon, 1993), and visual acuity (von Noorden, 1973; von Noorden, Dowling and Ferguson, 1970) are all severely affected in monocularly deprived monkeys. The effects of reverse occlusion on these visual functions have not been studied in monkeys.

The enormous anatomical, physiological and behavioural effects of early monocular deprivation prompted a separate but related set of investigations on the link between these effects and the clinical entity of amblyopia. This condition has long been recognized (Duke-Elder and Wybar, 1973) as a developmental visual disorder and it is nearly always found associated with a condition in which one eye is disadvantaged or with a disturbance of binocular correlation. Beginning shortly after the initial studies of the effects of monocular deprivation, attention was directed toward study of the consequence of rearing animals with either strabismus or anisometropia in order to study the neural underpinnings of the other major types of amblyopia.

Models of strabismic amblyopia

Strabismus is a deficit of the oculomotor control system leading to a misalignment of the two eyes. There are several ways of creating experimental strabismus in animals. The most common methodology is to induce the strabismus surgically by cutting or removing part of the medial rectus muscle to create a divergent strabismus (exotropia) or the lateral rectus muscle to create a convergent strabismus (esotropia). The strabismic condition can also be created optically (Smith, Bennett, Harwerth and Crawford, 1979; Bennett, Smith, Harwerth and Crawford, 1980; Crawford and von Noorden, 1980; van Sluyters and Levitt, 1980; Mower, Burchfiel and Duffy, 1982) by use of prisms worn by the animal.

As in humans, experimentally induced strabismus in animals creates different results, depending on the direction of the misalignment and the way in which it was produced. Because of its relevance to the work conducted in this study, the focus of this section will be on surgically created strabismus. Basically, four possible results are found in experimental strabismus: amblyopia, suppression of the image in one eye, loss of

binocular function and anomalous retinal correspondence. Numerous physiological results that may underlie strabismic amblyopia have been described, but the most investigated topic is the loss of binocularity of cortical cells. Once again, Hubel and Wiesel (1965) were the first researchers to report a loss of binocular cells in the striate cortex of strabismic cats, a conclusion confirmed repeatedly by many other researchers in both cats (Yinon, Auerbach, Blank and Friesenhausen, 1975; Yinon, 1976; Singer, von Grünau and Rauschecker, 1980; van Sluyters and Levitt, 1980; Berman and Murphy, 1982; Levitt and van Sluyters, 1982; Mower, Burchfiel and Duffy, 1982; von Grünau, 1982; Kalil, Spear and Langsetmo, 1984, Grant and Berman, 1991) and strabismic monkeys (Kiorpes, Kiper, O'Keefe, Cavanaugh and Movshon, 1998; Mori, Matsuura, Zhang, Smith and Chino, 2002). In addition, this loss of binocularity in strabismic animals seems only to apply to cells located in the primary visual cortex (area 17), since von Grünau (1982) reported no loss of binocular cells in the lateral suprasylvian sulcus (area LS). This latter result can possibly be explained by the fact that the receptive fields of cells located in area LS are much larger than those found in area 17 (Hubel and Wiesel, 1969; Spear and Baumann, 1975, Grant and Berman, 1991) so that they remain binocularly activated as the strabismus develops. Finally, there is general agreement that the period of vulnerability to disrupt binocular function in strabismic cats extends to 3 months of age (Yinon, 1976; Berman and Murphy, 1981; Levitt and van Sluyters, 1982).

Concurrent with the severe reduction of cortical binocularity observed in strabismic cats, behavioural tests reveal a loss of stereoscopic depth perception. With respect to the latter visual capacity, only a few studies have tested stereopsis directly. The remainder have inferred the presence or absence of stereopsis on the basis of comparison of monocular and binocular performance on depth judgments in situations where monocular depth cues were minimal. The ability of strabismic cats to perceive depth under binocular viewing condition only corresponds to their monocular performance or the monocular performance of normal cats (Mitchell, Kaye and Timney, 1979; Timney, 1990; Distler and Hoffman, 1991; Mitchell, Ptito and Lepore, 1994; Ptito, Bouchard, Lepore, Quessy, Di Stefano and Guillemot, 1995) and on this basis it has been argued that they lack exclusively binocular cues to depth of which stereoscopic vision is by far the most accurate.

As for possible mechanisms of image suppression, there have been studies showing inhibition of the cortical response from the deviated eye by stimulating of the non-deviated eye (Singer, von Grünau and Rauschecker, 1980; Freeman and Tsumoto, 1983; Crewther and Crewther, 1993). Results obtained from strabismic cats revealed that in neurons that retain binocularity to adulthood, two different mechanism of adaptation to ocular misalignment exist. First, for some neurons, the non-deviated eye dominates the response for high spatial frequencies; and second, other neurons adapt through active suppression of the monocular response to stimulation of the strabismic eye when the non-deviated eye is simultaneously stimulated (Crewther and Crewther, 1993). Cortical cells with anomalous retinal correspondence are not found in area 17 but in the lateral suprasylvian gyrus of the cat, which contains several areas of secondary visual cortex (Grant and Berman, 1991; Sireteanu and Best, 1992) and in area 18 of the visual cortex (Cynader, Gardner and Mustari, 1984). Anomalous retinal correspondence is found only when the angle of strabismus is constant and moderate, that is, less than 10° (Grant and Berman, 1991). There is also study of a reduction in the number of cells in the visual cortex that are driven by the deviated eye of esotropic cats (Kalil et al., 1984).

The physiological deficits in esotropic strabismic cats are accompanied by a reduction in visual acuity (Jacobson and Ikeda, 1979; Cleland, Crewther, Crewther and Mitchell, 1982; Mitchell, Ruck, Kaye and Kirby, 1984c; Crewther and Crewther, 1990; Ptito et al., 1995) and in contrast sensitivity, especially for high spatial frequencies (Jacobson and Ikeda, 1979; Singer, von Grünau and Rauschecker, 1980; von Grünau and Singer, 1980; Holopigian and Blake, 1983; Mitchell et al., 1984c). Behavioural measurements of visual acuity of strabismic cats showed that the visual acuity in the deviated eye of esotropic cats was about 2-3-fold lower than that of the fellow non-deviated eye, which has been reported by some investigators to be slightly below normal (Jacobson and Ikeda, 1979) but normal by others.

A number of behavioural studies have been conducted on the visual abilities of strabismic monkeys. Von Noorden and Dowling (1970) and Baker, Grigg and von Noorden (1974) both reported that strabismic monkeys had lower visual acuity in the deviated eye. Severe deficits in contrast sensitivity were reported (Harwerth et al., 1983; Kiorpes et al., 1998; Kozma and Kiorpes, 2003) while Kiper and Kiorpes (1994) reported

that strabismic monkeys had deficits in both contrast detection and contrast discrimination. Finally, strabismic monkeys also suffer from deficits in contour integration (Kozma and Kiorpes, 2003), spatial phase discrimination (Kiper, 1994) and on measures of Vernier acuity (Kiorpes, 1992; Kiorpes et al., 1993). Similarly to human amblyopes, Kiorpes (1992) reported that the deficits in Vernier acuity were larger than the deficits in grating acuity in strabismic monkeys.

Models of anisometropic amblyopia

Anisometropia refers to a difference in the refractive state of the two eyes. One eye can be put out of focus by rearing an animal with a substantial concave lens over the eye that is sufficiently powerful so that the defocus error cannot be overcome by accommodation. This technique provides very similar effects on spatial vision as seen in human amblyopia: the out-of-focus eye shows reduced contrast sensitivity at medium and high spatial frequencies in both cats (Eggers and Blakemore, 1978; Maguire, Smith, Harwerth and Crawford, 1982) and monkeys (Smith, Harwerth and Crawford, 1985). Another method used in primates to defocus the retinal image is to instill atropine into the eye in order to paralyze accommodation (Boothe, Kiorpes and Hendrickson, 1982). The most complete study of the behavioural, anatomical and physiological results of atropinization on the monkey's visual system was conducted by Mosvhon and colleagues (Hendrickson et al., 1987; Kiorpes et al., 1987; Movshon et al., 1987). As with monocular deprivation, the main effect of atropinization was seen in the visual cortex of the animals. The cells stimulated by the atropinized eye had reduced contrast sensitivities, with the most pronounced deficits occurring at high spatial frequencies. Behavioural measurements of contrast sensitivity functions revealed a similar pattern of results. No neurophysiological effects were found in the lateral geniculate nucleus but large effects were seen outside layer IV of the primary visual cortex where a modest shift of ocular dominance towards the normal eye and a loss of binocular cells were observed. Finally, there was considerable interanimal variability in the magnitude of the visual deficits. Later, Kiorpes et al. (1998) in a quantitative comparison of the behavioural and neurophysiological deficits in area 17 of anisometropic monkeys found that the latter deficits were smaller than the former. In particular, a proportion of the cortical neurons driven by the amblyopic eye responded physiologically to spatial frequencies that the

animals could not see behaviourally. They concluded that a complete explanation of the neural deficits found in human amblyopia could not be sought in terms of events in area 17 alone. More recently, Kozma and Kiorpes (2003) have shown than anisometropic monkeys had deficits in contour integration and that these deficits were not clearly related to their deficits in contrast sensitivity.

Visual deficits in human amblyopia

Historically, our understanding of the neural deficits that underlie the visual losses in amblyopia has been derived from two different approaches (Hess, 1995). The first source of information and most direct insight has emerged from neurophysiological studies performed on animals (described above), while the second source of information has come from human psychophysical studies (described below). The animal model of monocular deprivation has provided the most robust results and has become the technique of choice for pursuing the fundamental mechanisms underlying human amblyopia. This form of deprivation corresponds closely to that produced by unilateral cataract in humans. In recent years, this work has been complemented by the use of functional imaging techniques applied directly on human amblyopes in an attempt to define the site(s) and nature of the underlying neural deficits of human amblyopia. The visual deficits found in human amblyopia that are the most related to spatial vision and to the topic of this study are summarized below. The visual deficits that have been explored in the past include visual acuity, Vernier acuity, contrast sensitivity and perceptual distortions.

Visual acuity

In a clinical setting, visual acuity is usually measured using a Snellen chart, where a patient is required to identify letters presented in rows of progressively smaller size. A patient is typically described as amblyopic if there is a difference of at least two Snellen lines between the acuity of the two eyes (von Noorden, 1996; Wright, 2003). When testing the visual acuity of amblyopic patients, it is always of interest and importance to compare visual acuity measures with symbols presented in a row to single symbols presented on a uniform background. Most amblyopic patients are capable of discriminating Snellen letters that are considerably smaller when they are presented one at a time against a uniform background than when the letters are presented in a row. On a

Snellen chart, amblyopic patients report that letters tend to run together, a phenomenon called the "crowding effect" (Irvine, 1948; Stuart and Burian, 1962; Pugh, 1958, 1962). Although a similar phenomenon is observed in normal people (Stuart and Burian, 1962; Flom, Weymouth and Kahneman, 1963), the effects in amblyopes are far more profound. Interestingly, under reduced illumination, the Snellen acuity of normal humans decreases, while that of strabismic amblyopes either remains the same, drops slightly, or even improves (von Noorden and Burian 1959a, 1959b).

Vernier acuity

Vernier acuity, a form of localization acuity, has been referred to as a hyperacuity (Westheimer, 1975) because it exceeds, by a considerable margin, the resolution acuity measured with Snellen letters or gratings, and is defined as the ability to detect an offset between two adjacent contours. Vernier acuity is substantially reduced in human amblyopia. Deficits in Vernier acuity in human amblyopia have been demonstrated with a wide variety of targets, including a bright vertical line or rows of lines (Freeman and Bradley, 1980; Levi and Klein, 1982a, 1982b; Flom and Bedell, 1985; Rentschler and Hilz, 1985), multiple contours as with gratings (Bradley and Freeman, 1985) or a sequence of dots (Flom and Bedell, 1985).

Levi and colleagues (Levi and Klein, 1983, 1985, 1986, 1990b, 1992a; Levi, Klein and Yap, 1987; Levi, Klein and Wang, 1994a; Wang, Levi and Klein, 1998) conducted a series of experiments in order to investigate the positional acuity of human amblyopes. They used a variety of positional acuity tests, including a bisection task, 2- and 3-line Vernier acuity, as well as Vernier acuity with dots or Gaussian blurred lines, edges and abutting multiple horizontal lines. The positional thresholds of the amblyopic eyes were significantly larger (10-fold) than those of the fellow normal eyes, and as expected, the results from the strabismic amblyopes were worse than that for the anisometropic amblyopes. There were fundamental differences between the spatial deficits in anisometropic and strabismic amblyopia. For anisometropic amblyopes, the losses in positional acuity were proportional to the losses in contrast sensitivity, so that improvement of the visibility of the stimuli by increasing their contrast eliminated the deficits. On the other hand, increasing the contrast of the stimuli for strabismic amblyopes had little effect on their positional acuity performance. Thus while the deficit

in positional acuity of anisometropic amblyopes could be explained by their reduced contrast sensitivity, the larger spatial deficits of strabismic amblyopes must be attributed to something other than their loss of contrast sensitivity.

In addition, Levi and Klein (1982a, 1982b, 1983, 1985) showed that anisometropic and strabismic amblyopes display a different pattern of acuity losses. For strabismic amblyopes, both Snellen and Vernier acuities were substantially greater than the deficits in grating acuity, while for anisometropic amblyopes, the deficits in both Snellen and Vernier acuities were proportional to the deficits in grating acuity.

Hess and colleagues (Hess and Holliday, 1992b; Hess and Field, 1994; Field and Hess, 1996; Demanins and Hess, 1996) tested positional acuity in amblyopic patients using Gabor patches. Information on this type of task as well as on the stimulus used is provided in detail in Chapter 3. The task of the subjects was to measure the accuracy with which a central Gabor element can be aligned against two reference fixed Gabors. The main findings of these studies were that the alignment accuracy thresholds were greater for strabismic amblyopes than for anisometropic amblyopes and that the deficits were scale independent, i.e. the alignment deficits were equally affected for all spatial scales. As the size of the Gaussian blobs increased, the deficits in alignment accuracy became larger in a proportional fashion. Because amblyopia is defined in terms of a loss of visual acuity, it might be thought the deficits could be restricted to, or larger with small targets (i.e. high spatial frequencies). Finally, the loss in positional acuity for anisometropic amblyopes could be predicted simply on the basis of the reduced visibility of the localization targets, while for strabismic amblyopes, their larger spatial localization deficits could not be explained in such terms. In these subjects, the spatial localization deficits remained even with stimuli designed to factor out contrast sensitivity deficits.

Contrast sensitivity

The first quantitative glimpse of the visual deficit in amblyopia came when researchers investigated the contrast sensitivity function in human amblyopes. Gstalder and Green (1971) were the first researchers to show that amblyopes had abnormal contrast sensitivity for high spatial frequencies, while their sensitivity for low spatial frequencies was normal. Later, numerous other studies (Levi and Harwerth, 1974, 1978, 1980, 1982; Hess and Howell, 1977; Harwerth and Levi, 1978; Bradley and Freeman,

1981, 1985; Abrahamsson and Sjöstrand, 1988) reported that amblyopes have abnormal contrast sensitivity over a wide range of spatial frequencies. Although the magnitude of the deficit depends on the severity of the amblyopia, both anisometropic and strabismic amblyopes exhibited similar *types* of deficits. In other words, contrast sensitivity is particularly reduced in human amblyopes, and this deficit becomes larger with increasing spatial frequency. Moreover, further studies have indicated that these deficits were exclusively neural in origin, since they were not affected by oculomotor (Hess, 1977a), optical (Hess and Smith, 1977), fixation (Hess, 1977b) or field size (Hess and Howell, 1978) factors.

Perceptual distortions

Although human amblyopes exhibit contrast sensitivity deficits, this information by itself does not predict what these patients actually see. Hess, Campbell and Greenhalgh (1978) presented to a group of human amblyopes a series of sinewave gratings of variable spatial frequencies and asked them to draw what they saw. Most amblyopes exhibited spatial distortions/discontinuities that included fading and reappearance of the gratings (temporal instability). In some cases, lines in the gratings appeared to be broken up, and in other cases, the dark bars of the gratings appeared thinner than the light ones. In situations where contrast thresholds were elevated, the grating appeared fragmented or distorted. Moreover, all these distortions were present for all orientations and over a wide range of retinal illuminances. Finally, the visual distortions were greatest for gratings of high spatial frequency, while gratings of low spatial frequency were free of distortions and stable. Recently, these results were confirmed by Barrett, Pacey, Bradley, Thibos and Morrill (2003). The fact that spatial distortions were mostly present at high spatial frequencies is perhaps not surprising considering the fact the amblyopic patients experience their greatest contrast sensitivity loss at high spatial frequencies.

A number of different research groups, using different visual tasks, have attempted to quantify these spatial distortions. One group used a spatial localization task in which the subjects had to judge the position of a vertical line with respect to two triangular targets (Bedell and Flom, 1981, 1983; Bedell, Flom and Barbeito, 1985) and showed that the errors of localization of the amblyopic eye of strabismic amblyopes were

10-fold larger than those measured with their preferred eye and those of normal subjects. The distortions perceived by the strabismic amblyopes were characterized by bending of vertical lines.

Another group of researchers used a shape completion task in which amblyopes were asked to construct circles with different radii around a fixation point to quantify the spatial distortions found in human amblyopes (Lagrèze and Sireteanu, 1991; Sireteanu, Lagrèze and Constantinescu, 1993). The subjects exhibited individual distortion patterns that included expansion, shrinkage and torsion of specific regions of the visual field. In the study of Sireteanu et al. (1993), the researchers also asked the amblyopic subjects to copy drawings of gratings of different spatial frequencies, and they closely replicated the drawings published by Hess et al. (1978). In other experiments in which amblyopes were required to align a light stimulus with two reference marks (Fronius and Sireteanu, 1989), the performance of the amblyopic eye was found to be severely affected in central vision, but spatial distortions were essentially absent in the peripheral field.

Functional imaging studies

The first study conducted with human amblyopes was performed almost a decade ago by Kabasakal et al., (1995). Using single-photon emission computed tomography (SPECT), these researchers reported that the response of the visual cortex of human amblyopes by light stimulation of the amblyopic eye was severely reduced in comparison to the normal eye. This reduced activity in the visual cortex of amblyopic patients was also confirmed using functional magnetic resonance imaging (fMRI) by Goodyear, Nicolle, Humphrey and Menon (2000), Barnes, Hess, Dumoulin, Achtman and Pike (2001), Choi et al. (2001), Lee et al. (2001), and positron-emission tomography (PET) by Imamura et al. (1997) and Choi et al. (2002). Interestingly, in amblyopic patients, abnormal activity levels were also found outside many visual cortex areas, including areas V2 and V3A (Imamura et al., 1997; Barnes et al., 2001) as well as in both the inferior temporal lobe and superior temporal lobe areas (Choi et al., 2002). The fact that abnormal activity patterns are observed in brain areas other than the primary visual cortex suggests that amblyopia does not result only from events in the primary visual cortex, but that other visual areas may play a role in the visual deficits in amblyopia. Unfortunately, most of our knowledge on animal models of human amblyopia has been limited to the

study of the primary visual cortex, but in an animal model of anisometropic amblyopia, Kiorpes et al. (1998) reported that cells in the primary visual cortex responded to spatial frequencies that anisometropic monkeys could not see in behavioural experiments, and suggested that extrastriate cortical areas may be affected even more. It is obvious that future animal research on the underlying mechanisms of amblyopia will have to include study of visual areas outside of area 17.

Neural basis of amblyopia

Clearly, positional accuracy in all amblyopes is much poorer than normal. In anisometropic amblyopes, the loss in positional accuracy at high spatial frequencies can be explained by their deficits in contrast sensitivity, but for strabismic amblyopes, this loss is often much larger than that predicted by their contrast sensitivity loss. Thus, the deficits found in strabismic amblyopes must be explained in other terms.

Amblyopia is a complex syndrome whose symptoms have so far defied simple explanations (Hess, Field and Watt, 1990, Hess, 2002). The spatial deficits found in human amblyopia cannot be simply mimicked by such procedures as optical blur as evidenced by the perceptual distortions described earlier. Recent studies have reported than human amblyopes have veridical blur perception (Hess, Pointer, Simmers and Bex, 2003; Simmers, Bex and Hess, 2003), such that amblyopic patients perceive blurred stimuli as well as normal humans even though their visual acuity and contrast sensitivity are dramatically reduced. On the basis of psychophysical studies in humans and physiological studies on animals, two competing ideas have taken centre stage of late as explanations for the spatial deficits in human amblyopia (Hess, 1982, 1995; Kiorpes and McKee, 1999; Asper, Crewther and Crewther, 2000b). One view, for which psychophysical evidence has been marshaled from studies of human strabismic amblyopes, is that the visual deficits are best explained by uncalibrated neural disarray (Hess, Campbell and Greenhalgh, 1978; Hess et al., 1990; Hess and Field, 1994; Field and Hess, 1996; Demanins, Wang and Hess, 1999b; Hess, 2002). According to this theory, the lack of spatial accuracy is a direct consequence of a disrupted (jittered or scrambled) topological mapping somewhere within the amblyopic visual system. Since cells in the visual cortex of human amblyopes may not be organized in an orderly fashion, the visual system is unable to accurately represent the spatial distribution of light

on the retina so that objects appear distorted. The competing idea, for which the strongest evidence has come from electrophysiological studies on animals, is neural undersampling (Levi and Klein, 1985, 1986, 1990b, 1996; Levi et al., 1987; Levi, Klein and Wang, 1994a; Wang, Levi and Klein, 1998; Sharma, Levi and Coletta, 1999). According to this theory, the deficits in spatial localization are caused by cellular loss serving the amblyopic eye in the visual cortex (and other visual cortical areas) of human amblyopes. Too few cells in the visual cortex of human amblyopes are activated by the amblyopic eye to provide an accurate representation of all points in the visual field. This situation is one that can lead to the phenomenon of aliasing where the output is represented as an alias or distorted version of the true stimulus.

According to Hess and Field (1993), the neural undersampling theory predicts that positional errors should be associated with equivalent errors in perceived contrast. The essence of the argument is that, in a positional acuity detection task, errors for position and contrast would be associated because one cannot distinguish between an aligned low contrast stimulus and a misaligned, high contrast stimulus. In order to test this hypothesis, Hess and Field (1994) designed an experiment in which strabismic amblyopes had to judge both the state of alignment and the relative contrast of Gabor patches. In this experiment, measurements were made of both the accuracy with which a central element could be aligned with respect to two reference stimuli that were in vertical (physical) alignment, and at the same time, the increment contrast needed to discriminate a contrast difference between the central and the reference Gabor patches. When the deficits for position and contrast were plotted for both the amblyopic and the normal eye, the slope of the best fitting line was very shallow (0.1), indicating that the large spatial deficits found in strabismic amblyopia were not associated with comparable contrast discrimination deficits. These results were incompatible with the neural undersampling theory. By contrast, tests of the perception of physical distortion of stimuli of the amblyopic eye were comparable with the alternative view, that the spatial deficits found in human amblyopes were due to uncalibrated neural disarray in the visual cortex of these patients (Hess and Field, 1994). Later, similar results were found in another group of strabismic amblyopes (Demanins and Hess, 1996).

The aim of this study

The primary focus of the study was to compare the deficits in spatial localization of amblyopic cats with those observed in human anisometropic and strabismic amblyopes. A second focus was to provide data that could assist resolution of the debate between competing views of the nature of the underlying deficits in amblyopia (uncalibrated neural disarray and neural undersampling). This research project has for its eventual goal a replication of studies by Hess and colleagues (Hess and Holliday, 1992a, 1992b; Hess and Field, 1994, Demanins and Hess, 1996) using cats rather than humans as subjects in an attempt to better understand the neural mechanisms responsible for human amblyopia. The unique feature of animal studies is the potential to document both the behavioural and physiological deficits (Cleland, Crewther and Crewther, 1985). The spatial localization deficits were measured in kittens monocularly deprived for periods of time known to produce permanent and substantial loss of cells that can be excited by the deprived eye. For this study, a series of experiments was designed in order to compare the performance of human amblyopes and amblyopic cats on a spatial localization task. These included the behavioural assessment of visual acuity, and the performance on a spatial localization task using either Gaussian blobs or Gabor patches in which the influence of contrast, the spatial frequency of the stimuli, the orientation of the spatial frequency and the separation of the stimuli could be investigated.

Chapter 2. METHODS

Since all the experiments described in this thesis employed similar testing procedures and were conducted on the same pool of experimental animals, this chapter is dedicated to a description of the subjects and their early visual histories, the stimuli and the apparatus used to test the subjects.

Subjects

Various types of manipulations of the early visual input of kittens were chosen in order to mimic the presumed early visual input of human deprivation and strabismic amblyopes. The goal of these manipulations was to induce moderate to severe amblyopia by varying the duration and the starting time of particular deprivation periods so as to produce animal models of either strabismic and deprivation amblyopia of different severity. This was achieved by performing early monocular eyelid suture to produce a model of deprivation amblyopia, and to surgically induce a strabismus in order to produce a model of strabismic amblyopia.

The studies were conducted on a total of 10 domestic cats *(Felis catus)* that were born and raised in a closed laboratory colony located in the Studley Animal Care Facility of Dalhousie University. The animals were housed at times in three different animal rooms under an 11/13 hour light/dark cycle. The behavioural experiments and the surgeries performed on the animals were in accordance with standards and regulations established by the Canadian Council on Animal Care (CCAC), and conducted following protocols approved by the University Committee on Laboratory Animals (UCLA). Two cats served as control animals, a normal cat (N1) and a cat for which an attempt to induce a strabismus by tenotomy of the lateral rectus muscle of one eye failed (N2). The experimental animals were assigned to one of three groups according to the length or type of early deprivation. The first group of three animals was raised with extended periods (1-3 months) of monocular deprivation (LMD1, LMD2 and LMD3); a second group of three animals was raised with a short period (6 days) of monocular deprivation imposed at different ages (SMD1, SMD2 and SMD3); and finally, a group of two animals was raised with surgically induced strabismic esotropia (S1 and S2). The particular periods of monocular deprivation that were used were chosen because they were known to produce

moderate to severe behavioural and physiological deficits (Mitchell and Timney, 1984). The rearing condition for one animal (cat LMD2) was virtually identical to that of an animal in an earlier study (cat 60B, Mitchell et al., 1977) for which electrophysiological recordings were made for area 17 after behavioural measurement of the recovery of vision of the deprived eye. In this animal, only 14 of the 75 cells (19%) recorded were assigned to the three ocular dominance groups dominated by the deprived eye.

Surgical manipulations

For cats LMD2 and LMD3, the surgical eyelid closure was performed before natural eye opening (Warkentin and Smith, 1937; Blakemore and Cummings, 1975; Beaver, 1980) so that the eyelids were first parted by gently pulling them apart by hand before performing the surgery. With the exception of cat LMD1, the occluded (deprived) eye was always the left eye. Eyelid closure was performed under gaseous halothane anesthesia supplemented with an initial intra-muscular injection of xylazine hydrochloride (2mg/kg). The palpebral conjunctiva was dissected free from both the upper and the lower lid margins in order to expose approximately 3 mm of the underlying tissue. The palpebral conjunctiva was then sutured shut with 3-0 chromic gut. Scarring of the palpebral eyelid margins was gently and carefully performed with the use of a scalpel fitted with a number 11 blade, so as to create a small amount of bleeding to promote healing of the eyelids together. Following the application of a broad-spectrum ophthalmic antibiotic (Chloramphenicol 1%), the exposed tissue of the eyelids were opposed and sutured together with 5-0 silk. At the end of the surgery, the animals received an intra-muscular injection of Penicillin G (0.08 cc/kg) and were placed in a heated recovery box. When the animals began to stand up and walk, they were returned to their mother in the colony room. During the periods of monocular deprivation, the eyelids were checked on a daily basis for any pinhole openings. If an opening was detected, corrective surgery was performed by use of the same surgical protocol described above. Finally, upon termination of the period of monocular deprivation, the animals were once more brought into the surgery room and anesthetized as described above. The closed eyelids were then carefully parted and the palpebral conjunctiva cut open with small scissors. Following recovery from the surgical procedure, the animals were returned to the colony room where thereafter they received normal binocular visual input.

With this technique introduced by Murphy and Mitchell (1987), the scarred palpebral eyelid tissue near the margins and the sutured palpebral conjunctiva heal together to form two occlusion layers. This is a change from the original surgery pioneered by Wiesel and Hubel (1963a, 1963b) and used previously in this laboratory (Mitchell et al., 1977a; Giffin and Mitchell, 1978) that employed only a single occlusion layer following surgical excision of the eyelid margins. The main advantage of the new procedure is that the eyelid margins with their sebaceous glands are maintained which improves the ability of the animal to hold its eye open after termination of the period of deprivation.

The technique employed to produce a strabismus was modeled closely on that performed by Mitchell et al. (1984c), which produced a stable deviation. As with the majority of the monocularly deprived animals, the strabismus surgery was performed on the left eye of both animals, using the same anesthetic protocol as the one used for the eyelid closures. The first step, after inducing anesthesia, was to remove the nictitating membrane of the left eye. A small hole was then made near the conjunctiva close to the insertion of the lateral rectus muscle of the left eye and enlarged by blunt dissection to allow the passage of a muscle hook. With the muscle held by the hook, a piece of muscle was removed and sectioned close to the globe of the eye. A maximum of five passages was made with the muscle hook in order to locate and sever any residual muscle fibers. At the end of the surgery, a broad-spectrum ophthalmic antibiotic (Chloramphenicol 1%) was placed on the eye and the animals received an intra-muscular injection of Penicillin G (0.08 cc/kg). After recovering in the heated recovery box, the kittens were returned to their mothers in the colony room. The esotropia produced was immediately noticeable and remained throughout all the behavioural testing.

Apparatus

The measurements employed two versions of a jumping stand that differed only in the manner of display of the visual stimuli. The original version of the jumping stand, for which the stimuli were prepared photographically, was used for the behavioural assessment of visual acuity. This version of the jumping stand required the animals to jump onto one of the stimuli for a food reward. For the measurement of alignment

accuracy, the stimuli were displayed on a computer monitor and required the animals to jump onto a glass plate placed above the face of the monitor.

The original jumping stand

Inspired by the jumping stand used by Lashley (1930) to study pattern vision in rats, the visual acuity of the animals was tested using a jumping stand originally described by Mitchell, Giffin, Wilkinson, Anderson and Smith (1976) and Mitchell et al. (1977b). The jumping stand (Figure 1) consisted of two main units, a jumping platform (A) and a visual stimulus box (B). The jumping platform was made from a rectangular piece of plywood measuring 19 cm wide x 1 cm thick x 44 cm long, onto which a trapezoidal-shaped starting box (C) was screwed with removable bolts. The dimensions of the starting boxes were sufficiently small so as to prevent the animals from turning easily inside the box. As the animals aged, a larger starting box was used. The openings of the two starting boxes used in this experiment measured 13 cm x 20 cm and 15 cm x 22 cm. The height of the jumping platform could be continuously adjusted using two yoked mechanical jacks (D) to a maximum of 72 cm above the visual stimulus box. These jacks were screwed to a wooden base (E) measuring 68 cm x 41 cm x 42 cm. The second unit of the jumping stand, the visual stimulus box, had a base measuring 68 cm x 42 cm x 41 cm. The top of the base was divided in half by a wedged shaped divider (3 cm high) and consisted of two locked trapdoors (F) measuring 30 cm x 35 cm, upon which the visual stimuli were placed. A 42 cm high wall (G) surrounded three sides of the visual stimuli box in order to prevent the animals from escaping.

The computerized version of the jumping stand

The apparatus used for all the other experiments described in this thesis was a computerized version of the original jumping stand (Figures 2A and B), that also consisted of two main units: a jumping platform (A) and a visual stimulus box (B). The jumping platform was made from a piece of plywood measuring 20 cm x 2 cm x 44 cm. Screwed to the plywood piece, there was a rectangular-shaped starting box (C) having dimensions of 18 cm x 22 cm x 40 cm. The opening of the starting box measured 15 cm x 20 cm. The starting box was fixed to two yoked laboratory jacks fastened to two base units made from plywood measuring 50 cm x 50 cm x 50 cm (D). Finally, the height of the jumping platform was adjusted by the use of two yoked mechanical jacks (E). The

second unit of the jumping stand, the visual stimulus box, had a base (F) measuring 70 cm x 74 cm x 50 cm. The visual stimuli were displayed on a computer monitor (G) that faced upward toward the starting box. The top of the visual stimulus box had an opening (H), measuring 32 cm x 25 cm that permitted the animals to see the visual stimuli presented on the monitor located 5 cm under a glass window onto which the animals jumped. Also, the top of the visual stimulus box was divided in half by a 3 cm high wedged shaped divider (I) in order to separate the left side of presentation from the right side of presentation of the computer monitor. A 77 cm high wall (J) surrounded the visual stimulus box in order to prevent the animals from escaping. The visual stimuli for most of the experiments were presented on a display monitor (13" NEC multisync color monitor model JC-1401P3A) controlled by a PC computer (the "old" version of the computerized jumping stand), while in the latest set-up, the stimuli were presented on a display monitor (17" Mitsubishi Diamond Scan 90e monitor) controlled by an Apple iMac computer. For experiments 2, 3A, 3B, 4A1, 4A2 and 4B, the "old" version of the computerized jumping stand was used, while the newest version of the jumping stand was used for Experiments 4C1, 4C2 and for cat LMD3 of Experiment 4B.

Behavioural testing procedure

Behavioural assessment of visual acuity

Stimuli

Pairs of square-wave gratings were used that were either prepared photographically or else were printed with a high quality ink jet printer. These gratings were surrounded on all sides by a 4 cm wide black border and had an overall dimension of 26 cm x 27 cm. The gratings had a Michelson contrast of 100% and a mean luminance of 55 cd/m^2. A total of 45 pairs of gratings, ranging from 32 mm to 1.058 mm were used. The gratings were approximately equated on a logarithmic scale, being separated by 1/6 of an octave for gratings having periods of 10 - 32 mm, 1/10 of an octave for gratings with periods between 3 - 10 mm, and 1/12 of an octave for gratings having periods below 3 mm. The stimuli were presented on the original jumping stand.

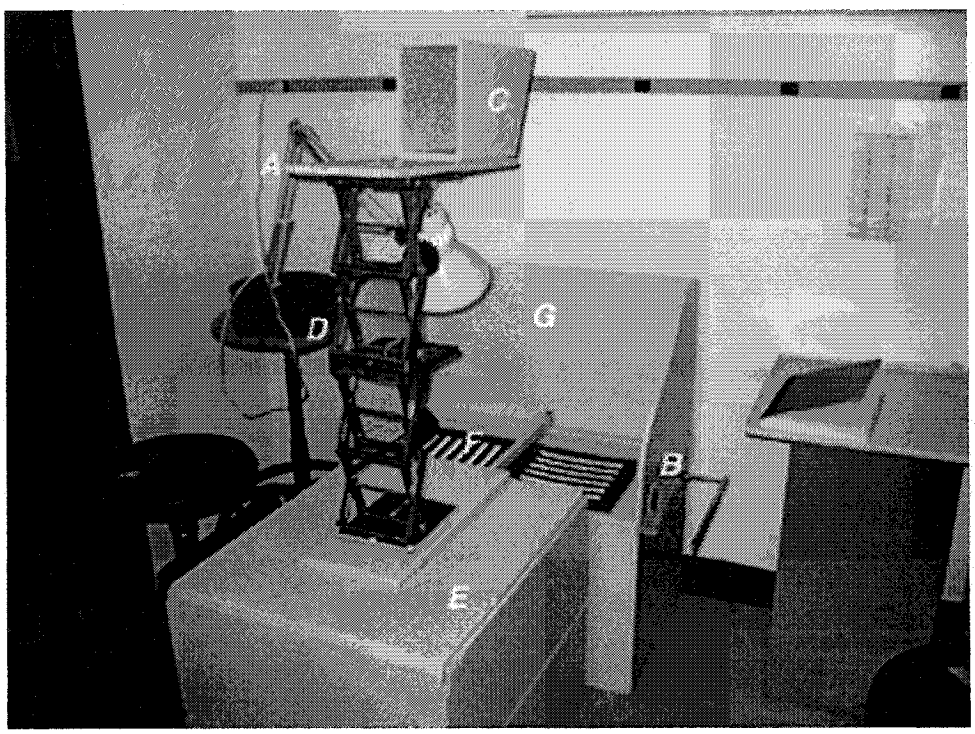
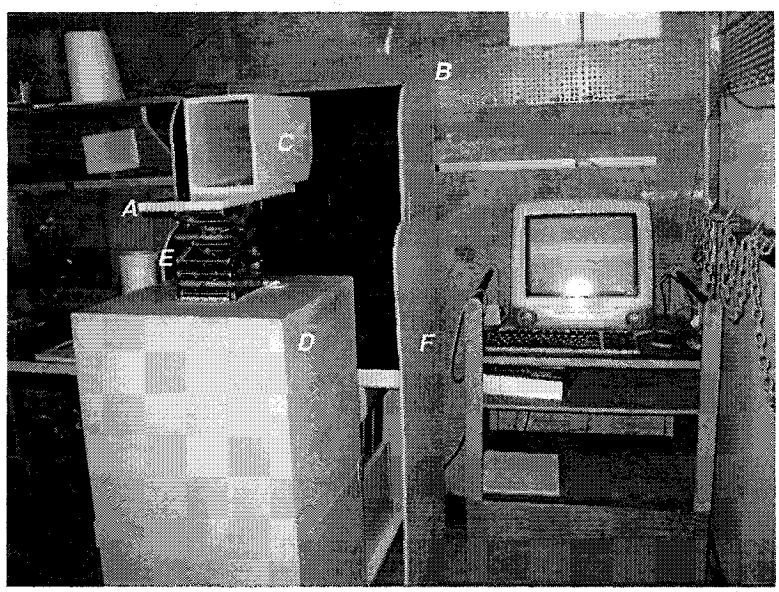


Figure 1. Photograph of the original jumping stand. See text for a complete description of the apparatus.

A



B

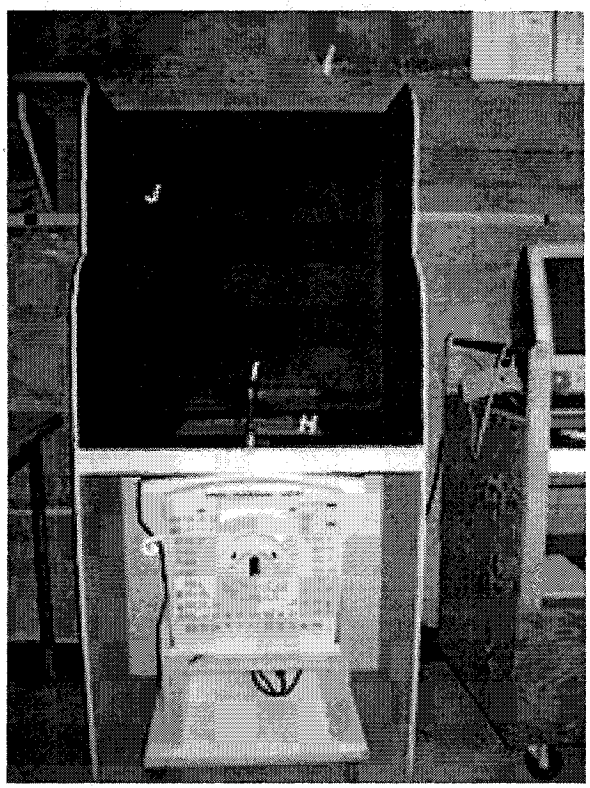


Figure 2. Two photographs (A and B) of the computerized version of the jumping stand taken from different viewpoints. See text for a complete description of the apparatus.

Procedure

Since the early description of Mitchell et al. (1976) and Mitchell et al. (1977b), the technique has been greatly refined in order to improve the level of performance of the animals. Notable improvements were the use of gratings equated on a logarithmic scale and the use of a discrimination task as opposed to a detection task.

The method of descending limits (Treutwein, 1995) and a two-alternative forced choice experimental protocol were used. The technique exploits the natural tendency of young kittens to jump and play. Most of the kittens were first introduced to the jumping stand when they were 4 weeks old. The goal of the training phase was to teach the kittens to enter and quickly leave the starting box on their own. For this purpose, the jumping platform was set at its lowest position, about 5 cm (stepping height) above the visual stimulus box so that the kittens could step onto the visual stimuli. The initial part of the training phase was for the kittens to discriminate between an opened trapdoor and the vertical square-wave grating with the largest period (32 mm) placed upon the closed trapdoor. At this initial stage, the kittens were coaxed by gentle pushes toward the vertical square-wave grating in order to facilitate the learning of the visual discrimination. A correct response was rewarded with petting and with a small portion of pureed chicken liver mixed with cat food presented on a wooden stir-stick. Once the kitten had made the correct response, the rewarded stimulus was switched from side to side until the kittens made ten consecutive correct responses. During this training phase, the kittens were prevented from making an incorrect choice toward the opened trapdoor.

The second part of the training phase required the kittens to discriminate between a closed trapdoor (a uniform gray stimulus) and the same vertical square-wave grating used in the initial training phase placed on the other closed trapdoor. Once more, the correct response was the vertical square-wave grating and this stimulus was moved from one side to the other in a random order. During the second training phase, the kittens were no longer prevented from making an error and the jumping platform was gradually raised so that the animals now had to jump rather than step onto the stimulus. When an incorrect jump was made, the kittens were denied the food reward and had to immediately repeat the trial until a correct response was made. The kittens were required to make ten consecutive correct jumps before passing to the third and final training phase.

This final training phase consisted of a discrimination between a vertical square-wave grating and a horizontal square-wave grating of the same period. The vertical square-wave grating was always the rewarded stimulus, and the kittens were required to make 20 consecutive correct jumps, or at least 36 out of 40 trials. Once more, the side of presentation of the rewarded stimulus was randomly assigned.

Following the successful completion of the final training phase, formal testing of visual acuity was initiated. The kittens were required to discriminate between a vertical square-wave grating (rewarded stimulus) and an identical square-wave grating presented horizontally (punished stimulus). The lateral position of the two square-wave gratings was interchanged from one trial to the next in a pseudo-random order (RRLRLLRLRR) that was modeled on the series introduced by Gellermann (1933). No more than two consecutive trials were presented with the stimuli in the same position. This procedure was used in order to prevent the kittens from learning the presentation order of the gratings, and also to prevent the occurrence of preferences for one side. This pseudo-random presentation of gratings has been used widely in the past and has also been used successfully for study of the visual acuity of visually deprived rats (Prusky, West and Douglas, 2000) and mice (Prusky and Douglas, 2003). The conduct of a daily session can be briefly summarized as follows. Each daily testing session consisted of many blocks of trials with gratings of progressively higher spatial frequencies that were incremented in small steps between blocks until a spatial frequency was reached at which point the animal could no longer maintain criterion performance. The criterion performance was defined as at least 7 correct jumps in a maximum of 10 trials on the same grating or 5 consecutive correct jumps. Visual acuity thresholds were defined as the highest spatial frequency for which criterion performance could be maintained. This brief summary of the procedure is expanded below.

Even with a well-trained kitten, a session began with gratings of low spatial frequencies, using spatial frequencies at least two octaves above their estimated threshold. Usually, the kittens only received one trial at each of the low spatial frequencies unless an error was made. In this case, the kittens were required to make five consecutive correct jumps or at least 7 correct jumps out of a maximum of 10 trials. When performance was errorless, the spatial frequency was increased by one step after

every trial, but within approximately an octave of the estimated threshold, the minimum number of trials was increased to 3. The minimum number of trials was yet again increased to 5 for the last 5 spatial frequencies closest to the estimated threshold. As illustrated in a representative testing session (Figure 3), a kitten typically progresses without difficulty until it reaches a spatial frequency where its performance falls dramatically below the success criterion. At this point, the testing session was terminated. Typically, kittens made very few incorrect jumps. Because of the small steps in spatial frequency between blocks of trials, the thresholds could be estimated very sharply as the performance dropped from flawless, or nearly so, to chance over a small fraction of an octave. On rare occasions where the kittens demonstrated poor motivation for the task, the procedure was repeated again starting at a spatial frequency an octave lower than the one failed. The inability of the kittens to discriminate between the two gratings at threshold was clearly noticeable because there was a dramatic change in the animal's behaviour. The kittens cried, became very agitated, repeatedly inspected both of the stimuli, tried to turn inside the starting box, and their performance dropped to chance. All these behavioural responses were clear indications that the kittens found the discrimination very difficult.

Finally, longitudinal daily measurements were made of both monocular (deprived or deviated eyes) and binocular (normal eye, non-deprived or non-deviated eyes) visual acuity. As the kittens grew, the height of the jumping stand was increased (up to a maximum of 72 cm high) according to the development of their visuo-motor coordination. For the testing sessions of the deprived eye or the deviated eye, a black opaque contact lens with a base curve matched to the average curvature of the cat's cornea (Freeman, 1980), was placed on the non-deprived eye or the non-deviated eye of the kittens. In order to prevent any irritation or discomfort to the animal's eye (Dzioba, Murphy, Horne and Mitchell, 1986) a few drops of an ophthalmic anesthetic (0.5% Proparacaine hydrochloride) was placed in the eyes before insertion of the contact lens. As a rule, the kittens were tested either binocularly or monocularly within the same testing session. Occasionally, testing of both acuities were conducted in the same session in which case the binocular tests were made first. The testing session for a trained kitten lasted approximately 45 minutes to an hour for each eye tested.

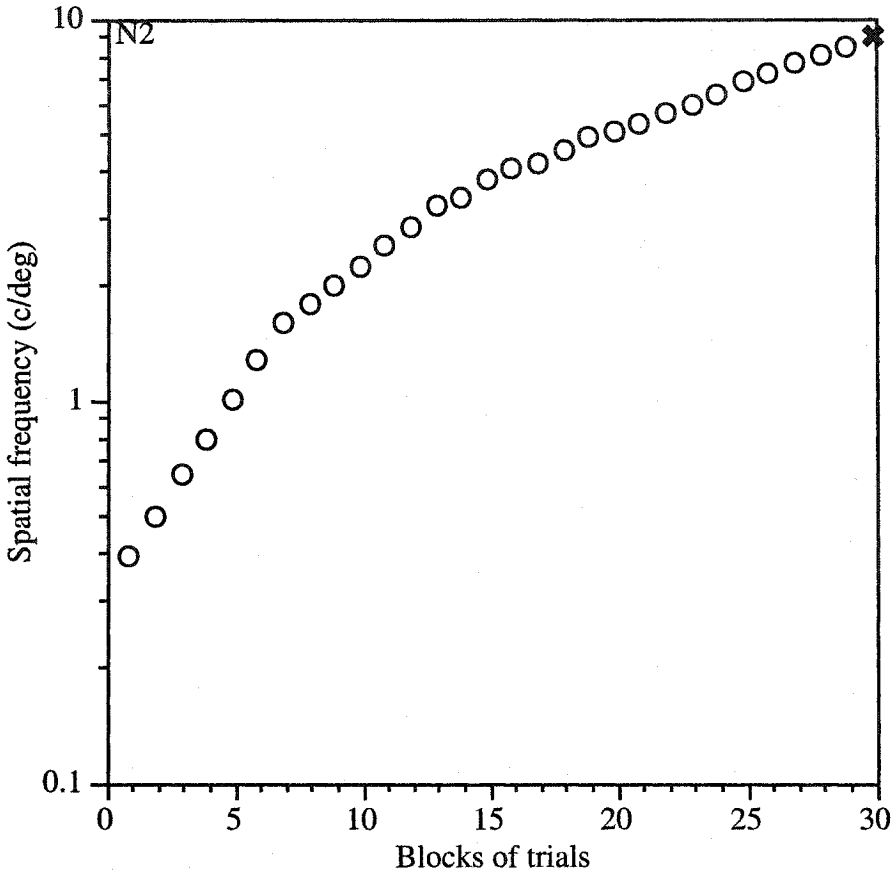


Figure 3. Representative testing session of cat N2 for the assessment of grating acuity. The open circles indicate that the animal achieved criterion levels of performance with gratings of a particular spatial frequency, while the black X indicates the spatial frequency where the animal failed. Normal visual acuity is 8.39 c/deg.

Alignment accuracy task

Stimuli

The stimuli used in this experiment were Gaussian blobs (i.e. having a luminance profile described by a Gaussian function) and were presented on the display monitor of the computerized version of the jumping stand. The description of the stimuli for this experiment and the rational for using this type of stimulus are described in greater detail in Chapter 3.

Procedure

The experimental procedure for this task was highly similar to the behavioural assessment of visual acuity described above. Testing on the alignment accuracy task began after the end of the behavioural assessment of visual acuity when the cats were 4-5 months old. The method of descending limits and a two-alternative forced choice task were employed in which the cats were required to jump toward a set of misaligned Gaussian blobs as opposed to an adjacent set of Gaussian blobs that were in physical alignment in the vertical plane. The correct (rewarded) response was to jump toward the set of misaligned Gaussian blobs and the cats were rewarded with petting and food. If a cat made an incorrect response, it received no reward and the trial was repeated. The lateral position of the two sets of stimuli was interchanged from one trial to the next in a pseudo-random order (RRLRLLRLRR). No more than two consecutive trials were presented on the same side of presentation. Daily measurements of binocular and/or monocular alignment accuracy tests were conducted until the performance of the cats reached threshold. In this experiment, threshold was defined as the smallest offset for which criterion performance could be maintained. Testing of the different sizes of the Gaussian blobs was random, but all the thresholds for the same blob size were gathered on a minimum of 3 testing days and up to 10 testing days.

Each daily testing session consisted of many blocks of trials with sets of Gaussian blobs of progressively smaller offsets. Below 20 mm, the offsets of the misaligned Gaussian blobs were diminished in regular steps, either by changing the size of the offsets in mm (or in pixels) and/or changing the height of the jumping platform. Between 20 mm and 10 mm, the offsets were diminished in steps of 2 mm, while between 10 mm and 5 mm, they were diminished in steps of 1 mm. For offsets between 5 mm and 2 mm,

the offsets were diminished by changing the size of the offsets by one pixel (0.25 mm). Finally, below 2 mm, the offsets of the Gaussian blobs were diminished by changing either the size of the offset in pixels, and/or changing the height of the jumping platform to produce steps equalized on a logarithmic scale (10 steps to an octave). The steps between adjacent offsets were as small as those of spatial frequency for the measurements of grating acuity. Where the vision was very poor with the deprived or the deviated eye, the offsets for these eyes were reduced in 1 mm steps beginning at 60 mm. The cats were tested with increasingly small offsets until they were unable to maintain criterion performance. At this point, the testing session was terminated. The criterion performance was defined as at least 7 correct jumps in a maximum of 10 trials with the same offset or 5 consecutive correct jumps.

A typical testing session began with an offset several octaves above threshold. Usually, the cats only received one trial in the upper third of the testing session unless an error was made. In this case, a corrective procedure was initiated and the cats were required to reach the criterion performance before being tested with a smaller offset. Within an octave of threshold, the minimum number of trials was increased to 3, and was once more increased to 5 trials for the last 5 offsets closest to the estimated threshold. On rare occasions when the cats demonstrated poor motivation, the procedure was repeated starting with an offset an octave lower than the one previously failed. In some cases, tests of alignment accuracy of both eyes were conducted on the same day in two separate testing sessions. The non-deprived or the non-deviated eye was tested in the first testing session, and then, after a rest period, the deprived or the deviated eye was tested in the second session. This latter testing session was performed monocularly with an opaque contact lens applied onto the non-deprived or non-deviated eye of the animals. But in most cases, the eyes were tested on different days. Each testing session lasted approximately 45 minutes to an hour for each eye.

Statistical analysis

Since the repeated thresholds obtained in all the tasks on each eye of each animal were essentially identical (i.e. no variability) formal statistical analysis was not necessary. Each animal represented a single case study and the non-deprived (or non-deviated) eye served as the control for the deprived or deviated eye.

Chapter 3. THE EXPERIMENTS

Experiment 1. Assessment of grating visual acuity

The goal of these measurements was to document the effects of various regimens of monocular deprivation and strabismus on grating acuity. For the monocularly deprived kittens, a second goal was to document the speed and extent of the recovery of grating acuity in the deprived eye. These measurements provided some interesting comparative data to previous behavioural assessment of visual acuity conducted in this laboratory that used different experimental protocols. In addition, these measurements provided an opportunity to train the animals on the jumping stand for the main experiments of this study at the optimum time, i.e. while the animals were young.

The subjects of this experiment were the 10 cats described in the previous chapter. In this section, the emphasis of the analysis will be on the visual deficits of the deprived eye or the deviated eye of the experimental animals. The rearing history of the experimental animals and a summary of the final visual acuities obtained with these animals can be found in Table 1.

Since the main focus of this experiment was to measure longitudinally the change in the vision of the deprived eye of the monocularly deprived kittens, testing of the non-deprived eye of these experimental animals was not conducted as frequently as was the tests of the vision of their deprived eye. For comparative purposes, a value of 8.39 cycles/degree (c/deg) that was achieved by normal animals and by the non-deprived or non-deviated eye of the experimental animals in this laboratory that were tested the longest and most frequently was used as the standard visual acuity against which the acuity of the non-deprived eye or the non-deviated eye of the experimental animals was compared. This value (8.39 c/deg) is referred to as the standard value that represents the average acuity of the visual acuity of the non-deprived/deviated eyes of the experimental animals at the age at which the measures of acuity described below were made.

Animal	Type of surgery	From (days of age)	To (days of age)	Grating acuity (c/deg)	Deficits in octaves
LMD1	MD	38	68	5.87	0.52
LMD2	MD	11	60	5.03	0.74
LMD3	MD	11	82	4.15	1.02
SMD1	MD	35	41	5.24	0.68
SMD2	MD	56	62	5.24	0.68
SMD3	MD	90	96	7.53	0.16
S1	esotropia	17	-	4.83	0.80
S2	esotropia	29	-	3.18	1.40

Table 1. Rearing history and final grating acuity of the deprived (or deviated) eye of the experimental animals. The deficit in acuity of these eyes has also been expressed in octaves with respect to normal value (8.39 cycles/degree).

Results

Initial behavioural observations of monocularly deprived kittens

Prior to the termination of the period of monocular deprivation, the kittens appeared normal in all respects and demonstrated normal visually guided behaviours identical to those found in normal kittens. For example, with the one open eye, the kittens played with each other, avoided objects located in the colony rooms, and appeared to have no difficulties whatsoever jumping onto cardboard boxes or various platforms located in the colony rooms or hit a small bouncing ball with their paws. Moreover, when the experimenter walked into the colony room, the kittens came toward him purring and willing to be picked up.

In dramatic contrast to the behaviour mediated by the non-deprived eye, following termination of the various periods of monocular deprivation, the kittens exhibited profound behavioural deficits when forced to use their deprived eye. As originally noted by Wiesel and Hubel (1963b), when forced to use their deprived eye, the kittens either froze or moved very slowly and gently bumped into walls and cardboard boxes in their path. They rarely jumped onto the top of familiar cardboard boxes or platforms. The kittens were at first unable to catch a bouncing ball and instead pounced toward the location where they heard the sound of the ball as it bounced and then moved slowly in order to search for where the ball had gone.

In addition to these anecdotal observations, the visual abilities of the kittens were assessed using a number of formal simple behavioural tests of visuomotor behaviours similar to those described by Hein and Held (1967) and Blakemore and van Sluyters (1974). The tests were conducted on the deprived eye of the monocularly deprived animals with an opaque hard contact lens placed in their non-deprived eye. The tests administered were visual following, visual startle and triggered visual placing. The visual following test assessed the ability of an animal to follow with its head and eyes an object such as the hand or a finger of the experimenter that was moved back and forth in front of the animal. The visual startle response is the reflex withdrawal of the head and eye blink in response to the sudden approach of an object. For the test of this response, the hand or finger of the experimenter was used as the "threatening" object. Finally, the triggered visual placing test examined the ability of the animals to extend their forelimbs to reach a

surface toward which the animal was lowered. For this test, the kittens were lowered toward the top of a counter. Initially, all the kittens failed all these visuomotor tests but as they recovered vision in their deprived eye (see below), all the tested behaviours returned. These behaviours began to emerge in crude form at about the time or shortly after the kittens passed the formal test for the presence of form vision on the jumping stand (see below). Eventually, on casual inspections, the kittens appeared to establish normal visually guided behaviours when using their deprived eye.

Formal tests of the kittens' visual abilities with their deprived eye were conducted on the jumping stand on a daily basis or nearly so. When first tested after termination of the period of monocular deprivation, the kittens appeared blind as described above. The formal definition of blindness on the jumping stand followed that described in early publications from this laboratory and are described more completely in Mitchell (1989). Briefly, blindness of the deprived eye was defined as the inability of an animal to discriminate the vertical square-wave grating from an opened adjacent trapdoor without searching for it with its paws or nose. When placed on the jumping stand, most of the monocularly deprived kittens became very agitated and would not voluntarily leave the starting box, even though this box was set at its lowest position (merely centimeters above the visual stimulus box). The kittens were gently pushed toward the visual stimulus, but they appeared unable to locate the vertical square-wave grating by use of visual clues alone. Sometimes, the kittens were unable to locate the closed trapdoor and in their attempts slipped and fell into the opened trapdoor. On those rare occasions, the kittens were immediately picked up and comforted before they were required to perform another trial. These unfortunate events seldom occurred and the kittens quickly learned to reach with one of their paws for the safe side of the visual stimulus box which they appeared to locate solely by use of tactile cues. After a few trials, the kittens would reach for the wooden divider and try to touch it with its paws. With one paw on the divider, it then actively pursued its search by exploring both sides of the visual stimulus box with each paw in turn until it eventually found the closed side on which the vertical square-wave grating was placed. After a successful trial, the vertical square-wave grating was moved to the other side of the visual stimulus box according to a quasi-random schedule. Over time, the kittens were able to find the vertical square-wave grating and step onto it

progressively faster so that it became unclear whether the kitten was relying exclusively upon tactile cues. To test for the possible ability to use visual information after ten consecutive correct trials of this sort, the jumping platform was gradually raised in order that the kittens had to jump rather than to walk toward the vertical square-wave grating. At this point, the kittens could not use tactile cues so that their judgments were based on visual cues alone. After ten consecutives correct jumps toward the closed trapdoor the animal was defined as having first recovered vision. This level of vision was referred to as the ability to locate the closed trapdoor (or avoid the open trapdoor) and probably represented at a minimum, the ability to make luminance discriminations.

Because of the rapid improvement of vision that typically followed, it was not possible to ascertain when the animal could first pass a formal test of luminance discrimination. However, it is likely that the ability to avoid an opened trapdoor could be performed by luminance cues alone without the animal having recovered any pattern vision. Once the kittens had passed this discrimination, formal tests for pattern vision were commenced with the trapdoor closed to enable tests of the ability to discriminate between adjacent horizontal and vertical square-wave gratings on the trapdoors. After ten consecutive correct responses to the vertical square-wave grating, the kittens were defined as having recovered pattern vision at which point formal tests of visual acuity were commenced.

Long-term monocularly deprived animals (LMD1, LMD2 and LMD3)

As mentioned above, the deprived eye of the monocularly deprived animals appeared blind in all aspects following the opening of this eye. The length of this period of blindness and the subsequent recovery of pattern vision of the deprived eye was further investigated on the jumping stand. These results are presented in Figure 4 and the final visual acuity values in Table 1. Following termination of the period of monocular deprivation, cat LMD1 was blind for 12 days. The next day, this animal was immediately able to discriminate a vertical square-wave grating from a horizontal square-wave grating and hence had recovered pattern vision. At the end of that day, the visual acuity of its deprived eye had reached 0.29 c/deg. Two weeks later, the visual acuity of its deprived eye had more than doubled to 0.51 c/deg. During the next two months of testing, the visual acuity improved to reach a stable level of 5.87 c/deg 74 days after signs of vision

first emerged. Cat LMD1 was tested for a further 11 days, but the visual acuity of its deprived eye did not improve during this time period, after which formal tests were concluded. In terms of the visual deficit, the visual acuity of its deprived eye represented a visual deficit of 0.52 octaves with respect to standard values.

Cat LMD2, which was monocularly deprived for twice as long as cat LMD1, was also blind for nearly double the time (23 days). Like cat LMD1, this animal passed the formal test of pattern vision the following day. At the end of that day, the visual acuity of its deprived eye reached 0.31 c/deg, after which it improved to reach a stable value of 5.03 c/deg 36 days after signs of vision first emerged. Testing was continued for 20 more days without any further improvement of visual acuity in its deprived eye, after which formal tests were concluded. The visual acuity of its deprived eye represented a visual deficit of 0.74 octaves with respect to standard values. Even though the recovery of vision of the deprived eye of cat LMD2 was somewhat quicker than for cat LMD1, its final visual acuity value was lower.

Unlike the two other long-term monocularly deprived animals, the recovery of vision of the deprived eye of cat LMD3 was not as smooth. Unlike the gradual improvement in visual acuity seen with the other cats, the improvement in visual acuity of the deprived eye of cat LMD3 increased in steps, followed by periods of stability, until it improved once more. Consistent with the fact that this animal received the longest period of monocular deprivation, the deprived eye was blind for 26 days but was still able to pass the formal test of pattern vision the following day. At the end of that day, the visual acuity of its deprived eye reached 0.19 c/deg. Over the next 67 days of testing, the visual acuity of its deprived eye subsequently improved in a step-like fashion before it reached a final stable value of 4.15 c/deg, which represented a deficit of 1.02 octaves with respect to standard values. Testing was continued for 5 consecutive days, but the visual acuity of its deprived eye did not improve during this time period, after which formal tests were concluded.

It can be concluded from these results that with increased length of monocular deprivation, the visual acuity deficits were greater and it took longer for vision to reach stable values.

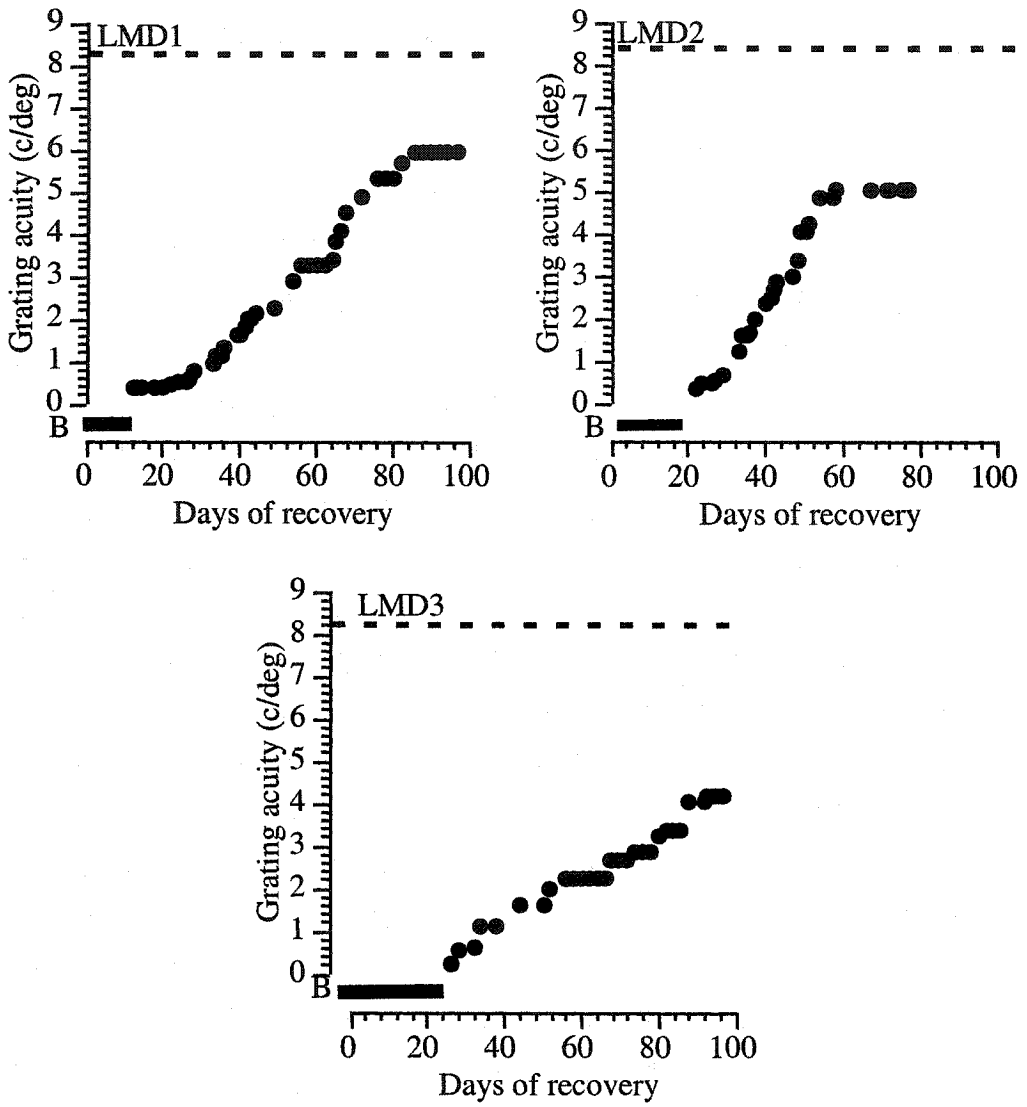


Figure 4. Recovery of the grating acuity (c/deg) of the deprived eye of the long-term monocularly deprived animals (LMD1, LMD2 and LMD3). The letter "B" and the black bar at the bottom of the graph indicate the duration of the period of blindness, while the dashed bar indicates normal visual acuity (8.39 c/deg).

Short-term monocularly deprived animals (SMD1, SMD2 and SMD3)

Short-term eye-lid closure also had detrimental effects on the visual abilities of the kittens, but these effects were considerably smaller than those found in long-term monocularly deprived animals. Following termination of the period of monocular deprivation, these kittens were also blind, but this period of blindness was substantially shorter than that found with the long-term monocularly deprived animals. The period of blindness of the short-term monocularly deprived animals lasted hours and not days. Moreover, the recovery of vision through the deprived eye of the short-term monocularly deprived animals (Figure 5) could be rapid. Table 1 also displays the final visual acuity recovered by the deprived eye of these experimental animals.

Cat SMD1 was blind for only a period of two hours after its deprived eye was opened. Five hours later, its deprived eye had already regained some pattern vision and had attained a visual acuity of 0.60 c/deg. From that point in time, the visual acuity of its deprived eye gradually increased over a period of 43 days, to just under 5 c/deg. For the next six weeks, this animal was tested only intermittently, but during this time, the visual acuity of its deprived eye increased to 5.24 c/deg. No further improvement occurred in the next month at which time testing was ended. The visual acuity of its deprived eye represented a visual deficit of 0.68 octaves with respect to standard values.

Even though cat SMD2 was monocularly deprived about 1 month later than cat SMD1, the initial recovery of vision of its deprived eye was similar. Cat SMD2 was also blind for a 2-hour period after the opening of its deprived eye, but regained pattern vision (0.71 c/deg) 3.5 hours after surgery. The visual acuity of its deprived eye gradually improved and reached the same stable value of 5.24 c/deg as cat SMD1 but after only 25 days of testing. Testing after 25 days (not shown) revealed no further change in grating acuity. As with cat SMD1, the final acuity of the deprived eye represented a visual deficit of 0.68 octaves with respect to standard values.

The recovery of grating acuity of the deprived eye of cat SMD3 was the fastest and most complete of all the monocularly deprived animals. Only 3 hours after the opening of its deprived eye, cat SMD3 was able to pass the formal test of pattern vision. At the end of the day (9 hours after surgery), the visual acuity of its deprived eye reached 1.0 c/deg. Afterwards, the visual acuity of its deprived eye improved rapidly and reached

a stable visual acuity of 7.53 c/deg after only 8 days of testing. In terms of the visual deficit, the visual acuity of its deprived eye represented a visual deficit of only 0.16 octaves with respect to standard values.

Closer analysis of the data revealed that there did not seem to be any simple relationship between the time of appearance of pattern vision and the age at which monocular deprivation was imposed. On the other hand, the final acuity recovered by the deprived eyes did show a general tendency to improve with delay in the onset of the period of deprivation. The one notable exception to this trend was the lack of any difference between the acuities achieved by cats SMD1 and SMD2. The results from this group of animals could have been affected by two facts. First, cat SMD1 gradually developed an esotropia several weeks after termination of the period of monocular deprivation. The esotropia was substantial and remains to this day some six years later. The esotropia that developed in cat SMD1 was similar in magnitude to that imposed surgically on cat S1, a point made evident by the photograph of Figure 6, in which the eye alignments of cats S1 and SMD1, as well as a normal cat are compared. Second, cat SMD3 was placed in a darkroom from birth for a one month period prior to the period of monocular deprivation. Both of these variables could have had an effect of the performance of these cats. One point that can be stated with certainty is that the recovery of vision for the short-term monocularly deprived animals was much faster than that found with the long-term monocularly deprived animals. Also, as stated above, there was a tendency for the deleterious effects on the visual acuity of the deprived eye to decline as deprivation was delayed to progressively later ages.

Strabismic animals (S1 and S2)

For both of the strabismic animals, tests of the visual acuity of the non-deviated eye preceded testing of the visual acuity of the deviated eye. The visual acuity of the deviated eye of cat S1 attained a value of 4.83 c/deg, while the deviated eye of cat S2 reached a value of only 3.18 c/deg. In terms of visual deficits, the difference in visual acuity between the non-deviated eye and the deviated eye of cat S1 was 0.80 octaves, while that of cat S2 was substantially larger, namely 1.40 octaves.

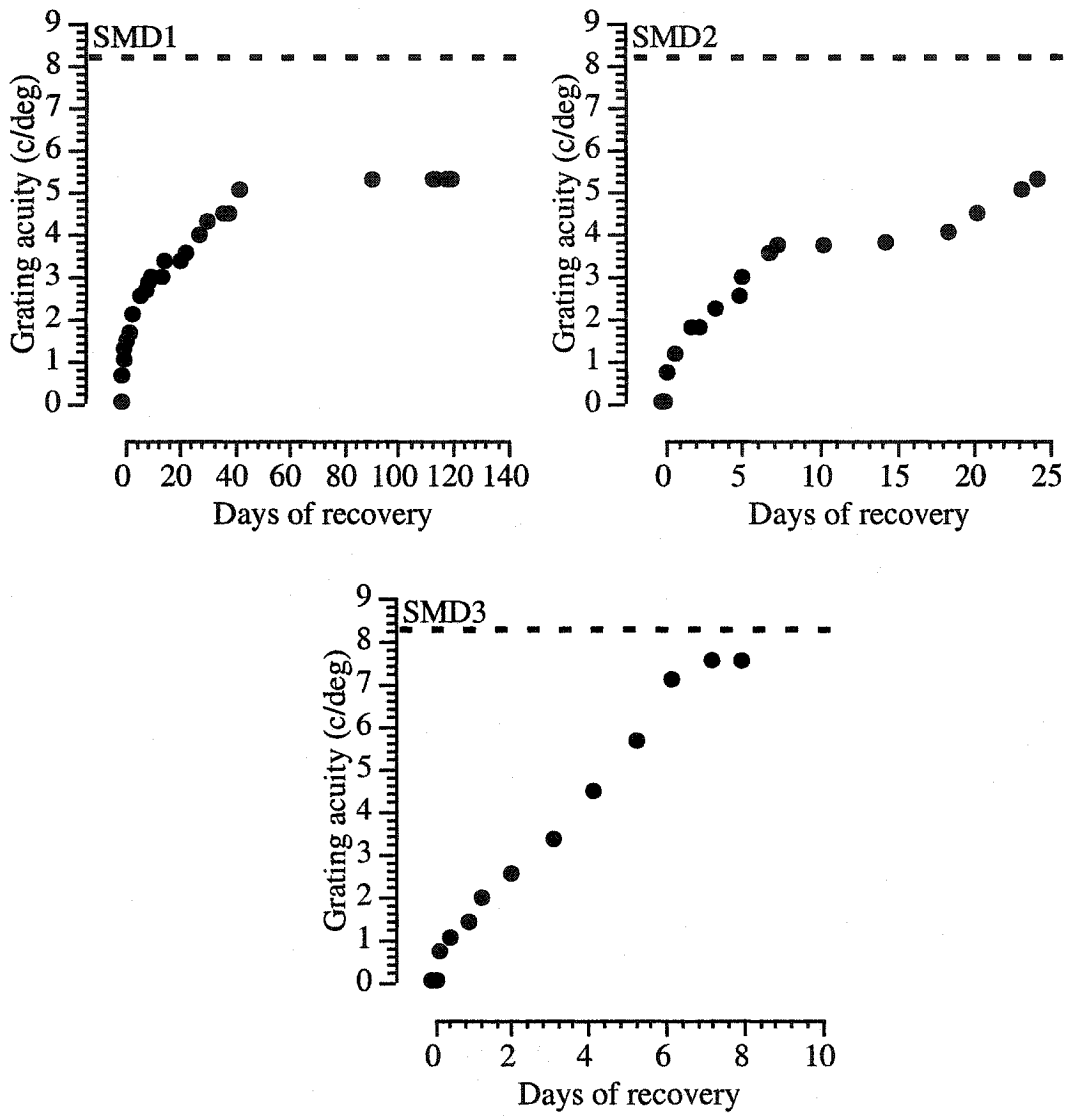


Figure 5. Recovery of the grating acuity (c/deg) of the deprived eye of the short-term monocularly deprived animals (SMD1, SMD2 and SMD3). The dashed line indicates normal grating acuity (8.39 c/deg).

Normal SMD1 S1

Figure 6. A photograph of the naturally occurring strabismus of cat SMD1 (middle) and of the esotropia induced surgically on cat S1 (right) to illustrate the esotropia that developed in the former after a 6 day period of monocular deprivation imposed at 5 weeks of age. A photograph of a normal cat (left) is shown for comparison. Note that in the normal cat, the pupillary axes appear divergent with respect to the optic axes as indicated by the two corneal reflexes from a distant light source. In contrast, the pupillary axes of both cats SMD1 and S1 are convergent in relation to their position in a normal cat to the extent that they coincide with the optic axes.

Discussion

A number of conclusions can be drawn from the results from the monocularly deprived animals. These conclusions mainly apply to the two long-term monocularly deprived animals that were visually deprived from birth (cats LMD2 and LMD3). First, the speed of the recovery of vision of the deprived eye declined with the length of monocular deprivation. Animals monocularly deprived for longer periods were blind for more extended periods of time. Second, the duration of the blindness period was also affected by the length of the monocular deprivation period. Animals deprived at a later age recovered the first signs of vision considerably earlier than animals deprived at younger ages. Third, as the length of the monocular deprivation period increased, so did the visual deficits of the deprived eye with respect to that of the non-deprived eye. Fourth, the age of onset of a short period of monocular deprivation also affected the final visual acuity of the deprived eye. Deprivation imposed at five weeks of age affected more negatively the visual acuity of the deprived eye than the same period of deprivation imposed at three months of age, when it had little effect on the final visual acuity of the deprived eye. Fifth, most of long-term monocularly deprived animals had larger visual deficits than short-term monocularly deprived animals, the only exception being cat SMD1 that developed a strabismus. Finally, the largest visual acuity deficits were observed with the deviated eye of the strabismic animals.

Altogether, these results are similar to those found in animals deprived for similar periods in previous published papers from this laboratory. For example, Mitchell et al. (1977a) and Giffin and Mitchell (1978) tested the visual acuity of a cat monocularly deprived until 60 days of age from the time of natural eye opening, a period identical to that of cat LMD2. This animal was blind for 10 days and the visual acuity of its deprived eye (4.45 c/deg) represented a deficit of 0.59 octaves with respect to its non-deprived eye. In comparison, cat LMD2, was blind for more than twice as long (23 days) and the visual acuity of its deprived eye represented a visual deficit of 0.74 octaves with respect to its non-deprived eye. The difference between the duration of the blindness period could be due to the fact that current monocular deprivation surgeries used double eyelid surgery as opposed to a single eyelid surgery. In addition, Giffin and Mitchell (1978) also tested cats monocularly deprived until 75 (cat 75B) and 90 (cat 90B) days of age from the time of

natural eye opening, a period similar to that experienced by cat LMD3. Cat 75B was only blind for 6 days, while cat 90B was blind for 12 days, as opposed to 23 days for cat LMD3. In contrast, the visual acuity of the deprived eye of cat 90B was lower (3.50 c/deg) that than of cat LMD3 (4.15 c/deg). However, the visual acuity of the non-deprived eye was not mentioned in the published paper so the visual acuity deficit in octaves could not be calculated. Moreover, the acuities measured for normal animals at that time were somewhat lower than those achieved now (approximately 7 c/deg). Using this value, the visual deficit of the deprived eye of cat 90B represented one octave. Unfortunately, the deprived eye of cat 75B became inflamed about a month after it was opened and testing was terminated. Similarly, Mitchell (1988) tested a cat monocularly deprived until 94 days of age from the time of natural eye opening, a period similar to that of cat LMD3. This animal was blind for 17 days, and the visual acuity of its deprived eye (3.45 c/deg) was also lower than the visual acuity of the deprived eye of cat LMD3 (4.15 c/deg). With respect to contemporary standard values, it represented a deficit in visual acuity of 1.02 octaves. Finally, Mitchell et al. (1984c) tested the visual acuity of two cats with an induced strabismus at day 21. The visual acuity of the deviated eye of these two animals was 3.72 c/deg (cat C112) and 3.53 c/deg (cat C113), while the visual acuity of the fellow non-deviated eye was respectively, 6.54 c/deg and 6.21 c/deg. Both of these animals had a visual acuity deficit of 0.81 octaves with respect to their non-deviated eye, a result that was nearly identical to cat S1 which had strabismic surgery performed at day 17.

With respect to methodological differences between the present study and past studies, some observations are noteworthy. It seems that the double eyelid closure performed in the present study did not negatively affect the recovery of vision with respect to the results found earlier by use of a single occlusion layer. It is true that the animals of the present study were blind for longer time periods, but their final visual acuity was higher. It could be argued that the higher visual acuity could be due to the use of a discrimination task as opposed to a detection task as was used in previous studies from this laboratory. However, because discrimination tasks are less sensitive to aliasing effects than detection tasks (Hall and Mitchell, 1991), it is more likely that the acuities tested with the latter task would be lower. Thus, it is just as likely that the better

performance of the animals of the present study could be attributed to additional refinements to the testing procedure introduced since the earlier studies such as the use of small increments in spatial frequency equated on a logarithmic scale.

Experiment 2. Alignment accuracy with Gaussian blobs

In human amblyopia, the main visual deficit concerns the coding of space. Hess and colleagues (Hess and Holliday, 1992b; Hess and Field, 1994; Demanins and Hess, 1996; Field and Hess, 1996) have extensively studied the spatial localization deficits in human amblyopia using Gabor patches. These stimuli are patches of sinusoidal grating enveloped in both the x- and y-dimension by a Gaussian envelope. The form of the Gabor functions was $G(x) = A \sin(x) \exp[-(x^2 + y^2)/(2s^2)]$, where A is the amplitude of the function, and s is the standard deviation of the Gaussian envelope defining the patch. These stimuli were used because performance on alignment accuracy with such stimuli cannot be determined by local luminance or contrast cues because of the absence of sharp edges in close proximity. Additionally, the relative influences of spatial scale and contrast can be assessed with this type of narrowband stimulus. This study has for its goal a replication of the studies of Hess and colleagues using the same tasks as they employed on human amblyopes on visually deprived cats for which the anatomical and physiological deficits could be predicted. The hope was that such comparisons could lead to a better understanding of the neural mechanisms responsible for human amblyopia.

The two main goals of this experiment were to document the visual deficits in spatial localization of cats with various forms of selected visual deprivation and to compare them to the previously published deficits observed in two main types of human amblyopia, namely anisometropic and strabismic amblyopia. Specifically, the performance was examined as a function of the size of the stimuli in an attempt to establish the extent to which the performance of cats and humans differ with changes in this parameter.

Methods

The subjects for Experiment 2 were drawn from the same pool of animals as those employed in Experiment 1. In contrast to the studies of Hess and colleagues mentioned above that employed Gabor patches as stimuli, the stimuli for this experiment were Gaussian blobs (Toet, van Eekhout, Simons and Koenderink, 1987; Toet and Koenderink, 1988). Using Gabor patches, Hess and Holliday (1992a, 1992b) and Demanins and Hess (1996) discovered that in most situations, the performance of both normal and amblyopic

subjects was based on the Gaussian envelope of the Gabor stimuli rather than the spatial frequency of the carrier. These stimuli share with Gaussian blobs two important features. First, because these stimuli are devoid of local spatial contrast cues in the sense that there are no sharp edges in close proximity, a pure measure of spatial localization can be obtained (Hess and Holliday, 1992a). Second, because these stimuli are spatially narrowband in comparison to the infinite range of spatial frequencies associated with the conventional bar stimuli used for measurement of Vernier acuity, it is likely that the same spatial mechanisms underlie the detection and the localization of the stimuli.

Three Gaussian blobs were used to measure the accuracy with which the central element could be aligned with respect to two reference stimuli (Figure 7). The outer two Gaussian blobs were in vertical alignment and measurements were made, by use of the computerized jumping stand and a Method of Descending Limits, of the minimum detectable horizontal misalignment of the middle Gaussian blob with respect to the other two, both with binocular viewing and with the deprived (or deviated) eye. The Gaussian blobs were separated from each other by 5 standard deviations and the stimuli had a Michelson contrast of 68.5%, a value that later experiments (Experiments 3a and 3b) showed was at least 20 or 37 dB above the contrast threshold for respectively, the deprived and non-deprived eye. The stimuli were presented on the display monitor and were viewed either binocularly or monocularly from a distance of 60 cm. To permit a constant separation between the Gaussian blobs of five standard deviations for all stimuli, it was necessary to reduce the viewing distance to 30 cm for the largest stimuli. The data obtained in the binocular viewing condition were used as an index of the alignment accuracy for the non-deprived (or non-deviated) eye so that each subject served as its own control. Data obtained in the past and supported by limited data from the experimental animals of this study indicate that the binocular performance is equal to the performance of the better of the two eyes tested monocularly (Giffin and Mitchell, 1978). A two-alternative choice task was employed in which the animals were required to jump toward the set of misaligned Gaussian blobs as opposed to an adjacent set of three Gaussian blobs that were in physical alignment. Since there was no difference in alignment accuracy for left or right offsets, the results were either pooled together or were tested using only a left offset. As with the preceding measure of grating acuity, the

lateral position of the two sets of stimuli was interchanged from one trial to the next in a pseudo-random order (RRLRLLRLRR).

Measurements of alignment accuracy were made at five spatial scales (Gaussian blobs with standard deviations of 5.7, 11.4, 22.9, 45.8 and 91.7 min of arc, where the stimuli were spatially scaled versions of one another (Figure 8). The order of measurement with the different stimulus sizes was chosen randomly. In most cases, alignment accuracy thresholds were obtained for one blob size each day. Depending on the level of motivation of the animals, thresholds of alignment accuracy for both the non-deprived (or non-deviated) eye and the deprived (or deviated) eye were obtained on the same day or on different days. In all cases where the thresholds were obtained during the same day, the performance was tested binocularly first before test of the deprived (or deviated) eye. Thresholds continued to be measured with all the blob sizes until the animal's performance on each blob size appeared to have stabilized on two consecutives measurements. At this point, formal measurements were begun with the different blob sizes chosen in random order until 3 to 10 alignment accuracy thresholds had been obtained for each eye for each stimulus set. Figure 9 displays a representative testing session for the alignment accuracy task of cat LMD3 using the 22.9 min Gaussian blobs.

For comparison purposes, tests of alignment accuracy were performed with one cat (LMD3) using the method of constant stimuli. This animal was tested with five selected offsets that straddled the thresholds found with the Method of Descending Limits. Each offset was presented randomly 20 times for a total of 100 trials per day for five days. For this experiment, only the 22.9 min Gaussian blobs were used and the Michelson contrast was slightly lower (50%) than that used with the method of limits (68.5%). Alignment accuracy thresholds were measured first for the non-deprived and then for the deprived eye. Five alignment accuracy thresholds were measured for each eye on different days.

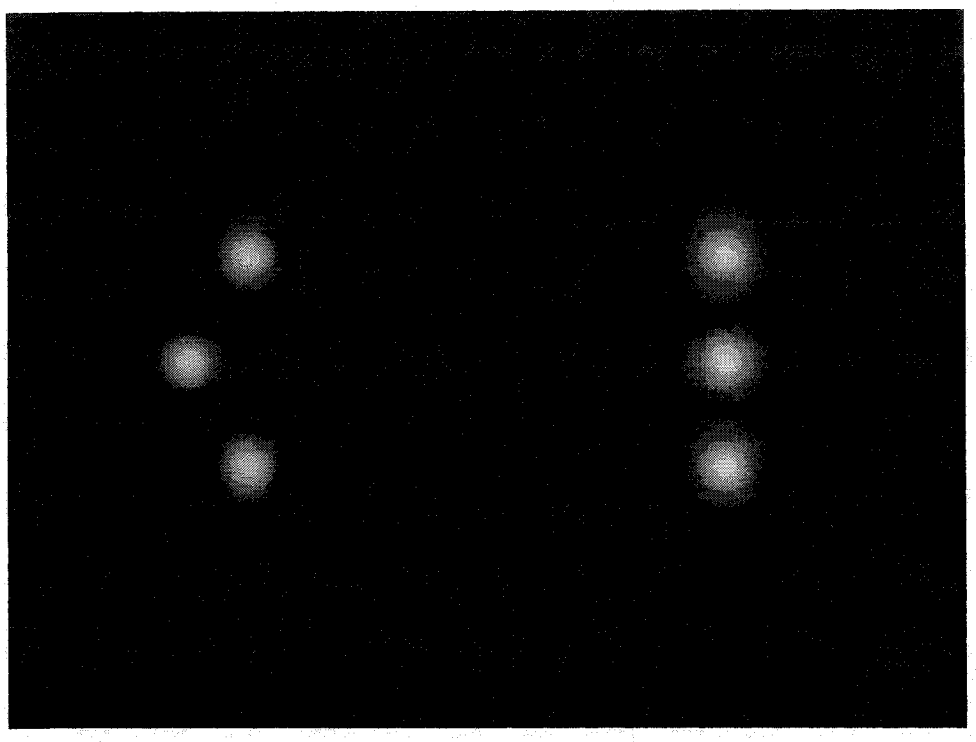


Figure 7. Illustration of the stimuli used in the alignment accuracy task with Gaussian blobs (Experiment 2). The task of the animals was to jump to the side with the misaligned set of Gaussian blobs (in this case, the left).

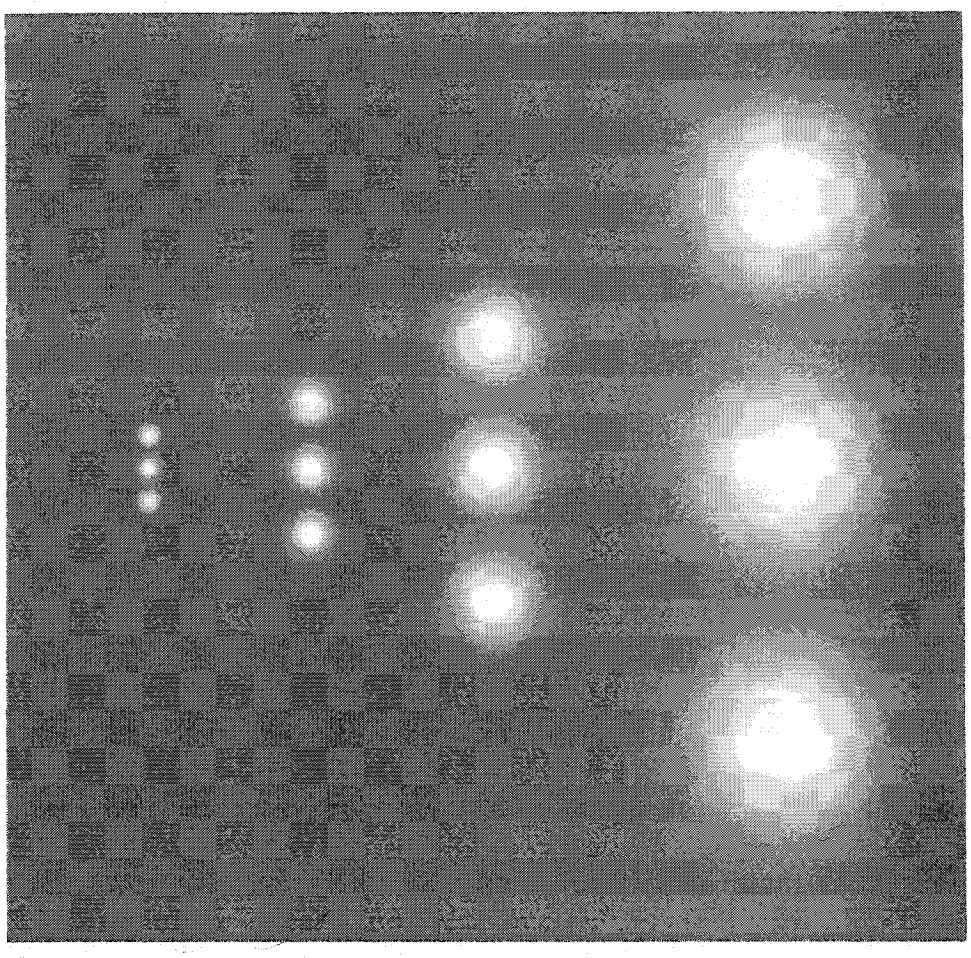


Figure 8. Illustration of the Gaussian blobs used in the alignment accuracy task. All stimuli are spatially scaled versions of one another. Gaussian blobs of 4 different sizes are shown.

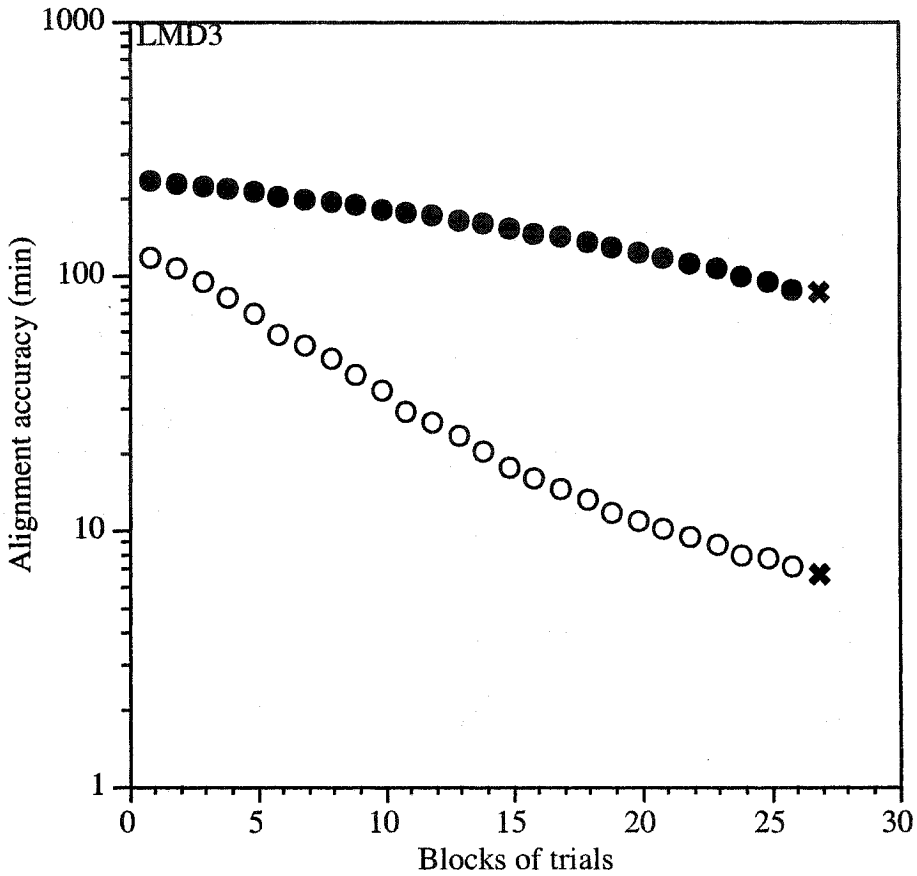


Figure 9. Representative testing session of cat LMD3 on the alignment accuracy task (Experiment 2) using the 22.9 min Gaussian blobs. Non-deprived (open circles) and deprived (filled circles) eyes are compared. The black "Xs" represent a failed offset.

Results

Figures 10, 11, 13 and 14 display the alignment accuracy thresholds, expressed in minutes of arc (min), as a function of the size of the Gaussian blobs (expressed in terms of the standard deviation) for each of the animal groups (normal, long-term monocularly deprived, short-term monocularly deprived and strabismic animals). A common feature of all the results was the fact that there was an approximately proportional relationship between alignment accuracy and the size of the Gaussian blobs. In other words, alignment accuracy appeared to be scaled with respect to Gaussian blob size, rather than having similar values for all spatial scales or else values that increased with decreasing blob sizes as might occur if the deficit was restricted to high spatial frequencies.

Normal animals (N1 and N2)

The results illustrated in Figure 10 show the alignment accuracy thresholds measured binocularly in the two control animals, N1 and N2. For both of these animals, it was possible to obtain alignment accuracy thresholds for all Gaussian blob sizes. Because cat N2 had better (lower) alignment accuracy thresholds than cat N1 with the smallest stimuli, this animal displayed more complete scaling of the thresholds with blob size. Nevertheless, it was readily apparent that alignment accuracy increased proportionally with blob size in a manner similar to that reported for normal humans (Toet et al., 1987; Toet and Koenderink, 1988; Hess and Holliday, 1992a). For cat N1, the difference in alignment accuracy thresholds between the smallest and the largest Gaussian blob sizes was 26-fold, while the corresponding value for cat N2 was 40-fold.

Long-term monocularly deprived animals (LMD1, LMD2 and LMD3)

The results illustrated in Figure 11 show the alignment accuracy thresholds of the normal and the fellow amblyopic eye of the long-term monocularly deprived animals (LMD1, LMD2 and LMD3) as a function of Gaussian blob size. There was an approximately proportional relationship between alignment accuracy of the non-deprived eye and the size of the Gaussian blobs.

It was only possible to measure alignment accuracy for two Gaussian blob sizes when testing the deprived eye of these animals. Measurements of alignment accuracy could not be made with the deprived eye for the two smallest Gaussian blob sizes. Moreover, it was not possible to obtain data even with the largest stimuli despite

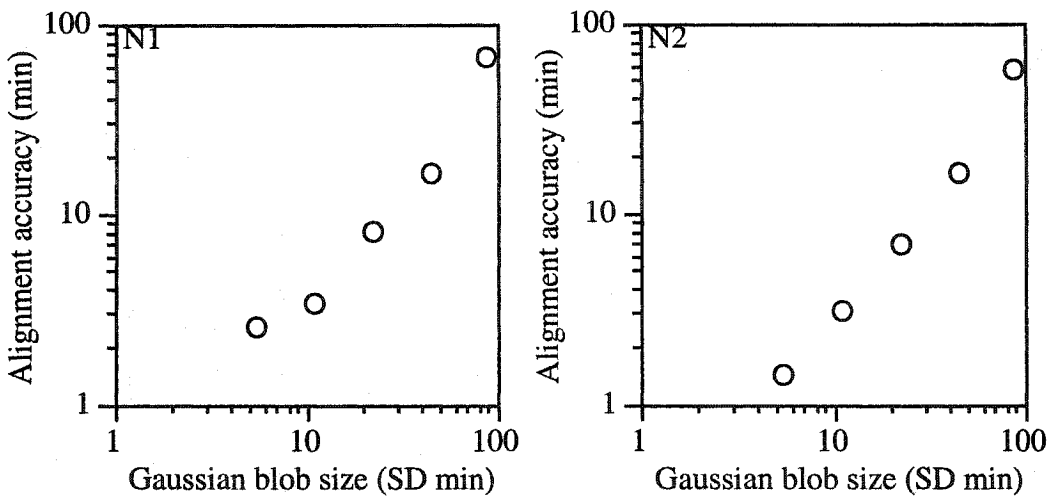


Figure 10. Alignment accuracy of the two normal animals (cats N1 and N2) as a function of the spatial scale of the Gaussian blobs expressed in terms of their standard deviation (SD min). Open circles indicate performance of the animals with binocular viewing.

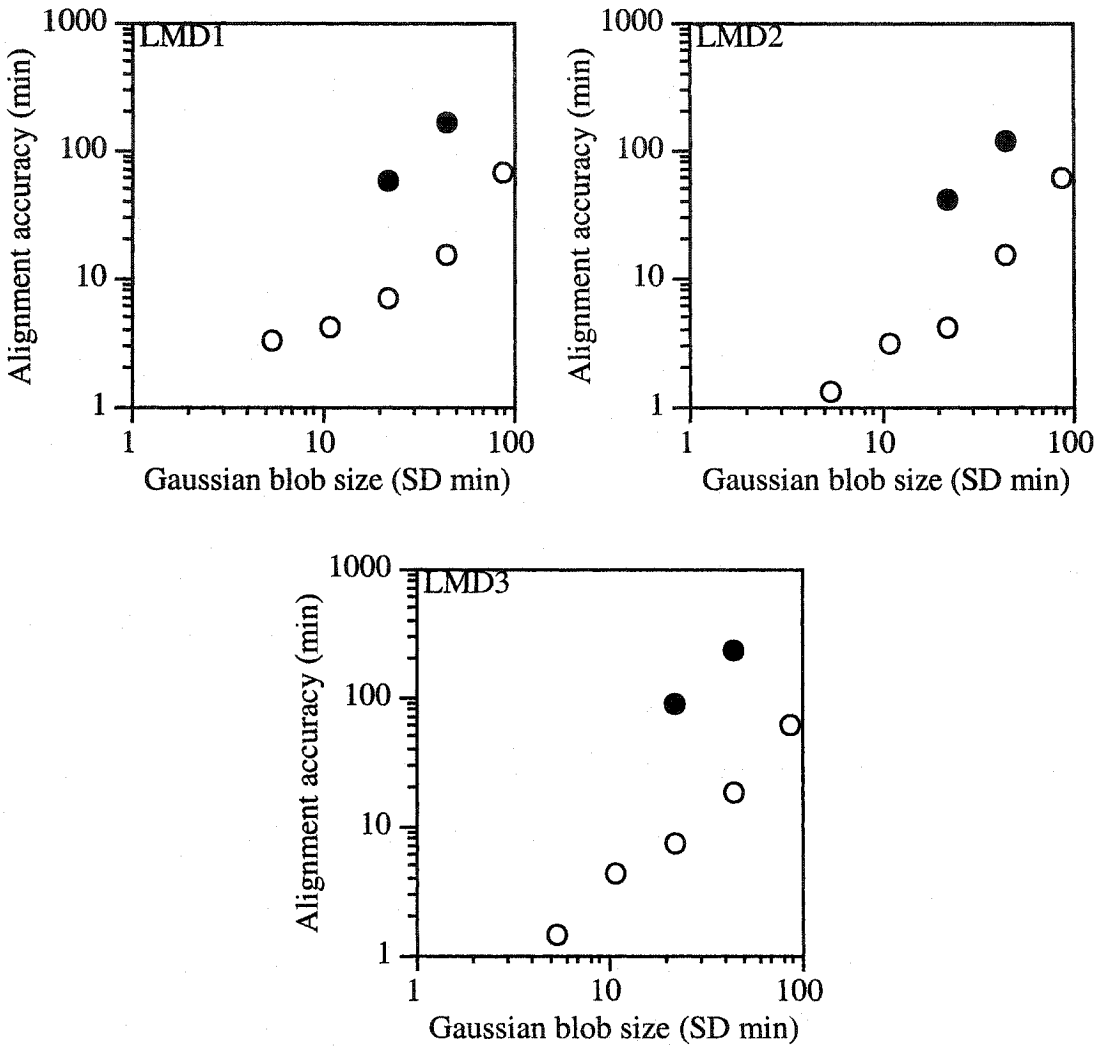


Figure 11. Alignment accuracy of the two eyes of the three long-term monocularly deprived animals (cats LMD1, LMD2 and LMD3) as a function of the spatial scale of the Gaussian blobs expressed in terms of their standard deviation (SD min). Non-deprived (open circles) and deprived (filled circles) eyes are compared. Measurements were possible for only two blob sizes (22.9 and 45.8 min) with their deprived eye.

their dimensions and obvious visibility. With these stimuli, the inability to measure alignment accuracy thresholds could be attributed to the limits on the maximum displacement set by the dimensions of the display screen of the monitor. However, the thresholds obtained with the two blob sizes with the deprived eye of these animals appeared to scale with Gaussian blob size.

The alignment accuracy thresholds of cat LMD1 show that the value measured with its non-deprived eye for the 22.9 min Gaussian blobs was 6.71 min of arc, while the value measured with its deprived eye was 56.35 min of arc, indicating an 8-fold difference in alignment accuracy between the two eyes. The ratio was somewhat larger for 45.8 min Gaussian blobs, where the alignment accuracy of the deprived eye (158.50 min of arc) was 11 times greater than the value measured with its non-deprived eye (14.32 min of arc).

The alignment accuracy thresholds measured with cat LMD2 exhibited similar trends to those observed with cat LMD1. For 22.9 min Gaussian blobs, the alignment accuracy of the deprived eye was approximately 10 times larger than that of its non-deprived eye (40.10 versus 3.98 min of arc). The alignment accuracy for 45.8 min Gaussian blobs was larger for both eyes than the values obtained with the smaller stimuli, but the ratio of the thresholds for the two eyes (a factor of 8) was comparable.

The alignment accuracy thresholds of the deprived eye of cat LMD3 for both blob sizes were slightly worse than those measured with the two other long-term monocularly deprived animals. The alignment accuracy thresholds measured with the 22.9 min Gaussian blobs were respectively, 6.98 and 85.94 min of arc for the non-deprived and the deprived eye, an approximately 12-fold ratio. For the 45.8 min of arc Gaussian blobs, the alignment accuracy of the deprived eye (225.60 min of arc) was 13 times worse than the corresponding values for the non-deprived eye (17.20 min of arc).

In addition, alignment accuracy with the 22.9 min Gaussian blobs was also measured using the Method of Constant Stimuli on this animal (cat LMD3). These tests were performed several months after the data were obtained with the Method of Limits and employed a contrast that was slighter lower. The results illustrated in Figure 12 show the percentage of correct responses as a function of the size of the offset presented in min of arc. The percentage of correct responses of both the non-deprived and the deprived eye

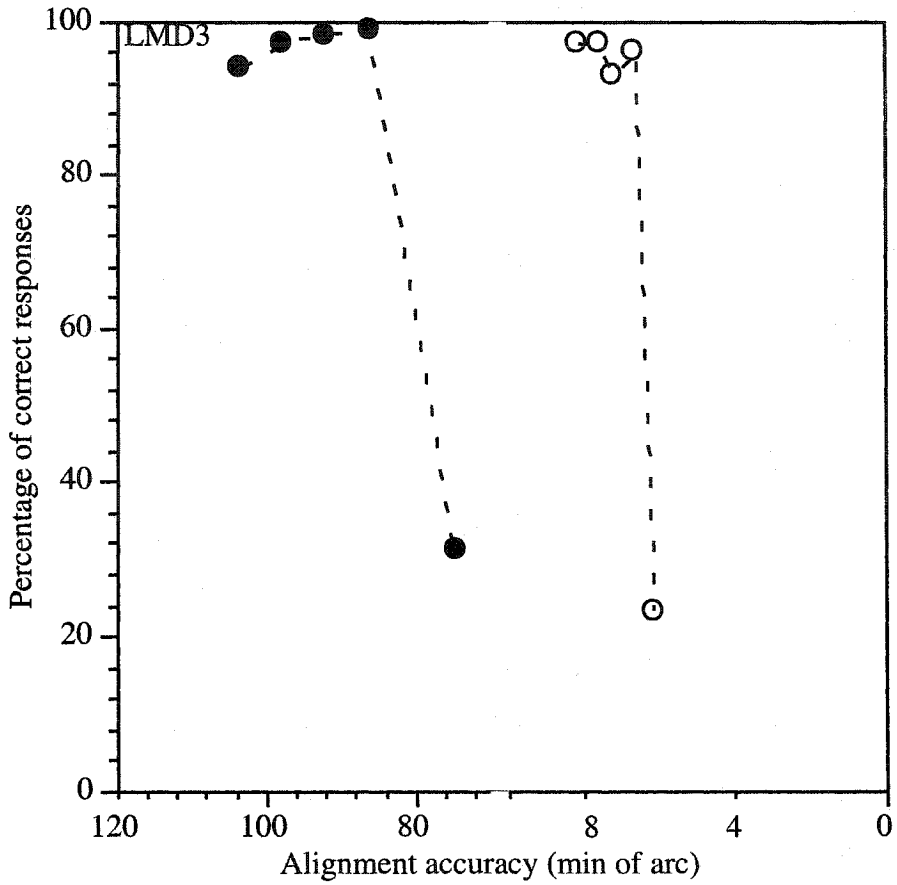


Figure 12. Frequency of seeing curve of cat LMD3 obtained with the Method of Constant Stimuli for the alignment accuracy task with Gaussian blobs. Non-deprived (open circles) and deprived (filled circles) eyes are compared.

was nearly perfect and varied between 93 and 99% for the largest offsets but fell dramatically below the success criterion for the smallest offsets. The precipitous decline in performance between the last two offsets was a possible reflection of the fact that the offsets employed were the smallest offsets employed for the measurements of alignment accuracy with the Method of Descending Limits. While it could be argued that a more sensitive estimate of the thresholds could be obtained with smaller differences in offsets than those that were employed, the important point that was established by this measurement was that the thresholds obtained with the Method of Constant Stimuli were of the same magnitude as those established with the Method of Descending Limits.

Short-term monocularly deprived animals (SMD1, SMD2 and SMD3)

The results illustrated in Figure 13 show the alignment accuracy thresholds of the normal and the fellow amblyopic eye of the short-term monocularly deprived animals (SMD1, SMD2 and SMD3) as a function of Gaussian blob sizes. Once more, there was an approximately proportional relationship between alignment accuracy thresholds and the size of the Gaussian blobs for the non-deprived eye of these animals. It was possible to make measurements of alignment accuracy with the deprived eye for one blob size for cat SMD1, three for cat SMD2 and four for cat SMD3.

For cat SMD1, it was only possible to measure alignment accuracy with the 22.9 min Gaussian blob with its deprived eye. The alignment accuracy of its deprived eye was 23 times larger (177.60 min of arc) than that of its non-deprived eye (7.81 min of arc). Indeed, this animal had the poorest alignment accuracy threshold of all the monocularly deprived animals, including all three of the long-term monocularly deprived animals. In addition, the threshold measured with its deprived eye was comparable to that measured with the deviated eye of the strabismic animals (see below). This result may not be coincidental as this animal developed an esotropic strabismus two months after termination of the short period of monocular deprivation.

Of all the monocularly deprived animals, cat SMD2 had the smallest alignment accuracy deficits. With this animal, it was possible to measure alignment accuracy thresholds for 11.4, 22.9 and 45.8 min Gaussian blobs. With 11.4 min Gaussian blobs, the alignment accuracy value measured with its non-deprived eye was 4.30 min of arc, while the value measured with its deprived eye was less than 3 times larger (11.4 min of

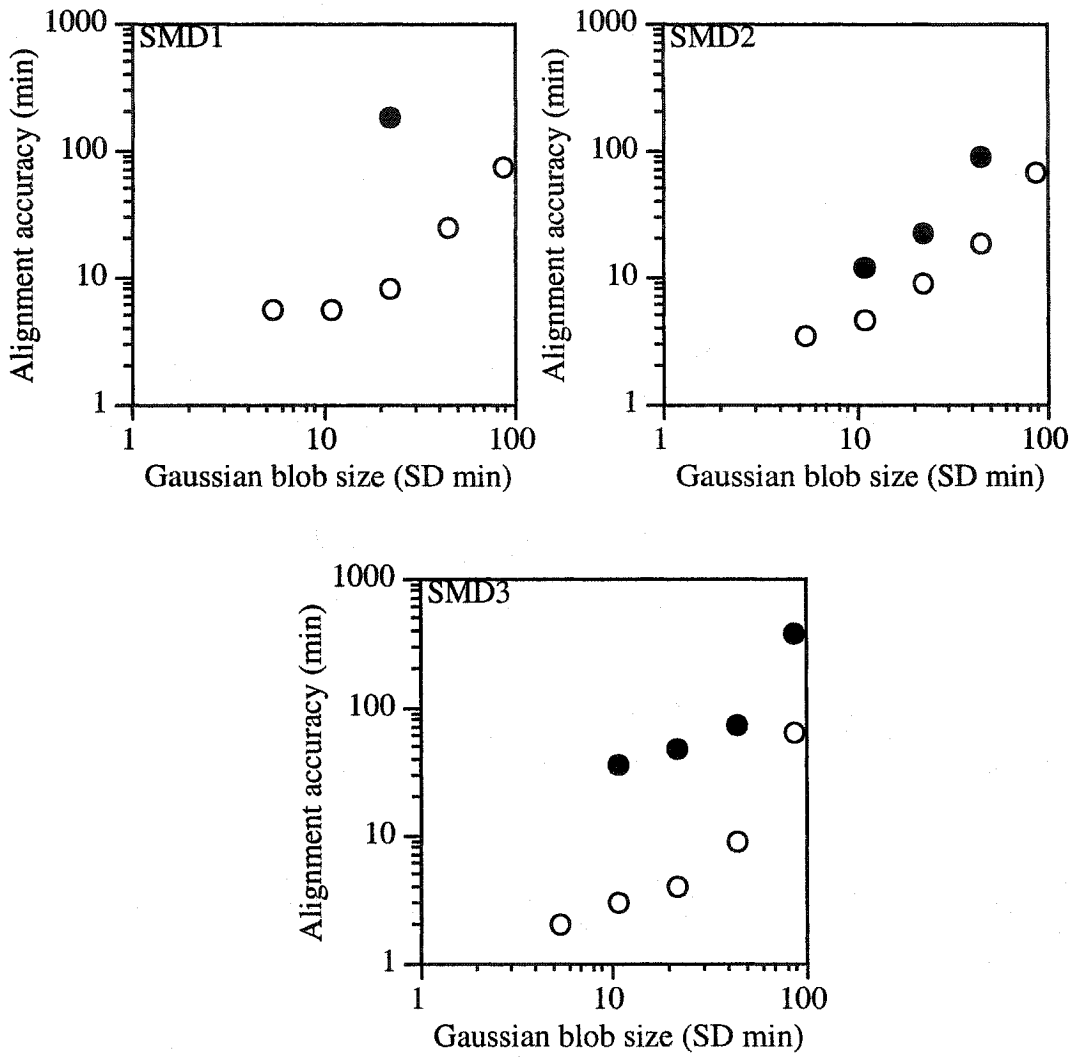


Figure 13. Alignment accuracy of the two eyes of the three short-term monocularly deprived animals (cats SMD1, SMD2 and SMD3) as a function of the spatial scale of the Gaussian blobs expressed in terms of their standard deviation (SD min). Non-deprived (open circles) and deprived (filled circles) eyes are compared. Measurements with their deprived eye were possible for only one blob size (22.9 min) for cat SMD1, three blob sizes (22.9 and 45.8 min) for cat SMD2 and four blob sizes (11.4, 22.9 and 45.8 min) for cat SMD3.

arc). A comparable result was obtained with 22.9 min Gaussian blobs, where the alignment accuracy of its deprived eye (21.50 min of arc) was only 2.5 times larger than that of its non-deprived eye (8.59 min of arc). The difference in alignment accuracy between the two eyes was greatest for the 45.8 min Gaussian blobs, where the alignment accuracy of its deprived eye (85.90 min of arc) was 5 times larger than that of the non-deprived eye (17.20 min of arc).

Even though it was possible to measure alignment accuracy of the deprived eye for four Gaussian blob sizes for cat SMD3, the ratio of the performance of the two eyes for the different blob sizes of this animal were similar to those found for the long-term monocularly deprived animals. These ratios ranged by a factor of 6 for the largest Gaussian blob size to 12 for the smaller stimuli. In addition, the absolute magnitude of the alignment accuracy for the two eyes were similar to those observed with the long-term monocularly deprived animals. Specifically, the values measured with the non-deprived eye of this animal were respectively, 2.86, 3.78, 8.60 and 60.20 min of arc with Gaussian blob sizes of 11.4, 22.9, 45.8 and 91.7 min of arc, while the corresponding values measured with its deprived eye were respectively 34.38, 45.80, 68.76 and 367.00 min of arc.

The results obtained for the animals that received short periods of deprivation at various ages were somewhat unexpected. Cat SMD1 exhibited huge deficits in alignment accuracy with its deprived eye, while cat SMD2 exhibited the smallest alignment accuracy deficit of all the animals tested. The results for cat SMD3 were similar to those of the long-term monocularly deprived animals, despite it being possible to measure alignment accuracy on a greater number of blob sizes. The results for cat SMD1 could be affected by the development of an esotropic strabismus, while the data for cat SMD3 may reflect the one-month period this animal spent in a darkroom immediately after birth.

Strabismic animals (S1 and S2)

The results illustrated in Figure 14 show the alignment accuracy thresholds of the normal and the fellow deviated eye of the two strabismic animals (S1 and S2) as a function of Gaussian blob sizes. As with the normal animals and the non-deprived eye of the monocularly deprived animals, the alignment accuracy of the non-deviated eye of both of these animals scaled with Gaussian blob sizes.

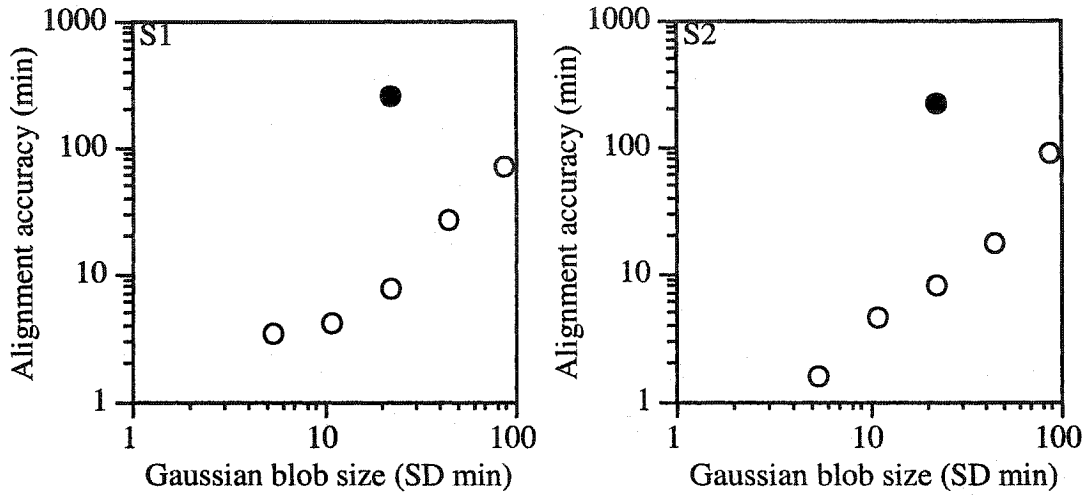


Figure 14. Alignment accuracy of the two eyes of the two strabismic animals (cats S1 and S2) as a function of the spatial scale of the Gaussian blobs expressed in terms of their standard deviation (SD min). Non-deviated (open circles) and deviated (filled circles) eyes are compared. For both animals, measurements were possible for only one blob size (22.9 min) with their deviated eye.

Of all the experimental conditions, the strabismic surgery created the largest deficits in alignment accuracy. With their deviated eye, it was possible to measure alignment accuracy on only the mid-size Gaussian blobs (22.9 min). For cat S1, the alignment accuracy value measured with its non-deviated eye was 7.47 min of arc, while the value measured with its deviated eye was 32 times larger (240 min of arc). The values were only slightly smaller for cat S2 where the alignment accuracy value measured with its deviated eye (212 min of arc) was 27 times larger than the alignment accuracy threshold of the non-deviated eye (7.77 min of arc).

Discussion

As illustrated in Figure 15, in terms of alignment accuracy deficits, the smallest deficits were observed in one animal (cat SMD2) from the group of animals that received short periods of deprivation. On the other hand, the two other animals from this group exhibited larger deficits. The spatial localization deficits of cat SMD1 were as large as those obtained with strabismic animals, while those of cat SMD3 were similar to those found in long-term monocularly deprived animals. The deficits were consistently larger for the long-term monocularly deprived animals, while the surgically induced strabismic animals exhibited the largest alignment accuracy deficits.

Alignment accuracy in normal cats followed a similar proportional relationship with stimuli size to that observed in normal humans (Toet et al., 1987; Toet and Koenderink, 1988; Hess and Holliday, 1992a). These animals demonstrated spatial localization performances that changed proportionally with spatial scale, so that as the size of the Gaussian blobs was increased, thresholds on the alignment accuracy task were elevated in proportion to the size of the stimuli.

The data for the non-deprived eye of the long-term monocularly deprived animals followed a very similar pattern to that observed with the normal animals with alignment accuracy thresholds increasing with blob size. Despite the fact that a high contrast was used for the alignment accuracy task, it was only possible to measure alignment accuracy thresholds on two blob sizes with the deprived eye. Possibly for reasons relating to their visibility, it was impossible to obtain data with the two smallest blob sizes. Measurements with the largest blob size were not possible because of the limits on the maximum displacement set by the dimensions of the display of the computer monitor.

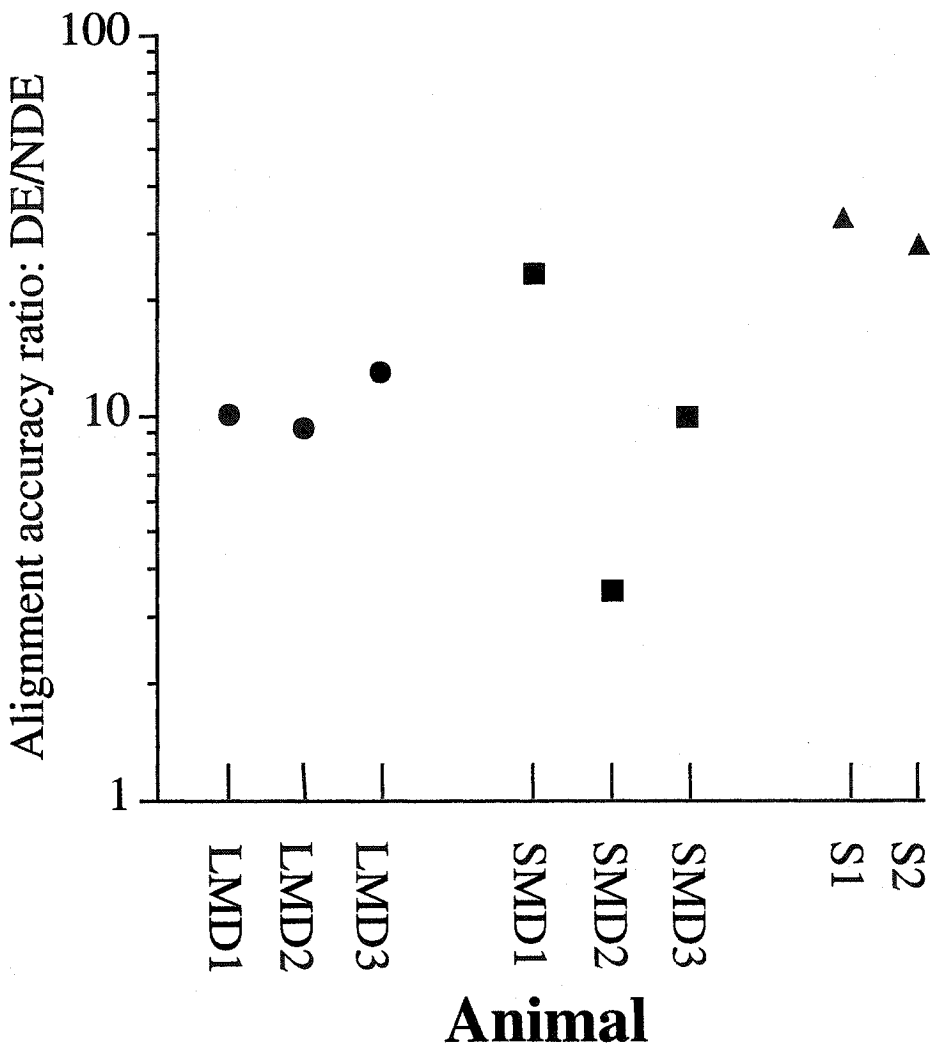


Figure 15. The ratio of the alignment accuracy of the deprived eye (DE) to the non-deprived (NDE) eye of each of the experimental animals. Different symbols are used to depict the results from the three deprivation conditions: long-term monocularly deprived animals (filled circles), short-term monocularly deprived animals (filled squares) and strabismic animals (filled triangles).

Alignment accuracy with the deprived eye was considerably worse (by a factor of 8-13) than that of the non-deprived eye. The data for the two blob sizes for which measurements were possible suggested that alignment accuracy also scaled with blob size for the deprived eye as well as with the non-deprived eye. This point was reinforced by the data from two short-term monocularly deprived animals (cats SMD2 and SMD3) where it was possible to obtain data for a wider range of blob sizes.

Similar to the long-term monocularly deprived animals, the alignment accuracy thresholds of the deprived eye of the short-term monocularly deprived animals were also considerably larger than those obtained with their non-deprived eye. The interocular difference was greatest for cat SMD1 (by a factor of 23) and smallest for cat SMD2 (by a factor of 2.5 – 5), while that of cat SMD3 (by a factor of 6 – 12) was similar to that observed in the long-term monocularly deprived animals. The fact that the alignment accuracy deficits were the greatest for the animal that was deprived at the earliest age (cat SMD1) was not a surprise since the period of monocular deprivation was initiated at the height of the sensitive period in area 17 (Hubel and Wiesel, 1970; Olson and Freeman, 1980). Moreover, this deficit was potentially compounded by the presence of a strabismus in its deprived eye that developed in the months following termination of the period of monocular deprivation. Past studies have shown that strabismus can occur spontaneously subsequently to monocular deprivation in both kittens (Sherman, 1972; Movshon, 1976a) and infant monkeys (Quick, Tigges, Gammon and Boothe, 1989).

For both of the surgically induced strabismic animals, it was only possible to obtain alignment accuracy thresholds for the mid-size blobs with their deviated eye. The interocular difference between the two eyes of the strabismic animals was the greatest (a factor of 27-32) of all the experimental animals.

One of the major findings of this experiment was that amblyopic cats demonstrated spatial localization deficits that changed with spatial scale in a manner similar to the effects observed in normal humans (Toet et al., 1987; Toet and Koenderink, 1988; Hess and Holliday, 1992a) as well as in human amblyopes (Hess and Holliday, 1992b; Demanins and Hess, 1996). As the size of the Gaussian blobs was increased, thresholds on the alignment accuracy task were elevated in proportion to the size of the stimuli. However, it is important to note that the alignment accuracy deficits

demonstrated by the amblyopic animals of the present study were substantially larger than those described in human amblyopes. A plausible explanation for these differences could be that the deprivation conditions in the present study were more severe than those experienced in human amblyopes. As yet, no data exist on the alignment accuracy of humans with deprivation amblyopia with stimuli of the sort employed in this study. Consequently, it might be thought that the closest data from the human literature to that induced by monocular deprivation in cats would be anisometropic amblyopia, where the amblyopia is presumably induced as a consequence of a defocused image in one eye. However, monocular deprivation with double eyelid suture would likely produce a far greater degree of deprivation than the blur produced by a refractive error.

The other major finding of the present experiment was that the deficits on the alignment accuracy task were independent of the deficits in grating acuity discussed in Experiment 1. In the latter task, grating acuities of the non-deprived (or non-deviated) eye and the deprived (or deviated) eye differed by a factor of between 1.11 and 2.64. In contrast, the comparable ratio for alignment accuracy thresholds between the non-deprived (or non-deviated) eye and the deprived (or deviated) eye varied between 3- and 32-fold. These results are illustrated in Figure 16 (the actual ratios between the two eyes for both tasks are presented in Table 2) where the magnitude of the grating acuity and alignment accuracy deficits are compared for each animal. If the deficits for grating acuity and alignment accuracy were equal, all the data points would lie close to a line with a slope of 1. However, all the data points fall well below this line, indicating that the magnitude of these two visual deficits were considerably different. The difference in performance between the two tasks is made even more evident when one compares the performance of cat SMD3. Even though the performance of cat SMD3 on the alignment accuracy task was similar to that of the long-term monocularly deprived animals, the grating acuity deficits for this animals were minimal. In fact, cat SMD3 had the best grating acuity following monocular deprivation of all the visually deprived animals. Taken together, the results obtained in the current study are similar to those found in human amblyopia where the deficits in Snellen or Vernier acuity can be substantially larger than deficits in grating acuity (Levi and Klein, 1982a, 1982b, 1983, 1985).

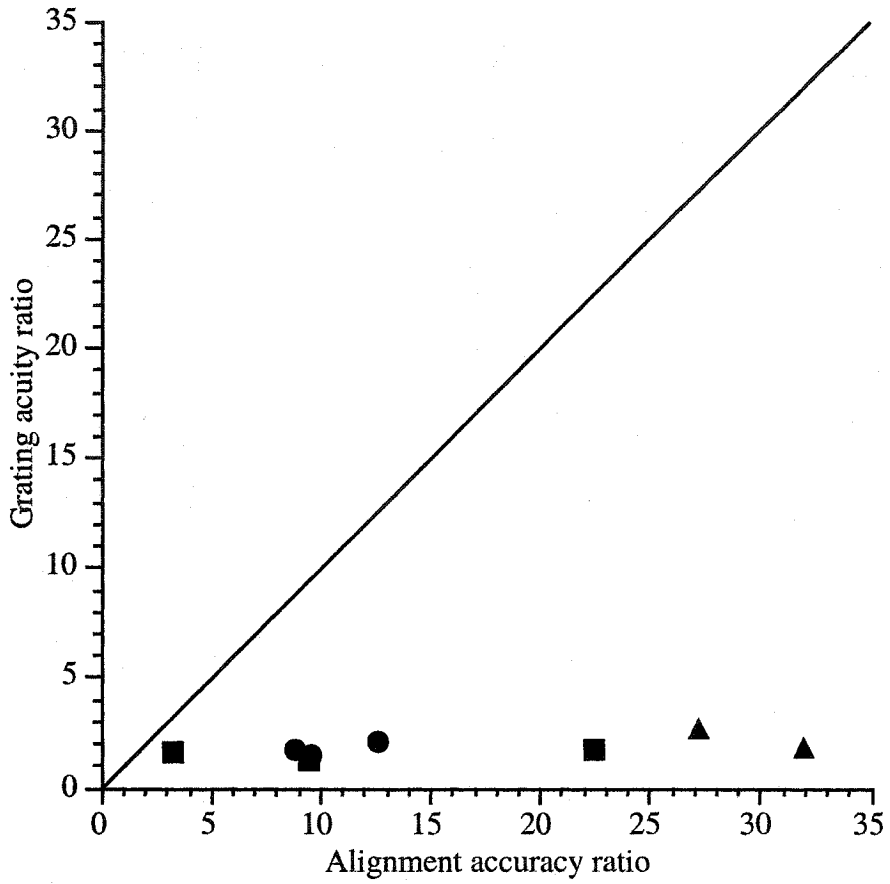


Figure 16. The ratio of the alignment accuracy between the normal and the fellow deprived or deviating eye (averaged across the scales for which measurements could be made) is plotted against the ratio of the grating acuities of the two eyes. Different symbols are used to depict the results from the three deprivation conditions: long-term monocularly deprived animals (filled circles), short-term monocularly deprived animals (filled squares) and strabismic animals (filled triangles). The line has a slope of 1.0 and indicates the situation where the deficits on the two measures are the same.

Animal	Alignment accuracy ratio	Grating acuity ratio
LMD1	9.74	1.43
LMD2	8.96	1.57
LMD3	12.72	2.02
SMD1	22.67	1.6
SMD2	3.39	1.59
SMD3	9.56	1.11
S1	32.1	1.74
S2	27.3	2.64

Table 2: Comparison of the alignment accuracy ratios and the grating acuity ratios between the non-deprived (or non-deviated) eye and the deprived (or deviated) eye of the experimental animals.

Experiment 3. The influence of contrast on alignment accuracy

One possible reason why human amblyopes have reduced alignment accuracy with their amblyopic eye relative to their fellow eye is that the visibility of the stimuli was poorer for the former eye. In other words, the alignment accuracy deficits could be related to their contrast sensitivity deficits. Although the experiments described to this point employed stimuli of very high contrast that should have been highly visible to both eyes, they may not have been *equally* visible to the two eyes of the visually deprived animals. In their studies on humans, Hess and colleagues (see below) addressed this possibility by equating the visibility of the stimuli to the two eyes by setting this contrast at the same multiple of the contrast thresholds for the two eyes. Using Gabor patches, they investigated the relationship between alignment accuracy and stimulus contrast both in normal subjects (Hess and Holliday, 1992a; Hess and Field, 1993; Hess and Hayes, 1993, 1994) and human amblyopes (Hess and Holliday, 1992b; Hess and Field, 1994; Demanins and Hess, 1996). Their results indicated that for all the strabismic amblyopes and for a minority of anisometropic amblyopes, contrast sensitivity was not correlated with the alignment accuracy deficits, while for most anisometropic amblyopes, the contrast sensitivity deficit completely defined the spatial localization deficits, since the deficits could be made to vanish by suitable manipulations of contrast (Hess and Holliday, 1992b; Hess and Field, 1994; Demanins and Hess, 1996). In normal humans, it was found that alignment accuracy was only minimally affected by contrast, such that thresholds were proportional to the 4th-root of contrast (Hess and Holliday, 1992a; Hess and Hayes, 1993, 1994). Since measurements of the dependence of alignment accuracy of Gaussian blobs on contrast have never been investigated for the cat, the goal of Experiment 3 was to investigate the contribution of contrast to alignment accuracy using a task highly similar to that used with human subjects. To permit this evaluation, the animals were tested on two different tasks. First, measurements of alignment accuracy were made as a function of the physical contrast of the stimuli (Experiment 3A), after which measurements of alignment accuracy were made with stimuli that were effectively equated for the two eyes by setting the contrast of the stimuli at equal distances from the contrast threshold for each eye (Experiment 3B).

Experiment 3A. Alignment accuracy as a function of the physical contrast of the Gaussian blobs

The subjects for both experiments (3A and 3B) were one normal animal (cat N2), the three long-term monocularly deprived animals (cats LMD1, LMD2 and LMD3) and one strabismic animal (cat S1). These visually deprived animals were chosen as subjects because they had the largest alignment accuracy deficits.

Methods

The testing procedure for Experiment 3A was identical to that of Experiment 2, with the only exception that the alignment accuracy task was performed using six different contrast levels (79.8, 40, 20, 10, 5 and 2.5%) with the 22.9 min Gaussian blobs. Examples of the stimuli used for this task are presented in Figure 17. As in Experiment 2, the task of the animals was to jump to the side with the misaligned set of Gaussian blobs. For all but one animal, the different contrast levels were tested in descending order of contrast levels, starting with the highest contrast level and ending with the lowest. For the normal animal (cat N2), the contrast levels were tested randomly. The animals were tested on one contrast level every day, and alignment accuracy thresholds for both the non-deprived (or non-deviated) eye and the deprived (or deviated) eye were obtained on the same day with the binocular tests preceding the tests of the deprived (or deviated) eye. In some cases, alignment accuracy thresholds with the highest contrast level (79.8%) were only tested monocularly. The alignment accuracy thresholds continued to be measured at all the contrast levels until the animal's performance appeared to stabilize and no further improvement occurred. Between two and ten alignment accuracy thresholds were obtained for each eye.

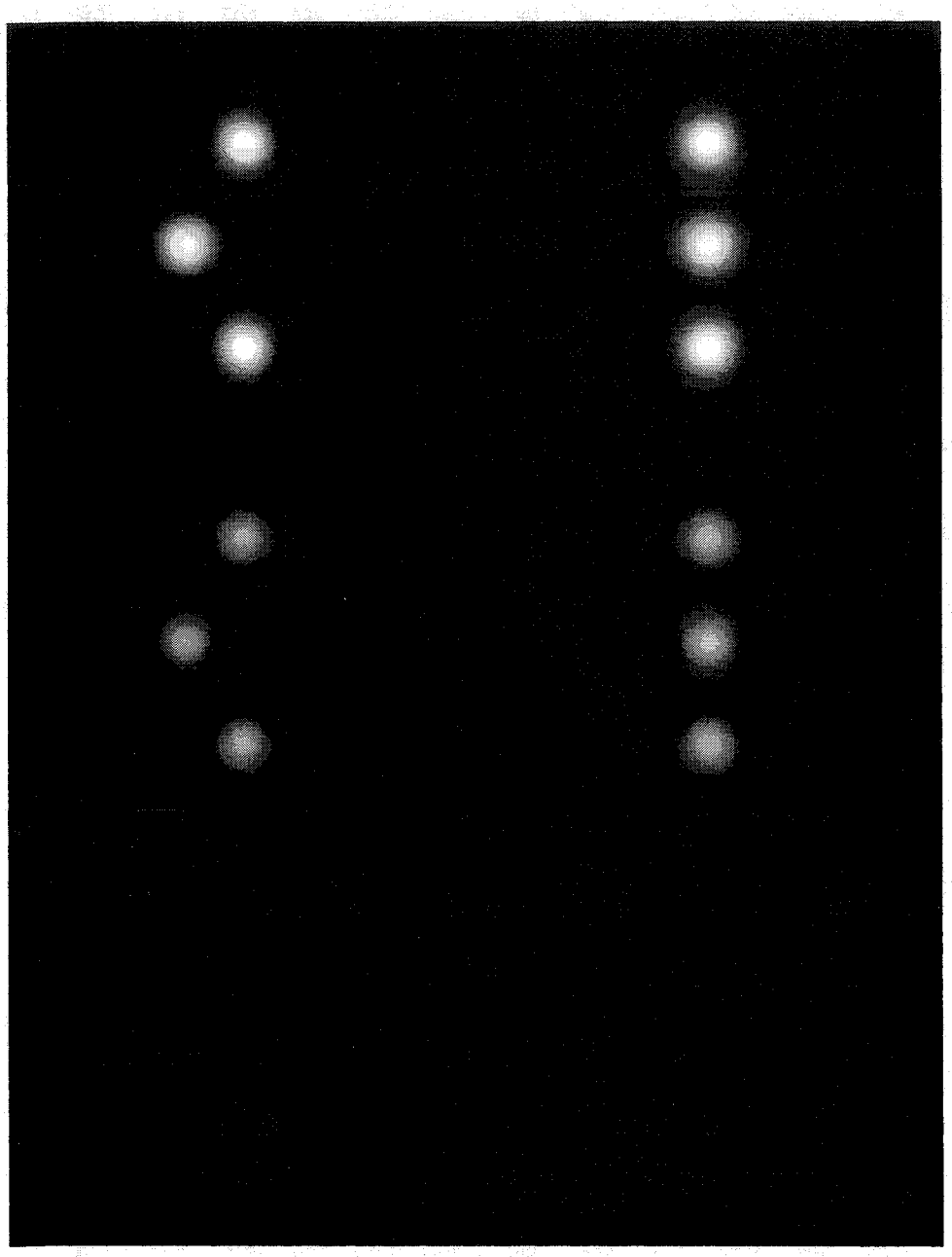


Figure 17. Illustrations of some of the stimuli used to study the effects of contrast on alignment accuracy (Experiment 3A). The Gaussian blobs are displayed at three levels of contrast with respect to the background. Because of printing artifacts, these stimuli are not exactly as seen by the animals.

Results

Figures 18, 19 and 20 display respectively the alignment accuracy thresholds as a function of stimulus contrast respectively for each of the animal groups (normal, long-term monocularly deprived and strabismic). A common feature of all the results was that the alignment accuracy thresholds for both eyes improved with increasing contrast and reached asymptotic levels with stimulus contrasts of about 40%. For the normal animal, there was approximately a 8-fold difference between the alignment accuracy thresholds obtained with the lowest and highest contrast.

Long-term monocularly deprived animals (LMD1, LMD2 and LMD3)

Alignment accuracy thresholds could not be measured at all contrasts with the deprived eye. For cat LMD1, it was possible to measure alignment accuracy thresholds for four contrast levels (79.8, 68.5, 40 and 20%) with its deprived eye. As with the normal animal, alignment accuracy thresholds for each eye reached asymptotic values at a contrast of 40%. However, whereas the alignment accuracy threshold of the non-deprived eye at these contrast levels was 6.60 min of arc, that of the deprived eye was nine times worse (57.30 min of arc). Interestingly, the interocular difference in alignment accuracy thresholds between the two eyes was the same (approximately 9-fold) for all contrast levels for which measurements were possible with both eyes.

The performance of cat LMD2 seemed to be better than for cat LMD1. Its alignment accuracy thresholds were smaller (better) than for cat LMD1, and it was possible to obtain data with its deprived eye with a lower contrast level (10%). Moreover, the alignment accuracy thresholds obtained with its non-deprived eye at the highest contrast levels were ten times better than those obtained with its deprived eye. At other contrast levels, the interocular differences varied between 10- and 12-fold, a ratio that was larger than that for LMD1.

Of all the long-term monocularly deprived animals, cat LMD3 showed the worst performance. Not only were the alignment accuracy thresholds larger than that of the two other animals, the interocular difference between the two eyes was also more substantial. It was possible to obtain data for four contrast levels with the deprived eye of this animal. At the highest contrasts, alignment accuracy with the non-deprived eye was 13 times better than that with the deprived eye (6.60 vs. 85.9 min of arc). At low

contrasts, the interocular difference in alignment accuracy between the two eyes increased to a factor of 14.

Strabismic animal (S1)

Finally, the results illustrated in Figure 20 show the alignment accuracy thresholds of the non-deviated and the deviated eye of the strabismic animal (S1) as a function of contrast. Considering the results obtained in Experiment 2, it was not a surprise that cat S1 had the worse performance of all the experimental animals. With this strabismic animal, it was only possible to obtain alignment accuracy thresholds for the deviating eye with stimuli of contrasts of 40% and higher. At the highest contrast levels, the alignment accuracy obtained was 7.60 min of arc for the non-deviated eye, and 246 min of arc for its deviated eye, an interocular ratio of 32.

Discussion

For all the animals, there was a steady improvement in alignment accuracy with increasing contrast until a contrast of either 40 or 68.5% beyond which the thresholds were at asymptotic levels. As expected, the alignment accuracy thresholds with the deprived eye of the experimental animals were considerable worse. Moreover, the interocular ratio between the two eyes increased with longer periods of monocular deprivation, and once more, the worst performance was from the strabismic animal. Clearly, the function describing the relationship between the alignment accuracy of the deprived eye and contrast did not appear to be shifted laterally with respect to that for the non-deprived eye as it would be if the performance of the deprived eye could be made equivalent to that of the non-deprived eye by presenting stimuli of higher contrast.

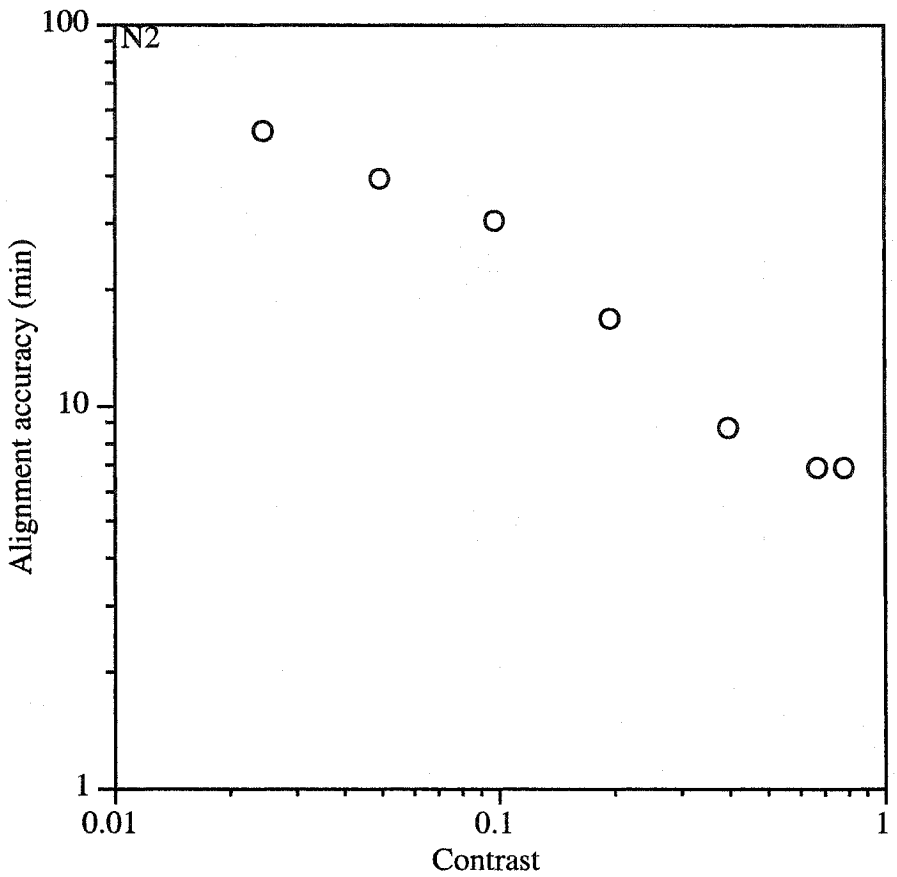


Figure 18. Alignment accuracy as a function of the physical contrast of the stimuli (22.9 min Gaussian blobs) for cat N2.

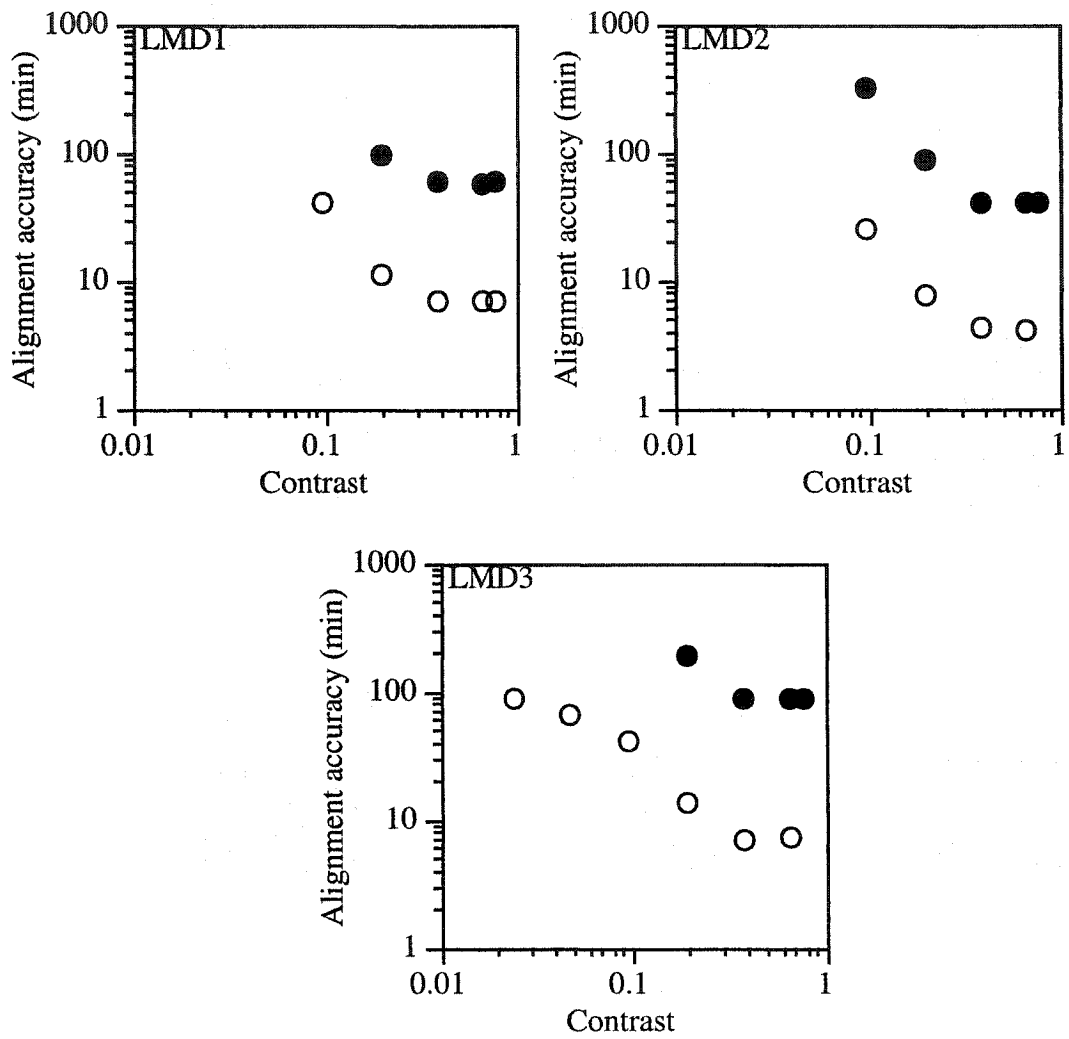


Figure 19. Alignment accuracy as a function of the physical contrast of the stimuli for cats LMD1, LMD2 and LMD3. Open and filled circles show the performance of the non-deprived eye and of the deprived eye, respectively. The measurements were made with the mid-size Gaussian blobs (22.9 min).

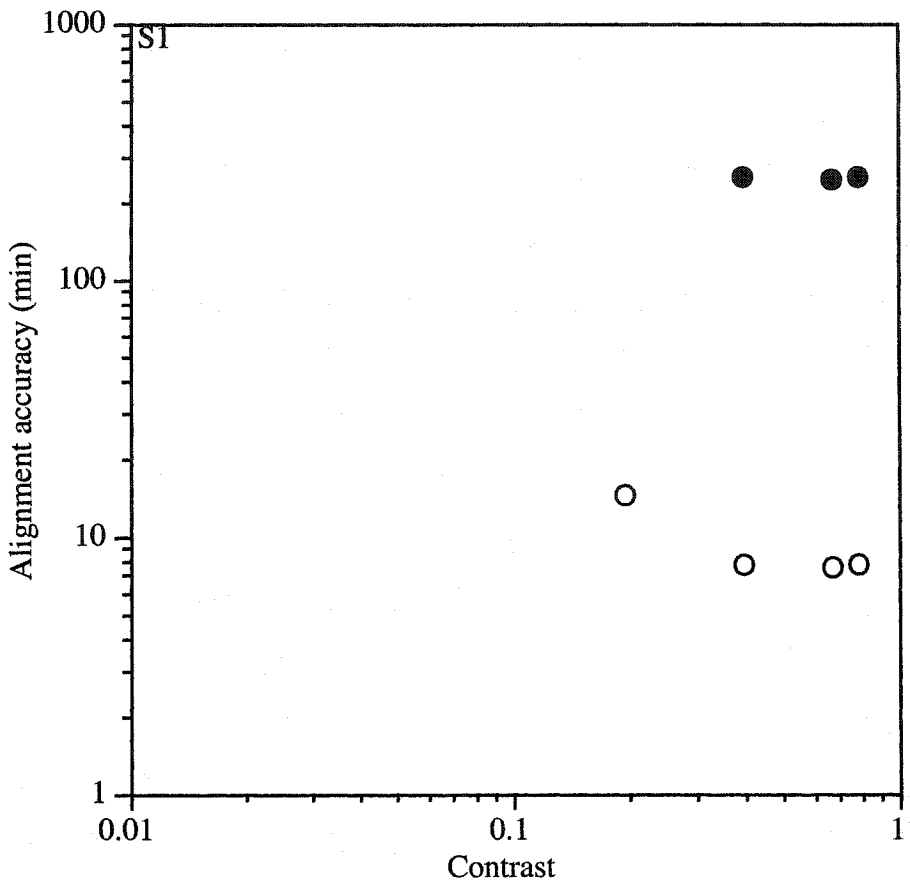


Figure 20. Alignment accuracy as a function of the physical contrast of the stimuli for cat S1. Open and filled circles show the performance of the non-deviated eye and of the deviated eye, respectively. The measurements were made with the mid-size Gaussian blobs (22.9 min).

Experiment 3B. Alignment accuracy as a function of the suprathreshold contrast of the Gaussian blobs

Because stimuli of a given physical contrast may appear to be of vastly lower contrast when viewed with the deprived (or deviated) eye, a more appropriate way to investigate the effects of contrast on alignment accuracy is to equate the effective contrast of the stimuli for each eye. One way to equate the apparent contrast of the stimuli for the two eyes would be to first establish the suprathreshold level of physical contrast of the stimuli as viewed by the non-deprived (or non-deviated) eye that matches their apparent contrast as viewed by the deprived (or deviated) eye. A second method, and the one adopted by Hess and Holliday (1992b) is to set the stimulus contrast for the two eyes at equal distances from their respective contrast thresholds. This particular choice was made for Experiment 3B because of the greater ease with which measures of contrast thresholds could be made as compared to measures of equal suprathreshold contrast.

This experiment permitted the investigation of the effects of stimulus contrasts for the two eyes that were incremented by the same amount (e.g. 10 dB) from their respective contrast thresholds. To allow this comparison, it was necessary first to measure the contrast thresholds for the Gaussian stimulus sets for each eye. Using the computerized jumping stand, these measurements were made for each eye by measurement of the contrast detection thresholds for those blobs for which alignment accuracy data could be made for the amblyopic eye.

A simple detection task was employed whereby the animals were first trained to jump towards an aligned set of Gaussian blobs as opposed to an adjacent blank field of the same luminance. On the basis of these measurements, the alignment accuracy thresholds were plotted as a function of the contrast of the stimuli with respect to their individual contrast thresholds. As in Experiment 3A, the middle-size Gaussian blobs (22.9 min) were used and the animals viewed the stimuli binocularly and monocularly. Between three and ten thresholds were gathered for each stimulus.

Results

Figures 21, 22 and 23 display respectively the alignment accuracy thresholds as a function of suprathreshold contrast for each animal group (normal, long-term monocularly deprived and strabismic animals). Hess and colleagues (Hess and Holliday, 1992a; Hess and Hayes, 1993, 1994) found that when plotted on a logarithmic scale, the relationship between alignment accuracy and contrast in normal humans was described by a slope of - 0.25 (4^{th}-root of contrast). When this relationship was plotted for the normal cat N2 (Figure 21), the slope was greater (- 0.64) than that observed in humans, indicating a greater dependence on contrast in cats.

Although equating the effective contrast of the stimuli for each eye brought the alignment accuracy thresholds of the two eyes closer together, the thresholds obtained with the deprived eye were always worse than that of the other eye and the difference between the two eyes increased with higher contrast. As illustrated in Figure 22, for both cats LMD1 and LMD2, the alignment accuracy thresholds for stimuli within 18-24 dB of the contrast thresholds for each eye were similar but still were worse for the deprived eye. For stimuli of higher contrast with respect to contrast threshold for each eye the performance of the deprived eye were worse by factors of 5-13.

Finally, the results illustrated in Figure 23 show the alignment accuracy thresholds of the non-deviated and the deviated eye of the strabismic animal (S1) as a function of the suprathreshold contrast levels. As expected from the results obtained in the previous experiments, the performance of cat S1 was the worst of all the experimental animals. The alignment accuracy of its deviated eye was appreciably worse (by a factor of 30) than that of the non-deviated eye at all contrast levels equated with respect to their individual contrast thresholds.

Discussion

These results demonstrated that in monocularly deprived cats, the alignment accuracy of the deprived eye for stimuli of low contrast measured with respect to the contrast threshold of this eye approached that of the non-deprived eye at equivalent contrast levels, but with high contrast stimuli the performance of the deprived eye was considerably worse. It can therefore be concluded that the elevated alignment accuracy of the deprived eye of the three long-term monocularly deprived animals cannot be

explained solely by the contrast threshold deficits of this eye. This conclusion was even more evident for the strabismic animal, a finding also consistent with observations made on human strabismic amblyopes (Hess and Holliday, 1992b; Hess and Field, 1994; Demanins and Hess, 1996). It can be concluded that for both monocularly deprived and strabismic cats, the deficits in alignment accuracy of the amblyopic cats were not due to their contrast sensitivity loss. As mentioned previously, Hess and colleagues (Hess and Holliday, 1992a; Hess and Hayes, 1993,1994) found that the performance on the alignment accuracy task of normal human was only minimally affected by contrast. In normal humans, the relationship between these two variables was fitted by a power function having a slope of - 0.25. By contrast, the relationship measured for one normal cat (N2) was greater (- 0.64), indicating a greater dependence on stimulus contrast for cats than for humans.

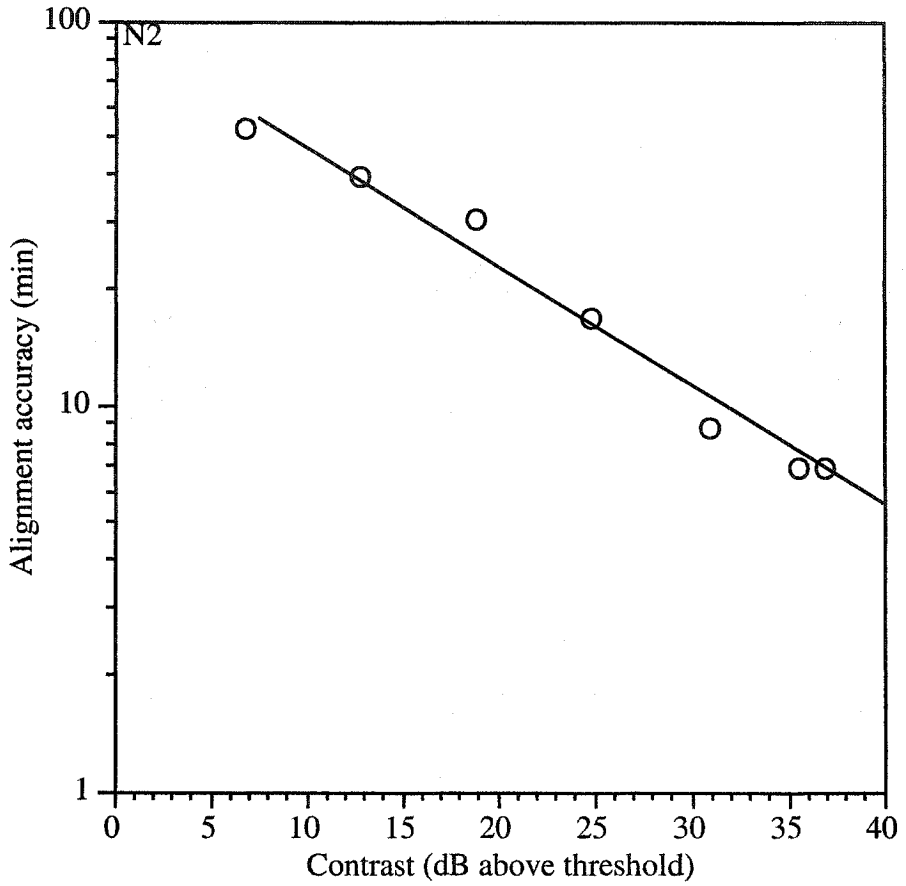


Figure 21. Alignment accuracy of cat N2 as a function of the contrast of the Gaussian blob stimuli plotted with respect to the contrast threshold for each eye. The best fitting line through the data has a slope of – 0.64.

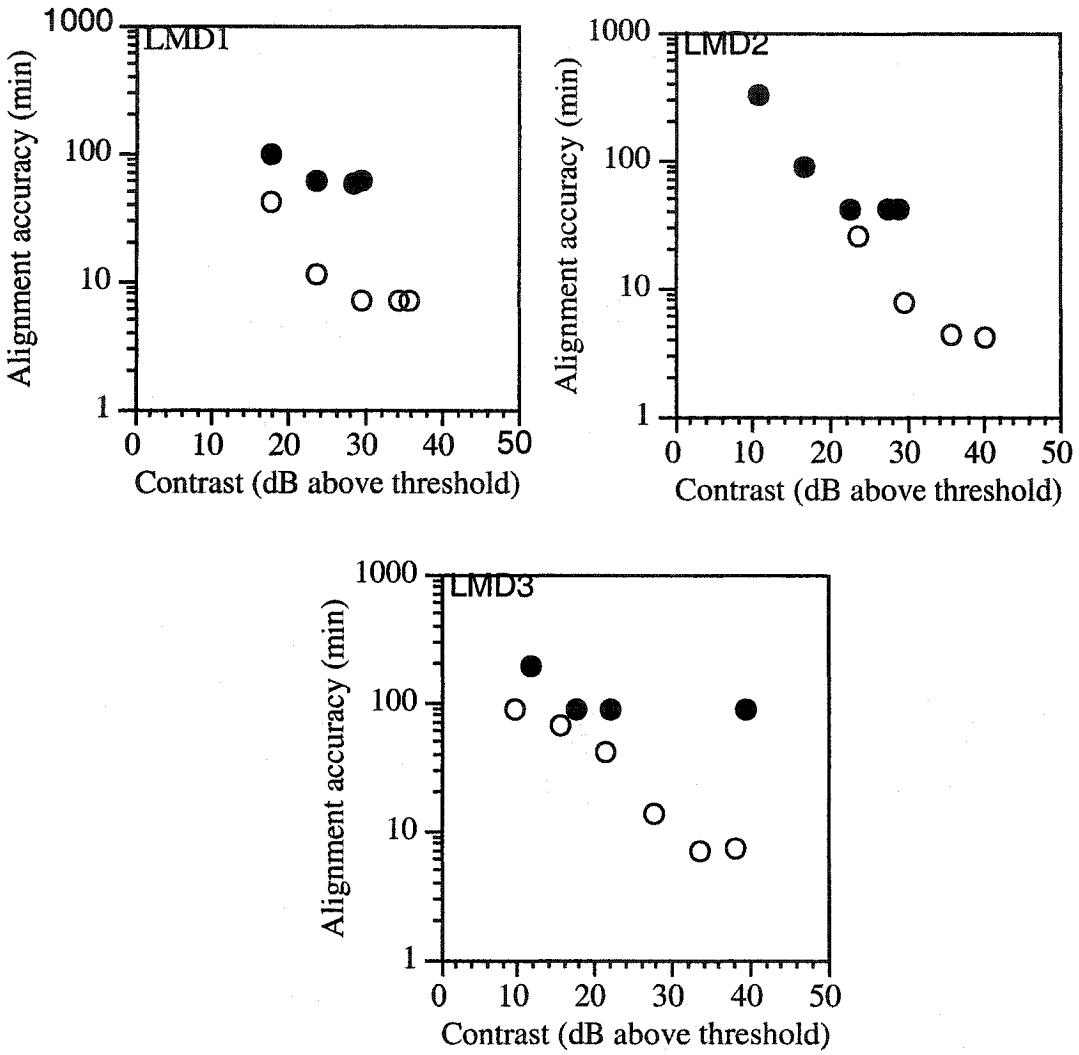


Figure 22. Alignment accuracy as a function of the contrast of the Gaussian blob stimuli plotted with respect to the contrast threshold for the stimuli for each eye. Data are shown for cats LMD1, LMD2 and LMD3. Results for the non-deprived (open circles) and deprived (filled circles) eyes are compared.

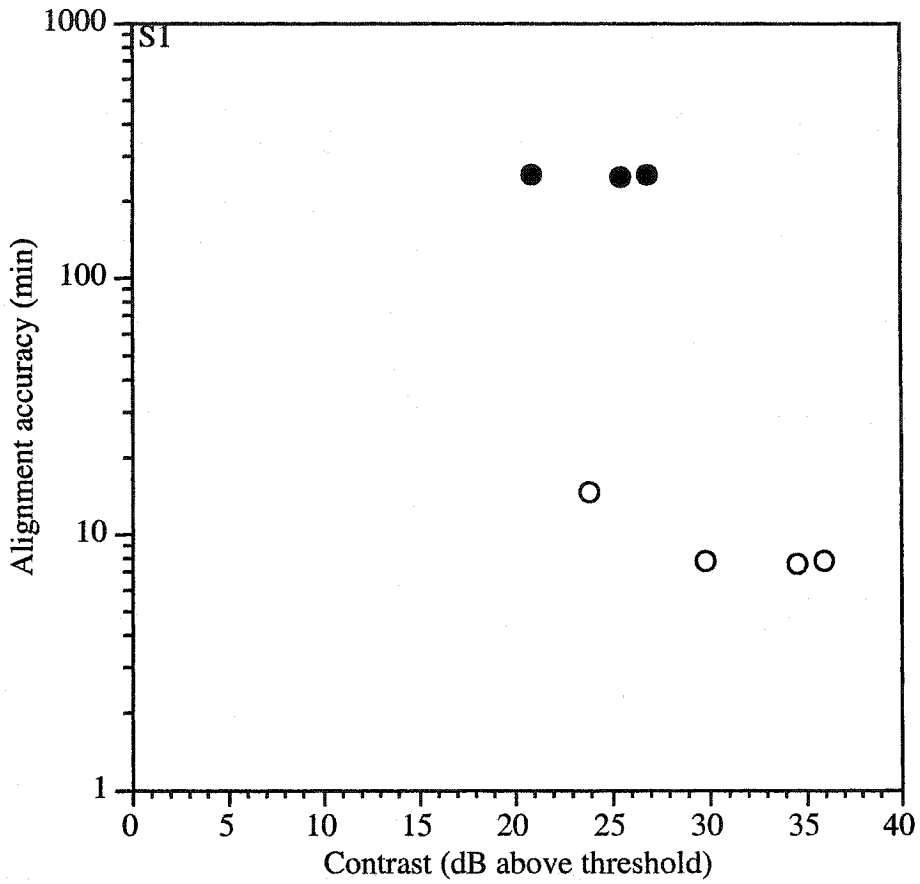


Figure 23. Alignment accuracy of cat S1 as a function of the contrast of the Gaussian blob stimuli plotted with respect to the contrast threshold for the stimuli for each eye. Results for the non-deviated (open circles) and deviated (filled circles) eyes are compared.

Experiment 4. The neural underpinnings of the spatial localization deficits in amblyopic cats

In human amblyopia, the spatial localization deficits are greater for strabismic amblyopes than for anisometropic amblyopes (Hess and Holliday, 1992b). Moreover, in anisometropic amblyopia, the spatial localization deficits can be predicted simply on the basis of the reduced visibility of the stimuli. The larger spatial localization deficits of strabismic amblyopes cannot be attributed to the contrast sensitivity loss (Levi and Klein, 1982b; Hess and Holliday, 1992b). For anisometropic amblyopes, their spatial localization deficits vanish at high contrasts while for strabismic amblyopes, this manipulation has little influence on their performance. Attempts to explain the larger spatial localization deficits in strabismic amblyopia have concentrated mainly upon two hypotheses, namely neural undersampling and uncalibrated neural disarray (both hypotheses are schematically illustrated in Figure 24). According to the neural undersampling hypothesis, too few cells are present in the visual cortex of human amblyopes in order to provide an accurate representation of all points in the visual field. On the other hand, the uncalibrated neural disarray hypothesis argues that the lack of spatial accuracy is a consequence of a disorganized topological mapping somewhere within the amblyopic visual system, whereby projections from a retinotopically orderly map at one level in the visual pathway to the next level become functionally disorganized and mislabeled (i.e. uncalibrated). Other explanations, including a combination of undersampling and uncalibrated neural disarray, have been offered (Kiorpes and McKee, 1999) and explored in ingenious psychophysical experiments. Experiments on human amblyopes that attempt to identify the most likely explanation rest upon certain assumptions that may be controversial and in the end lead to conclusions that cannot be verified at an anatomical or physiological level. One of the many appeals of animal models of amblyopia is the potential to replicate the results of psychophysical tests of amblyopic humans in visually deprived kittens thereby providing the opportunity to verify the conclusions with regard to the anatomical and physiological deficits.

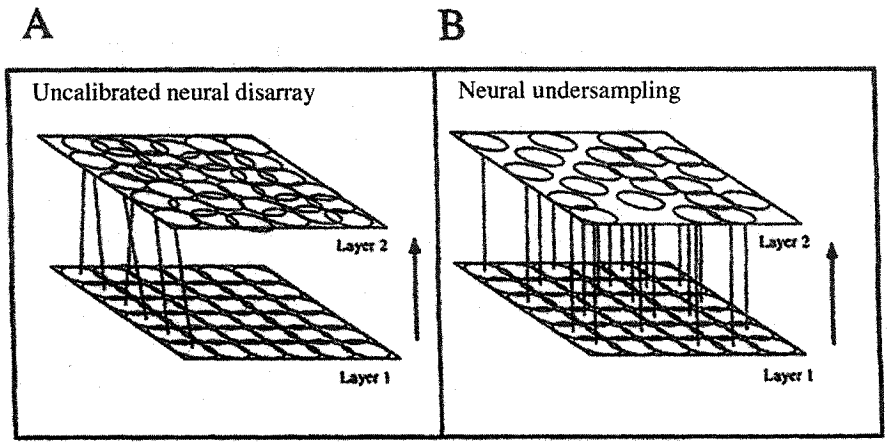


Figure 24. A schematic representation of two theories concerning the neural basis of the spatial localization deficits. A. According the uncalibrated neural disarray theory, the lack of spatial accuracy is a direct consequence of a disrupted (jittered or scrambled) topological mapping somewhere within the amblyopic visual system. A given cell's responses from layer 1 are mislabeled (i.e. coming from the wrong position in space), thereby resulting in an associated positional distortion in the cells from layer 2. B. According to the neural undersampling theory, the deficits in spatial localization are caused by cellular loss in the visual cortex (and other visual cortical areas) of human amblyopes. Too few cells are present in the visual cortex of human amblyopes in order to provide an accurate representation of all points in the visual field. As noted by Hess and Field (1993), stimuli that fall between the gaps can produce both errors in position and contrast.

In an elegant set of experiments, Hess and Field (1993, 1994) devised tests that attempt to distinguish between neural undersampling and uncalibrated neural disarray as an explanation for the poor vision in amblyopia as well as in the peripheral visual field of normal subjects. The test of neural undersampling rests on the well-known concept of univariance that has been a cornerstone of our understanding of colour matching.

As a general concept, the principle of univariance states that the response of a cell is one-dimensional, such that certain values of a wide variety of stimuli to which the cell is responsive can produce an equivalent level of neural excitation. In the cases of two variables such as position and stimulus contrast, changes in position from the optimum value can produce equivalent responses to a change of contrast. In other words, because of univariance, changes in stimulus position and contrast will covary. This covariance also applies to the situation where information about a given variable is determined from the response of a large population of cells. Moreover, the addition of any noise in the response of cells will effectively increase the confusion of both position and contrast. On the basis of these ideas, Hess and Field (1993, 1994) and Field and Hess (1996) developed an argument that with neural undersampling, positional inaccuracy, as reflected by deficits in alignment accuracy, would be accompanied by errors of contrast discrimination of similar magnitude. By contrast, the uncalibrated neural disarray hypothesis does not predict any link between alignment accuracy errors and contrast discrimination errors.

In order to test this hypothesis in human amblyopia, Hess and Field (1994) compared the ratio of spatial localization errors between the normal and the fellow amblyopic eye of strabismic amblyopes with the ratio of contrast discrimination thresholds between the two eyes of the same subjects. They found that for strabismic amblyopes, the spatial localization deficits were not associated with deficits in contrast discrimination of similar magnitude. The contrast deficits were in fact considerably smaller than the spatial localization deficits, a result incompatible with neural undersampling as the underlying cause of the alignment inaccuracy.

Although this conclusion, as well as the argument for a correlated positional and contrast discrimination deficits has not received universal acceptance (e.g. Levi and Klein, 1996), the ability to apply the same psychophysical tests on visually deprived

animals as used on human amblyopes provides a potential way to assess the ability of these tests to identify the nature of the neural losses. For example, monocularly deprived kittens are known to experience a loss of connections between the deprived eye and the visual cortex, so that it might be anticipated that the psychophysical tests used by Hess and Field (1993, 1994) would produce results consistent with neural undersampling on such animals.

The experiments conducted by Hess and Field (1993, 1994) employed Gabor patches. In order to use the same tests on the animals, it was first necessary to check whether alignment accuracy thresholds of cats obtained with such stimuli produced equivalent results as those obtained by use of Gaussian blobs. The following preliminary experiments (4A and 4B) represent control experiments that examine the performance of cats with Gabor patches, while Experiment 4C describe experiments that compare the alignment accuracy deficits with the deficits of contrast discrimination, using tests modeled closely on those employed on human amblyopes.

Experiment 4A. The influence of the carrier spatial frequency and its orientation on alignment accuracy

On the basis of three observations, it was shown that alignment accuracy of human subjects is determined by the size (spread) of the Gaussian envelope of Gabor patches (Toet and Koenderink, 1988: Hess and Holliday, 1992a, 1992b). First, alignment accuracy with Gabor patches was essentially invariant with the carrier spatial frequency (Toet and Koenderink, 1988; Kooi, De Valois and Switkes, 1991; Hess and Holiday, 1992a). Second, thresholds were unchanged when the central Gabor patch was rotated 90° with respect to the two flanking stimuli (Kooi et al., 1991; Hess and Holliday, 1992a). Finally, alignment accuracy thresholds changed with the overall size of the Gabor patches in a proportional manner (Toet and Koenderink, 1988; Hess and Holliday, 1992a, 1992b). It thus appears that the carrier spatial frequency of Gabor patches has no influence on spatial localization. Two experiments were conducted in order to investigate if alignment accuracy in cats, like humans, is determined by the spatial scale of the stimuli and not the carrier spatial frequency. In the first experiment (Experiment 4A1), alignment accuracy was investigated where the carrier grating of the middle Gabor patch was horizontal (rotated 90°) while that of the two outer reference Gabor patches

was vertical (Figure 25), while in the second experiment (Experiment 4A2), alignment accuracy was investigated with Gabor patches of various spatial frequencies (Figure 26).

Methods

For both experiments, the normal animal (cat N2) served as subject. The subject was first tested on Experiment 4A1 then on Experiment 4A2. In Experiment 4A1, the outer Gabor patches were vertical but the middle Gabor patch was horizontal, while in Experiment 4A2, all the Gabor patches were vertical. The testing procedure for both experiments was essentially identical to that of Experiment 2 with the exception that Gabor patches were used rather than Gaussian blobs. Binocular measurements of alignment accuracy were made using three Gabor patch sizes (11.4, 22.9 and 45.8 min) with spatial frequencies of 1, 2 or 4.2 c/deg. The Michelson contrast of the stimuli was set at 0.72. For both experiments, the order of presentation of the stimuli was random. Between four and six alignment accuracy thresholds were measured for each stimulus.

Results

Figure 27 displays the alignment accuracy thresholds for the Gabor patches as a function of the carrier spatial frequency for both experiments (Experiment 4A1, open circles; Experiment 4A2, filled triangles). The results showed that irrespective of the carrier spatial frequency or its orientation, the alignment accuracy thresholds increased with spatial scale. This is revealed by the vertical shift of the data for the different stimulus sizes. More importantly, for any one stimulus size, thresholds were virtually identical across carrier spatial frequency and relative orientation. Interestingly, the alignment accuracy thresholds obtained for the two smallest Gabor patch sizes (11.4 and 22.9 min) were slightly smaller when the middle Gabor patches were rotated 90° (Experiment 4A1) than that obtained with the experiment where all the Gabor patches were vertical (Experiment 4A2). Indeed, the alignment accuracy thresholds for Experiment 4A1 were 6.59 and 8.08 min of arc, while that for Experiment 4A2 were respectively 7.56 and 10.02 min of arc. These small differences in alignment accuracy thresholds may be attributable to the fact that different experimenters tested this animal on the two tasks. With the largest Gabor patch (45.8 min), the alignment accuracy thresholds were identical for both tasks (27.22 min of arc).

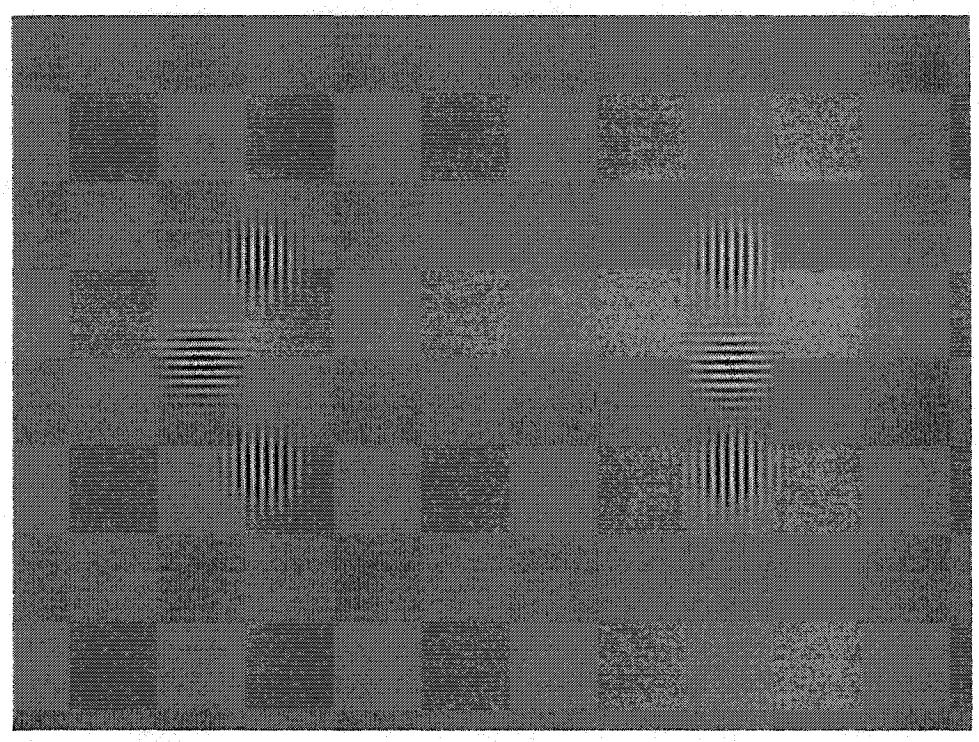


Figure 25. Illustration of the stimuli used in the alignment accuracy task with the middle Gabor patch rotated 90° (Experiment 4A1). The task of cat N2 was to jump to the side with the misaligned set of Gabor patches (in this case, the left).

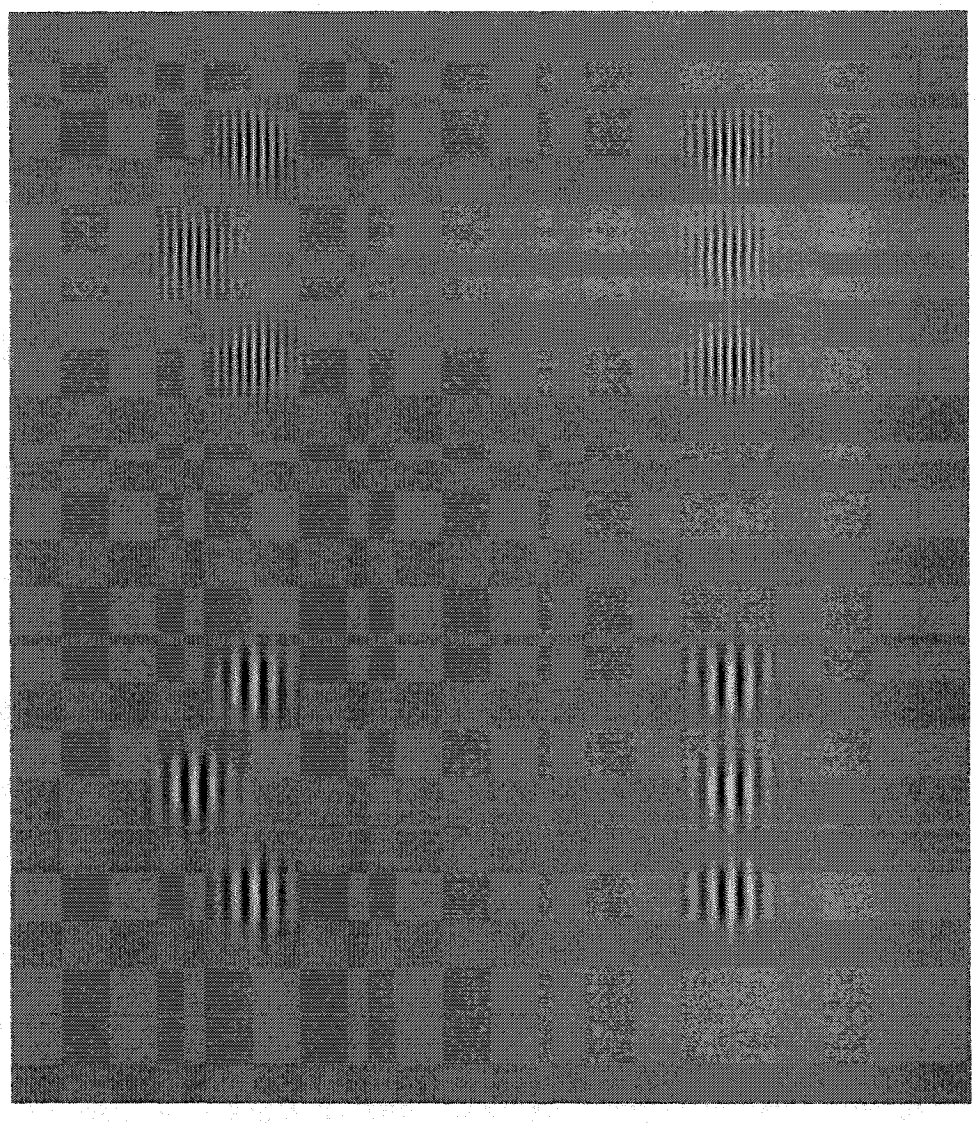


Figure 26: Illustration of two sets of stimuli used in the alignment accuracy task with Gabor patches presented with various carrier spatial frequencies (Experiment 4A2). The task of cat N2 was to jump to the side with the misaligned set of Gabor patches (in this case, the left).

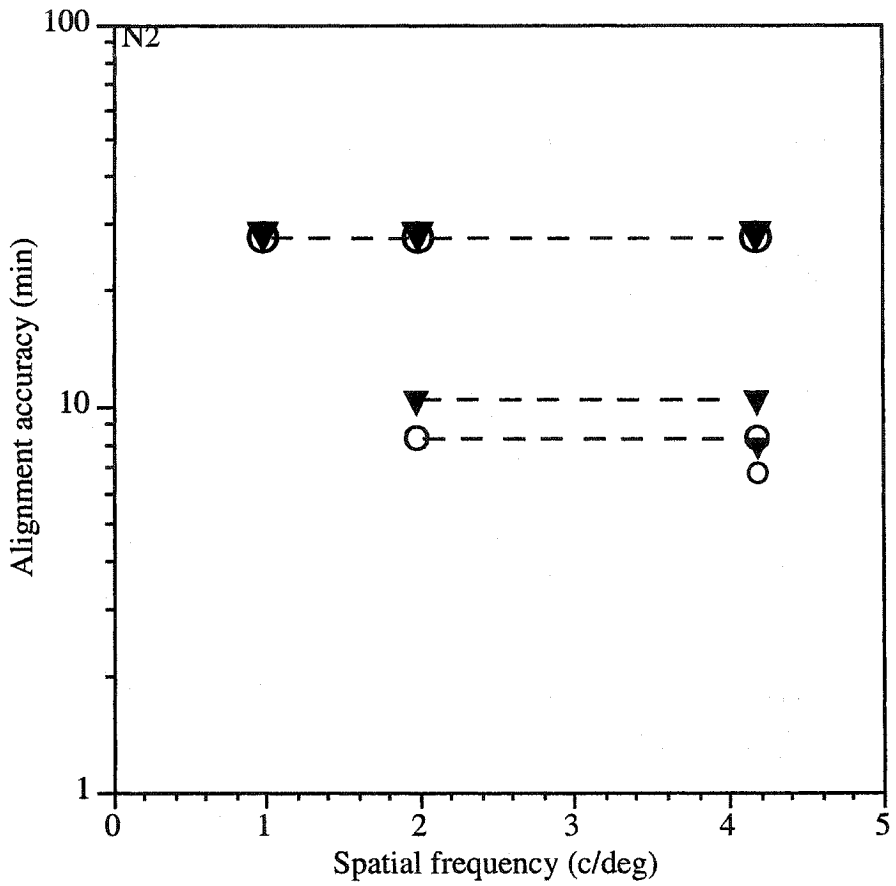


Figure 27. Comparison of the results of the normal cat N2 on the alignment accuracy task with the middle Gabor patches rotated 90° (Experiment 4A1, open circles) and the alignment accuracy task with Gabor patches of various spatial frequencies (Experiment 4A2, filled triangles). Different sizes of the symbols are used to represent the different stimulus sizes that were employed (small: 11.4 min; medium: 22.9 min; large: 45.8 min).

Discussion

The results obtained in both experiments were in agreement with human data (Toet and Koenderink, 1988; Kooi et al., 1991; Hess and Holliday, 1992a) that indicated that alignment accuracy is determined by the size of the Gaussian envelope of the Gabor patches. Similar to human data, the results obtained with a cat showed that alignment accuracy thresholds increased with Gabor patch size in a linear fashion and were independent of the carrier spatial frequency and its orientation for a fixed Gabor patch size. Additionally, human data obtained with Gaussian blobs (Toet et al., 1987) and the results obtained in Experiment 2 of the current study, reinforce the notion that it is the size of the Gaussian envelope that determines spatial localization. Taken together, these results suggest that both human and cats subjects do not use the carrier spatial frequency to align the stimuli.

Experiment 4B.The influence of stimulus separation on alignment accuracy

Hess and colleagues investigated the effects of Gabor patch separation on spatial localization in normal humans (Hess and Hayes, 1993, 1994) and in strabismic amblyopes (Demanins and Hess, 1996). The results showed that in the normal population, there was a shallow relationship between alignment accuracy and stimulus separation. By contrast, for most of the strabismic amblyopes (7 out of 9), the alignment accuracy thresholds of the amblyopic eye increased with stimulus separation. In the original experiment on alignment accuracy with Gabor patches, Hess and Holliday (1992b) used an inter-Gabor separation of 10 standard deviations. Due to the limits imposed by the dimensions of the display monitor, stimulus separations of 5 standard deviations were used to investigate alignment accuracy in this study. Nevertheless, even with smaller stimulus separation, cats performed like humans in the sense that alignment accuracy thresholds increased with the spatial scale of the stimuli. That being said, it is still of interest to establish whether alignment accuracy thresholds would have improved with use of a wider separation. This experiment, which was of a pilot nature, investigated the effects of stimulus separation on alignment accuracy in cats using Gaussian blobs.

Methods

The subjects for this experiment were one of the short-term monocularly deprived animals (cat SMD1) and the two strabismic animals (cats S1 and S2). The testing procedure for Experiment 4B was essentially identical to that of Experiment 2, with the exception that the separation between the stimuli varied (Figure 28). The Gaussian blobs were separated from each other by 5, 10, 15, 20 or 25 standard deviations and Michelson contrast was set at 68.5%. Tests of binocular alignment accuracy were made with only one Gaussian blob size (11.4 min). Each separation was tested individually, starting with the smallest separation and ending with the largest one. Six alignment thresholds were gathered for each stimulus.

Additionally, tests of binocular alignment accuracy with smaller stimulus separation were performed on cat LMD3 using one Gaussian blob size of (11.4 min). These stimuli were separated from each other by 2, 3, 4 or 5 standard deviations and the Michelson contrast was set at 0.50. Alignment accuracy thresholds were measured for each separation in decreasing order of separation. Three alignment accuracy thresholds were gathered for each stimulus.

Results

Figure 29 displays the alignment accuracy thresholds plotted against the size of the separation between the Gaussian blobs for separations equal to or larger than 5 standard deviations. A common feature of all the results was the fact that the alignment accuracy thresholds increased with stimulus separation. For cat SMD1, the alignment accuracy thresholds increased by a factor of 13 (from 6.13 to 80.20 min of arc) over the range of separations examined. The increase in alignment accuracy thresholds for the two strabismic cats (S1 and S2) was of comparable magnitude.

In contrast, the pattern of results obtained with stimulus separations of 5 standard deviations or less (data not shown) was different from that obtained with larger stimulus separations. Indeed, for all stimulus separations below 5 standard deviations, the alignment accuracy thresholds were identical for each stimulus separation examined (3.61 min of arc).

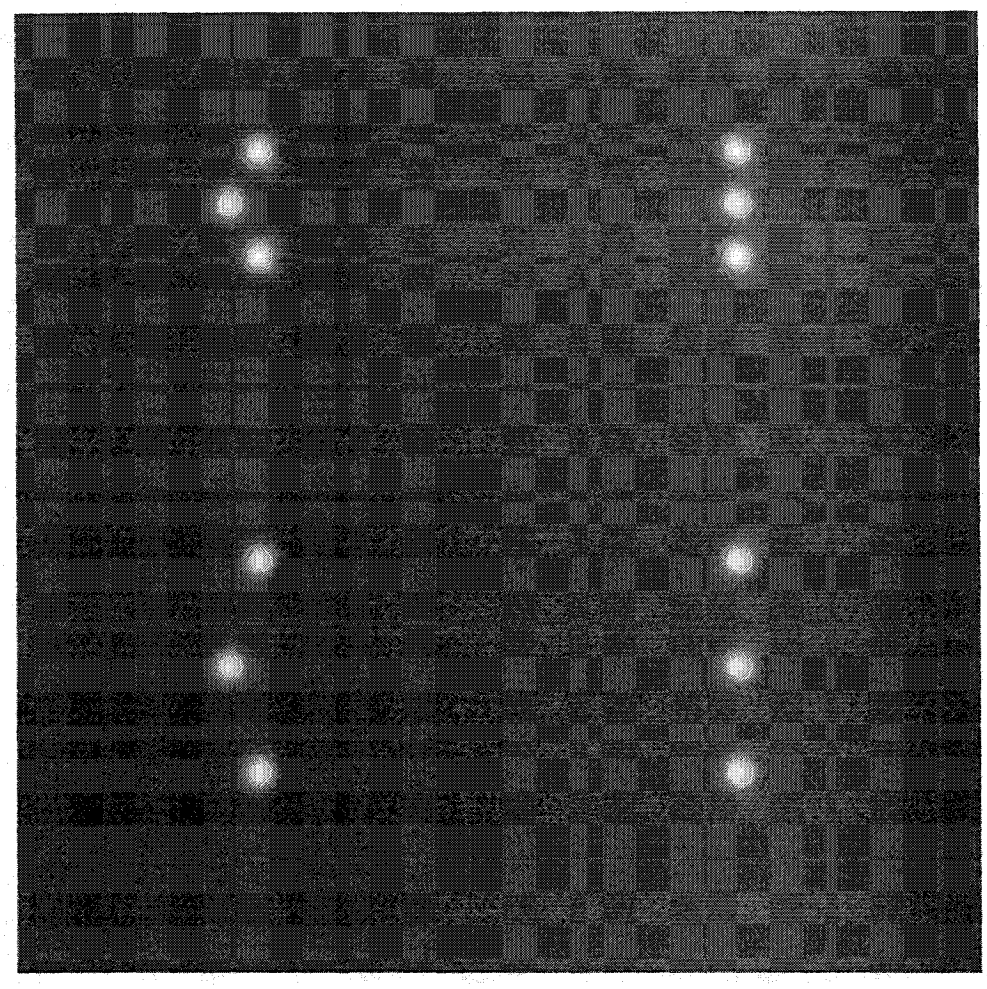


Figure 28. Illustration of some of the Gaussian blobs used in the alignment accuracy task as a function of stimulus separation (Experiment 4B). Stimulus separation of 5 (top) and 10 (bottom) standard deviations are shown. The task of the animals was to jump to the side with the misaligned set of Gaussian blobs (in this case, the left).

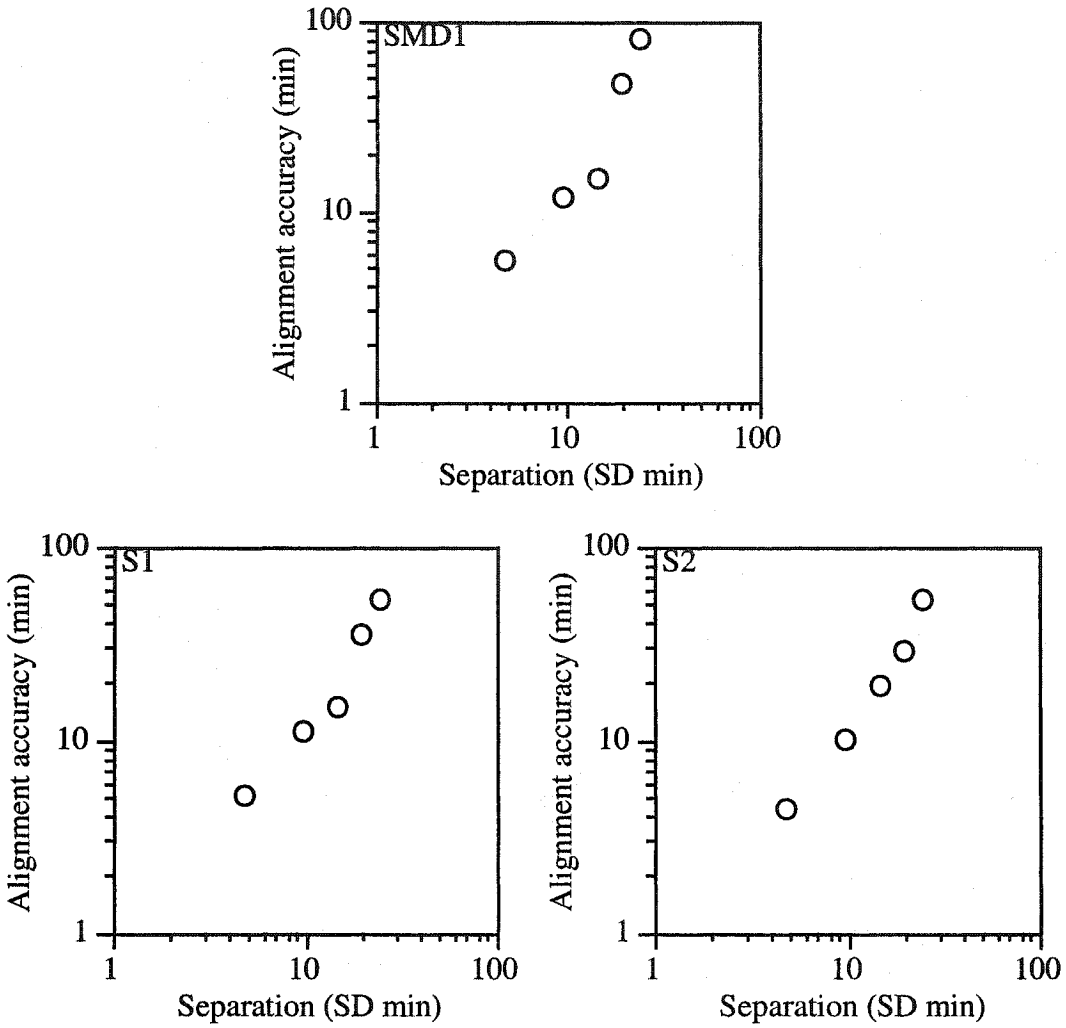


Figure 29. Alignment accuracy of the experimental animals (SMD1, S1 and S2) as a function of stimulus separation with binocular viewing (Experiment 4B).

Discussion

For stimulus separations of 5 standard deviations or less, the alignment accuracy was constant. However, for stimulus separations larger than 5 standard deviations, the alignment accuracy thresholds increased with separation in a monotonic manner. In normal humans, Hess and Hayes (1993, 1994) reported that alignment accuracy thresholds were essentially constant for all separations. When strabismic amblyopes were tested, Demanins and Hess (1996) reported that the spatial localization deficits increased with stimulus separation. Although the scope of the experiment conducted on cats was limited in that the effects of stimulus separation on the alignment accuracy of the deprived (or deviated) eye of the experimental animals was not tested, it appeared that the non-deprived (or non-deviated) of the experimental animals behaved like the amblyopic eye of humans. This result may be due to the fact that the fellow normal eye of strabismic animals, including cat SMD1 with its naturally occurring strabismus, may not be normal. Taken together, these results suggest that the separation of the stimuli can have some influence in alignment accuracy but only after a specified separation is reached, at which point the alignment accuracy thresholds increases with separation.

Experiment 4C. Are the spatial localization deficits in amblyopic cats due to neural undersampling or uncalibrated neural disarray?

The following experiment was very similar to the study of Hess and Field (1994) on human strabismic amblyopes that tested the hypothesis of neural undersampling as an explanation of the deficits of spatial localization. Whereas human subjects were required simultaneously to make dual judgments of alignment and relative contrast, the measurements of alignment accuracy and contrast discrimination in cats were conducted in separate testing sessions (respectively, Experiments 4C1 and 4C2).

Methods

This experiment was performed on three of the visually deprived animals, namely two long-term monocularly deprived animals (cats LMD2 and LMD3) and one strabismic animal (cat S1). For Experiment 4C1, alignment accuracy was measured for both eyes for the one Gabor patch size (22.9 min) for which measurements could be obtained for both eyes (Figure 30). The orientation of the spatial frequency (0.63 c/deg) of the Gabor

patches was vertical and the Michelson contrast was set at 50%. With the exception of cat LMD3, the alignment accuracy thresholds for each eye were measured on the same day, beginning with the non-deprived (or non-deviated) eye for five consecutive days. For cat LMD3, the alignment accuracy thresholds of each eye were measured on separate days alternating between the non-deprived and its deprived eye. As with the other two experimental animals, five alignment accuracy thresholds were obtained for each eye.

Once these alignment accuracy thresholds were gathered, the animals were then tested on their ability to make contrast discriminations (Experiment 4C2). For this experiment, the same stimuli were used, but all the Gabor patches were aligned. The task of the animals was to jump toward the side where the contrast of the middle Gabor patches was lower or higher than that of the two outer reference Gabor patches (Figure 31). Contrast discrimination thresholds were obtained for contrast increments and decrements beginning with contrast increments. Five contrast thresholds were gathered for both contrast increments and decrements. Because the results for the two were very close, the results were averaged together for calculation of the ratios between the thresholds for non-deprived (or non-deviated) eye and the deprived (or deviated) eye of the experimental animals.

Results

The alignment accuracy and contrast discrimination thresholds of all the experimental animals (LMD2, LMD3 and S1), as well as the ratio between the non-deprived (or non-deviated) eye and the deprived (or deviated) eye are presented respectively in Tables 3 and 4.

The differences between the alignment accuracy of the two eyes of each animal were substantial and very close to the values obtained with Gaussian blobs of the same size (Experiment 2), that is, the ratios of the performance between the two eyes ranged from 12 to 36. By contrast, the ratios for the contrast discrimination thresholds of the two eyes were substantially smaller to the extent that they did not exceed a factor of 2 for any animal. The substantial differences between the performances of the two eyes on the two tasks are made more evident in the graph shown in Figure 32. If the performance of the two eyes on the alignment accuracy and contrast discrimination tasks were identical, the

data would follow a line having a slope of 1. All the data fell well below this line reflecting the fact that performance on the two tasks was very different.

Discussion

The results clearly show that amblyopic cats, like human strabismic amblyopes (Hess and Field, 1994), exhibit far larger deficits in alignment accuracy than for contrast discrimination, indicating that these two deficits were not correlated, as would be expected on the basis of neural undersampling. In this sense, the results for both monocularly deprived and strabismic cats failed to support the proposal that the positional uncertainty is a result of neural undersampling. This conclusion may seem somewhat surprising in view of the frequently documented loss of connections with the deprived eye of animals monocularly deprived for periods of time as extensive as those experienced by cats LMD2 and LMD3. Fortunately, there exists data on the likely shifts of ocular dominance among cells in area 17 of cat LMD2. Cat 60B, reported by Mitchell et al. (1977a) was monocularly deprived for a similar period and allowed a period of binocular recovery afterward sufficient for the vision of the deprived eye to recover to a stable level. Electrophysiological recordings made at that time revealed that only 14 of 75 cells (19%) could be classified as dominated by the deprived eye. The failure to find a close link between the deficits in alignment accuracy and contrast discrimination can be explained in at least two ways. First, the assumption of univariance may not be true in the form provided by Hess and Field (1993, 1994). And second, it may be that a loss of connections in the visual cortex may masquerade as, or be accompanied by, neural disarray. Finally, the large differences between the interocular positional and contrast discrimination ratios could also be interpreted as evidence that the two tasks tap independent mechanisms

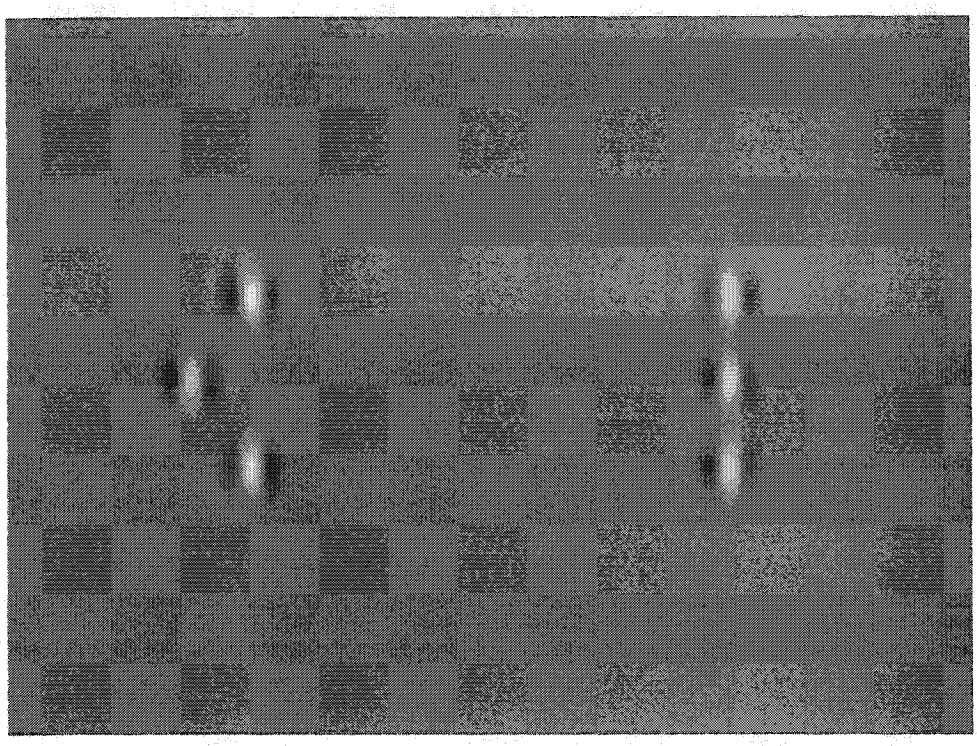


Figure 30. Illustration of the stimuli used in the alignment accuracy task with Gabor patches (Experiment 4C1). The task of the animals was to jump to the side with the misaligned set of Gabor patches (in this case, the left).

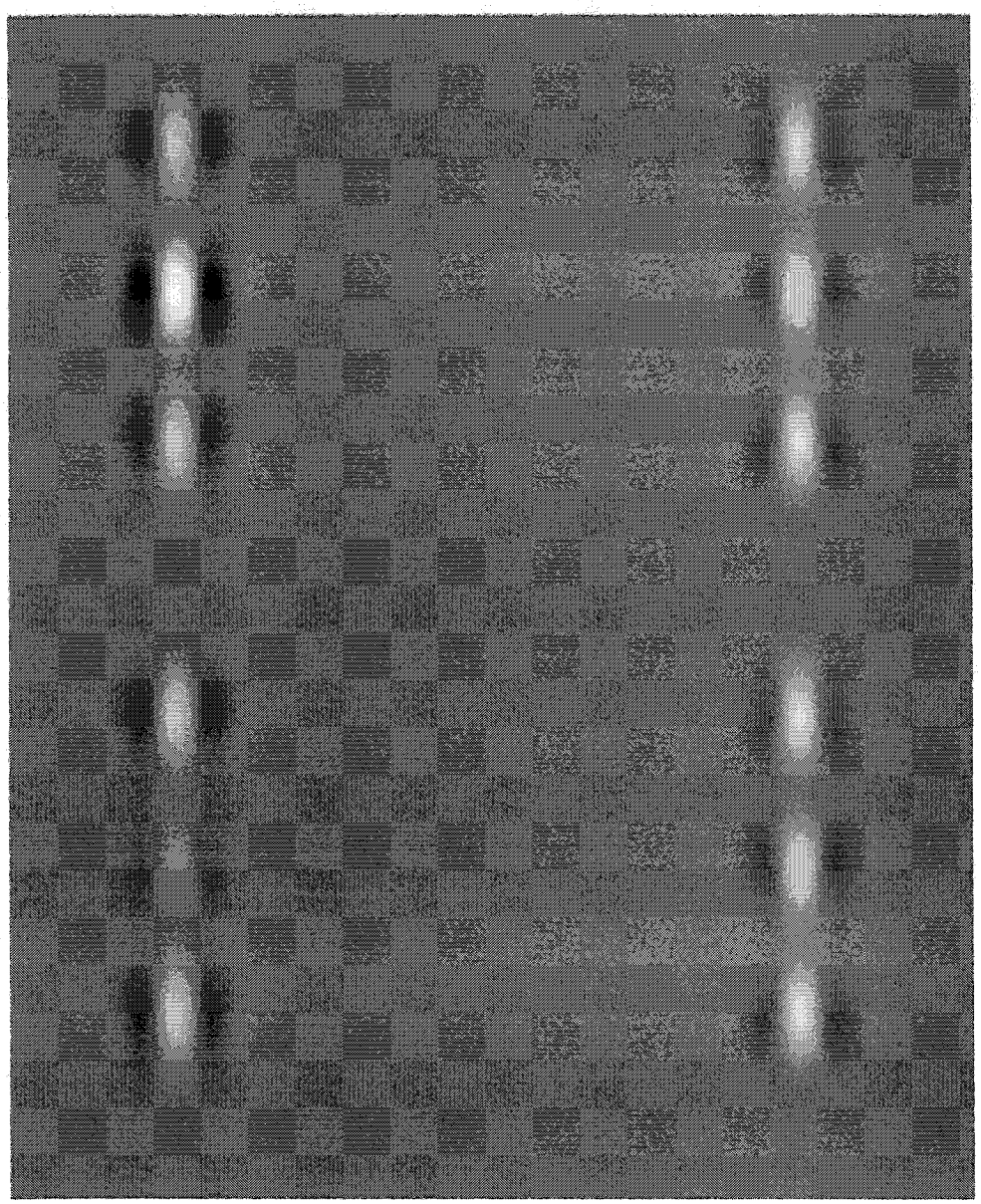


Figure 31. Illustration of the stimuli used to investigate the contrast deficits with the alignment accuracy task with Gabor patches (Experiment 4C2). In the top left side of the illustration, the middle Gabor patch has a high contrast, while in the bottom left of the illustration, the middle Gabor patch has a lower contrast. Because of printing artifacts, these stimuli are not exactly as seen by the animals.

Animal	Alignment accuracy of the non-deprived or the non-deviated eye (min of arc)	Alignment accuracy of the deprived or the deviated eye (min of arc)	Interocular ratio
LMD2	3.61	41.71	11.56
LMD3	7.28	85.20	11.71
S1	7.28	262.87	36.12

Table 3: The ratio of the positional errors between the non-deprived (or non-deviated) eye and the deprived (or deviated) eye of the experimental animals.

Animal	Increment contrast ratio	Decrement contrast ratio	Averaged ratio
LMD2	1.66	1.51	1.59
LMD3	1.68	1.58	1.63
S1	2.11	1.68	1.90

Table 4: The ratio of contrast discrimination thresholds between the non-deprived (or non-deviated) eye and the deprived (or deviated) eye of the experimental animals.

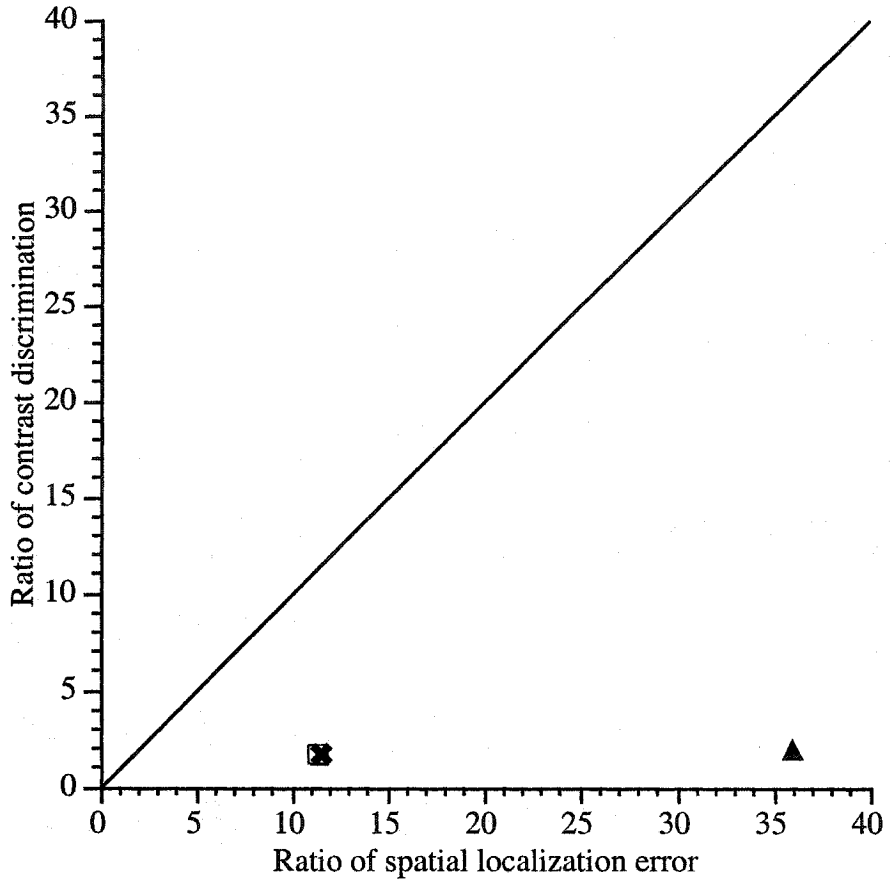


Figure 32. The ratio of the positional errors between the two eyes of the experimental animals is compared to the ratio of the contrast discrimination thresholds. Different symbols are used to depict the results of the three subjects: LMD2 (open square), LMD3 (black X) and S1 (filled triangle). The errors in alignment accuracy are substantially greater than those of contrast discrimination. The line has a slope of 1.0 and indicates the situation where the deficits on the two measures are the same.

Chapter 4. GENERAL DISCUSSION

It is generally agreed that amblyopia is a heterogeneous condition with a number of identifiable types that are categorized with respect to an associated optical or oculomotor abnormality that is thought to have played a causal role by disrupting coordinated binocular visual input. The two most common types are anisometropic and strabismic amblyopia that are associated with respectively, unequal refractive states between the two eyes and strabismus. For this study, monocular deprivation by eyelid suture and surgically induced strabismus were used as animal models of two forms of human amblyopia, namely deprivation and strabismic amblyopia. They are the two most commonly studied animal models of human amblyopia and a considerable amount of information has been generated from study of these two models concerning the neural basis of amblyopia. Although there are no studies on alignment accuracy in deprivation amblyopia, numerous studies have revealed fundamental differences in the underlying causes of the spatial localizations deficits between anisometropic and strabismic amblyopes. With respect to this study, the germane difference between these two types of amblyopia is that for the former, the loss in alignment accuracy can be fully explained by the losses in contrast sensitivity, while for the latter, the deficits in alignment accuracy and contrast sensitivity appear to be uncorrelated so that they represent two independent deficits. The close similarity between the spatial localization deficits observed in the visually deprived animals of this study and those of human amblyopes strengthens even more the use of cats as a valuable animal model of human amblyopia and the use of monocular deprivation and surgically induced strabismus as useful techniques to investigate the neural basis of human amblyopia.

Grating acuity

Despite the modification to the surgical procedure used for monocular eyelid closure that used two occlusion layers as opposed to one, and the changes to the behavioural testing of grating acuity from a detection to a discrimination task, the speed and the extent of the recovery of vision of the deprived eye of the visually deprived animals of this study were very similar to previous data from this laboratory (Mitchell et al., 1977a; Giffin and Mitchell, 1978; Mitchell et al., 1984c; Mitchell, 1988). As in past

studies, the speed of recovery of the vision through the deprived eye was negatively correlated with the length of the monocular deprivation period. For cats LMD2 and LMD3, the period of blindness increased with the length of deprivation. Moreover, the duration of blindness was also influenced by the age of onset of monocular deprivation. For the short-term monocularly deprived animals, the period of blindness lasted for only hours, as opposed to days or weeks. Additionally, with increasing length of monocular deprivation there was a corresponding increase in the size of the final acuity deficits. On the other hand, the deficit in grating acuity decreased with delay in the onset of the period of deprivation. At one extreme, cat SMD1, that was deprived for 6 days at 5 weeks, exhibited a substantial final deficit in the acuity of the deprived eye (0.68 octaves) while at the other extreme, cat SMD3, that was deprived for the same period beginning at 90 days of age, eventually recovered near-normal visual acuity in its deprived eye (7.53 c/deg). But it must be said that the final grating acuity value obtained for cat SMD1 was confounded with its naturally occurring strabismus. All these findings were to be expected on the basis of the known profile of the sensitive period for monocular deprivation in the visual cortex (Olson and Freeman, 1980). Finally, of all the experimental animals, the strabismic animals had the largest deficits in grating acuity.

As summarized in Table 1, the deficits in grating acuity of the deprived (or deviated) eye were relatively small when expressed in terms of octaves. Indeed, the deficits in octaves ranged from 0.16 to 1.40. With only two exceptions (cats LMD3 and S1), all the grating acuity deficits were less than one octave (a factor of two). As emphasized below, the deficits in grating acuity of the monocularly deprived animals were independent of the deficits in alignment accuracy, a result that is in remarkable agreement with data from human amblyopes (Levi and Klein, 1982a, 1982b, 1983, 1985).

Alignment accuracy with Gaussian blobs

As mentioned in the Introduction, one of the goals of this study was to apply to visually deprived cats the same stimuli and psychophysical probes employed in the studies of Hess and colleagues (Hess and Holliday, 1992b; Hess and Field, 1994, Demanins and Hess, 1996) on human amblyopes, in an attempt to better understand the neural mechanisms responsible for human amblyopia.

The stimuli employed in this study differed in two ways from those employed by Hess and colleagues in human amblyopes. First, Gaussian blobs were employed as opposed to Gabor patches on the basis of the finding that for humans, alignment accuracy was in fact determined by the dimension of the Gaussian envelope. Second, the stimuli were separated by 5 standard deviations as opposed to 10, a difference that was dictated by the dimensions of the display monitor at the minimum observation distance that could be used. A pilot study examined the effects of stimulus separation on alignment accuracy in order to assess whether the thresholds would have been any better if the stimuli had been separated by 10 standard deviations as they were for the prior human studies. The data clearly show (Figure 29) that alignment accuracy worsens as the stimuli are separated by more than 5 standard deviations, indicating that performance may have been optimal for the animals of this study.

Previously, four studies have investigated the effects of stimulus separation on humans using either Gaussian blobs (Toet et al., 1987) or Gabor patches (Hess and Hayes, 1993, 1994; Demanins and Hess, 1996). For normal humans, the results were similar irrespective of the type of stimulus use: the alignment accuracy thresholds were independent of stimulus separation (Toet et al., 1987, Hess and Hayes, 1993, 1994). However, the results were mixed for strabismic amblyopes (Demanins and Hess, 1996). For the majority of the strabismic amblyopes (7 out of 9), alignment accuracy thresholds increased with larger separations, while for the two remaining subjects, the alignment accuracy thresholds were constant at all separations. The results obtained with the animals of this study were limited by the fact that the deprived (or deviated) eyes of the visually deprived animals were not tested. Many other researchers have investigated the effects of stimulus separation on spatial localization in Vernier or bisection tasks using various stimuli, including dots (Sullivan, Oatley and Sutherland, 1972; Beck and Schwartz, 1979; Beck and Halloran, 1985; Klein and Levi, 1987; Yap, Levi and Klein, 1987), lines (Squillace and Bien, 1970; Westheimer, 1984; Levi and Klein, 1990a), bars (Squillace and Bien, 1970; Burbeck, 1987), gratings (Whitaker and MacVeigh, 1991), horizontal Gabor bars (Levi and Klein, 1992b) arrows (Squillace and Bien, 1970) and abutting sinusoidal gratings (Whitaker, 1993). All of these studies, except three (Burbeck, 1987; Levi and Klein, 1990a; Whitaker, 1993) reported an almost linear

increase in acuity with stimulus separation. Burbeck (1987) showed that the alignment accuracy thresholds using bars rose sharply at small separations but quickly reached asymptotic levels. On the other hand, Levi and Klein (1990a) showed that alignment accuracy thresholds gradually increased with separations up to two degrees, after which the alignment accuracy thresholds were constant. Finally, Whitaker (1993) showed that when the separation was small relative to the spatial frequency, the offset thresholds were a constant fraction (approximately 1%) of the period, but once the separation exceeded the period, the thresholds increased rapidly. Taken together, it would be tempting to conclude that with broadband stimuli, alignment accuracy thresholds increase with stimulus separation, while for narrowband stimuli (such as Gabor patches), alignment accuracy is constant irrespective of stimulus separation. Similar results have been reported for studies on the effects of stimulus separation on the Vernier acuity of the amblyopic eye of human amblyopes. Levi and Klein (1982b) found that Vernier thresholds doubled with each 2.5-fold increase in separation, while Levi et al. (1987) found that the bisection thresholds were more or less a constant fraction of the separation.

The results obtained with amblyopic cats in the current study followed the same pattern of results found in human amblyopes. One of the major findings of the current study was that alignment accuracy scaled with stimulus size. Indeed, in both normal animals and normal humans (Toet et al., 1987; Toet and Koenderink, 1988; Hess and Holliday, 1992a; Hess and Hayes, 1994), alignment accuracy increased proportionally with the size of the stimuli. Moreover, the same relationship between alignment accuracy and spatial scale was true for the amblyopic eye of both cats and humans (Hess and Holliday, 1992b; Demanins and Hess, 1996). It thus appears that in both cats and human, the spatial localization deficits are not fixed in size but instead appear to increase in size with spatial scale in a proportional manner. In other words, the neural representation of space in both visually deprived cats and amblyopic humans appears to be disrupted equally at all spatial scales. Since positional acuity tasks test the ability to detect fine details, one would expect that both human amblyopes and visually deprived animals would exhibit deficits with small stimuli but not large ones. To the contrary, previous measurements made with human amblyopia together with the data of the current study obtained from visually deprived animals indicate that the alignment accuracy deficits

were independent of stimulus sizes. These results provide very strong support for the claim that visually deprived cats provide a valid animal model for human amblyopia, a conclusion that has been challenged in recent years (Kiorpes and McKee, 1999.

Despite the qualitative similarities between the results of amblyopic and human amblyopes, there were some quantitative differences. For example, although there was a comparable proportional relationship between alignment accuracy and stimulus size, the alignment thresholds of the visually deprived animals were much larger than those found in human amblyopes (Hess and Holliday, 1992b). The interocular differences in alignment accuracy of the visually deprived animals exceeded between 6- and 30-fold for all but one animal (cat SMD2). By contrast, the largest deficit in spatial localization for human anisometropic amblyopes was of the order of a factor of 2 (Hess and Holliday, 1992b), while for the strabismic amblyopes, the spatial localization deficits ranged from a factor of 2 to 25 (Hess and Holliday, 1992b; Demanins and Hess, 1996). Although generally larger in magnitude than those observed in human amblyopes, the pattern of the deficits in alignment accuracy followed the same pattern as the deficits in grating acuity. For both tasks, the deficits observed in the long-term monocularly deprived animals were, with the exception of cat SMD1 that developed a strabismus, larger than those found with the short-term monocularly deprived animals. Additionally, the strabismic animals, as well as cat SMD1 with its deprivation-induced strabismus, had the largest alignment accuracy deficits of all the experimental animals. These results parallel the results found in human amblyopia where the deficits in alignment accuracy of strabismic amblyopes were significantly larger than those exhibited by anisometropic amblyopes (Hess and Holliday, 1992b). A plausible explanation for the larger deficits in amblyopic cats as opposed to human amblyopes is that the deprivation conditions for the former were more severe than those experienced by human amblyopes in early postnatal life. Monocular deprivation with double eyelid suture would very likely produce a far greater degree of deprivation than the blur produced by a refractive error, the probable cause of anisometropic amblyopia.

The other major finding of this study was that the spatial localization deficits on the alignment accuracy task were considerably larger than the deficits in grating acuity. In the latter task, there was at most only a 2-fold difference between the grating acuities of the non-deprived (or non-deviated) eye and the deprived (or non-deviated) eye. In contrast, on the alignment accuracy task, the interocular difference between the two eyes was as large as 32-fold. This difference in performance between the two tasks is made more evident in Figure 16. In human amblyopia, Hess and colleagues (Hess and Holliday, 1992b; Hess and Field, 1994, Demanins and Hess, 1996) reported a similar lack of correlation between the deficits in contrast sensitivity and those on alignment accuracy, a finding also found in amblyopic cats. Hess and Holliday (1992b) added that the deficits in contrast sensitivity were a poor predictor of the deficits found in spatial localization.

Taken together, the fact that the deficits in alignment accuracy were so much greater than the grating acuity deficits provide strong support for the assertion that the visual loss of the deprived animals of this study represents a genuine amblyopic defect. The spatial localization deficits found in both amblyopic cats and human amblyopes scaled with stimulus size rather than being of a constant size or limited to just high spatial frequencies. The results reinforce the use of broadband spatial stimuli in order to differentiate contrast sensitivity deficits from spatial localization deficits.

An interesting feature to emerge from the results of short-term monocularly deprived animals was the different pattern of results obtained for SMD1, as compared to the other animals of the group. The deficits of alignment accuracy for this animal were as large as those observed in long-term monocularly deprived animals and were of comparable magnitude to those exhibited by the two strabismic animals. Coincidently, this animal developed an esotropia over a period of several months following termination of a 6 day period of monocular deprivation that ended when the animal was 6 weeks old. On this basis, it could be argued that the strabismus, although it developed comparatively late, affected the development of visual pathways in a dramatic way resulting in alignment accuracy deficits as severe as those seen in cats made strabismic by surgery on an extraocular muscle. The results from this animal suggest further that strabismus, no matter whether it occurred after surgery or after deprivation, has similar effects on the development of the central visual pathways and that these may occur comparatively late

in development. In a sense, the results from this animal more closely resemble the data from the animals rendered strabismic by surgery than even the long-term monocularly deprived cats. Consequently, it could be argued that this animal potentially represents a separate class of experimental group that could be designated as deprivation-induced strabismus.

Comparison with previous measurements of Vernier acuity

It is of interest to analyze the results on alignment accuracy using the smallest Gaussian blob size (5.7 min) with previous measurements of Vernier acuity of normal cats. Murphy and Mitchell (1991) found that Vernier acuity thresholds measured with grating stimuli varied between 1.2 and 1.3 min of arc in normal animals. In this study, half of the animals tested (cats N2, LMD2, LMD3, SMD3 and S2) had alignment accuracy thresholds with their fellow normal eye close to that range (1.23-1.89 min of arc). Even more remarkable was the fact that one of the experimental animal of this study, cat LMD2, which was monocularly deprived for 8 weeks, had an alignment accuracy threshold (1.23 min of arc), a value almost identical to that of cat C229 (1.22 min of arc) of Murphy and Mitchell (1991) that was monocularly deprived for 6 weeks. Moreover, the Vernier acuity of the latter animals with its deprived eye was 15 times worse than that of its non-deprived eye. Taken together, the results obtained with the deprived eye of the monocularly deprived cats show that for positional acuity tasks, the performance of these animals represent a hypoacuity as opposed to a hyperacuity.

To what extent are the deficits in spatial localization explained by the loss of contrast sensitivity?

Unfortunately, no studies have investigated alignment accuracy in deprivation amblyopes, but Hess and colleagues (Hess and Holliday, 1992b; Hess and Field, 1994; Demanins and Hess, 1996) reported that fundamental differences exist between anisometropic and strabismic amblyopes with respect to the underlying causes of the spatial localization deficits. For the vast majority of anisometropic amblyopes, the loss in contrast sensitivity provides a complete explanation of their spatial localization deficits, while for strabismic amblyopes, their contrast sensitivity deficits appears to be uncorrelated with their spatial localization deficits so that they represent independent deficits.

In the current study, the effects of contrast on alignment accuracy were investigated in three long-term monocularly deprived animals and one strabismic animal. When the perceived contrast was equated for each eye of the visually deprived animals, the results indicated that at low contrast levels, the alignment accuracy was constrained by the reduced contrast sensitivity of the deprived (or deviated) eye, while at higher contrast levels, the performance of the deprived eye became progressively worse than that of the fellow eye even though the effective contrast was equated with respect to threshold. The performance of the strabismic animal was considerably worse than that of the long-term monocularly deprived animals and large differences remained between the two eyes even when the stimulus contrast was equated with respect to the contrast threshold for each eye. Thus, like human strabismic amblyopes, the spatial localization deficits of strabismic cats were not due to their contrast sensitivity deficits (Hess and Holliday, 1992b; Hess and Field, 1994; Demanins and Hess, 1996). In other words, the poor performance of both strabismic cats and strabismic humans is not due to the poor visibility of the stimuli. Concerning the long-term monocularly deprived animals, it is clear from the results obtained in the current study that their spatial localization deficits cannot be fully explained by their contrast sensitivity deficits since for stimuli of high contrast, the former deficits were always substantially larger than those expected on the basis of the stimulus contrast with respect to contrast threshold. In that sense, the findings from monocularly deprived animals differed from that of human anisometropic amblyopes. Taken together, these results suggest that the neural underpinnings of deprivation, anisometropic and strabismic amblyopia are different.

Comparison of alignment accuracy with Gaussian or Gabor stimuli

Two studies (Toet and Koenderink, 1988; Hess and Holliday, 1992a) noted that normal human alignment accuracy with Gabor patches was determined by the overall Gaussian envelope rather than by the spatial frequency of the carrier. This was revealed by both an invariant alignment accuracy thresholds with spatial frequencies (Toet and Koenderink, 1988; Hess and Holliday, 1992a) and even more impressive by the absence of any changes in thresholds when the middle Gabor patch was rotated 90° with respect to the two flanking Gabor patches (Hess and Holliday, 1992a). A similar set of results was observed with the normal cat N2. Thresholds were invariant both with carrier spatial

frequency and with the relative orientation of the central Gabor patch with respect to the two flanking Gabor patches (as illustrated in Figure 27). Moreover, the alignment thresholds also increased proportionally to the size of the Gabor patches, irrespective of the carrier spatial frequency. These results suggests that for both cats and humans the visual system does not encode the relative phase of each of the Gabor patches in order to determine position, but instead performance is limited by the envelope size of the stimuli. This finding was previously reported for humans by other researchers that used Gabor patches with horizontal carrier gratings (Toet and Koenderink, 1988; Kooi et al., 1991; Hess and Holiday, 1992a) in order to investigate alignment accuracy. With these stimuli, it was evident that humans do not use the individual bars of the gratings to determine if the Gabor patches are in alignment. Even when non-narrowband stimuli are employed, as with classic Vernier stimuli with multiple lines, there is general agreement that localization thresholds are independent of spatial frequency (Hess and Holliday, 1992a).

Although the amblyopic eyes of the visually deprived animals were not tested with Gabor stimuli as a function of carrier spatial frequency, it is of interest to mention the results of tests of Vernier acuity of human amblyopes with gratings of various spatial frequencies (Levi and Klein, 1982a, 1982b). In the non-amblyopic eye of the human subjects, Vernier acuity was independent of spatial frequency within one octave of the resolution limit. Interestingly, the amblyopic eye of anisometropic amblyopes showed the same pattern of results, but the results for the amblyopic eye of strabismic amblyopes were rather different. For these subjects, Vernier acuity decreases with spatial frequency beginning at very low spatial frequencies. A similar conclusion has been drawn on the basis of measurements of another hyperacuity, namely a bisection task (Levi and Klein, 1983).

Bradley and Freeman (1985) tested human amblyopes on a Vernier acuity task using vertical sine-wave gratings of various spatial frequencies. They found that Vernier acuity was best at low spatial frequencies and largest at high spatial frequencies. Although the exact nature of the amblyopic classification of the subjects was not specified, all but one of the subjects had a strabismus.

Later, Levi, Klein and Wang (1994b) investigated Vernier acuity with abutting cosine gratings of various spatial frequencies. Similarly to normal subjects, the Vernier thresholds of anisometropic amblyopes improved with increasing spatial frequency, but they were significantly larger and the optimal Vernier thresholds were not as low. As expected, the performance of the strabismic amblyopes was worse. For these subjects, it was only possible to obtain Vernier thresholds for a limited range of spatial frequencies. Even at low spatial frequencies, the thresholds were huge, and with high spatial frequencies, it was difficult to obtain data.

Thus, it appears that the Vernier acuity of anisometropic and strabismic amblyopes behave in different ways as a function of spatial frequency. Whereas anisometropic amblyopes behave like normal subjects, the Vernier acuity of the amblyopic eye of strabismic amblyopes becomes worse with increasing spatial frequency. In opposition to Bradley and Freeman (1985), who argued that the poor performance of strabismic amblyopes on this type of Vernier acuity task could be explained by their contrast sensitivity loss, Levi et al. (1994b) found that the elevated Vernier thresholds were not simply related to elevated contrast detection thresholds. They found that interocular differences in Vernier acuity were significantly worse than the differences in contrast sensitivity. For example, for one of their subjects the Vernier acuity of the amblyopic eye was 25 times worse than that of the fellow normal eye, while the interocular difference between the two eyes was only a factor of 2 in terms of contrast sensitivity.

The nature of the spatial localization deficit in amblyopia

As mentioned previously, the spatial localization deficits of human anisometropic amblyopes are smaller than those of strabismic amblyopes (Hess and Holliday, 1992b). Moreover, the spatial localizations deficits of the former group of amblyopes can be predicted in their entirety by their loss in contrast sensitivity, while for the latter group of amblyopes, substantial spatial localization deficit remains even when the deficits in contrast sensitivity are factored out. A number of proposals have been advanced to explain the neural basis of spatial deficits in human amblyopia: including, but not limited to, abnormal neural response properties (Eggers and Blakemore, 1978; Movshon et al., 1987; Crewther and Crewther, 1990; Kiorpes et al., 1998), poor synchronization of

neuronal responses (Roelfsema, Konig, Engel, Sireteanu and Singer, 1994), anomalous interactions between cells (Polat, Sagi and Norcia, 1997), uncalibrated neural disarray (Hess et al., 1978; Hess, Field and Watt, 1990; Hess and Field, 1993, 1994; Field and Hess, 1996; Demanins et al., 1999b; Hess, 2002) and neural undersampling (Levi and Klein, 1985, 1986, 1990b, 1996; Levi et al., 1987; Levi et al., 1994a; Wang et al., 1998; Sharma et al., 1999).

Most of the experimental work that has explored the neural basis of amblyopia has been derived from psychophysical studies on human amblyopes. One proposal investigated in this way was suggested by Polat et al. (1997) who argued that the spatial localization deficits in human amblyopes were due to anomalous interactions between normal cells in an otherwise normal topographical arrangement. However, the two proposals that have received the most attention for the neural deficits in amblyopia are neural undersampling and uncalibrated neural disarray. According to the neural undersampling theory, too few cells in the visual cortex of human amblyopes can be influenced through the amblyopic eye in order to provide an accurate representation of all points in the visual field. Alternatively, the uncalibrated neural disarray proposes that the lack of spatial accuracy is a direct consequence of a disrupted topological mapping somewhere within the amblyopic visual system. According to Hess and Field (1994), neural undersampling predicts comparable errors in both localization and contrast discrimination, while neural disarray predicts an associated deficit for discriminating image distortion. In order to test these theories they devised two experiments. In the first experiment, they asked strabismic amblyopes to make both a position judgment and a contrast judgment. Using a set of three Gabor patches where the middle Gabor patch was misaligned, the strabismic patients were asked to make two separate decisions. First, they had to judge whether the middle Gabor patch was to the left or to the right of the two outer reference Gabor patches. Second, they had to decide whether the middle Gabor patch was of higher or lower contrast than the two outer reference Gabor patches. Rather than being closely correlated, it was found that the spatial localization deficits were significantly larger than the contrast discrimination deficits, a result that did not support neural undersampling. In the second experiment, Hess and Field (1994) asked strabismic amblyopes to make a position judgment and a distortion judgment. For this experiment,

they used a radial sinusoid stimulus (a bull's eye target) in which the individual rings had a sinusoidal luminance profile (the distortions were created by adding jitter to the stimuli). Strabismic amblyopes were required to judge whether the middle bull's eye target was to the left or to the right of the two outer reference targets, and second, to judge if the middle target was more or less distorted than the two outer undistorted reference targets. They found that the strabismic amblyopes were grossly inaccurate on both measures. Moreover, there was a strong correlation (slope of 0.87) between the two measures, a result consistent with the predictions of uncalibrated neural disarray.

In this study, a similar test of the first experiment conducted by Hess and Field (1994) was applied to amblyopic cats and the results were comparable to those observed in human amblyopes. The interocular deficits in contrast discrimination were approximately a factor of two, a small fraction of the ratio of the alignment accuracy for the two eyes. As with human amblyopes, the results of the current study were incompatible with neural undersampling. On the other hand, it does appear that the proposal of a correlation between deficits in contrast discrimination and spatial localization deficits in neural undersampling as proposed by Hess and Field (1994) may have to be revisited. Taking into account the durations of the monocular deprivation periods used in the present study that are known to produce a shift in ocular dominance of cells in the primary visual cortex of cats, there is no doubt that these visually deprived animals had a loss of cells in the visual cortex. Thus according to Hess and Field (1994), the visually deprived animals in the current study should have comparable deficits in contrast discrimination and spatial localization, but this was not the case. It does appear that the tests devised by Hess and Field (1994) is not sensitive enough to detect cellular loss in visually deprived animals. Moreover, given the fact that the deficits in contrast discrimination are by definition limited (ranging from 0 to 1) and that the spatial localizations deficits are infinite, the absence of correlation between the two deficits may be not surprising. Finally, it may be that these two visual deficits are independent of each other and using contrast sensitivity as a predictor for spatial localization deficits may not be the most suitable approach. The conclusions of Hess and colleagues have not gone unchallenged. For example, Levi's group maintains that undersampling may still be the main factor underlying the localization errors in amblyopia and questions the assertion

that undersampling predicts closely linked deficits of localization and contrast discrimination. However, Levi et al. (1994a, 1994b) mention that undersampling alone could not fully explain the loss of position acuity in strabismic amblyopes, and propose that extra noise at higher stages of visual processing may contribute. Later, Levi and Klein (2003) provided additional evidence for added noise. In three other studies, Levi and colleagues (Levi and Klein, 1996; Wang et al., 1998; Levi et al., 1999) pointed out that both neural underampling and neural uncalibrated disarray contribute to amblyopic spatial localization deficits, but Hess (2002) still maintains that the evidence for neural undersampling is not overwhelming. Of course, it may be that the spatial localization deficits of strabismic amblyopes may result from a combination of both neural undersampling and uncalibrated neural disarray. Indeed, it could be argued that any process that leads to undersampling through random disconnection of one eye from cortical cells may simultaneously introduce a certain degree of spatial disarray so that the two proposed mechanisms may never occur in isolation.

REFERENCES

Abrahamsson, M. & Sjöstrand, J. (1988). Contrast sensitivity and acuity relationship in strabismic and anisometropic amblyopia. *British Journal of Ophthalmology, 72,* 44-49.

Antonini, A., Gillespie, D. C., Crair, M. C. & Stryker, M. P. (1998). Morphology of single geniculocortical afferents and functional recovery of the visual cortex after reverse monocular deprivation in the kitten. *Journal of Neuroscience, 18,* 9896-9909.

Antonini, A. & Stryker, M. P. (1993). Rapid remodeling of axonal arbors in the visual cortex. *Science, 260,* 1819-1821.

Antonini, A. & Stryker, M. P. (1996). Plasticity of geniculocortical afferents following brief or prolonged monocular occlusion in the cat. *Journal of Comparative Neurology, 369,* 64-82.

Asper, L., Crewther, D. & Crewther, S. G. (2000a). Strabismic amblyopia. Part 1: Psychophysics. *Clinical and Experimental Optometry, 83,* 49-58.

Asper, L., Crewther, D. & Crewther, S. G. (2000b). Strabismic amblyopia. Part 2: Neural processing. *Clinical and Experimental Optometry, 83,* 200-211.

Baker, F. H., Grigg, P. & von Noorden, G. K. (1974). Effects of visual deprivation and strabismus on the response of neurons in the visual cortex of the monkey, including studies on the striate and prestriate cortex in the normal animal. *Brain Research, 66,* 185-208.

Barnes, G. R., Hess, R. F., Dumoulin, S. O., Achtman, R. L. & Pike, G. B. (2001). The cortical deficit in humans with strabismic amblyopia. *Journal of Physiology (London), 533,* 281-297.

Barrett, B. T., Pacey, I. E., Bradley, A., Thibos, L. N. & Morrill, P. (2003). Nonveridical visual perception in human amblyopes. *Investigative Ophthalmology and Visual Science, 44,* 1555-1567.

Beaver, B. V. (1980). Sensory development of *Felis catus*. *Laboratory animals, 14,* 199-201.

Beck, J. & Halloran, T. (1985). Effects of spatial separation and retinal eccentricity on two-dot vernier acuity. *Vision Research, 25,* 1105-1111.

Beck, J. & Schwartz, T. (1979). Vernier acuity with dot test objects. *Vision Research, 19,* 313-319.

Bedell, H. E. & Flom, M. C. (1981). Monocular spatial distortion in strabismic amblyopia. *Investigative Ophthalmology and Visual Science, 20,* 263-268.

Bedell, H. E. & Flom, M. C. (1983). Normal and abnormal space perception. *American Journal of Optometry and Physiological Optics, 60,* 426-435.

Bedell, H. E., Flom, M. C. & Barbeito, R. (1985). Spatial aberrations and acuity in strabismus and amblyopia. *Investigative Ophthalmology and Visual Science, 26,* 909-916.

Bennett, M. J., Smith, E. L., Harwerth, R. S. & Crawford, M. L. J. (1980). Ocular dominance, eye alignment and visual acuity in kittens reared with an optically induced squint. *Brain Research, 193,* 33-45.

Berman, N. & Murphy, E. H. (1982). The critical period for alteration in cortical binocularity resulting from divergent and convergent strabismus. *Developmental Brain Research, 2* 181-202.

Blake, R. (1979). The visual system of the cat. *Perception and Psychophysics, 26,* 423-448.

Blakemore, C. & Cummings, R. M. (1975). Eye-opening in kittens. *Vision Research, 15,* 1417-1418.

Blakemore, C., Garey, L. J. & Vital-Durand, F. (1978). The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex. *Journal of Physiology (London), 283,* 223-262.

Blakemore, C. & Van Sluyters, R. C. (1974). Reversal of the physiological effects of monocular deprivation in kittens: further evidence for a sensitive period. *Journal of Physiology (London), 237,* 195-216.

Blakemore, C., Vital-Durand, F. & Garey, L. J. (1981). Recovery from monocular deprivation in the monkey. I. Reversal of physiological effects in the visual cortex. *Proceedings of the Royal Society of London B,* 213, 399-423.

Blasdel, G. G. & Pettigrew, J. D. (1978). Effect of prior visual experience on cortical recovery from the effects of unilateral eyelid suture in kittens. *Journal of Physiology (London), 274,* 601-619.

Boothe, R. G., Dobson, V. & Teller, D. Y. (1985). Postnatal development of vision in human and nonhuman primates. *Annual Review of Neuroscience, 8,* 495-545.

Boothe, R. G., Kiorpes, L. & Hendrickson, A. (1982). Anisometropic amblyopia in *Macaca nemestrina* monkeys produced by atropinization of one eye during development. *Investigative Ophthalmology and Visual Science, 22,* 228-233.

Bradley, A. & Freeman, R. D. (1981). Contrast sensitivity in anisometropic amblyopia. *Investigative Ophthalmology and Visual Science, 21,* 467-476.

Bradley, A. & Freeman, R. D. (1985). Is reduced vernier acuity in amblyopia due to position, contrast or fixation deficits? *Vision Research, 25,* 55-66.

Burbeck, C. A. (1987). Position and spatial frequency in large-scale localization judgments. *Vision Research, 27,* 417-427.

Burbeck, C. A. (1988). Large-scle relative localization across spatial frequency channels. *Vision Research, 28,* 857-859.

Chandna, A., Pennefather, P. M., Kovács, I. & Norcia, A. M. (2001). Contour integration deficits in anisometropic amblyopia. *Investigative Ophthalmology and Visual Science, 42,* 875-878.

Choi, M. Y., Lee, D. S., Hwang, J. - M., Choi, D. G., Lee, K. – M., Park, K. H. & Yu, Y. S. (2002). Characteristics of glucose metabolism in the visual cortex of amblyopes using positron-emission tomography and statistical parametric mapping. *Journal of Pediatric Ophthalmology and Strabismus, 39,* 11-19.

Choi, M. Y., Lee, K. - M., Hwang, J. - M., Choi, D. G., Lee, D. S., Park, K. H. & Yu, Y. S. (2001). Comparison between anisometropic and strabismic amblyopia using functional magnetic resonance imaging. *British Journal of Ophthalmology, 85,* 1052-1056.

Chow, K. L. & Stewart, D. L. (1972). Reversal of structural and functional effects of long-term visual deprivation in cats. *Experimental Neurology, 34,* 409-433.

Cleland, B. G., Crewther, D. P., Crewther, S. G. & Mitchell, D. E. (1982). Normality of spatial resolution of retinal ganglion cells in cats with strabismic amblyopia. *Journal of Physiology (London), 326,* 235-249.

Cleland, B. G., Crewther, S. G. & Crewther, D. P. (1985). The cat as a model for visual deprivation. *Australian and New Zealand Journal of Ophthalmology, 13,* 263-269.

Cleland, B. G., Mitchell, D. E., Gillard-Crewther, S. & Crewther, D. P. (1980). Visual resolution of retinal ganglion cells in monocularly deprived cats. *Brain Research, 192,* 261-266.

Crair, M. C., Ruthazer, E. S., Gillespie, D. C. & Stryker, M. P. (1997). Relationship between the ocular dominance and orientation maps in visual cortex of monocularly deprived cats. *Neuron, 19,* 307-318.

Crawford, M. L. J. & Marc, R. E. (1976). Light transmission of cat and monkey eyelids. *Vision Research, 16,* 323-324.

Crawford, M. L. J. & von Noorden, G. K. (1980). Optically induced concomitant strabismus in monkeys. *Investigative Ophthalmology and Visual Science, 19,* 1105-1109.

Crewther, D. P. & Crewther, S. G. (1990). Neural site of strabismic amblyopia in cats: spatial frequency deficit in primary cortical neurons. *Experimental Brain Research, 79,* 615-622.

Crewther, S. G. & Crewther, D. P. (1993). Amblyopia and suppression in binocular cortical neurons of strabismic cat. *Neuroreport, 4,* 1083-1086.

Cynader, M., Gardner, J. C. & Mustari, M. (1984). Effects of neonatally induced strabismus on binocular responses in cat area 18. *Experimental Brain Research, 53,* 384-399.

Daw, N. W. (1995). *Visual Development.* New York, NY: Plenum Press.

Daw, N. W., Fox, K., Sato, H. & Czepita, D. (1992). Critical period for monocular deprivation in the cat visual cortex. *Journal of Neurophysiology,* 67, 197-202.

Demanins, R. & Hess, R. F. (1996). Positional loss in strabismic amblyopia: interrelationship of alignment threshold, bias, spatial scale and eccentricity. *Vision Research, 36,* 2771-2794.

Demanins, R., Hess, R. F., Williams, C. B. & Keeble, D. R. T. (1999a). The orientation discrimination deficit in strabismic amblyopia depends upon stimulus bandwidth. *Vision Research, 39,* 4018-4031.

Demanins, R., Wang, Y. – Z. & Hess, R. F. (1999b). The neural deficit in strabismic amblyopia: sampling considerations. *Vision Research, 39,* 3575-3585.

Derrington, A. M. & Hawken, M. J. (1981). Spatial and temporal properties of cat geniculate neurones after prolonged deprivation. *Journal of Physiology (London), 314,* 107-120.

Dews, P. B. & Wiesel, T. N. (1970). Consequences of monocular deprivation on visual behaviour in kittens. *Journal of Physiology (London), 206,* 437-455.

Distler, C. & Hoffmann, K. – P. (1991). Depth perception and cortical physiology in normal and innate microstrabismic cats. *Visual Neuroscience, 6,* 25-41.

Duke-Elder, S. & Wybar, K. (1973). *System of ophthalmology, Vol. VI, Ocular motility and strabismus.* London, UK: Henry Kimpton.

Dzioba, H. A., Murphy, K. M., Horne, J. A. & Mitchell, D. E. (1986). A precautionary note concerning the use of contact lens occluders in developmental studies on kittens, together with a description of an alternative occlusion procedure. *Clinical Vision Sciences, 1* , 191-196.

Eggers, H. M. & Blakemore, C. (1978). Physiological basis of anisometropic amblyopia. *Science, 201,* 264-267.

Field, D. J. & Hess, R. F. (1996). Uncalibrated distortions *vs* undersampling. *Vision Research, 36,* 2121-2124.

Flom, M. C. & Bedell, H. E. (1985). Identifying amblyopia using associated conditions, acuity, and nonacuity features. *American Journal of Optometry and Physiological Optics, 62,* 153-160.

Flom, M. C., Weymouth, F. W. & Kahneman, D. (1963). Visual resolution and contour interaction. *Journal of the Optical Society of America, 53,* 1026-1032.

Fox, R. & Blake, R. R. (1971). Stereoscopic vision in the cat. *Nature (London),* 233, 55-56.

Freeman, R. D. (1979). The consequences of a "consolidation" period following brief monocular deprivation in kittens. In R. D. Freeman (Ed.) *Developmental Neurobiology of Vision* (pp. 99-107). New York, NY: Plenum Press.

Freeman, R. D. (1980). Corneal radius of curvature of the kitten and the cat. *Investigative Ophthalmology and Visual Science, 19,* 306-308.

Freeman, R. D. & Bradley, A. (1980). Monocularly deprived humans: nondeprived eye has supernormal Vernier acuity. *Journal of Neurophysiology, 43,* 1645-1653.

Freeman, R. D. & Tsumoto, T. (1983). An electrophysiological comparison of convergent and divergent strabismus in the cat: electrical and visual activation of single cortical cells. *Journal of Neurophysiology, 49,* 238-253.

Fronius, M. & Sireteanu, R. (1989). Monocular geometry is selectively distorted in the central visual field of strabismic amblyopes. *Investigative Ophthalmology and Visual Science, 30,* 2034-2044.

Ganz, L. & Fitch, M. (1968). The effect of visual deprivation on perceptual behavior. *Experimental Neurology, 22,* 638-660.

Ganz, L. & Haffner, M. E. (1974). Permanent perceptual and neurophysiological effects of visual deprivation in the cat. *Experimental Brain Research, 20,* 67-87.

Ganz, L., Hirsch, H. V. B. & Tieman, S. B. (1972). The nature of perceptual deficits in visually deprived cats. *Brain Research, 44,* 547-568.

Gellermann, L. W. (1933). Chance orders of alternating stimuli in visual discrimination experiments. *Journal of Genetic Psychology, 42,* 206-208.

Giffin, F. & Mitchell, D. E. (1978). The rate of recovery of vision after early monocular deprivation in kittens. *Journal of Physiology (London), 274,* 511-537.

Goodyear, B. G., Nicolle, D. A., Humphrey, G. K. & Menon, R. S. (2000). BOLD fMRI response of early visual areas to perceived contrast in human amblyopia. *Journal of Neurophysiology, 84,* 1907-1913.

Grant, S. & Berman, N. J. (1991). Mechanism of anomalous retinal correspondence: maintenance of binocularity with alternation of receptive-field position in the lateral suprasylvian (LS) visual area of strabismic cats. *Visual Neuroscience, 7,* 259-281.

Gstalder, R. J. & Green, D. G. (1971). Laser interferometric acuity in amblyopia. *Journal of Pediatric Ophthalmology, 8,* 251-256.

Hall, S. E. & Mitchell, D. E. (1991). Grating acuity of cats measured with detection and discrimination tasks. *Behavioural Brain Research, 44,* 1-9.

Harrad, R. A. & Hess, R. F. (1992). Binocular integration of contrast information in amblyopia. *Vision Research, 32,* 2135-2150.

Harwerth, R. S., Crawford, M. L. J., Smith, E. L. & Boltz, R. L. (1981). Behavioral studies of stimulus deprivation amblyopia in monkeys. *Vision Research, 21,* 779-789.

Harwerth, R. S. & Levi, D. M. (1978). A sensory mechanism for amblyopia: psychophysical studies. *American Journal of Optometry and Physiological Optics, 55,* 151-162.

Harwerth, R. S., Smith, E. L., Boltz, R. L., Crawford, M. L. J. & von Noorden, G. K. (1983). Behavioral studies on the effect of abnormal early visual experience in monkeys: spatial modulation sensitivity. *Vision Research, 23,* 1501-1510.

Hein, A. & Held, R. (1967). Dissociation of the visual placing response into elicited and guided components. *Science, 158,* 390-392.

Hendrickson, A. E., Movshon, J. A., Eggers, H. M., Gizzi, M. S., Boothe, R. G. & Kiorpes, L. (1987). Effects or early unilateral blur on the macaque's visual system. II. Anatomical observations. *Journal of Neuroscience, 7,* 1327-1339.

Hess, R. F. (1977a). Assessment of stimulus field size for strabismic amblyopes. *American Journal of Optometry and Physiological Optics, 54,* 292-299.

Hess, R. F. (1977b). Eye movements and grating acuity in strabismic amblyopia. *The Ophthalmology Resident* 225-237.

Hess, R. F. (1982). Developmental sensory impairment: amblyopia or tarachopia? *Human Neurobiology, 1,* 17-29.

Hess, R. F. (1995). Amblyopia: a tale of two approaches. *Ophthalmology, Physiology and Optometry, 15,* 395-397.

Hess, R. F. (2002). Sensory processing in human amblyopia: snakes and ladders. In M. Moseley & A. Fielder (Eds.) *Amblyopia: a multidisciplinary approach* (pp. 19-42). Boston, MA: Butterworth Heinemann.

Hess, R. F. & Anderson, S. J. (1993). Motion sensitivity and spatial undersampling in amblyopia. *Vision Research, 33,* 881-896.

Hess, R. F., Campbell, F. W. & Greenhalgh, T. (1978). On the nature of the neural abnormality in human amblyopia: neural aberrations and neural sensitivity loss. *Pflugers Archiv (European Journal of Physiology), 377,* 201-207.

Hess, R. F., Dakin, S. C., Tewfik, M. & Brown, B. (2001). Contour interaction in amblyopia: scale selection. *Vision Research, 41,* 2285-2296.

Hess, R. F. & Field, D. (1993). Is the increased spatial uncertainty in the normal periphery due to spatial undersampling or uncalibrated disarray? *Vision Research, 33,* 2663-2670.

Hess, R. F. & Field, D. J. (1994). Is the spatial deficit in strabismic amblyopia due to loss of cells or an uncalibrated disarray of cells? *Vision Research, 34,* 3397-3406.

Hess, R. F., Field, D. J. & Watt, R. J. (1990). The puzzle of amblyopia. In C. Blakemore (Ed.) *Vision: coding and efficiency* (pp. 267-280). Cambridge, UK: Cambridge University Press.

Hess, R. F. & Hayes, A. (1993). Neural recruitment explains "Weber's law" of spatial position. *Vision Research, 33,* 1673-1684.

Hess, R. F. & Hayes, A. (1994). The coding of spatial position by the human visual system: effects of spatial scale and retinal eccentricity. *Vision Research, 34,* 625-643.

Hess, R. F. & Holliday, I. E. (1992a). The coding of spatial position by the human visual system: effects of spatial scale and contrast. *Vision Research, 32,* 1085-1097.

Hess, R. F. & Holliday, I. E. (1992b). The spatial localization deficit in amblyopia. *Vision Research, 32,* 1319-1339.

Hess, R. F. & Howell, E. R. (1977). The threshold contrast sensitivity function in strabismic amblyopia: evidence for a two type classification. *Vision Research, 17,* 1049-1055.

Hess, R. F. & Howell, E. R. (1978). The influence of field size for a periodic stimulus in strabismic amblyopia. *Vision Research, 18,* 501-503.

Hess, R. F., McIlhagga, W. & Field, D. J. (1997). Contour integration in strabismic amblyopia: the sufficiency of an explanation based on positional uncertainty. *Vision Research, 37,* 3145-3161.

Hess, R. F., Pointer, J. S., Simmers, A. & Bex, P. (2003). Border distinctness in amblyopia. *Vision Research, 43,* 2255-2264.

Hess, R. F. & Smith, G. (1977) Do optical aberrations contribute to visual loss in strabismic amblyopia? *American Journal of Optometry and Physiological Optics, 54,* 627-633.

Hess, R. F., Wang, Y. - Z., Demanins, R., Wilkinson, F. & Wilson, H. R. (1999). A deficit in strabismic amblyopia for global shape detection. *Vision Research, 39,* 901-914.

Hoffmann, K. - P. & Cynader, M. (1977). Functional aspects of plasticity in the visual system of adult cats after early monocular deprivation. *Philosophical Transactions of the Royal Society of London B, 278,* 411-424.

Holopigian, K. & Blake, R. (1983). Spatial vision in strabismic cats. *Journal of Neurophysiology, 50,* 287-296.

Horton, J. C. & Hocking D. R. (1996). Pattern of ocular dominance columns in human striate cortex in strabismic amblyopia. *Visual Neuroscience, 13,* 787-795.

Horton, J. C. & Stryker, M. P. (1993). Amblyopia induced by anisometropia without shrinkage of ocular dominance columns in human striate cortex. *Proceedings of the National Academy of Sciences of the United States of America, 90,* 5494-5498.

Hsiao, C. F. & Sherman, S. M. (1986). Alpha and beta cells projecting from the retina to lamina A of the lateral geniculate nucleus in normal cats, monocularly deprived cats, and young cats. *Experimental Brain Research, 61,* 413-431.

Hubel, D. H. & Wiesel, T. N. (1959). Receptive fields of single neurons in the cat's striate cortex. *Journal of Physiology (London), 148,* 574-591.

Hubel, D. H. & Wiesel, T. N. (1962). Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *Journal of Physiology (London), 160,* 106-154.

Hubel, D. H. & Wiesel, T. N. (1965). Binocular interaction in striate cortex of kittens reared with artificial squint. *Journal of Neurophysiology, 28,* 1041-1059.

Hubel, D. H. & Wiesel, T. N. (1969). Visual area of the lateral suprasylvian gyrus (Clare-Bishop area) of the cat. *Journal of Physiology (London), 202,* 251-260.

Hubel, D. H. & Wiesel, T. N. (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *Journal of Physiology (London), 206,* 419-436.

Hubel, D. H. & Wiesel, T. N. (1998). Early exploration of the visual cortex. *Neuron, 20,* 401-412.

Hubel, D. H., Wiesel, T. N. & LeVay, S. (1977). Plasticity of ocular columns in monkey striate cortex. *Philosophical Transactions of the Royal Society of London B, 278,* 377-409.

Imamura, K., Richter, H., Fischer, H., Lennerstrand, G., Franzén, O., Rydberg, A., Andersson, J., Schneider, H., Onoe, H., Watanabe, Y. & Långström, B. (1997). Reduced activity in the extrastriate cortex of individuals with strabismic amblyopia. *Neuroscience Letters, 225,* 173-176.

Irvine, S. R. (1948). Amblyopia ex anopsia: observations on retinal inhibition, scotoma, projection, light difference discrimination and visual acuity. *Transactions of the American Ophthalmological Society, 66,* 527-575.

Jacobson, S. G. & Ikeda, H. (1979). Behavioural studies of spatial vision in cats reared with convergent squint: is amblyopia due to arrest of development? *Experimental Brain Research, 34,* 11-26.

Jones, K. R. & Spear, P. D. & Tong, L. (1984). Critical periods for effects of monocular deprivation: differences between striate and extrastriate cortex. *Journal of Neuroscience, 4,* 2543-2552.

Kabasakal, L., Devranoglu, K., Arslan, O., Erdil, T. U., Sönmezoglu, K., Uslu, I., Tolun, H., Isitman, A. T., Ozker, K. & Önsel, Ç. (1995). Brain SPECT evaluation of the visual cortex in amblyopia. *Journal of Nuclear Medicine, 36,* 1170-1174.

Kalil, R. E., Spear, P. D. & Langsetmo, A. (1984). Response properties of striate cortex neurons in cats raised with divergent or convergent strabismus. *Journal of Neurophysiology, 52,* 514-537.

Keech, R. V. & Kutschke, P. J. (1995). Upper age limit for the development of amblyopia. *Journal of Pediatric Ophthalmology and Strabismus, 32,* 89-93.

Kim, D. – S. and Bonhoeffer, T. (1994). Reverse occlusion leads to a precise restoration of orientation preference maps in visual cortex. *Nature (London), 370,* 370-372.

Kind, P. C., Mitchell, D. E., Ahmed, B., Blakemore, C., Bonhoeffer, T. & Sengpiel, F. (2002). Correlated binocular activity guides recovery from monocular deprivation. *Nature (London), 416,* 430-433.

Kiorpes, L. (1992). Effect of strabismus on the development of vernier acuity and grating acuity in monkeys. *Visual Neuroscience, 9,* 253-259.

Kiorpes, L., Boothe, R. G., Hendrickson, A. E., Movshon, J. A., Eggers, H. M. & Gizzi, M. S. (1987). Effects or early unilateral blur on the macaque's visual system. I. Behavioral observations. *Journal of Neuroscience, 7,* 1318-1326.

Kiorpes, L., Kiper, D. C. & Movshon, J. A. (1993). Contrast sensitivity and vernier acuity in amblyopic monkeys. *Vision Research, 33,* 2301-2311.

Kiorpes, L., Kiper, D. C., O'Keefe, L. P., Cavanaugh, J. R. & Movshon, J. A. (1998). Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *Journal of Neuroscience, 18,* 6411-6424.

Kiorpes, L. & McKee, S. P. (1999). Neural mechanisms underlying amblyopia. *Current Opinion in Neurobiology, 9,* 480-486.

Kiorpes, L. & Movshon, J. A. (2003). Neural limitations on visual development in primates. In L. M. Chalupa & Warner J. S. (Eds.) *The visual neurosciences* (pp. 159-173). Boston, MA: The MIT Press.

Kiper, D. C. (1994). Spatial phase discrimination in monkeys with experimental strabismus. *Vision research, 34,* 437-447.

Kiper, D. C. & Kiorpes, L. (1994). Suprathreshold contrast sensitivity in experimentally strabismic monkeys. *Vision Research, 34,* 1575-1583.

Klein, S. A. & Levi, D. M. (1987). Position sense of the peripheral retina. *Journal of the Optical Society of America A, 4,* 1543-1553.

Kooi, F. L., De Valois, R. L. & Switkes, E. (1991). Spatial localization across channels. *Vision Research, 31,* 1627-1631.

Kovács, I., Polat, U., Pennefather, P. M., Chandna, A. & Norcia, A. M. (2000). A new test of contour integration deficits in patient with a history of disrupted binocular experience during visual development. *Vision Research, 40,* 1775-1783.

Kozma, P. & Kiorpes, L. (2003). Contour integration in amblyopic monkeys. *Visual Neuroscience, 20,* 577-588.

Lagrèze, W. - D. & Sireteanu, R. (1991). Two-dimensional spatial distortions in human strabismic amblyopia. *Vision Research, 31,* 1271-1288.

Lashley, K. S. (1930). The mechanism of vision: I. A method for rapid analysis of pattern-vision in the rat. *Journal of Genetic Psychology, 37,* 453-460.

Lee, K. – M., Lee, S. – H., Kim, N. – Y., Kim, C. – Y., Sohn, J. – W., Choi, M. Y., Choi, D. G., Hwang, J. – M., Park, K. H., Lee, D. S., Yu, Y. S. & Chang, K. H. (2001). Binocularity and spatial frequency dependence of calcarine activation in two types of amblyopia. *Neuroscience Research, 40,* 147-153.

Lehmkuhle, S., Kratz, K. E., Mangel, S. C. & Sherman, S. M. (1978). An effect of early monocular lid suture upon the development of X-cells in the cat's lateral geniculate nucleus. *Brain Research, 157,* 346-350.

Lehmkuhle, S., Kratz, K. E., Mangel, S. C. & Sherman, S. M. (1980). Spatial and temporal sensitivity of X- and Y-cells in dorsal lateral geniculate nucleus of the cat. *Journal of Neurophysiology, 43,* 520-541.

Lehmkuhle, S., Kratz, K. E. & Sherman, S. M. (1982). Spatial and temporal sensitivity of normal and amblyopic cats. *Journal of Neurophysiology, 48,* 372-387.

LeVay, S., Wiesel, T. N. & Hubel, D. H. (1980). The development of ocular dominance columns in normal and visually deprived monkeys. *Journal of Comparative Neurology, 191,* 1-51.

Leventhal, A. G. & Hirsch, H. V. B. (1983). Effects of visual deprivation upon the morphology of retinal ganglion cells projecting to the dorsal lateral geniculate nucleus of the cat. *Journal of Neuroscience, 3,* 332-344.

Levi, D. M. & Harwerth, R. S. (1974). Brightness contrast in amblyopia. *American Journal of Optometry and Physiological Optics, 51,* 371-381.

Levi, D. M. & Harwerth, R. S. (1978). A sensory mechanism for amblyopia: electrophysiological studies. *American Journal of Optometry and Physiological Optics, 55,* 163-171.

Levi, D. M. & Harwerth, R. S. (1980). Contrast sensitivity in amblyopia due to stimulus deprivation. *British Journal of Ophthalmology, 64,* 15-20.

Levi, D. M. & Harwerth, R. S. (1982). Psychophysical mechanisms in humans with amblyopia. *American Journal of Optometry and Physiological Optics, 59,* 936-951.

Levi, D. M. & Klein, S. (1982a). Hyperacuity and amblyopia. *Nature (London), 298,* 268-270.

Levi, D. M. & Klein, S. (1982b). Differences in vernier discrimination for gratings between strabismic and anisometropic amblyopes. *Investigative Ophthalmology and Visual Science, 23,* 398-407.

Levi, D. M. & Klein, S. A. (1983). Spatial localization in normal and amblyopic vision. *Vision Research, 23,* 1005-1017.

Levi, D. M. & Klein, S. A. (1985). Vernier acuity, crowding and amblyopia. *Vision Research, 25,* 979-991.

Levi, D. M. & Klein, S. A. (1986). Sampling in spatial vision. *Nature (London), 320,* 360-362.

Levi, D. M. & Klein, S. A, (1990a). The role of separation and eccentricity in encoding position. *Vision Research, 30,* 557-585.

Levi, D. M. & Klein, S. A, (1990b). Equivalent intrinsic blur in spatial vision. *Vision Research, 30,* 1971-1993.

Levi, D. M. & Klein, S. A. (1992a). The role of local contrast in the visual deficits of humans with naturally occurring amblyopia. *Neuroscience Letters, 136,* 63-66.

Levi, D. M. & Klein, S. A. (1992b). "Weber's law" for position: the role of spatial frequency and contrast. *Vision Research, 32,* 2235-2250.

Levi, D. M. & Klein, S. A. (1996). Limitations on position coding imposed by undersampling and univariance. *Vision Research, 36,* 2111-2120.

Levi, D. M. & Klein, S. A. (2003). Noise provides some new signals about the spatial vision of amblyopes. *Journal of Neuroscience, 23,* 2522-2526.

Levi, D. M., Klein, S. A. & Sharma, V. (1999). Position jitter and undersampling in pattern perception. *Vision Research, 39,* 445-465.

Levi, D. M., Klein, S. A. & Wang, H. (1994a). Amblyopic and peripheral vernier acuity: a test-pedestral approach. *Vision Research, 34,* 3265-3292.

Levi, D. M., Klein, S. A. & Wang, H. (1994b). Discrimination of position and contrast in amblyopic and peripheral vision. *Vision Research, 34,* 3293-3313.

Levi, D. M., Klein, S. A. & Yap, Y. L. (1987). Positional uncertainty in peripheral and amblyopic vision. *Vision Research, 27,* 581-597.

Levitt, J. B., Schumer, R. A., Sherman, S. M., Spear, P. D. & Movshon, J. A. (2001). Visual response properties of neurons in the LGN of normally reared and visually deprived macaque monkeys. *Journal of Neurophysiology, 85,* 2111-2129.

Levitt, F. B. & van Sluyters, R. C. (1982). The sensitive period for strabismus in the kitten. *Developmental Brain Research, 3,* 323-327.

Loop, M. S. & Sherman, S. M. (1977). Visual discriminations during eyelid closure in the cat. *Brain Research, 128,* 329-339.

Loop, M. S., Smyly, E. C., Millican, C. L. & Greifer, C. F. (1981). Acuity, luminance, and monocular deprivation in the cat. *Behavioural Brain Research, 2,* 323-334.

Maguire, G. W., Smith, E. L., Harwerth, R. S. & Crawford, M. L. J. (1982). Optically induced anisometropia in kittens. *Investigative Ophthalmology and Visual Science, 23,* 253-264.

Malach, R., Ebert, R. & van Sluyters, R. C. (1984). Recovery from effects of brief monocular deprivation in the kitten. *Journal of Neurophysiology, 51,* 538-551.

McKee, S. P., Levi, D. M. & Movshon, J. A. (2003). The pattern of visual deficits in amblyopia. *Journal of Vision, 3,* 380-405.

Mioche, L. & Singer, W. (1989). Chronic recordings from single sites of kitten striate cortex during experience-dependent modifications of receptive-field properties. *Journal of Neurophysiology, 62,* 185-197.

Mitchell, D. E. (1988). The extent of visual recovery from early monocular or binocular visual deprivation in kittens. *Journal of Physiology (London), 395,* 639-660.

Mitchell, D. E. (1989b). Sensitive periods in visual development in the kitten: the effects of early monocular deprivation. In P. Kellaway & J. L. Noebels (Eds.) *Problems and concepts in developmental neurophysiology* (pp. 45-74). Baltimore, MD: John Hopkins University Press.

Mitchell, D. E. (2003). The effects of selected forms of early visual deprivation on perception. In L. M. Chalupa & J. S. Werner (Eds.) *The visual neurosciences* (pp. 189-204). Boston, MA: The MIT Press.

Mitchell, D. E., Cynader, M. & Movshon, J. A. (1977a). Recovery from the effects of monocular deprivation in kittens. *Journal of Comparative Neurology, 176,* 53-63.

Mitchell, D. E. Giffin, F. & Timney, B. (1977b). A behavioral technique for the rapid assessment of the visual capabilities of kittens. *Perception, 6,* 181-193.

Mitchell, D. E., Giffin, F., Wilkinson, F., Anderson, P. & Smith, M. L. (1976). Visual resolution in young kittens. *Vision Research, 16,* 363-366.

Mitchell, D. E. & Gingras, G. (1998). Visual recovery after monocular deprivation is driven by absolute, rather than relative, visually evoked activity levels. *Current Biology, 8,* 1179-1182.

Mitchell, D. E., Gingras, G. & Kind, P. C. (2001). Initial recovery of vision after early monocular deprivation in kittens is faster when both eyes are open. *Proceedings of the National Academy of Sciences of the United States of America, 98,* 11662-11667.

Mitchell, D. E., Kaye, M. & Timney, B. (1979). Assessment of depth perception in cats. *Perception, 8,* 389-396.

Mitchell, D. E., Murphy, K. M. & Kaye, M. G. (1984a). Labile nature of the visual recovery promoted by reverse occlusion in monocularly deprived kittens. *Proceedings of the National Academy of Sciences of the United States of America, 81,* 286-288.

Mitchell, D. E., Murphy, K. M. & Kaye, M. G. (1984b). The permanence of the visual recovery that follows reverse occlusion of monocularly deprived kittens. *Investigative Ophthalmology and Visual Science, 25,* 908-917.

Mitchell, D. E., Ptito, M. & Lepore, F. (1994). Depth perception in monocularly deprived cats following part-time reverse occlusion. *European Journal of Neuroscience, 6,* 967-972.

Mitchell, D. E., Ruck, M., Kaye, M. G. & Kirby, S. (1984c). Immediate and long-term effects on visual acuity of surgically induced strabismus in kittens. *Experimental Brain Research, 55,* 420-430.

Mitchell, D. E. & Timney, B. (1984). Postnatal development of function in the mammalian visual system. In I. Darian Smith (Ed.) *Hanbook of physiology. Section I: The nervous system, Vol. 3, Part 1: Sensory processes* (pp. 507-555). Bethesda, MD: American Physiological Society.

Mitzdorf, U. & Neumann, G. (1980). Effects of monocular deprivation in the lateral geniculate nucleus of the cat: an analysis of evoked potentials. *Journal of Physiology (London), 304,* 221-230.

Mori, T., Matsuura, K., Zhang, B., Smith, E. L. & Chino, Y. M. (2002). Effects of the duration of early strabismus on the binocular responses of neurons in the monkey visual cortex (V1). *Investigative Ophthalmology and Visual Science, 43,* 1262-1269.

Movshon, J. A. (1976a). Reversal of the physiological effects of monocular deprivation in the kitten's visual cortex. *Journal of Physiology (London), 261,* 125-174.

Movshon, J. A. (1976b). Reversal of the behavioural effects of monocular deprivation in the kitten. *Journal of Physiology (London), 261,* 175-187.

Movshon, J. A. & Blakemore, C. (1974). Functional reinnervation in kitten visual cortex. *Nature (London), 251,* 504-505.

Movshon, J. A. & Dürsteler, M. R. (1977). Effects of brief periods of unilateral eye closure on the kitten's visual system. *Journal of Neurophysiology, 40,* 1255-1265.

Movshon, J. A., Eggers, H. M., Gizzi, M. S., Hendrickson, A. E., Kiorpes, L. & Boothe, R. G. (1987). Effects or early unilateral blur on the macaque's visual system. III. Physiological observations. *Journal of Neuroscience, 7,* 1340-1351.

Movshon, J. A. & van Sluyters, R. C. (1981). Visual neural development. *Annual Review of Psychology, 32,* 477-522.

Mower, G. D., Burchfiel, J. L & Duffy, F. H. (1982). Animal models of strabismic amblyopia: physiological studies of visual cortex and the lateral geniculate nucleus. *Developemental Brain Research, 5,* 311-327.

Murphy, K. M. & Mitchell, D. E. (1987). Reduced visual acuity in both eyes of monocularly deprived kittens following a short or long period of reverse occlusion. *Journal of Neuroscience, 7,* 1526-1536.

Murphy, K. M. & Mitchell, D. E. (1991). Vernier acuity of normal and visually deprived cats. *Vision Research, 31,* 253-266.

Olson, C. R. & Freeman, R.D. (1975). Progressive changes in kitten striate cortex during monocular deprivation. *Journal of Neurophysiology, 38,* 26-32.

Olson, C. R. & Freeman, R. D. (1978). Monocular deprivation and recovery during sensitive period in kittens. *Journal of Neurophysiology, 41,* 65-74.

Olson, C. R. & Freeman, R. D. (1980). Profile of the sensitive period for monocular deprivation in kittens. *Experimental Brain Research, 39,* 17-21.

Pointer, J. S. & Watt, R. J. (1987). Shape recognition in amblyopia. *Vision Research, 27,* 651-660.

Polat, U., Sagi, D. & Norcia, A. M. (1997). Abnormal long-range spatial interactions in amblyopia. *Vision Research, 37,* 737-744.

Popple, A. V. & Levi, D. M. (2000). Amblyopes see true alignment where normal observers see illusory tilt. *Proceedings of the National Academy of Sciences of the United States of America, 97,* 11667-11672.

Prusky, G. T. & Douglas, R. M. (2003). Developmental plasticity of mouse visual acuity. *European Journal of Neuroscience, 17,* 167-173.

Prusky, G. T., West, P. W. R. & Douglas, R. M. (2000). Experience-dependent plasticity of visual acuity in rats. *European Journal of Neuroscience, 12,* 3781-3786.

Ptito, M., Bouchard, P., Lepore, F., Quessy, S., Di Stefano, M. & Guillemot, J.-P. (1995). Binocular interactions and visual acuity loss in esotropic cats. *Canadian Journal of Physiology and Pharmacology, 73,* 1398-1405.

Ptito M., Lepore, F. & Guillemot, J. – P. (1991). Stereopsis in the cat: behavioral demonstration and underlying mechanisms. *Neuropsychologia, 29,* 443-464.

Pugh, M. (1958). Visual distortion in amblyopia. *British Journal of Ophthalmology, 42,* 449-460.

Pugh, M. (1962). Amblyopia and the retina. *British Journal of Ophthalmology, 46,* 193-211.

Quick, M. W., Tigges, M., Gammon, J. A. & Boothe, R. G. (1989). Early abnormal visual experience induces strabismus in infant monkeys. *Investigative Ophthalmology and Visual Science, 30,* 1012-1017.

Rentschler, I. & Hilz, R. (1985). Amblyopic processing of positional information. Part I: Vernier acuity. *Experimental Brain Research, 60,* 270-278.

Roelfsema, P. R., König, P., Engel, A. K., Sireteanu, R. & Singer, W. (1994). Reduced synchronization in the visual cortex of cats with strabismic amblyopia. *European Journal of Neuroscience, 6,* 1645-1655.

Sharma, V., Levi, D. M. & Coletta, N. J. (1999). Sparse-sampling of gratings in the visual cortex of strabismic amblyopes. *Vision Research, 39,* 3526-3536.

Sharma, V., Levi, D. M. & Klein, S. A. (2000). Undercounting features and missing features: evidences for a high-level deficit in strabismic amblyopia. *Nature Neuroscience, 3,* 496-501.

Shatz, C. J. & Stryker, M. P. (1978). Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation. *Journal of Physiology (London), 281,* 267-283.

Sherman, S. M. (1972). Development of interocular alignment in cats. *Brain Research, 37,* 187-203.

Sherman, S. M., Hoffmann, K. - P. & Stone, J. (1972). Loss of a specific cell type from dorsal lateral geniculate nucleus in visually deprived cats. *Journal of Neurophysiology, 35,* 532-541.

Sherman, S. M. & Spear, P. D. (1982). Organization of visual pathways in normal and visually deprived cats. *Physiological Reviews, 62,* 738-850.

Sherman, S. M. & Stone, J. (1973). Physiological normality of the retina in visually deprived cats. *Brain Research, 60,* 224-230.

Simmers, A. J. & Bex, P. J. (2004). The representation of global spatial structure in amblyopia. *Vision Research, 44,* 523-533.

Simmers, A. J., Bex, P. J. & Hess, R. F. (2003). Perceived blur in amblyopia. *Investigative Ophthalmology and Visual Science, 44,* 1395-1400.

Simmers, A. J., Ledgeway, T., Hess, R. F. and McGraw, P. V. (2003). Deficits to global motion processing in human amblyopia. *Vision Research, 43,* 729-738.

Singer, W., von Grünau, M. & Rauschecker, J. (1980). Functional amblyopia in kittens with unilateral exotropia. I. Electrophysiological assessment. *Experimental Brain Research, 40,* 294-304.

Sireteanu, R. & Best, J. (1992). Squint-induced modification of visual receptive fields in the lateral suprasylvian cortex of the cat: binocular interaction, vertical effect and anomalous correspondence. *European Journal of Neuroscience, 4,* 235-242.

Sireteanu, R., Lagrèze, W. – D. & Constantinescu, D. H. (1993). Distortions in two-dimensional visual space perception in strabismic observers. *Vision Research, 33,* 677-690.

Skottun, B. C., Bradley, A. & Freeman, R. D. (1986). Orientation discrimination in amblyopia. *Investigative Ophthalmology and Visual Science, 27,* 532-537.

Smith, E. L., Bennett, M. J., Harwerth, R. S. & Crawford, M. L. J. (1979). Binocularity in kittens reared with optically induced squint. *Science, 204,* 875-877.

Smith, E. L., Harwerth, R. S. & Crawford, M. L. J. (1985). Spatial contrast sensitivity deficits in monkeys produced by optically induced anisometropia. *Investigative Ophthalmology and Visual Science, 26,* 330-342.

Spear, P. D. & Baumann, T. P. (1975). Receptive-field characteristics of single neurons in lateral suprasylvian visual area of the cat. *Journal of Neurophysiology, 39,* 1403-1420.

Spear, P. D. & Hou, V. (1990). Retinal ganglion-cell densities and soma sizes are unaffected by long-term monocular deprivation in the cat. *Brain Research, 522,* 354-358.

Spear, P. D., Tong, L. & Langsetmo, A. (1978). Striate cortex of binocularly deprived kittens respond to visual stimuli through the closed eyelids. *Brain Research, 155,* 141-146.

Squillace, A. S. & Bien, A. R. (1970). The functional relation between alignment accuracy and vertical separation of alignment marks. *Human Factors, 12,* 599-604.

Stuart, J. A. & Burian, H. M. (1962). A study of separation difficulty: its relationship to visual acuity in normal and amblyopic eyes. *American Journal of Ophthalmology, 53,* 471-477.

Sullivan, G. D., Oatley, K. & Sutherland, N. S. (1972). Vernier acuity as affected by target length and separation. *Perception and Psychophysics, 12,* 438-444.

Swindale, N. V., Vital-Durand, F. & Blakemore, C. (1981). Recovery from monocular deprivation in monkey. III. Reversal of anatomical effects in the visual cortex. *Proceedings of the Royal Society of London B, 213,* 435-450.

Timney, B. (1990). Effects of brief monocular deprivation on binocular depth perception in the cat: a sensitive period for the loss of stereopsis. *Visual Neuroscience, 5,* 273-280.

Toet, A., van Eekhout, M. P., Simons, H. L. J. J. & Koenderink, J. J. (1987). Scale invariant features of differential spatial displacement discrimination. *Vision Research, 27,* 441-451.

Toet, A. & Koendernik, J. J. (1988). Differential spatial displacement discrimination thresholds for Gabor patches. *Vision Research, 28,* 133-143.

Trachtenberg, J. T., Trepel, C. & Stryker, M. P. (2000). Rapid extragranular plasticity in the absence of thalamocortical plasticity in the developing primary visual cortex. *Science, 287,* 2029-2032.

Treutwein, B. (1995). Adaptive psychophysical procedures. *Vision Research, 35,* 2503-2522.

Van Hof-Van Duin, J. (1976). Early and permanent effects of monocular deprivation on pattern discrimination and visuomotor behavior in cats. *Brain Research, 111,* 261-276.

Van Sluyters, R. C. (1978b). Reversal of the physiological effects of brief periods of monocular deprivation in the kitten. *Journal of Physiology (London), 284,* 1-17.

Van Sluyters, R. C. & Levitt, F. B. (1980). Experimental strabismus in kittens. *Journal of Neurophysiology, 43,* 686-699.

Von Grünau, M. W. (1982). Comparison of the effects of induced strabismus on binocularity in area 17 and the LS area in the cat. *Brain Research, 246,* 325-329.

Von Grünau, M. W. & Singer, W. (1980). Functional amblyopia in kittens with unilateral exotropia. II. Correspondence between behavioural and electrophysiological assessment. *Experimental Brain Research, 40,* 305-310.

Von Noorden, G. K. (1967). Classification of amblyopia. *American Journal of Ophthalmology, 63,* 238-244.

Von Noorden, G. K. (1973). Experimental amblyopia in monkeys. Further behavioral observations and clinical correlations. *Investigative Ophthalmology, 12,* 721-726.

Von Noorden, G. K. (1996). *Binocular Vision and Ocular Motility: theory and management of strabismus.* St. Louis, MO: Mosby.

Von Noorden, G. K. & Burian, H. M. (1959a). Visual acuity in normal and amblyopic patients under reduced illumination. I. Behavior of visual acuity with and without neutral density filter. *Archives of Ophthalmology, 61,* 533-535.

Von Noorden, G. K. & Burian, H. M. (1959b). Visual acuity in normal and amblyopic patients under reduced illumination. II. The visual acuity at various levels of illumination. *Archives of Ophthalmology, 62,* 396-399.

Von Noorden, G. K. & Crawford, M. L. J. (1978b). Morphological and physiological changes in the monkey visual system after short-term lid suture. *Investigative Ophthalmology and Visual Science, 17,* 762-768.

Von Noorden, G. K. & Dowling, J. E. (1970). Experimental amblyopia in monkeys. II. Behavioral studies in strabismic amblyopia. *Archives of Ophthalmology, 84,* 215-220.

Von Noorden, G. K. Dowling, J. E. & Ferguson, D. C. (1970). Experimental amblyopia in monkeys. I. Behavioral studies of stimulus deprivation amblyopia. *Archives of Ophthalmology, 84,* 206-214.

Wang, H., Levi, D. M. & Klein, S. A. (1998). Spatial uncertainty and sampling efficiency in amblyopic position acuity. *Vision Research, 38,* 1239-1251.

Warkentin, J. & Smith, K. U. (1937). The development of visual acuity in the cat. *Journal of Genetic Psychology, 50,* 371-399.

Westheimer, G. (1975). Visual acuity and hyperacuity. *Investigative Ophthalmology, 14,* 570-572.

Westheimer, G. (1984). Line-separation discrimination curve in the human fovea: smooth or segmented? *Journal of the Optical Society of America A, 1,* 683-684.

Whitaker, D. (1993). What part of a vernier stimulus determines performance? *Vision Research, 33,* 27-32.

Whitaker, D., Bradley, A., Barrett, B. T. & McGraw, P. V. (2002). Isolation of stimulus characteristics contributing to Weber's law for position. *Vision Research, 42,* 1137-1148.

Whitaker, D. & MacVeigh, D. (1991). Interaction of spatial frequency and separation in vernier acuity. *Vision Research, 31,* 1205-1212.

Wiesel, T. N. (1982). Postnatal development of the visual cortex and the influence of environment. *Nature (London), 299,* 583-591.

Wiesel, T. N. & Hubel, D. H. (1963a). Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. *Journal of Neurophysiology, 26,* 978-992.

Wiesel, T. N. & Hubel, D. H. (1963b). Single-cell responses in striate cortex of kittens deprived of vision in one eye. *Journal of Neurophysiology, 26,* 1003-1017.

Wiesel, T. N. & Hubel, D. H. (1965a). Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *Journal of Neurophysiology, 28,* 1029-1040.

Wiesel, T. N. & Hubel, D. H. (1965b). Extent of recovery from the effects of visual deprivation in kittens. *Journal of Neurophysiology, 28,* 1060-1072.

Wright, K. W. (2003). Visual development and amblyopia. In K. W. Wright & P. H. Spiegel (Eds.) *Pediatric Ophthalmology and Strabismus* (pp. 157-171). New York, NY: Springer.

Yap, Y. L., Levi, D. M. & Klein, S. A. (1987). Peripheral hyperacuity: three-dot bisection scales to a single factor from 0 to 10 degrees. *Journal of the Optical Society of America A, 4,* 1554-1561.

Yinon, U. (1976). Age dependence of the effect of squint on cells in kitten's visual cortex. *Experimental Brain Research, 26,* 151-157.

Yinon, U., Auerbach, E., Blank, M. & Friesenhausen, J. (1975). The ocular dominance of cortical neurons in cats developed with divergent and convergent squint. *Vision Research, 15,* 1251-1256.