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MODIFICATION OF VISUAL FUNCTION BY EARLY VISUAL EXPERIENCE

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Summary

Physiological experiments, involving recording from the visual cortex in young kittens and monkeys, have given new insight into human developmental disorders. In the visual cortex of normal cats and monkeys most neurones are selectively sensitive to the orientation of moving edges and they receive very similar signals from both eyes. Even in very young kittens without visual experience, most neurones are binocularly driven and a small proportion of them are genuinely orientation selective. There is no passive maturation of the system in the absence of visual experience, but even very brief exposure to patterned images produces rapid emergence of the adult organization. These results are compared to observations on humans who have "recovered" from early blindness. Covering one eye in a kitten or a monkey, during a sensitive period early in life, produces a virtually complete loss of input from that eye in the cortex. These results can be correlated with the production of "stimulus deprivation amblyopia" in infants who have had one eye patched. Induction of a strabismus causes a loss of binocularity in the visual cortex, and in humans it leads to a loss of stereoscopic vision and binocular fusion. Exposing kittens to lines of one orientation modifies the preferred orientations of cortical cells and there is an analogous "meridional amblyopia" in astigmatic humans. The existence of a sensitive period in human vision is discussed, as well as the possibility of designing remedial and preventive treatments for human developmental disorders.

Zusammenfassung

Physiologische Experimente über die elektrischen Entladungen der Zellen im visuellen Cortex bei jungen Katzen und Affen vermitteln neue Einsichten in die Hintergründe von Entwicklungsstörungen des menschlichen Zentralnervensystems. Im visuellen Cortex von norma-

len Katzen und Affen sind die meisten Zellen selektiv empfindlich auf die Richtungsorientierung von sich bewegenden Kanten und werden von beiden Augen aktiviert. Auch bei sehr jungen Kätzchen ohne visuelle Erfahrung werden die meisten Zellen binokulär angeregt; eine kleine Anzahl von Zellen ist bereits richtungsspezifisch orientiert. Ohne visuelle Erfahrung erfolgt keine (passive) Reifung des Systems, jedoch genügt schon eine sehr begrenzte Erfahrung mit Bildmustern, um die Organisation des erwachsenen Gehirns kurzfristig entstehen zu lassen. Diese Beobachtungen entsprechen Erfahrungen bei menschlichen Patienten, welche von frühkindlicher Blindheit befreit werden konnten. Deckt man bei Kätzchen oder beim jungen Affen während einer empfindlichen Periode im frühen Lebensalter ein Auge zu, so bleibt die Hirnrinde gegenüber Erregungen von seiten dieses Auges fast völlig unerregbar. Dieser Befund entspricht wahrscheinlich der durch Reizentzug bedingten Amblyopie bei Kleinkindern mit einseitigem Augendeckverband. Experimentell induzierter Strabismus verunmöglicht die binokuläre Erregung des visuellen Cortex; beim Menschen führt Strabismus zum Verlust des Raumsehens und des binokulären Fusionsvermögens. Exponiert man kleine Katzen mit monotonen Linienmustern, so wird die Richtungsspezifizität der corticalen Zellen in einer bestimmten Weise eingeschränkt. Analog dazu ist die meridionale Amblyopie bei astigmatischen Menschen. In diesem Zusammenhang wird das Problem der kritischen Periode in der Entwicklung des visuellen Wahrnehmungsvermögens beim Menschen diskutiert; dabei ergeben sich Ansätze für therapeutische und praeventive Massnahmen bei zerebralen Entwicklungsstörungen.

Introduction

Clinical ophthalmologists have always known that certain abnormalities in the early visual experience of an infant can lead to persistent and largely irreversible deficiencies in visual ability later in life. Only in the last ten years or so have we begun to understand some of the reasons for these developmental disorders. Physiological experiments on the visual system, particularly the visual cortex of the cat and the monkey, have shown that many of the properties of visual neurones are dependent on the animal's early visual experience. This physiological work has provided insight into clinical conditions that were poorly understood, has given new hope for preventive, therapeutic and remedial treatment, but equally has produced data about the plasticity of individual nerve cells, which might be of more general interest to the biologist.

In this brief review of experimental work performed in many laboratories, partly in my own at Cambridge, I shall consider three subjects of clinical interest and shall try to show how

physiological research has increased our understanding and even provided clues to possible methods of treatment.

The Consequences of Early Blindness

Clinical observations

Many philosophers have considered the question: if a man who had been blind from birth, because of some defect in the optics of his eyes, suddenly had his sight restored, would he really be able to perceive? Some thought that this would be the ultimate answer to the ancient debate between the Empiricists (who believed that visual experience itself is essential for the development of visual perception) and the Nativists (who maintained that the ability to perceive was innately given and required no active use of the visual system). The perfect clinical case study does not exist. Usually blindness due to the early cataract or traumatic corneal opacity does not occur at birth, so the child has nearly always had some degree of visual experience before the onset of blindness. Also, there is usually some kind of very crude visual capacity, such as brightness discrimination or the ability to see large moving objects, despite the cloudiness of the eyes. So, deprivation is rarely complete and almost never extends from birth. Nevertheless, observations on people who have been cured by the removal of a cataractous lens or by a corneal transplant have provided fascinating information about the effects of reduced visual input early in life. VON SENDEN (1960) has collected accounts of many such cases, from ancient times, and his conclusion is that recovery of real visual function after early blindness is very rare. Generally these unfortunate people are able to make only the crudest use of visual information, such as discriminating brightness and colour and recognizing movement. GREGORY and WALLACE (1963) in a thorough case study came to the same conclusion: their patient became increasingly depressed because he could not use his new sensations. He reverted to the life of a blind person. In another recent study ACKROYD, HUMPHREY and WARRINGTON (1974) found that their patient, who was blind from the age of three, never recovered any useful visual ability. She too was disappointed with the "failure" of the treatment.

It is obvious, then, that the observation of previously blind adult humans is not a perfect way to discover the inherent, innate capacities of the visual system. Years of deprivation might be expected to lead to degenerative changes in the visual pathway and an increasing dependence on the other senses. A much more satisfactory way of studying the genuine early capabilities and maturation of the visual system is to observe the visual skills of very young infants. New behavioural methods are now enabling developmental psychologists to

measure such things as visual acuity in extremely young babies. It is now quite clear that the resolution of an infant improves very gradually from birth to at least six months of age (ATKINSON, BRADDICK and BRADDICK, 1974; TELLER, MORSE, BORTON and REGAL, 1974; LEEHEY, MOSKOWITZ-COOK, BRILL and HELD, 1975). It seems reasonable to conclude that certain slow changes are taking place in the immature visual system and that deprivation of visual experience prevents at least some of these maturational processes from occurring.

Physiological observations

In the past fifteen years, initially through the pioneering work of Jung and his colleagues (JUNG, 1961; BAUMGARTNER, BROWN and SCHULZ, 1965) and of HUBEL and WIESEL (1962, 1968) on the visual cortex of the cat and the monkey, we have learned a great deal about the normal organization of neurones in the visual pathway. In the visual cortex, just four synapses away from the photoreceptors themselves, there is an elegant neuronal machine for the analysis of pattern and movement. Each cortical neurone usually responds not to sudden overall changes in the illumination of the retina, but only to the presence of a light-dark border - an edge - moving across a particular part of the retina, the receptive field of the cell. Moreover these neurones are <u>orientation selective</u>: they respond best when the edge is at a particular orientation and the response declines as the edge is rotated away from the optimum orientation. Some cortical cells can be remarkably selective for orientation, only responding reliably for a total range of angles of about $\pm 10^{\circ}$. Presumably, then, these cells (which we almost certainly also possess in our visual cortex) are responsible for detecting the presence of the edges of objects in the visual field and for identifying the orientations of those edges.

Cortical neurones are clustered together according to their preferred orientations, so that if a microelectrode is driven exactly perpendicularly through the visual cortex, it records from a series of cells with very similar preferred orientation. But if the electrode moves diagonally through the cortex it finds groups of cells with the same orientational preference, with sudden, progressive small changes in orientation from one group to the next. This has been taken as evidence for the grouping of cells in radially distributed <u>orientation columns,</u> running from the surface to the white matter. All the cells in each column or sheet of tissue have in common the same preferred orientation.

In addition to being orientation selective, the majority of cortical cells receive similar signals from roughly corresponding regions of the two retinas - they are binocularly driven. They also show very precise interaction if both eyes are stimulated simultaneously with a

single moving edge. If the object has the correct retinal disparity (with its images correctly positioned on the receptive fields in both eyes) the neurone will usually respond much more strongly than for stimulation of either eye alone. But if the disparity of the images is even slightly wrong, the response will be occluded. Hence cortical cells can be disparity- or distance-selective, and since the optimal disparity varies from cell to cell, they can signal information about the relative distances of objects in space and hence contribute to stereoscopic vision (BARLOW, BLAKEMORE and PETTIGREW, 1967; BISHOP, 1973).

Naturally, the discovery of this intricate and complicated organization in the cortex of the adult cat and monkey led to an interest in its early maturation. It is known that visuo-motor co-ordination develops only gradually in kittens, during the first four weeks (NORTON, 1974) and that acuity continues to improve up to at least 3 months of age (MITCHELL, REARDON, GIFFIN, WILKINSON, ANDERSEN and SMITH, 1976).

An early, preliminary study of the visual cortex in very young, visually inexperienced kittens (HUBEL and WIESEL, 1963) emphasized how completely developed it was, even at only eight days of age, when the actual number of synaptic contacts per neurone is only about 1% of that in the adult (CRAGG, 1972). HUBEL and WIESEL (1963) found, in a small sample of cortical cells, that most had input from both eyes, responded more to one orientation of edge than any other and were even organized into a kind of orientation columnar arrangement. Their recent work on very young monkeys (WIESEL and HUBEL, 1974) has also emphasized the degree of genetic pre-specification in the cortex with much fuller evidence for an apparently normal columnar map.

However, BARLOW and PETTIGREW (1971) and PETTIGREW (1974) pointed out that there are large differences between the kinds of specificity exhibited by immature cortical cells and those in normal adult cats. They found that neurones in very young kittens, or those deprived of visual experience by closing the lids of both eyes, are very rarely genuinely orientation selective, although they often have a selectivity for the direction of movement. Also, although they confirmed the binocularity of immature cortical cells, they found that they never showed the precise disparity-selectivity found in the adult. So they emphasized the importance of early visual experience in not only maintaining the specificity of cortical cells but also generating their orientation and disparity-selectivities.

In a recent study, BLAKEMORE and VAN SLUYTERS (1975) have re-examined this issue, keeping in mind Barlow and Pettigrew's strict criteria for true orientation selectivity. They confirmed that even the cortex of very young inexperienced kittens does possess a proportion (up to about 20%) of cells with genuine orientation selectivity. Interestingly, these

innately specified cells tend to be of a particular type (simple cells) which respond well to stationary as well as moving lines, and they are also much more strongly dominated by one eye or the other, rather than being equally responsive to both.

However, BLAKEMORE and VAN SLUYTERS (1975) agreed that many cortical neurones in animals of all ages that have been deprived of visual experience are much less highly specified. They classified cells into 5 groups:

a) Orientation selective cells

b) Orientational bias cells (not strictly selective but responding slightly more strongly for one orientation, or axis of movement, than for the orthogonal)

c) Pure direction selective cells (responding to patterns of any shape moving in one direction)

d) Non oriented cells (responding to movement in any direction)

e) Visually unresponsive cells (which could not be excited at all).

Fig 1 shows the way that the proportions of these various classes of neurones change during the first few weeks of life in normal kittens (unfilled symbols) and those deprived of visual experience (filled symbols). Obviously, vision promotes an extremely rapid increase in the percentage of truly orientation selective cells, even during the first few days after a kitten opens its eyes.

Certainly everyone is agreed that very long periods of visual deprivation cause a great loss in responsiveness and stimulus specificity in the visual cortex (WIESEL and HUBEL, 1965 a; PETTIGREW, 1974; BLAKEMORE and VAN SLUYTERS, 1975). This correlates well with the general inability of humans who have recovered from early blindness to make use of their visual systems.

The Consequences of Monocular Deprivation

Physiological observations

Although covering both eyes does not seem to disrupt the binocularity of cortical cells in the cat, covering just one eye certainly does. If the lids of one eye are closed, even for a brief period, at any time between about 3 weeks and 3 months of age, the input from that eye to the cortex is made virtually completely ineffective. Almost all cells can only be excited through the experienced eye (HUBEL and WIESEL, 1970). This profound change is not due simply to the reduction in retinal illumination produced by lid-suture, because it also occurs if the eye is covered by a diffuser and the other eye by a transparent neutral density filter that attenuates the mean illumination by the same amount (BLAKEMORE,
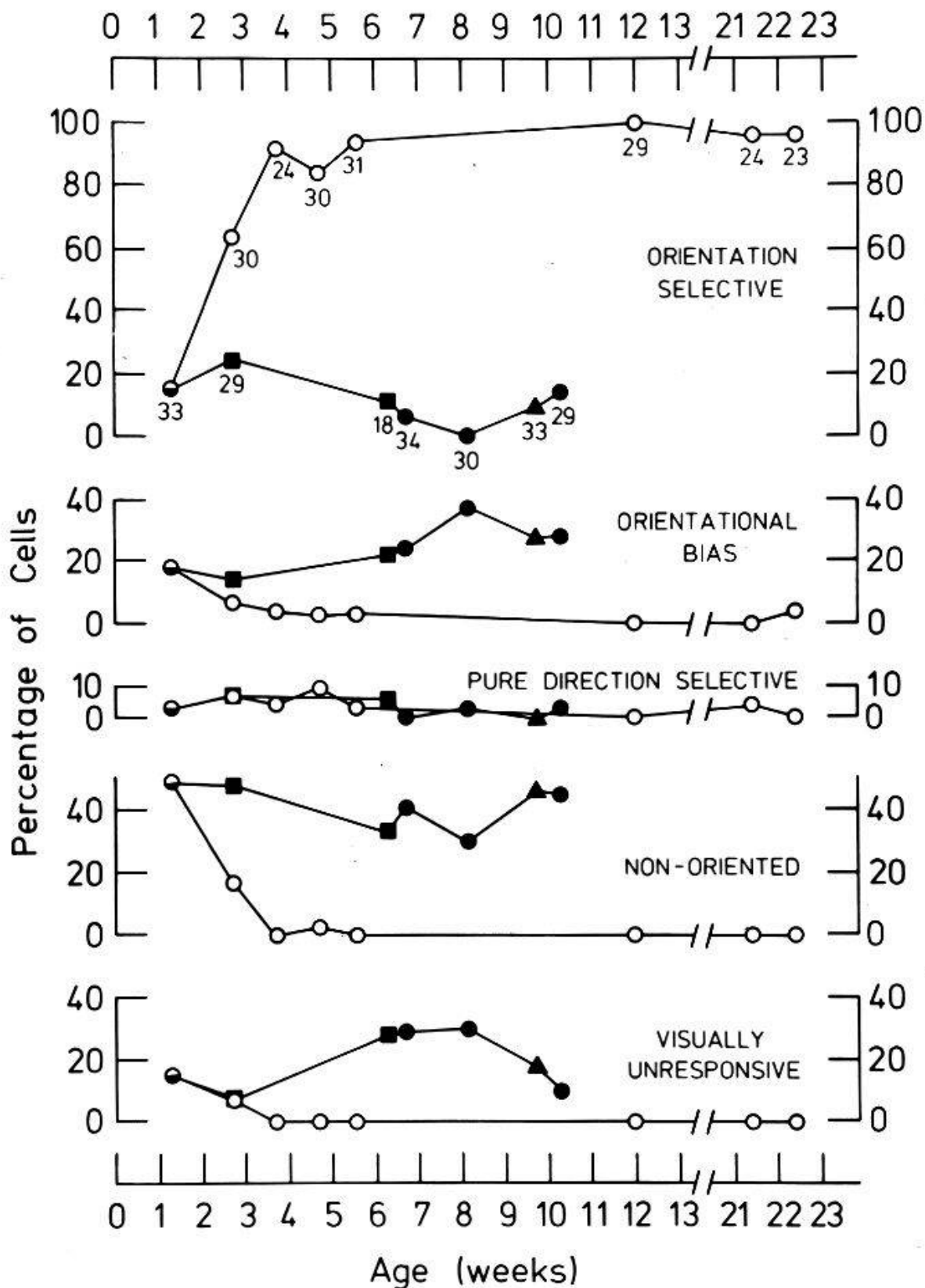
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Figure 1. The effects of visual experience and binocular deprivation on the proportions of different types of cortical neurones in young kittens. (See text for description of cell types). The open circles refer to normal kittens whose eyes were open from about 8 days of age. The solid symbols indicate kittens who were binocularly deprived until recording, using a variety of techniques (Dark rearing = squares; binocular lid suture = circles; suture of the nictitating membrane across the eye = triangle.) The abscissa indicates the age at recording. The numbers next to the symbols show the total number of neurones in the sample from each animal, used to calculate the percentage of different cell types shown on the ordinates. (Redrawn from Blakemore and Van Sluyters, 1975.)

VAN SLUYTERS and MOVSHON, 1976). At the peak of the 3 week to 3 month sensitive period, at about 4 weeks of age, just six hours of monocular vision can produce shifts in the ocular dominance of cortical cells (PECK and BLAKEMORE, 1975).

If the deprived eye is opened after a period of monocular deprivation, the kitten at first appears almost totally blind when the other eye is covered (WIESEL and HUBEL, 1963; BLAKEMORE and VAN SLUYTERS, 1974a). There is little improvement in the visual ability of the kitten if both eyes are left open after the end of the sensitive period and the changes in the cortex seem quite permanent (WIESEL and HUBEL, 1965b). This led Hubel and Wiesel to propose that the loss of input from a deprived eye is essentially an irreversible degenerative change.

Clinical observations

Monocular deprivation in monkeys also causes a shift in the ocular dominance of cortical cells and the sensitive period for these effects certainly starts at birth and is at its height during the first few weeks of life (BAKER, GRIGG and VON NOORDEN, 1974).

In human infants, too, there is evidence for rapid and dramatic changes in the visual cortex if one eye is covered. Patching an eye is often essential in the treatment of trauma to the lids or the cornea, or after surgery on the eye. But if a child's eye is patched, even briefly, early in life, the acuity of that eye can be drastically reduced even though the optics of the eye and the retina might be quite normal. This so-called stimulus deprivation amblyopia has recently been studied in some detail by VON NOORDEN (1973) and AWAYA, MIYAKE, IMAIZUMI, SHIOSE, KANDA and KOMURO (1973) in response to the findings of neurophysiologists.

They discovered that even very short periods of covering (for example, just one week) can lead to severe and persistent amblyopia in the deprived eye, especially if the patching occurs during the first year of the child's life.

Here then is a warning for the clinician, which comes directly from the physiological observations: if an eye must be patched during the first year, patch as briefly as possible, and if at all possible, patch both eyes, not one, because in that case binocularity may not be lost.

The Consequences of Early Strabismus

Clinical observations

In very young babies the two eyes are not continuously correctly aligned and at times they drift into extremely divergent or convergent positions. Most babies gain fusional control of

their eyes at about 2 months of age but quite a high proportion develop a permanent mis-alignment of the visual axes - a strabismus or squint. There are many possible reasons for the onset of strabismus such as traumatic damage to the extraocular muscles or their nerve supply, a difference in refractive power in the two eyes (anisometropia), or a difference in magnification (aniseikonia).

The perceptual consequences of a squint are very varied, but one common feature is a total loss of normal binocular fusion and stereoscopic vision. The strabismic child can almost ne-ver use disparity information to judge the relative distances of objects. In addition, parti-cularly for inward squints (esotropia), the squinting eye becomes amblyopic. Strabismus amblyopia also cannot be corrected completely later in life, even if the eyes are surgi-cally aligned by a muscle resection operation.

Physiological observations
An artificial strabismus can be induced in a young kitten or monkey by sectioning one of the rectus muscles of the eye. If this is done early in life there are again remarkable chan-ges in the organization of the visual cortex (HUBEL and WIESEL, 1965; BAKER et al, 1974). But instead of one eye losing its input entirely, the proportion of binocularly driven neu-rones is simply reduced. Cells tend to become very heavily dominated by one eye or the other. In kittens the effects are similar for inward squint (esotropia) and outward squint (exotropia) (VAN SLUYTERS and BLAKEMORE, unpublished observations).
Presumably, this loss of binocularity is the cause of the loss of binocular vision and stereop-sis in strabismic humans.

New correlates
Very recently a new line of research, involving perceptual experiments, has provided more evidence for the loss of binocular cortical neurones in strabismic humans. The studies have utilized some of the well known perceptual after-effects. For instance, if you look at a line tilted about 15° away from the vertical for a few minutes, then afterwards a truly vertical line will seem rotated in the other direction for a short time. If you adapt to a pattern mo-ving in one direction, then look at a stationary pattern, it seems to move in the opposite direction. These so-called tilt- and movement-after-effects have been attributed to the properties of cells in the visual cortex (BLAKEMORE and SUTTON, 1969). The effects will transfer from one eye to the other: adaptation through one eye alone causes a distortion of patterns subsequently viewed with the other eye. This interocular transfer of the after-effects in normal observers is presumably due to the fact that their cortical cells receive signals from both eyes.

It turns out that such after-effects will <u>not</u> transfer interocularly, or with very reduced strength, in people who have suffered from strabismus early in life and no longer have stereoscopic vision (MOVSHON, CHAMBERS and BLAKEMORE, 1972; MITCHELL and WARE, 1974; MITCHELL, REARDON and MUIR, 1975). This adds weight to the argument that strabismus has reduced the binocularity of their cortical cells. HOHMANN and CREUTZFELDT (1975) have extended this work by showing that reduced interocular transfer only occurs in humans in whom the strabismus first appeared before the age of 2-3 years. Here is further evidence of a sensitive period in human development.

The Consequences of Early Selective Pattern Deprivation

Physiological observations

Not only binocularity but even orientation selectivity is influenced by a kitten's early visual experience. If a kitten is kept in the dark and only ever exposed to a pattern of horizontal lines in one eye and vertical in the other, its cortical cells mainly become monocularly driven and their preferred orientations closely match that seen by the eye early in life (HIRSCH and SPINELLI, 1970).

Similarly, as shown in Fig 2, if the kitten is simply exposed binocularly to stripes of one orientation, cortical cells remain binocularly driven but in general their preferred orientations are close to those seen early in life. Cells preferring orientations far from that of the stripes tend to be very broadly tuned (BLAKEMORE and COOPER, 1970). The modification of preferred orientation has now been confirmed in nine independent laboratories (e.g. PETTIGREW and GAREY, 1974; TRETTER, CYNADER and SINGER, 1975; IMBERT and BUISSERET, 1975; SPENCER and COLEMAN, 1976). However, STRYKER and SHERK (1975) have recently had difficulty in reproducing the effect by simply exposing kittens in a striped environment, though they have observed the phenomenon in kittens exposed to stripes in goggles worn by the animal. Perhaps this should be taken to emphasize the importance of controlling the stimulus on the retina for these modifications to occur.

The sensitive period for these modifications in orientation selectivity also seems to occur during the same 3 week to 3 month period (BLAKEMORE, 1974) with peak sensitivity at 4 weeks, when only a few hours of exposure can cause profound changes (BLAKEMORE and MITCHELL, 1973; PETTIGREW and GAREY, 1974; TRETTER et al, 1975). Very recently SPENCER and COLEMAN (1976) have demonstrated changes in the pattern of dendrites of cortical cells in stripe-reared kittens, which might help to explain the physiological alterations.
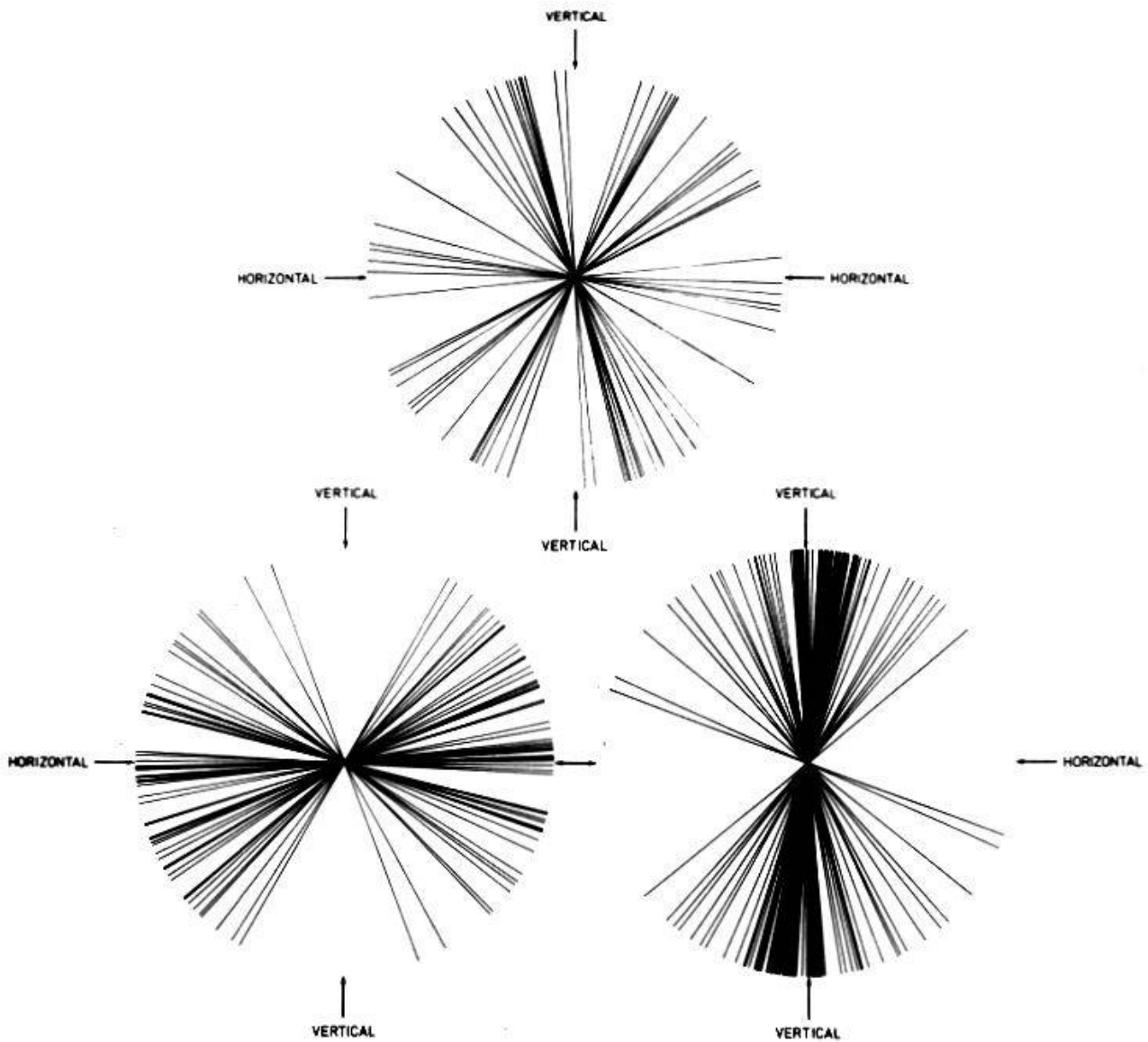
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Figure 2. The effects of exposure of kittens in environments consisting of stripes of a single orientation. Each line in these polar diagrams shows the preferred orientation of one cortical neurone.
Each diagram represents one animal: the one above is from a normal adult cat, the two below are from kittens reared in a horizontal environment (on the left) and a vertical environment (on the right). (Data from Blakemore and Cooper, 1970.)

Clinical observations

Exposure to one orientation, perhaps not surprisingly, produces a specific acuity deficit in the kitten. Edges of the experienced orientation can be resolved and responded to, but the opposite orientation is not seen so clearly (BLAKEMORE and COOPER, 1970). Indeed the actual acuity of the cat differs by up to a factor of two for the experienced and inexperienced orientations (MUIR and MITCHELL, 1975).

These experiments in cats led to the fortuitous rediscovery of a condition that has been cal-
led amblyopie astigmatique (MARTIN, 1890) or meridional amblyopia. Humans that have suf-
fered from extreme astigmatism early in life are left with a reduction in acuity for patterns
of the orientation that was originally out of focus on the retina, even after perfect optical
correction of the astigmatic eye (MITCHELL, FREEMAN, MILLODOT and HAEGERSTROM,
1973). These humans have presumably suffered the same kind of modification of orientation
selectivity as kittens exposed to a striped environment.

Here, then, is another suggestion to the clinician. Astigmatism is easy to diagnose and to cor-
rect. If this is not done early in life there will be persistent deficiencies in visual ability.

New Strategies of Treatment

It is clear that, in this field, much helpful information has been given to the clinician by
the physiologist. But it is, of course, the hope that this interchange of ideas will pass bey-
ond the phase of mere correlations between clinical disorder ans physiological phenomenon,
mere explanations of the diseases. It would be most rewarding to see positive suggestions
for new methods of treatment, or new signs to look for, as a result of physiological research.
The warnings about the dangers of early occlusion and astigmatism are good examples and
there are more instances where physiological results offer new hope for preventive or reme-
dial treatment.

Reverse occlusion

Although the effects of monocular deprivation in kittens cannot be changed simply by ope-
ning the deprived eye, they can be completely reversed by closing the experienced eye at
the same time. BLAKEMORE and VAN SLUYTERS (1974a) studied the consequences of this
reverse suturing procedure in kittens and found that if it was done early in the sensitive
period, at 5 weeks, the deprived eye could take over completely in the visual cortex: all
cells could become dominated by the re-opened eye. The later the reverse suturing was de-
layed, the less the reversal in ocular dominance. MOVSHON and BLAKEMORE (1974) have
analysed the speed of the change in ocular dominance after reverse suturing and have found
that it can be very rapid. As shown in Fig 3, the process is virtually complete in about 10
days if the kitten is reverse sutured at 5 weeks of age.

As well as proving that the changes in the cortex caused by monocular deprivation are not
simply degenerative and irreversible, the experiments provide hope for the treatment of hu-
man amblyopia. By a carefully designed schedule of reverse patching it may be possible to
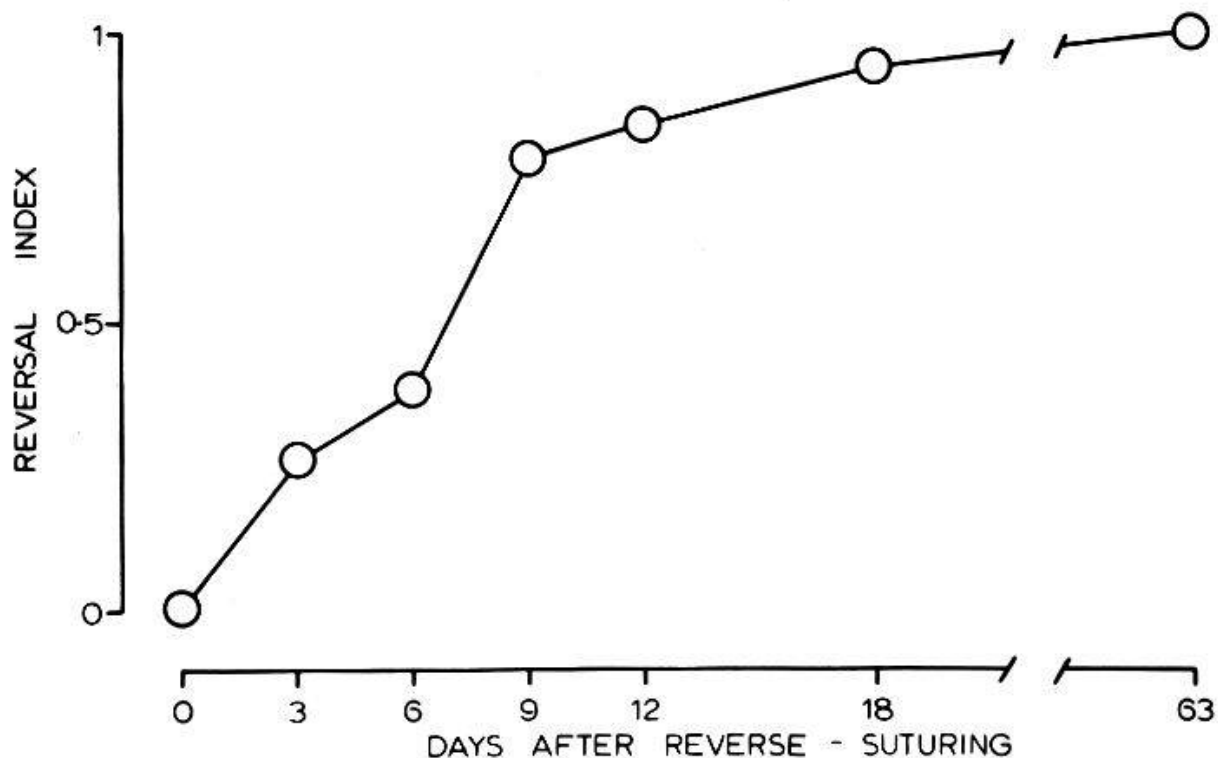
Figure 3. Reversal of the ocular dominance of cortical neurones produced by reverse suturing at 5 weeks of age. Each symbol plots the results for one animal. The abscissa shows the number of days after reverse suturing at which the recordings were taken. The result plotted at zero on the abscissa is from an animal that was simply monocularly deprived in the right eye from natural eye opening until 5 weeks. The ordinate plots the "reversal index": the proportion of all visually responsive cells that were more strongly influenced by the initially deprived eye. Hence the first animal, monocularly deprived until 5 weeks had an index of zero. The other animals had the right eye opened and the left closed at 5 weeks and had various periods of time to use the initially deprived eye. (Data from Movshon and Blakemore, 1974.)

restore effective connections from an amblyopic eye and, if the timing is just right, the proportion of binocular cells created may be high enough to permit some kind of stereoscopic function.

Maintenance of binocularity despite strabismus

BLAKEMORE and VAN SLUYTERS (1974b) made an unexpected observation that may provide hope for the treatment of young children with strabismus. They noticed that many kittens reared in a striped environment develop a natural strabismus. Their eyes can be divergent or convergent. However, their cortical cells are still binocularly driven.

It seemed possible that the peculiar nature of the visual environment is responsible for the failure to adopt correct eye position and the maintenance of binocularity. For it does not

matter where the eyes are pointing in a repetitive pattern of stripes; each eye will see roughly the same thing - an edge of a particular orientation. Hence, in a striped environment, binocular cells will receive simultaneous signals from both eyes even if the eyes are strabismic.

Blakemore and Van Sluyters extended this observation by showing that kittens with a surgically-induced strabismus will _also_ not lose binocularity in the cortex if they are regularly exposed in a striped environment.

This observation offers a little hope for a simple preventive treatment. It is possible that if strabismic infants are exposed to a striped pattern for a few minutes each day, they may retain sufficient cortical binocularity to avoid the loss of binocular function later in life. When accurate surgical correction of the squint can be made, such children may have normal stereopsis and not suffer from strabismus amblyopia.

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