

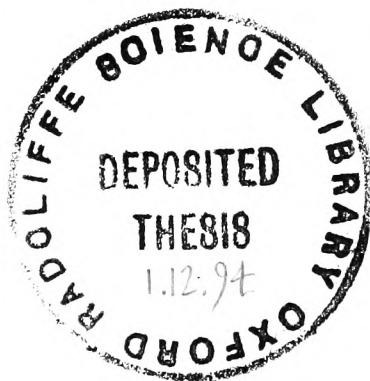
Mechanisms of Binocular Integration in the Mammalian Primary Visual Cortex

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Linacre College
1994



ABSTRACT

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D.Phil. thesis
Trinity Term, 1994

Mechanisms of Binocular Integration in the Mammalian Primary Visual Cortex

Combining the images seen by the two eyes into a single percept is one of the most challenging computational tasks that the visual cortex has to solve. The first stage at which information from the two retinae converges on individual neurons is the primary visual cortex, V1 or area 17. Here, I describe anatomical segregation and interocular suppression as two mechanisms for obviating potential interocular conflict.

I have studied V1 of the common marmoset (*Callithrix jacchus*), a New World monkey, with both neurophysiological and anatomical methods. Although similar in most respects to V1 of the Old World macaque, layer 4 of the normal adult marmoset has a predominance of binocular cells which corresponds to a lack of segregation of geniculo-cortical afferents into ocular dominance (OD) columns. Brief early monocular deprivation (MD) causes a physiological shift in OD towards the open eye, even when followed by long-term binocular recovery. Two marmosets subjected to 3 weeks of MD from 3 weeks of age exhibited clear afferent segregation in at least parts of V1. Brief disruption of correlated binocular inputs may have served to preserve, and probably enhance the normally transient columnar OD pattern of juvenile marmosets.

I have analysed responses of single neurons in cat area 17 to binocular stimuli under conditions that result in perceptual suppression of vision in one eye in humans. In normal animals, a paradigm of binocular contour rivalry was tested. The response of a binocular cell in V1 to an optimally oriented grating in one eye is powerfully depressed when gratings of very different orientation are suddenly presented to the other eye, while contours of matching orientation cause the well-known disparity-selective facilitation. However, neuronal responses to persistent rivalrous stimuli do not often exhibit spontaneous alternations between states of dominance and suppression, which might be expected in view of alternations of perceptual dominance in humans under such conditions. Whether or not suppression is triggered by rivalrous contours depends on the immediate history of visual stimulation. Binocular responses are consistently depressed below monocular control levels only when stimulation through one eye with contours of inappropriate orientation is preceded by stimulation of the other eye with a grating of optimum orientation, while there is no suppression with simultaneous stimulus onset: thus neurons display **interocular control of responsiveness**.

In most squinting humans, single vision is maintained through unilateral or alternating suppression. In cats and monkeys that have been rendered strabismic early in life, dominant-eye responses of striate cortical neurons to optimum gratings are dramatically reduced when gratings of *any* orientation, whether matching or orthogonal, are presented to the non-dominant eye. Like rivalrous suppression in normal animals, this phenomenon is characterized by independence of disparity, broad spatial frequency tuning and dependence on the sequence of stimulation. I propose that reciprocal inhibition between neighbouring ocular dominance columns in V1, over a number of orientation domains, mediates interocular suppression in both normal and strabismic subjects, vetoing signals from one eye in situations that would otherwise cause double vision and confusion.

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STATEMENTS

All experiments and analyses reported in this thesis were performed by me. The technique for flat-mounting marmoset visual cortex (Chapter 2) was developed in collaboration with Dr Peter Kind.

No part of my thesis has been accepted or is currently being submitted for any degree or diploma or other qualification in this University or elsewhere.

Oxford, 20 June, 1994

Frank Sengpiel

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1. INTRODUCTION

The primary visual cortex is probably one of the most extensively studied, and best described, areas of the mammalian central nervous system, in structural as well as in functional and in developmental respects. But it was not until just over a hundred years ago, that the crucial importance of the striate area at the occipital pole of the cerebral cortex for conscious visual perception was revealed.

As early as the 17th century, the French scientist and philosopher René Descartes had postulated in his *Traité de l'homme* that in the brain there had to be some kind of representation of the physical images projected onto the back of the two eyes (Fig. 1-1):

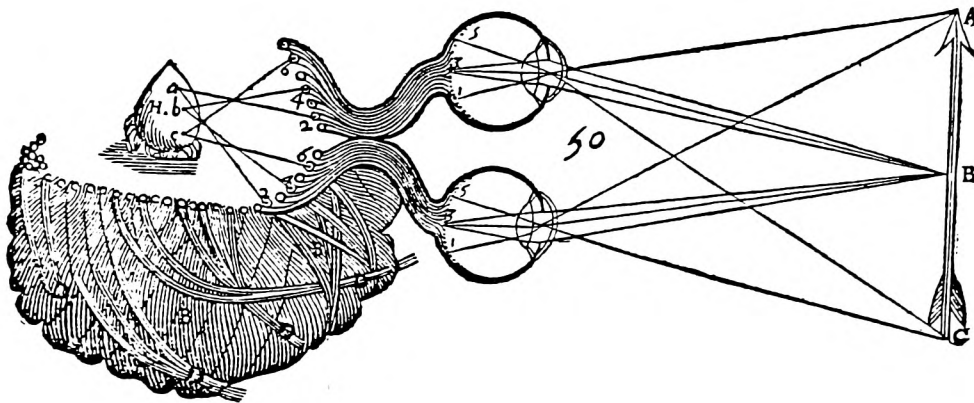


Figure 1-1: Representation of the retinal images of object ABC on the "internal surface of the brain" (the walls of the ventricles) as proposed by Descartes (Fig. 50 from *L'homme*, 1664)

"... Whence, just as the different ways in which these rays [that come from points *A*, *B*, and *C*] exert pressure on points *1*, *3*, and *5* trace a figure at the back of the eye corresponding to that of object *A*, *B*, *C* ..., so, evidently, the different ways in which tubules *2*, *4*, and *6*, and the like are opened by filaments *1-2*, *3-4*, and *5-6* ... must also ... trace on the internal surface of the brain a figure corresponding to that of object *A*, *B*, *C* (... une figure qui se rapporte à celle de l'objet *A*, *B*, *C*, sur la superficie interieure du cerveau)..."

However, Descartes thought that it was not those figures 'imprinted on the internal surface' of the brain that gave rise to perception, "... but only those traced in spirits on the surface of [the pineal] gland *H*, where the seat of imagination and common sense is, that should be taken ... to be the forms or images that the rational soul will consider directly when ... it will imagine or sense any object."

Even Thomas Willis, who, in his *Cerebri Anatome* of 1664, was the first to postulate that the cerebral cortex itself is the seat of perception, memory and voluntary action, regarded the cortex as a homogeneous sheet made of 'cortical' grey and 'medullary' white substance. On February 2, 1776, the Italian medical student Francisco Gennari made a discovery that proved this view wrong: in cross-sections of ice-hardened human brains he found what he called the 'third' substance, a whitish stripe or a pair of parallel stripes lying horizontally through the cortex (Gennari, 1782, cited by Glickstein & Rizzolatti, 1984). He wrote that this stripe: "... is somewhat obscure in the anterior part of the brain, but it can be detected more and more clearly in the posterior part of the brain. Moreover, in the medial part of the posterior lobe of the brain ... is the place in which I observed this substance of which I am speaking most elegantly coalesced into a small, very white line. In no other place in the cortex have I seen this line more clearly..."

This easily identifiable area containing the *stria of Gennari* became subsequently known as the *striate cortex*. But despite known anatomical differences between certain parts of the cerebral cortex, it was still generally agreed around the middle of the 19th century that functions that depend on an intact cortex could not be localized within it but were thought to be diffused throughout it (Glickstein & Whitteridge, 1987).

The first major discovery to change that view was made by the French physician Paul Broca. He reported aphasia in four patients with a lesion in a circumscribed region in the left frontal lobe which has since become known as Broca's area (Broca, 1861). The localization of brain functions was soon to be widely recognized, and twenty years after Broca's report the German physiologist Hermann Munk was the first correctly to identify the occipital lobes as essential for vision (Munk, 1881):

"If one extirpates the whole cortex on the one side of the occipital lobe the monkey becomes hemiopic. He is blind, cortically blind for those halves of both retinae which are on the side of the lesion..."

From a compilation of case studies of human hemianopia the Swedish neuropathologist Henschen (1892, cited by Glickstein & Whitteridge, 1987) finally concluded that the striate cortex on the lips and banks of the calcarine fissure is the primary visual area ("Sehsphäre") of the cortex. In his seminal work on the cytoarchitecture of the cerebral cortex, Brodmann (1909) described this region as "Feld 17", *area 17*, a term which is used synonymously with *striate cortex* and *V1* to refer to the primary visual cortex.

The first reasonably accurate mapping of the visual field on the striate cortex was achieved by the Japanese physician Tatsuji Inouye (1909, cited by Glickstein & Whitteridge, 1987). He had studied Japanese soldiers who suffered from visual field deficits as a consequence of bullet injuries to the occipital cortex received during the Russo-Japanese War of 1904-05. He found that the horizontal meridian is mapped at the base of the calcarine fissure, the upper visual field on its lower bank and lip and the lower visual field on the upper bank and lip. Furthermore, the central visual field is mapped caudally and the periphery towards the anterior end of the calcarine fissure.

Thus, it had been shown that, quite similar to the fashion envisaged by Descartes (1664), *the visual field is represented retinotopically on the primary visual cortex* (see Talbot & Marshall, 1941). However, for another fifty years nothing was known about *how* information about the visual world is encoded at the level of single neurons, the anatomical and functional units of the brain. This changed radically when Hubel and Wiesel (1962) published their work on "Receptive fields, binocular interaction and functional architecture in the cat's visual cortex", the first of a series of remarkable papers that eventually won them the Nobel Prize in Medicine in 1981.

1.1. The primary central visual pathway

In mammals, the projection from the retina *via* the dorsal lateral geniculate nucleus (dLGN, LGN) of the thalamus to the primary visual cortex constitutes the major central visual pathway. Other sites receiving direct retinal projections (apart from the tiny input to the suprachiasmatic nucleus) are the superior colliculus (SC) of the midbrain and several nuclei of the pretectal region. These areas are important for the control of eye movements and the mediation of various visual reflexes, respectively, but are not considered here further.

In primates, the retinal ganglion cells project to the dLGN in such a manner that axons of cells in the nasal hemiretina (i.e. medial to the fovea) cross in the optic chiasma to terminate in the contralateral dLGN, while the axons originating from ganglion cells in the temporal hemiretina do not cross but terminate in the ipsilateral dLGN. Thus, each LGN receives inputs from the ipsilateral halves of the two retinae which in turn represent the contralateral visual hemifield. This pattern of partial decussation was first described in words by Isaac Newton in his *Opticks* (1704) and, in 1750, depicted by the British ophthalmologist and surgeon John Taylor (Fig.1-2). However, inputs from the two eyes are separate at that stage, as the retinal ganglion cells project to different laminae of the LGN. In humans and Old World primates, the LGN is six-layered, consisting of two ventrally located magnocellular layers (1 and 2) and four dorsally located parvocellular layers (3, 4, 5, and 6); laminae 1, 4, and 6 are connected to the contralateral eye and laminae 2, 3, and 5 to the ipsilateral eye.

In cats and other carnivores which show a similar pattern of decussation of optic nerve fibres (although there is a considerable crossed projection from the temporal retina especially for W and Y ganglion cells; see Stone & Fukuda, 1974b; Kirk et al., 1976a,b), the LGN consists of four main cellular layers, with laminae A and C receiving input from the contralateral retina and laminae A1 and C1 being innervated by the ipsilateral retina (Guillery, 1970). Relay cells of all laminae (in both primates and

carnivores) in turn project to the striate cortex, where the vast majority of geniculate terminals is found in layer 4, the granular layer. However, termination of afferents from the two eyes remains largely segregated, giving rise to the so-called ocular dominance bands (see below and Chapter 2).

The work presented in this thesis is concerned with binocular stimulus integration in the primary visual cortex. However, in order to analyse and interpret the neuronal mechanisms that enable the striate cortex to fulfill this computational task, it is important first to review briefly the response properties of those cells which provide the sensory input to area 17 neurons.

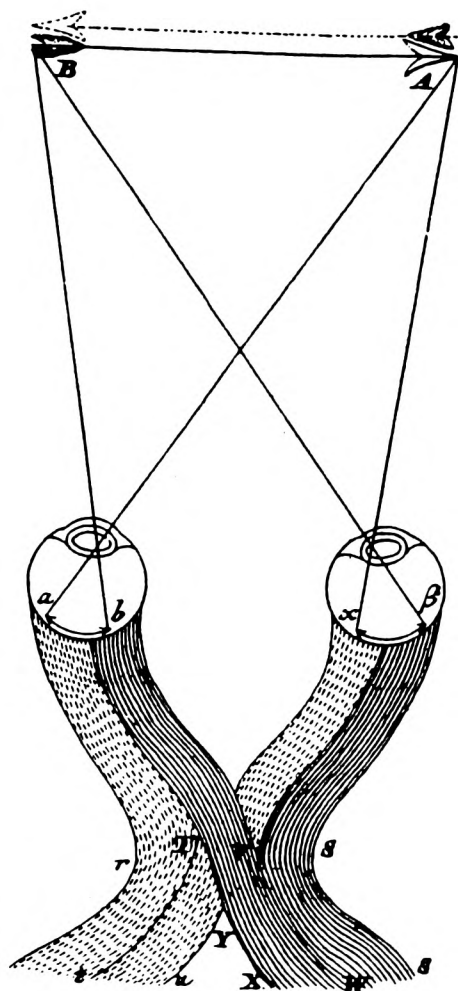


Figure 1-2: The partial decussation of optic nerve fibres from the two eyes in the optic chiasma of humans was first illustrated by John Taylor (1750).

1.1.1. Receptive fields of retinal ganglion cells

Cat retinal ganglion cells were the first cells of the mammalian visual system whose physiology was studied by means of single-unit recording. As demonstrated earlier by Hartline (1938) for single optic nerve fibres in the frog, Kuffler (1953) found that for each cat ganglion cell there is a specific area of the retina and therefore of the visual field, where stimulation with light causes a change in the cell's discharge pattern. This area is called the *receptive field* of the cell. Kuffler showed that mammalian retinal ganglion cells generally possess *concentric antagonistic* receptive fields composed of a roughly circular centre and an annular surround. He distinguished two classes of retinal ganglion cells which are present in approximately equal numbers: the 'on'-centre and the 'off'-centre cells. 'On'-centre cells are excited when light is shone on the central region or light is switched off in the periphery, and their spontaneous discharge is inhibited and responses generated by central illumination antagonized when the surround is illuminated. 'Off'-centre cells respond in a reverse fashion.

Later, Cleland and Levick, and Stone and co-workers found that with respect to their patterns of discharge when stimulated visually as well as their axonal conduction velocities there are three main physiological classes of ganglion cells, namely X, Y, and W cells (Cleland et al., 1971; Stone & Hoffmann, 1972; Cleland & Levick, 1974a,b; Stone & Fukuda, 1974a). All of those can be either of the 'on'-centre or the 'off'-centre type.

Morphologically, three main types of ganglion cells can be distinguished as well, namely α , β and γ cells (Boycott & Wässle, 1974). Cleland et al. (1975) and Levick (1975) succeeded in identifying α with Y cells and β with X cells. The small W (γ) cells form a rather heterogeneous group, projecting mainly to the superior colliculus (SC), with a minor projection to the LGN C laminae. X cells represent about 45% of all retinal ganglion cells. They have medium-size somata and small dendritic arbors, and they project exclusively to the LGN (mainly the A laminae) with medium conduction velocity. X cells show the highest spatial resolution, respond to small spots with *sustained* discharge and integrate stimuli in a *linear* way across their receptive fields

(Enroth-Cugell & Robson, 1966). In contrast, Y cells (around 10% of the total) have large somata, extensive dendritic fields and thick, rapidly conducting axons which often bifurcate and project to both LGN (A and C laminae) and SC. They respond *transiently* to rather large stimuli, in particular moving ones, and integrate *non-linearly* across their receptive fields (Enroth-Cugell & Robson, 1966).

Ganglion cells of the macaque retina can be subdivided into two main groups, originally named 'tonic' and 'phasic' cells (Gouras, 1968). Retinal ganglion cells in the latter group, with fast conducting axons (Gouras, 1969), almost exclusively project to the magnocellular layers of the LGN: they are now named $P\alpha$ or M cells, while the 'tonic', so-called $P\beta$ or P cells, which show linear spatial summation and have medium conduction velocities, project to the parvocellular layers (Blakemore & Vital-Durand, 1981; Shapley et al., 1981).

1.1.2. Receptive fields of neurons in the lateral geniculate nucleus

Hubel (1960) first recorded from single units in the cat's lateral geniculate nucleus and found that the organization of their receptive fields closely resembles the concentric organization of retinal ganglion cell receptive fields. However, he noted that the antagonism between the centre and the surround is somewhat enhanced, a finding confirmed by Cleland et al. (1971). This enhancement is likely due to postsynaptic GABAergic inhibition (Sillito & Kemp, 1983). Anatomically, more than 90% of the neurons in the LGN are relay cells (Lin et al., 1977) which interact with one another by means of dendrodendritic synapses. Local inhibitory interneurons are sparse but show extensive ramification of dendrites; they are activated either directly by monocular retinal afferents or disynaptically by axon collaterals of relay cells (Kato et al., 1971; Dubin & Cleland, 1977), and they also receive descending input from layer 6 of the cortex (see below). All relay cells receive direct excitatory input from a single or a few retinal ganglion cells from one eye, and there is virtually no convergence of input from both the 'on' and 'off' channels or both X and Y pathways of the retina (Cleland et al.,

1971; Hoffmann et al., 1972). Therefore, the classification devised for retinal ganglion cells can be applied to LGN neurons as well.

1.1.3. Influences of corticofugal feedback on responses of LGN neurons

Although there appears to be no significant transformation of receptive field properties from the retinal ganglion cells to the lateral geniculate, it seems unlikely that the LGN simply acts as a relay station on the way to the primary visual cortex. One cue to its integrative function may be provided by the fact that it receives extensive back-projections from about 50% of the layer 6 pyramidal cells of the striate cortex (Gilbert & Kelly, 1975) which actually outnumber the ascending geniculocortical projections (Robson, 1983). The corticofugal projections are roughly retinotopically organized, thus completing a feedback loop between sites in LGN and striate cortex that represent the same region in the visual field (Holländer, 1970). The corticogeniculate terminals synapse preferentially on dendritic shafts of GABAergic inhibitory interneurons, with synapses occurring three times as often on interneuron dendrites as on relay cell dendrites (Weber et al., 1989). These interneurons in turn inhibit LGN relay cells mainly postsynaptically in a feed-forward fashion (Dubin & Cleland, 1977).

The striate cortex should be capable of exerting a strong modulatory influence on visual response properties of LGN neurons *via* the described circuitry. Indeed, two main effects of corticofugal influence have been established. The first relates to the above-mentioned enhancement of the centre-surround antagonism in LGN compared to the retina. When stimulated with moving bars of varying length, most LGN cells exhibit pronounced length tuning (Cleland et al., 1983; Jones & Sillito, 1991). This is significantly reduced when the corticogeniculate input is eliminated by aspiration of areas 17 and 18 (Murphy & Sillito, 1987). Further evidence for the enhancement of geniculate length tuning through cortical feedback derives a) from the fact that layer 6 cells display optimal bar lengths in the range required to provide the appropriate inhibitory input to length tuned LGN cells (Grieve & Sillito, 1991a) and b) from the sensitivity of the strength of the surround antagonism in the LGN to the alignment of

centre and surround stimuli, reflecting input from orientation-tuned cells (Sillito et al., 1993).

Pronounced orientational selectivity is a property that emerges at the level of the primary visual cortex (see below), although weak orientational biases have been reported for LGN neurons (Vidyasagar & Urbas, 1982; Shou & Leventhal, 1989) and even for retinal ganglion cells (Levick & Thibos, 1980). Alignment dependence of surround inhibition is, however, seen for any absolute stimulus orientation and can, therefore, not be explained by an LGN cell's preference for a single orientation but only by convergence of inhibitory inputs from cortical cells with a range of preferred orientations (Sillito et al., 1993).

Binocular interactions constitute the second major effect of corticofugal feedback on receptive field properties in the LGN. In agreement with the aforementioned strictly monocular retinal input of all geniculate neurons, Hubel (1960), Hubel and Wiesel (1961) failed to record any cells that could be discharged by monocular stimulation of both eyes. However, Sanderson et al. (1971) reported weak excitatory receptive fields for 11 out of 113 LGN cells, and some cells show subliminal excitation (Schmielau & Singer, 1977; Xue et al., 1987). When the neuronal discharge level is raised by stimulating the dominant eye ('conditioning stimulus') and a test stimulus is presented to the 'silent' eye at the corresponding position in the visual field, a majority of LGN cells exhibits inhibitory binocular interactions. (Singer, 1970; Sanderson et al., 1971; Schmielau & Singer, 1977; Kato et al., 1981; Xue et al., 1987). As inhibition through the non-dominant eye is not abolished by ablation of areas 17 and 18, it was initially concluded (Sanderson et al., 1971) that binocular interactions are mediated by neurons whose dendrites cross the borders from one LGN layer to another (Guillery, 1966) or which receive inputs from collaterals of principal cells in other layers (Kato et al., 1971). However, by comparing binocular interactions before and during reversible inactivation of areas 17 and 18 by cooling, Schmielau and Singer (1977) found that most of the inhibition and all of the subliminal excitation elicited by stimulation of the 'silent' eye is actually mediated through the cortical loop.

1.2. Receptive fields and functional architecture of the striate cortex

The following paragraphs are intended to give a review of the functional and structural organization of the striate cortex of cats and primates particularly with respect to its integrative capacities and the underlying microcircuitry.

1.2.1. Receptive fields of neurons in the primary visual cortex

Diffuse light, a stimulus which quite effectively drives most retinal ganglion cells and even the majority of geniculate neurons, fails to elicit significant responses from area 17 neurons. However, small stationary spots of light switched on and off and, more so, moving spots evoke responses from many cortical cells (Hubel, 1959), while others remain largely unresponsive. Obviously, processing of visual information in the primary visual cortex is accompanied by a substantial transformation of receptive field properties. Since the seminal work of Hubel and Wiesel (1962, 1968) it is known that the two main response properties that emerge at the level of the primary visual cortex are

- 1) *orientation selectivity*, and
- 2) *binocularity*.

Using narrow bars (slits) of light, dark bars against a lighter background or borders between areas of different brightness ('edges'), Hubel and Wiesel (1962) demonstrated that for virtually all cells in cat striate cortex the orientation of the stimulus, whether it is moving or flashed stationarily, is critical for eliciting a vigorous response. If the stimulus orientation differs by 90° from the so-called *preferred orientation*, it will evoke very little or no discharge. This finding was later repeated for macaque monkeys (Hubel & Wiesel, 1968), with the one important exception that units in layer 4C, the layer receiving the main geniculate input, resemble geniculate neurons with their concentrically organized receptive fields and a lack of orientation selectivity. Subsequently, such 'non-oriented' cortical cells have been reported, though they are less common, in other layers of primate cortex (e.g. Livingstone & Hubel, 1984).

In contrast to retinal ganglion cells and the lateral geniculate, where the vast majority of cells can be monocularly driven only through one eye (see above), a majority of cells in the primary visual cortex of both cats (Hubel & Wiesel, 1962) and macaques (Hubel & Wiesel, 1968) can be discharged through either eye and are, therefore, termed *binocular*. In order to describe the relative strength of the (excitatory) input from each eye to a cell, Hubel and Wiesel (1962) devised a scheme of seven *ocular dominance groups*: all cells that could be driven only through the contralateral eye or only through the ipsilateral eye were placed in ocular dominance group 1 (OD1) and OD7, respectively. Cells with much stronger input from one than from the other eye were classified as OD2 (contralateral eye dominant) or OD6 (ipsilateral eye dominant), each of these groups including cells with only subliminal input from the non-dominant eye. Cells showing weak dominance of the contralateral or the ipsilateral eye were classified as OD3 and OD5, respectively, and cells with equal inputs from both eyes as OD4. For cat striate cortex, a proportion of 80% binocular cells (OD2-6) was reported in the original work by Hubel & Wiesel (1962), with an overall bias in the ocular dominance (OD) distribution towards the contralateral eye, even in the part of V1 where the centre of the visual field is represented (Hubel & Wiesel, 1962; Blakemore & Pettigrew, 1972). In contrast, Hubel and Wiesel (1968) suggested that in the macaque only about 60% of all striate neurons are binocular, with no significant bias in the OD distribution towards either eye and a marked paucity of OD4 cells. On the other hand, others have reported about 80% binocularity in the macaque primary visual cortex (e.g. Blakemore et al., 1978).

Hubel and Wiesel (1962) observed that, despite generally having binocularity and orientation selectivity in common, responses of cortical cells fell into two main classes, named simple and complex, respectively. That dichotomy was subsequently confirmed, albeit modified by some authors (see Henry, 1977, for review), and is followed in this work.

Simple cells

According to the original definition by Hubel and Wiesel (1962), all those cortical cells are classified as *simple* whose receptive fields consist of distinct 'on' and 'off' subregions and whose responses to stationary or moving stimuli can be predicted from the arrangement of these regions. Generally, simple cell receptive fields consist of two to five more or less elongated (roughly rectangular) subregions which are arranged in parallel, with neighbouring zones being of opposite response type and mutually antagonistic.

Experimental data indicate that simple cells perform a *linear summation* of visual input both within each subregion and across their receptive fields (Movshon et al., 1978a), and their receptive field organization has been successfully modelled by fitting Gabor functions (sine wave functions multiplied by a two-dimensional Gaussian) to the spatial response profile as obtained by stimulation with stationary bars of light (Daugman, 1980; Jones & Palmer, 1987; Freeman & Ohzawa, 1990).

As a result of its linear properties, a simple cell's discharge increases when an optimally oriented stimulus is lengthened, provided it remains within the discharge region. A simple cell's *preferred orientation* corresponds to the orientation of the long axis of its subregions, when the stimulus is a stationary or moving bar of sufficient length. However, for shorter stimuli the orientation tuning broadens, and for moving spots the strongest, so-called axial, response may be elicited by motion *along* the preferred axis of orientation, i.e. orthogonal to the preferred axis of bar motion (Wörgötter & Eysel, 1991). For moving bars and gratings, the *preferred direction* of motion of a simple cell can sometimes be inferred from an asymmetry in the receptive field structure with respect to 'on' and 'off' zones (Hubel & Wiesel, 1962), but is often independent of contrast and therefore not accounted for by simple summation of 'on' and 'off' responses.

Another consequence of the linear behaviour of simple cells is their sinusoidally modulated response to drifting gratings at all spatial frequencies that elicit significant discharge (though often partially rectified because of the absence of high maintained

discharge). Fourier analysis, therefore, yields a first-order component of the response at the drift frequency of a sinusoidally modulated grating that is equal to or greater than the zero-order component or mean discharge (for review see Skottun et al., 1991), thus providing a quantitative criterion for distinguishing simple from complex cells.

Complex cells

By default, Hubel and Wiesel (1962) defined those cortical cells as *complex* which do **not** give spatially separate 'on' and 'off' responses to stationary spots of light. The great majority of complex cells have rather uniform receptive fields, and mixed 'on'/'off' responses of similar strength can be evoked throughout the spatial extent of the receptive field. Only a small fraction of complex cells possess obvious inhibitory sidebands flanking the central discharge region. When separate 'on' and 'off' regions can be discerned, they are not mutually antagonistic.

Complex cells are *nonlinear* in their spatial summation across the receptive field (Movshon et al., 1978b). To drifting sinusoidal gratings they generally respond with an elevation of the mean firing rate though a modulated discharge is seen at low spatial frequencies in some complex cells. The receptive fields of complex cells appear to be made up of a number of non-superimposed 'subunits' that have summing characteristics similar to the receptive fields of simple cells. The spatial frequency selectivity of the complex cells is correlated with the dimensions of these 'subunits' (Movshon et al., 1978b).

Like simple cells, all complex cells show orientation selectivity, and a majority displays some degree of direction selectivity. However, the orientation tuning of complex cells is, on average, less sharp than that of simple cells (Henry et al., 1974; Rose & Blakemore, 1974).

'Standard' and 'special' complex cells have been discriminated by Gilbert (1977) on the basis of presence and absence, respectively, of length summation over the full extent of the receptive field's excitatory discharge region.

Hypercomplexity

Hubel and Wiesel (1965) described a third class of visual cortical cells, termed *hypercomplex*, that was characterized by optimal responses to stimuli restricted in length at one end or both and a marked decrease or even total suppression of response when the stimulus length was further increased. Later, this property was found to be associated with otherwise typical simple or typical complex cells that are now generally referred to as end-stopped or end-inhibited. The so-called end-zones at one or either end of the long axis of the receptive field show the same orientation preference as the central discharge region (Orban et al., 1979). The length preference has been shown to at least in part result from GABA-mediated inhibitory inputs (Sillito & Versiani, 1977). These are thought to originate from cells with receptive fields much longer than the recipient cell's excitatory central region, but centred on the same region (Bolz et al., 1989; Grieve & Sillito, 1991a). Recent evidence suggests that an *excitatory* input to layer 4 from layer 6 cells with *short* receptive fields contributes to the generation of length tuning (Grieve & Sillito, 1991b).

Streaming versus hierarchy in primary visual cortex

When Hubel and Wiesel (1962, 1965a) originally described the responses of neurons in the visual cortex as simple, complex, and hypercomplex, that classification implied a hierarchy in which cells with more 'complex' receptive fields were thought to derive their inputs from those with 'simpler' receptive fields: projections from geniculate neurons would converge onto simple cells which in turn would project upon complex cells (Hubel & Wiesel, 1962). Support for this hypothesis came from the fact that simple cells are predominantly found in the layers that receive geniculocortical afferents.

However, in contradiction to the hierarchical scheme, cells from *all* classes receive monosynaptic geniculate input as revealed by electrical stimulation of the optic radiation (Bullier & Henry, 1979a). Furthermore, response properties do not appear to depend on the 'ordinal position' of the cells, i.e. on whether they receive mono-, di- or

polysynaptic afferent input. Rather, a correlation between receptive field properties of cortical neurons and the type of their geniculate input has been found (Hoffmann & Stone, 1971; Bullier & Henry, 1979b): the input from X- and Y-dLGN cells onto individual cortical cells remains separate (Martin & Whitteridge, 1982, 1984). These data suggest that the X- and Y-*streams* found in the retina and LGN are preserved to some extent at the cortical level: most complex and many simple cells receive excitatory input from Y cells, while all end-inhibited simple cells and half of the simple cells without end-inhibition receive X-cell input (Bullier & Henry, 1979b). It should, however, be noted that even though the Y-stream makes a significant contribution to the strength of the excitatory response of many area 17 cells, its contribution to most receptive field properties is not distinguishable from non-Y-type inputs (Burke et al., 1992).

A clear correlation between morphology and physiology of area 17 neurons, as demonstrated for retina and LGN, has not been found, although the stellate cells of layer 4 have been shown predominantly to have simple receptive fields (Gilbert & Wiesel, 1979). On the other hand, pyramidal cells as well as, for instance, the inhibitory basket cells can have simple or complex response properties and can receive X- or Y-type geniculate inputs (Gilbert & Wiesel, 1979; Martin et al., 1983).

1.2.2. Functional architecture of the primary visual cortex

The integrative capacities of the primary visual cortex depend largely on the high degree of intra-areal connectivity, both in the vertical dimension, i.e. across the cortical layers, and in the horizontal dimension (for a review see Gilbert, 1983). This rich connectivity results in diverse circuitries, which may serve to explain many established physiological properties of V1 as well as novel visual response properties that will be described in the course of this thesis (Chapter 3 and Chapter 4). The basic features of the overall functional organization of area 17 in cats and macaques will also be reviewed for comparison with my findings on the functional architecture of marmoset visual cortex (Chapter 2).

Vertical connectivity

According to Brodmann, the mammalian primary visual cortex is, like all other cortical areas, anatomically subdivided into six more or less distinct layers, which for the monkey have been named as follows (Brodmann, 1904-05, 1909)¹:

- I. Lamina zonalis (layer 1)
- II. Lamina granularis externa (layer 2)
- III. Lamina pyramidalis (layer 3)
- IV. { IVa. Lamina granularis interna superficialis (layer 4A)
- { IVb. Lamina intermedia (layer 4B)
- { IVc. Lamina granularis interna profunda (layer 4C)
- V. Lamina ganglionaris (layer 5)
- VI. Lamina multiformis (layer 6)

Alternative schemes have been suggested by von Bonin (1942), who subdivided layer 3 into 3A and 3B (with 3B apparently being equivalent to Brodmann's 4A) and layer 4 into 4A and 4B, and by Hassler and Wagner (1965) who considered Brodmann's sublayer 4B, the layer containing the stria of Gennari, as sublayer 3C. The lamination scheme proposed by Lund (1973) follows that of Brodmann with some modifications of the borders of layers 4B and 4C, and is now widely accepted.

Layer 1 contains mainly axonal and dendritic arborization and few cells, the so-called Cajal-Retzius cells. Layers 2 and 3 consist mainly of small pyramidal cells and smooth stellate cells; the border between these layers is poorly defined in Nissl stained material. The occurrence of spiny stellate cells (beside aspiny stellate cells) distinguishes Brodmann's layer 4 from the other layers, with sublayer 4C showing the most prominent cell condensation in area 17. Layers 5 and 6 both consist of large pyramidal neurons but can be clearly distinguished in Nissl stained sections, where layer 5 appears as a pale and layer 6 as a dark band.

For the macaque, the following pattern of intrinsic vertical connections has been revealed by anterograde and retrograde transport of small amounts of horseradish

¹ For simplicity, and to avoid confusion with abbreviations like V1, arabic numerals will be used subsequently.

peroxidase (HRP) injected into single cortical layers. Geniculocortical terminals of the magnocellular pathway are found in layer 4C α , while cells in the parvocellular layers of the LGN project to both layers 4C β and 4A (Lund, 1973; Hendrickson et al., 1978; Blasdel & Lund, 1983). Further geniculate inputs to layers 1 and 6 (Hubel & Wiesel, 1972a; Blasdel & Lund, 1983) and to cytochrome oxidase-rich regions (so-called 'blobs') in superficial layers (Livingstone & Hubel, 1982) have been described. Layers that receive prominent input from lamina 4C are 4A (from 4C β), 4B (from 4C α) and 5A (Fitzpatrick et al., 1985). Both layers 4A and 4B project to layers 2 and 3, which also receive minor projections from layers 5A and 5B (Blasdel et al., 1985). HRP injections into layer 5 revealed projections intrinsic to this layer, while the most prominent input comes from layers 2/3. Layer 6 in turn receives its major input from layer 5, as well as inputs from layer 4B, layers 2/3, 4A, and 4C α ; layer 6 pyramidal neurons project mainly to layers 2/3, 4A and 4C (Blasdel et al., 1985).

The circuitry derived from anatomical studies is in good agreement with the spatio-temporal distribution of synaptic activities as revealed by current source density analysis (Mitzdorf & Singer, 1979).

For the cat, six layers can be distinguished within area 17 similar to the macaque monkey (O'Leary, 1941; Otsuka & Hassler, 1962), although they do not stand out as distinctly in Nissl preparations. Again, layer 4 is defined by the presence of spiny stellate cells. Geniculocortical axons mainly terminate in layer 4, up to the layer 3/4A border, with some collaterals being sent to upper layer 6: synapses are excitatory, and are mainly found on dendritic spines (LeVay & Gilbert, 1976). A partial segregation of X cell input (to lower layer 4) and Y cell input (to upper layer 4 and the layer 3/4A border) may be present (Gilbert & Wiesel, 1979, 1983; but see Martin & Whitteridge, 1984; Humphrey et al., 1985). The great majority of layer 4 cells possess small receptive fields of the simple type, and many of them show end-inhibition (Hubel & Wiesel, 1962; Gilbert, 1977). Smooth stellate cells show extensive axonal arborization within layer 4, while spiny stellate cells predominantly project to the superficial layers, with collaterals remaining within layer 4 (Gilbert & Wiesel, 1979).

Layers 2 and 3 contain mainly standard complex cells (often end-stopped) with small to intermediate receptive field sizes (Gilbert, 1977). Their axons branch richly within the superficial layers (see below) and project to both the underlying layer 5 (Gilbert & Wiesel, 1979) and to other cortical areas, among them areas 18, 19 and suprasylvian areas (Gilbert & Kelly, 1975), as well as to the contralateral hemisphere *via* the corpus callosum (Innocenti, 1980).

Layer 5 consists of standard and special complex cells whose intrinsic axon collaterals project mainly to layer 6, which contains a mixture of simple cells (in the upper part) and complex cells with very long receptive fields (Gilbert, 1977). Layer 6 axon collaterals branch primarily in layer 4, where they are restricted to either the upper or the lower half (Gilbert & Wiesel, 1979). The projection sites of the infragranular layers are subcortical: from layer 5 to the superior colliculus, pretectum and striatum and from layer 6 to the lateral geniculate nucleus and the claustrum (Gilbert & Kelly, 1975).

Current source density analysis of electrically evoked potentials yielded similar results regarding excitatory pathways in cat area 17 (Mitzdorf & Singer, 1978). Recently, *in vivo* and *in vitro* intracellular recordings have demonstrated that connections intrinsic to area 17 (the great majority of which are excitatory; see Kisvárdy et al., 1986) rather than the thalamic afferents provide the main excitatory input arriving at any V1 neuron, in particular in supragranular layers (Douglas et al., 1989; Nicoll & Blakemore, 1993).

Horizontal connectivity

Intracellular injections of HRP first demonstrated the existence of long-range connections within area 17 (Gilbert & Wiesel, 1979). The anatomical substrate of these connections, axon collaterals of pyramidal cells and spiny stellate cells travelling tangentially to the cortical surface over distances of up to 4 mm, show a clustered distribution (Gilbert & Wiesel, 1983). They form excitatory synapses predominantly on apical dendrites of pyramidal cells (Luhmann et al., 1990b). Extracellular axonal

tracing revealed that these horizontal connections are highly convergent, each small HRP injection site receiving input from regularly spaced clusters of cells covering a large area (Rockland & Lund, 1982). The axon collaterals of a single pyramidal cell can form clustered projections within its own layer and in another layer, where they are in register with the former: the cortical area covered by the clusters often appears to represent a part of the visual field larger than the cell's receptive field (Gilbert & Wiesel, 1983). In the cat, the clustered pattern of tangential connections evolves from an unclustered neonatal pattern during the second postnatal week through rapid rearrangement (Callaway & Katz, 1990; Luhmann et al., 1990a; Lübke & Albus, 1992).

It has been suggested (Mitchison & Crick, 1982) that the clustering results from the fact that axons link cells with similar orientation preferences. Supporting evidence has come from cross-correlation analysis of horizontal interactions between pairs of recording sites separated by up to 2 mm, showing excitatory interactions between, or common input to, cells with similar preferred orientations as well as the same eye preference (Ts'o et al., 1986).

Long-range intrinsic connections might serve to mediate neuronal responses beyond the classical receptive field (e.g. Nelson & Frost, 1978, 1985; Gilbert & Wiesel, 1990) and to synchronize firing of spatially separate cells if they respond to the same visual stimulus (e.g. Gray et al., 1989), thus binding the activity of feature-detecting neurons, which respond to a particular object, into coherent representations (for review see Singer, 1990).

In contrast to excitatory pyramidal-cell projections, inhibitory projections of GABAergic cells are mostly shorter than 1 mm and only loosely clustered (Albus et al., 1991). These inhibitory intrinsic connections are widely thought to play a key role in the generation or at least the sharpening of cortical orientation and direction selectivity (see Eysel, 1992), although there is some evidence (Chapman et al., 1991) that the underlying orientation selectivity of receptive fields in V1 arises from convergence of excitatory inputs from geniculate cells with aligned receptive fields, as originally proposed by Hubel and Wiesel (1962). Evidence in favour of the involvement of

intracortical inhibition in the generation of both directional and orientational tuning has come mainly from experiments in which the action of the principal cortical inhibitory transmitter, γ -aminobutyric acid (GABA), is blocked by antagonists such as bicuculline, resulting in broadening or even loss of tuning (Sillito, 1975, 1977, 1979; Wolf et al., 1986). A number of models has been put forward to explain the sharpness of cortical orientation selectivity in terms of either cross-orientation inhibition (first described by Morrone et al., 1982) or iso-orientation inhibition (for a review see Ferster & Koch, 1987). The latter posits that each cell is inhibited by other cells with partially overlapping receptive fields and similar orientation preferences, thus reducing its receptive field width relative to the length. Iso-orientation inhibition was first demonstrated using stimuli presented outside the classical receptive field (Blakemore & Tobin, 1972), but has recently been shown to originate from within the classical receptive field just like cross-orientation inhibition (DeAngelis et al., 1992).

Strong evidence for the sharpening of orientation selectivity through cross-orientation inhibition comes from experiments in which small cortical sites about 500 μm away from the recording site, with close to orthogonal preferred orientations, are inactivated by iontophoresis of GABA, resulting in an increase in response to non-preferred orientations for the neuron at the recording site (Eysel et al., 1990; Crook et al., 1991; Crook & Eysel, 1992). Inactivation of iso-orientation sites at horizontal distances of 500-1000 μm from a directionally selective cell often results in an increase in response at the recording site in either the preferred or the non-preferred direction (Eysel et al., 1988; Crook et al., 1992). The predominant mechanism for the underlying inhibition appears to be hyperpolarization rather than shunting inhibition (Douglas et al., 1991; Berman et al., 1991; Ferster & Jagadeesh, 1992).

Overall functional patterns

In their seminal work on cat and monkey area 17, Hubel and Wiesel (1962, 1963, 1968, 1974a) noted that, beside the continuous but somewhat sloppy retinotopic progression of receptive fields positions across the cortex, two key neuronal response properties are

mapped in an orderly, more or less discrete fashion over the surface of the primary visual cortex. In oblique electrode tracks penetrating all layers of V1, orderly successions of both preferred orientation and OD are frequently observed for neurons recorded along the track, while in tracks normal to the cortical surface both parameters hardly vary at all. Hubel and Wiesel (1962, 1963) concluded that the visual cortex is, similar to other sensory cortical areas (cf. Mountcastle, 1957, for cat primary somatosensory cortex) organized into *columns* that run perpendicularly to the cortical surface and contain cells with very similar response properties.

For both orientation preference and ocular dominance, a so-called *hypercolumn* (Hubel & Wiesel, 1974b) may be defined as a slab of visual cortex which consists of a set of columns rendering a complete local representation of the mapped feature, i.e. a full set of orientations (180°) and both eyes, respectively. The width of a hypercolumn of orientation or of OD is roughly 1 mm each in cat and macaque, resulting in small *modules* (Hubel, 1982) subtending 1 mm^2 of cortical surface which can encode all orientations present in a small part of the visual field for both eyes. Neighbouring modules analyse neighbouring but overlapping parts of the visual field. The average receptive field size of cells in V1 increases with eccentricity (i.e. the distance from the fovea or area centralis), but so does the average shift of receptive fields across one OD hypercolumn as the cortical magnification factor decreases (Daniel & Whitteridge, 1961; Tootell et al., 1982). Thus, at least for the upper layers of V1, both parameters (receptive field size and the reciprocal of magnification) remain roughly matched (Hubel & Wiesel, 1974b).

The exact overall patterns of OD and orientation columns and their topographical relationship to each other have been a subject of some controversy. Hubel and Wiesel (1963, 1968, 1974a) had described long sequences of small, clockwise or counterclockwise, shifts in preferred orientation when moving along the cortical surface; however, they also encountered areas in which orientations changed rapidly and apparently irregularly. The overall pattern of orientation columns has been visualized by a variety of techniques that allow monitoring of neuronal or metabolic activity during

or after exposure of the paralysed animals to gratings of a particular orientation. These techniques include the so-called 2DG method (autoradiography of uptake of radioactively labelled 2-deoxyglucose; e.g. Hubel et al., 1977b; Singer, 1981), the use of voltage-sensitive dyes (Blasdel & Salama, 1986) and imaging of intrinsic optical signals (Bonhoeffer & Grinvald, 1991). The latter revealed that iso-orientation domains (at least in cat visual cortex) only partly show the appearance of elongated bands with intervening lines of abrupt change in orientation preference ('fractures'; Blasdel & Salama, 1986) but are rather arranged in pinwheel-like patterns, with every orientation occurring once around the central singularities of orientation (Bonhoeffer & Grinvald, 1991). These patterns are in good agreement with the electrophysiological data as well as with the majority of theoretical models for the organization of orientation maps (e.g. Swindale, 1982).

Overall patterns of ocular dominance have been observed by means of three principally different approaches. Following intravitreal injection of tracers which are transported anterogradely across the retinogeniculate synapse, the distribution of geniculocortical terminals can be visualized (LeVay et al., 1978, 1980; Hendrickson et al., 1978). Alternatively, following monocular enucleation, the cytochrome oxidase, i.e. metabolic, activity of cells driven by the remaining eye can be mapped (Horton & Hubel, 1981; Hess & Edwards, 1987), or metabolic activity of cells driven by one eye can be visualized with the 2DG method after monocular stimulation of that eye (Kossut et al., 1983; Tieman & Tumosa, 1983; Löwel & Singer, 1993). The results obtained by all techniques show marked differences in the shape and regularity of OD domains in V1 of cats and various monkey species, which shall be discussed in detail later (Chapter 2).

It was first suggested that iso-orientation and OD bands intersect each other at right angles (Hubel & Wiesel, 1974a,b), a hypothesis that appeared to be contradicted by results of 2DG mapping of orientation columns (Hubel et al., 1978). However, recently employed imaging techniques revealed that the singularities of 'orientation centres' (Bartfeld et al., 1991) are aligned with the centres of OD columns (Bartfeld & Grinvald,

1992; Obermayer & Blasdel, 1993), and, to some extent, with local concentrations of high cytochrome oxidase activity ('blobs') in macaques (Humphrey & Hendrickson, 1983; but see Bartfeld & Grinvald, 1992): at the edges of OD columns, domains of iso-orientation indeed form parallel bands that tend to intersect the borders of the OD columns at angles of approximately 90° (Obermayer & Blasdel, 1993).

1.3. Functional development of the striate cortex

As functional capacities of the mammalian primary visual cortex such as binocular integration develop and mature postnatally and are subject to experience-dependent plasticity, the normal physiological development and some of the effects of altered visual experience will be described briefly here. With respect to the functional development of area 17, cats have been studied most extensively, and only data obtained from that species will be reviewed here. Many of the findings, however, apply to the development of the striate cortex of primates as well: relevant studies on primates will be discussed in Chapter 2.

1.3.1. Normal development

On average, lid-opening in kittens occurs on the eighth postnatal day, with the two eyes usually opening on the same day, but occasionally up to six days apart (Blakemore & Cummings, 1975). At that time, the optical quality of the eyes is poor and improves dramatically during the second and third postnatal week; by six weeks of age it is adult-like (for review see Movshon & Van Sluyters, 1981).

Recordings from kittens on the day of eye-opening, i.e. animals without patterned visual experience, showed that responsiveness of V1 neurons is considerably weaker than in adults, but all fundamental qualitative response properties (binocularity, orientation and direction selectivity) are present in at least some cells in the naive cortex, although even these cells lack the precision of stimulus specificity seen in the adult cortex (Hubel & Wiesel, 1963b; Blakemore & Van Sluyters, 1975; Frégnac & Imbert, 1978). The OD distribution appears to be adult-like, with the majority of cells being clearly binocularly driven (e.g. Hubel & Wiesel, 1963b). In layer 4, where the incidence of monocular cells is the highest, kittens show the normal periodic variation in eye dominance (Blakemore et al., 1975). However, geniculocortical terminals in one-week-old kittens, as revealed by transneuronal transport of ^3H -proline, are not yet obviously segregated (LeVay et al., 1978).

In the naive kitten cortex, more than a third of all cells are orientation selective or show an orientation bias (Blakemore & Van Sluyters, 1975). In contrast to the situation in adult cats, the orientation selective units are often monocular and most of them are simple cells found in layer 4 (Blakemore & Van Sluyters, 1975). Furthermore, it appears that, unlike in the adult cat, preferred orientations are not evenly distributed in the visually inexperienced animal but are biased towards vertical and horizontal orientations (Frégnac & Imbert, 1978).

In a normal visual environment, the cat's primary visual cortex develops near-adult overall properties within the first five postnatal weeks, with respect to both ocular segregation (LeVay et al., 1978) and orientation selectivity (Blakemore & Van Sluyters, 1975; Frégnac & Imbert, 1978; Thompson et al., 1983). Over the same period, most of the synaptogenesis takes place, followed by a partial loss of synapses until adult levels are reached at about three months of age (Cragg, 1975). Spatial resolution and contrast sensitivity also greatly improve during the early period, although they take longer to mature fully (Derrington & Fuchs, 1981).

1.3.2. Consequences of experimental manipulations; sensitive periods and binocular competition

Much of our present knowledge about plastic changes in primary visual cortex is derived from effects of altered visual experience, i.e. monocular or binocular deprivation (MD, BD), reverse occlusion, dark-rearing, rearing in a restricted visual environment, or artificially induced strabismus (for reviews see Blakemore, 1978; Movshon & Van Sluyters, 1981; Wiesel, 1982; Mitchell & Timney, 1984).

The physiological effects of MD produced by unilateral eye-lid suture were first described by Wiesel and Hubel (1963), who reported a drastic shift in ocular dominance towards the experienced eye in kittens that had been monocularly deprived from birth. When tested behaviourally, the deprived eye seemed to be functionally blind. This condition, which is presumably equivalent to the well-known clinical condition of *amblyopia*, has been shown to result from the lack of patterned input through the

occluded eye rather than from the attenuation of retinal illumination (Blakemore, 1976). From a number of anatomical and physiological studies it appears that two different mechanisms are contributing to the cortical effects of MD. First, there is a shrinkage of territory occupied by geniculocortical terminals from the deprived eye, accompanied by an expansion by the same amount of space innervated by the non-deprived eye (Shatz & Stryker, 1978). Thus, in layer 4, where afferents from each eye normally occupy about 50% of the available territory, a continuously deprived eye comes to control only 20-30%. This figure roughly equals with the percentage of cells in layer 4 dominated by the deprived eye. However, outside layer 4, virtually **all** cells, even those that lie above or below regions of layer 4 that are dominated by the deprived eye, are dominated by the non-deprived eye, suggesting a second mechanism, presumably involving changes in intracortical connectivity (Movshon & Van Sluyters, 1981; Blakemore, 1988).

There is evidence indicating that the time-course of deprivation effects differs for the two mechanisms: MD imposed at as late as one year of age can still change the OD distribution in supragranular layers (Daw et al., 1992) without having any effect on the relative sizes of OD bands in layer 4 (Shatz & Stryker, 1978). Numerous physiological and anatomical studies have shown that the effects of MD as well as reverse occlusion (re-opening of the deprived and suturing of the non-deprived eye) on ocular dominance in layer 4 of cats and monkeys critically depend on the onset and duration of the periods of deprivation, leading to the concept of a *sensitive period* in the functional development of V1 (introduced by Hubel & Wiesel, 1970; for review see Mitchell & Timney, 1984). It appears that in the cat susceptibility to the effects of pattern-deprivation in one eye starts at around two weeks of age (i.e. very shortly after eye-opening), reaches its maximum during the fifth postnatal week (Olson & Freeman, 1980), when one day of MD (Movshon & Dürsteler, 1977) or even less (8 hours: Freeman & Olson, 1979) can produce significant effects, and ends at approximately 10 weeks of age, judged by lack of effect of MD on OD bands in layer 4 (Shatz & Stryker, 1978). Also, reverse occlusion performed after 10 weeks of age has little effect on the (overall) OD distribution while it causes a complete shift towards the initially deprived

eye if imposed in five-week old kittens (Blakemore & Van Sluyters, 1974), indicating that during the sensitive period functional connections can be both broken and re-established (Mitchell & Timney, 1984). However, it should be noted that a short but physiologically optimal period of reverse occlusion followed by a period of binocular vision results in severe bilateral amblyopia (i.e. reduced visual acuity in both eyes), although the OD distribution and qualitative receptive field properties in V1 are normal (Murphy & Mitchell, 1986). This discrepancy is puzzling; it has been hypothesized that after reverse occlusion arborizations of geniculate afferents from both eyes are enlarged compared to normal animals, resulting in larger receptive fields, overlapping OD columns and, therefore, poorer visual acuity in both eyes (Murphy & Mitchell, 1986).

In comparison to MD, the effects of binocular deprivation (BD) and of dark-rearing on the ocular dominance of area 17 neurons are less pronounced: most of the visually responsive cells remain binocularly driven (Wiesel & Hubel, 1965; Blakemore & Van Sluyters, 1975; Frégnac & Imbert, 1978). However, after long periods of deprivation from the time of normal eye-opening, at least a third of the cells are visually unresponsive, and fewer than one-fifth exhibit normal orientation selectivity; these 'normal' cells tend to be monocular (Blakemore & Van Sluyters, 1975; Frégnac & Imbert, 1978). There seems to be no passive maturation of response properties during prolonged periods of binocular pattern deprivation, rather a progressive degradation may be seen in comparison to the visually naive cortex (Blakemore & Van Sluyters, 1975). However, in kittens that have been dark-reared from birth for as long as four months, i.e. beyond the sensitive period as conventionally defined by vulnerability of geniculocortical terminals to MD, 80% of cortical cells regained cortical orientation selectivity within four weeks (Cynader & Mitchell, 1980) and animals recovered normal visual acuity within four months of visual experience (Timney et al., 1978). Furthermore, in terms of cortical OD kittens dark-reared for four months superficially seem to be as susceptible to MD as much younger normal animals: reopening one eye causes a dramatic shift in OD in favour of that eye (Cynader & Mitchell, 1980). This has been interpreted as a sign that by dark-rearing the sensitive period is delayed or

extended; it appears that both the age of the animal and its previous visual experience are important in determining the response of the visual cortex to its visual input (Cynader & Mitchell, 1980). However, it is possible that the mechanism of these late shifts in OD is somewhat different from the effects seen in young animals: they might depend largely on the selective increase in excitability of cells as a result of the onset of visual stimulation through the open eye rather than competitive loss (see below) of responsiveness through a deprived eye.

The striking difference in the effects of MD versus BD and artificial strabismus has been attributed to a competitive interaction between the two eyes in the cortex (Wiesel & Hubel, 1965). Binocular competition is thought to favour the consolidation of geniculocortical terminals representing the eye that more often activates the postsynaptic layer 4 neuron (cf. Hebb, 1949). Experimental evidence in support of the hypothesis that the site of binocular competition indeed is the primary visual cortex has come from two studies employing a cylindrical lens in front of one eye which correctly focuses only contours of a single orientation. In the study by Cynader and Mitchell (1977) the other eye received normal visual experience, while Rauschecker and Singer (1979) monocularly deprived and reverse-sutured their kittens, exposing the initially deprived eye through the cylindrical lens. Under both conditions, when competition is possible only between oriented (i.e. cortical) units, cells selective for the correctly focused orientation were significantly more frequently dominated by the eye having the lens than cells tuned to other orientations.

The idea of binocular competition is not only helpful in understanding the physiological effects of a variety of rearing conditions on area 17; it is also consistent with the accompanying morphological changes observed in the LGN (for reviews see Blakemore, 1978; Movshon & Van Sluyters, 1981; Mitchell & Timney, 1984). Most prominent is the finding that cells in the deprived layers of the LGN of long-term MD animals are 30-40% smaller in cross-sectional area than cells in the layers innervated by the non-deprived eye (e.g. Wiesel & Hubel, 1963a). The fact that this apparent shrinkage is restricted to the binocular segment of the LGN (Guillery & Stelzner, 1970)

lends further support to the hypothesis of binocular competition. In addition, in a so-called "critical segment" of the binocular visual field in which the retina of the non-deprived eye has been lesioned, the LGN laminae innervated by the deprived eye do not undergo marked shrinkage (Guillery, 1972). The close correlation between the relative sizes of left- and right-eye OD columns in layer 4 of area 17 on the one hand and the changes in cells size in the A laminae of the LGN on the other hand (e.g. Sherman et al., 1974; Movshon & Dürsteler, 1977) suggest that the effects of MD and reverse occlusion observed in the LGN are secondary to the cortical effects. Thus, the size of an LGN cell seems to depend on its success in making and maintaining synaptic contacts in area 17 (Movshon & Van Sluyters, 1981; Mitchell & Timney, 1984).

The consequences of artificial strabismus will be discussed in detail in Chapter 4. It should be noted here that the period during which imposition of squint disrupts cortical binocularity appears to be identical with the sensitive period for MD (Levitt and Van Sluyters, 1982a).

In a number of studies it has been shown that apart from their ocular dominance other receptive field properties of neurons of area 17 such as orientation preference and receptive field size are subject to plastic changes during early postnatal development when animals are reared in restricted visual environments (e.g. Blakemore & Cooper, 1970; Blakemore & Van Sluyters, 1975). As plasticity of the above-mentioned properties is not within the scope of this thesis, the reader is here referred to reviews by Blakemore (1978), Movshon and Van Sluyters (1981), and Frégnac and Imbert (1984).

1.4. Aims of work reported here

Work presented in this thesis examines several aspects of binocular integration in the mammalian primary visual cortex. First, binocular integration in the classical sense, i.e. convergence of excitatory inputs from the two eyes onto neurons in V1, is studied in a small New World primate, the common marmoset. Functional architecture of marmoset area 17 and the effects of early monocular deprivation are described using both electrophysiological and anatomical techniques. Comparison with Old World primates (including man) centres on differences in the combination of signals from the two eyes with respect to underlying mechanisms and their evolution.

In the remaining chapters, truly binocular interactions in mammalian V1 are studied by means of dichoptically presented stimuli. While previous work has focused on facilitatory interactions, on conditions for their development and on neural correlates of stereoscopic depth discrimination, I shall give evidence of as yet undescribed mechanisms of interocular suppression. In Chapter 3, I describe binocular stimulation paradigms that elicit suppression in area 17 of normal adult cats and show their close relation to conditions under which the perceptual phenomenon of binocular rivalry is observed in humans. An animal model for clinical suppression in strabismic patients is presented in Chapter 4; consequences of surgically-induced strabismus for binocular integration in striate cortex are analysed in exotropic and esotropic cats as well as in an esotropic monkey. The effects of dark-rearing and reverse occlusion on the development of interocular interactions in cat area 17 are reported in Chapter 5, and the conditions required for the development of connections that underlie the observed forms of binocular integration in the mammalian primary visual cortex are outlined. Finally, conclusions are drawn with respect to the presumed evolution of binocular integration in higher vertebrates.

2. FUNCTIONAL ARCHITECTURE AND PLASTICITY OF THE MARMOSET PRIMARY VISUAL CORTEX

The two principal response properties that distinguish neurons in area 17 from those at the preceding stages in the primary visual pathway, are binocularity and orientation selectivity; both ocular dominance (OD) and preferred orientation are mapped across the cortical surface in an orderly, columnar fashion (see *Introduction*). Although this holds for primates as well as for carnivores, there are important differences between the two groups (as represented by macaques and cats, respectively) with respect to the visual development and the manner in which it is affected by the environment, i.e. visual experience. These differences are highlighted by effects of altered visual experience on ocular dominance and the patterns of segregation of geniculocortical afferents.

In contrast to cats, the eyes of primates are open at birth and possess clear optic media (Movshon & Van Sluyters, 1981). Moreover, inputs from the two eyes to layer 4 of V1, as visualized by transneuronal labelling, start visibly to separate in their distributions in the macaque three weeks before birth, prior to any visual experience (Rakic, 1976), while in the cat an apparently uniform overlap of terminal arbors is seen up to a postnatal age of one week (LeVay et al., 1978). Therefore, in this respect it appears that the monkey visual cortex is more mature at birth than that of cats. This notion derives further support from evidence that in the macaque the sensitive period (susceptibility to altered visual experience; see *Introduction*) starts immediately at or very shortly after birth, as compared to the beginning of the third postnatal week in the cat. Monocular deprivation (MD) during the first three postnatal weeks results in almost the same shrinkage of deprived-eye OD columns as does long-term MD (LeVay et al., 1980; Swindale et al., 1981).

Like in the cat, the sensitivity to monocular deprivation differs in duration within and outside layer 4C of macaque V1. The sensitive period, as defined by plasticity of OD bands and paralleled by changes in the OD distribution in layer 4C (Hubel et al., 1977a; Blakemore et al., 1978, 1981), ends at eight to ten weeks of age (LeVay et al.,

1980; Blakemore, 1988), thus coinciding with the natural period of afferent segregation. In contrast, a shift in OD distribution in supra- and infragranular layers towards the open eye can be produced when MD is imposed as late as in the second half of the second year of life (Hubel et al., 1977; Blakemore et al., 1978). This marked difference suggests that the underlying mechanisms of response to MD differ as well (Blakemore, 1988); the physiological changes seen in layer 4C seem simply to reflect anatomical changes in the distribution of geniculocortical afferents, while those in other layers may depend on a redistribution or changes in synaptic efficacy of the terminals of interneurons or the axon collaterals of pyramidal cells in the cortex (Blakemore et al., 1982).

There is evidence that the segregation of geniculocortical terminals and, hence, the physiological changes in the ocularity of layer 4C neurons are produced by 'competition' between inputs from the two eyes (see *Introduction*): re-opening of a deprived eye and suturing the initially non-deprived eye ('reverse occlusion'), if performed within the first two months of life, results in an **expansion** of cortical territory controlled by the initially deprived eye, anatomically as well as physiologically (LeVay et al., 1980; Blakemore et al., 1981; Swindale et al., 1981). In contrast, simply re-opening the deprived eye and allowing binocular visual experience does not cause any reversal of the effects of MD with respect to either the relative size of OD bands in layer 4C (Swindale et al., 1981) or the OD distribution (Blakemore et al., 1981), suggesting that the ratio rather than absolute amount of activity relayed through the two eyes' afferents determines the percentage of synaptic territory that each eye comes to control during the period of segregation of terminals (Blakemore, 1988).

Numerous anatomical studies have demonstrated segregation of the geniculocortical afferents into well-defined OD columns in all Old World primates (*Macaca*: LeVay et al., 1975, 1980, 1985; *Cercopithecus*, *Erythrocebus*, *Papio*: Hendrickson et al., 1978; *Pan*: Tigges & Tigges, 1979; *Myopithecus*: Florence & Kaas, 1992), including man (Hitchcock & Hickey, 1980; Horton & Hedley-Whyte, 1984). For New World monkeys, however, results vary with the species examined. In the spider monkey

(*Ateles ater*) and the capuchin monkey (*Cebus apella*) OD columns were clearly demonstrated anatomically (Florence et al., 1986; Hess & Edwards, 1987; Rosa et al., 1988) and electrophysiologically (Hubel & Wiesel, 1968; Rosa et al., 1992). In contrast, transneuronal label with radioactive amino-acids revealed only weak ocular segregation in both the squirrel monkey (*Saimiri*: Hendrickson & Wilson, 1979; Tigges et al., 1984) and the owl monkey (*Aotes*: Rowe et al., 1978).

Transneuronal labelling also reveals no evidence of OD columns in the adult common marmoset, *Callithrix jacchus* (Spatz, 1979). Rather, terminal label is uniform throughout layer 4. Interestingly, Spatz (1989) observed OD columns of the order of 200-300 μm wide in lower layer 4 of juvenile marmosets; however, this early ocular segregation disappeared during the first postnatal year (Spatz, 1989). The presence of these early OD bands may be an inherent immature arrangement or might depend on the nature of early visual experience. MD by neonatal lid-suture does not seem to disturb this juvenile pattern of ocular segregation (DeBruyn & Casagrande, 1981).

DeBruyn and Casagrande (1981) suggested that, comparing Old World monkeys and New World primates (such as marmosets), there might be a difference in the degree of ocular segregation rather than in the fundamental organization of geniculocortical afferents. Spatz (1989), however, postulated two separate mechanisms for producing OD bands: one for initiating and another for maintaining ocular segregation. The OD bands seen in the juvenile marmoset might disappear during adolescence as a result of increasing terminal overlap. These two hypotheses are not mutually exclusive. As DeBruyn and Casagrande (1981) examined the effects of MD on ocular segregation at an age when it is still normally present (Spatz, 1989), a further study is required to test whether experimental manipulation of the balance between inputs from the two eyes for a relatively brief period early in life can reveal afferent segregation that persists in the **adult** marmoset.

The second organizing principal of functional architecture of the primary visual cortex is the grouping of cells with similar orientation preference into orientation columns. This phenomenon was first demonstrated electrophysiologically for macaque

V1 by Hubel and Wiesel (1968, 1974a) and later confirmed by means of 2DG autoradiography (Hubel et al., 1977b) and voltage-sensitive dyes (Blasdel & Salama, 1986). Data from one spider monkey included in the study of Hubel and Wiesel (1968) and recent work on *Cebus* monkeys (Rosa et al., 1992) showed a similar columnar arrangement of preferred orientations in V1 of these species of New World monkeys.

Here, single-unit recording techniques are employed to examine receptive fields and functional organization of V1 in the adult common marmoset. Data from normally reared animals are compared to those obtained from animals that had been subjected to early monocular deprivation with subsequent binocular visual experience. Furthermore, the pattern of deprived-eye afferents in layer 4 of animals with short-term MD is visualized by transneuronal labelling techniques and compared to the pattern of cytochrome oxidase activity in the supragranular layers.

2.1. Methods

Animals

Nine adult common marmosets (*Callithrix jacchus*) bred in an isolated colony were used in this study. Two of them (MN1 and MN2) were normally reared; seven were monocularly deprived within the first three weeks postnatally for various lengths of time (see Table 2-1). The conjunctiva was dissected from the upper and lower eyelids and sutured with absorbable chromic collagen under alphaxalone-alphadolone (Saffan®, Pitman-Moore) anaesthesia. The lid margins were then sutured with fine silk. After re-opening, the refractive state of both eyes was assessed at regular intervals by streak retinoscopy (for details see Troilo & Judge, 1993).

Table 2-1: Start and duration of MD, eye deprived, results of refractometry, and ages of animals at the time of the experiment; type of experiment performed

Animal	Eyelid suture on day	Eye deprived	Duration of MD (weeks)	Refraction of deprived eye at age of		Age at time of expt. (months)	Type of experiment
				~3 mo.	~6 mo.		
MD1	19	left	5	-6.9	-8.3	17	recording
MD2	10	right	15	-2.8*	-6.3	12	recording
MD3	6	right	5	-3.8	-0.3	14	eye inject.
MD4	7	right	3	-12.0	-12.5	11	eye inject.
MD5	6	right	5	-3.1	-7.4	16	recording
MD6	23	right	3	-0.8	-7.9	19	eye inject.
MD7	25	left	3	+2.4	-4.9	21	eye inject.

* measured after 4 months

Electrophysiology

Surgery

Two normal and three MD animals were used for single-unit recording. Anaesthesia was induced with ketamine hydrochloride (30 mg/kg i.m.; Vetalar®, Parke-Davis) and maintained during surgery with i.v. alphaxalone-alphadolone. Tracheotomy was performed for intubation. During electrophysiological recording animals were anaesthetized and paralysed with a continuous i.v. infusion of sodium pentobarbitone (1-2 mg/kg/h Sagatal®, RMB) and pancuronium bromide (0.2 mg/kg/h Pavulon®, Organon Teknika). The sterile infusion solution further contained 5% glucose and 0.9% NaCl and was administered at a rate of 1.2 ml/h. Electroencephalogram (E.E.G.) and electrocardiogram (E.C.G.) were constantly monitored and the dose of barbiturate increased if necessary to maintain anaesthesia, judged by continuous slow-wave E.E.G. The animal was artificially hyperventilated with room air plus carbon dioxide (CO₂); stroke rate (30-35/min) and volume or inspired CO₂ were adjusted to maintain an end-tidal CO₂ level of 4.5-5.0%. Body temperature was kept at 38°C by means of a feedback-controlled heating-pad.

The animal was placed in a stereotaxic frame that leaves the visual field unobstructed and permits the head to be rotated around the horizontal interaural axis and a vertical axis through the centre of the head (Eldridge, 1979b). Stability of the head was achieved by cementing a bolt to the skull and attaching it to the stereotaxic frame.

Pupils were dilated with atropine hydrochloride (2% w/v). Chloramphenicol (0.5% w/v) was applied to prevent infection of the corneae. Zero-power contact lenses were placed on each cornea and 3-mm artificial pupils were placed in front of the lenses as well as additional corrective lenses in order to produce focused retinal images for a viewing distance of 57 cm or 114 cm. By means of a reversible ophthalmoscope (Eldridge, 1979a), the optic discs and foveae were back-projected and plotted on the screen.

For recording from area 17, a small craniotomy was made over the occipital cortex, ca. 7-9 mm lateral to the midline and ca. 9-10 mm posterior to the interaural line (cf.

Stephan et al., 1980). Tungsten-in-glass micro-electrodes (Merrill & Ainsworth, 1972) were advanced, by means of a stepping-motor microdrive, into the cortex either vertically or at an angle of ca. 20° away from the midsagittal plane, the latter producing penetrations almost tangential to the cortical layers. In the MD animals, all penetrations were made in the hemisphere contralateral to the deprived eye. The exposed cortex was protected and prevented from pulsation by sealing with agar.

Recording and visual stimulation

Spikes were conventionally amplified and displayed on an oscilloscope screen and an audio monitor. Single units were isolated at regular intervals (ca. 100 µm) along each electrode track. They were characterized qualitatively with moving and stationary bars, edges or spots of light of medium contrast back-projected by means of an overhead projector on to a translucent tangent screen. Receptive fields in both eyes were plotted with moving bars as 'minimum response fields' (Barlow et al., 1967) on the tangent screen, on which the projections of the foveas and the optic discs were also mapped by means of a reversible ophthalmoscope (Eldridge, 1979a). Cells were classified into seven ocular dominance groups (Hubel & Wiesel, 1962), and the remaining tests performed on the dominant eye. Orientational and directional selectivity were determined according to Blakemore and Van Sluyters (1975). Receptive fields were assessed with flashed stimuli in order to reveal any separate 'on' and 'off' subregions, and units were classified as simple or complex (Hubel & Wiesel, 1962; Blakemore & Price, 1987).

Orientation and spatial frequency tuning of some units were assessed quantitatively by means of drifting sinusoidal gratings. Gratings of mean luminance 36 cd/m² and variable contrast (up to a maximum of about 0.95) were generated by an image synthesizer ('Picasso', Innisfree) and presented on a Tektronix 608 cathode-ray tube screen (display size, 10 x 10 cm) in front of the animal (distance, 57 or 114 cm). External control of the 'Picasso' as well as data acquisition and analysis were performed by a Visual Stimulation package ('VS'; Cambridge Electronic Design, CED) running on

an IBM-386 computer. Orientations and spatial frequencies, respectively, were varied pseudorandomly. Responses from five trials were averaged to obtain data for tuning curves. Spontaneous activity was assessed by presenting a uniform screen of the same luminance as the mean luminance of the gratings.

Histology

At the end of each electrode penetration small electrolytic lesions ($3\ \mu\text{A} \times 3\ \text{sec}$) were made along the track during withdrawal of the electrode. Animals were given an overdose of pentobarbitone and perfused transcardially with phosphate-buffered saline followed by 4% paraformaldehyde. Electrode tracks were reconstructed from 50- μm coronal sections stained with cresyl violet.

Transneuronal labelling and metabolic mapping

Three days prior to perfusion, four additional MD animals were deeply anaesthetized with Saffan. The back of the deprived eye was exposed by bluntly dissecting the conjunctiva from the upper lid and rotating the eye-ball downwards by means of a suture through the dorsal conjunctiva. With a fine Hamilton syringe, an injection of 1 mg of wheat germ agglutinin-conjugated horseradish peroxidase (WGA-HRP, Sigma) in 10 μl of sterile saline was made into the vitreal body of the deprived eye. The total volume was administered in four small doses at 15-sec intervals at different positions in the vitreous.

Animals were given an overdose of barbiturate and perfused transcardially with 2% glutaraldehyde in phosphate buffer. Perfusion time was limited to four minutes in order to allow subsequent flat-mounting. To visualize the overall pattern of geniculocortical afferents, flat-mounts of V1 and V2 were made from at least one hemisphere in each of the four animals. After a coronal cut anterior to V2, the calcarine fissure was opened, and a sagittal cut was made along the dorsal edge of the operculum. The position of this cut was chosen in such a way as to allow subsequent flattening of the cortex without

producing any tension in the tissue that would grossly distort afferentation patterns. However, a separation of neighbouring parts of V1 was thus inevitable. A second releasing cut was made at the posterior pole of the calcarine sulcus. The white matter was carefully removed using cotton wool swabs and blunt-end surgical forceps, and the grey matter flattened and clamped between two microscope slides, such that gentle pressure was exerted on the tissue. After 24h of post-fixation in 2% glutaraldehyde + 30% sucrose in phosphate buffer, tangential frozen sections were cut at 40 μ m. Complete sections were obtained from all layers of the visual cortex except layer 6.

The HRP was visualized using a tetramethyl-benzidine (TMB) reaction modified after Mesulam (1978). Sections were pre-soaked in acetate-buffered aqueous solution containing 5 mg of TMB (Sigma) in 2.5 ml ethanol and 100 mg of sodium nitroferricyanide per 100 ml. After 20 min the enzymatic reaction was initiated by adding 0.3% H₂O₂ solution; it was stopped 20-30 min later. Sections were washed, briefly dehydrated in ethanol and HistoClear®, and coverslipped with DePeX. Sections were viewed and photographed under dark-field conditions using cross-polarizing filters (Illing & Wässle, 1979). Under these viewing conditions, regions with a high density of HRP reaction product show up light, corresponding to territory occupied by geniculocortical terminals from the injected eye ('OD bands'). Their outlines were *camera lucida* drawn at low magnification, assigning the boundaries between dark and light regions by eye. As Price et al. (1994) show, such by-eye judgements correspond quite reliably to a level of density of label midway between the values of adjacent peaks and troughs.

Sections corresponding to the upper third of the cortex (layers 2 and 3) were mounted and reacted for cytochrome oxidase activity after Wong-Riley (1979). Briefly, sections were reacted for two to four hours at 37°C in a phosphate buffered solution of cytochrome C (40 mg/100 ml) and sucrose (2 g/100 ml) in the presence of diaminobenzidine (50 mg/100 ml).

2.2. Results

Normally reared animals: Electrophysiology of V1

In two normal animals six penetrations running at oblique angles through the cortical layers were made and 144 cells of all layers characterized with respect to ocular dominance, orientational and directional selectivity and receptive field type.

All cells had parafoveal receptive fields centred at eccentricities between 0.7° and 3° . Receptive field sizes of 139 cells varied from 0.4° to 4.7° in length and from 0.3° to 2.8° in width. The average receptive field size was $1.23^\circ \pm 0.57^\circ$ in length by $1.02^\circ \pm 0.41^\circ$ in width (mean $\pm$ SD). Mean length-to-width ratio was 1.36 ± 0.65 . In both animals, a mean disparity of 4° of the receptive fields in the two eyes was found, most likely due to the divergence of the visual axes observed with paralysis.

Receptive field types

Generally, receptive field properties in marmoset primary visual cortex closely resembled those previously described for cats and macaques. A clear majority of cells (104 of 144 units, 72%) were complex-like and showed mixed 'on'- and 'off'-responses to small flashed stimuli. Five of them (two each in layers 2/3 and 5, one in layer 6) were clearly 'end-stopped', responding little to stimuli that were longer than their receptive fields. Upon stimulation with drifting sinusoidal gratings of optimal orientation, responses of complex cells at optimal spatial frequencies were unmodulated. Spatial frequency tuning of 13 complex cells showed band-pass characteristics with optimal frequencies in the range of 1 to 3 cycles per degree (c/deg) and 'cut-off' frequencies (i.e. highest spatial frequencies that just elicited neuronal discharge) of 3 to 9 c/deg.

Twelve out of 144 cells (8%) were characterized as simple, showing discrete areas of 'on'- and 'off'-responses to flashed stationary spots and bars. Five of the simple cells were located in layer 4.

The remaining 28 neurons (19% of the total) were non-oriented. Of these, the great majority were found in layer 4 where they made up about two thirds (17 out of 25) of all units.

As found in macaque monkeys, most cells (71%) showed clear orientation selectivity upon stimulation with bars of sufficient length-to-width ratio. Fig. 2-1A gives an example of a layer 5 complex cell. For 13 complex cells, a Fourier analysis was performed of the responses to drifting gratings varying pseudorandomly in direction of drift (see Wörgötter & Eysel, 1987; Wörgötter et al., 1990). Curves were fitted to the data points, taking into account the zero- to eighth-order Fourier components, and tuning widths were calculated. Half width at half height varied from 14° to 32° (mean $\pm$ SD, $22.1^\circ \pm 5.9^\circ$). Few cells (9%) were orientation biased (cf. Blakemore & Van Sluyters, 1975), responding above spontaneous activity to any orientation of either bar or grating, yet preferring one orientation. Out of 116 orientation selective or orientation biased cells, 24 (21%) were direction selective (qualitative judgement; cf. Blakemore & Van Sluyters, 1975), some cells being virtually unresponsive to motion in null-direction (see Fig. 2-1B). Most of the directionally tuned units were found in layer 5 (10 cells = 20% of the 50 cells recorded in that layer) and in layer 6 (6 units = 27% of 22 units). The occurrence of orientational and directional selectivity with respect to cortical layers is summarized in Table 2-2.

Table 2-2: Distribution of orientation and direction selectivity among cortical layers (NO, non-oriented; OB, orientation biased; OS, orientation selective; DS, direction selective); percentage of all cells (N = 144) in brackets. In accordance with previously published work on *Callithrix*, the nomenclature of cortical layers follows Hassler & Wagner (1965) who regard Brodmann's (1909) sublayers 4A and 4B as 3B and 3C, respectively. Their layer 4 is Brodmann's 4C.

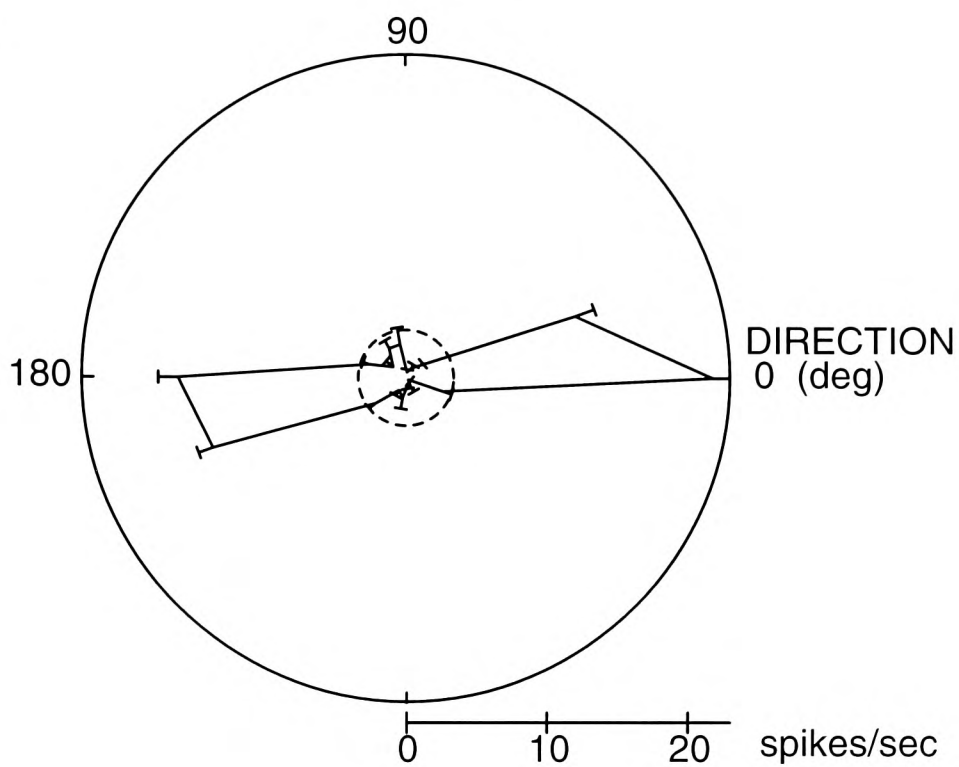
layers	NO cells	OB cells	OS cells	DS cells	Σ cells
2+3	2	1	44	7	47
4	17	3	5	1	25
5	5	7	38	10	50
6	4	2	16	6	22
all	28 (19%)	13 (9%)	103 (72%)	24 (17%)	144

An orderly succession of preferred orientations of the recorded neurons was observed along most of the penetrations, as illustrated in Figs 2-2**B** and 2-3**B**. From these sequences of orientation shifts, by projecting the electrode tracks on to the cortical surface, it was inferred that a 180°-range of orientations was covered by a block of VI some 400-800 μm wide. However, breaks in the regular sequences and shifts in preferred orientation of more than 50° within 100 μm were not uncommon.

Figure 2-1

Orientation tuning of a layer 5 complex cell (**A**) and of a direction selective layer 6 complex cell (**B**), both of ocular dominance group 4. Mean discharge rates in spikes/sec (+ SEM, $n = 5$ presentations per data point) are plotted as a function of the direction of drift of sinusoidal gratings (contrast = 0.45; spatial frequency 2.0 c/deg, i.e. cycles per degree of visual angle; drift frequency 4 Hz) presented to the contralateral eye; 0 deg signifies rightward motion, 90 deg, upward motion. The radius of the dashed circle in the centre indicates the mean spontaneous activity level during 5 presentations of a blank screen interleaved with the grating presentations and of the same mean luminance as the test gratings.

A



B

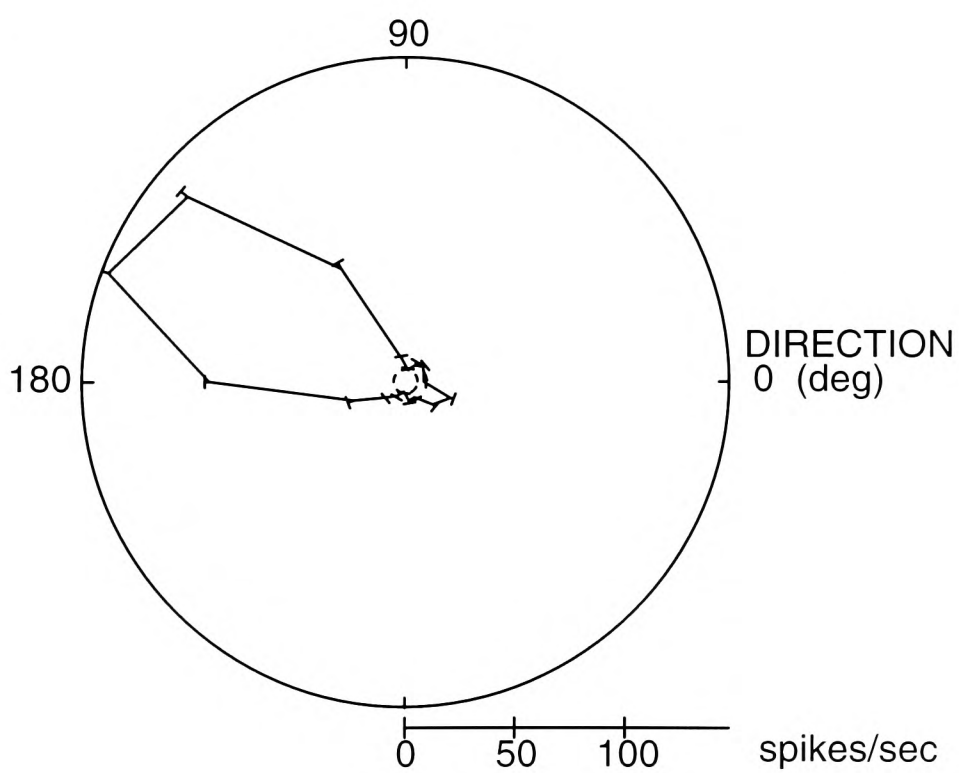


Figure 2-2

Orientation selectivity and ocular dominance in an electrode penetration through area 17 in a normal marmoset (MN1).

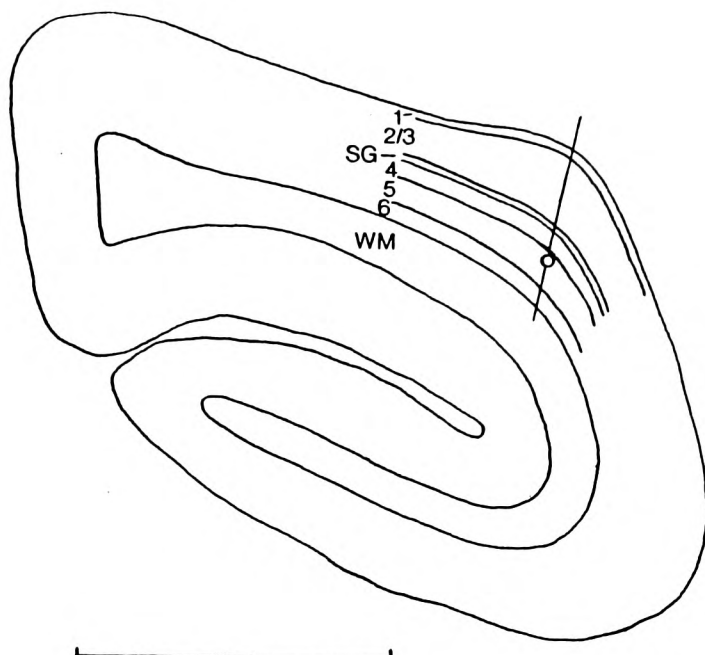
A: Histological reconstruction of the penetration passing through the lateral operculum in the coronal plane, angled medially by 10°. Lines indicate the borders of cortical layers 1, 2/3AB, 3C (stria of Gennari; SG), 4, 5, and 6; WM, white matter. An open circle marks the position of a lesion in upper layer 5. Scale bar, 5 mm

B: Sequence of preferred orientations of cells recorded along the electrode track in **A**. The preferred orientation of each cell is plotted against the distance (in μm) along the track; squares indicate orientation selective cells and triangles orientation biased cells; clearly direction selective cells are indicated by filled symbols. The sign convention for orientation is orthogonal to that for direction (see legend to Fig. 2-1): 0 deg = horizontal, 90 deg = vertical. Circles in the row marked 'NO' signify non-oriented units.

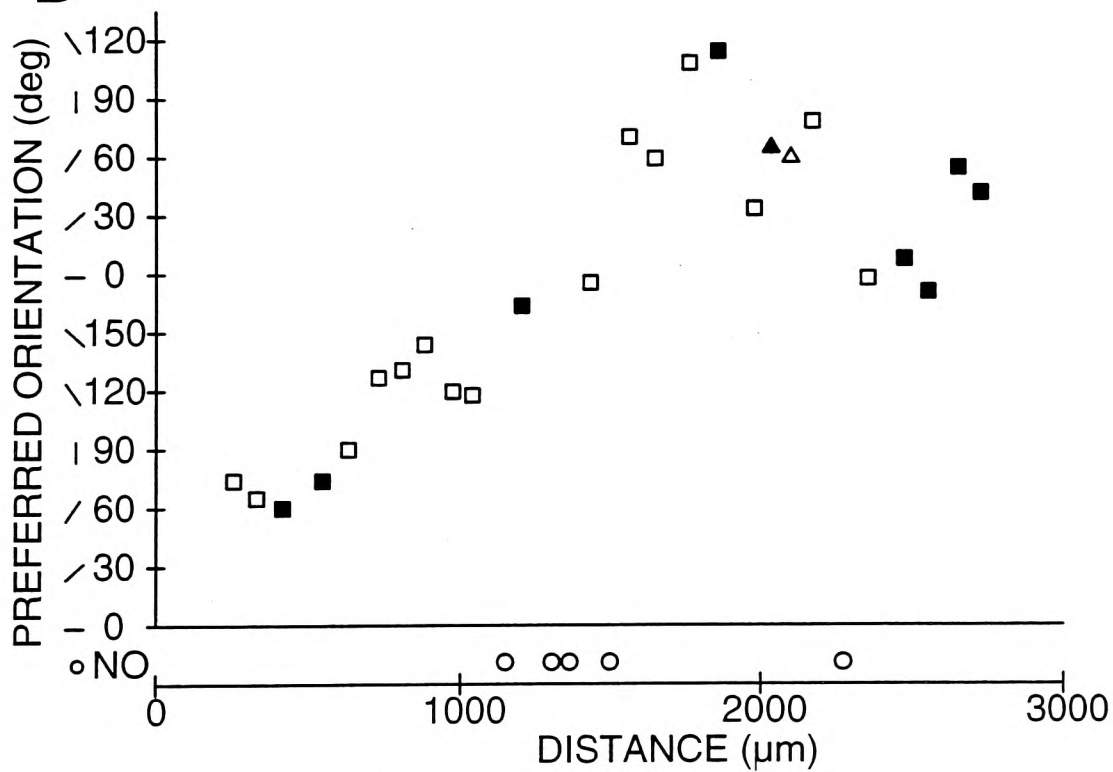
C: Sequence of ocular dominance of cells recorded along the electrode track in **A**. The ocular dominance of each cell (represented by a filled circle) is plotted against the distance (in μm) along the track. Note that there are transitions between (weak) contralateral and ipsilateral eye dominance, respectively, covering roughly two full cycles of dominance.

Borders of cortical layers are indicated on the scale below part **C**, and the position of the lesion in upper layer 5 is marked by an arrow.

A



B



C

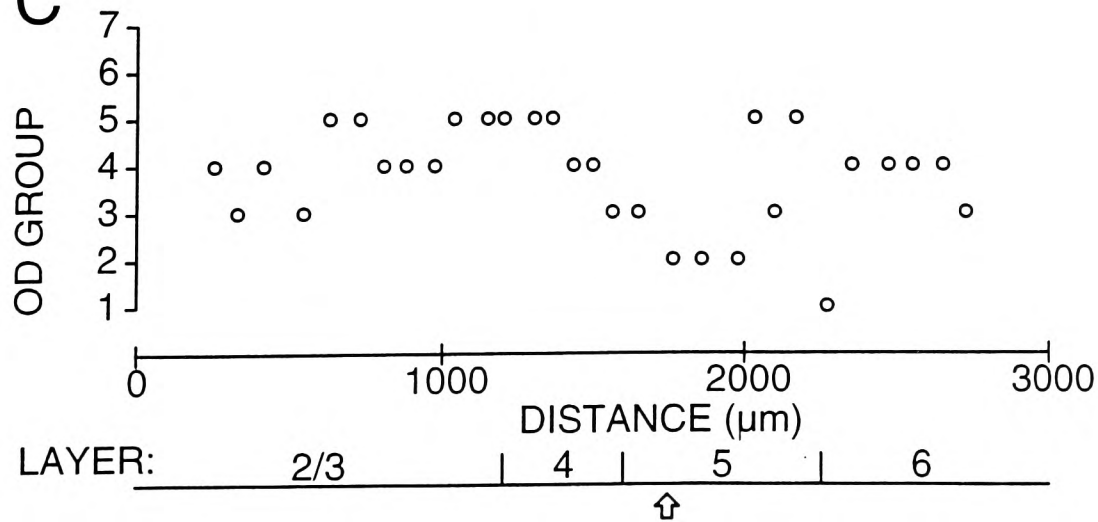


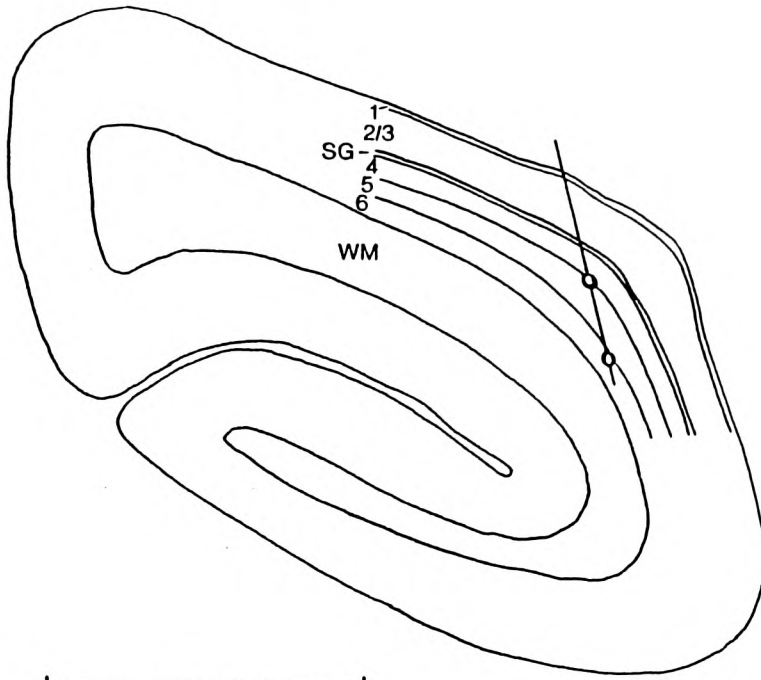
Figure 2-3

Orientation selectivity and ocular dominance in an electrode penetration through area 17 in a normal marmoset (MN2), presented as in Fig. 2-2.

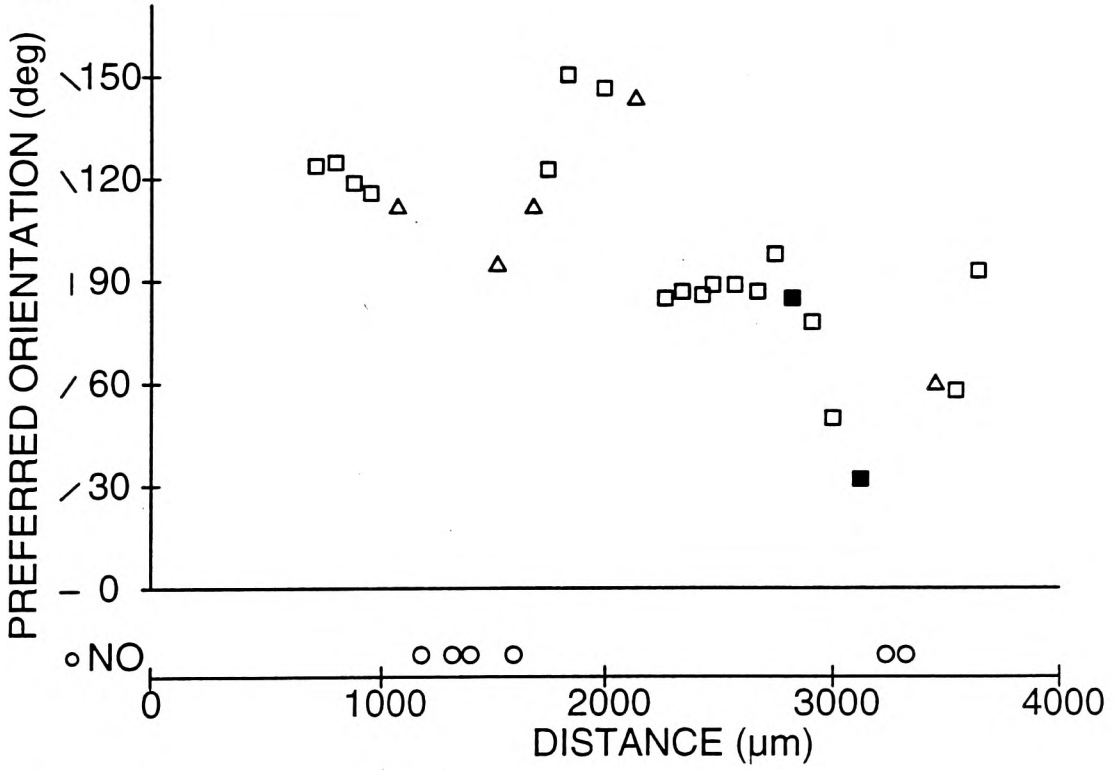
A: Histological reconstruction of the penetration passing through the lateral operculum in the coronal plane. Cortical layers and the positions of marking lesions, one at the layer 4/5 border and another at the top of layer 6, are indicated. Scale bar, 5 mm

B and C: Sequences of preferred orientations (**B**) and of ocular dominance (**C**) of cells are plotted against distance along the electrode track shown in **A**; all conventions as in Fig. 2-2. One lesion lay at the layer 4/5 border and the other marked the location of two non-oriented units in upper layer 6 (see arrows on scale below **C**).

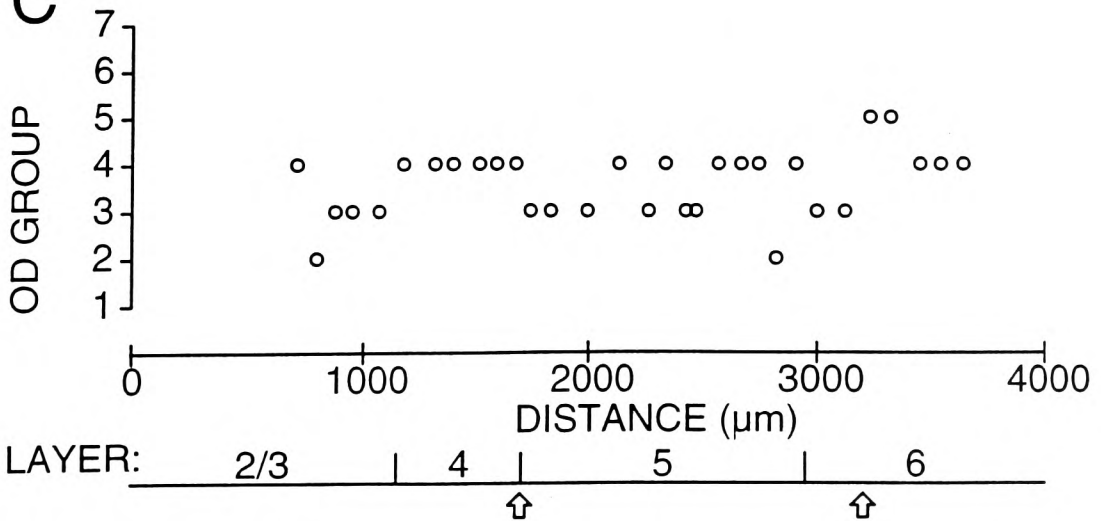
A



B



C



Ocular dominance

The overall OD distribution of marmoset V1 is not significantly biased towards either eye. A striking feature is the high percentage of neurons that can be equally well driven through either eye: of 144 cells, 66 (46%) were classified in ocular dominance group 4 (OD4), while only few cells were strictly monocular (OD1 + OD7: 6 cells = 4%) or strongly dominated by one eye (OD2 + OD6: 18 cells = 13%). Due to the small number of cells dominated by one eye or the other, clear shifts in ocular dominance along penetrations, corresponding to OD columns, were usually difficult to discern (see Fig. 2-3C). However, in some tracks, such as that illustrated in Fig. 2-2C, there did seem to be shifts back and forth in dominance. In this particular case, roughly two complete cycles of dominance appeared to be covered in the full extent of the penetration, equivalent to a width of approximately 350 μm across the cortical surface for each individual OD column. There is no statistically significant difference (χ^2 -test: $p > 0.1$) between cortical layers in the OD distributions of neurons, which are shown in Fig. 2-4. Cells in layer 4, which receives the main geniculate projection, do not show a higher degree of ocular segregation than do cells in supra- and infragranular layers. Indeed, if anything cells were more binocularly balanced in dominance in layer 4 than outside it. This applies equally to oriented cells in layer 4 as well as to non-oriented cells, of which 12 (out of 17) were classified as OD4.

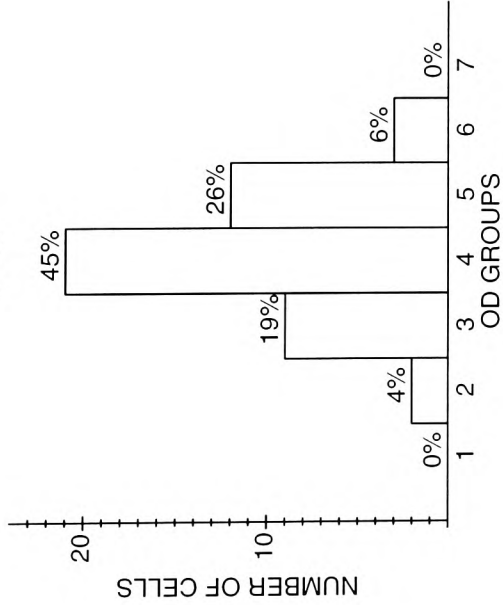
Colour sensitivity

The sensitivity of cortical neurons to chromatic stimuli was tested in one of the two normal animals, a male. Apart from of a single red-'on'-centre geniculate fibre, I failed to isolate any units with obvious chromatic selectivity.

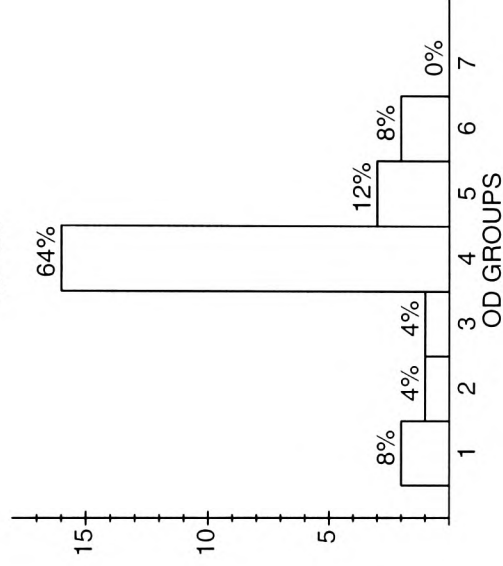
Figure 2-4

Ocular dominance histograms for each cortical layer accumulated from two normal adult marmosets. The numbers of cells recorded in the respective layers are shown above each histogram. Percentages of cells in each OD group are given.

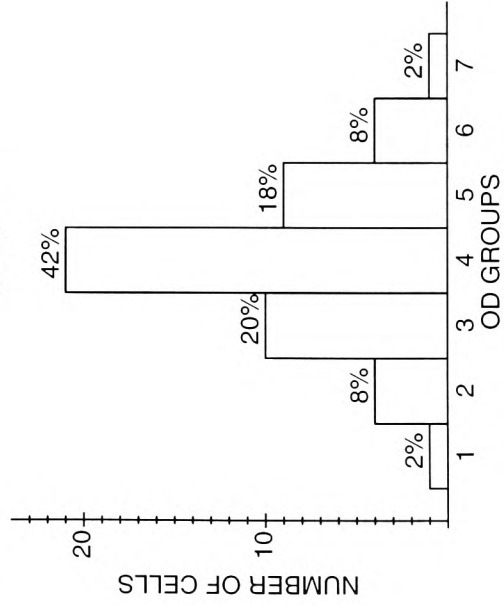
layers 2/3
N = 47



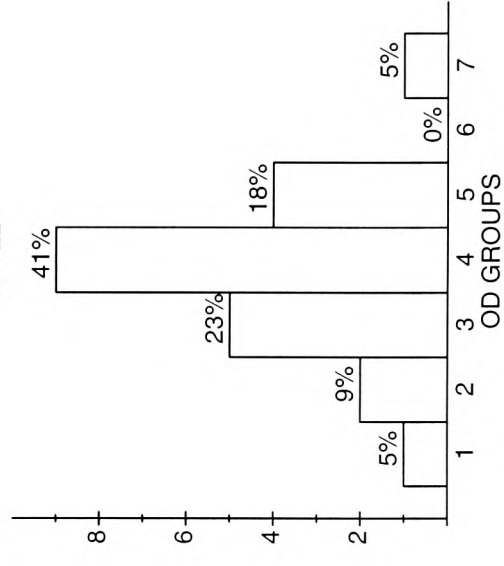
layer 4
N = 25



layer 5
N = 50



layer 6
N = 22



Monocularly deprived animals: Electrophysiology of V1

In three MD animals eight penetrations were made, all in the hemisphere contralateral to the deprived eye. Responses of 139 neurons were quantified as described above.

In two animals (MD2 and MD5), the average disparity of receptive fields in the two eyes (4° and 5°, respectively) did not differ from that in normal animals, while for marmoset MD1 a divergence of the visual axes of about 14° was found.

Ocular dominance

Of all cells, 68% were classified as OD7. Both in the supragranular layers (2/3) and in layer 5, responses were almost exclusively elicited through the ipsilateral, non-deprived eye. This held for each of the three MD animals that I recorded from (see Fig. 2-5 for accumulated OD histograms for all cortical layers). In just one track an adjacent pair of two non-oriented cells was encountered in layers 2/3, both of which were driven solely through the deprived eye (Fig. 2-7C).

More frequently, clusters of cells responding to stimulation of the deprived eye were found in layer 4 as well as in layer 6. Their locations were histologically confirmed by means of marking lesions that were easily identifiable in Nissl stained sections. The estimated tangential width of these patches (projected on to the cortical surface), taking into account all cells that were grouped OD1 to OD4, was 200-300 µm (Figs 2-6 and 2-7). Intervening clusters of cells dominated by the non-deprived eye were wider (ranging from 300-600 µm). I calculated an index OD_{eye} for the relative strength of deprived and non-deprived eye inputs to layers 4 and 6 by weighting the OD data as follows:

$$OD_{non-dep.} = \frac{0*n[OD1] + 1*n[OD2] + 2*n[OD3] + 3*n[OD4] + 4*n[OD5] + 5*n[OD6] + 6*n[OD7]}{6*N}$$

$$OD_{deprived} = 1 - OD_{non-dep.}$$

with $n[ODx]$ being the number of cells attributed to each OD group and N the total number of cells (58). I obtained values of $OD_{non-dep.} = 0.66$ and $OD_{deprived} = 0.34$.

Receptive field properties

While the OD distribution was strongly affected by MD, this was generally not the case for orientation selectivity or directionality. In MD animals, 79% of all cells were orientation selective or orientation biased and 13% were directionally tuned, compared to 81% and 17%, respectively, in normal animals (see Table 2-3). There was, however, a significantly higher proportion of non-oriented or orientation biased cells in layer 6 of the deprived animals (18 out of 22 units = 82%) than in layer 6 of normal animals (7 out of 23 units = 30%), this being largely due to the fact that no cell dominated by the deprived eye was orientation selective. Also, the only two cells dominated by the deprived eye that were found outside layers 4 and 6 were non-oriented (see Fig. 2-7).

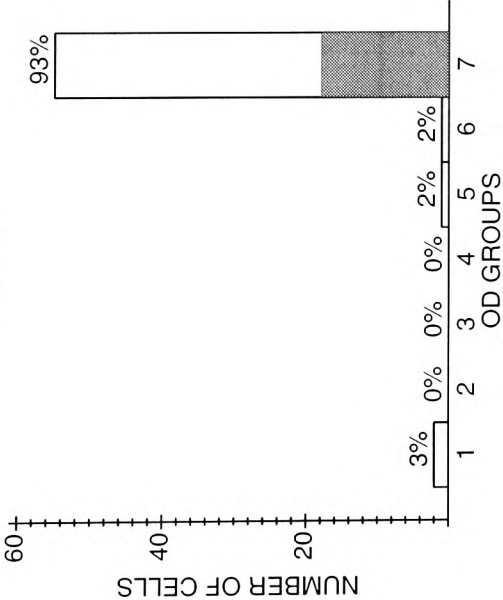
Table 2-3: Distribution of orientation and direction selectivity among cortical layers in MD animals. NO, non-oriented; OB, orientation biased; OS, orientation selective; DS, direction selective (always also OS or OB); percentage of all cells (N = 139) in brackets.

layers	NO cells	OB cells	OS cells	DS cells	Σ cells
2+3	4	3	52	7	59
4	12	6	8	1	26
5	1	3	18	8	22
6	12	13	7	2	32
all	29 (21%)	25 (18%)	85 (61%)	18 (13%)	139

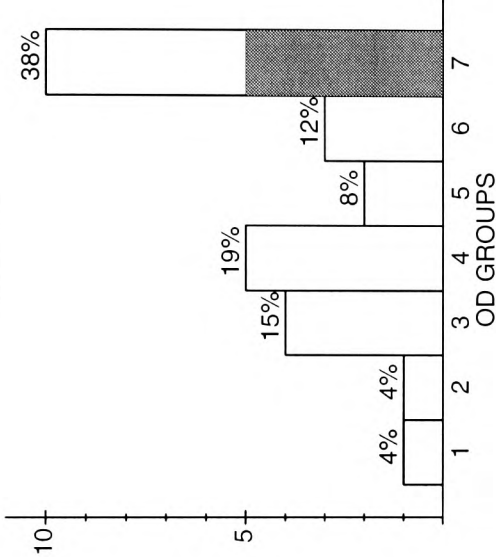
Figure 2-5

Pooled ocular dominance histograms for each cortical layer obtained from three monocularly deprived marmosets. The numbers of cells recorded in the respective layers are shown above each histogram. Percentages of cells in each OD group are given. The shaded bars represent cells recorded from the apparently exotropic animal MD1.

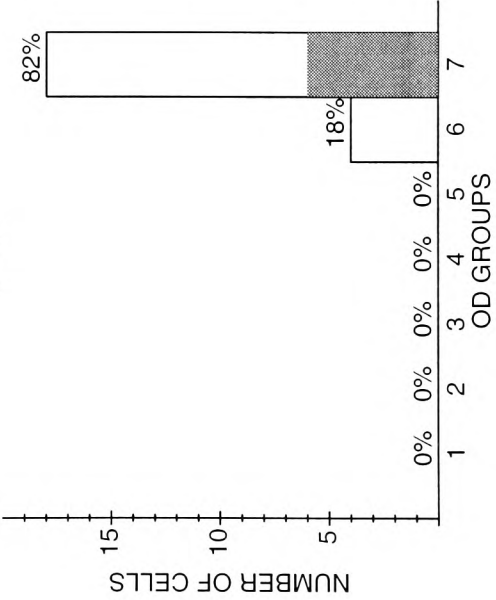
layers 2/3
N = 59



layer 4
N = 26



layer 5
N = 22



layer 6
N = 32

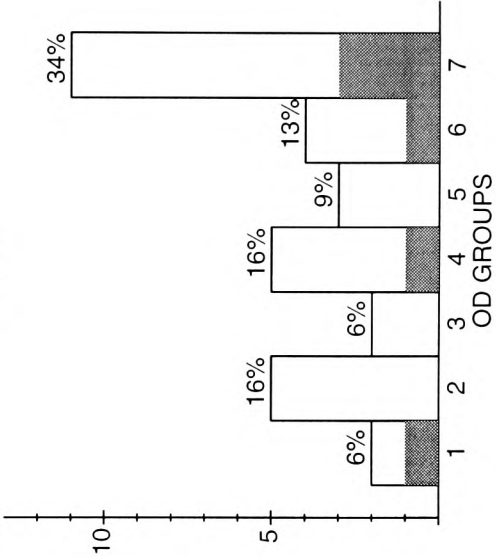


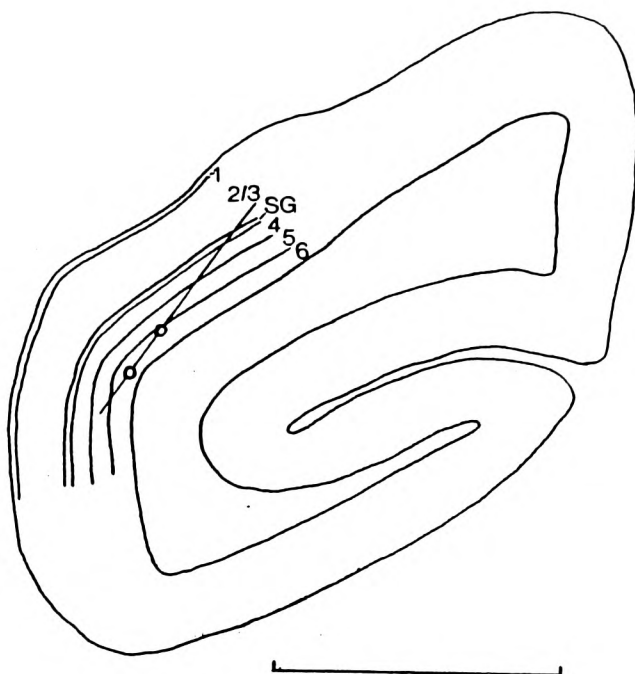
Figure 2-6

Orientation selectivity and ocular dominance in an electrode penetration through area 17 in marmoset MD2, which had been monocularly deprived for 15 weeks from day 10, and recorded at 12 months.

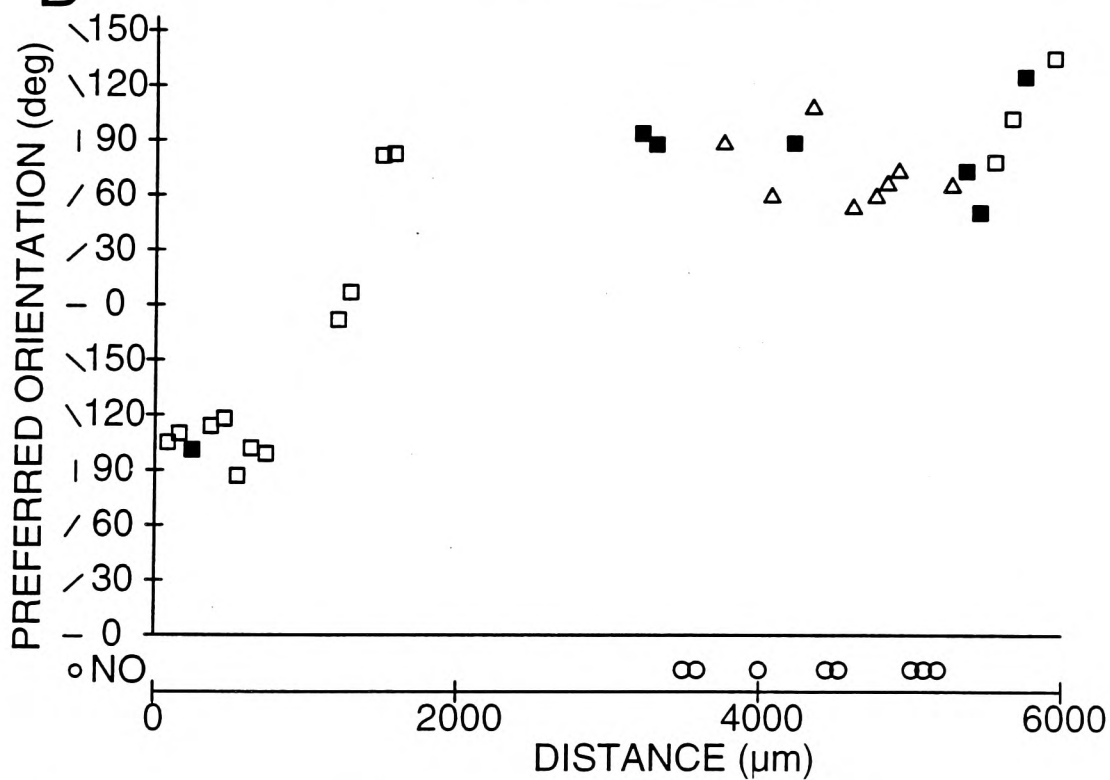
A: Histological reconstruction of the penetration, passing tangentially through the lateral operculum of the left hemisphere. Cortical laminae (see Fig. 2-2) and the positions of two marking lesions in layer 6 are indicated. Scale bar, 5 mm

B and **C:** Sequences of preferred orientations (**B**) and of ocular dominance (**C**) of cells are plotted against distance along the electrode track shown in **A**; all conventions as in Fig. 2-2. Three clusters of cells dominated by the deprived (contralateral) eye were found in layer 6, two of which were marked by lesions (see arrows on scale below **C**).

A



B



C

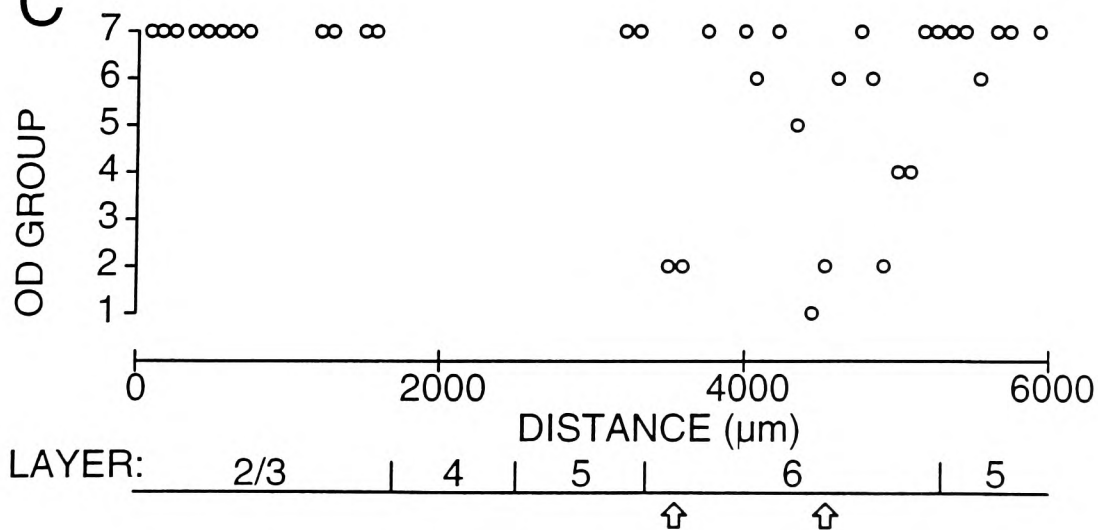


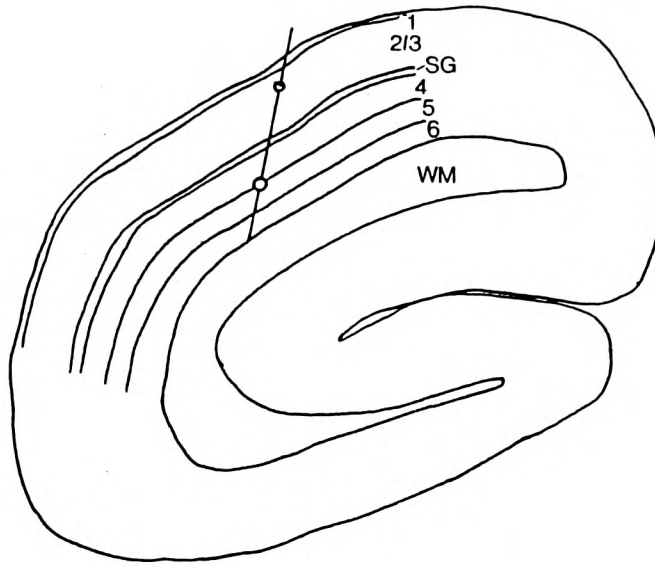
Figure 2-7

Orientation selectivity and ocular dominance in an electrode penetration through area 17 in marmoset MD5, which had been monocularly deprived for 5 weeks from day 6, and recorded at 16 months.

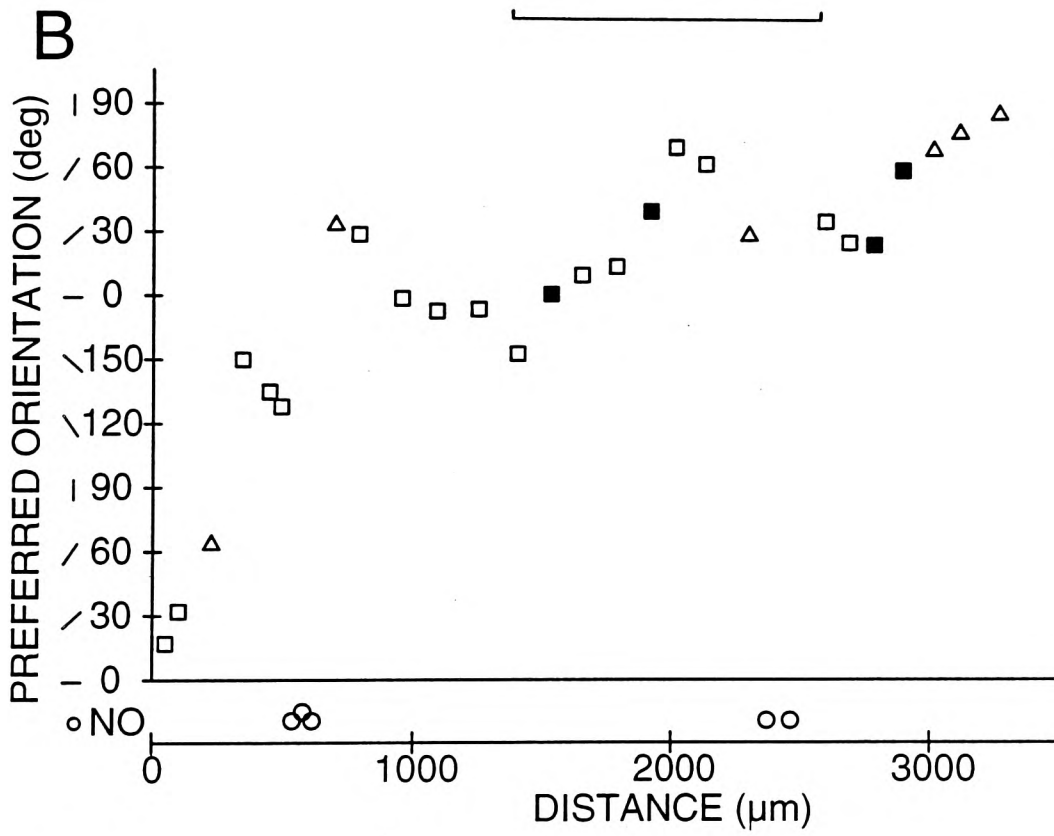
A: Histological reconstruction of the penetration, angled laterally to pass through the lateral operculum of the hemisphere contralateral to the deprived eye. Cortical laminae (see Fig. 2-2) and the positions of two marking lesions are indicated. Scale bar, 5 mm

B and **C:** Sequences of preferred orientations (**B**) and of ocular dominance (**C**) of cells are plotted against distance along the electrode track shown in **A**; all conventions as in Fig. 2-2. The lower borders of two clusters of cells dominated by the deprived eye, one in layer 2/3, one in the lower half of layer 4, were marked by lesions (see arrows on scale below **C**). Note that all cells dominated by the deprived eye, even those outside layers 4 and 6, were non-oriented.

A



B



C

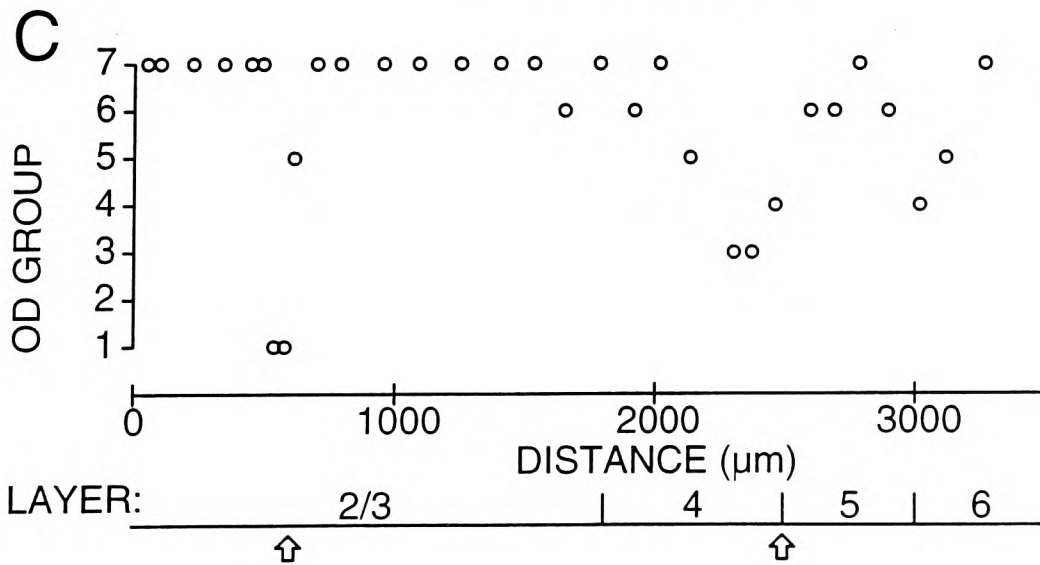


Figure 2-8

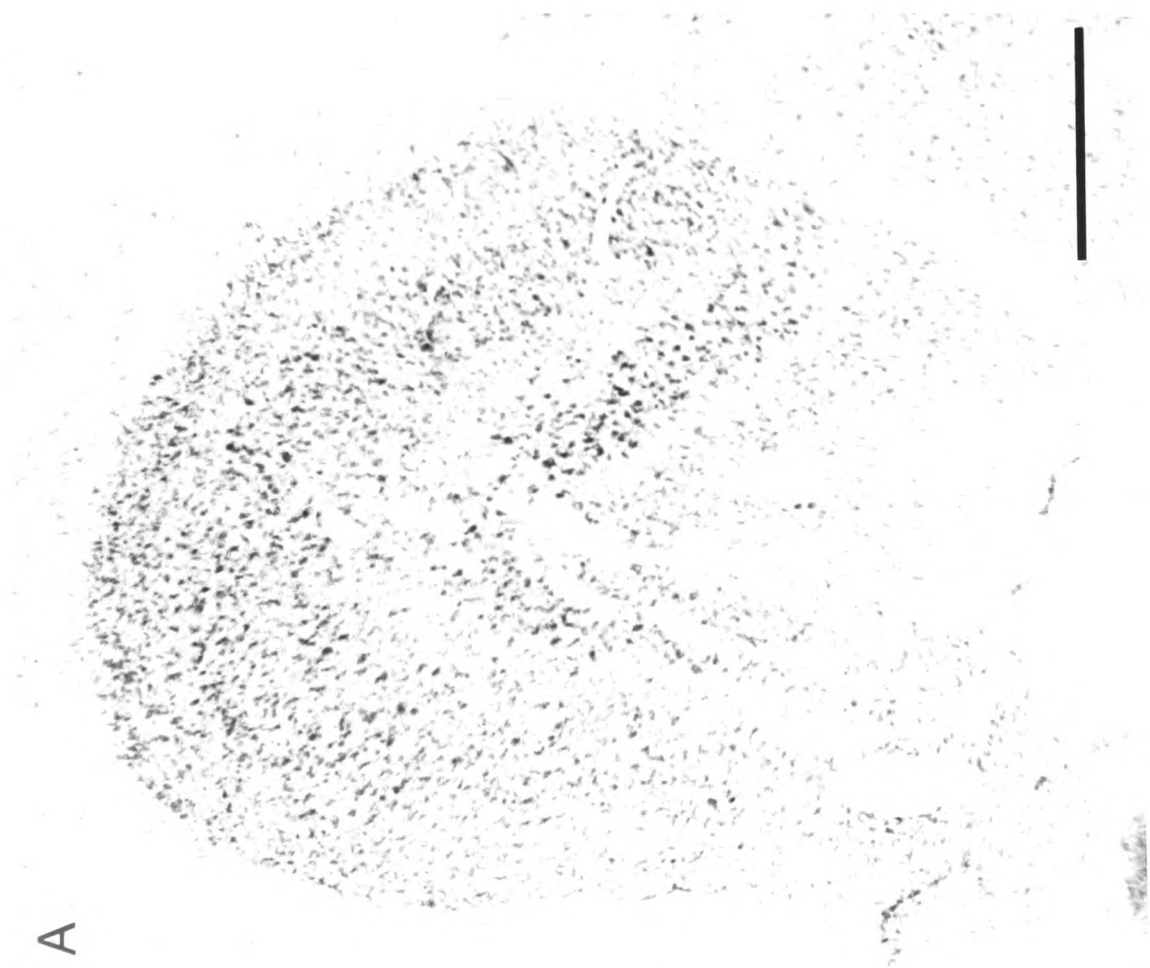
Photomicrographs of Nissl-stained coronal sections through the lateral geniculate nuclei of monocularly deprived marmoset MD2 (right eye sutured for 15 weeks from day 10). The animal was 12 months old when it was sacrificed.

A: LGN contralateral to the deprived eye;

B: LGN ipsilateral to the deprived eye.

Note the darker appearance of cells in laminae innervated by the non-deprived eye.

Scale bars, 500 μm .



A



B

Figure 2-9

Photomicrographs of coronal sections of the right LGN, contralateral to the deprived eye, of monocularly deprived marmoset MD7 (left eye sutured for 3 weeks from day 25). The deprived eye had been injected WGA-HRP.

A: Light-field photograph of Nissl-stained section.

B: Dark-field photograph of section reacted for HRP. Light regions indicate laminae that receive input from the deprived eye (1 and 4); note that label in the layers innervated by the ipsilateral (non-deprived) eye (2 and 3) is denser than background label outside the LGN, suggesting either that there is some 'spillover' of label (LeVay et al., 1978) or that laminar segregation is not total in the marmoset. A finger of dense label (marked with arrows) pushes down from layer 4 into layer 3 in the posteroventral half of the LGN (see text).

Scale bars, 500 μm .

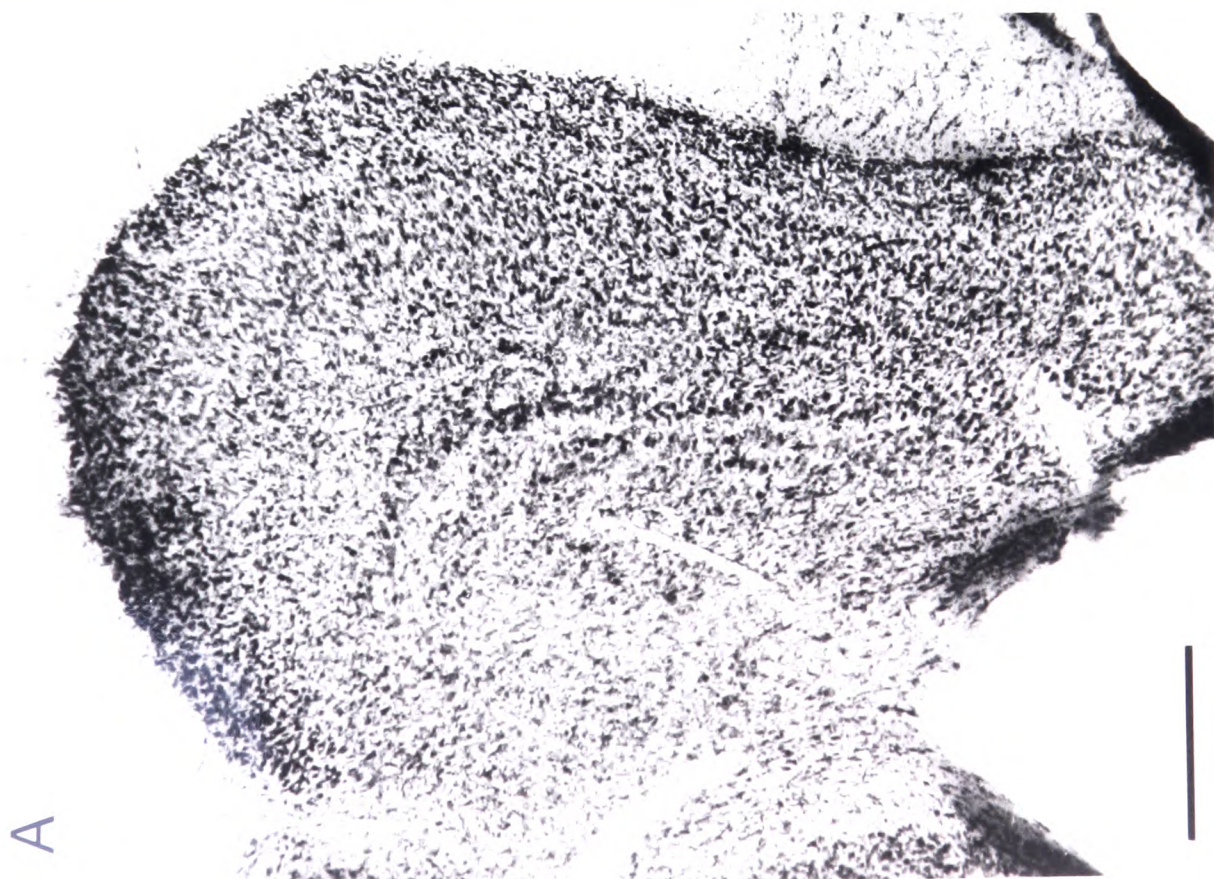
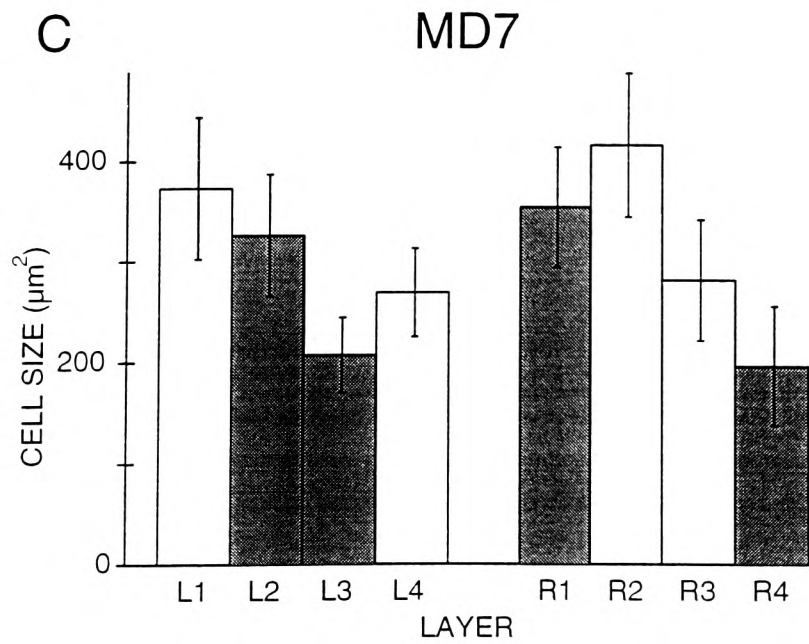
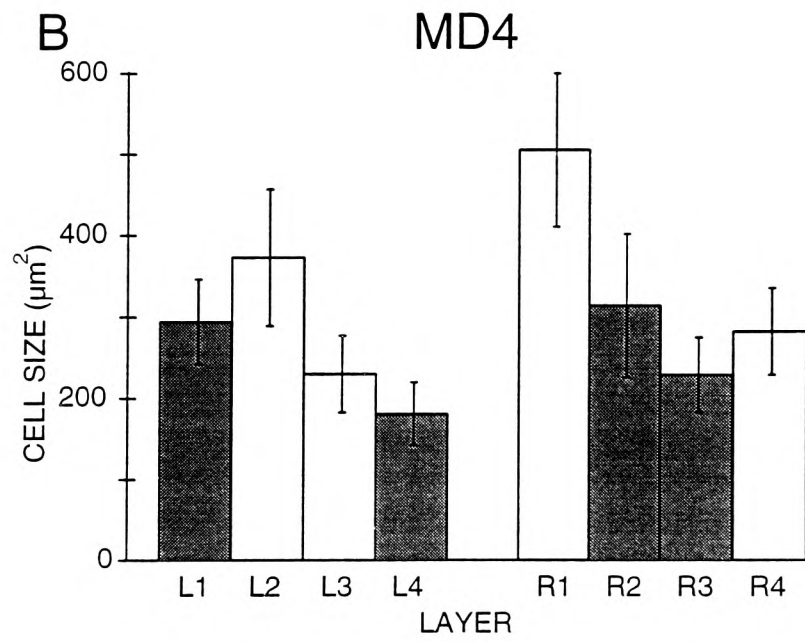
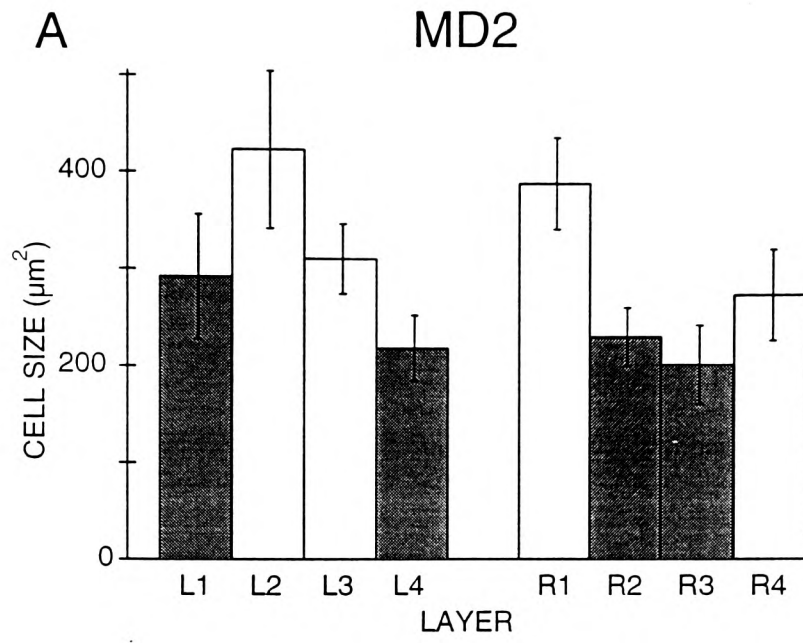


Figure 2-10

Cell sizes in the LGNs of MD marmosets MD2 (**A**), MD4 (**B**), and MD7 (**C**). Average sizes ($\pm$ SD) are given as cross-sectional areas of cells sampled from the central part of the nucleus (i.e. receiving input from the central part of the retina of either eye). At least 50 cells per lamina and hemisphere were *camera lucida* drawn from high-power fields at the centre of each lamina; only cells with a clearly visible nucleus were drawn (see Movshon & Dürsteler, 1977) and the cross-sectional areas of their outlines determined with a graphics tablet. The shaded bars represent LGN layers receiving input from the deprived eye (the right eye in animals MD2 and MD4, the left eye in MD7).



Anatomical effects of monocular deprivation

Lateral geniculate nucleus

In the four animals that had received intra-ocular injections of WGA-HRP the basic four-layered lamination pattern described by Spatz (1978) was confirmed. In hemispheres ipsilateral to the injected eye, dense label was confined to layers 2 (magnocellular) and 3 (parvocellular). In hemispheres contralateral to the injected eye dense label was found in layers 1 (magnocellular) and 4 (parvocellular). Some apparent 'spillover' of label (LeVay et al., 1978) was observed, especially from lamina 4, opposite to the injected eye, to lamina 3 (see Fig. 2-9B). It is not clear whether this corresponds to imprecision of the boundaries of termination in the marmoset LGN or 'leakage' of label into inappropriate layers. Certainly, in some places in the posteroventral portion of the parvocellular layers (see Fig. 2-9B), there appeared to be genuine irregularities in the boundaries (as described by Spatz, 1978). These uncertainties about laminar borders in the LGN render quantification of transneuronal labelling in the cortex problematical.

In all monocularly deprived animals a relative shrinkage of cells was found in laminae innervated by deprived eye, compared to cells in laminae innervated by the non-deprived eye. This laminar difference in cell sizes was greatest, both in magno- and in parvocellular layers, in animal MD2 that had been monocularly deprived for 15 weeks (see Fig. 2-8), and least conspicuous in animals MD6 and MD7 (see Fig. 2-9A), which had been deprived for only three weeks, starting at about three weeks of age. Differences in cell sizes were quantified by measuring cross-sectional areas of cells in the central part of the LGN in both hemispheres of animals MD2, MD4, and MD7. From each animal, at least 50 cells per hemisphere and lamina were drawn with a *camera lucida* and measured with a graphics tablet (for details see Movshon & Dürsteler, 1977). Results are summarized in Fig. 2-10. There were highly significant ($p < 0.01$) differences in cell size in the same hemisphere between layers innervated by the normal eye and those innervated by the deprived eye for both magno- and parvocellular layers in all three animals. A 'morphological index' MI of the deprivation effect (Dürsteler et al., 1976) was calculated for magno- and parvocellular layers (MI_M , MI_P):

$$MI_M = \frac{1}{4} \cdot (I_1/C_1 + C_2/I_2 + C_2/C_1 + I_1/I_2),$$

$$MI_P = \frac{1}{4} \cdot (I_4/C_4 + C_3/I_3 + C_3/C_4 + I_4/I_3);$$

with I_x and C_x being the mean cell area in layer x of the LGN ipsilateral (I) or contralateral (C) to the deprived eye. It was $MI_M = 1.57$ and $MI_P = 1.39$ for animal MD2; $MI_M = 1.45$ and $MI_P = 1.27$ for MD4; $MI_M = 1.16$ and $MI_P = 1.37$ for MD7.

Pattern of geniculocortical afferents

In one of the four MD marmosets that had received injections of WGA-HRP into the deprived eye, only a small part of the LGNs and, therefore, of V1 had been labelled successfully: data from this marmoset (MD4) are not included in this study.

In another animal (MD3), the transneuronal labelling of geniculocortical input did not show evidence of segregation of afferents when examined immediately after processing for HRP reactivity. In frontal sections, terminal label formed a continuous band in layer 4 and, though considerably weaker, in layer 6, throughout the primary visual cortex (Fig. 2-11). Also, flat-mounts of both the opercular and the calcarine part of V1 did not reveal conspicuous patchiness of terminal label. However, in this animal label was extremely dense and background fairly high: faint waxing and waning of density of label might have been undetectable. Indeed, when the HRP reaction product had faded considerably a year later, it did show some patchiness but had become too light for quantitative examination.

In marmosets MD6 and MD7 (both lid-sutured from about 3 to 6 weeks of age), a clear segregation of geniculocortical afferents in flat-mounts of both hemispheres was found in most of V1. Input from the deprived eye to layer 4 was largely confined to elongated patches or short bands some 250 to 400 μm wide, as illustrated in Fig. 2-12. Transneuronal label in intercalating regions was sparser but above background label as seen in adjacent area V2. There was a tendency for both the heavily labelled 'islands' and the intervening regions to decrease in width with increasing eccentricity of the part of the visual field represented (see Figs 2-13, 2-14). The average width of a pair of light

and dark bands was $660 \text{ mm} \pm 80 \text{ mm}$ (mean $\pm$ SD) in MD6 and $700 \text{ mm} \pm 60 \text{ mm}$ in MD7, respectively.

The segregation of geniculocortical afferents was sharpest in the dorsal lip and the ventral lip and bank of the calcarine fissure, i.e. in the representation of paracentral vision. This was also the region in which the patches receiving input from the injected eye showed the most regular arrangement in parallel bands. In the opercular part, i.e. the dorsolateral surface of V1, onto which the central retina is mapped (Spatz, 1979) and where recordings were made, afferent label was almost uniform (in MD6) or consisted of rather irregular, poorly delineated patches (in MD7); it was of a lower density than in the representation of the paracentral visual field in the calcarine cortex. For the most peripheral part of the visual field, which is mapped on to the posterior part of the dorsal bank of the calcarine fissure (Spatz, 1979), no afferent segregation was seen in either MD6 or MD7. Complete reconstructions of deprived-eye terminal label in both hemispheres are shown in Fig. 2-13 and Fig. 2-14 for MD6 and MD7, respectively. The zones of deprived-eye afferents were more 'insular' than those attributable to the non-deprived eye, in particular in MD7. The OD stripes with deprived-eye input appeared to be somewhat larger in the contra- than in the ipsilateral hemisphere; this difference was less obvious in MD6 than in MD7. In the segregated regions, the overall cortical territory occupied by deprived-eye afferents, as measured with a graphics tablet, was 39% in the ipsilateral hemisphere and 43% in the contralateral hemisphere in MD6 and 34% and 39%, respectively, in MD7.

In order to compare my results to values given for other species, the hypothetical number of OD hypercolumns was calculated according to Florence and Kaas (1992): the square of the average width of a pair of OD columns was taken as the size of a hypercolumn, by which the area of striate cortex was divided. I measured the size of area 17 with a graphics tablet for both hemispheres in MD6 and MD7, and obtained means of 210 mm^2 and 215 mm^2 , respectively (cf. Fritschy & Garey, 1986a). Thus, the number of ocular dominance hypercolumns was calculated to be 480 in MD6 and 440 in MD7, respectively.

Figure 2-11

Dark-field photograph of a coronal section through the occipital cortex of the left hemisphere, contralateral to the deprived eye, in marmoset MD3. This animal had been monocularly deprived for 5 weeks, starting 6 days after birth. Transneuronal label (light) shows geniculocortical afferents for the deprived eye, which had been injected with WGA-HRP. A dense band of label with no apparent waxing and waning can be seen in layer 4 along both banks of the calcarine fissure, representing V1. Medial, to the right. Scale bar (bottom right), 1 mm.

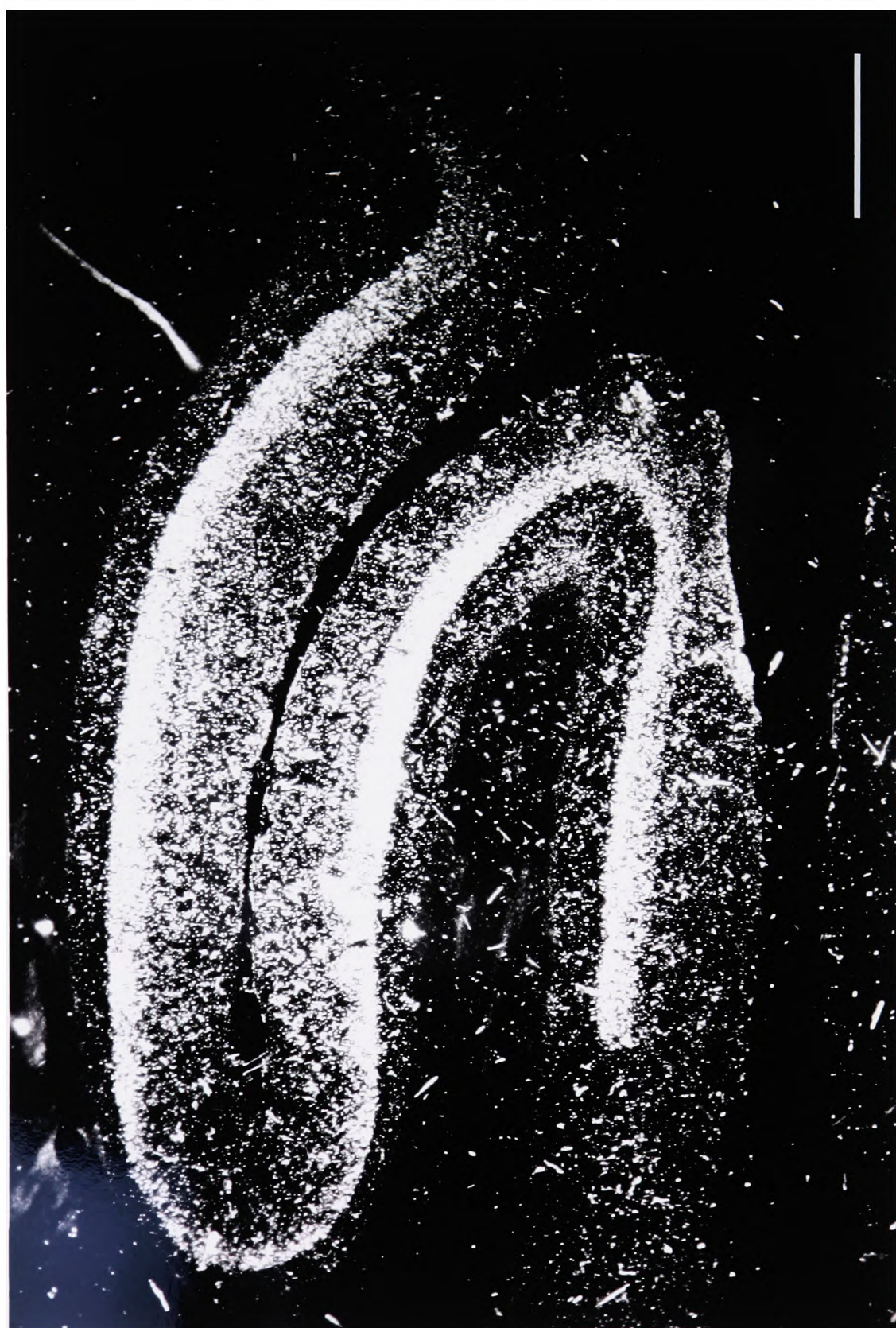


Figure 2-12

Ocular dominance patterns in layer 4 of an adult marmoset that had been monocularly deprived for 3 weeks from day 25 (MD7). Montage of dark-field photographs of a tangential section through lower layer 4 in the ventral bank of the calcarine fissure, obtained from a flat-mount of the right hemisphere (contralateral to the deprived eye). Light regions reflect the distribution of geniculocortical terminals ('ocular dominance bands') labelled after an injection of WGA-HRP into the deprived eye. The V1/V2 border is at the top, the ventral lip of the calcarine fissure to the left and the bottom of the calcarine fissure to the right. Scale bar (bottom), 1 mm.

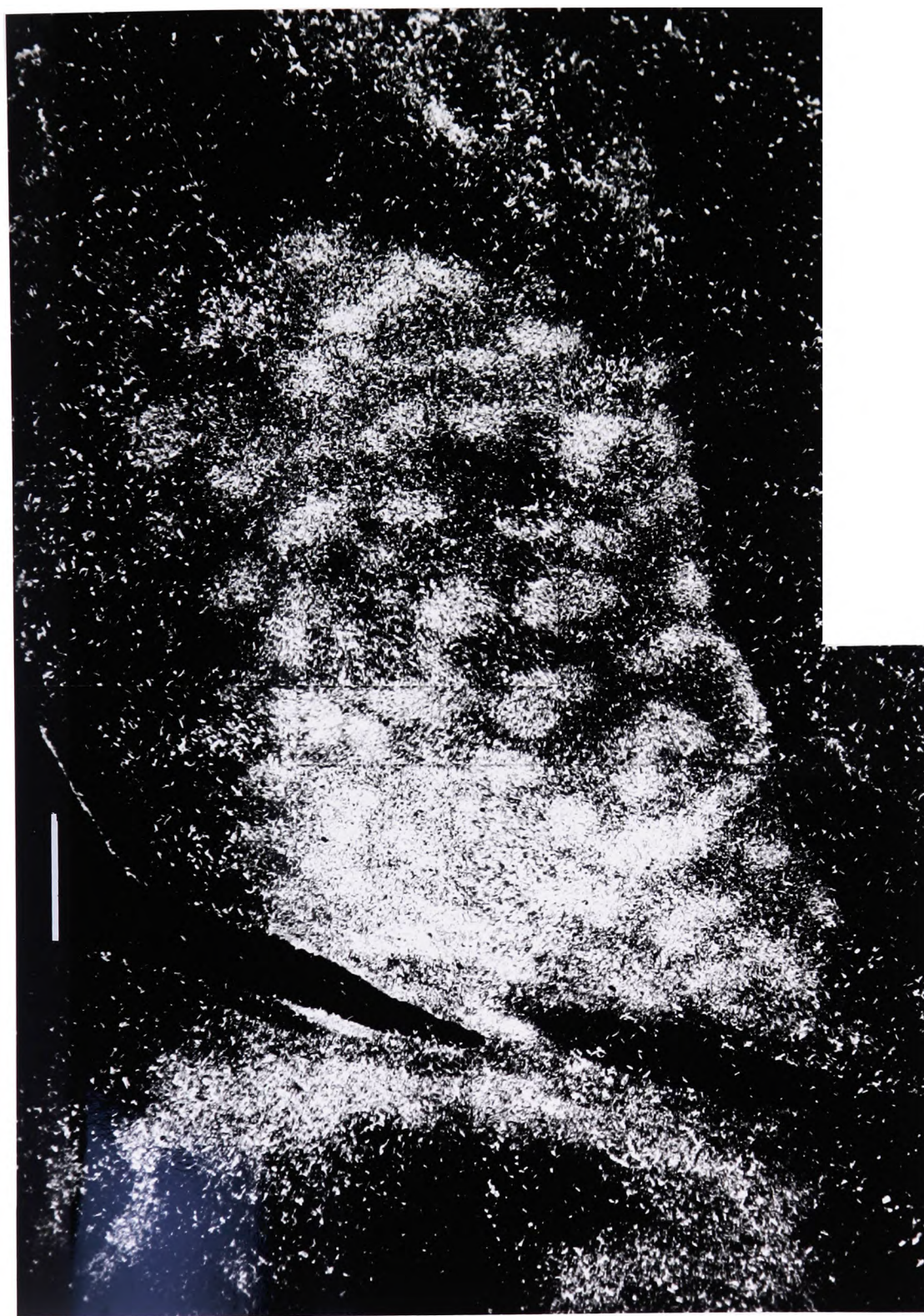


Figure 2-13

Complete reconstruction of afferent segregation in V1, contralateral (top) and ipsilateral (bottom) to the deprived eye in marmoset MD7. Light regions correspond to territory occupied by deprived-eye terminals. Due to the flattening procedure (see *Methods*), the V1/V2 border remains intact in the flat-mounts, while parts representing the centre of V1 near the occipital pole of the cortex are no longer joined. For the reconstruction of each hemisphere, *camera lucida* drawings of the extent of label (see *Methods*) in three adjacent sections through layer 4 were superimposed. For the montages shown here, drawings representing the operculum (left), the ventral lip and bank of the calcarine (centre top) and the dorsal bank and lip of the calcarine fissure (right) are arranged to reflect the actual neighbourhood relationships. The centre of each montage corresponds to the occipital pole of the cortex.

A: Hemisphere **contralateral** to the deprived eye;

B: Hemisphere **ipsilateral** to the deprived eye.

Scale bars, 5 mm.

A



B

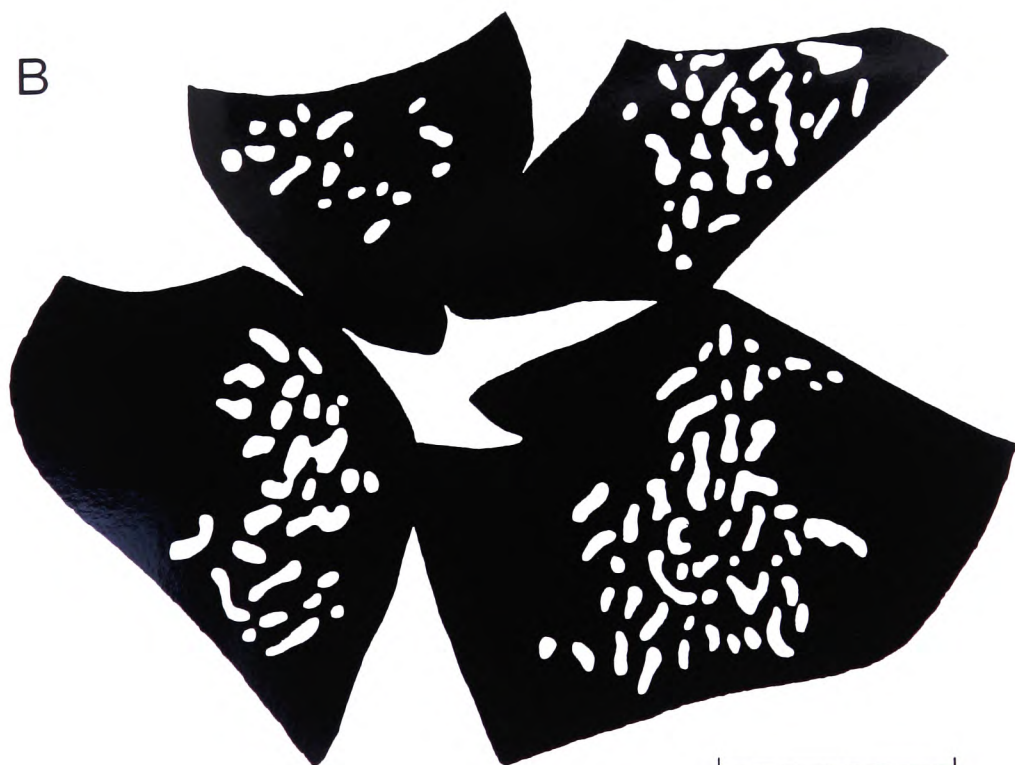


Figure 2-I4

Complete reconstruction of afferent segregation in V1, contralateral (top) and ipsilateral (bottom) to the deprived eye in marmoset MD6 (deprived from day 23 for 3 weeks). Light regions correspond to territory occupied by deprived-eye terminals. The montages were obtained in the same way as for the ones in Fig. 2-13.

A: Hemisphere **contralateral** to the deprived eye;

B: Hemisphere **ipsilateral** to the deprived eye.

Scale bars, 5 mm.

A



B



Pattern of metabolic (cytochrome oxidase) activity in the cortex

Flat-mounts of supragranular layers of V1 of animals MD4, MD6 and MD7 were processed for cytochrome oxidase (CO) activity. 'Blobs' of increased enzymatic activity were evident in most of V1, spaced fairly regularly at centre-to-centre inter-'blob' distances of 300 to 450 μm (Fig. 2-15A). Interestingly, the 'blobs' are most conspicuous in the operculum, the representation of the central visual field, while they become less and less distinct with increasing eccentricity and are barely detectable in the dorsal bank of the calcarine, where the periphery of the visual field is represented. For the right hemisphere (contralateral to the deprived eye) of marmoset MD7, I superimposed sections processed for CO activity with those reacted for geniculocortical terminal label, using blood vessels as landmarks to guide alignment, and found that CO 'blobs' were just as frequent and as discernible in areas receiving deprived-eye afferents as outside those areas. In the regions where both OD bands and CO 'blobs' could be clearly defined, a total 231 CO 'blobs' were counted, 88 of which had their centres within deprived-eye territory, 129 outside and 14 on the border of OD patches. Thus (whether the borderline 'blobs' were ignored or divided equally between inside and outside the OD bands), 41% of all CO 'blobs' were in areas densely innervated by the deprived eye: this value is in good agreement with an overall territory of 39% being occupied by deprived-eye patches (see above). Moreover, the CO 'blobs' showed a definite tendency to be aligned with the centres of OD bands, as demonstrated in Fig. 2-15B for the right hemisphere of MD7: for 124 CO 'blobs' that were located between two borders of OD patches that were roughly parallel to the axis of orientation of these patches, the distances a and b ($a < b$) from these two borders were measured and a coefficient $d = 2a/(a+b)$ was calculated. (For CO 'blobs' exactly aligned with the centre of an OD stripe or an 'inter-stripe', $d = 1$, for those on the border of OD patches, $d = 0$.) I obtained a mean $d = 0.68$ (SD = 0.27), which differs highly significantly ($p < 0.001$) from $d = 0.5$ which would have been expected, had the CO 'blobs' been randomly distributed.

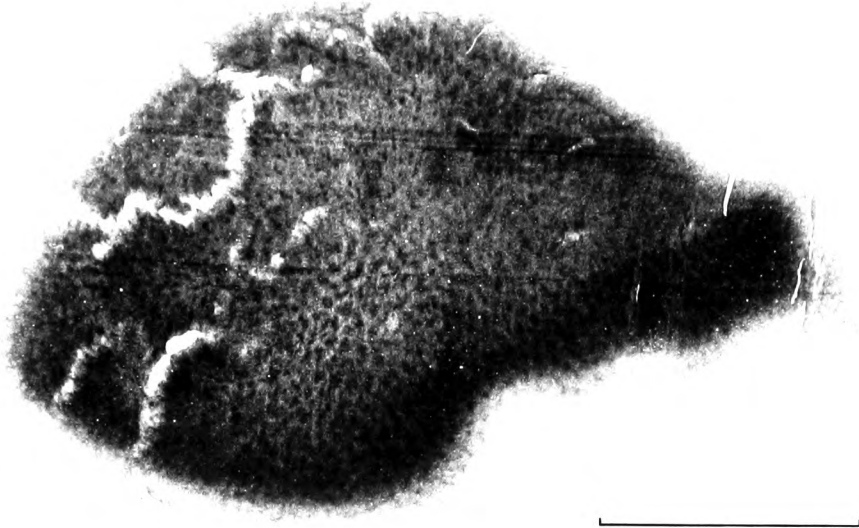
Figure 2-15

Pattern of cytochrome oxidase (CO) activity in superficial layers of V1 in a monocularly deprived marmoset.

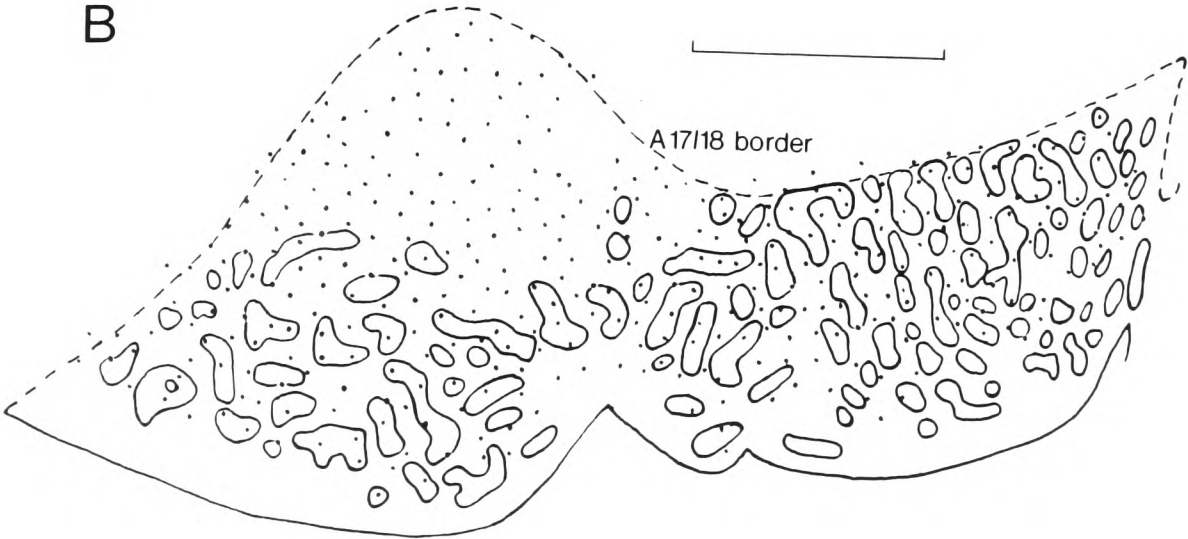
A: Photomicrograph showing CO 'blobs' in flat-mounted area 17 of the hemisphere contralateral to the deprived eye in marmoset MD7. This animal had been monocularly deprived for 3 weeks from day 25. Dark stain indicates CO-rich regions. Scale bar, 1 cm.

B: Alignment of OD bands and CO 'blobs' in V1 of marmoset MD7. The outlines of zones densely innervated by deprived-eye geniculocortical terminals (see Fig. 2-12) and the centres of regions of high CO activity (see part **A**) have been superimposed, using blood vessels as landmarks to aid alignment. Only the operculum and the ventral bank and lip of the calcarine cortex, where CO 'blobs' can be clearly distinguished, are shown. Scale bar, 5 mm.

A



B



2.3. Discussion

Functional architecture of V1 in normal animals

The basic properties of receptive fields in V1 of normal marmosets were shown to be very similar to those described for cat area 17 (Hubel & Wiesel, 1962) and macaque V1 (Hubel & Wiesel, 1968). All cells could be driven by light or dark bars (and frequently by spots) that were flashed in or moved through their receptive fields. Also, it was possible to distinguish between simple and complex cells, as defined by Hubel and Wiesel (1962), the majority of cortical neurons having complex-like receptive fields; some of the complex cells were 'end-stopped' ('hypercomplex' according to Hubel and Wiesel's original nomenclature; see *Introduction*).

For 81% of the units the response strength, when using bar stimuli, critically depended on the stimulus orientation. The remaining 19% of cells were not obviously selective for stimulus orientation and these were mainly found in layer 4 and, to a lesser extent, also in layer 6. Layer 6 receives a direct geniculocortical input, although a significantly weaker one than layer 4 (Spatz, 1979); therefore, it may be that cells that receive a direct geniculate projection tend to be non-oriented or weakly orientation-tuned in marmosets.

In macaques, the laminar distribution of non-oriented or poorly oriented cells is somewhat controversial: initially, Hubel and Wiesel (1968) reported only a few non-oriented cells, in layer 4, [while showing regular columnar progressions of orientation with closely spaced recordings through all layers in a spider monkey (*Ateles ater*)]. Later they described all cells in layer 4C of the macaque as not orientation selective (Hubel & Wiesel, 1974a). Blakemore et al. (1978) confirmed a concentration of non-oriented cells in layer 4C, but also saw a small percentage of non-oriented cells in other layers, especially the lower part of the supragranular layers. Dow (1974) also demonstrated non- or weakly-oriented cells in supra- and infragranular layers, and Schiller et al. (1976) found a relatively even distribution of non-oriented cells over all layers. More recently, Livingstone and Hubel (1984) have reported that cells lying

within cytochrome oxidase 'blobs' in the upper layers are frequently non-oriented, though Bartfeld and Grinvald (1992) have shown that many such neurons are selective but often broadly tuned for orientation. The discrepancy between these studies is at least partly explained by variation in the criteria for orientation selectivity. My data on the marmoset appear to be in line with the findings of Blakemore et al. (1978). In the New World *Cebus* monkey Rosa et al. (1992) encountered non-oriented cells almost exclusively in layer 4C β , while half of the units in layer 4C α were described as strongly orientation selective; similar results were reported by Hawken and Parker (1984) and Livingstone and Hubel (1984) for the macaque. The present data do not suggest such a subdivision for the marmoset's layer 4 α and 4 β , respectively: however, some uncertainty remains regarding the upper border of layer 4 and the equivalence between species in its subdivisions.

The orderly succession of preferred orientations of neurons recorded along most tracks is suggestive of a regular columnar organization of the representation of orientation preference similar to that described for cats (Hubel & Wiesel, 1962, 1963; Albus, 1979; Grinvald & Bonhoeffer, 1991), macaque monkeys (Hubel & Wiesel, 1968, 1974a, 1977b; Blasdel & Salama, 1986; Obermayer & Blasdel, 1993) and spider monkeys (Hubel & Wiesel, 1968). The surface distance covering a 180° range (a 'hypercolumn') of orientations was, according to my estimate, approximately 500-1000 μ m, similar to values obtained by the same method in capuchin monkeys (Rosa et al., 1992: ca. 900 μ m) or by means of imaging techniques in cats (Grinvald & Bonhoeffer, 1991) and in macaques (Blasdel & Salama, 1986).

The present study revealed some interesting differences in the pattern of cortical binocularity between marmosets and macaques. In V1 of the marmoset the majority of cells receive inputs of similar strength from the two eyes, while just 4% of all cells appear to be strictly monocular. In contrast, in macaque striate cortex a more substantial proportion of cells appears to be exclusively driven through one eye (OD1 or 7), estimates ranging from 28% (Schiller et al., 1976) to about 40% (Hubel & Wiesel,

1968); however, specifically for cells outside layer 4C, Blakemore et al. (1978) reported as few as 14% monocular cells.

In layer 4, where many neurons are monocular in cat, and the vast majority are monocular in macaque and capuchin monkey (e.g. Hubel & Wiesel, 1968; Blakemore et al., 1978; LeVay et al., 1980; Rosa et al., 1992), most cells in the marmoset seem to receive equal inputs from both eyes (OD4). Even the non-oriented units display substantial binocularity, unlike in the capuchin monkey (Rosa et al., 1992) and macaque (Hubel & Wiesel, 1968; Blakemore et al., 1978; but see also Schiller et al., 1976). This suggests that there exists substantial overlap in the terminals of the left- and right-eye geniculate projections to layers 4 and 6 of the marmoset, unlike the well-segregated OD columns in macaque and capuchin monkeys (LeVay et al., 1975, 1978, 1980; Hess & Edwards, 1987; Rosa et al., 1988).

Results of physiological recording in the normal marmoset are in good agreement with the transneuronal labelling experiments, which failed to demonstrate OD columns in V1, but instead revealed continuous bands in both layers 4 and 6 (Spatz, 1979). It would be interesting to record from layer 4 of juvenile marmosets in which OD bands have recently been demonstrated (Spatz, 1989), to study whether this early, transient anatomical segregation has a physiological correlate.

It appears that binocular integration in marmoset visual cortex takes place in the layer(s) receiving direct geniculate input, while in cat and macaque integration of inputs from the two eyes occurs one synapse further on.

Physiological effects of monocular deprivation

In the marmosets that had been monocularly deprived early in life the majority of cells in V1 were driven solely through the non-deprived eye (68%), particularly outside layers 4 and 6 (90%). Isolated clusters of cells responding to stimulation through the deprived eye were found in layers 4 and 6, which receive afferent input from the LGN, but were very rare in other layers. The laminar pattern of ocular dominance in response

to early MD resembles that described in the cat (Shatz & Stryker, 1978) and macaque (LeVay et al., 1980), with two reservations.

First, the deprived eye is still capable of driving cells in layer 6 in the marmoset. However, a subthreshold input from the deprived eye to layer 6 may be present in MD cats or macaques as well, but possibly be suppressed by intracortical inhibition (cf. Sillito et al., 1981; Mower & Christen, 1989). The fact that all layer 6 cells dominated by the deprived eye displayed weak or no orientation selectivity may reflect the non-orientation selective nature of geniculate input; orientation selectivity probably arises largely from intracortical circuitry (for a review see Ferster & Koch, 1987).

Second, the high percentage of binocularly driven cells in layer 4 (as well as in layer 6) of the MD marmosets contrasts with a preponderance of monocular units (driven through either the experienced or the normal eye) in MD cats and macaques (Shatz & Stryker, 1978; Blakemore et al., 1978; LeVay et al., 1980). This may be due to a capacity of layer 4 in marmoset V1 to maintain binocularity (cf. results from normal animals), even under altered visual experience, or to a recovery of binocularity during the prolonged period of normal visual experience that followed the period of MD in all of the experimental animals.

LeVay et al. (1980) demonstrated that a nine-day closure beginning at three weeks of age in macaques produced "the full anatomical and physiological effects" of MD. Since all of the eye-lid sutures in this study were performed similarly early in life and lasted for at least three weeks, it may not be surprising that the severity of the physiological effects did not show obvious variations with the duration of deprivation for the paradigms that were tested. Simply re-opening the deprived eye (at ages of six to sixteen weeks) apparently had very little effect on restoring functional inputs to cells outside layers 4 and 6. In this respect, my study replicates for the marmoset similar findings in macaque V1 (Blakemore et al., 1981). It, therefore, seems likely that the binocularity of cells within layers 4 and 6 in marmosets subjected to early MD with subsequent binocular recovery results from maintaining rather than regaining binocular inputs.

Anatomical effects of monocular deprivation

Following injections of WGA-HRP into an eye that had been monocularly deprived early in life, segregation of transneuronal label in V1 into OD bands was found in two adult marmosets. While in both animals afferents were clearly segregated in the dorsal lip and in the ventral bank and lip of the calcarine fissure, segregation was seen in only one of these animals in the part of V1 on to which the central visual field is mapped (the dorsolateral operculum).

The periodicity of the OD patches in marmosets MD6 and MD7 is similar to that seen in juvenile normal animals (Spatz, 1989). Ocular segregation also resembles in appearance and periodicity the pattern described by DeBruyn and Casagrande (1981) for two 5-month-old marmosets that had been monocularly deprived from birth: 200-300 μm -wide patches of denser label representing deprived-eye afferents were found in the lower half of layer 4, in both banks of the calcarine fissure, overlying continuous weaker terminal label throughout layer 4.

No data are available from this or the earlier study by DeBruyn and Casagrande (1981) on the pattern of geniculocortical terminals representing the non-deprived eye. It would be interesting to know whether such afferents occupy territory complementary to that of the deprived-eye terminals or whether they innervate layer 4 continuously (see below). The latter would be compatible with the hypothesis that in normal animals some afferent segregation does exist but is concealed by a high degree of terminal overlap, while in MD animals the arbors of deprived-eye terminals decrease in size, thus rendering segregation visible (DeBruyn & Casagrande, 1981).

Mechanisms of afferent segregation and response to MD

Using the same axon tracing technique as Spatz (1989), I have demonstrated a preservation, probably an enhancement, of afferent segregation in **adult** marmosets that had been subjected to brief monocular deprivation early in life, while in normally reared animals the fluctuations in the density of geniculocortical terminal label in layer 4 seen in young animals disappear by about one year of age. The retention of afferent

segregation appears to be a genuine effect of MD; however, the possibility cannot be excluded that binocular 'decorrelation' due to strabismus after early MD (see data from animal MD1) might be the cause of continuing ocular segregation. (Eye alignment of the marmosets used in the anatomical studies was not assessed.)

The disappearance of OD columns in marmoset V1 during normal postnatal development, as demonstrated by Spatz (1989), contrasts with findings in both cats and macaques, in which geniculocortical terminals from the two eyes **increase** in the degree of segregation into ocular dominance bands and remain separate throughout life. The **formation** of ocular dominance bands in cats is partly dependent on the presence of some form of visual input, since it is disrupted or at least delayed by dark-rearing starting at birth (Swindale, 1981; Mower et al., 1985; Stryker & Harris, 1986) and is prevented by tetrodotoxin blockade of activity in both eyes (Stryker & Harris, 1986). However, this does not hold for the macaque, where BD actually exaggerates physiological OD columns (see LeVay et al., 1980).

The **relative size** of terminal territories in layer 4 devoted to each eye depends on the **nature** of the early visual experience in the two eyes: following early MD in cats (Shatz & Stryker, 1978) and macaques (LeVay et al., 1980; Swindale et al., 1981) much of the area of layer 4 that would normally become exclusively occupied by the deprived eye is taken over by the experienced eye. Thus, the anatomical data are in good agreement with physiological evidence which shows a comparable bias in the ocular dominance distribution of layer 4 cells towards the non-deprived eye in both cats (Shatz & Stryker, 1978) and macaques (Blakemore et al., 1978, 1981). The ocular dominance of layer 4 cells may indeed simply be a reflection of the pattern of geniculocortical afferents representing the two eyes (Hubel et al., 1977a; Blakemore, 1988).

In marmosets, too, there is a fairly clear correlation between the amount of space occupied by terminals originating from either eye and the OD distribution of cells of layer 4 and layer 6. The fraction of territory densely innervated by terminals from the deprived eye is similar to that observed in macaques (38% after three weeks of MD, according to Swindale et al., 1981) and compares favourably with the physiological

index of deprived-eye dominance of cells in layers 4 and 6, obtained from three MD animals in this study. However, it has to be borne in mind that the distribution of terminal label, as revealed by transneuronal transport, does not always reflect the functional distribution and efficacy of synaptic connectivity. For instance, Blakemore and Van Sluyters (1975) found clear physiological OD columns in all layers of 7-day-old kittens, at a time when geniculocortical afferent segregation apparently has not yet been initiated (LeVay et al., 1978). Recently, Friedlander et al. (1992) have shown that, apart from a variable reduction in the size of deprived-eye terminal arbors, MD results in smaller boutons of deprived-eye axons compared to normal and non-deprived-eye axons, and a reduced number of synapses per bouton in cat area 18. Moreover, they found an **increased** density of boutons on deprived-eye arbors compared to arbors of the non-deprived eye. Similar structural changes might underlie the anatomical effects of MD that were observed in marmoset V1. In particular, an increase in the density of boutons on deprived-eye terminals might result in zones of high-density label after tracer injections into the deprived eye, while one would expect to find rather continuous label after injections into the non-deprived eye due to the expansion in terminal arbor size (see Swindale et al., 1981). If, however, OD bands were found, this would indicate a stabilization of the early ocular segregation through temporary 'decorrelation' of inputs from the two eyes (rather than a competitive capture of deprived-eye territory by the non-deprived eye): such sharpening of OD columns by brief MD has been reported for the case of a 7-week-old kitten that had been monocularly deprived from day 21 to day 31 (Shatz et al., 1977), similar to the pattern in strabismic animals (Shatz et al., 1977; Löwel & Singer, 1993). Once complete segregation is established, it is not reversed by restoration of binocular vision, presumably because of the lack of overlap as a substrate for interactions between left- and right-eye terminals.

In the normally reared marmoset correlated input from the two eyes apparently serves to enhance binocular input not only for cells **outside** layer 4 but also **within** layer 4. In contrast, in the macaque only cells outside layer 4 come to be binocularly driven, while neurons within layer 4, which often receive binocular inputs at birth, are mainly

monocular in normal adults, with ocular dominance corresponding to the bands of geniculocortical termination in which they lie (Hubel et al., 1977a). Therefore, different mechanisms are likely to underlie the development of ocular dominance within and outside layer 4 in macaques (Blakemore, 1988). In marmosets, the mechanism initially creating modest afferent segregation in layer 4 may be superseded during normal development (with correlated binocular input) by increasing binocularity.

Shape and overall pattern of OD bands

The tendency of OD bands to fragment into insular patches seems more pronounced in the marmoset than in other monkeys studied so far, and is thus more similar to the pattern observed in cats (LeVay et al., 1978; Anderson et al., 1988). This appearance may have one of two causes: first, the pattern of OD bands may have been affected by prolonged binocular vision following the re-opening of the deprived eye; a change of pattern from one of narrow stripes to patches of nearly normal width has been demonstrated for macaques with similar regimens of MD and subsequent binocular experience, with no recovery in the overall proportion of territory occupied by the deprived eye (Swindale et al., 1981). This possibility could easily be tested by studying the distribution of transneuronal label in infant marmosets subjected to MD without binocular recovery. It would also be interesting to know the shape of segregated regions in the normal young marmoset. (Spatz, 1989, examined only coronal sections.)

Second, the overall OD pattern may reflect geometrical constraints in the combination of left and right LGN inputs to layer 4 in order to obtain a retinotopic map that is locally isotropic within each ocular dominance column (Jones et al., 1991): the rather beaded appearance of the cat's OD pattern has been interpreted as the result of convergence of elliptically shaped LGN layers onto a primary visual cortex of similar shape. The macaque's striate cortex also takes the form of an ellipse that is about two times longer than wide but is innervated by roughly circular LGN laminae, resulting in OD bands that run perpendicularly to the long axis of V1 (Jones et al., 1991). In the marmoset, the shape of the LGN has been described as highly variable (Fritschy &

Garey, 1986b), but generally appears to be similar to that of the macaque's LGN. However, reconstructions from my flat-mounted material suggest that the marmoset's V1 may be only 1.5 times longer than wide. In that case, the difference in shape between LGN laminae and V1 would be rather small, similar to the situation in the cat. The solution of the mapping problem - preservation of local isotropy in layer 4 - might therefore look similar too. However, a more detailed quantitative study would be needed to test this assumption.

Comparison with other primates

The segregation of ocular inputs to V1 in MD marmosets exhibits a periodicity similar to OD patterns found in the New World monkeys *Cebus apella* (300-400 μm per column; see Hess & Edwards, 1987; Rosa et al., 1988) and *Ateles ater* (350-400 μm ; see Florence et al., 1986). In Old World monkeys, the widths of ocular dominance columns vary from 300 μm in *Myopithecus talapoin* (see Florence & Kaas, 1992) to 440 μm in macaques (Florence & Kaas, 1992; LeVay et al., 1985). As the striate cortex of the marmoset is significantly smaller (see above), the number of hypothetical OD hypercolumns (~ 460) is much lower than in any of the above species (≥ 1500 , see Florence & Kaas, 1992). It rather compares to the number calculated for the bushbaby *Galago* (~ 330 ; see Florence & Kaas, 1992), a prosimian of similarly small-sized striate cortex, in which OD bands of about 300 μm width have been demonstrated (Glendenning et al., 1976; Casagrande & Skeen, 1980).

Taken together, these data suggest that the *average width* of ocular dominance columns rather than the *number of cortical modules* is relatively constant across primate species (see Fig. 2-16). Moreover, ocular dominance bands of similar width are found in cat striate cortex (LeVay et al., 1978; Anderson et al., 1988) and even in the tectum of the "three-eyed frog" (Constantine-Paton & Law, 1978) where axons from two eyes co-innervate one tectal lobe due to implantation of a third eye primordium into the embryo. It therefore appears that universal mechanisms of self-organization rather than species-specific factors underlie and determine the width of ocular dominance bands; a number

of models for the formation of ocular dominance patterns based on interactions between afferents of opposite 'types' representing the two eyes have been put forward (e.g. von der Malsburg, 1979; Swindale, 1980).

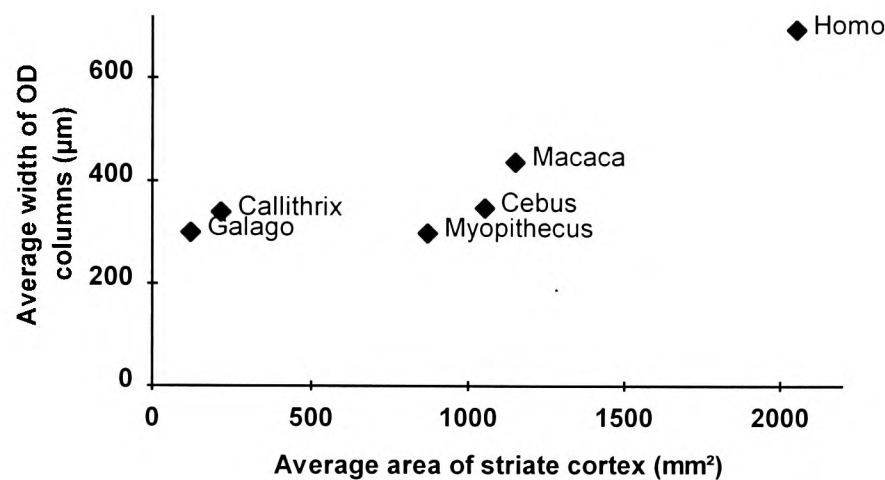


Figure 2-16: Average width of OD columns is plotted against surface area of striate cortex for a number of primate species. (Values for *Galago*, *Myopithecus*, *Cebus*, *Macaca* and *Homo* are taken from Florence & Kaas, 1992; see there for full references).

A puzzling implication of the species-dependence of the number of OD hypercolumns (and, similarly, of the number of orientation hypercolumns) is that the area of visual field of a given eccentricity that is analysed by a cortical module is not species-invariant. One might therefore expect that the average receptive field size at a given retinal locus is much bigger, for instance, in the marmoset than it is in the macaque in order to enable a cortical module to analyse fully the part of the visual field represented (see Hubel, 1982). That seems at least partly true: Hubel and Wiesel reported parafoveal (0-4° of eccentricity) receptive field sizes between $0.25^\circ \times 0.25^\circ$ and $0.5^\circ \times 0.75^\circ$, whereas I found receptive fields of, on average, $1.02^\circ \times 1.23^\circ$ (at 0.7-3° of eccentricity). This could indicate either a better resolution or a higher degree of 'over-

sampling' of the visual scene in macaque compared to marmoset striate cortex. The latter is more likely to be true, as the minimum separable visual acuity of marmosets (2' according to Ord & Samorajski, 1968) matches that of rhesus monkeys. Due to the small sample size, the present study does not allow any definitive statement on the spatial resolving power of individual neurons in marmoset visual cortex.

Phylogeny of OD segregation

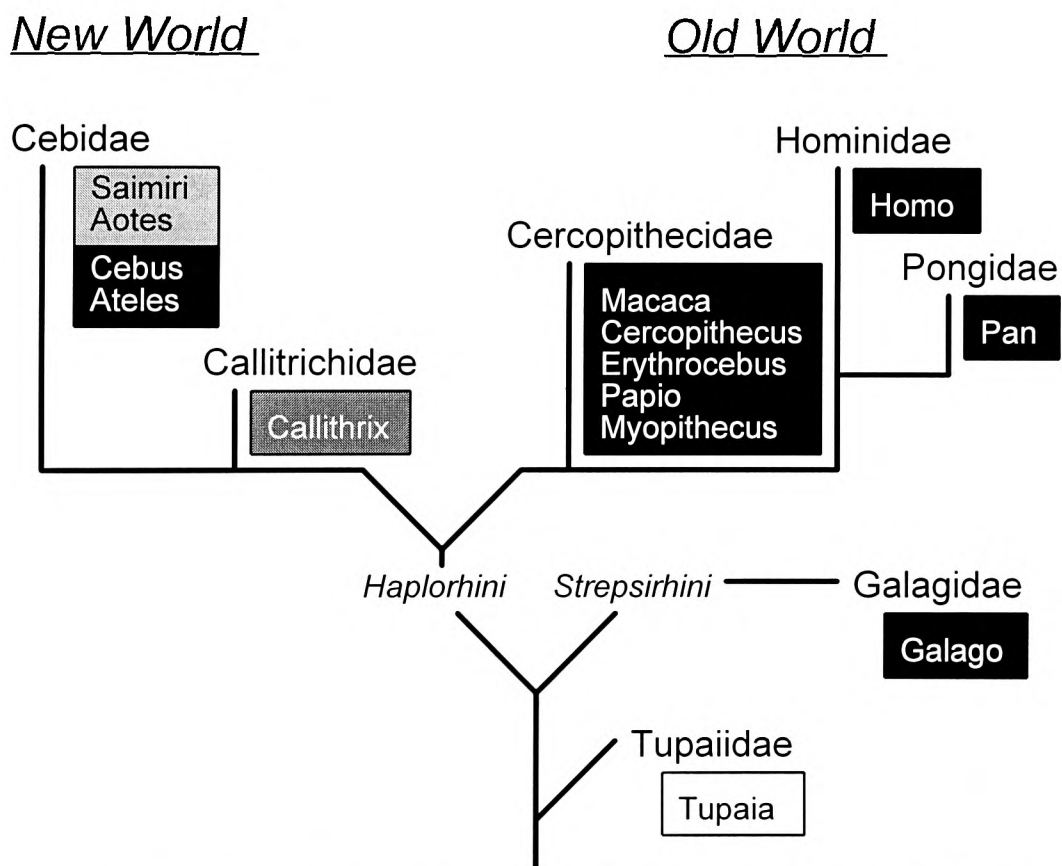


Figure 2-17: Phylogenetic tree of Old and New World primates, modified after Florence et al. (1986; see for full references). Genera with clear OD segregation in the normal adult are shown in black boxes, those with weak segregation in light grey and those with experience-dependent segregation in dark grey boxes. Absence of any afferent segregation (unfilled box) applies only to the tree shrew, *Tupaia*.

My findings support the notion that a weak tendency for segregated inputs characterized early ancestors of modern New and Old World monkeys, which was enhanced in highly-developed species in both lines of descent (Fig. 2-16; Florence & Kaas, 1992). While the tree shrew, *Tupaia glis*, being closest to the common ancestors of New and Old World monkeys, does not exhibit any segregation of geniculocortical afferents (Casagrande & Harting, 1975; Hubel, 1975), it appears that at least at some point during ontogeny **all** contemporaneous New World primates (like Old World monkeys) have the capacity for segregation of geniculocortical afferents (see Fig. 2-17). In some species, such as *Callithrix*, this capacity may be demonstrable only during infancy or by altering the animal's early visual experience.

Cytochrome oxidase (CO) 'blobs'

In three MD marmosets, V1 was processed for cytochrome oxidase (CO) activity. In all of them 'blobs' of high enzymatic activity were found: they were most distinct in the representation of the central visual field. Anatomical and physiological studies suggest an involvement of these insular zones of increased metabolic activity in the processing of colour information (e.g. Livingstone & Hubel, 1984, 1988). Like in Old World primates (including man), the density of cones, i.e. photoreceptors that contain visual pigments of different spectral sensitivities, is highest in the fovea of the marmoset's retina and decreases rapidly towards the periphery (Troilo et al., 1993). The topography of CO 'blobs' in V1 may reflect this distribution. However, no data are as yet available on the neurophysiological basis of colour vision in marmosets. In view of the sex-dependent polymorphism of the visual pigments (Travis et al., 1988) it would surely be worth paying more attention to colour sensitivity of striate neurons than was possible in the scope of this study.

There is evidence in other primates that the pattern of CO 'blobs' is in register with that of OD bands and that both periodic patterns are affected by imbalance of stimulation between the two eyes. After monocular enucleation, CO 'blobs' in supra-granular layers are aligned with columns receiving input from the remaining eye in

macaques (Horton & Hubel, 1981) as well as in the New World capuchin monkey (Hess & Edwards, 1987). Even in cats, where CO 'blobs' have recently been reported (Murphy et al., 1991), there is some evidence that they are aligned with the centres of OD columns (Murphy et al., 1991; but see Boyd & Matsubara, 1993). In marmosets the situation seems rather different. There is a clear pattern of CO 'blobs' in normal adults (Malach, 1992; Spatz et al., 1992) but no hint of a corresponding array of OD stripes in layer 4. It is conceivable that CO 'blobs' are aligned with the OD pattern seen in young marmosets, since I observed a rough correlation between CO 'blobs' and the OD structure present in mature animals after early MD (see Fig 2-15B). The CO 'blob' pattern was, however, most distinct in the poorly segregated regions of V1 in these animals, representing the central part of the visual field. In cats, a dissociation of afferent segregation and the emergence of CO 'blobs' has recently been observed following disruption of layer 4 cell generation (Kind et al., 1993). It appears that a columnar organization of the major geniculocortical terminals is not a necessary condition for the development of CO-rich regions. The possible interdependence of these two systems deserves further investigation.

3. INTEROCULAR SUPPRESSION IN THE PRIMARY VISUAL CORTEX: A POSSIBLE NEURAL BASIS OF BINOCULAR RIVALRY

With respect to vision, perhaps the most distinctive feature of many carnivores and all primates, including humans, compared to other mammals is the frontal position of their eyes. Although the panoramic vision, seen, for instance, in rabbits, is sacrificed, a highly advantageous capacity has been gained: *stereoscopic vision* and, in consequence, acute *depth perception*. As the two eyes are horizontally separate they see the world from slightly different points of view. Wheatstone (1838) demonstrated that the resulting difference in the two retinal images is the crucial requisite for stereopsis. However, despite that difference in the two eyes' images, we normally experience binocular single vision rather than *diplopia* (double vision) or *confusion* (conflicting images seen in the same position in space).

On the locus in space known as the horopter, each point in the visual world is said to project upon *corresponding points* on the retinae of the two eyes. Points on the two retinae are classically defined as corresponding if they give rise to the same sense of 'visual direction' through the two eyes (Hering, 1879). The retinal images of points that lie closer or further than the horopter (or surface of single vision) are said to fall on non-corresponding positions: for points closer than the plane of focus the image in one eye is nasally offset compared to that in the other eye, while for points behind the plane of focus there is a temporal offset. These offsets have become known, respectively, as crossed and uncrossed retinal *disparities* and are thought to be the essential cues for the high-performance depth discrimination that stereopsis enables us to do: at a distance of 40 cm, a depth difference of as little as 25 μm can be discriminated under optimal conditions (Bishop, 1983).

Obviously, we are able to fuse slightly disparate retinal images to form a single stereoscopic percept. However, this is possible only over a very restricted range of disparity, called Panum's fusional area (Panum, 1858; Mitchell, 1966), which, for

example, at a distance of 40 cm represents a depth in space of only 12 mm (Bishop, 1983). Outside of this area are regions of space in which individual objects fall on entirely non-corresponding retinal points and hence should be seen in two different visual directions. However, we are usually unaware of such double vision, suggesting the operation of a suppressive mechanism.

In order to explain our ability to see objects singly even when they stimulate non-corresponding retinal points, Panum (1858) suggested that any point on the retina of one eye actually corresponds to a certain *area* on the other retina. Interestingly, this idea resembles the modern concept of receptive field disparities as a neurophysiological basis of stereoscopic depth perception: Barlow et al. (1967) and Nikara et al. (1968) showed that there are binocular cells in cat striate cortex whose receptive fields are in non-corresponding positions on the two retinae. Similarly, neurons have been found in macaque V1 that selectively respond to crossed or uncrossed stimulus disparities (Poggio & Fisher, 1977; Poggio et al., 1988). It should, however, be emphasized that the majority of cells have receptive fields in roughly corresponding positions in both eyes and respond best to binocular stimuli of zero or near-zero disparity, and, therefore, presumably constitute the neurophysiological correlate of binocular single vision (Bishop, 1983).

When images that are so dissimilar that they cannot be fused impinge on corresponding retinal areas in the two eyes continuously over an extended time period, simultaneous vision of both ('false fusion': Wolfe, 1983) quickly gives way to alternating periods of perceptual dominance and suppression of each monocular stimulus: the visual field breaks up into a set of fluid patches, within which perception is dominated completely by the image viewed by one eye, before switching, after a few seconds, to the image seen by the other eye. This psychophysical phenomenon became known as "*Wettstreit der Sehfelder*" (see Helmholtz, 1910) or ***binocular rivalry*** (see review by Fox, 1991). It was actually first described by Du Tour (1760), who noted alternations in perceived colour when the two eyes viewed different colours. This *colour rivalry* seemed to support his (false) view that normal single vision is merely a

consequence of the fact that only the information from one eye is perceived at any one time.

However, the phenomenon commonly described as binocular rivalry is that of *contour rivalry*. A first account of contour rivalry was given by Wheatstone (1838). When viewing the two halves of the stereogram shown below (Fig. 3-1) with a stereoscope, he noted that the letter within the circle changed 'alternately from that which would be perceived by the right eye alone to that which would be perceived by the left eye alone' and that at the moment of change fragments of both letters seemed to intermingle. Wheatstone (1838) further observed that it "... does not appear to be in the power of the will to determine the appearance of either of the letters."



Figure 3-1: First demonstration of contour rivalry (Fig. 25 from Wheatstone, 1838).

Subsequent work addressed the issue of what controls the alternations between the two eyes' images. Helmholtz (1910), studying rivalry between orthogonally oriented gratings or pairs of lines, maintained that involuntary shifts in attention between the two eyes cause the rivalry phenomenon and claimed that he could at will prevent the occurrence of binocular rivalry by turning his attention to one of the two rivalrous stimuli ("... auch hier kann ich beliebig das Bild des einen oder anderen [Linien-]Paares festhalten, wenn ich meine Aufmerksamkeit darauf richte...").

However, Breese (1899) showed that *binocular rivalry cannot be explained solely in such 'psychical' terms but must have a physiological component*: if subjects try to 'hold' one of a pair of rivalrous stimuli, the percentage of time that this stimulus is seen can be increased considerably, but the number of alternations in a given period of time

does not change significantly. Breese (1899, 1909) further demonstrated that the rate of alternations *is* affected when, for example, the luminance of the stimuli is changed.

Breese's experiments also revealed that binocular rivalry is a *stochastic process*. Consequently, statements made on the duration of phases of dominance and suppression in binocular rivalry always refer to averages taken over a large number of cycles. The distribution of durations (x) of individual phases of rivalry can be fitted with a gamma (Γ) distribution (Fox & Herrmann, 1967; Lehky, 1988) by the equation

$$f(x) = \frac{t^k \cdot x^{k-1} \cdot e^{-tx}}{\Gamma(k)} \quad \text{where } \Gamma(k) = (k-1)!$$

The parameters t and k can be obtained from the experimental data as

$$k = \frac{\bar{x}^2}{\sigma^2} \quad \text{and} \quad t = \frac{\bar{x}}{\sigma^2},$$

where $\bar{x}$ is the mean and σ^2 the variance of the measured phase durations.

Another important statistical property of binocular rivalry is that the durations of successive periods of dominance or suppression are independent, as has been shown by autocorrelation analysis (Fox & Herrmann, 1967).

Levelt (1965) related the rivalrous phase durations to what he called *stimulus strength*, defined as 'the power of contralateral suppression' that a monocularly presented stimulus exerts. He gave evidence that the stimulus strength of a pattern is directly related to both the 'amount of contour per area' and the 'strength' of contours in that pattern. This contour strength increases with contrast, luminance and size of the stimulus as well as with the sharpness of the contours. It was shown by Levelt (1965) and confirmed by Fox and Rasche (1969) that *increasing the stimulus strength in one eye* does not affect the dominance period of that eye but *produces a decrease in the average duration of dominance of the other eye*.

A number of neural models has been developed to account for these various characteristics of binocular rivalry (Matsuoka, 1984, Lehky, 1988, Blake, 1989, Mueller, 1990). They are based on the assumption that an autonomous oscillator operates at some stage of binocular interaction in the processing of visual information.

Albeit differing in detail, all theories postulate that the oscillating circuitry involves *reciprocal inhibition between populations of monocular neurons*, resulting in alternating blockage of signals from the two eyes. The inhibition is generally believed to be of the feedback rather than the feedforward type in order to account for the alternations of perceptual dominance (Matsuoka, 1984; Mueller, 1990; Lehky & Blake, 1991; but see Blake, 1989). The most instructive model may be that of the binocular integration circuit as an astable multivibrator (Fig. 3-2), proposed by Lehky (1988). In this simple flip-flop circuit, two transistors Tl and Tr (analogous to neurons receiving input from the left and right eye, respectively) are connected *via* two capacitors Cl and Cr in a manner resembling reciprocal inhibition. The variable resistors Rl and Rr symbolize the strength of the inhibitory coupling. The duration that one side is 'dominant' depends on the time constant of the capacitor that is charged through the **other** side. The charging of the capacitor up to the threshold, where the circuit flips over to the opposite state, may be considered as adaptation of inhibition, and a decrease in capacitor time constant as an increase in stimulus strength (Lehky, 1988). The stochastic properties of binocular rivalry can be readily simulated by adding random noise to the reciprocal inhibition (Lehky, 1988).

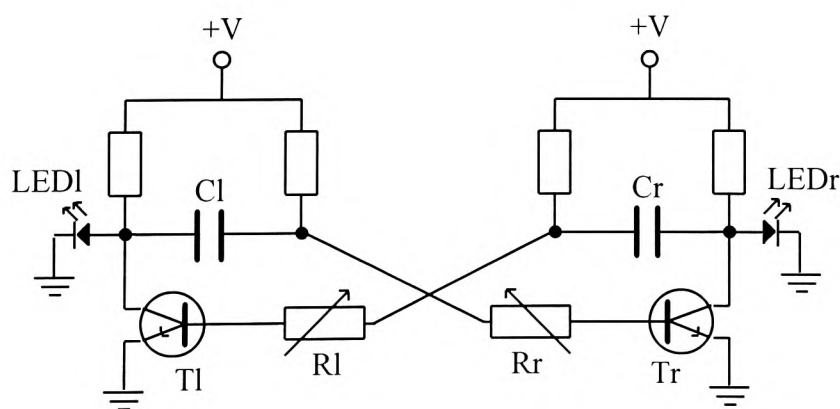


Figure 3-2: Circuit diagram of astable multivibrator (adapted from Lehky, 1988).

Most of the more recent psychophysical studies on binocular rivalry are concerned with the site and nature of the interocular interactions that perceptually suppress information from one eye at a time. It has been demonstrated that, while the dominance phases represent a state of normal sensitivity comparable to monocular viewing (Fox & Check, 1966; Wales & Fox, 1970), rivalry suppression is an inhibitory state in which detectability of any stimulus changes is non-selectively decreased except increments in contrast (Blake & Fox, 1974a). Among other parameters, increment detection thresholds for the duration of flashes are increased by about 0.5 log units (Wales & Fox, 1970), and detection of motion (Fox & Check, 1968) as well as detection of changes in spatial frequency and orientation of gratings presented to the suppressed eye are impaired (Blake & Fox, 1974a; Blake & Lema, 1978).

The notion of binocular rivalry as alternating monocular viewing finds support in recordings of human visual evoked potentials (VEPs) during stimulation with sinusoidal gratings modulated in counterphase: the magnitude of VEPs evoked by dichoptic stimuli of orthogonal orientations seems to be roughly equal to that during monocular stimulation (Apkarian et al., 1981). Moreover, the rhythmic EEG response to flicker stimulation in one eye is suppressed during episodes of rivalry produced by presentation of a stationary grating to the other eye (Lansing, 1964).

The non-selectiveness of suppression, including a decrease in detectability even of contour-free stimuli (Wales & Fox, 1970), and the wide variety of stimulus parameters that evoke binocular rivalry if dissimilar in the two eyes (e.g. contour, colour, or motion) suggest that rivalry takes place at an early stage in the visual pathway, prior to the postulated parallel streaming of visual information (Van Essen & Maunsell, 1983; Livingstone & Hubel, 1987, 1988). However, problems for this notion derive from studies that reported adaptational after-effects of equal strength whether the adapting stimulus was visible continuously (during monocular viewing) or only intermittently (during binocular rivalry). These after-effects include the threshold elevation after-effect (Blake & Fox, 1974b; Blake & Overton, 1979) and the motion after-effect (Lehmkuhle & Fox, 1975; O'Shea & Crassini, 1981). From these data, it appears that

the site of the relevant adaptation, which is likely to reside at least in part in V1 (e.g. Maffei et al., 1973), is located **before** that of binocular rivalry in the visual pathway. However, recently Lehky and Blake (1991) found a reduction of the threshold elevation after-effect when conditions were such that the adapting stimulus was visible only 10% of the time, implying that neurons undergoing adaptation are located **at or after** the site of rivalry suppression.

In summary, much of the available psychophysical evidence as well as the neural models of binocular rivalry suggest that the underlying interocular suppression takes place in the periphery of the visual pathway, possibly between pools of monocular cells. The orientation-dependence of binocular rivalry requires either that these cells are themselves orientation-selective, or that they receive inhibition from such neurons. This has led Lehky and Blake (1991) to suggest that the site of the alternation is either the lateral geniculate nucleus, where neurons are monocular and essentially lack orientation selectivity but receive extensive back-projections from orientation-selective cells in layer 6 of the primary visual cortex (Gilbert & Kelly, 1975), or in layer 4 of area 17, where cells tend to be monocular and are non-oriented in the monkey (Hubel & Wiesel, 1968) but usually orientation-selective in the cat (Hubel & Wiesel, 1962).

Despite the compelling nature of the rivalry phenomenon, rather little is known of its possible neural origin. Logothetis and Schall (1989a, b) related neuronal activity in area MT of the superior temporal sulcus (STS) of awake monkeys to a behavioural indicator of the perception of rivalry in a motion discrimination task. Although a small fraction of cells in MT (about 15%) behaved in a manner correlated with the monkey's judgement of direction of movement, an equal fraction behaved in the opposite fashion; and the majority were unaffected. The results were therefore somewhat inconclusive. More in line with the recent models of binocular rivalry, Varela and Singer (1987) reported periodic suppression of responses in the A and A1 laminae of the anaesthetized cat LGN during stimulation of the two eyes with stimuli differing in orientation. However, Moore et al. (1992) recently failed to confirm these findings.

In their analysis of binocular interactions for simple and complex cells in cat area 17, Ohzawa and Freeman (1986a,b) also saw no strong interocular influences that might account for binocular rivalry. Most striate neurons showed little difference in response to an optimally oriented grating presented to one eye when an orthogonal grating was simultaneously presented to the other eye.

I recorded from both the dLGN and area 17 in adult cats, using identical visual stimulation procedures for both structures, to re-evaluate the role each cell population may play in classical contour rivalry.

3.1. Methods

Animals and surgery

All data presented here were obtained from five normal adult cats bred in a closed laboratory colony.

Standard electrophysiological techniques for single-cell recording were employed (see Blakemore and Price, 1987). Anaesthesia was induced with ketamine hydrochloride (30 mg/kg i.m.; Vetalar®, Parke-Davis) and maintained with alphaxalone/alphadolone (Saffan®, Pitman-Moore) i.v. during tracheal cannulation and the exposure of the brain *via* a very small craniotomy and durotomy. During recording the animal was anaesthetized and paralysed with a continuous i.v. infusion of sodium pentobarbitone (1-2 mg/kg/h, as needed to maintain anaesthesia; Sagatal®, RMB) and gallamine triethiodide (10 mg/kg/h; Sigma) in 0.9% sterile saline. The infusion solution further contained 5% glucose and was administered at a rate of 3 ml/h. The animal was artificially hyperventilated (ventilator 7025, Ugo Basile) with room air plus carbon dioxide (CO₂); stroke rate and volume were adjusted to maintain an end-tidal CO₂ level of 4.5-5.0%. E.E.G. and E.C.G. were constantly recorded to monitor the state of anaesthesia. Body temperature was kept at 38°C by means of a feedback-controlled heating-pad.

The animal was placed in a stereotaxic frame that leaves the visual field unobstructed and permits the head to be rotated around the horizontal interaural axis and a vertical axis through the centre of the head (Eldridge, 1979b). Stability of the head was achieved by cementing a bolt to the skull and attaching it to the stereotaxic frame.

Pupils were dilated with atropine hydrochloride, and the lids and nictitating membrane retracted with phenylephrine. Chloromycetin was applied to prevent infection of the corneae. Zero-power contact lenses were placed on each cornea and 3-mm artificial pupils were placed in front of the eyes as well as additional lenses for correction of refractive errors.

Tungsten-in-glass micro-electrodes (Merrill & Ainsworth, 1972) were advanced, by means of a stepping-motor microdrive, at stereotaxic positions (Horsley & Clarke, 1908) corresponding to the centre of the visual field in the LGN (A6.5, L9) and area 17 (P5, L1.5). The craniotomy was sealed with agar to protect the exposed cortex and to minimize pulsations. Furthermore, prednisolone acetate (Deltastab®, The Boots Co.) was administered i.m. to prevent inflammation and cortical oedema.

Recording and visual stimulation

Spikes were conventionally amplified and displayed on an oscilloscope screen and an audiomonitor. Single units were isolated using a Schmitt-trigger window discriminator. They were characterized qualitatively with moving and stationary bars or spots of light, of medium contrast, back-projected by means of an overhead projector on to a translucent tangent screen. Receptive fields in both eyes were plotted on the tangent screen, on which the projections of the areae centrales and the optic discs were also mapped by means of a reversible ophthalmoscope (Eldridge, 1979a). LGN cells were classified as 'On'- or 'Off'-centre and as linear (X) or non-linear (Y) in their responses to a phase-reversing grating (Enroth-Cugell & Robson, 1966). Cortical neurons were classified as simple or complex according to Blakemore and Price's (1987) description of Hubel and Wiesel's (1962) original criteria: only cells with distinct spatially summing and antagonistic 'On' and 'Off' areas were termed simple. This qualitative classification was confirmed during quantitative recording by Fourier analysis of the response to drifting, sinusoidally modulated gratings: for simple cells the first-order component, F_1 , of the response (modulation at the drift frequency of the gratings) is greater than the zero-order component, F_0 (mean discharge) for all spatial frequencies up to the optimum, while for complex cells $F_1 < F_0$ holds for all but very low spatial frequencies (Movshon et al., 1978a,b; Skottun et al., 1991).

The ocular dominance (OD) of binocularly driven neurons was classified on the seven-point scale of Hubel and Wiesel (1962). For quantitatively tested units, the subjective classification was confirmed: for cells of OD2 or OD6 the response elicited

through the dominant eye was at least three times that elicited through the non-dominant eye at the respective optimal orientations; for cells of OD3 or OD5 the ratio of response strengths was between 1.5 and 3, and for cells of OD4 it was below 1.5.

For quantitative tests, the two eyes were stimulated independently by means of two high-resolution cathode-ray tube screens (Tektronix 608) viewed at a distance of 57 cm *via* two pairs of front-silvered mirrors. These mirrors, placed at angles of 45° to the animal's midsagittal plane in front of each eye, produced a temporal horizontal displacement of the visual axes and guaranteed that either eye could view only one of the two CRT screens ('dichoptic' stimulation). The total display area on each screen consisted of a circular region subtending 10 cm, i.e. 10° of visual angle at a viewing distance of 57 cm, in diameter. Each screen was adjusted in position to bring the receptive field in that eye to the centre of the display. Drifting, sinusoidally modulated gratings (mean luminance 17.5 cd/m²) were generated by a 'Picasso' (Innisfree) image synthesizer. External control of the Picasso as well as data acquisition and analysis were performed by a Visual Stimulation software package ('VS'; Cambridge Electronic Design). This package allows a range of different stimuli, including a blank stimulus with no modulated pattern on the screen, to be pseudorandomly interleaved. Responses to each individual stimulus are averaged over a number of trials included in the randomized sequence. These data as well as data for individual and accumulated peristimulus time histograms (PSTHs) can be output for hardcopies and/or further analysis.

Cells were first stimulated monocularly with gratings drifting at a temporal frequency optimized by ear to determine tuning curves for orientation and spatial frequency: during these tests a uniform field of the same space-averaged luminance was presented to the corresponding region of the field of the other eye. Each individual presentation lasted 1.25 sec while the blank periods between presentations lasted 1 sec.

Binocular interactions were then tested by constantly stimulating one eye (generally the dominant eye) with a full-field (10° diameter) drifting grating (the '**conditioning stimulus**') of optimum orientation and spatial frequency and medium contrast [between 0.18 and 0.35, where Michelson contrast = (maximum-minimum luminance)/(2 x mean

luminance)], and intermittently presenting to the other eye drifting gratings varying in orientation, spatial frequency, or contrast. The time course of the onset of those gratings was always a step-function. During intervening periods of monocular stimulation the second eye viewed a homogeneous field of the same space-averaged luminance as the 'conditioning' stimulus. This 'blank' stimulus was preferred over a dark field in order to avoid stimulation by changes in brightness and in view of the observation that prolonged closure of one eye results in occasional rivalrous suppression of the open eye's image (Wales & Fox, 1970; Ellingham et al., 1993). In some experiments the *spatial offset* (initial spatial phase) of the grating shown to the non-dominant eye was varied while the relative phase of the conditioning (dominant-eye) grating was held constant. When both stimuli were optimally oriented, such a spatial offset corresponds to relative *interocular phase disparity* (Ohzawa & Freeman, 1986a). The two gratings always drifted at the same temporal frequency - either 2 or 4 Hz. Each epoch of binocular stimulation lasted 5 sec and the periods of monocular stimulation in between also lasted 5 sec, unless specified otherwise.

Mean discharge rates and standard errors of the mean were calculated from at least four trials for each condition. Tuning curves of interactions were obtained by relating the responses during binocular stimulation to those during the immediately preceding periods of monocular stimulation.

A cell was considered to show ***binocular interaction*** if the response to binocular stimulation differed significantly (in a two-tailed *t*-test) in strength from the response to stimulation of the dominant eye alone.

The time-course of suppression for rivalrous stimuli was studied comprehensively in 5 cells that showed clear suppressive interaction. An optimal conditioning grating was presented to the dominant eye and 5 seconds later a grating of orthogonal orientation and high contrast was introduced to the other eye and was left on for a 30-sec stimulation period. The latency and consistency of suppression were judged from peri-stimulus time histograms (PSTHs) of individual trials and from PSTHs accumulated over 7 to 10 such trials.

Finally, in four cells that showed clear suppression for rivalrous stimulation in the standard procedure, the effects of different temporal sequences of presentation were studied. The response was averaged over a 5-sec period of binocular stimulation with orthogonally oriented gratings in the two eyes, preceded by either 1) an optimal conditioning grating shown to the dominant eye alone; 2) the orthogonal grating presented alone to the other eye; or 3) a blank screen of the same mean luminance presented to both eyes.

Histology

At the end of each electrode penetration small electrolytic lesions were made along the track during withdrawal of the electrode. Animals were given an overdose of pentobarbitone and perfused transcardially with phosphate-buffered saline followed by 4% paraformaldehyde. Electrode tracks were reconstructed from 50- μ m coronal sections stained with cresyl violet.

3.2. Results

Lateral Geniculate Nucleus

In two animals I studied quantitatively 17 LGN cells in laminae A and A1, 12 X-cells and 5 Y-cells, all monocularly driven by conventional stimuli. All receptive field centres were within 5° of the area centralis. For binocular stimulation, the display for the 'silent' eye was centred on the position corresponding to that of the receptive field in the dominant eye, determined by prior recording from neighbouring cells in the adjacent lamina, dominated by the other eye.

Most of these LGN cells had no obvious selectivity for orientation (see Fig. 3-3A), but some showed small but clearly significant biases in preference (cf. Vidyasagar & Urbas, 1982; Shou & Leventhal, 1989). In every case, the orientation and direction of movement giving the largest response were used as the steady monocular stimulus during binocular testing. In 7 LGN cells (41%) the binocular responses differed significantly from responses through the dominant eye alone. In all these cases, the interaction was entirely suppressive: in this sample I saw no significant augmentation of the response even when the stimuli were identical in the two eyes. Presumably, grating stimuli, like the single light bars employed by Kato et al. (1981), do not reveal binocular facilitation of the type found by Schmielau and Singer (1977) with stationary flashing spots.

Figure 3-3 shows results for a typical on-centre Y-cell, recorded in lamina A of the LGN. Part A is a polar plot of mean response as a function of direction of drift (and therefore of orientation) for a grating presented monocularly to the receptive field in the contralateral eye. Response did not vary consistently with orientation for this cell. Part B illustrates the results of the binocular stimulation procedure (see *Methods*). The receptive field in the contralateral eye was continuously stimulated with a 'conditioning' stimulus, in this case a near-vertical grating, drifting leftward (direction of drift 202.5° , corresponding to the largest value on the polar plot). Gratings of various directions of drift were then presented intermittently in random sequence to the corresponding region

of the ipsilateral eye. Filled circles plot mean responses during presentations with the interocular difference of directions of drift indicated on the abscissa, while the corresponding unfilled circles plot the mean discharge during the periods of monocular stimulation immediately preceding presentations with that particular binocular combination. In order to take account of any chance fluctuations in responsiveness, as indicated by variation in these monocular control values, the level of response during binocular stimulation as a percentage of the corresponding monocular response was calculated:

$$\frac{(\text{binocular response} - \text{monocular response}) \times 100\%}{(\text{monocular response} - \text{spontaneous discharge})}$$

Part **C** plots this *binocular interaction function*; binocular inhibition (about 40% reduction in response for this cell) was essentially independent of the orientation and direction of drift of the gratings shown to the 'silent' eye.

The behaviour of all the other LGN cells that showed binocular interaction was essentially similar, the mean response through the dominant eye being suppressed by an average $26.7\% \pm 11.1\%$ SD during stimulation through the 'silent' eye with gratings of any orientation. In addition to the mean discharge (F_0 Fourier component), I also examined the modulated response of these cells (the first harmonic component, F_1) but saw no obvious difference in the suppressive influence on these two components.

For LGN neurons, the extent of inhibition did not vary with the relative interocular spatial phase of the two gratings, either for iso-oriented gratings (confirming the observation of Xue et al., 1987a) or for orthogonal stimulus orientations (see Fig. 3-4). However, the magnitude of inhibition did depend on the spatial frequency of the gratings presented to the silent eye (cf. Moore et al., 1992), its maximum being at a spatial frequency close to that eliciting the strongest excitation in the dominant eye. Fig. 3-5B shows the results of an experiment (on the same cell as for Figs 3-3 and 3-4) in which the spatial frequency of gratings presented to the silent eye was varied. The dependence of inhibition on spatial frequency was similar to the selectivity for spatial frequency for the excitatory response through the dominant eye alone (Fig. 3-5A), whether the gratings in the two eyes were iso-oriented or orthogonal to each other.

Figure 3-3

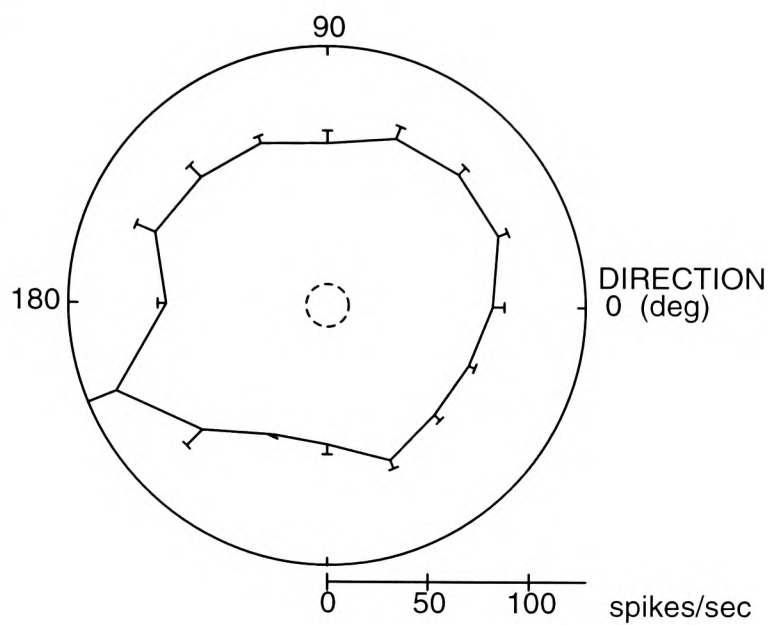
Orientation tuning and binocular interaction for an on-centre Y-cell recorded in lamina A of the LGN.

A: Mean response in spikes/sec ($\pm$ SEM, $n = 4$) is plotted on polar coordinates as a function of the direction of drift of a grating (contrast = 0.7; spatial frequency 0.28 c/deg, i.e. cycles per degree of visual angle) presented to the receptive field in the contralateral eye alone; 0 deg signifies rightward motion of a vertical grating and 90 deg corresponds to upward drift of a horizontal grating. The radius of the interrupted circle in the centre represents the mean spontaneous discharge measured during blank presentations interleaved with the grating presentations and of the same mean luminance as the test gratings. This LGN cell, like most in this sample, was essentially non-oriented.

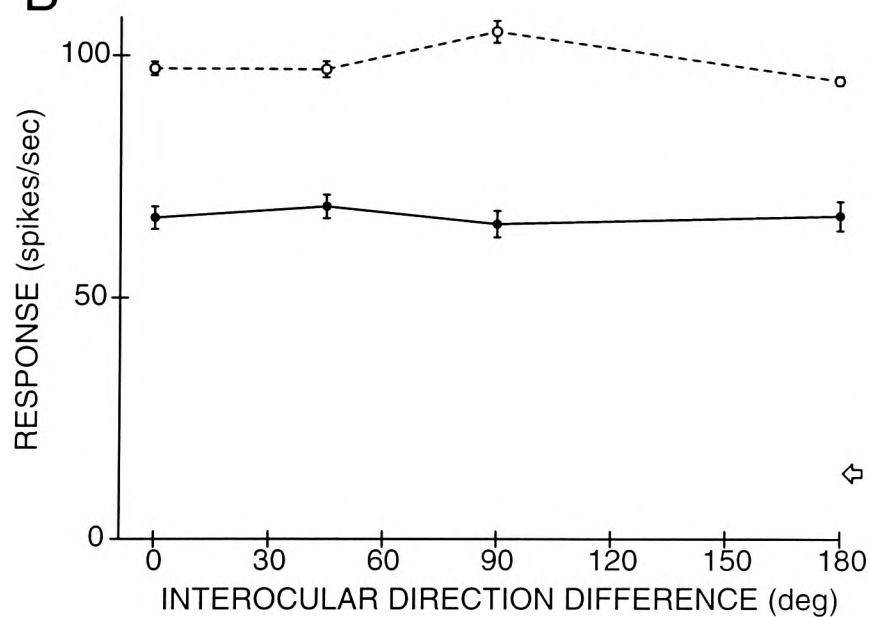
B: Results of the binocular interaction protocol. The contralateral eye was continuously stimulated with a 'conditioning' stimulus whose direction of drift was 202.5°, corresponding to the largest value on the polar plot in **A** (contrast = 0.7; spatial frequency = 0.28 c/deg), and a randomized sequence of gratings of various directions of drift (same spatial frequency and contrast) were presented to the corresponding region of the ipsilateral eye for binocular presentations each lasting 5 sec with 5 sec periods of the conditioning stimulus alone in between. Filled circles ($\pm$ SEM, $n = 4$) joined by solid lines plot the mean firing rate during binocular stimulation with gratings differing in direction of drift in the two eyes by the angle shown on the abscissa. Unfilled circles ($\pm$ SEM, $n = 4$) linked by interrupted lines plot mean responses during the periods of monocular stimulation preceding presentations with the particular combination of gratings plotted on the abscissa. The arrow indicates the level of spontaneous discharge.

C: *Binocular interaction function*, plotting the difference between unfilled and filled symbols in **B**, as a function of the interocular difference in direction of drift. The ordinate plots $(\text{binocular response} - \text{monocular response}) / (\text{monocular response} - \text{spontaneous activity}) \times 100\%$. Thus -100% would indicate complete suppression down to the level of spontaneous discharge.

A



B



C

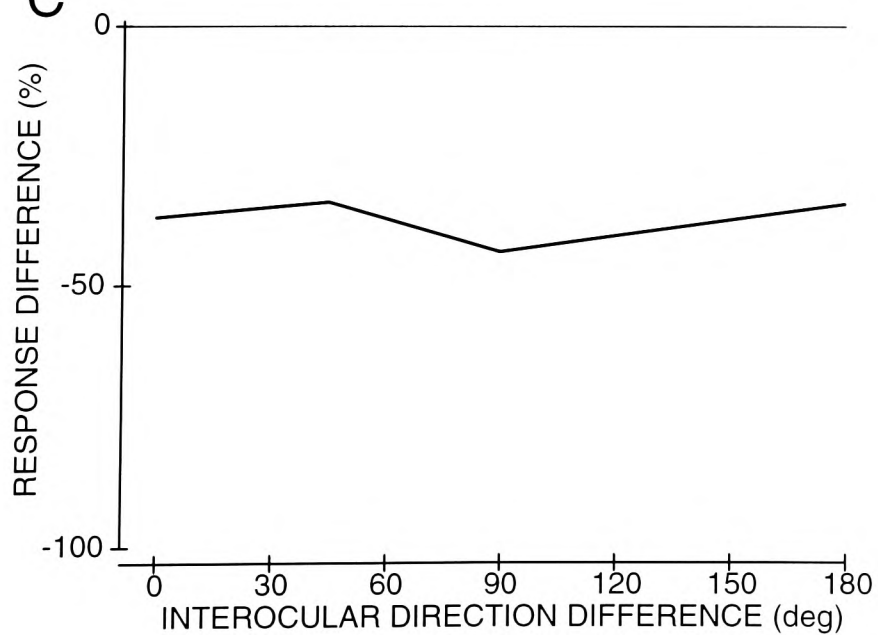


Figure 3-4

Binocular responses of the LGN cell shown in Fig. 3-3 as a function of the spatial offset of the grating in the 'silent' eye relative to that of the stimulus in the dominant eye. The initial spatial phase of the drifting grating presented to the dominant eye was fixed at an arbitrary value while that of the grating presented to the other eye was varied in phase from presentation to presentation. The spatial offset or phase angle between the two gratings is plotted on the abscissae.

A: Filled circles show the results for iso-oriented gratings (contrast = 0.7; spatial frequency = 0.28 c/deg in both eyes), while the unfilled circles plot the control values during monocular stimulation preceding presentations at each particular value of relative spatial phase. Filled and unfilled triangles plot comparable data for orthogonally oriented gratings. The arrow indicates the mean level of spontaneous discharge during blank presentations.

B: Binocular interaction functions (see Fig. 3-3C) as a function of relative spatial phase for iso-oriented (solid curve) and orthogonal gratings (interrupted curve). Note that in both cases the depth of suppression is essentially independent of spatial offset.

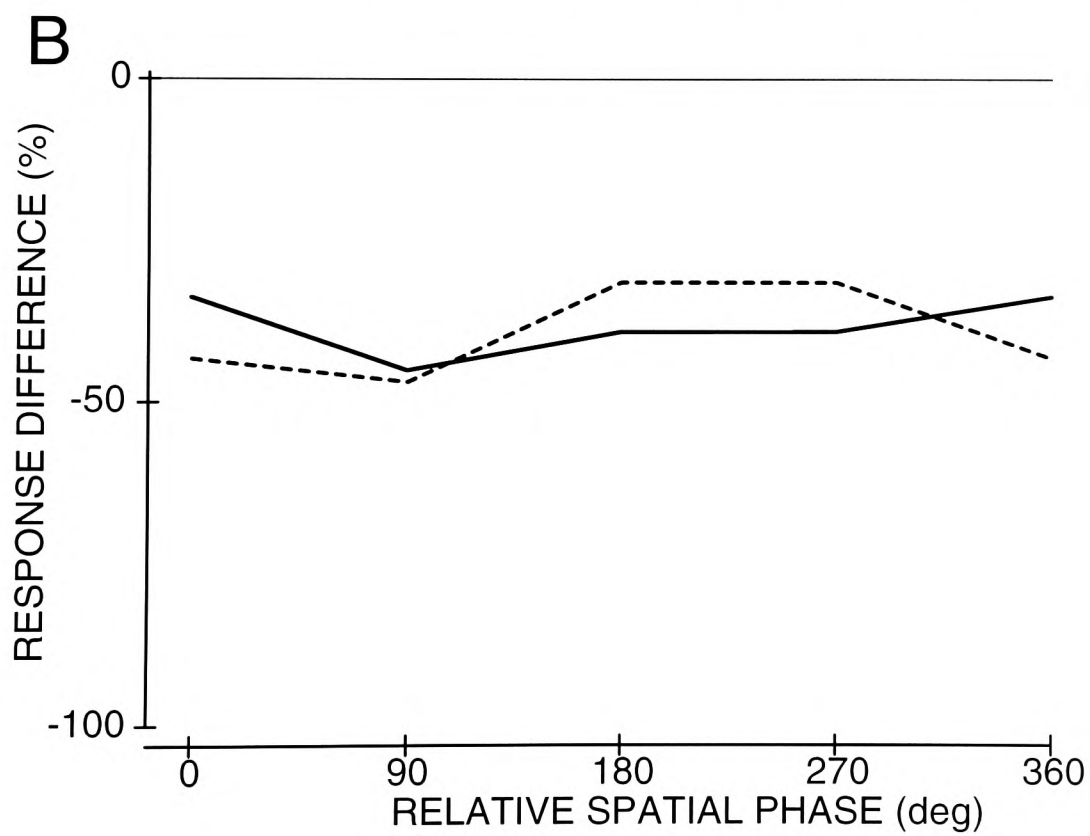
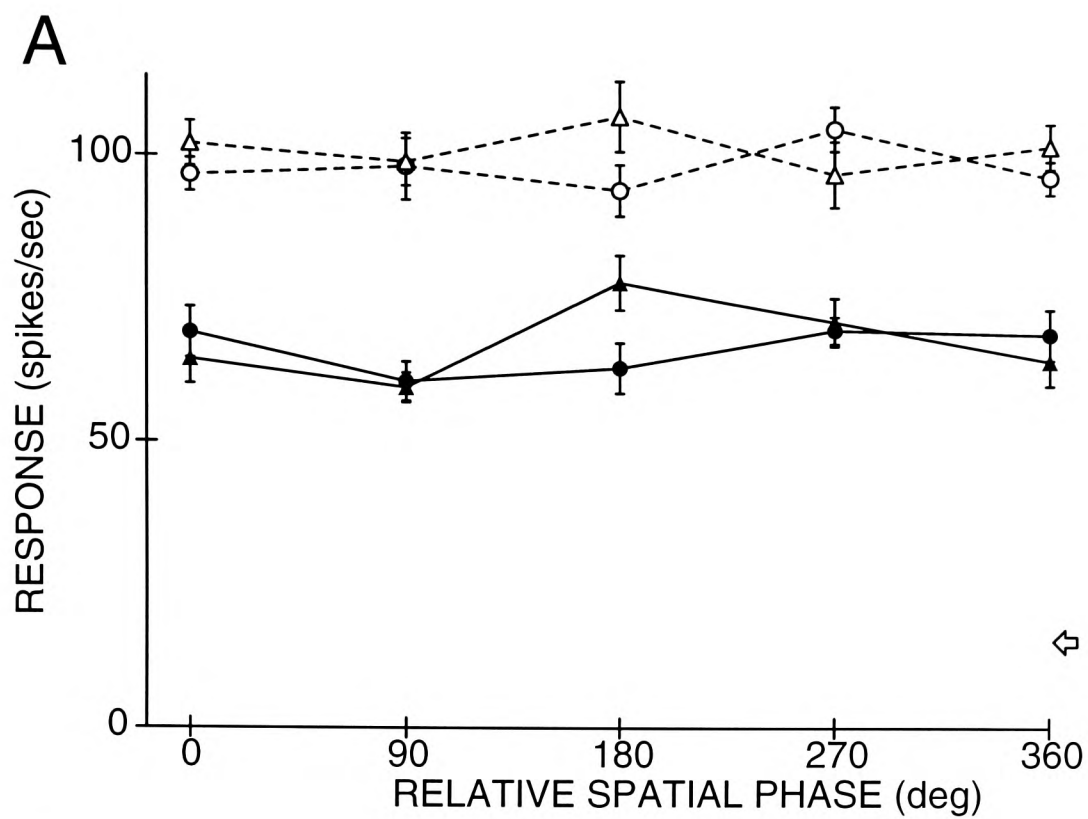
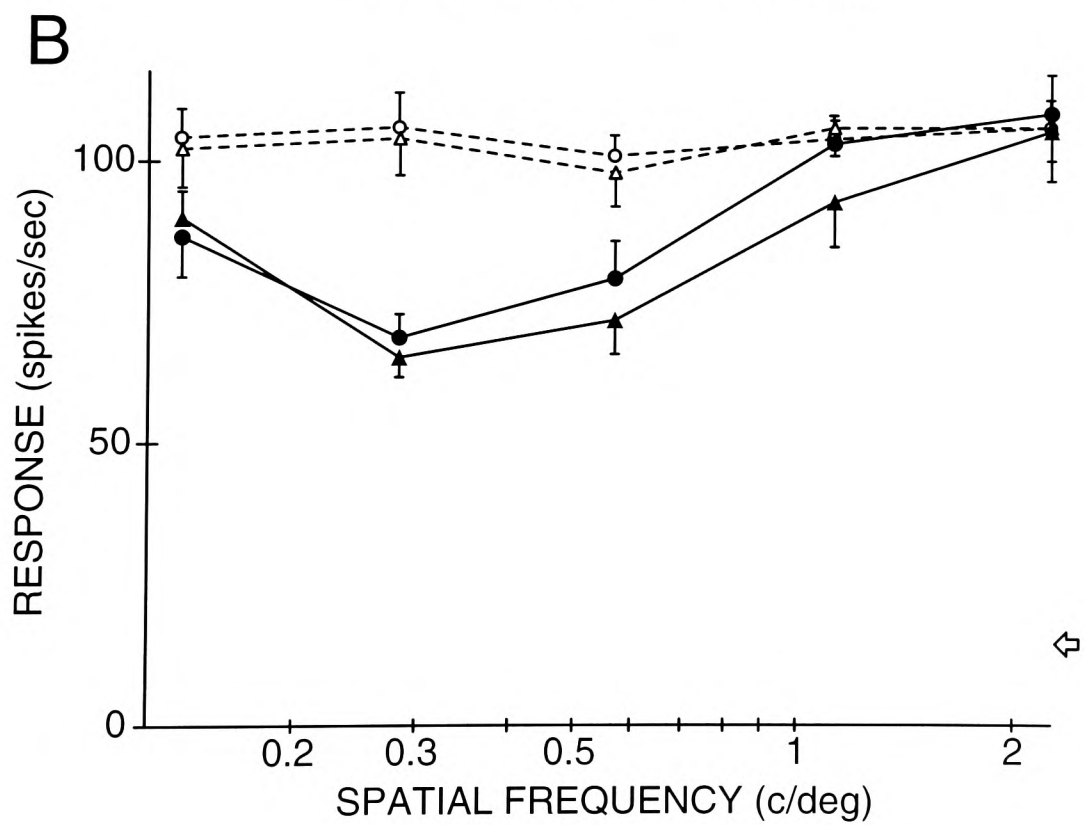
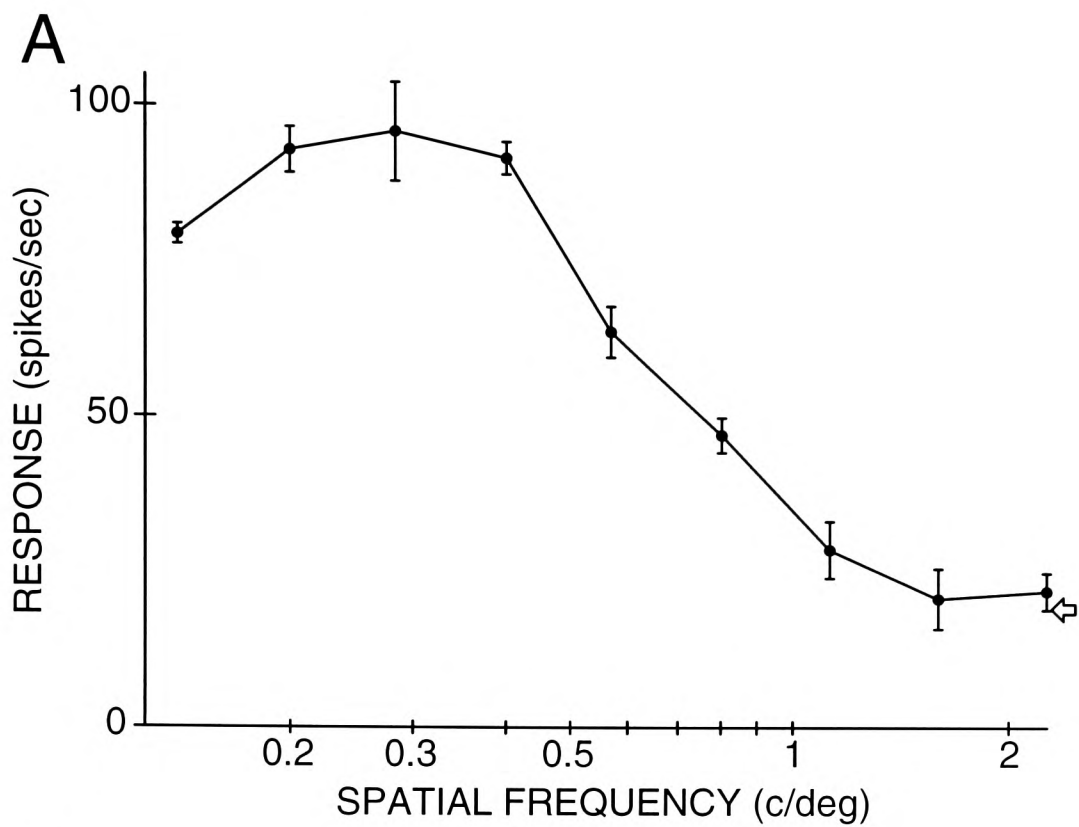


Figure 3-5

Spatial frequency tuning of monocular responses and of interocular suppression for the same LGN cell as in Fig. 3-3.

A: Spatial frequency tuning curve for the dominant (contralateral) eye alone; mean responses ($\pm$ SEM, $n = 4$) are plotted. The receptive field was stimulated with a randomly interleaved series of drifting gratings (direction of drift = 202.5° ; contrast 0.7) which differed in spatial frequency. The arrow indicates the mean spontaneous discharge during blank presentations.

B: Binocular suppression as a function of the spatial frequency of gratings presented to the 'silent' eye. The dominant eye was stimulated continuously with an optimal drifting grating (direction = 202.5° ; spatial frequency = 0.28 c/deg; contrast = 0.7) and gratings of either the same orientation (filled circles) or the orthogonal orientation (filled triangles), of various spatial frequencies, were presented intermittently to the silent eye. The filled symbols, joined by solid lines, plot mean responses ($\pm$ SEM; $n = 4$) during binocular stimulation, while the corresponding unfilled symbols show the mean discharge rate during the immediately preceding epochs of monocular stimulation. The arrow indicates the mean spontaneous discharge during blank presentations.



Area 17

In five animals I obtained quantitative results from 52 cells of the primary visual cortex, 16 of which were simple and 34 complex. The remaining two cells, both recorded in layer 4, were classified as non-oriented, based on quantitative assessment of their monocular orientation tuning curves. Both were monocularly driven, but they had spike waveforms typical of cells rather than axons, and they did not have the obvious centre-surround organization and vigorous responses typical of LGN cells. 45 cells (87%) were binocularly driven by conventional stimuli. Receptive field centres were all within 4° of the area centralis. Stimulation of the non-dominant eye produced statistically significant effects on the response to stimulation through the dominant eye for 46 cells (88% of the total), including all binocular cells outside layer 4.

Orientation-independent suppression for monocular units in layer 4

Of the 18 units recorded within layer 4, 5 (28%) were monocularly driven, a higher proportion than in the sample from all other layers (2/34 cells; 6%). Four of these 18 cells in layer 4 (7.7% of the total sample), three simple and one non-oriented, all monocularly driven by conventional stimuli, showed significant suppression¹ for gratings presented to the 'silent' eye, independent of the interocular orientation difference, very similar to that described above for LGN neurons (Fig. 3-6). In particular, the suppression exerted by even an iso-oriented grating presented to the 'silent' eye was essentially independent of interocular phase difference, in contrast to the phase-selective (i.e. disparity-selective) interaction typical of binocularly driven cells (e.g. Barlow et al., 1967; Ohzawa & Freeman, 1986a, b). Spatial frequency tuning for this non-orientational suppression seen in some cells in layer 4 was not tested.

¹In the following, the term 'suppression' is used for cortical binocular interactions in which the response through one eye is reduced by introduction of some stimulus in the other eye. Similar interactions in the LGN are referred to as 'inhibition'. Interocular suppression (in the cortex) appears to depend on the sequential history of stimulation (see below), while the interocular inhibition seen in the LGN is independent of the history of stimulation.

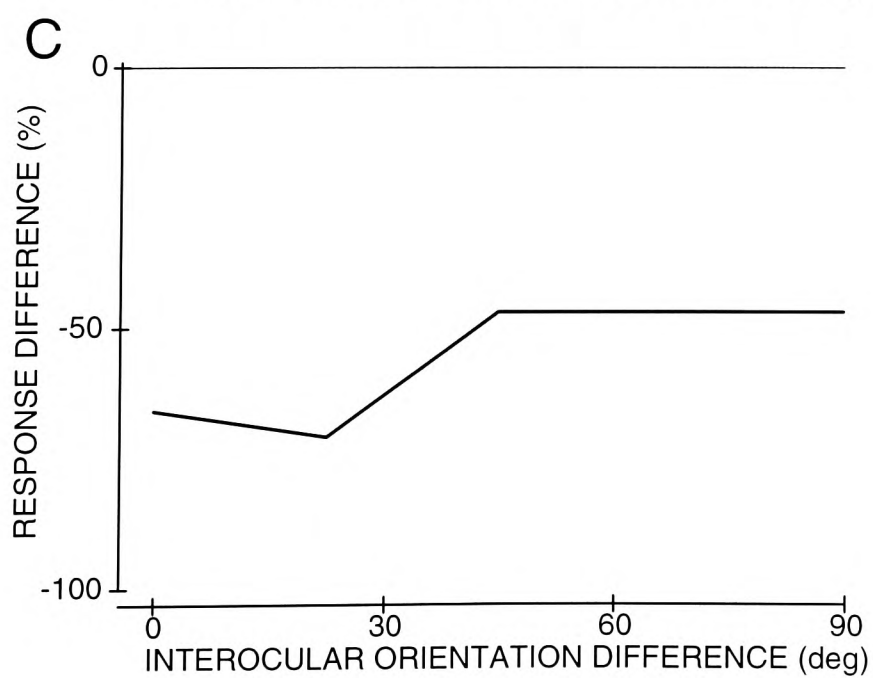
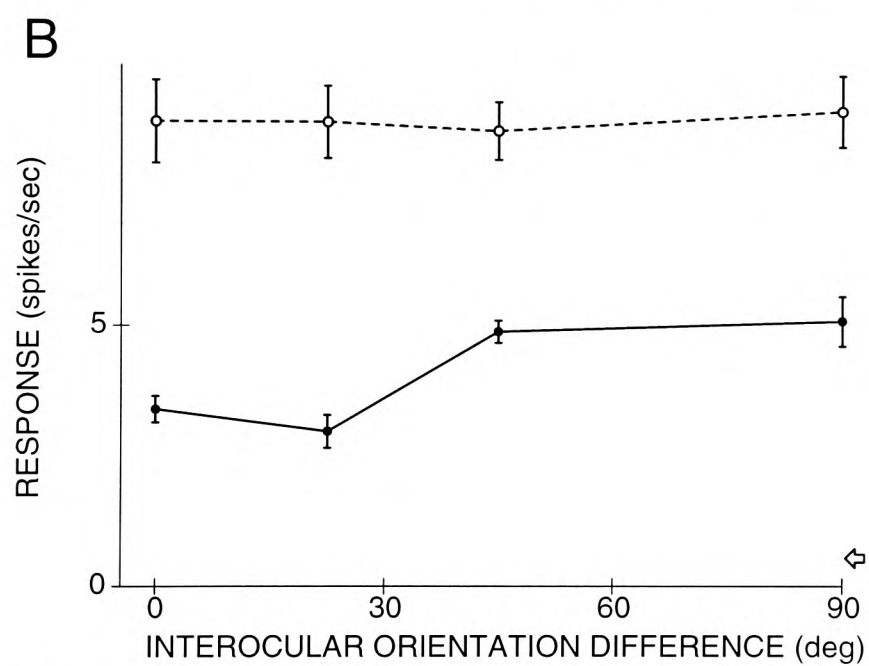
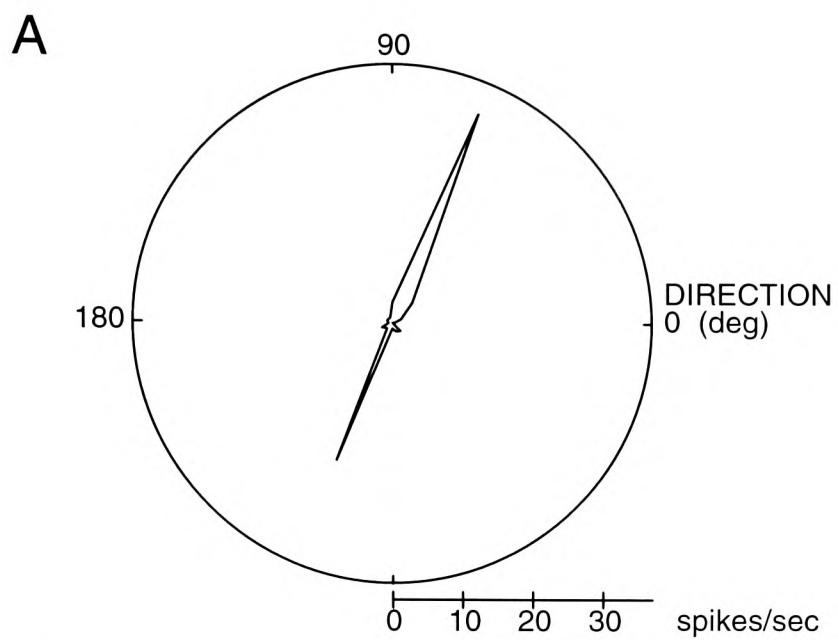
Figure 3-6

Orientation tuning of binocular interactions in a simple cell recorded in layer 4 of area 17, which was monocularly driven by conventional stimuli.

A: Polar plot of orientation selectivity for gratings (contrast = 0.7; spatial frequency = 0.8 c/deg) presented to the dominant (contralateral) eye alone. In this case the spontaneous discharge rate, which was only 1.3 spikes/sec, and the standard error (4.3 spikes/sec at the optimal orientation) are not plotted to avoid confusion.

B: Results of the binocular stimulation procedure, plotted as in Fig. 3-3B, except that the abscissa indicates the difference in **orientation** between the two eyes, rather than direction of motion. Gratings (contrast = 0.7; spatial frequency = 0.8 c/deg) were presented to the non-dominant eye at four different orientations, over a 90° range of directions, clockwise from the optimal stimulus, which was being presented continuously to the dominant eye (contrast = 0.35; spatial frequency = 0.8 c/deg). Filled circles plot mean responses ($\pm$ SEM; $n = 6$) during binocular stimulation, while unfilled circles show the means during the preceding periods of monocular stimulation. The low level of monocular response compared to that in **A** is largely due to the lower stimulus contrast, partly to fatigue during continuous stimulation. Note that even identically oriented gratings (zero on the abscissa) produced strong suppression: variation of spatial phase under these conditions revealed no obvious disparity-dependent facilitation in this and another three monocular units recorded in layer 4.

C: Binocular interaction function, showing the degree of suppression as a function of the interocular orientation difference, as in Fig. 3-3C.



None of the binocularly excitable cells in layer 4 showed this type of non-orientation-selective suppression, nor was it seen in other layers, even among monocular cells. The other monocular cell and three of the binocular cells recorded in layer 4 lacked any significant binocular interactions. Five of the 13 binocular cells in layer 4 showed interocular suppression dependent on orientation, as described below. Table 3-1 summarizes the results for all 52 cells with respect to their laminar position.

Table 3-1: Occurrence of orientation-dependent suppression (ODS) and orientation-independent suppression (OIS) in area 17. The final column gives the average percentage suppression, below the monocular level, caused by orthogonally oriented gratings.

Cortical layer	Total number of cells	OIS: Number of cells	ODS: Number of cells	Percentage of suppression with orthogonal gratings ($\pm$ SD)
2/3	28	0	17	41.4% ($\pm$ 24.4%)
4	18	4	5	30.1% ($\pm$ 20.5%)
5/6	6	0	3	34.8% ($\pm$ 32.2%)
All	52	4	25	36.8% ($\pm$ 24.6%)

Orientation-dependent interocular suppression

For 42 out of the 45 binocular units I observed the expected facilitation of the dominant eye's response when the other eye was simultaneously stimulated with a grating of optimal orientation. For most complex cells (and they constituted the majority of my sample), this facilitation was largely independent of spatial offset in the non-dominant eye (i.e. the interocular phase disparity of the gratings), while all simple cells and some complex cells showed facilitation at one spatial phase and inhibition when the gratings

were 180° out of phase in the two eyes, with cyclical variation in the strength of response as the relative phase (or disparity) was progressively shifted (Fig. 3-7; cf. Ohzawa & Freeman, 1986a, b).

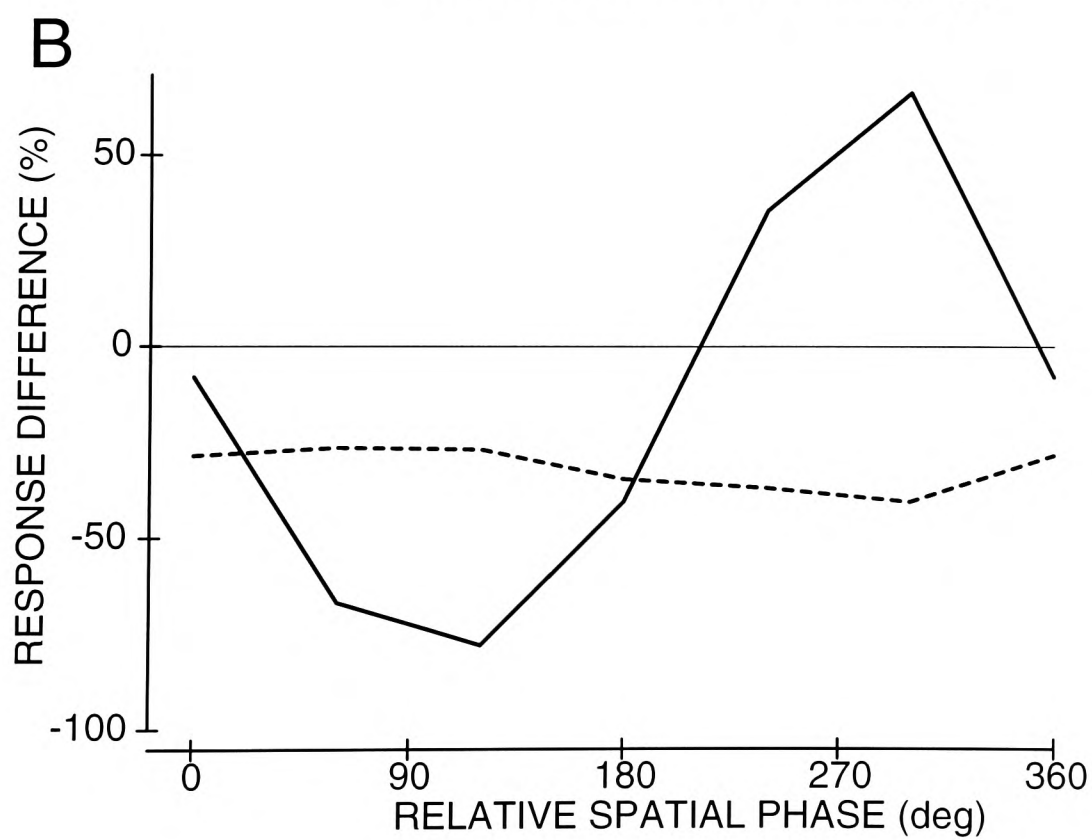
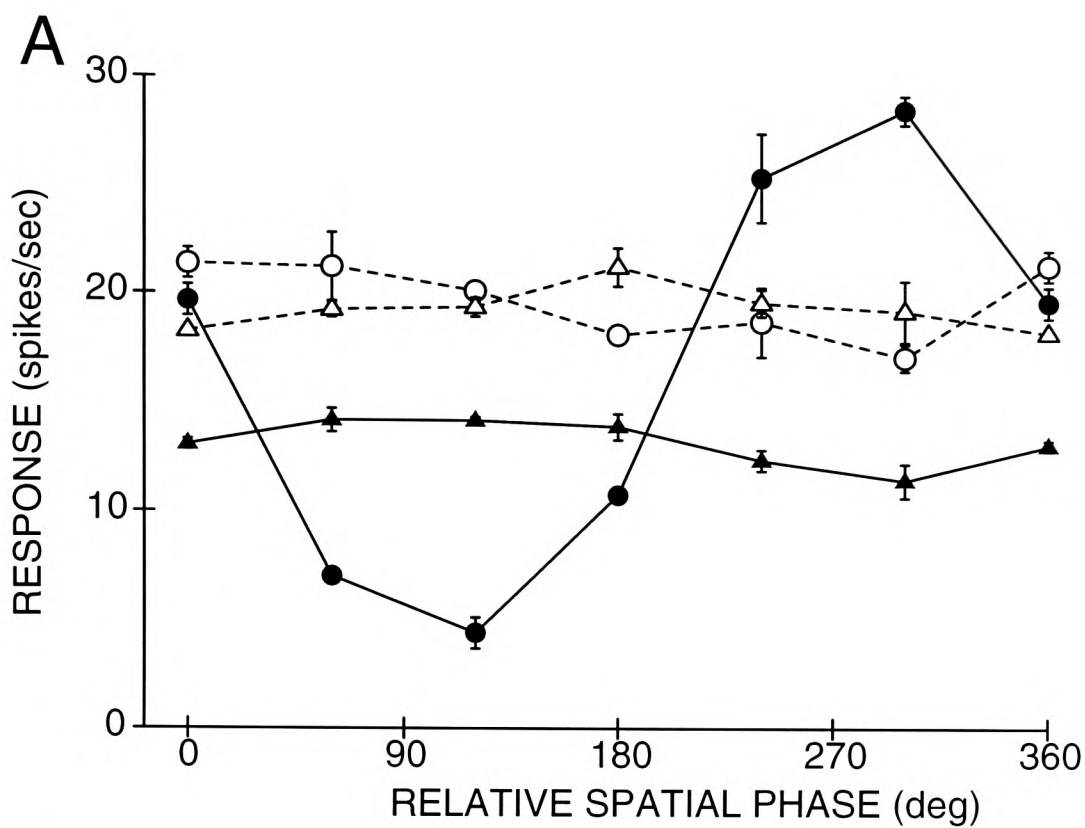
All 45 binocular cells were tested for the orientation-selectivity of binocular interaction. When the non-dominant eye was stimulated with a high-contrast (0.7) grating oriented *orthogonal* to the optimal orientation being shown to the dominant eye, 25 cells (56% of the binocularly driven units) showed statistically significant suppression (t -test, $p < 0.05$), reducing the mean spike rate by between 15% and 90% of the monocular response through the dominant eye (average 52.4%; SD = 20.5%). The suppression with orthogonal stimulation did not vary convincingly with the spatial offset of the grating in the non-dominant eye in any of the cells tested. This held for not only complex but also simple cells, in which the facilitatory and inhibitory effects with matched gratings were always clearly disparity selective. Fig. 3-7 analyses the effects of spatial offset, for both iso-oriented and orthogonal gratings, for a typical disparity-selective simple cell recorded in the supragranular layers. In part **A**, filled circles plot the response of the cell during binocular stimulation with gratings of the same (optimal) orientation in the two eyes, as a function of the spatial offset of the gratings, while the open circles show the corresponding control responses with monocular stimulation in the dominant eye alone. Part **B** plots binocular interaction as a function of spatial offset for iso-oriented gratings (solid curve) and orthogonal gratings (interrupted function). For matched gratings the variation in response is roughly sinusoidal, from occlusion to facilitation, as the relative disparity is changed (cf. Ohzawa & Freeman, 1986a, b). By comparison, with orthogonally oriented gratings the clear (roughly 30%) suppression is essentially independent of spatial phase.

Figure 3-7

Binocular responses of a layer 2/3 simple cell as a function of the spatial offset of the grating in the non-dominant eye relative to that of the stimulus in the dominant eye. The initial spatial phase of the optimally oriented drifting grating presented to the dominant eye was fixed at an arbitrary value while that of the grating presented to the other eye was varied in phase. The spatial offset or phase angle between the two gratings is plotted on the abscissae.

A: Filled circles show the results for iso-oriented gratings (contrast = 0.35; spatial frequency = 0.56 c/deg in both eyes), while the unfilled circles plot the control values during monocular stimulation preceding presentations at each particular value of spatial offset. Filled and unfilled triangles plot comparable data for orthogonally oriented gratings. The arrow indicates the mean level of spontaneous discharge during blank presentations.

B: Binocular interaction functions (see Fig. 3-3C) as a function of spatial phase for iso-oriented (solid curve) and orthogonal gratings (interrupted curve). Note the characteristic cyclical variation as a function of spatial offset with matched gratings, shifting from 67% binocular facilitation at the optimum disparity to 78% inhibition at the worst. On the other hand, presentation of an orthogonal grating in the non-dominant eye simply suppressed the response by about 30% regardless of its spatial phase.



Both facilitation (with matched orientations) and suppression (with inappropriately oriented gratings) increased in strength with the contrast of the stimulus in the non-dominant eye (Fig. 3-8); so, for comparison between cells, the orientation-dependence of interocular interactions was always tested with gratings of 0.7 contrast presented to the non-dominant eye. For cells that were clearly disparity selective, care was taken to optimize the spatial offset, to generate the maximum facilitation with matched and near-matched orientations (Blakemore et al., 1972). Fig. 3-9 shows the analysis for a representative complex cell recorded in layer 2/3, in a form similar to that for Fig. 3-3. Part **A** is a polar plot of the individual monocular orientation/direction tuning curves through the dominant and non-dominant eyes, respectively. Part **B** shows the results of binocular stimulation with different interocular orientation differences, with the continuous conditioning grating being presented either to the dominant eye (red lines and symbols), or to the non-dominant eye (blue lines and symbols). The two binocular interaction functions (**C** and **D**) reveal a sharp change from facilitation for small orientational differences to marked suppression for larger values. Facilitation in this particular cell was independent of spatial phase, so these functions were definitely not contaminated by variations in spatial phase with orientational difference.

Another example is shown in Fig. 3-10, for a complex cell recorded in layer 4. For this neuron, suppression of the response through the non-dominant eye by stimulation of the dominant eye was much weaker than vice versa (compare Figs 3-10**C** and **D**) and facilitation was seen over a wider range of interocular orientation differences.

For most cells, responses to dichoptic iso-oriented gratings of opposite direction of drift were also tested. While in simple cells either facilitation or suppression was seen (probably depending on the relative interocular phase of the two gratings), most complex cells showed facilitation of a magnitude comparable to that obtained for identical directions of drift. For a majority of the complex cells, instead of an elevated mean discharge a frequency-doubled response, i.e. a modulation at twice the drift frequency of the gratings, was observed, as if the cells were responding to a sinusoidally modulated counter-phased grating (cf. Ohzawa & Freeman, 1986b).

Figure 3-8

Contrast dependence of suppression by orthogonal gratings in a layer 2/3 complex cell of ocular dominance group 5 (slightly dominated by the ipsilateral eye). The contrast of the optimally oriented drifting grating presented to the dominant eye (direction = 22.5° ; spatial frequency = 0.56 c/deg) was fixed at 0.35 while that of the grating presented to the other eye was varied.

A: Plot of responses against log contrast of the gratings shown to the non-dominant eye. Filled circles ($\pm$ SEM) joined by solid lines plot the mean firing rate during binocular stimulation while unfilled circles ($\pm$ SEM) linked by interrupted lines plot mean responses during the corresponding periods of monocular stimulation preceding the presentations with the particular contrast (in the non-dominant eye) shown on the abscissa. The arrow indicates the mean level of spontaneous discharge during blank presentations.

B: Binocular interaction (see Fig. 3-3C) as a function of contrast of the grating presented to the non-dominant eye.

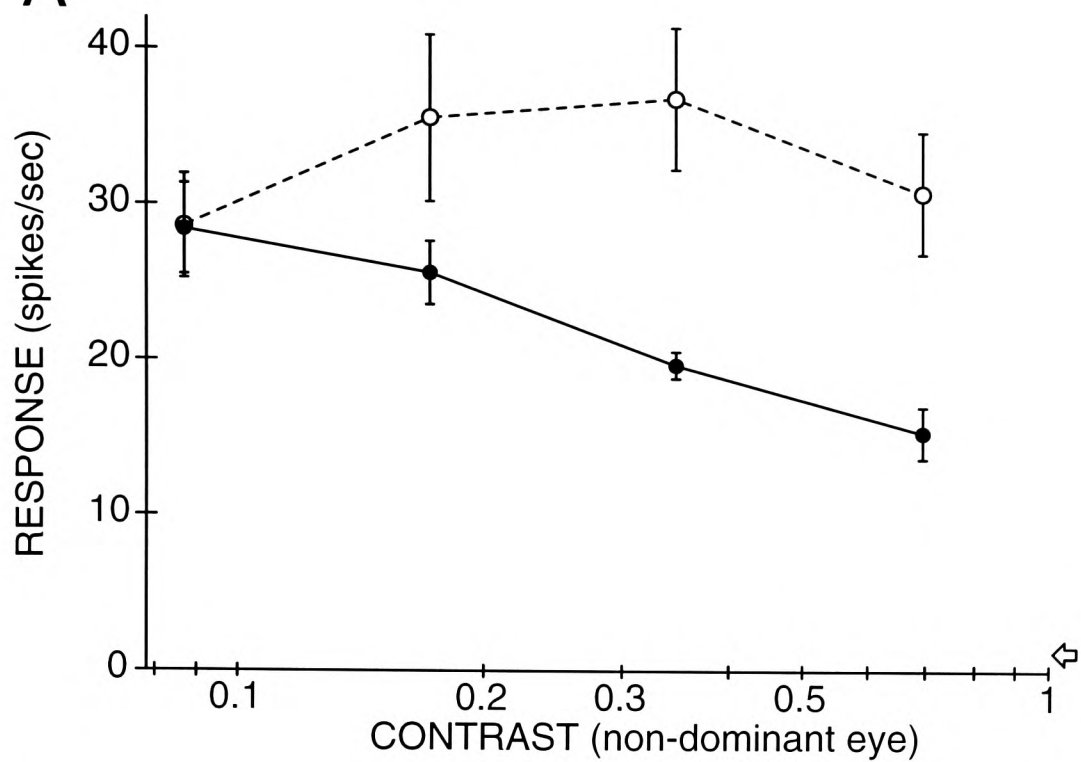
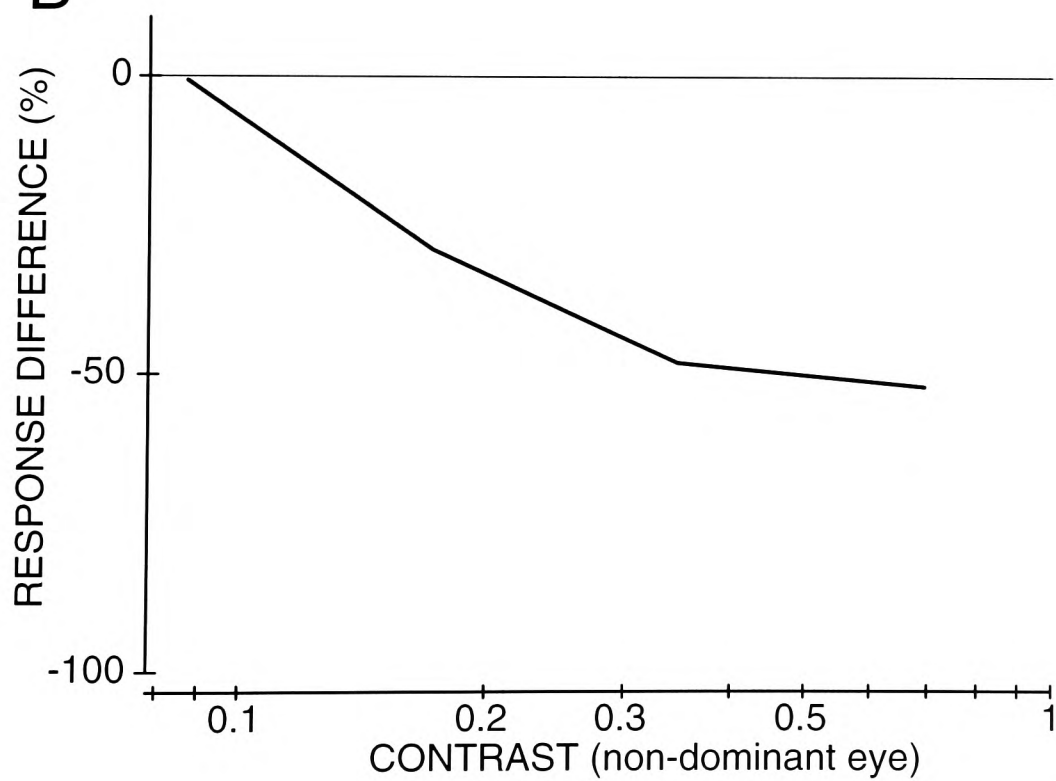
A**B**

Figure 3-9

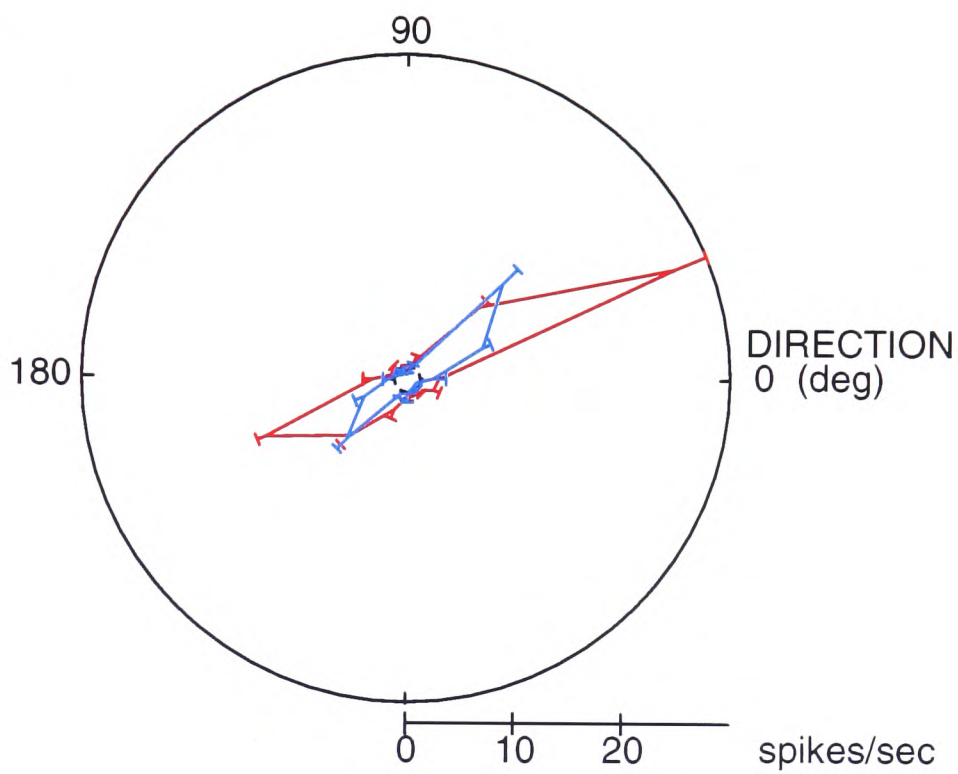
Orientation dependence of binocular interactions in a layer 2/3 complex cell (same cell as in Fig. 3-8).

A: Polar plots of orientation tuning curves obtained with monocular stimulation through the ipsilateral eye (red) and the contralateral eye (blue), with gratings of 0.7 contrast and a spatial frequency of 0.56 c/deg. Mean levels of spontaneous discharge were 0.9 and 1.5 spikes/sec during data collection for ipsilateral and contralateral stimulation, respectively.

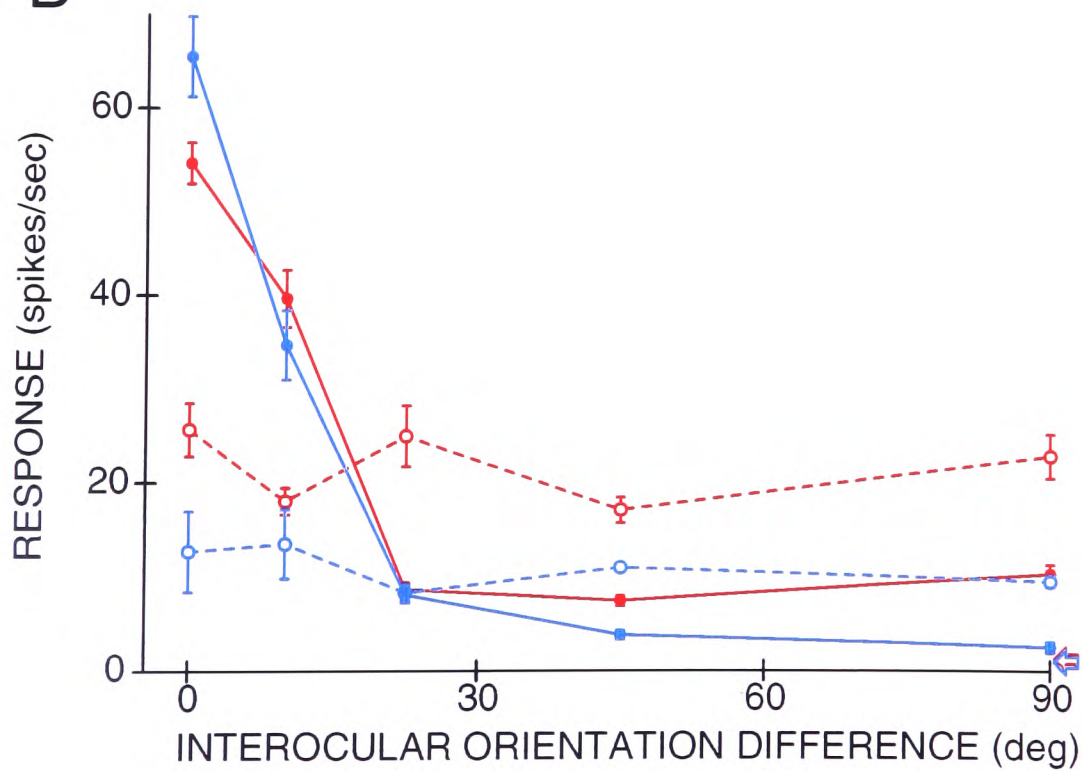
B: Results of the binocular interaction protocol, as in Fig. 3-6B. Filled circles ($\pm$ SEM) joined by solid lines plot the mean firing rate during binocular stimulation with gratings differing in orientation by the angle shown on the abscissa. Unfilled circles ($\pm$ SEM) linked by interrupted lines plot mean responses during the corresponding periods of monocular stimulation preceding the presentations with the particular orientation difference shown on the abscissa. For the red curves ($n = 8$), a drifting 'conditioning' grating of optimal orientation (direction = 22.5° ; spatial frequency = 0.56 c/deg; contrast = 0.35) was presented continuously to the dominant, ipsilateral eye and gratings of five different orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the contralateral eye. For the blue curves, the 'conditioning' grating (direction = 22.5° , spatial frequency = 0.56 c/deg, contrast = 0.7) was presented continuously to the contralateral eye and gratings of various orientations (same spatial frequency and contrast) were shown to the ipsilateral eye. In this complex cell, the facilitation for matched orientations was independent of spatial phase.

C, D (following page): Binocular interaction functions, as in Fig. 3-3C, with the 'conditioning' grating being presented to the dominant eye (in **C**) or the non-dominant eye (in **D**).

A



B



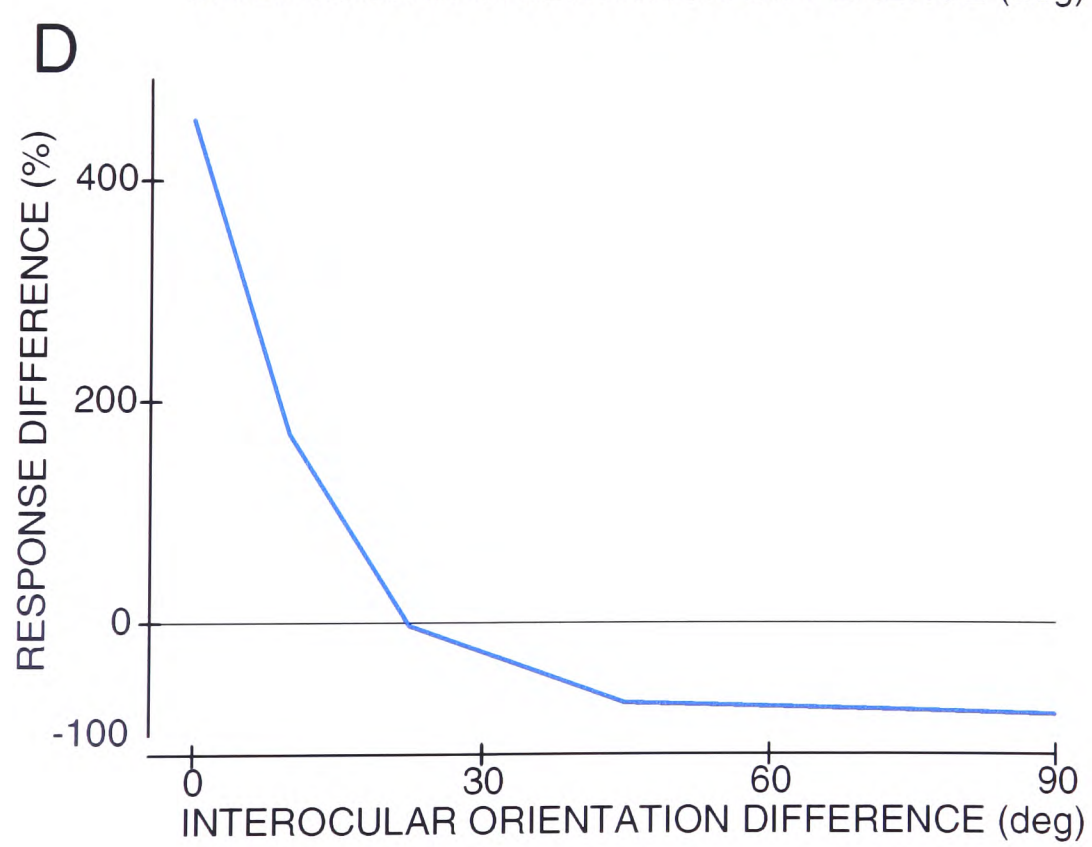
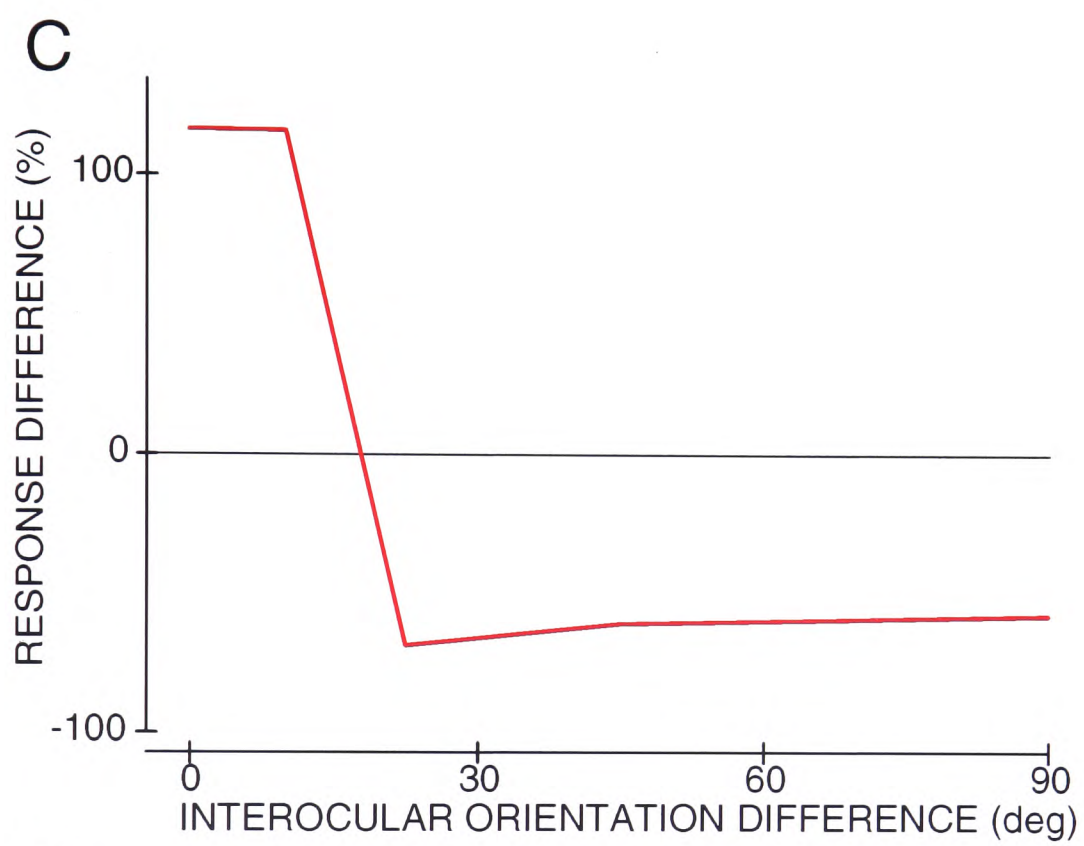


Figure 3-I0

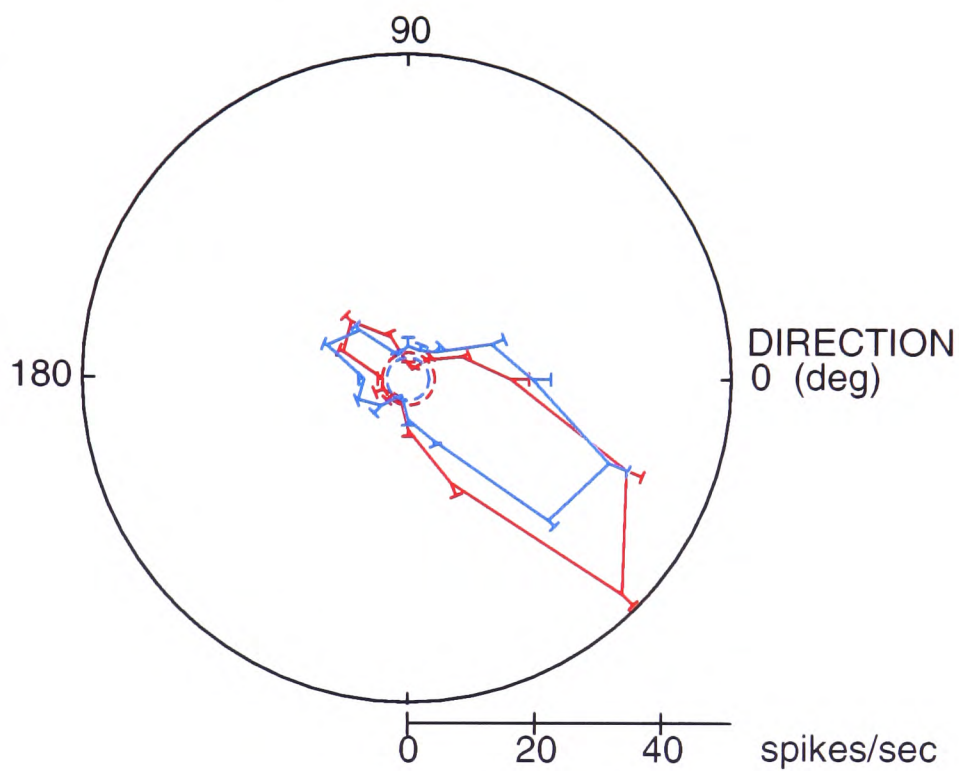
Orientation dependence of binocular interaction for a complex cell of ocular dominance group 4 recorded in layer 4.

A: Monocular orientation tuning curves (as in Fig. 3-3A) obtained through the ipsilateral (red) and the contralateral eye (blue) with gratings of contrast = 0.7 and spatial frequency = 0.4 c/deg (dashed circles indicate spontaneous discharge).

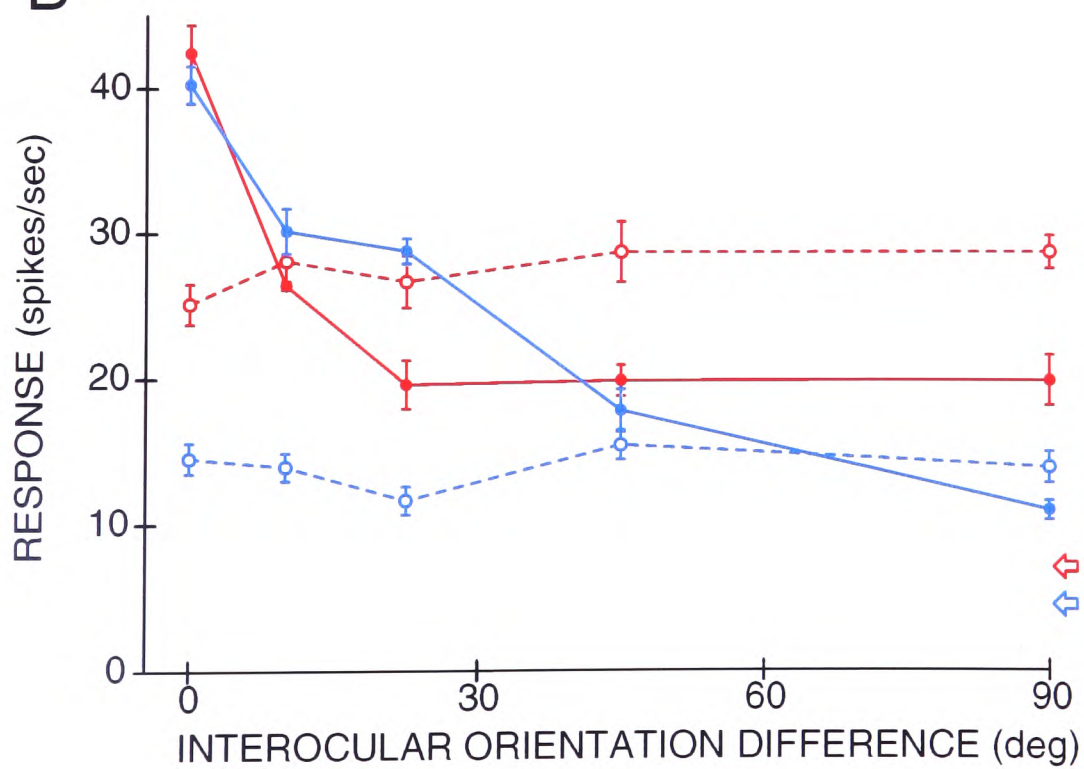
B: Binocular responses (solid lines, filled circles $\pm$ SEM) as a function of orientation difference between the two eyes, as in Fig 3-9B. For the red curves ($n = 5$), gratings of optimal orientation (direction = 315°) were presented to the ipsilateral eye (spatial frequency = 0.4 c/deg, contrast = 0.35) and gratings of varying orientation (same spatial frequency, contrast = 0.7) to the contralateral eye. For the blue curves ($n = 8$), the 'conditioning' grating (direction of drift = 315°) was presented to the contralateral eye (spatial frequency = 0.4 c/deg, contrast = 0.35) and gratings of various orientations (same spatial frequency, contrast = 0.7) to the ipsilateral eye. In each case, the unfilled circles and interrupted lines plot the control values obtained in the immediately preceding periods of monocular stimulation.

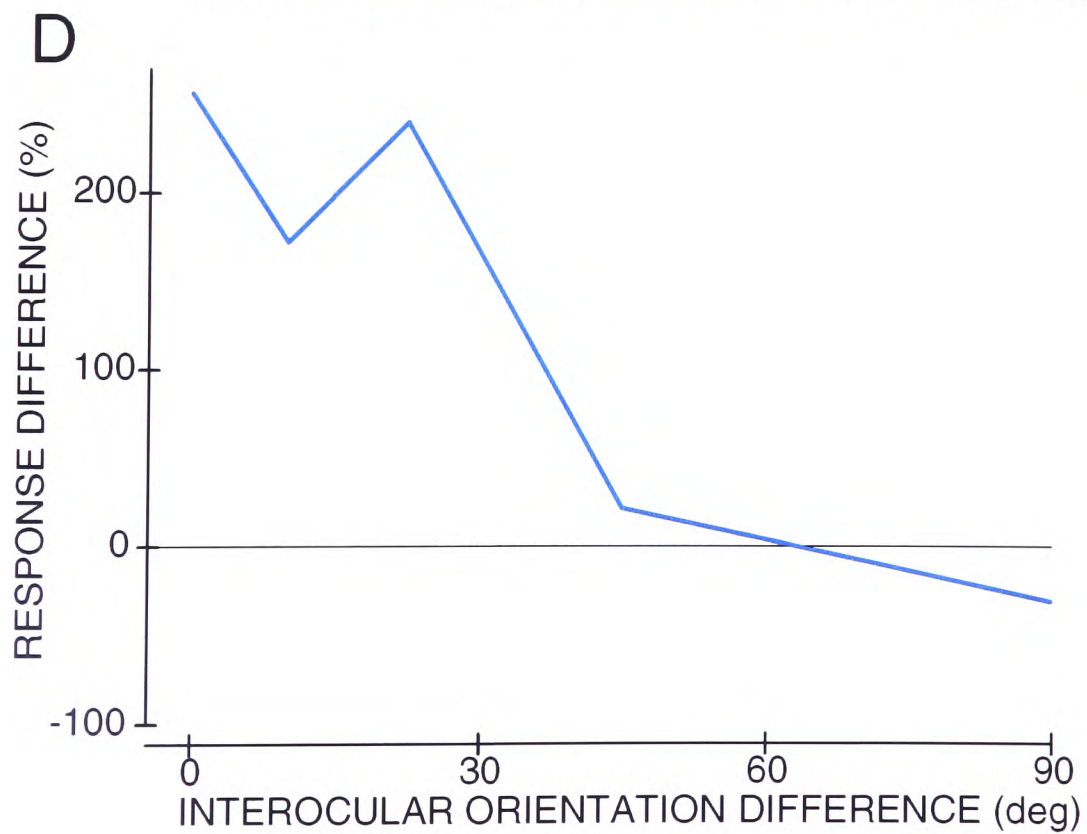
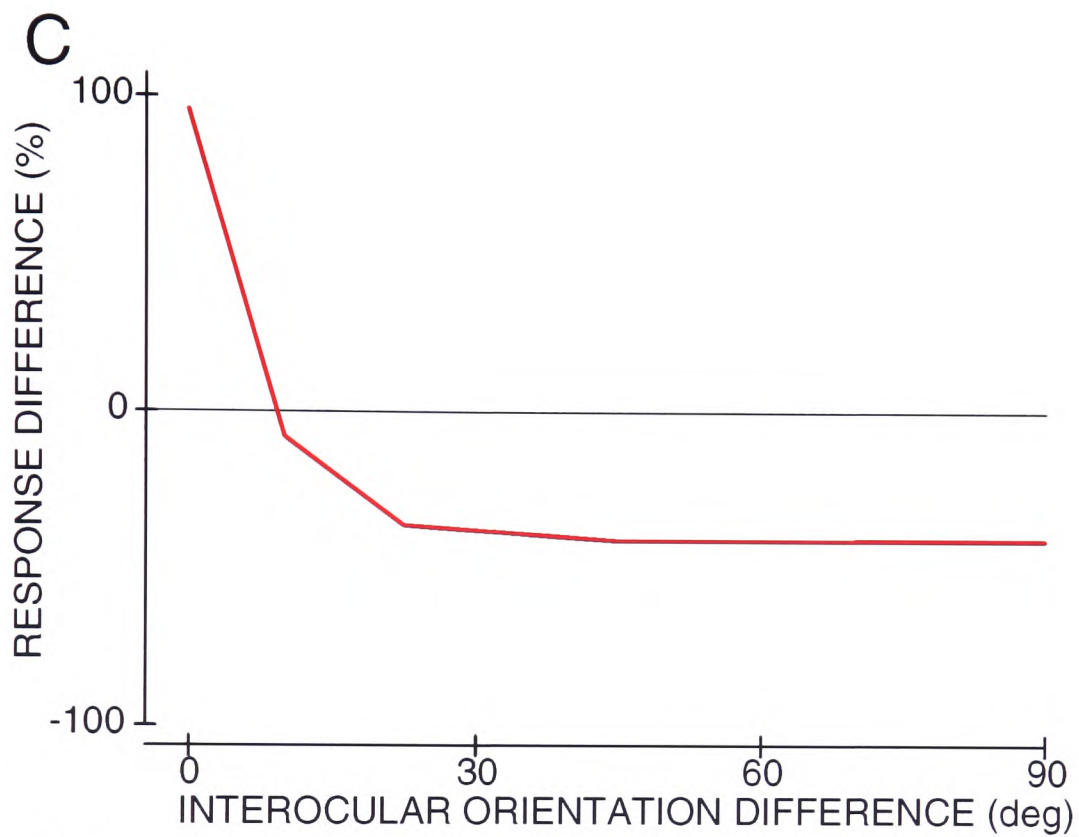
C, D (following page): Binocular interaction functions, as in Fig. 3-3C, with the 'conditioning' grating being presented to the dominant eye (in **C**) or the non-dominant eye (in **D**).

A



B



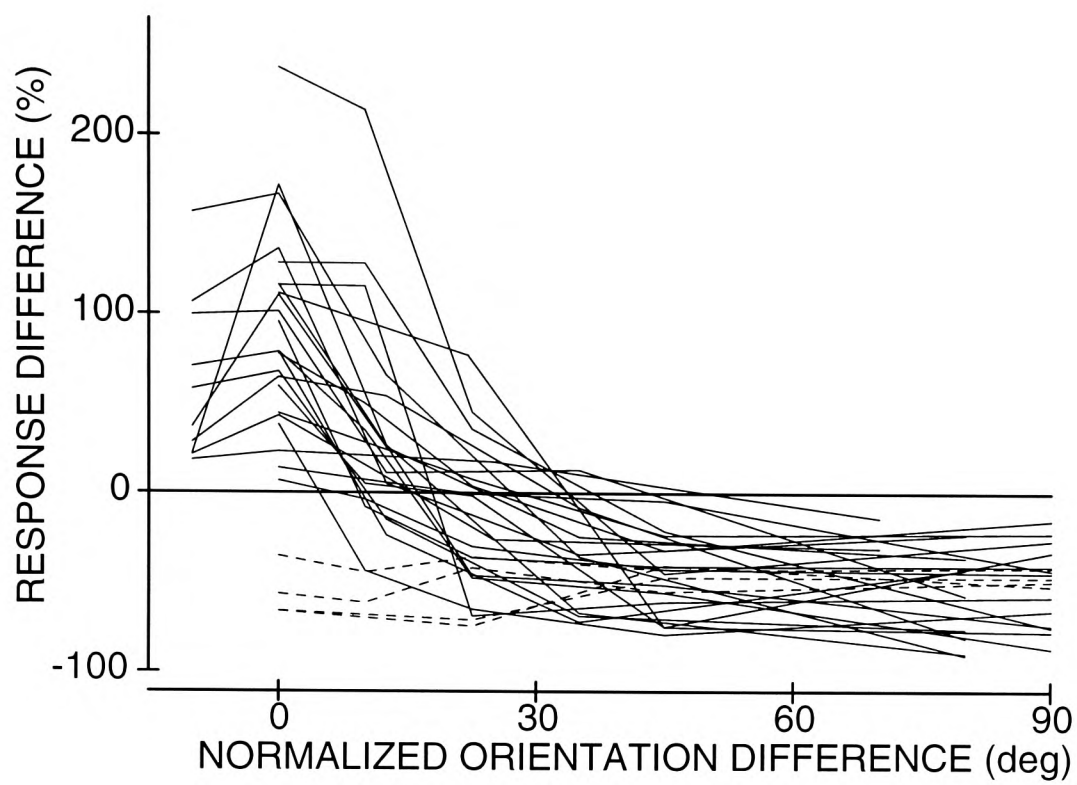


Many binocular cells had small but distinct differences in optimal orientation between the two eyes (Fig. 3-9A shows a clear example). These were undoubtedly partly caused by the slight in-cyclotorsion that commonly occurs on paralysis; but, since the angular difference in tuning varied from cell to cell in individual animals, some of the variation was due to genuine orientational disparity, as described by Blakemore et al. (1972) and Nelson et al. (1977). Since the abscissae of the raw interaction functions, such as those of Figs 3-9 and 3-10, do not take into account differences in monocular orientational preference, maximum binocular facilitation did not always occur at zero orientational difference. In order to take account of these lateral shifts in the binocular interaction functions, I have pooled the functions for 27 cortical cells (chosen to represent the range of variation) in Figure 3-11, normalizing them on the abscissa by shifting them to bring maximum facilitation to zero. Examination of this family of functions suggests that there is a continuum of tuning for interocular orientational difference, although it is surely significant that the four cells for which suppression was virtually independent of orientational difference (interrupted functions) were all monocular units recorded in layer 4 (including that illustrated in Fig. 3-6).

Among all the cells that exhibited iso-orientational facilitation and cross-orientational suppression, the transition between the two occurred at between 5° and 70° from the peak (after normalization), although for most it was between about 15° and 35° , with a mean of 22° . There was a weak ($r = 0.31$) but not quite significant correlation between the threshold normalized orientation difference for the appearance of suppression and the half-width of monocular orientation tuning. Moreover, there was also a clear correlation between the depth of suppression with orthogonal gratings and the half-width of monocular orientation tuning ($r = 0.64$; $p < 0.002$). In other words, cells with narrower orientation tuning tended to be suppressed at smaller orientational differences and to have stronger suppression than did cells with broader orientational tuning.

Figure 3-11

Binocular interaction functions for 27 cortical cells, as in Figs. 3-9C,D and 3-10C,D, showing the range of variability in the depth of suppression and in the threshold interocular orientation difference for the onset of suppression. For comparison of the relation between strengths of facilitation and of suppression on the one hand and the threshold orientational difference for the transition between the two on the other hand, all tuning curves with maximum facilitation at an orientational difference other than zero, have been normalized by shifting them leftwards to peak at zero. Included are the four monocular units recorded in layer 4 (data plotted as interrupted lines) that were judged to have suppression essentially independent of interocular difference in orientation (see Fig. 3-6). Results from binocularly driven neurons, which showed clear variation of suppression with orientational disparity, are plotted as continuous lines.



Spatial frequency tuning of suppression

For 12 cells, the spatial-frequency tuning of suppression was determined by presenting a conditioning grating of optimal orientation and spatial frequency to the dominant eye and intermittently introducing orthogonal gratings of various spatial frequencies to the other eye, always drifting at the same temporal frequency. Although maximal or near-maximal suppression was generally observed when the two stimuli were matched in spatial frequency, the spatial-frequency tuning of suppression was usually wider, and never narrower, than that for the monocular responses elicited through either eye alone. Often, clear suppression was exerted by gratings of spatial frequencies too high to elicit any excitatory monocular responses from the cell in question (see Fig. 3-12). Fig. 3-13 shows the spatial-frequency dependence of suppression in all 12 cells tested, each normalized to the spatial frequency that elicited the maximum response when presented to the dominant eye alone (zero on the abscissa).

Comparison of dichoptic suppression and cross-orientation inhibition

It appears that the characteristics of rivalrous suppression on the one hand and suppression elicited monocularly by cross-oriented gratings on the other hand (DeAngelis et al., 1992) are largely similar, as regards, for example, the breadth of spatial frequency tuning and the independence of spatial phase. In the present work, orientation tuning of suppression by monocularly superimposed gratings was not examined systematically, partly because a direct comparison of responses obtained through monocular *versus* dichoptic stimulation is difficult: a stimulus of a given contrast presented to the dominant eye is likely to differ in efficiency compared with an identical stimulus presented to the non-dominant eye. However, Fig. 3-14 exemplifies, for a layer 2/3 complex cell, that the orientation tuning of monocular and dichoptic suppression, respectively, differs only in degree rather than qualitatively. In this case, the tuning for dichoptic stimulation appears to be displaced downward compared to that for monocular stimulation, suggestive of a higher level of non-orientational suppression upon which orientation-selective facilitation is superimposed.

Figure 3-12

Spatial frequency dependence of rivalrous suppression in a layer 2/3 complex cell (same cell as for Figs 3-8 and 3-9), analysed as in Fig. 3-5.

A: Spatial frequency tuning of monocular responses obtained through the dominant eye (filled circles, $\pm$ SEM; $n = 4$) and the non-dominant eye (unfilled circles). The arrow indicates the spontaneous discharge.

B: The dominant eye was stimulated with an optimally oriented grating of optimal spatial frequency (0.56 c/deg), while the non-dominant eye was intermittently stimulated with orthogonally oriented gratings whose spatial frequency varied in random sequence. Responses during binocular stimulation are plotted as filled circles (mean $\pm$ SEM, $n = 8$) and the comparable monocular responses as unfilled circles. Note that a grating of 1.13 c/deg (to which the cell did not respond when presented at the optimum orientation to either eye) produced very significant suppression when presented at the orthogonal orientation in the non-dominant eye.

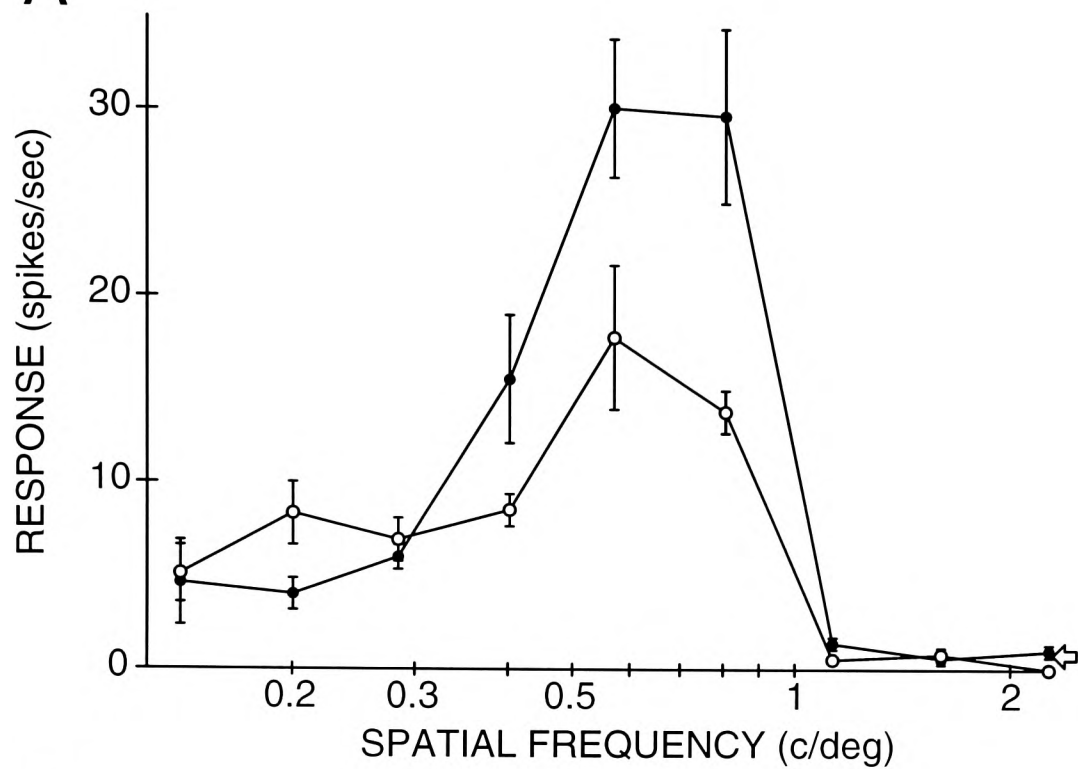
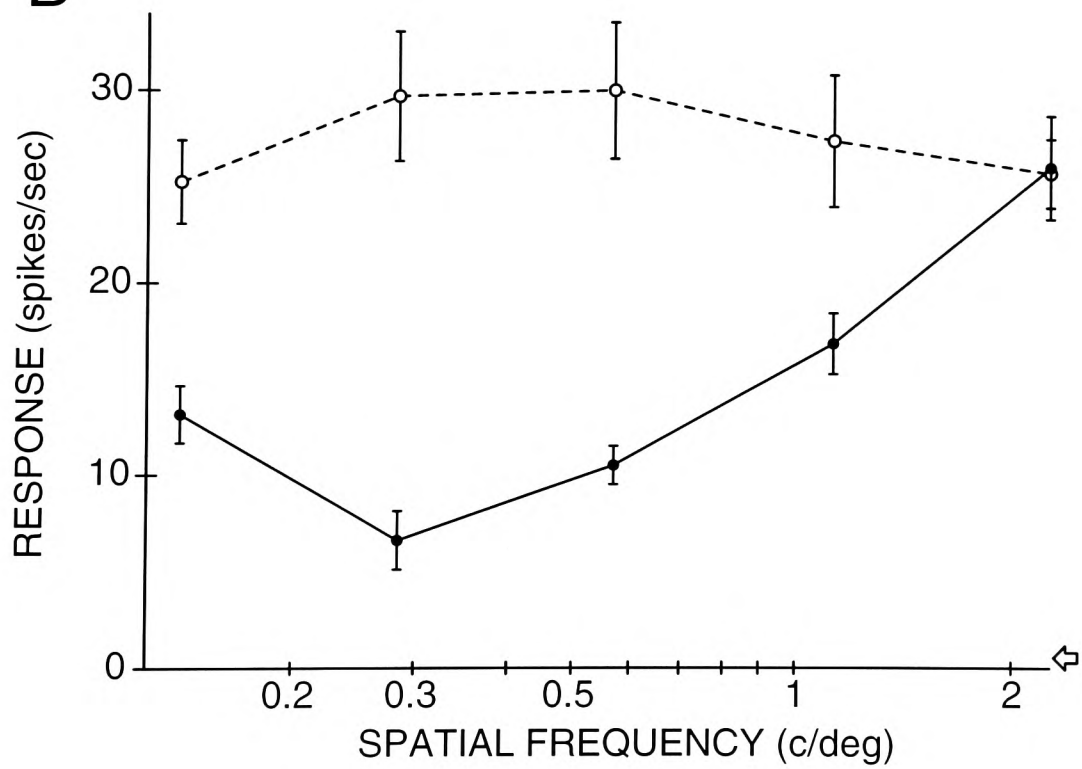
A**B**

Figure 3-13

Spatial frequency tuning of rivalrous suppression, shown as binocular interaction functions for all 12 cells in which it was studied in detail (cf. Fig. 3-12 for one example). Tuning curves have been normalized to the spatial frequency that elicited the maximum excitation when presented to the dominant eye alone (corresponding to a value of zero on the abscissa). For each of the cells, the dominant eye was then stimulated with a grating of optimal orientation and spatial frequency, while the non-dominant eye was intermittently stimulated with orthogonally oriented gratings of spatial frequencies of ± 1 and ± 2 octaves and the same as that in the dominant eye.

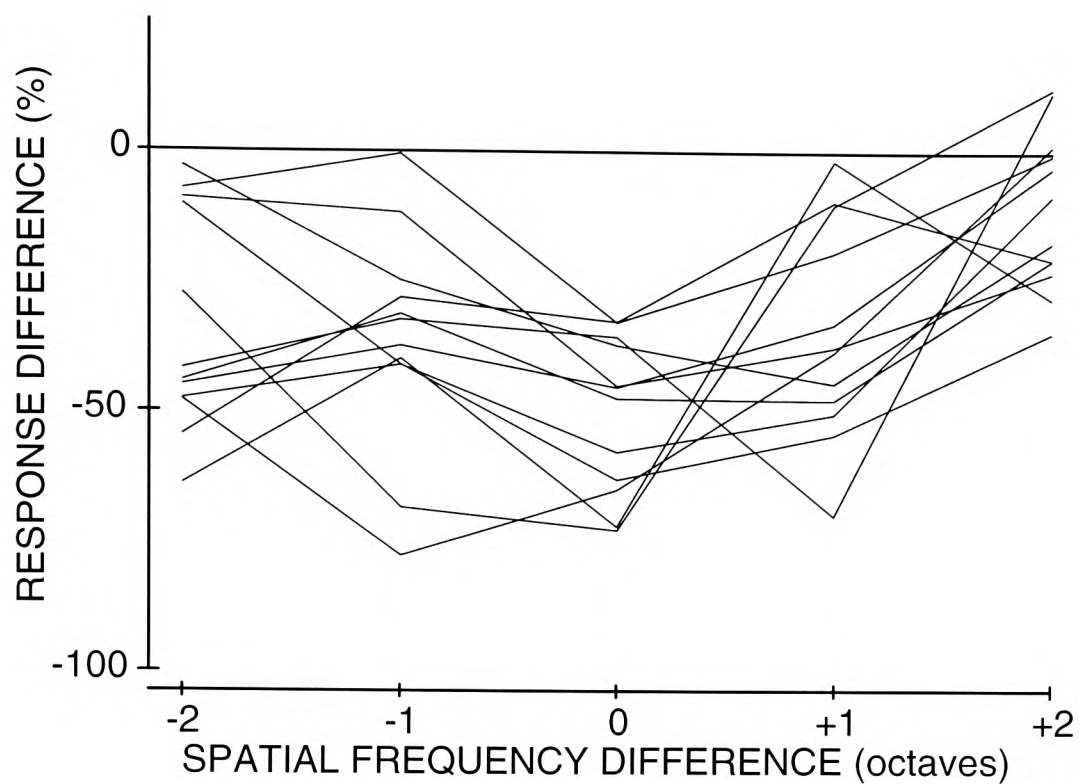


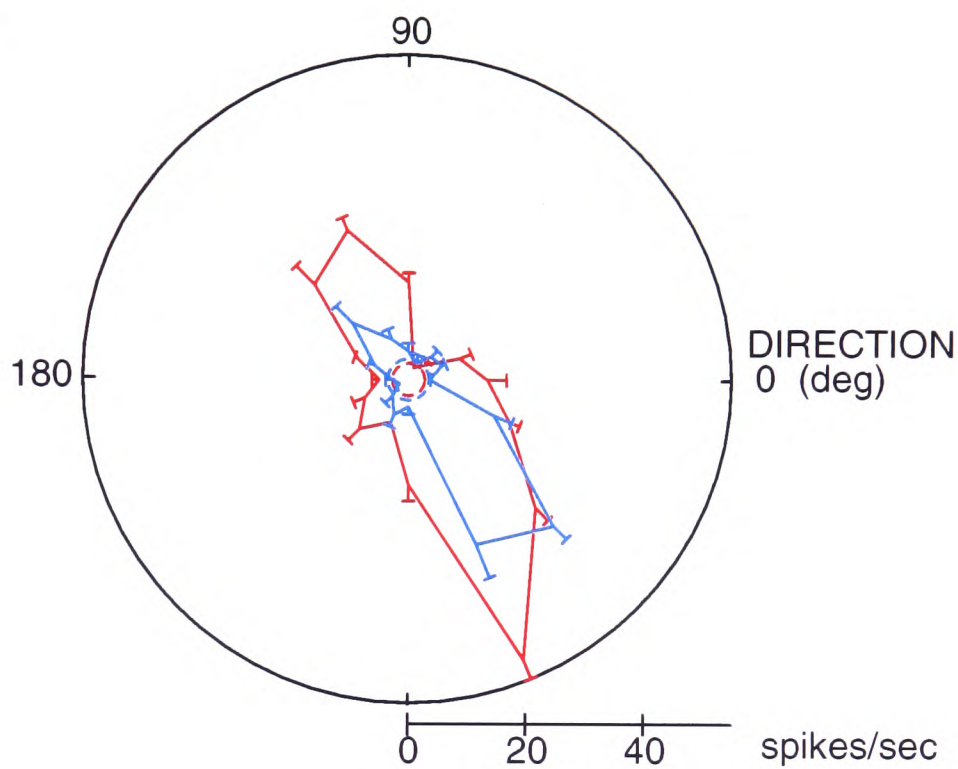
Figure 3-14

Comparison of dichoptic (rivalrous) and monoptic suppression in a layer 2/3 complex cell of OD group 5.

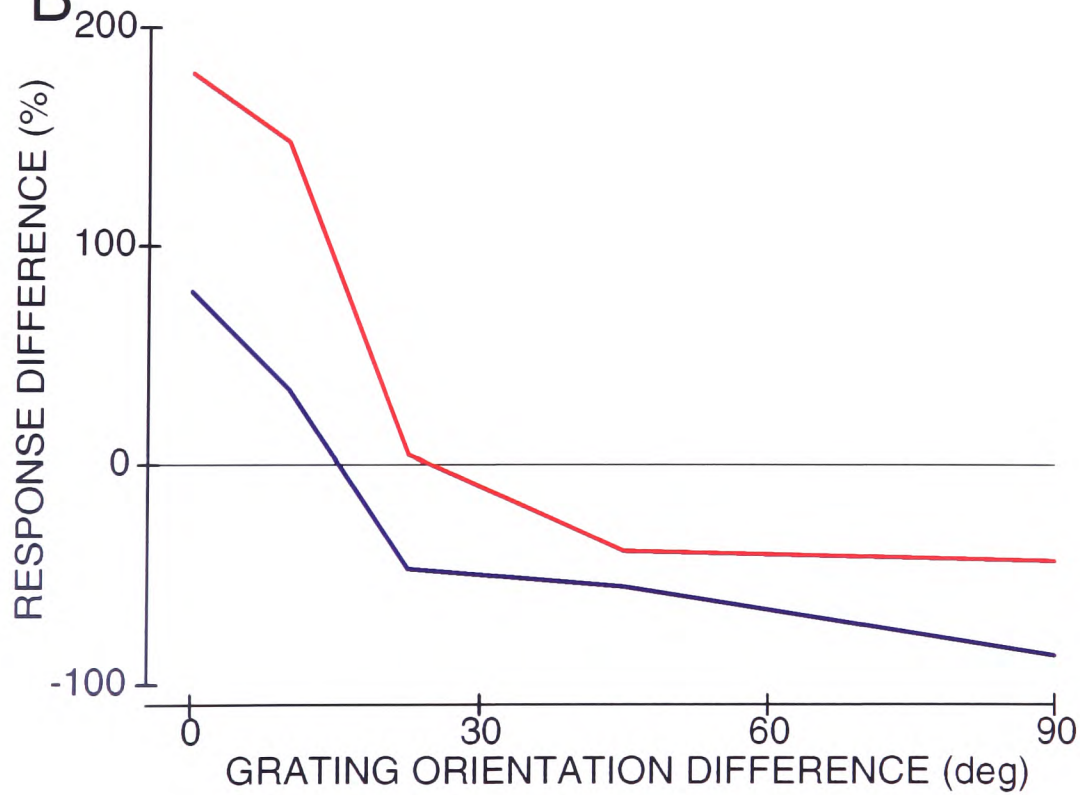
A: Polar plots of orientation tuning curves obtained with monocular stimulation through the ipsilateral eye (red) and the contralateral eye (blue), with gratings of 0.7 contrast and a spatial frequency of 0.4 c/deg. Interrupted circles indicate the very similar mean levels of spontaneous discharge during these two determinations.

B: Interaction functions for binocular stimulation (violet line) and for monoptic stimulation with superimposed gratings (red line). The ipsilateral (dominant) eye was stimulated continuously with an optimally oriented grating (direction of drift = 292.5° , spatial frequency = 0.4 c/deg, contrast = 0.18). For the binocular interaction function (see Fig. 3-3C), gratings of various orientations (same spatial frequency, contrast = 0.7) were intermittently presented to the non-dominant eye, while for the monoptic interaction function they were intermittently superimposed on the stimulus being presented to the dominant eye. (The phase of the superimposed gratings was matched, so for zero orientation difference the test stimulus was a single grating of contrast 0.88.) The difference of orientations between the two stimuli is plotted on the abscissa. The difference between the response to the two gratings (whether presented dichoptically or superimposed in the dominant eye) and that to the conditioning grating alone is plotted on the ordinate as a percentage of the response the conditioning grating (after subtraction of the spontaneous discharge).

A



B



Time-course and stability of suppression

In order to judge the latency and consistency of suppression produced by rivalrous stimuli I examined peri-stimulus time histograms (PSTHs) from both the binocular stimulation procedure described above and from experiments in which orthogonally oriented gratings were presented to the two eyes for as long as 30 sec. Suppression of the response to the optimal conditioning stimulus usually commenced quite sharply, some 60 - 250 msec (mean of 13 cells: 120 msec; SD = 54 msec) after the presentation of an orthogonally oriented grating in the other eye (e.g. Fig. 3-15B). However, in some accumulated PSTHs, suppression appeared to turn on more gradually, due to statistical scatter of latency between individual trials of rivalrous stimulation (e.g. Fig. 3-15A). Suppression was strongest over a subsequent phase of 1-3 sec, with slight recovery to a tonic level, which was then sustained over the remainder of the period of binocular stimulation (Fig. 3-15A,B).

I was interested to see whether the pattern of response during prolonged binocular stimulation would reveal spontaneous shifts between two stable states, suppressed and unsuppressed, which might be expected in view of the fact that **perceptual** dominance switches from one eye to the other every few seconds during binocular rivalry. PSTHs accumulated over several presentations with prolonged binocular stimulation never showed clear switches in firing rate: Fig. 3-15A shows a representative example for a layer 2/3 complex cell. However, the oscillations of binocular rivalry would not be expected to be precisely phase-locked to the stimulus onset, but to vary randomly from trial to trial and hence to be diluted by averaging. Therefore, histograms from individual trials were inspected; but for this cell there was no obvious variation of suppression over time (Fig. 3-15B), nor did its overall magnitude vary substantially from trial to trial.

Figure 3-15

Peri-stimulus time histograms (PSTHs) of the response of a layer 2/3 complex cell to a rivalrous stimulus.

A: PSTH accumulated over 10 trials. The cell was initially stimulated through the dominant eye alone with a grating of optimal orientation and spatial frequency (contrast = 0.35). After 5 sec (marked with an arrow), an orthogonally oriented grating of optimal spatial frequency (contrast = 0.7) appeared in the non-dominant eye. Binocular exposure continued for the entire 30-sec period marked by the horizontal bar. Bin width, 116 msec.

B: PSTH for a typical single trial.

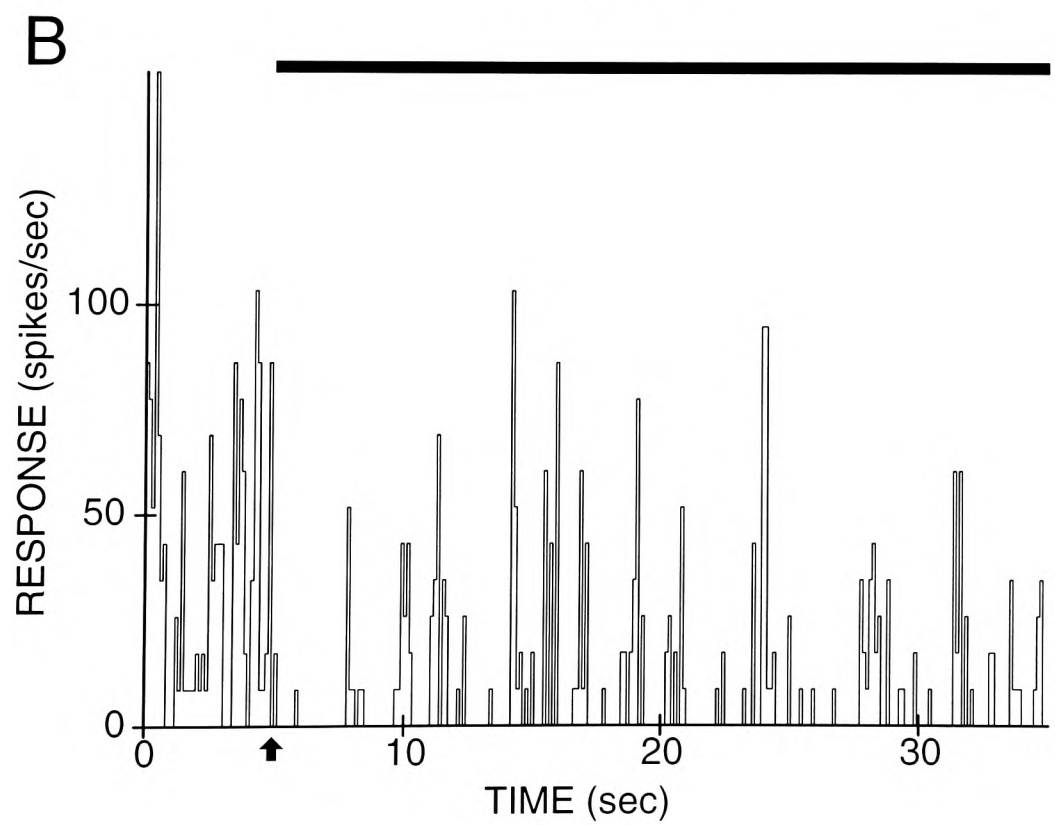
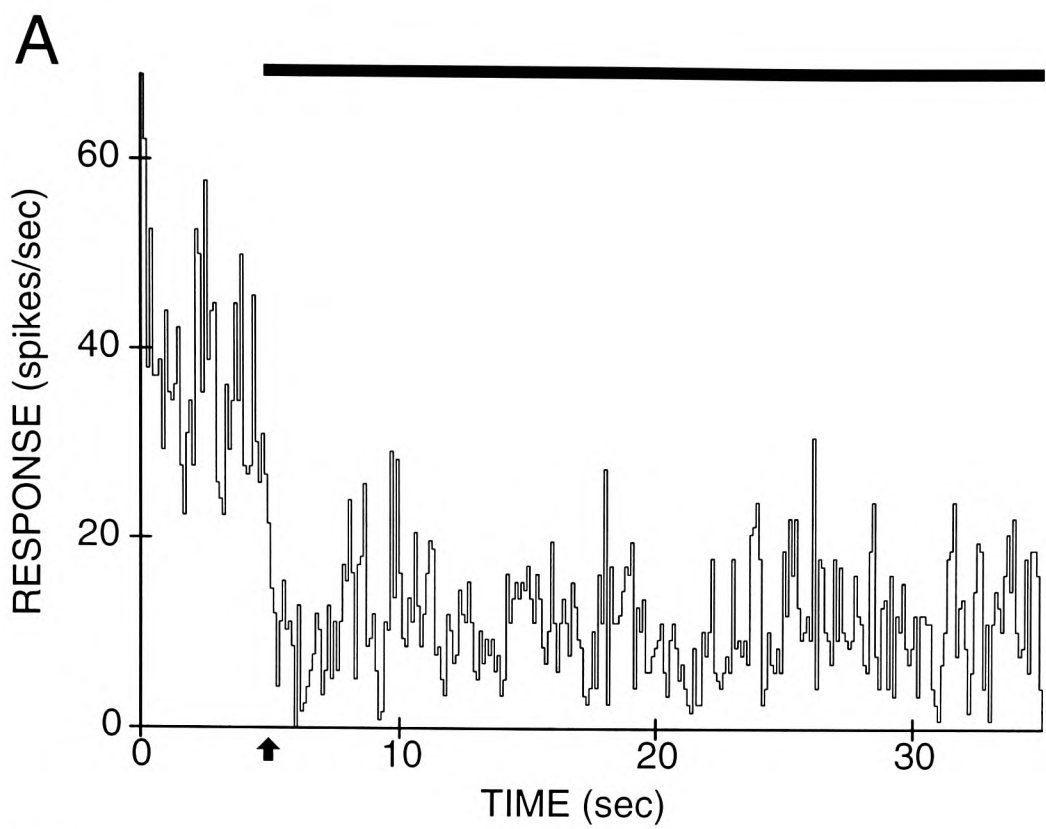


Figure 3-16

Fourier analysis of responses of two cells to orthogonally oriented drifting gratings presented for half a minute. For each 30-sec trial, a fast Fourier transformation (FFT) of the individual PSTH (256 bins of 116 msec each) was performed, and the resulting amplitude spectra were accumulated over the total number of trials.

A: Amplitude spectrum of the response of the layer 2/3 complex cell shown in Fig. 3-15, accumulated over 10 trials. The amplitude of response modulation (ordinate) is plotted against the frequency of the Fourier components (abscissa), up to the Nyquist limit of 4.31 Hz.

B: Amplitude spectrum of the response of the layer 2/3 simple cell shown in Fig. 3-17, accumulated over 9 trials. Note that the only clear peak in response modulation is at 4.04 Hz, corresponding to the drift frequency of the gratings.

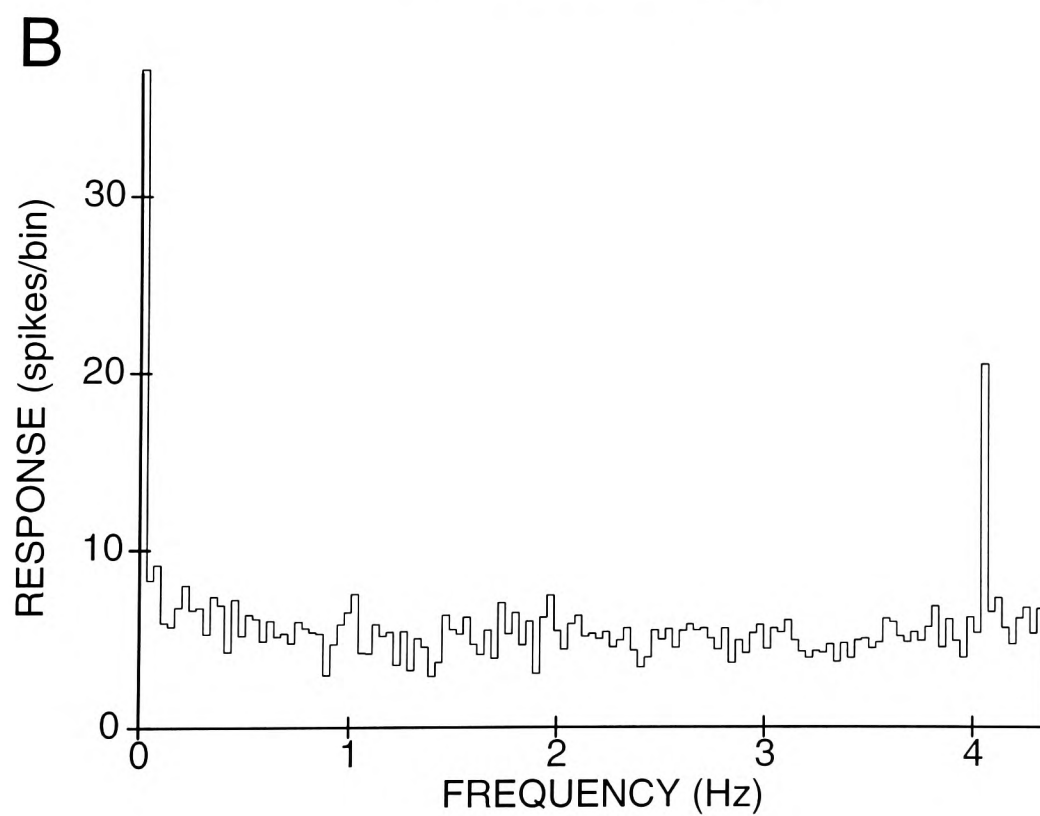
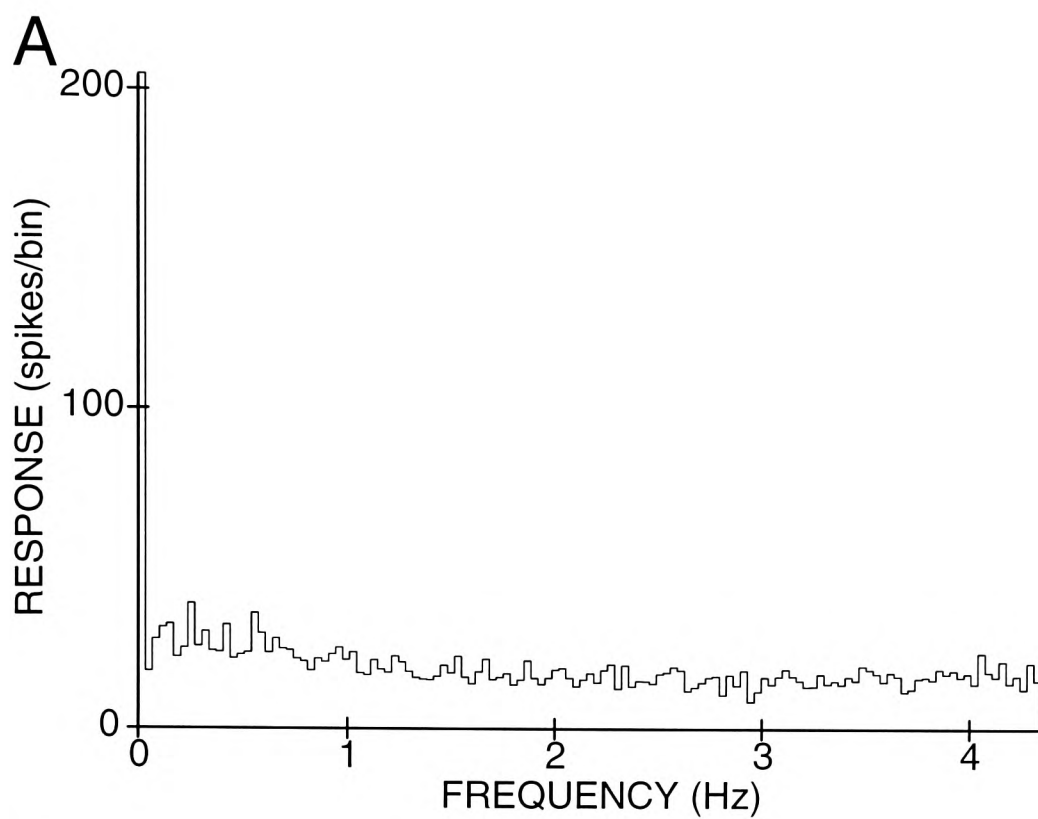
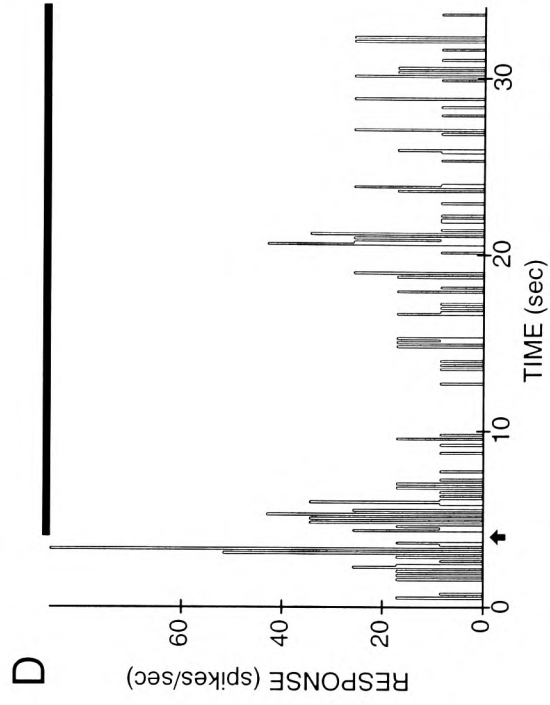
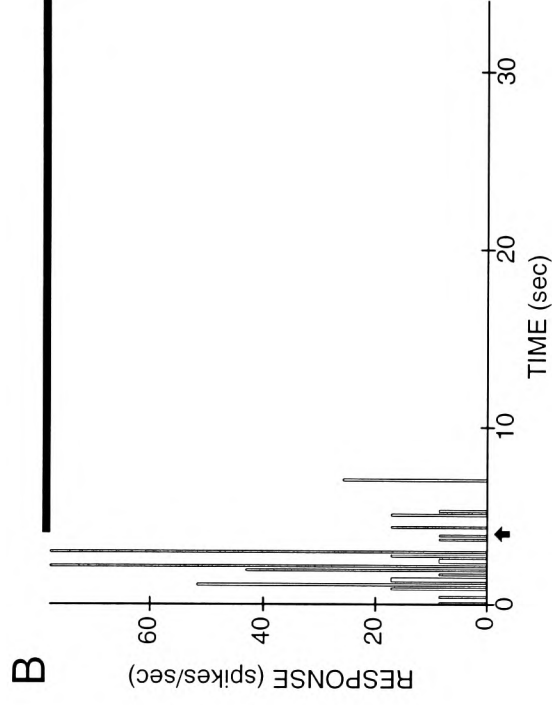
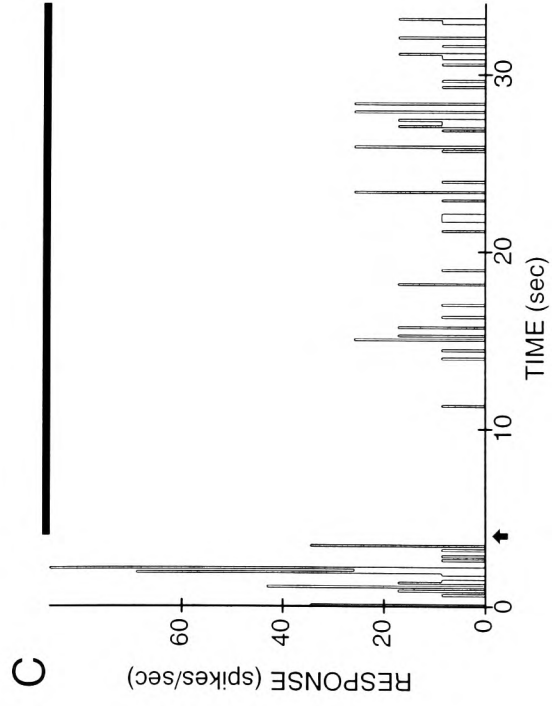
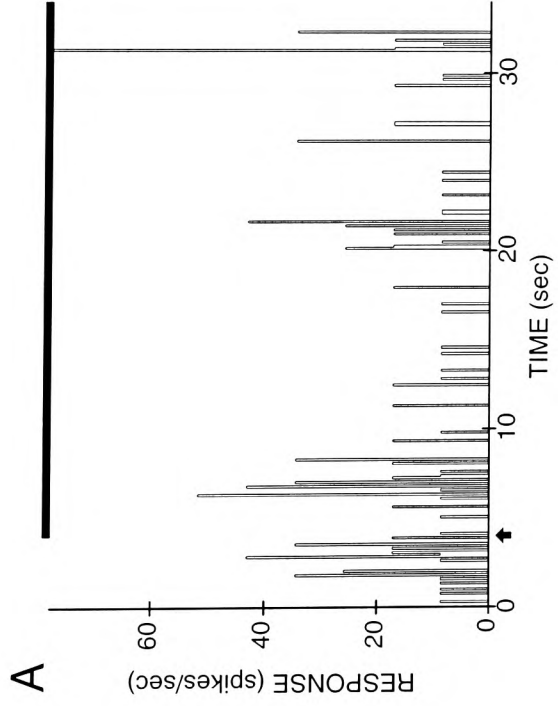


Figure 3-17

Peri-stimulus time histograms of the response of a layer 2/3 simple cell to a rivalrous stimulus, as in Fig. 3-15. All histograms represent single-trial responses. For 4 sec, the cell was stimulated through the dominant eye alone with a grating of optimum orientation and spatial frequency (contrast = 0.35). Arrows mark the onset of stimulation of the non-dominant eye with an orthogonal grating of optimum spatial frequency (contrast = 0.4). Bin width, 116 msec. Note the enormous variation in the pattern of response during the periods of rivalrous stimulation.



For most cells, fluctuations of response during suppression (after the onset transient) appeared to be within the normal range of response variability seen when stimulating the first eye alone. In no case did trial-by-trial Fourier analysis reveal significant cycling within this prolonged phase of suppression. Fig. 3-16 exemplifies this for the cells shown in Figs 3-15 and 3-17, respectively. However, due to the stochastic nature of the oscillations in rivalry, this finding was not really surprising, since random noise (see Lehky, 1988) would dilute any underlying periodicity.

In some cells the overall magnitude and/or pattern of suppression did differ from trial to trial. Fig. 3-17 shows a particularly striking case of a simple cell recorded in the supragranular layers that exhibited distinct inter-trial differences in its response to cross-oriented gratings. On some trials, profound suppression was observed immediately after the onset of binocular stimulation, but the cell's response recovered considerably after several seconds (Fig. 3-17C). On others, the response seemed unaffected for several seconds after the onset of the rivalrous stimulus but then was clearly suppressed for a further period of several seconds (Fig. 3-17A,D). On one presentation, the neuron ceased responding completely from shortly after the onset of the stimulus in the second eye and this total suppression was sustained for the full half-minute period (Fig. 3-17B).

Influence of the order of stimulus presentation

I came to suspect that the striking suppression that I saw in the majority of cells, which has not been reported by others (Ohzawa & Freeman, 1986a, b; DeAngelis et al., 1992), might depend on the particular temporal sequence that I employed, with the rivalrous stimulus being introduced against a pre-existing background response caused by stimulation of the other eye. For four cells (1 simple, 3 complex), distinctive in no respect other than that they showed clear suppression in the standard binocular interaction experiments, I examined the dependence of suppression on the temporal pattern of stimulation and the nature of the reduction in responsiveness during stimulation with various protocols of monocular and binocular stimulation.

The procedure used and the results obtained are illustrated in Fig. 3-18 for a supragranular simple cell. For the PSTHs in parts A, B, and C, spikes were accumulated over 10-sec stimulus presentations, the second half of which always consisted of simultaneous stimulation of the dominant eye with a grating of optimal orientation and of the other eye with an orthogonal grating of identical contrast and spatial frequency. The only difference between these *experimental* runs was the nature of stimulation during the 5-sec period immediately preceding each binocular presentation, which was:

- a) a **blank screen** of the same mean luminance was presented to **both eyes**; or
- b) the **orthogonal grating** was presented alone to the **non-dominant eye**; or
- c) the **optimal conditioning grating** was shown alone to the **dominant eye** (as in the standard procedure described above).

For *control* data, I also examined the response as a function of contrast during 5-sec presentations of the optimal grating to the dominant eye alone with the other eye viewing only a blank screen, preceded by either:

- 1) a blank screen presented to both eyes; or
- 2) an initial 5-sec period of stimulation of the dominant eye (to control for possible effects of 'fatigue' caused by the prior monocular stimulation in condition (c) above).

The magnitude of the response during the second 5-sec epoch of each of the five conditions is compared in Fig. 3-18D. There are no significant differences except for condition (c), where the sudden introduction of the orthogonal grating in the non-dominant eye while the cell is already responding through the dominant eye results in pronounced suppression. When orthogonal gratings were exposed to the two eyes with synchronized onset (condition (a)) no obvious suppression was seen, confirming the observations of Ohzawa and Freeman and DeAngelis et al. (1992).

For each of the four cells, the various sequences of stimulation described above were performed with the contrast of the suppressive grating in the non-dominant eye fixed at 0.7, while that in the dominant eye varied from presentation to presentation.

This provided data for the construction of contrast gain functions (relating response to the contrast of the stimulus in the dominant eye) under each of the five experimental and control conditions. For all four neurons, these functions were very similar for all control and experimental conditions except condition (c), which results in suppression. This is illustrated in Fig. 3-18E for the one simple cell in the sample: when rivalrous binocular stimulation followed a preceding period of activation through the dominant eye alone, there was distinct suppression (filled circles) over the entire range of suprathreshold contrasts in the dominant eye: indeed the magnitude of response was reduced by more than 50% below that in the monocular control condition (unfilled circles), the reduction reaching statistical significance ($p < 0.05$) at all contrasts tested. On the other hand, there was little or no suppression under the other two protocols (filled triangles and squares, respectively), even though the stimulus conditions during the actual epoch of data collection were identical.

A reduction in the response to a grating of a particular contrast in the dominant eye could be due to either a simple rightward shift of the response *versus* contrast function (i.e. an elevation of contrast threshold without a change in gain), or a reduction of the slope or gain of the function (or a combination of both effects). Fig. 3-19 illustrates the nature of the change in gain elicited under condition (c) for all four cells studied in detail. Average firing rate over the second 5-sec period in each trial is plotted against the contrast of the grating in the dominant eye. Filled circles show responses in the suppressed state (condition (c)) while unfilled circles plot results for the corresponding control condition (2). Fig. 3-19A shows results for the same cell as for Fig. 3-18, while parts **B**, **C**, and **D** summarize the results for the other three cells. For all four cells the absolute reduction in response was greater the higher the contrast of the stimulus in the dominant eye (with contrast in the 'suppressing' eye fixed). In other words, suppression results from a reduction in contrast gain. Although I did not explicitly determine the contrast thresholds of cells in the suppressed and unsuppressed states, extrapolation of the gain curves back to the level of background activity in each part of Fig. 3-19 suggests that there is little difference in threshold.

Figure 3-18

Dependence of binocular suppression on the temporal sequence of stimulation for a representative layer 2/3 simple cell.

Three experimental conditions were employed in which the cell was stimulated for 10-sec periods. In each case, during the second half of the 10-sec epoch a drifting grating of optimal orientation was shown to the dominant eye together with an orthogonal grating presented to the non-dominant eye. The only difference between these three conditions was the nature of stimulation during the 5-sec period immediately preceding this binocular exposure:

- a) Blank screen presented to both eyes, with simultaneous onset at the start of the period of binocular stimulation (filled triangles).
- b) Orthogonal grating presented alone to the non-dominant eye with the dominant eye viewing a blank screen (filled squares).
- c) Optimal grating presented alone to the dominant eye (filled circles).

A,B,C: PSTHs (each the average of six 10-sec presentations) of responses in the three experimental conditions a, b and c above. For these results the contrast of the gratings in both eyes was set at 0.7. The unfilled and filled bars above each PSTH indicate the periods of stimulation of the dominant and the non-dominant eye, respectively. Only when the stimulus appeared in the non-dominant eye while the cell was already responding through the dominant eye (**C**), was there obvious suppression during the period of binocular stimulation, the start of which is marked by small arrows.

D: Histogram comparing responses (mean $\pm$ SEM, $n = 6$) under the three experimental conditions (a, b, c) described above and two further controls:

- 1) The dominant eye alone was stimulated during the second 5 sec, preceded by 5 sec of presentation of a blank screen of the same mean luminance (unfilled triangle).
- 2) The dominant eye was stimulated for the entire 10 sec period and the response was measured during the latter 5 sec of each presentation (unfilled circle), in order to control for adaptation or 'fatigue' (i.e. progressive reduction in response) under experimental condition (c) above. (This cell displayed some fatigue for contrasts > 0.2 .)

For both controls, the non-dominant eye viewed a blank screen.

E: Contrast response functions for all five conditions. In each case the contrast of the gratings shown to the dominant eye was varied across presentations. The interrupted line indicates the mean level of spontaneous discharge measured during blank presentations with no pattern presented to either eye. Only when the cell was already responding, because of prior presentation of the optimal grating to the dominant eye, did the orthogonal grating in the other eye cause obvious suppression (filled circles).

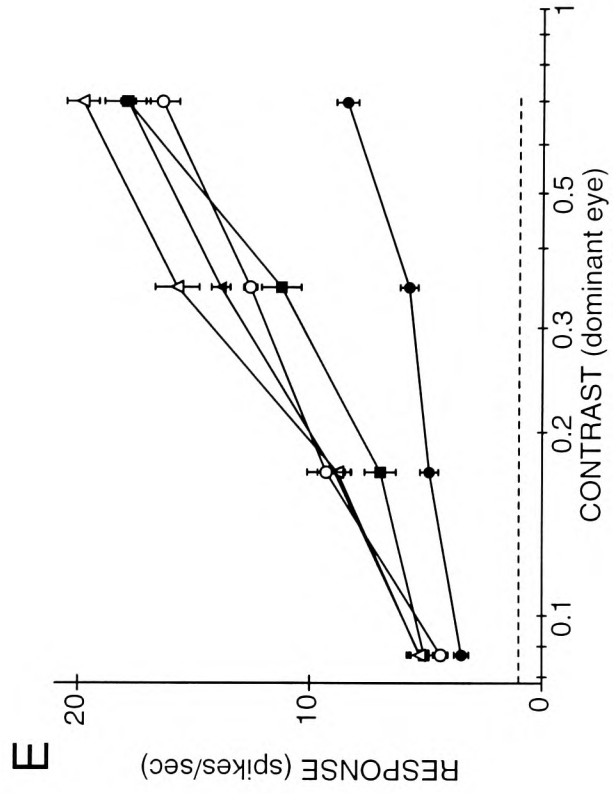
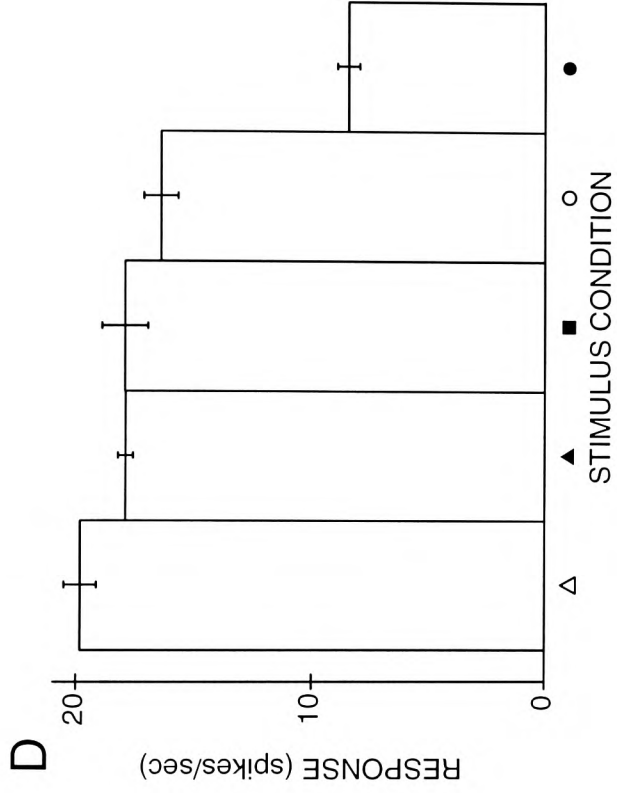
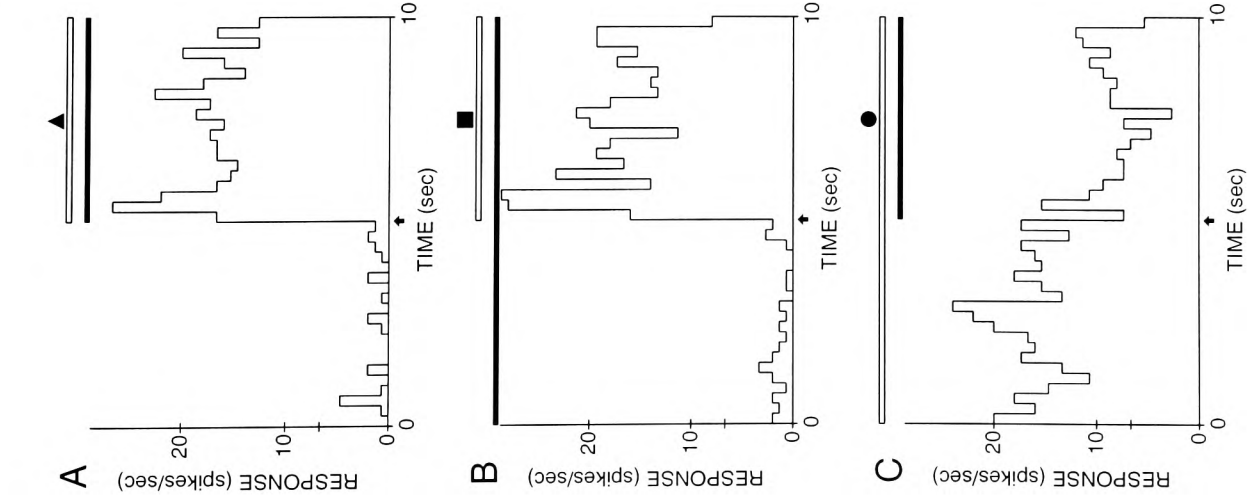
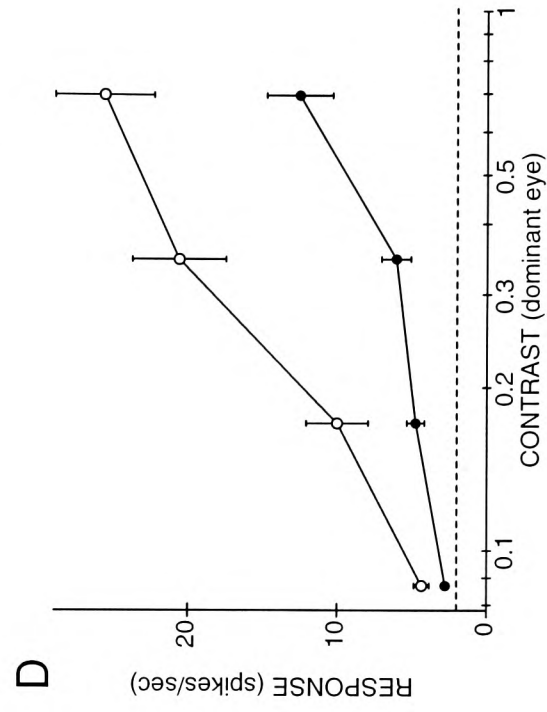
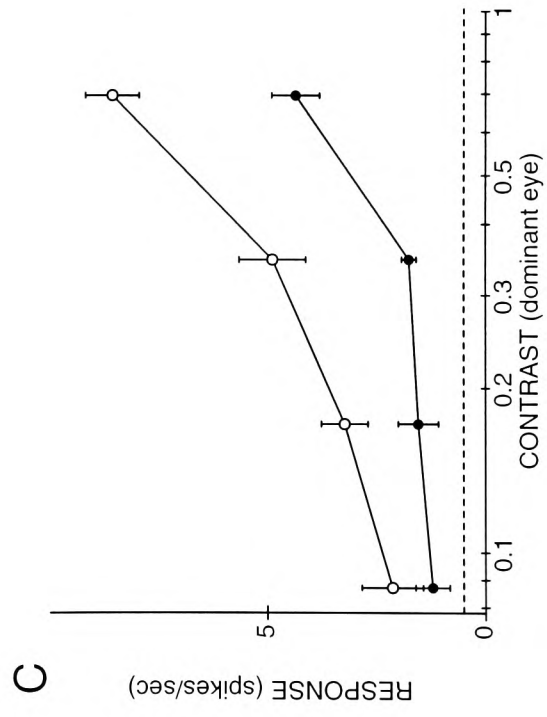
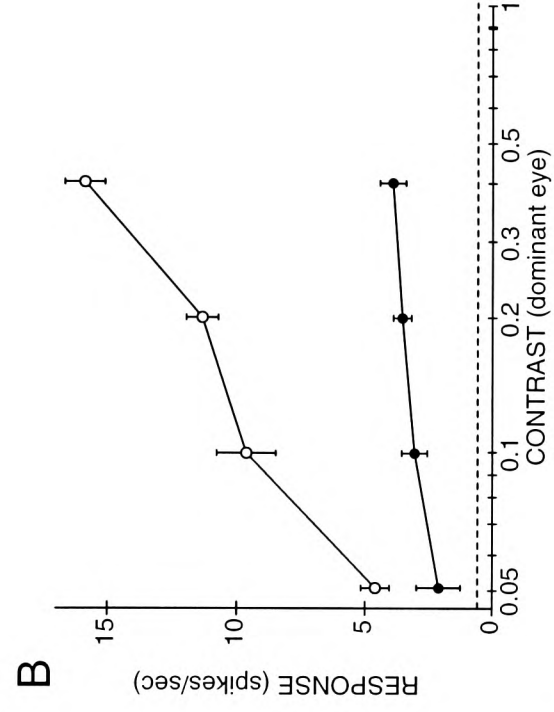
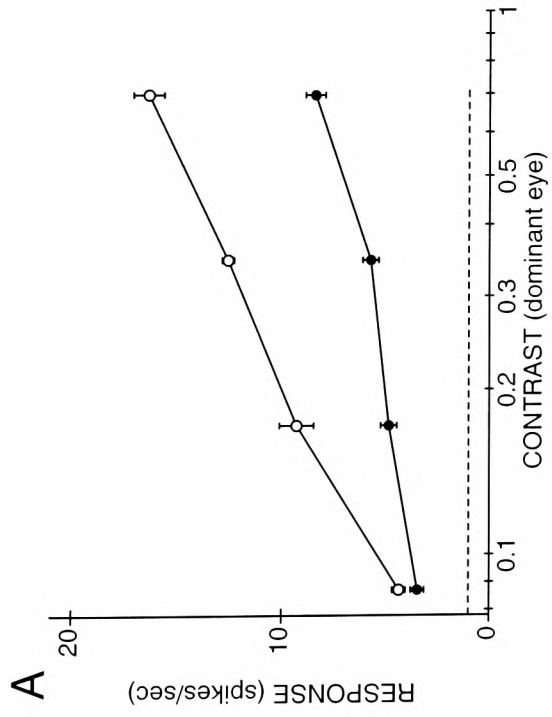


Figure 3-19

Response *versus* contrast functions for experimental condition (c), in which binocular stimulation with orthogonal gratings was preceded by monocular presentation of an optimal grating to the dominant eye (filled circles), and the corresponding control condition (2) (unfilled circles; see legend to Fig. 3-18). The contrast of the grating shown to the dominant eye was varied under each condition to provide the data for these functions. Mean responses in spikes/sec ($\pm$ SEM, $n = 6$ presentations per data point in all parts) are plotted against the contrast of the optimally oriented drifting grating shown to the dominant eye. The interrupted lines indicate the mean level of spontaneous discharge measured during blank presentations with no pattern presented to either eye. Part **A** depicts responses from the simple cell of Fig. 3-18, and **B**, **C** and **D** show results from three complex cells recorded from layers 2/3 (**B**, **C**) and 5 (**D**).



3.3. Discussion

The site of rivalry

Although the phenomenon of binocular rivalry has been well known for more than a century and its characteristics have been thoroughly defined by psychophysical investigation, the neural mechanism responsible for this virtually complete suppression of perception through one eye at a time has remained elusive. Even the site of its occurrence in the visual pathway is still a matter of conjecture, though the wide variety of stimulus parameters that evoke binocular rivalry if dissimilar in the two eyes (e.g. contour, colour, or motion) suggests that the process takes place in the periphery of the visual pathway, prior to the postulated parallel streaming of visual information (Van Essen & Maunsell, 1983; Livingstone & Hubel, 1988). This notion receives further support from the fact that rivalry occurs independently in patches of the visual field whose angular dimensions seem to relate to the magnification factor in the precise topographic representations of the field seen only early in the pathway (see Blake et al., 1992).

At first thought, the fact that rivalry manifests itself as virtual blanking of input from one eye suggests that the underlying physiological mechanism resides at a point prior to the combination of signals from the two eyes. Indeed, current theoretical models of rivalry postulate reciprocal feedback inhibition between or on to groups of **monocular** cells (Matsuoka, 1984; Lehky, 1988; Blake, 1989). Furthermore, since contour rivalry is orientation-dependent, these cells should themselves be orientation selective or should derive inhibition from orientation selective neurons. Cells of the LGN seem good candidates because they generally receive excitatory input (or at least suprathreshold excitation) from only one eye, and they have extensive back-projections from orientation selective binocular cells in layer 6 of primary visual cortex (Gilbert & Kelly, 1975), which can exert inhibition as well as facilitation (Schmielau & Singer 1977; Tsumoto et al., 1978). Indeed, Varela and Singer (1987) reported that a majority of LGN cells in the anaesthetized cat showed long-latency suppression of activity when

stimulated binocularly, specifically with gratings differing substantially in orientation in the two eyes.

As part of the present study, the role of the LGN was also investigated but not a single case of orientation-selective suppression was seen during dichoptic stimulation. Although the sample of LGN cells was not large, the results do agree with recent findings by Moore et al. (1992). Although almost half the cells I studied showed clear interocular inhibition when a grating was presented to the silent eye, it was independent of the orientation of the stimulus. My procedure more closely resembled that of Varela and Singer (1987) than did that used by Moore et al. (1992). In particular, dichoptic gratings were employed that were always matched in drift frequency, and the stimulus was presented to the dominant eye for several seconds before the onset of the stimulus to the silent eye, rather than both starting simultaneously, as in the protocol of Moore et al. (1992). The remaining minor differences in Varela and Singer's experiment (square-wave rather than sinusoidal gratings and slightly higher contrast) seem unlikely to be critical. In searching for reasons for the discrepancy in results I wonder whether the lack of randomized interleaving in Varela and Singer's (1987) study might have caused chance fluctuations in excitability to produce the apparent effects of stimulus orientation that they saw during prolonged periods of binocular stimulation.

Four out of five monocularly driven units recorded in layer 4 of area 17 displayed a pattern of binocular suppression strikingly similar to the inhibition seen in the LGN, being independent of interocular spatial phase or orientation difference. (Indeed, these effects seen in layer 4 may be simply a reflection of the properties of geniculate neurons that provide input to such cells: further work is needed to see whether they also involve, at least in part, intracortical interactions). Just as I found for these monocular cells of layer 4, Ohzawa and Freeman (1986a, b) reported that 7.8% of simple cells as well as 8.2% of complex cells (all but one of them monocular) showed non-phase-specific suppression by iso-oriented gratings presented to the non-dominant eye.

My data imply that, contrary to the speculations of Leaky and Blake (1991), monocular cells in the LGN and layer 4 of area 17 are unlikely to provide the

physiological substrate for the suppression underlying binocular rivalry. The results are incompatible with models predicting the site of rivalry to be prior to binocular convergence. Rather, they indicate that *orientation-selective binocular neurons* in the primary visual cortex represent the earliest stage (at least in cats) at which such interaction occurs.

One line of psychophysical evidence that has been extensively explored involves the measurement of perceptual after-effects induced by prior adaptation to a stimulus that is only intermittently perceived because it is presented to one eye, with a rivalrous stimulus shown to the other eye (see Lehky & Blake, 1991). If the site of rivalry were prior to that of the neural change underlying adaptation, after-effects induced under such conditions of partial visibility should be weaker than following uninterrupted viewing of the adapting stimulus. Some years ago, a variety of after-effects, e.g. the threshold elevation after-effect (Blake & Fox, 1974; Blake & Overton, 1979) and the motion after-effect (Lehmkühle & Fox, 1975; O'Shea & Crassini, 1981), were reported to be of equal strength after normal adaptation and after adapting monocularly with a rivalrous stimulus present in the other eye (thus reducing the fraction of time for which the adapting stimulus was actually visible). This was taken to imply that the adaptation process occurs **before** the site of rivalry suppression. However, recently Lehky and Blake (1991) did find a reduction of the threshold elevation after-effect when the conditions were such that the adapting grating was visible only 10% of the time during rivalry, suggesting that neurons undergoing adaptation are located **at or after** the site of rivalry suppression. Taking into account the orientation selectivity of such after-effects (Blakemore & Campbell, 1969; Blakemore & Nachmias, 1971) and the fact that they partially transfer from one eye to the other (Gilinsky & Doherty, 1969; Mitchell et al., 1975), it seems likely that the earliest site for the relevant adaptation is the primary visual cortex and that at least some of the neurons involved are binocularly driven. Thus the psychophysical findings of Lehky and Blake (1991) are compatible with my neurophysiological results.

Logothetis and Schall (1989a, b) recorded from area MT in awake monkeys trained to perform a motion discrimination task. They found that only about two fifths of direction selective cells displayed variation of responsiveness with the perceptual choice of the monkey, and in about half of these responsiveness was inversely correlated with the direction of motion being perceived by the monkey (as judged by its behavioural responses). By comparison, I found that more than half the binocular cells studied in cat area 17 were significantly and selectively suppressed by rivalrous stimuli; this type of suppression, if it also occurs in primates, could be the origin of the properties of those cells in MT whose behaviour does parallel the animal's behavioural indication of rivalry.

Stimulation procedures that reveal suppression in the cat cortex could be employed in experiments on various stages of the visual pathway in awake primates, trained to indicate their perceptual experience, in order to define the site or sites of rivalrous interaction. Very recent evidence indicates that, as in cats, orientation-dependent suppression does not occur in the monkey's LGN (Lehky & Maunsell, 1993).

The nature of interocular inhibition and suppression

The origin of the non-oriented inhibition seen in about half the LGN cells studied (Fig. 3-3) remains uncertain. It could conceivably be due to direct inhibitory interaction between right-eye and left-eye laminae of the LGN, *via* inhibitory interneurons (Guillery, 1966); but it could also involve the feedback projection from layer 6 of the cortex, the lack of selectivity for orientation perhaps being due to a combination of inhibitory inputs to each LGN cell from cortical neurons in a range of neighbouring orientation columns. Very recently, it has been suggested that the non-dominant-eye inhibitory input arises from the perigeniculate nucleus (Wang et al., 1994).

The non-orientational suppression that was seen in most monocularly driven cells recorded in layer 4 (Fig. 3-6) may be a simple reflection of the properties of their geniculate inputs. However, it seems likely that most of the interocular suppressive effects seen at the cortical level are due to intracortical mechanisms. For one thing, the

maximum levels of suppression seen at the cortex were generally stronger than those in LGN cells.

The fact that suppression in most cortical cells appears tuned for interocular orientation difference might also be taken as a distinctive cortical property. However, it is possible that the characteristic orientation-dependent interaction functions for suppression (Figs 3-9, 3-10) are generated by the sum of strong facilitation for gratings of similar orientation and non-oriented suppression (like that seen in the LGN, for monocular cortical cells in layer 4, and for the majority of cortical cells in strabismic animals; see Chapter 4). Indeed, my data provide some support for the idea that suppression is generated at all orientational differences, but is swamped by conventional binocular facilitation when the orientations are matched:

First, binocular interaction functions (Fig. 3-11) nearly always showed a smooth transition from facilitation, for gratings of similar orientation in the two eyes, to suppression, for larger angular differences. Hence, the narrower the tuning of binocular facilitation for orientational disparity, the smaller the angular difference at which suppression appeared. If suppression were restricted to a narrow range of angular differences centred on the orthogonal, one would expect to find no binocular interaction at all over an intermediate range of orientational differences, especially in cells showing binocular facilitation only over a narrow range of near-iso-orientations.

Second, the family of binocular interaction functions in Fig. 3-11 suggests that there is a continuum of tuning, between equal suppression at all orientational differences to broad facilitation with a narrow range of suppression around the orthogonal. In these terms, the monocular units of layer 4 might differ from the rest of the population only in lacking facilitatory interaction for matched stimuli.

Finally, binocular suppression in many respects resembles monocular suppression from within the receptive field (Morrone et al., 1982; Bonds, 1989; DeAngelis et al., 1992; see Fig. 3-14). It has recently been shown that monoptically elicited suppression occurs at all orientations, including the cell's preferred orientation for excitation, but is usually concealed by facilitation (Nelson, 1991; DeAngelis et al., 1992). One possible

function of such non-specific inhibition may be normalization of the response of each cell with respect to local image contrast (Bonds, 1989; DeAngelis et al., 1992). It is conceivable that binocular and monocular suppression have similar anatomical substrates (see also Chapter 6) and are *both* non-selective for relative orientation.

If the dependence of response on the orientation difference of binocular stimuli were indeed the result of facilitatory interactions, of various strengths, being superimposed on a background of uniform, non-orientational suppression, the apparent tuning of dichoptic suppression would simply depend on the range of orientation differences over which inhibition exceeds facilitation.

An obvious candidate for the origin of suppressive effects in the cortex is intrinsic connections between adjacent ocular dominance columns. Although intrinsic horizontal excitatory connections predominantly link cortical neurons of similar orientation (Ts'o et al., 1986; Schwarz & Bolz, 1991), inhibitory connections appear to be more uniformly distributed across orientation and ocular dominance columns (Somogyi et al., 1983; Kisvárdy & Eysel, 1993; Kisvárdy et al., 1993b), connecting areas of both similar and orthogonal orientation preferences. One possible implementation of interocular suppression is reciprocal inhibition between cells dominated by the two eyes, lying in neighbouring ocular dominance columns. Since the majority of excitatory synapses on neurons in area 17 derive from closely neighbouring cells rather than from thalamic afferents (Kisvárdy et al., 1986; Douglas & Martin, 1991; Nicoll & Blakemore, 1993) the responses of cortical neurons are likely to depend crucially on 'amplification' of input from the thalamus operating through this local excitatory circuitry (Douglas et al., 1989; Douglas & Martin, 1991), at least in some layers of the cortex (Nicoll & Blakemore, 1993). Perhaps inhibitory interactions between adjacent ocular dominance columns, responsible for suppressive interocular interactions, modulate the gain of this local excitatory circuitry (see Fig. 3-20). The resultant interocular suppression might be overcome by binocular facilitation when the images in the two eyes are sufficiently similar.

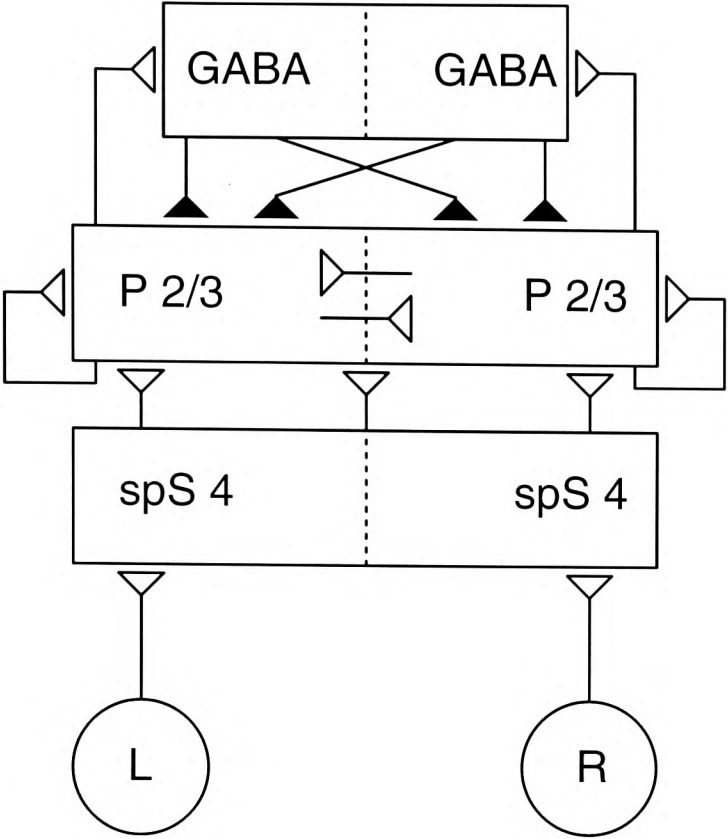
The arrangement of intracortical circuitry responsible for suppression might generate oscillatory behaviour, perhaps because of gradual fatigue in the inhibitory output from the ocular dominance column that happens to be dominant, leading to sudden 'capture' of dominance by inhibition from the other column (see Lehký, 1988). The fact that perceptual rivalry takes place independently in patches of the visual field, scaled in size in relation to the magnification factor of the representation in the striate cortex (Blake et al., 1992), implies that the suppressive influences operate over small domains within ocular dominance columns, roughly constant in anatomical size across the visual cortex.

The similarity of peak spatial frequency for the monocular excitatory responses of binocular neurons and the suppressive effects produced by an orthogonal grating in the other eye (Figs 3-12, 3-13) suggest that the interaction responsible occurs mainly between neurons with similar preference for spatial frequency. Compatible with this finding is a recent psychophysical study showing that rivalry occurs most readily for dichoptic stimuli matched in spatial-frequency content (Yang et al., 1992). On the other hand, the spatial-frequency tuning for suppression was clearly broader than that for facilitation in most cells tested and suppression could often be generated by gratings too high in spatial frequency to produce any response from the cell in question when presented at the optimal orientation (Fig. 3-12). This implies that the suppressive signal derives from a population of other cortical neurons whose spatial frequency preferences cover a broader range than that of the tuning curve of the receiving cell. Similarly, the lack of sensitivity to spatial phase for suppressive effects could be taken to mean that the suppressive signal is drawn from a group of cells whose receptive fields are spatially scattered.

The population of cells showing powerful interocular suppression was not distinctive in any obvious respect. Indeed the continuous variation in the strength of suppression across the population (see Fig. 3-11) suggests that suppression is a general phenomenon in the cortex, simply graded in potency and not restricted to a particular class of neuron.

Figure 3-20

Schematic diagram of a cortical microcircuitry in normal cat cortex that could generate binocular responses of the type described above. Circles marked 'L' and 'R' represent left and right eye inputs to spiny stellate cells in layer 4 of V1 ('spS 4'). Layer 2/3 pyramidal cells are indicated as 'P 2/3', GABA-ergic interneurons as 'GABA'. Open and filled triangles represent excitatory and inhibitory synapses, respectively. Vertical interrupted lines separate cells with predominantly left-eye excitatory input from those with predominantly right-eye excitatory input. For further explanation see text.



Interocular suppression as the basis of perceptual switching in rivalry

Perhaps the best evidence that suppression in the striate cortex does play a part in contour rivalry is its dependence on the sequence of stimulation. Only when a conflicting stimulus is introduced into one eye while the cell is already responding through the other eye does obvious suppression occur (see Fig. 3-18). To some extent, this gross non-linearity has a parallel in perceptual rivalry. If perception is already dominated by a grating in one eye and a contrasting stimulus suddenly appears in the other eye, the latter will usually capture and dominate perception for some time. On the other hand, if two different gratings are simultaneously exposed to the two eyes, they are initially both perceived (false fusion; see Wolfe, 1983).

The reductions in responsiveness that occur after adaptation to a high-contrast stimulus and during exposure to superimposed iso-oriented gratings (of different drift frequency) in one eye are characterized by an elevation of the threshold contrast of cortical cells and a rightward shift of the response *versus* contrast function without a change in its slope (Bonds, 1991; Ohzawa et al., 1985; Morrone et al., 1987). By comparison, interocular suppression, like 'cross-orientation inhibition' seen with superimposed orthogonal gratings (Morrone et al., 1987), is manifested as a reduction in the gain of response as a function of contrast in the suppressed eye without an obvious increase of threshold contrast (Fig. 3-19), that is, the **relative** strength of suppression is independent of the contrast of the stimulus eliciting the suppressed response.

Imagine the overall pattern of activity in the striate cortex under conditions that provoke suppression (and perceptual rivalry in humans). Initial stimulation with, say, a vertical grating in the left eye will activate cells in columns tuned to vertical, especially strongly within ocular dominance columns devoted to the left eye. Now, the sudden appearance of a horizontal grating in the right eye will suppress activity extensively throughout the left-eye OD columns, while evoking a sudden surge of activity in columns tuned to horizontal in the right-eye OD columns. Interpretative mechanisms might assign perception according to local maxima of activity across the entire population of neurons in the striate cortex, thus resolving perceptual ambiguities.

Perceptual suppression of one eye is not just an entertaining phenomenon seen only under laboratory conditions. Situations that lead to rivalry occur all the time during the normal viewing of three-dimensional scenes containing a large range of binocular disparities. The images of objects much closer and further than the fixation point obviously fall on entirely non-corresponding retinal areas, outside the range of receptive field disparities of cortical neurons. For these parts of the scene, each cortical region will receive conflicting inputs from the two eyes. Local suppression, equivalent to rivalry, eliminates confusion by allowing only one eye at a time to see within each area that cannot be fused (see Blake & Camisa, 1978). Thus the suppressive mechanism revealed in binocular rivalry may be valuable in vetoing input from one eye under normal conditions of interocular conflict that occur very frequently in natural viewing.

The origin of spontaneous perceptual alternation

One of the most distinctive characteristics of rivalry (and of other forms of unstable perception, such as that of ambiguous figures) is the alternation between the two sensory experiences, typically occurring every few seconds during continuous viewing (Levelt, 1965; Mueller & Blake, 1989). Theories of rivalry have postulated the existence of oscillating circuitry, driving groups of monocularly dominated neurons alternately into one of two relatively stable states, with a duty cycle of switching dependent on the 'strengths' of the stimuli in the two eyes (Levelt, 1965; Lehky, 1988). The arrangement of intracortical circuitry that I suggest is responsible for suppression might indeed generate oscillatory behaviour, perhaps because of gradual fatigue in the inhibitory output from the ocular dominance column that happens to be dominant, leading to sudden 'capture' of dominance by inhibition from the other column (see Lehky, 1988). It might then be expected that individual neurons would show such temporal patterns of activity, switching from responsive to suppressed states every few seconds during the presentation of rivalrous stimuli.

No such switching behaviour was seen in the standard binocular interaction procedure, but this is not surprising in view of the fact that individual binocular

exposures were short (only 5 sec). However, even in the few experiments in which I examined activity during prolonged (30-sec) exposure to orthogonal gratings, only one unit, illustrated in Fig. 3-17, clearly showed the kind of unstable behaviour that might be expected. On some trials, this cell's response to an optimal stimulus in the dominant eye was completely and tonically suppressed by the appearance of a rivalrous stimulus in the other eye: on other trials there did appear to be switching between suppressed and virtually unsuppressed states over the 30-sec period. It is conceivable that the apparent instability displayed by this cell was simply due to inherent variability of response during long periods of continuous stimulation.

Further work is needed to determine whether instability is indeed a feature of suppressive interactions and particularly to see whether fluctuations in suppression are correlated between groups of neurons, which might be expected if perceptual alternation is determined by the behaviour of populations of cells. Perhaps the perceptual alternation in rivalry depends on the properties of a sub-population of cells, or maybe its temporal characteristics are simply different in the cat. Of course, there is also the distinct possibility that the characteristics of the circuitry involved were affected by the anaesthetized state of the animals in this study. The lack of eye movement might also have reduced spontaneous alternation of suppression: certainly, perceptual switches in rivalry are often triggered by changes in fixation (see Helmholtz, 1910).

It is also conceivable that, although interocular suppression resulting from initial conflict between the eyes appears to originate in the striate cortex, subsequent *spontaneous* switches in eye dominance may only occur in some 'higher' visual area. They may be triggered by the reduced level of response during rivalrous stimulation (due to suppression of activity in the striate cortex) and, hence, increased response variability. Although the circuitry of area 17 seems to provide a mechanism by which an image in one eye can veto perception of a conflicting stimulus in the other eye, further work is needed to explain the spontaneous perceptual alternations that occur in rivalry.

4. INTEROCULAR SUPPRESSION IN AREA 17 OF STRABISMIC CATS AND MONKEYS

Strabismus, or misalignment of the visual axes of the two eyes in the horizontal plane, is a common visual disorder in humans and also in monkeys reared in captivity (Kiorpes and Boothe, 1981). Various categories can be discerned clinically, with respect to the direction of squint, state of fixation, presumed aetiology etc. (for reviews see Duke-Elder & Wybar, 1973; von Noorden, 1990). Convergent strabismus is referred to as *esotropia*, divergent strabismus as *exotropia*. Both esotropic and exotropic deviations can be either alternating or unilateral. In the latter (more frequent) case only one eye is used for fixation, while the other permanently deviates. About 15% of strabismic humans (so-called '*alternators*') show alternating fixation patterns, switching fixation from one eye to the other either indiscriminately or for certain viewing distances or directions of gaze. With esotropia (about 80% of all cases of strabismus) unilateral fixation is much more common than with exotropia, as is *amblyopia* (= "blunt vision"), a condition defined as a loss in visual acuity which persists once refractive errors have been corrected, in the absence of any recognizable pathology of the eye. It has been suggested that the lower incidence of strabismic amblyopia in exotropic patients is primarily due to the prevalence of alternating fixation (Mitchell, 1988). This notion receives support from the observation that patients with untreated large-angle esotropia of early onset commonly display alternating 'cross-fixation' but do not show amblyopia in either eye, while early surgical alignment, although permitting the development of peripheral fusion, frequently results in amblyopia in the operated eye (Good et al., 1993). In conventionally treated large-angle esotropia as well as in congenital small-angle esotropia, peripheral fusion may then function as a 'lock' and prevent one eye from experiencing adequate visual stimulation of the fovea (Good et al., 1993).

The most frequently observed form of human strabismus is accommodative esotropia. In this case, a hypermetropic refractive error in one or both eyes is thought to result in an excessive amount of accommodative convergence and, consequently, the

development of a squint (Mitchell, 1988). Non-accommodative forms of strabismus (about 1/3 of cases) include congenital as well as paralytic squint. The latter, a manifestation of paresis of one or more extraocular muscles, constitutes only a small minority of cases (~ 2%).

Most humans who develop strabismus at an early age do not suffer obvious double vision (diplopia) or confusion despite the fact that the images of each feature in the visual scene fall on geometrically non-corresponding points in the two retinae and corresponding points are stimulated by different features. In some cases, single vision (haplopia) in strabismus is attributed to the phenomenon of harmonious *anomalous retinal correspondence* (ARC), in which functional correspondence is shifted to match the angle of squint. The two images of a single object give rise to a single sensation of visual direction despite the misalignment of the eyes, and there is even rudimentary stereoscopic vision (for reviews see Nelson, 1988; Schor, 1991). The classical concept of ARC postulates that the two retinotopic maps are projected onto the cortex out of register to generate binocular cortical neurons with receptive fields on **functionally** (rather than geometrically) corresponding points. Presumably, this reorganization of binocular inputs would have to occur during the sensitive period of visual cortical plasticity (see Hohmann & Creutzfeldt, 1975; Banks et al., 1975) and would then be maintained throughout life.

Alternatively, single vision in small-angle strabismus might be provided without such a shift in retinal correspondence through expanded sensory fusion (see Nelson, 1988; Schor, 1991): an extension of Panum's fusional area may result from a selective loss of disparity channels tuned to high spatial frequencies that would normally sense diplopia for small disparities (Holopigian et al., 1986). Much more commonly, double vision as well as confusion (resulting from dissimilar images being present simultaneously in corresponding parts of the two retinae) is obviated through partial or global *suppression* of information from one eye (see below).

In the past thirty years much has been learned about the anomalies of binocular vision associated with strabismus, from both psychophysical and neurophysiological

studies. Since the pioneering work of Hubel and Wiesel (1965), artificially induced strabismus has been widely investigated and has provided an increasingly convincing animal model of certain kinds of human squint. Misalignment of the eyes can be induced optically, by means of prisms placed in front of the eyes, or surgically, by interfering with the extraocular muscles. The latter technique involves removal of the muscle body (myectomy) or section of the muscle tendon (tenotomy) of either the lateral rectus (to generate esotropia) or the medial rectus (to give exotropia). More recently, natural, congenital strabismus has also been reported in cats (Grünau & Rauschecker, 1983; Hoffmann & Schoppmann, 1984) and in monkeys (Kiorpes & Boothe, 1981). Different forms of experimental strabismus have yielded a variety of results with respect to responses of neurons in the primary visual pathway, prevailing fixation patterns and the occurrence strabismic amblyopia (for review see Mitchell, 1988).

There is general agreement that strabismus, whether convergent (esotropia) or divergent (exotropia), leads to a marked reduction in the proportion of binocular neurons in the primary visual cortex, directly excitable through either eye, in both cats (e.g. Hubel & Wiesel, 1965; Yinon et al., 1975; Blakemore, 1976; Van Sluyters & Levitt, 1980; Singer et al., 1980; Mower et al., 1982; Tremain & Ikeda, 1982; Crewther & Crewther, 1990) and monkeys (e.g. Baker et al., 1974; Crawford & von Noorden, 1979, 1980; Crawford et al., 1984). This loss of binocularity has been taken to underlie the defects of binocular summation and stereopsis in strabismic animals (von Grünau, 1979) and humans (Lema & Blake, 1977; Levi et al., 1979). It has been interpreted as a consequence of a lack of correlation of activity relayed through the two eyes (Hubel & Wiesel, 1965; Blakemore, 1976; Van Sluyters & Levitt, 1980). The sensitive period for disruption of cortical binocularity through artificial strabismus coincides with that for monocular deprivation in the cat (Levitt & Van Sluyters, 1982a,b; see *Introduction*).

There is some neurophysiological evidence concerning the possible basis of the harmonious anomalous correspondence and residual stereopsis observed in some strabismic humans. Shlaer (1971) found that, in area 17 of kittens reared with a small

prism-induced vertical squint, the relative vertical positions on the retinae (vertical disparities) of the receptive fields of binocular neurons were shifted in the direction to compensate for the induced misalignment. After rearing with optically induced rotational misalignment of the eyes, Shinkman and Bruce (1977) and Dürsteler and von der Heydt (1983) also reported some degree of compensation in the positional or orientational disparity of the receptive fields of surviving binocular cells in kitten striate cortex. In area 18 (Cynader et al., 1984) and in the lateral suprasylvian cortex of strabismic cats (Sireteanu & Best, 1992) some binocular neurons appear to have receptive fields in anomalously corresponding retinal positions, which might allow registration of the images seen by the two eyes.

In the majority of cases of strabismus in humans, diplopia and confusion are avoided through suppression of vision in one eye, in particular in the central visual field (Sireteanu & Fronius, 1981; Sireteanu, 1982). In people who alternate fixation, such interocular suppression also switches from eye to eye, depending on which eye currently being used for fixation. In those who habitually fixate with the non-squinting eye, the deviating eye, which commonly suffers strabismic amblyopia (see above), is usually permanently suppressed when both eyes are open. Little is known of the site and nature of the suppressive mechanism that results in the virtual blanking of vision in the non-fixating eye, although psychophysical evidence points to a cortical origin (Blake & Lehmkuhle, 1976; Hess, 1991).

The origin of the neurophysiological deficits associated with strabismic amblyopia has also been a matter of controversy for a long time. From a number of studies, it now appears that sites and severity of acuity losses in strabismic cats vary with the techniques employed to induce squint (Cleland et al., 1985; Crewther & Crewther, 1988). The most radical form of surgically induced strabismus includes myectomy of two extraocular muscles and removal of connective tissue on one side of the eyeball, resulting in almost complete paralysis of the operated eye (Ikeda & Wright, 1976). Convergent strabismus produced that way has been reported to cause not only a shift in ocular dominance towards the normal eye (Tremain & Ikeda, 1982) but also to reduce

the spatial resolving power of LGN X-cells which receive input from the central retina of the operated eye (Ikeda & Wright, 1976; Jones et al., 1984), a relative shrinkage of these LGN cells (Tremain & Ikeda, 1982) and even a reduction in spatial resolution and contrast sensitivity of X-cells in the area centralis of the squinting eye (Ikeda & Tremain, 1979).

If, in contrast, esotropia (like exotropia) is induced by the surgically milder procedure of tenotomy of just one extraocular muscle, spatial resolution of retinal ganglion cells in the operated eye of strabismic cats and of geniculate X-cells receiving input from that eye are normal even in the presence of behavioural amblyopia (Cleland et al., 1982; Crewther et al., 1985; Crewther & Crewther, 1988). In these cats, the earliest site of acuity deficit may be the primary visual cortex (Crewther & Crewther, 1990; but see Blakemore & Eggers, 1978). It appears that the peripheral spatial sensitivity loss associated with the more severe surgical procedures is a side-effect of the surgery itself (Mitchell, 1988). This idea receives support from studies on the immediate, transitory acuity losses following tenotomy of the medial or lateral rectus (Mitchell et al., 1984). Most notable among the direct consequences of surgical induction of squint are temporary ischemia of the anterior segment of the eye (see Von Noorden, 1990, for review), interruption of proprioception from the severed extraocular muscles (see Frégnac & Imbert, 1984, for review) and drastic impairment of ocular motility (e.g. Cynader & Harris, 1980). These complications are not found to anywhere near the same extent in strabismic patients; milder forms of artificially induced squint are therefore likely to be better models of most cases of human strabismic amblyopia which is generally of cortical origin (e.g. Wald & Burian, 1944; Hess & Smith, 1977; for review Von Noorden, 1980; but see Arden et al., 1980).

The present study is concerned with the neurophysiological origin of strabismic suppression and its possible relationship to strabismic amblyopia. Analysis of visually evoked potentials in cats (Sclar et al., 1986) and of the responses of striate neurons (Xue et al., 1987b) suggests that binocular summation is generally lost in long-term esotropic cats, while some binocular facilitation is retained in the apparently monocularly driven

cells found in exotropes (see also Cynader et al., 1984). Interocular inhibition, as assessed by visually stimulating cells through one eye while electrically stimulating the optic nerve of the other side, showed asymmetries in esotropes but not in exotropes (Freeman & Tsumoto, 1983): responses through the deviating eye were more efficiently suppressed by the normal eye than *vice versa*. Only one very recent study has employed true binocular stimulation, of the kind that actually leads to suppression in humans, to investigate the neural mechanism of suppression in amblyopic cats: detailed analysis of responses of a few binocular units in area 17 showed some disinhibition of the responses through the deviating eye under monocular rather than binocular stimulation (Crewther & Crewther, 1993).

Here I present electrophysiological evidence that surgically induced strabismus (both exotropia and esotropia) virtually abolishes the disparity-specific binocular interactions that are such distinctive features of normal striate neurons, and leaves pronounced, non-specific interocular suppression in the majority of monocular or weakly binocular cells.

4.1. Methods

Animals

Data presented here were obtained from five strabismic cats as well as from one rhesus monkey (*Macaca mulatta*) bred in a laboratory colony.

All cats were rendered strabismic by tenotomy on postnatal day 10, i.e. just after eye-opening. In two cats, the right eye was made exotropic under ketamine hydrochloride general anaesthesia and with topical anaesthetic (Amethocaine) instilled in the conjunctival sac. Through a small incision in the conjunctiva, the medial rectus muscle was secured with a muscle hook and it was disinserted from its attachment to the globe. In three other animals, tenotomy of the lateral rectus of the right eye was performed in the same way to induce esotropia. Recovery was rapid, with no evidence of pain or distress. The animals were checked frequently for the first few days after surgery to be sure that the lids of the operated eye remained open and thereafter to ensure that the operated eye did not return to its normal position (a not uncommon occurrence after simple tenotomy). All strabismic animals were reared in an open colony room until at least one year of age.

Prior to the electrophysiological experiments, the fixation patterns of four cats (DS2, CS1, 2 and 3) were assessed by means of the *cover tests* (Duke-Elder & Wybar, 1973). The animal was held facing the observer, who attracted its attention to his face by making movements and noises with his mouth. A window behind the observer provided a distinct reflection in the cat's corneae, which aided judgement of eye movement. A piece of card was then used to cover and uncover one eye at a time, or was moved quickly from eye to eye, and the resulting patterns of fixation and refixation were judged. Even for the animal with the smallest squint (CS1), I was fairly confident that this procedure established whether the cat habitually fixated with the non-operated eye (monocular squint) or whether it could hold fixation with either eye (alternating squint). The fifth animal (DS1) had a very large-angle exotropia and it was evident from the orientation of its head during locomotion and active exploration of moving objects that it habitually employed the non-squinting eye for fixation.

Table 4-1 summarizes the test results and gives the angle of squint for each cat, estimated from the separation of the projections of the areae centrales during the recording experiment (see below). Values were corrected for the average divergence (4°) of the visual axes observed in normal paralysed cats (Nikara et al., 1968). Although it is difficult to estimate the angle of strabismus accurately in awake cats, I had the feeling that it was usually larger than the value seen under paralysis.

Observation of reflex eye movements during rotation of the head and spontaneous changes of fixation suggested that, for four of the animals, the operated eye was quite mobile and that movements were roughly conjugate, except in extreme duction towards the tenotomized muscle. Only in CS2, which had an esotropia of very large angle (Table 4-1), were movements of the deviating eye much more restricted.

Table 4-1: Direction and angle of squint, and fixation patterns of strabismic cats

Animal	Direction and angle of squint	Fixation pattern
DS1	exo 30°	normal eye only
DS2	exo 8°	alternating
CS1	eso 4°	normal eye only
CS2	eso 34°	normal eye only
CS3	eso 10°	normal eye only

The rhesus monkey (identification #115) was 11 years old at the time of recording. It had received a myotomy of the lateral rectus in the right eye at the age of 19.5 weeks (4.5 months), and had developed an esotropia of about 30° (20° after paralysis, judged by plots of the foveae). It fixated unilaterally with the unoperated eye and showed reduced motility of the squinting eye, which could not be abducted further than to the midline of the visual field. Both eyes were slightly hypermetropic (+1 D). A

preferential looking test with Teller acuity cards (Teller et al., 1978) was performed a day prior to the recording. With the unoperated eye, the monkey could detect gratings of up to 19.5 c/deg (tested with both eyes open) and failed at 28.5 c/deg. The test revealed clear amblyopia in the deviating eye: with the normal eye patched, the monkey's performance was above or at criterion level for up to 3.6 c/deg and fell below criterion level for a grating of 4.9 c/deg. Thus, the acuity deficit in the deviating eye was 2.4 octaves compared to the normal eye.

Surgery

For the cats, surgical procedures were as described in the previous chapter. All micro-electrode penetrations were made at stereotaxic positions corresponding to the representation of the centre of the visual field in the primary visual cortex, area 17, of the left hemisphere (P5, L1.5).

For the macaque, anaesthesia was induced with ketamine hydrochloride (20 mg/kg i.m.) and maintained with alphaxalone/alphadolone (Saffan®) i.v. during tracheal cannulation and the exposure of the brain *via* a very small craniotomy and durotomy. During recording the animal was anaesthetized and paralysed with a continuous i.v. infusion of sodium pentobarbitone (2 mg/kg/h, supplemented if necessary to maintain anaesthesia) and pancuronium bromide (Pavulon®, 0.1 mg/kg/h). The infusion solution was administered at a rate of 6 ml/h. The animal was artificially hyperventilated with room air plus carbon dioxide (CO₂); stroke rate and volume were adjusted to maintain an end-tidal CO₂ level of 36-40 mm Hg. E.E.G. and E.C.G. were constantly recorded to monitor the state of anaesthesia. Body temperature was kept at 37.5°C by means of a feedback-controlled heating-pad.

Pupils were dilated with atropine hydrochloride, and the lids retracted by means of fine sutures. Chloromycetin was applied to prevent the corneae from infection. Gas-permeable contact lenses were placed on each cornea and 3-mm artificial pupils were placed in front of the eyes as well as additional lenses for focusing the visual stimuli

(see below) on the retinae. A 15Δ prism¹ was placed base-out in front of the right eye in order to reduce its deviation so as to bring the receptive fields in the two eyes to the centres of the two cathode-ray tube (CRT) displays (see below).

In the macaque, a single, long micro-electrode penetration was made in V1 of the right hemisphere just posterior to the lunate sulcus, angled at 10° towards the midline. The craniotomy was sealed with agar to protect the exposed cortex and to minimize pulsations. Furthermore, prednisolone acetate was administered i.m. to prevent inflammation and cortical oedema.

Recording and visual stimulation

Recording and visual stimulation procedures in cats and monkey were identical to those described in Chapter 3. Briefly, receptive fields of single units were plotted on a translucent tangent screen and characterized qualitatively with moving and stationary bars or spots of light of medium contrast projected on to the screen (see Blakemore & Price, 1987).

For quantitative tests, animals dichoptically viewed two CRT screens via front-silvered mirrors. The screens were placed at a distance of 57 cm (for the cats) or 114 cm (for the monkey) from the animal. The positions of the receptive fields in the two eyes were mapped onto the centres of the screens. In case of monocular units, the display for the 'silent' eye was centred on the position corresponding to that for the dominant eye, determined by mapping background activity or by prior recording from neighbouring cells dominated by that eye.

Drifting sinusoidal gratings (mean luminance 17.5 cd/m^2) were generated by a 'Picasso' (Innisfree) image synthesizer. External control of the Picasso as well as data acquisition and analysis were performed by a Visual Stimulation package ('VS', Cambridge Electronic Design). Monocular tuning curves were obtained as described in the previous chapter. Binocular interactions were then tested by constantly stimulating the dominant eye with a drifting grating (the 'conditioning' stimulus) of optimum

¹ Δ signifies prism diopter; $1\Delta = 0.573^\circ$

orientation and spatial frequency and medium contrast [0.18 - 0.35, where contrast = (maximum-minimum luminance)/(2 x mean luminance)], and intermittently presenting to the other eye drifting gratings varying in orientation, spatial frequency, or spatial offset (for details see Chapter 3). A cell was considered to show *binocular interaction* if the response to binocular stimulation differed significantly (in a two-tailed *t*-test) in strength from the response to stimulation of the dominant eye alone.

Histology

At the end of each electrode penetration small electrolytic lesions were made along the track during withdrawal of the electrode. Animals were given an overdose of pentobarbitone and perfused transcardially with phosphate-buffered saline followed by 4% paraformaldehyde. Electrode tracks were reconstructed from 50- μ m coronal sections stained with cresyl violet.

4.2. Results

Cats

In each cat, two to four vertical penetrations were made, and cells were recorded from all layers of the striate cortex, usually at intervals of about 100 μ m. In the two exotropic animals, 87 cells were recorded, 38 of which (11 simple, 27 complex) were quantitatively tested for binocular interaction, after initial monocular characterization. In the three esotropic animals, 112 units were recorded and 47 were tested binocularly (12 simple, 35 complex). The receptive field centres of all cells were within 4 deg of the area centralis.

Stimulation of the non-dominant eye statistically significantly affected the response to stimulation through the dominant eye for 28 cells from exotropic animals (74% of the total of 38 quantitatively analysed units) and for 30 cells (64% of the total 47) recorded from esotropic cats.

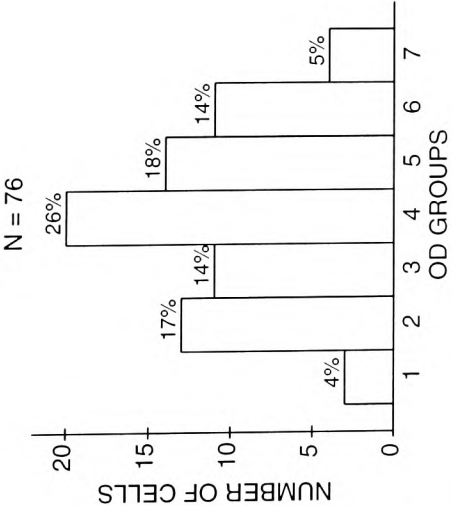
Monocular response properties

In all strabismic animals, the proportion of cells in which responses could be elicited through stimulation of either eye ('binocular' cells) was distinctly lower than in normal cats. Of the total of 199 units, only 62 (31%) were binocular, compared to 91% in the sample of 76 units recorded from five normal animals under identical conditions. For the individual strabismic animals, the fraction of neurons that were exclusively driven through one eye (ocular dominance (OD) groups 1 or 7; Hubel & Wiesel, 1962) varied between 56% (in CS2) and 76% (in CS3). Only 3% of all cells were equally well driven through either eye (OD group 4), compared to 26% in the normal animals. OD distributions for each of the five strabismic cats, as well as an accumulated histogram of the data from the five normal animals, are shown in Fig. 4-1.

Figure 4-1

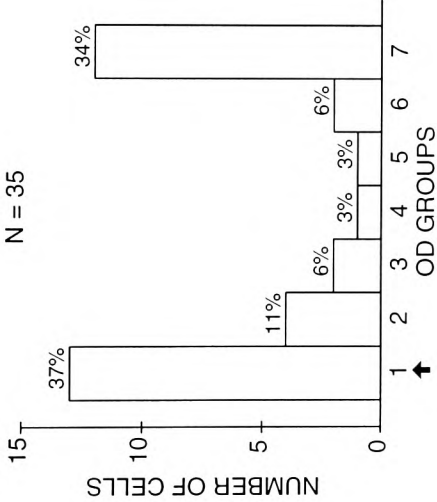
Ocular dominance (OD) distributions of cells recorded from normal and strabismic cats. The top left histogram ('NORMAL') shows accumulated data from five normal animals, while the remaining histograms represent individual OD distributions for each of the five strabismic animals, subdivided into exotropes (one, DS2, being the only animal with alternating fixation) and esotropes. Animal identification (see Table 4-1) and the total number of cells recorded are given at the top of each histogram. Neurons were classified in one of seven OD groups following the scheme devised by Hubel and Wiesel (1962): cells in groups 1 and 7 are monocularly driven by the contralateral and ipsilateral eye, respectively; cells in group 4 are equally responsive through the two eyes. Since recordings in the squinting animals were taken from the hemisphere contralateral to the operated eye, OD group 1 (filled arrows) signifies complete dominance of the operated eye, while OD group 7 represents cells exclusively driven through the non-operated eye.

NORMAL

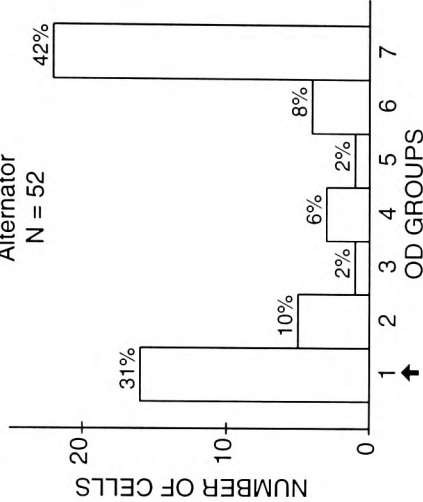


EXOTROPES

DS1
N = 35

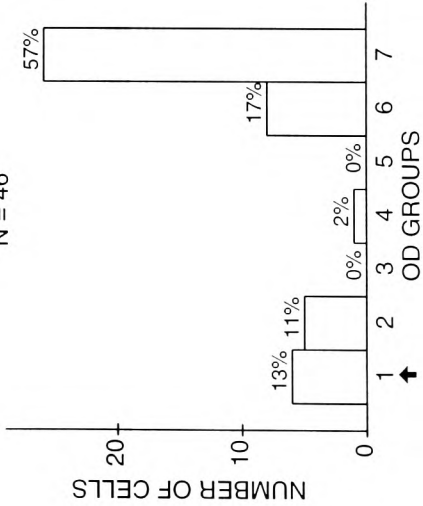


DS2
Alternator
N = 52

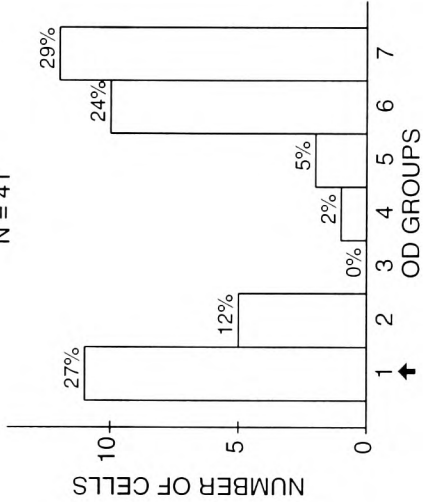


ESOTROPES

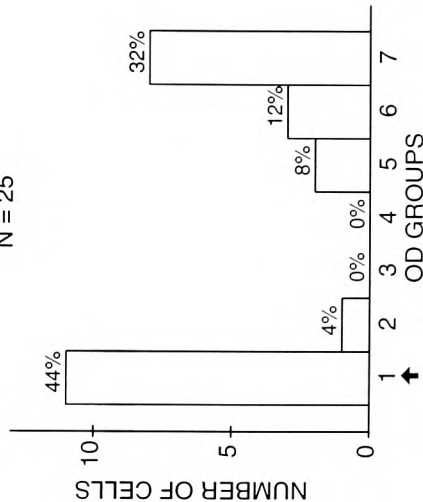
CS1
N = 46



CS2
N = 41



CS3
N = 25



Four of the five strabismic animals showed no obvious bias in the OD distribution towards either eye. Only in CS1 (4° of esotropia) was the histogram apparently skewed towards the non-deviating eye. This bias was nominally statistically significant (χ^2 -test, $p < 0.005$), but such a result might well be produced by non-uniform sampling across the cortical OD columns (see **Discussion**). Certainly there was no consistent difference between the form of the OD distribution in the animals that habitually fixated with their non-operated eye and the one animal (DS2) with alternating fixation (and therefore presumably without severe amblyopia).

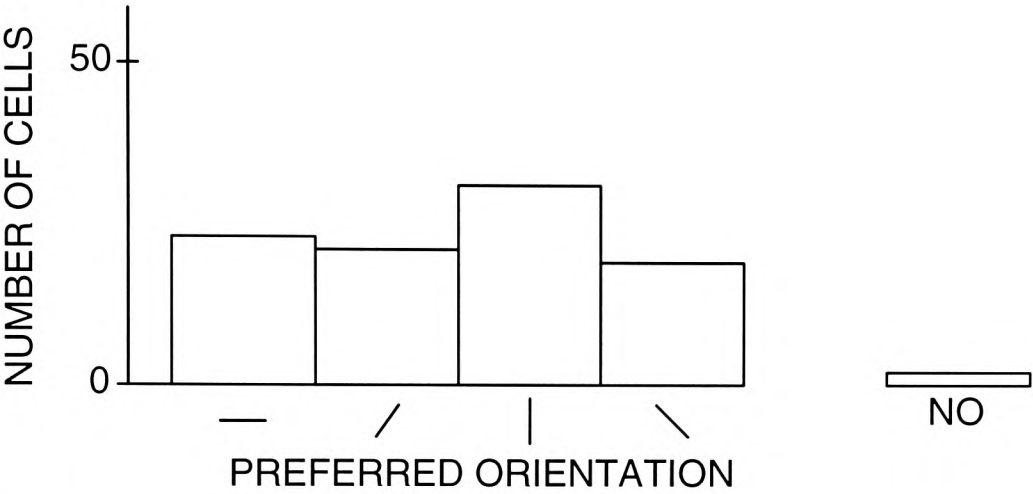
Apart from the breakdown of binocularity, cells recorded from the strabismic cats did not show any obvious abnormalities, irrespective of whether they were dominated by the non-operated or by the deviating eye. There was no evidence of a shift of correspondence (ARC) to compensate for the squint. In each penetration, all the receptive fields encountered, of both monocular and binocular cells, were on roughly geometrically corresponding points in the two eyes (relative to the projections of the *areae centrales*).

The sharpness of orientational tuning was quantitatively assessed for a sample of cells dominated by each eye in all strabismic cats. A Fourier analysis of the responses to drifting gratings varying pseudorandomly in direction of drift was performed (see Wörgötter & Eysel, 1987; Wörgötter et al., 1990). Curves were fitted to the data points, taking into account the zero- to eighth-order Fourier components, and tuning widths were calculated. For 33 cells dominated by the operated eye, the mean half-width at half-height was $24.4^\circ \pm 8.3^\circ$ (SD). For 48 cells dominated by the non-deviating eye, mean half-width at half-height was $21.3^\circ \pm 8.4^\circ$, and for 44 cells recorded from normal animals the mean value was $22.2^\circ \pm 7.0^\circ$, similar to that reported by others (e.g. Henry et al., 1974; Rose & Blakemore, 1974).

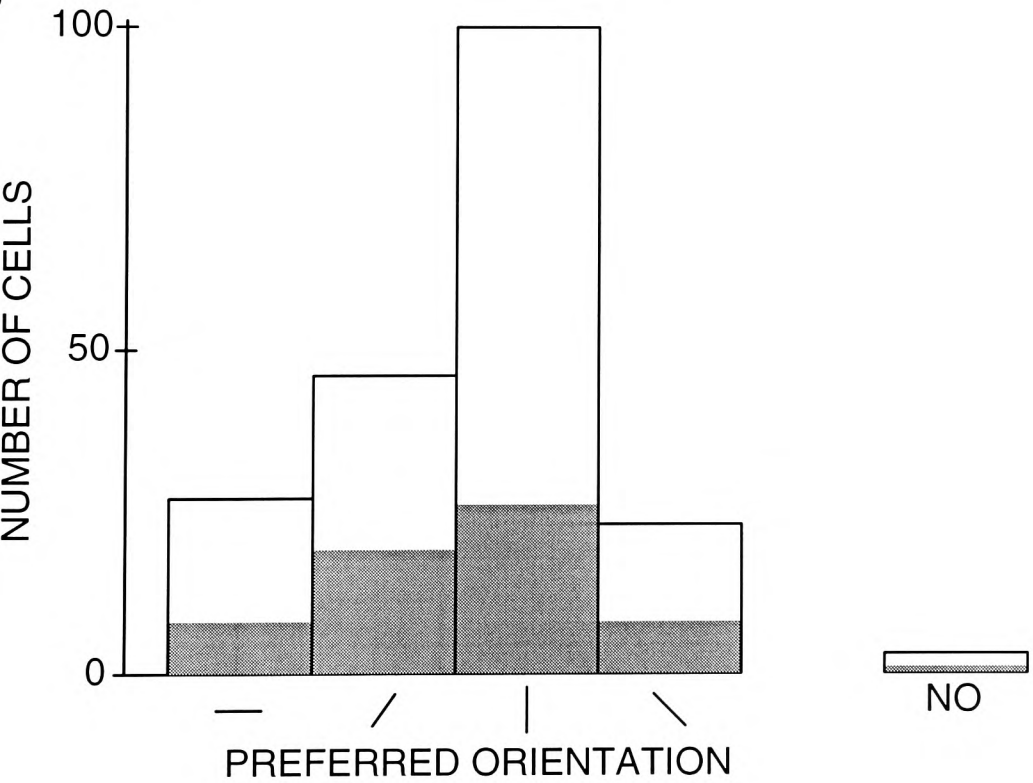
Figure 4-2

Distribution of preferred orientation for 96 cells recorded from V1 in six normal cats (**A**) and, 199 cells from five strabismic cats (**B**). Numbers of cells are plotted against orientation preference, classified into one of four bins of $\pm 22.5^\circ$, corresponding to near-vertical (|) near-horizontal (—) and near-oblique (/ and \). The shaded bars in part **B** represent binocular cells (OD groups 2-6).

A



B



Although the **precision** of orientational selectivity of cells dominated by the squinting eye appeared unimpaired, the distribution of **preferred** orientations of cells recorded from strabismic cats differed markedly from that found in normal control animals (Fig. 4-2). While in the latter all orientations were roughly equally represented, neurons from the squinting cats showed a clear bias towards **vertical** preferred orientations, irrespective of whether cells were dominated by the deviating or the normal eye and whether they were monocularly or binocularly driven. However, among the binocular cells the incidence of near-vertical preferred orientations was slightly lower (42%) than in the total population (50%).

Tuning curves for spatial frequency were determined by measuring responses to gratings of optimal orientation and direction of motion, all drifting at the same temporal frequency but varying pseudorandomly in spatial frequency from presentation to presentation. The value of spatial frequency, on the high-frequency side of the tuning curve, at which the response of the cell fell to the spontaneous level was taken as the 'neural acuity' or cut-off spatial frequency of the cell. Although the sample of quantitatively analysed cells dominated by the operated eye was relatively small, in none of the five strabismic cats were cut-off frequencies significantly lower for cells dominated by the deviating eye compared with those dominated by the non-operated eye of the same animal, although a minor (non-significant) difference, by an average 0.3 cycles/deg, was found in esotropic cat CS1. However, I did not systematically test neural acuity through the deviating eye in binocular cells dominated by the normal eye, for which Crewther & Crewther (1990) have reported mean differences in neural acuity in cats with behavioural amblyopia.

Strabismus virtually eliminates orientation-dependent binocular facilitation

For disparity-selective cells in area 17 of normal cats (e.g. Barlow et al., 1967; Nikara et al., 1968), including a proportion of those that appear to be monocularly driven, iso-oriented dichoptic gratings produce facilitation or summation at one relative interocular phase and occlusion when the gratings are 180° out of phase in the two eyes (Ohzawa

and Freeman, 1986a, b). Before studying the effects of varying the orientation of the grating presented to the non-dominant eye, I displayed gratings of identical orientation, direction, and spatial and temporal frequency (optimum for the dominant eye) to the two eyes and altered the relative spatial phase (or disparity) to search for such disparity-selective interactions.

The results are summarized in Table 4-2. Out of 85 cells tested in all five strabismic animals, only eight (9%) showed any enhancement of the monocular response when an identical grating was introduced to the other eye, and only five exhibited genuine facilitation in the sense that the binocular response was more than the sum of the monocular responses (see Fig. 4-3A for a typical example). There were no obvious differences between animals (whether esotropic or exotropic, alternators or non-alternators) in the proportion of cells showing binocular summation (Table 4-2). All but one of the eight neurons demonstrating some degree of binocular enhancement (which were encountered in all layers of the cortex) were initially classified as binocularly driven (i.e. they were responsive through either eye alone) and they included all four cells of OD group 4 and three out of eight of the cells that were only slightly dominated by one eye (OD groups 3 and 5). For these cells, the amount of summation (or facilitation) did not vary significantly with the relative interocular phase (disparity) of iso-oriented gratings, with one exception (Fig. 4-4): a weak cyclical variation of the strength of facilitation (but no occlusion), indicative of rudimentary disparity-sensitivity, was displayed by the only simple cell in this group (recorded from CS1, with small-angle esotropia).

Table 4-2: Occurrence of orientation-dependent *summation* and orientation-independent *suppression* in area 17 of strabismic cats: numbers in brackets refer to strictly monocular units (OD groups 1 or 7). Rows marked OD4 refer to cells that were equally responsive through either eye alone (OD group 4). The final two columns give the average percentage suppression, below the monocular level, caused by an iso-oriented grating ($\Delta\text{Or} = 0^\circ$) and an orthogonally oriented grating ($\Delta\text{Or} = 90^\circ$) presented to the non-dominant eye, for all cells showing orientation-independent suppression.

Cat (cf. Table 4-1)	Eye dominant for cell	Total number of cells tested	Sum- mation: number of cells	Sup- pression: number of cells	Depth of suppression for $\Delta\text{Or} = 0^\circ$ $\Delta\text{Or} = 90^\circ$ (mean $\pm$ SD)	
DS1	normal	11 (8)	0	9 (7)	67% $\pm 16\%$	60% $\pm 14\%$
	exo	9 (3)	1	6 (2)	51% $\pm 26\%$	58% $\pm 32\%$
	OD4	0	0	0	/	/
DS2 (Alter- nator)	normal	9 (5)	0	5 (3)	56% $\pm 21\%$	45% $\pm 33\%$
	exo	7 (4)	0	4 (2)	46% $\pm 4\%$	48% $\pm 16\%$
	OD4	2	2	0	/	/
CS1	normal	10 (6)	0	6 (3)	47% $\pm 20\%$	44% $\pm 8\%$
	eso	6 (3)	1(1)	0	/	/
	OD4	1	1	0	/	/
CS2	normal	11 (6)	2	5 (4)	60% $\pm 16\%$	55% $\pm 14\%$
	eso	7 (5)	0	5 (3)	55% $\pm 9\%$	44% $\pm 12\%$
	OD4	1	1	0	/	/
CS3	normal	8 (7)	0	7 (6)	48% $\pm 27\%$	45% $\pm 16\%$
	eso	3 (3)	0	0	/	/
	OD4	0	0	0	/	/

Figure 4-3

Peri-stimulus time histograms (PSTHs) chosen to represent the variety of responses observed during binocular stimulation in strabismic cat cortex. PSTHs were accumulated over 6-8 trials; bin width, 125 ms. Each cell was initially stimulated with a grating of optimal orientation and spatial frequency (contrast = 0.35) through the dominant eye alone (indicated by an unfilled horizontal bar above the histogram). After 5 sec (marked with an arrow) a grating of the same spatial frequency (contrast = 0.7) and either the same orientation (indicated as || above PSTH) or orthogonal orientation (| —) appeared in the non-dominant eye. Binocular exposure continued for the 5-sec period marked by the filled bar.

A: Complex cell from exotrope DS1, slightly dominated by the operated eye (OD3), displaying close-to-normal tonic facilitation for iso-oriented gratings.

B: Complex cell from esotrope CS1, exclusively driven through the operated eye (OD1). This very unusual cell showed transient augmentation following stimulation of the silent eye with gratings of any orientation, even orthogonal-to-optimum.

C,D: Complex cell from esotrope CS2, excitable only through the non-operated eye (OD7). For this cell, the latency of orientation-independent suppression was around 375 ms for both iso-oriented (**C**) and orthogonally oriented gratings (**D**).

E: Complex cell from exotrope DS1, dominated by the deviating eye (OD1). This cell exhibited interocular suppression, with relatively rapid onset, irrespective of interocular orientation difference.

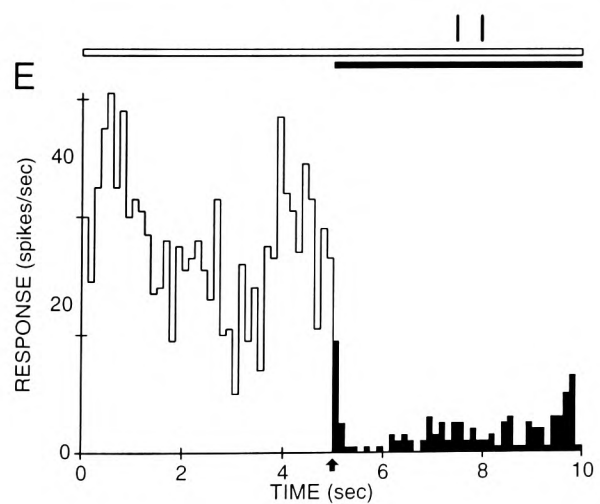
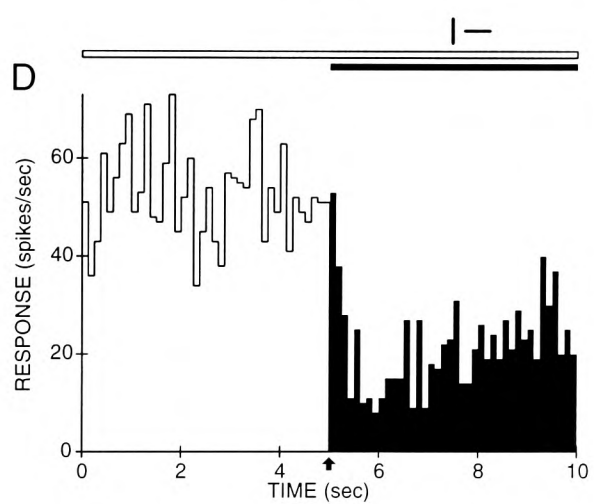
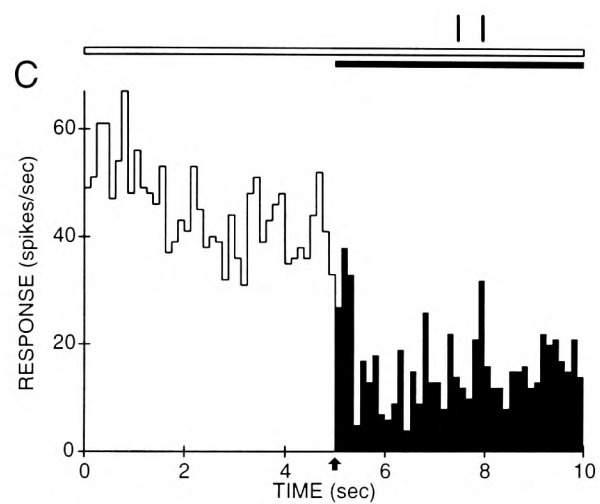
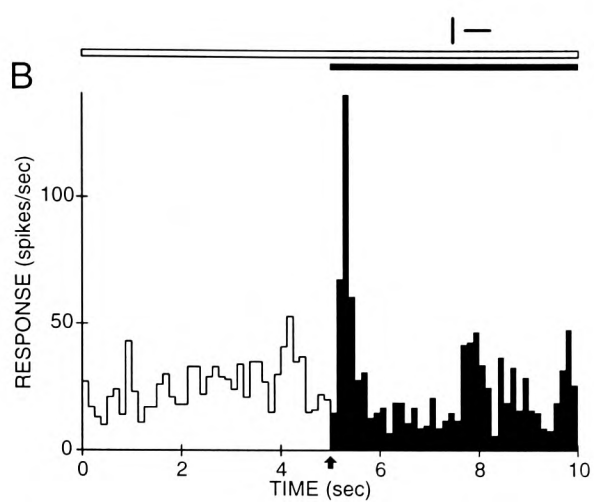
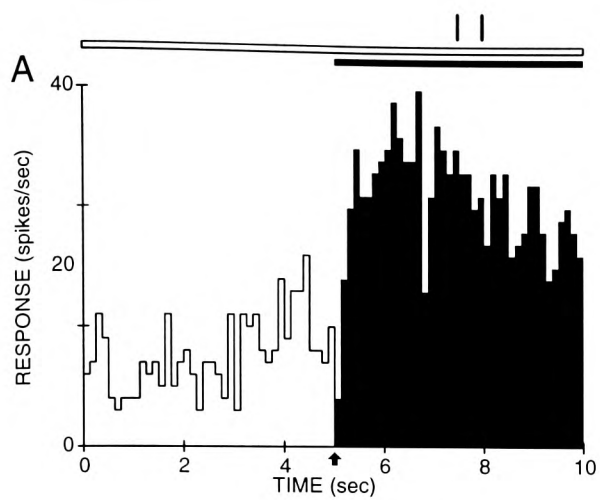


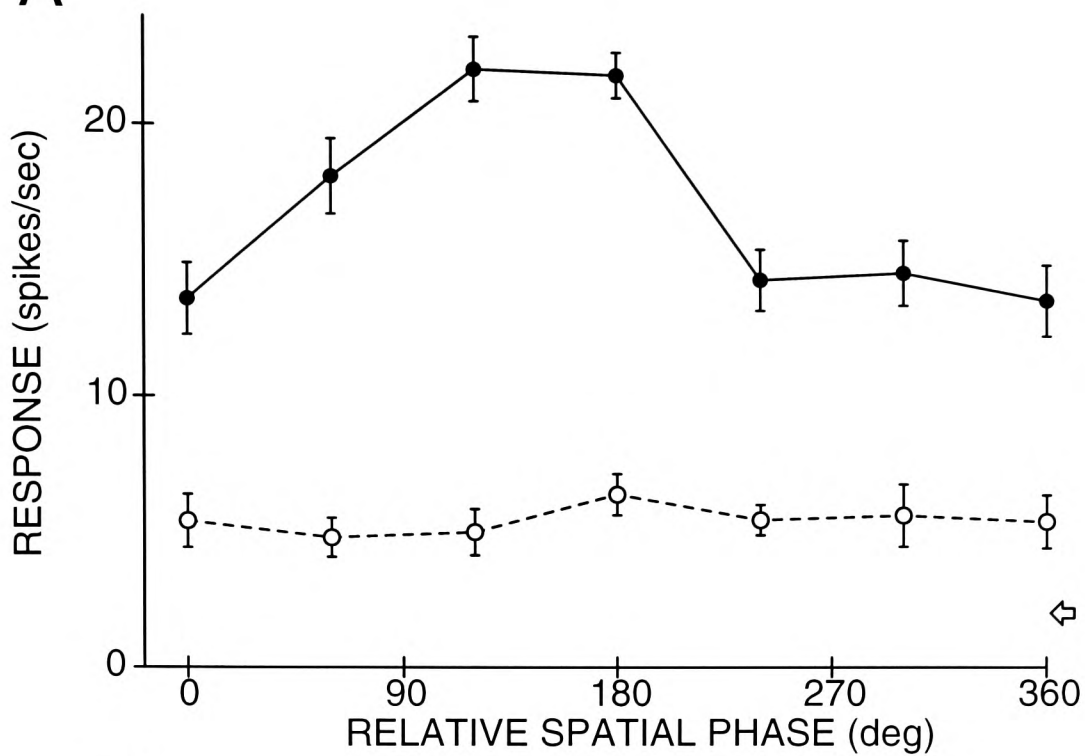
Figure 4-4

Binocular responses as a function of relative disparity for a simple cell, recorded in esotrope CS1, which was equally responsive through either eye alone (OD group 4). The spatial phase of the optimally oriented drifting grating presented to the operated eye (contrast = 0.35; spatial frequency = 0.56 c/deg, i.e. cycles per degree of visual angle) was fixed at an arbitrary value while that of the grating presented to the other eye was varied in phase.

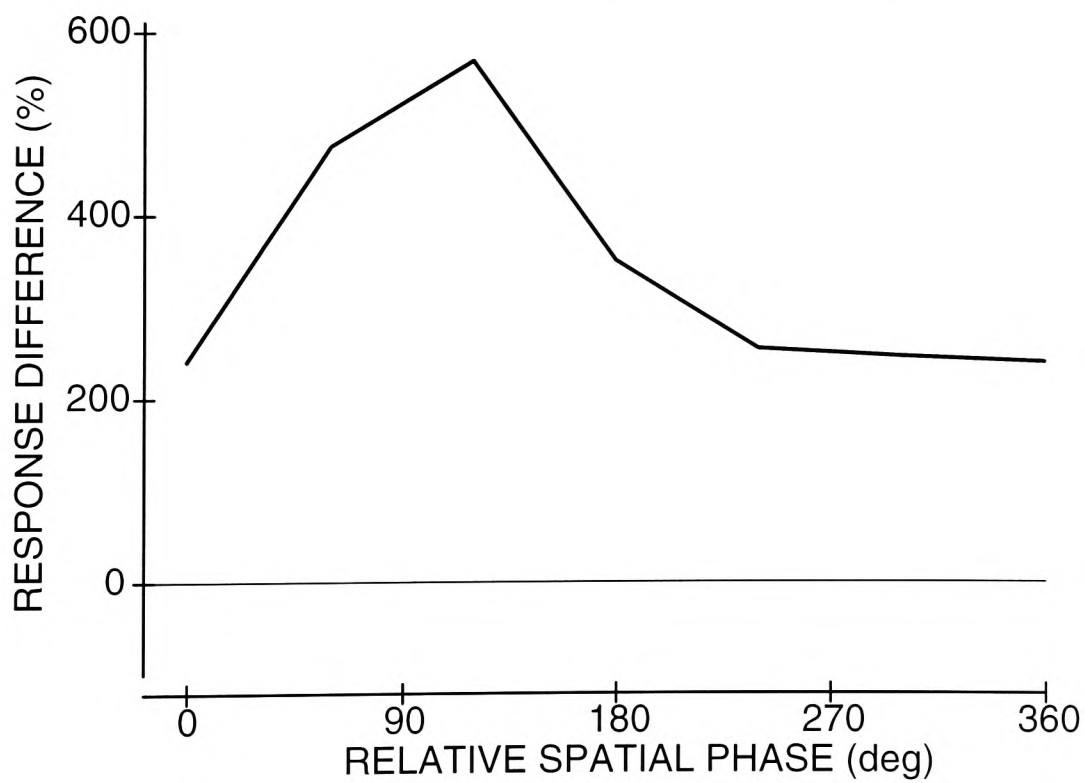
A: Mean responses in spikes/sec ($\pm$ SEM, $n = 4$ presentations per data point) are plotted against the spatial offset or phase angle between the two gratings. Unfilled circles plot the control values during preceding periods of monocular stimulation. The arrow indicates the mean level of spontaneous discharge, measured during blank presentations.

B: *Binocular interaction function*, plotting the difference between the response to the two gratings and that to the conditioning grating alone as a percentage of the response to the conditioning grating (after subtraction of the spontaneous discharge), at each relative interocular phase.

A



B



In the previous chapter, I showed that the majority of binocular striate neurons in normal cats show interocular suppression when stimulated binocularly with orthogonally oriented gratings, under conditions identical to those used in this study. Among the seven binocular cells in strabismic animals that exhibited binocular summation/facilitation, five showed varying degrees of suppression with orthogonal or near-orthogonal gratings. An example (a complex cell slightly dominated by the deviating eye in exotropes DS1) is shown in Figure 4-5. Polar plots in Fig. 4-5A represent direction/orientation tuning curves obtained through each eye monocularly. Part **B** illustrates interocular interactions: the dominant (operated) eye was continuously stimulated with an optimally oriented, drifting grating while gratings of various directions of drift (and therefore different orientations) were presented intermittently, in pseudorandom sequence, to the corresponding region of the visual field in the other (non-operated) eye. Filled circles plot responses during these binocular presentations as a function of interocular difference in orientation, while the corresponding unfilled circles at the same position on the abscissa plot the mean discharge during the periods of monocular stimulation immediately preceding binocular presentations with that particular combination of orientations.

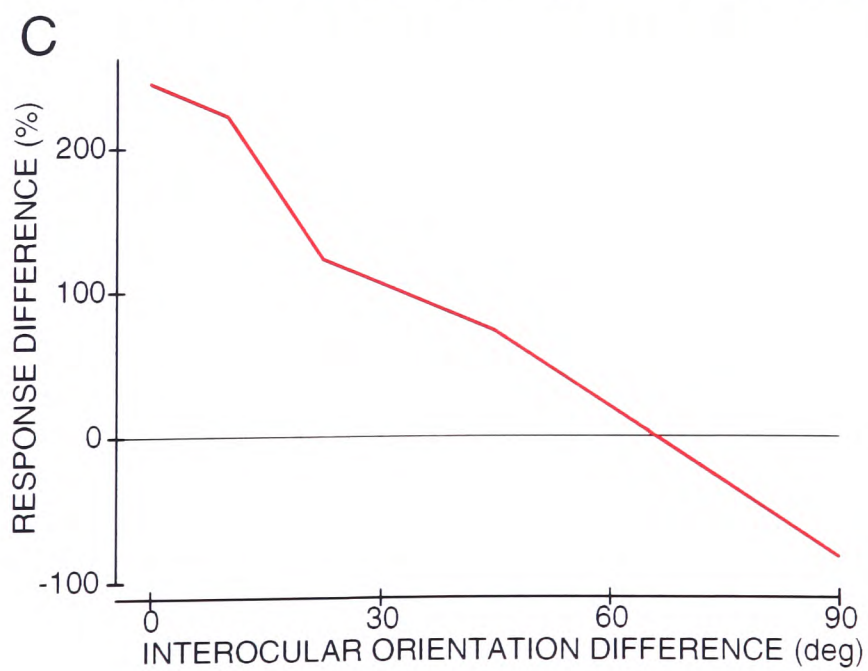
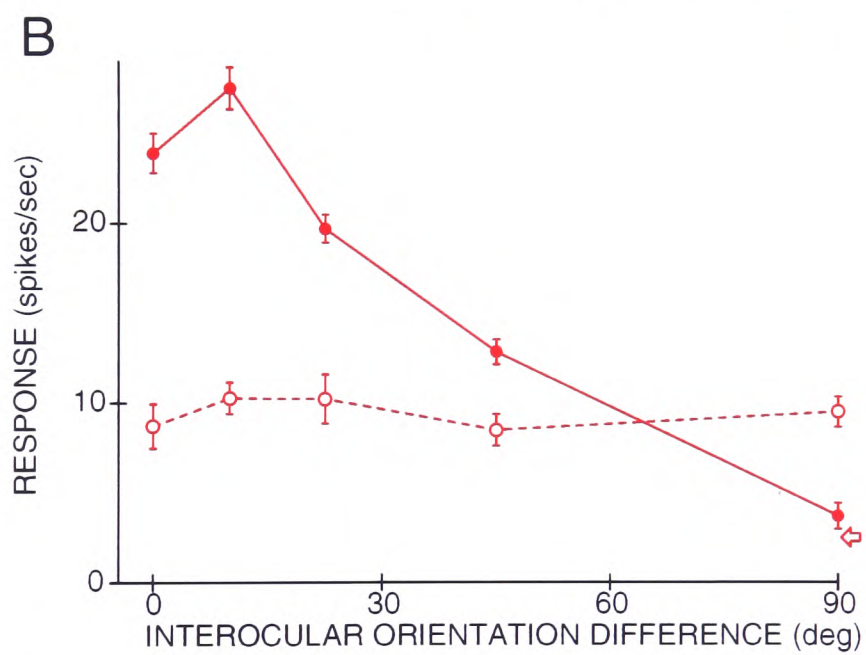
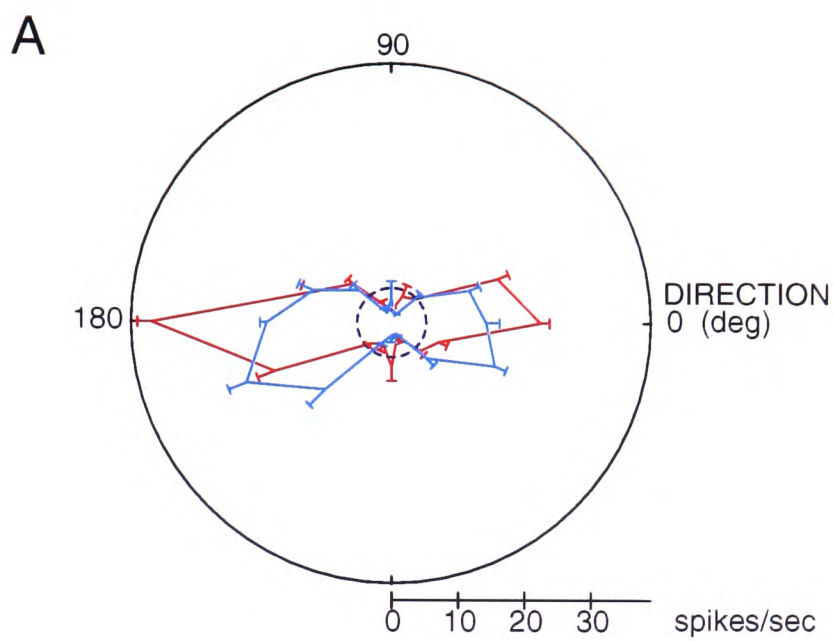
Figure 4-5

Orientation dependence of binocular interactions in a layer 5 complex cell from exotrope DS1. This cell (the same as in Fig. 4-3A) was slightly dominated by the operated eye (OD3).

A: Polar plot of orientation tuning curves obtained with monocular stimulation through the deviating (dominant) eye (red lines) and the normal (non-dominant) eye (blue lines), respectively. Mean responses ($\pm$ SEM, $n = 4$) are plotted as a function of the direction of drift of a grating (contrast = 0.7) of optimal spatial frequency (0.56 c/deg, i.e. cycles per degree of visual angle) presented to one eye alone. The interrupted circle in the centre indicates the mean level of spontaneous discharge.

B: Results of the binocular interaction protocol. The dominant eye was continuously stimulated with a 'conditioning' stimulus whose direction of drift was 180° , corresponding to the optimum obtained from the polar plot in **A** (contrast = 0.18; spatial frequency = 0.56 c/deg). The abscissa indicates the difference in orientation between the stimuli shown to the two eyes. Gratings (contrast = 0.7; spatial frequency = 0.56 c/deg) were presented to the non-dominant (normal) eye at five different orientations, over a 90° range, clockwise from the orientation of the optimal conditioning stimulus. Each filled circle ($\pm$ SEM, $n = 6$; joined by solid red lines) plots the mean firing rate during the periods of binocular stimulation with gratings differing in orientation (and direction of drift) in the two eyes by the angle shown on the abscissa. Each unfilled circle ($\pm$ SEM, $n = 6$; linked by interrupted red lines) plots mean responses during the periods of monocular stimulation preceding those presentations with the particular combination of gratings plotted on the abscissa. The arrow indicates the mean level of spontaneous discharge, measured during blank presentations.

C: *Binocular interaction function*, plotting the response difference as a percentage of the corresponding monocular response (see text), at each interocular orientation difference.



However, 28 out of the 35 binocularly driven cells tested (80%) did *not* show any augmentation of the response to a grating in the dominant eye alone when an identical grating was added to the non-dominant eye, whatever its relative spatial phase, despite the fact that the latter stimulus would make the cell respond when presented on its own.

The one monocular cell exhibiting some excitatory binocular interaction was very abnormal in that a clear but *transient* augmentation of the response (lasting for only about 0.6 sec) was observed immediately after the appearance of the grating in the silent eye, irrespective of the orientation of the silent-eye stimulus (see Fig. 4-3B). The *tonic* discharge over the remainder of the 5-sec period of binocular stimulation did not differ significantly from the dominant-eye response.

None of the remaining 49 apparently monocularly driven units tested showed *any* increase in response during binocular stimulation, whatever the orientation of the gratings. Indeed, 30 of them (60%) exhibited consistent interocular suppression, whatever the stimulus in the silent eye (see below).

Orientation-independent interocular suppression

The majority of all cells, even 17 out of the 35 that responded to monocular stimulation of either eye, were profoundly *suppressed* when the non-dominant eye was stimulated while the cell was responding to an optimal grating in the dominant eye: the level of response was reduced by up to 90% compared to that elicited monocularly through the dominant eye. Unlike in normal animals (Chapter 3), this interocular suppression was usually virtually independent of the orientation of gratings shown to the non-dominant eye, i.e. suppression of the dominant-eye response was just as strong when the grating in the other eye was of the same orientation as the optimal grating in the dominant eye as when it was orthogonal (whatever its spatial phase) (see Fig. 4-3C,D). This was the case for 24 units (63% of the total) from exotropic animals as well as for 23 units (49% of the total) from esotropes.

Fig. 4-6 shows an example of a complex cell, monocular driven through the non-deviating eye, recorded in the supragranular layers in the large-angle esotropic cat, CS2.

Part **A** is a polar plot showing the orientation tuning of this neuron for stimulation through the dominant eye. Fig. 4-6**B** illustrates binocular interactions in the same manner as Fig. 4-5**B**, plotting the binocularly elicited response (filled circles) against the difference in orientations between the optimally oriented grating present in the dominant eye and gratings of various orientations presented to the silent eye; unfilled circles at the same position on the abscissa again plot the mean discharge during the periods of monocular stimulation immediately preceding binocular presentations with that particular combination of orientations. In order to take account of any chance fluctuations in responsiveness, as indicated by variation in the monocular control values, the level of response during binocular stimulation was calculated as a percentage of the corresponding monocular response:

$$\frac{(\text{binocular response} - \text{monocular response}) \times 100\%}{(\text{monocular response} - \text{spontaneous discharge})}$$

Part **C** plots this *binocular interaction function*: interocular suppression (about 75% reduction in response for this cell) was essentially independent of the orientation of the gratings shown to the silent eye. Further examples of non-selective suppression are shown for two simple cells recorded from exotropic animals, one dominated by the non-operated eye of the non-alternator, DS1 (Fig. 4-7), the other dominated by the operated eye of the alternator, DS2 (Fig. 4-8), as well as for a complex cell dominated by the operated eye of esotrope CS2 (Fig. 4-9).

Orientation-independent suppression was seen for cells in all cortical layers but was more frequent among neurons from supragranular layers (33 out of 51 units) and infragranular layers (8/12) than in layer 4 (6/22).

Figure 4-6

Orientation tuning of binocular interactions in a layer 2/3 complex cell recorded in esotropic cat CS2, which was monocularly driven through the non-operated (ipsilateral) eye (OD7).

A: Mean response (+ SEM, $n = 4$) is plotted on polar coordinates as a function of the direction of drift of a grating (contrast = 0.7; spatial frequency 0.56 c/deg) presented to the dominant (non-operated) eye alone.

B: Results of the binocular interaction protocol, as in Fig. 4-5B. The dominant eye was continuously stimulated with a 'conditioning' stimulus whose direction of drift was 202.5° , corresponding to the optimum obtained from the polar plot in **A** (contrast = 0.35; spatial frequency = 0.56 c/deg). The abscissa indicates the difference in *orientation* between the stimuli shown to the two eyes. Filled circles ($\pm$ SEM, $n = 8$) plot the mean firing rate during binocular stimulation with gratings differing in orientation in the two eyes by the angle shown on the abscissa. Each unfilled circle ($\pm$ SEM, $n = 8$) plots mean responses during the periods of monocular stimulation preceding those presentations with the particular combination of gratings plotted on the abscissa. The arrow indicates the mean level of spontaneous discharge. Note that even identically oriented gratings (zero on the abscissa) produced strong suppression.

C: *Binocular interaction function*, plotting the response during binocular stimulation, expressed as a percentage of the corresponding monocular response (see text), at each interocular orientation difference. Strength of suppression was constant (about 75% of the monocular responses) over the range of orientation differences tested.

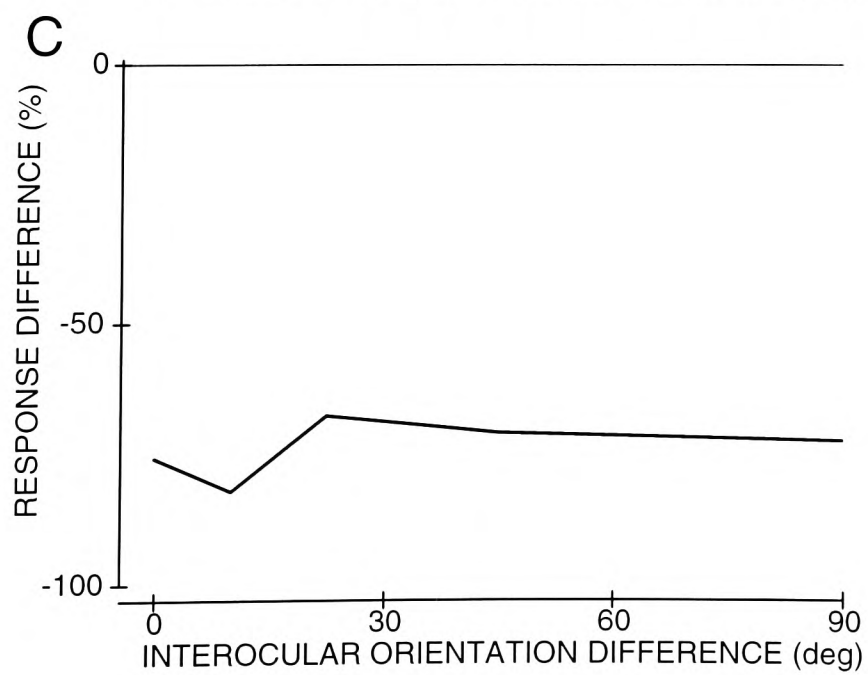
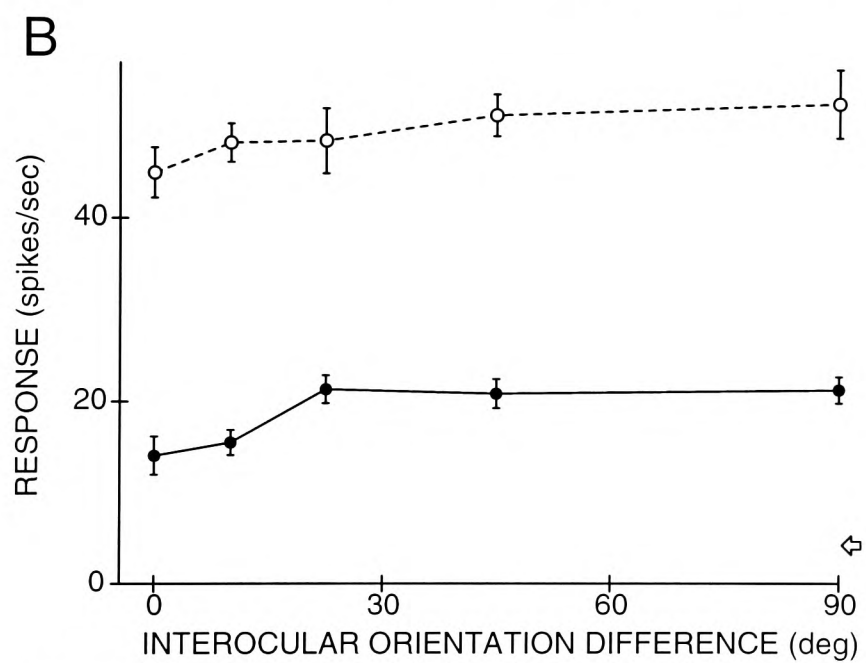
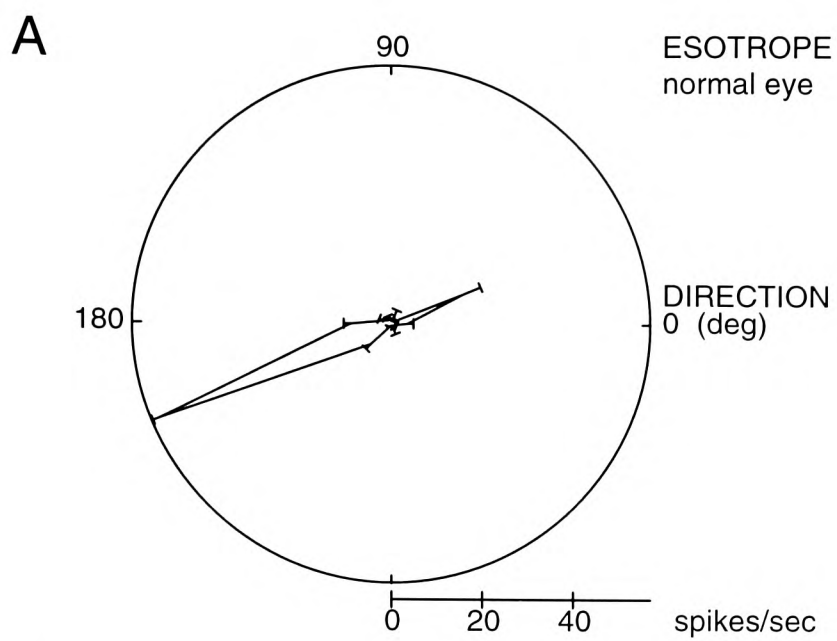


Figure 4-7

Orientation-independent interocular suppression in a layer 2/3 simple cell from exotrope DS1, exclusively driven through the non-operated (ipsilateral) eye (OD7).

A: Polar plot of orientation tuning curve for monocular stimulation through the dominant eye, with gratings of 0.7 contrast and a spatial frequency of 0.56 c/deg ($n = 5$).

B: Result of the binocular interaction protocol, as in Fig. 4-5B. A drifting 'conditioning' grating of optimal orientation (direction = 180° ; spatial frequency = 0.56 c/deg; contrast = 0.35) was presented continuously to the dominant, ipsilateral eye and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the contralateral eye ($n = 8$).

C: *Binocular interaction function*, plotting the response difference (see Fig. 4-5C) as a function of the interocular difference in orientation.

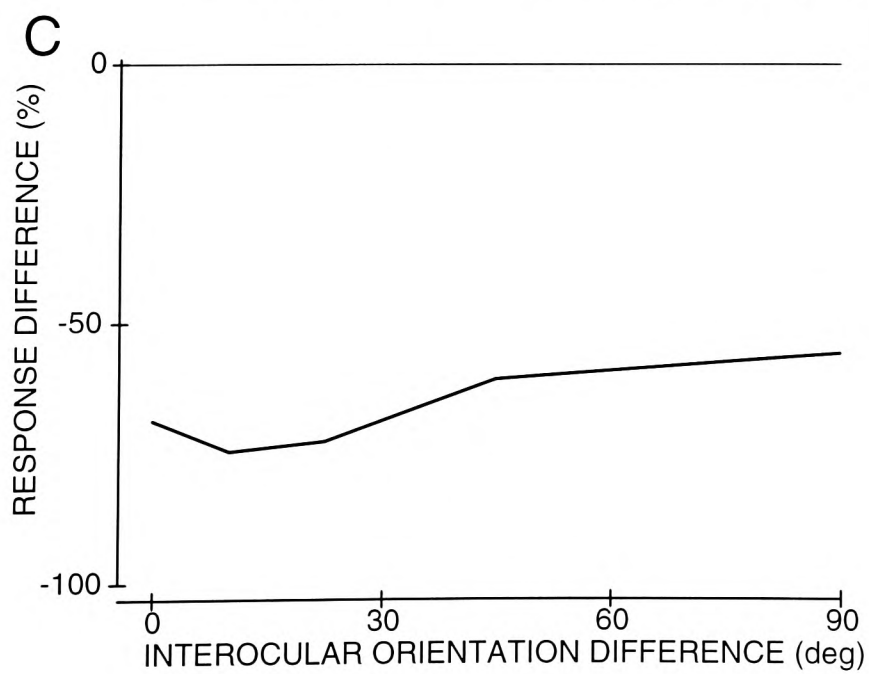
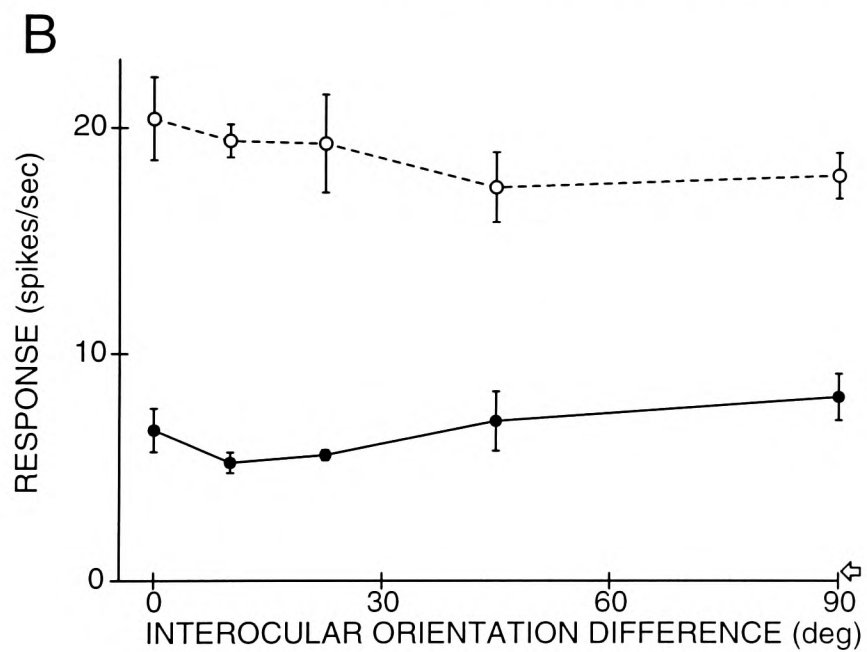
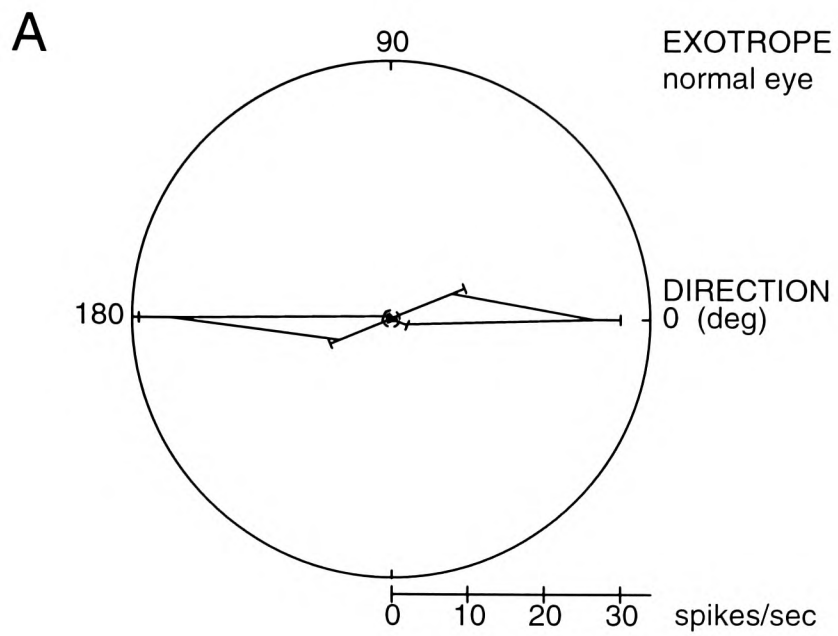


Figure 4-8

Orientation-independent interocular suppression in a layer 2/3 simple cell from exotrope DS2, strongly dominated by the operated (contralateral) eye (OD2).

A: Polar plot of orientation tuning curve for monocular stimulation through the dominant eye, with gratings of 0.7 contrast and a spatial frequency of 0.8 c/deg ($n = 5$). The interrupted circle in the centre indicates the mean level of spontaneous discharge.

B: Result of the binocular interaction protocol, as in Fig. 4-5B. A drifting 'conditioning' grating of optimal orientation (direction = 292.5° ; spatial frequency = 0.8 c/deg; contrast = 0.35) was presented continuously to the dominant, contralateral eye and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the ipsilateral eye ($n = 7$).

C: *Binocular interaction function*, plotting the response difference (see Fig. 4-5C) as a function of the interocular difference in orientation.

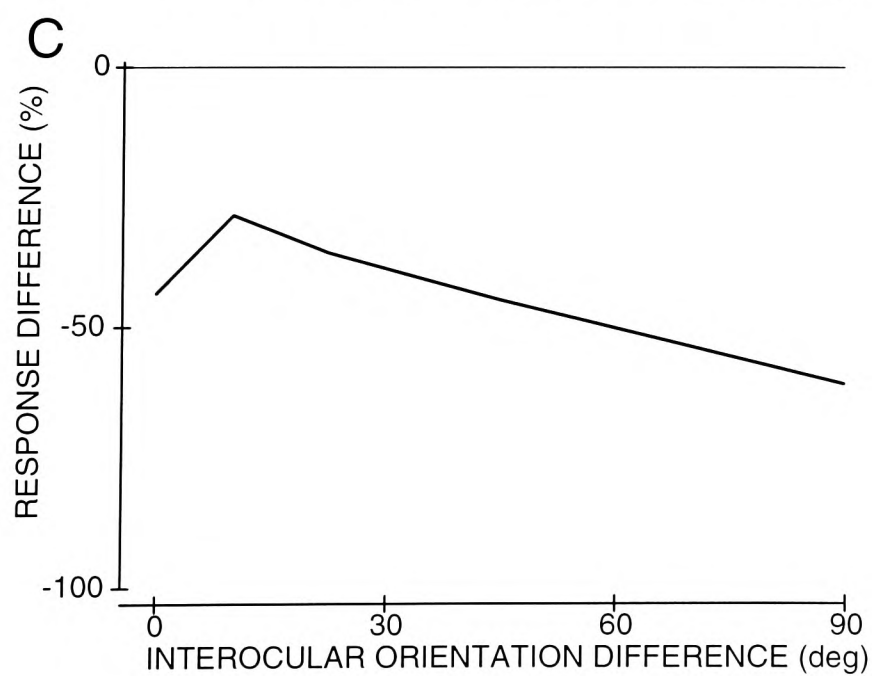
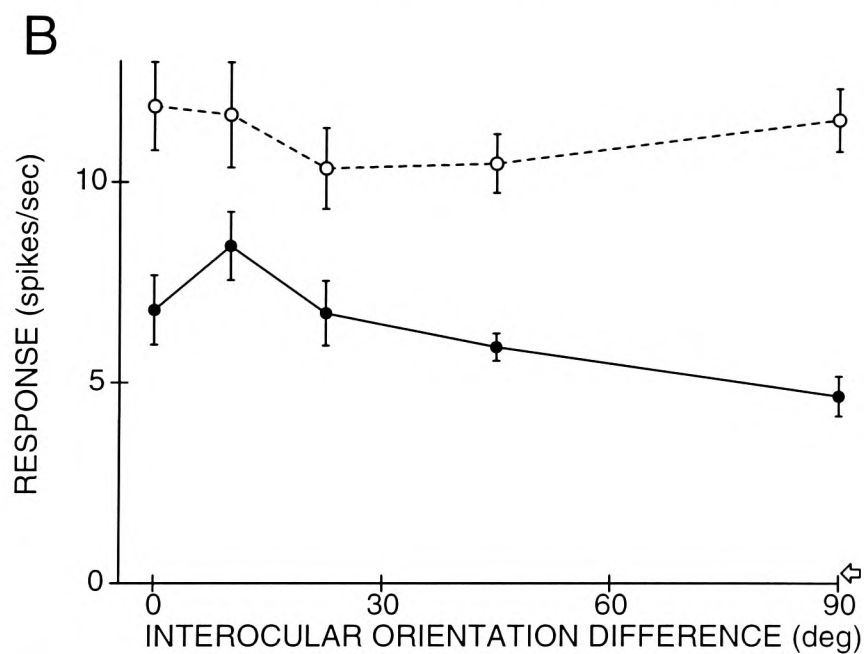
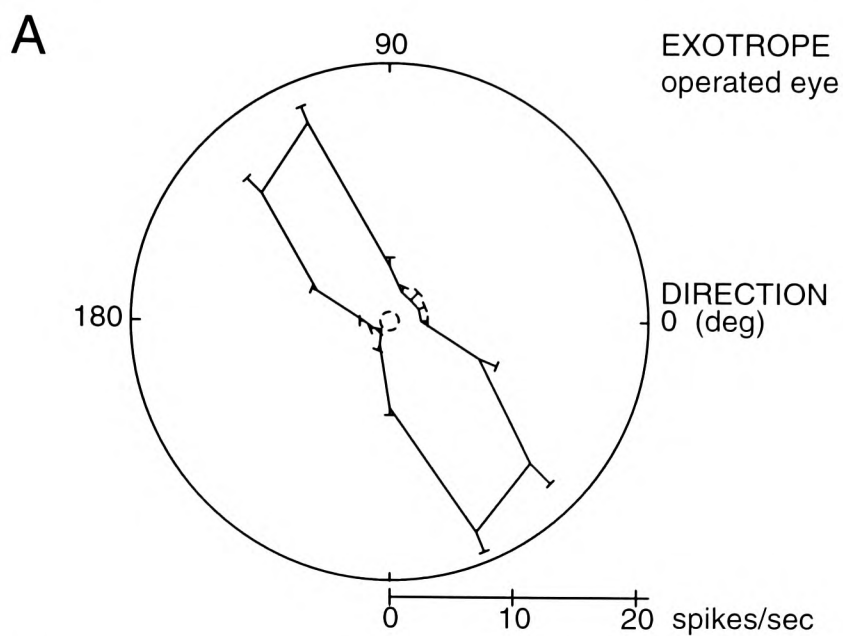


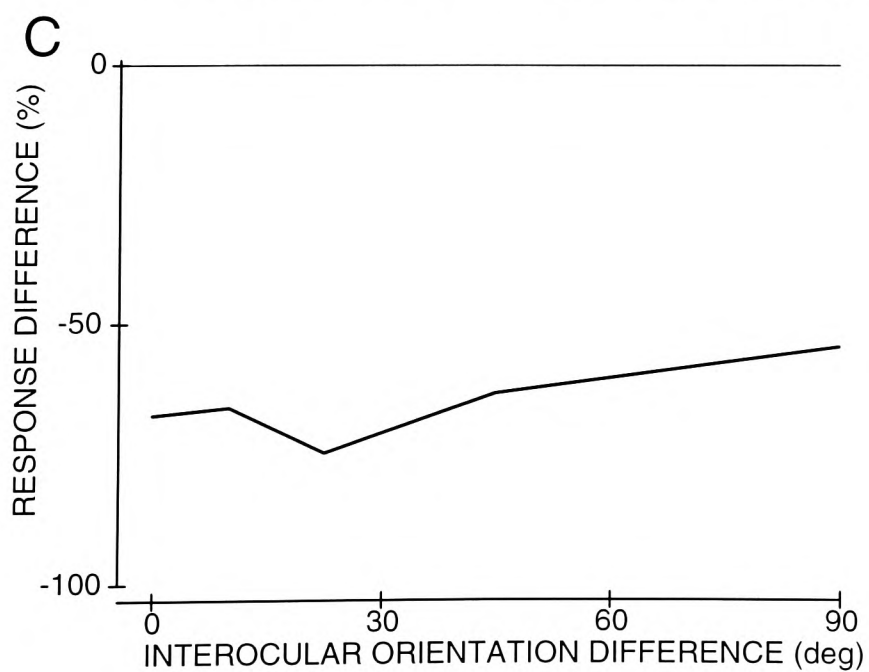
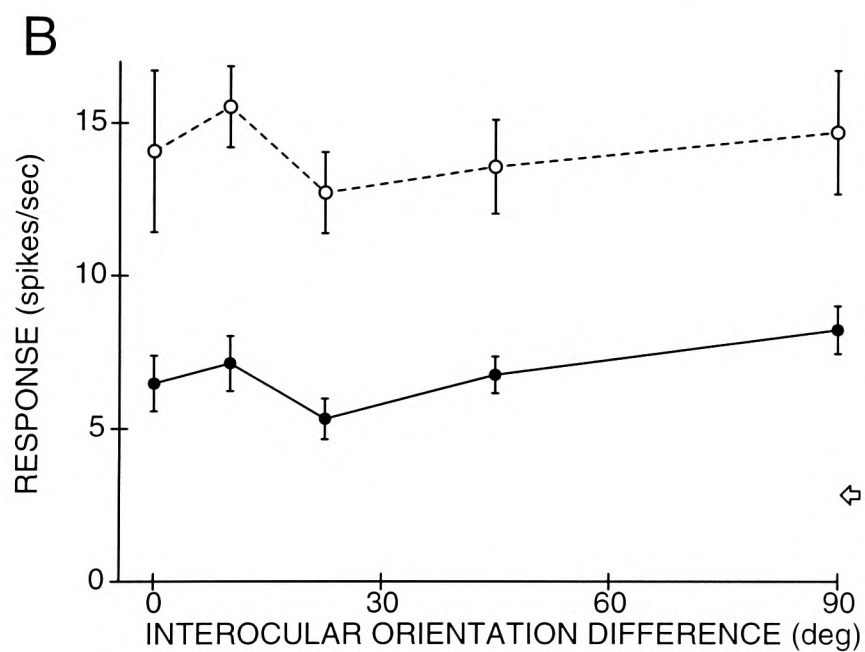
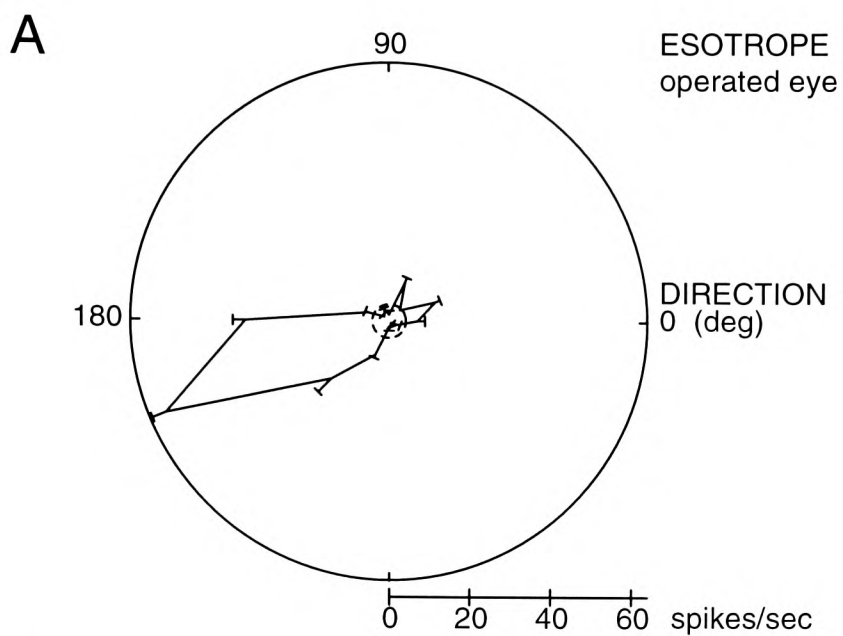
Figure 4-9

Orientation-independent interocular suppression in a layer 2/3 complex cell from esotrope CS2, dominated by the deviating (contralateral) eye (OD1).

A: Polar plot of orientation tuning curve, for monocular stimulation through the dominant eye, with gratings of 0.7 contrast and a spatial frequency of 0.56 c/deg ($n = 4$).

B: Result of the binocular interaction protocol, as in Fig. 4-5B. A drifting 'conditioning' grating of optimal orientation (direction = 202.5° ; spatial frequency = 0.56 c/deg; contrast = 0.35) was presented continuously to the operated eye and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the non-operated eye ($n = 8$).

C: *Binocular interaction function*, plotting the response difference (see Fig. 4-5C) as a function of the interocular difference in orientation.



Suppression in exotropic and esotropic animals

In both exotropic animals, for all cells that showed clear interocular suppression except one (see below), the suppression was essentially independent of orientation, whichever eye dominated the cell. This was also true in the esotropes for cells dominated by the non-squinting eye. In one of the three esotropic animals (CS2; with a very large squint), this non-selective suppression was also seen in cells dominated by the deviating eye (Fig. 4-9). In another esotrope, CS3, none of only three cells tested that were dominated by the deviating eye showed any significant binocular interaction. In the third esotrope (CS1, with a small-angle squint) just one of six apparently monocular cells that were dominated by the operated eye, displayed interocular suppression but *only* for gratings of orthogonal or near-orthogonal orientation in the non-operated eye.

For all animals, the incidence and magnitude of interocular suppression are summarized in Table 4-2 (see above). For those cells judged to show suppression independent of orientation, the average magnitude of suppression is shown, for both iso-oriented and orthogonal gratings in the non-dominant eye. It is worth noting that the mean depth of suppression was stronger, though only slightly, in the animals with large-angle squints (DS1, CS2) than in the others.

Selective iso-orientational binocular suppression

In contrast to the prevailing non-selective suppression, just two units displayed clear interocular suppression only when the orientation of the grating presented to the non-dominant eye was *similar* to the optimal orientation of the conditioning stimulus in the dominant eye and not at all when it was orthogonal. This selective iso-orientational suppression was again independent of relative interocular phase (disparity). One of these cells was a simple cell dominated by the deviating eye in the large-angle exotrope, DS1, the other a complex cell dominated by the non-operated eye in the large-angle esotrope, CS2 (see Fig. 4-10).

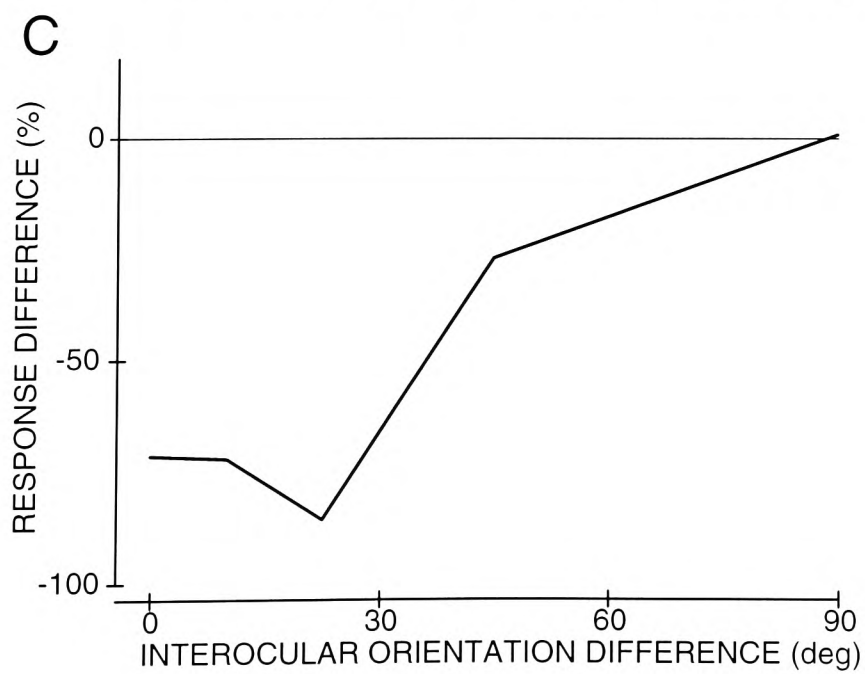
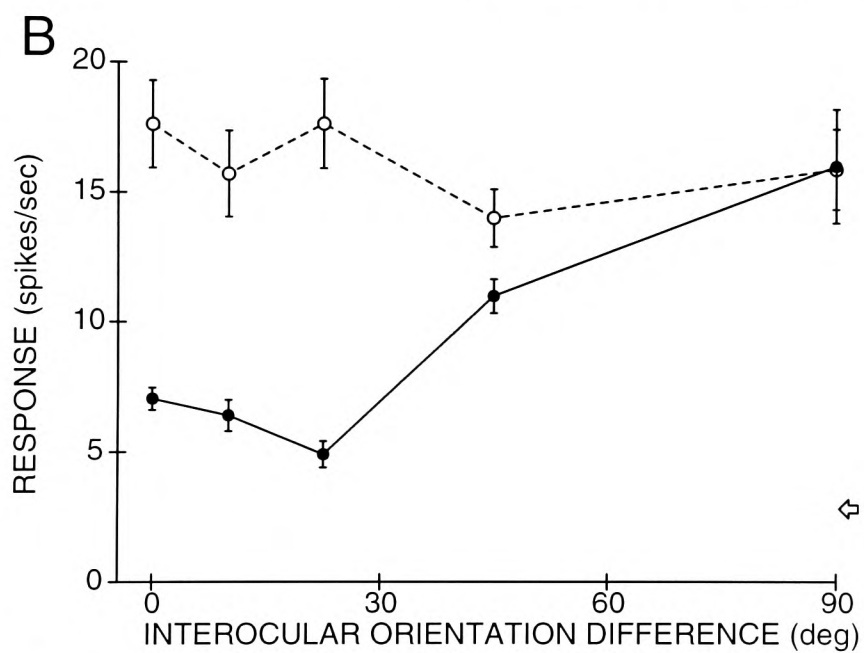
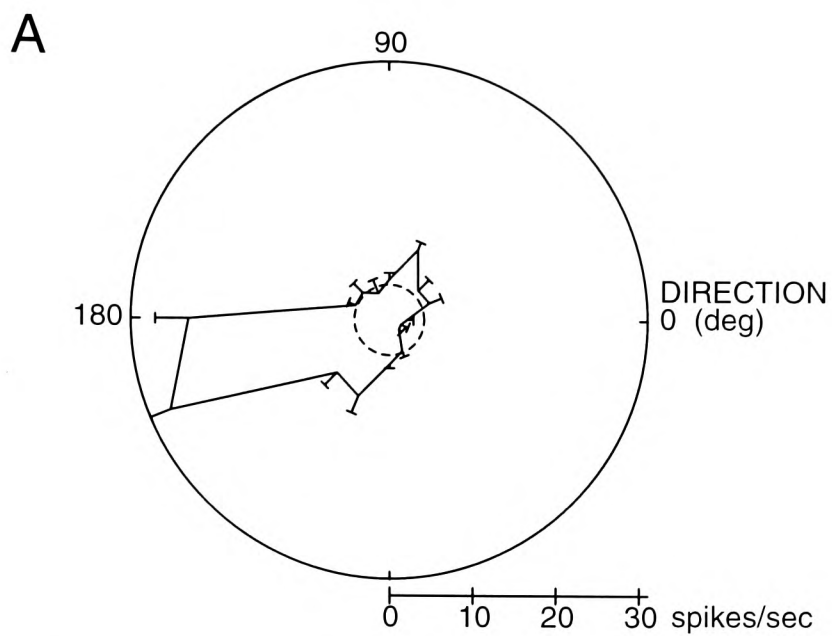
Figure 4-10

Orientation dependence of interocular suppression in a layer 2/3 complex cell from esotrope CS2. This cell was strongly dominated by the operated eye (OD2).

A: Polar plot of orientation tuning curve, for monocular stimulation through the dominant eye, with gratings of 0.7 contrast and a spatial frequency of 0.56 c/deg ($n = 4$).

B: Result of the binocular interaction protocol, as in Fig. 4-5B. A drifting 'conditioning' grating of optimal orientation (direction = 202.5° ; spatial frequency = 0.56 c/deg; contrast = 0.35) was presented continuously to the deviating eye and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the non-operated eye ($n = 8$). In this cell, suppression operated only at relatively small interocular orientation differences.

C: *Binocular interaction function*, plotting the response difference (see Fig. 4-5C) as a function of the interocular difference in orientation.



*Influence of spatial phase and spatial frequency on suppression:
positional specificity*

I tested all cells that were significantly suppressed by iso-oriented gratings to see whether this effect was dependent on the relative spatial phase between the two eyes: in no case was there significant modulation of the depth of suppression with interocular phase. This held for both complex and simple cells (Fig. 4-11).

In 28 cells with clear interocular suppression, the spatial-frequency tuning of the suppressive signal was also determined. With the 'conditioning' grating presented to the dominant eye always at the optimal spatial frequency, I presented drifting gratings of the same orientation to the other eye and varied the spatial frequency from presentation to presentation in pseudorandom sequence. The strongest suppression was invariably produced by gratings of similar spatial frequency to the optimum for excitation in the dominant eye. However, in most cells suppression was elicited over a range of spatial frequencies *broader* than the spatial-frequency tuning for excitation, and never over a narrower range. Fig. 4-12B shows the spatial frequency tuning of suppression for the simple cell illustrated in Figs 4-7 and 4-11. This unit, like several others tested, was strongly suppressed by gratings of a spatial frequency too high to elicit a significant response in the dominant eye alone. Gratings of ± 1 octave around the optimum spatial frequency caused roughly equal suppression in the majority of the 28 cells tested (see Fig. 4-12C).

Figure 4-11

Binocular responses of the simple cell shown in Fig. 4-7 as a function of the spatial phase of the grating in the silent (deviating) eye relative to that of the stimulus in the dominant eye. The triggering point of the optimally oriented drifting grating presented to the dominant eye (contrast = 0.35; spatial frequency = 0.56 c/deg) was fixed at an arbitrary value while that of the grating presented to the other eye was varied in phase. The relative spatial phase between the two gratings is plotted on the abscissa. Filled circles show the results for iso-oriented gratings, while the unfilled circles plot the control values during preceding periods of monocular stimulation. Filled and unfilled squares plot comparable data for orthogonally oriented gratings. Note that even for iso-oriented gratings suppression was independent of relative interocular phase.

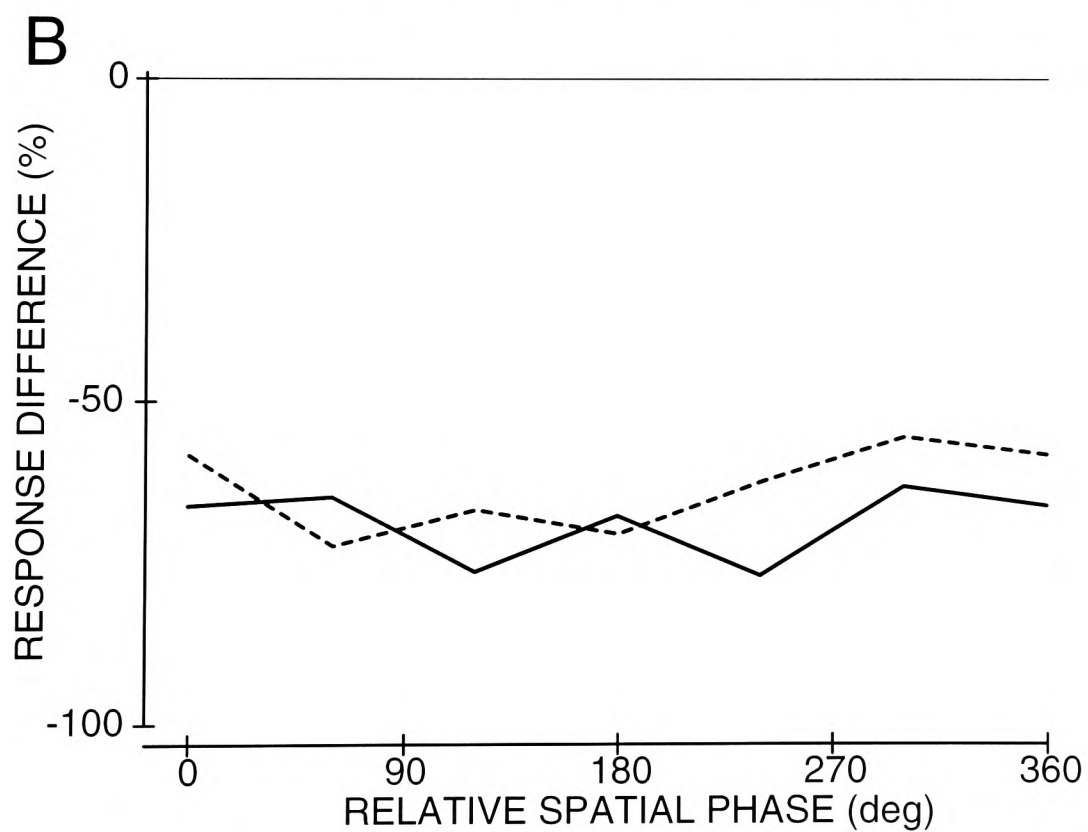
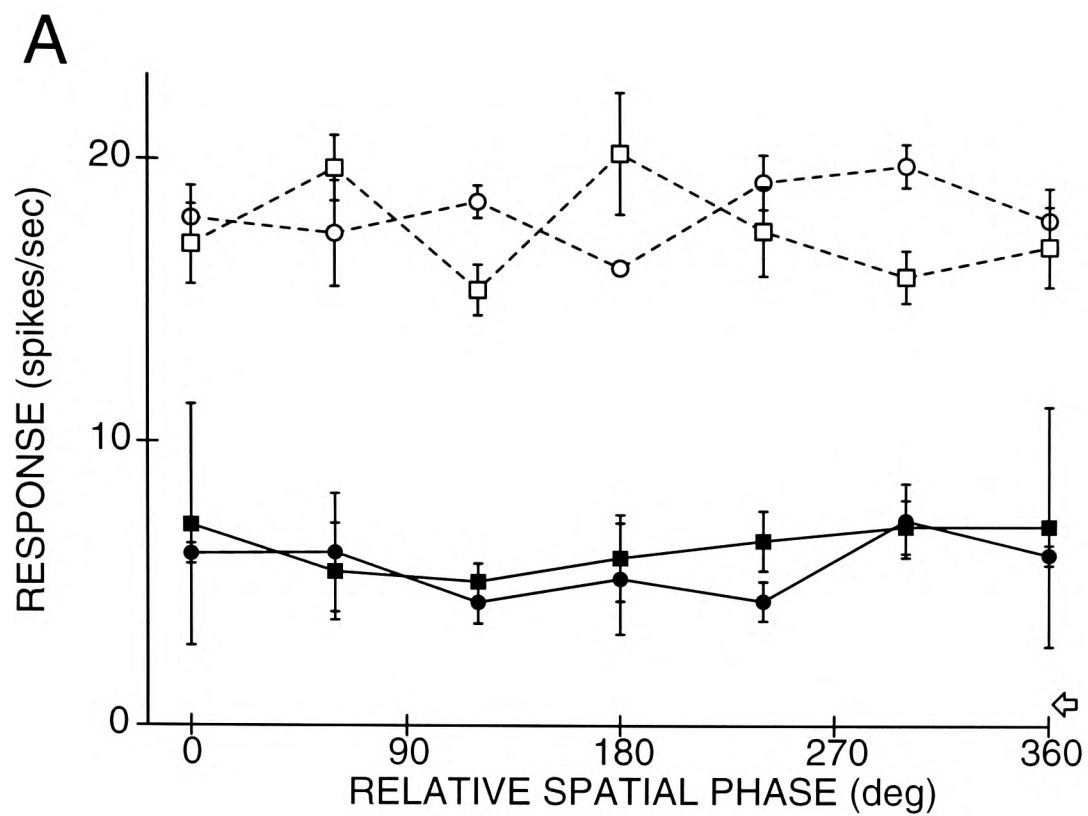


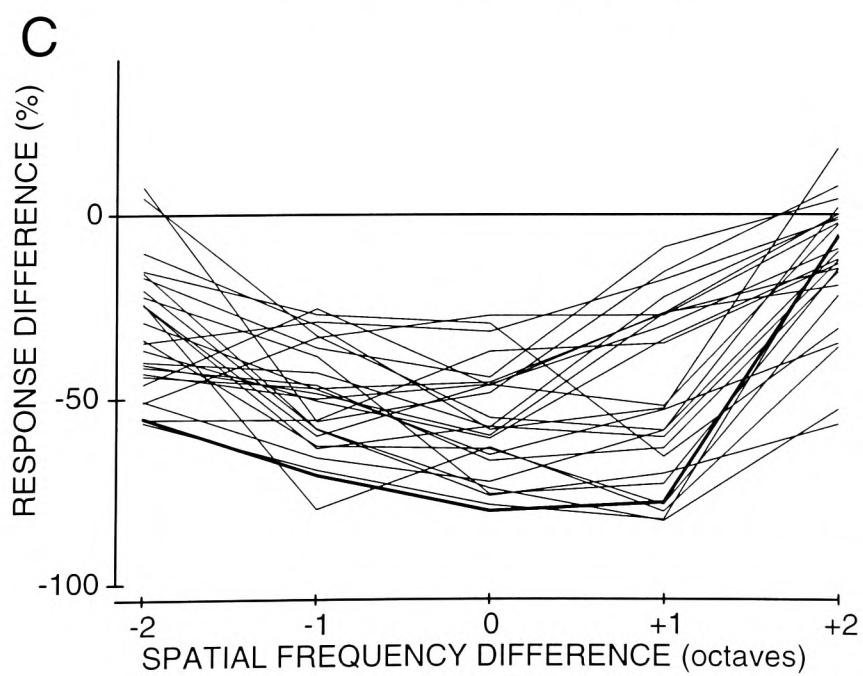
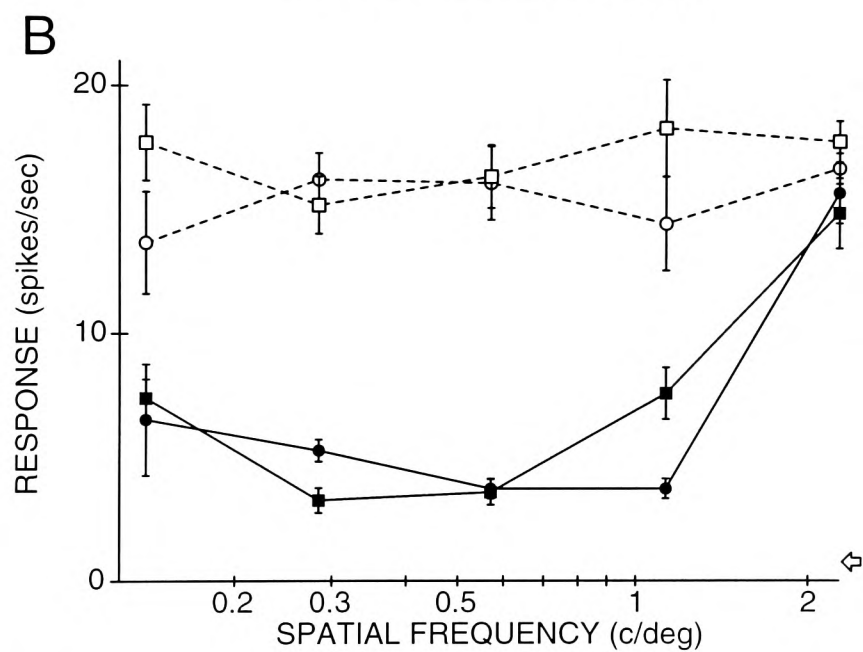
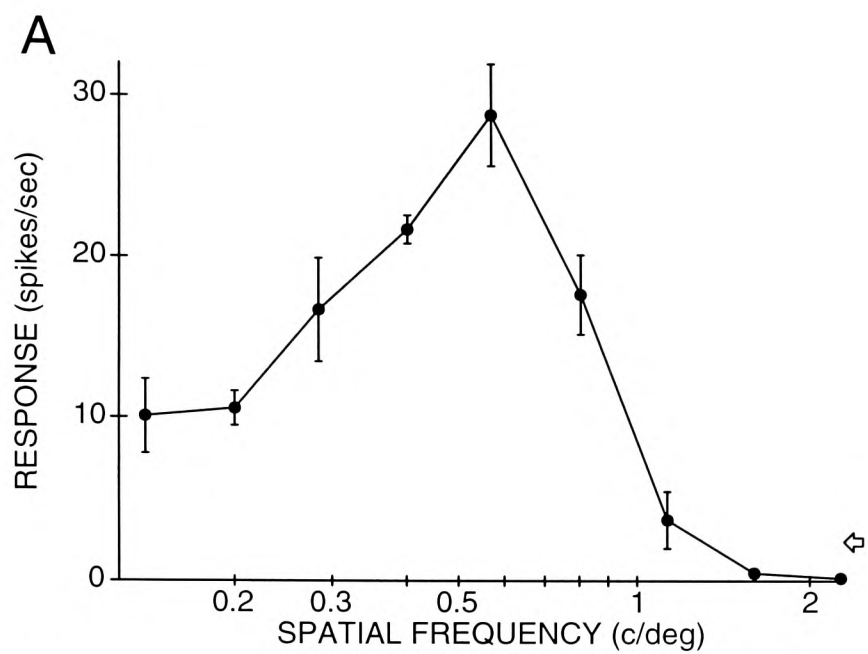
Figure 4-12

Spatial frequency dependence of suppression in strabismic cat area 17.

A: Spatial frequency tuning of monocular responses (filled circles, $\pm$ SEM; $n = 5$) obtained through the dominant (non-operated) eye, for a layer 2/3 simple cell, recorded from exotrope DS1 (same cell as for Figs 4-7 and 4-11). The arrow indicates the mean spontaneous discharge.

B: Binocular responses as a function of the spatial frequency of the grating in the silent (deviating) eye. The dominant eye was stimulated with an optimally oriented grating of optimal spatial frequency (0.56 c/deg), while the non-dominant eye was intermittently stimulated with gratings whose spatial frequency varied in random sequence. Filled circles show the results for iso-oriented gratings, while the unfilled circles plot the control values during preceding periods of monocular stimulation ($n = 6$). Filled and unfilled squares plot comparable data for orthogonally oriented gratings ($n = 6$).

C: Spatial frequency tuning of suppression for iso-oriented gratings, shown as binocular interaction functions for all 28 cells in which it was studied in detail. Tuning curves have been normalized to the spatial frequency that elicited the maximum excitation when presented to the dominant eye alone (corresponding to a value of zero on the abscissa). For each of the cells, the dominant eye was then stimulated with a grating of optimal orientation and spatial frequency, while the non-dominant eye was intermittently stimulated with orthogonally oriented gratings of spatial frequencies of ± 1 and ± 2 octaves or the same as that in the dominant eye. The binocular interaction function for the cell shown in parts **A** and **B** is given as a thick line.



For six cells, the dependence of the depth of suppression on the exact **position** of the suppressive stimulus was tested. In these experiments, the iso-oriented grating presented to the non-dominant eye occupied a circle of 4° diameter whose position was pseudorandomly varied, being centred on a position that either geometrically corresponded to the receptive field centre in the dominant eye or was offset by $\pm 3^\circ$ vertically and/or horizontally. For all cells tested, suppression was strongest when the position of the suppressive stimulus corresponded exactly to that of the excitatory stimulus presented to the dominant-eye receptive field, and was much weaker or absent for all other positions (Fig. 4-13).

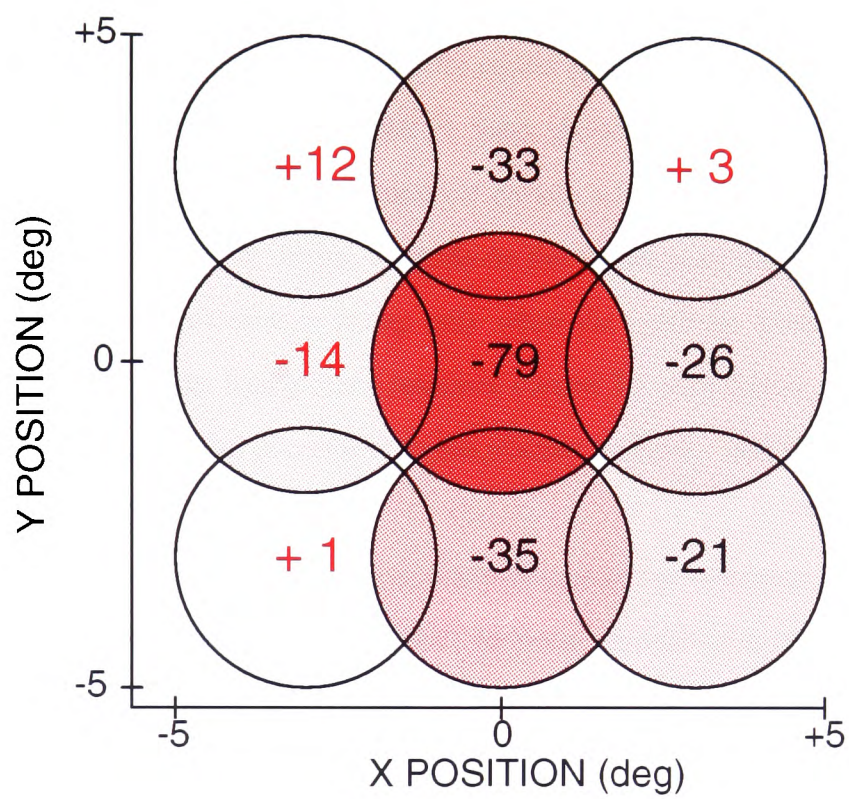
Time-course of suppression

In order to judge the latency of onset and consistency over time of interocular suppression I examined accumulated peri-stimulus time histograms (PSTHs) during the sudden introduction of a suppressive, iso-oriented grating to the silent (or non-dominant) eye, while the cell was responding to a conditioning stimulus in the other eye. For most of the 29 cells studied, suppression commenced quite sharply 100-200 ms after the onset of binocular stimulation (see Fig. 4-3E); however, in some accumulated PSTHs, suppression appeared to turn on more gradually, mostly due to statistical scatter of latency between individual trials. For 6 cells, the latency of onset of suppression was as long as 400-800 ms (Fig. 4-3C,D). Suppression was generally strongest in the first second after the onset, followed by a slight recovery, but was always sustained at a significant tonic level throughout the 5-sec period tested (Fig. 4-3C,D,E).

Figure 4-13

Position dependence of suppression in a layer 2/3 complex cell recorded from esotrope CS2 (same cell as for Figs 4-3C,D and 4-6).

The diagram shows depth of interocular suppression as a function of position of the stimulus presented to the silent eye. The dominant eye was stimulated with an optimally oriented grating of optimal spatial frequency, filling a circle of 4° diameter, while identical gratings of the same size were intermittently shown to the silent eye in pseudorandomly varied positions. In both eyes, the background (around the 4° grating patch) was of the same luminance as the mean for the grating. Positions and stimulus size are represented as circles in an X-Y plot of the receptive field in the silent eye, with $X=0$, $Y=0$ indicating the position that geometrically corresponded to the centre of the receptive field in the dominant eye. Numbers in the circles give the average percentage suppression ($n = 5$ trials) below the monocular level for the respective positions of the silent-eye stimulus; depth of suppression is roughly colour coded (0%, white; 100%, saturated red). Black numbers indicate statistically significant deviation from 0; red, non-significant.



Suppression depends on the sequence of stimulus presentation

The strong interocular suppression that I saw in such a large proportion of neurons from strabismic animals might be thought to contradict the preliminary observations of Xue et al. (1987b), who reported that long-term squint results in a complete loss of binocular interaction. In the previous chapter, I have shown that the orientation-dependent interocular suppression seen in normal cat cortex, which may underlie the perceptual phenomenon of binocular rivalry, depends on the temporal sequence of stimulation of the two eyes. Suppression is strong only when the rivalrous stimulus is introduced against a pre-existing background response caused by stimulation of the other eye. Here, I have used similar procedures to see whether this gross non-linearity also applies to strabismic suppression.

Responses were measured during 5-sec binocular presentations in which the two eyes were simultaneously stimulated with *identical* gratings of orientation, optimal for the dominant eye. The contrast of the grating in the silent (or non-dominant) eye was fixed at 0.7 and the contrast in the dominant eye was varied, providing data for the construction of a contrast-response function. The only difference between *experimental* runs was the nature of stimulation during the 5-sec period immediately preceding each binocular presentation, which was *either*:

- a) a blank screen of the same mean luminance presented to *both eyes*; or
- b) the identical to optimum grating shown *alone* to the non-dominant eye; or
- c) the optimal conditioning grating presented *alone* to the dominant eye.

For *control* data, I also examined the response as a function of contrast during 5-sec presentations of the optimal grating to the dominant eye alone with the other eye viewing only a blank screen, preceded by *either*:

- 1) a blank screen to both eyes; or
- 2) an initial 5-sec period of stimulation of the dominant eye (to control for possible effects of 'fatigue' caused by the initial monocular stimulation in condition (c) above).

Contrast-gain functions (relating response to the contrast of the stimulus in the dominant eye) were then constructed for these two monocular control conditions and for the three forms of binocular stimulation, which differed only in the immediate histories of stimulation. I examined three apparently monocular cells and one weakly binocular neuron that showed clear suppression but were not distinctive in any other way. All four cells tested showed clear suppression under condition (c), but little or none under stimulus conditions (a) or (b), compared with monocular controls (2) and (1), respectively.

Figures 4-14A,B,C show accumulated PSTHs of responses of a representative neuron, a supragranular complex cell recorded from esotrope CS2, for the highest contrast (0.7) under all three experimental conditions. The magnitude of the response during the second 5-sec epoch of each of all five conditions is compared in Fig 4-14D. Fig. 4-14E illustrates contrast-response curves. When binocular stimulation followed a brief period of activation through the dominant eye alone (condition (c): filled circles), the magnitude of response was reduced by about 70% below that in the monocular control (condition (2): unfilled circles) over the entire range of suprathreshold contrasts in the dominant eye; the reduction reaching statistical significance ($p < 0.05$) at all contrasts tested. Even though the binocular stimulus conditions were identical during the 5-sec periods of measurement, there was little or no suppression, especially at medium to high stimulus contrasts in the dominant eye, under the other two experimental conditions.

Figure 4-14

Dependence of response on the temporal sequence of stimulation for the monocularly driven layer 2/3 complex cell shown in Figs 4-3C,D and 4-6.

Three experimental conditions were tested, in each of which drifting gratings (0.7 contrast) of **identical** orientation, optimum for the dominant eye, were simultaneously presented to both eyes during the second half of a 10-sec period. The only difference between these three conditions was the nature of stimulation during the 5-sec period immediately preceding this binocular exposure:

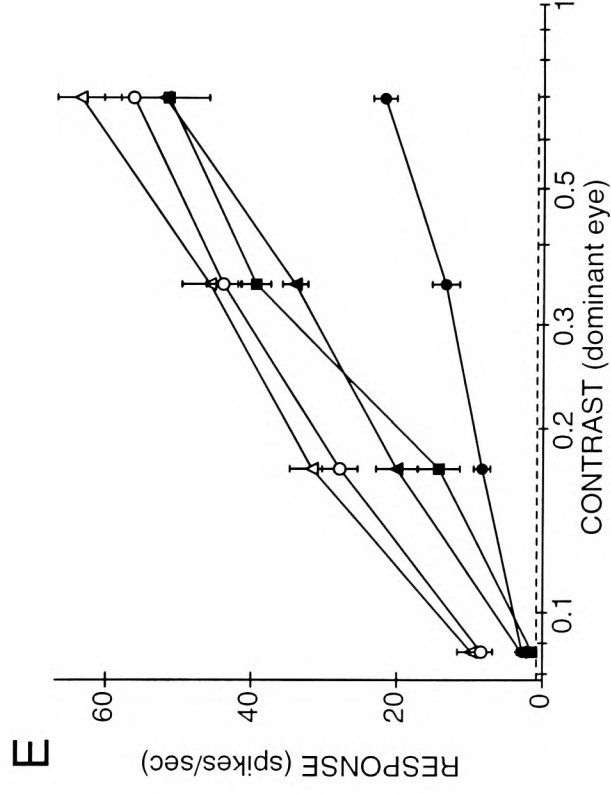
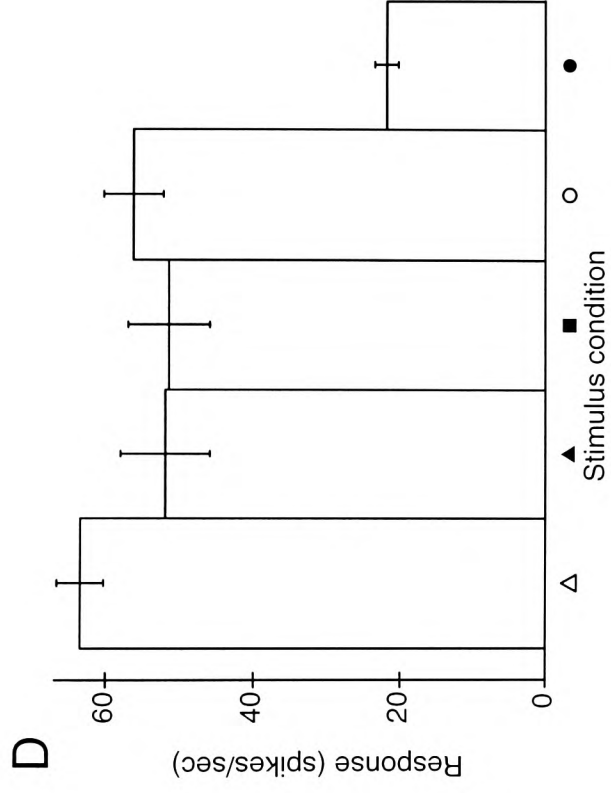
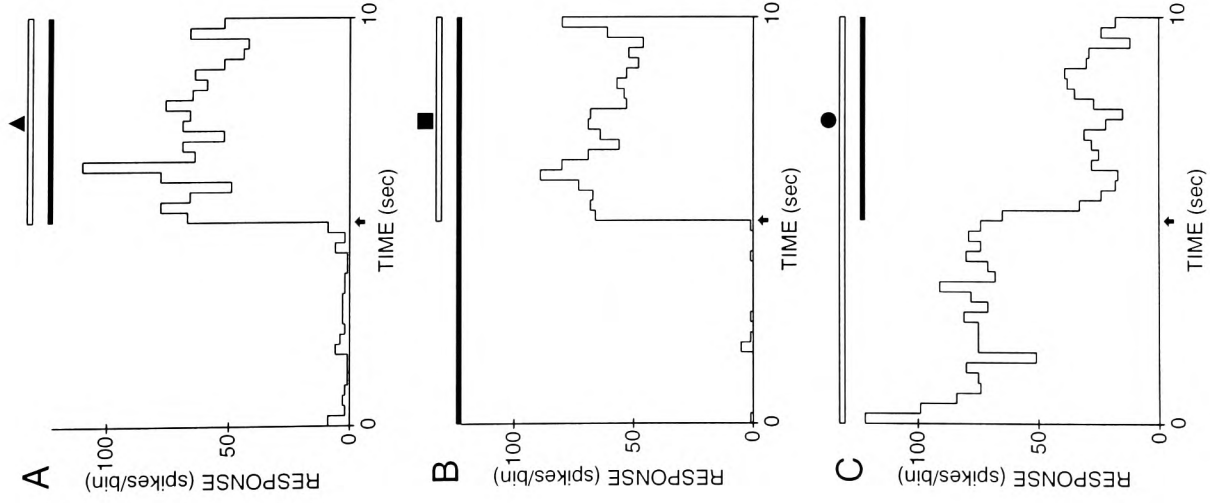
- a) Filled triangle: blank screen presented to both eyes for the first 5 sec, with simultaneous onset in the two eyes at the start of the period of binocular stimulation.
- b) Filled square: grating presented alone to the silent eye with the dominant eye viewing a blank screen for the first 5 sec.
- c) Filled circle: optimal grating presented alone to the dominant eye during the initial 5 sec.

A,B,C: PSTHs (each the average of five 10-sec presentations) of responses in the three experimental conditions a, b and c above. The filled and unfilled bars above each PSTH indicate the periods of stimulation of the silent and the dominant eye, respectively. Only when the stimulus appeared in the silent eye (arrow) while the cell was already responding through the dominant eye (**C**), there was strong suppression during the period of binocular stimulation.

D: Histogram comparing responses (mean $\pm$ SEM, $n = 5$) under the three experimental conditions (a, b, c) described above and two further controls:

- 1) Unfilled triangle: the dominant eye alone was stimulated for the second 5 sec, preceded by 5 sec of presentation of a blank screen of the same mean luminance.
- 2) Unfilled circle: the dominant eye was stimulated for the entire 10 sec period and the response was measured during the latter 5 sec of each presentation, in order to control for adaptation or 'fatigue' under experimental condition (c) above. In both cases, the non-dominant eye viewed a blank screen.

E: Contrast response functions for all five conditions. In each case the contrast of the optimally oriented gratings shown to the dominant eye was varied across presentations. The interrupted line indicates the mean level of spontaneous discharge measured during blank presentations with no pattern presented to either eye. Only when the cell was already responding, because of prior presentation of the optimal grating to the dominant eye, did the orthogonal grating in the other eye cause obvious suppression (filled circles).

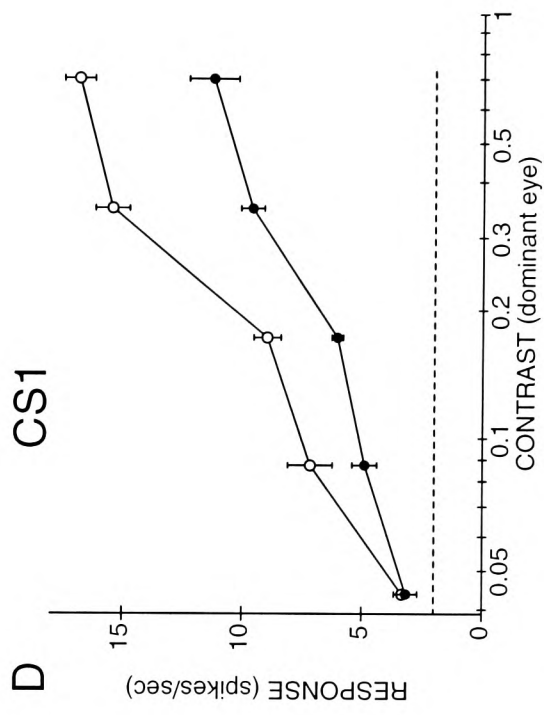
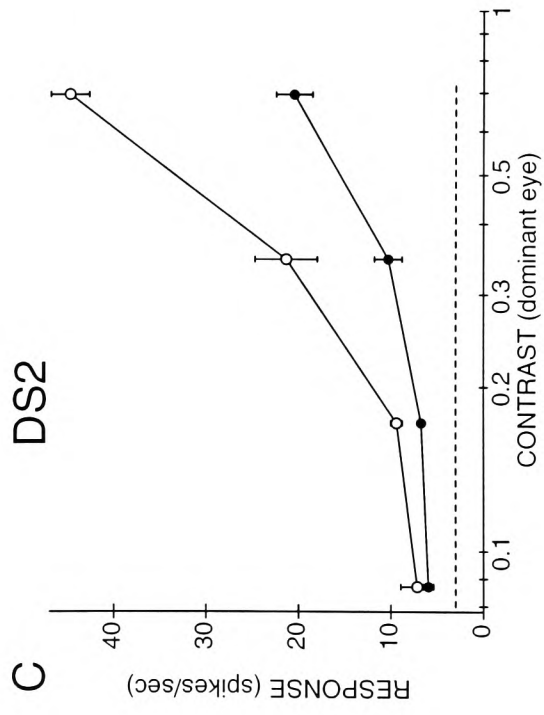
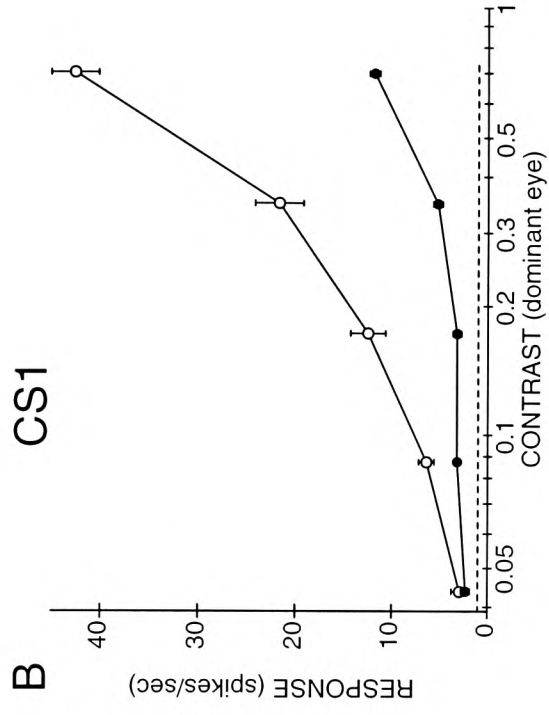
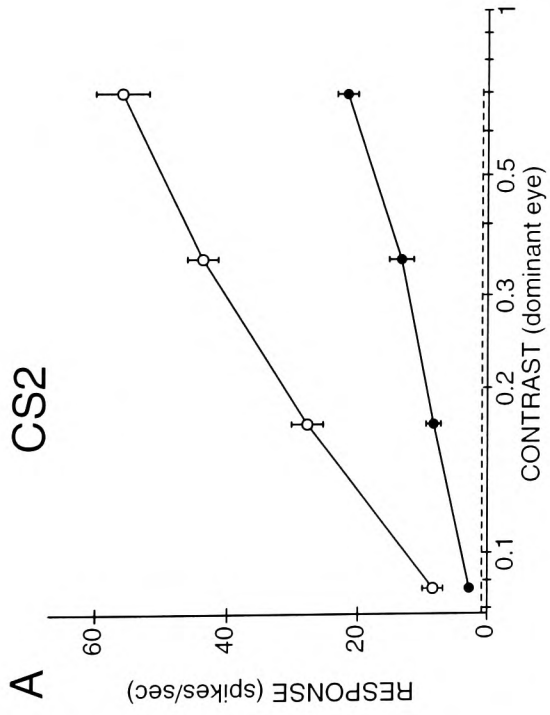


Suppression results from a reduction in contrast gain

In the previous chapter, I showed that the decrease in response during rivalrous suppression is due to a decrease of the slope of the contrast gain function, with little shift in threshold. Fig. 4-15 illustrates the nature of suppression for the four cells from strabismic animals that were tested according to the procedure described above (except that the gratings in the two eyes were of the **same** orientation rather than orthogonal for the similar experiments in normal cats; see Figs 3-18 and 3-19). Average firing rate over the second 5-sec period in each presentation is plotted against the contrast of the grating in the dominant eye. Unfilled circles plot results for the control condition (2) (stimulation through the dominant eye alone) while filled circles show responses in the suppressed state (condition (c)). Fig. 4-15A shows results for the same cell as for Fig. 4-14, while the other parts of Fig. 4-15 summarize the results for three more fully analysed cells. The pattern was similar for all four cells. The reduction in response was greater the higher the contrast of the stimulus in the dominant eye (with contrast in the 'suppressing' eye being fixed) and the control and suppressed curves meet very close to the level of background activity. In other words, suppression results from a reduction in the slope of the contrast response curve (contrast gain). Although the contrast thresholds of cells in the suppressed and unsuppressed states were not systematically measured, extrapolation of the gain curves back to the level of background activity in each part of Fig. 4-15 suggests that there is little difference in threshold.

Figure 4-15

Response *versus* contrast functions for experimental condition (c), in which binocular stimulation was preceded by presentation of an optimal grating to the dominant eye (filled circles), and the corresponding control condition (2) (unfilled circles; see legend to Fig. 4-14) are shown for all four cells that were fully tested. Mean responses in spikes/sec ($\pm$ SEM, $n = 5$ presentations per data point in part **A**, $n = 6$ in parts **B,C,D**) are plotted against the contrast of the optimally oriented drifting grating shown to the dominant eye (the non-deviating eye for all four cells). The interrupted lines indicate the mean level of spontaneous discharge measured during blank presentations with no pattern presented to either eye. Part **A** depicts responses from the monocularly driven complex cell of Fig. 4-14. Parts **B** and **D** show results from two apparently monocular simple cells recorded from the small-angle esotrope CS1. Contrast response functions in **C** were obtained from a complex cell that was dominated by the non-operated eye but clearly responded to stimulation of the operated eye alone, in the alternator DS2.



Monkey

In the esotropic rhesus monkey (#115), 55 cells were recorded in one penetration (see Fig. 4-16), 25 of which were quantitatively tested with dichoptic stimuli. Receptive field centres of all cells were within 2 deg, for most cells within 1 deg of the fovea.

In this animal, like in the cats, the loss of binocularity was severe: only 22 cells (40%) received excitatory inputs from both eyes, while 33 cells (60%) were strictly monocular by conventional tests. Regular alternations of ocular dominance of cells recorded along the electrode track are illustrated in Fig. 4-17B. The overall OD distribution (Fig. 4-17C) shows a marked skew towards the non-operated eye; however, in the small sample of cells recorded from layer 4C, units driven by either eye were equally represented (see Fig. 4-17B). Response properties (i.e. orientation selectivity, spatial acuity) of neurons dominated by the deviating eye were normal, compared to those of neurons dominated by the fixating eye that were recorded from the same cortical layers. As in the strabismic cats, there was no evidence of anomalous retinal correspondence of the receptive fields of binocular cells.

Of 25 quantitatively tested units, 11 showed significant binocular interactions. The results are summarized in Table 4-3 with respect to the laminar position of the cells.

Orientation-dependent binocular interactions

In just two cells, located in layer 4B, orientation-dependent binocular facilitation was observed (cf. Chapter 3 and above). Both were complex cells slightly dominated by the fixating eye (OD3). They showed clear facilitation (>100% of the response to the 'conditioning' stimulus) when the deviating eye was stimulated with gratings of near-optimum orientation and little or no suppression when stimulated with gratings of widely differing orientations in the two eyes (see Fig. 4-18).

Figure 4-16

Coronal section through striate cortex of monkey #115, showing electrode penetration angled at 10° towards the midline. Three electrolytic lesions, one near the upper border of layer 4B, one just above the layer 5/6 border and the third within layer 6, are marked with arrows. Scale bar, 500 µm.



Figure 4-17

A: Sequence of preferred orientations of cells recorded along the electrode track (reconstructed in Fig. 4-16) from esotropic monkey #115. The preferred orientation of each cell is plotted against the distance (in μm) along the track; squares indicate orientation selective and triangles orientation biased cells; clearly direction selective cells are indicated by filled symbols. Circles in the row marked 'NO' signify non-oriented units.

B: Sequence of ocular dominance of cells recorded along the electrode track in **A**. The ocular dominance of each cell (symbolized by a filled circle) is plotted against the depth (in μm) along the track.

Borders of cortical layers are indicated on the scale below part **C**, and the positions of lesions at the layer 4A/4B border, at the layer 5/6 border and in layer 6, respectively, are marked by arrows. Note that most of the clearly direction selective cells (filled symbols in **A**) were located in layers 4B and 6, confirming observations by Hawken et al. (1988).

C: Ocular dominance distribution of all 55 neurons recorded in this animal. Classification of cells in one of seven OD groups (OD1 to OD7, plotted on the abscissa) followed the scheme devised by Hubel and Wiesel (1962). As recordings were made from the hemisphere contralateral to the operated eye, OD7 signifies complete dominance of the deviating eye (marked with arrow), while OD1 represents cells exclusively driven through the non-operated eye.

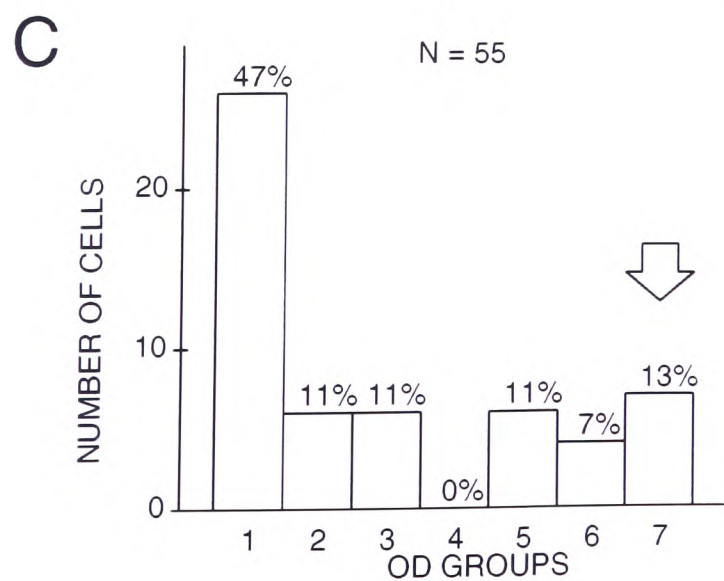
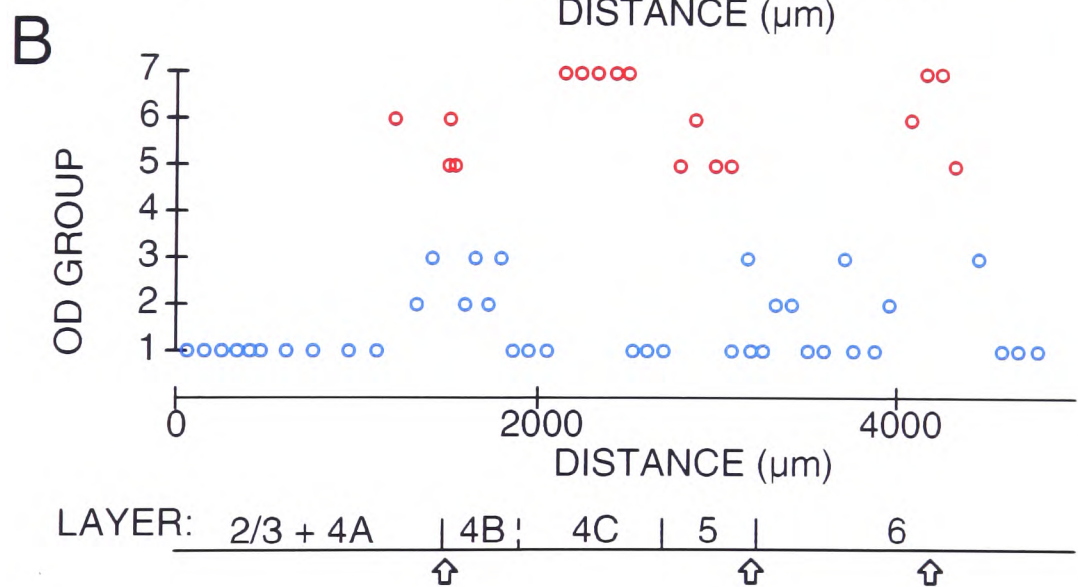
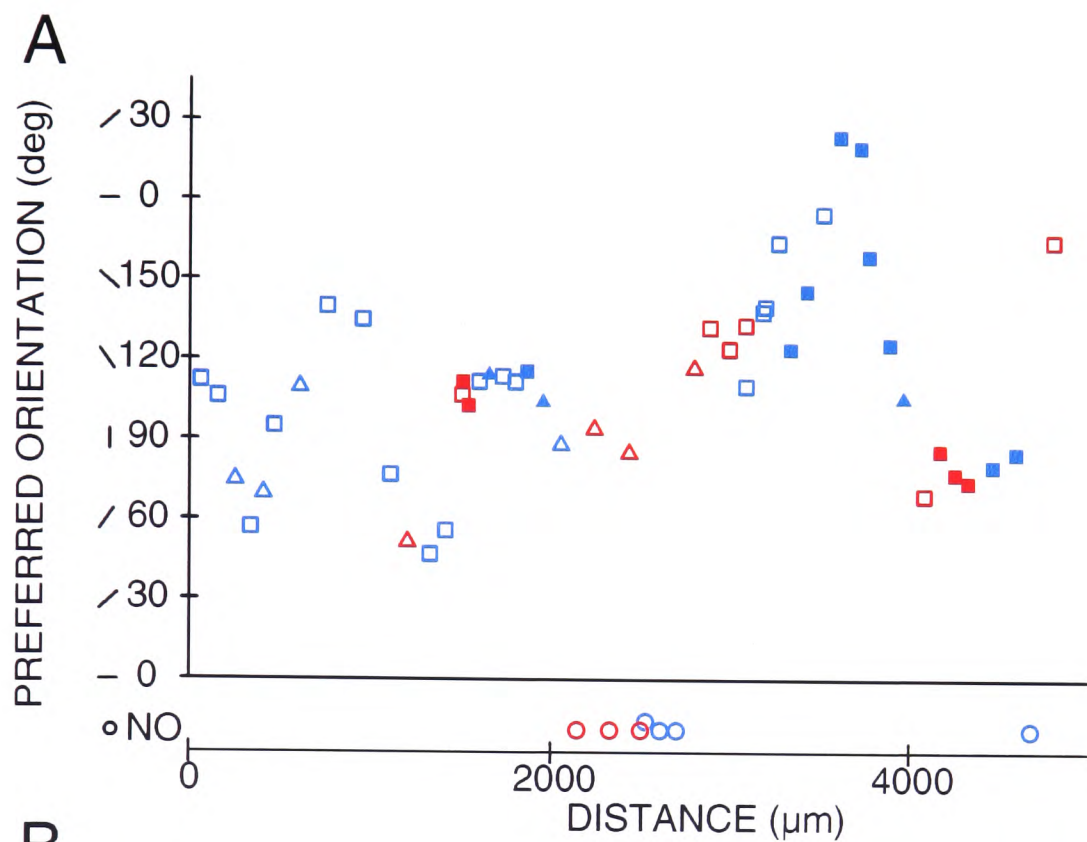


Table 4-3: Occurrence of orientation-dependent *facilitation* and orientation-independent *suppression* in V1 of esotropic rhesus monkey #115, with respect to cortical layers. One cell recorded at the upper border of layer 4C α is included in the group of cells from layer 4B. The final two columns give the average percentage suppression, below the monocular level, caused by an iso-oriented grating ($\Delta\text{Or} = 0^\circ$) and an orthogonally oriented grating ($\Delta\text{Or} = 90^\circ$) presented to the non-dominant eye, for all cells showing orientation-independent suppression.

Layer	Total number of cells tested	Facilitation: number of cells	Suppression: number of cells	Percentage of suppression for $\Delta\text{Or} = 0^\circ$ $\Delta\text{Or} = 90^\circ$ (mean $\pm$ SD)	
2/3,4A	9	0	0	/	/
4B,C α	6	2	3	61% $\pm$ 22%	61% $\pm$ 31%
4C β	1	0	0	/	/
5	1	0	0	/	/
6	8	0	6	45% $\pm$ 32%	57% $\pm$ 32%

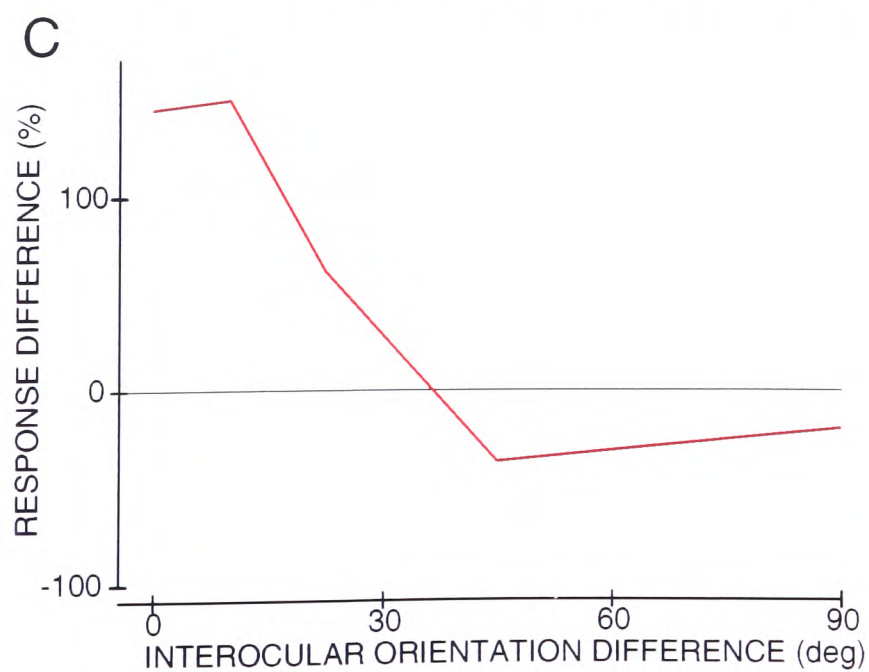
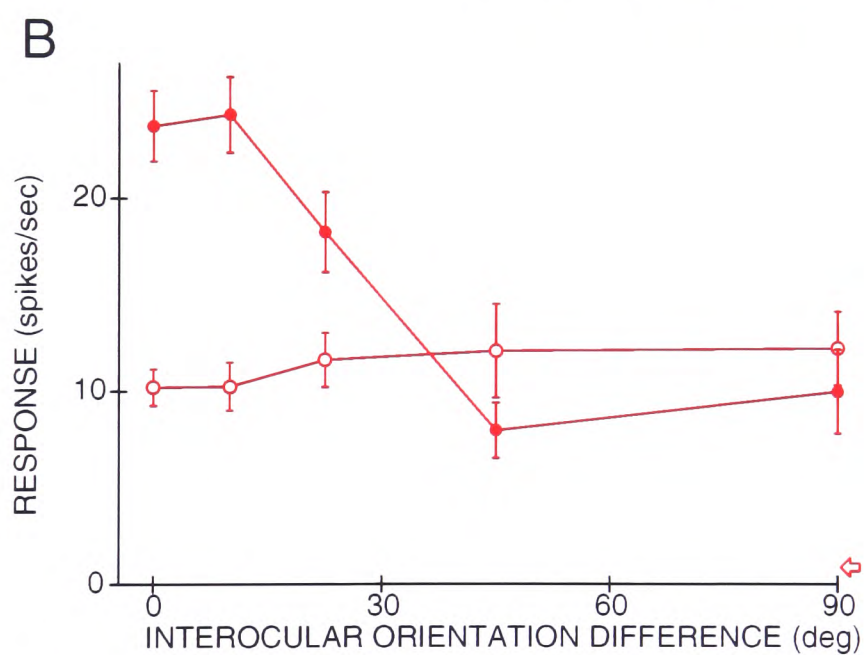
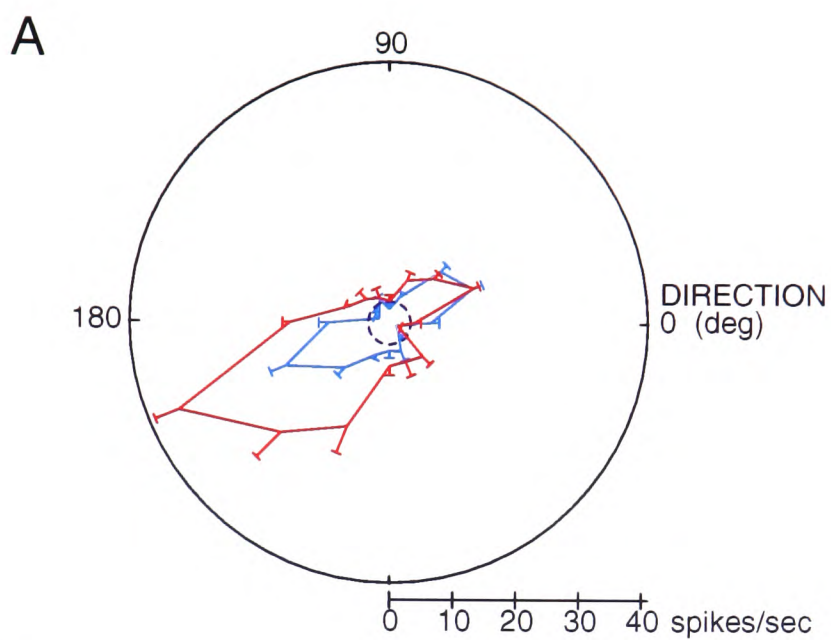
Figure 4-18

Orientation dependence of binocular interactions in a layer 4B complex cell from monkey #115. This cell was mildly dominated by the non-operated eye (OD3).

A: Polar plot of orientation tuning curves, for monocular stimulation through the normal (dominant) eye (red lines) and the deviating (non-dominant) eye (blue lines), respectively. Mean responses ($\pm$ SEM, $n = 4$) are plotted as a function of the direction of drift of a grating (contrast = 0.7) of optimal spatial frequency (4.52 c/deg). The interrupted circle in the centre indicates the mean level of spontaneous discharge.

B: Result of the binocular interaction protocol, as in Fig. 4-5B. A drifting 'conditioning' grating of optimal orientation (direction = 202.5°; spatial frequency = 4.52 c/deg; contrast = 0.18) was presented continuously to the dominant, contralateral eye and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the ipsilateral eye ($n = 7$).

C: *Binocular interaction function*, plotting the response difference (see Fig. 4-5C) as a function of the interocular difference in orientation.



Orientation-independent interocular suppression

Perhaps the most surprising finding of this study (compared with that in the strabismic cats) is the layer-specific occurrence of orientation-independent suppression. In 9 out of 25 quantitatively analysed units, dominated by either the normal eye (6 cells) or the operated eye (3 cells), the response to the optimum stimulus presented to the dominant eye was significantly reduced by introducing a stimulus of *any* orientation to the non-dominant eye; an extreme example, with a response reduction of up to 97%, is shown in Fig 4-19. However, none of the 9 cells studied in the supragranular layers displayed orientation-independent suppression, while it was seen for 3 of the 6 cells (50%) recorded from layers 4B/4C α and for 6 out of 8 units (75%) in layer 6. When present, suppression in this animal was characterized by a broad tuning for spatial frequency and a lack of sensitivity for spatial phase, just as I observed in strabismic cats.

For one simple cell recorded from layer 6, it was found that interocular suppression, although largely independent of interocular orientation difference in terms of the reduction of the mean discharge (F_0 response), varied significantly in strength when the response *modulation* (F_1 response) was measured (Fig. 4-20): for drifting gratings of similar orientation, but not for orthogonally oriented gratings, the sinusoidal response modulation characteristic of all simple cells was greatly reduced.

Figure 4-19

Orientation-independent interocular suppression in a layer 6 simple cell from monkey #115, exclusively driven through the non-operated (contralateral) eye (OD1).

A: Polar plot of orientation tuning curve, for monocular stimulation through the dominant eye, with gratings of 0.7 contrast and a spatial frequency of 1.6 c/deg ($n = 4$). This neuron was not spontaneously active.

B: Result of the binocular interaction protocol, as in Fig. 4-5B. A drifting 'conditioning' grating of optimal orientation (direction = 45° ; spatial frequency = 1.6 c/deg; contrast = 0.18) was presented continuously to the dominant, ipsilateral eye and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the contralateral eye ($n = 7$).

C: *Binocular interaction function*, plotting the response difference (see Fig. 4-5C) as a function of the interocular difference in orientation.

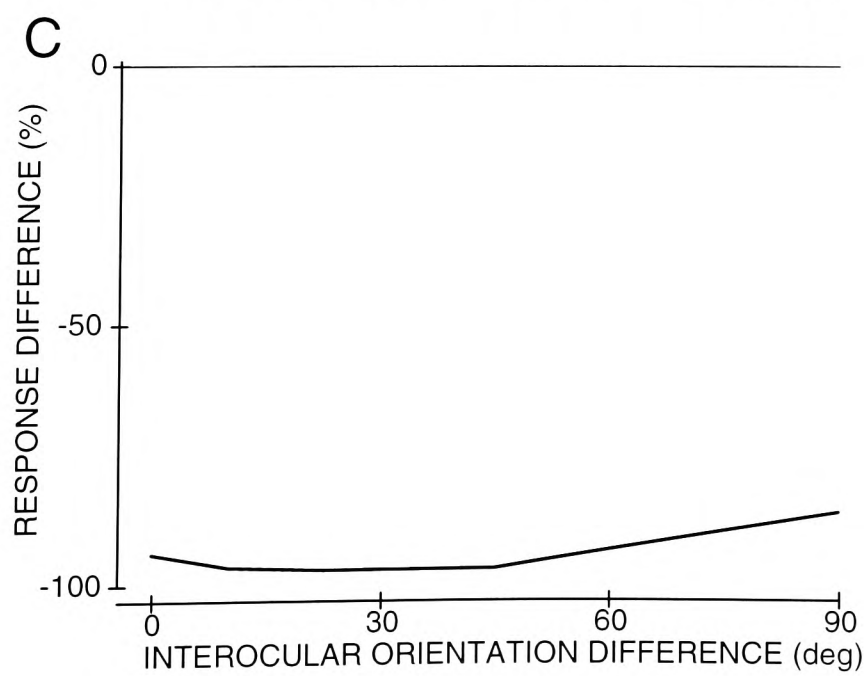
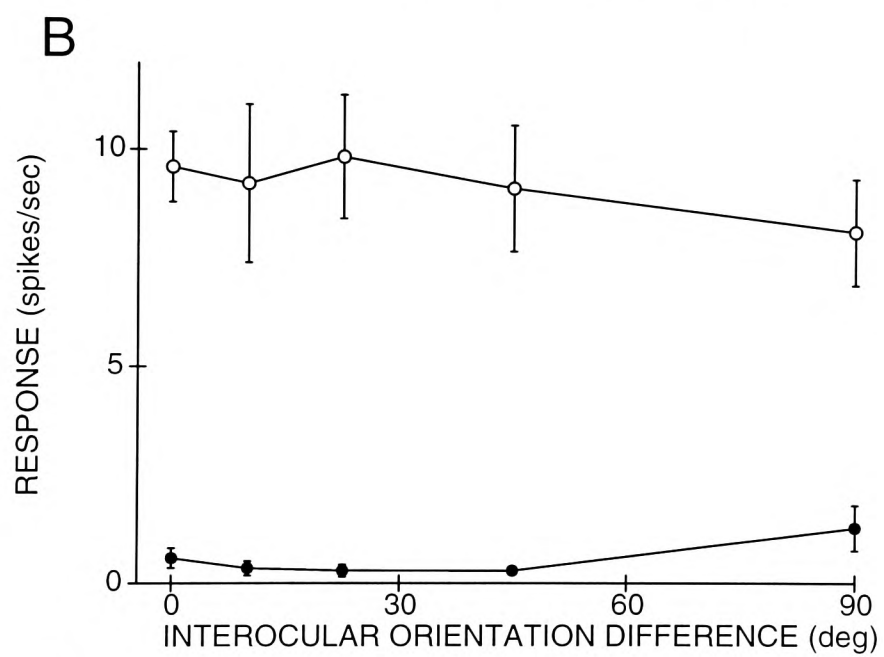
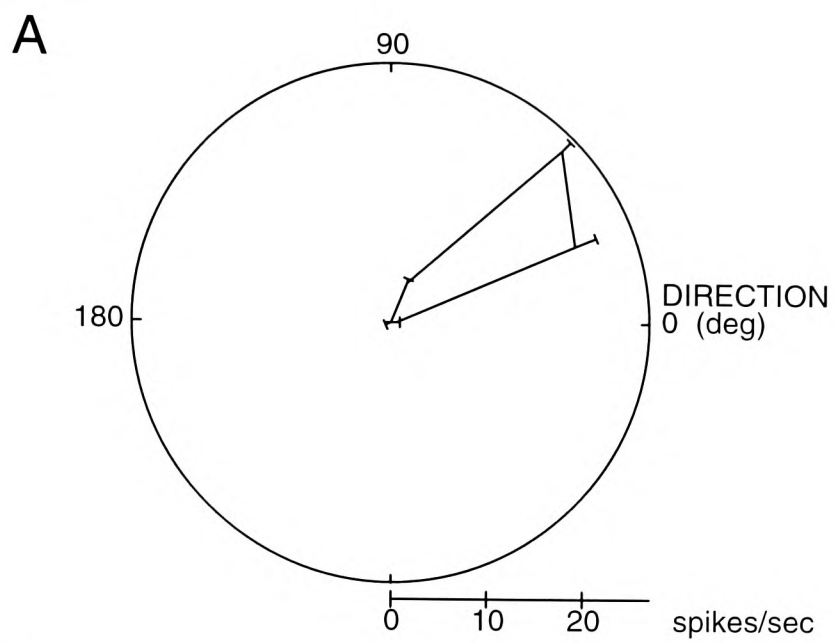


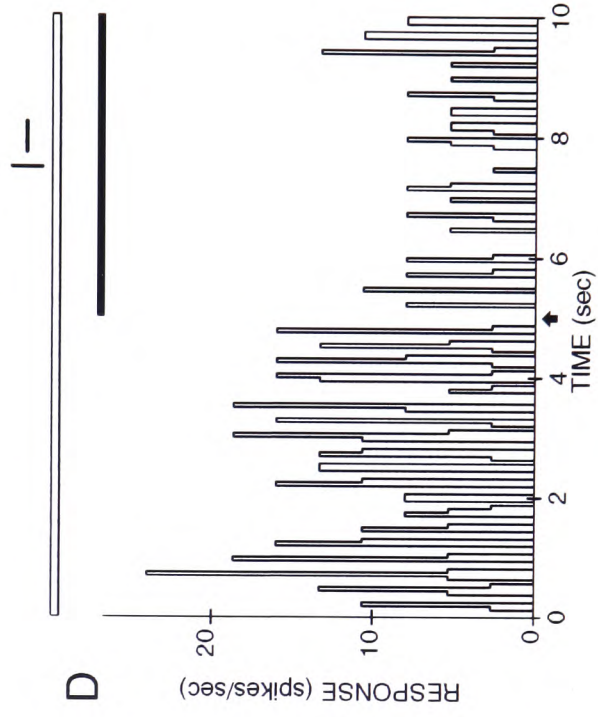
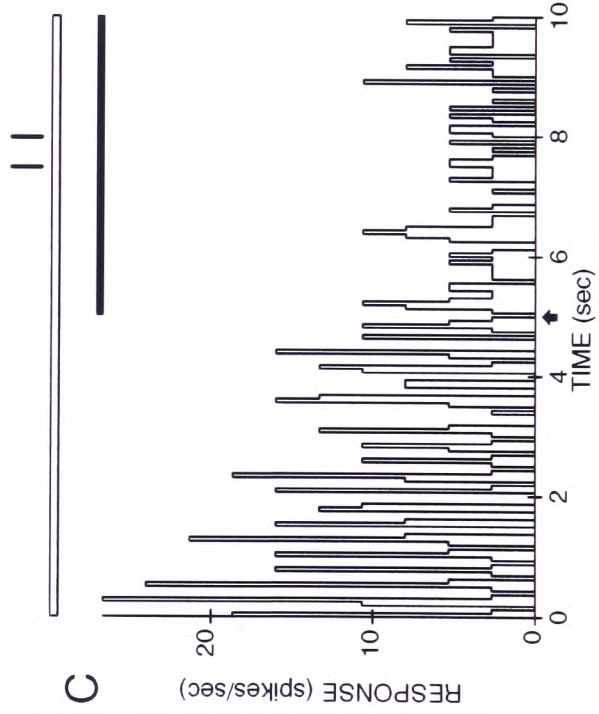
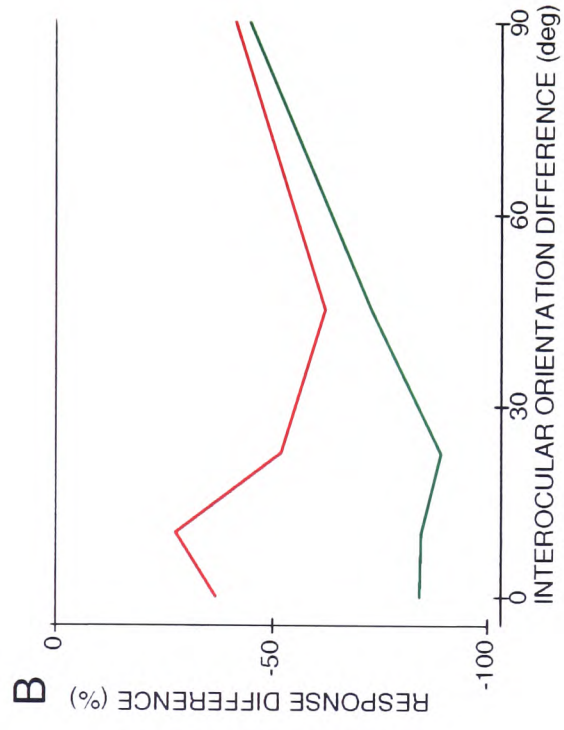
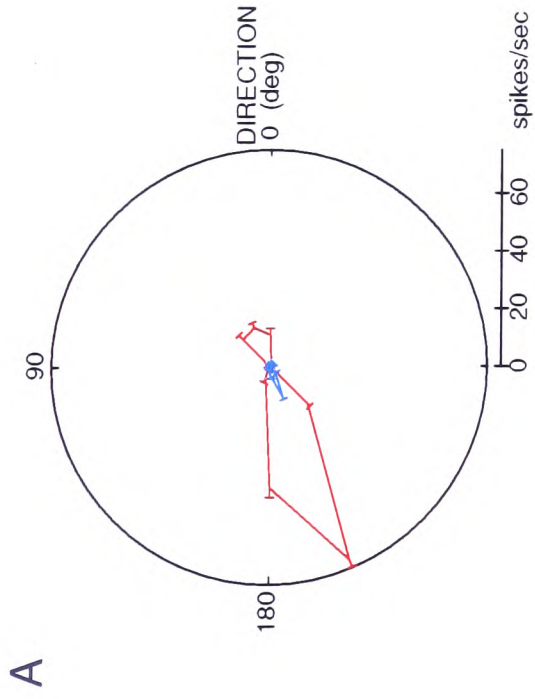
Figure 4-20

Interocular suppression in a layer 6 simple cell from monkey #115, strongly dominated by the non-operated (contralateral) eye (OD2).

A: Polar plots of orientation tuning curves obtained with monocular stimulation through the dominant eye (red lines) and non-dominant eye (blue lines), respectively, with gratings of 0.7 contrast and a spatial frequency of 2.26 c/deg ($n = 4$). This neuron was not spontaneously active.

B: Result of the binocular interaction protocol, plotting response during binocular stimulation as a percentage of the corresponding monocular response, at each interocular orientation difference. A drifting 'conditioning' grating of optimal orientation (direction = 202.5° ; spatial frequency = 2.26 c/deg; contrast = 0.18) was presented continuously to the non-operated eye and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the operated eye ($n = 7$). The red line represents the standard *binocular interaction function* (see Fig. 4-6C) for the mean neuronal discharge, while the green line shows the relative depression of the first-order Fourier component of responses during binocular *versus* monocular stimulation.

C,D: PSTHs of single-trial responses to dichoptic gratings of identical (**C**) and orthogonal orientations (**D**), respectively (for further explanations, see Fig. 4-3); bin width, 62.5 msec.



4.3. Discussion

Cats

Monocular response characteristics

As expected, the fraction of striate neurons receiving *supra-threshold* excitatory inputs from both eyes was very much reduced in all the strabismic animals. The proportion of binocularly driven cells ranged from 24% to 44% in five animals (average, 31%), compared to 91% in the control sample from normal cats. These values are in good agreement with the results of previous studies, which have shown between 15% and 31% binocular units in squinting cats and from 80 to 91% in normal animals studied with similar techniques (e.g. Hubel & Wiesel, 1962, 1965; Blakemore, 1976; Van Sluyters & Levitt, 1980; Mower et al., 1982; Crewther & Crewther, 1990).

In the samples from both exotropic animals and two of the esotropes, roughly equal numbers of cells were dominated by each eye, but in one esotrope (CS1) the OD distribution was clearly biased in favour of the non-deviating eye (see Fig. 4-1). However, the 46 units from this animal were recorded along three electrode tracks angled almost perpendicular to the cortical surface; therefore it is quite conceivable that such a nominally statistically significant skewing of the OD distribution could have been produced by uneven sampling across the OD columnar pattern of the cortex. On the other hand, it must be said that similar biases, and always towards the non-operated eye, have been reported by others for esotropic cats with definite amblyopia in the deviating eye (Mower et al., 1982; Tremain & Ikeda, 1982), although others have failed to confirm such a shift in OD (Crewther & Crewther, 1990). The possible contribution of competitive effects on the OD structure of the cortex to the aetiology of strabismic amblyopia remains a confused but intriguing question.

The properties of receptive fields studied through the operated eye in these strabismic cats were indistinguishable from those through the other eye in the same animals and from those in normal cats, in all but one respect. I saw neither unusual

scatter of receptive field positions in the deviating eye (cf. Yinon et al., 1975) nor any evidence for anomalous retinal correspondence (as reported by Shlaer et al., 1971, Cynader et al., 1984, and by Sireteanu & Best, 1992, for some neurons in area 17, area 18 and the lateral suprasylvian cortex, respectively). However, the large angles of strabismus in all animals but CS1 might have precluded compensatory shifts in receptive-field disparity.

In accordance with the majority of previous studies (e.g. Hubel & Wiesel, 1965; Freeman & Tsumoto, 1983; Kalil et al., 1984; but see Chino et al., 1983), the narrowness of orientational tuning was found to be unaffected by strabismus in cells driven by either the normal or the deviating eye. However, like Kalil et al. (1984), I found the overall distribution of preferred orientations to be skewed towards vertical. Singer et al. (1979, 1980) and Cynader et al. (1984) also reported an anisotropy in the orientation distribution of area 17 and area 18 respectively, in squinting cats, but they found an *under-representation* of vertical preferences. Sireteanu and Singer (1980) interpreted this reported preponderance of cells preferring horizontal orientations as a physiological correlate of the 'vertical effect' in human strabismic amblyopia (the fact that the visual acuity for vertical gratings is usually about $\frac{1}{2}$ octave worse than that for horizontal gratings in the squinting eye of esotropic subjects). The inconsistency of results from different studies on strabismic cats, which could simply be the result of sampling biases, renders this correlation less likely. What is needed to settle this point is a comprehensive study of orientation preferences in animals with known amblyopia, in which the vertical effect has been behaviourally demonstrated.

In none of the five strabismic cats, even CS1, which had a biased OD distribution, did I see an obvious deficit in spatial resolving power of cortical cells driven through the operated eye. This confirms results of Blakemore and Eggers (1978) from three exo- and three esotropic animals with tenotomy-induced squint. However, in a recent study of five tenotomized cats with convergent squint and behavioural amblyopia, Crewther and Crewther (1990) did find subtle deficits in neural acuity for cells driven through the operated eye, in particular for cells with strong input from the normal eye. There was a

difference in the **mean** acuity of cells through the two eye, though, interestingly, the best acuities through the squinting eye (which would surely be expected to limit the behavioural capacity) were not very different from those through the normal eye. The possible contribution of changes in the spatial resolution of cortical neurons to strabismic amblyopia certainly deserves further study.

Binocular interactions

In normal cats, most binocular neurons show distinct binocular summation and often facilitation when both eyes are stimulated at the appropriate retinal disparity (e.g. Barlow et al., 1967; Nikara et al., 1968; Freeman & Ohzawa, 1986a,b), as long as the stimuli are roughly matched in orientation (Blakemore et al., 1972; Nelson et al., 1977). Even the majority of apparently monocular cells in normal cats (except in layer 4 itself; see Chapter 3), receive subliminal excitatory input from the silent eye, which can be revealed by the effects of binocular stimulation (Kato et al., 1981). Previous studies (Xue et al., 1987b; Cynader et al., 1984) have shown that such binocular interactions are reduced or absent for monocular cells in strabismic cats. I too found only one monocular unit out of 50 that showed any evidence of excitatory interaction during binocular stimulation, and that in the very unusual form of a transient facilitation at the onset of the stimulus in the silent eye (see Fig. 4-3B).

On the other hand, my results establish that the majority of apparently monocular neurons in strabismic animals *do* receive significant input from the silent eye, but its net effect is powerfully inhibitory. Moreover, by contrast with both facilitatory and suppressive interactions in normal cats (Blakemore et al., 1972; Nelson et al., 1977; see Chapter 3) the interactions in strabismic cats are largely independent of the parameters of the stimulus presented to the non-dominant eye. Suppression with iso-oriented gratings, independent of spatial phase, similar to the interactions I saw, was also seen by Freeman and Ohzawa (1988) in a small proportion of apparently monocular cells in monocularly deprived cats.

Iso-orientational facilitation and cross-orientational suppression similar to that seen in the majority of cells in normal cats (Chapter 3) was displayed by just five of the 85 cells studied in strabismic animals (see Fig. 4-5). However, none of these cells exhibited normal disparity selectivity, and even 28 out of the 35 binocular cells tested (80%) did *not* show any binocular summation. There were no obvious differences between esotropic and exotropic, or between alternating and non-alternating animals in the fraction of cells showing binocular summation. Together, these findings might well account for the failure of binocular summation at threshold or subthreshold contrast levels in strabismic humans (Levi et al., 1979), as well as the loss of stereopsis and the lack of interocular transfer of visual after-effects in most strabismic patients (e.g. Movshon et al., 1972; Ware & Mitchell, 1974; Mitchell et al., 1975). It is worth noting that some strabismic observers do exhibit residual binocular interactions (Hess, 1978; Anderson et al., 1980); such capacities may depend on the proportion of cortical cells still showing positive binocular interaction.

It would be worth testing whether, with the contrast of the dominant-eye stimulus set to threshold, subthreshold facilitation through the silent eye could be revealed in monocular units that do not show suppression through that eye. However, that seems rather unlikely, as there is anatomical evidence suggesting that in V1 of strabismic cats and primates, clustered intracortical connections (which are the presumed substrate of excitatory interactions) are restricted to cortical columns of like ocular dominance (Löwel & Singer, 1991; Tychsen & Burkhalter, 1992).

Site and nature of interocular suppression

The neural origin of the profound interocular suppression experienced by strabismic observers has been a matter of speculation for some time (e.g. Blake & Lehmkuhle, 1976; Hess, 1991). Psychophysical investigations have utilized the phenomenon of adaptation caused by prolonged exposure to high-contrast gratings (Blakemore & Campbell, 1969), which is, because of its orientation-dependence, thought to depend on neural effects in the visual cortex. Blake and Lehmkuhle (1976) showed that a grating

presented to one eye of a strabismic alternator is capable of producing adaptation, i.e. an elevation of contrast threshold, even if the eye viewing it is perceptually suppressed at the time. If the site of suppression were at or prior to that of the neural change underlying adaptation, any after-effect should be diminished or absent. Blake and Lehmkuhle (1976) concluded that suppression occurs *after* the site of grating adaptation which is assumed to be the primary visual cortex.

In contrast, Hess (1991) found that strabismic amblyopes, who show grating adaptation when viewing monocularly with their amblyopic eyes, do not exhibit threshold elevation through the amblyopic eye after adapting under binocular viewing conditions. Hess' data suggest that suppression takes place *at* the site of adaptation, probably in V1. The apparent contradiction between his findings and those of Blake and Lehmkuhle (1976) led Hess (1991) to speculate that sites and mechanisms of suppression might differ in alternating and amblyopic squinters. On the other hand, Lehky and Blake (1991) have recently shown that, in normal observers, the magnitude of threshold elevation resulting from adaptation to a grating made invisible because of binocular rivalry does depend on the contrast of the adapting pattern (and hence the time for which it is perceived), and this made them revise their views about the site of the interaction underlying rivalry. Similar experiments are needed in strabismic humans.

Physiological data presented here provide strong support for the notion that the primary visual cortex is indeed the site of interocular suppression in strabismus; the results do not suggest a difference in that respect for alternating and unilaterally fixating animals, nor for exotropes and esotropes. The suppressive interactions seen at the cellular level clearly resemble pathological suppression in strabismic humans in their relative independence of stimulus parameters, in particular in the virtual absence of selectivity for orientation (see Holopigian et al., 1988).

Inhibitory interocular interactions that are independent of relative orientation are seen in the lateral geniculate nucleus (LGN) of normal animals (Moore et al., 1992; Chapter 3). One might then argue that the interocular suppression seen in the cortex of

strabismic animals is simply due to the loss of excitatory binocular interactions in the cortex itself, revealing the non-specific interactions actually taking place in the LGN.

For several reasons I believe that this is not the case. For one thing, interactions at the subcortical level are usually much weaker than those that seen in the cortex. Second, interocular suppression in the LGN, unlike that in the cortex, does not appear to depend on the temporal sequence of stimulus presentation: it can be observed with simultaneous onset of stimulation in both eyes (Moore et al., 1992) as well as with stimulation of the dominant eye preceding silent-eye stimulation (Chapter 3). Third, the occasional occurrence of orientation-dependent interocular suppression (see Fig. 4-10) might be taken as an indication that inhibitory inputs derive from oriented cortical units but usually appear non-selective in strabismic animals because of convergence of inputs tuned to different orientations. Finally, interocular suppression in the cortex of strabismic cats is clearly *less* prominent in layer 4, which receives the main geniculate input, than in supra- and infragranular layers (where it reached significance for two-thirds of all cells studied).

Given current knowledge of the microcircuitry of the primary visual cortex (see Douglas et al., 1989; Douglas & Martin, 1991), it seems likely that intracortical inhibitory connections, mainly within cortical layers 2/3, form the substrate for interocular suppression in strabismus, which is then fed down to infragranular layers. In view of the fact that suppression in strabismic cats is largely independent of the orientation and spatial phase of the suppressive stimulus and occurs for a wide range of spatial frequencies in the suppressing eye, the inhibitory inputs responsible are likely to derive from a pool of cells with somewhat scattered receptive fields (but roughly in retinal correspondence with the excitatory inputs from the dominant eye; see Fig. 4-13) and a wide range of preferred orientations and spatial frequencies.

It is tempting to speculate that the suppressive mechanism is depends on reciprocal inhibitory connections between neighbouring ocular dominance columns dominated by the right and left eyes (cf. Chapter 3). At first thought, this hypothesis seems to be at odds with a recent anatomical study showing that intrinsic horizontal connections

between OD columns are selectively lost in V1 of strabismic kittens: following cortical injections of fluorescent beads into one OD column, clusters of retrogradely labelled cells were predominantly (75-90%) found in territories activated by the *same* eye (Löwel & Singer, 1992). However, even in normal animals, up to 75% of retrogradely labelled clusters are found in columns of like ocular dominance (Yoshioka et al., 1992). Furthermore, these clusters of cells probably mainly indicate regions sending excitatory projections to the injection site, since inhibitory connections form only a small fraction of all intrinsic projections in V1 (see Kisvárdy et al., 1986) and they are more uniform in their distribution (Somogyi et al., 1983; Albus et al., 1991). It is therefore conceivable that the reduction in horizontal connectivity between columns of opposite eye dominance observed in strabismic animals is due to a selective loss of excitatory but not inhibitory connections (see Levi et al., 1979). This notion receives further support from the finding that synchronization of neuronal responses in V1 of strabismic cats is reduced between cells dominated by different eyes, again reflecting a lack of long-range excitatory interactions (König et al., 1993).

Contrast gain control and alternation of suppression

Interocular suppression in the cortex of strabismic cats exhibits a gross non-linearity in that it depends critically on the immediate history of visual stimulation (Fig. 4-14). A neuron is switched into the suppressed mode only when the monocular suppressive stimulus appears while the cell is already being activated through the other eye. To some extent, there is a perceptual parallel of this non-linearity in that perceptual suppression also does not occur when stimuli are briefly presented simultaneously to the two eyes of strabismic amblyopes: both are seen, 'falsely fused' (Wolfe, 1986). Moreover, my data suggest that the percentage suppression of response is largely independent of the contrast of the suppressed stimulus (see Fig. 4-15). This suggests that, if suppression results from interocular inhibition, that inhibition may be divisive rather than subtractive, in contrast with reductions in responsiveness that occur during exposure to conflicting *monocular* stimuli (iso-oriented gratings of different drift frequency) in one eye and that are characterized by an elevation of threshold contrast

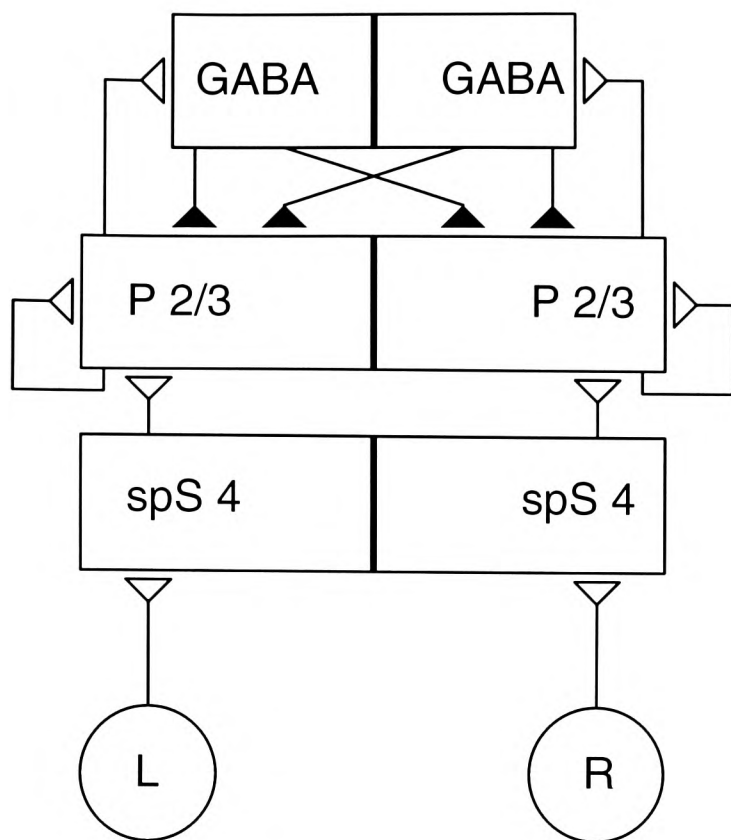
and a rightward shift of the contrast gain function without a change in slope (Morrone et al., 1987).

The interocular control of contrast gain in strabismic suppression clearly resembles that seen in normal cat cortex (Chapter 3). I argued that the responsiveness of cortical neurons is likely to depend crucially on 'amplification' performed by local excitatory circuitry within the same ocular dominance column (cf. Douglas et al., 1989; Nicoll & Blakemore, 1993). The intrinsic excitatory circuitry mediating this local amplification may indeed be unaffected by squint (Löwel & Singer, 1992; König et al., 1993). Perhaps surviving inhibitory connections between adjacent ocular dominance columns modulate the gain of this local intrinsic excitation. A model of the proposed cortical microcircuitry is presented in Fig. 4-21.

The very long latencies of suppression observed for some neurons in this study (Fig. 4-3C,D) may reflect a slow build-up in the attenuation of the excitatory amplifier. The alternations in eye dominance experienced by many strabismic subjects (those without deep amblyopia) might either occur spontaneously, possibly due to adaptation or fatigue of the inhibitory neurons responsible (Lehky, 1988), or be triggered by visual stimuli appearing in the fovea of one eye. Such fatigue might also explain why interocular suppression is seen only with staggered but not with simultaneous binocular stimulus presentation: preliminary stimulation through one eye alone could cause fatigue of inhibitory interneurons in that eye's OD columns, so that when the other eye is subsequently stimulated, inhibition from its columns exceeds that in the reverse direction, leading to suppression.

Figure 4-21

Schematic diagram of a cortical microcircuitry in strabismic cat cortex that could generate binocular responses of the type described above (compare Fig. 3-20). Circles marked 'L' and 'R' represent left and right eye inputs to spiny stellate cells in layer 4 of V1 ('spS 4'). Layer 2/3 pyramidal cells are indicated as 'P 2/3', GABA-ergic interneurons as 'GABA'. Open and filled triangles represent excitatory and inhibitory synapses, respectively. Thick vertical lines separate cells with exclusively left-eye excitatory input from those with exclusively right-eye excitatory input. For further explanations see text.



Suppression and amblyopia

Schor (1991) has suggested that chronic suppression resulting from strabismus, if present during the sensitive period for development of the visual system, might actually precipitate amblyopia in the deviating eye. The region of the visual field most affected by acuity loss in the squinting eye of human amblyopes is indeed correlated with the central region of the suppression scotoma (Sireteanu & Fronius, 1981). However, the strengths of suppression and amblyopia were found to be inversely correlated in a group of patients with strabismic or anisometropic amblyopia (Holopigian et al., 1988).

Recently, Harrad and Hess (1992a) found that suppression, determined as the elevation of contrast threshold in the amblyopic eye caused by a masking grating in the normal eye, is more powerful in strabismic amblyopia than in many cases of anisometropic amblyopia (after normalization for monocular threshold differences), suggesting that the relationship between suppression and amblyopia is not straightforward. Harrad and Hess (1992b) proposed that the nature of suppression is different for different types of amblyopia, and that the depth of suppression is inversely related to the degree of binocularity, i.e. the percentage of surviving binocular neurons (see Blake, 1989). This notion is supported by my finding that, in strabismic cats, striate neurons with more or less balanced inputs from the two eyes show binocular interactions closest to normal (cf. Chapter 3), at least in terms of their orientation selectivity, whereas the majority of cells with weak or no direct input from one eye exhibit profound suppression.

My results further suggest that neural suppression of either eye in alternators (like cat DS2) as well as of the fixating eye in non-alternating animals is of roughly the same strength, i.e. not obviously dependent on angle of squint or state of fixation. However, no suppression was seen among cells dominated by the deviating eye in two convergent strabismic cats. In one of them (CS3) the small number of cells studied does not allow any further conclusions. The other (CS1) was characterized by small-angle esotropia, an apparent shift in ocular dominance towards the non-operated (fixating) eye and perhaps even a slight neural acuity deficit in the deviating eye. This animal seemed the most

likely among the cats included in this study to have been deeply amblyopic in the central part of the visual field of the deviating eye. The finding that cells in this animal, with receptive fields in the area centralis of the deviating eye, were not suppressed by stimuli in the other eye is reminiscent of the inverse correlation between the strengths of amblyopia and suppression in strabismic humans (Holopigian et al., 1988). Suppression appears to decrease once deep amblyopia is established, as if there were no longer a 'need' for strong suppression of the amblyopic eye to eliminate double vision. The relationship between the degree of interocular suppression and the angle of squint, mobility of the eye, and presence of amblyopia deserve further examination. So too does the question of whether non-selective suppressive interactions are mainly limited to the central visual field, as for strabismic suppression in humans (Sireteanu & Fronius, 1981; Sireteanu, 1982). In the periphery of the visual field, some degree of surviving binocular facilitation might be expected (see Sireteanu, 1982).

Suppression in strabismus and in binocular rivalry

Apart from the fact that interocular suppression in the cortex of strabismic cats is usually independent of relative orientation, it is remarkably similar in its characteristics to the suppression produced by dichoptic gratings of differing orientation in normal cat cortex (Chapter 3). Both phenomena show broad spatial frequency tuning, with clear suppression often being exerted by gratings of spatial frequencies too high to elicit any excitatory monocular responses from the cells tested. Also, both types of interocular suppression are independent of relative spatial phase, even for identical dichoptic stimuli for strabismic animals. Third, strabismic suppression and rivalrous suppression are of roughly equal strength (about 50% of monocular responses) and occur in similar proportions of neurons. Finally, and most importantly, both phenomena exhibit the same dynamics of interocular gain control. These similarities add weight to the suggestion that, even in normal animals, suppression is essentially non-selective for orientation but is swamped by powerful facilitation for matching stimuli (see Chapter 3).

My results strongly support the view that the neural mechanisms underpinning suppression in binocular rivalry and strabismus, respectively, are similar if not identical. This notion finds support in a recent study showing similar suppression of pattern reversal evoked potentials in normal observers experiencing binocular rivalry and in unilaterally fixating strabismic subjects (McCulloch et al., 1992).

Psychophysical investigations have also revealed similarities between rivalry and strabismic suppression. Most notably, the two phenomena build up with similar 'rise times' after an initial period of perceptual fusion (Wolfe, 1986). Moreover, if stimuli in the two eyes of a strabismic amblyope are made equally visible by attenuating the stimulus in the dominant eye, alternating suppression occurs, similar to binocular rivalry in normal subjects (Leonards and Sireteanu, 1993). However, threshold elevation in strabismic suppression (although varying among subjects) is usually much greater than in binocular rivalry (Holopigian et al., 1988). Also, rivalry suppression is more affected by interocular spatial-frequency differences than is strabismic suppression (Schor, 1977) and appears more strongly to reduce the visibility of short wavelength stimuli (Smith et al., 1985). It is conceivable that these differences between the two phenomena reflect minor modifications of the underlying neural network. The greater depth of suppression in strabismics may, for instance, simply be due to a higher *number* of cells involved in reciprocal inhibition rather than to a fundamental difference in the neural mechanism itself (see Blake, 1989). On balance there is reason to believe that the pathological suppression associated with strabismus evolves from the same neural circuitry that produces alternating suppression in normal binocular rivalry, and that both are due to inhibitory interaction between OD columns in the striate cortex.

Monkeys

Ocular dominance distribution

As in the strabismic cats, the fraction of striate neurons receiving direct inputs from both eyes was small in the strabismic monkey. At 40%, the proportion of binocularly driven cells was much reduced compared with values between 60% and 80% reported for normal animals (Hubel & Wiesel, 1968; Schiller et al., 1976; Blakemore et al., 1978). Furthermore, for cells outside layer 4C, a clear bias in the OD distribution towards the non-operated eye was observed. More radical shifts in the OD distribution towards the non-operated eye have been reported for monkeys in which unilateral esotropia was induced by myectomy of the lateral rectus, resection of its antagonist and anchoring of the eye in its deviated position for a week (Von Noorden & Dowling, 1970). These animals all exhibited a depletion of binocularly driven cells and a predominance of cells dominated by the normal eye; they were also severely amblyopic in the operated eye (Von Noorden & Dowling, 1970; Von Noorden, 1973a; Baker et al., 1974; Harwerth et al., 1983), with the exception of two monkeys in which esotropia had been induced comparatively late (at 92 and 511 days of age). When esotropia was induced in the first five weeks of life, within two weeks from the operation OD shifts were observed in favour of the non-deviated eye that were similar in magnitude to those reported following comparable periods of monocular deprivation (Crawford & Von Noorden, 1979). In a monkey that was made esotropic at 13 weeks of age, no such shift was found.

The preponderance of cells dominated by the non-operated eye in the animal studied here (with esotropia induced after 19.5 weeks) most likely reflects a sampling bias, as only one electrode penetration was made (see above). Notably, in layer 4 equal numbers of cells were driven by the normal and the operated eye, respectively. Whatever the effect of squint on ocular dominance, the degree of behavioural amblyopia in the operated eye was quite pronounced (2.4 octaves) despite the late onset of

strabismus, a result that has not been observed before. The question which factors determine the development of amblyopia in strabismus remains an open issue.

Binocular interactions

While two neurons with clear excitatory inputs from both eyes (despite the convergence of the visual axes by 30°) displayed facilitatory interactions selective for stimulus orientation, 36% of all cells, dominated by either the normal or the deviating eye, were suppressed by stimuli of *any* orientation presented to the other eye. Thus, at the single-cell level, binocular interactions in the esotropic macaque were comparable in type and magnitude to those observed in the five strabismic cats. These similarities provide strong vindication for the use of cats to study the effects of strabismus, at least with respect to the mechanisms of suppression. However, an intriguing difference between cats and monkey was found in the laminar distribution of orientation-independent suppression: while in the cat this phenomenon was present among equal proportions of cells in all layers outside layer 4, it appeared to be confined to layers 4B and 6 in the macaque (for the relatively small sample of cells studied here). The absence of suppression among 9 cells recorded from layers 2/3 certainly provides strong support for the hypothesis that interactions at the cortical level (beyond layers 2/3 in the macaque) rather than at the subcortical level (in the LGN) underpin this phenomenon. The observation of an orientation-dependent effect of suppression on the firing *pattern* in one simple cell (Fig. 4-20) may be interpreted in terms of non-linear convergence of inputs representing the two eyes, as has been argued by Freeman and Ohzawa (1988) in a similar case.

The laminar distribution of orientation-independent suppression in monkey V1 may have to be interpreted in the context of the generally higher laminar specificity of certain response properties in monkey V1 as compared with cat area 17. Possibly, interocular suppression in the monkey is more pronounced for neurons of the magnocellular ('M') pathway: neurons in the magnocellular layers of the LGN project to cortical layer 4C α which sends projections to layer 4B. The magnocellular pathway then diverges, with

one stream of processing going *via* layers 2/3 to the thick cytochrome oxidase stripes of V2 (see Livingstone & Hubel, 1988), and another (together with that from layer 6, which also contains a high proportion of direction selective units; Hawken et al., 1988), projecting directly to area MT (V5) of the superior temporal sulcus. On the basis of the present findings one might then predict a high incidence of orientation-independent suppression in higher-order motion processing areas.

Alternatively, the predominant occurrence of interocular suppression in the deep cortical layers may be one functional correlate of the degree of inhibitory connectivity, which has been shown to be richer in infragranular layers of macaque V1 than in any other layer apart from the upper border of layer 2 (Somogyi et al., 1981). More experiments are needed in order to confirm and extend the present results. Moreover, a study of binocular interactions in V1 of normal monkeys is required for comparison.

5. CONSEQUENCES OF DARK-REARING AND OF REVERSE OCCLUSION FOR BINOCULAR INTEGRATION IN CAT PRIMARY VISUAL CORTEX

In the preceding chapters I have analysed binocular interactions in normal adult cats and in cats that had discordant binocular experience because of strabismus from the time of eye-opening until adulthood. The establishment of binocular excitatory inputs to visual cortical neurons, as demonstrated through standard, *monocular* stimulation, is known to depend critically on concordant binocular experience during the so-called sensitive period of cortical development (see *Introduction*). The susceptibility of the primary visual cortex to manipulation of its inputs has a very similar time course for different experimental paradigms such as monocular deprivation, reverse occlusion and artificial strabismus. In the cat, it starts at about two weeks of age, peaks between four and five weeks and lasts until more than three months of age (see *Introduction*). Here, a first attempt is made at determining in more detail the requirements for the establishment of the two types of interocular interactions, which I have suggested, in the two previous chapters, underlie binocular integration: 1) iso-orientational disparity-selective interaction (or disparity-independent facilitation), and 2) orientation-independent suppression.

I have chosen two experimental paradigms that, under certain conditions, ultimately result in relatively normal binocularity, unlike the situation in strabismus. These are: 1) dark-rearing, and 2) reverse occlusion, both followed by normal binocular experience. Dark-rearing from birth leads to severe deficits both behavioural and at the level of neuronal responses in V1 (see *Introduction* and Mitchell & Timney, 1984). However, if its duration does not exceed four months, then a subsequent period of binocular recovery will result in a restoration of close-to-normal visual acuity within four months of visual experience (Timney et al., 1978). Also, relatively brief dark-rearing has little effect on the overall OD distribution, with the majority of cells displaying responses,

albeit weak and erratic, to stimulation of either eye (Blakemore & Van Sluyters, 1975; Maffei & Bisti, 1976; Frégnac & Imbert, 1978).

While early reverse occlusion of sufficient duration, with no subsequent binocular vision, leads to recovery of vision in the initially deprived eye and a bias in the OD distribution towards that eye, a short but physiologically optimal period of reverse occlusion with subsequent binocular vision results in a normal degree of cortical binocularity but, paradoxically, severe bilateral amblyopia (Murphy & Mitchell, 1986, 1987).

Here, I ask whether normal binocular interactions develop in V1 of cats subjected to altered visual experience during the sensitive period develop under conditions that lead to conventional binocularity of a normal level. In other words, is a normal OD distribution well correlated with interactions underlying normal binocular function and can it therefore be taken as an easily obtainable indicator for the latter?

5.1. Methods

Animals

Data were obtained from three cats. One animal, RO1, was monocularly deprived on postnatal day 8. Under halothane anaesthesia and with topical anaesthetic (Amethocaine) instilled in the conjunctival sac, the conjunctiva was dissected from the upper and lower lid margins and sutured with fine absorbable chromic collagen. The lid margins were then sutured with fine silk. During the period of deprivation, the sutured eye was checked daily for any openings between the lids. On postnatal day 29, the eyelids were re-opened under general anaesthesia, any thickened conjunctival tissue was carefully removed, and topical antibiotic was applied. The initially non-deprived eye was then lid-sutured for 9 days, before the lids were re-opened in the same way. The experiment was performed after a further period of 31 days of normal binocular vision (i.e. the animal was 10 weeks old by that time).

One cat, DR1, was reared in absolute darkness from birth until 5 weeks of age. Precautions were taken to ensure that the animal was never exposed to light during this period (for details see Kind, 1993). Subsequently, the animal had normal visual experience until the age of 15 months, when the recording experiment was carried out. A second animal, DR2, was dark-reared from birth to 100 days (~ 14 weeks) of age, and thereafter had normal binocular experience for another 100 days. This cat developed a severe bilateral convergent strabismus, the amplitude of which was determined as 20° during paralysis. (The other two cats, RO1 and DR1, had normal ocular alignment.) Similar ocular misalignments have been reported previously as a consequence of long-term dark-rearing (Cynader, 1979; Kaye et al., 1982), while in normally reared kittens normal eye alignment develops during the first two postnatal months (Olson & Freeman, 1978). After removal from the dark room, DR2 showed no signs of visually guided behaviour but improved slowly over subsequent weeks.

Surgery, recording and histology

All experimental procedures were as described in the previous chapters. All micro-electrode penetrations were made at stereotaxic positions corresponding to the representation of the centre of the visual field in the primary visual cortex, area 17.

5.2. Results

Reverse-occluded cat RO1

In the reverse-sutured animal, 24 cells (4 simple, 17 complex) were recorded in one electrode track in the left hemisphere, ipsilateral to the initially deprived eye; 21 cells were quantitatively tested for binocular interaction, after initial monocular characterization. Receptive field centres had eccentricities of 2 to 3 deg.

Monocular response properties

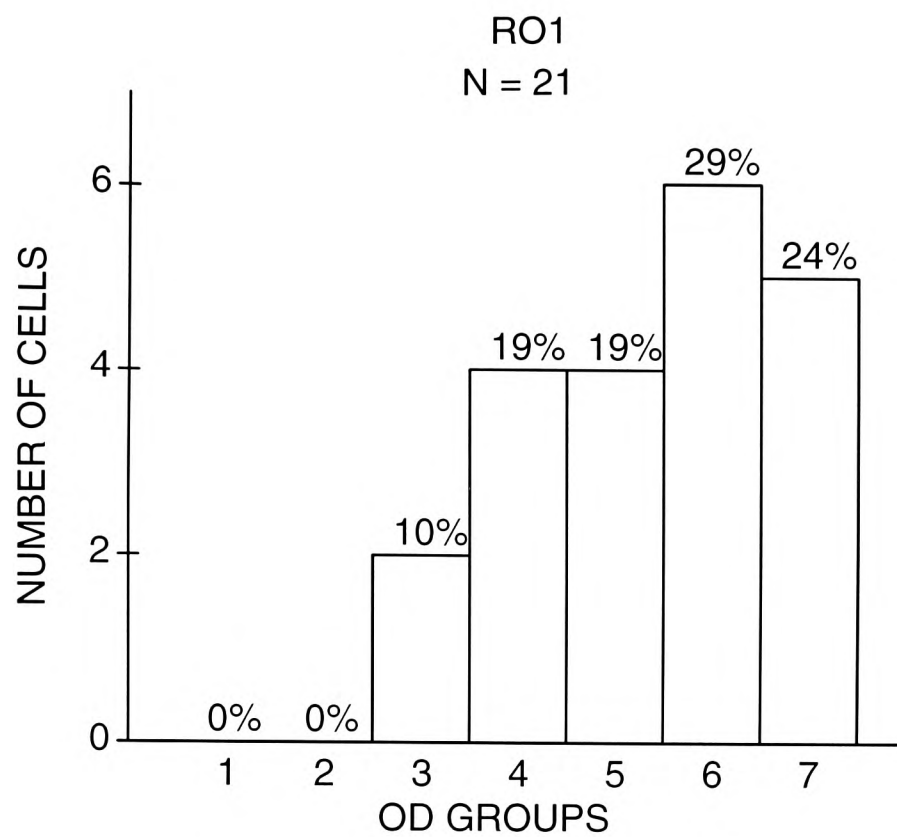
Of 24 cells, 19 (81%) were binocular by conventional definition, while 5 (19%) could only be driven through the left, initially deprived eye. The overall OD distribution is shown in Fig. 5-1. The apparent skew towards the initially occluded eye, albeit nominally significant, may well represent a sampling bias due to the small sample size. However, this bias might also reflect the fact that the shift in OD towards the initially deprived eye would have been virtually total at the time of onset of binocular vision, after 9 days of reverse occlusion beginning at about 4 weeks of age (Movshon, 1976). In any case, the percentage of binocular cells is within the normal range (see Chapter 4).

Neural acuities were measured as cut-off spatial frequencies, as described in the previous chapter. All 24 cells were tested through the initially deprived eye which was dominant for all but two of them. The mean acuity ($\pm$ SD) of 1.32 ± 0.55 c/deg was significantly lower ($p < 0.005$) than that obtained for a control sample of 61 cells recorded from normal (adult) animals under identical conditions (1.92 ± 0.60 c/deg). The mean acuity of cells dominated by the initially deprived eye reached only about 2/3 of that value. However, it has to be borne in mind that this animal was only 69 days old when the experiment was carried out: at that age neural acuity of normally reared animals has reached at best 3/4 of adult levels (cf. Derrington & Fuchs, 1981).

For 9 neurons with clear inputs from the initially open eye (OD groups 3-5), acuity was also measured through that eye. The value obtained of 1.29 ± 0.45 c/deg (mean $\pm$ SD) was virtually identical to that for cells dominated by the initially sutured eye.

Figure 5-1

Ocular dominance (OD) distribution of cells recorded from reverse-occluded cat RO1. Neurons were classified in one of seven ocular dominance groups following the scheme devised by Hubel and Wiesel (1962). Since recordings were made from the hemisphere ipsilateral to the initially deprived eye, OD group 7 represents cells exclusively driven through that eye, while OD group 1 signifies cells with excitatory input from the initially open eye only.



Binocular interactions

As described in the previous chapters, a cell was taken to display binocular interactions if the introduction of a grating of any orientation to the cell's non-dominant eye significantly affected the response to an optimal grating already present in the dominant eye. This was the case for 19 of the 21 cells tested. For 16 cells, varying degrees of binocular summation were observed when the stimuli in the two eyes had matching or similar orientations (and directions of drift). Of these 16 neurons, nine (56%, but only 43% of the entire sample tested) displayed significant interocular suppression when the two gratings had orthogonal orientations. An example for orientation-selective interactions of this kind, resembling those seen in the majority of binocular cells in normal animals (see Chapter 3) is shown in Fig. 5-2.

One monocular cell, located in layer 4, exhibited interocular suppression which was independent of interocular orientation differences (as in layer 4 of normal animals; Chapter 3), while two neurons showed suppression but only when the gratings in the two eyes substantially differed in orientation. Both of these cells were dominated by the initially deprived eye (OD6 and OD7, respectively) and did not show any binocular summation with matched gratings. One of them, a monocularly driven simple cell recorded in layer 4, is illustrated in Fig. 5-3.

Figure 5-2

Orientation dependence of binocular interactions in a layer 2/3 simple cell from reverse-occluded cat RO1. This cell was mildly dominated by the initially deprived eye (OD5).

A: Polar plot of orientation tuning curves obtained with monocular stimulation through the ipsilateral (dominant) eye (red) and the contralateral (non-dominant) eye (blue), respectively. Mean responses ($\pm$ SEM, $n = 5$) are plotted as a function of the direction of drift of a grating (contrast = 0.7) of optimal spatial frequency (0.4 c/deg) presented to each eye alone. The interrupted circles in the centre indicate the mean levels of spontaneous discharge measured during these two determinations of tuning.

B: Results of the binocular interaction protocol. The dominant eye was continuously stimulated with a 'conditioning' stimulus whose direction of drift was 90° , corresponding to the optimum obtained from the polar plot in **A** (contrast = 0.35; spatial frequency = 0.4 c/deg). Gratings (contrast = 0.7; spatial frequency = 0.4 c/deg) were presented to the non-dominant (normal) eye at five different orientations, over a 90° range, clockwise from the orientation of the optimal conditioning stimulus. The abscissa indicates the difference in orientation between the stimuli shown to the two eyes. Filled circles ($\pm$ SEM; joined by solid lines) and unfilled circles ($\pm$ SEM; linked by interrupted lines) plot the mean firing rates during binocular stimulation with gratings differing in orientation by the angle shown on the abscissa and during the preceding periods of monocular stimulation, respectively ($n = 10$). The arrow indicates the mean level of spontaneous discharge, measured during interleaved blank presentations.

C: Binocular responses as a function of relative phase disparity, with gratings of matched orientation. The spatial phase of the optimally oriented drifting grating presented to the dominant eye (contrast = 0.35; spatial frequency = 0.4 c/deg) was fixed at an arbitrary value while that of the identically oriented grating presented to the other eye was varied in phase. Mean responses in spikes/sec ($\pm$ SEM, $n = 5$) are plotted against the relative phase difference between the two gratings. Unfilled circles plot the control values during preceding periods of monocular stimulation.

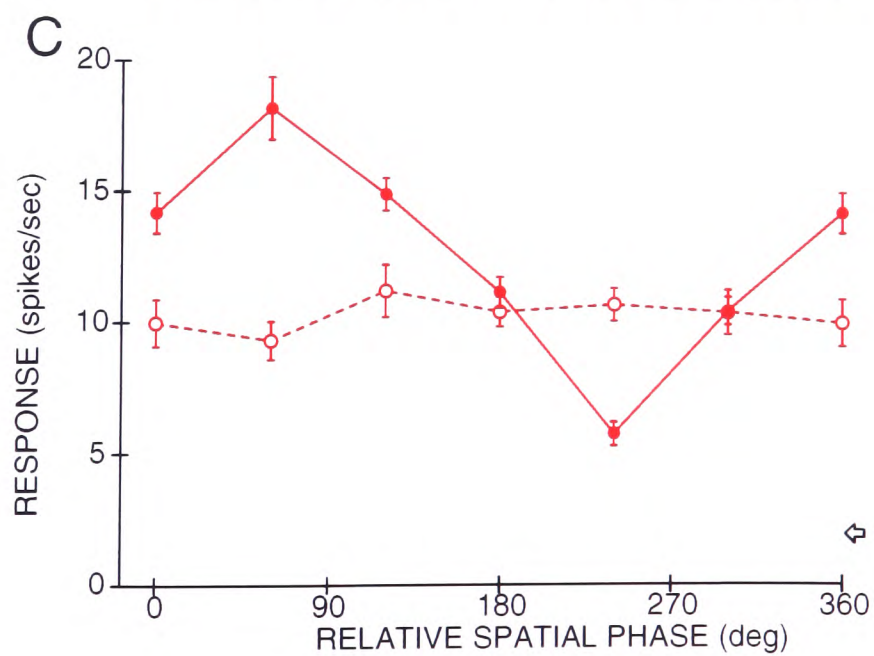
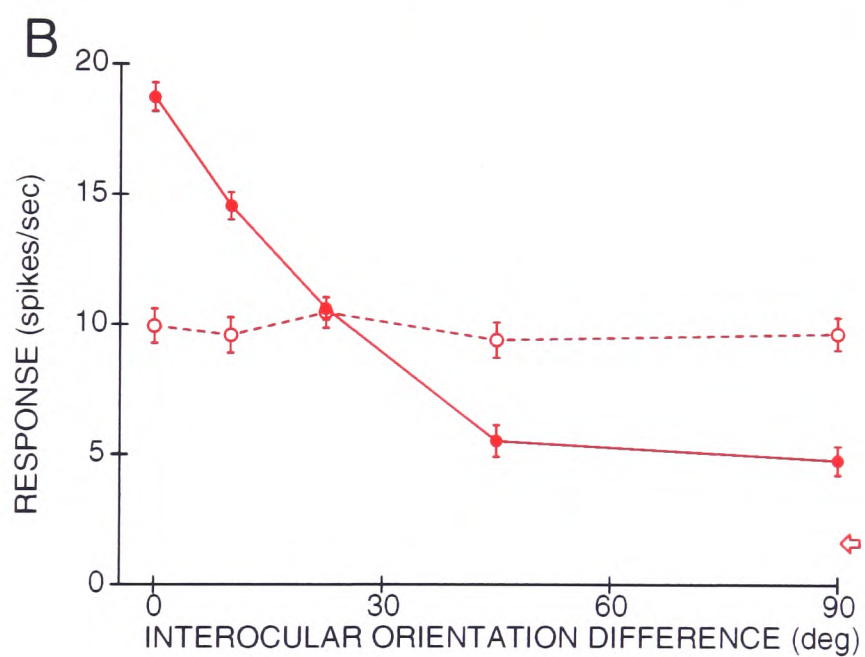
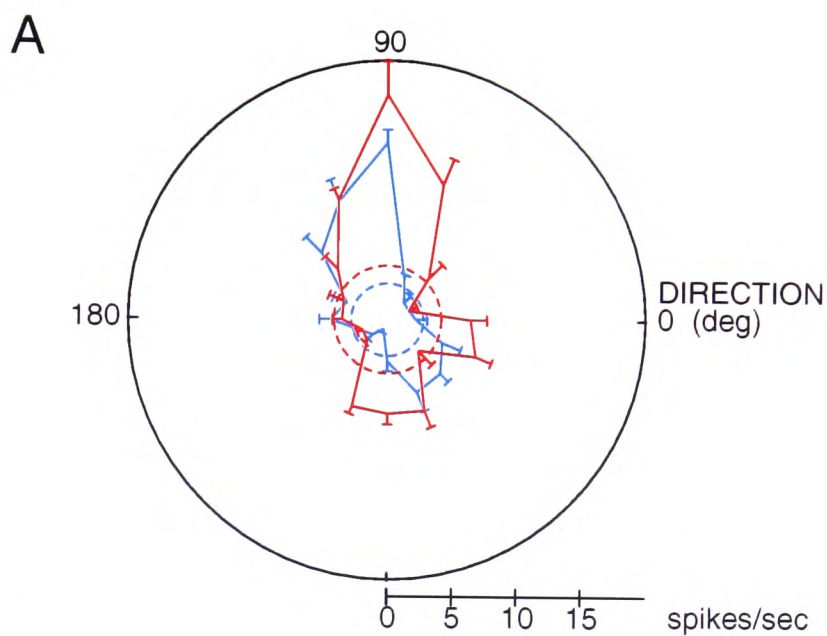
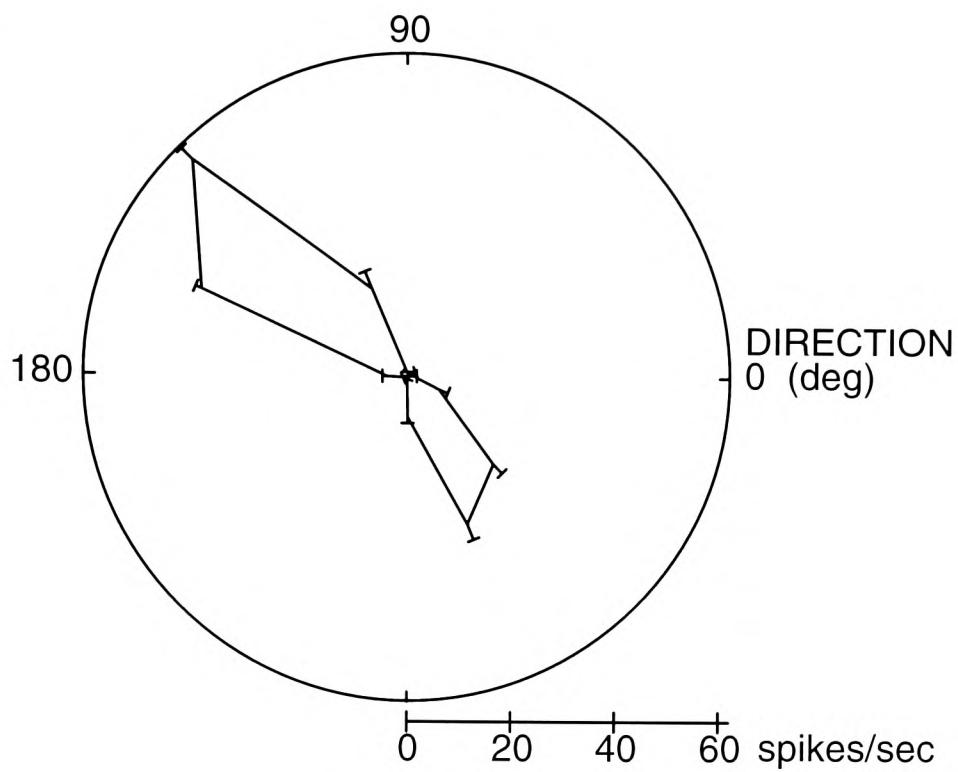
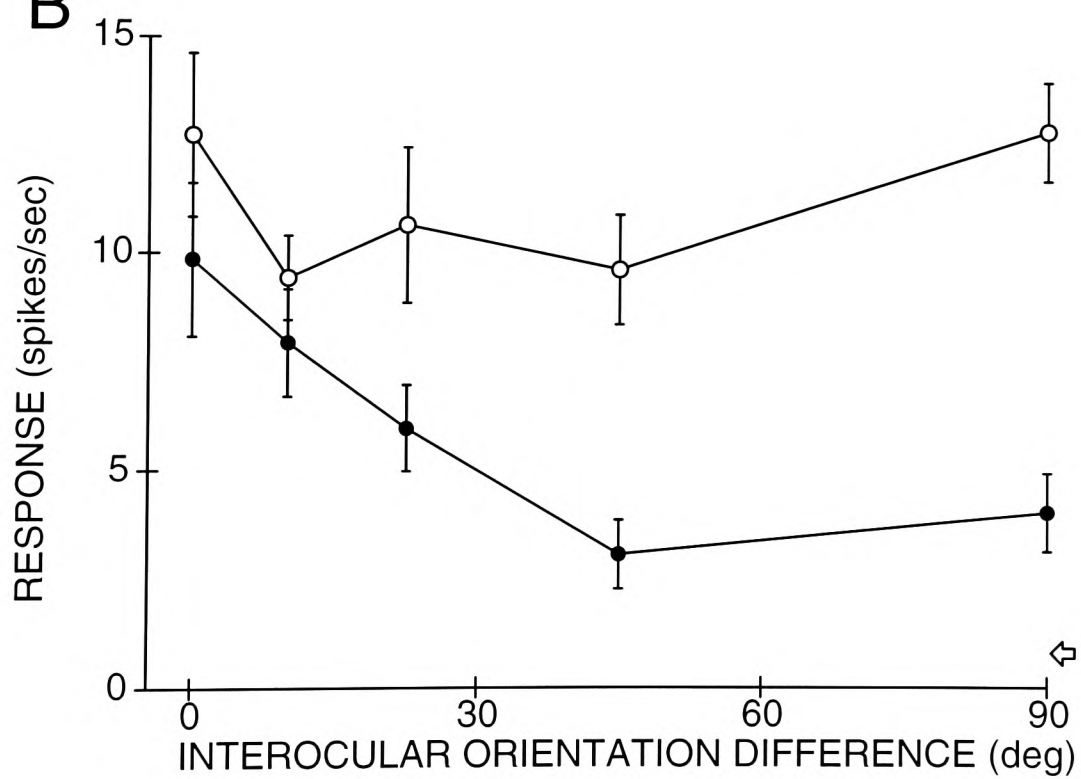


Figure 5-3

Orientation dependence of binocular interactions in a layer 4 simple cell from reverse-occluded cat RO1. This cell was excitable only through the initially deprived eye (OD7).

A: Polar plot of orientation tuning curve obtained with monocular stimulation through the ipsilateral (initially deprived) eye. Mean responses (+ SEM, $n = 5$) are plotted as a function of the direction of drift of a grating (contrast = 0.7) of optimal spatial frequency (0.4 c/deg). This cell displayed no spontaneous activity.

B: Results of the binocular interaction protocol, as in Fig. 5-2B. A drifting 'conditioning' grating of optimal orientation (direction = 135° ; spatial frequency = 0.4 c/deg; contrast = 0.35) was presented continuously to the dominant, ipsilateral eye and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the contralateral eye ($n = 8$). This neuron exhibited marked adaptation during conditioning stimulation (compare these monocular responses with best response in A).

A**B**

Short-term dark-reared cat DR1

In this animal (dark-reared until 5 weeks and then given normal vision until 15 months), 23 cells were recorded in one electrode track in the left hemisphere; 15 cells (1 simple, 14 complex) were quantitatively tested for binocular interaction, after initial monocular characterization. Receptive field centres were all within 2 deg of the area centralis.

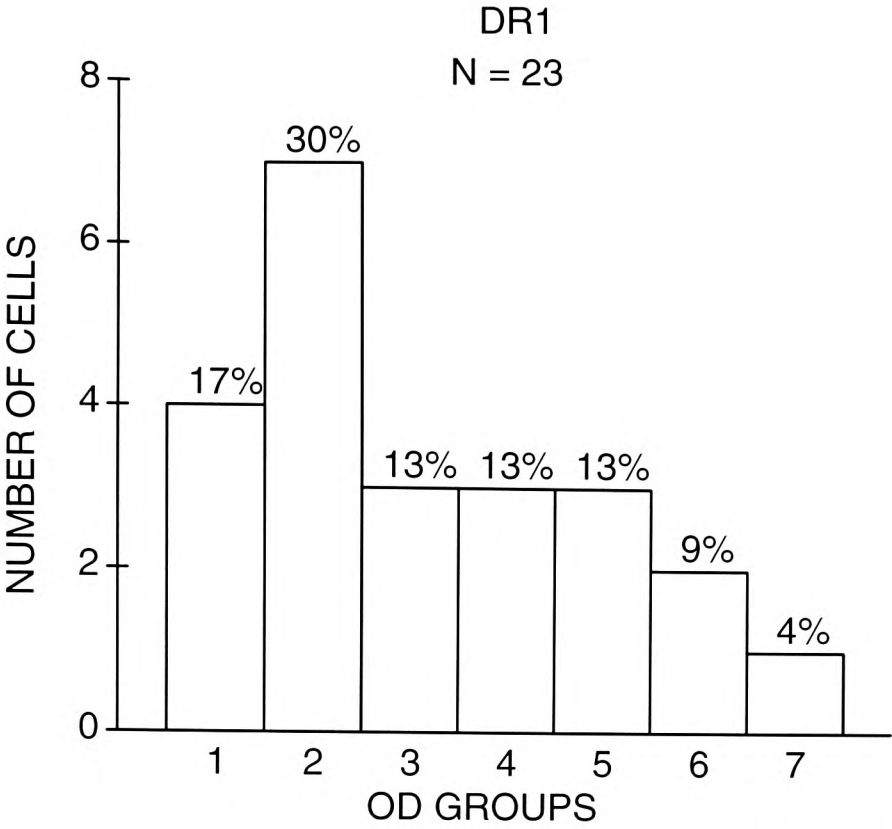
Monocular response properties

The overall OD distribution for 23 cells is illustrated in Fig. 5-4; 18 cells (78%) responded to stimulation of either eye, while 5 (22%) were monocularly driven. These percentages are comparable to those reported for normal animals, although the *degree* of binocularity appears to be somewhat reduced compared to normal animals (cf. top left histogram in Fig. 4-1).

Acuties (cut-off spatial frequencies) were determined for 19 neurons; cells responded up to a mean 2.15 c/deg (SD, 0.61 c/deg). For 61 neurons from 5 normal animals, acuities of 1.92 ± 0.60 c/deg were measured (see above). Thus, there was no obvious deficit in spatial resolving power at the neural level.

Figure 5-4

Ocular dominance (OD) distribution of cells recorded from short-term dark-reared cat DR1. Neurons were classified in one of seven OD groups following the scheme devised by Hubel and Wiesel (1962).



Binocular interactions

For 10 of the 15 cells tested, the introduction of gratings to the non-dominant eye significantly affected the response to an optimal grating already present in the dominant eye, while a third of the cells in this sample did not show any binocular interactions at all. Among the latter were two monocular cells located in layer 4 as well as 3 cells outside layer 4 that were strongly dominated by the contralateral eye (OD group 2).

Eight neurons displayed binocular summation for stimuli that were similar in orientation (and direction of drift) in the two eyes. Seven of them displayed significant interocular suppression when the two gratings had orthogonal orientations, thus showing orientation-selective interactions resembling those seen in the majority of binocular cells in normal animals (see Chapter 3). A particularly striking example is shown in Fig. 5-5. Two cells recorded from infragranular layers, one of OD group 6, the other of OD group 7, exhibited suppression for gratings of any interocular orientation differences, similar to the behaviour of most cells in strabismic animals.

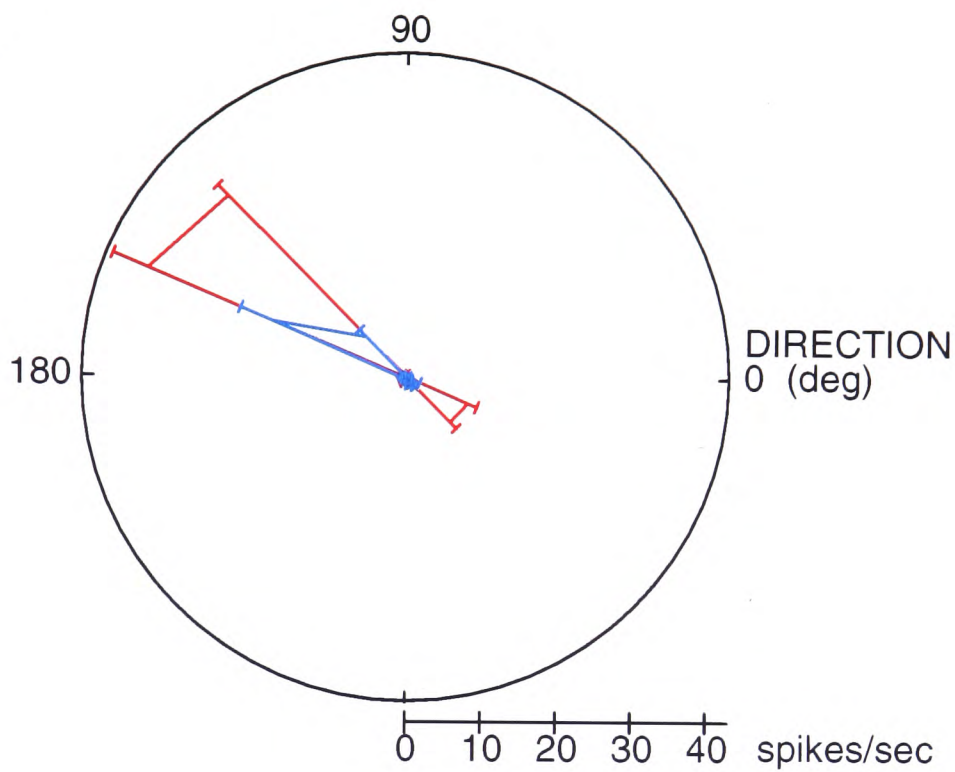
Figure 5-5

Orientation dependence of binocular interactions in a layer 6 complex cell from dark-reared cat DR1. This cell was mildly dominated by the ipsilateral eye (OD5).

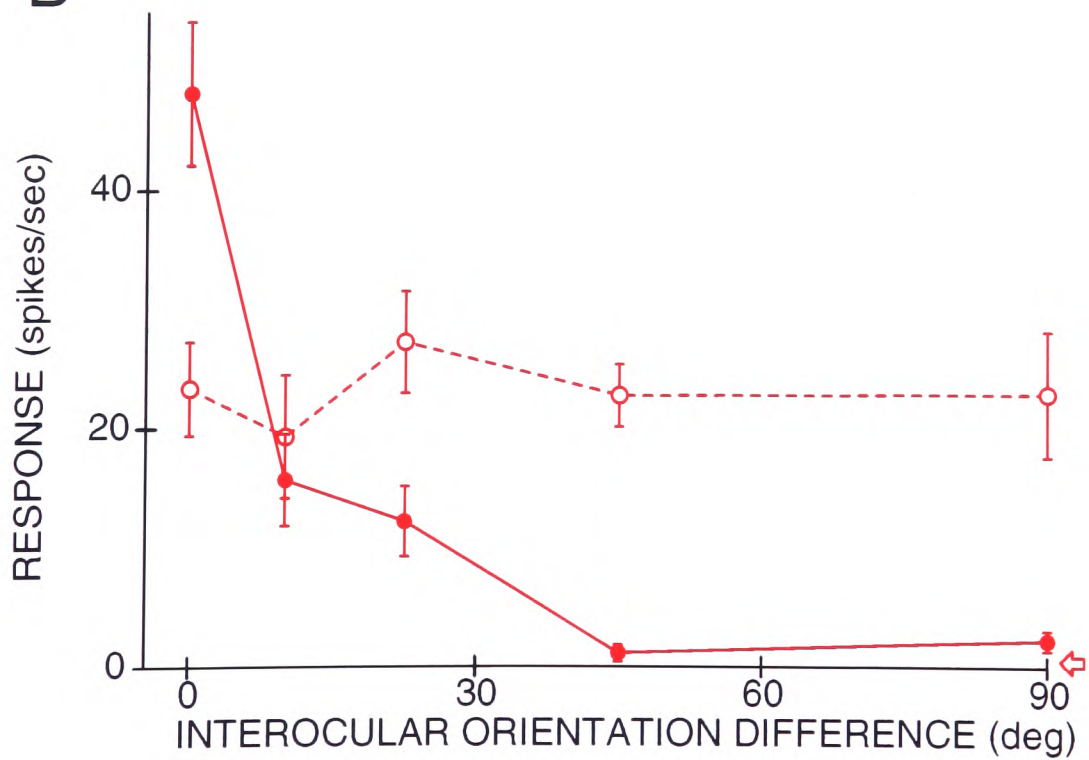
A: Polar plot of orientation tuning curves obtained with monocular stimulation through the ipsilateral (dominant) eye (red) and the contralateral (non-dominant) eye (blue), respectively. Mean responses (+ SEM, $n = 4$) are plotted as a function of the direction of drift of a grating (contrast = 0.7) of optimal spatial frequency (1.13c/deg) presented to one eye alone. Spontaneous discharge was only 0.4 spikes/sec.

B: Results of the binocular interaction protocol, as in Fig. 5-2B. The dominant eye was continuously stimulated with a 'conditioning' stimulus whose direction of drift was 157.5° , corresponding to the optimum obtained from the polar plot in **A** (contrast = 0.35; spatial frequency = 1.13 c/deg), and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the contralateral eye ($n = 6$). The arrow indicates the mean level of spontaneous discharge, measured during blank presentations.

A



B



Long-term dark-reared cat DR2

In this animal (dark-reared until 14 weeks followed by normal vision until about 28 weeks), 31 cells were recorded in three electrode tracks; 9 cells (all complex) were quantitatively tested for binocular interaction, after initial monocular characterization. Receptive field centres were within 3 deg of the area centralis.

Monocular response properties

The responsiveness of neurons recorded from this long-term dark-reared cat (with pronounced convergent strabismus) appeared much reduced, on average, when compared with cells recorded from both normal and other experimental animals, including the shorter-term dark-reared cat. The majority of cells (21 out of 31, or 68%) was monocularly driven (see Fig. 5-6); I have found similar proportions of monocular neurons in cats with surgically induced squint (cf. Chapter 4, Fig. 4-1).

For 21 neurons, the cut-off spatial frequency, for which responses fell to the spontaneous level, was determined. The mean neural acuity ($\pm$ SD) was 1.99 ± 0.56 c/deg; it did not differ significantly from that found in normal adult animals (see above).

I estimated the half-width at half height of orientation tuning curves of 9 neurons (for details see Chapter 4). Mean half-width ($\pm$ SD) was $31.7^\circ \pm 12.9^\circ$; another two units were non-oriented. Compared to a mean half-width of 22.2 ± 7.0 for 44 cells recorded from normal animals, orientation-selectivity in the sample from the long-term dark-reared cat DR2 was significantly worse ($p < 0.005$).

Figure 5-6

Ocular dominance (OD) distribution of cells recorded from long-term dark-reared cat DR2. Neurons were classified in one of seven ocular dominance groups following the scheme devised by Hubel and Wiesel (1962).

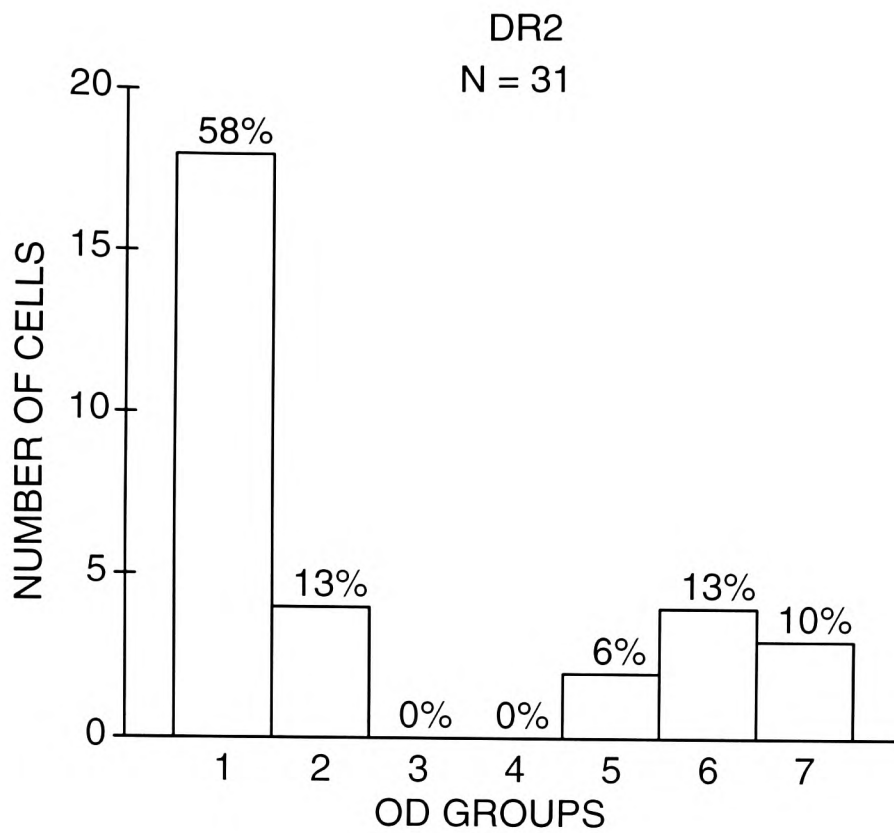


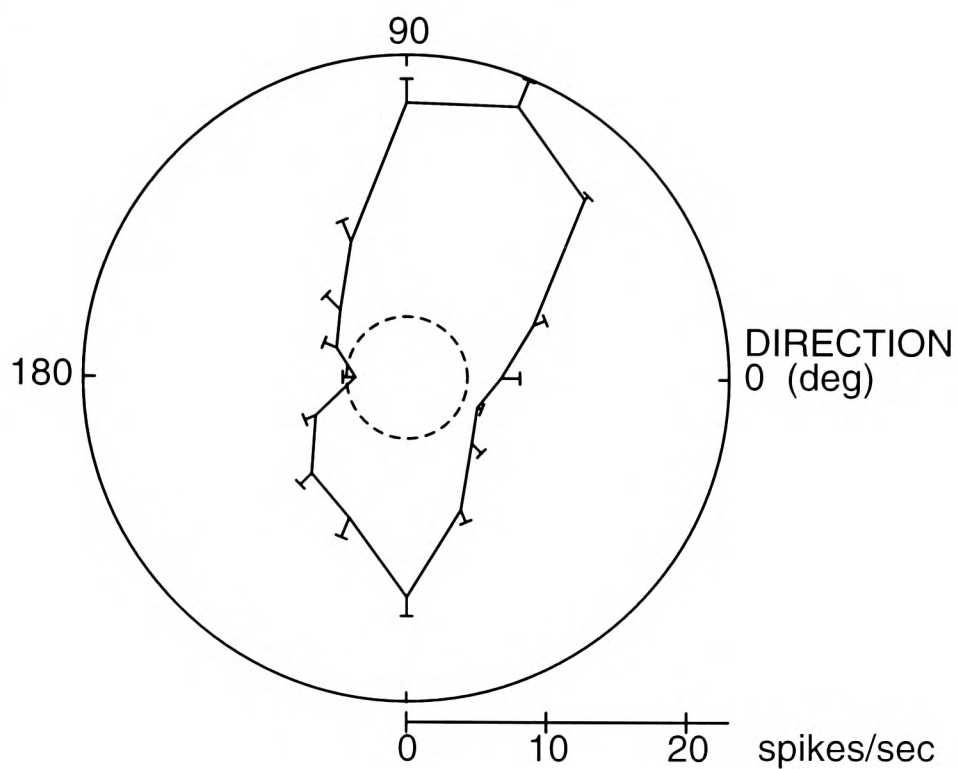
Figure 5-7

Orientation dependence of binocular interactions in a layer 5 complex cell from dark-reared cat DR1. This cell could be driven only through the contralateral eye (OD1).

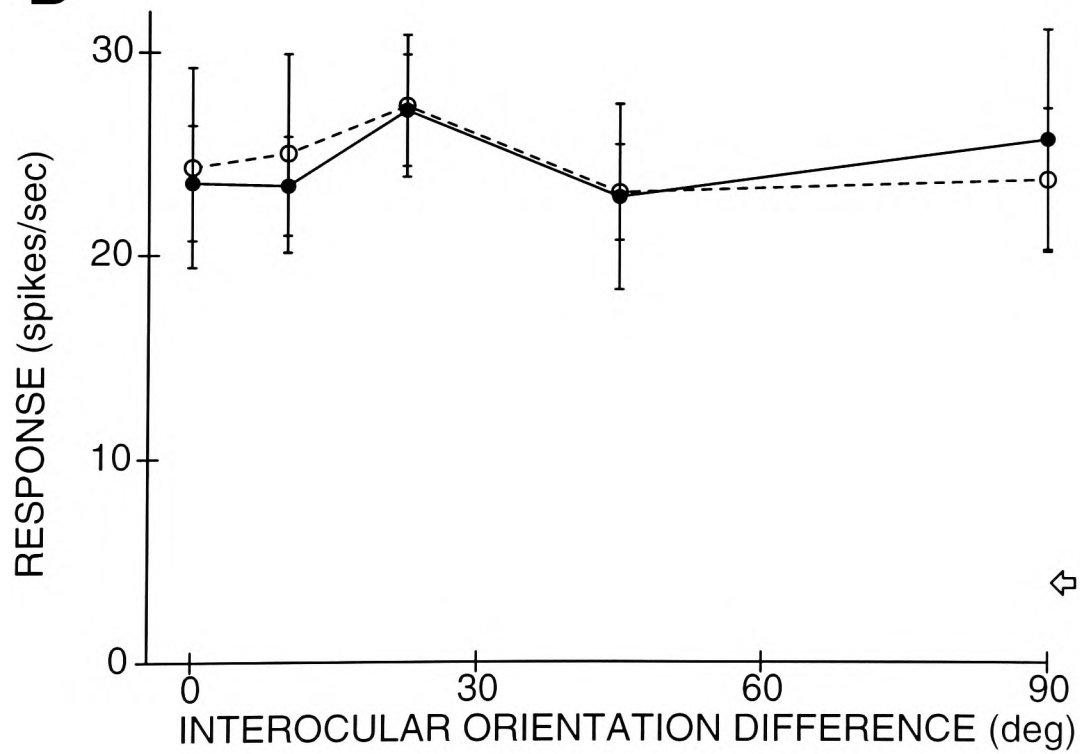
A: Polar plot of orientation tuning curves obtained with monocular stimulation through the contralateral (dominant) eye. Mean responses ($\pm$ SEM, $n = 5$) are plotted as a function of the direction of drift of a grating (contrast = 0.7) of optimal spatial frequency (0.56 c/deg). The interrupted circle in the centre indicates the mean level of spontaneous discharge.

B: Results of the binocular interaction protocol, as in Fig. 5-2B. The dominant eye was continuously stimulated with a 'conditioning' stimulus of optimal direction of drift (67.5° ; contrast = 0.35; spatial frequency = 1.13 c/deg), and gratings of various orientations (same spatial frequency, contrast = 0.7) were shown intermittently to the silent (ipsilateral) eye ($n = 5$). The arrow indicates the mean level of spontaneous discharge, measured during blank presentations. There were no binocular interactions, either excitatory or inhibitory, with any combination of orientations.

A



B



Binocular interactions

Only nine of the 31 cells could be tested binocularly with the stimulation paradigm employed in previous experiments, since the remaining cells gave unreliable responses or adapted dramatically during conditioning stimulation of the dominant eye.

Of these nine cells, only one showed weak binocular summation when gratings of matching orientations were presented to the two eyes. None of the remaining eight cells showed any significant effects, when a grating of any orientation was introduced to the non-dominant or 'silent' eye, while the dominant eye was being stimulated with a grating of optimal orientation and spatial frequency. This is illustrated in Fig. 5-7 for a complex cell that was driven by the contralateral eye.

5.3. Discussion

Early disruption of binocular experience

Preliminary data presented here appear to indicate that some cortical cells display near-normal orientationally-tuned binocular interactions in cats deprived of normal binocular stimulation during the first 5 weeks of life (either through reverse occlusion or dark-rearing) but given a substantial subsequent period of binocular vision. Such rearing conditions allow binocularity, as conventionally defined (i.e. excitability through either eye), to develop. Both in the reverse-occluded animal, RO1, and in the short-term dark-reared animal, DR1, binocular summation was observed for a majority of cells when dichoptic stimuli had similar orientations in the two eyes. Most of those, and more than 40% of **all** cells (9 out of 21 in RO1 and 7 out of 15 in DR1) showed interocular suppression for orthogonally oriented gratings, a fraction only slightly lower than that found in normal animals (25 out of 52 cells = 48%; see Chapter 3). On the other hand, orientation-independent suppression, which is the norm in strabismic cats (Chapter 4), was displayed by very few neurons in cats RO1 and DR1.

The effects on conventional binocularity of reverse-suturing followed by binocular vision, as observed in RO1, are in agreement with previous reports (Murphy & Mitchell, 1986, 1987). The preponderance of cells dominated by the initially occluded eye may be due to the relatively brief period of binocular recovery, as compared to rearing paradigms employed by Murphy and Mitchell, but is more likely to reflect a sampling bias or simply a persistent effect of the virtually total shift in dominance likely to have been caused by the period of reversal starting at only 4 weeks of age (see Movshon, 1976). My data on neural acuities may correlate with behavioural findings by Murphy and Mitchell (1986, 1987) of bilateral amblyopia despite quite normal conventional binocularity; however, the apparent acuity deficit that I found is more likely due to the young age of the animal studied (cf. Derrington & Fuchs, 1981).

The present data do not suggest that the bilateral amblyopia seen after reverse occlusion is precipitated by some form of abnormal binocular integration (such as a

predominance of interocular suppression), as may be the case in strabismus. However, it has to be borne in mind that the initial effect of unilateral lid-suture is a pronounced inhibitory influence of the deprived eye on responses elicited through the non-deprived eye, before functional inputs from the deprived eye disappear completely with more prolonged deprivation (Freeman & Ohzawa, 1988). If a similar effect were to be seen after reverse occlusion, with the reverse-sutured eye establishing suppression upon responses from the initially deprived eye, then it might contribute to the deterioration of vision in the initially non-deprived eye during the subsequent period of binocular experience. Clearly, a study of binocular interactions immediately after the end of the period of reverse occlusion is needed to shed more light on this issue.

As expected, the cat subjected to five weeks of dark-rearing followed by binocular experience until adulthood had recovered virtually normal receptive field properties, when tested with conventional monocular stimuli (for review see Mitchell & Timney, 1984). For the small sample of cells studied, binocular interactions were largely normal with respect to the orientation-tuning of summation and suppression. On the other hand, the number of cells exhibiting no obvious binocular interactions (5/15) was rather high in this animal. Since all cells that showed binocular facilitation with iso-oriented stimuli were of the complex type and I did not study their tuning for disparity, no conclusions can be drawn as to whether a neural substrate for disparity sensitivity and, therefore, stereopsis was present in this animal.

It has been shown that dark-rearing prevents maturation of neuronal response properties, if prolonged beyond the third postnatal week (Blakemore & Van Sluyters, 1975). From previous work it is known that under normal rearing conditions neurons in kitten V1 develop adult-like disparity selectivity (i.e. phase-dependent binocular facilitation and occlusion, respectively) between 3 and 5 weeks of age (Pettigrew 1974; Freeman & Ohzawa, 1992); in parallel, maturation of binocular depth perception is observed (Timney, 1981). However, the above data suggest that the **capacity** of V1 to develop normal binocular interaction may survive during short-term dark-rearing until

after 5 weeks of age, arguing in favour of the idea of an extension of the sensitive period under these conditions (see Mitchell & Timney, 1984).

Effects of long-term visual deprivation

Data obtained from the long-term dark-reared cat DR2 imply that prolonged total deprivation results in a loss of any binocular interaction and the capacity to redevelop it. Presumably this means that intrinsic cortical connections between neurons of opposite eye dominance are lost and cannot be regained. While recovery of monocular response properties is substantial during subsequent binocular experience, even after more than three months of dark-rearing, neither binocular facilitation nor suppression are observed. This finding is in line with behavioural observations of a severe deficit in stereopsis of cats raised with similar regimens of dark-rearing and recovery (Kaye et al., 1982). Interestingly, this was true not only for animals that developed convergent squint following exposure to light, but also for orthotropic animals: in a depth discrimination task they all performed just as poorly binocularly as they did monocularly.

Apparently, long-term dark-rearing results in a permanent effective loss of connections underlying binocular interactions, irrespective of eye (mis)alignment. It would be worth testing this hypothesis on cats reared under conditions identical to those for DR2 but showing normal ocular alignment, in particular in view of evidence that cats raised with binocular lid-suture do display some phase-specific interactions (Ohzawa & Freeman, 1988). On the other hand, long-term monocular lid-suture leads to a loss of any functional input from the deprived eye (Freeman & Ohzawa, 1988), similar to the situation seen in the present study after long-term dark-rearing.

Anatomically, the development of (excitatory) clustered horizontal connections in cat cortex has been studied in some detail. In normally reared animals, injection of retrograde tracers reveals crude clusters of labelled cells even from the end of the first postnatal week. This pattern is refined through a decrease of the proportion of labelled cells between clusters, until the adult organization appears by the end of the first postnatal month (for review see Katz & Callaway, 1992). Apparently, neither dark-

rearing nor binocular deprivation affect the emergence of crude clusters (Luhmann et al., 1990a; Callaway & Katz, 1991; Lübke & Albus, 1992); they do, however, prevent the refinement of the early pattern (Callaway & Katz, 1990, 1991), and prolonged deprivation degrades the clustered organization of horizontal connections (Luhmann et al., 1990a). On the other hand, if normal vision is restored to a binocularly deprived animal at six weeks of age, then the crude clusters present at that stage will refine to a normal adult state by three months (Katz & Callaway, 1992).

Nothing is as yet known about specific effects of deprivation on the pattern of intrinsic inhibitory connections, particularly between neurons of opposite ocularity. In summary, available anatomical data support the notion that binocular deprivation (dark-rearing) initially delays the development of intracortical connections, which may well form the substrate for or at least contribute to binocular interaction, and later leads to their disruption.

From work presented in this and the preceding chapter it appears that both the **presence** of patterned binocular visual experience during early postnatal life and the **correlation** of the images relayed through the two eyes are crucial for the development and the nature of intracortical connections underlying binocular interactions. Absence of (patterned) input from one or both eyes eventually results in a truly monocular primary visual cortex, while a mismatch of the two eyes' images (as in squint) allows the retention only of inhibitory connections between neurons of opposite ocular dominance.

6. CONCLUDING REMARKS

And they came to Beth-sa'ida. And some people brought him a blind man, and begged him to touch him. And he took the blind man by the hand, and led him out of the village; and when he had spit on his eyes and laid his hands upon him, he asked him, "Do you see anything?" And he looked up and said, "I see men; but they look like trees, walking." Then he laid his hands upon his eyes; and he looked intently and was restored and saw everything clearly. - Mark 8, 22-25

Vision, though seemingly effortless, is a highly demanding computational process, whose complexity is reflected in the fact that more than a third of our cerebral cortex is devoted to it. In the macaque cortex more than 30 areas have been identified, that analyse features of the retinal images such as form, colour, motion, and depth (Van Essen et al., 1992). As we now know, much of the performance of the visual cortex in analysing the visual scene is subject to and dependent upon visual experience: functions have to be 'learned', i.e. implemented at the neuronal level.

One particularly challenging problem that obviously cannot be dealt with in the retina is to integrate the images seen by the two eyes in order to generate a single percept. The work that I have presented here shows two ways in which the primary visual cortex may resolve the conflict between inputs from the two eyes as they converge upon a single functional structure. One way is *anatomical segregation*, as observed to varying degrees in layer 4 of V1 in animals with frontally-positioned eyes, including carnivores and all Old and New World monkeys that have been studied so far. Data on the New World marmoset, with transient formation of OD columns in juvenile animals and stabilization of segregation in monocularly deprived animals, suggest that the mechanism of anatomical segregation plays an important role during the establishment and consolidation of geniculocortical afferentation but may not be necessary during adulthood.

The physiological process of *interocular gain control* may serve not only to adjust the sensitivity of cortical cells to match the prevailing contrast range in the visual scene (Freeman & Ohzawa, 1990) but appears to ensure that, through *interocular suppression*,

signals from one eye are vetoed under viewing conditions that would otherwise lead to diplopia and confusion. Suppression during binocular rivalry and strabismic suppression are prominent examples.

On the other hand, frontal eye position is a prerequisite for *co-operation* between the two eyes, which results from the convergence of inputs from cells driven by one eye or the other onto binocularly excitable neurons. Physiologically, binocular facilitation is observed for patterns that are identical or sufficiently similar in the two eyes and of small interocular disparity.

It may well be that afferent segregation and interocular suppression are phylogenetically older than binocular convergence and summation. The capacity for the formation of ocular dominance columns, for instance, is present in the tectum of the frog, where no binocular neurons are found: implantation of a third eye during larval development leads to fibres from two eyes (normal plus supernumerary) innervating one tectal hemisphere, competing with each other and segregating into columns of a width similar to OD columns in the primary visual cortex of higher mammals (Constantine-Paton & Law, 1978). The mechanisms of ocular segregation and interocular suppression are likely to have evolved in parallel with a shift in eye position from lateral to more frontal, present in particular among predatory mammals. This shift enabled predators, while hunting, to view their prey with higher image quality, as the optic axes of both eyes and the central specialization of the retina, where resolution is higher than in the periphery by several orders of magnitude, became directed towards the centre of the frontal visual field. But the increasing degree of overlap of the visual fields of the two eyes gives rise to potential interocular conflict.

However, the closer the visual axes of the two eyes came to being parallel, the more the degree of matching of the two images increased, eventually reaching near 100% in normal viewing for objects in the centre of the visual field that lie in the plane of fixation. The acquisition of frontal eye positions allowed for the development of highly specific co-operative interactions between inputs from the two eyes in V1, which I suggest were superimposed upon pre-existing suppressive interactions. Not only does

summation of inputs result in decreased detection and discrimination thresholds at low contrast and/or low luminance (Blake & Fox, 1973, for review; Bearnse & Freeman, 1994), but also, and more important for us, small disparities of the (two-dimensional) images of objects that lie before or behind the plane of focus are utilized to compute the third dimension, depth. Stereoscopic depth perception, as displayed by feline carnivores and by primates, has proved highly advantageous, apparently compensating for the disadvantage of losing panoramic vision associated with laterally-positioned eyes.

I have analysed two situations in which a single stereoscopic percept (which represents neither the left nor the right eye's image but a computed, 'resolved' view) cannot be achieved. Strabismic subjects permanently experience a form of 'utrocular' vision (vision with each eye separately, as opposed to 'ambicocular' vision with both eyes together) at least in the central part of the visual field, and normal observers do so too during binocular rivalry. The image signalled by the non-dominant eye is perceptually suppressed, while that present in the dominant eye is perceived. I have been able to show that in normal and strabismic cats neuronal responses to a stimulus in one eye are indeed suppressed by introducing a second stimulus to the other eye, under conditions similar to those causing perceptual suppression in normal and squinting human observers.

The similarity of properties of interocular suppression at the neuronal level in a binocular rivalry paradigm on the one hand and in strabismus on the other hand led me to propose that the underlying mechanisms are essentially the same. The fact that suppression is essentially independent of orientation in strabismus strongly supports my view that the orientation-dependent binocular interactions observed in normal animals represent the sum of orientation-independent suppression plus disparity-selective facilitation (and occlusion) for matching orientations. The situation seen in strabismic animals (and humans) may then resemble the phylogenetically older state of utrocular vision associated with more laterally placed eyes (Walls, 1951; reviewed by Schor, 1991), while the 'newer' mechanism of binocular summation needed to mediate ambicocular vision fails to develop.

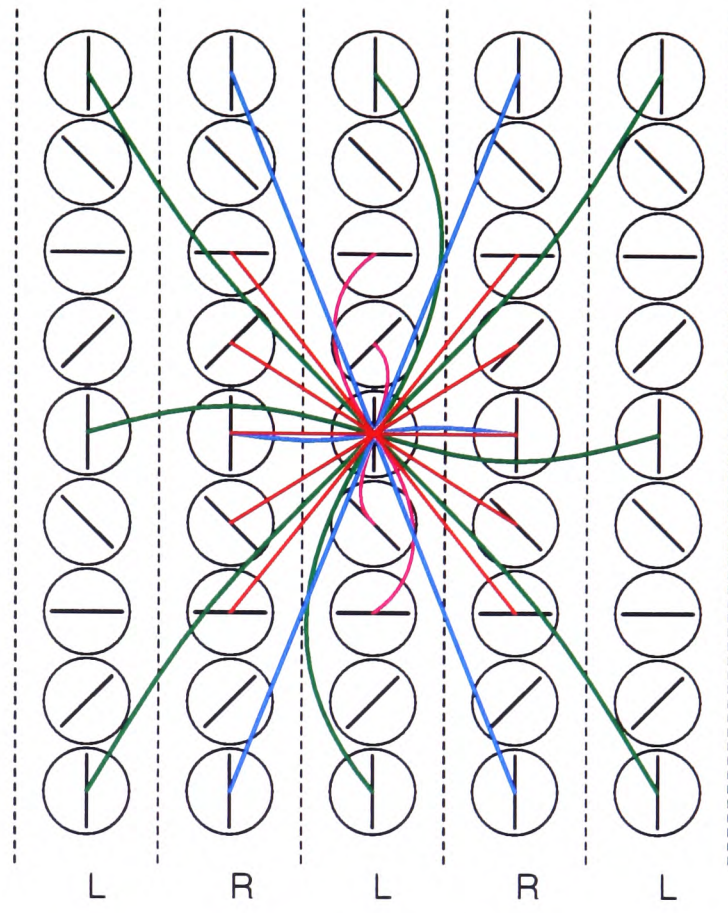
Interestingly, stereoblind humans with a childhood history of strabismus perform better in a task of eye-of-origin discrimination for grating patterns than normal subjects (Blake & Cormack, 1979), lending support to the notion of greater independence of vision through the two eyes in strabismus. It might be worth studying the balance between binocular facilitation and interocular suppression in a species with an intermediate eye position like the ferret, where the optical axes diverge by 32° as compared to 8° in the cat (Johnson, 1901).

A possible anatomical substrate for the two types of binocular interactions postulated above is schematically illustrated in Fig. 6-1. Blue and green lines symbolize excitatory connections between clusters of cells of same-eye dominance and opposite-eye dominance, respectively; red and purple lines represent inhibitory connections. In normal animals (**A**), excitatory intrinsic connections in the primary visual cortex between regions of similar orientation preference (Ts'o et al., 1986; Schwarz & Bolz, 1991) may mediate disparity-sensitive binocular facilitation. In addition, there is evidence for widespread non-orientation-selective inhibitory connections both within and between OD columns (see Somogyi et al., 1983; Kisvárdy et al., 1993b). Large basket cells found in layers 3, 4, and 5 appear to be the likeliest candidates to provide the rather long-range ($> 500 \mu\text{m}$) inhibitory input to target cells representing the whole range of orientations (Kisvárdy, 1992; Kisvárdy & Eysel, 1993; Kisvárdy et al., 1993a). I suggest that in strabismic animals (**B**) excitatory intrinsic connections *between* neighbouring OD columns are selectively lost, leaving only inhibitory projections and, therefore, pronounced non-specific interocular suppression in the majority of cells.

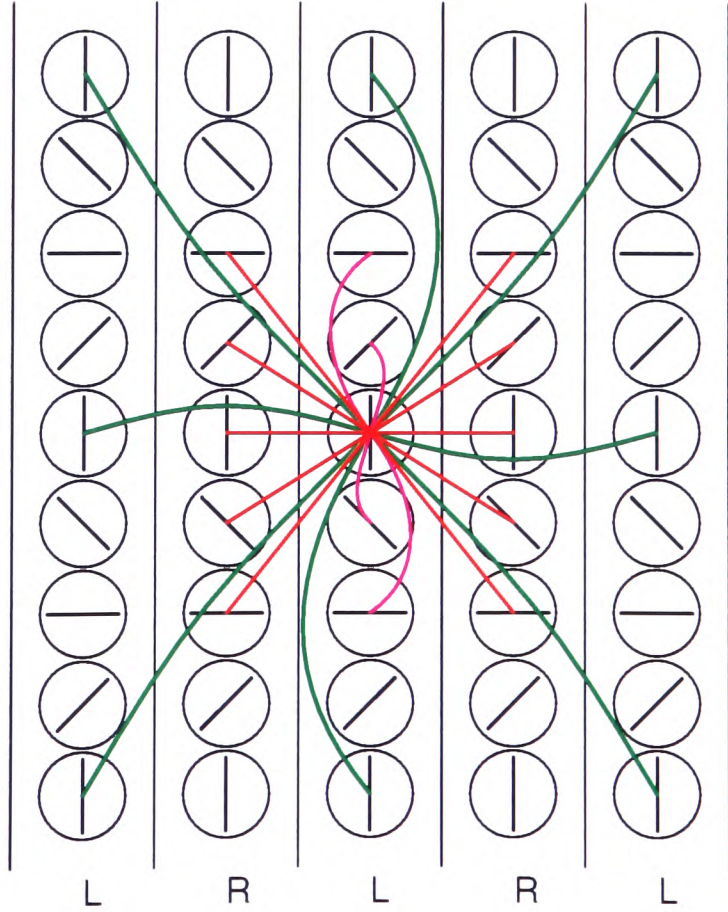
Figure 6-1

Schematic diagram of intrinsic horizontal connections that might underlie binocular integration in normal (**A**) and strabismic (**B**) animals. A surface view of orientation and ocular dominance domains is shown. Parallel slabs or 'columns' marked 'L' and 'R' represent left-eye and right-eye OD columns, respectively. In normal animals, these columns are only weakly segregated in supra- and infragranular layers (symbolized by the interrupted lines in **A**), while they are clearly delineated in strabismic animals (solid lines in **B**). Columns of cells with similar orientation preference are depicted as circles with an oriented line inside. Thick green and blue lines represent excitatory projections, which selectively connect neurons of similar orientation preference, while thinner purple and red lines show widespread, non-selective inhibitory connections, respectively, within and between neighbouring OD columns; see text for further explanation.

A



B



In order to characterize the nature of suppressive interactions in V1 in more detail, simultaneous recordings from pairs of neurons separated by various distances, and therefore potentially differing in ocular dominance and/or orientation preference, need to be made. The part that local connections between two recording sites in neighbouring ocular dominance columns play in generating interocular suppression could be directly demonstrated by iontophoretically inactivating cells at one of the two sites (by application of the inhibitory transmitter GABA).

The hypothesis that strabismus interrupts normal excitatory interactions between the two eyes, but leaves inhibitory connections between cortical ocular dominance domains unaffected, needs to be tested with anatomical and immunohistochemical techniques: this would require, for example, a combination of cortical injections of fluorescent beads (retrogradely to label cells projecting to the injection site) and visualization of ocular dominance domains, as well as labelling of all GABA-ergic neurons [e.g. by staining for glutamic acid decarboxylase (GAD), the rate limiting enzyme in the synthesis of GABA]. Retrogradely labelled cells in columns of **opposite** ocularity should be predominantly GABA-positive in strabismic animals.

The most intriguing and most challenging question arising from this work must be: what triggers the switches between perceptual dominance and suppression? A study on V1 neurons in awake behaving monkeys tested in a binocular rivalry paradigm (see Logothetis & Schall, 1989a,b) may provide further evidence in that respect. However, while the kind of interocular suppression that I have demonstrated at the neuronal level is clearly related to situations of interocular image conflict, it is conceivable that a perceptual phenomenon like alternation of eye dominance may not have an immediate physiological correlate at an early stage of visual processing.

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