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INTEROCULAR INTERACTIONS IN ESOTROPIA

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INTRODUCTION

The visual system of adult mammals is characterized by an highly topographic ordering of projections (for a review see Ref. 37). Since the pioneering studies of Hubel and Wiesel (24) experimental work, particularly on the cat, has provided a large body of evidence indicating that the highly ordered set of visual connections is in large part genetically programmed yet its ultimate arrangement is shaped by visual experience (45) . At birth, in fact, the visual system is still immature and most susceptible to changes in its morpho-functional organization. Indeed, the early postnatal life represents a 'critical period' for the normal development of connections between the visual afferents and their cortical and subcortical targets. If during the critical period the individual's eyes are submitted to unequal stimulation as a result of experimental manipulations or ocular pathologies, binocular convergence of the two eyes' inputs is lost or severely impaired and binocular functions are damaged as well (for a review see Ref. 5).

Clinical evidence indicates that congenital unilateral strabismus is one of the conditions that leads in humans to permanent binocular sensory anomalies and to monocular spatial vision deficits. Our understanding of the neural alterations responsible for the functional vision defects associated with ocular misalignment is based primarily on the findings from investigations on the animal models of strabismus. Naturally occurring strabismus is rare in animals but surgical procedure have typically been employed to create an ocular misalignment in young animals.

I. *Different susceptibility to strabismus of the binocular interactions in striate and extrastriate cortex.*

Hubel and Wiesel (25) were the first to demonstrate that strabismus induced during the critical period of plasticity modifies the functional architecture of the primary visual cortex. In normal animals, owing to the convergence of retinothalamic inputs from the two eyes onto single neurons of area 17, the majority of striate cells is binocularly activated. Cortical binocularity, that is already present at 3 weeks of age, is however invariably lost when unilateral ocular deviation is induced in the early postnatal life (25, 43, 29). The absence of binocular interactions in the primary visual cortex is likely to be responsible for many of the binocular vision deficits found in strabismic subjects (e.g. reductions in stereopsis, binocular summation and interocular transfer of masking and adaptation phenomenon; Ref. 1, 22, 33).

It is generally agreed that the deleterious effect of strabismus -either convergent

(esotropia) or divergent (exotropia)- on the cortical binocularity is due to the spatial incongruence of the two monocular inputs. Because of the visual axes' misalignment the two retinal images are not spatially correspondent and the lack of visual correlation in the inputs conveyed to the cortex precludes coincident binocular activation of cortical neurons.

Binocular matching between the two eyes' inputs is, however, differentially interfered with at different regions of the visual cortex. In fact, binocular activation that is severely impaired in areas 17 and 18 (9) is largely preserved in the extrastriate lateral suprasylvian area (LSA) of strabismic cats (44, 31, 20). In figure 1 the effect of esotropic deviation on binocularity of both the striate and the extrastriate cortex is represented. It is shown as in normal cats (Fig. 1A) the vast majority of cortical cells is binocularly activated, even though the proportion of binocular neurons is higher in LSA (92%) than in area 17 (76%). In esotropic cats (Fig. 1B) the number of binocular neurons is drastically reduced in area 17 (20% of the cells is binocularly driven) whereas it is only slightly decreased in LSA (83% of the cells is binocularly driven).

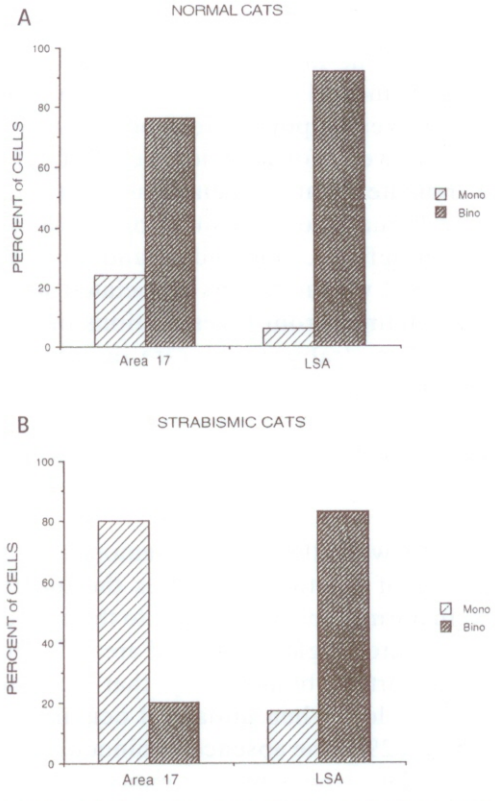

Fig. 1. - *Percentage of monocular and binocular neurons recorded in area 17 and LSA of normal and esotropic cats.*

From Ref. 11.

The neural substrate of the different susceptibility to image misalignment displayed by area 17 and LSA is not fully understood. We argued that the main mechanism for maintenance of binocular interactions in the extrastriate cortex might reside in the widespread callosal projections that in LSA are far more expanded than in area 17 and link together cortical loci with a larger retinotopic representation (35). One may expect that the misaligned retinal images representing heterotopic portions of the visual field could be brought into register through the callosal route and that cortical binocular activation of LSA could be attained by convergence onto single neurons of the direct geniculo-cortical input of one eye and the callosally transmitted input of the other eye. Our experimental evidence indicates, however, that binocularity of LSA is only partially sustained by callosal connections since a sizeable proportion of neurons is still binocularly driven in strabismic callosotomized cats (11).

It is most likely that the different impairment of binocular activation in area 17 and LSA might stem from specific influences exerted by the spatially conflicting inputs on the mechanisms underlying information processing in the two areas. Compared to striate neurons, the spatial properties displayed by LS cells are relatively crude. Neurons receptive fields (RF) are large (39, 42) with low contrast sensitivity and broad orientation selectivity (32, 21). We found that spatial frequency tuning and spatial resolution of LSA cells is poor, their highest resolving power being 2c/dg (10, 34). However, even though LSA lacks the fine-grained vision that is peculiar of area 17, it is able to perform basic discrimination of patterns and shapes, as indicated by behavioural studies on cortically lesioned cats (3, 2). In light of these observations it is conceivable that the coarse spatial analysers of LS cortex could be less affected by the retinal-image misalignment than the spatially acute and position-dependent visual processors of the striate cortex. In area 17 binocular convergence of the mismatched inputs is precluded by the small RF size of neurons and by their high sensitivity for the spatial features of the stimulus. In LSA the rather lax spatial requirements of neurons may preserve binocular activation by allowing at least a rough binocular match between the two spatially incongruent informations.

II. *Competitive interactions between the eyes.*

It has been frequently reported that in the striate cortex of esotropic animals the proportion of neurons excited through the deviated eye is reduced (9, 44) and their functional effectiveness is impaired (5 bis, 6). Several lines of evidence (8, 16, 36) indicate that decreased responsiveness to the strabismic input may reflect an imbalancement in the competitive interocular interactions that subserve functional maturation and maintenance of the visual connections. During postnatal development the axonal inputs from the two eyes compete for a common target. Competitive binocular interactions, which are driven by activity-dependent mechanisms, can be imbalanced by visual perturbations that impede correlated firing of the retinal afferents from the two eyes (36). Indeed both, the lack of coincidence

between the two monocular inputs in strabismus as well as the unequal stimulation of the two eyes in monocular deprivation, disrupt correlated activity in the two eyes' projections and imbalance the use-dependent competition in favour of the normal eye which establishes a functional advantage over either strabismic or deprived eye.

By comparing the number of neurons driven by each eye in the striate and extrastriate cortex of esotropic cats the expected, consistent prevalence of the non-deviated eye is found (Fig. 2). Interestingly, however, the relative failure of the esotropic eye to activate neurons is less severe in LSA than in the area 17. This finding supports the idea that effectiveness of the strabismic input is largely dependent on coincident activation of the visual projections from both eyes. Binocular activation of the LSA neurons implies that activity in the afferents to the extrastriate cortex must be, at least roughly, coincident. Thus, in LSA, through the general mechanism that strengthens coactivated inputs, effectiveness of the esotropic input is better preserved than in area 17 whose cortical afferents lack of binocularly correlated activity.

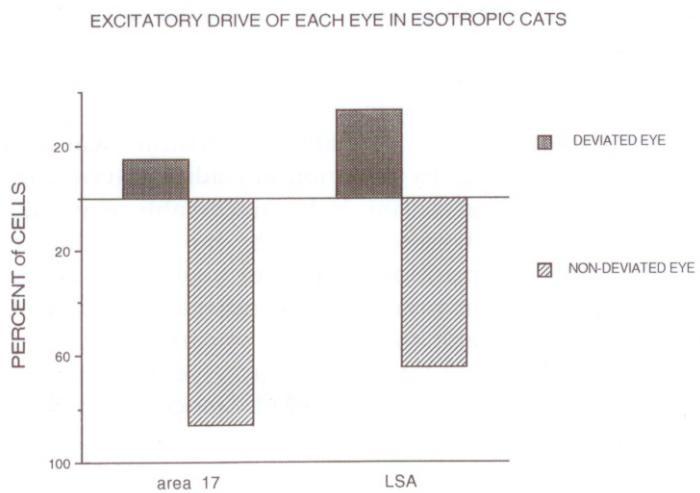

Fig. 2. - *Relative effectiveness of the deviated and the non-deviated eye in driving neurons in area 17 and LSA.*

From Ref. 11.

III. *Interocular inhibitory interactions.*

The decreased visual effectiveness of the strabismic eye has been interpreted as a functional consequence of strabismus, aimed to suppress the deviated eye input for preventing diplopic vision by retinal-image misalignment. According to the electrophysiological reports, visual information from the deviated eye might be suppressed in the striate cortex by interocular mechanisms that inhibit the activity

of neurons driven by the deviated eye when the non-deviated eye afferents are stimulated (16). The inhibitory effect might be especially severe on the input conveyed by the ipsilateral retinal projections of the esotropic eye which appear to be almost ineffective in driving neurons in the striate cortex (29, 38).

It may be argued that inhibitory influences on the strabismic input, if they are acted by interocular mechanisms, can be prevented by interrupting the visual pathways that subserve interactions between the eyes. This is done by the section of the optic chiasm that abolishes the crossed retinal projections and spares the uncrossed retinal pathways of either eye. The role of postnatal development must be, however, taken into account. It is possible that interocular inhibition, being established early in life, might yield morpho-functional changes in the esotropic afferents (27, 19) which eventually result in a permanent deficit of transmission from the deviated eye. If this is the case, suppression of the esotropic input in adult animals may be prevented only if the interocular interactions are impeded at birth, that is if the chiasm is severed at the same time as strabismus is induced. Thus, esotropic cats with the early section of the optic chiasm are a suitable preparation to test whether the two eyes inputs can develop comparable visual effectiveness when reciprocal influences between the eyes are absent during the postnatal maturation.

Four cats were submitted, at 3 weeks of age, to the section of the optic chiasm and, at the same time, to the surgical induction of esotropia. In these four animals, as adults, we recorded from area 17 of both sides and, in two of them, also from the LSA ipsilaterally to the deviated eye. The results (12) show that visual cortices of early split-chiasm esotropes are normally responsive to visual stimuli. Since direct transmission of the contralateral eye input is abolished by the section of the crossed retinal pathway, in both hemispheres the neurons are monocularly driven by stimulation of the ipsilateral eye. The total number of neurons, as well as the response properties of cells activated by either eye in the corresponding hemisphere are equivalent. Thus, with regard to the main question addressed by this study, i.e. the role of interocular influences in the impairment of the strabismic eye input, our data point out that interruption of interocular interactions at birth prevents the functional disadvantage of the deviated eye. In fact we found that the uncrossed afferents from the esotropic are as effective as that from the non-deviated eye in driving cortical neurons.

An additional and rather unexpected finding of the above cortical recordings, concerns the presence, only in the hemisphere connected to the esotropic eye, of a consistent proportion of cells that could not be monocularly driven yet responded to the simultaneous stimulation of both eyes. This means that to be activated these neurons required the direct input from the deviated eye and the indirect, callosally transmitted, input from the non-deviated eye, neither of the two alone being effective. These cells seems to be more represented in LSA (40% of the encountered neurons) than in area 17 (23% of the encountered neurons) (Fig. 3), possibly for the greater chance of binocular convergence provided by the enlarged callosal connections and the coarse spatial properties of the LS cortex.

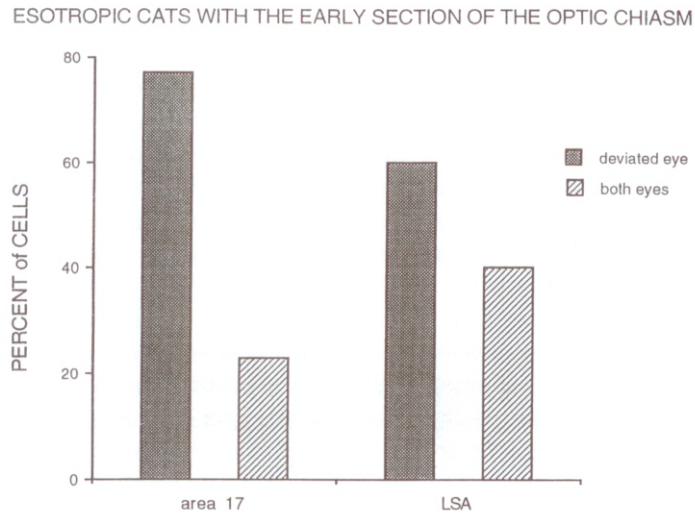

Fig. 3. - *Responsiveness of the neurons recorded in area 17 and LSA ipsilaterally to the deviated eye in early split-chiasm esotropic cats.*

From Ref. 12.

The occurrence of these neurons suggests that cortical binocular activation is attempted by the callosal transmission of the non-deviated input to the esotropic cortex. The interhemispheric pathway, however, is not successful in achieving a proper binocular convergence of inputs since the neurons cannot be separately driven by each eye but need concurrent stimulation of both visual pathways. In addition the callosal route shows a functional asymmetry because solely the non-deviated eye input is transferred by callosal connections. Whether the attempt for binocular activation exhibited by the esotropic cortex has a functional outcome is, at present, object of investigation in our laboratory.

IV. *Reversible interocular inhibition.*

Experimental data on animals (5 bis, 6, 29) as well as clinical reports in humans (15), point out that convergent strabismus has a more disruptive effect on cortical binocularity and on visual capabilities of the deviated eye than divergent squint. In addition esotropic cats exhibit a behavioural suppression of the nasal field of the deviated eye (26, 28, 38). This latter finding parallels electrophysiological results showing that the greatest failure in driving striate cells through the esotropic eye occurs in the region of cortex where is represented the input from the temporal retinal afferents, corresponding to the suppressed nasal field (29).

The behavioural field loss might be related to a greater developmental vulnerability of the ipsilateral retinal pathway that, compared to the crossed retinal projections, seems to be more affected by any imbalance in visual stimulation of the two eyes during postnatal development. Indeed a nasal field loss analogous to

that occurring in esotropes has been shown in cats with unequal alternating monocular exposure (41) and a more severe impairment of the temporal than of the nasal pathway has been documented in monocularly deprived cats (4).

It is assumed that when the two eyes are unequally stimulated, as in monocular deprivation, the normally-experienced eye gains a competitive advantage that leads to suppression of the non-experienced eye. However the suppressive effect is, at least partially, reversible since visual capabilities of the deprived eye are improved after enucleation of the normal eye, both in cats (30) and monkeys (23). These results support a role for competitive interocular processes in the loss of excitatory drive from the deprived eye. Removal of the normal eye is effective in removing suppression because it abolishes the interocular competitive interactions. Competition explains the efficacy of the established clinical practice of patching the non-deviated eye in human strabismics. This treatment, popularized at the turn of the century, is shown to be rather effective in improving visual performance of the strabismic eye, possibly because the lessening of interocular competition by occlusion of the 'good' eye reduces a suppressive effect on the deviated eye. All together these observations are suggestive of a common mechanism underlying the functional inhibition of strabismic and deprived eyes, a sort of active inhibition of the inputs that is exerted through interocular mechanisms.

We wandered whether also the behavioural field loss that is manifested by esotropic cats might depend on an active suppression of the ipsilateral input and then, whether the full extent of the visual field might be recovered by removing the inhibitory interocular influences. Following this line of reasoning we sectioned the optic chiasm in adult esotropic cats and compared the extension of the visual field before and after the section.

Seventeen adult cats were raised with early induced esotropia. In all of them we measured the extention of the visual fields of either eye by behavioural perimetry methods. Perimetric measurements (fully described in Ref. 13) were performed by scoring the orienting responses to visual stimuli presented at different eccentricities in the visual field while the cat's fixation was surely directed toward the midline of the perimeter (0° position). In all the cats we documented the loss of the nasal portion of the strabismic field (Fig. 4).

In eight of these animals the optic chiasm was sectioned and the extention of the nasal field measured after the section was compared to that assessed before chiasmotomy. Results of the perimetric testing indicate that in all cats the difference in rate of orienting responses recorded before and after the section is highly significant at all test angles within the nasal portion of the strabismic field (Wilcoxon signed ranks test). Indeed, as reported in Figure 5, following the chiasm section, the extent of the nasal hemifield of the esotropic eye is strikingly increased in all animals.

Recovery of the behavioural field loss after the chiasm section demonstrates that the temporal retinal input from the strabismic eye is not permanently lost yet functionally suppressed. Thus, the nasal field deficit assessed in esotropic cats with intact optic pathways cannot be attributed to morpho-functional abnormalities

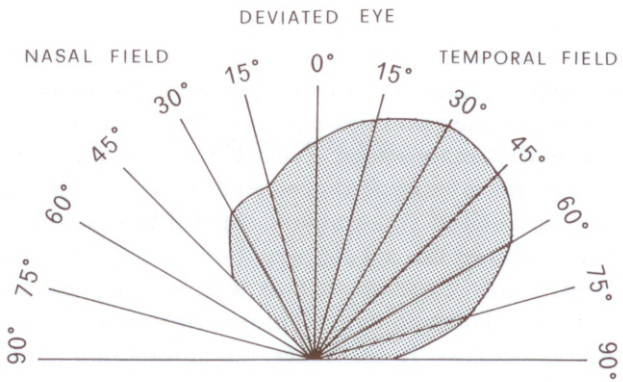

Fig. 4. - *Graph showing the results of perimetric testings in seventeen esotropic cats with intact optic pathways.*

For each test angle in the two hemifields the length of the corresponding line represents the mean percentage of correct orienting responses. Full length lines indicate 100% correct performance.

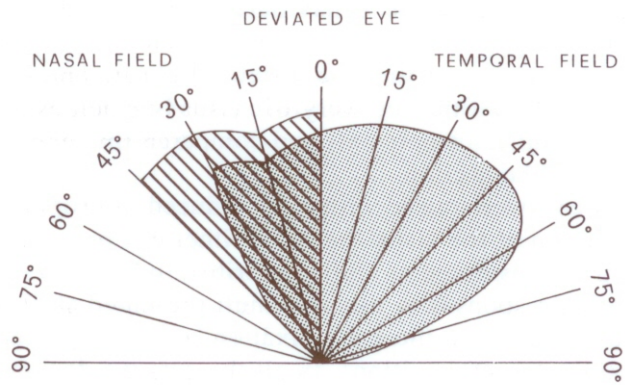

Fig. 5. - *Graph showing the results of perimetric testings in eight esotropic cats before and after the chiasm section.*

The dashed area represents the extent of the nasal field measured after chiasmotomy. Conventions are the same as in Figure 4.

of the visual afferents occurring during postnatal maturation (27, 19). Instead the neural mechanism for the field defect seems to lie in the continuos inhibition of the esotropic input that is acted through the interocular pathways. By the chiasm section are impeded the direct interactions between the eyes and with them is also impeded the competitive advantage of the non-deviated eye that yields the specific failure of the esotropic eye in responding within the nasal hemifield.

CONCLUSIONS

Ocular deviation disturbs synchrony of inputs from the two eyes during development and this alters the interocular balance of inputs. Hence competitive interactions between the eyes lead to the loss of binocular convergence and to the marked dominance of the non-deviated eye. The competitive advantage of this eye reduces both the excitatory drive to the cortex and the behavioural visual capabilities of the strabismic eye.

Our experimental evidence suggests that the esotropic input, released by interocular influences by the chiasm section recovers at least as much effectiveness to achieve orienting reactions in the previously neglected nasal field. The finding that responsiveness through the strabismic eye may be restored well into adulthood indicates that functional impairment of the esotropic input prior of chiasmotomy does not reflect developmental changes of the visual afferents yet the active inhibition exerted by interocular mechanisms.

As far as effectiveness in driving cortical neurons is concerned, we found that the excitatory drive of the ipsilateral strabismic input, which is the one mostly impaired in esotropic animals, is fully preserved when the interocular interactions are impeded at birth. Preliminary data (17) suggest however that improvement in the ability to drive striate cells may also occur in esotropic cats in which the section of the optic chiasm was performed during their adult life. In addition, in these esotropic split-chiasm animals there is a change in the spatial properties of the cells (18) that might parallel a partial recovery of visual capacities.

At present, the nature and the site of neural mechanisms underlying decreased effectiveness of the strabismic input are not entirely determined. Recent electrophysiological reports (7) suggest that the striate cortex is the most probable location. Results of our experiments of cortical recording support this possibility. Our behavioural data confirm that competitive interocular interactions play the main role in the functional impairment of the esotropic eye and point out that one of the inhibitory mechanism is an active (and reversible) suppression that is established over the strabismic input through the crossed retinal pathways.

SUMMARY

In cats the unilateral convergent strabismus surgically induced in the early postnatal life causes monocular spatial vision deficits and loss of binocular activation of the primary visual cortex. It is assumed that the asynchrony of inputs from the two eyes, by disrupting binocular convergence, leads to umbalanced binocular interactions that favour the non-deviated eye. The competitive advantage of this eye reduces both the excitatory drive to the cortex and the behavioural visual capabilities of the strabismic eye that exibits the loss of the nasal portion of the visual field.

Our experimental evidence indicate that the esotropic input, released by interocular

influences by the chiasm section, recovers at least as much effectiveness to achieve orienting reactions in the previously neglected nasal field. In addition we found that the excitatory drive of the ipsilateral strabismic input, which is the one mostly impaired in esotropic animals, is fully preserved when the interocular interactions are impeded at birth and it is greatly improved in the esotropic cats with section of the optic chiasm performed in adulthood.

All together these results suggest that functional impairment of the esotropic input prior of chiasmotomy does not reflect developmental changes of the visual afferents yet the active inhibition exerted by interocular mechanisms.

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