European Journal of Neuroscience, Vol. 5, pp. 501–508

Squint Affects Synchronization of Oscillatory Responses in Cat Visual Cortex

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Key words: striate cortex, exotropia, cross-correlation analysis, oscillation, temporal coding, binding problem

Abstract

As shown previously, neurons in various areas of the cat's visual cortex respond to appropriate visual stimuli with oscillatory activity in the frequency range of 30–70 Hz. It has been suggested that synchronization of such responses serves to define assemblies of coherently active cells which represent individual visual objects. In this study, we have investigated this putative binding mechanism in the visual cortex of strabismic cats. We used six adult cats in which divergent squint had been induced surgically at the age of 3 weeks. Multiunit activity was recorded from area 17 with arrays of four or five closely spaced microelectrodes. Subsequently, auto- and cross-correlation functions were computed for all spike trains. To quantify the oscillatory nature of the responses and the strength of synchronization between spatially remote sites, damped sine wave functions were fitted to the correlograms. Analysis of responses obtained from 202 recording sites showed that the vast majority of cells had become monocular. Auto-correlation analysis revealed that the proportion of oscillatory firing patterns was similar to that observed in normal cats. However, cross-correlation analysis of 153 response pairs demonstrated that synchronization was reduced significantly between cells dominated by different eyes while it was as frequent and strong as in normal cats between cells dominated by the same eye. These findings indicate that strabismus not only causes a reorganization of afferent inputs but also affects intracortical interactions. Since strabismic cats lack tangential intracortical connections between territories connected to different eyes and are unable to combine signals conveyed by the two eyes these results support the notion that response synchronization is achieved by cortico-cortical connections and serves as a mechanism for feature binding.

Introduction

Theoretical considerations on the neuronal substrate of cognitive processes have led to the hypothesis that synchronous firing of neurons might play an important role in the processing of visual information (Milner, 1974; von der Malsburg, 1981, 1986; Shimizu *et al.*, 1986). Specifically, it has been suggested that temporal synchrony serves to 'tag' feature-detecting neurons which respond to a particular object present in the visual field, and thus binds activity of distributed cortical neurons into coherent representations.

Recent experimental studies in the cat and monkey visual system provide supportive evidence for this hypothesis (for reviews see e.g. Singer, 1990; Engel *et al.*, 1992a). In cats, several studies have demonstrated that spatially separate cells within a visual area can synchronize their spike discharges with zero phase lag (Ts'o *et al.*, 1986; Eckhorn *et al.*, 1988; Gray *et al.*, 1989; Engel *et al.*, 1990). In addition, response synchronization has been observed between neurons located in different visual areas (Eckhorn *et al.*, 1988; Engel *et al.*, 1991a; Nelson *et al.*, 1992) and even between cells of different hemispheres (Engel *et al.*, 1991b). In the visual system of monkeys, synchronization of spatially separate neurons has been demonstrated within striate cortex (Ts'o and Gilbert, 1988; Krüger and Aiple, 1988), and within extrastriate regions such as the caudal superior temporal sulcus (Kreiter and Singer, 1992; Engel *et al.*, 1992b) and the inferior temporal cortex (Gochin *et al.*, 1991).

A key finding is that the response synchronization depends critically on the stimulus configuration. We could recently demonstrate that spatially separate cells synchronize their discharges only if they respond to the same visual stimulus. However, if responding to two independent stimuli, they fire in an uncorrelated manner. First made in cat visual cortex (Gray *et al.*, 1989; Engel *et al.*, 1991a,c), this observation has now been confirmed in motion-sensitive visual areas of macaque monkeys (Kreiter *et al.*, 1992). Taken together, the ample evidence for correlated firing of neurons and the findings on the stimulus dependence of response synchronization support the hypothesis that synchrony may serve as the 'glue' which binds highly distributed neurons into unique assemblies which are thus able to represent particular visual objects (Singer, 1990; Engel *et al.*, 1992a).

Several studies indicate that such a synchronization of distributed neurons is frequently associated with oscillatory activity in the gamma range. As shown in cat striate cortex, local groups of neurons tend to engage in synchronous bursts which recur at frequencies of 30–70 Hz (Gray and Singer, 1987, 1989; Gray *et al.*, 1990; Ghose and Freeman, 1992). Although they are, in principle, independent of

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Received 18 May 1992, revised 17 December 1992, accepted 8 January 1993

the synchronization which may occur between spatially distant neurons, these oscillations might play an important role in the operation of a dynamic temporal binding mechanism. As we have suggested recently (Engel *et al.*, 1992a,c), oscillatory firing patterns may offer certain advantages for establishing synchrony over large distances such as, for instance, across the cerebral hemispheres (Engel *et al.*, 1991b). In accordance with this hypothesis, oscillatory firing patterns have also been observed in various extrastriate areas of cat visual cortex (Eckhorn *et al.*, 1988; Engel *et al.*, 1991a). In monkeys, oscillatory activity in the gamma frequency range has been demonstrated in extrastriate motion-sensitive visual areas of both awake and anaesthetized animals (Kreiter and Singer, 1992; Engel *et al.*, 1992b), in the striate cortex (Livingstone, 1991; Maunsell and Gibson, 1992) and in inferotemporal visual cortex (Nakamura *et al.*, 1992). It should be noted, however, that one group has recently failed to disclose oscillatory activity in monkey visual cortex (Young *et al.*, 1992).

We have now investigated the occurrence of synchrony and of oscillatory responses in the primary visual cortex of strabismic cats. In area 17 of normal cats, most neurons receive binocular input (Hubel and Wiesel, 1962). However, induction of squint early in development leads to a breakdown of binocularity, and thus the majority of cells in striate cortex become responsive to stimulation of one eye only (Hubel and Wiesel, 1965). Behavioural and psychophysical experiments show that strabismic animals and humans lose the ability to integrate information from the two eyes (for review see Duke-Elder and Wybar, 1973; von Noorden, 1990). In order to avoid double vision, two different strategies are employed, which are typically associated with different types of squint. Strabismic individuals either fixate with both eyes in an alternating manner and suppress the signals from the currently non-fixating eye, or they always use the same eye for fixation and consistently suppress the other. In the first case, these subjects develop normal monocular vision in either eye, whereas in the second case vision in the suppressed eye becomes amblyopic. Typically, alternating fixation is found in individuals with divergent squint, whereas convergent strabismus frequently leads to amblyopia of one eye (Ikeda and Tremain, 1979; Jacobson and Ikeda, 1979; Mower and Duffy, 1983; Mitchell *et al.*, 1984; von Noorden, 1990). Based on the available behavioural evidence it can be predicted that the mechanisms for feature binding are altered in either of these cases.

If binding is indeed mediated by correlated firing of neurons at the level of the visual cortex, the following hypotheses should prove to be true: since monocular vision is unimpaired in humans and cats with squint and alternating fixation (Duke-Elder and Wybar, 1973; Ikeda and Tremain, 1979; von Noorden, 1990), cells receiving input from the same eye should be capable of synchronizing their responses. In addition, response parameters of striate cortical neurons such as their oscillatory temporal structure should be the same as in normal animals. In contrast, no synchronization should be observed between cells with different ocular dominance, because squinters cannot bind features across the two eyes. In this study, we set out to investigate these predictions in cats with surgically induced divergent squint by recording with multiple electrodes from area 17 and subjecting the data to correlation analysis. Some of the results have been presented in abstract form (König *et al.*, 1990).

Materials and methods

Animal preparation

In six cats, divergent strabismus, or exotropia, was induced at the age of 3 weeks by cutting the medial rectus muscle of one eye under ketamine–xylazine anaesthesia. At the age of 3–6 months, we measured the pupillary alignment using the photographic technique described by Sherman (1972) and von Grünau (1979). For this purpose, each cat was restrained manually and several flashlight snapshots of the animal's head were taken. Subsequently, the distances between the corneal reflexes and the pupils were measured on the photoprints. The ratio of the reflex distance over the pupillary distance can be taken as a reliable indicator of eye alignment (Sherman, 1972; von Grünau, 1979). In normal cats aged >2 months, this ratio is in the range of 0.94–0.97. Smaller values indicate divergent strabismus (von Grünau, 1979). The values measured in our experimental subjects were 0.88, 0.89, 0.92, 0.92, 0.92 and 0.93, respectively. Thus, all cats used in this study were exotropic.

The cats were prepared for electrophysiological recording when they were older than 6 months. Preparation and maintenance of the animals followed standard techniques which have been described in detail previously (Engel *et al.*, 1990). Briefly, anaesthesia was induced by an i.m. injection of ketamine hydrochloride (10 mg/kg) and xylazine hydrochloride (2.5 mg/kg). After tracheotomy, the animal's head was placed in the head-holder of a stereotactic instrument. At the end of the preparation, the animal's skull was cemented to a metal rod and eye and ear bars were removed. Throughout the experiment, the cat was respirated with a mixture of 70% N_2O, 30% O_2 and 0.2–1% halothane. To eliminate painful stimuli local anaesthetics were applied to all wound edges. Eye movements were prevented by continuous i.v. infusion of hexacarbacholinbromide (1–2.5 mg/h). Glucose and electrolytes were supplemented via a gastric catheter. The electrocardiogram and electroencephalogram were monitored during the whole experiment, and the values of end-tidal CO_2 and rectal temperature were kept in the range of 3–4% and 37–38°C, respectively.

Recording

We recorded extracellularly with teflon-coated platinum–iridium wires (Mioche and Singer, 1988) from the central representation of area 17. For this purpose, we used arrays of several electrodes with a spacing of 0.4–1.0 mm. Multiunit activity was obtained by amplification and filtering of the electrode signals in the frequency range of 1–3 kHz. This signal was fed through a Schmitt trigger whose threshold was set to at least three times the noise level and, after digitizing at 1 kHz, was stored on disk.

Prior to quantitative measurements, the receptive fields of the recorded cell groups were mapped with manually projected stimuli onto a tangent screen located 100 cm in front of the cat. Because of the small interelectrode distances the receptive fields of cells responding through the same eye were usually overlapping. However, due to the exotropia the receptive fields for the two eyes were located at widely different positions on the screen, separated by 10–30°. In addition to the receptive field size and position, we assessed the cells' preferred stimulus orientation and, by comparing responses to stimulation through the left and right eye, we estimated their ocular dominance. According to their ocular dominance, the recorded neurons were grouped in five classes. Units which were exclusively driven by the eye ipsilateral or contralateral to the recorded hemisphere were grouped in classes 1 or 5, respectively. Units responding to one eye at least twice as strongly as to the other were grouped in classes 2 and 4, respectively. Units responding more evenly to stimulation of either eye were grouped in class 3.

For quantitative confirmation of the ocular dominance classification and for correlation measurements, visual stimuli were projected from a computer-controlled optical bench onto the tangent screen. In cases where the recorded cell groups were dominated by the same eye, visual

stimuli were presented to the dominant eye only. When the cell groups had the same orientation preference a stimulus was selected that matched this preference. When their orientation preferences differed, we presented two superposed stimuli with the respective optimal orientations as well as single light bars whose orientation was intermediate between the respective preferences. In cases where cell groups with different ocular dominance were recorded two stimuli were presented simultaneously in the receptive fields of both eyes. In all of these cases, two sets of measurements were performed: first, the cell groups were tested with simultaneous presentation of stimuli that matched their respective orientation preferences. Second, orientations intermediate to those preferred by the respective cell groups were chosen and presented to the two eyes simultaneously. In these measurements, stimuli were carefully matched with respect to their size, orientation, speed and direction of motion in order to provide the two eyes with highly coherent information. Response pairs where one of the two cell groups was rated in ocular dominance class 3 were tested by presenting a single stimulus in the receptive fields of the eye preferred by the cell group with asymmetric ocular dominance. To test whether the synchronization depended on the ocular dominance of the cells we selected for further statistical evaluation the data from those stimulus conditions which gave the strongest cross-correlation. For each stimulus trial, light bars were moved forward and backward across the receptive fields. The movement direction was always perpendicular to the longer axis of the light bar. Trials lasted for 10 s and were repeated at intervals of 15 s. At least 10 responses to the same stimulus were recorded.

Data processing

For quantitative evaluation of the strength of the responses and their temporal correlation we used a standard procedure which has been described previously (Engel *et al.*, 1990). For all responses, we compiled peristimulus time histograms to confirm the manual ocular dominance assessments. Furthermore, auto-correlation and cross-correlation functions were calculated for the spike trains in the first and second half of each 10 s trial, corresponding to forward and backward movements of the stimulus, respectively. In all our measurements, the correlograms computed from at least ten individual trials of each block were summed up to yield a single correlation function. To quantify the oscillatory temporal structure of the responses and the strength of synchronization, a damped sinusoid (Gabor function) was fitted to each of the correlograms. For this purpose, we employed the Marquardt–Levenberg algorithm (Press *et al.*, 1986). The error estimate of the data points of the correlation function, which we assumed to be proportional to the square root of its value, is exploited by the algorithm which supplies values and error estimates for amplitude and frequency of the correlogram modulation, as well as the decay constant of the envelope, and its phase shift and offset. As a measure of the modulation which is independent of the overall response strength we computed a 'relative modulation amplitude' by dividing the amplitude of the Gabor function by its offset. We then tested the relative modulation amplitude against zero on the 5% level. In order to exclude significantly but very weakly modulated correlation functions we rejected all correlation functions with a relative modulation amplitude of <0.10. Correlation functions with a relative modulation amplitude between 0.10 and 0.20 were classified as weak and are shown separately in the statistics. This method was applied to both auto- and cross-correlation functions. Although primarily designed to detect correlograms with multiple troughs and peaks, this method also detects correlograms which only have a centre peak and eventually two adjacent troughs. These two types of correlation functions were distinguished by computing the ratio of the decay constant (τ) over the period time (T). Correlation functions were classified as 'oscillatory' if τ/T exceeded a value of 0.8, or as 'single-peaked' if τ/T was <0.8 (Engel *et al.*, 1990). It should be noted, however, that in the latter case, the recorded cells typically also show the burst-and-pause firing pattern which we term an oscillation (Engel *et al.*, 1992a,c), but due to the considerable variability of the interburst intervals the peak-and-trough modulation is blurred if correlograms are averaged over several trials (Gray *et al.*, 1990; Engel *et al.*, 1990). The shift predictors, which we computed as a control for all correlograms, exhibited no modulation.

Results

We recorded from a total of 202 sites. For 115 of these recording sites, the ocular dominance assessment was confirmed quantitatively. The ocular dominance distribution of the entire data sample is shown in Figure 1. At the majority of the recording sites (137 of 202), the responses were strictly monocular (Fig. 1A, ocular dominance classes 1 and 5), with a slight preponderance of the eye contralateral to the recorded hemisphere. At 44 sites, responses were binocular but dominated by one eye (ocular dominance classes 2 and 4). At the remaining 21 recording sites responses from the two eyes were similar (ocular dominance class 3). The same U-shaped ocular dominance distributions were found if data were displayed separately for each experimental animal. This observation is in accordance with previous studies (Hubel and Wiesel, 1965) and confirms that the induction of strabismus had been effective. Cells dominated by the normal and by the operated eye were recorded with similar probability (Fig. 1B).

Computation of auto-correlation functions revealed that most of the responses in strabismic cats exhibited an oscillatory modulation. An example of a strongly modulated auto-correlation function is shown in Figure 2A. Quantitative analysis of the entire sample showed that at 139 of 202 recording sites (69%) the responses had an oscillatory temporal structure. This proportion is virtually identical to that found in normal cats (68%, Engel *et al.*, 1990). Moreover, oscillatory responses were equally frequent for cells driven by the operated and the intact eye (Fig. 2B). Thus, squint induction does not seem to affect the temporal structure of the neuronal responses as such.

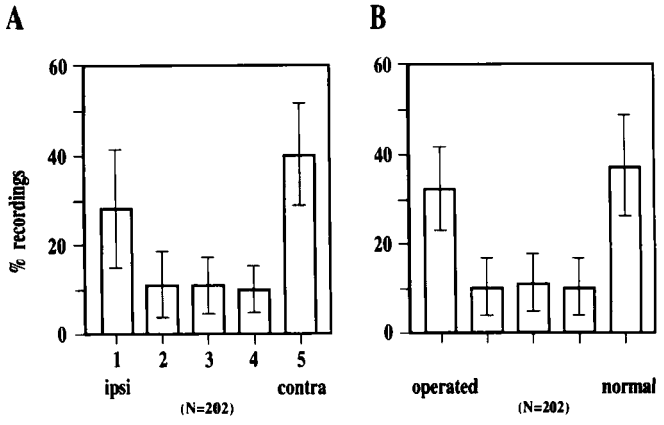

FIG. 1. Averaged ocular dominance distribution for the six cats used in this study. (A) Classification of cells with respect to dominance of the eye ipsi- and contralateral to the recorded hemisphere. (B) Classification according to dominance of the operated and the normal eye. Error bars indicate the standard deviation.

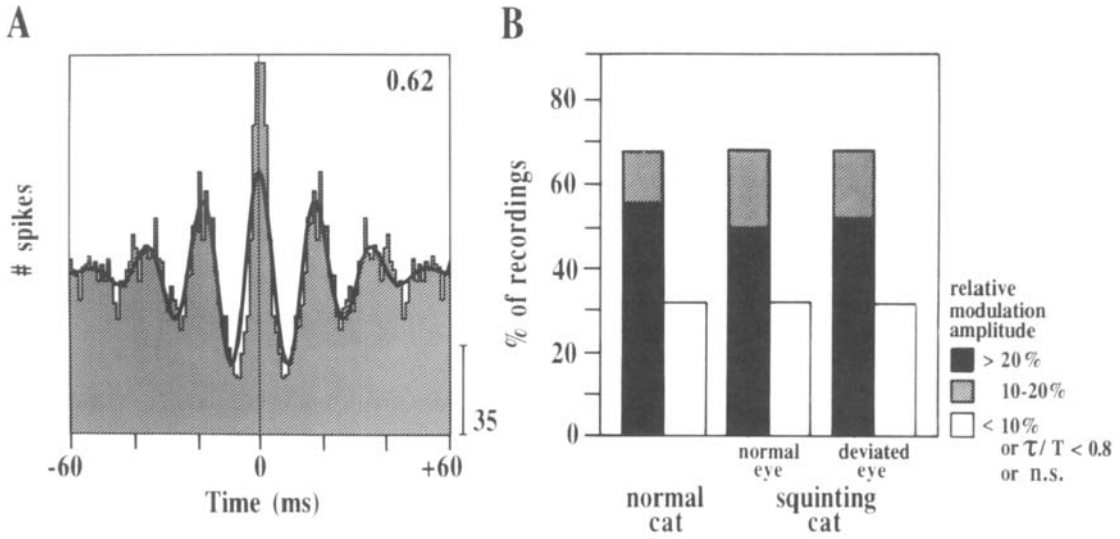

FIG. 2. Incidence of oscillatory responses in strabismic cats. (A) Example of an auto-correlation function of a strictly monocular recording with a relative modulation amplitude of 0.62. The correlogram was computed from responses to ten stimulus presentations. The presence of multiple peaks and troughs in the correlogram indicates that the burst-and-pause firing pattern of the recorded cell group had a fairly narrow frequency spectrum. The thick continuous line corresponds to the Gabor function fitted to the correlogram. (B) Comparison of the incidence of oscillatory responses in normal (left, data taken from Engel *et al.*, 1990) and strabismic cats. For the latter, neurons dominated by the normal and the operated eye are represented separately in the middle and right columns, respectively. The correlation functions are classified according to their relative modulation amplitude and the ratio of decay constant (τ) over the period time (T) (see Materials and methods). The black columns indicate the percentage of auto-correlograms with a strong modulation (relative modulation amplitude of more than 0.20 and $\tau/T \geq 0.8$). Hatched columns indicate the proportion of responses with a weak rhythmicity (relative modulation amplitude between 0.10 and 0.20 and $\tau/T \geq 0.8$). Unfilled columns represent cases where the relative modulation amplitude was below 0.10, where $\tau/T < 0.8$ or where our rating procedure did not detect a significant modulation (n.s.).

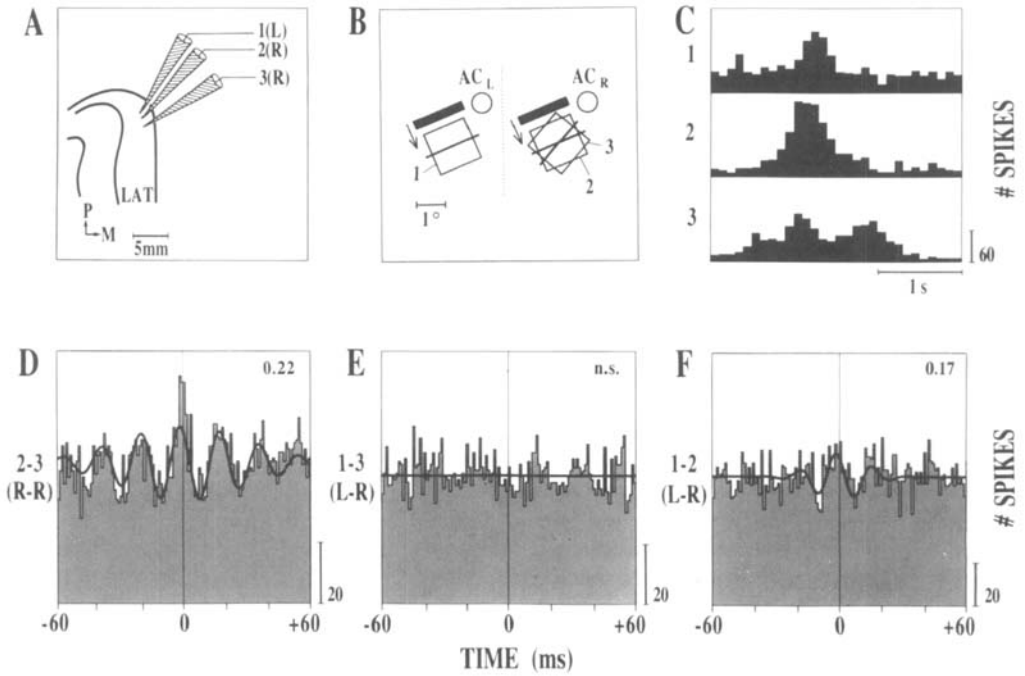

FIG. 3. Temporal correlation between spatially separate neurons in strabismic cats. (A) Position of the recording electrodes in area 17 of the right hemisphere. Electrodes 1 and 2 were separated by 0.4 mm, and electrodes 2 and 3 by 0.8 mm. (B) Receptive fields of the three recorded cell groups. The cells at electrode 1 responded exclusively to stimulation through the left eye (L), whereas the cells recorded with electrodes 2 and 3 were exclusively driven by the right eye (R). All cells responded to light bars with a 112° orientation. The spatial separation of the receptive fields for the left and right eye was actually 15° and thus larger than shown in the figure. (C) Peristimulus time histograms of responses of the three cell groups, added up over ten successive trials. All of the responses exhibited an oscillatory temporal structure (data not shown). (D, E, F) Cross-correlograms between the responses of the three cell groups computed for blocks of ten stimulus presentations. Synchronization was weak (1−2) (F) or absent (1−3) (E) between cells with different dominance but strong for cells with the same ocular dominance (2−3) (D). The thick black line superimposed onto each of the correlograms represents the fitted Gabor function. The numbers in the upper right corners indicate the relative modulation amplitude. LAT, lateral gyrus; P, posterior; M, medial; AC_L, projection of left area centralis onto the tangent screen; AC_R, projection of right area centralis onto the tangent screen; n.s., not significant.

However, cross-correlation analysis revealed that synchronization between spatially separate cell groups was profoundly altered in strabismic cats. Figure 3 shows an experiment where we recorded simultaneously with three electrodes from area 17 (Fig. 3A). One of the recorded cell groups was dominated by the left eye, whereas the responses at the other two electrodes were dominated by the right eye. All cell groups preferred similar stimulus orientations (Fig. 3B). Cross-correlation analysis showed that strong synchronization (relative modulation amplitude >0.20) occurred only between the two cell groups dominated by the right eye (Fig. 3D). Synchronization between responses of cells dominated by the left and right eye was either weak (1−2, Fig. 3F, relative modulation amplitude <0.20) or absent (1−3, Fig. 3E).

Analysis of the whole data sample corroborated this result and showed that temporal correlation occurred mainly between responses of cells that were driven by the same eye. The whole data sample comprised a total of 153 response pairs. Cross-correlation analysis was applied only to pairs of recording sites with a spatial separation of <2 mm. This restriction was chosen to facilitate comparison with data from normal cats (Gray *et al.*, 1989; Engel *et al.*, 1990). Both the probability and the strength of synchronization clearly depended on the ocular dominance of the recorded cells. As shown in Figure 4, 41 of the 66 pairs of recordings with the same ocular dominance (62%) showed a strong synchronization, i.e.the correlogram had a relative modulation amplitude of >0.20. In most of the cases where synchronization was observed it occurred with a phase lag of <3 ms. In 19 cases, significant cross-correlograms showed only a centre peak without clear additional side peaks. The strength of synchronization did not depend on whether both cell groups responded to the normal eye or to the operated eye. In contrast, the large majority of pairs of recordings with different ocular dominance showed flat cross-correlograms. Strong synchronization (i.e. relative modulation amplitude >0.20) occurred in only two of the 57 cases (3%, Fig. 4). One third of the significant correlograms in this group showed a phase shift of >3 ms (Fig. 4),

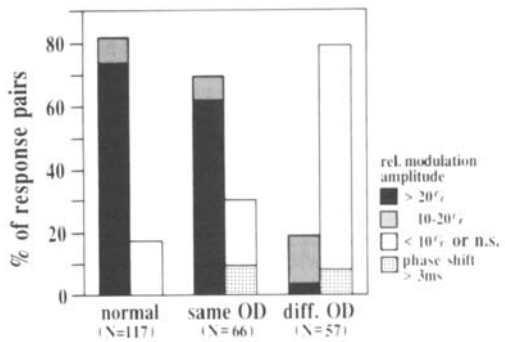

FIG. 4. Incidence and strength of response synchronization as a function of ocular dominance. The leftmost histogram shows data from normal cats. To enable comparison with the present data, only recordings from cell groups with a spatial separation of <2 mm were included (data taken from Engel *et al.*, 1990). The centre histogram represents the correlograms of recordings from cell groups with the same ocular dominance (i.e. pairs with ocular dominances 1/1, 1/2, 2/2, 4/4, 4/5, 5/5; see Materials and methods), and the histogram to the right the correlation of cells with different ocular dominance (i.e. the combinations 1/4, 1/5, 2/4, 2/5). Black columns represent cases with strong synchronization, i.e. correlograms with a relative modulation amplitude of >0.20 and a phase shift of <3 ms. Hatched columns indicate weak correlations, i.e. cases where the correlograms had a relative modulation amplitude between 0.10 and 0.20 and a phase shift of <3 ms. Dotted columns represent cases where the correlograms had a modulation amplitude of >0.10, but showed a phase shift of >3 ms. Unfilled columns comprise correlation functions which did not show a significant modulation (n.s.) or had a relative modulation amplitude of <0.10.

indicating the abnormal character of these residual interactions. In two of the 57 cases, single-peaked correlograms were found for pairs of recordings with different ocular dominance. With respect to strength of response synchronization, the difference between pairs of recordings with the same and different ocular dominance was highly significant ($P < 0.001$; *U*-test).

Response pairs where one of the two cell groups was rated in ocular dominance class 3 ($n = 30$) were always tested with presentation of a single stimulus to the eye preferred by the cell group with asymmetric ocular dominance. These pairs showed strong synchronization in six of 30 cases (20%), which is intermediate between pairs of cell groups with the same ocular dominance and pairs with different ocular dominance (Fig. 4). Statistical testing revealed that this value differs significantly ($P < 0.001$; *U*-test) from that of cell pairs with the same ocular dominance but not from that of pairs with different ocular dominance ($P > 0.01$; *U*-test).

The temporal correlation between responses of cell groups with the same ocular dominance was in several respects similar to that found in normal cats for recording distances of <2 mm (Engel *et al.*, 1990). First, the frequency of occurrence of strong synchronization was comparable (Fig. 4). In normal cats, strong synchronization of neuronal responses was found in 73% of recordings with an electrode separation of <2 mm. Single-peaked correlograms occurred in 24% of the cases. The slight difference between the respective distributions of relative modulation amplitudes in normal and strabismic cats was statistically not significant ($P > 0.1$; *U*-test). Second, as in normal cats, synchronization usually occurred without a phase lag (Gray *et al.*, 1989; Engel *et al.*, 1990). Third, synchronization did not depend on differences in preferred orientation (Table 1) (Gray *et al.*, 1989; Engel *et al.*, 1990).

In three cases, we studied the influence of the stimulus configuration on the synchronization of cell groups with different ocular dominance. Figure 5 illustrates a case in which one of the cell groups responded only to the right eye while the other was binocular with a strong dominance of the left eye. If the receptive fields of both eyes were stimulated simultaneously with their respective preferred stimuli, the responses of the two cell groups were entirely uncorrelated (Fig. 5A, B). The same was true when the two sites were activated with stimuli which had the same orientation and moved coherently over the receptive fields of both eyes (Fig. 5C, D). However, when a single stimulus was presented to the right eye only, the responses of the two cell groups were synchronized (Fig. 5E, F), and this occurred although the cell group dominated by the left eye was activated only weakly. Qualitatively similar results were obtained for the other two cases. Thus, residual interactions between cells of different ocular dominance, which may occur during monocular stimulation, become suppressed by binocular stimulus presentation.

Discussion

Previous physiological studies of the striate cortex of exotropic cats have focused on changes in the response properties of individual cortical cells. Since the classical work of Hubel and Wiesel (1965) numerous investigators have confirmed that squint induction during early development leads to a breakdown of cortical binocularity (Yinon *et al.*, 1975; Yinon, 1976; Blakemore, 1976; Singer *et al.*, 1979; van Sluyters and Levitt, 1980; Berman and Murphy, 1982; Levitt and van Sluyters, 1982; Freeman and Tsumoto, 1983; Kalil *et al.*, 1984). The lack of correlation in the retinal images at anatomically corresponding loci triggers a competitive interaction between inputs from the two eyes on their common target cells in the cortex. As a result, most cells become responsive only to stimulation of either the left or the right

TABLE 1. The dependence of cross-columnar synchronization in strabismic cats on differences in preferred orientation. Only pairs of responses with the same ocular dominance are included

ΔOP[1]	Cross-correlation function		
	oscillatory	single peak	flat
0–22° (n = 30)	47%	20%	33%
45° (n = 21)	48%	38%	14%
67–90° (n = 15)	53%	33%	30%

[1]Difference in preferred orientation.

eye. These monocular cells are not interspersed randomly, but are grouped to ocular dominance columns which extend through the whole depth of the cortex and are in register with the terminal fields of left and right eye afferents in layer IV (Hubel and Wiesel, 1965; Löwel and Singer, 1992).

In the present study, we have extended the search for squint-induced changes of cortical organization by studying the temporal correlation between responses of simultaneously recorded neurons. This approach revealed that early induced strabismus not only causes a rearrangement of thalamo-cortical connections but also influences profoundly the temporal relations between the responses of spatially distributed groups of cells. The neurons in area 17 of exotropic cats exhibit oscillatory responses similar to those observed in normal cats. However, response synchronization occurred almost exclusively between cells with the same ocular dominance and was weak or absent between cells with different ocular dominance. Synchronization between cell groups with the same ocular dominance was found to be similar to that observed in normal animals with respect to strength and average phase relationship. In addition, casual observations suggest that the synchronization between responses of binocular cells with different ocular dominance depends on whether stimuli are presented to both eyes or to one eye only.

Several arguments relate the changes in temporal correlations between distributed responses to alterations of visual perception. Strabismic subjects consistently lose the ability to integrate signals from the two eyes into a single percept. However, preservation of normal monocular vision of both eyes is common in exotropic squinters who usually adopt the strategy of alternating fixation (Duke-Elder and Wybar, 1973; von Noorden, 1990). It is likely that the same is true for exotropic cats, as behavioural data indicate that these exhibit alternating fixation and preserve normal monocular grating acuity but lose all functions requiring binocular cooperativity, such as stereopsis and binocular enhancement of resolution (Ikeda and Tremain, 1977; Mitchell *et al.*, 1984; von Grünau and Singer, 1979; Sireteanu *et al.*, 1982). In addition, there is physiological evidence suggesting that the contrast sensitivity of monocularly evoked potentials and monocular receptive field properties of cortical neurons tend to be normal in exotropic cats (Freeman and Tsumoto, 1983; Freeman *et al.*, 1983; Kalil *et al.*, 1984; Sireteanu and Best, 1992). Based on these previous studies, we assume that the cats used in the present study also lost the ability for binocular integration while preserving normal monocular vision. They resembled in all of the measured variables the exotropic cats which have been raised previously in this laboratory and in which behavioural testing has revealed preserved monocular vision but disrupted binocular integration (Sireteanu *et al.*, 1982). Accepting this extrapolation as valid the present results indicate a correlation between the occurrence or absence of response synchronization on the one hand and the presumed ability or inability to bind visual signals into coherent percepts on the other. Thus, the lack of synchronization between cells dominated

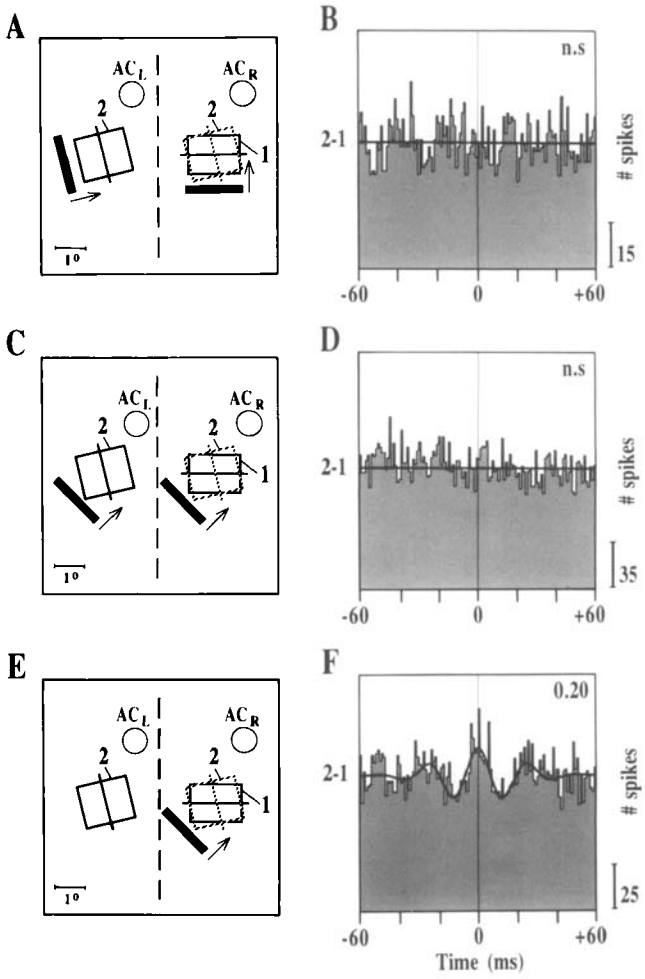

FIG. 5. Dependence of response synchronization on the stimulus configuration. Recordings were taken from two cell groups in area 17 of the right hemisphere separated by 0.8 mm. Cell group 1 was exclusively driven by the right eye and had a preferred stimulus orientation of 90°. Cell group 2, which preferred a stimulus oriented at 22°, was dominated by the left eye, but responded weakly also to stimulation of the right eye. (A, C, E) Receptive field locations and stimulus configurations (same conventions as in Fig. 3). (B, D, F) Cross-correlograms for the responses elicited with the respective stimulus configuration. The thick continuous line represents the function fitted to each correlogram. (A, B) When cell groups 1 and 2 were activated by optimally oriented stimuli presented to the respective dominant eye (left for group 2, right for group 1), the cross-correlation function showed no significant modulation (n.s.). (C, D) When stimuli with the same orientation (45°) were presented to both eyes, the responses were also uncorrelated. In this case, the two stimuli chosen were intermediate between the respective preferred orientations, but still elicited responses in both cell groups. The respective cross-correlation function showed again no significant modulation. (E, F) However, when the two cell groups were activated by a single stimulus presented to the right eye only, the summed cross-correlogram now exhibited a significant correlation (relative modulation amplitude 0.20). Note that in this case group 2 was activated via the non-dominant eye. All correlograms represent the sum over 4–6 blocks of ten trials which were recorded in an interleaved manner during presentation of the various stimulus configurations.

by different eyes corresponds to the presumed inability to integrate signals from the two eyes into a single percept. Likewise, the persistence of temporally structured responses and the normal synchronization of these responses between cells dominated by the same eye relate well to the presumed preservation of the ability to bind signals conveyed by the same eye. Finally, there appears to be a relation between the

occurrence of interocular rivalry and the breakdown of response synchronization upon dichoptic stimulation. Exotropic squinters cannot achieve binocular vision even if the visual stimuli fall on corresponding retinal loci in the two eyes. Rather than becoming fused and bound into a single percept these stimuli are processed separately and give rise to rivalrous percepts. The present finding that binocular cells with differing ocular dominance synchronize their responses when activated through one eye only but desynchronize when stimulated dichoptically may be taken as a reflection of such rivalry. In conclusion, then, there appears to be a correlation between the occurrence of response synchronization and binding of stimuli into single percepts. We consider this correspondence as support for the hypothesis that synchronization on a millisecond time scale mediates the binding of responses of spatially distributed cells in the visual cortex and provide a mechanism for the formation of assemblies of coherently active neurons which, as a whole, serve as representations of particular visual objects (von der Malsburg, 1981, 1986; Gray *et al.*, 1989; Singer, 1990; Engel *et al.*, 1992a).

When considered in the context of previous anatomical results from strabismic animals the present data have implications concerning the neuronal substrate of response synchronization. Strabismus enhances the segregation of afferents from the two eyes (Shatz *et al.*, 1977). In addition, it leads to a reorganization of the tangential intracortical connections which, in normally raised cats, link cortical columns irrespective of the origin of their thalamic afferents. However, in cats that were made exotropic during early development, these tangential pathways preferentially interconnect columns served by the same eye and are largely absent between territories dominated by different eyes (Löwel and Singer, 1992). Thus, there is a close correlation between the absence of response synchronization among distributed cells, the segregation of thalamic afferents and the lack of tangential connections, suggesting a causal relationship between these phenomena. The following arguments suggest that the reorganization of intracortical connections, rather than the segregation of thalamic afferents, is responsible for the lack of synchronization between columns with different ocular dominance. Previous studies on interareal (Engel *et al.*, 1991a) and interhemispheric interactions (Engel *et al.*, 1991b) have shown that response synchronization does not depend on common subcortical input. Rather, the study of interhemispheric interactions has provided direct evidence that response synchronization is mediated by cortico-cortical connections. Groups of cells in the left and right area 17 synchronize their respective responses when activated with coherent stimuli although they do not receive common thalamic input, and this synchronization is abolished when the corpus callosum is sectioned. Because of this evidence that response synchronization can be achieved in the absence of subcortical common input we consider it unlikely that the lack of synchronization between columns with different ocular dominance, as shown here, is due to enhanced segregation of thalamic input. Rather, we suggest that response synchronization within area 17 is also achieved mainly by the intracortical tangential connections. This possibility is further supported by the fact that these connections share essential features of organization with the callosal connections such as reciprocity, laminar distribution and synaptic connectivity. Taken together, these considerations suggest that the squint-induced reorganization of tangential intracortical connections is primarily responsible for the absence of synchronization between columns with different ocular dominance in strabismic animals.

In summary, then, we conclude that the altered capacity for perceptual grouping observed in squinters is the result of an altered probability of response synchronization which, in turn, is brought about by experience-dependent changes in the architecture of synchronizing intracortical connections. If this relationship holds true, our results may have important implications for understanding the visual processing and the development of the visual system in normal animals. As in squinting animals, the capacity for the binding of certain features into coherent percepts will depend on the functional architecture of intracortical connections and, hence, will at least in part reflect the correlations between visual signals experienced during early development.

Acknowledgements

The authors thank Anja Herrmann for technical assistance and Renate Ruhl-Völsing for her invaluable help in the preparation of the figures, and the staff of the animal house for excellent animal care.

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