Visual interhemispheric transfer to areas 17 and 18 in cats with convergent strabismus

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Abstract

Commissural connections between primary visual cortical maps of the two hemispheres are essential to unify the split representation of the visual field. In normal adult cats, callosal connections are essentially restricted to the border between areas A17 and A18, where the central vertical meridian is projected. In contrast, early convergent strabismus leads to an expanded callosal-receiving zone, as repeatedly indicated by anatomical experiments. We investigated here the functional correlates of this widespread distribution of callosal terminals by analysing transcallosal visual responses in five anaesthetized and paralysed 4–10-month-old cats whose right eye had been surgically deviated on postnatal day 6. After acute section of the optic chiasm, single-unit activity was recorded from A17 and A18 of the right hemisphere while the left eye was visually stimulated. A total of 108/406 units were transcallosally activated. While they were more frequent at the 17/18 border (46% of the units recorded within this region), numerous transcallosally activated units were located throughout A17 (16%), A18 (27%) or within the white matter (17%). In all regions, transcallosally driven units displayed functional deficits usually associated with strabismus, such as decreased binocularity and ability to respond to fast-moving stimuli, and increased receptive field size. Many units also displayed reduced orientation selectivity and increased position disparity. In addition, transcallosal receptive fields were manifestly located within the hemifield ipsilateral to the explored cortex, with almost no contact with the central vertical meridian. Comparison with data from normal adults revealed that strabismus induced a considerable expansion of the callosal receiving zone, both in terms of the cortical region and of the extent of the visual field involved in interhemispheric transfer, with implications in the integration of visual information across the hemispheres.

Introduction

In higher mammals, restricted portions of the visual cortical areas A17 and A18 of the two hemispheres are reciprocally interconnected by axons running through the corpus callosum (CC). In cats, these axons originate from and terminate in the 17/18 border (Innocenti & Fiore, 1976; Houzel *et al*., 1994), where the central vertical meridian (CVM) of the visual field and a narrow adjacent portion of both hemifields are topographically represented (Choudhury *et al*., 1965; Berlucchi & Rizzolatti, 1968; Leporé & Guillemot, 1982; Payne, 1990a,b, 1991; Payne & Siwek, 1991; Milleret & Buser, 1993).

This specific adult pattern of interhemispheric connectivity is not innate but rather emerges during the first 4 postnatal months, under normal viewing conditions, from the reshaping of initially exuberant projections. Indeed, in young kittens, callosal axons originate from a large extent of both A17 and A18 (Innocenti *et al*., 1977), and their terminals within the contralateral hemisphere are widely distributed, although only the 17/18 border is invaded by abundant callosal terminals reaching its superficial-most layers (Innocenti, 1981;

Innocenti & Clarke, 1984; Kennedy *et al*., 1987; Elberger, 1993; Aggoun-Zouaoui & Innocenti, 1994; Aggoun-Zouaoui *et al*., 1996). In agreement with these anatomical data, transcallosal visual responses within the cortex are already limited to the 17/18 border upon eye opening, i.e. from the second postnatal week onwards. However, the mature response properties of transcallosally driven neurons, including the spatial distribution of their receptive fields, only develop gradually during the subsequent weeks with normal sensory experience (Milleret *et al*., 1994).

When images seen by both eyes are misaligned during early life, thalamocortical and intracortical networks responsible for the coding of ocularity, stimulus contrast, spatial frequency and velocity are not assembled properly (Boothe *et al*., 1985). Unavoidably, the disrupted equilibrium between right and left visual inputs also interferes with the development of interhemispheric connections, leading to a widespread distribution of both callosal projecting neurons (Innocenti & Frost, 1979; Berman & Payne, 1983; Elberger *et al*., 1983; but see Bourdet *et al*., 1996) and callosal terminals (Lund *et al*., 1978; Lund & Mitchell, 1979; Berman & Payne, 1983) throughout both A17 and A18 of the adult. However, it remains unknown how far the profuse callosal terminals actually penetrate the cortex, whether they establish functional synapses and, if so, what are the actual locations and functional characteristics of their postsynaptic targets. Here we examine these issues by analysing the cortical distribution and response properties of transcallosally driven units recorded

within the lateral gyrus of acutely chiasmotomized adults cats raised with unilateral convergent strabismus. Comparison with data obtained in identical conditions from normal cats (Milleret *et al.*, 1994) indicates that strabismus induces major alterations in the connections responsible for interhemispheric integration of the visual field representation. Preliminary results have appeared elsewhere (Milleret & Houzel, 1991a; Milleret, 1994).

Materials and methods

Five cats, born from different litters in our colony, were used in this study. They were in good health and had no apparent malformations or pathologies. All manipulations and surgical interventions were carried out in accordance with the European Communities Council Directive concerning preparation and maintenance of higher mammals during neuroscience experiments.

Induction of convergent strabismus

At postnatal day 6, i.e. a few days before natural eye opening and while callosal projections are still exuberant (Innocenti *et al.*, 1977), the right eye of each animal was made esotropic. Unilateral convergent deviation was preferred because it is known to induce a more pronounced stabilization of callosal terminals than divergent squint (Lund & Mitchell, 1979). Under Saffan anaesthesia (1.2 mL/ kg, i.m. 10.8 mg/kg of Alfaxolone and 3.6 mg/kg of Alfadolone acetate, Genusxpress, York, UK), the right lateral rectus muscle was completely removed. Local (Neomycin, 350 000 U/mL, Roussel Diamant, France; Rifamycin, 10 mg/mL, MSO-Chibret, France) and general (Extencilline, 1 MU/kg, Specia Rhône-Poulenc Rorer, France) antibiotics were administered and the eyes were checked daily. All kittens recovered rapidly, showed no sign of pain or discomfort, and developed a manifest convergent squint. Four to 10 months later, strabismus angle was assessed using the corneal reflex method (Sherman, 1972) and was found to range between 6 and 13° across animals (see Table 1).

Section of the optic chiasm

Animals were anaesthetized with Saffan (initial, i.m. as above; additional, 1 : 1 in saline, i.v. *ad libitum*) to undergo section of the optic chiasm. While the electrocardiogram and the rectal temperature were continuously monitored, cats were installed on their back in a stereotaxic apparatus. After local anaesthetic (Xylocain) infusion, the bony palate was drilled to expose the dura, which was incised. The underlying optic chiasm was then cut in the midsagittal plane. Antibiotics were given both locally (Cébénicol, 80 mg/mL, Chauvin, France) and i.m. (Extencilline). Completeness of the section was verified during postmortem using gold-chloride staining (Schmued, 1990).

Electrophysiological recordings

Since primary visual cortical responsiveness and receptive field size can be rapidly modified after chiasmotomy in adult cats (Milleret & Buser, 1984, 1993), electrophysiological recordings were performed systematically 3 days after the optic chiasm section to allow direct comparison with other experimental series. Animals were re-anaesthetized with Saffan as described earlier. After tracheal and venous cannulation, electrocardiogram, temperature and expired CO_2 probes were placed for continuous monitoring. Animals were installed in a stereotaxic frame and prepared for acute electro-physiological recording. The scalp was incised and a large craniotomy was performed overlying visual areas A17 and A18 of

TABLE 1. Number of cortical units recorded in areas 17 and 18 of the right hemisphere of the five unilateral convergent strabismic cats with acute split chiasm and either an intact or severed corpus callosum

| Cat | (Angle of strabismus) | Number of cells recorded in areas 17 and 18 | | | |
		c	i	NV	Total
Intact corpus callosum					
CV1	(9°)	24	35	14	73
CV2	(6°)	7	30	17	54
CV5	(13°)	38	12	30	80
CV6	(11°)	8	77	24	109
CV7	(6°)	31	57	2	90
Total		108	211	87	406
After section of the corpus callosum					
CV6		0	50	0	50
CV7		0	55	0	55
Total		0	105	0	105

c, units activated through visual stimulation of the contralateral eye via the transhemispheric pathway; i, units activated exclusively through visual stimulation of the ipsilateral eye via the retinogeniculocortical pathway; NV, nonvisually driven cells. Since no contralateral responses were obtained after section of the corpus callosum, the 108 units which displayed a contralateral response were considered to be transcallosally activated.

the right hemisphere. The nictitating membranes were then retracted with Neosynephrin (5%, Ciba Vision Opthalmics, France) and the pupils dilated with Atropine (1%, MSD, Chibret). Scleral lenses were placed to protect the cornea and focus the eyes on a screen placed 57 cm ahead. Animals were then paralysed with Flaxedil (10–15 mg/ kg/h, Specia), provided by continuous infusion in a mixture of Saffan (3.6 mg/kg/h), plasmagel and glucose, and artificially ventilated. Multiunit extracellular activity was sampled using tungsten micro-electrodes (1–2 MΩ at 1 kHz), amplified, band-pass filtered between 1 and 3 kHz and audio-monitored. Single-cell spike activity was selected through a window discriminator, audio-monitored on a second channel, and occasionally stored for quantitative analysis using a CED–1401plus interface (Cambridge Electronic Devices, Cambridge, UK).

Four to seven electrode penetrations were performed per cat, in the coronal plane and towards the midline, with 20–40° inclination relative to the vertical. Their standard stereotaxic coordinates were P_5 to A_{10} and L_1 to L_4, so as to explore the representation of the centre and the lower quadrant (down to –20°) of the visual field within A17 and A18 (cf. Tusa *et al.*, 1978, 1979). To minimize sampling bias, guarantee the exploration of all cortical layers and include the white matter (WM) in our analysis, single units were recorded at regular intervals of 100 μm, over a total course of 2000–5000 μm. Finally, two small electrolytic lesions (10μA DC, 15 s) were made along each track for subsequent reconstruction. After the recording session, the animal was perfused through the heart with Ringer solution followed by fixative (3% paraformaldehyde, 0.5% glutaraldehyde and 4% sucrose in 0.1 M phosphate buffer). The stereotaxically blocked brain was frozen and cut in 50-μm-thick sections, processed alternately to reveal Nissl substance or cytochrome oxidase activity (Wong-Riley, 1979). The areal and laminar locations of each recording site were determined from the reconstructed tracks. Note that in strabismic animals, as in normal adults, the cytoarchitectonically defined '17/18 transition zone' appeared as a cortical ribbon elongated in a roughly parasagittal direction and about 1 mm wide (cf. Payne, 1990b; Milleret *et al.*, 1994).
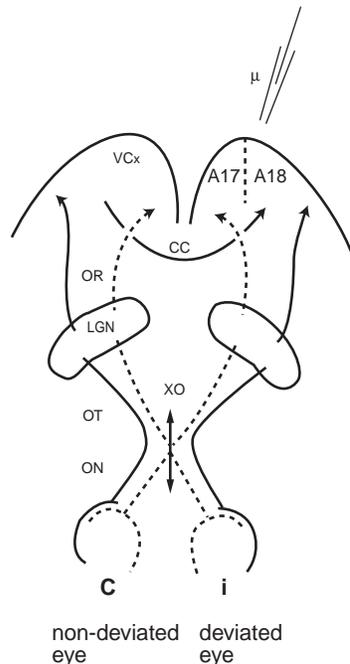
FIG. 1. Experimental design. In strabismic cats subjected to midsagittal section of the optic chiasm (XO), crossed fibres coming from the nasal retinas are severed while uncrossed fibres originating from the temporal retinas are intact and project to the visual cortex (VCx) via the optic nerve (ON), the optic tract (OT), the dorsal lateral geniculate nucleus (LGN) and the optic radiations (OR). Visual units recorded (μ) in areas 17 (A17), 18 (A18) or at the 17/18 border (dotted line) of the right hemisphere may be visually stimulated through the ipsilateral (i, right) deviated eye via the retinogeniculocortical pathway or through the contralateral (c, left) nondeviated eye via the interhemispheric route. CC, corpus callosum.

Analysis of visual responses properties

Visual stimuli (50 Cd/m^2) of various shapes, sizes and velocities were projected manually or using a computer-controlled optic bench onto the faintly illuminated tangent translucent screen (13 Cd/m^2). Stimuli were presented to each eye successively and the following properties were analysed: (i) Response strength was rated into four classes of increasing discharge levels: < 2, 2–3, 3–4 and $> 4 \times$ mean spontaneous activity. (ii) Ocular dominance was determined by comparing the strength of responses to visual stimulation of each eye successively. Note that in the split-chiasm preparation, crossing fibres from the nasal hemiretinae are interrupted; thus, for units recorded within the right hemisphere, responses to right eye stimulation involve the ipsilateral retinogeniculocortical pathway, whereas responses to left eye stimulation result from the activation of the indirect interhemispheric route (Berlucchi & Rizzolatti, 1968; Fig. 1). It is important to point out that the nondeviated (left) eye was chosen to analyse interhemispheric transfer because it has a better acuity than the deviated eye (Ikeda & Tremain, 1979; Chino et al., 1980) and it does not display any nasotemporal asymmetry (Ikeda & Jacobson, 1977; Cynader et al., 1984; Kalil et al., 1984; Sireteanu & Best, 1992). (3) Orientation selectivity was assessed by comparing responses to light bars of different orientations. Units were classified as orientation selective (S) or nonselective (NS). (4) Velocity sensitivity was determined using moving stimuli of optimal orientation and direction. Units were categorized as low-pass, broadband, tuned or high-pass, according to the criteria defined by Orban et al. (1981). (5) Precise limits of the receptive fields (RFs) were mapped as the 'minimum response fields'. (6) Spatial location of the RFs within the visual field was inferred relative to the position of the optic discs and the area centrales, whose projections were verified several times during the experiment (Vakkur et al., 1963; Milleret et al., 1988). (7) RF size (in degrees^2) was derived from careful plots drawn on the tangent screen. (8) For each binocular unit, the disparity in RFs position was evaluated as the angular distance between the centres of its two RFs. (9) Finally, the RF overlap index (OI) was calculated using the formula: $[B/(I + C - B)] \times 100$, where I and C are the size of the ipsilateral and the contralateral RF of a given binocular unit, respectively, and B is the visual field area common to both RFs.

Control section of the corpus callosum

Cortical responses driven by the contralateral eye in strabismic split-chiasm animals could in principle either be mediated through the corpus callosum or result from system-wide reorganization following the early induced modification of sensory experience. To distinguish between these possibilities, the effects of acute callosotomy were investigated in two animals (Table 1; CV6 and CV7). Prior to these recording sessions, a larger craniotomy was performed to expose the entire lateral gyrus of both hemispheres. After having recorded a substantial number of units from the right cortical hemisphere, with an incidence of contralateral responses comparable with that observed in other CC-intact animals, anaesthesia was increased temporarily. The dura was reflected along the interhemispheric cleft and the venous sinus was pushed aside. A blunt spatula was then inserted vertically between the hemispheres and advanced with a stereotaxic holder so as to cut the posterior 2/3 of CC (standard stereotaxic coordinates: H_0 from A_3 to A_8; $H_{+4.5}$ from A_8 to A_{15}). The next day, the left hemisphere was first tested for its functionality by recording a few responses to visual stimulation of the ipsilateral (left) eye; recordings were then pursued within the right hemisphere, and responses to both eyes were explored systematically. Whatever their areal location (Table 2), the 105 units recorded in this condition responded exclusively to visual stimulation of the ipsilateral eye (Table 1). Therefore, contralateral visual responses were considered to involve strictly the corpus callosum. Completeness of the callosotomy was verified postmortem on 50-μm-thick myelin stained frontal sections.

Results

Of the 406 units recorded in the right hemisphere of five early strabismic adult cats with acute chiasmotomy and intact corpus callosum, 108 responded to visual stimulation of the contralateral (nondeviated) eye, and were thus driven through the transcallosal pathway (Table 1). Other units either responded exclusively to visual stimulation of the ipsilateral eye through the geniculocortical pathway ($n = 211$) or were visually unresponsive ($n = 87$). The following sections examine the distribution and functional characteristics of transcallosally driven units (TC units) only. Since their characteristics did not differ among animals of different ages and with different strabismus angles, data from all five animals were pooled together and then compared with data obtained previously from eight normally reared (NR) adult cats (Milleret et al., 1994) and one additional animal.

Location of transcallosally driven units

Most TC units of strabismic animals were located within the grey matter of the visual cortex (Table 2). The highest incidence of TC units was observed at the 17/18 border, where it reached 46.5% (47/

TABLE 2. Incidence of the different types of cortical units recorded in strabismic (CV) cats before and after section of the corpus callosum

	Area 17			17/18 border			Area A18			White matter			
	c	i	NV	c	i	NV	c	i	NV	c	i	NV	Total (n)
Convergent strabismic cats (CV)													
With intact corpus callosum													
n	23	79	40	47	37	17	29	63	17	9	32	13	406
%TC (%)	16			46.5		27			17				
After section of the corpus callosum													
n	0	33	0	0	41	0	0	31	0	0	0	0	105
%TC (%)	0			0			0			–			
Normally reared adult cats (NR)													
With intact corpus callosum													
n	1	105	19	58	26	25	0	49	2	0	11	2	298
%TC (%)	1			53			0			0			

c, i and NV, as in Table 1, with 'c' corresponding to transcallosal responses. n, number of cells; %TC, percentage of transcallosally activated units. (NR), controls, normally reared adult cats.

101 units recorded in this region). TC units were also present in A17 (16%, 23/142 units) and A18 (27%, 29/109 units), as far as 4600 μm away from the 17/18 border (Fig. 2). Whatever their areal location, they were often grouped as clusters of 4–7 units and were distributed throughout all cortical layers (except in layer I of A18), with strong biases towards deep layers at the 17/18 border and superficial layers in A17 (Fig. 3). Additional TC units (17%, 9/54 units) were recorded within the WM, 100–500 μm below the inferior limit of the 17/18 border or A18 (Fig. 4).

These results differ markedly from those obtained with NR adults (Table 2; Figs 2 and 3). While strabismus neither prevented callosal terminals from establishing functional synaptic contacts nor modified the percentage of TC units at the 17/18 border (46.5 vs. 53%; χ^2 with Yates's correction, $P < 0.05$), it greatly disrupted their laminar distribution since they are normally located mainly in layer II/III (χ^2 with Yates's correction, $P < 0.05$). More importantly, convergent squint resulted in numerous cortical units within both A17 and A18 being driven through the CC, while such units are virtually absent in normal animals (Fisher's exact test, $P < 0.0001$). Strabismus also tended to increase the proportion of TC units within the WM (17 vs. 0%, Fisher's exact test, $P = 0.18$) although the difference between NR and strabismics is not significant because of too low a sampling in the former group.

Strength of transcallosal responses (Fig. 3)

All TC units of strabismic animals were not equally driven through the transcallosal pathway. At the 17/18 border, most TC responses were clear and reproducible (class 2, 55% of TC units) or even strong (class 3, 30%); other responses were either irregular and poor (class 1, 11%) or conversely, extremely vigorous ones (class 4, 4%). Whereas vigorous responses were confined to supragranular layers, TC units of various strength classes were recorded from all layers. In A17 and A18, most TC units belonged to classes 1 and 2, but a few class 3 responses were recorded from supra- and granular layers. Clear and strong TC responses were recorded several millimetres away from the 17/18 border, medially in A17 or laterally in A18. Finally, within WM, most TC units belonged to class 2 and only a few ones were of class 1.

These observations indicate that interhemispheric connections formed in strabismic animals were capable of mediating vigorous postsynaptic responses in a large portion of the lateral gyrus of the target hemisphere, including those regions that are normally devoid
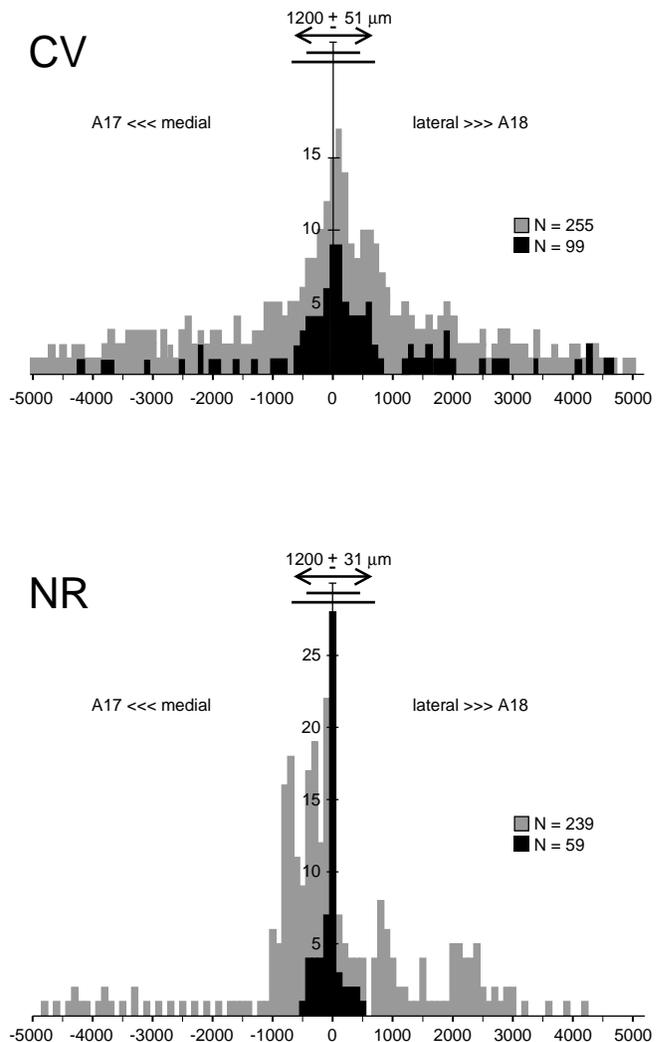

FIG. 2. Tangential distribution of cortical units recorded in convergent strabismic (CV) and normally reared (NR) cats, either activated (transcallosal units in black) or nonactivated (grey) through the transcallosal pathway. Abscissa, tangential distance (in μm) of the recorded cortical units from the centre of the 17/18 border; negative values correspond to more medial locations in A17 while positive values correspond to more lateral locations in A18. Ordinate, number of units. Double-headed arrow, short and long lines indicate mean, minimum and maximum width of the 17/18 border, respectively. N, number of units.
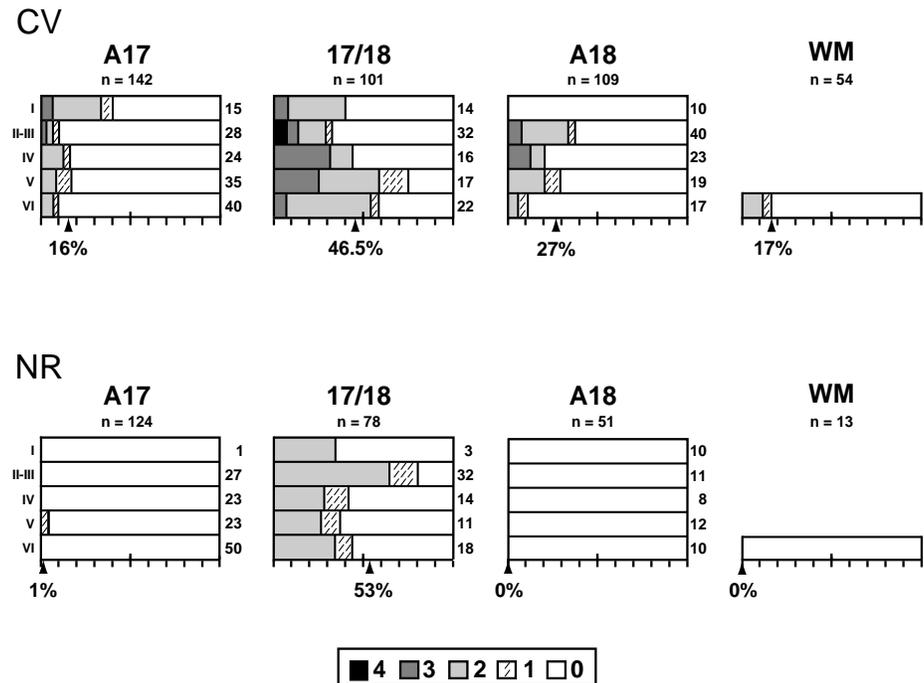
FIG. 3. Strength of transcallosal responses with respect to area and laminar location in strabismic (CV) and normally reared cats (NR). For each lamina (roman numbers), bars indicate the percentage of TC units relative to the total number of recorded units indicated on the right. Shading represents response strength. Arrows indicate the mean percentage of transcallosally responding units in each region. WM, white matter.

of callosal inputs. Moreover, the mean TC response level at the 17/18 border was even higher in strabismics than in NR adults since only class 1 and 2 responses are usually found in the latter group (χ^2 test with Yates's correction, $P < 0.05$).

Ocular dominance of transcallosal units (Fig. 5)

While some TC units responded exclusively to visual stimulation of the left (contralateral) eye, the majority responded additionally to visual stimulation of the right eye through the ipsilateral geniculo-cortical pathway (14/23 in A17; 19/47 at the 17/18 border; 23/29 in A18 and 7/9 in WM). Although the proportion of binocular TC units recorded in strabismics seems high (58%), it is significantly lower than in NR controls (95%, χ^2 with Yates's correction, $P < 0.05$), indicating that the binocularity of many TC units is disrupted by strabismus. Indeed, once computed relative to the entire population of recorded (TC and non-TC) units and corrected for the ≈33% chiasmotomy-induced decrease in binocularity, the overall proportion of binocular cells in our sample (CV: 13% in A17; 25% at the 17/18 border; 28% in A18) appears very similar to previously reported values (13–43% depending on author, see Boothe et al., 1985).

Comparing the strength of the responses to each eye allowed the establishment of ocular dominance in our sample. When all TC units were pooled together, global ocular dominance distribution was U-shaped, indicating that either the contralateral or the ipsilateral eye dominated TC-driven units. However, responses through the contralateral (left, nondeviated) eye were stronger than through the ipsilateral (right, deviated) eye for 61% of the TC units. Sorting TC units according to their areal location revealed marked regional differences. At the 17/18 border, ocular dominance distribution was biased towards the contralateral eye, which contrasts with the situation observed in NR adults where the ipsilateral eye dominates the population of TC units (χ^2 test with Yates's correction, $P < 0.05$). This difference could, in theory, be attributed to the reduced efficacy of the deviated eye (Boothe et al., 1985; Milleret, 1994; Kiorpes & McKee, 1999). Surprisingly, however, the deviated eye dominated in A18 and there was no ocular bias in A17.

Orientation selectivity of transcallosal units (Fig. 6)

From 108 recorded TC units, 58% were selective for orientation (S). When sorting TC units according to their areal location, the percentage of S units varied from 72% at the 17/18 border to 62% in A18 and 48% in A17; all nine TC units recorded in WM were nonselective (NS). Since nearly all (97%) TC units are selective in NR adults, these results indicate that convergent squint markedly reduced the orientation selectivity of TC units recorded at the 17/18 border (McNemar χ^2 test with Yates's correction, $P < 0.0001$), as has been reported to be the case for the whole population of visual cortical cells in strabismic, nonchiasmotomized cats (Yinon et al., 1975; Mower et al., 1982; Chino et al., 1983; but see Berman & Murphy, 1982; Kalil et al., 1984).

The distribution of the preferred orientations encoded by the selective TC units showed that the vertical orientation was under-represented in all explored regions. This is in contrast with NR adults for which all orientations are equally represented (χ^2 test with Yates's correction, $P < 0.05$). Thus, the 'vertical effect', i.e. the decrease in the proportion of visual cortical units encoding vertical orientations occurring after early horizontal strabismus (Singer et al., 1979; Cynader et al., 1984; Chino et al., 1991; Sireteanu & Best, 1992; but see Berman & Murphy, 1982; Kalil et al., 1984) is also obvious within the subpopulation of TC units. As in NRs, binocular units in strabismics displayed the same orientation selectivity regardless of which eye was stimulated.

Velocity sensitivity of transcallosally activated units (Fig. 7)

Slow-moving stimuli were generally more effective in driving TC units in strabismics, as indicated by the prevalence of low-pass units at the 17/18 border (64%), in A17 (61%), as well as in WM (5/9 units). However, faster stimuli were more effective in A18, where the majority of TC units (52%) were high-pass. Again, binocular units exhibited no apparent difference in velocity sensitivity whether one eye or the other was stimulated.

Motion sensitivity of TC neurons located at the 17/18 border appeared to be profoundly affected by strabismus since most of them
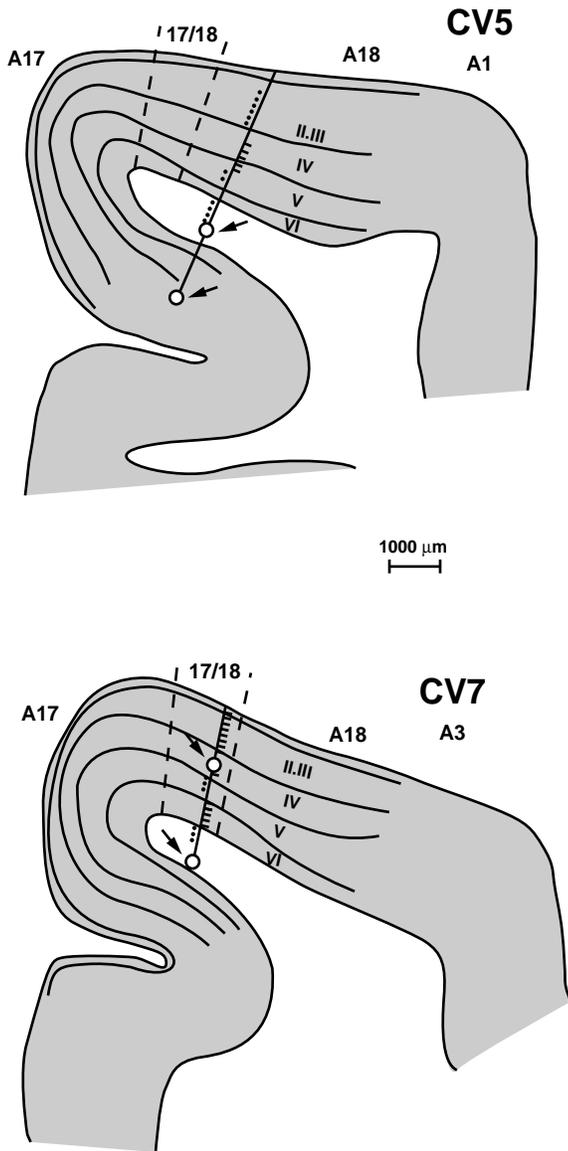
FIG. 4. Examples of two recording tracks with transcallosal (TC) responses within the white matter of convergent (CV) strabismic cats. Top, cat CV5, track through A18, stereotaxic plane A1. Bottom, cat CV7, track at the 17/18 border, stereotaxic level A3. Tracks were reconstructed with respect to two electrolytic lesions (arrows). Dots, TC activated units; bars, exclusively ipsilaterally driven units (i). Areal and laminar (roman numbers) boundaries are indicated. Notice that some units were located several hundred micrometers below the lower limit of layer VI.

are broadband in NR adults (62%, χ^2 test with Yates's correction, $P < 0.05$). We thus confirm that strabismus induces an alteration of motion processing mechanisms at the single neuron level within primary visual cortical areas (Chino *et al.*, 1983, 1988).

Receptive field characteristics of transcallosally activated units

As described earlier, some TC units received exclusively transcallosal inputs, while others received additionally ipsilateral geniculocortical inputs. Their receptive fields (RFs) will therefore be referred as TC-RFs or GC-RFs depending on the pathway used to map them.

Sizes of transcallosal and geniculocortical RFs

TC units of strabismics, whether of S or NS type, displayed a great variability in TC-RF size, which ranged from 3 to 120 degrees^2
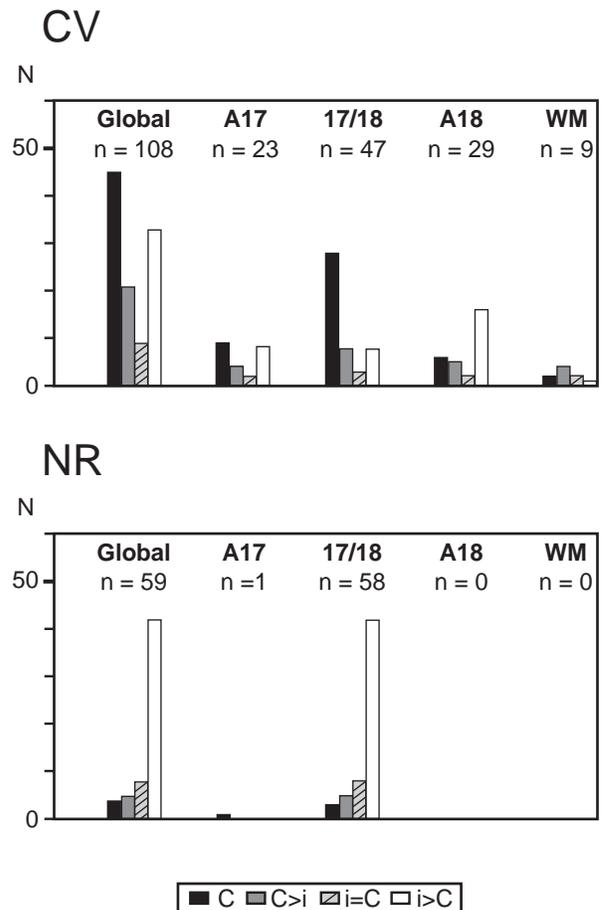

FIG. 5. Ocular dominance of transcallosal units recorded in A17, at the 17/18 border, in A18 and in white matter (WM) of convergent strabismic (CV) and normally reared (NR) cats. Units were ranked into four classes according to the relative strength of response to contralateral and ipsilateral eye stimulation: c, units activated only through the contralateral (nondeviated) eye; c > i, units activated preferentially through the contralateral eye; c = i, units activated equally through both eyes; i > c, units activated preferentially through the ipsilateral (deviated) eye. Since this graph only includes TC responses, there is no class 'i' (purely ipsilateral response). Global, all units pooled together. N and n, number of units.

(Fig. 8). Mean size was 34 degrees^2 and did not differ significantly between regions (A17, 30.6 ± 2.8 degrees^2; 17/18 border, 37.9 ± 7.2 degrees^2; A18, 30.4 ± 10.6 degrees^2). Since mean RF size for TC units recorded at the 17/18 border in NR adults is 11 ± 1.5 degrees^2, strabismus apparently induced a significant increase in RF size. Our data thus indicate that this expansion also involves the subpopulation of TC units and does not only occur in A17 as had been previously reported (Berman & Murphy, 1982; Chino *et al.*, 1983, 1988).

For most of the 38 binocular TC units analysed in our sample (13 in A17, nine at the 17/18 border, 14 in A18 and two in WM), the respective geniculocortical and transcallosal RFs were of almost identical size (unpaired *t*-test, $P = 0.84$; see Fig. 11). This similarity was also observed in normal cats and is therefore unaffected by strabismus.

Spatial distribution of TC-RFs (Fig. 9)

While the TC-RFs of a few units recorded within A17 and A18 abutted or intersected the CVM, most other TC-RFs (including those
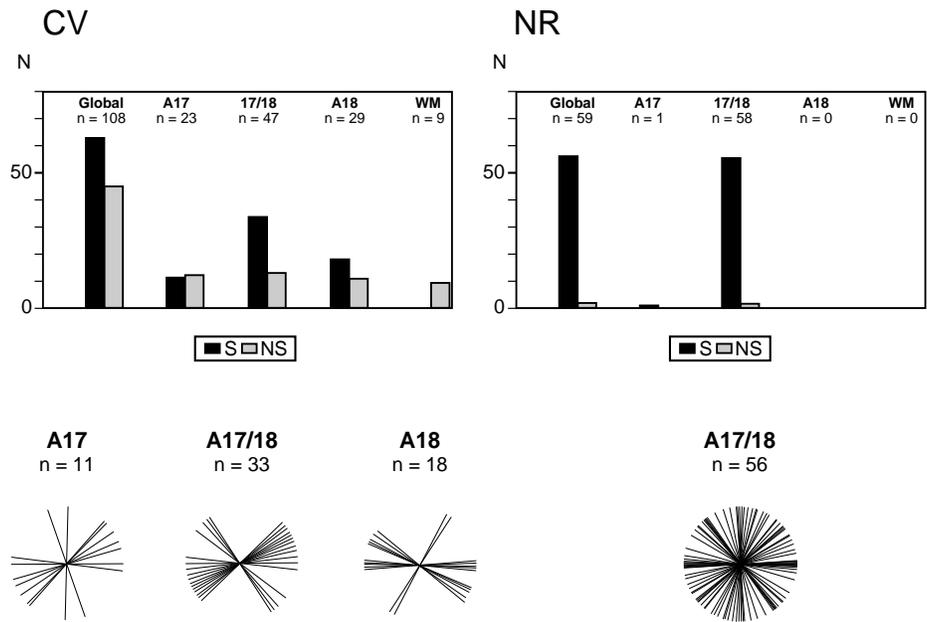
FIG. 6. Orientation selectivity of transcallosal units recorded in A17, at the 17/18 border, in A18 and in white matter (WM) of convergent strabismic (CV) and normally reared (NR) cats. Top, distribution of orientation selective (S) and nonselective (NS) units in each explored region. Global, all data pooled together. Bottom, polar diagrams showing the distribution of the preferred orientations encoded by S units. N, n, number of units.

of all units recorded at the 17/18 border) were manifestly located within the right hemifield so that no contact with the CVM was observed. The medial-most and lateral-most limits of TC-RFs were, respectively, localized at −1° and +15° azimuth, apart from the CVM for units recorded in A17, +2° and +19° for the 17/18 border and −1° and +14° for A18; the mean azimuth of the centres of the TC-RFs were +4.9 ± 0.3° for A17, +9.5 ± 0.3° for the 17/18 border and +6.5 ± 0.3° for A18. As a result, the 'callosal visual field', i.e. the portion of visual field transferred to the target hemisphere through the CC, spans a similar width in all the explored cortical areas (mean = 16 ± 1°) and is located in the ipsilateral hemifield, off the CVM by some degrees, more especially within the 17/18 border.

In all explored regions, most TC-RFs were located within the lower half of the visual field, from 0 to −20° of elevation, corresponding to what was expected from the cortical location of the recording sites. Another parameter that was basically unchanged is the width of the callosal visual field (14° in NR vs. 16° in strabismics). In contrast, the azimuthal positions of the TC-RFs of units recorded at the 17/18 border were manifestly altered. A comparison of the ranges of coordinates of their centres (from −4.5° to +6° in NR vs. +4.5° to +15° in strabismics), of their medial-most limits (−3° to +4° vs. +2° to +14°) and of their lateral-most edges (−6° to +8° vs. +7° to +19°) reveals that strabismus markedly shifted the callosal visual field towards the ipsilateral hemifield. Since there is very little overlap between the callosal visual fields or between the TC-RFs centres of both groups, the previously mentioned increase in TC-RF size cannot account for this displacement, which indeed reflects some genuine reorganization in the topographical representation of the callosal visual field at the 17/18 border.

Spatial distribution of the GC-RFs (Fig. 10)

In all explored regions, most GC-RFs of TC units were located between +5° and −20° elevation. While only a few GC-RFs (from units recorded within A17, WM or 17/18 border) reached the CVM, most of them, including all GC-RFs in A18, were located within the left hemifield, so that contact with the CVM was absent. The medial-most and lateral-most limits of GC-RFs were, respectively, localized at an azimuth of +9° and −16° for units recorded within A17, +3° and

−16° for the 17/18 border and −3.5° and −23° for A18, while the mean azimuth of their centres were −6 ± 1.4°, −7.2 ± 0.8° and −12.6 ± 1.1°, respectively. Thus, although the width of the portion of visual field 'seen' through the GC-RFs of the TC units varied between 19° and 25° according to the area, it was always markedly displaced towards the contralateral hemifield.

The spatial distribution of GC-RFs of TC units recorded from the 17/18 border of strabismic cats was similar to that observed in NR controls regarding elevation as well as width of the portion of visual field seen through this pathway (20° in NR vs. 19° in strabismics). Similar to TC-RFs, the main difference concerned the azimuthal position of the RFs, which were markedly shifted toward the contralateral hemifield in strabismics. However, there was a considerable degree of overlap between the distributions of GC-RFs in NR and in strabismics (medial-most edge, −5° to +2.5° in NR vs. −9° to +3° in strabismics; centres, −9° to +4° vs. −10.5° to −4°; lateral-most edge, −13° to +7° vs. −11° to −16°, respectively) suggesting that this effect could merely reflect the increased size of GC-RFs (discussed earlier), requiring no profound reorganization of topographical maps.

Disparity in position between RFs of binocular TC units

As expected from the global spatial distributions described above, TC-RFs and GC-RFs of binocular TC units generally did not match in position. Both amplitude and direction of this position disparity were not constant but varied from one unit to another, including within the course of a single recording track (Fig. 11).

Correcting the data for strabismus angle by superimposing the projections of both area centrales showed that TC-RFs were always located within the hemifield ipsilateral to the explored cortex, while GC-RFs were located within the contralateral hemifield (Figs 11 and 12A), except for one unit whose two RFs were both located in the ipsilateral hemifield (see Fig. 12A, A17, RF centres joined by a dotted line). Moreover, the two RFs of most binocular units differed in elevation (9/13 in A17, 9/9 at the 17/18 border, 9/14 in A18 and 1/2 in WM; Fig. 12A). Their disparities in position ranged from 6 to 21° (mean receptive field size, m = 12°) in A17, from 17 to 21° (m = 18.7°) at the 17/18 border, from 14 to 27° (m = 19°) in A18 and
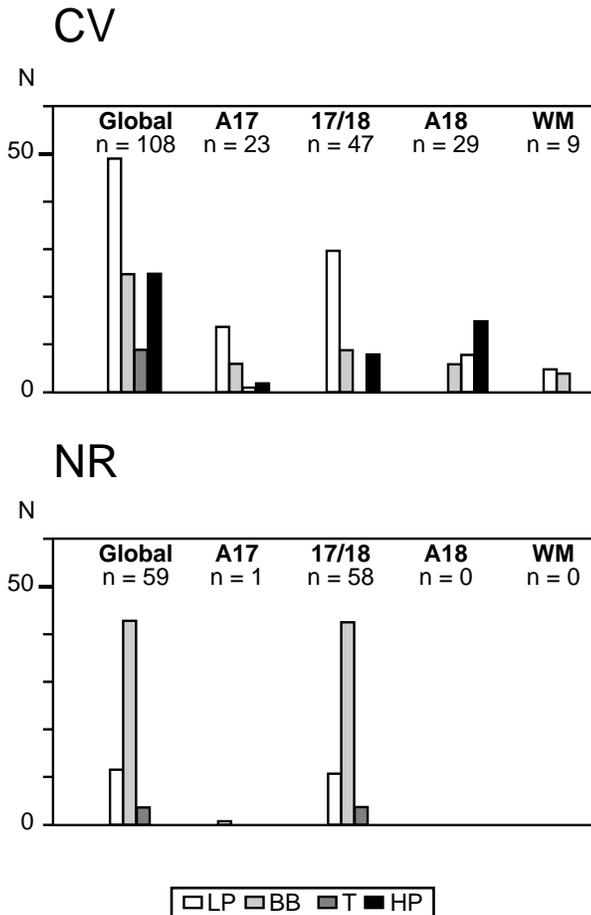
CV

NR

FIG. 7. Velocity sensitivity of transcallosal (TC) units recorded in A17, at the 17/18 border, in A18 and in white matter (WM) of convergent strabismic (CV) and normally reared (NR) cats. LP, low pass; BB, broadband; T, tuned; HP, high pass. Global, data pooled for all regions. N and n, numbers of TC units.

CV

NR

FIG. 8. Distribution of the sizes of the transcallosal receptive fields of units recorded from A17, the 17/18 border, A18 and white matter (WM) in convergent strabismic (CV) and normally reared (NR) cats. Global, all units polled together. S, orientation-selective units; NS, nonselective units. N and n, number of units; m, mean receptive field size; bin width, 10 degrees^2.

from 12 to 13° in WM (Fig. 12B). Furthermore, TC-RFs and GC-RFs of binocular TC units were never superposed (Figs 11 and 12C); they overlapped partially in one case (Fig. 11; overlap index = 11.6%) and not at all for all others 37 units, yielding a very low mean overlap index (0.3 ± 0.3%).

Comparison with results from NR adults (Figs 11 and 12) revealed that unilateral strabismus did not affect the match in selectivity for orientation, direction, velocity and sizes observed between TC and GC inputs converging on binocular TC units recorded at the 17/18 border. In contrast, it raised the mean position disparity from 3.1 ± 0.4° up to 18.7 ± 0.4° and lowered the mean overlap index for RF pairs from 22 ± 4.7% down to 0%. This observation confirms that early strabismus affects the ability of primary visual cortical cells to encode disparity (Yinon *et al.*, 1975; Cynader *et al.*, 1984; but see Grant & Berman, 1991) and indicates that the same effect occurs for TC units. Units with large disparity are reminiscent of the binocular units with abnormal RF position reported by Di Stefano *et al.* (1991) in suprasylvian cortex of strabismic cats (see Discussion).

When RF positions were corrected, not for strabismus angle (Fig. 13), but were shifted so as to mimic the awake situation, i.e. when the two area centrales projections were separated by the squinting angle measured in each animal, some GC-RFs moved
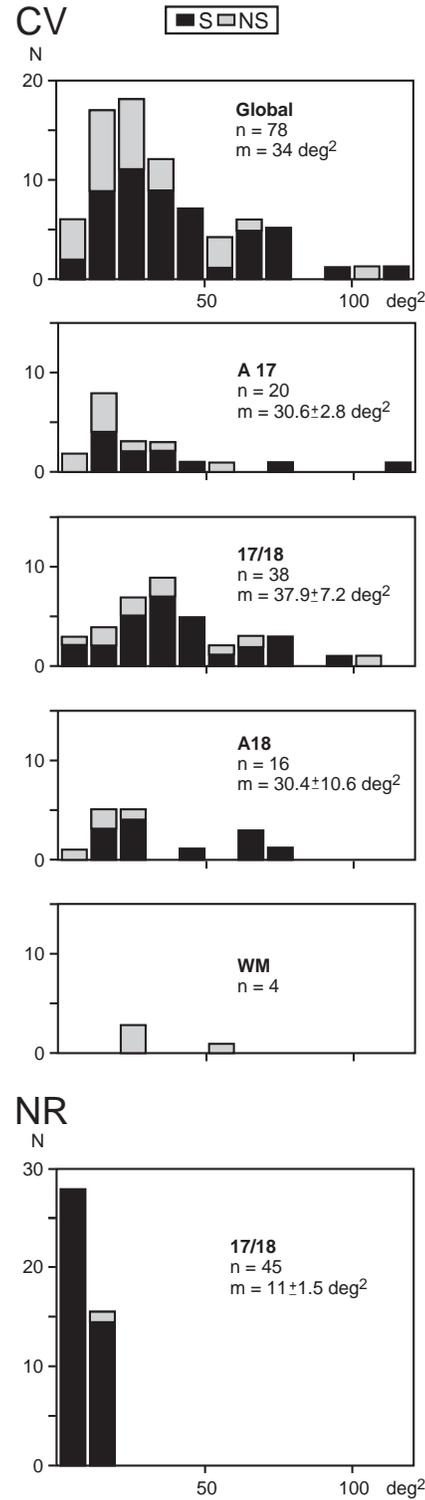
toward the CVM and the ipsilateral hemifield, thus closer to the corresponding TC-RFs (centres of such pairs are joined by dotted lines in Fig. 13A). However, disparities between RF pairs (Fig. 13B) remained quite large, ranging from 1 to 12° (m = 6.5°) in A17, from
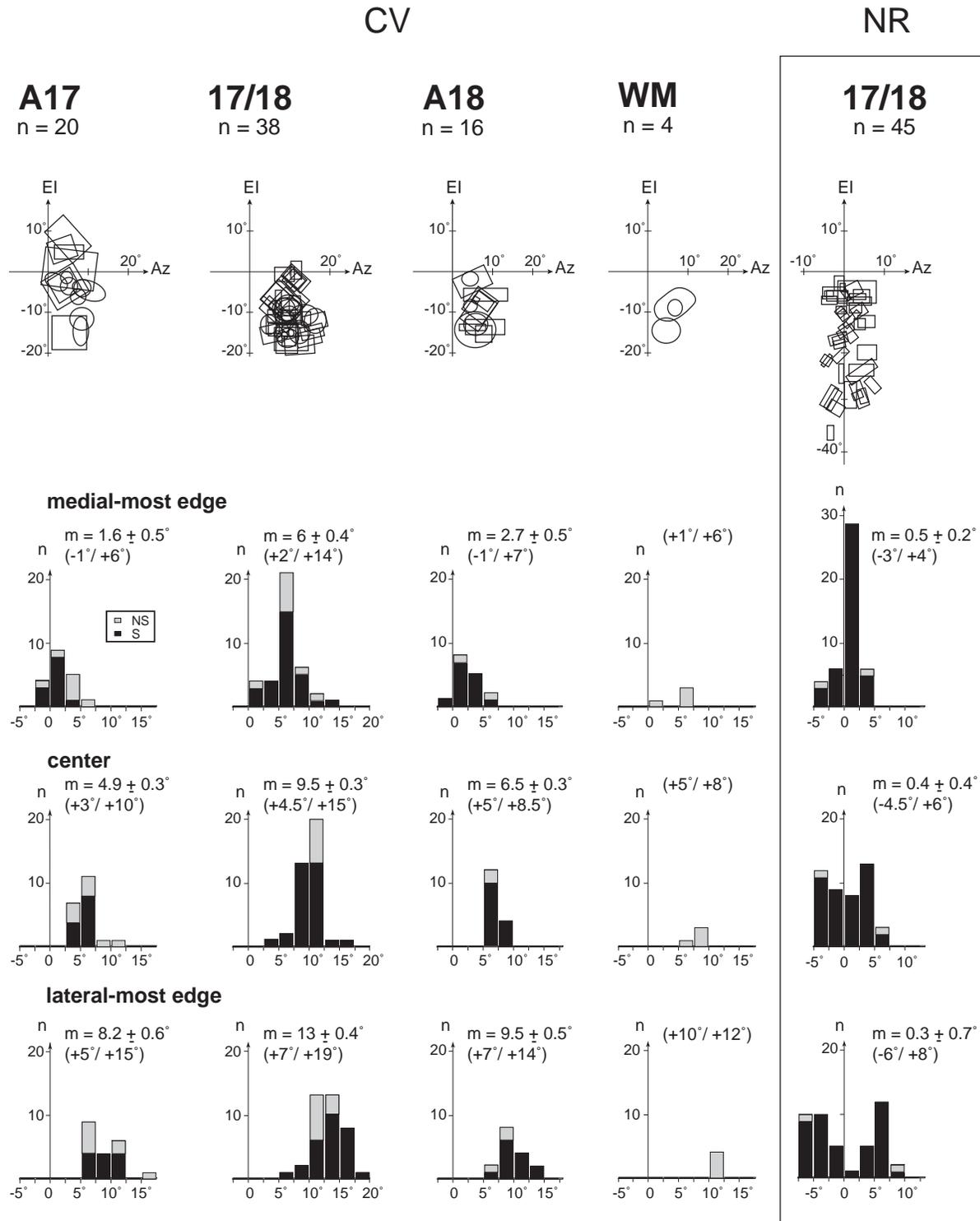
FIG. 9. Spatial distribution of the transcallosal receptive fields (TC-RFs) of transcallosal units recorded in A17, at the 17/18 border, in A18 and in white matter (WM) of convergent strabismic (CV) and normally reared (NR) cats, mapped through the left, nondeviated eye, contralateral to the explored cortex. Upper part, spatial distribution within the visual field. El, elevation axis (central vertical meridian of the visual field); Az, azimuth axis. Rectangles and circles, contours of the minimum response field of orientation-selective and nonselective TC units, respectively. Lower part, azimuths of medial-most limits, centres and lateral-most limits of the TC-RFs represented within the upper part. S, units selective for orientation; NS, nonselective units. m, mean values; into brackets, minimal and maximal values. n, number of units.

7 to 13° (m = 10°) at the 17/18 border and from 6 to 20° (m = 11.2°) in A18. In addition, the global amount of overlap increased only slightly (5.4 ± 2.5 vs. 0.3 ± 0.3%; compare Figs 12C and 13C),

with only 6 TC units in A17, 2 at the 17/18 border and 1 in WM exhibiting overlapping RFs (their centres are indicated by arrows in Fig. 13A).
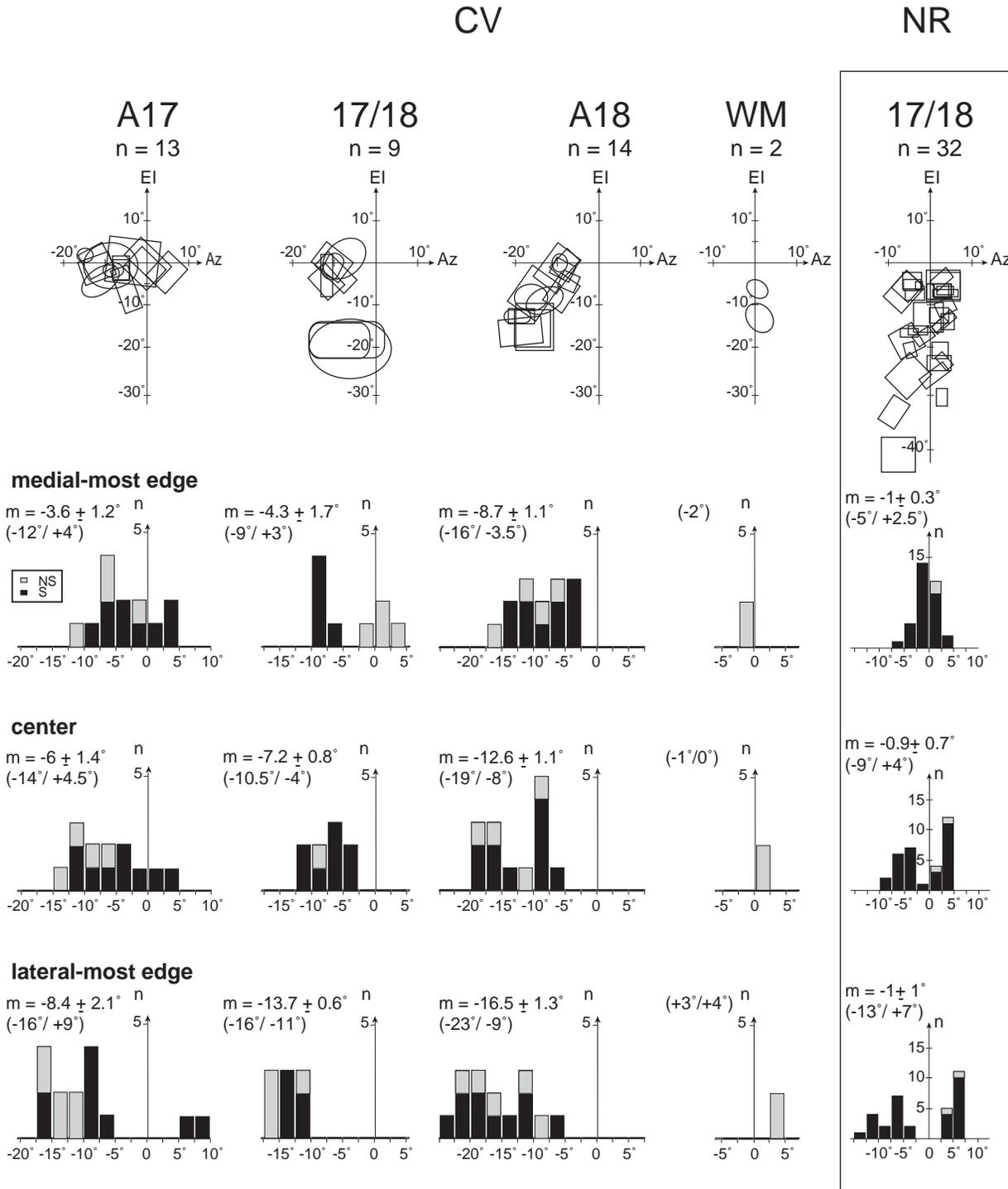
FIG. 10. Spatial distribution of the geniculocortical receptive fields of the TC units recorded in A17, at the 17/18 border, in A18 and in white matter (WM) of convergent strabismic (CV) and normally reared (NR) cats, mapped through the right, deviated eye, ipsilateral to the explored cortex. Same legend as Fig. 9.

Discussion

This study addresses the question of whether interhemispheric integration of visual information depends on early sensory experience, more specifically on congruent binocular visual inputs. We investigated to what extent the functional pattern of callosal connectivity between primary visual cortical areas might be affected in adult cats raised with unilateral convergent strabismus by comparing the characteristics of transcallosal visual responses with those previously described for normally reared animals. The results indicate that such disruption of binocularity does induce major alterations. In the following paragraphs, we will discuss the effects at the level of the callosal efferent neurons, of their contralateral terminals and finally of callosal recipient cells.
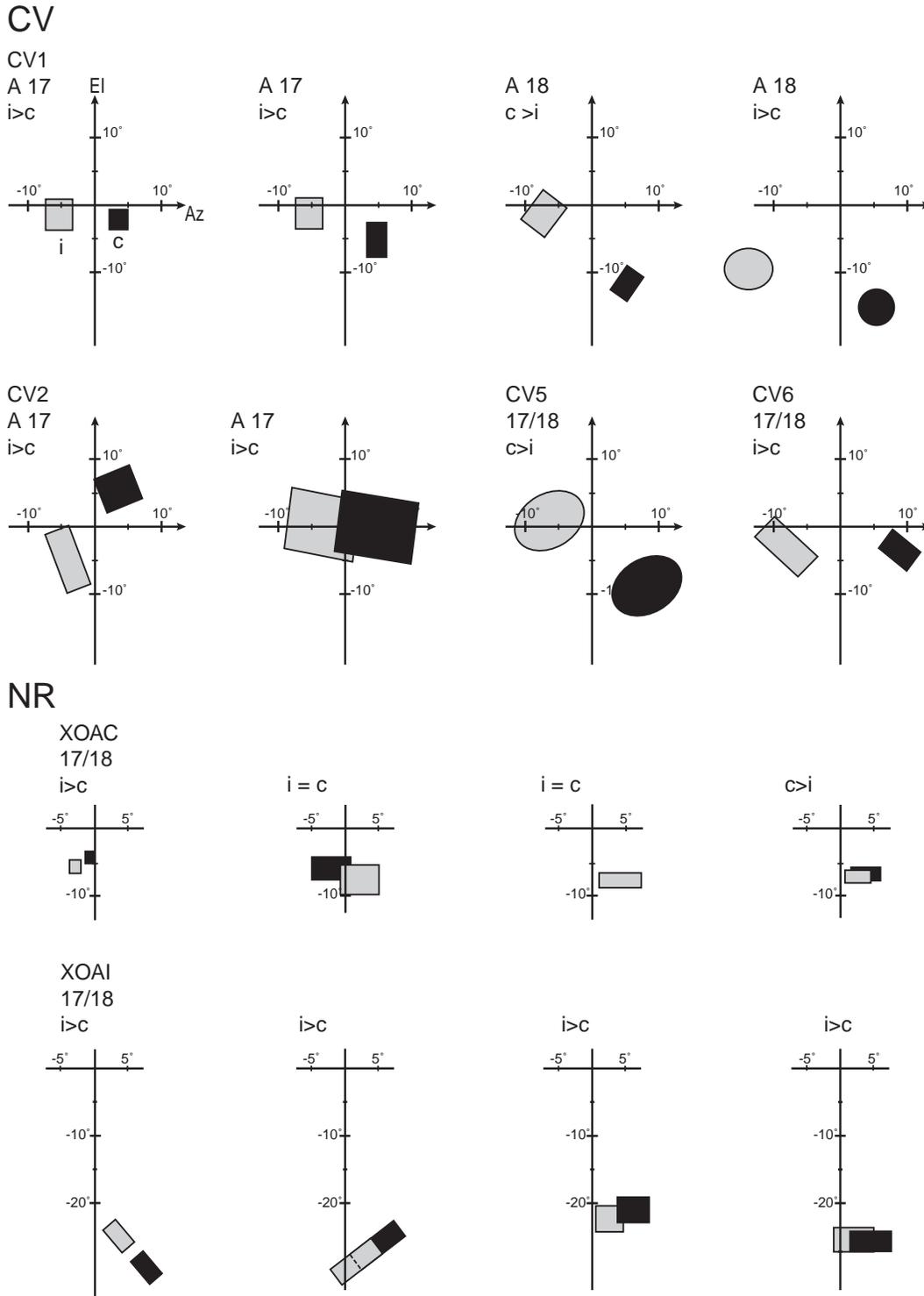
FIG. 11. Spatial location of the receptive fields of eight representative binocular transcallosal (TC) units recorded in different cortical areas of four convergent strabismic (CV) and two normally reared (NR) animals (cats CV1, CV2, CV5, CV6 and XOAC, XOAI, respectively), after off-line realignment of the eyes (see text). El and Az, elevation and azimuth axes. Rectangles and circles, contours of the minimum receptive fields of the orientation selective and nonselective units, respectively. i (grey) and c (black), receptive fields mapped by visually stimulating the ipsilateral eye (GC-RF) or the contralateral eye (TC-RF), respectively. i > c, i = c and c > i indicate the ocular dominance of each TC unit as in Fig. 5.

Effects of strabismus on the cortical distribution of callosal neurons

The precise cortical distribution of callosal projecting neurons in strabismic cats is still an open issue. Most anatomical studies indicate that the callosal efferent zone in strabismics is, as in young kittens, wider than in normal adults and involves large parts of areas 17 and 18. However, recent work by Bourdet et al. (1996) contradicts this view and suggests that the callosal efferent zone of strabismics is as well restricted to the 17/18 border as it is in NR adults.
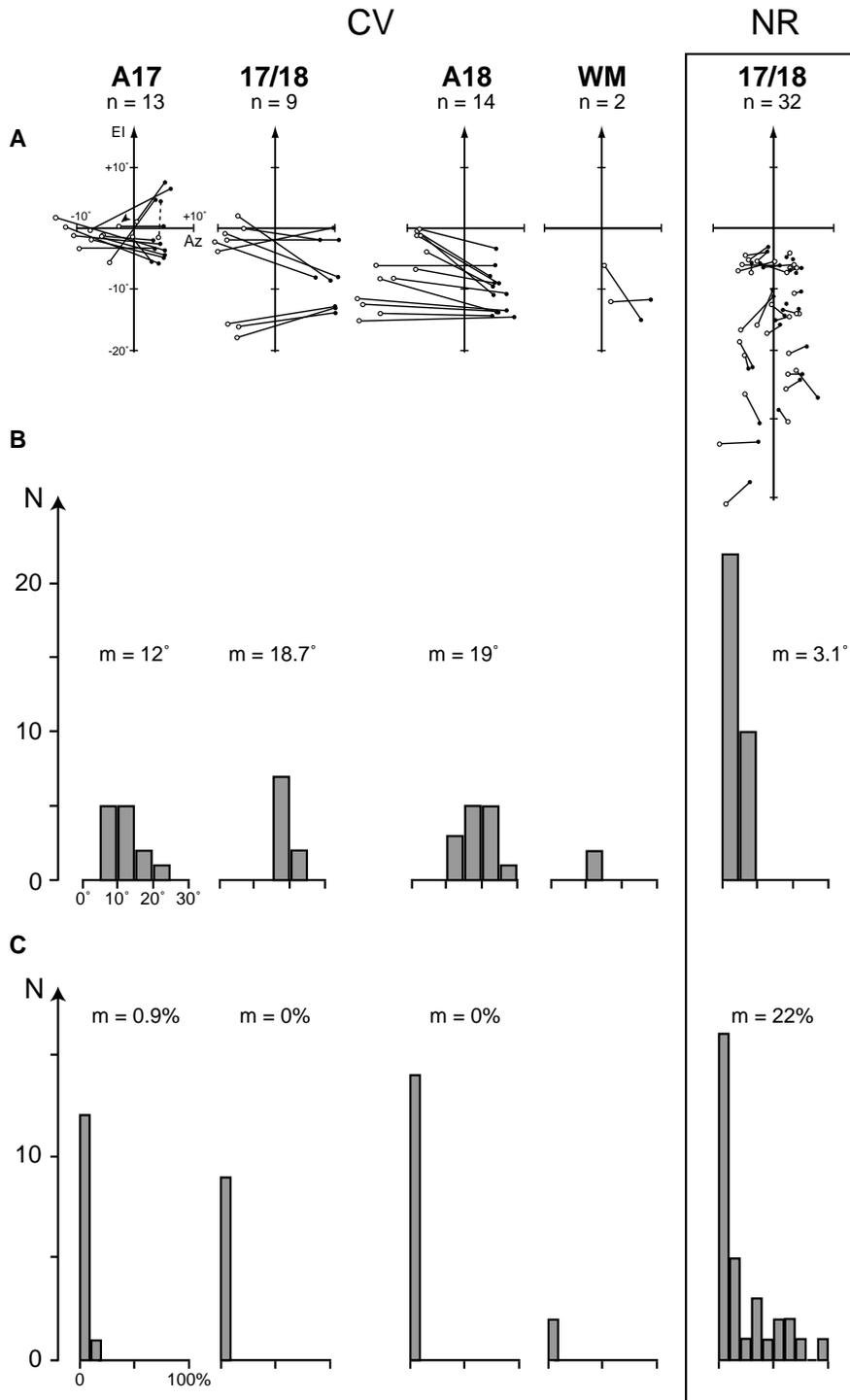
FIG. 12. Position disparity of the receptive fields of binocular transcallosal (TC) units recorded in A17, the 17/18 border, A18 and white matter (WM) of convergent strabismic (CV) and normally reared (NR) cats, after off-line realignment of the eyes. (A) Position of pairs of geniculocortical receptive field (GC-RF; open circle) and transcallosal receptive field (TC-RF; black dot) centres in the visual field for each binocular cell. The dotted line indicates the only binocular TC unit whose GC-RF and TC-RF were both located within the hemifield ipsilateral to the explored cortex. El and Az, elevation and azimuth axes. Arrow points to the pairs with partially overlapping RFs. (B) Distribution of GC-RF centre to TC-RF centre angular distances for binocular TC units recorded in the different explored regions, ranked into six classes. m, mean disparity. (C) Distribution of overlap indices between GC-RFs and TC-RFs for binocular units recorded within each explored region; m, mean overlap index. n, number of units.

Two observations favour the hypothesis of an extended callosal efferent zone. (i) Comparison of the spatial distribution of TC-RFs indicates that the 'callosal visual field' is shifted ipsilaterally in strabismic compared with normal cats. Although a reorganization of the retinotopic map within the normally located callosal efferent zone (17/18 border) cannot be ruled out, it is likely that signals from the peripheral-most callosal visual field are conveyed through the CC by efferent neurons located outside the 17/18 border. (ii) Along the same line, the fact that TC units located within A17 and A18 in strabismics responded better to slow- and fast-moving stimuli, respectively,

suggests that they were driven by callosal neurons located in corresponding areas of the contralateral hemisphere. It is thus likely that strabismus leads to stabilization of some widespread callosal projecting neurons known to be present at birth and which normally loose their callosal axon during the first postnatal months (Innocenti *et al.*, 1977).

Effects of strabismus on callosal terminals

Our electrophysiological results provide the first demonstration that callosal terminals are able to establish effective functional synaptic
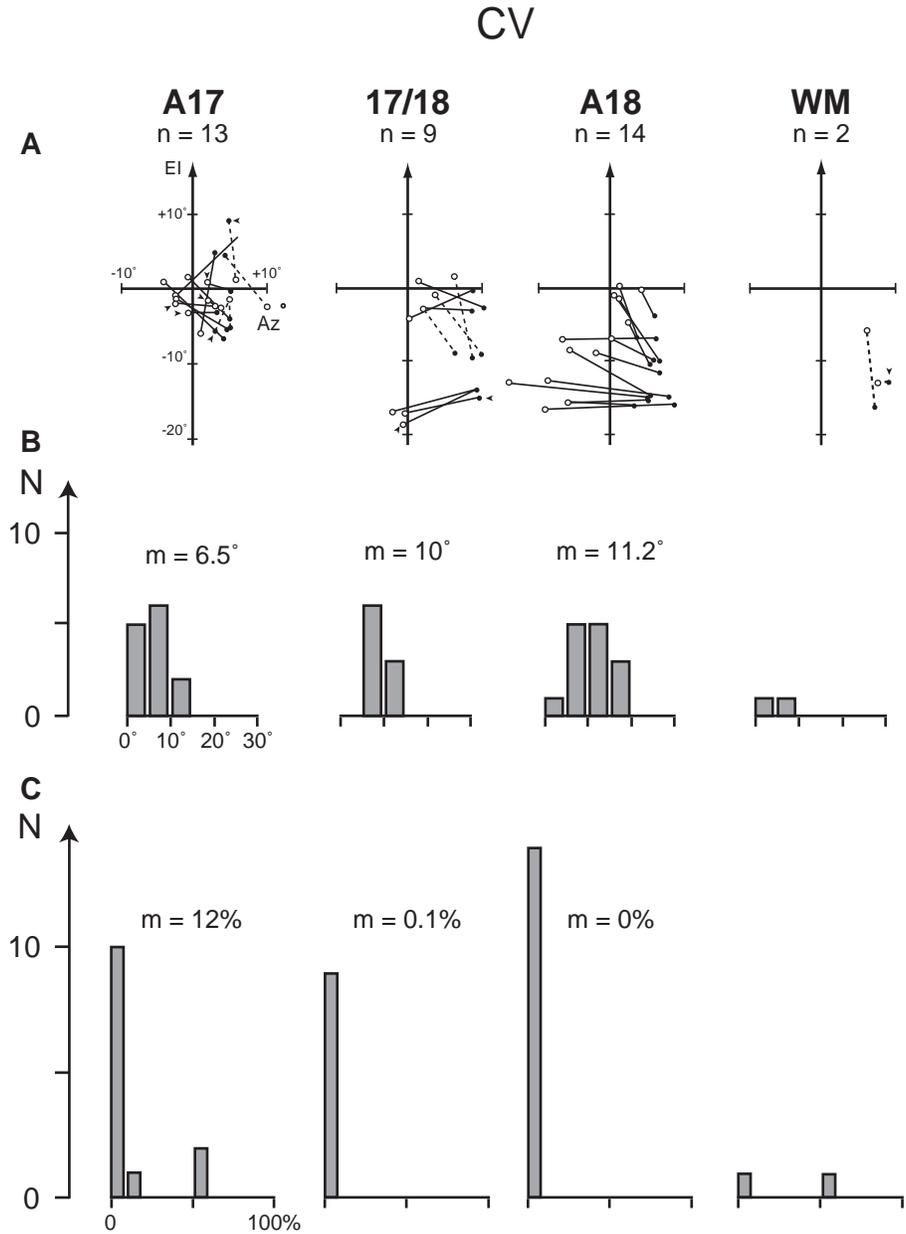
CV

FIG. 13. Position disparity of the receptive fields of binocular transcallosal units recorded in A17, the 17/18 border, A18 and white matter (WM) of convergent strabismic cats, after shifting the geniculocortical-receptive fields by the angle of strabismus determined for each animal. A–C, same nomenclature as in Fig. 12.

contacts within primary visual areas after strabismus. Remarkably, as recorded after acute chiasm split, the TC responses mediated by these newly formed connections could be stronger than in NR adults. Further, our observations corroborate previous anatomical data showing that early strabismus induces an expansion of the callosal terminal territories in the adult. Specifically, we confirm that the callosal terminal territories are conspicuously expanded within the hemisphere ipsilateral to the convergent eye (Berman & Payne, 1983), since TC responses were recorded as far as 4 mm away from the 1 mm wide region to which they are normally confined. Recordings from the hemisphere contralateral to the deviated eye in one additional animal (20 TC units out of 83 recorded along three tracks, with the following distribution: A17, 4 TC units out of 42; 17/18 border, 15/15; A18, 1/26; data not shown) suggest that a similar expansion occurs within this hemisphere, as predicted by Lund & Mitchell (1979). Further investigation will be required to assess any

possible asymmetries in the portion of the callosal visual field represented in each hemisphere.

The callosal terminal zone was also significantly extended in its radial dimension, since TC units were found throughout all cortical layers whereas they are normally almost restricted to layers II/III. Given that the percentage of TC units encountered at the 17/18 border was not higher in strabismic than in NR adults, their modified laminar distribution might be interpreted as resulting from a local redistribution of callosal terminals. In contrast, the high incidence and the location of TC units in regions that are normally void of callosal terminals might result from a tangential sprouting of axonal arbors arising from 'normally' located callosal projecting neurons, i.e. from the opposite 17/18 border region and/or from projections originating from areas 17 and 18. While the first mechanism cannot be excluded, the arguments detailed in the previous section suggest a participation of the second mechanism.

Interestingly, a few TC units were found within the WM, which we believe are likely to be subplate neurons for the following reasons. (i) These few units were located far below the cortical grey matter, as indicated by postmortem histological reconstruction of the recording tracks. (ii) The tungsten-coated electrodes we used allowed us to distinguish unequivocally between activity derived from fibres and from cell bodies. (iii) TC units have been reported in the WM of 2-week-old normally reared kittens (Milleret *et al*., 1994), i.e. when numerous subplate neurons are still present (Luskin & Shatz, 1985), as well as in monocularly deprived or enucleated adults (Houzel *et al*., 1992; Houzel and Milleret, 1994) where some subplate target cells might have been preserved. (iv) Conversely, no TC units were recorded from the WM of normally reared animals older than 2 weeks, nor in dark-reared adults (Milleret & Houzel, 1991b); two conditions known to allow the normal elimination of transient subplate cells (Reid & Daw, 1995). Although confirmation will require further investigation, it is tempting to suggest that subplate elements are maintained after unbalanced, abnormal visual experience and serve as postsynaptic targets for converging geniculocortical and callosal terminals in adulthood (Friauf *et al*., 1990; Hermann *et al*., 1994).

Effects of strabismus on callosal recipient neurons

Alterations in the properties of TC visual responses such as decreased binocularity, orientation selectivity, proportion of vertically orientated and high-velocity tuned cells, or enlarged RF size and position disparity, merely reflect the known effects of strabismus on the overall population of cortical neurons of primary visual areas (Boothe *et al*., 1985; Kiorpes & McKee, 1999). In other words, several functional characteristics of callosally recipient neurons within the cortical representation of the 'callosal visual field' are affected by strabismus in the same way as noncallosally recipient neurons located within or outside this cortical region.

In addition, the topography of the cortical representation of the callosal visual field is genuinely affected, since it appears to be represented three times in the primary cortex of strabismics, whereas it was only mapped once at the 17/18 border in NR. The portion of visual field transferred through the corpus callosum is also markedly shifted away from the central vertical meridian and towards the ipsilateral half of the visual space. This ipsilateral shift is compatible with the involvement of the CC in the extended ipsilateral representation in suprasylvian areas of strabismic cat (Di Stefano *et al*., 1991).

Interestingly, whereas transcallosal RFs were shifted toward the ipsilateral hemifield, geniculocortical RFs merely increased in size but remained in their usual position, indicating an unbalanced effect on the two pathways. Whereas most TC units were binocularly activated in strabismics, and although their respective TC and GC inputs still matched for orientation, velocity and size specificity, the two RFs systematically displayed a large disparity instead of being superimposed as in NRs. Thus, the spatial integration of converging TC and GC afferents appears to be specifically modified after strabismus. Since the magnitude and direction of disparity between pairs of RFs varied greatly among units recorded in a single animal, they cannot be directly related to the angle of strabismus itself. The large disparities observed are more likely due to true heterotopic connections, involving callosal terminals conveying inputs from a given portion of space and synapsing onto cortical cells that receive, directly or through local circuits, geniculocortical inputs from another spot of visual space. When measured after correction for strabismus angle, the retinotopic mismatches appear substantial and even larger than the disparities observed in 2-week-old, visually inexperienced NR kittens (mean position disparity was $12.6 \pm 1.1°$ at eye opening

vs. $18.7 \pm 0.4°$ in adult strabismics; mean overlap index for RF couples was 1.8 ± 0.9 vs. 0%; Milleret *et al*., 1994). Thus, a simple 'freezing' of the normal maturational mechanism is not sufficient to account for this effect, which appears rather to be a consequence of an active process such as widespread sprouting (discussed earlier). On the other hand, the fact that disparities were still significant after the data were analysed using the awake-like position of the visual axes indicates that the RF shift does not result from an adaptive mechanism involving harmonious abnormal retinal correspondence (see Grant & Berman, 1991). As a consequence, callosal connections between primary visual cortices do not seem suited to contribute to depth perception along the CVM (see Jeeves, 1991 for review), since, as far as the retinotopic congruence of the transcallosal and the ipsilateral temporal retinogeniculocortical pathways are concerned, strabismus does not appear to be compensated for.

Although abnormal callosal connections between primary visual cortices seem to cause the deficit in depth perception in strabismus, callosal connections between suprasylvian areas of strabismics (Di Stefano *et al*., 1991) and Siamese cats (Marzi *et al*., 1980, 1982; Zeki & Fries, 1980) appear to contribute to the preserved cortical binocularity in these areas, where RFs are much larger than in primary visual areas and binocular units display disparate but still overlapping receptive fields (Von Grunau, 1982; Marzi *et al*., 1986; Grant & Berman, 1991; Sireteanu & Best, 1992). Differences in connectivity might account for the different susceptibility of both areas to strabismus; while striate cortex receives its main input from the lateral geniculate nucleus, a structure that is markedly affected by strabismus, suprasylvian areas receive major inputs from extrageniculate pathways, particularly from the superior colliculus, which is only weakly affected by eye deviation (Gordon & Gummow, 1975). Additionally, the larger RFs and broader functional tuning of suprasylvian neurons, as compared with striate cortical neurons, impose looser constraints for the convergence of ipsilateral and callosal inputs onto recipient cells (Marzi *et al*., 1982) which thereby maintain a higher degree of binocular activation.

In contrast, the observation that TC units recorded within A17 and A18 responded better to slow- and fast-moving stimuli, respectively, suggests that connections formed between abnormally located callosally projecting cells and abnormally located callosal recipient neurons were established according to a rough topographical rule. Furthermore, the distribution of velocity tuning profiles observed in strabismic adults are reminiscent of those from 2- to 4-week-old NR kittens (cf. Milleret *et al*., 1994), and suggest that the maturation of these mechanisms has been frozen after the eyes were misaligned.

Therefore, our study reveals that functional characteristics of visual callosal transfer might be affected differentially by early strabismus, depending on the rule governing the connections subserving them. Based on a series of elegant experiments combining optical recording, deoxyglucose labelling and retrograde tracing, Schmidt *et al*. (1997a, 1997b) concluded that long-range corticocortical connections – intrahemispheric as well as interhemispheric – are selected during development according to perceptual grouping criteria and thereafter link domains of similar ocularity or orientation selectivity. These connections are considered to be the substrate for long-range, stimulus-specific synchronization of visual responses, a phenomenon that is proposed to serve as a mechanism for dynamic tagging of visual responses, as belonging to neuronal assemblies (reviewed in Singer & Gray, 1995). It was shown that in strabismic cats, the intrahemispheric synchronization of visual responses between neurons of different ocularities is disrupted as a result of the elimination of the underlying intrahemispheric connectivity (König *et al*., 1993). Thus, in view of the present results, it would

be of particular interest to investigate how far this holds for interhemispheric synchronization.

Abbreviations

CC, corpus callosum; CVM, central vertical meridian of the visual field; GC, geniculocortical; m, mean receptive field size; NR, normally reared; NS, orientation nonselective; OI, overlap index; RF, receptive field; S, orientation selective; TC, transcallosal; WM, white matter.

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