THE JOURNAL OF COMPARATIVE NEUROLOGY 396:493–510 (1998)

Area-Specific Laminar Distribution of Cortical Feedback Neurons Projecting to Cat Area 17: Quantitative Analysis in the Adult and During Ontogeny

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ABSTRACT

Corticocortical pathways can be classified as feedback and feedforward, in part according to the laminar distribution of the parent cell bodies. Here, we have developed exhaustive sampling procedures to determine unambiguously this laminar distribution. This shows that individual extrastriate areas in the adult cat have highly stereotyped proportions of supragranular layer neurons with respect to the total population of neurons back-projecting to area 17. During development, these adult laminar patterns emerge from an initially uniform radial distribution through a process of selective reorganization, which is highly specific to each area. Injections of fluorescent retrograde tracers were made in area 17. In areas 19, 20, posteromedial lateral suprasylvian area, and anteromedial lateral suprasylvian area, we defined a projection zone as the region containing retrogradely labeled neurons. In the neonate, counts of labeled neurons throughout the projection zones show constant percentages of 40% in the supragranular layers. During development, there is an area-specific reduction in the percentage of supragranular labeled neurons generating the laminar distributions characteristic of each area. Numbers of labeled neurons were estimated at different eccentricities of the projection zone. This finding indicates that during development there is a relative decrease in the numbers of labeled neurons of the periphery of the projection zone in the supragranular layers but not in the infragranular layers. This decrease is accompanied by a relative decrease in the dimensions of the supragranular projection zone with respect to the infragranular projection zone. These findings suggest that each extrastriate area precisely adjusts the proportions of supragranular layer neurons back-projecting to striate cortex in part by developmental changes in the divergence-convergence values of individual neurons. This shaping of corticocortical connectivity occurs relatively late in postnatal development and could, therefore, be under epigenetic control. J. Comp. Neurol. 396:493–510, 1998.

Indexing terms: visual cortex; corticocortical; striate cortex; retrograde labeling; topography

Areas of the neocortex are richly interconnected, and the density and laminar organization of the connections between individual visual areas are thought to be a key feature underlying the cortical processing of visual information. This principle has been thoroughly documented in primates in which rostrally directed projections allow outflow of activity from area 17 toward circumstriate cortex (feedforward pathways). These projections largely originate from supragranular layers, target layer 4 and contrast with the reciprocal, caudal directed projections (feedback pathways), which largely originate in infragranular layers and terminate outside of layer 4 (Kuypers et al., 1965; Cragg, 1969; Spatz et al., 1970; Tigges et al., 1973; Lund et al., 1975; Kaas and Lin, 1977; Spatz, 1977; Wong-Riley, 1978; Van Essen and Zeki, 1978; Rockland and Pandya, 1979; Wall et al., 1982; Maunsell and Van Essen, 1983; Weller et al., 1984; Kennedy and Bullier, 1985; Weller and Kaas, 1985; Barbas, 1986, 1995; Boussaoud et al., 1990; Sousa et al., 1991; Distler et al., 1993; Salin and Bullier, 1995; Barbas and Rempel-Clower, 1997).

Grant sponsor: BIOMED; Grant number: PL 951604; Grant sponsor: MNESR; Grant number: 95079.

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Received 9 December 1997; Revised 25 February 1998; Accepted 9 March 1998

These laminar patterns of the organization of cortical connections suggest an anatomical hierarchical ranking of primate cortical areas (Maunsell and Van Essen, 1983; Van Essen et al., 1990; Felleman and Van Essen, 1991). Anatomical studies in cat and to a lesser extent in rat also showed that there are laminar patterns in corticocortical connectivity that are coherent with the feedforward and feedback classification (Symonds and Rosenquist, 1984a,b; Bullier et al., 1984; Dreher, 1986; Coogan and Burkhalter, 1990, 1993). In the cat, consideration of the laminar patterns of these connections has suggested similar hierarchical ranking of the visual cortical areas (Felleman and Van Essen, 1991; Scannell et al., 1995).

In this way, despite some doubt on the physiologic significance of hierarchical schemes (Nowak et al., 1995; Crick and Koch, 1998), the vast majority of pathways connecting cortical areas can be classified as feedback or feedforward, and furthermore, there is increasing evidence that each type of pathway fulfills different roles. Feedforward, & pathways are thought to be responsible for relaying activity from lower to higher areas and to play directly a role in visual perception (Zeki, 1993; Bullier et al., 1994; Hubel, 1995; Vanduffel et al., 1997). The role of feedback pathways has been more difficult to pin down (Sandell and Schiller, 1982), although recent evidence suggests that they are involved in gain control of their target areas (Bullier et al., 1996) and may play a role in visual imagery (Miyashita, 1995; Ishai and Sagi, 1995).

Despite the functional importance of feedback and feedforward pathways for understanding cortical processing, we have little insight as to how feedback laminar patterns emerge during development in cat (Kato et al., 1991). A characteristic feature of corticogenesis is that many connections formed early in development are eliminated before adulthood (Goodman and Shatz, 1993; O'Leary, 1992) by processes of axonal elimination and possibly cell death (Cowan et al., 1984; Stanfield, 1984; Price and Blakemore, 1985; Bates and Killackey, 1984). In the present study in the cat, we focus on the development of feedback pathways from separate extrastriate areas to area 17. Quantitative techniques show that in the adult, the laminar distribution of neurons participating in these pathways is highly characteristic of each area. This contrasts with the neonate in which there is a uniform laminar distribution of neurons across extrastriate areas. By evaluating, simultaneously, the tangential and radial distributions of labeled neurons, we are able to show that this dynamic area-specific reorganization of the laminar distribution in part involves changes in the axonal spread of individual neurons.

MATERIALS AND METHODS

Anaesthesia and surgery

Results are based on the quantitative analysis of injections of retrograde tracers in visual cortices after 22 injections in 18 neonates (postnatal day [PND] 3–32; Table 1) and 13 injections in 12 adult cats. Newborn and adult cats were premedicated for surgery with dexamethasone (Soludecadron: 1mg/kg) and chlorpromazine (Largactil, 0.5–1 mg/kg) injected intramuscularly. Animals were then anesthetized with ketamine hydrochloride (Ketalar, 10–30 mg/kg). Adults were placed in ear-bars. The young animals were held in a head-holding device. In each animal, a small rectangular flap of bone was excised from the skull along the central sinus overlying the primary visual area. All the procedures used follow the national and European regulations concerning animal experiments and have been approved by the authorized national and veterinary agencies.

TABLE 1. Experimental Cases[1]

NEWBORN[2]	Age at injection	Age at perfusion
K 139	3	9
K 186 (50 microns)	3	10
K 124 (FB & DY)	3	9
K 1 (FB & DY)	4	10
K 180	4	17
K 4	7	14
K 135	7	13
K 136	7	13
K 128	8	18
K 129	15	25
K 178 (20 microns)	15	22
K 165	17	26
K 152	19	26
K 138	21	27
K 179 (30 microns)	22	29
K 130 (FB & DY)	25	32
K 5 (FB & DY) (30 microns)	26	33
K 131	32	38

[1]Age in postnatal days.
[2]Section thickness is 40 microns unless indicated otherwise in parentheses. FB, Fast Blue; DY, Diamidino Yellow.

Injection of retrograde tracers

Single injections of a fluorescent tracer (either Fast Blue [FB] or Diamidino Yellow [DY]) were made in area 17 at various postnatal ages between birth and adulthood (Table 1). The dyes (0.1–0.7 µl) were injected at a concentration of 3% with a Hamilton microsyringe. Injections in adults and kittens were made in a stereotype fashion, mostly in the bank of the interhemispheric fissure, and except for K152, in such a way as to span the full depth of the cortex. The injection in K186 also involved the underlying white matter. An example of an injection site restricted to the gray matter is shown on Figure 1. The black zone represents the crystal deposit of the dye, and the gray region corresponds to the estimated uptake zone, defined by the region of high color density (Bullier et al., 1984; Kennedy and Bullier, 1985).

After a 6- to 13-day survival period (Table 1), the animals were deeply anesthetized and perfused through the heart with 2.7% saline, followed by 8% paraformaldehyde in phosphate buffer (0.1 M; pH 7.4). After 45 minutes fixation, the brain was rinsed with an increasing concentration solution of sucrose (8% to 30%). The brains were then blocked in the coronal plane and were cut on a freezing microtome. Section thickness was 20–50 microns (Table 1). One in two sections (newborns) or one in three sections (adults) were immediately mounted from saline solution onto gelatin-coated slides.

Examination of material

The sections were left without coverslips and were observed with oil-immersion objectives under ultraviolet light with a Leitz fluorescent microscope equipped with a D-filter set (355–425 nm). The characteristics of neurons labeled with FB and DY are described by Keizer et al. (1983). Neurons labeled by FB exhibit a blue coloration in their cytoplasm, whereas those labeled by DY exhibit a yellow nucleus. Neurons were plotted using a magnification of 10×25. In the different cortical regions, the spatial

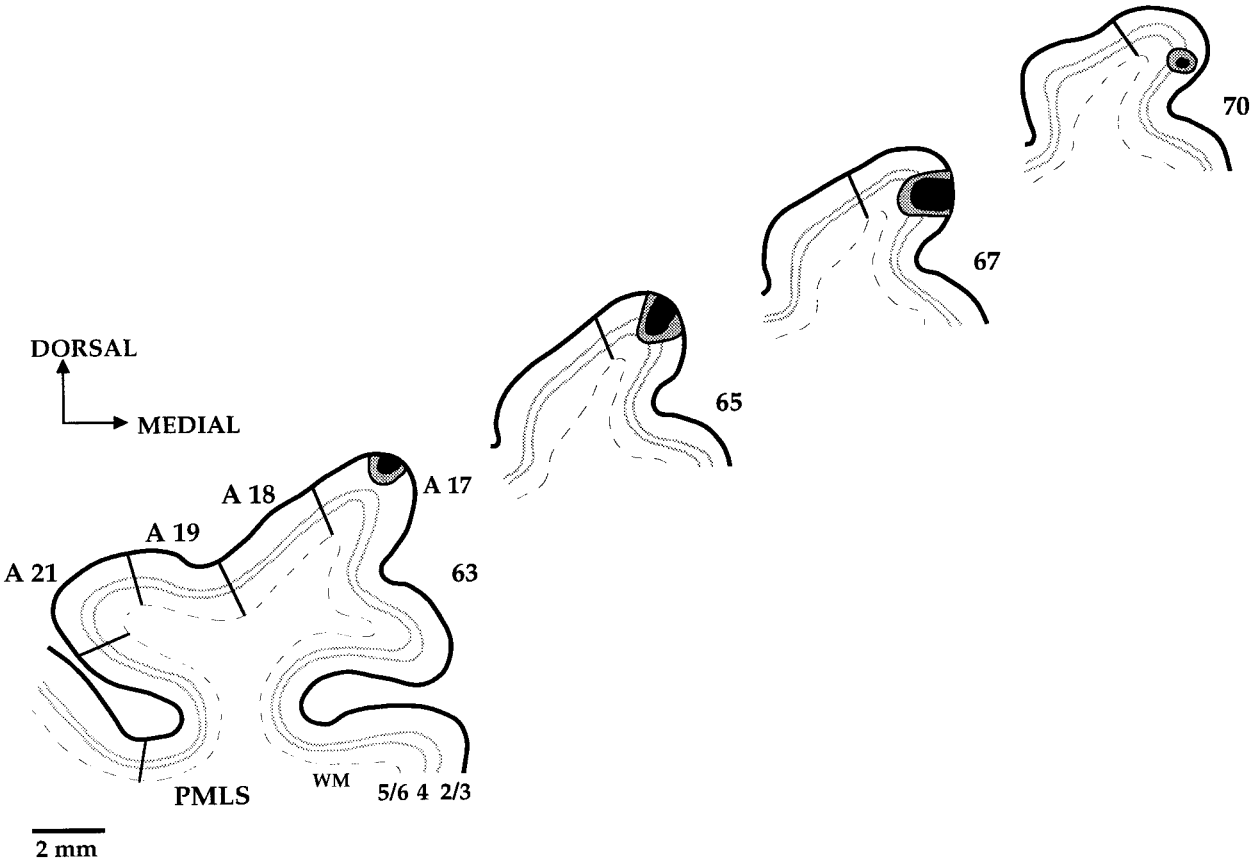

Fig. 1. Reconstruction of a Fast Blue injection site (black area) in area 17 of a newborn kitten. Gray stippling represents the uptake zone. Dashed lines represent white matter limits. Solid gray lines represent locations of layer 4. A, area; WM, white matter; PMLS, posteromedial lateral suprasylvian area. Numbers 63–70 refer to section number. High numbers are anterior.

locations of labeled neurons were charted by means of an X-Y plotter electronically coupled to the microscope stage. After plotting, sections were counterstained either for Nissl substance or for cytochrome oxidase activity (Wong-Riley, 1979; Price, 1985) and back-projected onto the charts of labeled neurons so as to trace cytoarchitectonic borders, including that of layer 4.

Location of injection sites

Injection sites were allocated to area 17, according to their location with respect to the cytoarchitectonic borders as revealed by Nissl stain or cytochrome oxidase (Price, 1985; Dehay et al., 1988). The pattern of thalamic labeling was examined to confirm that the pick-up zone of retrograde tracer was restricted to the cortical area injected (Dehay et al., 1988).

Areal and laminar distribution of labeled neurons

A quantitative study was carried out by counting neurons in the supra- and infragranular layers. Estimation of proportions of labeled neurons in each compartment is made by counting labeled neurons at regular intervals throughout the projection zones in areas 19, posteromedial lateral suprasylvian area (PMLS), anteromedial lateral suprasylvian area (AMLS) and area 20. This method allowed us to determine the percentage of labeled neurons in the supragranular layers. Percentage of supra was calculated from the following equation: (number of supra / [number of supra + number of infra]) $\times$ 100. The limits of cortical areas were determined on Nissl-stained sections. In some cases, sections were stained for cytochrome oxydase to confirm the position of the border of areas 18 and 19. For areas PMLS and AMLS, the labeling was restricted on the medial bank of lateral suprasylvian sulcus and clearly separated along the rostrocaudal axis. Area 20 labeling was restricted to the ventral part of the posterolateral gyrus.

Statistical tests

Comparison of the laminar distributions between each group of animals (kitten and adults) in the different subdivisions of the projection zones (periphery, center, and core) as well as the changes in the relative dimensions of the separate projection zones within the supra- and infragranular layers used the nonparametric Mann-Whitney U test (Tables 2–4).

RESULTS

Definition of terms used to describe labeling in the cortex

Retrograde tracers were injected in the target area, area 17, and the radial and tangential distribution of retro-

TABLE 2. Percentage of Labeled Supragranular Neurons in Areas 19, PMLS, AMLS, and 20 After Injection in Area 17 and Statistical Comparisons Between Adult and Newborn Values[1]

	Area 19		Area PMLS		Area AMLS		Area 20	
	S (n)	% Supra	S (n)	% Supra	S (n)	% Supra	S (n)	% Supra
Adults								
CAT 1	28 (4115)	27.7	23 (2657)	20.4			5 (73)	0
CAT 2	25 (1873)	28.9	14 (373)[2]	18.5				
CAT 5	18 (1186)	31.0						
CAT 6 (FB)	25 (2651)	23.6	22 (751)	21.2	30 (281)	2.5	14 (236)	0
CAT 6 (DY)	23 (4370)	29.8	20 (1418)	22.2	33 (377)	2.4	17 (341)	0
BK 17							4 (242)	0
BK 23							7 (486)	0
BK 25							7 (104)	0
BK 29							9 (167)	0
BK 30							4 (113)	0
BK 35			14 (281)	21.7				
BK 50			25 (1001)[2]	18.3			5 (117)	0
BK 52			26 (1506)	15.6			9 (180)	0
Mean (STD)		28.2 (2.8)		19.7 (2.4)		2.5 (0.1)		0 (0)
Newborn								
K 186	23 (6511)	43.0	27 (2740)[2]	38.5			11 (761)	0
K 139							6 (280)	0
K 124 (FB)			9 (149)	33.6			5 (27)	0
K 124 (DY)			5 (285)[2]	33.0			5 (66)	0
K 1 (FB)							2 (598)	0
K 1 (DY)							2 (212)	0
K 180							7 (75)	0
K 4							3 (456)	0
K 135							5 (138)	0
K 136							5 (167)	0
K 128							4 (158)	0
K 129							4 (120)	0
K 178			20 (1929)	34.3				
K 165	14 (5131)	35.5	7 (2331)[2]	36.3				
K 152	5 (1818)	42.0	6 (239)	49.8	7 (215)	43.2	3 (169)	0
K 138			4 (121)	36.4	6 (361)	41.6	3 (111)	0
K 179	17 (1438)	48.1	14 (1236)	43.5				
K 130 (DY)	8 (438)	48.6			10 (755)	56.0	5 (120)	0
K 130 (FB)			5 (294)	56.5	8 (534)	42.1		
K 5 (FB)							4 (197)	0
K 5 (DY)							4 (216)	0
K 131			6 (182)	38.5	6 (489)	43.6	7 (151)	0
Mean (STD)		43.4 (5.3)		40.0 (7.7)		45.3 (6.0)		0 (0)
Statistics (p)		=0.009*		=0.0006*				ns

[1]PMLS, posteromedial lateral suprasylvian; AMLS, anteromedial lateral suprasylvian; supra, supragranular layer neurons; S, number of sections; n, number of neurons; STD, standard deviation; ns, not significant; FB, Fast Blue; DY, Diamidino Yellow.
[2]Sections available for half of the projection zone.
*Significant at 95% (Mann-Whitney U test).

TABLE 3. Percentage of Supragranular Layer Neurons in the Periphery, the Center, and the Core of Projection Zones in the Posteriomedial Lateral Suprasylvian Area (PMLS) and Statistical Comparison Between Adult and Newborn Values[1]

	Periphery of density profile		Center of density profile		Core of projection zone	
	% of neurons	% Supra	% of neurons	% Supra	% of neurons	% Supra
Adults						
CAT 1	18.1	4.9	81.9	24.2	52.8	28.2
CAT 2	14.0	1.9	86.0	21.7	55.0	27.5
CAT 6 (FB)	27.2	15.3	72.8	23.5	54.5	24.9
CAT 6 (DY)	16.7	4.2	83.3	25.8	52.8	28.6
BK 35	15.2	15.3	84.8	21.6	52.3	22.6
BK 50	32.7	6.7	67.3	25.2	32.7	19.4
BK 52	35.2	9.7	64.8	18.9	45.9	22.1
Mean (STD)	22.7 (8.8)	8.3 (5.4)	77.3 (8.8)	23.0 (2.4)	49.4 (8.0)	24.8 (3.5)
Newborn						
K 186	18.2	21.0	81.2	43.8	46.1	41.6
K 124 (FB)	31.3	34.1	68.7	34.4	42.7	32.1
K 124 (DY)	24.6	31.4	75.4	33.5	54.0	37.0
K 178	38.2	34.7	61.8	34.4	42.4	34.2
K 165	30.1	31.8	69.9	38.6	40.5	40.1
K 152	27.2	58.4	72.8	46.5	63.2	45.0
K 179	29.6	41.0	70.4	44.6	46.6	39.9
K 138	11.2	45.4	88.8	26.4	70.4	26.1
K 130 (FB)	17.8	69.2	82.2	53.3	46.2	51.1
K 131	12.4	14.3	87.6	43.2	56.2	35.8
Mean (STD)	24.1 (8.8)	38.1 (16.4)	75.9 (8.8)	39.9 (7.9)	50.8 (9.9)	38.3 (7.0)
Statistics (p)	=0.80 (ns)	=0.0013*	=0.80 (ns)	=0.0006*	=0.99 (ns)	=0.0018*

[1]Supra, supragranular layer neurons; STD, standard deviation; ns, not significant; FB, Fast Blue; DY, Diamidino Yellow.
*Significant at 95% (Mann-Whitney U test).

gradely labeled neurons were analyzed in the source areas (areas 19, 20, PMLS, and AMLS). The regional extent within the source area containing labeled neurons is referred to as the projection zone (Fig. 2C). Because brains were cut in the coronal plane, successive sections intersect the projection zone along a rostral-caudal axis, making it

TABLE 4. Length (in mm) of Neurons Density Profile in Supra- and Infragranular Compartments in Area PMLS After Injection in Area 17[1]

	Infra	Supra	Ratio
Adults			
CAT 1	5.55	2.82	0.51
CAT 2*	1.73	0.72	0.42
CAT 6 (FB)	4.08	2.80	0.69
CAT 6 (DY)	4.32	2.52	0.58
BK 35	4.16	2.70	0.65
BK 50*	5.32	3.22	0.61
BK 52	6.59	2.82	0.43
Mean (STD)			0.56 (0.11)
Newborn			
K 186*	5.35	3.96	0.74
K 124 (FB)	3.25	3.86	1.19
K 124 (DY)*	5.60	5.25	0.94
K 178	1.80	2.40	1.33
K 165*	5.15	5.12	0.99
K 152	2.05	2.30	1.12
K 138	2.27	2.29	1.01
K 130 (FB)	2.06	2.34	1.14
K 131	3.03	2.67	0.88
Mean (STD)			1.04 (0.18)
Statistics (*P*)			=0.0009*

[1]PMLS, posteromedial lateral suprasylvian; FB, Fast Blue; DY, Diamidino Yellow; STD, standard deviation; infra, infragranular; supra, supragranular.
*Significant at 95% (Mann-Whitney U test); sections available for half of the projection zone.

possible to construct a neuron density profile (density profile) in this axis (Fig. 2D). The density profile sums the numbers of supra- and infragranular layer neurons found on single sections. At peripheral levels of the projection zone, neuron counts are low and increase steadily to reach maximal levels at the center of the projection zone. The areal extent of the projection zone is defined by a peripheral threshold value (5–10% of the peak value at the center of the projection zone). The rostral and caudal quarter of the density profile is designated the periphery and the central half the center of the density profile.

The density profiles provide one-dimensional reconstructions of the projection zone so that the medial and lateral part of each individual section passing through the center of the projection zone corresponds to part of the periphery of the projection zone (Fig. 2). The central part of each section passing through the center of the density profile corresponds to the core of the projection zone.

Qualitative description of the laminar distribution of labeled neurons

Examples of the radial distribution of labeled neurons at different rostrocaudal levels of projection zones in area AMLS, PMLS, area 19, and area 20 are shown in Figures 3–6. In the adults, retrogradely labeled neurons are typically more extensive in the infragranular layers compared with the supragranular layers. This finding is particularly clear in AMLS (Fig. 3) and PMLS (Fig. 4). It is also the case but to a lesser extent in area 19 (Fig. 5). Area 20 is an exception in so far as no labeled neurons are present in supragranular layers (Fig. 6). For example, in the center of the adult projection zones (top left-hand sections in Figs. 3–6) the medial-lateral extent of labeling in infragranular layers is greater than in the periphery of the projection zones (bottom left-hand sections in Figs. 3–6). These observations illustrate two related and characteristic features of the adult projection zone: infragranular layer neurons extend further than do supragranular layer neurons and the proportion of supragranular layer neurons is higher in the center of the projection zone than at more peripheral levels (Salin et al., 1992).

In the neonate the tangential extent of labeled supragranular neurons was nearly identical to that of the infragranular layers, contrary to what is observed in the adult. This finding is particularly clear in AMLS and PMLS (Figs. 3, 4) but could also be detected in area 19 (Fig. 5).

Density profiles and the influence of sampling frequency

To compare the proportions of labeled neurons in supra- and infragranular layers, we have prepared density profiles from individual sections taken at regular intervals throughout the projection zones. This procedure was repeated for all cases listed in Table 2.

Typical density profiles obtained from two adults are shown in Figure 7A,B. There is a steady decrease in the numbers of labeled neurons per section as one goes from the center of the density profile toward the periphery, and peak values are higher in infragranular layers compared with supragranular layers. The density profiles show an uneven profile, which could reflect the patchy distribution of neurons in PMLS that project to area 17 (Shipp and Grant, 1991; Montero, 1981; Sherk and Ombrellaro, 1988). The density profiles suggest that the percentage of labeled supragranular layer neurons per section is significantly higher in the center of the density profile compared with the periphery. Adjacent sections- even toward the center- can return widely different percentages of labeled supragranular layer neurons. For example, adjacent sections return 14% and 34% in the density profile analyzed in Figure 7A and 7% and 36% in that of Figure 7B. In both adults, near-zero values of supragranular layer neurons are found in the periphery of the density profile.

The variation of the percentages of supragranular layer neurons from section to section points to the caution required when attempting to estimate the laminar distribution for a particular density profile and underlines the necessity of sampling adequate numbers of sections. Figure 7C–F illustrates the influence of sampling frequency on calculations of proportions of supragranular layer neurons in two adults. In the density profile shown in Figure 7C, low sampling frequencies return percentages ranging from 9% (3 sections) to 33% (2 sections), whereas the highest frequency returns a global value of 20% (20 sections and 2,500 neurons). In the density profile shown in Figure 7D, low frequencies return percentages ranging from 4% (3 sections) to 22% (3 sections). In this animal, stable values of 16% were obtained with 13–25 sections involving counts of between 500 and 1,500 neurons.

The density profiles in the newborns show important differences with those of the adults (compare Figs. 7 and 8). In contrast to the adult, newborn percentages of supragranular layer neurons were well above zero even at the most peripheral levels of the density profiles so that percentages of supragranular layers were relatively higher in the periphery of the newborn compared with the periphery of the adult (Fig. 8). For instance in the newborn shown in Figure 8a values in the periphery of the neuron density profile range from 16 to 47%, whereas in the adult shown in Figure 7A they range from 0 to 6%.

An important consequence of these differences is that stable estimations of percentages of supragranular neurons are obtained in the neonates with a lower sampling frequency than is required in the adults. In the neonate shown in Figure 8D low frequencies returned percentages

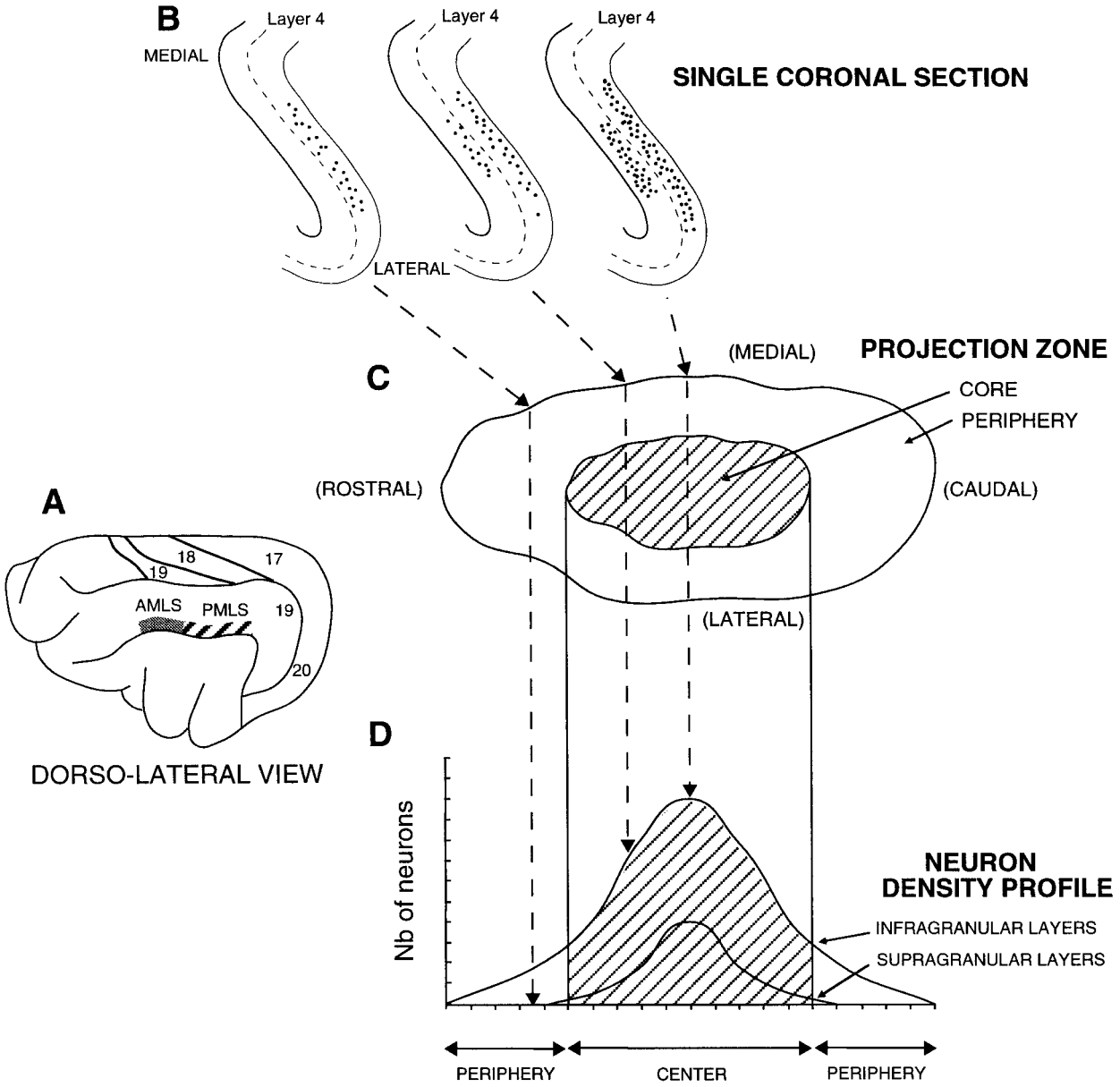

Fig. 2. Schematic representation of terms used to describe the radial and tangential distribution of labeling. **A:** Dorsolateral view of a cat brain showing the location of areas 17, 18, 19, 20, anteromedial lateral suprasylvian (AMLS) area, and posteromedial lateral suprasylvian (PMLS) area. **B:** Coronal sections from different levels of the projection zone. Dots represent retrogradely labeled neurons in area PMLS after injection of retrograde tracer in the area 17. **C:** Schematic representation of the projection zone showing core and peripheral regions. **D:** Neuron density profile showing the distribution of labeling in supra- and infragranular layers in the central and peripheral parts of the density profile. Nb, number of neurons.

ranging from 40% (2 sections) to 65% (3 sections), and a stable value of 60% was returned with 10 sections. Similar results were obtained in the neonate shown in Figure 8C in which low frequencies gave a maximal difference of 15%.

Percentages of supragranular neurons were calculated from density profiles similar to those shown in Figures 7 and 8 (Table 2). In three of the newborns and two of the adults, one limb of the density profile was incomplete, although the peak was clearly present. In these animals only the complete limb of the density profile was retained so that the number of sections used corresponds to the number of sections required to evenly sample the density profile from its peak to either its rostral or caudal limit (Table 2). With this proviso, density profiles were considered complete if the lowest threshold was inferior to 15% of the peak value. In fact, the mean minimal thresholds in adults was below 3.5% and was not significantly different from that in kittens.

Generation of area-specific laminar distributions

In the adult each extrastriate cortical area showed a highly specific laminar distribution of retrogradely labeled neurons (Table 2). Area 19 returned a mean value of 28% (range, 27.7–31%), area PMLS 20% (range, 15.6–22.2%),

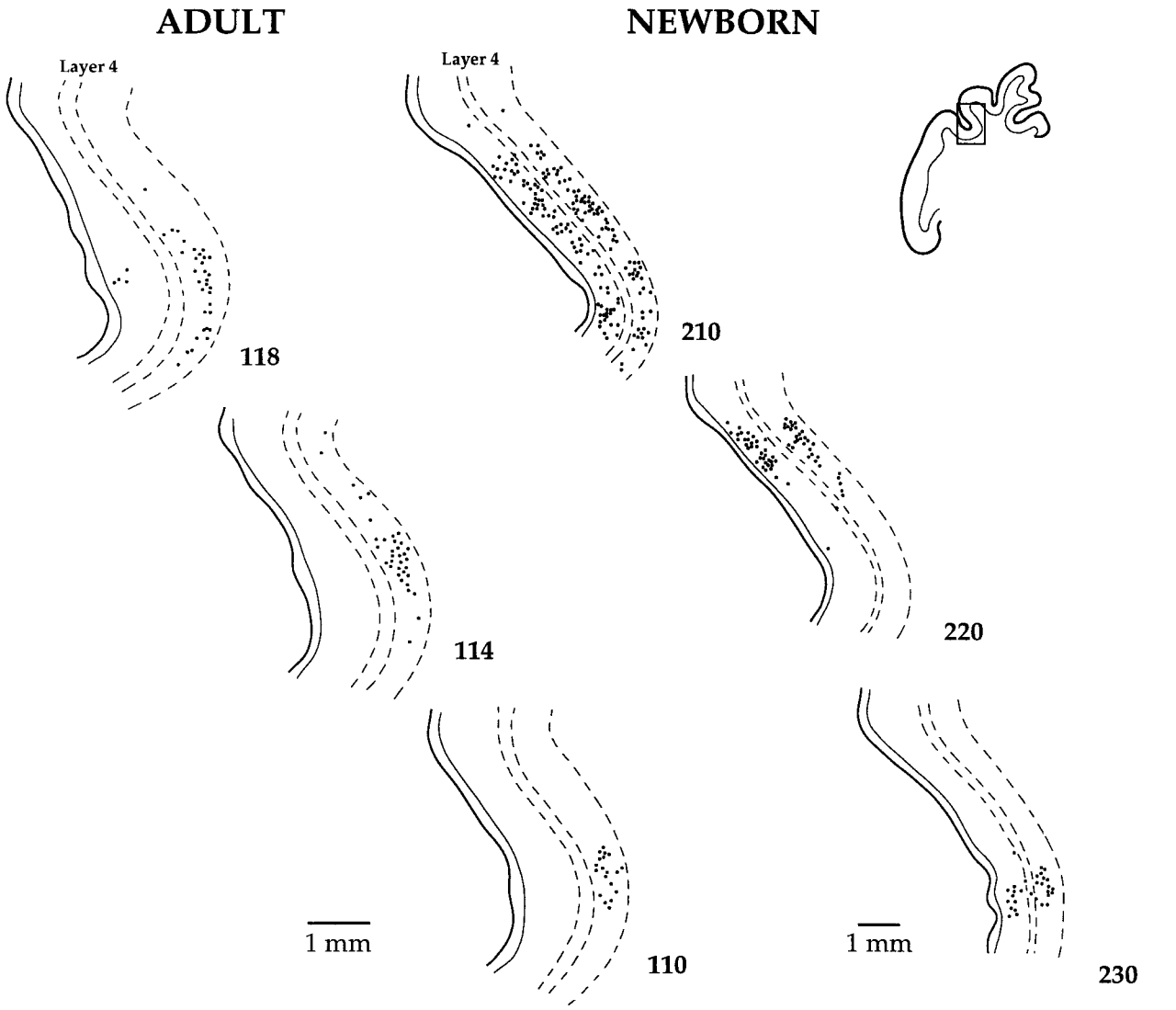

Fig. 3. Laminar distribution of labeled neurons in the anteromedial lateral suprasylvian area (AMLS) after injection in area 17 in adult and newborn kitten. Sections 118 (adult) and 210 (newborn) are from the center of the density profile, sections 110 (adult) and 230 (newborn) are from the periphery of the density profile. **Inset:** low-power view of the cortex showing the location of area AMLS. Medial is to the right.

area AMLS 2.5% (range, 2.4–2.5%), and zero percent in area 20. The small range of values obtained within each group for the density profiles for each area showed no significance, whereas the differences between areas were highly significant (all cases $P < 0.05$).

In contrast to the adults, neonates showed remarkably similar percentages of supragranular layer neurons in areas 19, PMLS, and AMLS (range, 40–45.3%; comparison between individual areas: all cases $P > 0.05$). Five newborns could be adequately sampled in area 19 and returned a mean value of 43% (Table 2). Statistical comparison of adults and neonates confirmed that there is a significant decrease in the percentage of supragranular layer neurons during development ($P < 0.01$). Percentages of labeled supragranular layer neurons in PMLS in 10 neonates ranged from 33% to 56% (mean, 40%), and once again the results in neonates and adults were statistically significantly different ($P < 0.001$) (Table 2). Five neonates could be adequately sampled in area AMLS (Table 2) and shows that there is a massive developmental reduction in the percentages of supragranular layer neurons going from an average of 45% in the neonate to 2.5% in the adult.

A large number of immature and adult brains were examined in area 20, and no labeled neurons were encountered at any age in supragranular layers (Table 2).

To conclude, within the neonates, percentages of labeled supragranular layer neurons in all three areas are similar. During development, there is a reduction in the proportion of supragranular layer neurons, which is specific for each area and which generates the laminar distribution characteristic for each area (Fig. 9).

Differences in the percentages of labeled supragranular neurons between periphery and center of density profiles of PMLS

The neonate and adult density profiles show important differences (Figs. 7, 8). Whereas in the neonate supragranu-

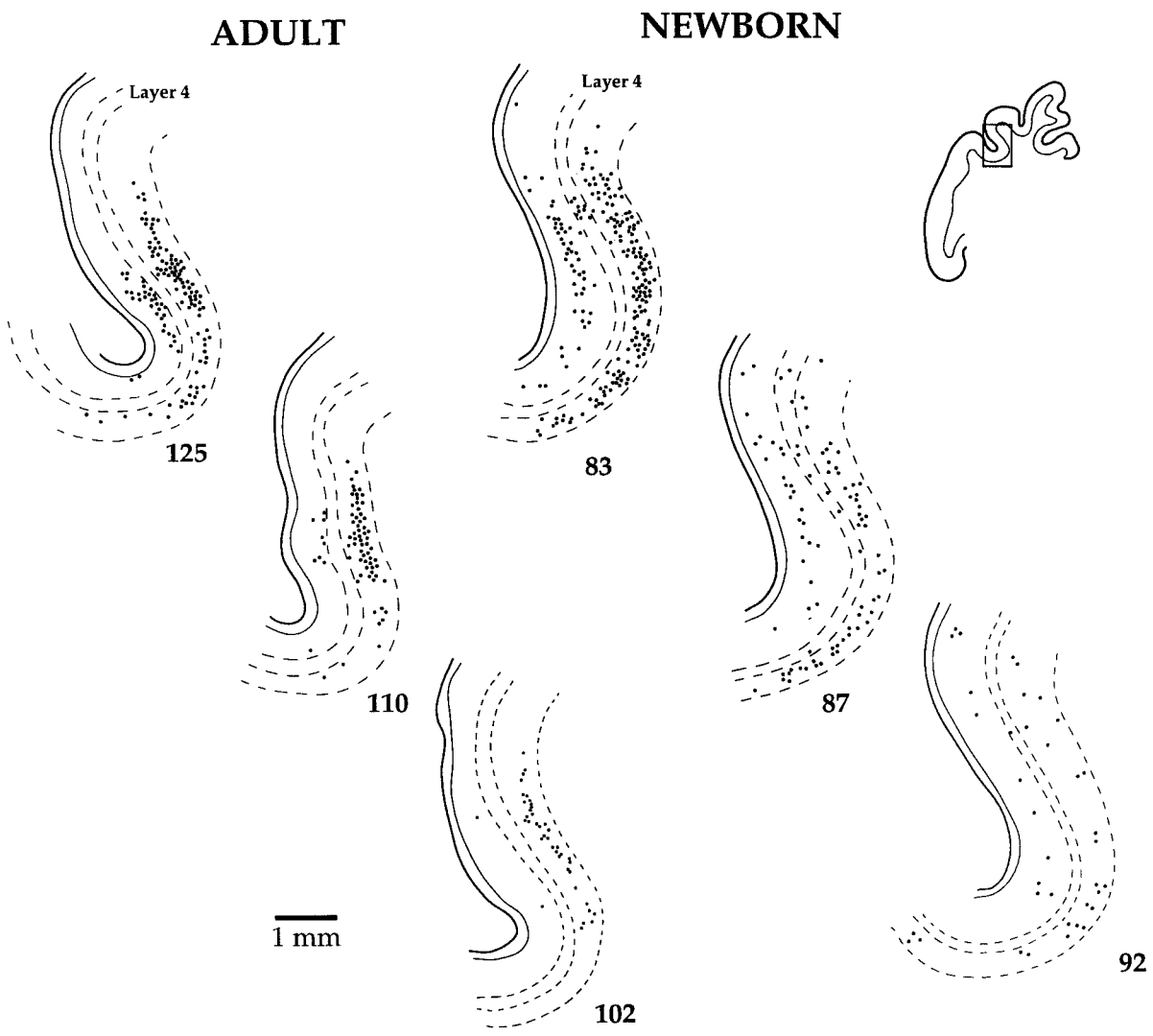

Fig. 4. Laminar distribution of labeled neurons in posteromedial lateral suprasylvian (PMLS) area after injection in area 17 in adult and newborn kitten. Conventions are as in Figure 3.

lar neurons are largely coextensive with infragranular neurons, this is not the case in the adult, suggesting that the reduction in the global percentages of supragranular neurons during maturation might be due to their progressive restriction to the center of the projection zone. In an attempt to investigate this issue, we have analyzed the developmental changes in the pooled proportions of supragranular neurons in the central and peripheral half of the density profiles of PMLS (Table 3).

Because approximately 76–77% of the neurons in the projection zones of both neonates and adults were located in the center of the density profile, restricting the estimation of the percentage of labeled supragranular layer neurons to the central half of all the density profiles in PMLS in both neonates and adults returned similar values to those obtained throughout the projection zone (compare PMLS values in Tables 2 and 3). However, when the percentages were calculated in the peripheral half of the projection zone, adult global values of 20% dropped to 8.3%, whereas values for kittens were maintained at 38% (Table 3).

The distributions of values per section of supragranular layer percentages obtained by pooling all sections from all the brains examined are shown in Figure 10. This shows that in the adult periphery, 65% of the sections have zero supragranular layer neurons, whereas this is only true for 3% of the sections in the periphery of the neonates. This analysis confirms that, whereas there are large and highly significant differences in the proportions of supragranular layer neurons between the center and periphery in the adults ($P < 0.0001$), this is not the case in the neonates ($P > 0.05$).

Differences between core and periphery of projection zones in PMLS

So far the results show that there is a greater reduction of supragranular layer neurons in the periphery of the density profile compared with its center. Here we shall address the issue of whether there is also a drop in

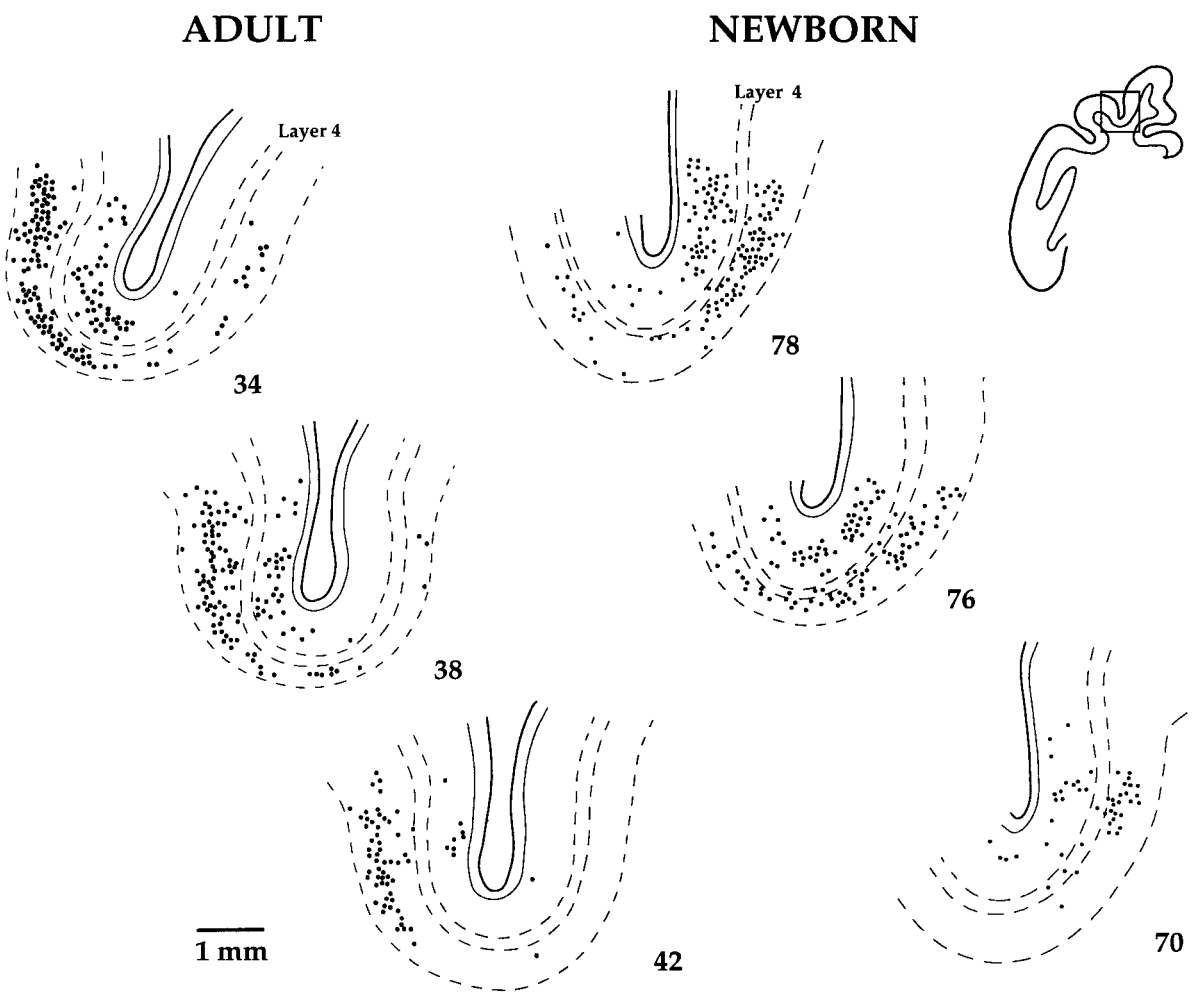

Fig. 5. Laminar distribution of labeled neurons in area 19 after injection in area 17 in adult and newborn kitten. Conventions are as in Figure 3.

proportions of supragranular neurons from central regions of the projection zone.

This question cannot be directly addressed by comparing neonatal and adult values obtained from the center of the density profiles, despite the large differences (adult, 23%; neonate, 40%; Table 3). The objection to making this comparison stems from the fact that sections from the central half of the density profiles include peripheral regions represented at the medial and lateral limit of the labeling on each section (see Fig. 2), because individual coronal sections in PMLS show that even in the center of the density profiles labeled infragranular layer neurons stretch further both medially and laterally (Fig. 4). For this reason, it could be that the observed differences between neonates and adults in the center of the density profile originates from supragranular layer neurons stretching out further into the medial and lateral part of the periphery of the projection zone.

To resolve this issue, we have compared the percentages of labeled supragranular layer neurons in the core of the projection zone in PMLS. To do this, we have divided those sections in the center of the density profile into three parts, the central half represents the core of the projection zone (Figs. 2, 11A).

The core of the projection zones in both neonates and adults contained approximately 50% of the total number of labeled neurons in the projection zone. The pooled values of the core of the projection zone in the adults is 25% of supragranular labeled neurons, which is significantly lower than the 38% found in the neonates ($P < 0.01$; Table 3). To further explore the developmental changes in labeled neuron distribution within the center of the density profile, we divided individual sections into 250-micron-wide segments running perpendicular to the cortical surface (Fig. 11). This method shows that, whereas in the neonate the lateral and medial periphery returns similar values to those obtained in the core, in the adult the mean of the distribution of the core values is 22% and is significantly higher than the peripheral values of 14% (Fig. 11).

Hence, this analysis confirms that the major developmental changes are detected in the periphery of the projection zone both mediolaterally and rostrocaudally. However, core values in the neonate are significantly higher than those in the adult, showing that although the selective loss of supragranular layer neurons occurs more extensively in the periphery of the projection zone, it also occurs in the core of the projection zone.

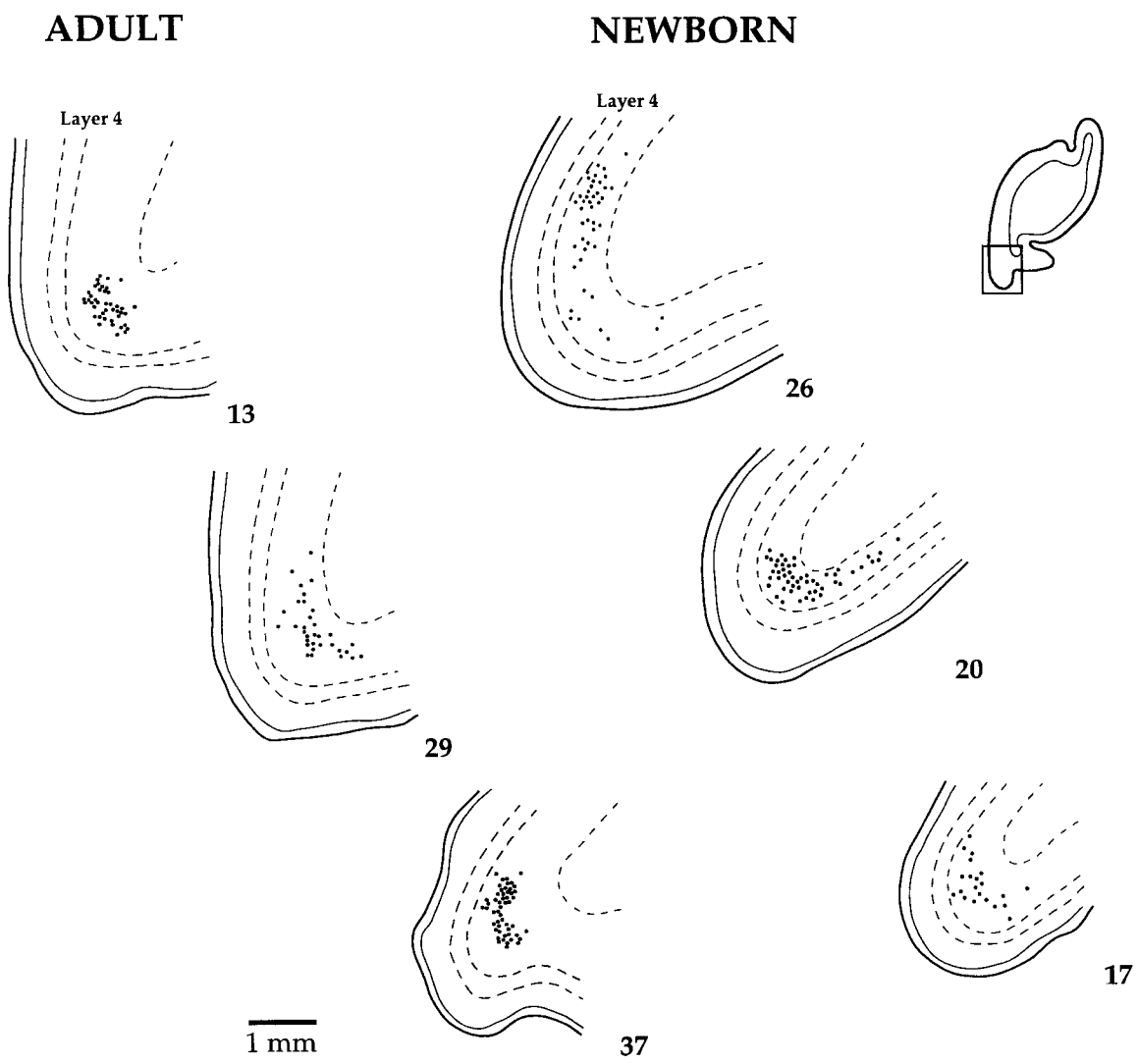

Fig. 6. Laminar distribution of labeled neurons in area 20 after injection in area 17 in adult and newborn kitten. Conventions are as in Figure 3.

Developmental changes in the dimensions of projection zones

The above findings suggest that developmental changes in the proportions of supragranular neurons might be the consequence of a change in the relative dimensions of the projection zones in upper and lower layers. To investigate this suggestion, we have measured the rostrocaudal length of the density profiles in adults and newborns by using thresholds of 5–10% of the peak value to establish the rostral and caudal limits of projection zones (Table 4). The changing dimension of the kitten brain and individual differences in the size of injection sites preclude estimating absolute change in the dimensions of the projections zone. However, the ratio of the dimensions in upper and lower layers does change significantly, going from 0.56 in the adults to 1.04 in the neonates ($P < 0.001$).

Developmental changes in the distribution of labeled neurons within supra- and infragranular projection zones

Elsewhere, we have defined convergence as the extent of a cortical source structure that contains neurons converging on an infinitely small region of the target structure and the divergence as the extent of the target structure innervated by an infinitely small region of the source structure (Salin et al., 1992; Kennedy et al., 1994). The surface area containing labeled neurons in each compartment reflects the convergence values of each population. In this way, a narrow distribution of labeled neurons indicates a restricted range of convergence values (Price et al., 1994). To investigate this issue, we have estimated within each layer the proportion of labeled neurons in the center and the periphery of the density profile as well as beyond the 5% threshold (Fig. 12). This investigation showed that, com-

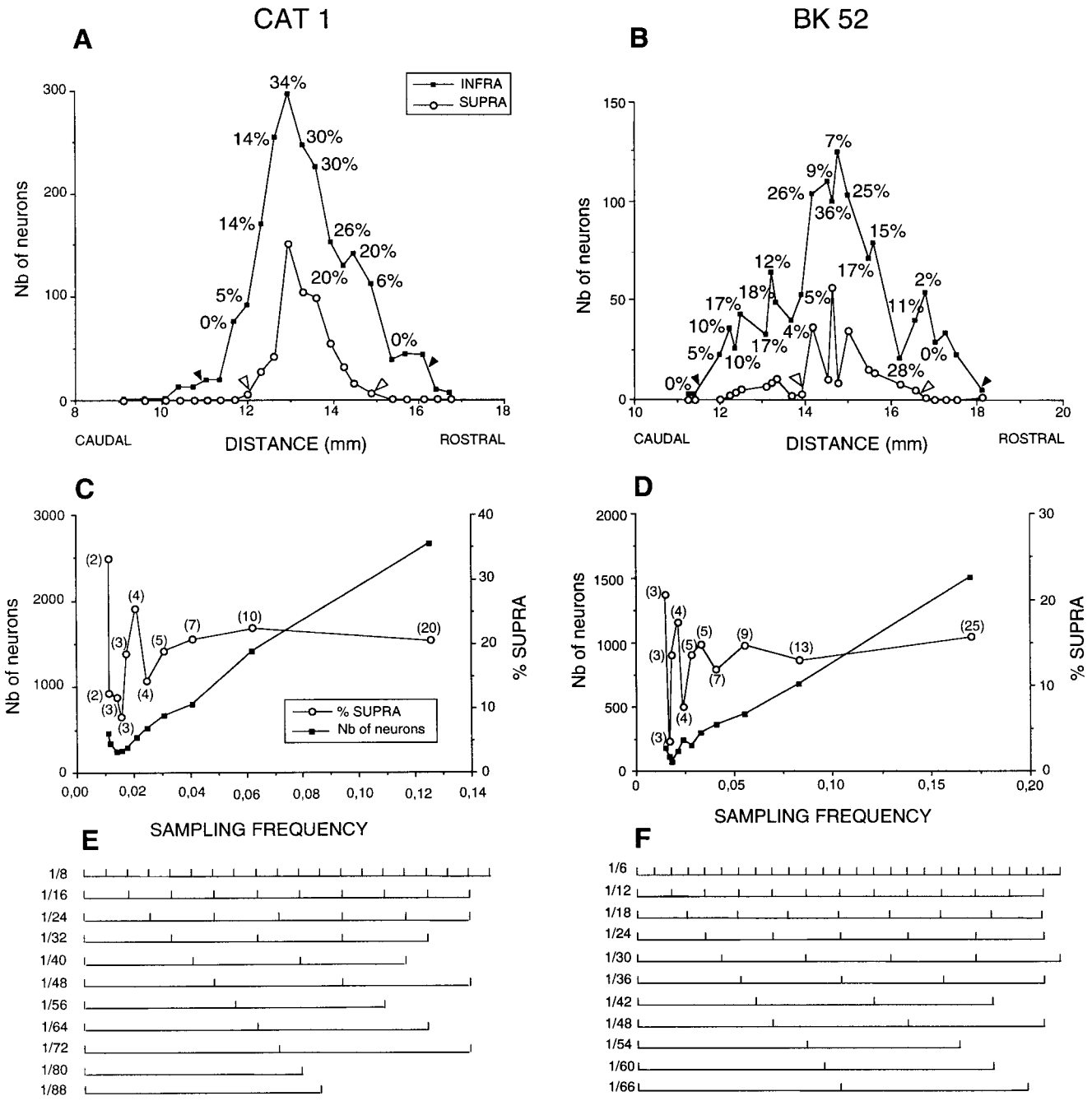

Fig. 7. Neuron density profiles and influence of sampling frequency on estimation of laminar distribution in the adult cat. **A,B:** Neuron density profile of posteromedial lateral suprasylvian area projection zone in the infragranular (black squares) and supragranular layers (open circles) in two adult cats (CAT 1 and BK52). Percentages refer to the proportion of supragranular layers neurons on each individual sections. Caudal to the left. Arrowheads indicate 5% of peak values used to determine the limits of the neuron density profiles (see Table 3). **C,D:** Influence of the sampling frequency on the proportion of supragranular layer neurons (SUPRA). Nb, number of neurons. **E,F:** Sections and sampling frequency procedure used in C and D above. Increasing the sampling frequency permits a reliable estimation of the percentage of supragranular layers neurons (open circles, right-hand scale). At each frequency, the number of labeled neurons is indicated (black squares, left-hand scale). Numbers in parentheses refer to the number of sections used to calculate the percentage as indicated in E and F.

pared with the neonates, the adult population had a significantly higher proportion of supragranular layer neurons in the center of the density profiles. This finding means that the center-periphery slope is significantly steeper in the adults than in the neonates, which suggests a developmental restriction of convergence values of individual supragranular layer neurons (Kennedy et al., 1994; Price et al., 1994). In infragranular layers, no differences

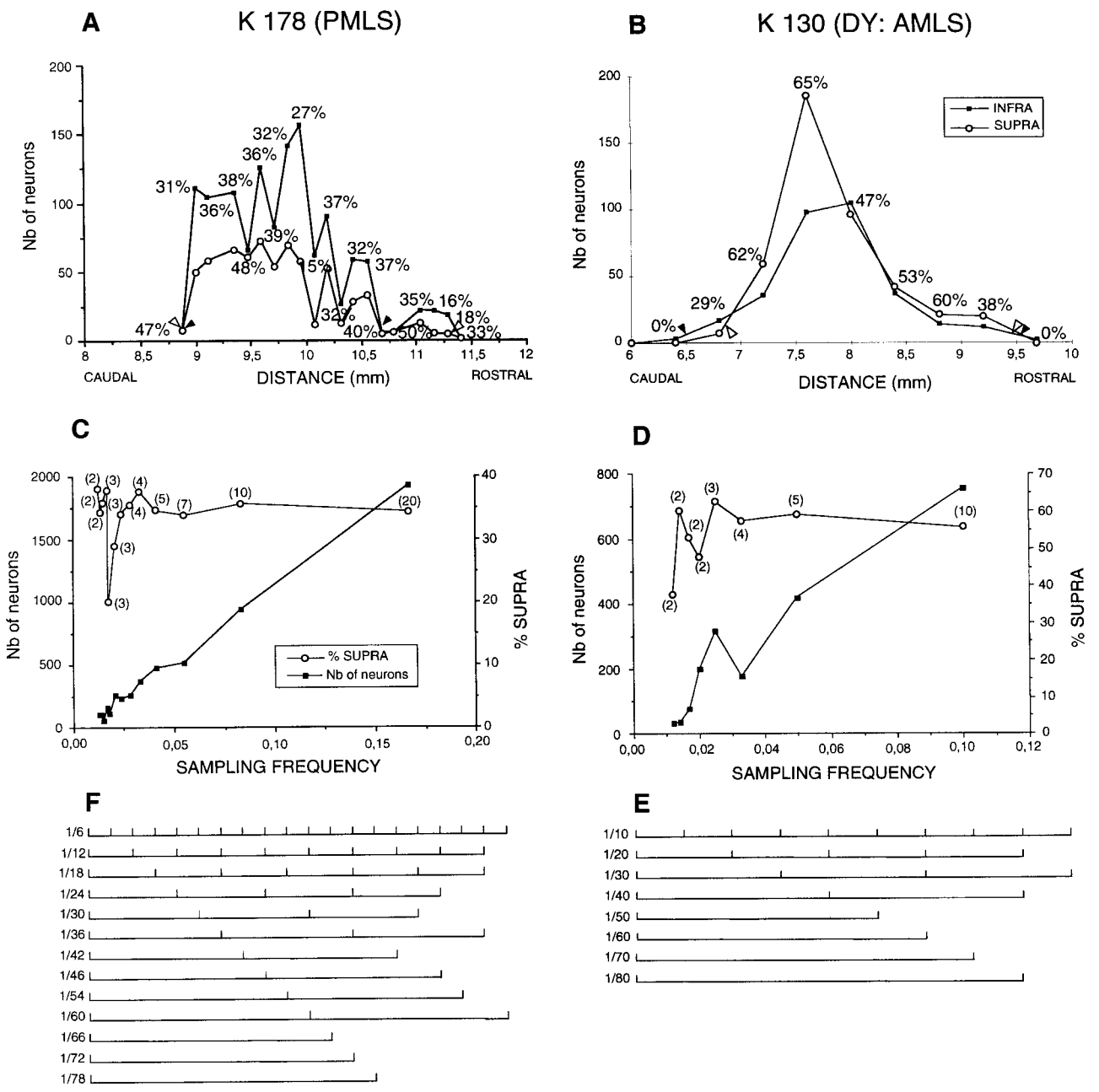

Fig. 8. Neuron density profiles and influence of sampling frequency on estimation of laminar distribution in the newborn. **A,B:** Posteromedial lateral suprasylvian (PMLS) area. Anteromedial lateral suprasylvian (AMLS) area infragranular (black squares) and supragranular layers (open circles) neurons. Percentages refer to the proportion of supragranular layer neurons on each individual sections. Caudal is to the left. Arrowheads indicate 5% of peak values used to determine the limits of the neuron density profiles (see Table 3). **C,D:** Influence of the sampling frequency on the proportion of supragranular layers neurons. **E,F:** Sampling frequency used in C and D above. Other conventions are as in Figure 7.

were found in the adults and neonates between the proportions of neurons in the center and periphery of density profiles, suggesting that during development divergence values may remain constant in this population.

Control for artifacts

Representation of visual space. The rostrocaudal location of the injection will determine the representation of visual space, which could conceivably influence the proportion of supragranular layer neurons. To examine whether this is the case, we have plotted the percentage of supragranular layer neurons against distance from the caudal limit of the brain. This method shows that there is no correlation between changes of cortical location of the injection site with respect to variations of percentages of labeled supragranular layer neurons (Fig. 13A).

Depth of injection. Although all injections were restricted to area 17 and all but one restricted to the gray

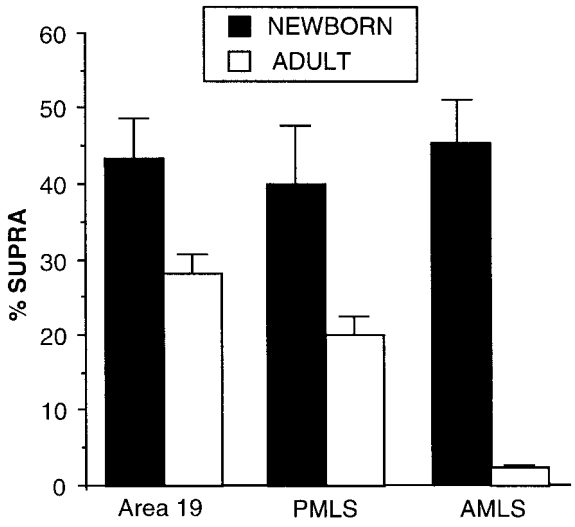

Fig. 9. Summary histogram of mean percentages of labeled supragranular layer neurons in areas 19, posteromedial lateral suprasylvian (PMLS), and anteromedial lateral suprasylvian (AMLS) in adults and neonates.

matter, here we need to address whether small variation in depth of injection could influence the laminar distribution. The influence of the depth of the injection was estimated by attributing a depth index to each injection site (Barone et al., 1995). Briefly, each section that includes the injection site is given an index according to the depth of the pick-up zone in the cortex (superficial to layers 2/3, 1; superficial to layer 4, 6; superficial to white-matter, 15). The sum of the values for sections intercepting the injection site at regular intervals generates the depth index for that injection. Figure 13B shows a scattergram for seven newborn injections that could be examined in this fashion and that show that depth of injection site did not influence the percentage of labeled supragranular layer neurons ($P > 0.05$). Depth of injection also failed to influence proportions of supragranular layer neurons in the five injections in adults that could be analyzed appropriately ($P > 0.05$).

DISCUSSION

The present results show that in the adult cortex each individual feedback pathways from area 19, PMLS, and AMLS have characteristic laminar distributions of parent neurons and that these distributions emerge during development from a distribution that is initially uniform across all three areas. We first need to consider the potential significance of the adult findings before discussing the possible developmental mechanisms.

Comparison of present results with other adult studies

Importance of sampling procedure. Numerous authors have noted the differences in the laminar distribution of parent cell bodies participating in corticocortical connections, and this finding, in addition to the laminar pattern of termination, has been used in a number of different sensory systems to propose a hierarchical ranking of cortical areas (Fitzpatrick and Imig, 1980; Maunsell and Van Essen, 1983; Weller et al., 1984; Ungerleider and Desimone, 1986; Barbas 1986; Colby et al., 1988; Friedman et al., 1986; Van Essen et al., 1990; Felleman and Van Essen, 1991; Barbas and Rempel-Clower, 1997). In this way, corticocortical pathways are seen to be either feedback, feedforward, or lateral. However, in their exhaustive review of the literature Felleman and Van Essen (1991) noted that the hierarchical status of nearly 17% of pathways between primate cortical visual areas remained essentially ambiguous. The present results indicate two potential sources of this ambiguity.

First, the nonhomogeneous organization of the projection zone can lead to miscalculation of the laminar distribution. The laminar distribution for a given pathway is not a fixed entity but rather fluctuates across the projection zone, showing maximal percentages of supragranular layer neurons in central and minimal values in the periphery. In the present study we illustrate this finding in adult PMLS where the central half of the density profile has twice the proportion of labeled supragranular neurons than does the peripheral half. Such large differences in percentages will artifactually influence the categorization of the laminar distribution if the sampling of the projection zone is not carefully controlled. If the exact dimensions of the projection zone are not known, then the sections may well not be taken at regular intervals throughout the entire projection zone, which introduces the possibility of a bias due to either oversampling of the periphery or of the center of the density profiles.

Second, the problem of the influence of eccentricity in the projection zone is compounded by the fact that there are large variations in the laminar distribution between adjacent sections. This variation is largely due to cortical folding and means that a relatively large number of sections need to be examined to obtain stable values.

These difficulties can be clearly seen when one compares the percentages of supragranular layer neurons projecting to area 17 in the present study with the quantitative data used by Felleman and Van Essen (1991) to rank visual cortical areas in the cat (Symonds and Rosenquist 1984a,b; Bullier et al., 1984). Symonds and Rosenquist (1984b) reported 47% labeled supragranular layer neurons in area 19 in a count of 95 neurons. Bullier et al. (1984) reported 46% on counts taken from four randomly selected central sections in two adults. In the present study, area 19 returns 28% in counts made over a hundred sections and over 10,000 neurons. Similarly, in PMLS Symonds and Rosenquist (1984b) reported 13% of labeled supragranular layer neurons in counts of 311 neurons. This finding is considerably lower that the 28% reported by the study of Bullier et al. (1984) based on randomly selected central sections. The exhaustive analysis of the present study shows that the two earlier studies were equally off and that the true figure for the distribution is 20%, in agreement with the 20% reported by Shipp and Grant (1991) in an exhaustive quantitative study.

Relevance of adult findings to hierarchical schemes. The present study shows that although an arduous task, it is indeed possible to demonstrate that each area that projects to area 17 has a characteristic percentage of labeled supragranular layer neurons. Felleman and Van Essen (1991), following the consideration of a large number of cortical pathways, have described the anatomical hierarchy of visual areas that span seven levels. According to this scheme, areas 18, 19, PMLS, and AMLS are on

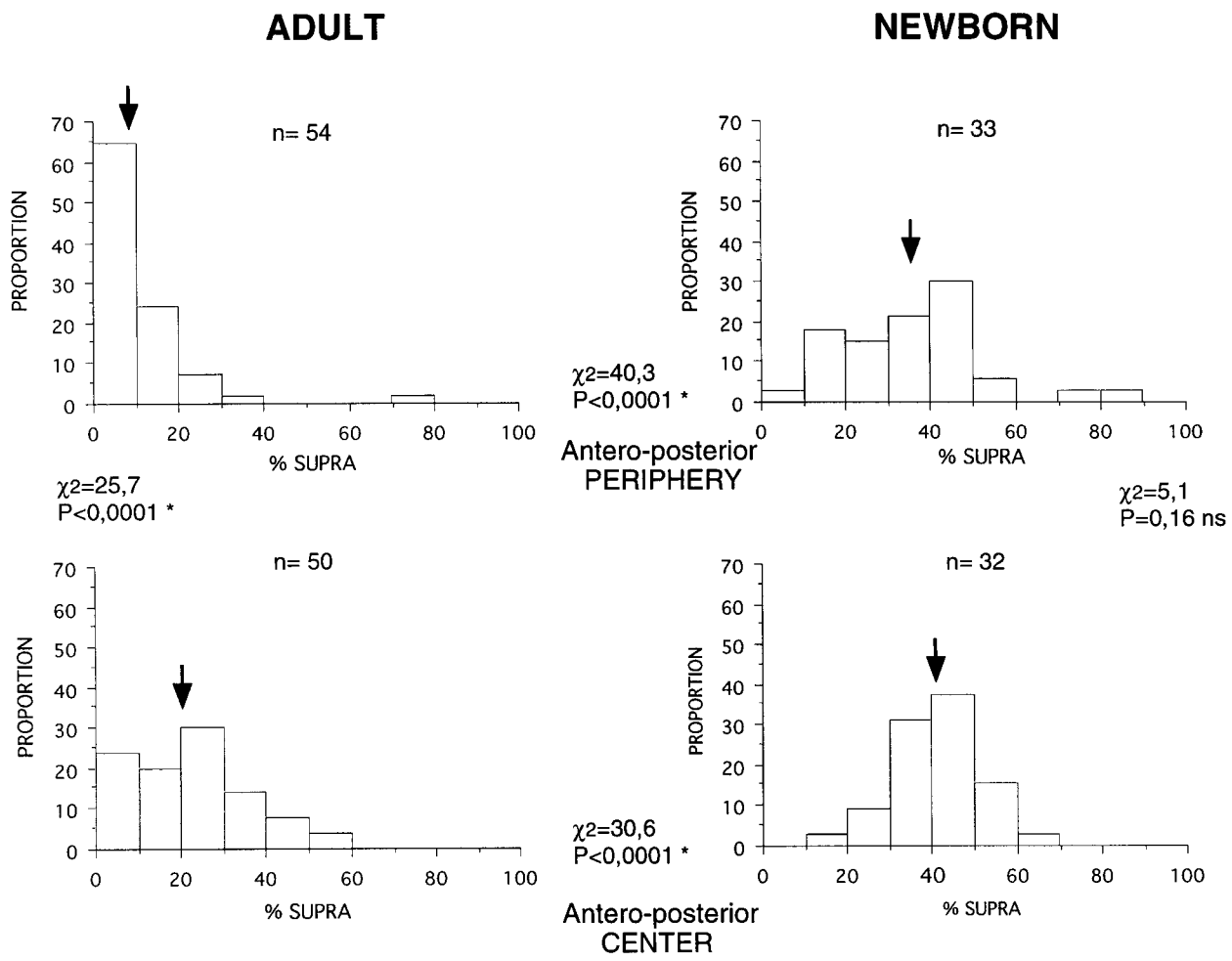

Fig. 10. Adult and newborn distribution of percentages of labeled supragranular layer neurons (SUPRA) for individual sections in posteromedial lateral suprasylvian (PMLS) area. Pooled values from the periphery (top) and center (bottom) of the projection zone. Arrows indicate mean values of the distribution. Statistical differences on the distribution calculated by using the χ^2 test.

levels 2, 3, 4, and 5 (Scannell et al., 1995). These considerations are relevant to the present findings because we show that levels 2, 3, 4, and 5 display a large decrease in the percentage of supragranular layer neurons.

Physiologic and behavioral studies suggest homologies between cat and monkey visual areas (Payne, 1993). Similarly, in adult monkey rigorously determined percentages of supragranular layer neurons projecting to area V1 also distinguish areas V2, V3, V4, MT, and FST (Barone et al., 1995; Barone, unpublished observations). Multiple anatomical criteria have been used to place V1,V2, V3, MT, and FST on separate and successive levels within an anatomical hierarchical scheme (Felleman and Van Essen 1991).

There are several lines of evidence which suggest that differences in the percentages of supragranular layer neurons could be of functional significance. First, there is increasing evidence that pyramidal cells in upper and lower layers could have different physiologic (Lagae et al., 1989; Nowak et al., 1995; Raiguel et al., 1995) and histochemical properties (Hof et al., 1996, 1997). Second, that the projection zone in the infragranular layers extends further than that in the supragranular layers suggests that the divergence of infragranular cortical neurons is higher than of supragranular layer neurons (Barone et al. 1995; Barbas, 1995). Together both of these features of upper and lower layer neurons could contribute to differences in the physiologic functions of feedback and feedforward pathways (Domenici et al., 1995; Nowak and Bullier, 1997).

Developmental studies

This study demonstrates a developmental reduction of the percentage of supragranular neurons in an ensemble of extrastriate cortical areas back-projecting to striate cortex in cat, a phenomena known to occur in primates (Kennedy et al., 1989; Meissirel et al., 1991; Barone et al., 1995). In cat, the laminar distribution of feedback neurons is still immature 1 month after birth. The late maturation of feedback projections from an early uniform distribution contrasts with the early development of feedforward pathways that has been demonstrated in monkey (Barone et al., 1995, 1996; Coogan and Van Essen 1996), cat (Price and Zumbroich, 1989), and rodent (Knutsen et al., 1997).

The development of feedback pathways in primate and carnivore both show a prolonged period of maturation.

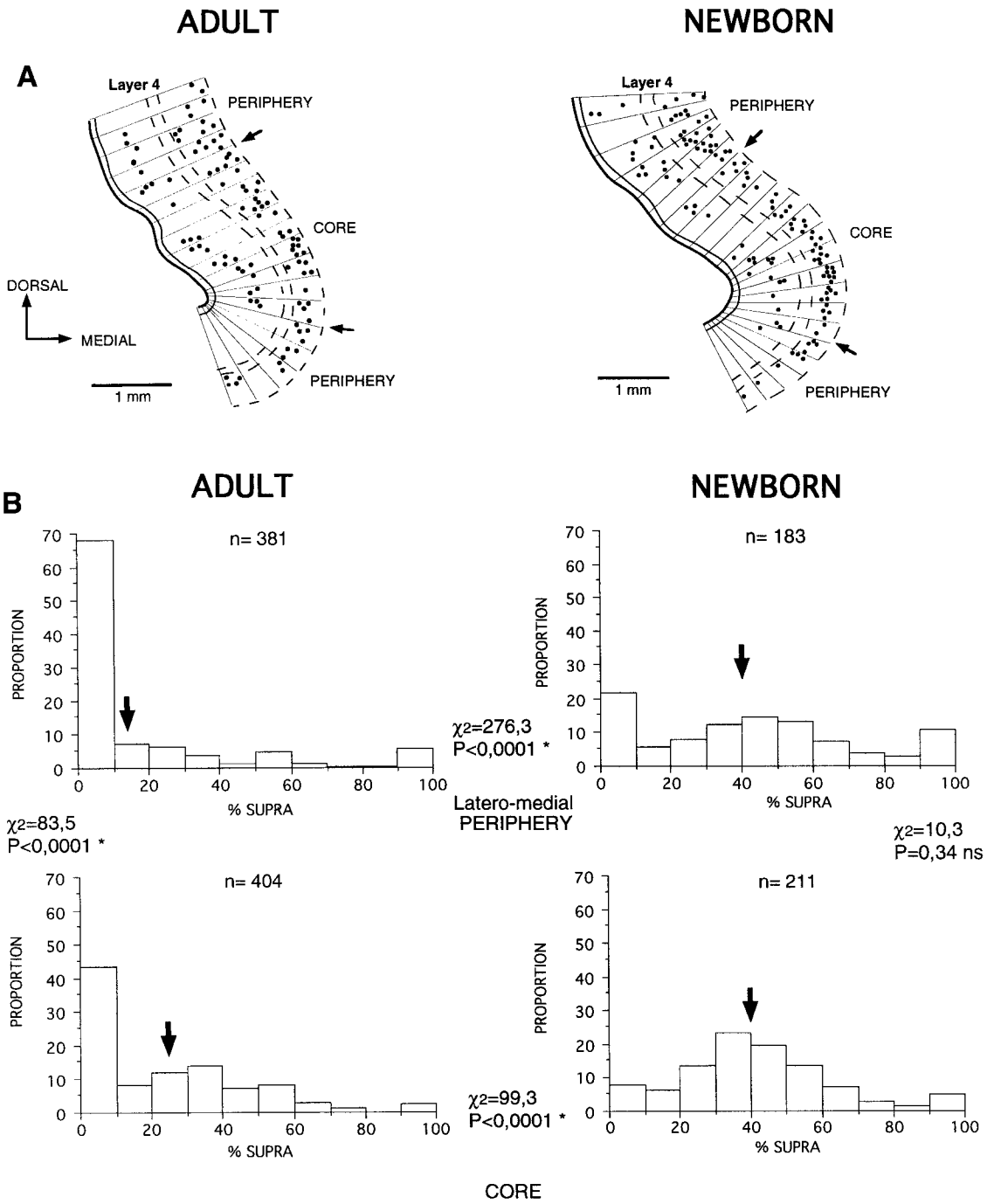

Fig. 11. **A:** Laminar distribution of labeled neurons in 250-micron-wide radial stripes in the posteromedial lateral suprasylvian area. Single sections show the positions of core and periphery. Arrows indicate the medial and lateral limits of the core of the projection zone on individual coronal sections. **B:** Pooled values from the periphery (top) and core (bottom) of the projection zone. Conventions are as in Figure 10.

However, in early fetal monkey, despite a high proportion of supragranular projecting neurons, areas that back-project to V1 can be differentiated from each other by their laminar distribution of neurons (Barone et al., 1995). This early areal specificity of feedback projections in monkey is observed right at the start of formation of corticocortical connections (E115). This finding contrasts with the uniform distribution across areas of projecting neurons in kitten and constitutes a primate feature.

The development of feedback corticocortical pathways in rodents may differ from that of monkey and cat. Coogan and Burkhalter (1988) made injections of retrograde tracers in area 17 of rat and monitored the laminar distribution of labeled neurons in area 18a at postnatal day (PND)

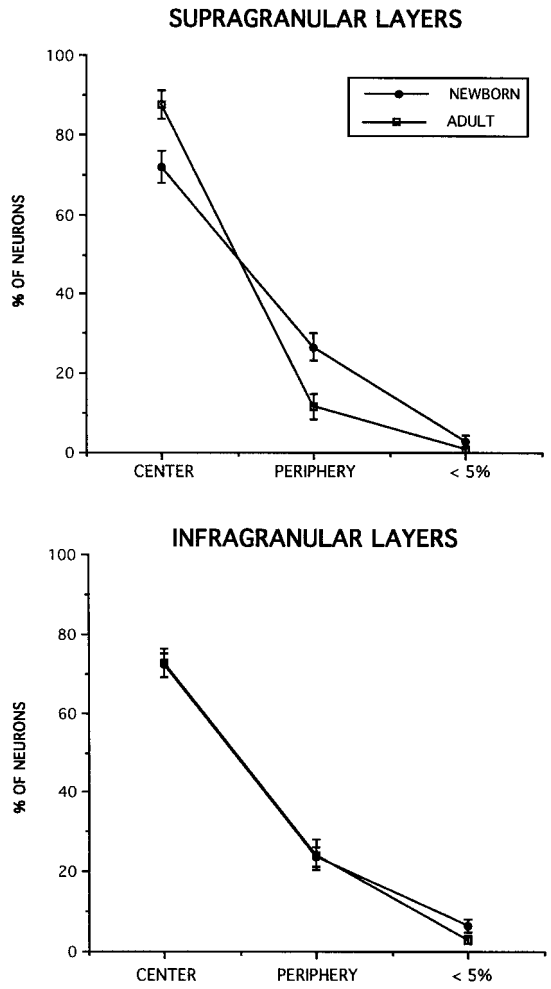

Fig. 12. Percentage of supragranular and infragranular layer labeled neurons in the center, periphery, and beyond the 5% threshold limit of the projection zone.

1 and 5. These authors found that the earliest formed projections at PND 1 originated predominantly from the infragranular layers. By PND 5, there is a significant increase in the proportion of supragranular layer neurons but the laminar pattern is still immature at this age. Coogan and Burkhalter's results suggest that there is no developmental excess of supragranular layer projection neurons, although the possibility cannot be excluded that it occurs at later stages, possibly during the period of eye opening.

What are the cellular mechanisms responsible for developmental changes in laminar patterns?

Simultaneous cortical injections of two distinguishable retrograde tracers separated by 2–4 mm in the adult monkey leads to a higher incidence of double-labeled neurons in infragranular layers compared with supragranular layer neurons (Kennedy and Bullier, 1985; Barbas, 1995). This result shows that infragranular pyramidal cells have higher divergence values (Bullier and Kennedy, 1987). Similar injections in the fetal monkey

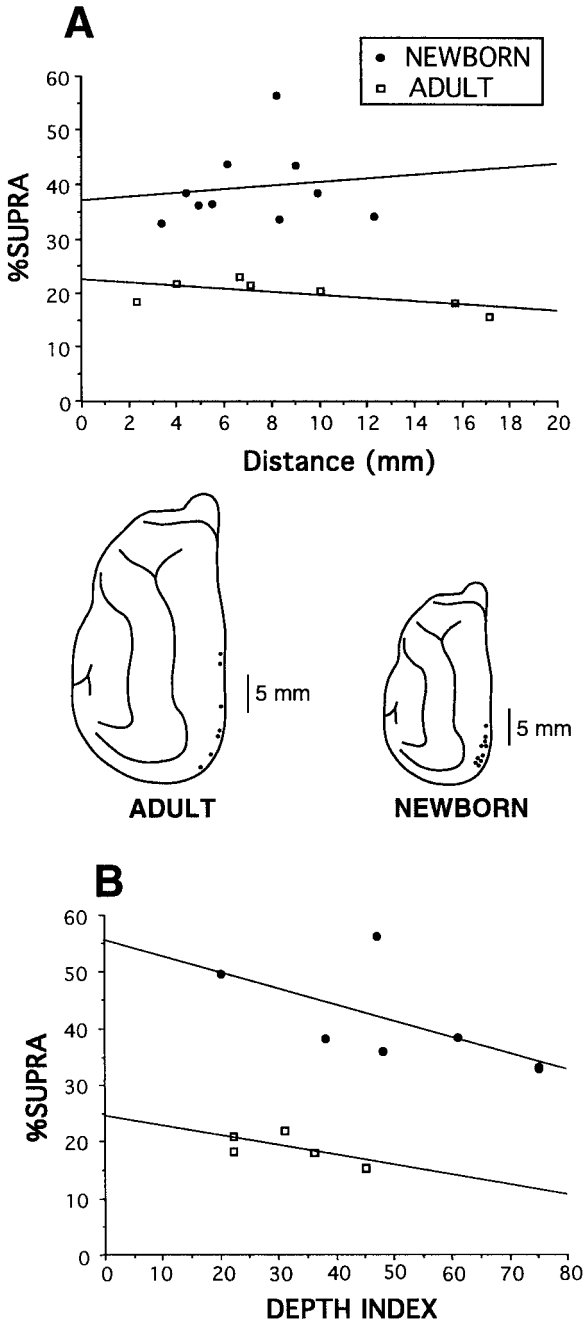

Fig. 13. Influence of the rostrocaudal position of injection site (**A**) and the depth of injection site (**B**) on proportions of labeled supragranular layer neurons (SUPRA) in newborn (black circles) and adults (open squares). The depth index reflects the depth of the injection site (see text), low values correspond to more superficial injections. This figure shows that the laminar distribution of labeled neurons in the posteromedial lateral suprasylvian (PMLS) area is not influenced by either the depth of the injection site ($P = 0.38$) or the rostrocaudal position of injection of the injection site ($P = 0.11$). Number of sections used to calculate the depth index: adults, 5; neonates, 3.

show that virtually all double-labeled neurons are located in supragranular layers (Barone et al., 1995). These results suggest a developmental decrease in the divergence values of supragranular layer neurons. In the present

study, we show that the developmental change in the laminar distribution of area 17 afferents is accompanied by a relative decrease in the proportion of supragranular layer neurons in the periphery of the projection zone. During development, it is known that there is a reduction in the divergence values of corticocortical projections (Kennedy et al., 1994; Price et al., 1994). The present findings suggest that in early feedback projections widely divergent projections specifically stem from supragranular neurons. However, the possibility remains that their axon terminals are restricted to the deep layers of their target (Caric and Price, 1996).

CONCLUSIONS

Here we show that rigorously determined laminar distributions of corticocortical connections rank individual extrastriate areas in an order that corresponds to the hierarchy proposed by others using multiple anatomical criteria (Felleman and Van Essen, 1991; Scannel et al., 1995). The present results show that a prolonged area-specific developmental process leads to the precise laminar pattern of extrastriate feedback connections that characterizes each area. Furthermore, there is evidence that developmental remodeling of corticocortical pathways of this sort could be a universal feature across sensory areas of the neocortex (Kennedy et al., 1996). Although the precise developmental mechanism remains unknown, it would seem that there is a differential modification of the divergence values of supra- and infragranular layer neurons.

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