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# Postnatal Development of Corticocortical Efferents from Area 17 in the Cat's Visual Cortex

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**We are interested in the postnatal development of corticocortical connections in the cat's visual cortex. In this study, we injected the anterograde tracer $^3$H-proline into visual cortical area 17 of kittens, aged 4–70 d, and adult cats to visualize the distribution of terminals of the association projections to areas 18, 19, 21a, and the lateral suprasylvian visual cortex. The density of anterograde label was quantified using computerized image analysis.**

**There was dense labeling at topographically appropriate locations in area 18 in animals of *all* ages. In 4- and 8-d-old kittens, other extrastriate areas (19, 21a and the lateral suprasylvian cortex) contained only *sparse* label, localized in a few solitary axons; these areas were *densely* labeled in animals aged 12 d or more. In kittens aged 4–20 d there was considerable, widespread label within fibers located in the white matter, and many of these axons lay underneath regions of extrastriate, and also striate, cortex that were almost certainly not destined to be persistently innervated by cells at the injection site. This pattern of extensive white matter label was not seen in animals older than 20 d.**

**In each extrastriate region, from the earliest age at which we identified *dense* cortical innervation from area 17, the terminals were distributed in clusters. At first these patches were mainly in infragranular layers, but later, during the second and third postnatal weeks, they began to appear in more superficial laminae. By 70 d, an adult-like distribution of terminals was found in each extrastriate area: most fibers appeared to end in layers II and III in areas 18, 19, and 21a and centered on layer IV in the medial bank of the middle suprasylvian sulcus in adult cats.**

**We suggest that the development of ipsilateral association projections from area 17 to extrastriate cortex is a 2-stage process. First, cells at a particular point in area 17 send immature fibers in a *nonspecific* fashion through white matter towards a very wide area of extrastriate cortex. Second, corticocortical axons penetrate extrastriate cortex mainly in patches at topographically appropriate regions and grow to their targets in a *specific* fashion.**

There is considerable reorganization of corticocortical projections during normal development of the mammalian cortex (Innocenti et al., 1977, 1986; Innocenti, 1981; O'Leary et al., 1981; Cusick and Lund, 1982; Ivy and Killackey, 1982; Dehay et al., 1984, 1988; Innocenti and Clarke, 1984a, b; Price and Blakemore, 1985a, b; Clarke and Innocenti, 1986; Kato et al., 1986; Luhmann et al., 1986; Price, 1986). Much of the remodeling of these pathways results from a loss of initial "exuberant" projections that link regions of brain that do not remain connected in the adult (see review by Cowan et al., 1984). The mechanism by which these early transient projections are eliminated is not well understood, but it is clear that normal visual experience is required early in postnatal life for full maturation of at least some of the corticocortical visual pathways (Lund et al., 1978; Innocenti and Frost, 1980; Rhoades and Dellacroce, 1980; Cusick and Lund, 1982; Innocenti et al., 1985; Luhmann et al., 1986). It is possible that interactions between the *terminals* (either growth cones or synapses) of axons generated early in development and their target areas determine whether particular connections will be retained or withdrawn.

Previous studies of the maturation of the cat's geniculocortical pathway demonstrate that afferents from the lateral geniculate nucleus (LGN) arrive in the subplate, immediately below the developing visual cortex, in prenatal development. These fibers then wait for a prolonged period until their target layers (IV and VI) are fully formed, before penetrating them early in postnatal life (Shatz and Luskin, 1986). Hence, it is interesting to ask whether a similar relationship could be true for the developing corticocortical pathways.

The functional properties of neurones in striate and extrastriate areas of the cat's visual cortex are immature during the immediate postnatal period but rapidly improve with normal visual experience (e.g., review by Sherman and Spear, 1982; Albus and Wolf, 1984; Blakemore and Price, 1987; Price et al., 1988; Zumbroich et al., 1988). It has been suggested that association projections play a role in the normal development of the visual responsiveness and the receptive field properties of at least some neurons in extrastriate visual cortex (Blakemore and Price, 1987). A knowledge of the nature and the timing of the anatomical changes that occur in the distribution of the terminals of association projections to extrastriate cortex is important when considering a possible functional role for these pathways in development.

There have been a few studies of normal postnatal changes

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in the distribution of the terminals of callosal connections (Innocenti, 1981; Innocenti and Clarke, 1984b) and ipsilateral association pathways to the area 17/18 border from both nonvisual and visual areas in the cat (Clarke and Innocenti, 1986). However, there has been no detailed analysis of developmental changes in the distribution of terminals of the major intrahemispheric corticocortical efferents from area 17 to other extrastriate visual cortical areas. Here we report the results of our study of the development of ipsilaterally projecting association fibers in the visual cortex of the cat. The experiments were carried out by injecting tritiated proline into area 17 at various ages and observing the resulting anterograde label in the extrastriate visual cortex.

## Materials and Methods

*Animals.* We performed successful experiments on 9 normal animals, 7 of which were kittens, aged 4 (2 animals), 8, 12 (2 animals), 20 and 70 d, and 2 of which were adult cats (both 1.75 kg). All animals were bred in an isolated colony.

*Surgical procedures for injection.* Anesthesia was induced with ketamine hydrochloride (20 mg/kg, i.m.) and maintained throughout the experiment with alphaxalone-alphadolone (Saffan, Glaxo) intravenously as needed. The electrocardiogram was monitored continuously.

The animal was placed in a stereotaxic frame (Eldridge, 1979), and an injection of tracer was made through a small craniotomy over the lateral gyrus on one side of the brain. After injection, the wound in the scalp was sutured, and the animal was allowed to recover.

*Injection of tracer.* L-(2,3,4,5-$^3$H) proline (100 Ci/ml; Amersham) was injected (125 nl/injection in animals aged 12 d or less; 250 nl/injection in animals older than 12 d) into area 17 through a glass micropipette (tip diameter about 50 $\mu$m) using a pulsatile pressure system (Picospritzer, General Valve Corporation). In most animals we made only one injection, several millimeters caudal to the coronal plane that runs through the external auditory meatuses (AP0). In each adult cat and the 20-d-old kitten, we made 2 well-separated injections into area 17 on the same side of the brain, one caudal to AP0 and the other about 5 mm further rostral, so as to increase the amount of data obtained from each animal. Because of the quite strict topographic nature of these projections (Montero, 1981a; Price and Blakemore, 1985a, b), the 2 injections always produced 2 separate patterns of anterograde labeling with no possibility of confusion in relating a particular injection site to its resulting region of label. For injections into rostral area 17, we lowered the tip of the pipette 3–4 mm down the medial bank of the lateral gyrus, and at caudal sites, where area 17 covers the crest of the lateral gyrus (Otsuka and Hassler, 1962), we injected at a depth of about 1 mm. Data presented here are from a total of 12 injection sites, 8 in kittens and 4 in adult cats.

*Histology.* Each animal survived for 24 hr before being deeply anesthetized with an overdose of sodium pentobarbitone and then perfused transcardially with a 4% solution of paraformaldehyde. The fixed brain was removed and left to equilibrate in phosphate buffer containing 10% sucrose. A 1-in-5 series of coronal sections of injected cortex and ipsilateral thalamus was cut at a thickness of 25 $\mu$m on a freezing microtome and mounted on gelatinized slides.

All slides were coated for autoradiography with Nuclear Research Emulsion (Ilford, K5), using a wire loop method (Jenkins, 1972). They were exposed in the dark at 4°C for 6 weeks and then developed in D19 (Kodak). Sections were analyzed fully before being counterstained with cresyl violet.

*Analysis.* Sections of cortex and thalamus were studied using bright- and dark-field microscopy. To study patterns of cortical labeling *quantitatively* and to allow detailed comparisons between results from animals at different ages, we used a computerized image-analyzer to measure the density of label within 50-$\mu$m-thick strips drawn as shown in Figure 1: (1) parallel to the cortical surface, curved as necessary to follow the contours of the cortex, along the cortical layer in which label was densest in coronal sections through the center of the labeled region (*tangential analysis*), and (2) orthogonal to the cortical surface, extending through all layers and running through the center of a patch of label in coronal sections (*radial analysis*). Mean background densities and their SDs and SEM were calculated from measurements taken at 10 points 250 $\mu$m apart in the same cytoarchitectonic area of cortex but distant from the major zone of anterograde labeling. We established a threshold equal to the mean background label +2 SD for tangential analysis and considered that when values for density along the 50-$\mu$m-wide strip drawn through a coronal section rose above threshold significant labeling was present. For radial analysis, a threshold equal to the mean background +2 SEM (i.e., $p$ about 0.05 in a $t$ test) was established, coronal sections from the center of the labeled region were chosen for study, and sampling strips were drawn orthogonal to the cortical surface through the middle of each of a number of labeled patches. Thus, we obtained a group of values for relative density at a series of cortical depths (separated by 250 $\mu$m in adult cats and 125 $\mu$m in kittens) and calculated mean values and SEM at each depth.

Data from both tangential and radial analyses are shown on scales of *normalized relative density*, in which 0 indicates no significant labeling (i.e., the threshold density) and a value of 1.0 corresponds to the highest density found along a sampling strip or, in the case of radial analysis, a *group* of sampling strips used to construct a graph.

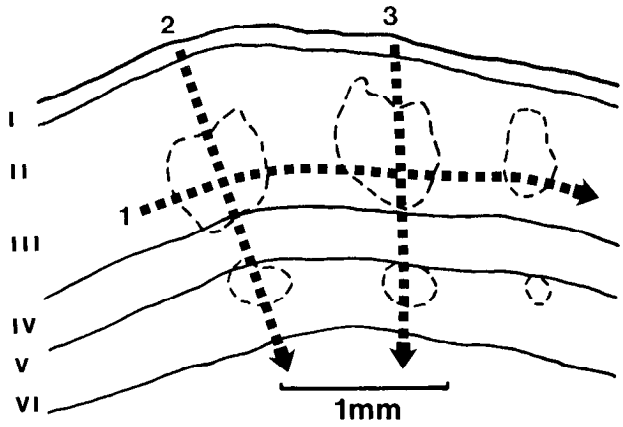


*Figure 1.* Diagram illustrating how we carried out the analyses of the relative density of label along sampling strips on a section through the visual cortex. This drawing shows a coronal section through area 19 in an adult cat and is traced from the computer screen. Laminae are marked, and the *narrow broken lines* outline the densest areas of label, as judged by eye. The computer measured the density of label in 50-$\mu$m-wide strips (*broad interrupted lines*). *Tangential* analysis (*line 1*) was carried out in the layer containing the highest density of label (in this case layer III). Densities along lines 2 and 3 were measured for *radial* analysis.

## Results

### Analysis of injection sites

The injection sites covered all cortical layers in area 17. Sometimes underlying white matter was involved to a limited extent, but in these cases the patterns of anterograde labeling were the same as those in animals of similar age in which white matter was not contaminated. To check that the injection sites were restricted to area 17 in both kittens and adult cats, we first used cytoarchitectonic criteria to locate the area 17/18 border (Garey, 1971; Anker and Cragg, 1974). In 4- and 8-d-old kittens, layers II and III are not yet fully formed (Shatz and Luskin, 1986), and the area 17/18 border was located by examining layer V, which is about 25% thicker in area 18 than in area 17 at all postnatal ages (Garey, 1971; Price, 1985).

#### *Thalamic labeling*

To confirm that the area 17/18 border was not covered by the injection sites, we examined the distribution of label in the LGN. The projection from area 17 to the LGN is present from birth and is arranged topographically in both cats and kittens. Any deposit of tracer in area 17 that avoids the areal boundaries will not label the medial or lateral edges of the LGN (Henderson

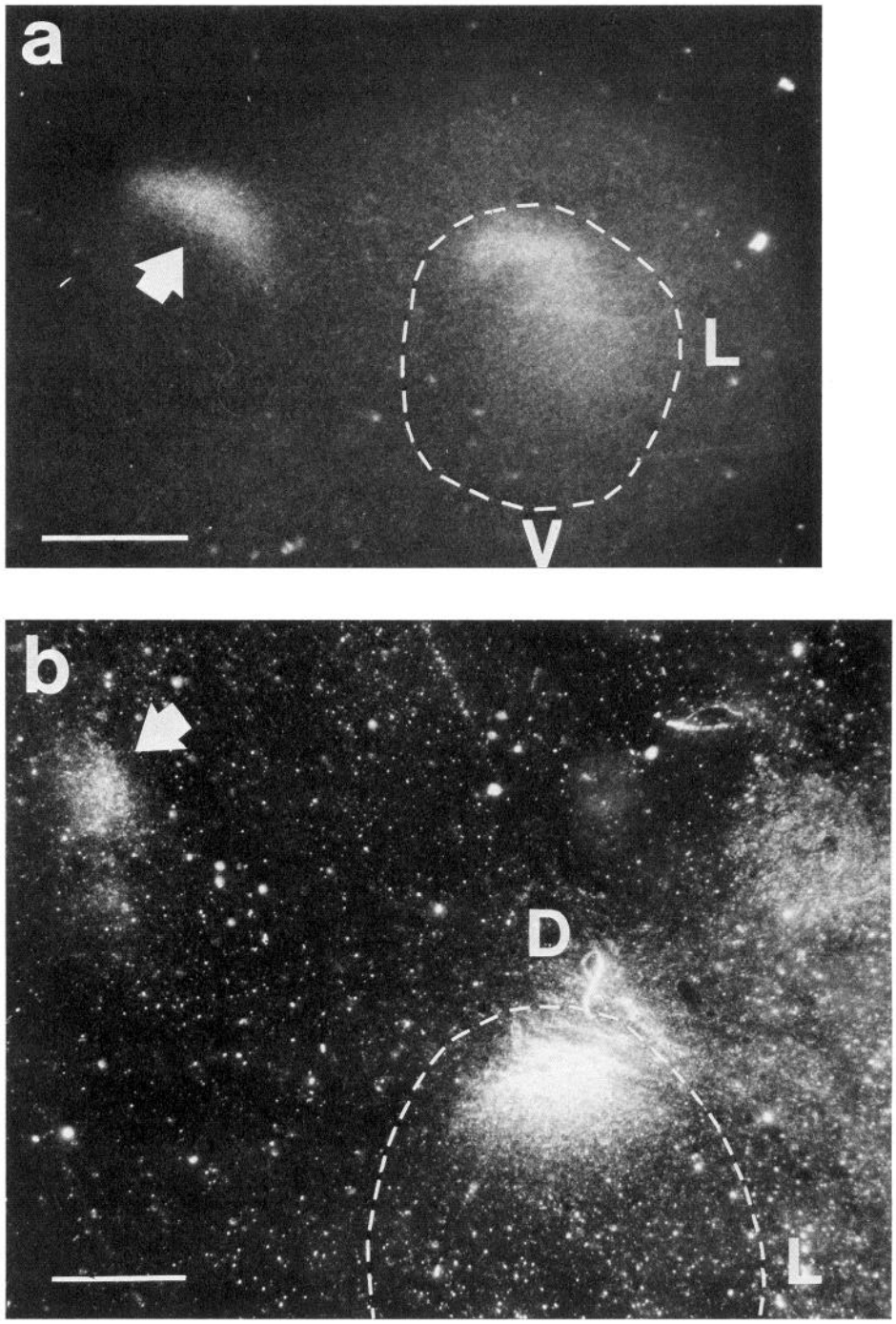


*Figure 2.* *a,* Dark-field photomicrograph of a coronal section through the right thalamus of a 4-d-old kitten with anterograde labeling resulting from an injection in the ipsilateral area 17. The borders of the LGN (identified in bright field) are marked with an *interrupted line* (*L,* lateral; *V,* ventral), and the *arrow* indicates label in the lateral posterior nucleus. Label in the LGN does not involve its medial and lateral boundaries. *b,* Dark-field photomicrograph of a coronal section through the right thalamus of an adult cat demonstrating anterograde thalamic labeling resulting from an injection in area 17. The borders of the LGN are marked with an *interrupted line* (*L,* lateral; *D,* dorsal), and the *arrow* indicates label in the lateral posterior nucleus. The label in the LGN does not involve the medial and lateral boundaries. Scale bars, 1 mm.

and Blakemore, 1986). All the injections considered here did indeed produce labeling that spared the medial and lateral borders of the LGN (Fig. 2).

Injections at all ages also labeled the region of the lateral posterior nucleus of the thalamus (Fig. 2); because of histological immaturity in the younger animals, we did not attempt to subdivide this nucleus into its medial and lateral parts (Raczkowski and Rosenquist, 1983; Kato, 1986).

## Cortical areas studied

Areas 17, 18 and 19 are distinguishable in Nissl-stained sections not only in adult cats (Garey, 1971) but also in kittens (Anker and Cragg, 1974; Price, 1985; Price and Blakemore, 1985a; Henderson and Blakemore, 1986). The criteria used to distinguish areas 17 and 18 are described above; areas 18 and 19 are distinguishable since layer VI is thicker and the large layer V pyramidal cells are more superficial in area 19 (Garey, 1971). There is considerable debate as to exactly how the suprasylvian visual cortex should be anatomically and functionally subdivided in the adult cat (e.g., Palmer et al., 1978; Sherk, 1986a; Updyke, 1986; Zumbroich et al., 1986), and cytoarchitectonic criteria do not appear to allow the identification of different subregions at any age. Fortunately, the middle suprasylvian sulcus is quite clearly formed in the kitten at the time of birth (Henderson and Blakemore, 1986), and the middle portion of the suprasylvian cortex can be subdivided into medial and lat-

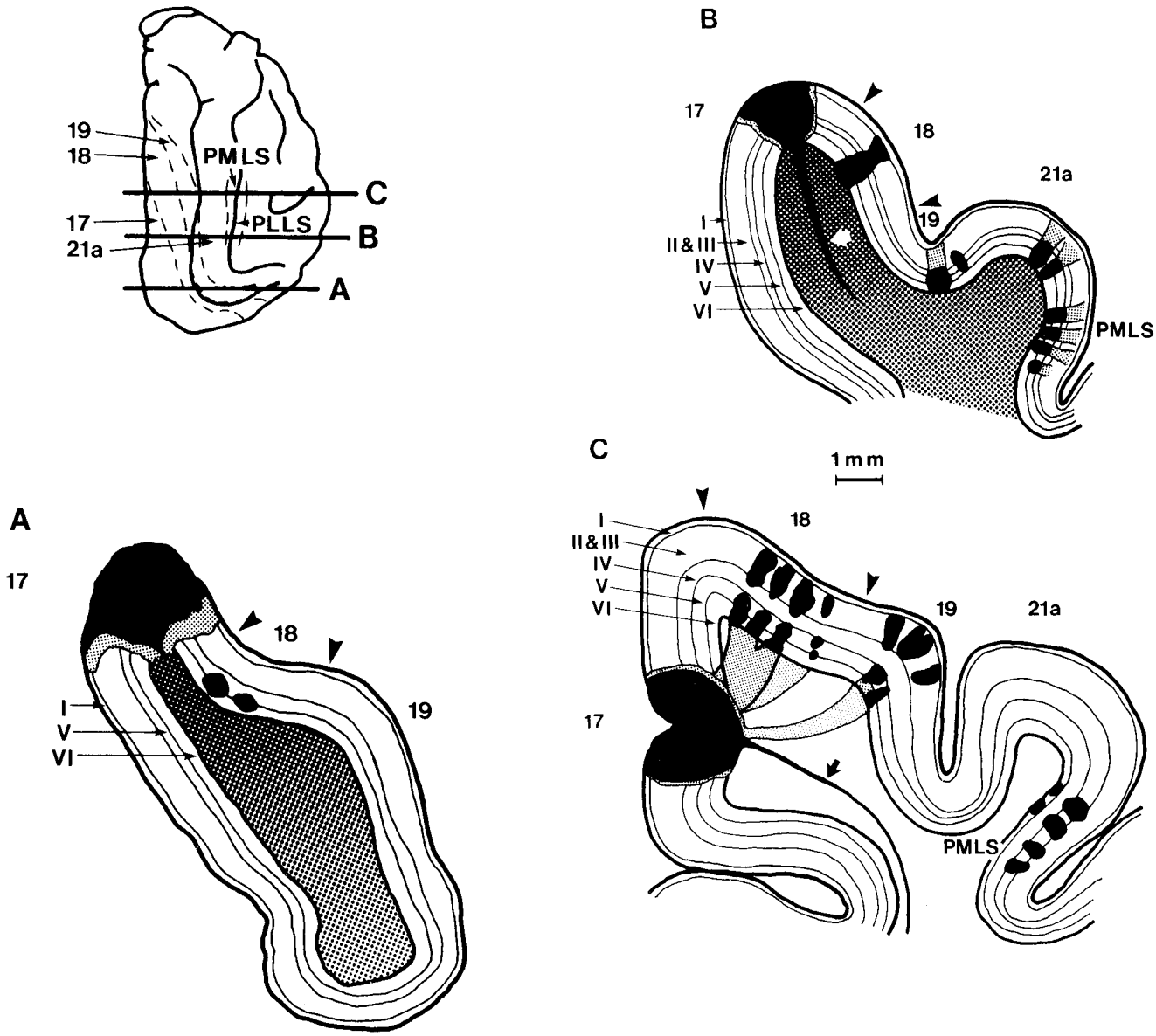


*Figure 3.* Summary of our main findings: camera lucida drawings of coronal sections through the right visual cortex of a 4-d-old kitten (*A*), a 12-d-old kitten (*B*), and an adult cat (*C*) are presented. The anteroposterior levels of the sections are indicated on the drawing representing the dorsal aspect of the right cerebral hemisphere of the cat (the locations of the cortical areas that we studied are shown). In the camera lucida drawings, the degree of shading is porportional to the density of label; the *filled areas* represent the injection sites in area 17, and in *B* and *C* labeled corticogeniculate axons could be seen (*arrows*). At 4 d, there was widespread anterograde labeling of white matter. In area 18, dense anterograde label was present in patches confined to layers V and VI, but only very sparse labeling was seen in other regions of visual cortex. At 12 d (*B*), extensive white matter labeling persisted, but by now all of the visual cortical areas lateral to area 17 contained dense, patchy label. In area 18, this label was distributed across layers II–VI, but in more lateral areas it was confined mainly to deep laminae. In adult cats (*C*), we found dense, patchy labeling of layers II, III, V, and VI in areas 18, 19, and 21a (label in 21a was seen only in sections further caudal to that drawn here and appeared similar to that in areas 18 and 19), and mainly in layer IV in the medial bank of the middle suprasylvian sulcus. Label in the white matter was confined to the fiber tracts leading from the injection site to the regions of cortical labeling. Throughout this developmental series, wherever there was dense labeling of the *gray* matter of extrastriate cortex, the location of this label was topographically related to the position of the injection site in area 17. Note that at 4 d only layers I, V, and VI are fully formed (Shatz and Luskin, 1986). *Arrowheads* indicate the areal boundaries.

eral banks at all ages, using the fundus of the suprasylvian sulcus as the boundary. It is likely that these 2 subdivisions largely correspond to the areas PMLS (posteromedial lateral suprasylvian cortex) and PLLS (posterolateral lateral suprasylvian cortex) of Palmer et al. (1978). In adult cats, visual area 21a lies between the lateral border of area 19 and the medial boundary of PMLS (Tusa and Palmer, 1980) and is distinguished by myeloarchitectonic criteria (Symonds and Rosenquist, 1984). Myelination is incomplete in very young kittens, and so it is not possible to use myelin staining for positively identifying area 21a in these animals, but it is likely that area 21a occupies the same relative position in kittens and adult cats.

## Labeling of cortex and white matter

The drawings in Figure 3 summarize our main findings. In general, we found that in kittens aged 20 d or less, but not in

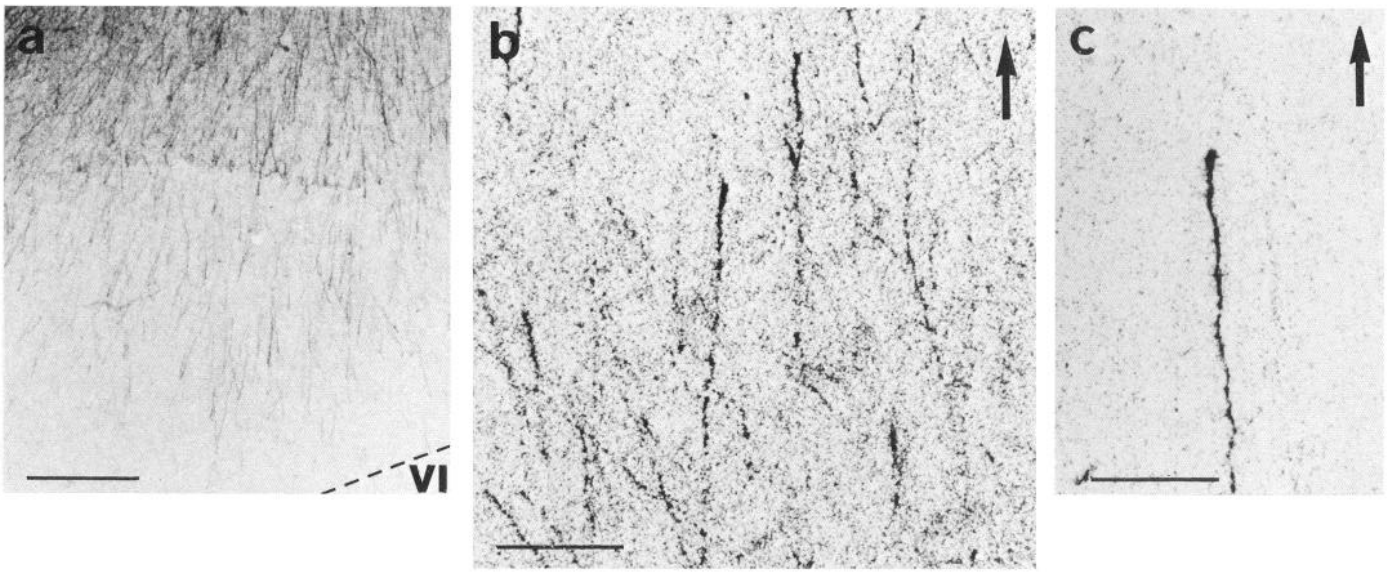


*Figure 4.* Bright-field photomicrographs of labeling of white matter in coronal sections from 4-d-old kittens. *a,* Labeling in white matter under area 17 at low-power magnification. The border of layer VI with the white matter is indicated. Scale bar, 200 μm. *b* and *c,* These sections, shown at higher magnification, contain labeled axons in the white matter under the cortex of the medial bank of the middle suprasylvian sulcus (*arrows* indicate the direction of the pial surface). Many of these axons end with a slightly enlarged, bulbous terminal. Similar axons were commonly seen under regions of area 17 outside the injection site, and beneath areas 18, 19, 21a and the medial bank of the middle suprasylvian sulcus in kittens aged between 4 and 12 d; however, they were not seen in animals older than 20 d. Scale bars, 100 μm.

older animals, a large proportion of the anterogradely transported label was widely distributed in the white matter underlying both striate and extrastriate cortex. In the youngest kittens, aged 4 and 8 d, the only cortical region containing patches of dense label was area 18; other areas were labeled only very sparsely. In older animals, other extrastriate cortical areas also became densely labeled. We observed marked developmental changes in the patterns of label in these areas of cortex.

*White matter labeling*

In kittens aged 4 to 20 d there was widespread, apparently indiscriminate, and continuous labeling of the white matter under the full mediolateral extent of areas 17, 18, 19, 21a, and the medial bank of the middle suprasylvian sulcus (Fig. 3). This label appeared mainly in fibers that fanned out from the point of injection through the white matter in all directions, with an even density and in a fairly well-ordered fashion (Fig. 4*a*). Many of these fibers did not appear to penetrate the overlying developing cortex in the regions towards which they seemed to project (Fig. 6, *b, c*). There was no evidence of tangential fluctuation in the density of label in the white matter under most cortical areas; however, we did observe a slightly increased density in some of the regions where the directly overlying *gray* matter contained dense patches of label specifically restricted to regions topographically related to the injection site (described below). In the rostrocaudal dimension, the diffuse labeling in the white matter extended several millimeters anterior and posterior to the coronal plane of the injection site but did not reach the rostral and caudal limits of each cytoarchitectonic area.

Examination of this white matter labeling in the young kittens, aged 4–20 d, under higher magnification revealed that much of it appeared to be located in axons that ended with slightly enlarged bulbous terminals. Examples of such profiles are shown in Figure 4, *b, c*. These terminal swellings had 2 general characteristics suggesting that they were not artifactual. First, they were very numerous in the youngest kittens (aged 4–12 d), were slightly less common at 20 d, and were never seen in the 10-week-old kitten and in adult cats, even though individual labeled axons could still be distinguished in the white matter at these later ages (Fig. 5*a*). Second, they were always found at the end of the portion of the axon contained in the section that was closest to the cortical gray matter and not at the other end (which presumably marked the point of severance of the axon at the cut face of the section).

In the 70-d-old kitten and adult cats, indiscriminate labeling of white matter was not seen, but we were able to follow bundles of labeled fibers traveling from the injection site through the white matter to *specific* targets in topographically related locations in the gray matter of extrastriate areas. In the 70-d-old kitten and adult cats we observed that not all of the axons *within* each bundle were arranged in a strictly parallel, well-ordered fashion (Fig. 5*a*). Individual fibers appeared to take a direct route towards their target, but they often crossed one another in an apparently random fashion as they approached the target zone, so that it looked as if they would terminate with some local disarray, even though the overall projection was arranged topographically (as suggested by Ferrer et al., 1988).

In adult cats and also in kittens of all ages we saw occasional profiles suggestive of the branching of axons running in the white matter (Fig. 5*b*). We observed such profiles only rarely, and there was no indication of an increased incidence at any age.

*Cortical labeling*

As shown in Figure 3, there was dense patchy labeling of the gray matter of area 18 in animals aged 4 d or more, whereas in other cortical areas anterograde labeling was *very sparse* at 4 and 8 d. In animals aged 12 d or more, areas 19, 21a, and the medial bank of the middle suprasylvian sulcus also contained dense patches of label.

*Topography of cortical labeling.* As can be seen in Figure 3,

the dense anterograde labeling in area 18 in kittens aged 4 d or more and in area 19 in animals aged 12 d or more was restricted to regions lying directly lateral to the injection site in area 17. Where the injection sites were centered approximately midway between the medial and lateral boundaries of area 17, the foci of labeling in areas 18 and 19 lay approximately midway between their medial and lateral boundaries. In cases in which the injection in area 17 was nearer the area 17/18 border, label lay correspondingly close to this border in area 18 and nearer to the lateral border of area 19. In kittens aged 12 d or more, injections into rostral area 17 labeled rostral regions of both area 21a and the medial bank of the middle suprasylvian sulcus (lying either directly lateral to or lateral and caudal to the injection site). Injections into caudal area 17 in kittens aged 12 d or more labeled caudal regions of area 21a and the medial bank of the middle suprasylvian sulcus (lying lateral and rostral to the injection site). These results are compatible with previous findings that the ipsilateral corticocortical projections in visual cortex are arranged topographically, even in very young kittens (Montero, 1981a; Price and Blakemore, 1985a).

*Clustering of cortical labeling.* As shown in Figures 3, 6*a*, 7, and 8, in animals at all ages at which there was dense cortical labeling in area 18 (from 4 d on) and areas 19, 21a and the medial bank of the middle suprasylvian sulcus (from 12 d on), this label was distributed in a series of clusters. Quantitative analysis confirmed that the density along the lamina in which the label was densest (see below) showed a clear periodic tangential variation (Fig. 9). The density of label in regions between these patches always remained slightly higher than the background. Comparison of *absolute* densities in different animals, even at the same age, was not possible because the overall density of label varied, probably mainly for technical reasons associated with the autoradiographic coating of sections.

*Radial distribution of cortical labeling.* As shown in Figure 11*a*, in area 18 of kittens aged 4 d the density of label was significantly higher than background in all layers except layer I and increased markedly with depth, rising to a peak in layers V and VI (see also Fig. 6*a*); the density of label was also significantly above background in underlying white matter. In area 18 of kittens aged 8–20 d the density of labeling remained above background in all cortical layers and also in the directly underlying white matter, but was greatest in layers V and VI and immediately below layer I (Figs. 7*a*, 11*a*). In these 8- to 20-d-old animals the relatively dense label just below layer I was viewed under higher magnification (Fig. 10), and it appeared as if the tracer was filling a series of highly branched, but quite restricted, terminal arborizations clustered along the lower border of layer I. This pattern was not seen in the 10-week-old kitten nor in adult cats.

In kittens aged 12–20 d the radial distribution of label in area 19 was similar in most respects to that in area 18 of *younger* kittens, aged 4 d. The density of label was greatest in deeper layers, peaked in layer VI, and was above background in more superficial layers and in white matter (Figs. 7*b*, 11*d*); the density of label in layer II was slightly increased above that in layers I and III (Fig. 11*d*), and higher magnification revealed a pattern of axonal branching similar to that seen immediately below layer I of area 18 in kittens aged 8–20 d (Fig. 10). The distribution of label in area 21a in kittens aged 12–20 d was essentially the same as that in area 19 of animals of the same age (Fig. 7*c*).

In the medial bank of the middle suprasylvian sulcus of kittens aged 12 and 20 d the density of label was above background in all layers below layer I and also in the white matter directly beneath, but it peaked in layers V and VI (Figs. 7*d*, 11*f*).

In areas 18, 19, and 21a of adult cats and a 10-week-old kitten, most of the label was in layers II and III, with an intermediate level in layers V and VI, distributed in patches aligned with the denser patches in the superficial layers. The density of label was

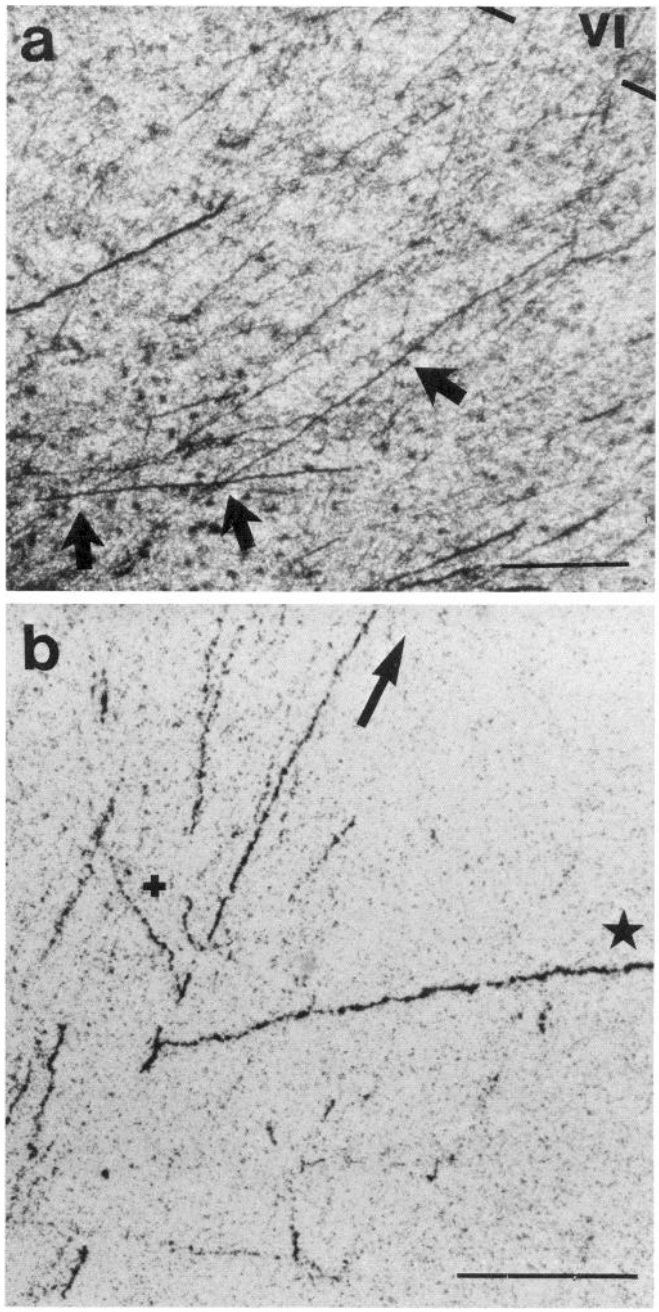


*Figure 5.* High-power bright-field photomicrographs. *a*, Labeled axons entering area 19 from the white matter in an adult cat; the border between layer VI and white matter is indicated. The figure illustrates our finding that many axons cross within a bundle of corticocortical fibers (example indicated by *arrows*). *b*, An axon traveling through the white matter in a 12-d-old kitten appears to give off 2 branches, one of which (★) travels into area 19, while the other (+) goes deeper into the white matter. The "main" axon (*arrow*) continues further laterally beyond area 19, although its eventual destination could not be discerned. Such profiles were relatively rare but could be found at all ages. Scale bars, 100 μm.

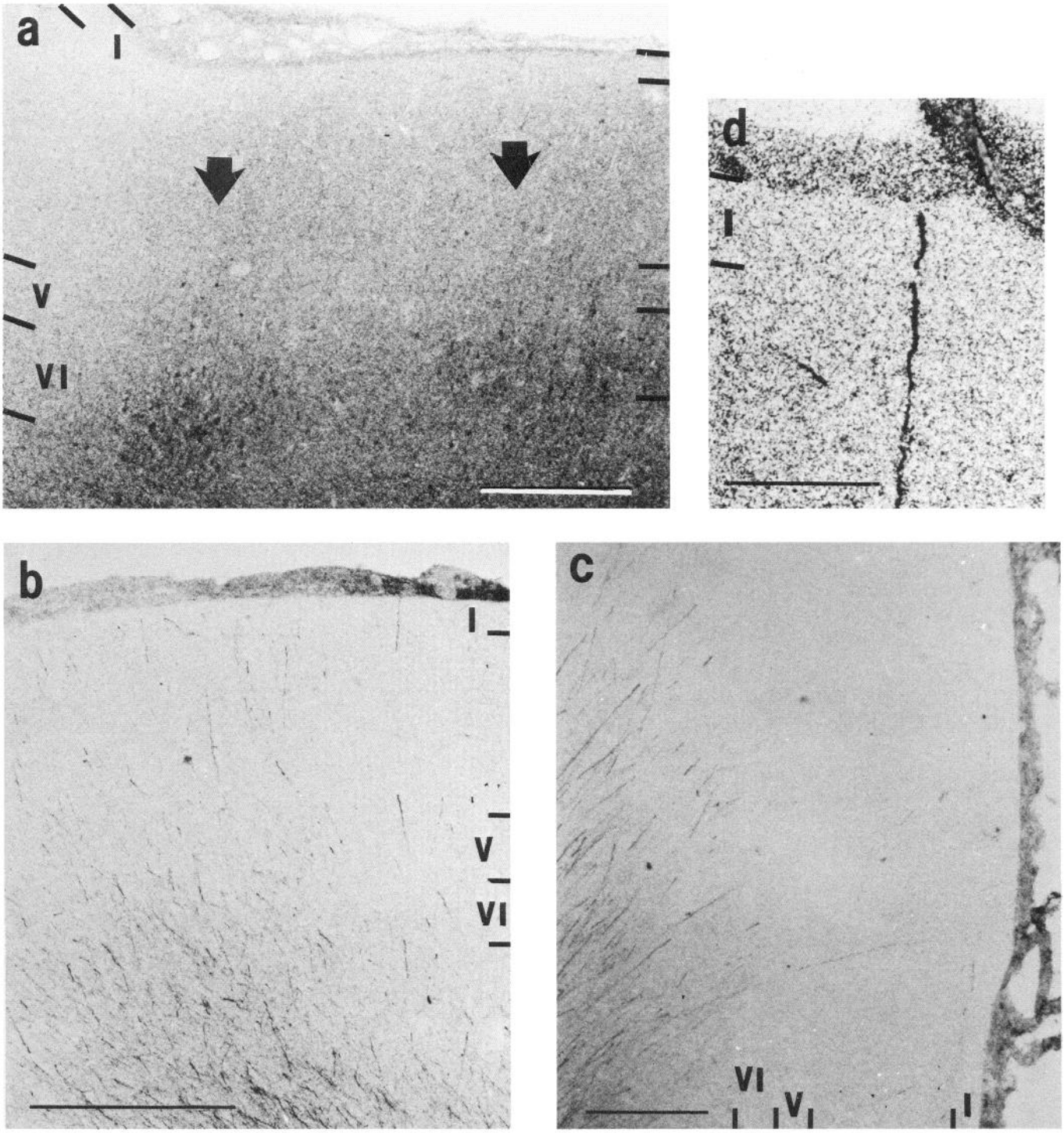


*Figure 6.* Bright-field photomicrographs of coronal sections from 4-d-old kittens. *a,* Two patches of label in area 18 (*arrows*) that were densest in infragranular layers. *b,* In a section through area 19, label is sparsely distributed in radial fibers in the gray matter but is denser in the underlying white matter. *c,* Label is very sparsely distributed in occasional individual radial axons in the gray matter of the medial bank of the middle suprasylvian sulcus but is denser in the underlying white matter. Scale bars in *a–c,* 500 μm. *d,* At higher magnification, a solitary labeled axon in area 19 can be seen running radially to the pial surface. The dense labeling above the pial surface is an artifact created by direct spread of tracer from the injection site over the surface of the brain. Scale bar, 100 μm. Note that at 4 d, layers II–IV are not yet fully formed (Shatz and Luskin, 1986).

relatively low, but was significantly higher than background, in other cortical laminae and the white matter immediately underneath the regions of gray matter labeling. An example of labeling of area 19 in an adult cat is shown in Figure 8*a*. Graphs of quantitative radial analysis are shown for areas 18 and 19 in Figure 11, *c, e.*

In the medial bank of the middle suprasylvian sulcus of adult cats and the 10-week-old kitten distinct patchy labeling was

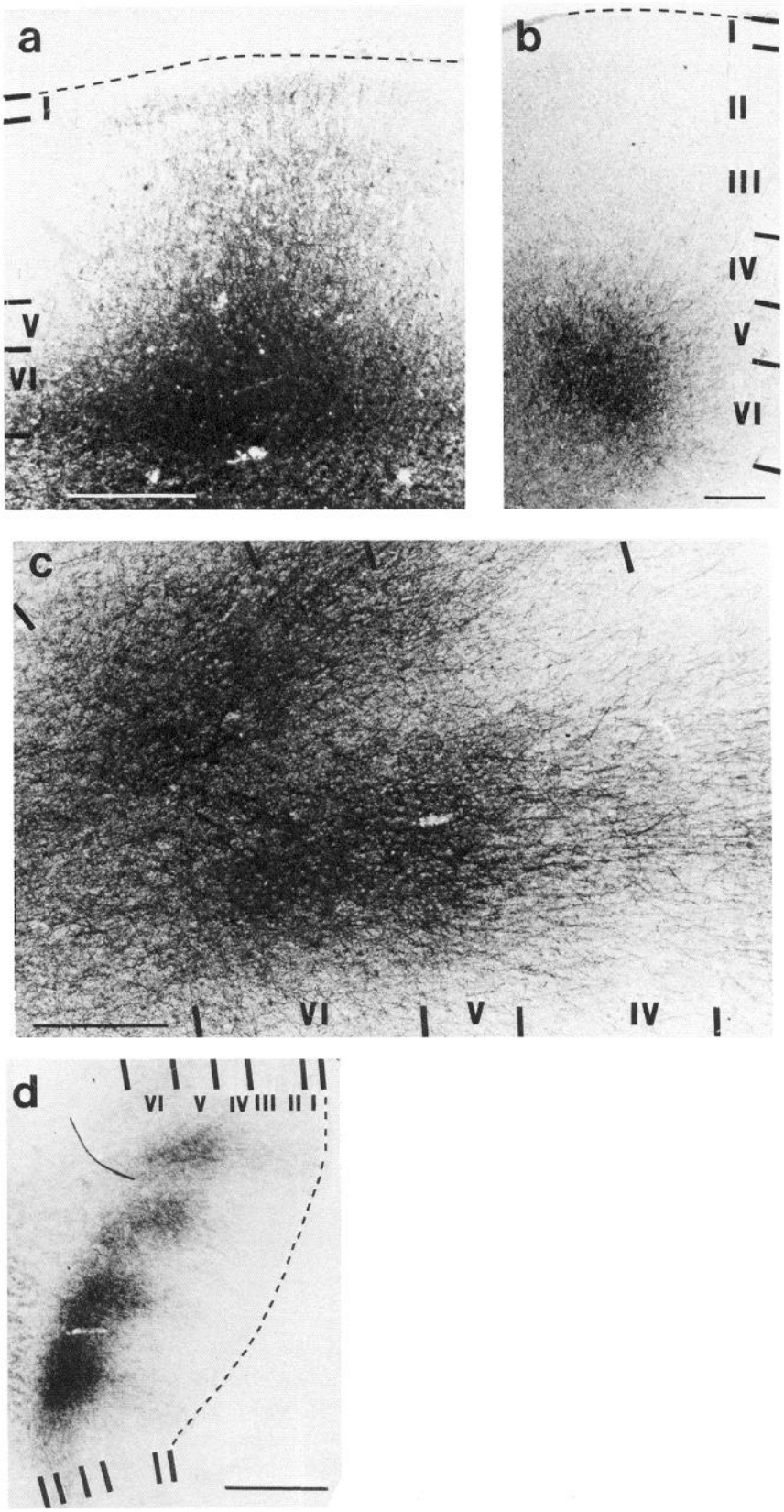


*Figure 7.* Bright-field photomicrographs of coronal sections from 8- to 12-d-old kittens. *a,* In area 18 of a kitten aged 8 d, a patch of label covers all laminae but is densest in deeper layers. There is also an increase in density immediately below layer I. Scale bar, 500 μm. In area 19 (*b*) and area 21a (*c*) of a kitten aged 12 d, label is densest in the deep cortical layers (V and VI) and is seen in a single distinct patch in area 19 and in 2 patches in area 21a. Scale bars, 200 μm. *d,* In the medial bank of the right suprasylvian sulcus of a 12-d-old kitten, label lies in a series of patches mainly in layers V and VI but also to a lesser degree in more superficial laminae. Scale bar, 1 mm.

centered on layer IV (Figs. 8*b,* 11*g*). In some sections there appeared to be a slightly elevated density in lower layer VI. However, this was variable and was not evident in the averaged data from several radial strips (see Fig. 11*g,* which shows only a gradual decrease in density both above and below layer IV, falling to insignificant levels in layer I).

*Sparse cortical labeling in 4- and 8-d-old kittens.* In kittens aged 4 and 8 d we found *very sparse* label in areas 17 (outside

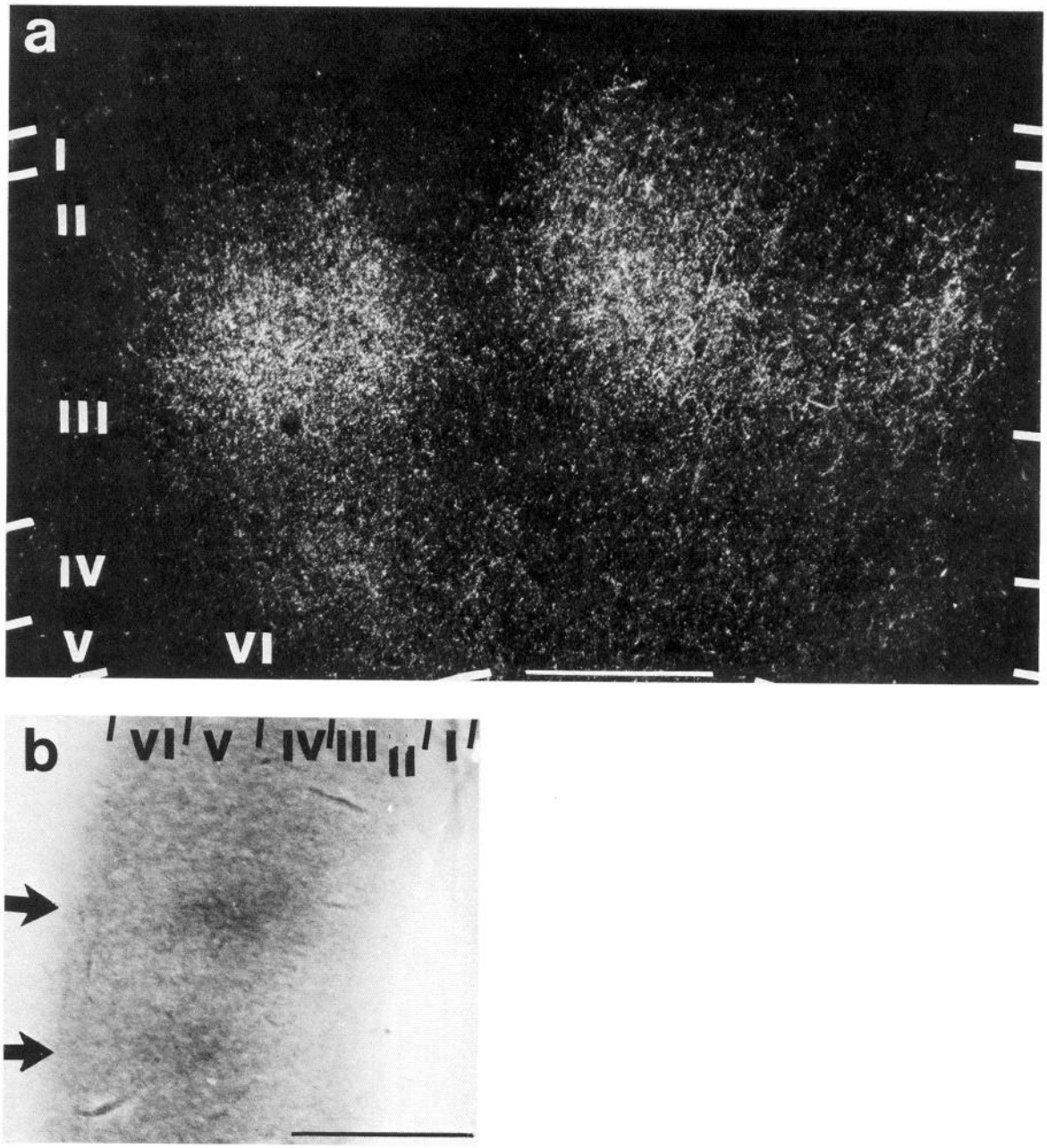


*Figure 8.* Labeling of extrastriate cortex in adult cats. *a,* Dark-field photomicrograph of a coronal section through area 19 of an adult cat showing label in 3 patches mainly in supragranular layers; a slightly increased density of label is seen in infragranular laminae. Scale bar, 500 μm. *b,* Bright-field photomicrograph of a coronal section through the medial bank of the suprasylvian sulcus showing label in 3 patches (*large arrows*), centered over layer IV. Scale bar, 1 mm.

the injection site), 19, 21a and the medial bank of the middle suprasylvian sulcus (Fig. 6, *b, c*); there was heavier labeling in the underlying white matter (described above). At higher magnification this label in the gray matter appeared to be localized within solitary axons that often ran directly all the way to the pial surface, roughly parallel to the cortical palisades of cell bodies and without evidence of branching, to terminate with slightly enlarged, bulbous endings (Fig. 6*d*). These fibers were distributed over the entire mediolateral extent of areas 17 (outside the injection site), 19, 21a and the medial bank of the middle suprasylvian sulcus (even though no injection site occupied more than about 50% of the mediolateral width of area 17) and were seen up to several millimeters rostral and caudal to the anteroposterior plane in which the injection was made. They were neither denser at, nor restricted to, sites topographically related to the position of the injection site in area 17. Such solitary fibers could not be identified after the major ingrowth of corticocortical fibers to a cortical area had occurred.

*Other cortical regions.* In no animal did we find labeling of the lateral bank of the suprasylvian sulcus, nor did we observe label in yet more lateral cortical areas, including nonvisual regions. These results are difficult to interpret since we never used

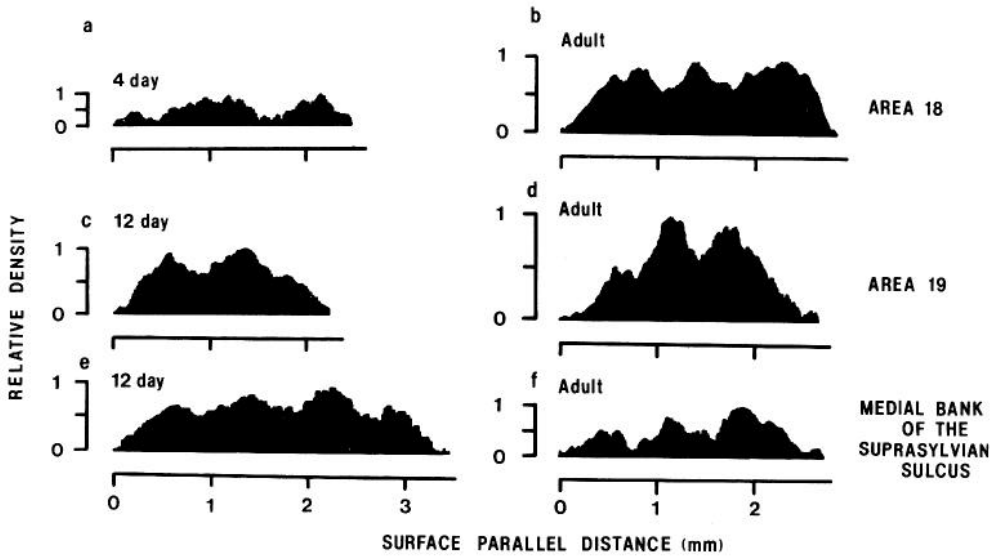


*Figure 9.* Graphs showing the results of *tangential* analysis in various extrastriate areas at different ages (method illustrated in Fig. 1). *Normalized relative density* is plotted, from 0 (indicating that the value is equal to the mean background density +2 SD) up to 1.0 (the greatest density found along the strip). Data in *a* and *b* are for area 18, in *c* and *d* for area 19, and in *e* and *f* for the medial bank of the middle suprasylvian sulcus. Data in *a, c,* and *e* are from kittens 4, 12, and 12 d old, respectively, and all measurements are in layer VI; *b, d,* and *f* show results from adult cats, from lamina III for areas 18 (*b*) and 19 (*d*) and lamina IV for the medial bank of the middle suprasylvian sulcus (*f*). In all cases there is evidence of a patchy distribution of label even in kittens in which corticocortical fibers have just penetrated the gray matter. The density remains above background between peaks.

survival times longer than 24 hr, which might conceivably have allowed label to reach more lateral areas of cortex. However, previous studies have shown that the lateral bank of the suprasylvian sulcus receives only a very weak projection from area 17 in adult cats (Grant et al., 1984; Symonds and Rosenquist, 1984).

## Discussion

We have used the anterogradely transported tracer, tritiated proline, to examine the postnatal development of the terminal distributions of corticocortical efferents from area 17 in the cat's visual cortex. In the youngest kittens we studied, aged 4 and 8

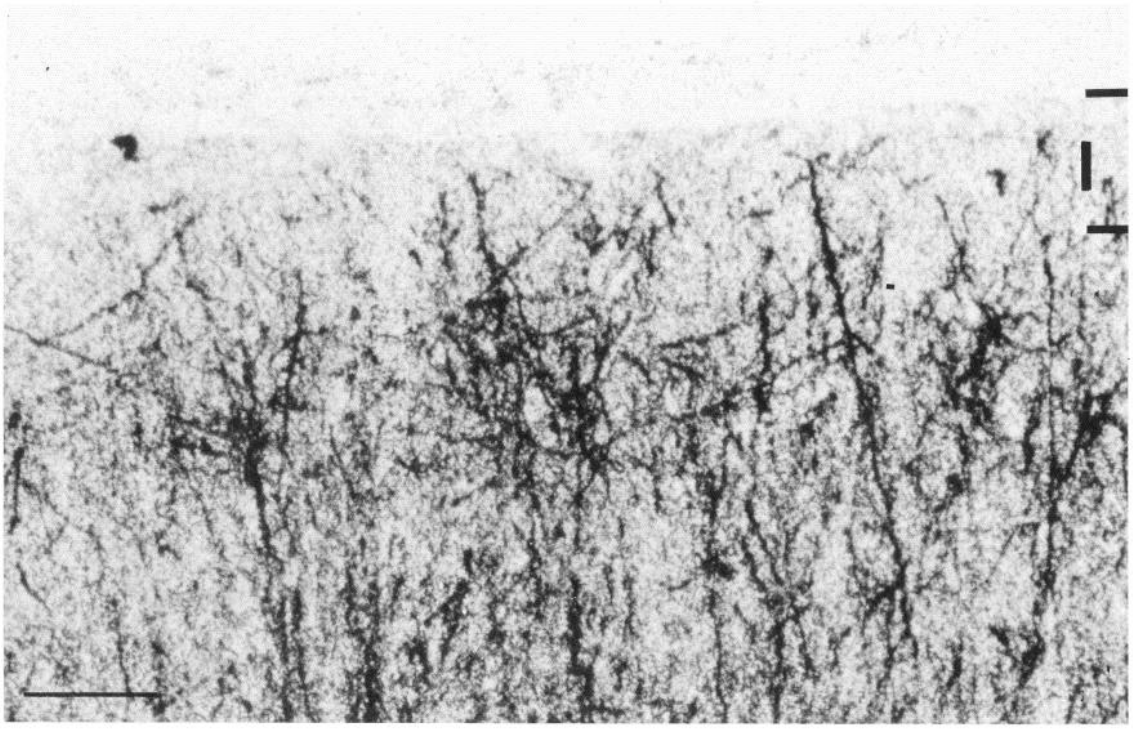

*Figure 10.* High-power bright-field photomicrograph of labeling immediately below layer I in area 18 in an 8-d-old kitten (seen at lower magnification in Fig. 7*a*). Scale bar, 100 $\mu$m.

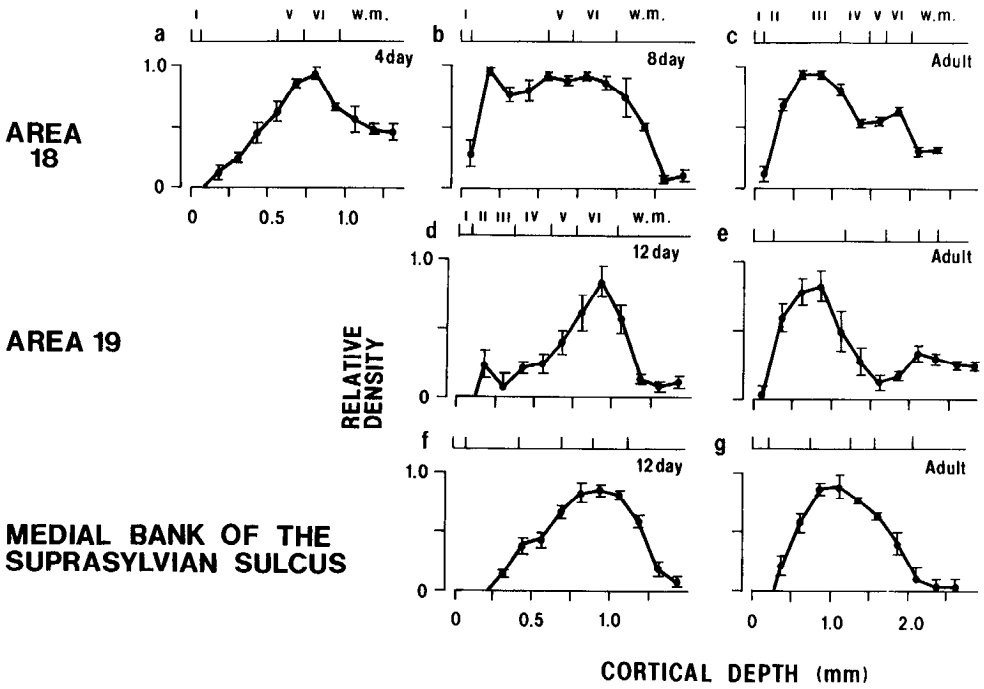


*Figure 11.* Quantitative data were obtained as illustrated in Figure 1 to generate these graphs, which show results from a *radial analysis* of the density of label through clusters of anterograde label in area 18 (*a–c*), area 19 (*d, e*), and the medial bank of the middle suprasylvian sulcus (*f, g*). Data are from kittens aged 4 d (*a*), 8 d (*b*), and 12 d (*d, f*) and from adult cats (*c, e, g*). In each graph, mean density values at a series of depths (±SEM) are expressed on a scale of relative density from 0 (a value equal to the mean background density +2 SEM) to 1.0 (highest *single* density measurement along any line used to generate that graph). Cortical laminae are indicated above each diagram (*w.m.*, white matter); note that the exact depths of the laminar boundaries vary slightly among graphs. In the youngest animals, the density of label is highest in deep layers; in adult cats, the density of label is highest in layers II and III for areas 18 and 19 and in layer IV for the medial bank of the middle suprasylvian sulcus. The *bulk* of corticocortical fibers first penetrate deep layers of area 18 earlier than they enter more lateral extrastriate areas. Note that label is always above background in the white matter, where tracer is in axons traveling towards their targets.

d, the only extrastriate region that contained *dense* label in the cortical plate itself was area 18; labeling in the gray matter of other cortical areas, while widespread at 4–8 d, was *very sparse* until 12 d and was mainly in unusual solitary radial axons terminating in expanded knobs in layer I. In animals aged 12 d or more, *dense* label was present in specific regions in all the extrastriate areas studied.

Our results suggest the following developmental sequence of events for all the pathways we examined in this study.

1. During development, axons from immature neurons in area 17 grow out through the white matter, extending underneath a wide area of the adjacent striate and extrastriate cortex. Much of this initial widespread axonal outgrowth may occur prenatally. These fibers will form persistent connections with only some of the regions that they travel towards. Whether or not these immature axons can penetrate the overlying cortex and eventually form persistent connections may depend largely on local interactions once growth cones have reached the border of cortical layer VI and the white matter.

2. As the kitten matures, at topographically appropriate points in each of a number of extrastriate cortical areas, corticocortical axons penetrate the gray matter in a specific fashion, entering in clustered bundles to terminate mainly in patches, located at early stages in deep cortical layers. The very sparse radial axons running up to layer I, seen in 4- and 8-d-old kittens prior to the major ingrowth of axons to extrastriate areas, may be a separate population (see below).

3. During the second and third postnatal weeks, association fibers continue to grow up through the cortical laminae, still maintaining a patchy tangential distribution, and increasing numbers of axons terminate in more superficial layers. At the same time, the diffuse population of axons that terminate subcortically and are unable to penetrate the overlying gray matter gradually disappears from the white matter, probably either because the axons are withdrawn or because the cell bodies of origin die. It is conceivable that immature fibers terminating in the white matter in young kittens are not lost but are rerouted to innervate an appropriate target.

4. By the third postnatal month the adult distribution of terminals is established within the cortex.

It is well recognized that, during the development of many pathways of the CNS, the terminal distributions of connections are initially diffuse and later narrow (e.g., Rakic, 1976; LeVay et al., 1978). Our general account of the maturation of terminals of ipsilateral corticocortical efferents from area 17 is in good agreement with previous studies of other ipsi- and contralateral corticocortical pathways in the cat. Transient projections from the auditory cortex to ipsilateral areas 17 and 18, and from area 17 through the corpus callosum to contralateral areas 17 and 18, terminate mainly around the layer VI/white matter border, and most do not enter the cortex before being eliminated (Innocenti, 1981; Innocenti and Clarke, 1984b; Clarke and Innocenti, 1986). The early exuberant callosal projections extend under a region of contralateral cortex that is wider than the zone that is eventually persistently innervated (Innocenti, 1981; Innocenti and Clarke, 1984b). Similarly, in the rat's visual cortex,

callosal axons terminate in the white matter under a wide region of the contralateral cortex in the immediate postnatal period and later invade overlying gray matter only in discrete regions destined to receive dense callosal input in the adult (Olivarria and Van Sluyters, 1985). In the monkey, much of the development of callosal projections in the visual cortex occurs prenatally and may involve processes similar to those described in the cat (Dehay et al., 1986, 1988). Early in gestation there is a widespread distribution of callosal projection neurons that later narrows to produce an adult-like pattern by the time of birth (Dehay et al., 1988). Although the terminal distribution of the initial exuberant callosal projection and its prenatal development in the monkey have yet to be described, it seems quite possible that many of the immature callosal axons may be distributed throughout a wide region of white matter but a smaller region of the contralateral gray matter, where they may be restricted to zones that will be innervated in the adult.

In the kitten, many of the transient projections from the auditory cortex to the white matter below ipsilateral areas 17 and 18 have bulbous endings somewhat like those that we saw on projections from area 17 to the white matter (Clarke and Innocenti, 1986). These bulbous swellings may well be growth cones, but it is also possible that they are synapses on subplate neurons. Early in the development not only of kittens but also of monkeys and humans, subplate neurons are numerous below the cortical plate, but their numbers later decrease during postnatal life (Rakic, 1977; Kostovic and Rakic, 1980; Chun et al., 1987; Wahle and Meyer, 1987). Subplate neurons are known to receive synapses, although the source of these inputs is as yet unclear (Rakic, 1977; Kostovic and Rakic, 1980; Chun et al., 1987).

In our study we were unable to demonstrate a major projection from area 17 to layer I of the medial bank of the middle suprasylvian sulcus during the first 3 postnatal weeks. Such a projection has been described by Kato et al. (1986). This may reflect technical differences: Kato et al. (1986) used HRP as their tracer, and since this substance is transported both anterogradely and retrogradely, it is often difficult to distinguish between retrograde label in the dendritic trees of neurons and genuine anterograde label. Another possible explanation is that Kato et al. (1986) injected tracer into area 18 as well as area 17.

As described in Results, some of our injection sites contaminated the white matter below area 17 to a limited extent. In cases of white matter involvement in the younger kittens, it is possible that tracer was taken up by cell bodies in the subplate below area 17 as well as by cells in the cortex itself. Such cells could have been transient subplate neurons, which are known to have long-range axons (Chun et al., 1987; Wahle and Meyer, 1987), and/or corticocortical neurons still migrating to layers II and III in area 17 that have not yet reached the cortex (Shatz and Luskin, 1986). The patterns of anterograde labeling we obtained in young kittens of similar age appeared similar irrespective of whether or not the injection sites contaminated white matter below area 17; involvement of the subplate was not a requirement for production of any of the patterns of labeling we observed in kittens. The axons of cells in the subplate may have been undetectable in our study because they were much less numerous than the axons of cells in the overlying cortical area 17 and/or the cells in the subplate may have projection patterns that overlap and are indistinguishable from those of neurones in the overlying gray matter of area 17.

Our data demonstrate that the association pathway from area 17 to area 18 matures ahead of the major projection from area 17 to more lateral extrastriate visual areas. Recent studies have shown that, during the first postnatal month, the development of the visual responsiveness and receptive field properties of neurons follows a similar time course in both striate and extrastriate visual cortical areas in the cat (Blakemore and Price, 1987; Price et al., 1988). It appears that the major functional properties of the various visual cortical areas mature largely in parallel, despite a hierarchical succession of development among the association pathways from area 17 to extrastriate areas.

Our description of the development of association connections supports the hypothesis that growing corticocortical axons do not possess *detailed* instructions on how to reach *specific* targets but are capable of forming permanent connections on the basis of local interactions at their terminals once they reach the matching part of another cortical region (or the white matter below it). This hypothesis is attractive because it implies that the amount of genetic information required for the specification of these pathways might be relatively small. It is parsimonious to suggest that the axons that actually invade the topographically appropriate regions of the cortical plate are simply a subset of the mass of early subcortical fibers, which are "validated" in some way by interaction with their targets. However, there remains the possibility that there are 2 quite distinct populations of association axons in young kittens; one that is specifically directed to its correct target and the other a numerous population of subcortical fibers whose function is obscure and which are ultimately eliminated.

It is interesting to speculate on the role played by the solitary axons that run to the pial surface of the cortex in areas 17, 19, 21a and the medial bank of the lateral suprasylvian sulcus at ages before the *major* invasion of gray matter by axons in the white matter occurs. It is possible that these axons are involved in detecting whether a particular cortical zone is appropriate for subsequent invasion by large numbers of fibers from a particular point in area 17.

Previous work using retrograde tracers injected into area 18 has demonstrated that both axonal elimination and cell death play important parts in the maturation of the laminar pattern and the appearance of a clustered distribution of association cells in area 17 projecting to area 18 in kittens (Price and Blakemore, 1985a, b). The question arises of whether the initial "inappropriate" area 17 to 18 projections that were shown by Price and Blakemore (1985a, b) to be eliminated early in postnatal development are the very fibers that we observed projecting to the white matter immediately below area 18 in this present study. This seems unlikely since the transient projections studied by Price and Blakemore (1985a) were highly topographic in their organization, even in newborn kittens, whereas the diffuse, transient white-matter projection described here was very broadly distributed and lacked topographic organization. Therefore, we favor the hypothesis that the selective invasion of the cortical plate by axons from the white matter establishes the overall topography in ipsilateral association pathways and that *subsequent* elimination of some of these invading axons generates clustering of the cells of origin of the connections.

The fact that periodic tangential clustering is so common among both the terminals and the cells of origin of many association pathways in the cat's visual cortex (Gilbert and Kelly, 1975; Montero, 1981a; Symonds and Rosenquist, 1984; Price and Blakemore, 1985a, b; Ferrer et al., 1988) suggests that it represents an important aspect of cortical organization in this

species, as it clearly does in others (e.g., Livingstone and Hubel, 1984). As yet, the functional significance of this clustering in the cat is unknown.

It has generally been thought that association projections in many mammalian species not only originate but also terminate mainly in supragranular cortical layers (Montero, 1981b), and our results confirm this for the pathways from area 17 to areas 18, 19, and 21a in adult cats. The majority of projections from area 17 to areas 18, 19, and 21a appear to avoid layer IV (the main recipient zone for thalamocortical inputs) in adult cats. The radial distribution of the terminals of corticocortical projections from area 17 to the medial bank of the middle suprasylvian sulcus in adult cats appears to be somewhat different. Our results are in agreement with those of others (Sugiyama, 1979; Montero, 1981b; Symonds and Rosenquist, 1984; Kato et al., 1986; Sherk, 1986a) and show that the majority of these fibers end in a series of patches centered on layer IV itself, but extending into layers III and V. This difference between the medial bank of the middle suprasylvian sulcus and other extrastriate areas might reflect the presence of a more direct intralaminar interaction between overlapping visual cortical and thalamic inputs in the medial bank of the suprasylvian cortex, as is suggested by recent studies (Sherk, 1986b).

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