

Postnatal development of the occipito-tectal pathway in the rat

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ABSTRACT. The postnatal development of the occipito-tectal pathway was studied by making single injections of ^3H -leucine into the striate cortex of rats ranging in age from newborn to postnatal day 50 (P50). After these injections, the earliest age at which autoradiographic labeling was found in the ipsilateral superior colliculus (SC) was P4. Two main stages were recognized in the development of the occipito-tectal pathway. In the first stage, from P4 to P9, the silver grain pattern over the SC was suggestive of axonal labeling. The label was tangentially and radially exuberant involving the prospective *stratum opticum*, the adjacent part of the *stratum griseum superficiale* and also the *strata intermediale*. A rough topographic order in the projection existed at least from P6. The second stage, from P9 to P17, was characterized by the ingrowth of axonal arbors into the collicular *strata superficiale* and by the disappearance of the tangentially exuberant projections. Quantitative estimations of the degree of tangential exuberancy of the projection showed that it underwent a reduction of almost 50% from P7 to P17. By P17, the radial and tangential patterns of termination of the occipito-tectal pathway appeared virtually mature. No projections to the contralateral SC were observed at any age. The results of the present study indicate that the mature topographic pattern of the occipito-tectal projection is attained through two separate steps which may involve a number of different mechanisms. In the first step, occipital axons grow orderly -although in an exuberant manner- towards their roughly appropriate tectal locations, remaining to a large extent confined to the collicular white matter. In the second step, further refinement of the topographic map is achieved both by selective growing of terminal arbors into tangentially restricted regions of the tectal surface, and, by retraction of tangentially exuberant projections.

KEY WORDS: *postnatal development, visual pathways, occipito-tectal, autoradiography, rat.*

Introduction

A striking feature of the nervous system is the high degree of precision with which its components are interconnected. In the sensory systems, the connections preserve the topography of incoming stimuli by forming maps of the external world within the central nervous system. Several sensory systems have been studied in an attempt to explain the nature of the mechanisms controlling the formation of orderly nerve patterns. So far, the most used has been the retino-tectal system of non mammalian vertebrates in which a lot of work has been done both during initial development in the embryo and during regeneration after optic nerve section in the adult (Sperry, 1963; Cowan, 1971; Gaze, 1974; Hunt and Jaccbsen, 1974). The mammalian system does, however, have the advantage that the upper layers of the superior colliculus (SC) also receive a projection from the layer V of the visual cortex (Lund, 1966), which is visuotopically organized and in register with the projection from the retina. Thus, the study of the occipito-tectal system is of interest because it is a pathway of cerebral origin rather than one arising from primary afferents, and it can be compared with the retino-tectal system from which most rules about development of topo-

graphic maps in the central nervous system have been inferred.

Previous studies on the developing cortico-tectal pathway with horseradish peroxidase (HRP) in the rat, have shown that the projection goes through a stage of exuberancy followed by gradual pruning to the more restricted mature pattern, this pruning involving a restriction in both the areal distribution of cortico-tectal neurons within the cortex (Thong and Dreher, 1986) and the distribution of their axonal terminals (Thong and Dreher, 1987).

However, the precise timing of the areal pruning of the terminal field in relation to its radial development is not known. In addition, it is unclear whether the occipito-tectal axons grow directly towards their visuotopically appropriate tectal regions or whether the topographic order is brought about by the selective pruning of an early diffuse projection.

In the present study, we sought to describe and analyze in detail the developmental sequence and timing of the tangential and radial patterns of the occipito-tectal terminal field. Precise knowledge of the form and timing of the

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POSTNATAL DAY 4

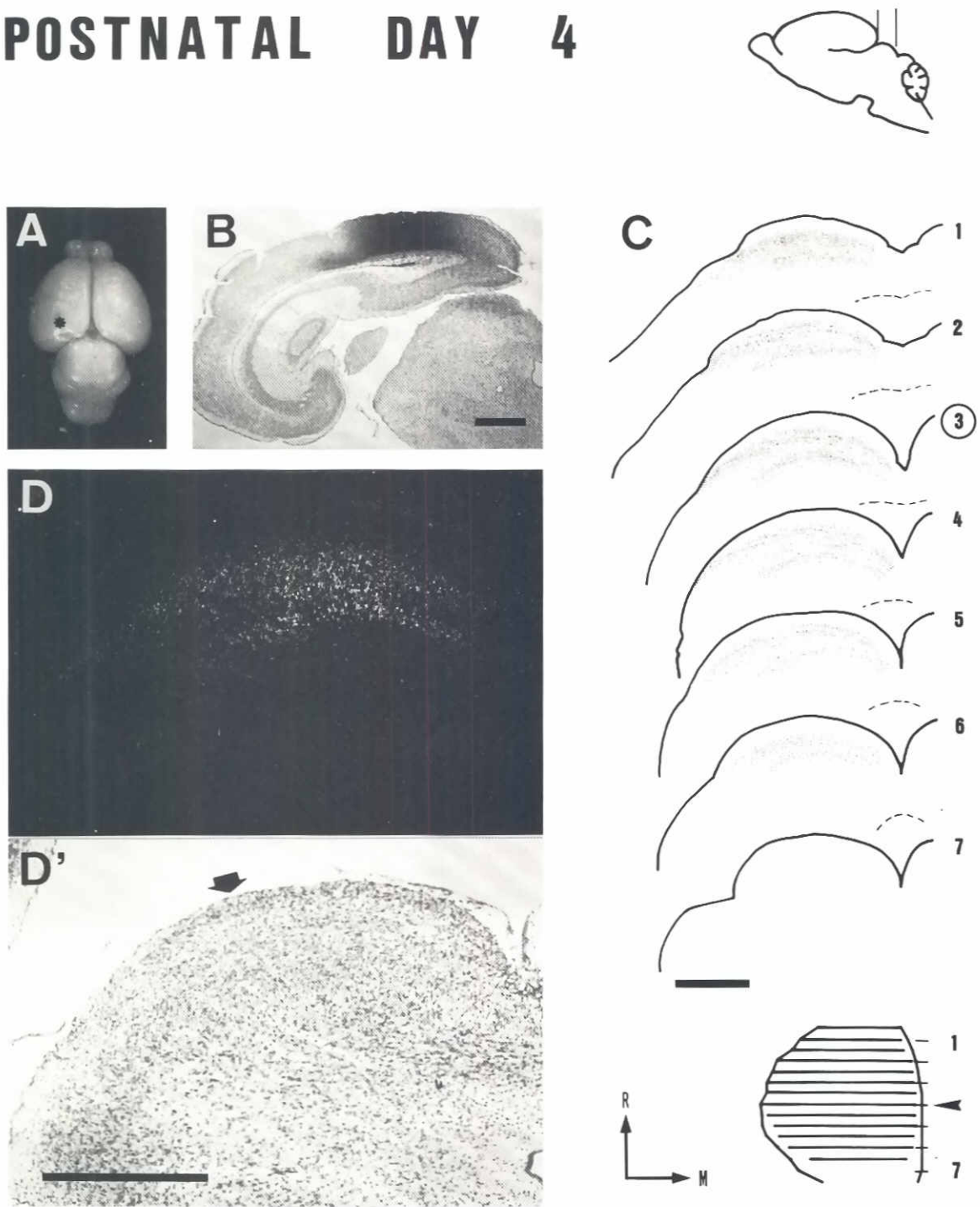


Fig 1-4. Autoradiographic tracing of the occipito-tectal projection in a rat injected with ^3H -leucine into the striate cortex on postnatal day 3 and sacrificed on postnatal day 4. **A.** Photograph of a dorsal view of the brain injected showing the location of the injection. **B.** Bright field photomicrograph of a coronal section through the site of injection. **C.** Camera lucida drawings of representative series of sections through the ipsilateral SC showing the distribution of anterograde labeling from the injection site shown in B. Numbers indicate rostrocaudal levels of the sections and the encircled number indicates the section from which photomicrographs shown in D were taken. At the bottom, tangential view reconstruction of the labeling in each section. The section used for establishing the degree of tangential exuberancy is pointed by an arrowhead. **D.** Dark- and bright field photomicrographs of the same coronal section through the SC showing the pattern of anterograde labeling from the injection site shown in b. Large arrows mark the point at which grain counting shown in Fig. 5 was made in a traverse across the SC. All scale bars = 0.5 mm.

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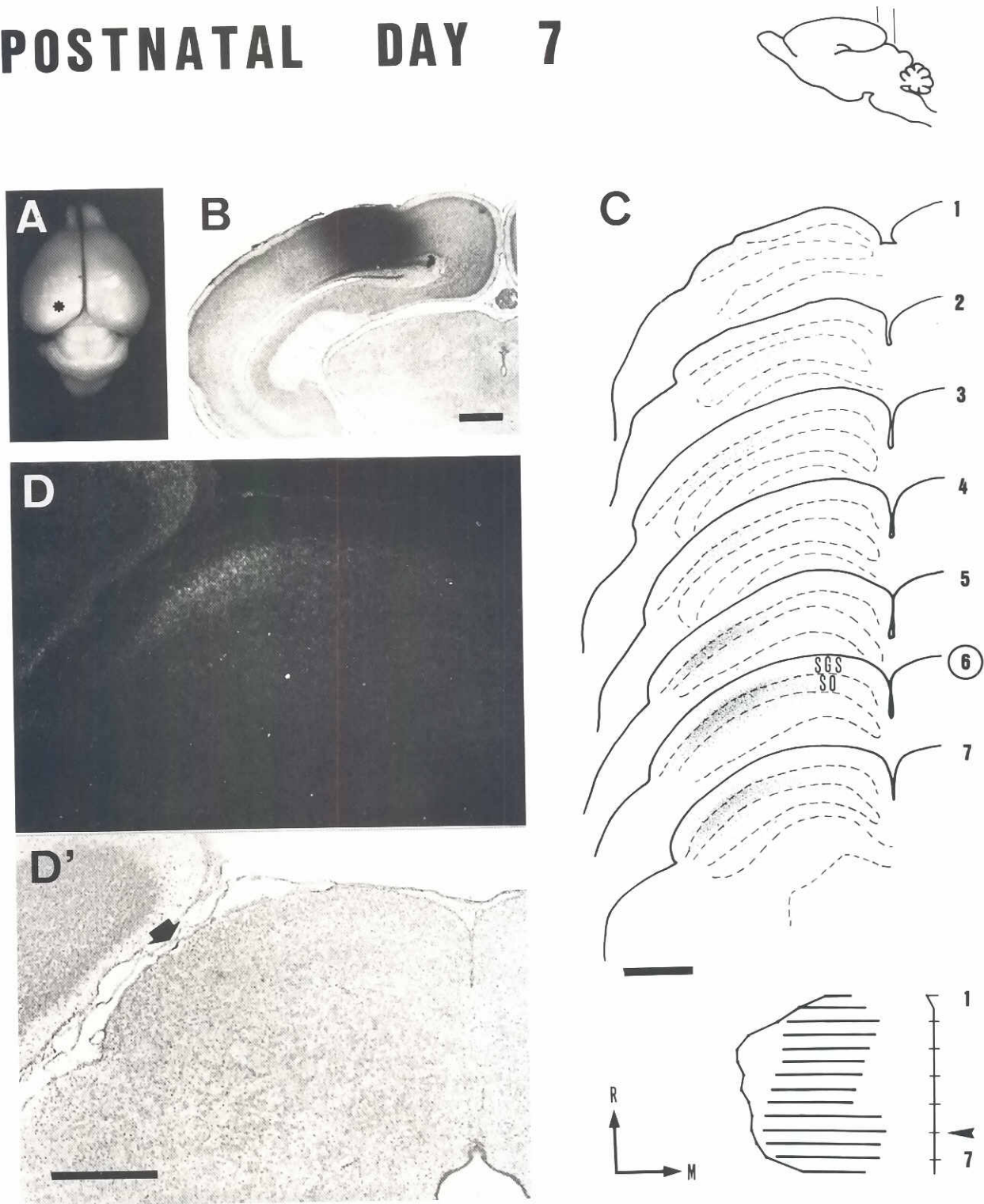


Fig 2. Autoradiographic tracing of the occipito-tectal projection in a rat injected with ^3H -leucine into the striate cortex on postnatal day 6 and sacrificed on postnatal day 7. The organization and conventions of this figure are as those described in Fig 1. SGS, stratum griseum superficiale; SO, stratum opticum. Scale bars = 0.5 mm.

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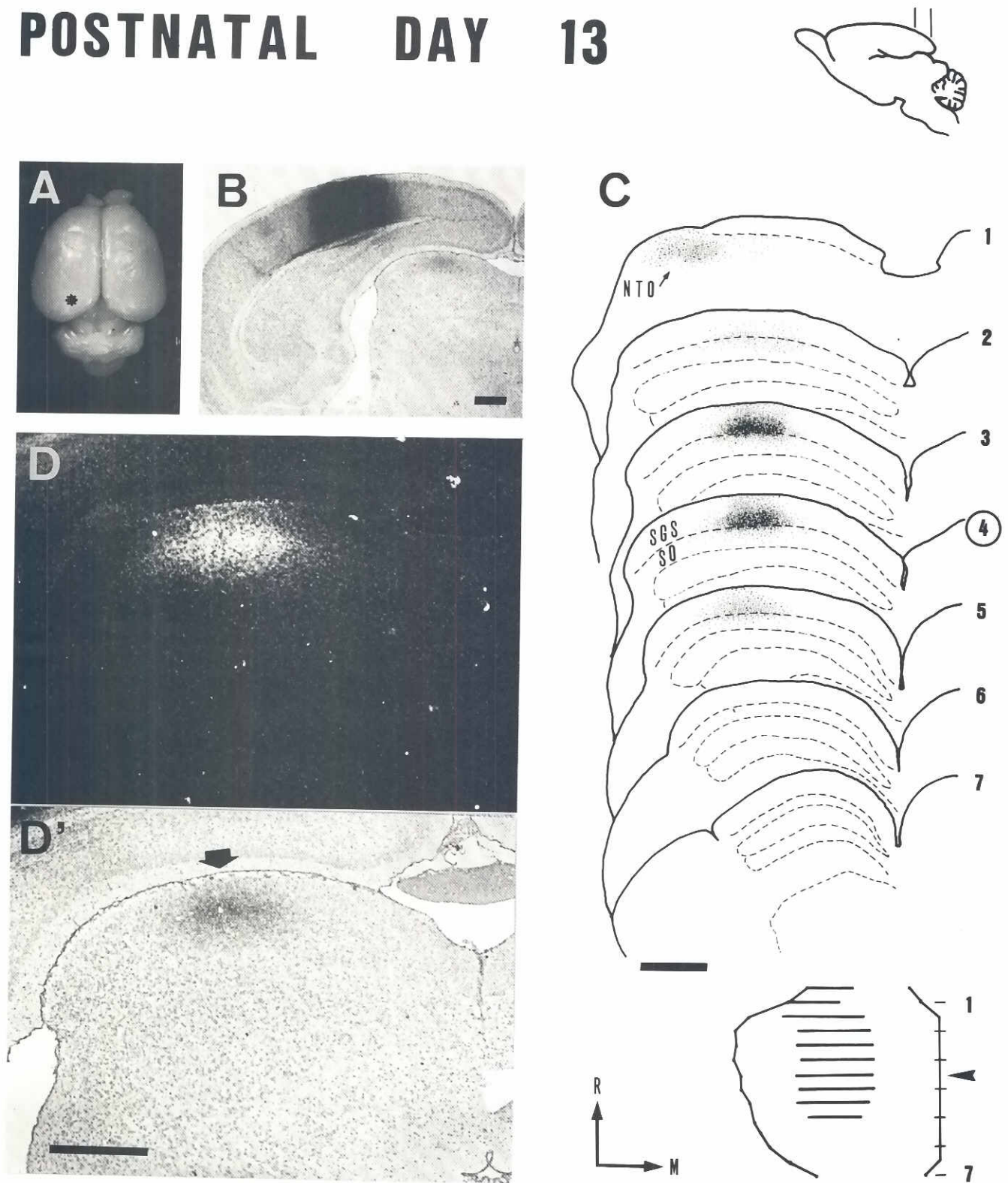


Fig 3. Autoradiographic tracing of the occipito-tectal projection in a rat injected with ^3H -leucine into the striate cortex on postnatal day 12 and sacrificed on postnatal day 13. The organization and conventions of this figure are as those described in Fig 1. NTO, nucleus of tractus opticus; SGS, stratum griseum superficiale; SO, stratum opticum. Scale bars = 0.5 mm.

POSTNATAL DAY 17

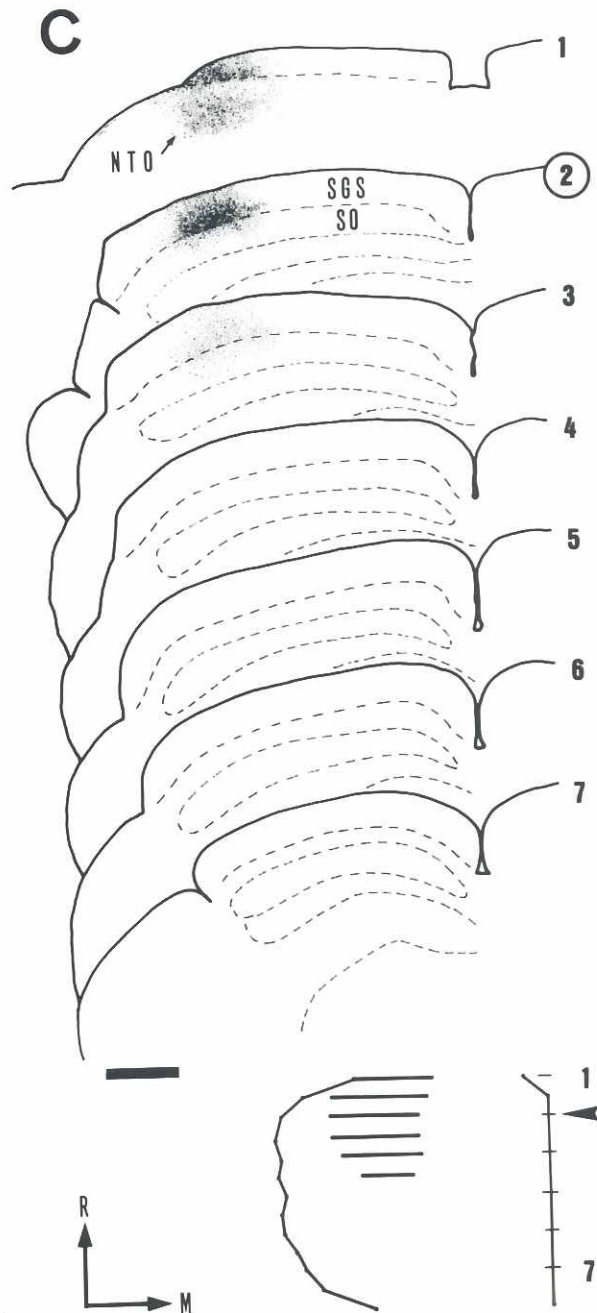
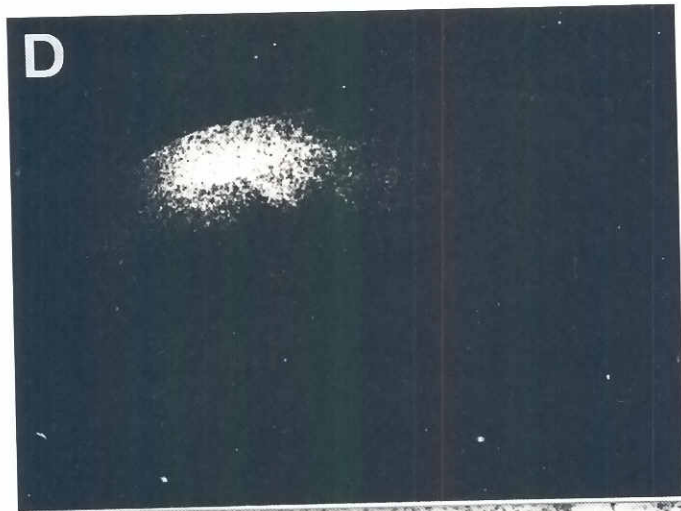
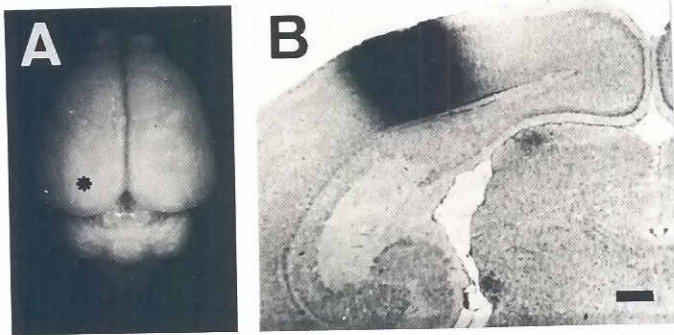
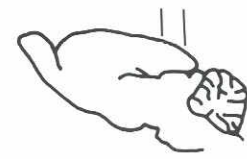


Fig 4. Autoradiographic tracing of the occipito-tectal projection in a rat injected with ^3H -leucine into the striate cortex on postnatal day 16 and sacrificed on postnatal day 17. The organization and conventions of this figure are as those described in Fig 1. NTO, nucleus of tractus opticus; SGS, stratum griseum superficiale; SO, stratum opticum. Scale bars = 0.5 mm.

occipito-tectal development together with its correlation with other events that occur during the ontogeny of the visual system is an important step towards identifying the mechanisms that guide the formation of these connections.

Results

After ^3H -leucine injections into the striate cortex, the earliest age at which anterogradely labeled axons were observed in the ipsilateral SC was P4. However, other projections like occipito-geniculate and occipito-spinal were evident from P1. No projections to the contralateral SC were observed at any time of development.

In animals studied on P4, the injections covered most of the prospective striate cortex (Fig. 1B). After these injections, the anterograde labeling spread over most of the tangential extension of the SC involving the prospective SO, adjacent part of the SGS and also the prospective *strata intermediale* (Fig. 1C-D). The labeling density was highest in rostral sections and gradually decreased backwards, until the caudalmost collicular sections which were free of label. Radially, we could distinguish a bilaminar pattern according to the differential density of the labeling which was higher in both the prospective SO and *stratum album intermedium* and lower in the region between them (Fig. 1C-D). This qualitative observation was supported by quantitative data from grain counting across a traverse of the labeled collicular region (Fig. 5).

In animals studied from P6 onwards, the injections covered only partial regions of the striate cortex. On P6, the anterograde labeling over the SC, although still diffuse compared to that seen in adult animals, was restricted to tangentially discrete regions of the tectal surface (Fig. 2). Furthermore, the center of these regions was always located in the expected position according to visuotopic maps of the adult occipito-tectal projection (Lund, 1966), indicating that the gross organization of the map was established at this early stage. Radially, the projection was almost restricted to the SO and the adjacent part of the SGS (Figs. 2 and 5). The density of labeling in the *strata intermediale* decreased from P4 onwards (Fig. 5); a light labeling could be observed in the prospective *stratum album intermedium* until P11.

From P9 to P17, substantial changes in the radial and tangential patterns of the occipito-tectal projection were observed. The radial changes were characterized by a gradual shift of the labeling towards the pial surface and by its increasing density over the ventral half of the SGS (Fig. 5). On P11, the middle region of the labeling had expanded upwards and included the ventral two thirds of the SGS. On P13 (Figs. 3 and 5), the labeling had reached the *stratum zonale*, and its maximum density and mediolateral spread was seen in the region of the SGS adjacent to the SO. By P15, the radial pattern of the projection was indistinguishable from that observed in the older animals included in this study, and was in agreement with previous descriptions of

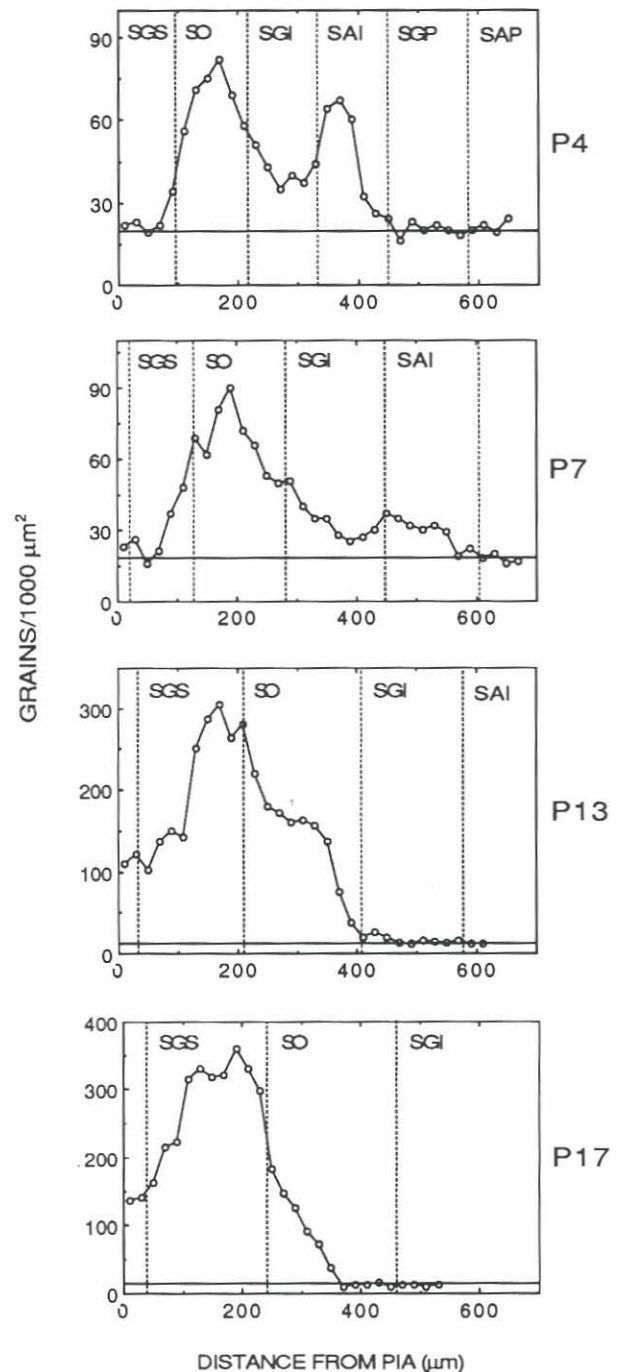


Fig. 5. Plots of grain density vs. distance from pial surface showing different patterns of termination of the occipito-tectal projection during postnatal development. The points at which the counts were made at 20 μm intervals across the SC are indicated by large arrows in the bright field photomicrographs of the SC in Figs. 1-4. Horizontal lines within the plots indicate the level of autoradiographic background and vertical dotted lines indicate the boundaries between collicular layers.

the adult occipito-tectal projection (Lund, 1966; Thong and Dreher, 1987). Labeling spread over the dorsal half of the SO, the SGS and the *stratum zonale*, with the maximum concentration and extent in the ventral half of the SGS.

The tangential extent of the occipito-tectal terminal field showed a gradual and strong reduction during the period studied. To estimate the degree of tangential exuberancy of the projection in different ages we used a quotient which corrected for both the size of the injection and the different growth rate between the cortex and the SC (see Materials and Methods). This analysis was based on injection sites that across ages, spanned approximately the same relative extent of the striate cortex (except for P4), and were located in approximately the same region within the striate cortex (as indicated by the position of the anterograde labeling at both the SC and the ipsilateral thalamus). As shown in Figure 6, the estimated degree of exuberancy reached a peak on P6, and between P7 and P17 it underwent a reduction of almost 50%.

By P17 (Figs. 4 and 5), the pattern of terminal distribution of the occipito-tectal projection was indistinguishable from that observed in P22 and P50 animals, and was consistent with previous descriptions of the adult occipito-tectal projection (Lund, 1966).

Discussion

Radial distribution of the occipito-tectal terminal field during development

The present study confirms the existence of a transient projection from the striate cortex to the collicular *strata intermediale* (Thong and Dreher, 1987) and in addition shows that this projection tends to remain confined to the prospective *stratum album intermedium*. In contrast to previous work reporting an increase in the density of the transitory projection to the *strata intermediale* between P7 and P10 (Thong and Dreher, 1987), we have found that the density of the transitory labeling decreases from P4 onwards. Our results are in line with previous studies suggesting that transient occipito-spinal (Jones, 1981; Adams *et al.*, 1983; Joosten *et al.*, 1987) retino-retinal (Bunt and Lund, 1981), retino-ventrobasal (Frost, 1984), visual callosal (Innocenti, 1981) and cortico-cerebellar (Distel and Hollander, 1980; Tolbert and Panneton, 1983) axons, all disappear without elaborating significant terminal arbors.

Tangential reduction of the occipito-tectal projection during development

We have estimated that from P7 to P17 the tangential exuberancy of the occipito-tectal projection undergoes a reduction of 50%. This estimation is consistent with previous qualitative reports of terminal fields occupying a larger proportion of the target than in the adult (Hollander *et al.*, 1979; Thong and Dreher, 1987) and with studies on the postnatal development of individual retinal ganglion cells axons in the SC of the hamster and mouse (Sachs *et*

al., 1986; Schneider *et al.*, 1987) which have reported selective collateral elimination from these axons.

If our estimation reflects a real age-related reduction in the tangential spread of the developing occipito-tectal terminal field, the question which arises is to what extent this reduction reflects the disappearance of exuberant axons confined to the SO before elaborating terminal arbors or, the pruning of exuberant branches of elaborated terminal arbors located within the SGS. The present observation that the entry of labeling into the SGS occurs only in a localized and central region of the total tangential extent of the labeling over the SO, suggests that although in a first stage occipito-tectal axons are exuberantly distributed in the collicular white matter, they enter the gray matter only in the tangentially restricted regions where they are found in the adult. Indeed, this interpretation is consistent with previous studies on callosal and associational development (Ivy *et al.*, 1979; Innocenti, 1981; Innocenti and Clarke, 1984). However, the present study shows that from P13 onwards the extent of the collicular labeling from a given injection into the striate cortex, is maximum at the level of the SGS. Since our measurements reflect the maximum extent of the total labeling and, since from P13 to P17 the degree of tangential exuberancy decreases about a half of the total reduction, it seems probable that at least some tangentially exuberant branches of terminal arbors located in the SGS are pruned during the last days of the second postnatal week. Furthermore, since rats first open their eyes by P12-14, it is possible that patterned visual experience may be responsible for the elimination of these axonal branches.

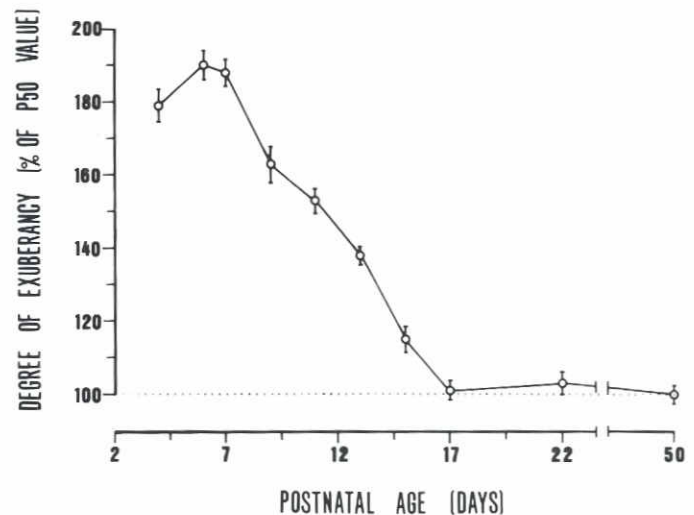


Fig. 6. Graph showing changes with age in the degree of tangential exuberancy of the occipito-tectal projection (see Materials and Methods). The values are expressed as percentages of the mean value obtained for P50 animals. Each dot represents the mean value of 3 or more experiments of a given age. Vertical lines indicate the standard error of the mean.

Emergence of the occipito-tectal topography

In the cat, the cortico-tectal projection has at least a rough topographic organization on P1 (Stein and Edwards, 1979). On the other hand, in the rabbit, a previous study has suggested that the cortico-tectal projection in the neonate may be composed of axons which arborize widely in the SGS and SO (Hollander *et al.*, 1979). In the rat we have found that from P6 onwards, tangentially discrete injections within the striate cortex result in tangentially discrete areas of anterograde labeling over the SC, and that the center of this labeling is always in the expected position according to topographic maps of adult animals (Lund *et al.*, 1966). Our findings suggest that, at least from P6, the projection has some topographic order. Furthermore, since at this age the degree of tangential exuberancy of the occipito-tectal projection is maximum, it follows that any topographic order observed on P6 could not have been brought about by the pruning of a diffuse projection. Therefore, it is possible that the orderliness existed before P6 but we were not able to recognize it due to the large size of the injections. This interpretation is consistent with previous studies on the developing thalamo-cortical (Crandall and Caviness, 1984; Naegele *et al.*, 1988), cortico-thalamic (Kato, 1987) and retino-tectal (Holt and Harris, 1983) systems in which the initial projections show a rough topographic organization.

Concluding remarks

The present study suggests that the development of the topographic pattern of the occipito-tectal projection is a multifactorial process which may involve several different mechanisms. First, the rough topographic organization found at early ages indicates that the initial occipito-tectal fibers do not randomly form collateral branches throughout the SC, but instead they are guided by some sort of active mechanism. This is consistent with the chemoaffinity hypothesis which states that complementary molecular gradients along the afferents and their targets are the basis for selective synaptogenesis (Sperry, 1963; Meyer and Sperry, 1976). Second, the decrease in the degree of tangential exuberancy of the occipito-tectal projection supports the notion that the refinement of topographic maps is achieved by selection of appropriate branches and retraction of incorrectly positioned branches (Gaze and Keating, 1972; Changeaux and Danchin, 1976). Our findings suggest that this retraction may be effected both before and after occipito-tectal axons have elaborated complex terminal arbors, and therefore, that separate sets of factors may be involved in selection of topographically appropriate projections.

Materials and Methods

Studies were performed on albino rats (Sprague-Dawley) ranging in age from postnatal day 1 (P1) to P50 (day of birth=P0): P1 (n=4), P2 (4), P3 (3), P4 (4), P6 (5), P7 (6), P9 (5), P11 (6), P13 (5), P15 (6), P17 (5), P22 (4), P50 (6). For surgery and sacrifice the animals were anesthetized as follows. Animals aged from P1 to P9 were anesthetized with 3% cloral hydrate (0.13 mg/g body

weight) supplemented with ether as needed. Animals older than P9, were anesthetized with 6% cloral hydrate (0.20 mg/g body weight). Over the prospective location of the striate cortex, a small opening was made in the skull and the dura, thus exposing the cortical surface. Single intracortical injections of 0.01-0.10 μ l (0.070 μ Ci/g body weight) of [4,5- 3 H] L-Leucine (50 μ Ci/ μ l; sp. act. 40-60 Ci/mM, Amersham) were made with the aid of a stereotaxic frame, via a glass micropipette (tip diameter = 50 μ m) attached to a 1- μ l Hamilton syringe.

After postinjection survival periods ranging from 24 to 48 hours, most animals were perfused transcardially with a warm 0.9% sodium chloride solution followed by cold 10% neutral formalin, and the brains were removed and placed in fresh fixative for 48 hours. Some of the youngest rat pups, were sacrificed by decapitation and the brains fixed in Carnoy's solution for 24 hours. All brains were dehydrated, embedded in paraplast and coronally sectioned at 10-15 μ m. From each brain, a one-in-five series of sections was processed for standard autoradiography as described by Cowan *et al.* (1972), using developer Kodak D-19, and finally counterstained with 1% cresyl violet.

The distribution of the labeling at the injection site was plotted onto camera lucida drawings of the cortical sections. The extent of the injection site was estimated by measuring under bright field illumination the mediolateral extent of the region in which black labeling completely obscured the neuropil at the level of layer V. By orthogonally projecting these drawings onto the tangential plane of the cortical surface, we made tangential view reconstructions of the injection site. The location of the injections was estimated by scaling and superposing the tangential view reconstructions onto a map of the adult visual cortical areas (Schober and Winkelman, 1975). These estimates were supported by the pattern of anterograde labeling in the ipsilateral thalamus and by citoarquitectonic criteria reported for the postnatal development of the rat visual cortex (Olavarria and Van Sluyters, 1985). Only those cases in which the injection site was restricted to the prospective striate cortex and involved lamina V are included in the present study.

The distribution of anterograde labeling at the SC (as seen under dark field microscopy) was plotted onto camera lucida drawings of the SC and then tangential view reconstructions of the terminal field were made as described for the injection sites. To quantitatively document radial patterns of anterograde labeling, grain counts along a traverse across the SC were made at 20 μ m intervals in the region of most dense labeling of each animal. These counts were made under x400 magnification with the aid of a graticule attached to the ocular of the microscope (Price and Wann, 1975).

To assess developmental changes in the degree of tangential exuberancy of the projection we chose from each age group three or more brains with similar relative size and location of the injection site. In these brains, we calculated the following quotient: proportion of mediolateral extent of the cortex covered by the injection site/proportion of mediolateral extent of the SC covered by the terminal field. For each brain, the extent of the cortex and the SC as well as the extent of the injection site and the terminal field were estimated by measuring their maximum mediolateral extent from the tangential view reconstructions above described (the section used to establish the spread of the terminal field is indicated with an arrow in the tangential view reconstructions of the SC shown at the bottom of Figs. 1-4).

In this quotient, the extent of the labeling becomes relative to the size of cortex/SC thus correcting for the different growth rate in both structures. We did not take measurements along the rostrocaudal dimension because the extent of terminal fields located caudally in the SC would be overestimated in relation to those

located more caudally, since labeled axons course rostrocaudally towards their sites of termination. Note that we have used the mediolateral extent of the whole hemisphere as an indication of the size of the striate cortex due to the inevitable inaccuracy in measuring its extent at the earlier ages. Throughout the paper, the ages expressed for the animals refer to the age at fixation, unless otherwise indicated.

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