

# Trigeminal Ganglion Cell Processes Are Spatially Ordered Prior to the Differentiation of the Vibrissa Pad

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**The rodent trigeminal system is characterized by the punctate organization of its afferents and neurons that replicate the distribution of mystacial vibrissae and sinus hairs on the snout. We have examined the development of topographic equivalence between the sensory periphery on the snout and the brainstem trigeminal nuclei in rats. Lipophilic tracers Dil (1,1'-dioctodecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate) and DiA [4-(4-dihexadecylaminostyryl)-N-methylpyridinium iodide] were used to label trigeminal ganglion cells and their processes differentially from discrete regions of the presumptive vibrissa field in fixed embryos. Our results show that trigeminal ganglion cell processes are spatially ordered as they reach their peripheral and central targets on embryonic day 12 (E12). Peripheral processes of dorsomedially situated ganglion cells course dorsally toward the presumptive vibrissa field, and those of ventrolaterally situated ganglion cells project ventrally. On E13, the central processes of dorsomedially situated ganglion cells enter the brainstem medially whereas those of ventrolaterally situated ganglion cells enter laterally. This spatial order of trigeminal ganglion cell processes precedes the emergence of vibrissa rows in the periphery and the differentiation of brainstem trigeminal nuclei. Thus, the subsequent transfer of the vibrissa-related pattern to the brainstem trigeminal nuclei occurs along a preexisting, spatially aligned bridge formed by the trigeminal ganglion cells.**

Primary sensory afferents that connect the periphery to the CNS navigate through a variety of substrates and across considerable distances before contacting target cells, yet these fibers succeed in conveying the spatial organization of the sensory periphery to central relay nuclei with remarkable precision. Understanding how this comes about has been a major endeavor in developmental neurobiology for many years.

Periphery-related neuronal patterns are a distinct feature of the rodent trigeminal system. In both rats and mice, the whiskers on the snout are arranged in five rostrocaudally aligned rows and the number of vibrissa follicles in each row is constant (Yamakado and Yohro, 1970; Van Exan and Hardy, 1980). During perinatal life, afferents and cellular elements of the central trigeminal pathway leading to the neocortex form facsimiles of the peripheral pattern (Woolsey and Van der Loos, 1970;

Van der Loos, 1976; Belford and Killackey, 1979; Killackey and Belford, 1979; Erzurumlu et al., 1980; Ivy and Killackey, 1982; Ma and Woolsey, 1984; Bates and Killackey, 1985). These central patterns are drastically altered if the trigeminal innervation of the vibrissa pad is disturbed during a sensitive period in development (Van der Loos and Woolsey, 1973; Belford and Killackey, 1980; Jeanmonod et al., 1981; Killackey and Shinder, 1981; Durham and Woolsey, 1984). In contrast, an array of vibrissal follicles develops, independent of trigeminal innervation, on an innervated embryonic mouse snout grown in culture (Andrés and Van der Loos, 1982, 1983).

The construction of vibrissa-related central patterns is thought to occur under the directive guidance of periphery (Van der Loos and Dörfel, 1978; Van der Loos and Welker, 1985; Woolsey, 1987). However, little is known about developmental strategies used by trigeminal ganglion cells to match topographically equivalent regions of the periphery and brainstem. Nor is it known how the punctate organization of the whiskers is transferred to afferent arbors and their target cells along the entire trigeminal neuraxis leading to the neocortex. In this study, we present evidence of an orderly patterning in the early outgrowth of trigeminal ganglion cell processes; this intrinsic spatial organization may provide a foundation upon which periphery-related patterns are elaborated.

## Materials and Methods

Timed-pregnant Sprague-Dawley rats were obtained from Taconic Farms. Day of sperm positivity is designated as embryonic day 0 (E0). Embryos were delivered by cesarian section, after overdosing the dams with sodium pentobarbital. At least six embryos were used for each time point (E11–E18). The heads were fixed in 8% paraformaldehyde (S. Senft, personal communication) in 0.1 M phosphate buffer. Small crystals of fluorescent tracers Dil (1,1'-dioctodecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate) and DiA [4-(4-dihexadecylaminostyryl)-N-methylpyridinium iodide] (Molecular Probes) (Godement et al., 1987) were inserted into emerging vibrissa rows in varying combinations (Fig. 1).

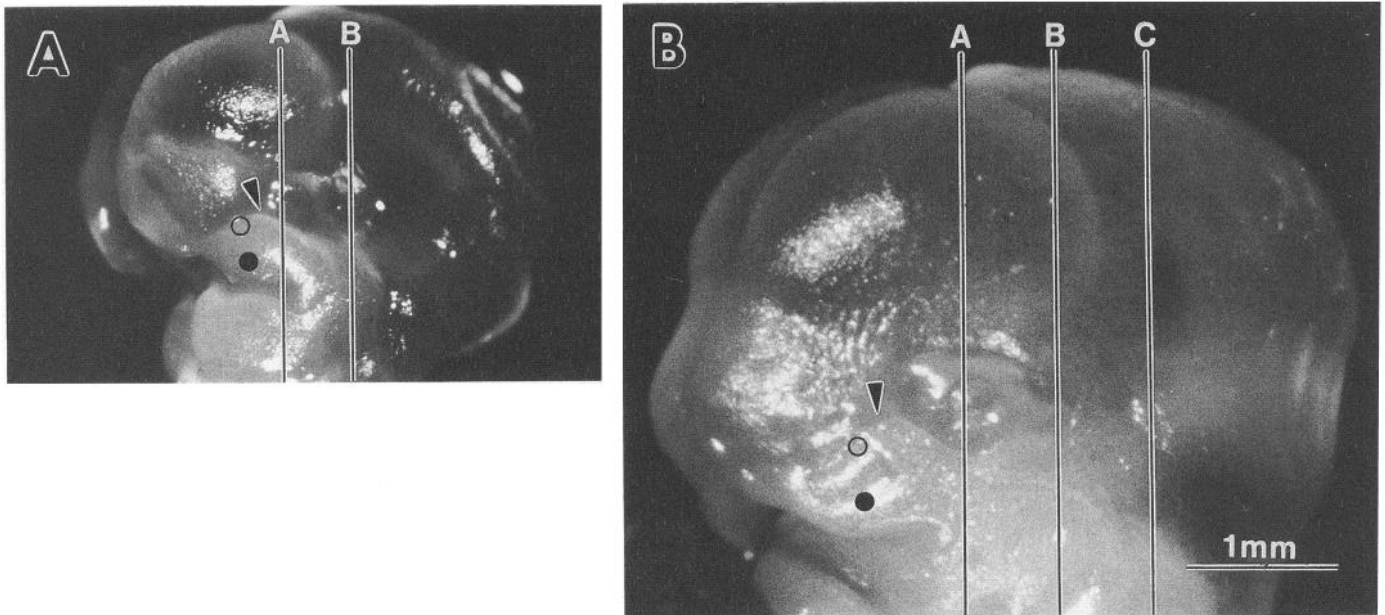
During morphogenesis of the vibrissa pad, the dorsal two rows of whiskers (rows A and B) arise from the lateral nasal process whereas the ventral three (rows C, D, and E) derive from the maxillary process; the two prominences are separated by the nasolacrimal groove (Yamakado and Yohro, 1979; Van Exan and Hardy, 1980). Before E14, prior to the appearance of vibrissa rows, crystals of Dil and DiA were placed either one in the lateral nasal process above the nasolacrimal groove and the other in the maxillary prominence, or one dorsally and the other ventrally, both in the maxillary process (Fig. 1). In older embryos, alternating crystals of Dil and DiA were placed in rows A, C, and E (caudally in rows A and E and rostrally in row C); in some cases, one crystal was placed rostrally and the other caudally in row C. Labeled heads were stored in fixative at 37°C for 2–8 weeks, embedded in 2.5% agar, and sectioned (100–200  $\mu$ m thick) on a vibratome. Sections were mounted on buffer; counterstained with 0.025% bisbenzimidazole; viewed with rhodamine, fluorescein, and ultraviolet filters; and photographed.

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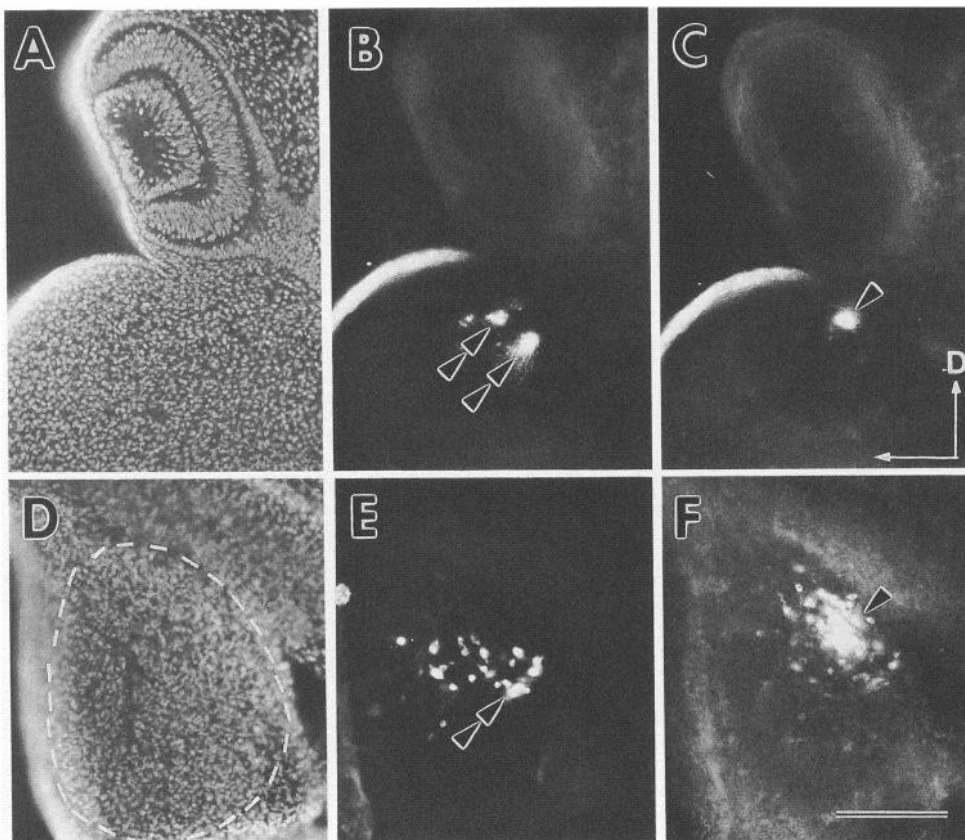
**Figure 1.** Photomicrographs of E12 (*A*) and E13 (*B*) rat heads. On E12 no vibrissal ridges are visible on the maxillary process, whereas on E13 shallow depressions within the maxillary process indicate the beginning of ridge formation. No vibrissal follicles are present at either age. *Arrowheads* point to the nasolacrimal groove that separates the lateral nasal process from the maxillary process. *Solid* and *open circles* indicate the position of Dil and DiA implants, respectively. The levels indicated by *lines A* and *B* on the E12 head correspond to coronal sections shown in Figure 2. *Lines A, B, and C* on the E13 head indicate the levels of coronal sections shown in Figure 3.

## Results

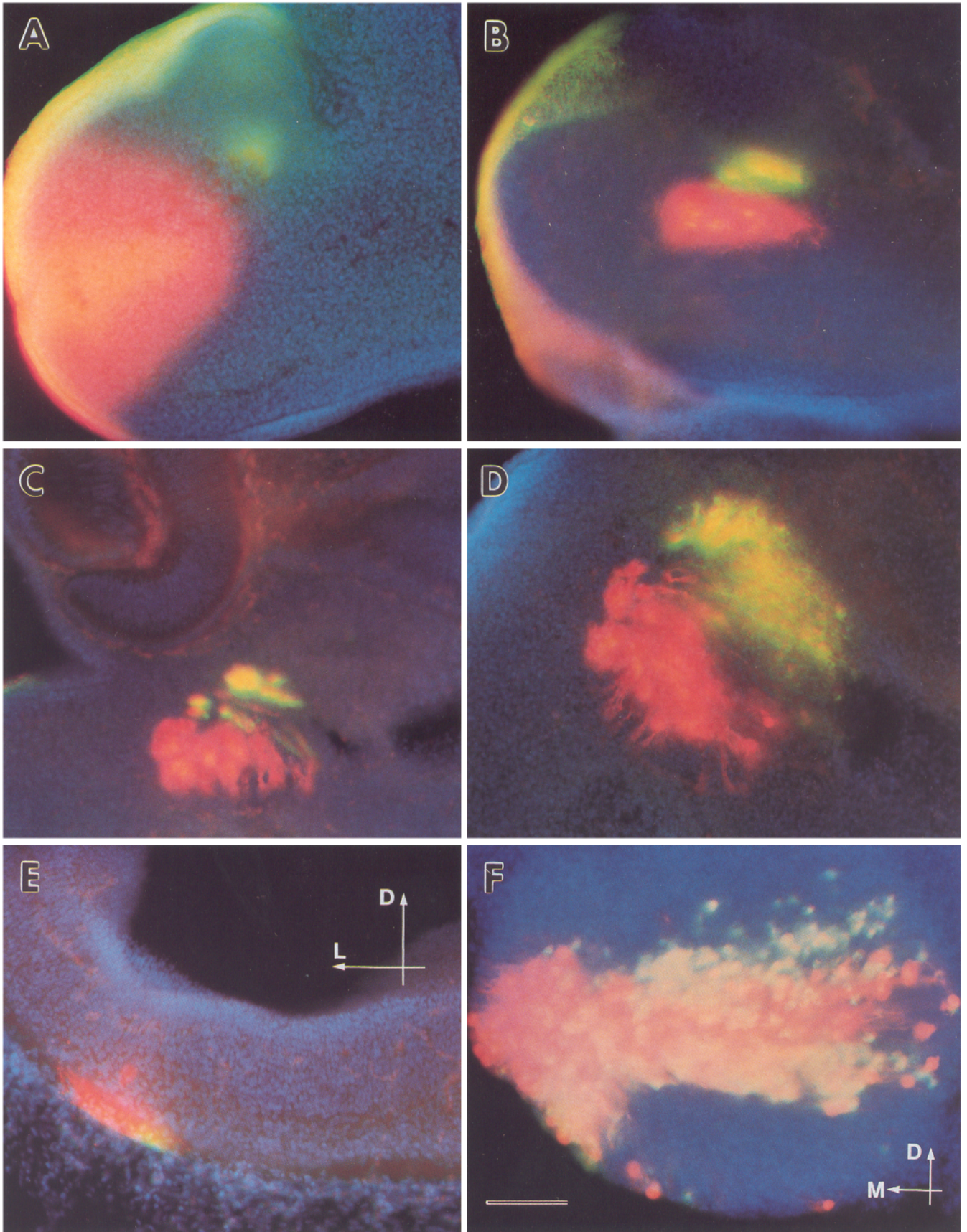
### *Trigeminal ganglion cells and their peripheral processes*

Although neurogenesis in the rat trigeminal ganglion begins after E9.5 (Rhoades et al., 1991), placement of carbocyanine dyes

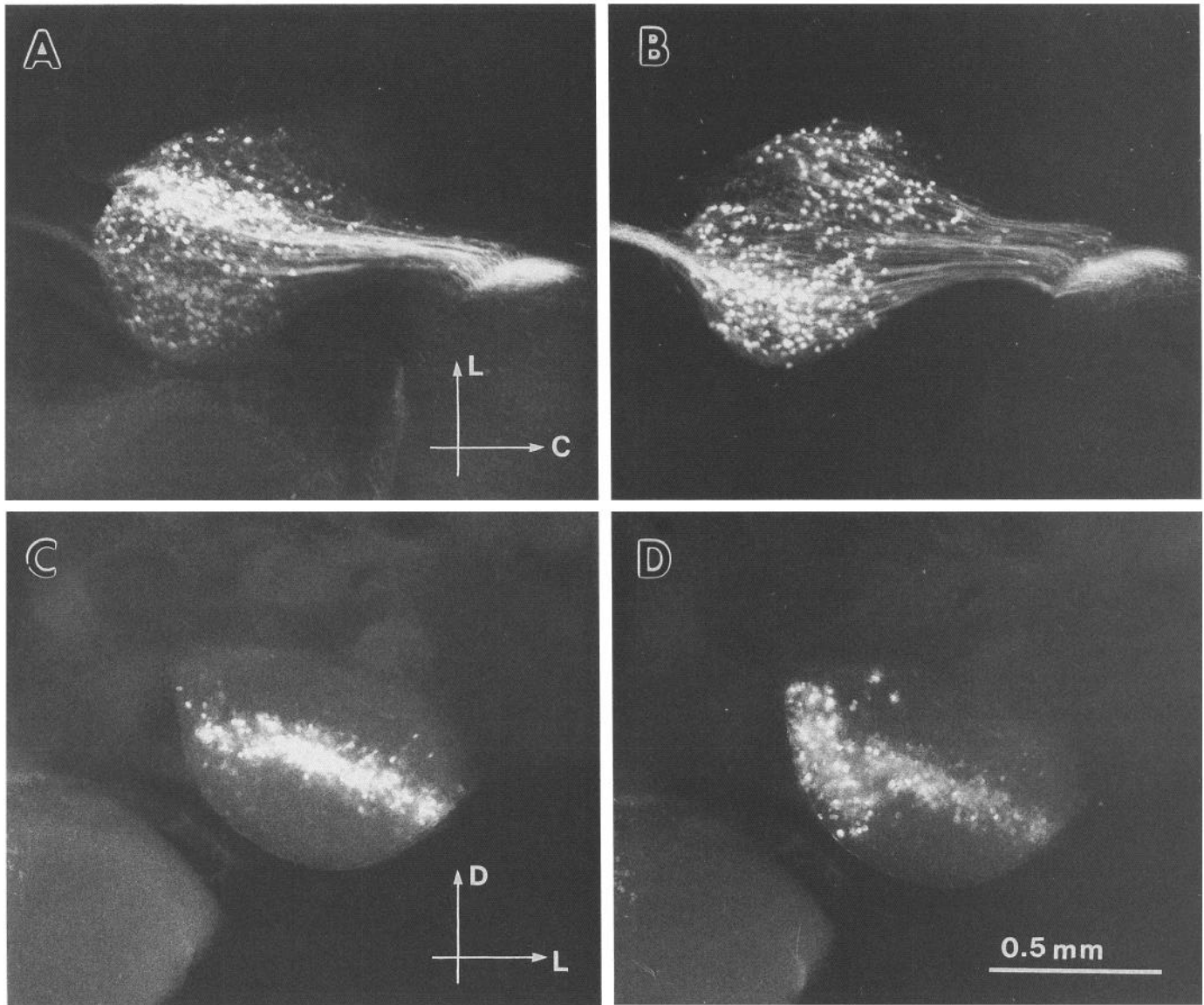
superficially in the differentiating snout on E11 did not label any ganglion cells. Only in those cases where the dye crystal was implanted deep within the mesenchyme, apposed to the emerging ganglion, were a few bipolar cell profiles encountered (data not shown). This observation suggests that processes of ganglion



**Figure 2.** Differential labeling in the infraorbital nerve and trigeminal ganglion following implantation of DiA dorsally and Dil ventrally in the maxillary process of an E12 rat. *A–C* are photomicrographs of the same coronal section at the level of the infraorbital foramen (plane *A* in Fig. 1*A*), and *D–F* are from one at the level of the trigeminal ganglion (plane *B* in Fig. 1*A*). *A* and *D* are photographed with a UV filter to show the cell nuclei stained with bisbenzimidium; *B* and *E* are photographed with a rhodamine isothiocyanate (RITC) filter to show Dil labeling, and *C* and *F* with a fluorescein isothiocyanate (FITC) filter to reveal the DiA labeling. DiA-labeled cells and processes are situated dorsal to Dil-labeled ones. *Broken line* in *D* outlines the trigeminal ganglion; *single arrowheads* point to DiA, and *double arrowheads*, to Dil labeling. *D*, dorsal; *L*, lateral. Scale bar, 200  $\mu$ m.



**Figure 3.** Triple exposure micrographs taken with UV, RITC, and FITC filters to document the spatial order in the trigeminal pathway. DiA was implanted dorsally and Dil ventrally on the maxillary prominence of an E13 rat. *A-E*, Coronal sections showing DiA (yellow-green) and Dil (red) labeling (see Fig. 1). *A*, Dil and DiA implantation sites on the maxillary process. *B-D*, Successively more caudal sections from the same case as in *A*. *E*, Caudalmost section, through the immature trigeminal tract. Note that the dorsoventral order within the nerve is translated into a mediolateral organization within the tract. *F*, A triple-exposure micrograph of the trigeminal ganglion from an E15 rat in which alternating crystals of DiA, Dil, and DiA were implanted in vibrissa rows A, C, and E, respectively. *D*, dorsal; *L*, lateral; *M*, medial. Scale bar, 150  $\mu\text{m}$ .



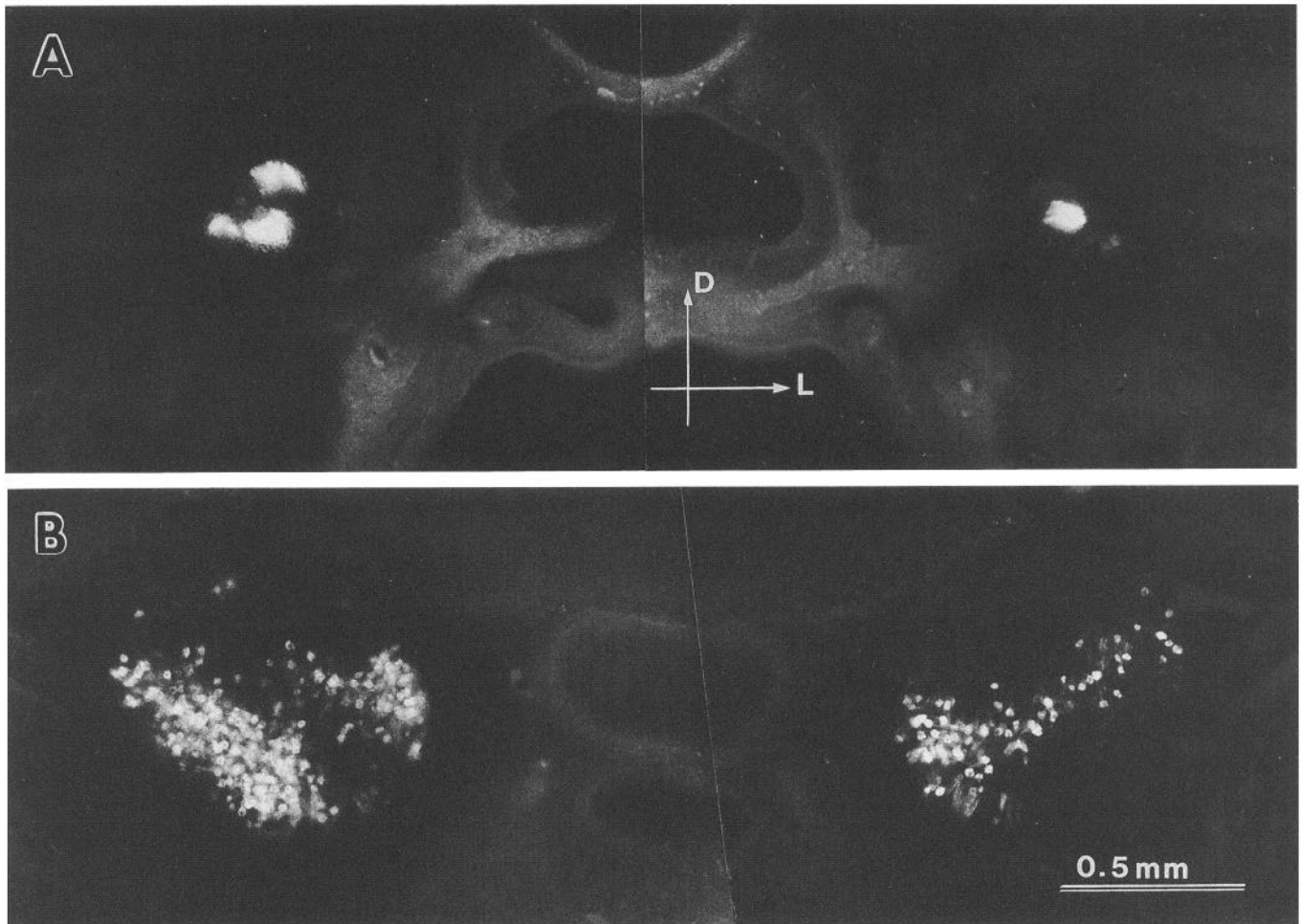
**Figure 4.** Topographic order in trigeminal ganglion of E15 rats. *A* and *B* show the same horizontal section from an animal in which the face was labeled with a dorsoventral sequence of Dil, DiA, and Dil in whisker rows A, C, and E, respectively. *A*, A single band of labeling in the middle of the ganglion is seen with the FITC filter (DiA labeling). *B*, Two bands of labeling are seen with the RITC filter (Dil labeling). *C* and *D*, Coronal section through another E15 trigeminal ganglion following placement of DiA (*C*, FITC filter) caudally and Dil (*D*, RITC filter) rostrally in row C. In *D*, many of the cells labeled with DiA also show through the RITC filter. *D*, dorsal; *L*, lateral; *C*, caudal.

cells first begin to grow out on E11 (cf. Erzurumlu and Killackey, 1983).

On E12, neurogenesis in the ganglion is occurring at peak levels but morphological differentiation of the vibrissa pad is not yet evident (English et al., 1980; Forbes and Welt, 1981; Altman and Bayer, 1982; Erzurumlu and Killackey, 1983; Rhoades et al., 1991) (see Figs. 1, 8). At this time, tracers placed dorsally and ventrally within the maxillary process revealed numerous labeled trigeminal ganglion cells and their axons. These labeled profiles were topographically aligned with respect to the dorsoventral axis of the face: when Dil was placed in the ventral part of the presumptive vibrissa field and DiA in the dorsal part, discrete fascicles of axons and specific groups of ganglion cells were labeled (Fig. 2).

On E13, shallow depressions along the maxillary process demarcate the presumptive location of vibrissa rows (Fig. 1). How-

ever, no evidence of vibrissa follicle development is visible. Ganglion cell axons directed toward the rudimentary vibrissa field form a roughly circular bundle of fascicles within the infraorbital foramen. These fascicles fan out as they approach the maxillary and lateral nasal processes. A distinct topography was evident along the entire trigeminal pathway (Fig. 3). Placements of Dil and DiA crystals along the dorsoventral axis of the presumptive vibrissa field led to labeling of discrete populations of axon fascicles, ganglion cell bodies, and central processes. Cells located in the dorsomedial portion of the ganglion extended peripheral processes that traveled in fascicles toward dorsal targets; cells situated ventrolaterally traveled likewise to ventral target fields. Thus, the spatial order of the developing infraorbital nerve fascicles was aligned with the dorsoventral axis of the presumptive vibrissa pad and consequently of future vibrissa rows. The topographic order of the ganglion cells with



**Figure 5.** Spatial order in the infraorbital nerve (*A*) and the trigeminal ganglion (*B*) of an E18 rat. On the left side, Dil was placed in rows *A* and *E*, whereas on the right side Dil was placed in row *C*. Both micrographs are photographed with an RITC filter. *D*, dorsal; *L*, lateral.

respect to their target fields was best seen in coronal or sagittal sections through the head: discrete injections of Dil and DiA in the periphery led to bands of labeled cells that were oriented dorsolaterally to ventromedially (Fig. 3).

Vibrissa rows (*A–E*) can be identified on the snout by E14 and become quite distinct on E15. At these ages, crystals of DiA, Dil, and DiA were placed in alternating rows (*A*, *C*, and *E*, respectively) on one side of the face, whereas Dil, DiA, and Dil crystals were applied likewise on the other side of the face. With such a procedure, the vast majority of cells as well as their processes were labeled differentially from corresponding loci in their peripheral fields (Figs. 4, 5; see also Fig. 7).

We were also able to place two different dye crystals along the rostrocaudal axis of a given vibrissal row in E14 and older embryos. The resultant labeling pattern showed that the rostrocaudal axis of the vibrissa pad is represented mediolaterally in the ganglion (Fig. 4). Between E14 and E18, the topography with respect to both the dorsoventral and rostrocaudal axes of the vibrissa pad becomes increasingly distinct in the trigeminal ganglion and in its projections (see Figs. 5, 7).

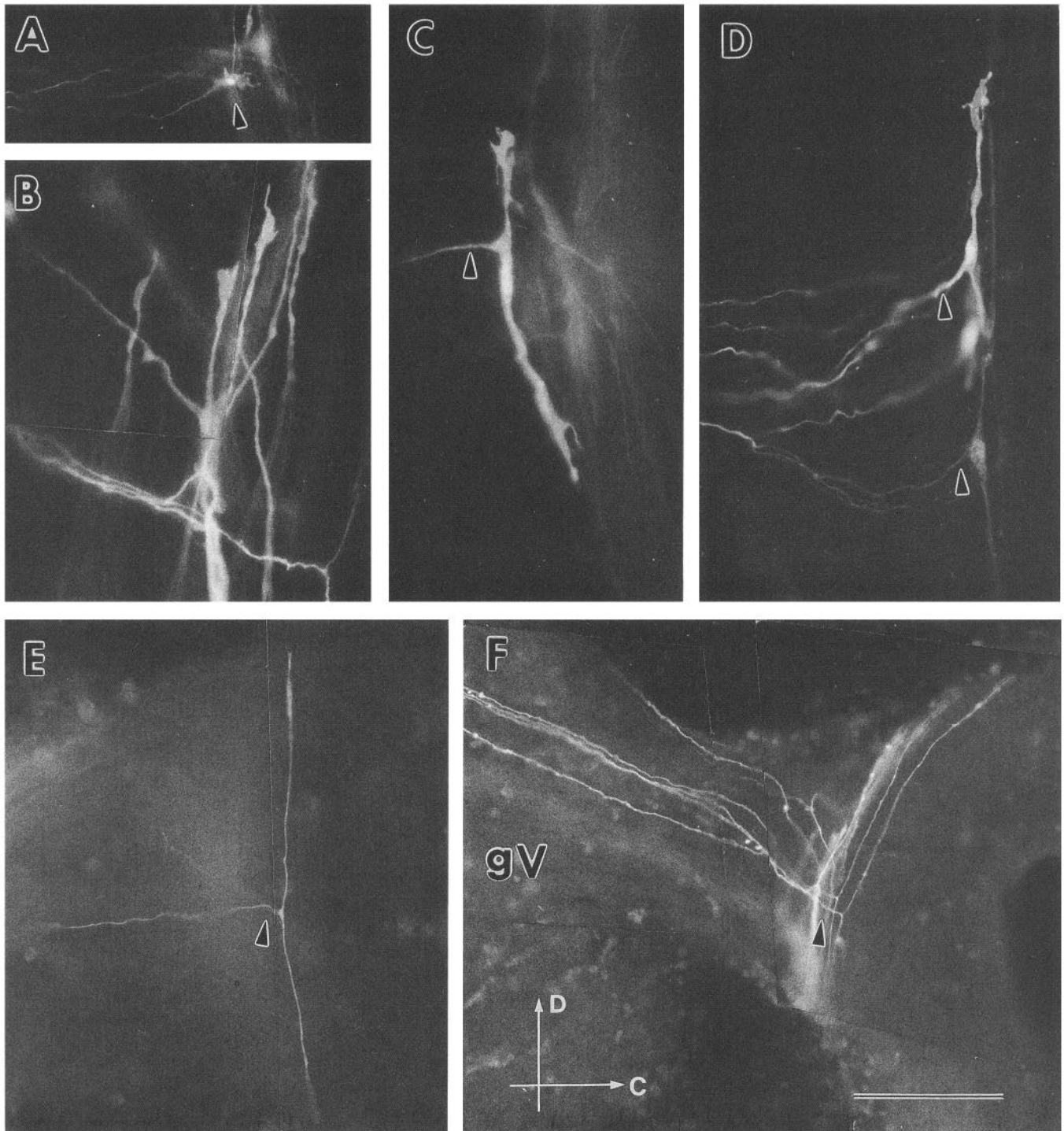
#### *Central processes and arbors of trigeminal ganglion cells*

The entry of trigeminal ganglion cell processes into the CNS is best seen in sagittal sections (Fig. 6*F*). On E12 and E13, tracer implants in the periphery revealed axons with large lamellate

growth cones approaching the rhombencephalon (Fig. 6*A*). As they encountered the surface of the brainstem on E13, these processes formed T-shaped swellings (about 125–150  $\mu\text{m}$  in length), presaging their bifurcation into the ascending and descending branches of the central trigeminal tract (Fig. 6). Growth cones with filopodia tipped the leading edges of the T-shaped swellings on both sides. Furthermore, at the leptomeningeal–CNS interface, the bifurcating fibers were not all of the same caliber: a subpopulation of labeled fibers was consistently thinner than others (Fig. 6*E*). These differences may be a reflection of the dual origin (placodal vs. neural crest) of the ganglion cells (Hamburger, 1961; LeDourain et al., 1986; Nichols, 1986), or they may reflect a differentiation into the large versus small fibers seen in the mature trigeminal tract.

Centrally directed processes of ganglion cells were also spatially ordered from the onset of trigeminal tract formation. As early as E13, axons of dorsally situated ganglion cells entered the brainstem medially, whereas those of ventrally situated ganglion cells entered laterally (Fig. 3). Thus, the dorsoventral axis of the peripheral field is rotated 90° and translated into a medial-to-lateral dimension within the brainstem. With further maturation of the hindbrain, this axis shifts an additional 90°, resulting in an almost upside-down representation of the face in the trigeminal tract (compare Figs. 3 and 7).

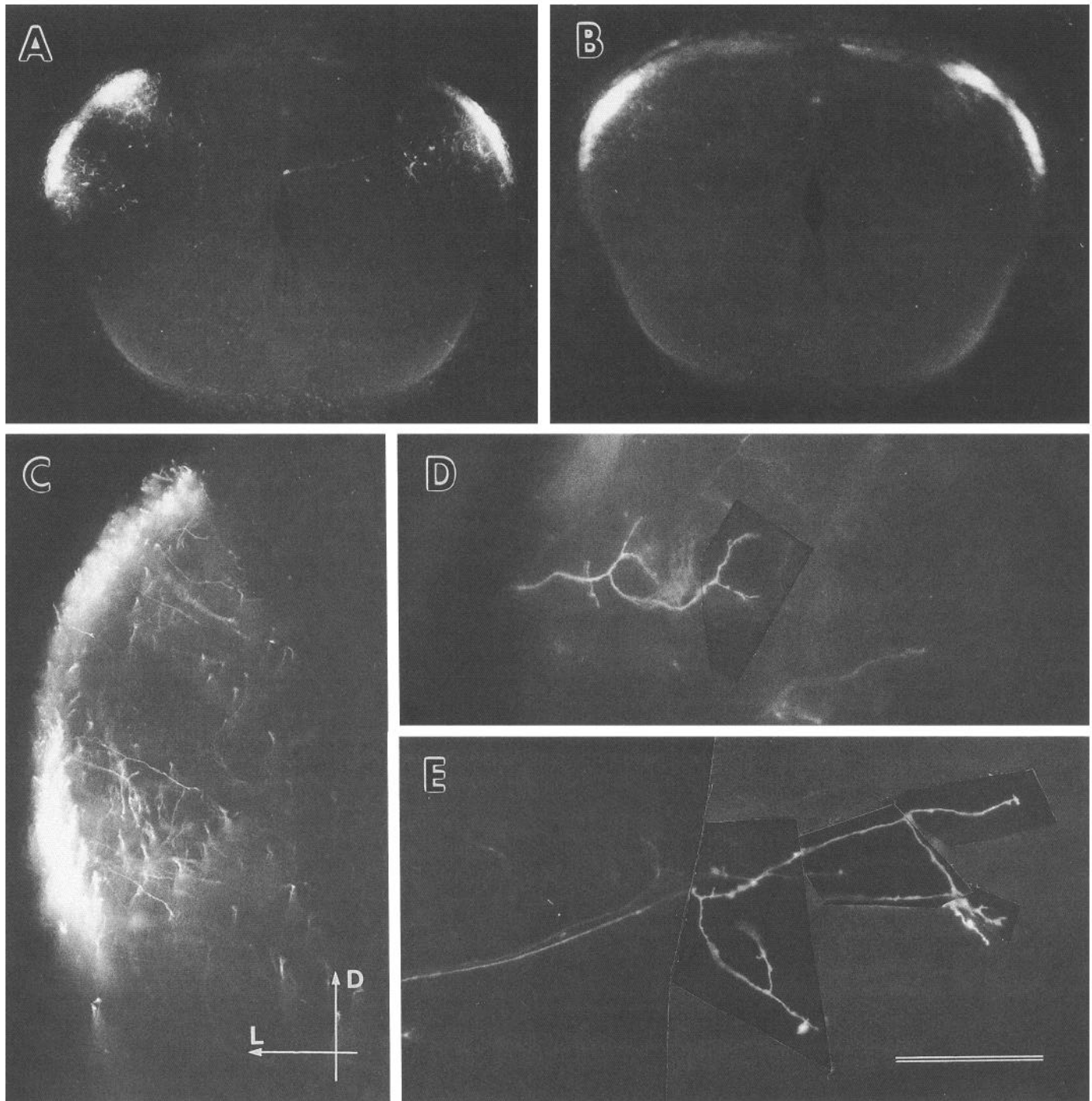
On E14 and later, axons contributing to the trigeminal tract



**Figure 6.** Profiles of growth cones that tip the central processes of trigeminal ganglion cells. All the micrographs are from E13 rat heads sectioned in the sagittal plane. The growth cones are large with lamellipodia and filopodia as they approach the CNS (*A*). Upon entering the developing brainstem, the leading edge of the central process bifurcates to form large, T-shaped swellings that presage the ascending and descending processes of the central trigeminal fibers (*B–D*). *E*, Some T-shaped processes are very thin. *F*, Low-power view of the bifurcating central processes at their entry point into the CNS. Arrowheads point to the bifurcation points of single fibers. *gV*, trigeminal ganglion; *D*, dorsal; *C*, caudal. Scale bar: 50  $\mu\text{m}$  for *A–E*; 200  $\mu\text{m}$  for *F*.

began emitting collaterals at right angles to the pial surface, to invade the newly forming brainstem sensory trigeminal nuclei (Fig. 7). Placement of alternating crystals of Dil and DiA in vibrissa rows A, C, and E also revealed that radial collaterals and their arbors, emitted from parent axons in the trigeminal tract, were segregated along the dorsoventral axis of the brain-

stem trigeminal nuclei, reflecting a 180° inversion with respect to the dorsoventral axis of the vibrissa pad. In addition, collateral branches were consistently longer within the subnucleus interpolaris of the brainstem trigeminal complex than those seen in the principal sensory nucleus (Fig. 7), despite the fact that invasion of both nuclei and arbor formation within all brainstem

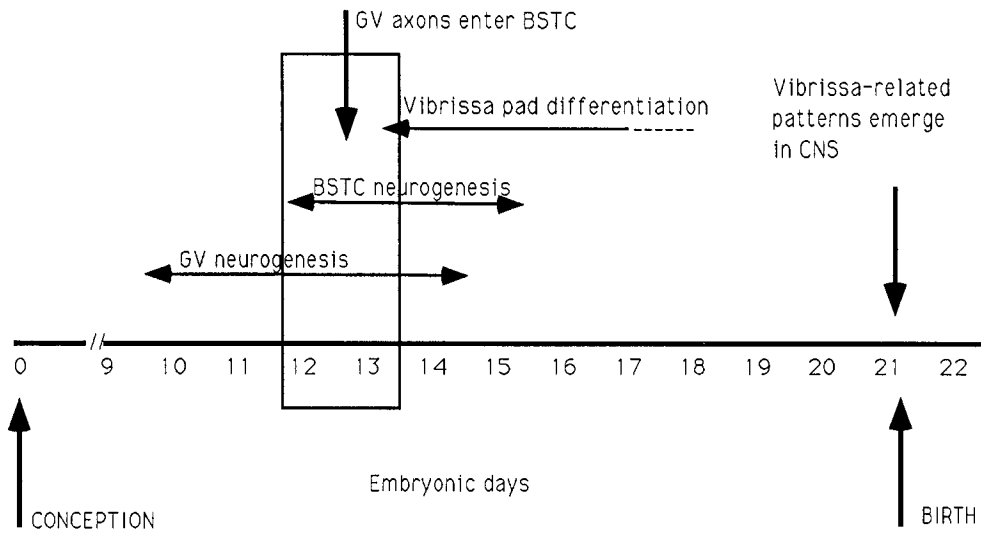


**Figure 7.** Topographic order in the trigeminal tract of E14 rats. Crystals of Dil, DiA, and Dil were placed in rows A, C, and E, respectively, on the left side of the face, and DiA, Dil, and DiA were implanted in rows A, C, and E, respectively, on the right side of the face. *A* and *B*, The same coronal section through the brainstem, photographed with an RITC (*A*) and an FITC (*B*) filter, revealed alternating bands of label in the trigeminal tract. Note that by this age, the dorsoventral axis of the face representation is shifted nearly 180° in the trigeminal tract. Higher-magnification views show that axons of the trigeminal tract have begun emitting radially oriented collaterals into the newly differentiated brainstem trigeminal nuclei. *C*, Labeling pattern in the subnucleus interpolaris of the brainstem trigeminal complex, seen with an RITC filter, in an E16 rat with Dil implanted in rows A and E. Note that the length and size of the arbors within the principal sensory nucleus (*D*) are considerably smaller than those in the subnucleus interpolaris (*E*). *D*, dorsal; *L*, lateral. Scale bar: 500  $\mu\text{m}$  for *A* and *B*; 200  $\mu\text{m}$  for *C*; 50  $\mu\text{m}$  for *D* and *E*.

trigeminal targets began around the same time. Thus, although the central primary afferent arbors have not yet segregated into the disjunctive patches characteristic of the more mature animal, they are focalized, at least with respect to the dorsoventral axis of the face.

## Discussion

Connectivity between the vibrissa pad and the brainstem trigeminal complex is established relatively early in development (Fig. 8). Previous studies have established that in the rat, tri-



**Figure 8.** Summary diagram of selected morphogenetic events that occur during the time that trigeminal ganglion cell processes bridge the periphery and the brainstem (BSTC). The rectangle indicates the period during which the trigeminal ganglion (GV) cell processes invade their peripheral and central targets. The data presented in this diagram have been compiled from Belford and Killackey (1979), Altman and Bayer (1980a–c), English et al. (1980), Forbes and Welt (1981), Erzurumlu and Killackey (1983), Rhoades et al. (1991), and the present study. For purposes of comparison, ages of the embryos in all these studies are adjusted so that the day of sperm positivity is E0.

geminal ganglion cells are generated between E9.5 and E14.5, with a peak of neurogenesis on E12 (Forbes and Welt, 1981; Altman and Bayer, 1982; Rhoades et al., 1991). The peripheral processes of these cells invade the superficial epidermis of the maxillary process after E13 (English et al., 1980; Erzurumlu and Killackey, 1983). Brainstem trigeminal nuclei follow a similar though shorter neurogenetic timetable, between E12 and E15 (Altman and Bayer, 1980a–c). Our study shows that newly differentiated trigeminal ganglion cells extend peripheral and central processes in an orderly fashion before the differentiation of their respective targets. Such order in initial outgrowth of primary sensory neurons has also been reported for the embryonic chick trigeminal and chick and rat dorsal root ganglia (Noden, 1980; Honig, 1982; Scott, 1982; Wessels et al., 1988).

#### *Possible role of chemospecific interactions in the establishment of topography*

During development, sensory axons may navigate along pathways labeled by ephemeral molecular cues (see Dodd and Jessel, 1988, for a review) or along gradients of target-derived diffusible “chemoattractants” (see Tessier-Lavigne and Placzek, 1991, for a review). One such example of chemotropic interaction between afferents and their targets is derived from tissue culture experiments involving the embryonic mouse trigeminal system. E10–E11 mouse trigeminal ganglion cells, when cocultured with maxillary and hyoid processes, extend neurites preferentially toward the maxillary process (Lumsden and Davies, 1983, 1986). Based on the assumption that at the time of explantation of the target tissues the maxillary process has not yet been explored by the pioneering trigeminal ganglion cell processes, Lumsden and Davies suggested that the epithelium of the maxillary process produces a specific “attractant” that guides the trigeminal neurites. Recently, Stainier and Gilbert (1990, 1991), using specific antibodies to newly differentiated trigeminal ganglion cells, showed that the pioneer axons of the mouse trigeminal ganglion invade their peripheral fields by E10 (Stainier and Gilbert, 1990). These observations leave open the possibility that, by the time the so-called “virgin” peripheral explants were taken for coculturing in Lumsden and Davies’ experiments, the pioneer trigeminal axons have already explored and perhaps even altered the state of differentiation of the target tissue.

Our results do not challenge the notion of chemotropic factors attracting trigeminal fibers to peripheral targets. However, if

chemotaxis were the only factor influencing the growth of ganglion cell processes, they would extend diffusely toward the source of the attractant. We show that there is a considerable degree of order between trigeminal fibers as they emerge from the ganglion. The mechanisms whereby this order remains to be determined. The order may be established by axoaxonal interactions mediated via cell surface molecules (Trisler, 1982, 1990; Trisler and Collins, 1987), or by differential gradients of target-associated molecules (Thanos et al., 1984; O’Leary et al., 1990; Baier and Bonhoeffer, 1992). It is highly likely that the chemical milieu within which the leading wavefront of axons and growth cones navigate toward their targets plays a major role in axonal pathway formation (Landmesser et al., 1988). The elaborate bifurcation of a single growth cone into a T-shaped swelling, which occurs only at the leptomeningeal–CNS interface of the brainstem, is also strongly suggestive of surface-associated positional cues.

#### *Spatial order in the trigeminal ganglion cell processes and the formation of somatotopy in the brainstem*

Previously, topographic order in the trigeminal ganglion projections has been noted in studies utilizing silver stains or retrograde labeling of ganglion cells in perinatal rats (Erzurumlu and Killackey, 1982, 1983; Rhoades et al., 1990). However, these studies do not provide direct clues as to whether or not the initial outgrowth of the trigeminal nerve is ordered. In an experiment addressing these issues, Davies and Lumsden (1986) counted the number of axonal profiles in different fascicles of serially sectioned segments of the infraorbital nerve in embryonic mice. They found that the number of axonal profiles in a given fascicle varied considerably over a distance of 200  $\mu\text{m}$ . They concluded that the early outgrowth of the trigeminal ganglion projection was diffuse and that vibrissa-related topography emerged from selective elimination of inappropriately connected fibers (Davies and Lumsden, 1984, 1986). However, the local axonal disorder reported by Davies and Lumsden (1986) does not imply a lack of global order in the trigeminal ganglion projections. Conversely, our observation of spatial order in the peripheral and central projections of the trigeminal ganglion cells (labeled from their peripheral target fields) need not preclude free exchange of fibers between neighboring fasciculi along short segments of the nerve. Finally, the overall spatial order at the outset of trigeminal path formation and at the peak of



trigeminal ganglion neurogenesis argues against the hypothesis that the somatotopic organization of trigeminal ganglion projections emerges from an early exuberance.

The observation of spatial order along axonal pathways is also related to the establishment of axial orientation of periphery-related maps along the rest of the trigeminal neuraxis. While the punctate arrangement of vibrissae on the snout is replicated by the segregation of afferents and neurons in the brainstem trigeminal complex, the ventrobasal thalamus, and the primary somatosensory cortex (Woolsey and Van der Loos, 1970; Van der Loos, 1976; Belford and Killackey, 1979; Erzurumlu et al., 1980; Ivy and Killackey, 1982; Ma and Woolsey, 1984; Bates and Killackey, 1985; Woolsey, 1987), the face map is oriented differently in each of these vibrissa representation areas (cf. Erzurumlu and Killackey, 1980; Bernardo and Woolsey, 1987). We have described a 180° inversion of the vibrissal map at the level of the brainstem. This shift is brought about by a gradual rotation in the positions of the central processes of ganglion cells due to the changing conformation of the brainstem. It is likely that a combination of axial ordering within fiber tracts and conformational changes in the developing brain is, to a considerable degree, also responsible for the absolute orientation of the map in the thalamus and cortex. At least a crude topography in the connections between dorsal thalamus and neocortex is seen prior to the appearance of barrels (Crandall and Caviness, 1984; Dawson and Killackey, 1985; Molnár and Blakemore, 1990), indicating that formation of such ordered connections in the CNS occurs independent of the sensory periphery. In fact, in anophthalmic mice, the axial orientation of the geniculocortical map develops normally in the absence of retinal input (Godement et al., 1979; Kaiserman-Abramoff et al., 1980; for map orientation in the Siamese cat, see also Guillery and Kaas, 1973; Shatz and Le Vay, 1979). Furthermore, while neonatal disruption of the vibrissa nerves alters the pattern of central representations, the orientation of the face maps is not affected (Belford and Killackey, 1979; Killackey and Belford, 1979). Even in the case of mice with supernumerary whiskers and corresponding extra barrels, the axial orientation of the face maps is unaltered (Welker and Van der Loos, 1986). Collectively, these observations argue for the existence of separate strategies for determining axial orientation of a peripheral map and periphery-related pattern formation (cf. Killackey, 1985; Welker and Van der Loos, 1986).

We propose that pattern formation in the rodent trigeminal system can be divided into two distinct phases. In the first phase, the axial framework of the trigeminal neuraxis is laid down in an orderly fashion without guidance from the periphery. This organization is "hard-wired" by the spatial arrangement of developing sensory afferents. In the second phase, peripheral patterns guide the modular patterning of neuronal elements within the constraints of this axial framework. The available data on the consequences of peripheral alterations in the formation of vibrissa-related patterns in the CNS strongly suggest that it is the second phase of vibrissa-related pattern construction that is extrinsically malleable and under directive guidance of the sensory periphery.

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