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Formation of topographic maps

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FORMATION OF TOPOGRAPHIC MAPS

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INTRODUCTION

Most sensory inputs to the central nervous system (CNS) are topographically arranged. For instance, the various retinofugal projections are topographically arranged in the retinoreceptive nuclei, the auditory projection connects tonotopically with the cochlear nucleus, and sensory projections terminate topographically in the primary sensory nuclei. The topography of these projections is continued through several relay nuclei as far as the cortex. Working out the mechanisms by which the topography of these various projections is set up has been a major focus of developmental neurobiology over the past 30 years or so. In this article we attempt to summarize some of this work and to present a coherent view of the development of topographic maps in the nervous system.

Historically, the general view held by neurobiologists was that there must be a single unifying mechanism by which topographic connections are set up. Four main classes of hypothesis were advanced:

1. The postsynaptic structure possesses a series of "addresses" on it, which tell ingrowing axons where to terminate.
2. The presynaptic axon terminals interact with one another on an informationless target structure, and arrange themselves topographically, by means of either positional labels or patterns of electrical activity.
3. Axons, as they grow, remain neighbors with axons that come from

neighboring neurons in the presynaptic structure, and therefore arrive at the postsynaptic structure already topographically arranged.

4. Axons grow out in a topographically arranged time sequence, and connect to a target generated in a matching temporal pattern.

All these hypotheses now to some extent appear correct, and in fact several different mechanisms cooperate to ensure the topography of sensory maps. (See Willshaw & von der Malsburg 1979, Fraser 1980, Fraser & Hunt 1980, Whitelaw & Cowan 1981 for reviews of theoretical issues.) In the following review we look at the evidence for each of the proposed mechanisms of map formation and try to delineate the role of each. We use as our model mainly the visual system, specifically the retinotectal and retinocollicular projections, since much of the work has been done on them. Much valuable information has also come from the study of the retinogeniculate projection; this subject was reviewed in the previous volume of this series (Shatz & Sretevan 1986), and readers are encouraged to read this article in association with the following.

RETINOTECTAL AND RETINOGENICULATE PROJECTIONS

Topography of Fiber Pathways

If topography is to be transmitted from one structure to another simply by axons from neighboring neurons remaining neighbors all the way to their target, then a topographic arrangement of the axons should be demonstrable at all points in their pathway. The topographic arrangement of axons in the optic nerve, for instance, should be just as precise as it is in the optic tectum. Early results suggested that this might indeed be the case (Attardi & Sperry 1963, Scalia & Fite 1974, reviewed in Horder & Martin 1978), but further examination of the topography of the axons in the retinotectal projections of a number of animals led to somewhat variable results.

THE OPTIC NERVE Order in the first part of the pathway, the optic nerve, ranges from very precise, as in fish with ribbon-shaped optic nerves (Scholes 1979), fairly precise, as in teleost fish (Rusoff & Easter 1980, Bodick & Levinthal 1980, Easter at al 1981, Bunt 1982) and chicks (Rager & Rager 1978, Rager 1980, Thanos & Bonhoeffer 1983), rather imprecise, as in frogs (Fawcett 1981, Reh et al 1983, Scalia & Arango 1983, Bunt & Horder 1983) and rats (Bunt & Lund 1982), to very imprecise, as in cats (Horton et al 1979). Since the accuracy of the topography of the axons in many species' optic nerves is considerably lower than that of their retinotectal terminations, the conclusion that axons must maintain their

neighbor relations in order to make topographic maps seemed unlikely. However, all the above studies suffered from the weakness that axon topography was being studied some time after axonal growth; perhaps the axons had become disarranged after they had grown (e.g. Cima & Grant 1982). Williams & Rakic (1985), however, examined the anatomy of axons and growth cones in serial EM sections of the embryonic monkey optic nerve, and found that growth cones frequently change the axons to which they adhere. One end of a growth cone might have its processes adherent to one set of axons, while the other end of the growth cone would be associated with a quite different group of axons. These findings collectively make untenable the idea that topography in the retinofugal projections is entirely a product of the maintenance of neighbor relations between axons.

THE OPTIC TRACT Studies of the optic tract in frogs and fish have revealed that the topography of axons in this part of the visual pathway is generally fairly precise, and that the topography of this order is different from that found in the optic nerve, thus indicating that a rearrangement of axon topography must occur in the region of the chiasma (Scalia & Fite 1974, Scholes 1979, Steedman 1981, Easter et al 1981, Fujisawa et al 1981a,b, Fawcett & Gaze 1982, Bunt 1982, Reh et al 1983, Fawcett et al 1984b). The topography is present from the earliest embryonic stages (Holt 1984, Holt & Harris 1983), and is particularly precise as axons grow onto the optic tectum itself (Fawcett & Gaze 1982, Reh et al 1983, Stuermer & Easter 1984a, Rusoff 1984). The optic tract is arranged so that circumferential retinal order is represented across one axis of the tract, and time of axon growth across the other, with the latest growing axons positioned most superficially. A similar ordering is found in the chick (Thanos & Bonhoeffer 1983). In mammals, time of axon arrival is represented across the depth of the tract as in lower vertebrates (Walsh et al 1983, Walsh & Polley 1985, Guillery et al 1982, Walsh & Guillery 1985, B. E. Reese, personal communication, Reese & Guillery 1987), and in the cat there is a map of circumferential retinal position across the other axis; however, this is a complex map, with each type of ganglion cell appearing to make a separate, overlapping map (Aebersold et al 1981, Torrealba et al 1982, Mastronarde 1984). As in the lower vertebrates, there is a change in fiber order in the region of the chiasma.

How is the mapping of circumferential order achieved? In frogs there is evidence for some form of active fiber guidance. In *Xenopus*, eyes can be reconstructed at embryonic stages to contain two nasal, ventral, or temporal half retinas. Despite such eyes producing a roughly normal number of axons, the nerve fibers only travel in the part of the optic tract that would contain axons from the appropriate half of a normal eye (Straznicky

et al 1979, Steedman 1981, Fawcett & Gaze 1982). The mechanism behind this active fiber guidance may involve axons specifically following axons from neighboring regions of the eye that have already reached the tectum, since some behavior of this kind is demonstrated by regenerating retinotectal axons (Gaze & Fawcett 1983; Fawcett 1985, Taylor & Gaze 1985). In the chick, however, mechanical factors may largely govern the pathway that axons take as far as the optic tectum. Injection of anti N-CAM (Neural Cell Adhesion Molecule) into the developing chick eye deranges the pathway of axons through the retina and into the optic nerve, and the axons displaced by this treatment remain displaced right into the optic tectum (Thanos et al 1984). Only when they reach the tectum do a few of the axons correct their pathway.

The observation of topographic ordering of axonal growth in the optic tract led to the hypothesis that ordered ingrowth of axons alone might be sufficient to order the retinofugal projections; the topography might be cleaned up later by axon-axon interactions (see below). However, a necessary prediction of such a hypothesis is that axons growing into the tectum from a completely anomalous route should be unable to form a normal topographic map. In the axolotl, Harris (1982) was able to make animals in which a single eye innervated an otherwise "virgin" tectum via a completely abnormal pathway, and such animals had normally ordered retinotectal projections. One is therefore led to the conclusion that the precise topography of axons as they grow onto the optic tectum is not a critical factor in establishing the topography of the axon terminations. There must be some form of addresses on the tectum that tell the axons where to terminate. (See *Chemoaffinity Labels* below.)

Ordering in the deep-to-superficial axis of the tract is clearly related to time of axon growth; the most recently grown axons are found superficially. This is presumably achieved by an affinity of growing axons for the glia limitans, or by mechanical factors. Could time of axon arrival be a topographic ordering factor? In frogs this is unlikely, since delaying axon growth does not affect the final topography of the retinotectal map (Feldman et al 1971, Holt 1984).

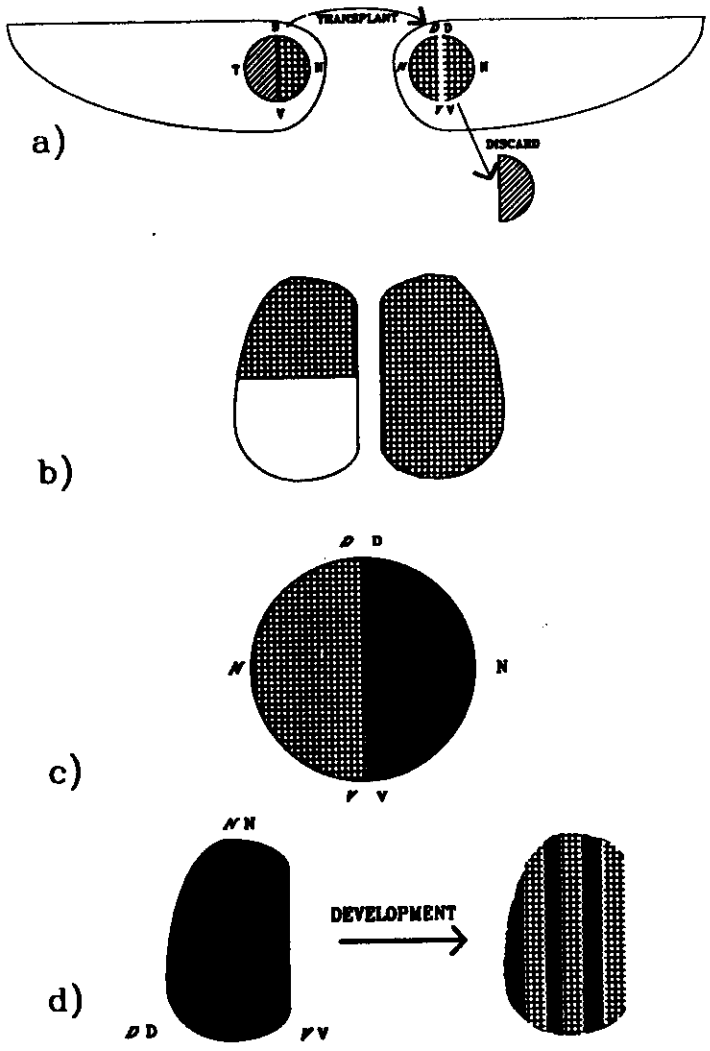
In the chick and frog there is evidence for specific interactions between axons from temporal retina, which tend to adhere to one another, as opposed to fibers from nasal retina, which do not (Gaze & Fawcett 1983, Bonhoeffer & Huf 1985, Halfter et al 1981). The role that these interactions play in the ordering of axonal growth is not clear.

Is there any functional reason that the optic tract should be so precisely ordered? One possible advantage of such an arrangement is that axons as they grow onto their target are immediately guided to the correct area in which to terminate. If axons were to grow in randomly, they would have to search much of the target structure for an appropriate termination site; as it is they are guided there directly.

Chemoaffinity Labels

The chemoaffinity hypothesis postulates the existence of chemical labels, distributed in a graded fashion across the retina and tectum, which allow each retinal cell to recognize its proper tectal termination site (Sperry 1944). In this section, we present evidence that argues compellingly that retinal ganglion cells do behave as though they bear quite finely graded "identities" that reflect their positions of origin. We also present evidence for positional labels of a much weaker and more elusive nature in the tectum.

RETINAL LOCUS SPECIFICITIES The most compelling evidence that retinal ganglion cells bear some label or characteristic by which they can be distinguished from one another comes from studies of compound eyes in *Xenopus*. Surgical techniques can be used in embryos to construct eyes by fusing various fragments of host and donor eye rudiments. For example, a nasal quadrant or half of a donor's right eye can be excised, rotated, and implanted in place of the temporal quadrant or half of a host's eye. (See Figure 1A.) As the compound eye grows, the grafted cells and their progeny can retain their original nasal-pole characteristics; the graft's projections to the tectum can make connections in register with the host's nasal retinal projections (see Figure 1B). Thus the graft continues to behave as though it were still in its original nasal position (Gaze et al 1963, Feldman & Gaze 1975, Gaze & Straznicky 1980, Straznicky 1981, Cooke & Gaze 1983, Willshaw et al 1983). Similar results can be obtained with sectors taken from any part of the eye; projections from wedges as small as about 30° can be resolved with electrophysiological techniques. Whether the mosaic of specificities is so fine-grained that each ganglion cell is distinguishable from its neighbors is not yet known. These experiments demonstrate that not only the ganglion cells, but also their axons, carry these specificities, and that the optic axons must be able to interact with one another in such a way as to ensure that axons bearing the same positional labels innervate the same area of the tectum. These interactions are independent of the actual position that the ganglion cells occupy in the compound eye. We emphasize that this form of axon-axon interaction is not likely to be mediated by a process of correlations of firing patterns (see below). Indeed, in compound eyes, ganglion cells that have the same embryological identity may well be situated at opposite poles of the retina and therefore have minimal similarity in their firing patterns. Thus, it seems reasonable to propose that there is a mechanism of axon-axon interaction, such as graded adhesion, that is independent of activity-mediated axon-axon interactions.



How and when do ganglion cells acquire their identities? To test whether retinal ganglion cells inherit their identities or whether they acquire them from neighboring tissue, whole eyes or parts of eyes may be inserted into new positions or new orientations in *Xenopus* embryos. Later, one may assess whether the optic axons form a map as though their cell bodies were still in their original locations or whether they form maps that are consistent with the cells' new positions (Hunt & Jacobson 1972, Sharma & Hollyfield 1974, Feldman et al 1983). In the previous paragraph, we cited some experiments that suggest that retinal cell identities are stable, but many data seem to suggest the opposite (Jacobson 1967, Hunt & Jacobson 1973, 1974, Cooke & Gaze 1983, Willshaw et al 1983, O'Rourke & Fraser 1986b).

Some of these apparent contradictions stem from the fact that cellular movements have a major influence on the final pattern of projections formed by a rotated retina or retinal graft and may confound the experimenter's intent in constructing a particular anatomical arrangement. Holt (1980) has shown that neural precursors can migrate from the optic stalk into the eye cup and reform an essentially normal retina after a surgical graft or rotation has been performed; and Ide et al (1984) have found that cells within a surgically halved eye can move to new positions and reconstitute a duplicate half-eye that maps as the mirror-image of the original half. In such cases, the final polarity of the maps reflects the original specificities of cells that have moved to positions unintended by the experimenters. Perhaps such cell movements within retinal grafts explain why some grafts seem to give completely or partially respecified maps whereas others yield maps that are strictly consistent with the original location and polarity of the grafted segment (Hunt & Jacobson 1973, Ide et al 1979, Cooke & Gaze 1983, Willshaw et al 1983).

We do not yet know how long during development such rearrangements can occur. A prolonged period of malleability might help to explain the intriguing results of O'Rourke & Fraser (1986b), who have studied the projections from an eye containing a temporal half-eye graft in dorso-ventrally inverted orientation. Their new vital-dye labeling techniques

Figure 1 (*a*) Construction of a double-nasal eye. Nasal half of right eye replaces temporal half of left eye to produce compound eye with normal dorso-ventral polarity. (*b*) When compound eye innervates a tectum lacking other retinal input (*right side*), the projection from each half-eye spreads out to cover the whole rostrocaudal extent of the tectum. When the compound eye innervates a tectum that also has input from a normal eye, the double-nasal eye's projection maps in register with the nasal half of the normal eye. (*c*, *d*) The two nasal halves are shown with different patterns to illustrate that their projections initially overlap but later segregate into bands. N: nasal; T: temporal; D: dorsal; V: ventral.

reveal that the graft initially projects in an inverted manner, which reflects its embryological origin; nevertheless, the projection from the subsequently produced cells is not inverted. Does this switch in polarity result from cell movements, from respecification of graft cell identities, or even from axon-axon interactions between graft and host tissue, or from other mechanisms, discussed below, that can influence the topography of the map quite independently of positional labels?

The physical nature of retinal "labels" or "specificities" is not understood. Do differentially distributed cell adhesion molecules constitute the labels? Recent experiments to examine this question have tested the adhesive behavior of cultured embryonic chick retinal axons. Bonhoeffer & Huf (1985) have shown that temporal axons strongly prefer to grow along other temporal axons and not upon nasal axons: nasal axons showed no preference. A complementary nasal-temporal distinction was shown by Halfter et al (1981), who found that tectal membranes adhere avidly to nasal retinal neurites but not to temporal neurites. Neither group found any differential behavior of dorsal versus ventral retina. Thus, these adhesion assays show dramatic nasal-temporal distinctions but do not reveal any of the fine-grain distinctions that are implied by other experiments on retinal specificities.

Another approach to searching for the basis of retinal specificities is to try to identify some cellular component that is differentially distributed across the retina. Liu et al (1983) have found that peanut agglutinin binds to chick retinal plexiform layers with a spatiotemporal gradient that begins near the center of the temporoventral quadrant and progresses toward the periphery. Trisler et al (1981) identified an antigen, dubbed TOP (toponymic), that is distributed in a stable gradient from ventronasal (low) to temporodorsal (high) retina. Constantine-Paton et al (1986) have discovered an antigen, probably a ganglioside, that is more densely distributed in the dorsal half of the rat retina than in the ventral half; the gradient first becomes apparent in the retina at embryonic day 17, the same age at which retinal axons begin to terminate in the tectum. The involvement of any of these gradients with the mechanisms underlying retinal specificities is still unknown.

TECTAL LOCUS SPECIFICITIES Experiments in which optic axons are forced to reach the tectum via abnormal routes demonstrate that the tectum bears markers that can align the retinal map to conform to an intrinsic tectal polarity. For example, ablation of one tectal lobe on the day of birth in hamsters induces the axons appropriate to the ablated tectum to recross the midline between the tecta; even though they enter via this abnormal pathway, they form a map that is "normal" in the sense that nasal axons

innervate caudal tectum, temporal axons innervate rostral tectum, and so forth (Finlay et al 1979). Similarly, axons from surgically implanted eyes can reach the tectum by a variety of abnormal routes but still form maps of proper orientation with respect to retinal landmarks (Sharma 1972b, Constantine-Paton 1981, Harris 1982). In addition, early rotations of the tectal primordium often lead to the establishment of ectopic optic tracts, but the retinotectal maps still become oriented normally with respect to the tecto-diencephalic border, wherever that happens to be (Chung & Cooke 1978).

The above experiments demonstrate that the tectum contains, at minimum, enough information to entrain the retinotectal map to the proper *polarity*. The following experiments indicate that the tectum actually bears *positional* markers rather than simply polarity markers. In other words, some physico-chemical property of tectal cells exists that serves not simply to orient the map but also to help position that individual components of the map. One such class of experiments involves the translocation of grafts of tectal tissue by exchanging rostral and caudal pieces of tectum; in many cases, cut retinotectal axons regrow to innervate the piece of tectum that they would normally innervate, despite the fact that this action brings them to the wrong place relative to the tectal borders and to the axons occupying the intact tissue (Levine & Jacobson 1974, Sharma 1975, Yoon 1980, Gaze & Hope 1983).

Examination of the distribution of retinotectal projections from partial or compound eyes also reveals that optic axons of a given retinal origin preferentially innervate the correct tectal location when they first reach the tectum (although rearrangements may occur later) (Crossland et al 1974, Straznicky et al 1981, Holt & Harris 1983, Holt 1984, O'Rourke & Fraser 1986a). Even when retinal axons are prevented from firing by application of tetrodotoxin, they are able to find approximately correct target regions with the tectum (Harris 1980, 1984, Meyer 1983, Schmidt & Edwards 1983) and lateral geniculate nucleus (Archer et al 1982, C. J. Shatz and M. P. Stryker, personal communication).

What is the nature of the interaction between retinal axons and tectal cells that underlies this selective innervation? The most popular hypotheses have focused on adhesion properties and have motivated experiments to test whether a given set of retinal cells, axons, or membranes adheres preferentially to the appropriate tectal membranes (Barbera 1975, Marchase 1977, Meyer 1982b, Fraser 1985). Intriguing evidence for such a mechanism comes from the experiments of Bonhoeffer & Huf (1982), who found that chick axons from temporal retina prefer to grow upon rostral (appropriate) rather than caudal (inappropriate) tectal cell monolayers. This preference is graded; for example, temporal axons grow more readily

on cells from the rostral 20% of the tectum rather than from cells taken from the 20% immediately caudal to that rostral strip. However, these results have not yet been replicated for nasal, dorsal, or ventral retinal axons. A transient gradient of TOP molecules (see above) has recently been found in the developing chick tectum (Trister & Collins 1987). The molecule is most abundant in ventral tectum and least abundant dorsally. This distribution is complementary to the retinal TOP gradient; thus, parts of the retina with high TOP concentrations connect to the parts of the tectum which initially have high TOP concentrations, while corresponding regions with low amounts of TOP also become connected. These results suggest, but do not prove, that preferential adhesion is the mechanism underlying topographic innervation of target tissue by afferent axons.

Plasticity in Retinotectal and Retinocollicular Projections

As explained in the preceding section, evidence is now good that the optic tectum bears positional labels that guide retinofugal fibers to an appropriate termination site. However, there is also much evidence that these labels are not absolute determinants of the termination sites of axons.

MISMATCH EXPERIMENTS One way of testing whether retinofugal axons are rigidly matched to a target region of the tectum is to create a size mismatch between retina and tectum by surgically reducing the size of either the retina or the tectum, so creating a situation in which half the tectum is denervated, or half the retina has its target removed. The fish and frog retinotectal projections show considerable plasticity following these manipulations. If half the tectum is ablated, the "dispossessed" axons that had innervated the ablated area of tectum generally gradually colonize the remaining half tectum, and the incumbent fibers retreat to make space for them. This leads to a "compressed" retinotectal map, with the entire retina represented over half a tectum (Gaze & Sharma 1970, Yoon 1971, Sharma 1972a, Cook 1979, Jacobson & Levine 1975, Ingle & Dudek 1977, Meyer 1977, Schmidt 1983) [although in *Rana* this only happens if the optic nerve also has been cut and allowed to regenerate (Udin 1977)]. Similarly, when half the retina is removed, thereby denervating half the tectum, the axons from the remaining half retina "expand" to cover the entire tectum (Horder 1971, Schmidt et al 1978, Udin & Gaze 1983).

Experiments in *Xenopus* yield the same type of result. Surgically constructed compound eyes contain only half the usual complement of retinal addresses but a roughly normal number of retina ganglion cells (see Figure 1a). Such compound eye maps are not confined to the "appropriate" half of the tectum, but expand to cover its entire surface (Figure 1b, right) (Gaze et al 1963, Straznicky et al 1974, 1981). Similarly, when half an eye

is removed at embryonic stages, and the remaining half rounded up to prevent regrowth, the projection from this half-sized eye, when mapped in adult frogs, covers the entire tectum (Straznicky et al 1980a).

Both expansion and compression are seen in the mammalian retinocollicular projection, but only during the first ten days or so of life; after this period plasticity is no longer demonstrable. Thus ablation of half the newborn hamster colliculus leads to a compressed map of the whole retina on the remaining colliculus (Schneider & Jhaveri 1974, Finlay et al 1979) [although it is comprised of a lower number of axons than normal (Udin & Schneider 1981)]. Similarly, ablation of part of the retina allows remaining axons to fill in vacated space on the colliculus (Frost & Schneider 1979).

In contrast, the chick is unusual in that its retinotectal projection appears to have little plasticity: when part of the eye is ablated at early embryonic stages, the remaining retina only connects to the positionally appropriate region of the tectum, leaving much of the tectal surface uninnervated (Crossland et al 1974, McLoon 1985).

A form of developmental plasticity known as "shifting connections" is seen in the fish and frog retinotectal projection. As an animal grows, both the retina and optic tectum grow with it, and new retinofugal fibers constantly arrive at and connect with the tectum. However, retina and tectum grow in very different ways, the retina by the addition of cells all round the ciliary margin, and the tectum by addition of cells to its caudomedial edge (Straznicky & Gaze 1971, 1972, Johns & Easter 1977, Beach & Jacobson 1979, Tay et al 1982, Raymond & Easter 1983). Gaze et al (1974) argued that in order to maintain a retinotopic map on the tectal surface, the earlier arriving axons would gradually have to shift their initial functional connections to a site more caudally in the tectum. It has since been demonstrated in *Xenopus* (Gaze et al 1979b, Fraser 1983), *Rana* (Reh & Constantine-Paton 1984, Fraser & Hunt 1986), goldfish (Easter & Stuermer 1984), and perciform fish (Rusoff 1984) that this process occurs. Birds and mammals develop over a much shorter period of time, and the retinofugal fibers innervate a target that is nearly fully developed, so one would not expect shifting connections to be so important in development.

These results point toward the existence of competitive interactions between optic fibers on the tectal surface. If each axon terminal competes to occupy as much space on the tectum as possible, then retinofugal axons will always occupy all the available tectal space. Many workers therefore attempted to develop theories of retinotectal map formation that did not rely on tectal labels at all, but used a combination of axonal guidance (see first section) and axonal competition. This period of theoretical uncertainty continued until (*a*) experimental evidence demonstrated that there must be positional labels on the tectum and that axonal pathway guidance was

not the main mechanism whereby the retinotectal map was set up, and (*b*) the significance of the phenomenon of ocular dominance stripes was understood.

OCULAR DOMINANCE STRIPES In fish and frogs, the retinotectal axons from one eye all project to the contralateral optic tectum. However, a variety of maneuvers can cause axons from both eyes to innervate the same tectum. When this is done, the projections from the two eyes, instead of intermixing, separate out into mutually exclusive ocular dominance stripes (Levine & Jacobson 1975, Law & Constatine-Paton 1980, Straznicky et al 1980b, Willshaw & Gaze 1986). Ocular dominance stripes may also be created in chicks (Fawcett & Cowan 1985). The axons from the two half eyes that constitute a "compound" eye also separate into stripes (Fawcett & Willshaw 1982, Ide et al 1983). (See Figure 1c,d.) In mammals, a proportion of the axons from each eye innervate the ipsilateral colliculus: initially this ipsilateral projection is spread diffusely, but during the first few days of life it segregates into eye-specific patches, which are probably equivalent to ocular dominance stripes (Graybiel 1975, Harting & Guillery 1976, Land & Lund 1979, Frost et al 1979, Williams & Chalupa 1982, Godement et al 1984).

A single unifying mechanism cannot explain both topographic mapping and ocular dominance stripe formation. Instead, at least two mechanisms must be invoked, which have been brought into conflict on the doubly innervated tectum. For instance, in the case of a double nasal compound eye (see Figure 1), the fibers from the two nasal poles of the retina grow to the caudal tectum, and initially their terminals overlap (J. W. Fawcett, D. J. Willshaw, and J. S. H. Taylor, unpublished results). This part of their behavior must be controlled by a system of retinal positional addresses, since the axons from the graft nasal pole behave like the normal nasal retina. However, the axon terminals from the two "nasal" poles now separate out into eye-specific stripes. On the basis of retinal positional labels they should be indistinguishable; therefore, another mechanism must be responsible. If there were a mechanism that caused each cell's axon to associate preferentially with the axons of its present retinal neighbors, then axons from the two nasal poles would subdivide their tectal territory, forming dominance areas. Similarly, embryologically equivalent axons from two separate eyes would occupy the same general region of the tectum, but, within that region, their tendency to associate with axons from neighboring ganglion cells would promote the formation of ocular dominance areas. Activity cues, discussed below, are likely to underlie this behavior.

REFINEMENT OF THE RETINOTECTAL MAP When the optic nerve of a frog or

fish is cut, the axons regenerate back to the tectum and make connections. Initially, the topographic accuracy of those connections is low, and an electrophysiologically recorded retinotectal map shows some degree of disorganization, as reflected in the large, diffuse morphology of the terminal arbors. However, in time the topography of the map improves, until it is as accurate as a normal one (Gaze & Jacobson 1963, Udin 1978, Meyer 1980, Humphrey & Beazley 1982, Schmidt & Edwards 1983, Rankin & Cook 1986), and the terminal arbors become smaller and more focused (Meyer 1980; Fujisawa et al 1982, Schmidt et al 1984, Stuermer 1984, Stuermer & Easter 1984b). There is also evidence that the accuracy of the fish and frog retinotectal map is rather low early in normal development, and improves with time (Gaze et al 1974; O'Rourke & Fraser 1986a). Again, the morphology of the terminal arbors reflects this topographic refinement; in young frogs, arbors are large relative to the size of the tectum, particularly in the rostro-caudal axis, but as the tectum grows the proportion of its area occupied by each arbor diminishes (Sakaguchi & Murphey 1985, Lázár 1973, Piper et al 1980, Fujisawa 1987).

In the newborn rodent, the topography of the retinocollicular projection is imprecise. A proportion of ganglion cells connect to completely inappropriate regions of the colliculus, and the terminals of the retinocollicular axons may extend over much of the length of the collicular surface. Over the first few days of life, the terminal arbors become focused to a localized area, and most of the ganglion cells that have sent their axons to inappropriate parts of the colliculus die. These mechanisms cooperate to refine the topography of the map substantially (Cowan et al 1984, Schneider & Jhaveri 1984, Fawcett & O'Leary 1985, Sachs et al 1986, O'Leary et al 1986). Similarly, in the developing chick, some axons make inappropriate projections that are not demonstrable later on (McLoon 1982, 1985).

How might the refinement of the map be achieved? Theoretically, it could be refined by axons gradually searching out correct tectal addresses with more and more precision. The available evidence, however, suggests that tectal labels are imprecise guides, at least in fish and frogs. Moreover, the ocular dominance stripe phenomenon suggests a mapping mechanism that is independent of retinal and tectal positional labels. The obvious alternative is a mechanism that acts by ensuring simply that neighboring ganglion cells project to neighboring tectal sites. How might information on the relative contiguity of ganglion cells be transmitted to the axon terminals? The most likely possibility is that neighboring ganglion cells have relatively synchronous patterns of electrical activity, and a mechanism exists that ensures that neighboring terminal arbors that fire synchronously are stable, whereas nonsynchronously firing terminals are unstable—a class of mechanism originally proposed by Stent (1973). Some

evidence indicates that neighboring ganglion cells do have correlated activity (Arnett 1978, Mastronarde 1983, Ginsburg et al 1984). This hypothesis, if correct, predicts that abolishing electrical activity in the retinofugal axons should disable both ocular dominance stripe formation and the refinement of a disorganized retinotectal map. Both these predictions turn out to be correct. Electrical activity in the eye can be blocked by injections of tetrodotoxin (TTX), and if this block is maintained over the relevant period, stripe formation (Meyer 1982a, Boss & Schmidt 1984, Reh & Constatine-Paton 1985), ocular dominance patch formation in hamsters (Holt & Thompson 1984), and map refinement (Meyer 1983, Schmidt & Edwards 1983) are prevented. The refinement of the rat retinocollicular projection by the preferential death of erroneously projecting cells is also disabled; retinal ganglion cell death becomes random in the presence of a TTX block (Fawcett & O'Leary 1985, O'Leary et al 1986).

The hypothesis that correlated firing leads to synaptic stabilization implies that simultaneous converging input produces a qualitatively different effect than the same amount of nonsimultaneous input. Recent research on glutamate receptors has revealed a possible mechanism whereby simultaneous activity could trigger events, such as increased calcium influx, which would not occur in response to noncorrelated activity: NMDA (*N*-methyl-D-aspartate) receptors conduct calcium currents when the receptors bind NMDA or glutamate and, at the same time, the membrane is depolarized by several excitatory inputs (MacDermott et al 1986, Ascher & Nowak 1987, Cull-Candy & Usowicz 1987, Jahr & Stevens 1987). Blocking these receptors with the antagonist APV (aminophosphonovaleric acid) by chronic application to the tectum of three-eyed tadpoles does not block optic nerve firing but does induce desegregation of retinotectal stripes (Cline et al 1987). This exciting result raises the question of whether NMDA receptors also mediate the contribution of activity to the formation of other topographic maps, such as those described below.

Mapping refinement in fish is prevented when all the ganglion cells are made to fire synchronously by rearing animals under stroboscopic illumination (Schmidt & Eisele 1985, Cook & Rankin 1986). However, simple competition for terminal space continues in the absence of electrical activity (Meyer & Wolcott 1984), and a retinotectal map possessing at least a crude degree of order can be formed (Harris 1980), presumably based entirely on tectal positional labels. Moreover, apart from the electrically controlled mechanism, terminal arbors can interact with one another on the basis of positional labels (see above).

The formation of experimentally induced ocular dominance stripes in chicks occurs while the animal is still in the egg, usually in the dark, and possesses a retina that is anatomically immature and unable to respond to light stimula (Rager 1976). Such stripes are formed in rodents during the period when the ipsilateral projection is becoming restricted into patches, topographic targeting errors are being corrected, the eyelids are closed, and the retinal circuitry is incomplete (Weidman & Kuwabura 1968). Assuming that these processes are all electrically driven, as the TTX experiments suggest, then spontaneous activity in the ganglion cells must be responsible. Such spontaneous activity has been observed in newborn rabbit optic nerve fibers, at an equivalent stage of retinal development (Masland 1977, McArdle et al 1977), and in dissociated rat retinal ganglion cells (Lipton & Harcourt 1984).

TERMINAL ARBORS A topographic map is made up of many terminal arbors, and the behavior of these determines the dynamic properties of the map as a whole. What do we know about the forces that shape terminals? The simplest model would be one in which terminal arbors constantly compete to occupy tectal space; success or failure in this competition would be governed by an impulse activity controlled mechanism, which would give a competitive advantage to the terminals making the most topographically appropriate connections. However, this picture appears to be oversimplified. Some evidence suggests that at a certain stage in their evolution, terminal arbors will withdraw their more far-flung branches even in the absence of competition. For instance, even in the presence of a TTX block, regenerated fish terminal arbors change in time from a diffuse to a more focused morphology (J. T. Schmidt, personal communication), and some evidence suggests that this is also the case in the developing rat retinocollicular projection (Fawcett & O'Leary 1985, O'Leary et al 1986). Similarly, Sretevan & Shatz (1986) report that terminal arbors in the cat geniculate are of normal size even when competition for terminal space is reduced by removing one eye; and in the peripheral nervous system, neuromuscular junction terminals reduce the number of muscle fibers they innervate, and therefore their size, even when competition is considerably reduced by decreasing the number of axons innervating the muscle (Brown et al 1976). Some terminals, however, increase their size in development rather than contract (Sur et al 1984). Although little evidence is available on the subject, it may be that the natural history of most terminal arbors is to focus themselves by retracting their more far-flung branches, regardless of competition from other arbors.

MATCHING OF SENSORY MAPS IN THE VISUAL SYSTEM

Virtually all visual nuclei receive multiple sets of inputs, which are aligned to bring the individual representations of external space into register. For

example, the superior colliculus receives input from the contralateral eye directly via the optic nerve and also, indirectly, via structures such as the striate cortex and the parabigeminal nucleus; the ipsilateral eye also sends both direct and indirect inputs; and the auditory and somatosensory systems additionally contribute topographic maps (Stein 1984). These inputs may be interdigitated or intermingled in the same laminae or may be superimposed in adjacent laminae, but in all cases, the maps are in topographic register with one another such that a single region in the visual field is represented in a small region of the nucleus. At least two mechanisms can contribute to the establishment of such congruence. First, chemospecific cues may be equally accessible to all populations and all of the afferent axons are equipped to read the cues properly. Second, visually-evoked firing patterns may provide the information that aligns one group of axons with respect to another. As we shall discuss in this section, the relative roles of these mechanisms can differ markedly in different nuclei and from species to species, with activity cues dominant in some cases and chemospecific cues dominant in others.

Isthmotectal Maps

This point is dramatically illustrated by examining the relation between the tectum (superior colliculus) and the midbrain structure known as the nucleus isthmi in amphibians (Grobstein et al 1978, Gruberg & Udin 1978), parabigeminal nucleus in mammals (Graybiel 1978, Sherk 1978), or nucleus isthmi pars parvocellularis in birds (Hunt & Künzle 1976). This nucleus receives a topographic input from the ipsilateral tectum (superior colliculus); the nucleus then sends a matching topographic map back to the ipsilateral tectum and, in amphibians and mammals, also sends a topographic map to the contralateral tectum. The uncrossed isthmotectal projection is quite capable of forming a topographically normal map in the absence of any visual input, as experiments using bilaterally enucleated frogs (Constantine-Paton & Ferrari-Eastman 1981) and birds (O'Leary & Cowan 1983) demonstrate.

Similarly, the role of visual input on the crossed isthmotectal/parabigeminotectal projection has been tested in several species. This projection relays visual input to the tectum from the ipsilateral eye, forming a map in register with the map from the contralateral eye (Keating & Gaze 1970, Glasser & Ingle 1978, Graybiel 1978, Gruberg & Udin 1978, Sherk 1978). In order to test whether visual information is used to bring these two maps into register, one may rear an animal with one eye rotated. This manipulation does not change the anatomical connectivity of the isthmic/parabigeminal axons in *Rana pipiens* or *Hyla moorei* frogs (Jacobson & Hirsch 1973, Beazley 1979, Kennard & Keating 1985) or in cats (H. Sherk, C. Peck, and S. B. Udin, unpublished observations); the two eyes' maps thus develop out of register.

In contrast, early eye rotations in *Xenopus* lead to dramatically different results (Gaze et al 1970, Keating 1974). Even though one eye is rotated while the other eye is normally oriented, the isthmotectal map on each tectum comes to be in register with the contralateral map on that tectum. For example, if the right eye is rotated 90° clockwise and the left eye is unrotated, both maps to the left tectum will be rotated 90° while both maps to the right tectum will be normal. Horseradish peroxidase tracing experiments have shown the morphological correlate of this arrangement to be the rerouting of isthmotectal axons; the axons enter the tectum normally and grow toward their normal termination sites but then develop abnormal trajectories that eventually enable them to form a reoriented map (Udin & Keating 1981, Udin 1983). Probably a given axon terminal becomes stabilized at a new position because there is an optimum correlation between its visually evoked activity and that of the adjacent retinotectal axons from the opposite eye. Ultrastructural evidence suggests that isthmotectal and retinotectal axons both terminate on tectal cell dendrites (Székeley & Lazar 1976, Udin & Fisher 1986). Presumably, a visual stimulus at the appropriate receptive field location will activate the retinotectal synapse and will somehow "ready" the dendrite; if the isthmotectal axon fires after an appropriate delay (due in part to the polysynaptic nature of the ipsilateral pathway), a further change occurs that helps to stabilize the recently activated isthmic axon.

Further evidence for the role of visual input in aligning the two maps during normal development is the fact that dark-rearing prevents the isthmotectal axons from establishing a normal topographic ipsilateral map (Keating & Feldman 1975).

Callosal Visual Connections

Another system in which visual activity influences the formation of retinotopic registration between two separate sets of input is the callosal projection in the mammalian visual cortex. In normal adult mammals, areas 17 and 18 in each hemisphere contain maps of all of the contralateral hemifield and a few degrees of the ipsilateral hemifield. These half-maps are "tied together" by callosal axons that relay information about positions along the vertical meridian from the 17/18 border in one hemisphere to the 17/18 border in the opposite hemisphere.

The adult callosal connections are sculpted out of the much more diffuse distribution that has been observed in newborn rodents (Lund et al 1984, Mooney et al 1984) and kittens (Innocenti 1981) [but not monkeys (Dehay et al 1986)]. Callosal axons originate from cells distributed throughout

areas 17 and 18; as normal development proceeds, most of these axons are eliminated from the callosum, leaving predominantly those axons originating from cells near the 17/18 border (Olavarria & Van Sluyters 1985). Despite the widespread origin of most early callosal axons, the axons normally arborize only in the appropriate area, the 17/18 border, from the earliest stages at which they enter the cortical plate (Innocenti 1981, Lund et al 1984, Mooney et al 1984, Olavarria & Van Sluyters 1984). One may hypothesize that visual input preferentially stabilizes connections between cells with the same receptive field locations. Under normal circumstances, this mechanism would ensure that cells with receptive fields near the vertical meridian remain interconnected via the corpus callosum but that other cells, with receptive fields farther from the vertical meridian, would fail to find corresponding targets and would die or withdraw their axons (Stanfield et al 1982, Innocenti & Clarke 1983, Stanfield & O'Leary 1985, Innocenti et al 1986), perhaps because of competition from topographically appropriate geniculocortical axons.

If visual input is a factor in stabilizing connections between cells with matching receptive field locations, then misalignment of the two eyes' visual fields as a result of strabismus should induce anomalous connections. For example, if convergent squint is induced in the one eye, then the cells at the 17/18 border will receive input from two different visual field positions from the two eyes. (See Figure 2.) Moreover, cells at some distance from the 17/18 border will receive input that normally should be relayed to the 17/18 border. Thus, one might expect to find more widespread zones of callosal cells and terminals, with their limits being separated from the 17/18 border by a distance corresponding to the degree and direction of strabismus. This prediction is only partially borne out. Misalignment of the eyes in kittens does lead to an expansion of the zone of callosal cells (Innocenti & Frost 1979, Berman & Payne 1983, Elberger et al 1983, but see Lund et al 1978), but there is no obvious correlation of the degree of expansion or the specific location of the ectopic cells with the magnitude of the strabismus or with the animals' fixation strategies. In many cases, the callosal terminal zone also is expanded, again with no clear correlation with the magnitude of the strabismus (Lund et al 1978, Lund & Mitchell 1979, Berman & Payne 1983). Much of the variability of results no doubt is due to poorly controllable factors such as variable degrees of convergence throughout the critical period and differing degrees of "suppression" of input from the strabismic eye. Firmer conclusions cannot be made, however, until more precise information about the detailed topography of the projections becomes available.

Monocular enucleation in neonatal rats leads to an ectopic band of callosal connections in the hemisphere ipsilateral to the remaining eye

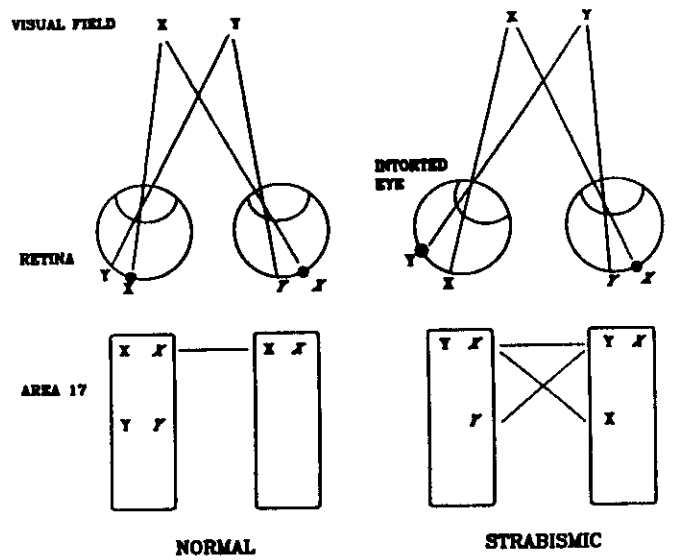


Figure 2 *Left*: In normal adult cats, the area centralis of each eye sees position X on the vertical meridian and transmits this input bilaterally via the lateral geniculate to the cortex near the border between areas 17 and 18. Callosal axons connect the 17/18 border regions but do not connect with areas with receptive fields distant from the vertical meridian (position Y). *Right*: In strabismic cats different connections are predicted. In this example, the left eye is deviated such that position Y rather than X falls on the area centralis. Thus the left eye relays input about position Y to the 17/18 border, while position X is represented in the right hemisphere. Callosal axons that connect cells with the same receptive field locations should connect more sites than normal.

(Olavarria et al 1979); a double representation of the vertical meridian, resulting from anomalous retinogeniculocortical connections, may underlie this extra band of callosal projections. As with studies of strabismic animals, clear interpretation of those results await studies of the projections' topography.

Direct Ipsilateral Retinofugal Maps

In contrast to the marked and obvious influence of visual input on the formation of binocular maps relayed by callosal fibers and by the nucleus isthmi, vision and activity seem to play little, if any, role on the formation of ipsilateral maps relayed directly from the retina. For example, the direct ipsilateral retinothalamic projections in *Xenopus* do not compensate

for an early eye rotation (Kennard 1981) even though the isthomotectal axons in the same animals can fully compensate for the same rotation. The ipsilateral retinothalamic axons instead continue to form connections consistent with their embryonic origin rather than their visual fields.

This lack of influence of visual activity on ipsilateral retinotectal axons is further borne out by examining the response of retinotectal axons to monocular enucleation in neonatal rodents. Some ipsilateral axons establish an expanded projection that retains the normal ipsilateral polarity, with the nasotemporal retinal axis mapped rostrocaudally on the tectum (Finlay et al 1979, Thompson 1979, Fukuda et al 1984, Reese 1986), while other axons may form a second projection of opposite polarity (Thompson 1979, Fukuda et al 1984); this latter projection presumably originates from cells with a "contralateral identity" that normally grow to the ipsilateral tectum and are then eliminated (Jeffery & Perry 1982, Martin et al 1983, Insausti 1984, Fawcett et al 1984a). Thus, the same eye, and even cells in the same region of that eye, can give rise to two opposite maps despite the mismatch of visually evoked firing that results. Some developmental process thus confers drastically different positional specificities upon neighboring retinal ganglion cells.

Little is known about the process that establishes ipsilateral versus contralateral identities in ganglion cells. Briefly, we may mention that ipsilaterally projecting cells are normally born according to a different schedule than contralaterally projecting cells (reviewed in Dräger 1985) and that hormonal (Hoskins & Grobstein 1985) and genetic abnormalities, such as the Siamese mutation in cats, can alter these schedules (Kliot & Shatz 1985) and can change the proportions of cells that project ipsilaterally versus contralaterally.

Registration of Visual and Somatic Maps in the Tectum

The tectum contains not only visual maps but also maps from receptors on the body surface (Wickelgren 1971, Stein 1984). The possibility that the visual maps help to establish the polarity or topography of these other maps has prompted several groups to test whether abnormal visual input to the tectum interferes with establishment of orderly somatosensory maps. Thus far, the evidence for interaction is scanty. Early eye enucleation allows the normally deep somatosensory inputs to innervate more superficial layers that have lost their retinal input (Rhoades 1980, Rhoades et al 1981, Harris 1982, 1983) but does not interfere with the formation of otherwise normal somatotopic maps. Similarly, abnormal visual input induced by a rotated eye does not cause any change in the orientation of the underlying somatosensory map (Harris 1983). However, if optic axons in hamsters are induced to form a mirror image map, the somatosensory map undergoes partial rearrangement, with formation of a partial mirror image map of the ipsilateral body surface superimposed on the normally organized contralateral body map (Mooney et al 1979).

Registration of Visual and Auditory Maps in the Tectum

The superior colliculus contains auditory and multimodal cells with auditory receptive fields that are aligned, at least crudely, with the corresponding maps of visual space when the eyes are centered in the orbit (Dräger & Hubel 1975, Chalupa & Rhoades 1977, L. R. Harris et al 1980, Knudsen 1982, Palmer & King 1982, Middlebrooks & Knudsen 1984, Meredith & Stein 1986). Auditory receptive fields tend to be quite large, and their geometrical centers are often not well-aligned with the visual fields of the same cells, but a better match of visual and auditory maps is achieved by considering auditory "best areas," the most responsive regions of the auditory receptive fields (Jay & Sparks 1984, Middlebrooks & Knudsen 1984).

An example of plasticity of auditory topography comes from the dramatic rearrangements that Knudsen (1983) has demonstrated in the developing barn owl, which displays an exceptionally well-developed ability to localize sound sources (Knudsen 1981). The barn owl is unusual in having multimodal auditory/visual units in all layers of the tectum, not just the intermediate and deep layers (Knudsen & Knudsen 1983). If one ear is plugged in an adult barn owl, the binaural imbalance produces a systematic shift in auditory best areas such that they are out of register with the visual fields; but if one ear is plugged in a young owl, then the auditory receptive fields shift to restore the registration of the auditory with the visual maps (Knudsen 1983). Behavioral tests indicate that the auditory map shifts only if visual input is provided during development; moreover, the magnitude and direction of the shift can be manipulated by rearing the owls with prisms that skew the visual input (Knudsen & Knudsen 1985). Thus, the auditory map organizes with respect to the visual map.

This situation seems reminiscent of the readjustments seen in the tectum of *Xenopus*, in which the ipsilateral eye's map, relayed via the nucleus isthmi, organizes with respect to the contralateral eye's map (Gaze et al 1963). In that system, developing isthmic axons change their termination sites in the tectum when they encounter changes in the visual map coming from the other eye (Udin & Keating 1981). By analogy, one might predict that auditory axons projecting from the owl's inferior colliculus would change their termination sites when they encounter a mismatched visual map in the tectum (Knudsen 1983). Instead, anatomical mapping in one owl reared with a plugged ear indicates that there is no anatomical shift in this connection (Knudsen 1985). At least two possible explanations can

be offered for this surprising result. One suggestion is that the auditory map becomes rearranged at some earlier stage in the auditory pathway (Knudsen 1985), but how visual information would be able to guide such a shift at such locations, where visual input is not available to guide the reorganization of the auditory map (Knudsen & Knudsen 1983), is unclear. Another possibility is that a physiological change in the excitatory and inhibitory processes that construct tectal auditory fields could underlie the observed auditory plasticity; the fact that many auditory fields are extremely large relative to the imposed auditory-visual shifts (Knudsen 1982) raises the possibility that intratectal processes could stably alter best-field locations, much as may occur transiently during eye position shifts in primates (Jay & Sparks 1987). The drawback of this model is that the auditory inputs from the inferior colliculus in owls already have best field maps (Knudsen & Knudsen 1983), and these maps would have to be suppressed in favor of newly constructed maps in the superior colliculus.

Not all species show comparable influences of the visual map upon the developing auditory map. King et al (1985) tested the effects of removing one eye and rotating the other eye by 180° in ferrets at the time of eye opening; the auditory map did not compensate for this discrepancy. Another way to test the possible instructive role of vision upon auditory maps is to rear animals in the dark. Rauschecker & Harris (1983) found that visually deprived kittens showed a shift of some auditory units to superficial layers of the superior colliculus and also noted that auditory fields of multimodal units were abnormally large, indicating that visual input normally plays a role in restricting auditory receptive field size in the colliculus.

TOPOGRAPHIC MAPS OUTSIDE THE VISUAL SYSTEM

The phenomenon of topographic mapping is by no means confined to the visual system. In the following section we examine present evidence on how topography is set up in some other parts of the brain.

Auditory System

The tonotopic maps of the auditory system provide opportunities to address some of the same questions discussed above concerning the mechanisms that establish topographic maps. The technical problems posed by the complicated, delicate, and poorly accessible sensory epithelium of the cochlea and by the difficulty of completely controlling auditory input have slowed progress in studying auditory development, but several systems are beginning to yield intriguing data.

The auditory system is characterized by a plethora of tonotopically organized structures, with representations of frequency mapped along one axis (Aitkin et al 1984). That many of these structures also show clear cytogenetic gradients has raised the question of whether gradients of neuron age provide cues to assist the formation of tonotopic maps (Altman & Bayer 1981). This mechanism seems to be plausible for some, but not all, sets of auditory nuclei. For example, in the chick, the primary brainstem nucleus (nucleus magnocellularis, NM) and the secondary brainstem nucleus (nucleus laminaris, NL) develop with corresponding gradients: the first-born cells in each area eventually mediate high frequencies whereas the last-born cells mediate low frequencies (Rubel et al 1976, Smith & Rubel 1979, Jackson et al 1982). Young & Rubel (1986) have examined the development of the map from NM to the ipsilateral NL. Both of these structures derive from the same ventricular epithelium, with NM arising before NL. The axons from NM initially grow dorsally toward the ventricular epithelium, where they contact and follow the appropriate NL cells as the cells migrate ventrally. Thus, the relative position or relative maturation of an NM axon and its NL target cells may underlie the striking precision with which the NM axons initially establish their tonotopic projections in NL.

In contrast, most developing or regenerating sets of connections among auditory nuclei are initially rather crudely organized and undergo a period of refinement that may entail restriction of arbor size and/or shifting of axonal connections (Jhaveri & Morest 1982, Jackson & Parks 1982, Zakon 1983, Young & Rubel 1986). Neuronal activity may well be an important factor in the process of refinement of tonotopic maps. For example, Young & Rubel (1986) find that refinement of the tonotopic organization of contralateral inputs to NL occurs in large part after the NL has become responsive to auditory input (Jackson et al 1982). In addition, Sanes & Constantine-Paton (1985) demonstrated that abnormal auditory input (clicks or 11 KHz and 14 KHz tones) interferes with the refinement of tonotopy in the inferior colliculus of developing mice; it is not yet known whether the abnormally broad tuning curves are the result of abnormally widespread axon arborization or of improper balance of inhibitory versus excitatory connections.

Somatosensory Systems

SPINAL CORD SENSORIMOTOR PROJECTIONS At first viewing, the "map" from muscle sensory afferents to motor neurons in the ventral horn seems rather crude, there being extensive overlap in the terminal zones of both sensory axons and motor dendrites corresponding to flexor and extensor muscles (Smith 1983, Lichtman et al 1984). However, physiological studies

show that the actual synaptic connections are highly precise (see review by Mendell 1984); for example, intracellular recordings demonstrate that a given spindle afferent makes remarkably few detectable connections onto antagonist motor neurons in either developing or adult frogs (Frank & Westerfield 1983, Lichtman & Frank 1984). Light microscopic comparisons of normal developing dorsal root ganglion (DRG) processes in rats and chicks also are consistent with the early establishment of a very orderly pattern of connections, both peripherally and centrally, without a preceding stage of more widespread or disorderly connections (Honig 1982, Scott 1982, Smith 1983, Tosney & Landmesser 1985a, Dodd & Jessell 1986).

Axon-axon guidance mechanisms may play a role in setting up these orderly connections. Sensory axons enter the limb in intimate association with emerging motor axons (Tosney & Landmesser 1985b), and the sensory axons require guidance by motor axons in order to reach muscles (Landmesser & Honig 1986, Scott 1986). The sensory axon acquires its identity, it has been suggested, as a result of contacting a given muscle; this imposed identity then enables the central process to synapse upon appropriate targets within the cord (Miner 1956, Hollyday & Mendell 1975, Honig 1982, Smith 1983, Frank & Jackson 1986). Thus, if one were to change the axons' peripheral connections during development, one would expect to find altered central connections. One way to alter peripheral connections is to delete some of the dorsal root ganglia and to allow the spared ganglia to expand into the vacated periphery. In bullfrog tadpoles, removal of DRG2, which provides most of the sensory input to the forelimb, induces DRG3 or DRG4 to innervate the arm (Frank & Westerfield 1983, Smith 1986). Anatomical (Smith 1986) and physiological methods (Frank & Westerfield 1983) demonstrate that some of the sensory cells in those ganglia innervate spindles in the arm and are able to synapse upon the newly appropriate motor neurons. In *Rana pipiens* tadpoles, removal of caudal DRGs leads to an expansion of the spared DRGs' peripheral territories but not to an anatomically visible change centrally (Davis & Constantine-Paton 1983); nevertheless, the extensive overlap of fields of adjacent DRGs may perhaps still allow for formation of physiologically appropriate connections. Partial removal of neural crest in chicks results in a limited expansion of afferents from the spared dorsal root ganglia (Scott 1984) and to a similarly limited rearrangement of connections within the spinal cord (Eide et al 1982). Although these deletion experiments show varying degrees of peripheral plasticity, all are consistent with the interpretation that afferents from a given muscle connect to motoneurons that innervate that muscle and not to antagonists or other inappropriate motoneurons.

Grafting experiments also lead to the conclusion that inducing a sensory cell's peripheral axon to innervate a given peripheral target somehow allows that cell's central process to find the appropriate targets in the cord. In bullfrog tadpoles, Smith & Frank (1987) replaced DRG2 with thoracic DRGs; they found that some of the grafted thoracic cells could innervate limb muscles and make highly specific monosynaptic connections onto corresponding motor neurons.

Does the sensory axon's central process find its appropriate motor neuron targets by using cues based on related activity patterns? In an effort to test this hypothesis, Frank & Jackson (1986) altered sensory input from the triceps during development by tenotomizing the muscle, or by suturing it to an antagonist tendon; in both cases, the inappropriate spindle activity did not interfere at all with establishment of precise connections of triceps spindle afferents onto triceps motoneurons.

The identities that DRG axons acquire during some critical period of development seem to remain stable throughout life. Frank & Westerfield (1982) found that the critical period probably ends at about stage 9, when limb muscles normally become innervated; DRG3 axons could replace ablated DRG2 axons in the limb and spinal cord only if DRG2 was removed prior to stage 9. Using older tadpoles as well as postmetamorphic frogs, Sah & Frank (1984) found that transected DRG2 axons regenerate and reestablish connections onto proper motoneurons with almost as much accuracy as normal.

THE PROJECTION OF RODENT VIBRISSAE TO THE CORTEX Rats, mice, hamsters, and guinea pigs have on their snouts rows of vibrissae, which together constitute the animal's most important tactile sensory organ. The importance of the vibrissae to the rat is reflected in the fact that their projection to the sensory cortex occupies a large proportion of its area. In layer IV of the cortex in the region of the vibrissal projection, the cortical cells are divided into groups (barrels), the pattern of which exactly corresponds to the pattern of the vibrissae on the snout (Woolsey & Van der Loos 1970). Each vibrissa can be mapped functionally to the corresponding barrel in the cortex (Welker 1976, Simons 1978). This cortical map is a third-order topographic projection; the axons innervating the hair follicles first project to the principal sensory nucleus and three subnuclei in the trigeminal nucleus in the medulla (Nord 1967, Arvidsson 1982); the neurons here project to the ventrobasal thalamus (Emmers 1965, Waite 1973, Shipley 1974, Verley & Onnen 1981), which in turn projects to the cortex. At each stage of this pathway, cytoarchitectonic or histochemical patches corresponding to the pattern of the vibrissae on the snout can be detected (Van der Loos 1976, Belford & Killackey 1979a,b, Woolsey et al 1979, Durham & Woolsey 1984).

Development The vibrissal projection develops from periphery to center. The trigeminal nucleus first receives innervation from the trigeminal ganglion before birth (Erzurumlu & Killackey 1983), whereas axons from the thalamus do not grow into layer IV of the cortex until after birth (Wise & Jones 1978, Crandall & Caviness 1984). The vibrissa-related organization of patches stained with succinate dehydrogenase (SDH) is first detected in the trigeminal nuclei around the time of birth, then in the thalamus on days 1–4, and in the cortex on days 3–6 (Killackey & Belford 1979, Erzurumlu & Killackey 1983). Similar results are reported for 2-deoxyglucose mapping of the vibrissal projection (Melzer et al 1986). However, a topographically organized set of connections between thalamus and cortex is present before the appearance of the anatomical specialization into whisker barrels (Dawson & Killackey 1985, Crandall & Caviness 1984), and indeed the thalamocortical projection is topographically organized in cortical layer VI before it has invaded layer IV. The projection from the vibrissae to the trigeminal nucleus is also topographically organized before barrels can be detected there by SDH histochemistry (Erzurumlu & Killackey 1983). The formation of barrels seems, therefore, to be the final phase of differentiation of an already topographically arranged projection. There is also some evidence to suggest that the topography of the projection to the cortex is less precise at birth than in adult animals, a notion that implies that some topographic refinement occurs during the early postnatal period (Crandall & Caviness 1984, Kossut & Hand 1984b, Melzer et al 1986). Electrical activity may play some role in this refinement. Removing the whiskers at birth reduces electrical activity in the trigeminal nerve; this does not prevent barrel formation, but it does lead to neurons in the barrel field having abnormal response properties, and to a decrease in the precision of the map (Durham & Woolsey 1978, Simons & Land 1986).

A precise topography exists in the pathway of axons from the vibrissae to the trigeminal nucleus; the axons from the whisker follicles grow out parallel to one another and fasciculate into bundles, each of which contains axons from a localized area of the whisker field (Erzurumlu & Killackey 1983). Whether this topographic arrangement of axons is necessary for axons to make topographic connections in the V nucleus has not been fully tested. However, if the overall number of axons innervating the whisker field is reduced prenatally by anti-NGF treatment, the fascicular pattern of the nerve is abnormal, whereas the barrel pattern in the cortex is unaffected (Sikich et al. 1986). This suggests that topographic mapping in the whisker projection does not depend on the maintenance of topography in the fiber pathway.

Plasticity The vibrissal projections show a very dramatic and precise form of plasticity. If one or more vibrissae are lesioned in a newborn animal, the corresponding barrels in the cortex and thalamus fail to develop, and the surrounding barrels expand to fill the vacated space (Van der Loos & Woolsey 1973, Weller & Johnson 1975, Killackey et al 1976, Jeanmonod et al 1977, Belford & Killackey 1979b, 1980, Woolsey et al 1979, Durham & Woolsey 1984, 1985). This plasticity is only present in the few days after birth. In order to have an effect on the barrels in the thalamus, lesions must be made before P4, whereas lesions up to P6 will still affect the barrel pattern in the cortex (Weller & Johnson 1975, Woolsey & Wann 1976, Killackey & Belford 1979, Woolsey et al 1979, Jeanmonod et al 1981). Electrophysiological studies give essentially the same results as the anatomical experiments, and also reveal that areas of cortex that have been denervated by whisker lesioning may receive an abnormal input from the fur surrounding the lesion (Waite & Taylor 1978, Pidoux et al 1979). Functional mapping with 2-deoxyglucose shows that the connections from an unlesioned vibrissa can expand to occupy territory vacated by lesioning (Kossut & Hand 1984a) and that the functional mapping corresponds closely to the altered barrel pattern (Durham & Woolsey 1985). The vibrissal projection exhibits a different form of expansion when the overall population of axons innervating the vibrissae is reduced by treating developing guinea pigs in utero with anti-NGF. The barrel pattern in such animals is quite normal, both in size and shape (Sikich et al 1986).

The cortical barrel field can also show compression. If an area of the cortex is lesioned, a normal number of barrels will develop, but they will skirt around the damaged area. The axons that would have innervated the damaged area must, therefore, have displaced axons from the neighboring region of the cortex, thus leading to a readjustment of the topography of the barrel field (Ito & Seo 1983).

SUMMARY

The catalogue of data presented here for many systems demonstrates that multiple mechanisms are involved in the formation of topographic maps. We are not yet in a position to explain why a particular mechanism appears to dominate in some situations and not in others. Certain generalizations can be made, however. First, at least some form of chemospecificity can be invoked to help explain connectivity in all of the experiments we have cited. Often, the differential identities of a population of neurons can be reflected in an orderly pattern of axon outgrowth and in the actively maintained preservation of neighbor relations as the axons grow toward their targets; such orderly arrangements are not obligatory, but, where present, they facilitate the speedy establishment of orderly maps when the

axons reach their target nuclei. Within a terminal zone, chemospecific cues may dominate and constrain a given axon to terminate in a specific location, but axon-axon interactions commonly supercede chemospecific matching. At least two forms of axon-axon interactions occur, one based on some sort of biochemical properties related to the axons' embryological identity and another based on the axons' electrical activity.

Tasks for the future are to identify the cellular bases of each of these mechanisms and to understand the situations in which each is manifested.

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