Target Recognition: Topographic Maps

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Synopsis: Topographic maps are a widespread organizing feature of the central nervous system whereby spatial relations between cells are preserved between the projecting set of neurons and the receiving set. Axon guidance cues and their receptors (especially ephrins and Ephs) are expressed in gradients in the projecting and receiving layers, which guide projecting axons into a crude topographic map. This crude map is refined by activity-dependent remodeling of axonal projections, in which neural activity in the projecting layer leads to the elimination of axonal projections not well correlated with their neighbors.

Target Recognition: Topographic Maps

Topographic maps are a widespread organizing feature of the central nervous system, especially in early sensory processing, whereby spatial relations between cells are preserved between the projecting set of neurons and the receiving set. That is, neighbors in the projecting set connect to neighbors in the receiving set. The effect is that neurons in higher circuits are arranged in a 'map' representing spatial or frequency information about the external world. As information moves toward higher processing centers, it remains organized topographically, so that, for example, neighboring columns of the visual cortex process information from neighboring areas of the visual world, and neighboring columns of the auditory cortex process sounds of similar frequencies.

Ongoing work has revealed two major themes in topographic map development. First, axon guidance cues and their receptors are expressed in gradients in the projecting and receiving layers, which guide projecting axons into a crude topographic map. Second, this crude map is then refined by activity-dependent remodeling of axonal projections, in which neural activity in the projecting layer leads to the elimination of axonal projections not well correlated with their neighbors. This article will focus mainly on the retinotectal projection because it is by far the best-characterized of the topographic maps, but we will also make reference to other systems, where the same general principles apply.

1. The purpose of topographic maps

At first glance, it might be unclear why sensory processing is organized topographically. There is no homunculus 'viewing' a projection of the outside world inside the brain, and it would seem that it is the pattern of connections that matters for information processing, not whether neurons processing neighboring stimuli in the external world are neighbors themselves. However, the topographic organization of sensory processing does have important functional benefits. Much of sensory processing relies on comparing neighboring stimuli, most notably in center-surround receptive fields that allow the visual system to analyze edges and motion. The spatial proximity of neurons that respond to neighboring stimuli makes this kind of processing more efficient, since the transmission of action potentials is costly in both energy and time. In addition, some diffusible cues, like nitric oxide, rely on near-neighbor relations. Some circuits rely directly on axon length for processing; for example, the auditory system calculates interaural time difference using coincident detectors with the delays inherent in action potential transmission to determine how long the sound from one ear must be delayed to match the timing of the sound from the other ear. In this case, the spatial arrangement of cell bodies relates directly to circuit function.

Perhaps more importantly, topographic mapping is efficient developmentally. An arbitrary spatial arrangement of neurons and their synapses, though theoretically possible, would require every connection to be specified individually, a daunting prospect in an organism with billions of neurons and trillions of synapses but only a few tens of thousands of genes. In contrast, topographic mapping allows axonal targets to be determined with only a few broad gradients and activity-dependent refinement of projections (see below). That is, the mechanism of topographic map formation may itself be the functional rationale behind topographic maps.

2. Historical perspective

The topographic organization of sensory processing has been recognized since the 19th century, but the mechanism by which maps are established was debated until Roger Sperry's classic experiments in the 1940's and 1950's led to his proposal of the 'chemoaffinity hypothesis.' Using the regenerative capacity of amphibian nervous systems, Sperry severed frog optic nerves and allowed the retinal axons to re-innervate their target, the optic tectum. Even if the optic nerve was artificially scrambled or if the eye was rotated 180º, axons always regrew to the correct targets according to the original topographic map. Strikingly, if the eye was rotated 180º, the frog behaved as if its visual world was upside-down, as if the formerly 'top' part of the eye, now on the bottom, re-connected to the 'top' part of the retinotopic map in the tectum. These classical experiments argued for the 'chemoaffinity hypothesis,' that axonal connections are specified by complementary molecular identification tags on the axon and its target. To overcome the problem that there could not be enough molecules to mark each cell individually, Sperry proposed overlapping and orthogonal gradients to mark each cell with its 'latitude and longitude.' This combinatorial code would provide each cell with a unique molecular identity defined by expression levels of each tag. This model has been broadly validated with some modifications (see below) in the last decade with the identification of these molecular tags, especially the Ephs and ephrins.

3. Axon guidance cues in topographic mapping

3.1 Ephs and ephrins

The axon guidance cues most involved in topographic mapping are the ephrins and the Eph receptor tyrosine kinases. The Eph receptors (discovered in an erythropoietin producing hepatocellular cell line) form the largest subfamily of receptor tyrosine kinases and are divided into two classes, EphA and EphB. Their ligands, the ephrins (Eph-receptor interacting proteins), are similarly divided into two classes, ephrin-A and ephrin-B; generally, EphAs bind ephrin-As while EphBs bind ephrin-Bs. Ephrin-As are glycosylphosphatidylinositol (GPI)-linked to the membrane, while ephrin-Bs are transmembrane proteins. In addition to 'forward signaling' from ligand to receptor, ephrins are also capable of 'reverse signaling' from receptor to ligand, most clearly with ephrin-Bs through their intracellular domain, but potentially also with ephrin-As through an unknown mechanism. Ephrins and Ephs can be both attractive and repulsive guidance cues, but function only when membrane-bound, suggesting that they guide axons through contact attraction or repulsion rather than long-range guidance.

3.2 Nasal-temporal mapping in the retinotectal projection

Retinal ganglion cell (RGC) axons project onto the optic tectum in non-mammalian vertebrates (the 'retinotectal' projection), and onto the superior colliculus in mammals (the 'retinocollicular' projection). In both cases, the projection is topographic, such that nasal axons project posteriorly, and temporal axons project anteriorly (Figure 1). (For simplicity, this article will refer to the retinotectal projection, with the understanding that similar principles apply in the retinocollicular projection.) Retinotectal topography can be observed by recording receptive fields of tectal neurons to see which part of the retina they respond to, and by anterograde and retrograde tracing, where a lipophilic dye is injected into the retina or tectum to see which part of the other layer is connected by RGC axons.

Classic experiments by Bonhoeffer and colleagues in the 1980's using the 'stripe assay' showed that temporal axons were selectively repelled by membranes from the posterior tectum. Retinal axons were allowed to grow on alternating stripes of membranes from anterior and posterior tectum. Temporal axons grew only on anterior stripes, while nasal axons grew indiscriminately (Figure 2). The directed growth of temporal axons was due to repulsion from posterior stripes rather than attraction to anterior stripes, because heat-inactivation of posterior membranes alone abolished the striped outgrowth pattern, while heat-inactivation of anterior membranes had no effect. These findings confirmed the central principle of the chemoaffinity hypothesis, but with a surprising twist: instead of the prevailing idea of attraction between matching tags on axons and their targets, these findings suggested repulsion between axons and inappropriate targets.

Eventually, ephrin-A2 and ephrin-A5 were identified as the critical ligands in the tectum, and EphA5 and EphA6 (EphA3 in chick) the receptors in RGCs. EphA receptors are expressed in a low nasal to high temporal gradient in RGCs, while Ephrin-As are expressed in a low anterior to high posterior gradient in the tectum (Figure 1d). The same principle holds in another retinal target in mammals, the dorsal lateral geniculate nucleus (dLGN) in the thalamus, where ephrin-A2 and ephrin-A5 are expressed in a high ventral-lateral-anterior to low dorsal-medial-posterior gradient (see Figure 4b). Knocking out or mis-expressing ephrin-A2/A5 disrupts retinotectal topography, though some retinotopy remains intact, suggesting that other molecules are involved (see below).

In the tectum, ephrin-A expression is thought to be patterned by the transcription factor Engrailed-2, which, like the ephrin-As, is expressed in a low anterior to high posterior gradient. In the retina, the nasal-temporal axis is patterned by the transcription factors BF1 (expressed nasally) and BF2 (expressed temporally), and SOHo1 and GH6 (expressed nasally). SOHo1 and GH6 repress EphA3 expression in chick, suggesting a mechanism by which a low nasal to high temporal gradient of EphA expression is created.

RGCs also express ephrin-As themselves, in a high nasal to low temporal gradient (Figure 1d). Ephrin-A5 has been shown to silence EphA3 responsiveness through *cis* interactions when the two are co-expressed (i.e., interactions on the same cell, as opposed to *trans* interactions between ephrin-A and EphA on different cells), suggesting that ephrin-A expressed on nasal axons could silence what little EphA receptor they do have. Thus, the counter-gradient of ephrin-A may enhance the gradient of EphA signaling in RGCs. Also, it has been suggested that ephrin-A expressed by early-arriving retinal axons might sharpen the tectal ephrin-A gradient, because nasal axonal arbors in the posterior tectum would express high ephrin-A on top of tectal ephrin-A, while temporal axonal arbors in the anterior tectum would express low ephrin-A.

Initially, tectal ephrin-As were thought to be purely repulsive. In this model, temporal axons expressing high levels of EphA receptor are repelled by the high levels of ephrin-A in the posterior OT/SC and therefore remain in the anterior tectum, while nasal axons expressing low levels of EphA receptor are unaffected by ephrin-A and continue to grow into the posterior OT/SC. Axon-axon competition and a hypothetical opposing gradient would explain why all axons did not simply crowd into the anterior tectum. (For a review of computational models of molecular gradients in retinotopic mapping, see Further Reading.)

However, recent findings suggest that ephrin-As have concentration-dependent biphasic effects. Ephrin-A2 promotes *in vitro* retinal axon outgrowth at low concentrations and inhibits it at high concentrations, with the tipping point between positive and negative effects for a particular axon varying depending on its nasal-temporal position. Nasal axon growth is promoted by ephrin-A2 up to a higher concentration than temporal axons. Each axon therefore terminates around the tipping point between a positive and negative response to ephrin-As. Another molecule mediating biphasic guidance is Engrailed-2. In addition to its

role in transcriptional regulation of tectal ephrin-A levels, Engrailed-2 attracts nasal axons but repels temporal axons. Unlike ephrins, Engrailed-2 passes directly into growth cones *in vitro* and may function by binding to intracellular signaling molecules rather than receptors; presumably, nasal and temporal growth cones differ in these intracellular molecules.

In frogs and fish, ephrin gradients act by controlling how far posterior the growing RGC axons extend: RGC axons grow 'up' an ephrin-A gradient, and depending on how much EphA receptor they express, they stop at a certain zone, which becomes the target. In contrast, in birds and mammals, axons substantially overshoot the target (though still biased toward the target), and the critical step for topographic mapping is selective interstitial branching near the target zone (Figure 3). This difference may be due to species differences in size and developmental timing: frog and fish RGC axons innervate the tectum early, when it is still very small (150-200 μm), and both the retina and tectum continue to grow as the retinotopic map is refined (see Section 4). In contrast, the optic tectum in chick and superior colliculus in mouse are relatively large (10,000 μm in chick, 2,000 μm in mouse) when RGC axons arrive and do not grow substantially during map refinement. In addition to mediating retinal axon extension, EphAs and ephrin-As are thought to mediate selective interstitial branching by blocking branching posterior to the target zone. As with axon extension, branching anterior to the target may be blocked by axon-axon competition or by ephrin-A biphasic action, in which branches need a certain threshold of ephrin-A (attractive at low concentrations) to grow.

A straightforward nasal-temporal mapping only applies to organisms with mostly monocular vision, where each retina projects mainly to the contralateral optic tectum. In organisms with binocular vision, such as humans, each retina projects to both sides of the brain. In the right retina, for example, the nasal half projects to the left side of the brain while the temporal half projects to the right side. Each retina therefore needs two topographic maps, and indeed, the human embryonic retina displays a bidirectional high central to low nasal/temporal gradient of EphA receptors, while the dLGN displays a complementary gradient of ephrin-As (Figure 4). Remarkably, this finding was predicted by Sperry almost a half-century ago.

3.3 Dorsal-ventral mapping in the retinotectal projection

Retinal axons also map topographically in the dorsal-ventral dimension. Dorsal RGCs map to the ventral tectum (lateral tectum in chick, superior colliculus in mouse) while ventral RGCs map to the dorsal tectum (medial tectum/SC). Until recently, dorsal-ventral mapping was poorly understood compared to anterior-posterior mapping, but in the last few years it has been shown that dorsal-ventral mapping is established by ephrin-Bs and EphBs, as well as Wnt-3 and its receptors Ryk and Frizzled.

Ephrin-Bs are expressed in a high dorsal to low ventral gradient in both the retina and the tectum, while EphBs are expressed in high ventral to low dorsal gradients (Figure 1d). Like EphAs, retinal gradients of ephrin-Bs and EphBs are set up by transcription factors: Vax2 (expressed ventrally) and Tbx5 (expressed dorsally). Ventral Vax2 represses ephrin-B expression, to create the high dorsal to low ventral ephrin-B gradient, while dorsal Tbx5 represses EphB expression, to create the high ventral to low dorsal EphB gradient.

In frogs, reverse signaling by EphBs in the tectum onto ephrin-Bs in RGCs mediates dorsal-ventral mapping: ephrin-B-expressing dorsal axons are attracted to EphB expressing cells in the ventral tectum. Ectopic expression of ephrin-B in ventral RGCs shifts their tectal projections ventrally, while expression of dominant-negative ephrin-B in dorsal RGCs shifts their projections dorsally. Chick and mouse dorsal-ventral mapping appears to be achieved by forward signaling from tectal ephrin-Bs to RGC EphBs: interstitial branches of EphB-

expressing ventral axons are attracted to ephrin-B-expressing cells in the medial tectum/SC. Knocking out EphB2 and EphB3 in mice causes axonal branches to project too far laterally.

In chick and mouse, the counteracting force that pulls axons toward the lateral tectum/SC is created by a Wnt-3 gradient as well as biphasic action by ephrin-B. Wnt-3 is expressed in a high medial to low lateral gradient in the tectum. The receptor Ryk, which mediates repulsive responses to Wnt-3, is expressed in a high ventral to low dorsal gradient in the retina, while the receptor Frizzled, which mediates attractive responses to Wnt-3, is expressed evenly in the retina (Figure 1d). The Ryk-mediated repulsive response and Frizzled-mediated attractive responses both drive interstitial branches laterally: high-Ryk-expressing ventral axons are repelled by Wnt-3 while low-Ryk-expressing dorsal axons are attracted to low Wnt-3 levels (such as those in the lateral tectum), though still repelled by high Wnt-3 levels. This lateral-driving effect of Wnt3 counteracts the effect of ephrin-B, which attracts axons medially. Ephrin-B itself may also have biphasic effects; in chick, high levels of ephrin-B can be repulsive, indicating that axons from a given DV retinal position has an 'optimum' level of ephrin-B that their interstitial branches grow toward.

3.4 Guidance cue gradients in other topographic maps

Although the role of guidance cue gradients in topographic mapping has been most thoroughly studied in the retinotectal projection, similar principles apply in other sensory projections, including a role for ephrins and Ephs. In the thalamocortical projection, ephrin-As and EphAs play double roles (Figure 5). In early development, EphA receptors are expressed in a high anterior to low posterior gradient in the thalamus, and ephrin-As are expressed in a high posterior to low anterior gradient in the ventral telencephalon. Thalamic axons pass through the ventral telencephalon en route to the cortex, so this initial mapping step sorts them into cortical areas. For example, axons from the anterior thalamus end up in the anterior cortex, in the motor cortex, while axons from more posterior regions of the thalamus end up more posteriorly in the cortex, e.g. in somatosensory or visual cortex. Ephrin-As and EphAs are then reused later in development: both are expressed in high medial to low lateral gradients, with EphAs in the ventrobasal thalamus and ephrin-As in somatosensory cortex (S1). These complementary gradients arrange a somatotopic map in an analogous way to the retinotectal map: EphA-expressing medial thalamic axons are repelled away from the ephrin-A-expressing medial S1 into the lateral S1. Thus, ephrin-As and EphAs are used twice in thalamocortical mapping: first at an intermediate target to mediate *inter*-areal mapping and then within cortical areas to mediate *intra*-areal mapping.

Ephrin-As and EphAs also play a role in topographic mapping between the hippocampus and septum, and between motor axons and muscles. In both cases, the mechanism is similar to that described for AP retinotectal mapping: high-EphA-expressing axons are repelled from high-ephrin-A areas of the target. In the auditory system, functional studies of topography have not yet been done, but there are gradients of EphA4 and ephrin-B2 that could form the basis of a tonotopic map in the avian nucleus laminaris, the target of axons from the nucleus magnocellularis, which is in turn the target of cochlear ganglion cells. Interestingly, ephrins have a conserved role in topographic mapping beyond vertebrates: in *Drosophila*, the single Eph and ephrin homologues are required for topographic mapping in the visual system. The reuse of Ephs and ephrins across different projections suggests an evolutionarily efficient modular approach to topographic mapping that would allow newly evolved projections to be patterned by co-opting a standard package of Eph and ephrin gradients.

4. Activity-dependent refinement of topographic maps

4.1 Correlated RGC firing is required for topographic map refinement

Molecular gradients are insufficient to establish a refined topographic map, most likely because they act over too long a range to ensure precise mapping at the cellular level. Moreover, in frogs and fish, retinotectal topography shifts throughout life, as the retina grows radially at the periphery while the tectum grows linearly at the posterior edge. Retinotopic map refinement occurs through correlated activity in RGCs, where cells that are close together fire around the same time, while cells that are far apart do not. Correlated retinal firing occurs naturally in vision: neighboring retinal ganglion cells have neighboring receptive fields, so they are likely to receive, and transmit, similar input. In amphibians and fish, where embryos develop externally, the retina becomes responsive to visual input around the time when axons arrive in the tectum, so normal visual input may suffice to provide the correlated firing patterns needed to refine retinotectal projections. However, in mammals, where embryonic retinas develop in the dark, correlated firing is provided by spontaneous 'retinal waves' of depolarization that move across the retina. These waves have been observed by multielectrode arrays as well as calcium imaging of depolarization. Because they occur every few minutes and the depolarization only lasts for a few seconds, cells that fire together temporally are very likely to be located together spatially.

Eliminating correlated retinal firing blocks the refinement of retinotectal mapping, as measured by the size of axonal arbors or receptive fields (Figure 5). Blockade of neuronal activity in the retina causes abnormally broad axonal arbors and receptive fields in the tectum, even though the basic shape of the topographic map remains intact, suggesting that molecular gradients suffice for a crude topographic map, but refinement requires activity. This finding holds whether neuronal activity is abolished pharmacologically, by intraocular injection of tetrodotoxin (TTX), or by genetic knockout, for example of voltage-dependent sodium channels. Importantly, it is not electrical activity in RGCs *per se* that matters, but correlated firing patterns. The β2 subunit of the nicotinic acetylcholine receptor (nAChR) is required for spontaneous waves of activity in the developing retina, but not for neuronal activity *per se*. Mice lacking β2 nAChR exhibit random spontaneous retinal activity instead of retinal waves, and indeed develop abnormally large axonal arbors, just like those of TTX-injected animals. Correlated retinal firing can be inhibited in fish, which lack retinal waves, by rearing them under stroboscopic illumination, which artificially increases correlation of firing between RGCs that are far apart; this treatment, like the β2 nAChR knockout, decreases retinotopic refinement.

Additional support for this model comes from artificial ocular dominance bands induced by transplanting extra eyes onto frog embryos, where normally only one eye innervates each tectum. Ectopic and native RGCs innervate the same tectum, and presumably express and encounter the same set of molecular gradients, yet the two projections gradually segregate into exclusive ocular dominance bands reminiscent of those discovered by Hubel and Wiesel in the cat visual cortex. Ectopic RGC innervation is presumably an extreme case of uncorrelated firing, as RGCs from two different eyes would be even more uncorrelated than RGCs far apart in the same eye. Ocular dominance bands are thus an extreme example of activity-dependent refinement of topography, as two sets of axons uncorrelated with each other segregate within a region defined by the coarse topography set up by molecular gradients.

4.2 Post-synaptic NMDA receptors induce map refinement by eliminating inappropriate connections

N-methyl-D-aspartate receptors (NMDARs) are ionotropic glutamate receptors that are blocked by a magnesium ion unless the dendrite is already depolarized, meaning that NMDARs act as 'coincidence detectors' that only activate when more than one synapse fires nearly simultaneously onto the dendrite. In long-term potentiation, Ca^{2+} influx through NMDARs activated by coincident stimulation leads to signaling that strengthens the synapse, and it is thought that a similar mechanism operates in the stabilization of synapses that are 'in sync' with their neighbors and the withdrawal of axonal branches from synapses that are 'out of sync.' Indeed, blocking NMDARs in post-synaptic tectal cells prevents retinotopic refinement of the pre-synaptic retinal axons. In addition, calcium/calmodulin-dependent kinase II (CaMKII), which is activated by NMDARs, is required in post-synaptic tectal dendrites for pruning pre-synaptic RGC axonal arbors. Time-lapse imaging in dually-innervated frog tecta shows that axonal branch elimination rates, but not addition rates, are higher in areas dominated by axons from the other eye. This bias is NMDAR-dependent, suggesting that correlated firing acts through NMDARs to eliminate axonal branches not well correlated with their neighbors.

The nature of the retrograde signal activated by post-synaptic NMDARs to axonal branches, telling them whether to stabilize or retract, remains unclear, although a few candidate mechanisms exist. Nitric oxide (NO) has been suggested as a retrograde messenger since NO synthetase is expressed in tectal cells and NO collapses growth cones *in vitro*. However, blocking NO synthetase appears to slow down, but not ultimately prevent, retinotopic refinement in mouse and chick, while it has no effect on refinement in frogs and fish. Brain-derived neurotrophic factor (BDNF) is produced by tectal neurons where it is released by neuronal activity, and it promotes axonal branching and synapse formation, making it a good candidate for an activity-dependent retrograde messenger. However, the effects on axonal branch dynamics of blocking neuronal activity do not match those of blocking BDNF, suggesting that BDNF may not directly mediate the effects of correlated neuronal activity, but rather modulates them in a complex way that is not fully understood. Work in fish suggests a role for arachidonic acid, a cleavage product of diacylglycerol; both applying arachidonic acid globally and inhibiting its release by post-synaptic cells block retinotopic refinement. Cell adhesion molecules may also serve as activity-dependent retrograde messengers. Applying antibodies against NCAM or glycoproteins to the tectum inhibits retinotopic map refinement. NCAM, N-cadherin, and glycoprotein L1 are inserted into the membrane in an activity-dependent fashion in other systems, suggesting that they may similarly be inserted by NMDAR activation to aid in axonal branch or synapse stabilization. These candidate mechanisms all seem to converge on inter-related pre-synaptic signaling pathways involving Ca^{2+}, phospholipase C (PLC), growth-associated protein 43 (GAP-43), Rho GTPases and others, ultimately influencing the actin cytoskeleton to cause stabilization or retraction of axonal branches.

5. Conclusions

Our understanding of the molecular mechanisms behind topographic mapping has increased greatly in the last decade. An emerging principle is that topographic mapping efficiently uses a relatively small number of genes to pattern connections among billions of neurons. Matching gradients of axon guidance cues in the target layer and their receptors in the projecting layer set up a coarse topographic map, while activity-dependent mechanisms refine this map to make it more precise by eliminating inappropriate connections. The conservation of the molecular principles of topographic mapping across phyla and across different neural projections suggests that these principles may be a basic method of nervous

system organization that evolution has repeatedly turned to. Future work will surely shed further light onto the development of topographic maps.

Word count: 4,067 words

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Figure Legends:

Figure 1. (A) Schematic of nasal-temporal and ventral-dorsal retinal axes. (B) The retinocollicular projection: ventral view of the human brain, showing the retina, lateral geniculate nucleus (LGN), and superior colliculus (SC). (C) The retinotectal projection: lateral view of a *Xenopus* embryo, showing the retina and tectum. (D) Schematic of retinotectal/retinocollicular topography and gradients of guidance cues and their receptors. Dorsal tectum in *Xenopus* corresponds to medial tectum in chick and medial SC in mouse; ventral tectum in *Xenopus* corresponds to lateral tectum/SC in chick and mouse.

Figure 2. The stripe assay. Membranes from anterior (white) and posterior (green) tectum are laid down in alternating stripes, and retinal pieces are explanted on them so that axons will grow over the stripes. Temporal axons avoid posterior membrane stripes, while nasal axons grow indiscriminately. Temporal selectivity is abolished by heat-inactivation of posterior membranes, but not anterior membranes.

Figure 3. In frogs and fish, axons stop growing near the eventual target zone (gray circle) and arborize there. In contrast, in birds and mammals, axons considerably overshoot the target

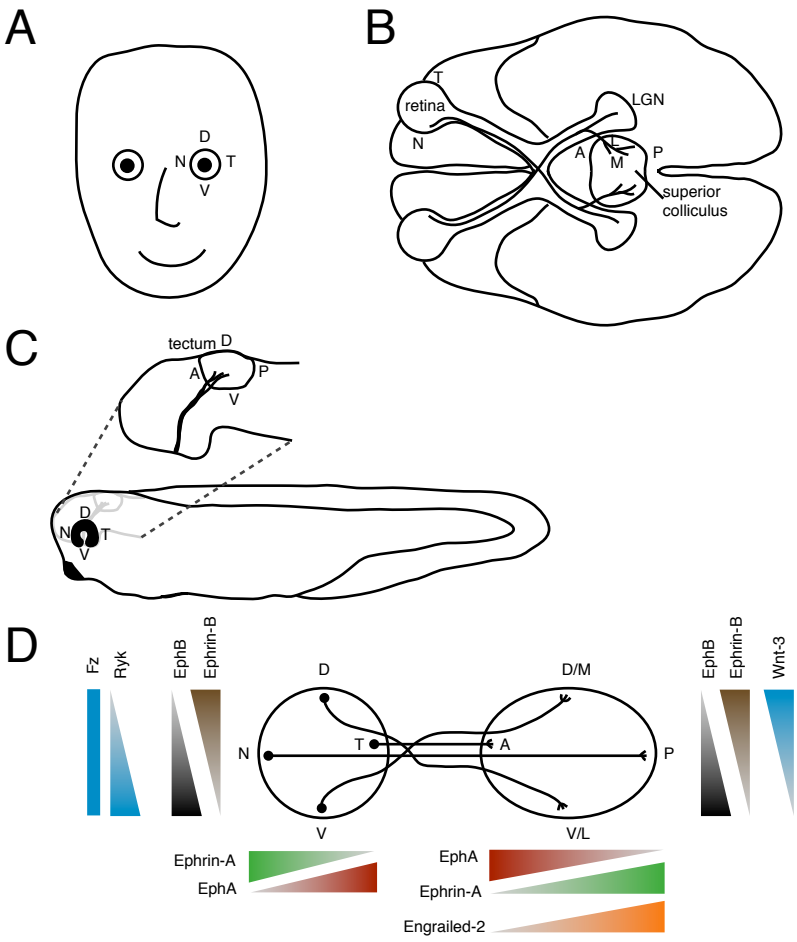
zone and selectively grow interstitial branches at the target zone. This difference may be due to the vastly different sizes of the tectum/SC between the two cases (bars).

Figure 4. Schematic of retinotopic mapping in organisms with binocular vision. (A) Nasal axons cross at the optic chiasm to the contralateral side of the brain, while temporal axons project to the ipsilateral side, so that each side of the brain processes the contralateral half of the visual field. (B) Topographic mapping between the retina and the dorsal lateral geniculate nucleus (dLGN) is achieved by a bi-directional high central to low nasal/temporal gradient of EphAs in the retina and a high ventral to low dorsal gradient of Ephrin-As in the dLGN.

Figure 5. Topography in the thalamocortical projection uses EphA and ephrin-A gradients twice. In early development, thalamic axons are sorted toward the correct cortical areas by an ephrin-A gradient at an intermediate target, the ventral telencephalon. Later on, thalamic axons are sorted within each cortical area by a second ephrin-A gradient.

Figure 6. Activity-dependent mechanisms are required to refine initially broad axonal arbors to create precise retinotopy. Refinement can be blocked by interfering with correlated neuronal activity in RGCs, for example with TTX, NMDAR antagonists, knockout of the β2 subunit of the nicotinic ACh receptor, rearing under stroboscopic conditions, etc.

Suggestions for cross-references:
Pathfinding: Guidance cues & guidepost cells; Growth cones; Ephrins and Eph receptors
Synapse Formation and Elimination: Developmental synaptic plasticity (roles of LTP & LTD); Synapse elimination and dynamics; Retrograde transsynaptic influences; Cell adhesion molecules at synapses
Target Recognition: Interstitial axon branching / collateral elimination; Patterned activity (bursting waves); Chemoaffinity hypothesis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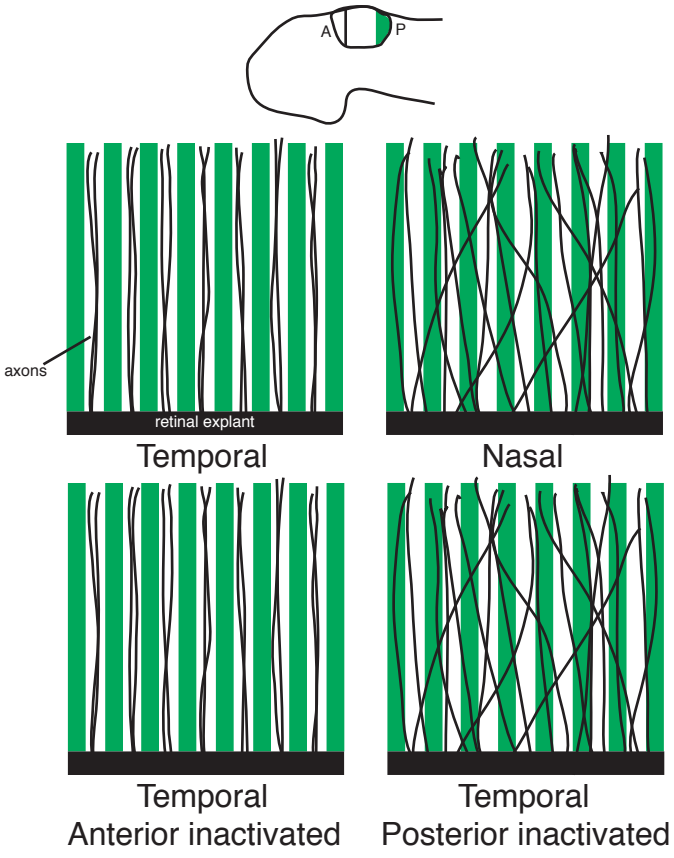
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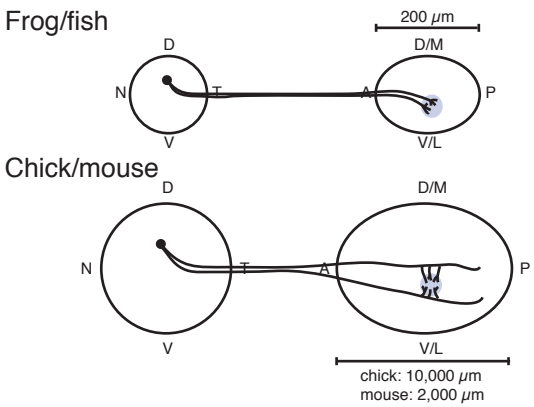
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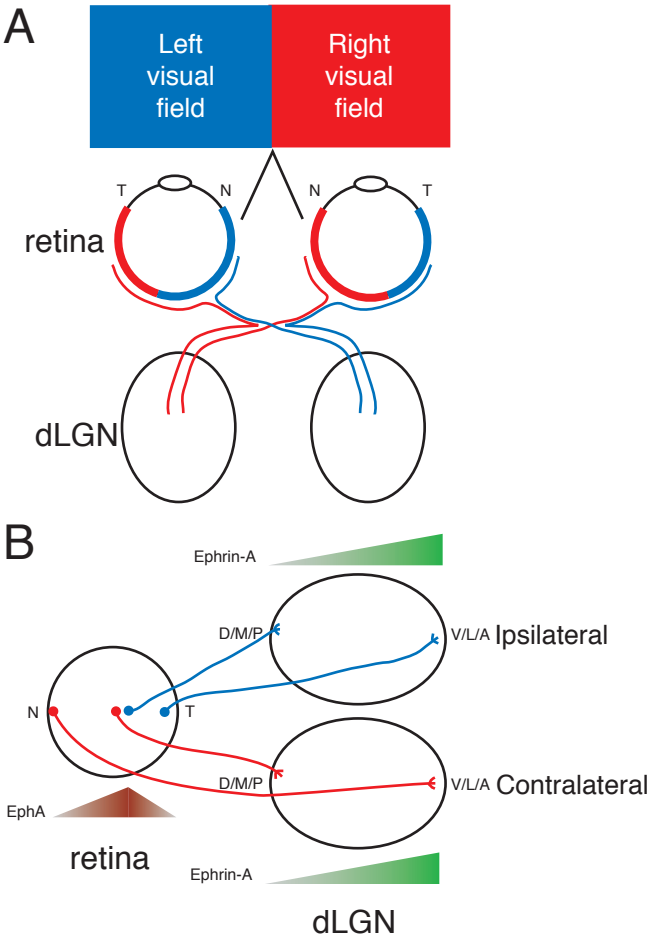
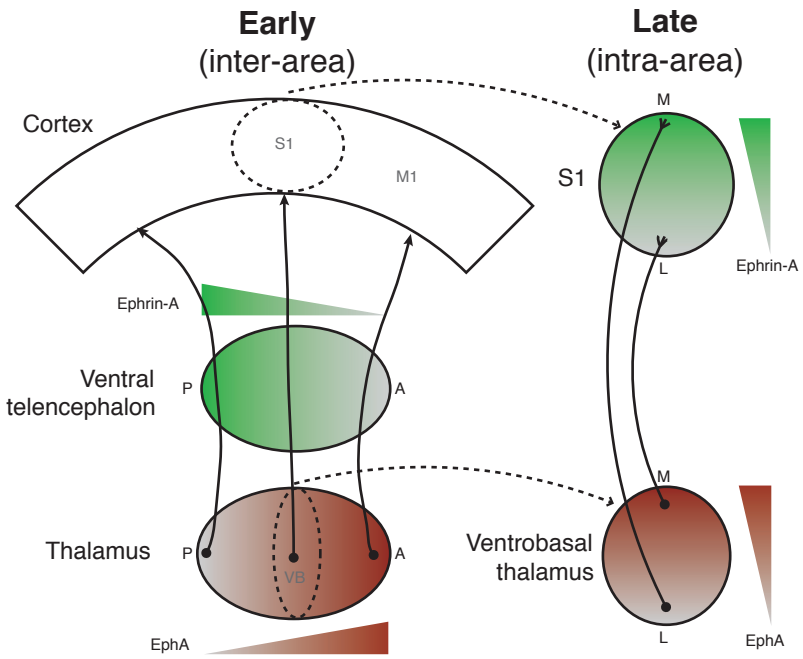
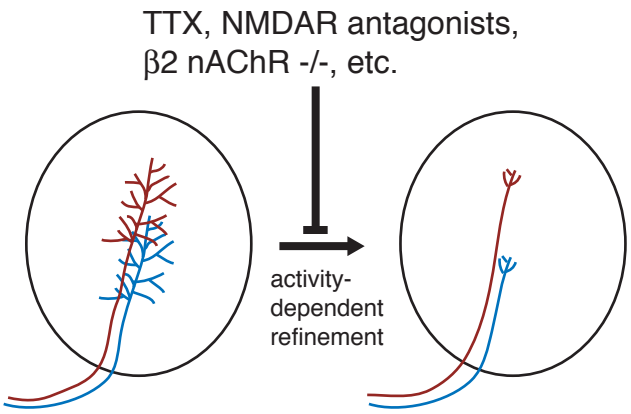
chick: 10,000 μm
mouse: 2,000 μm


A
Left visual field
Right visual field
T
N
N
T
retina
dLGN
B
Ephrin-A
D/M/P
V/L/A
Ipsilateral
N
T
D/M/P
V/L/A
Contralateral
EphA
retina
Ephrin-A
dLGN


Early
(inter-area)
Late
(intra-area)
Cortex
S1
M1
Ephrin-A
Ventral
telencephalon
P
A
Thalamus
P
A
VB
EphA
S1
M
L
Ephrin-A
M
L
Ventrobasal
thalamus
EphA


TTX, NMDAR antagonists,
β2 nAChR -/-, etc.
activity-
dependent
refinement