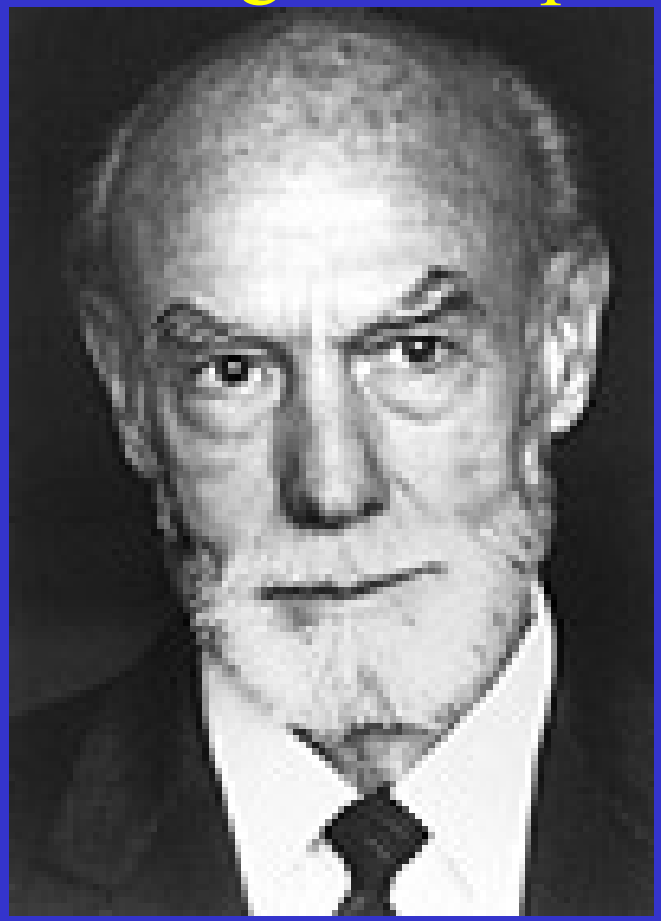
Lecture 6:
Non-Cortical Visual Pathways

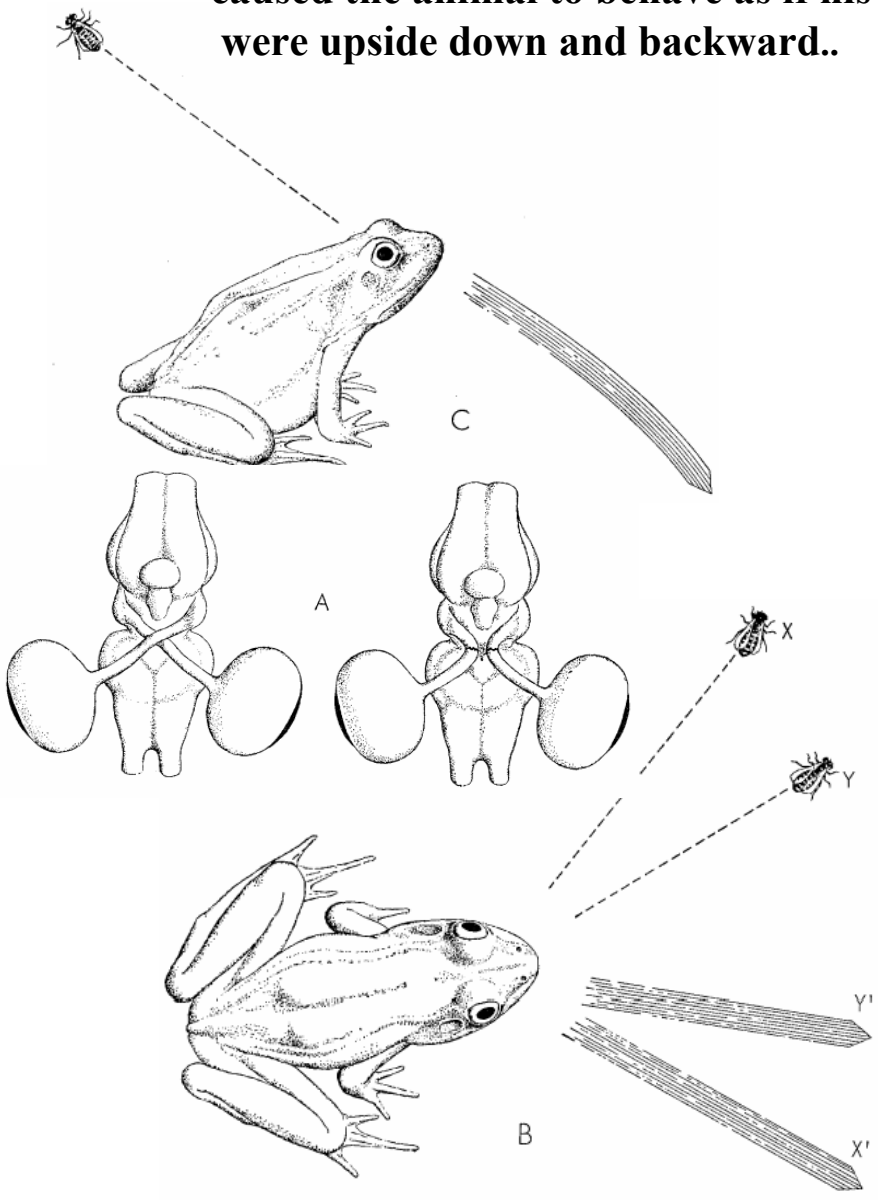
Roger W. Sperry



The problem of central nervous reorganization after nerve regeneration and muscle transposition. R.W. Sperry. Quart. Rev. Biol. 20:311-369 (1945).
Regulative factors in the orderly growth of neural circuits. R.W. Sperry. Growth Symp. 10: 63-67 (1951).
Cerebral organization and behavior. R.W. Sperry. Science 133:1749-1757 (1961).
Chemoaffinity in the orderly growth of nerve fiber patterns and connections. R.W. Sperry. Proc. Nat. Acad. Sci. USA 50: 703-710 (1963).

The Nobel Prize in Physiology or Medicine 1981 "for his discoveries concerning the functional specialization of the cerebral hemispheres"
(with Hubel and Wiesel)

180^{O}Rotation of the eye followed by regeneration caused the animal to behave as if his world were upside down and backward..

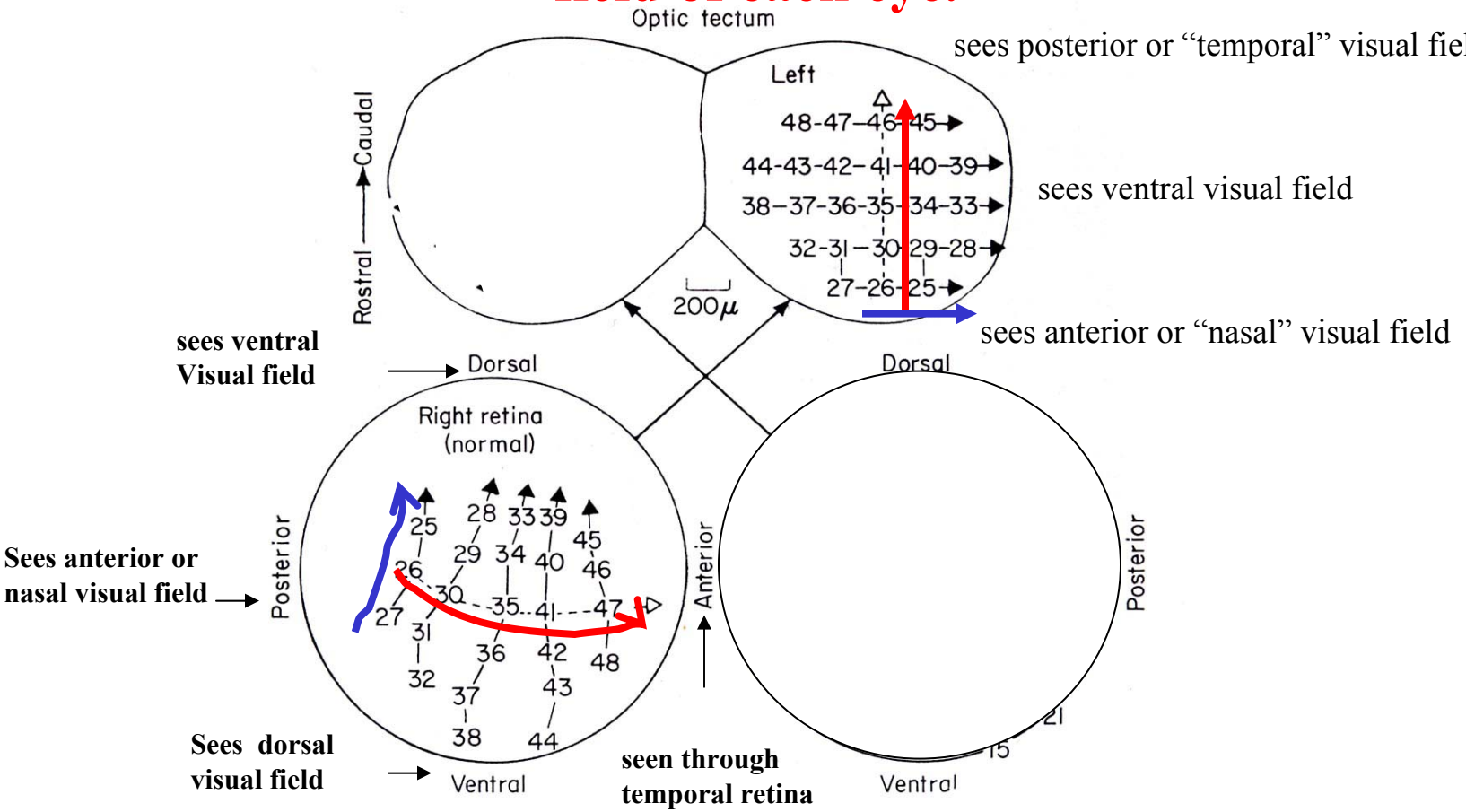


The animals never learned to adapt their behavior. Therefore activity was not involved.

Uncrossing the optic chiasm caused the animal to behave as if his left and right visual fields had been flipped about the vertical Midline.

Sperry RW (1956) The eye and the brain. Sci. Amer. 194(5):48-52.

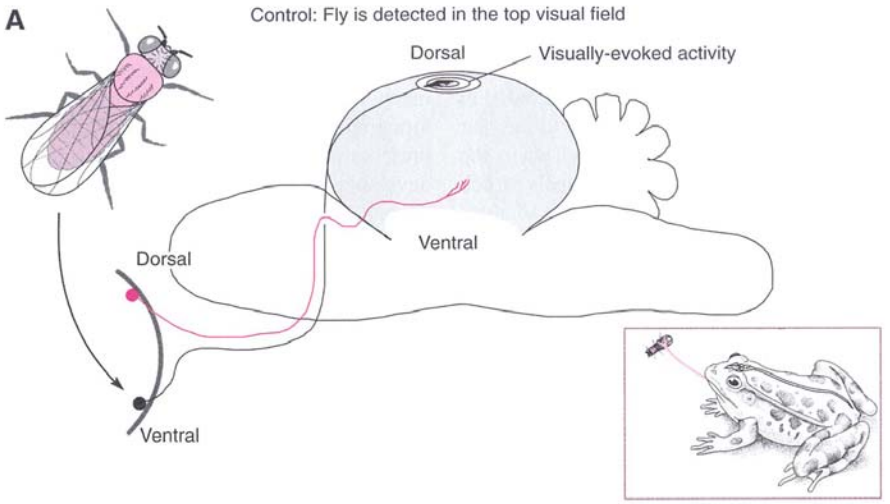
The retinotectal projection can be mapped with extracellular recording electrodes while small spots are positioned in the visual field of each eye.

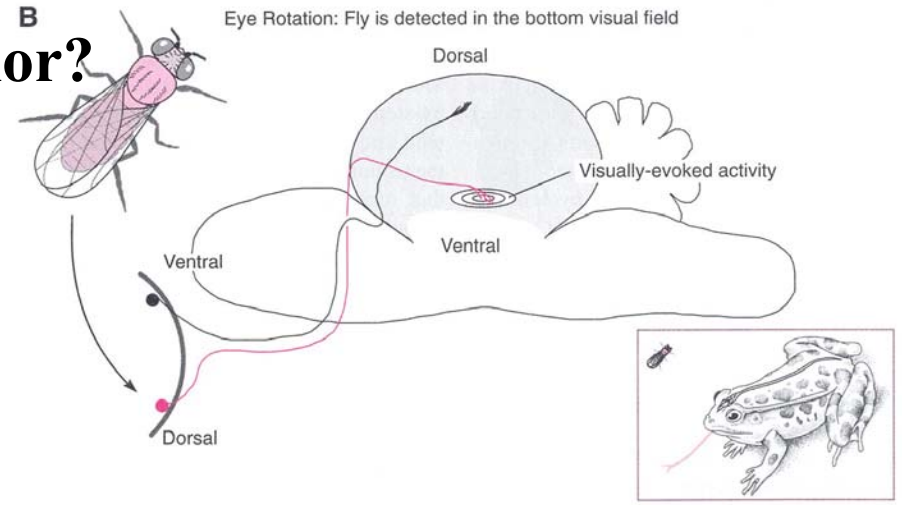


Modified from:
Jacobson (1968),
Devel. Biol.17:202.

The lens inverts the image. Therefore, posterior visual field is projected through nasal retina, Anterior visual field is projected through temporal retina, dorsal visual field through ventral retina and and ventral visual field through dorsal retina.

Dorsoventral misdirected striking behavior results because the retina projects back to its original loci in the tectum regardless of the orientation or the retina relative to the visual field





Why does this alter the behavior?

The tectum to motor pattern projection is fixed.
For example,
stimulating a point in dorsal tectum in a blind frog will cause the animal to strike toward the dorsal visual. This is because
The dorsal tectum is driven by ventral retina and ventral retina is normally activated by objects in the dorsal visual field.

Retino-tectal synaptogenesis involves continuous sprouting of retinal axons as the projections shift caudally in a continually enlarging tectum

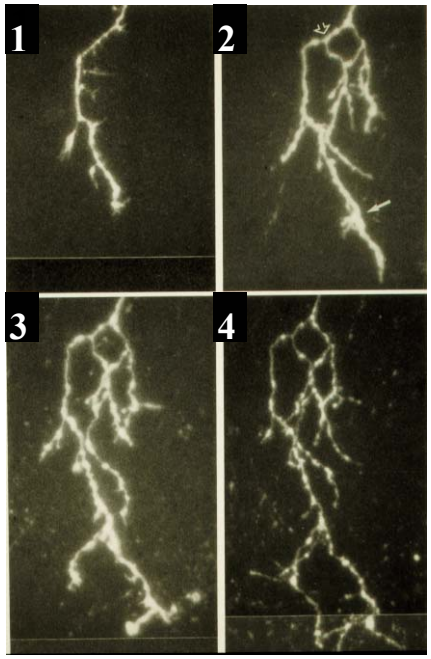
Confocal Microscopy Used to Label Single Retinal Arbors During Growth

Di1 (liphilic dye) injected into retina at ~ st 39-41 (~ 6-8 mm tadpole)

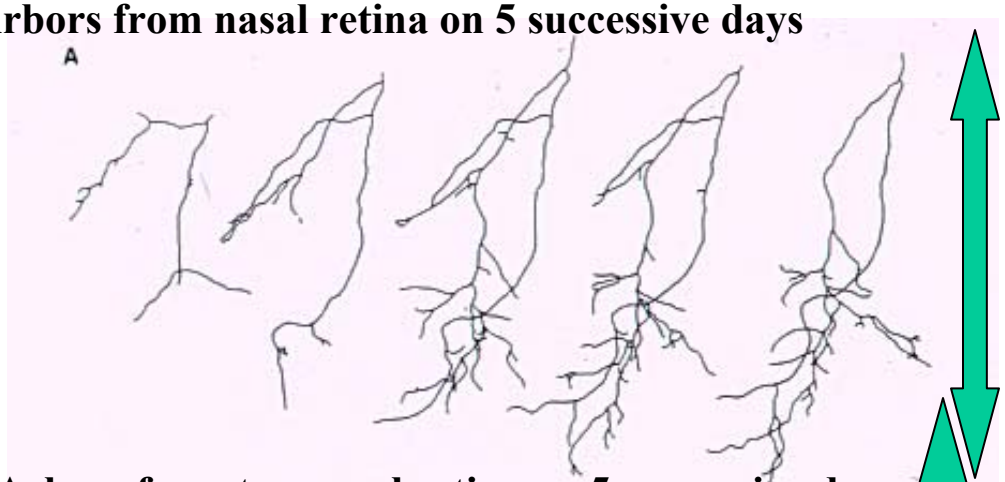
After 18-24 hrs to allow dye to transport to the terminal arbors. At st 45/46 the arborizations of labeled axons were imaged in the optic tectum on sucessive days.

From: O'Rourke & Fraser, (1990) Neuron 5:159

Nasal arbor on 4 succesive days

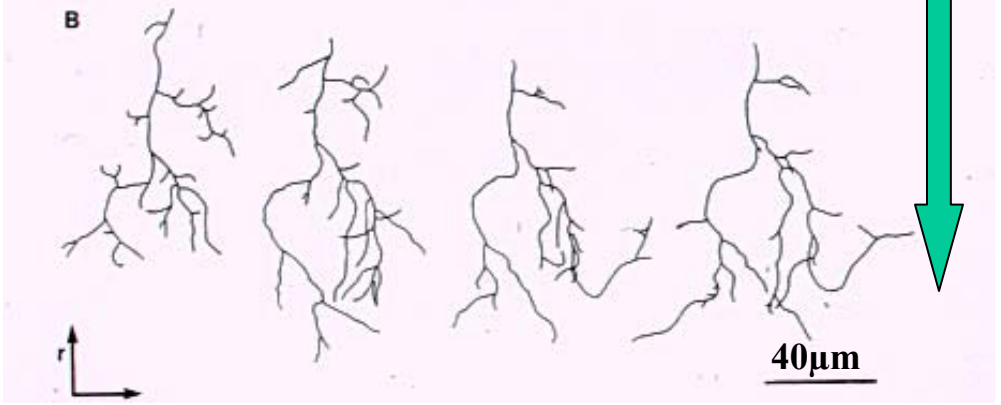


Arbors from nasal retina on 5 successive days



full rostral-caudal extent of the tectum

Arbors from temporal retina on 5 successive days



Arbors are highly dynamic structures in tadpoles. Synapses are continually being made and broken as the retina grows in circles and the tectum grows only at its caudal medial edge.Reh & Constantine-Paton (1984) J Neurosci.

BDNF Application to the Optic Tectum of Tadpoles Causes the Formation of More Synaptic Puncta On Each Terminal and an Elaboration Of the Arbor

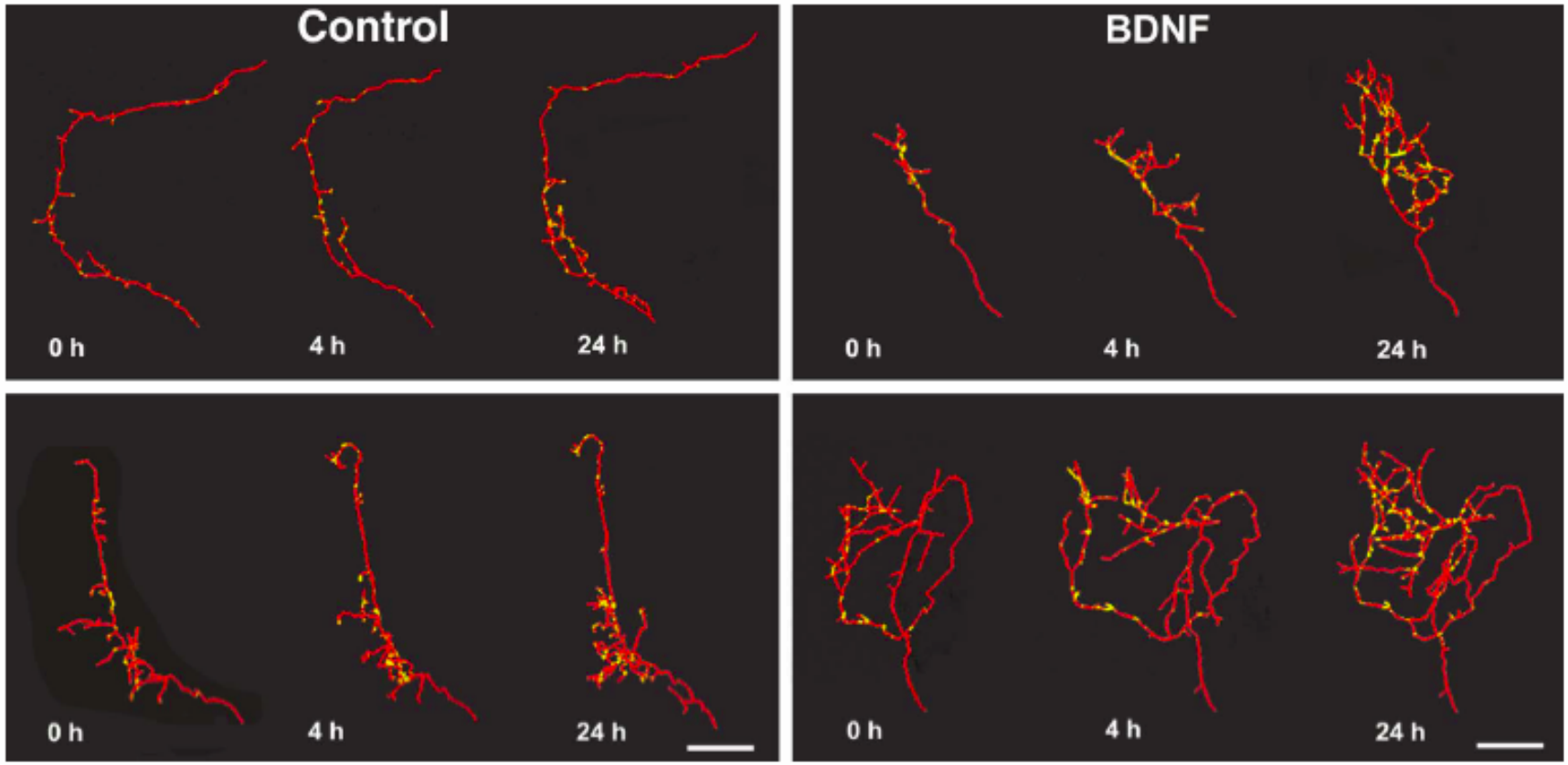
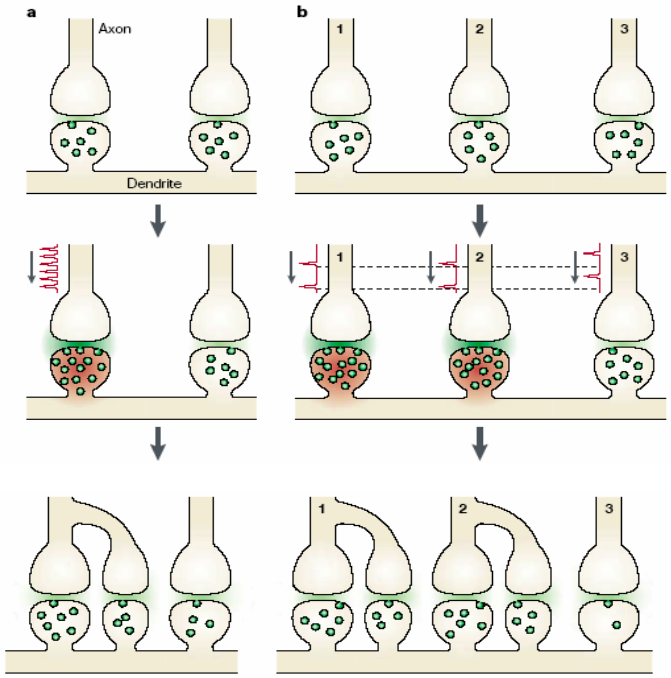


Fig. 6. BDNF increases RGC axon arborization and GFP-synaptobrevin puncta *in vivo*. Tracings of representative three-dimensional arbors illustrate the effects of BDNF on axon arbor complexity and synapse number. Individual RGC axons double-labeled with GFP-synaptobrevin and DsRed were visualized by confocal microscopy in the live, developing tadpole after direct tectal injection of vehicle solution (control) or BDNF. BDNF not only increases axon arbor complexity but also increases the number and density of GFP-synaptobrevin clusters per axon terminal. Note the high proportion of branch points with synaptic clusters in these arbors. Scale bar, 20 μm.

Alsina B., et al., (2001) Nature Neurosci. 4: 1093-1102

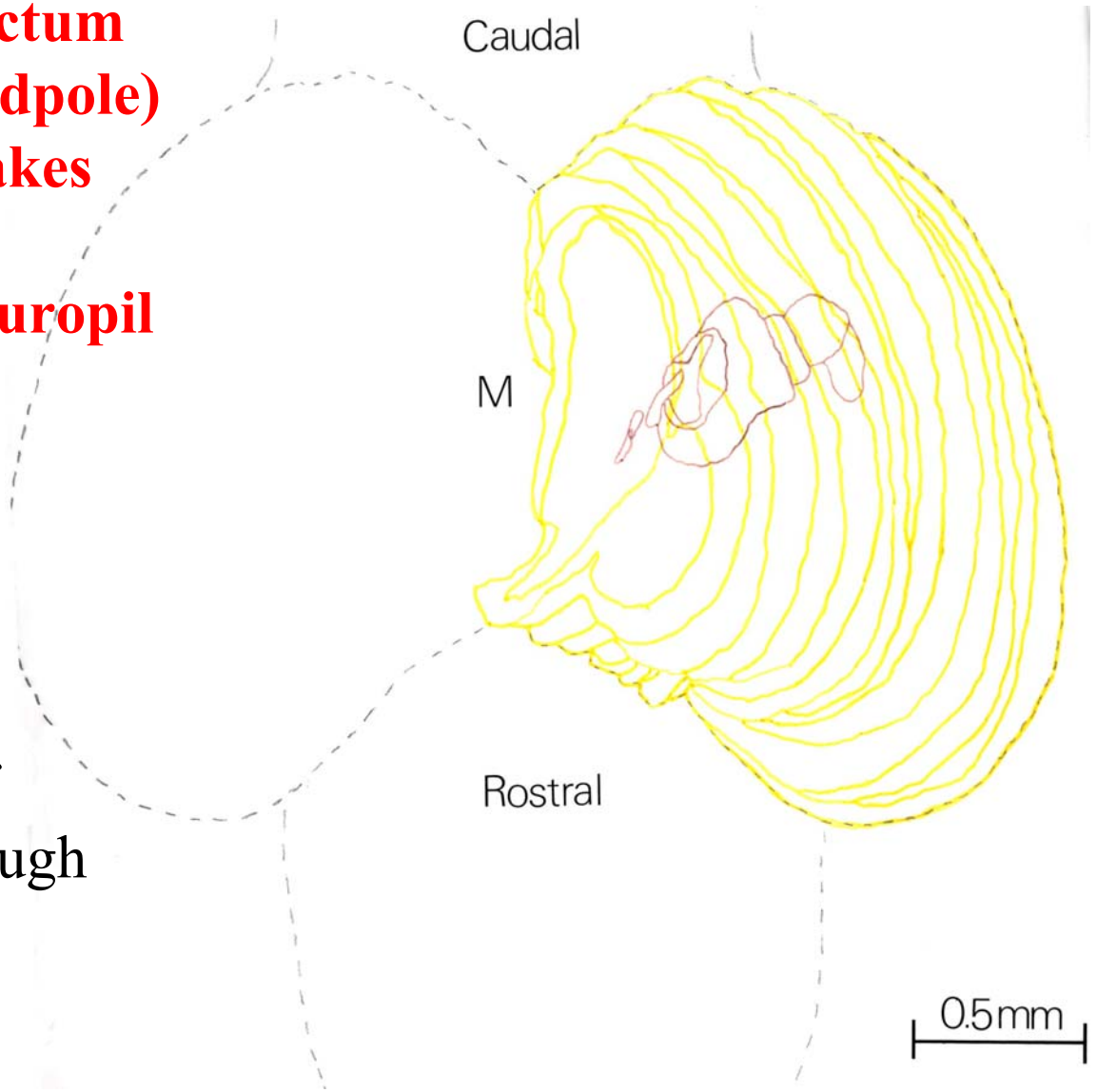
Figure 2 | **Neurotrophins as synaptic morphogens. a** | Top: Constitutive secretion of neurotrophins (NTs) from postsynaptic dendrites results in a low-level of extracellular NTs at the synapse, which is required for maintenance of normal synaptic function, including the capability for the induction of long-term potentiation (LTP). Middle: Following intense synaptic activity, a transient high level of postsynaptic calcium (for example, accompanying the induction of LTP) results in a high level of NT secretion that raises the local extracellular NT concentration (possibly corresponding to early-phase LTP). Bottom: High NT levels locally trigger sprouting of nerve terminal arbors and dendritic spines, leading to the formation of new synapses (possibly corresponding to late-phase LTP). **b** | The NT hypothesis for activity-dependent refinement of connections. Top: Synapses made by the terminals of different axons co-innervating the same postsynaptic dendrite are maintained in a normal functional state by the low-level constitutive secretion of NTs. Middle: Correlated activity in axon 1 and axon 2 causes large postsynaptic depolarization (and spiking) immediately following synaptic activation at axon 1 and axon 2, resulting in a transient high level of calcium and a high level of NT secretion. By contrast, uncorrelated activity in axon 3 does not experience postsynaptic spiking at the time of its synaptic activation, and therefore does not secrete high levels of NT. Bottom: Terminals of axon 1 and axon 2 sprout and new spines are formed in response to local high levels of NT. The synapse made by axon 3 may lose its postsynaptic supply of NT, owing to the directed transport of NT-containing granules towards adjacent synapses with correlated activity, leading to synaptic weakening and eventually withdrawal of the nerve terminal.



Poo M (2001) NatureNeuro. Review 2:24-33

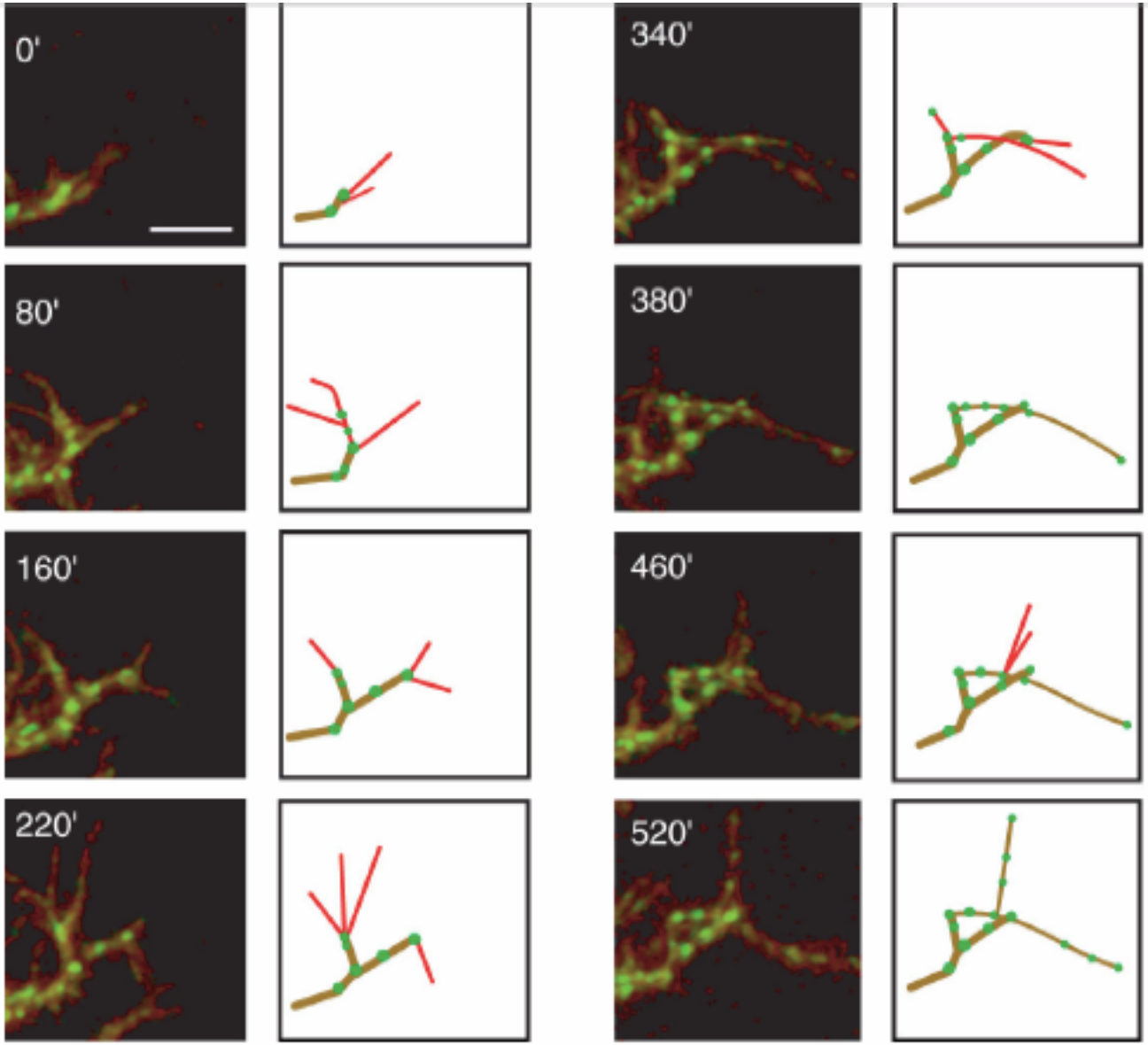
In a more mature tectum (metamorphosing tadpole) each retinal arbor takes up a much smaller proportion of the neuropil

Envelope of a single (large) retinal arbor Labeled from the retina. Traced from a complete sequence of thin plastic section through an entire tectum.



Zebrafish with sparse labeling of tectal cells with ds-red and post-synaptic densities labeled with eGFP tagged PSD-95.

Imaged with 2-photon microscopy



Niell CM et al., (2004) Nature Neurosci. 7:254-261.

Figure 4 Dendrite growth occurs by an iterative sequence of selective filopodial stabilization and punctum formation. Still images from a time-lapse series, accompanied by a schematic rendering for clarity. Green represents PSD-95:GFP puncta, red lines are newly formed (often transient) branches, and brown are persistent branches. Scale bar, 5 µm.

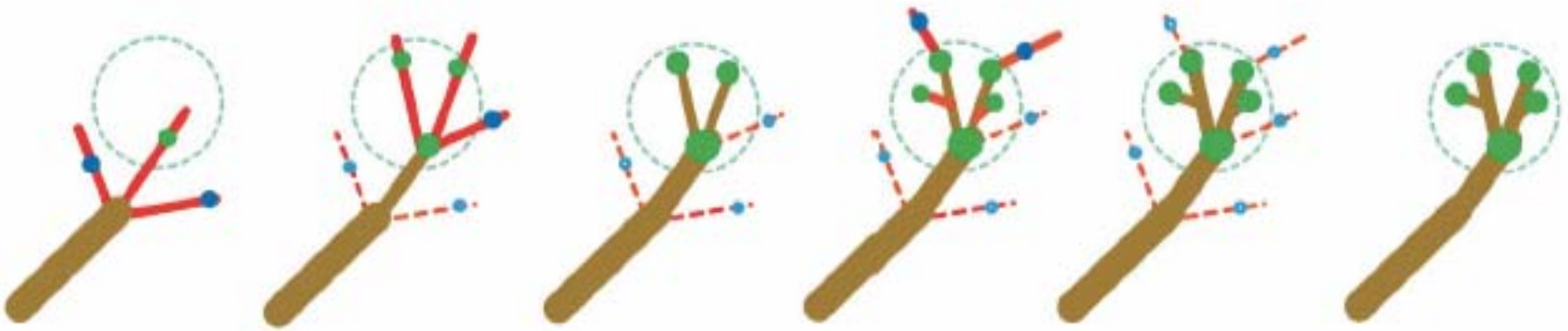
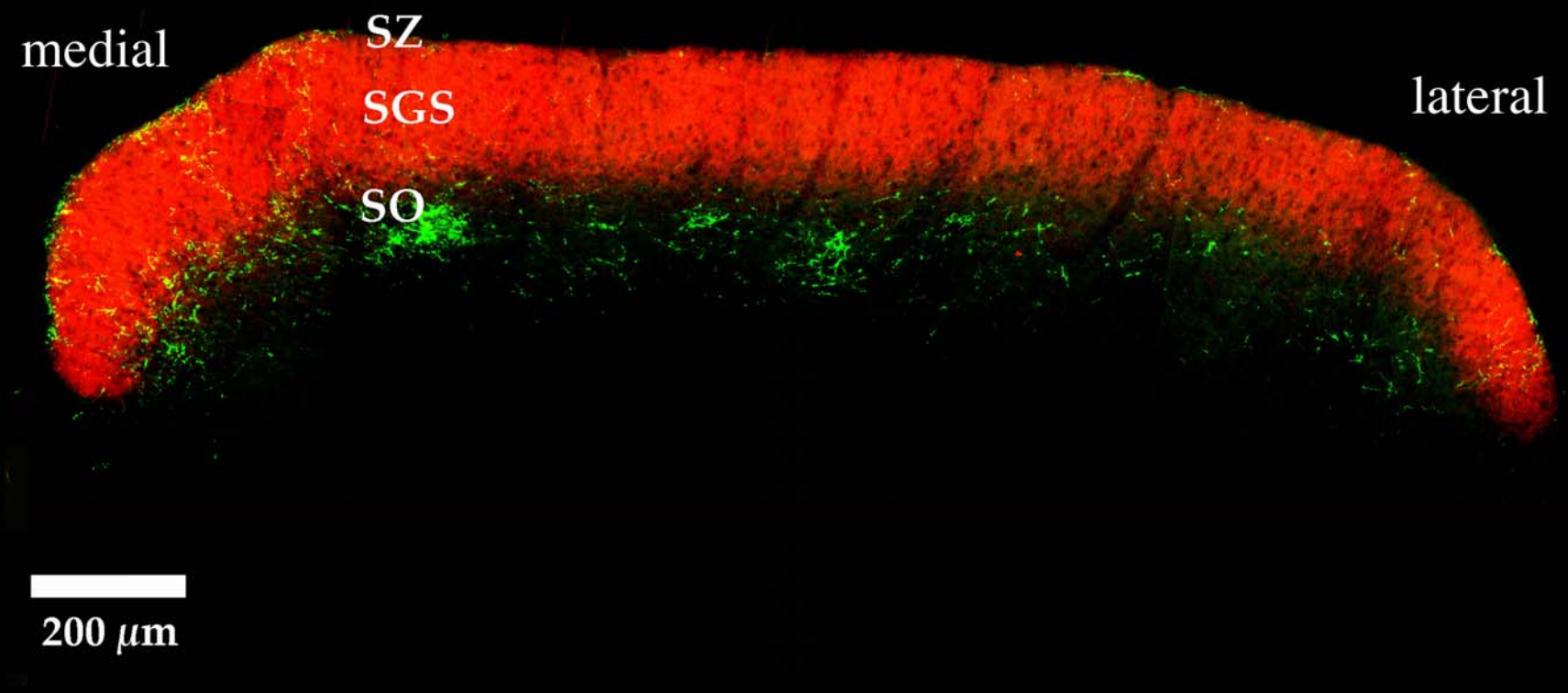
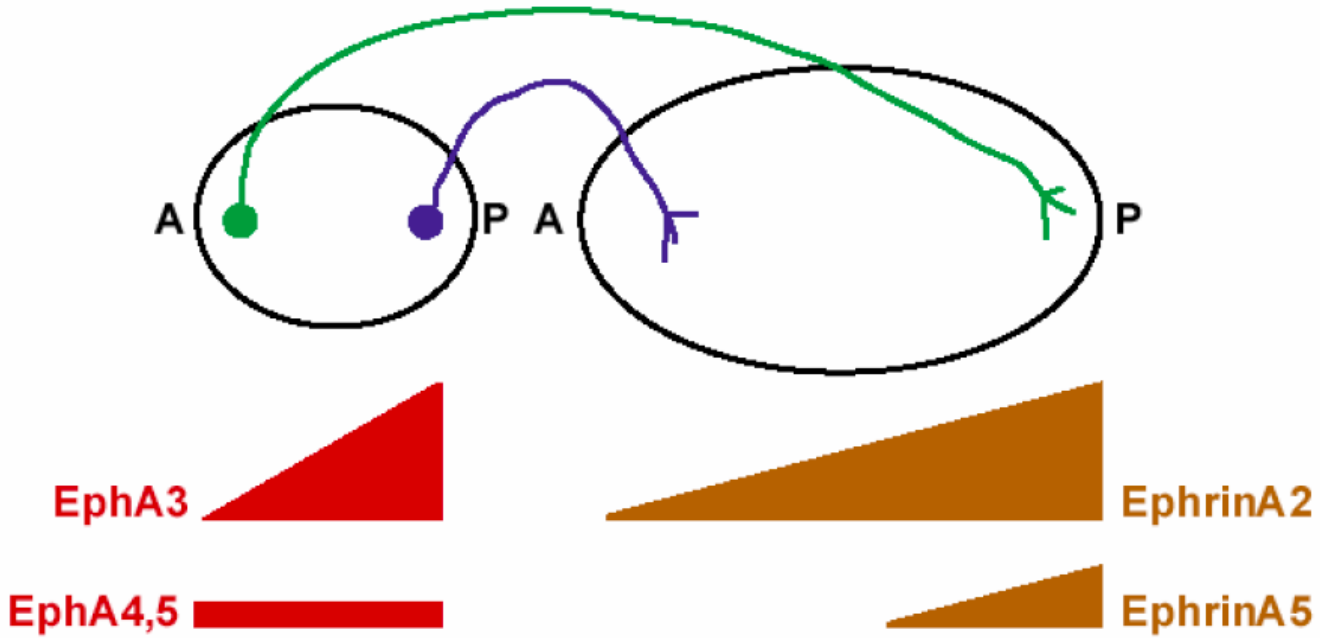


Figure 6 Model of synaptotropic guidance of dendrite growth. A number of filopodia (solid red) extend from a dendritic branch. Those that encounter correct partners and form synaptic contacts (green dots) are stabilized as new branches (brown), whereas those that establish inappropriate contacts (blue dots) are retracted (dashed red). Successive rounds of selective stabilization result in arborization within a field of appropriate synaptic connections (dashed green region).

Superficial Visual Layers of the Superior Colliculus



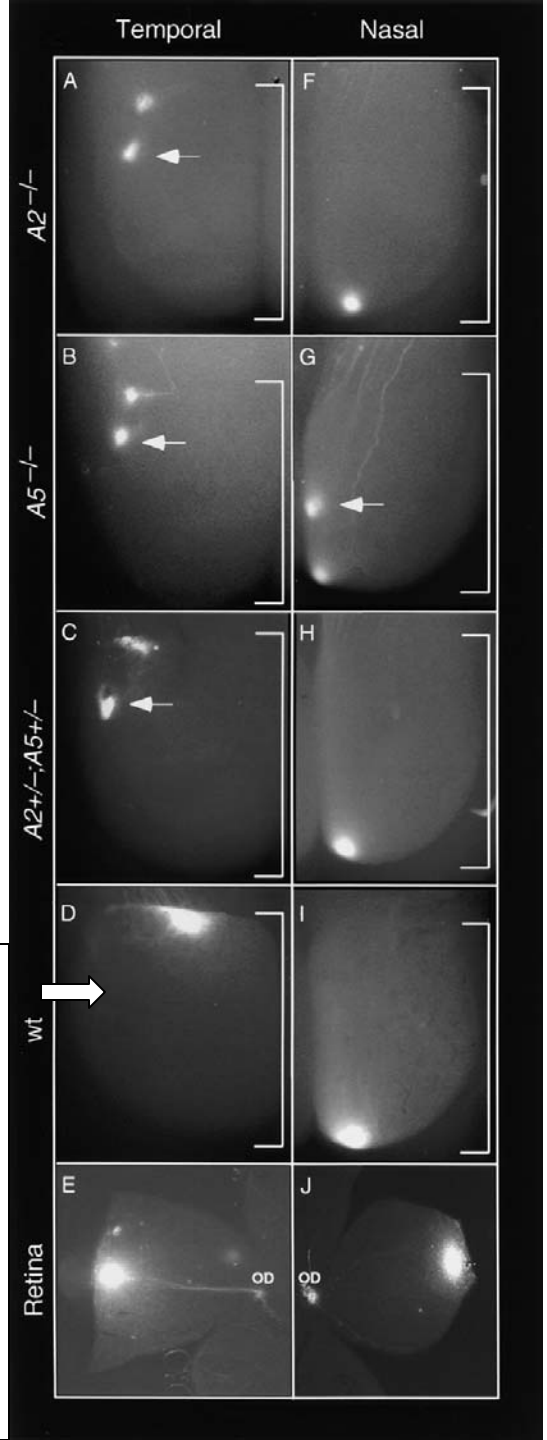
Eph and Ephrins in the Retinotectal System



Small injections of an anterograde tracer into one retinal pole (either temporal or nasal) terminate at multiple loci when Ephrin A2 or Ephrin A5 is mutated
The effect is most pronounced in the double mutant (A2-/-;A5-/-)

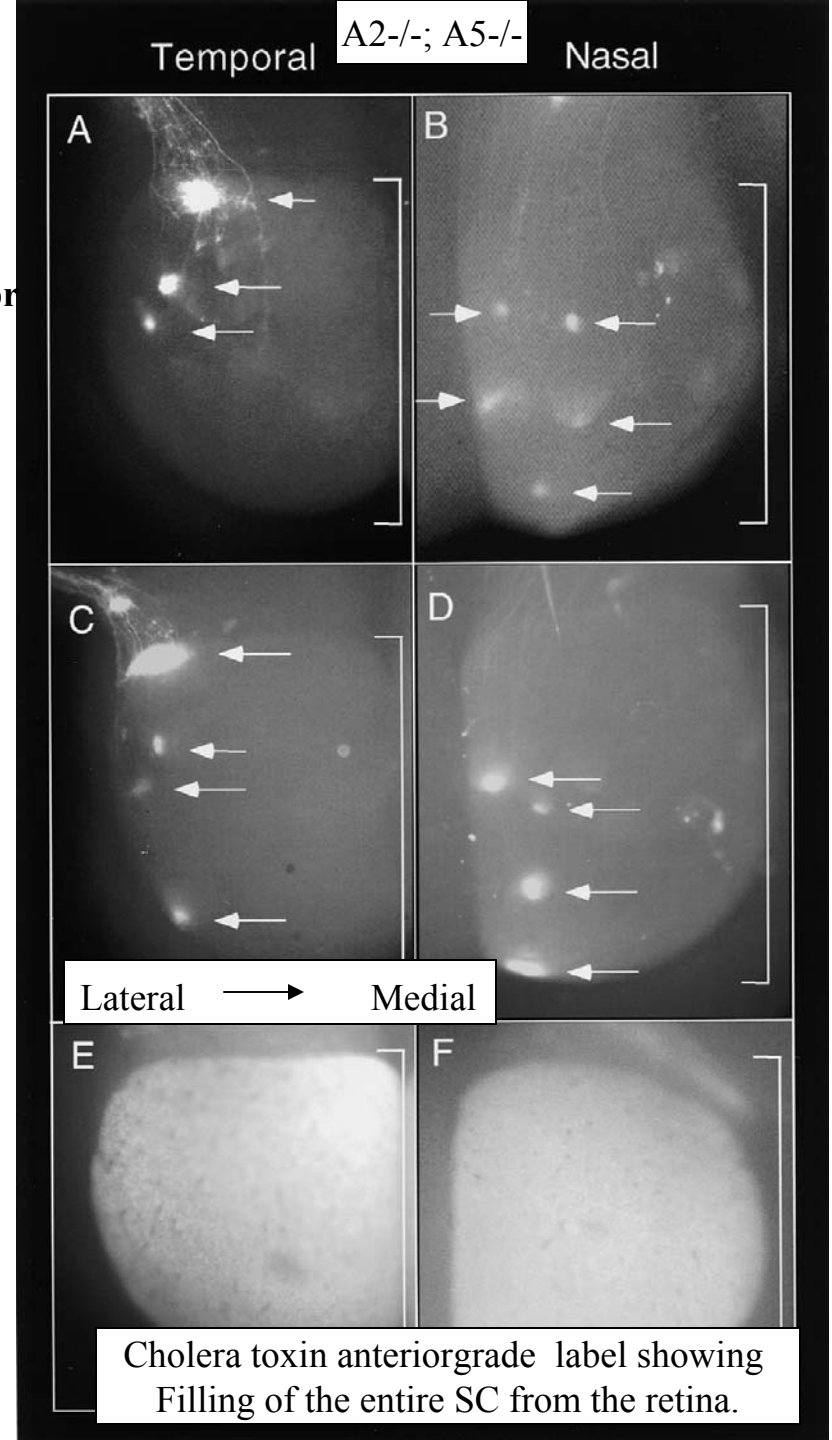
Wildtype shows only one locus of termination

Double mutants also show some abnormal targeting along the dorsoventral (mediolateral) Axis of the SC



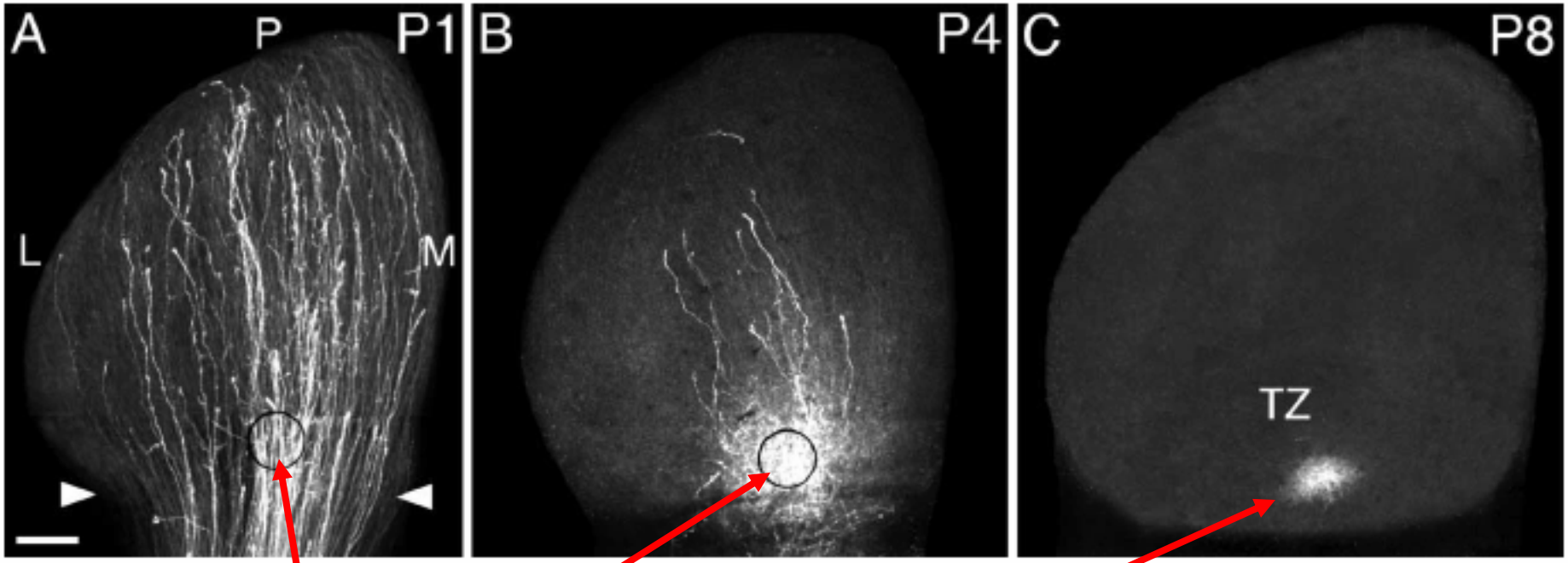
Anterior

Posterior



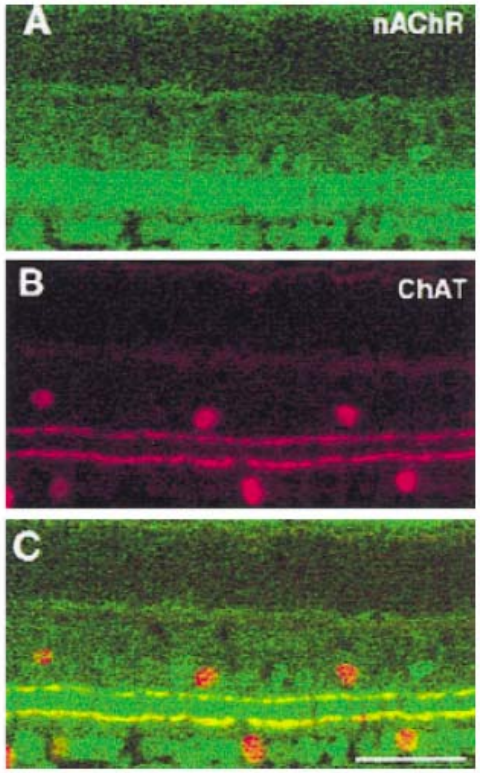
Cholera toxin anteriorgrade label showing Filling of the entire SC from the retina.

Normal Refinment of the Projection From a Temporal Retinal Locus to a Rostral Position in the Contralateral Tectum

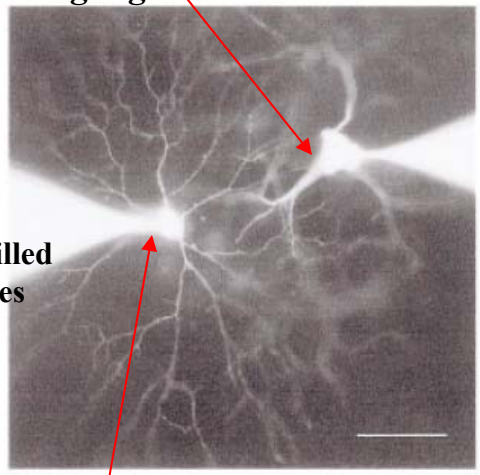


Appropriate topographic locus

Starburst amacrine cells in the retina are cholinergic and produce spontaneous bursts of activity that are correlated with depolarizations in ganglion cells.

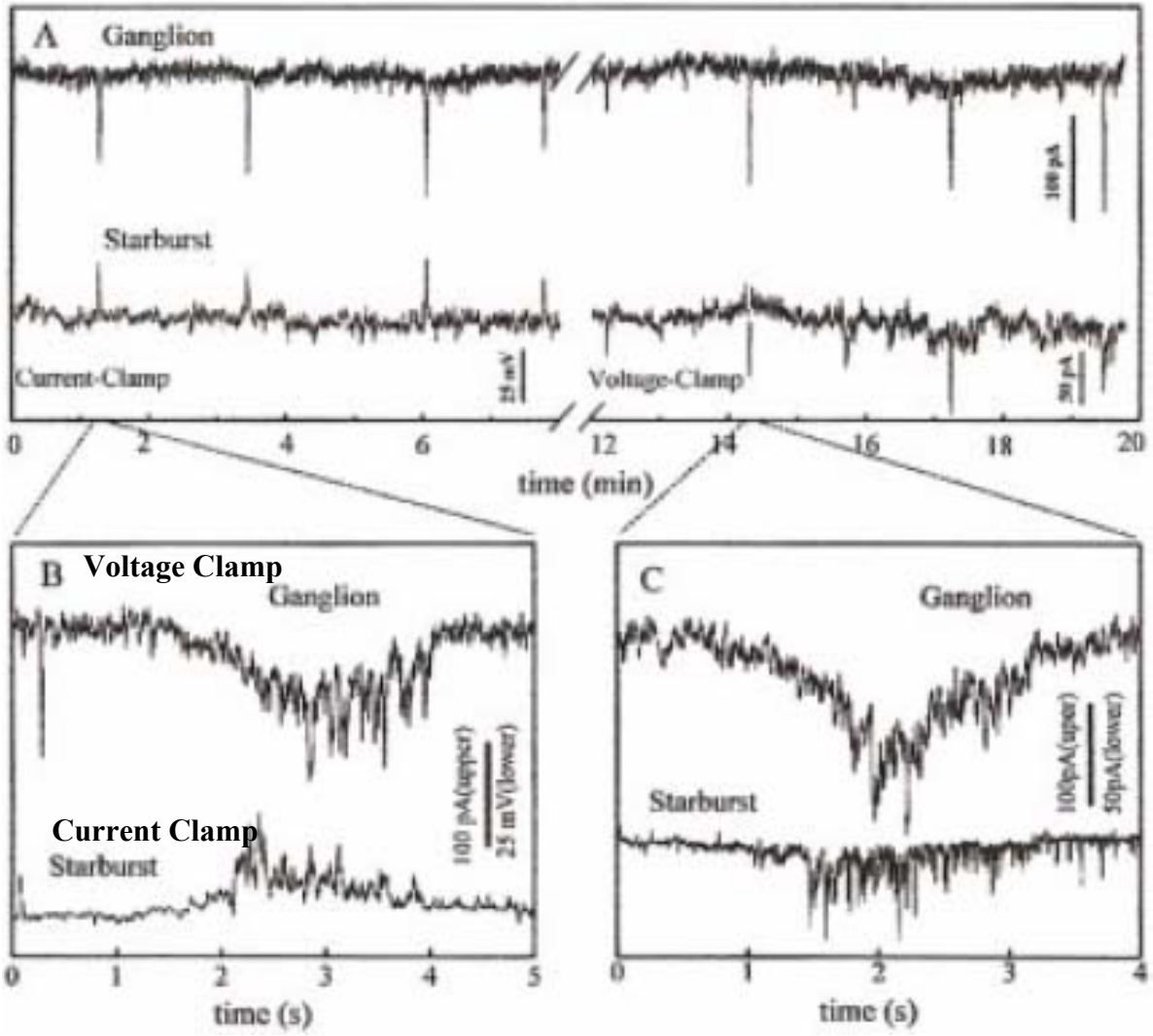


Retinal ganglion cell



Lucifer yellow filled electrodes

Starburst amacrine cell



Zhou ZJ, (1998) J. Neurosci. 18:4155-4165

Retinal activity on multi-electrode arrays

QuickTime™ and a
Video decompressor
are needed to see this picture.

QuickTime™ and a
Video decompressor
are needed to see this picture.

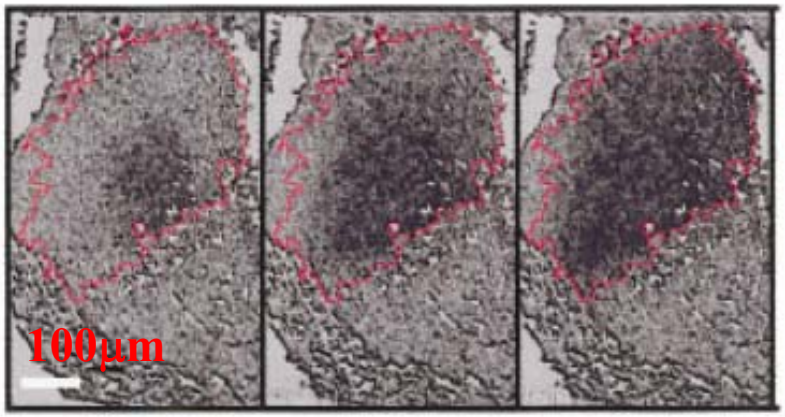
P4 WT

P4β$^{-/-}$

Each dot represents a position on the array where a discrete unit could be selected
Size of each dot represents average firing rate recorded over 500msec on that electrode
Movie represents 5 minutes of recording played 5x as fast.

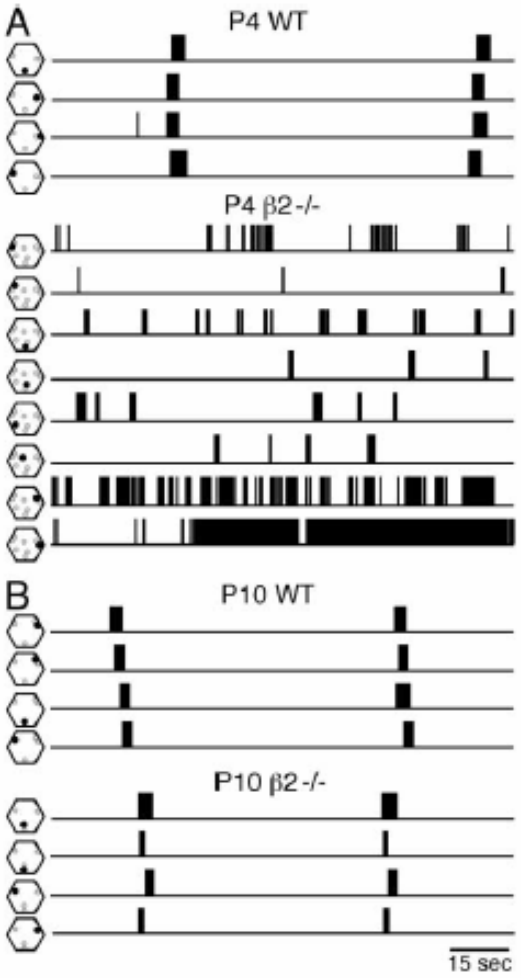
Temporal Pattern of retinal bursts as seen on multi-electrode arrays.

Ca+ fluorescent imaging of a single retinal wave



0.05 sec intervals

$\beta_2^{-/-}$mice have disrupted retinal waves during the first week.



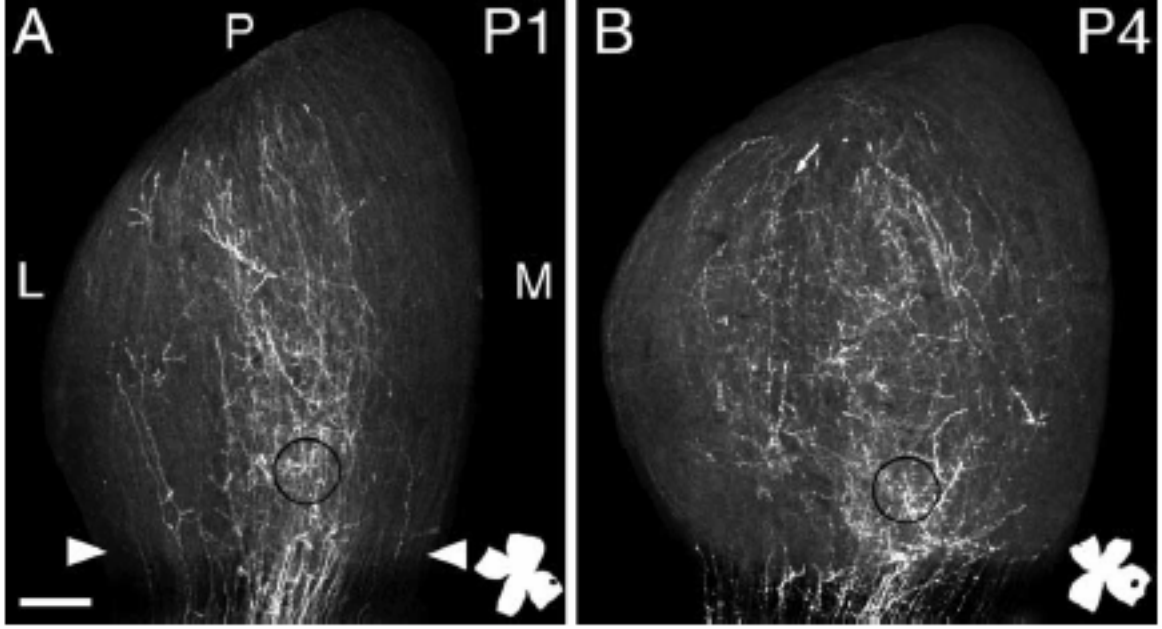
Waves are blocked by nACh receptor antagonists. The nAChRs on ganglion and amacrine cells contain the β_2 nicotinic cholinergic receptor subunit.

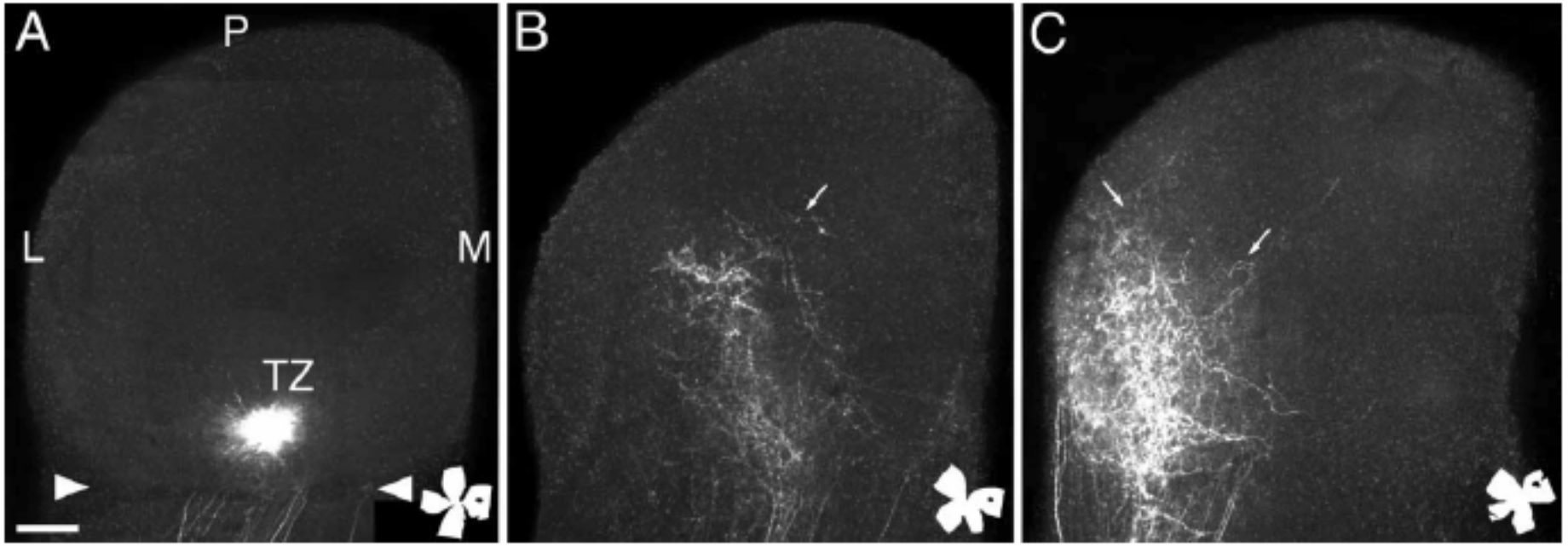
$\beta_2^{-/-}$mice have normal retinal waves during the second week.

Figure 1. β2$^{-/-}$ Retinas Have Altered Firing Patterns during the First Postnatal Week

Zhou, (1998)

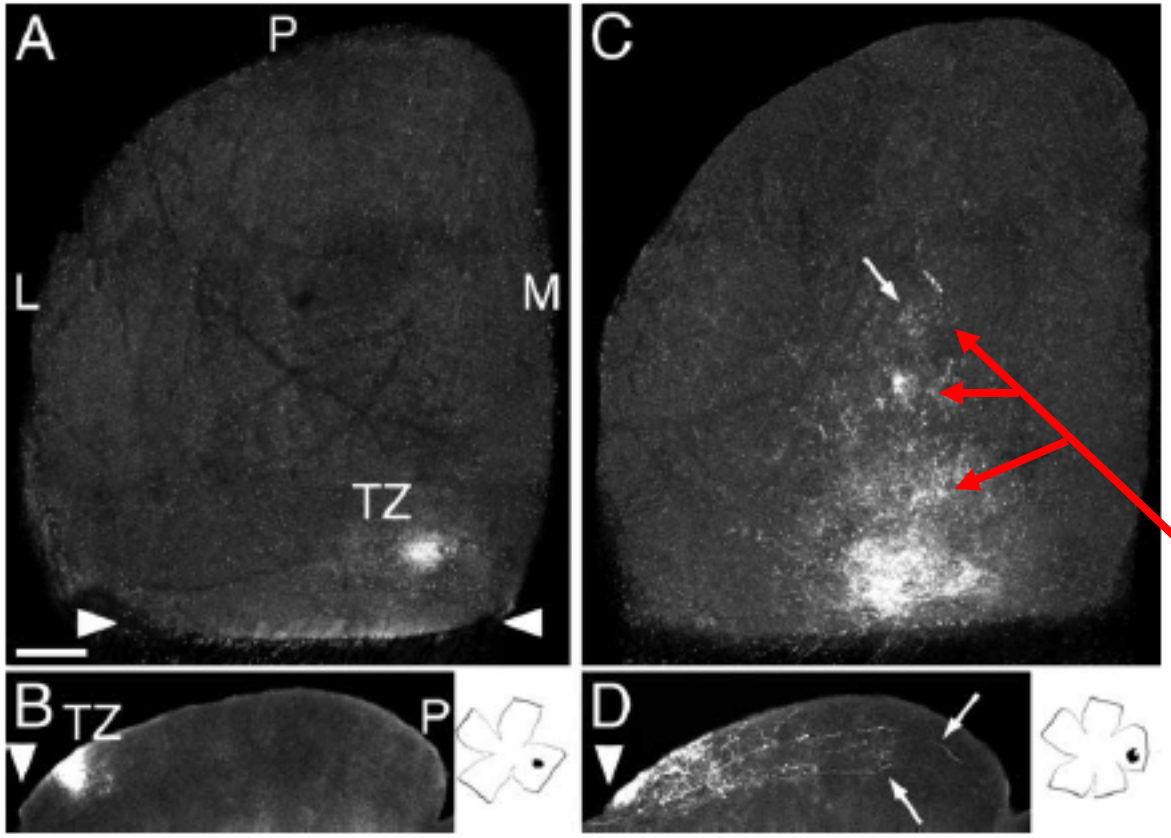
Mc Laughlin et al., 2002 Neuron 40:1147-1160.


A
P
P1
L
M
B
P4


A
P
L
M
TZ
B
C

$\beta_2^{-/-}$ mutants never refine their maps even though activity is normal after P8 when glutamate driven by the developing photoreceptor to bipolar to ganglion/amacrine network develops

P20 WT

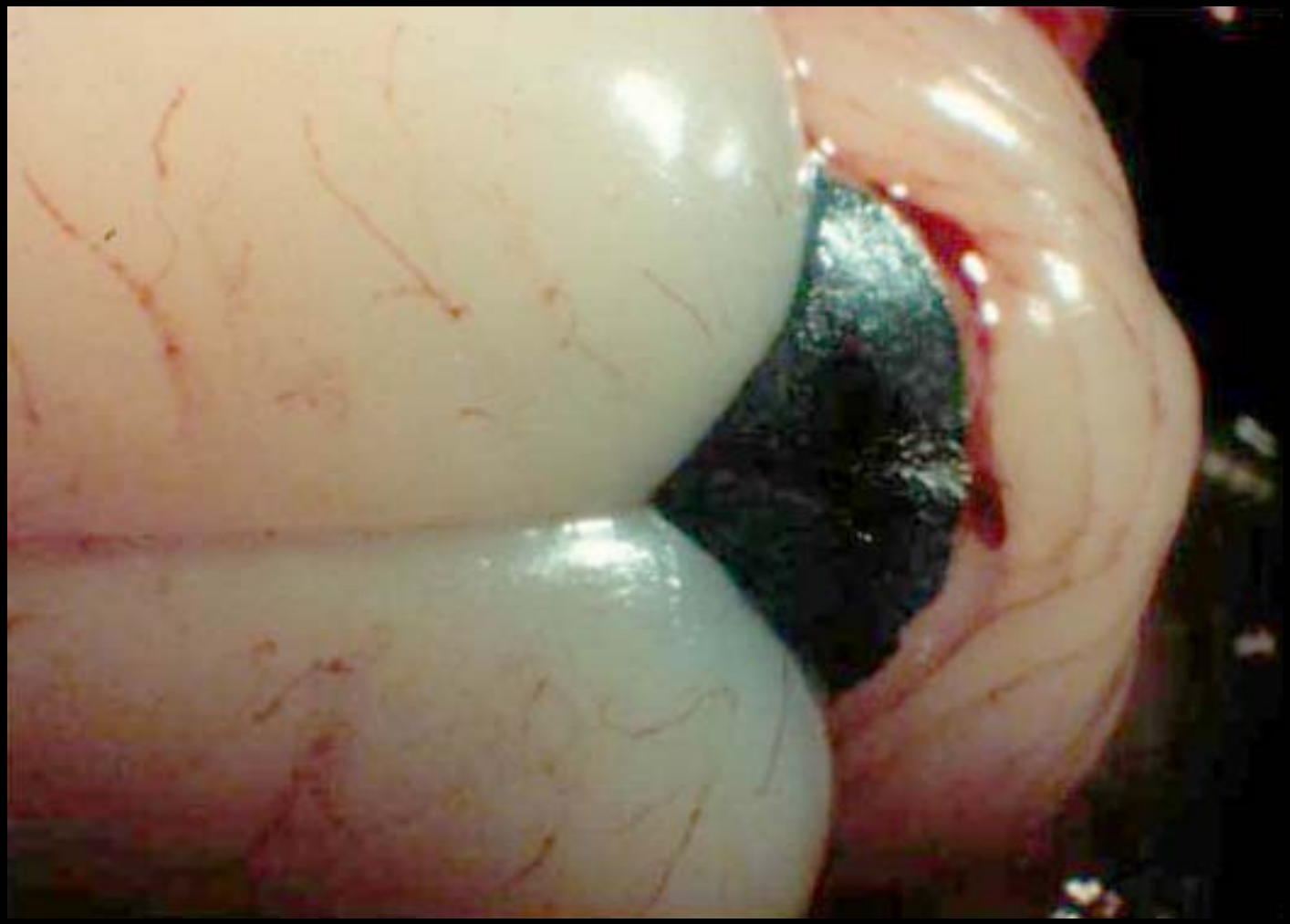


P20 $\beta_2^{-/-}$

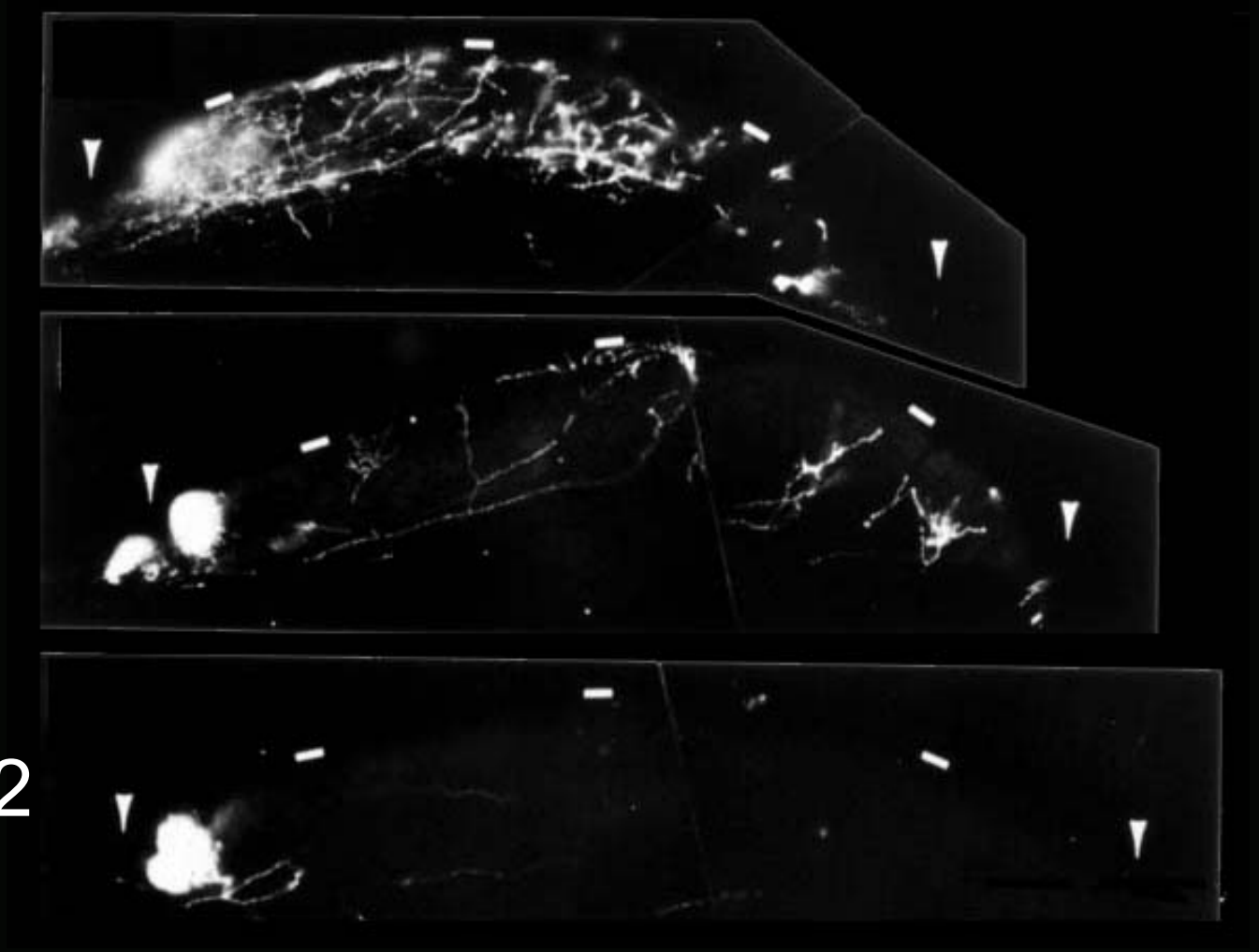
saggital section

Note: "increased clumpiness" of the projection

NMDA receptors are blocked by implanting Elvax over the colliculus

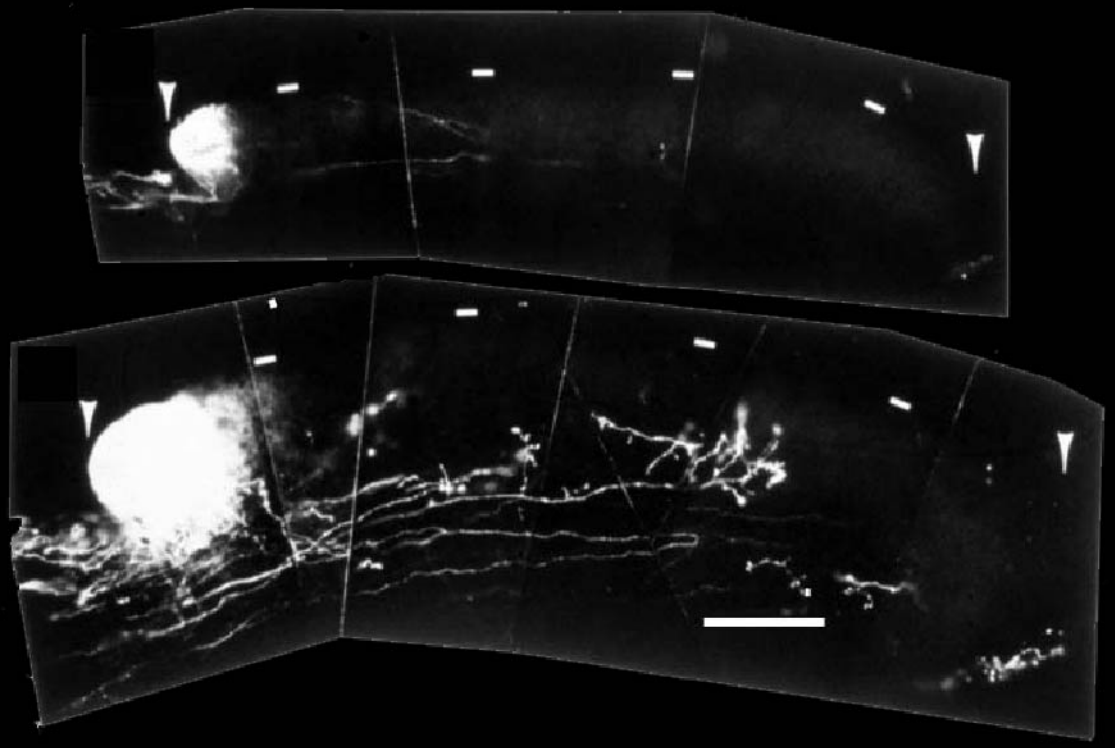


Development of the contralateral retinal projection



from Simon and O'Leary, 1992

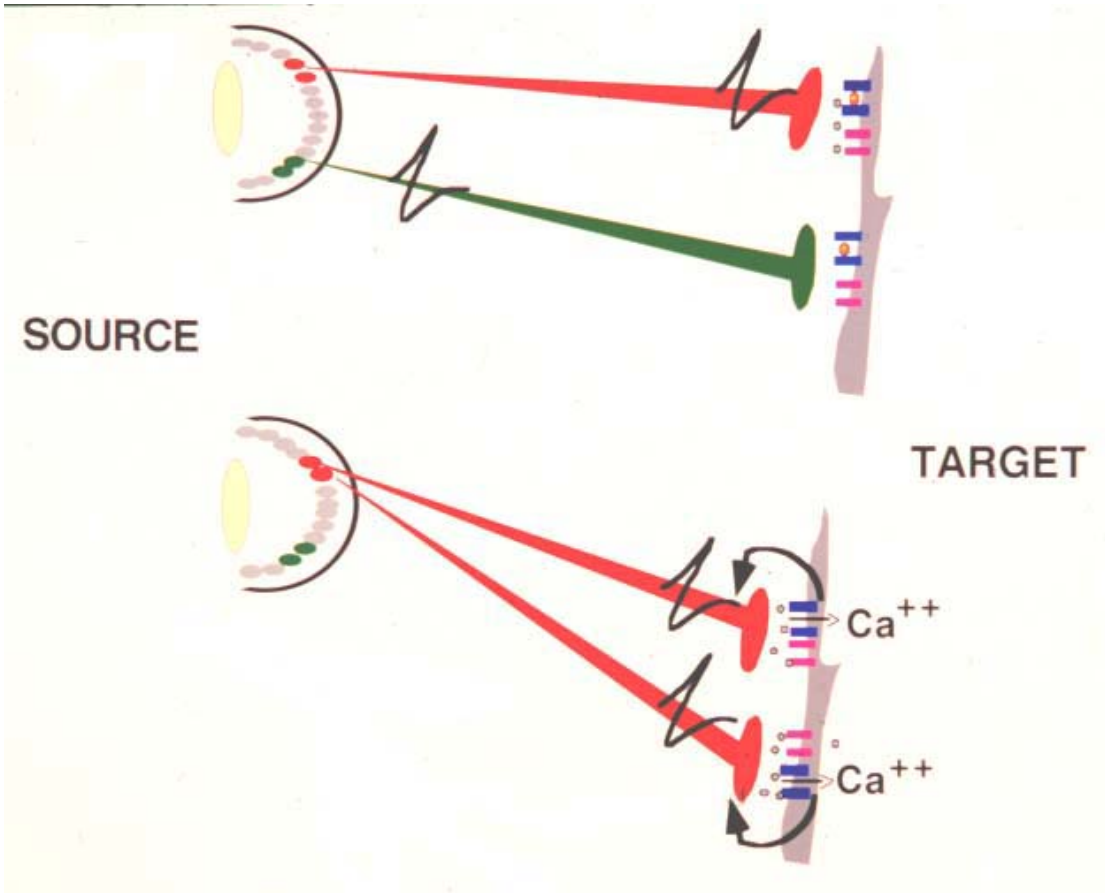
NMDA receptor blockade from birth prevents the refinement of retinotopy in the contralateral projection



From: Simon, et al., 1992

Point to point order is determined by nearest-neighbor activity dependent sorting

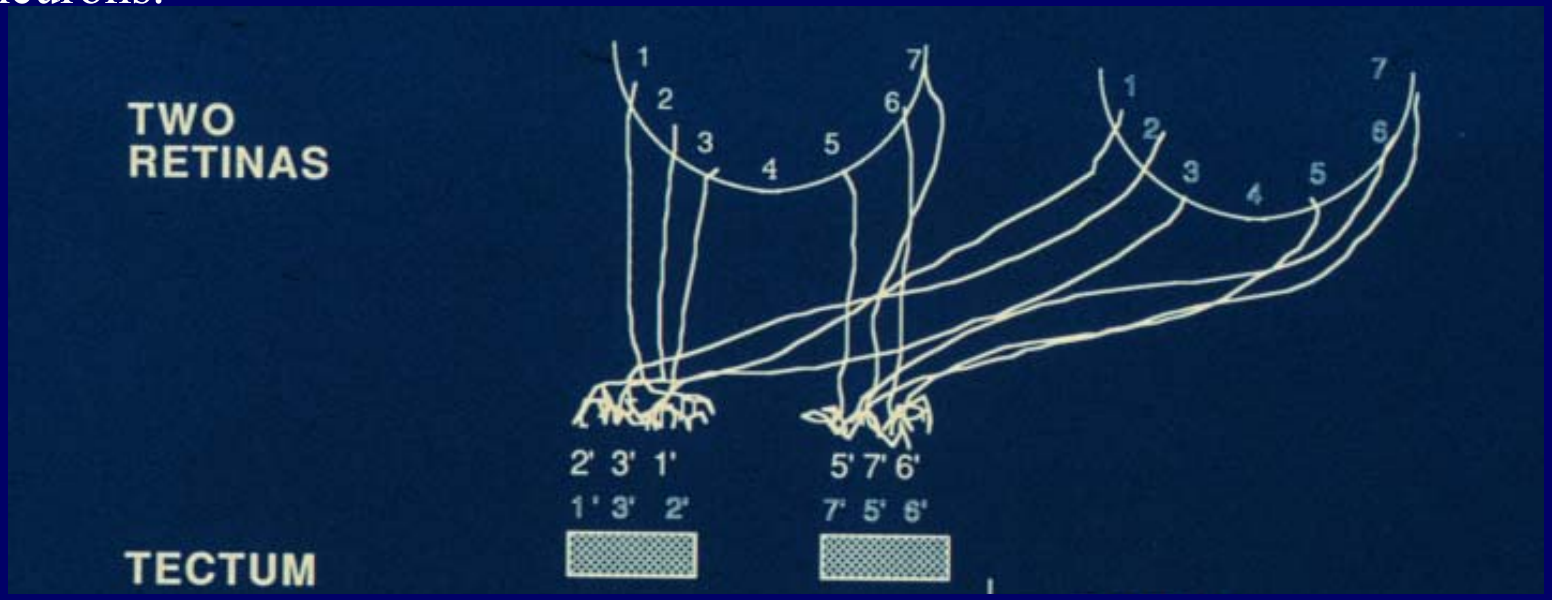
Neighboring pre-synaptic neurons tend to have correlated activity



Chemoaffinity,(cell-cell interactions) among genetically pre-labeled axons and their targets does not predict sorting of synaptic terminals once they reach their target. The retinal projections have an exceptionally high degree of point to point order

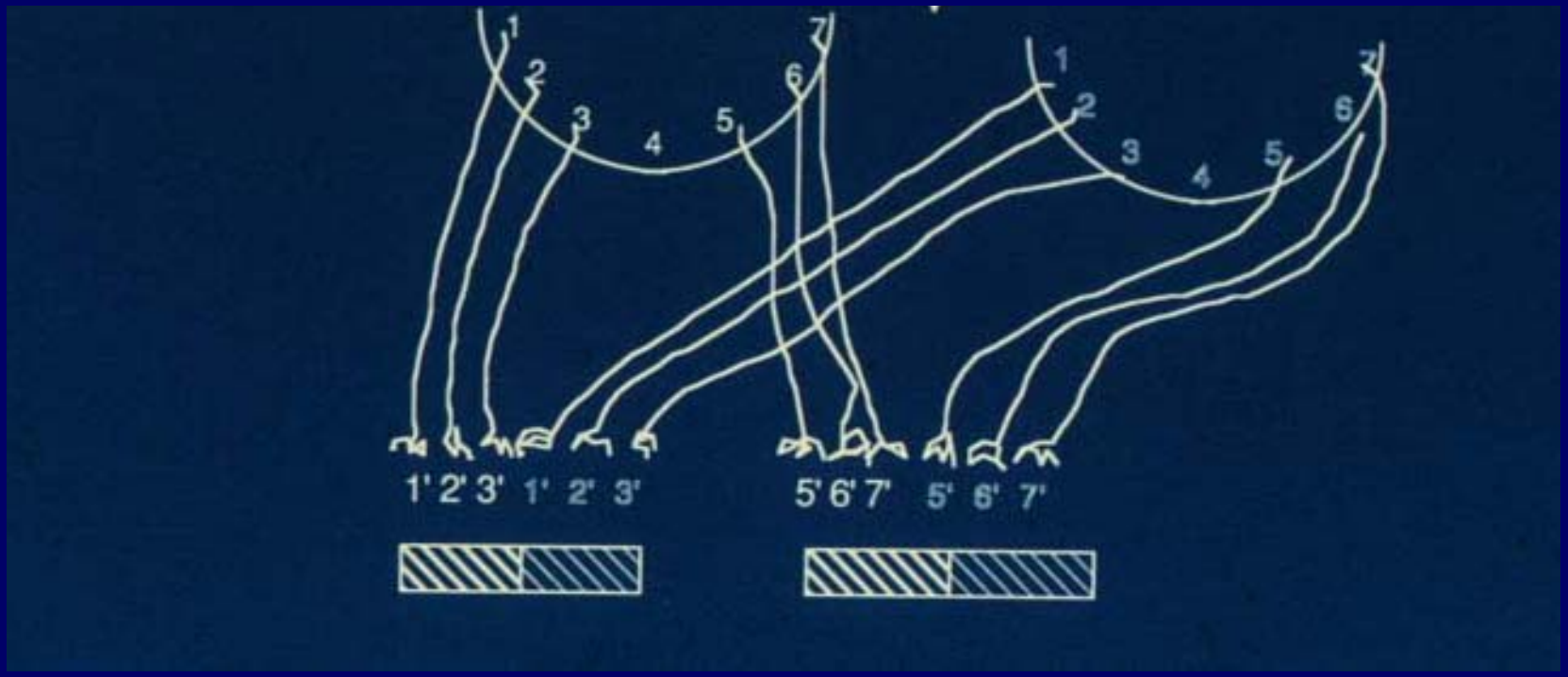
Testing the hypothesis that:

Nearest neighbor sorting and not "chemoaffinity" dictates position of synapses locally by maximizing zones where terminals from neighboring ganglion cells converge on common target neurons.

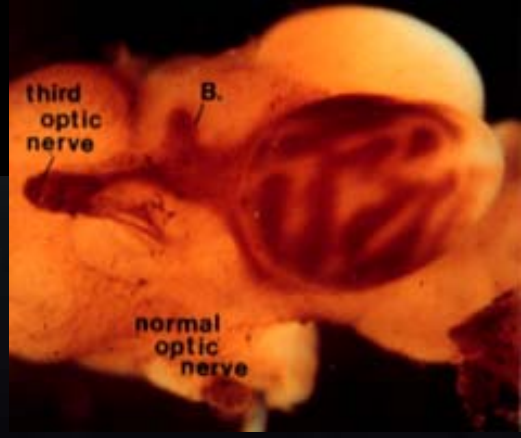


Test by challenging the chemoaffinity targeting by a second pre-specified set of retinal ganglion cells

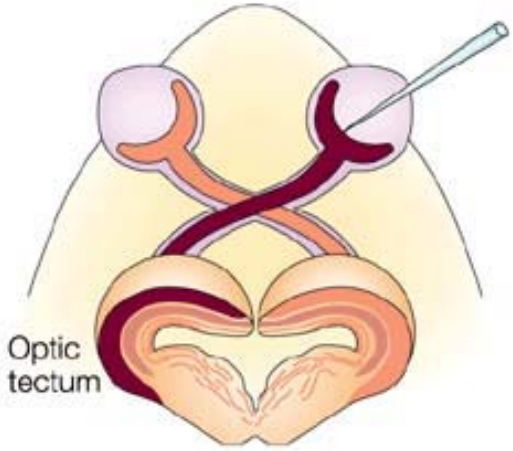
Two identically ‘specified’ retina’s should segregate their synaptic zones in the tectum if inputs from nearest retinal neighbors tend to terminate together.

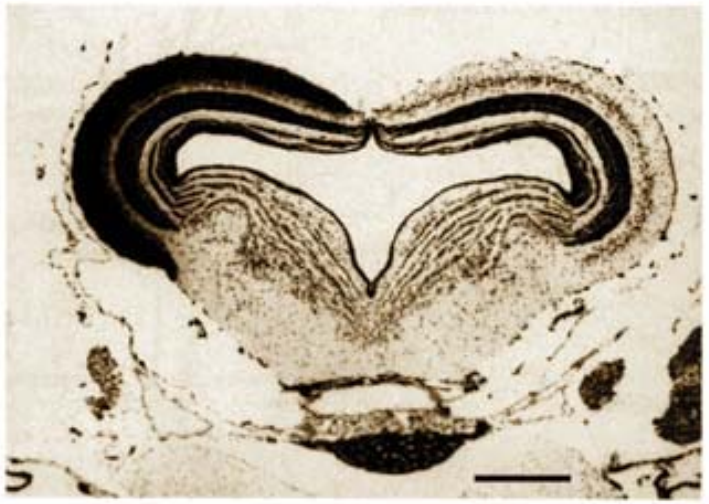


Three-eyed frogs show "induced" ocular dominance columns whenever 2 retinal projections compete for space in one tectal lobe.

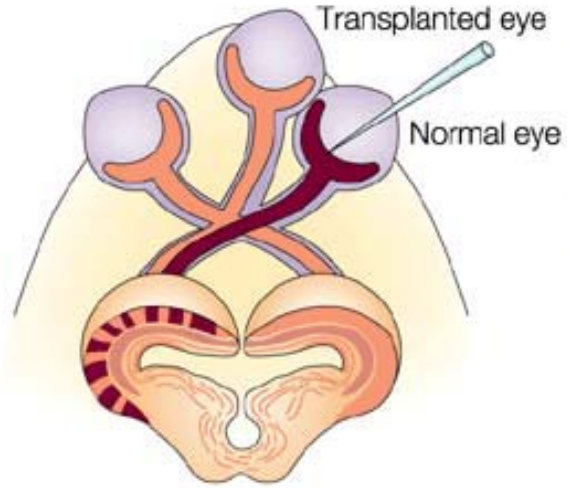


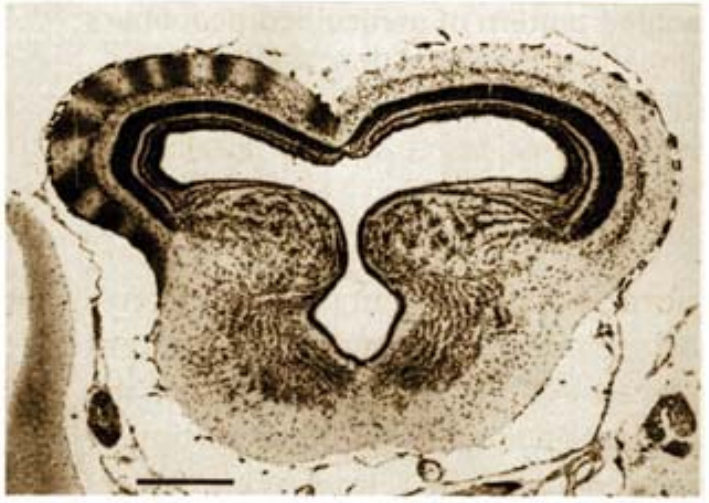
Implant a supernumerary eye in early neural tube stage embryos. and label the terminal zone with an anterograde label.





A segregated terminal zone develops with axons from the two maps of visual space represented in alternate striped zones.





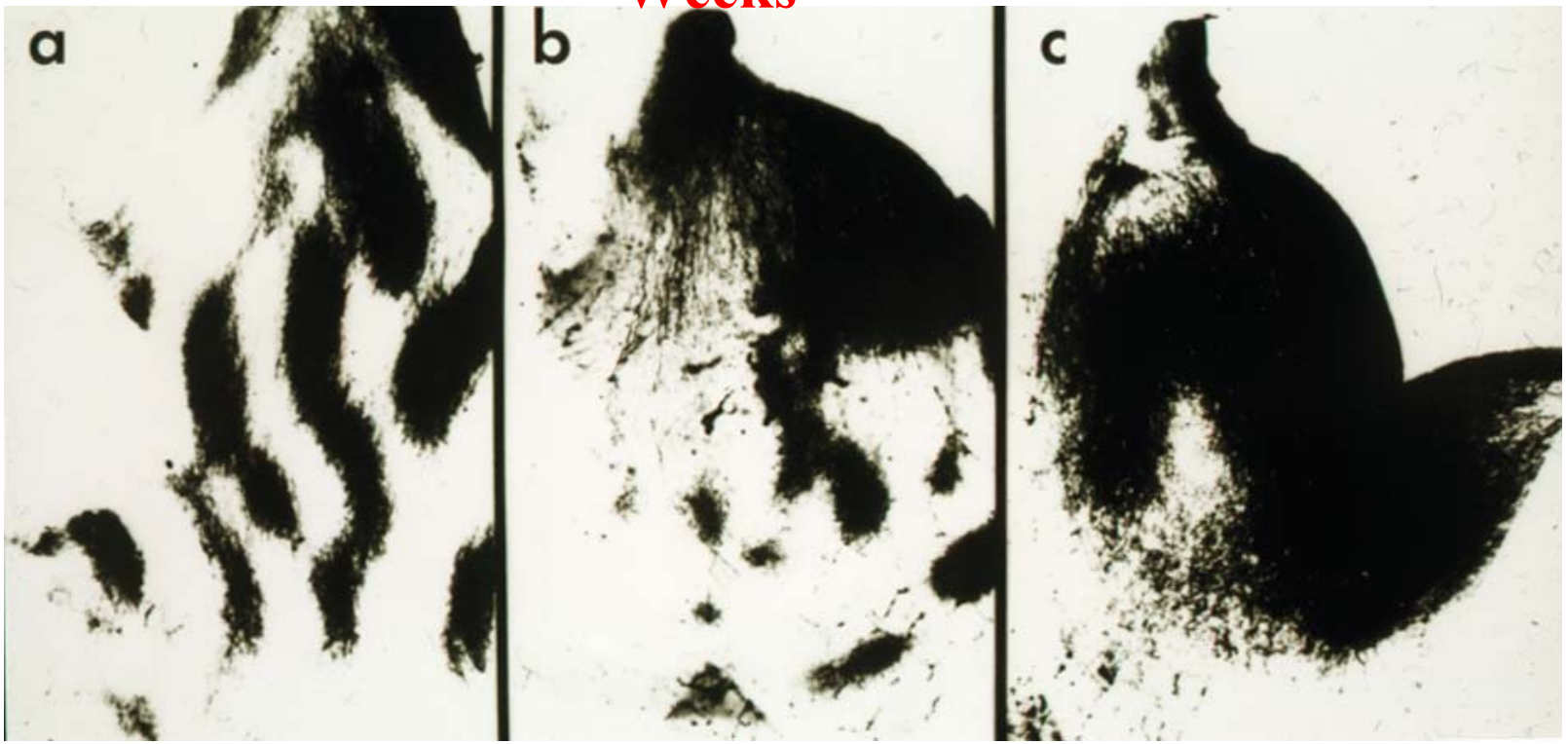
Constantine-Paton and Law, (1978) Science, 202:639
Law & Constantine-Paton (1981) J. Neurosci. 1:741.

Chronic Application of the NMDA Receptor Blocker AP-5 Causes A Desegregation of Eye-Specific Stripes In Amphibian Tecta

SHAM

AP5 After 2.5 Weeks

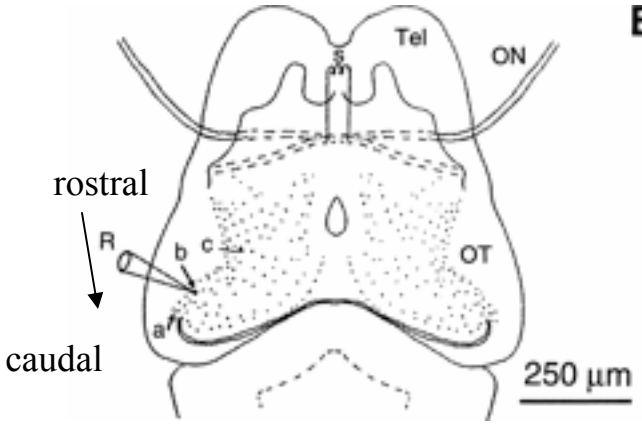
AP5 After 4 Weeks

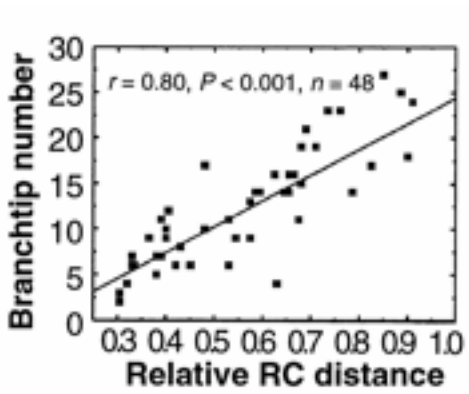


When AP5 is removed the stripes reappear in 2 weeks

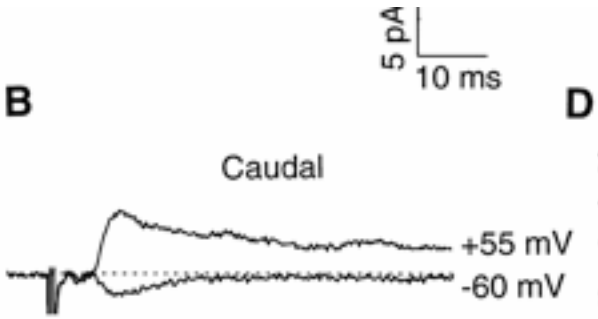
From: Cline, Debski & Constantine-Paton, 1987

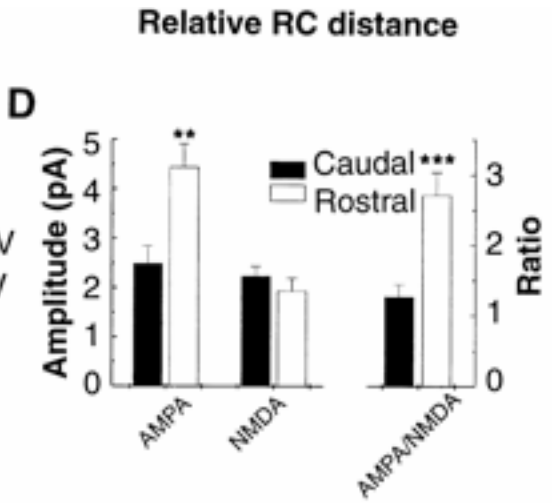
The Tectum of Xenopus Allows Analysis of the Differentiation of Glutamate Currents With Time Because of a Rostral to Caudal Gradient Of Differentiation

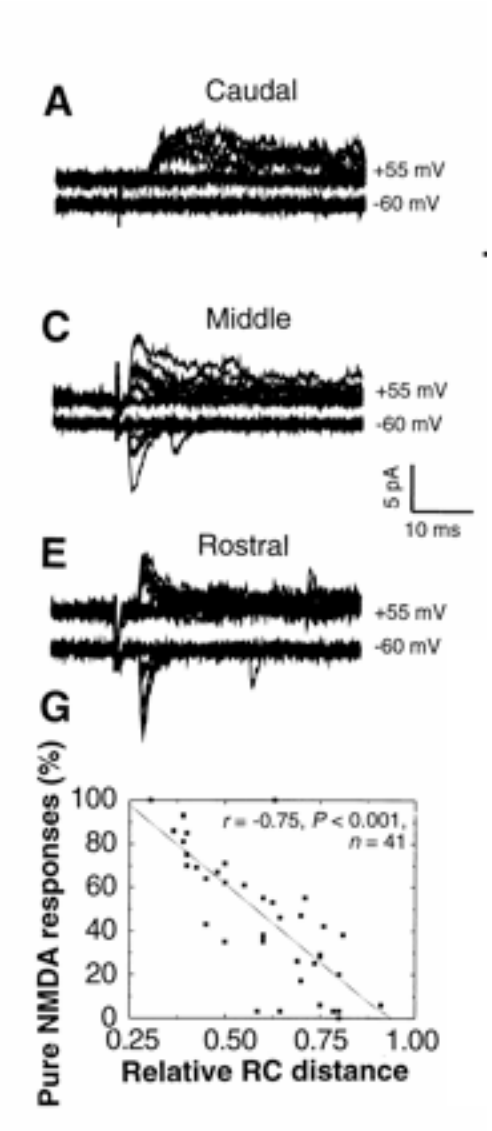




caudal → rostral



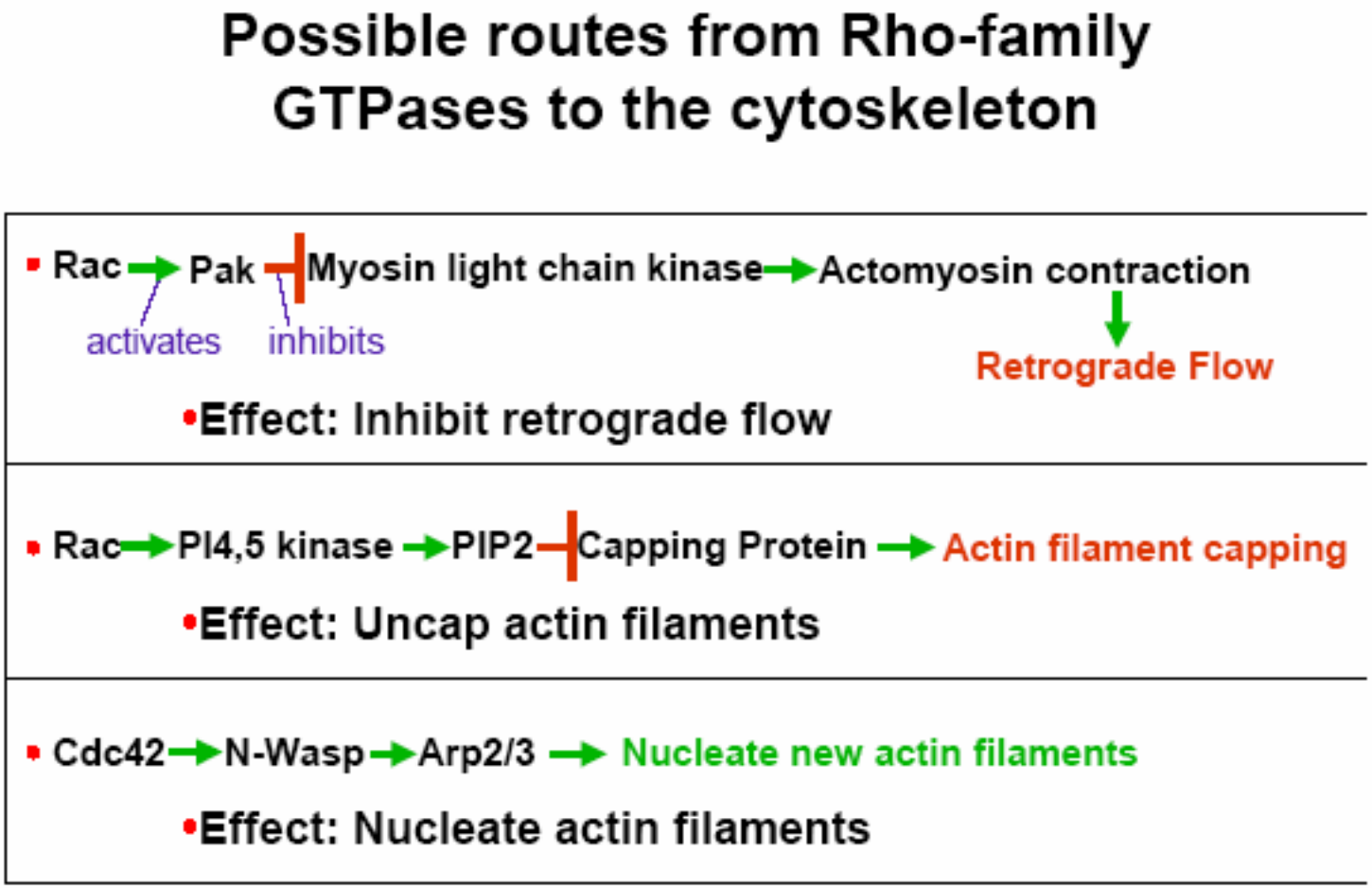




caudal → rostral

Wu et al., (1996) Science 1274:972-976

Review From Paul Garrity



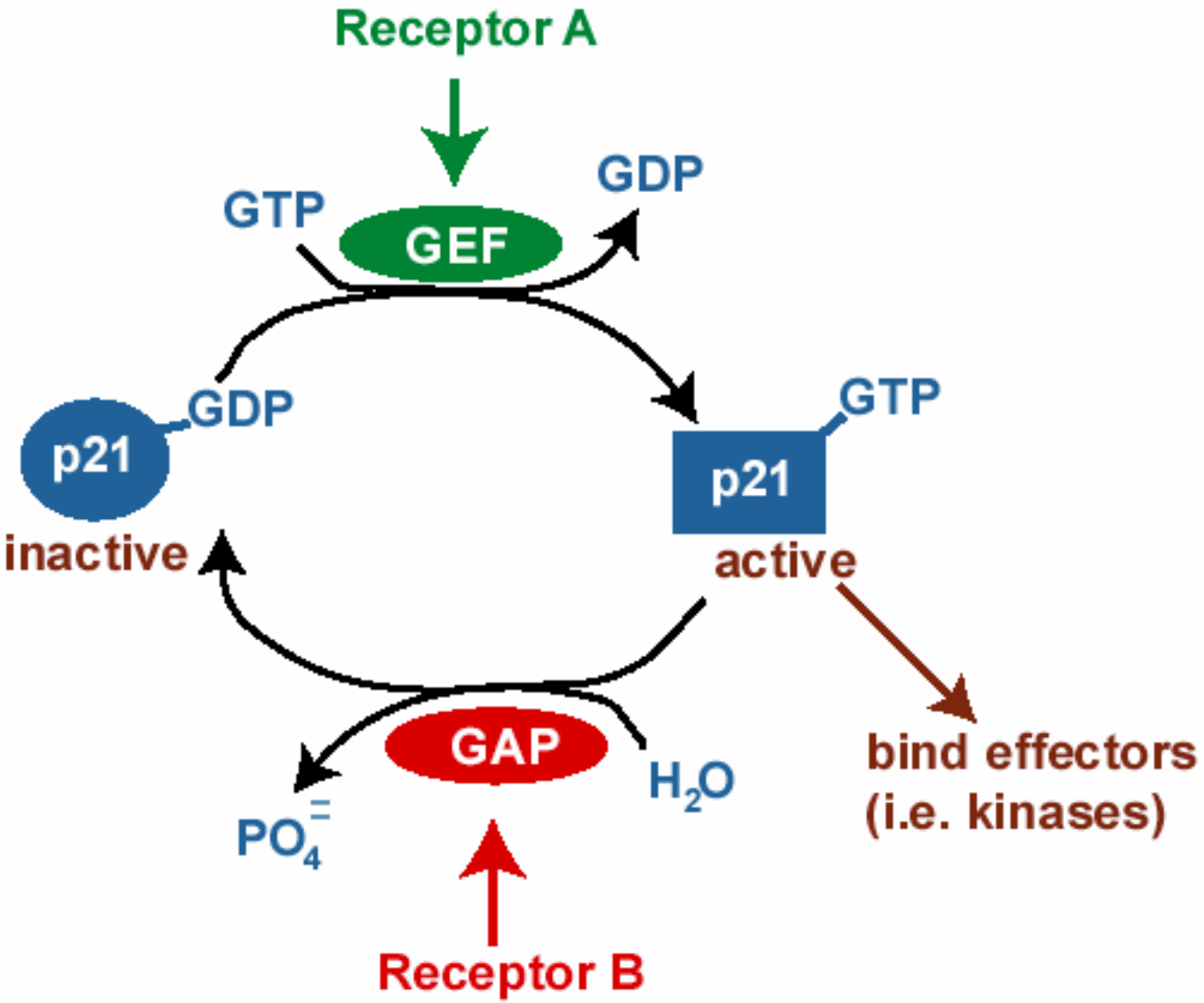
Rho family GTPases act as molecular switches

- members of the ras superfamily of p21 GTPases
- subject to both positive and negative regulation by:

  - guanine nucleotide exchange factors (GEFs) (positive)

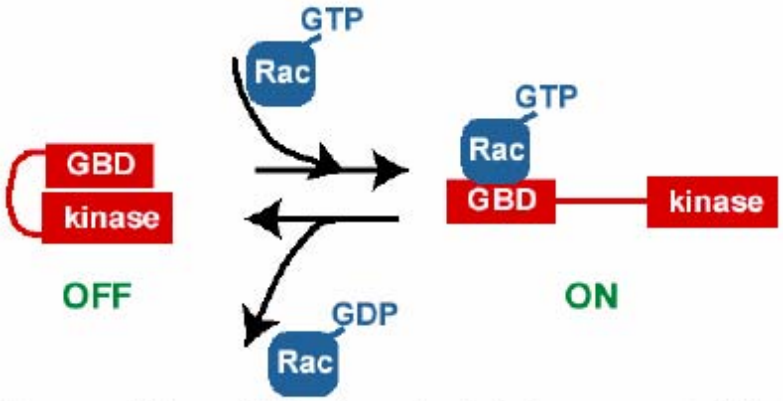
  - GTPase activating proteins (GAPs) (negative)

The p21 GTPase cycle



How can putting a Rho-family GTPase into the GTP-bound regulate an effector?

- One example: PAK (a serine/threonine protein kinase) is activated by binding to Rac^{GTP} and $cdc42^{GTP}$



- Crystallographic and biochemical data suggest this type of activation mechanism may be used in many RhoGTPase-effector interactions.