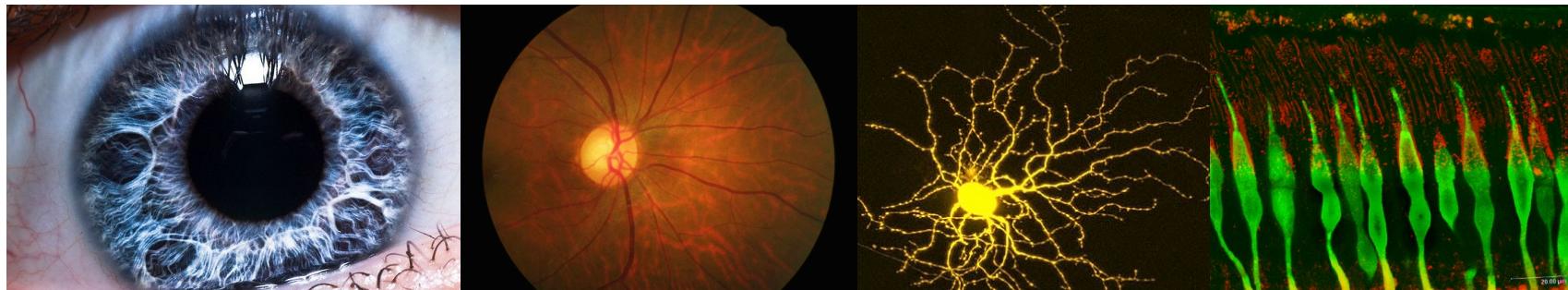


Development and function of visual circuits

It's all about molecule and activity

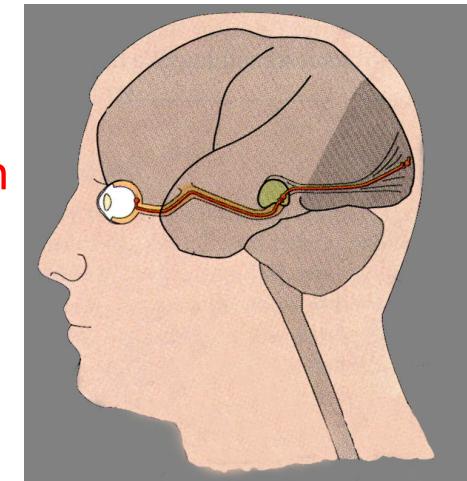
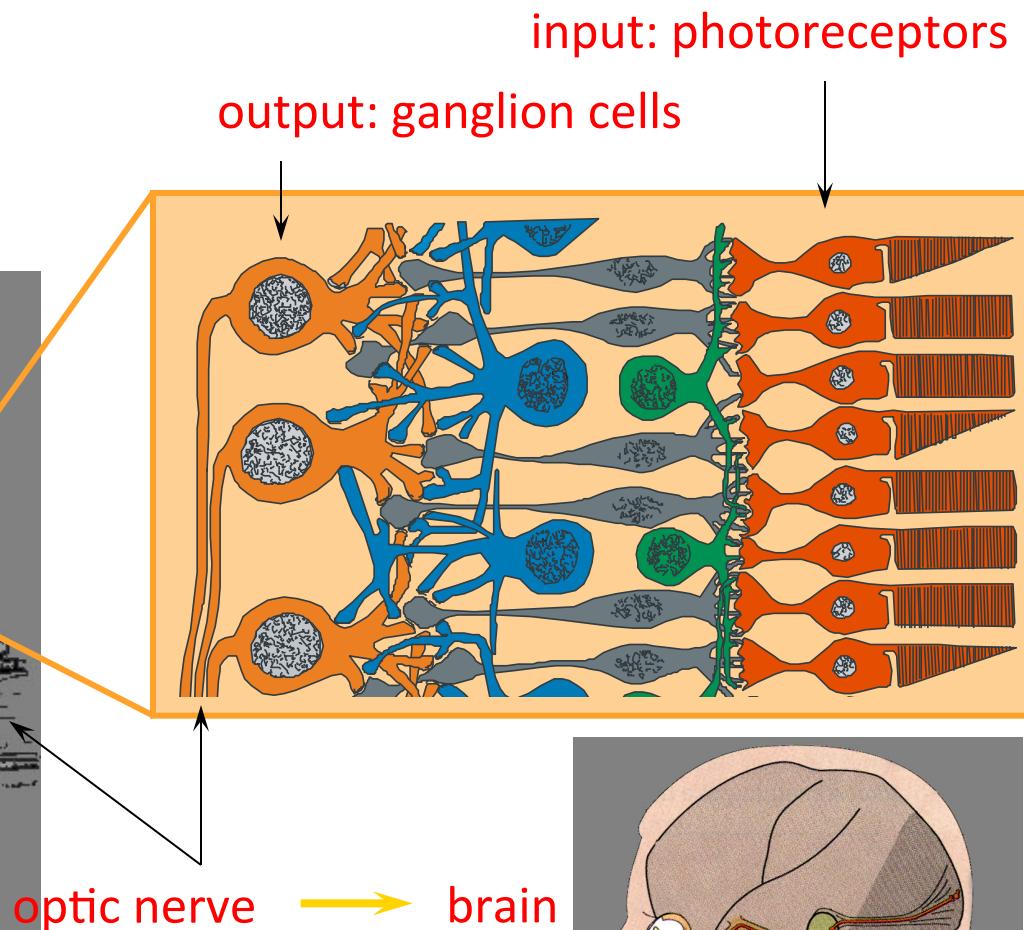
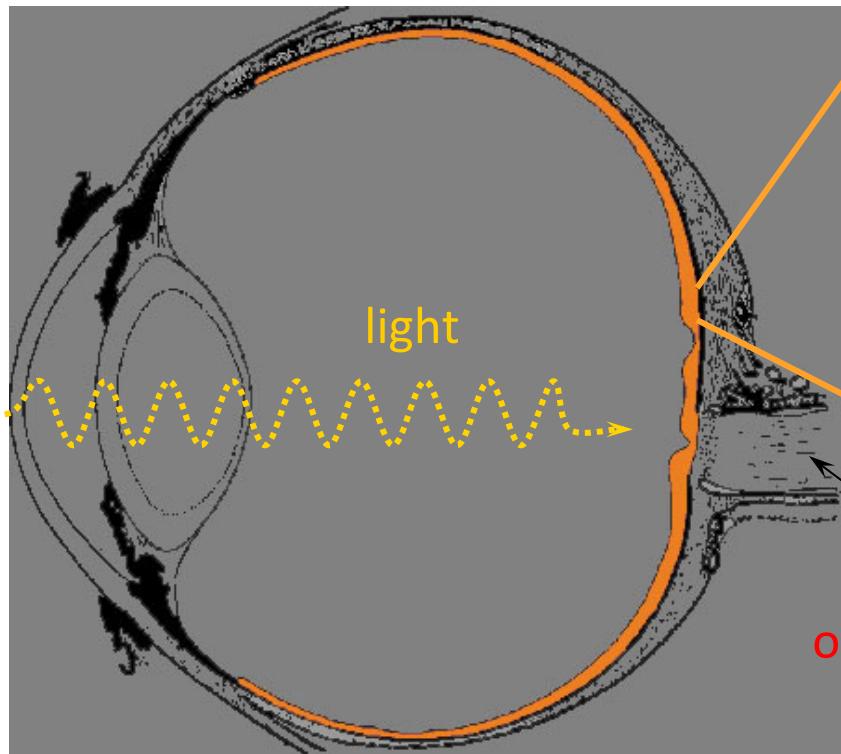
复旦大学
张嘉漪



Outline for Part I: activity

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 - Retinofugal visual pathway - from eye to brain
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- Q&A

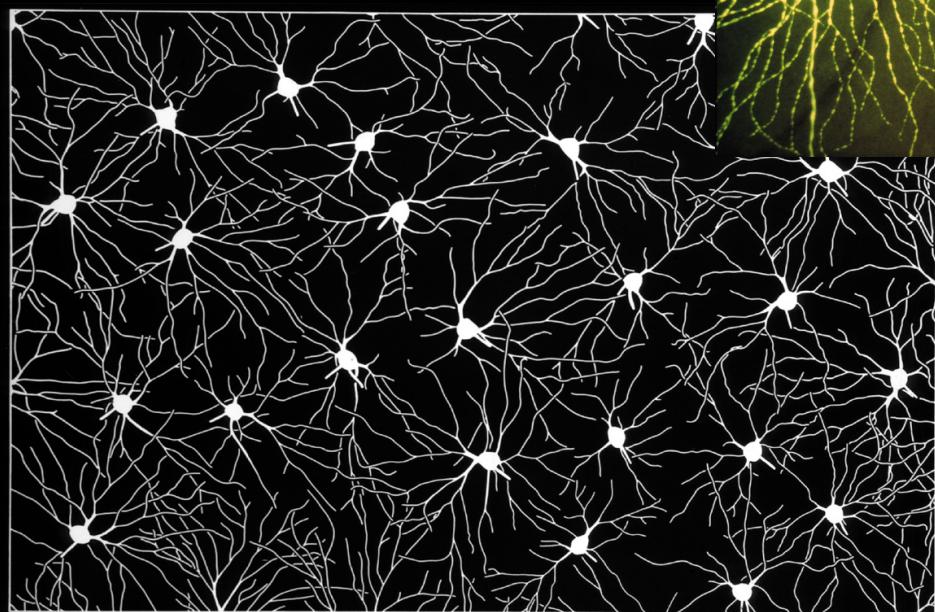
Brief anatomy of vision



Retinal mosaics and parallel processing

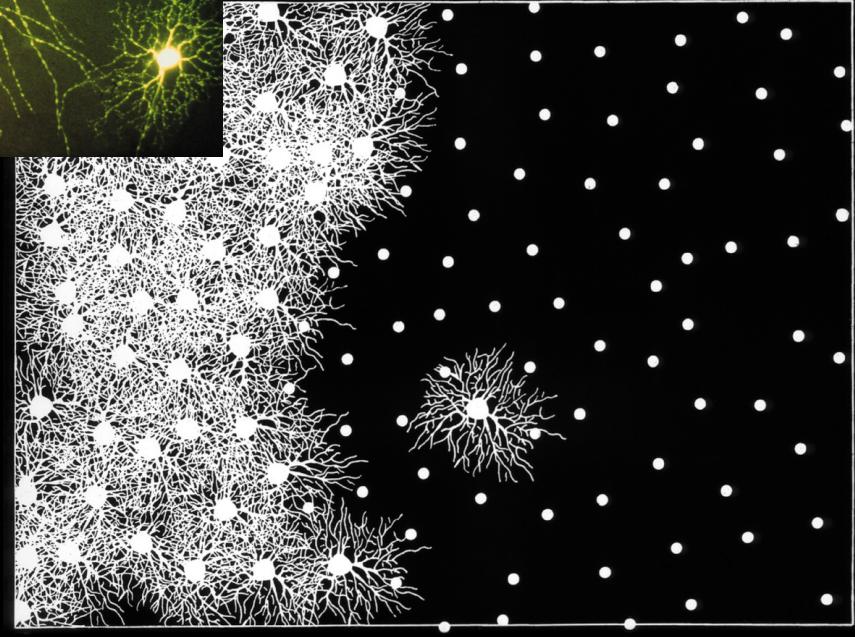
Cat:

ON alpha ganglion cell



150 μm

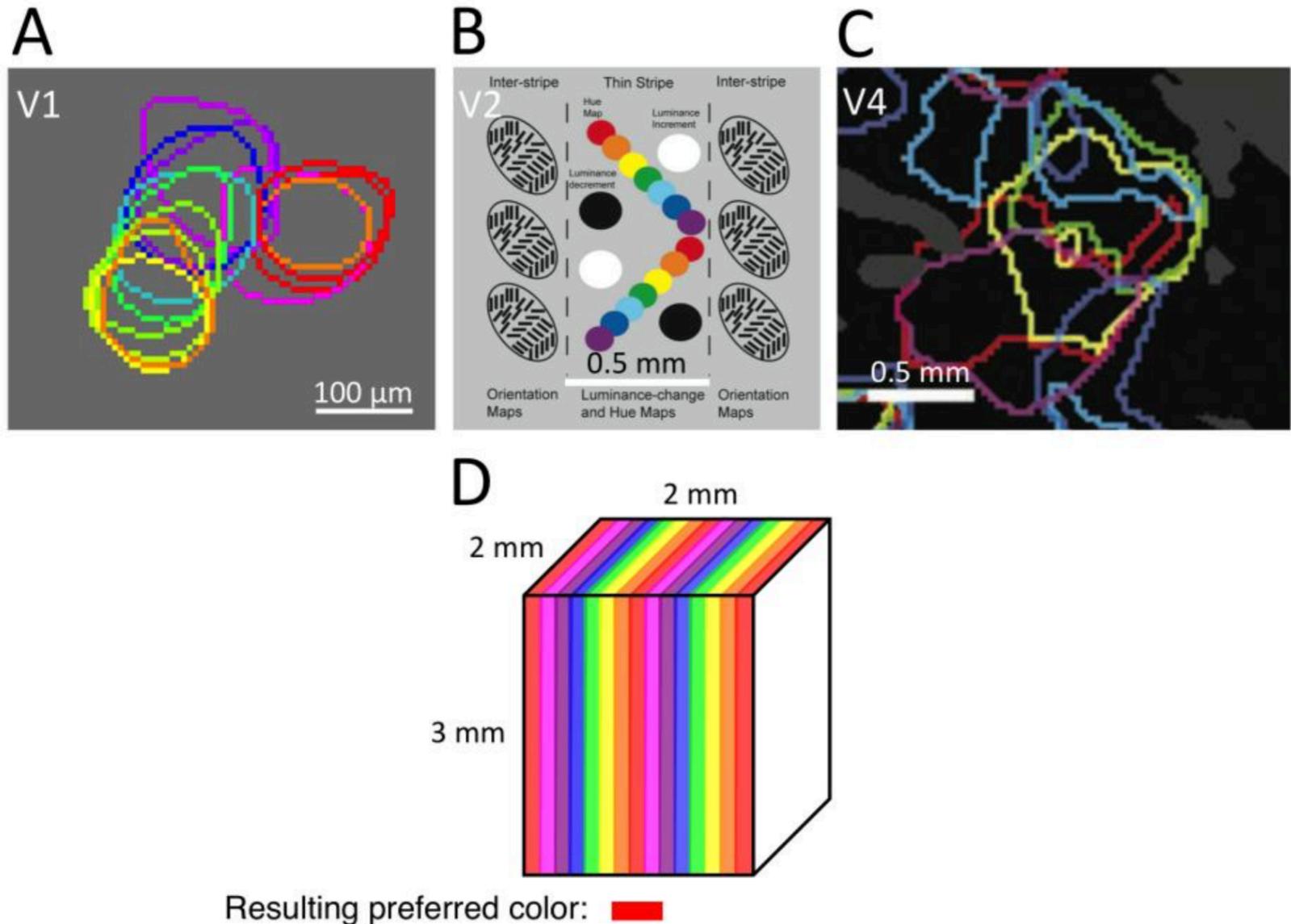
ON beta ganglion cell



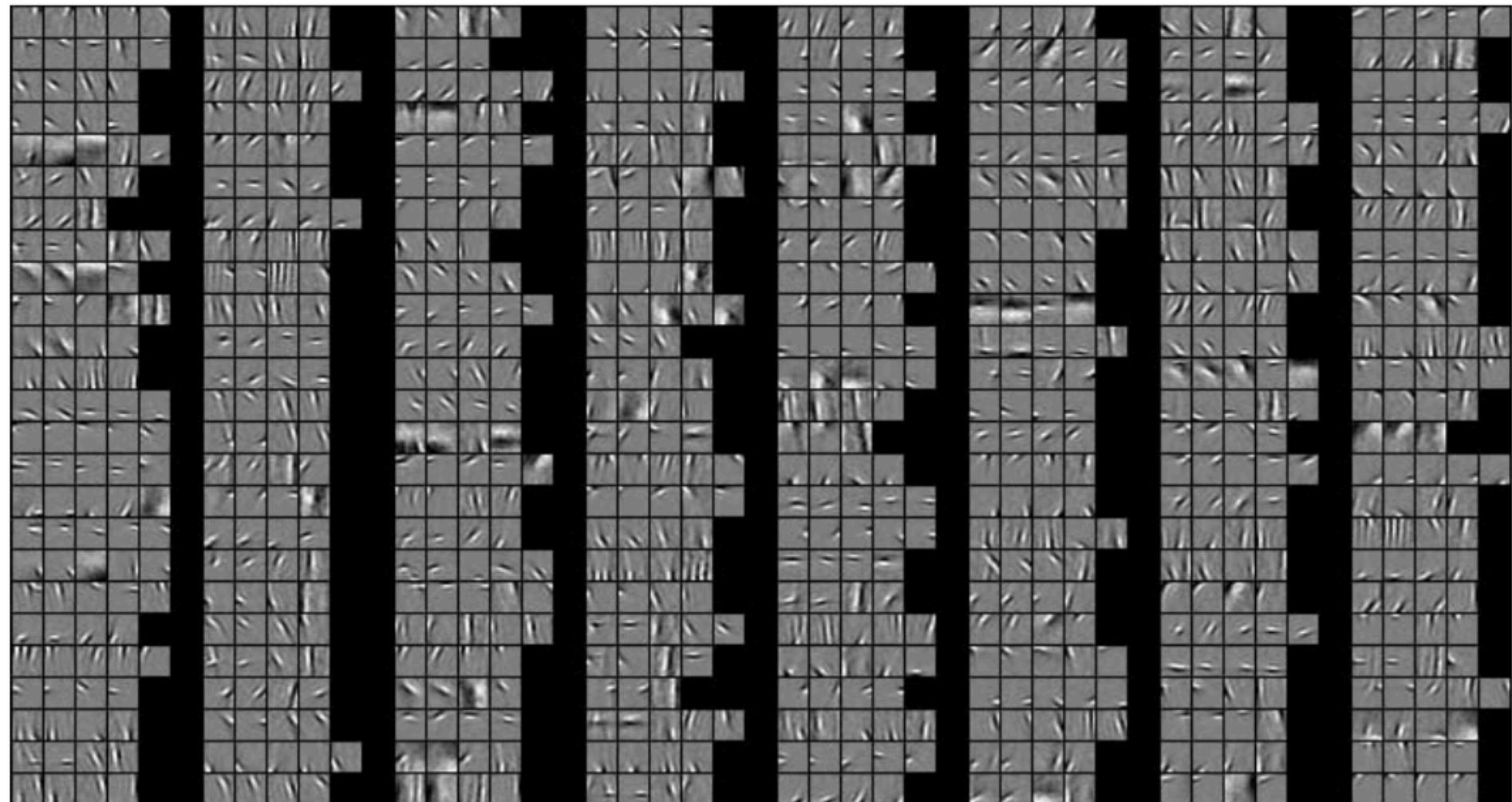
150 μm

courtesy of Heinz Wässle

Visual maps in the monkey V1, V2 and V4



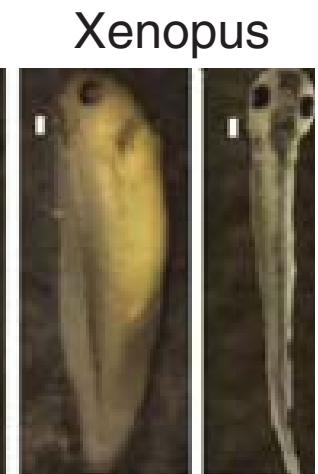
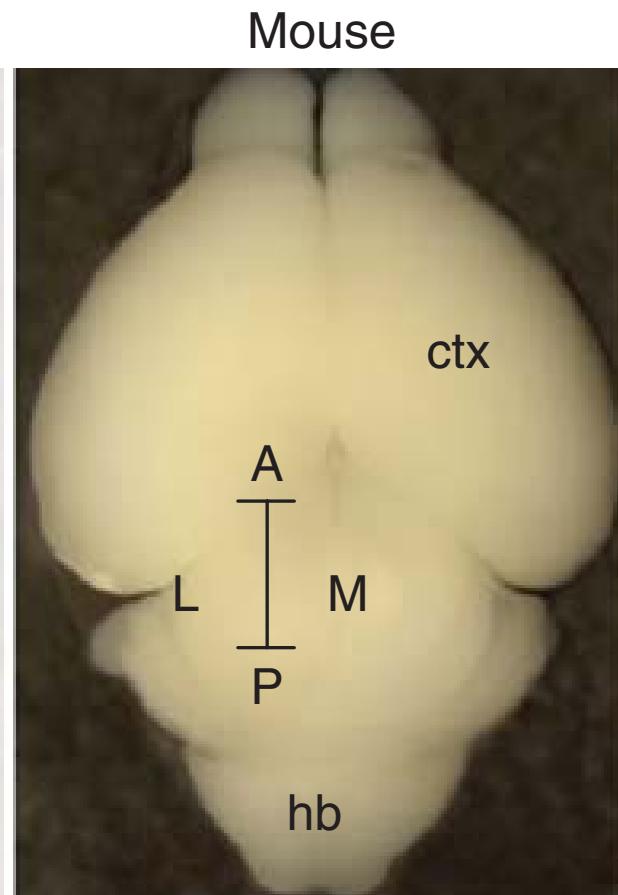
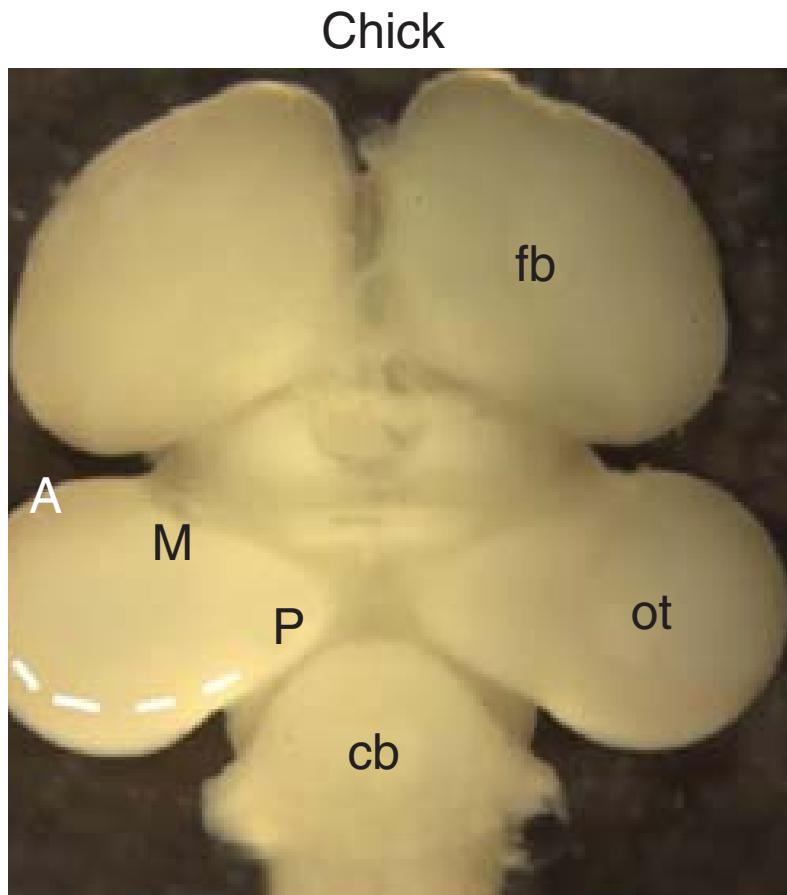
Model for receptive fields in V2



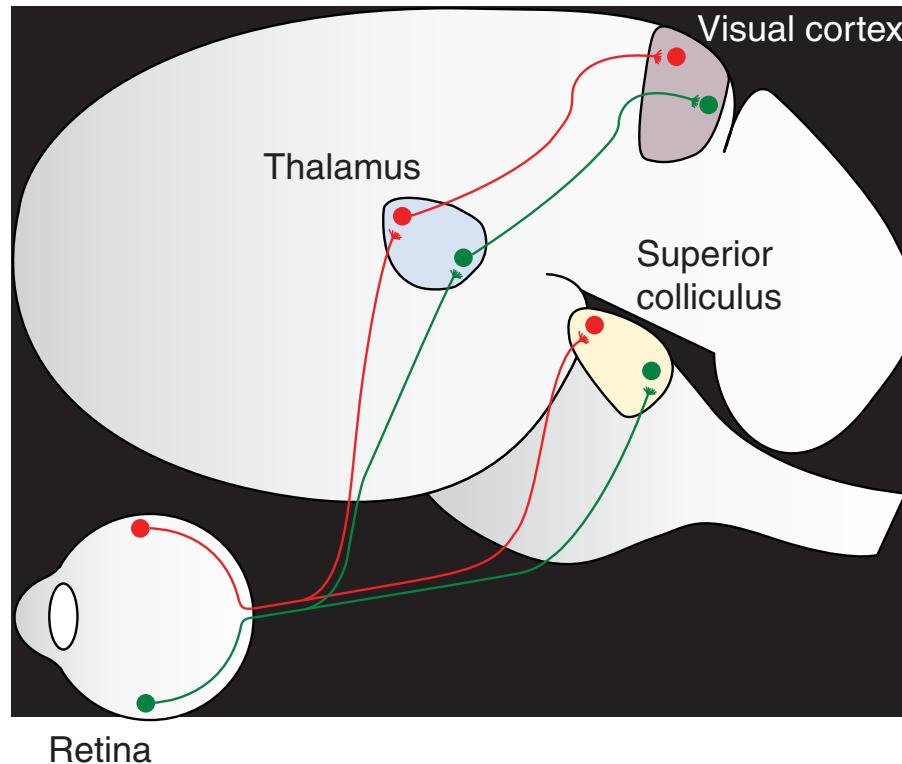
Visual function is highly preserved in different species



Overview – retinofugal pathway

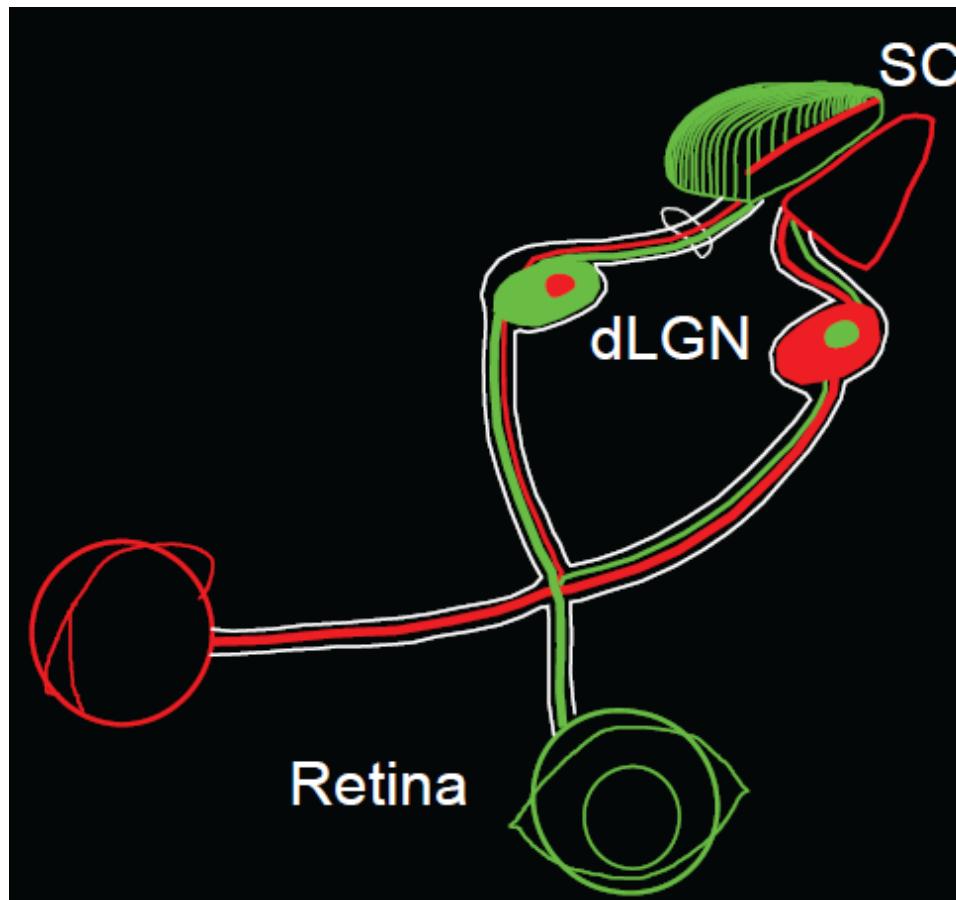


Overview – retinofugal pathway in mice

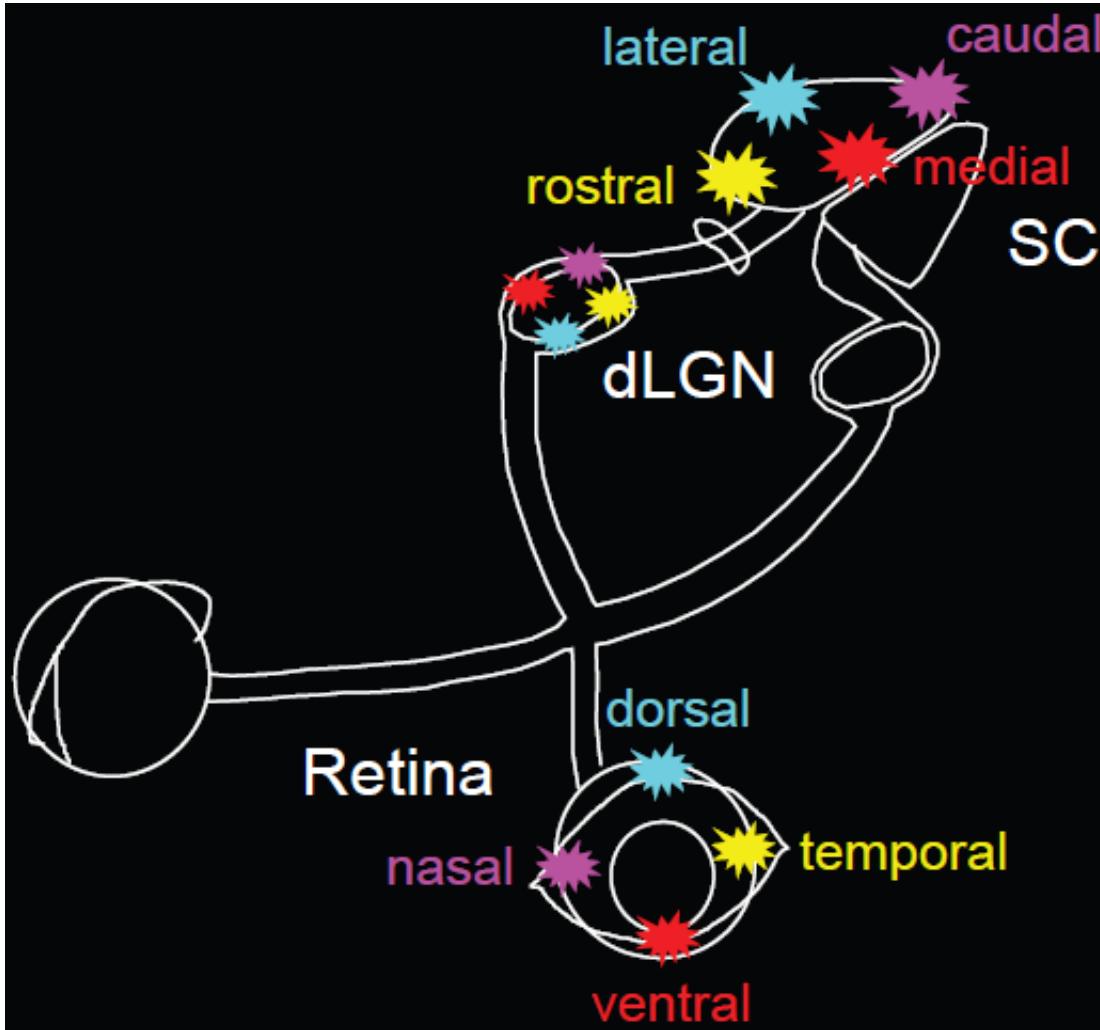


Visual maps

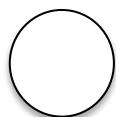
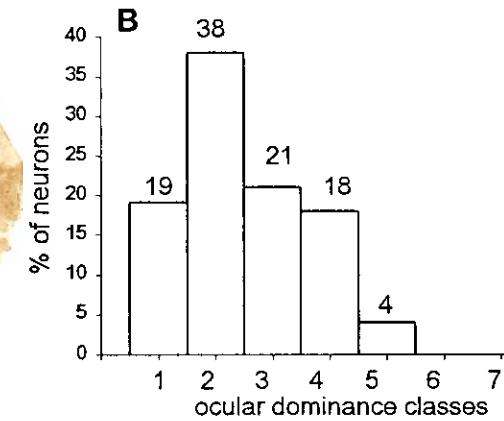
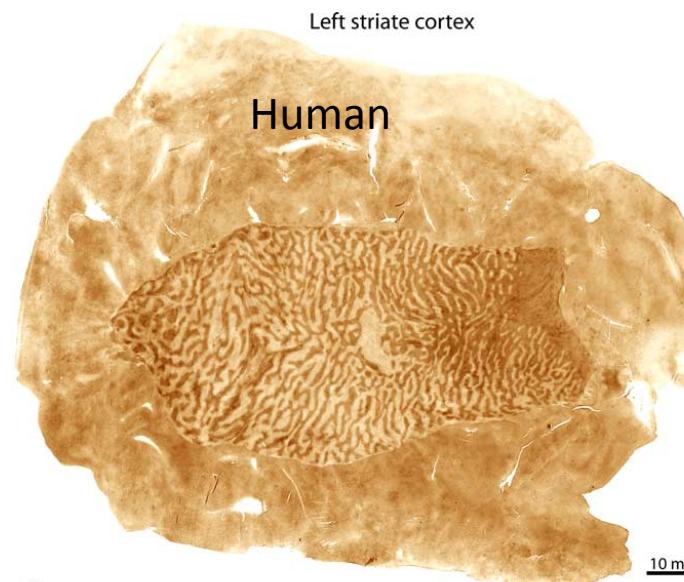
Anatomical visual maps – Eye-specific segregation (mice)



Anatomical visual maps – Retinotopic map (mice)



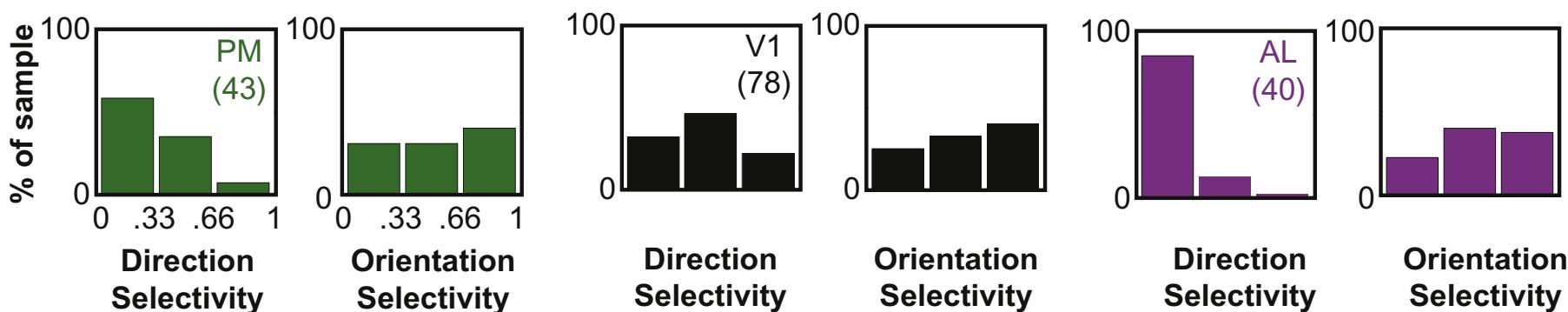
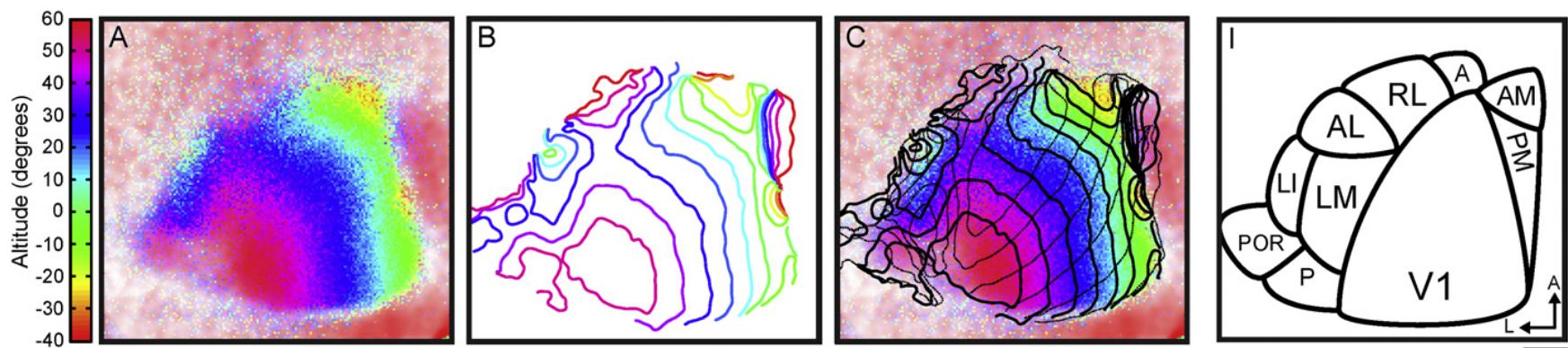
Anatomical and functional visual maps – ocular dominance columns



LeVay, Wiesel and Hubel, *J. Comp. Neurol.* (1980)
Adams et al, *J. Neurosci.* (2007)

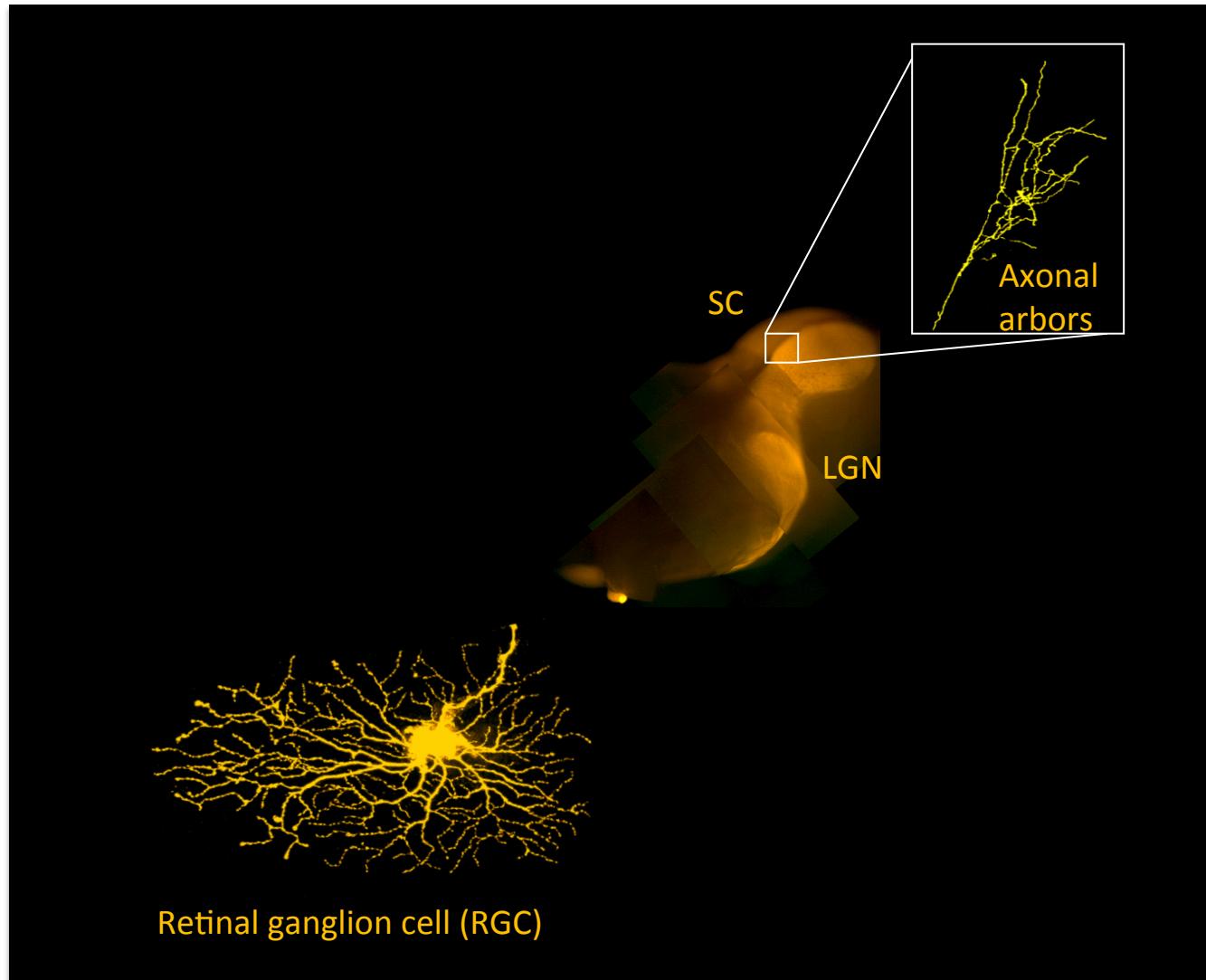
Functional visual maps – Orientation and direction selective maps (mice)

Visual Cortex

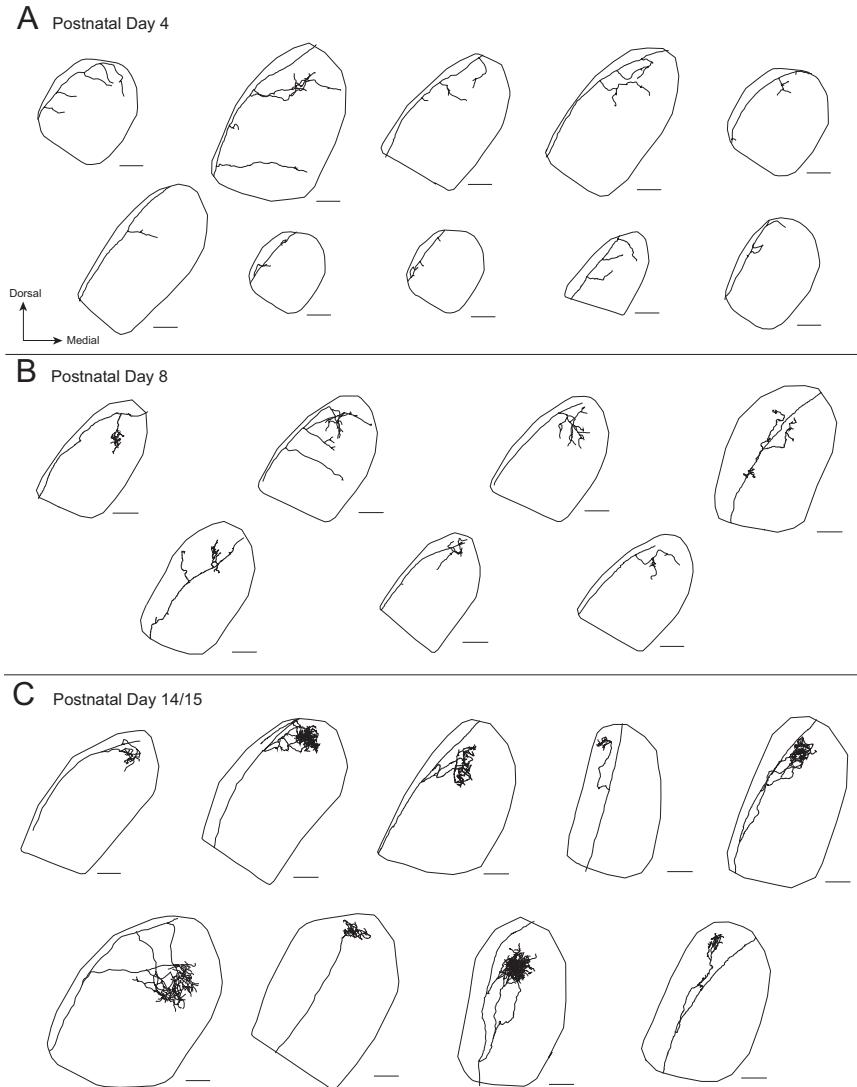


Development of visual maps

Development of visual maps – single cell level

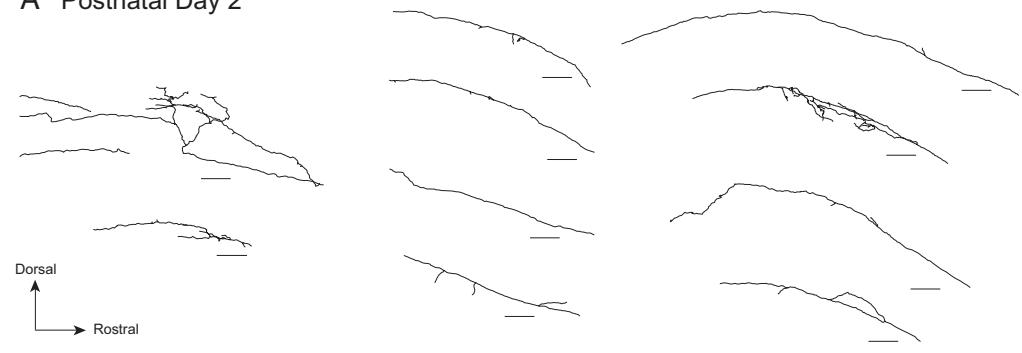


Development of visual maps – single RGC axon in LGN

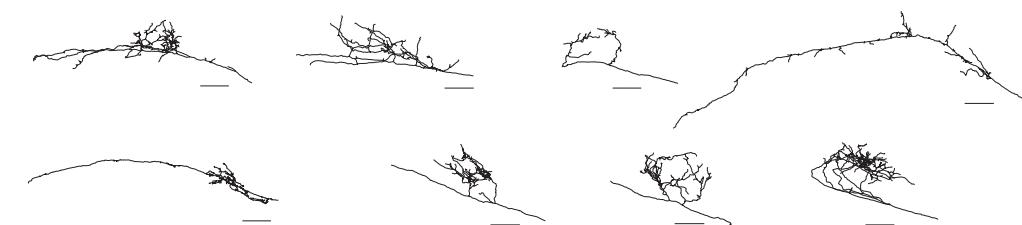


Development of visual maps – single RGC axon in SC

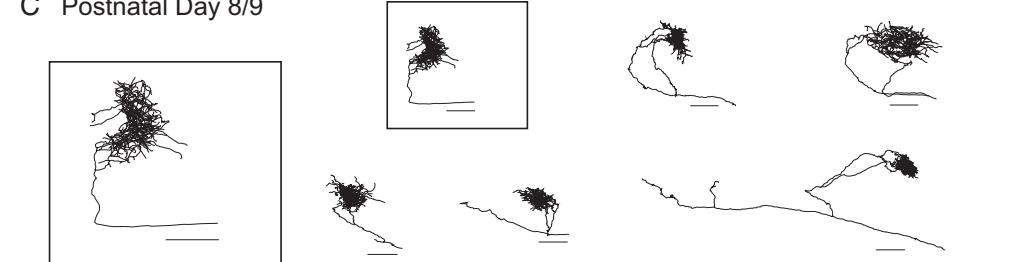
A Postnatal Day 2



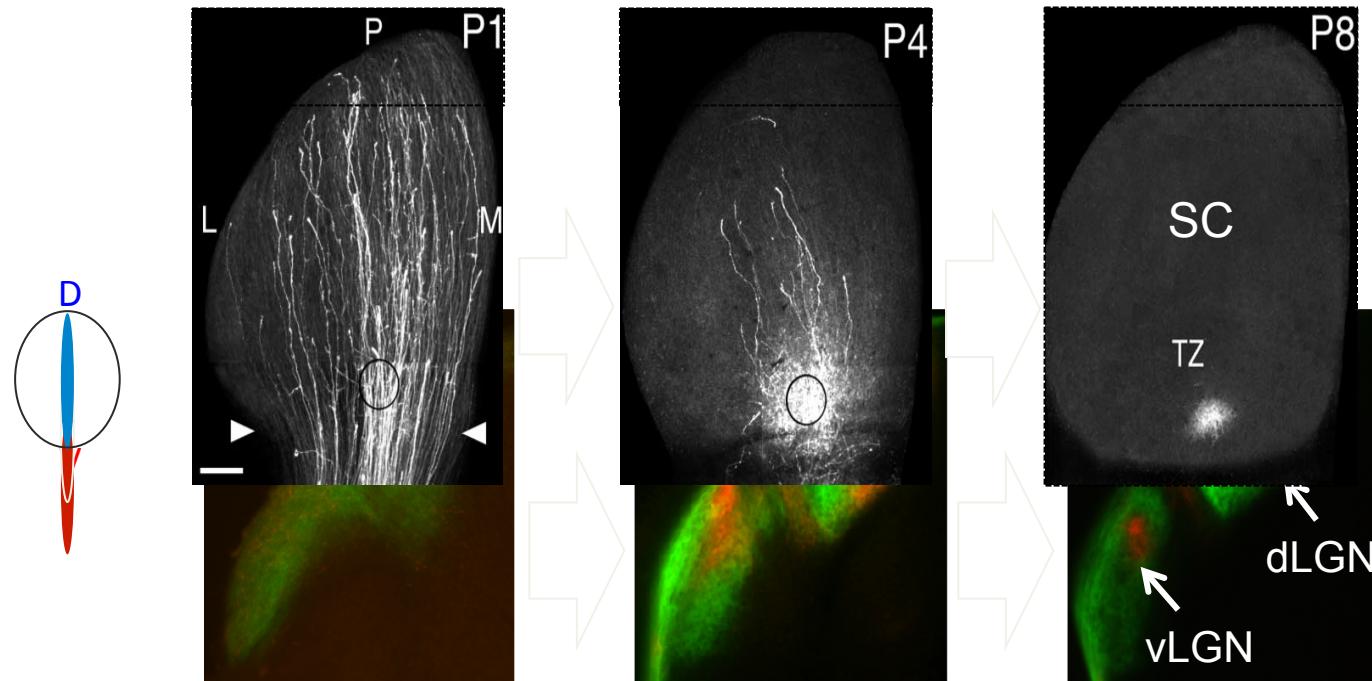
B Postnatal Day 4



C Postnatal Day 8/9



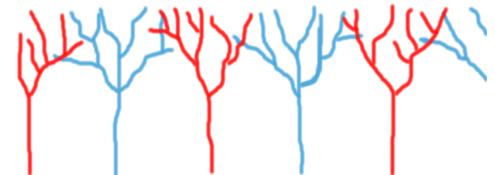
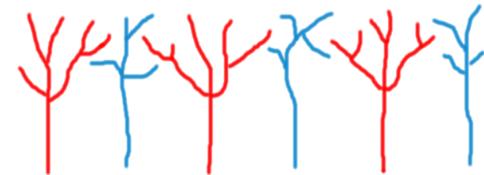
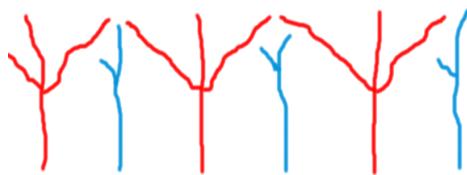
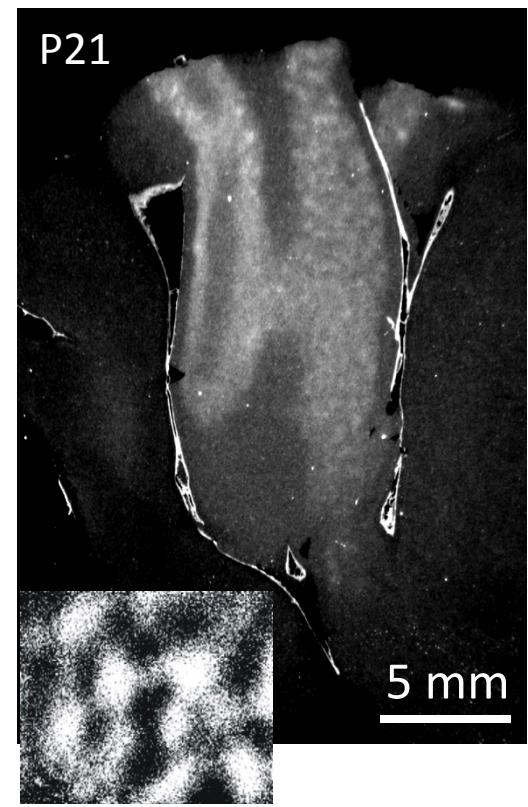
Development of visual maps – retinotopic and eye-specific segregation



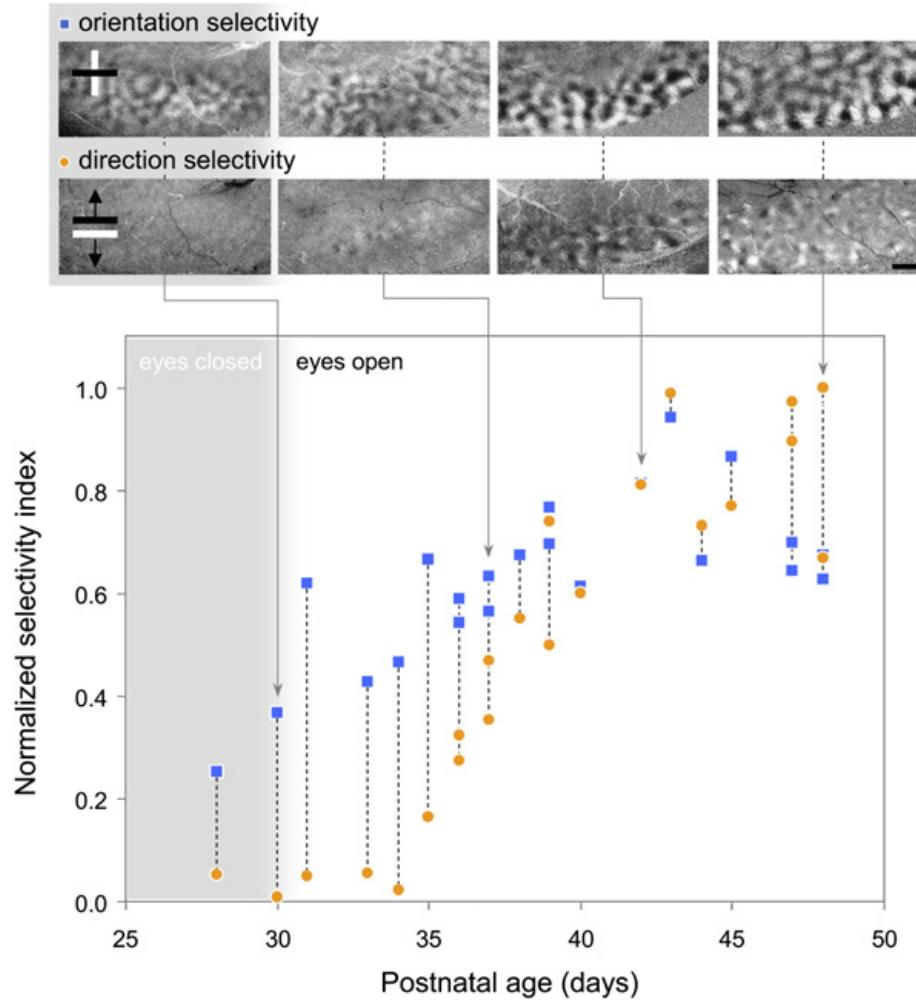
TZ: target zone

McLaughlin et al. (2003)
unpublished data

Development of Ocular dominance map



Development of orientation and direction selective maps

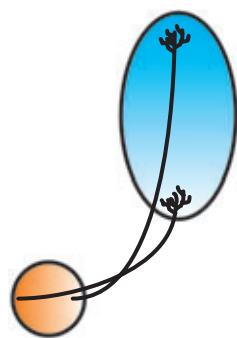


How do these maps develop?

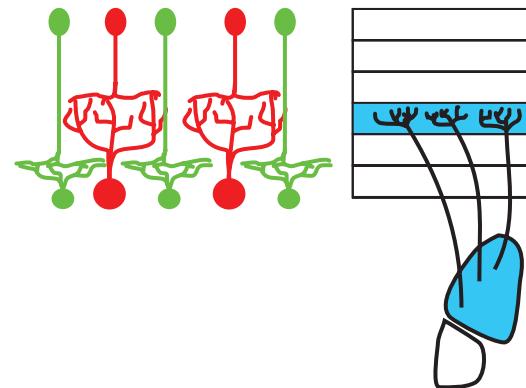
Molecules + Activity

Molecules – next lecture!

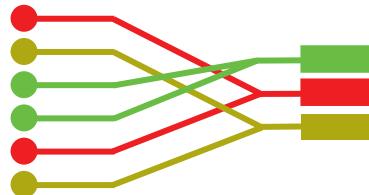
a Graded axon guidance cues



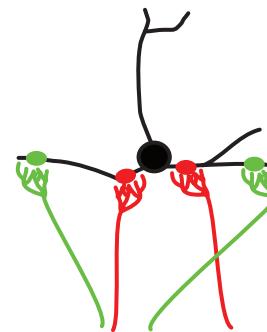
b Homophilic adhesion cues



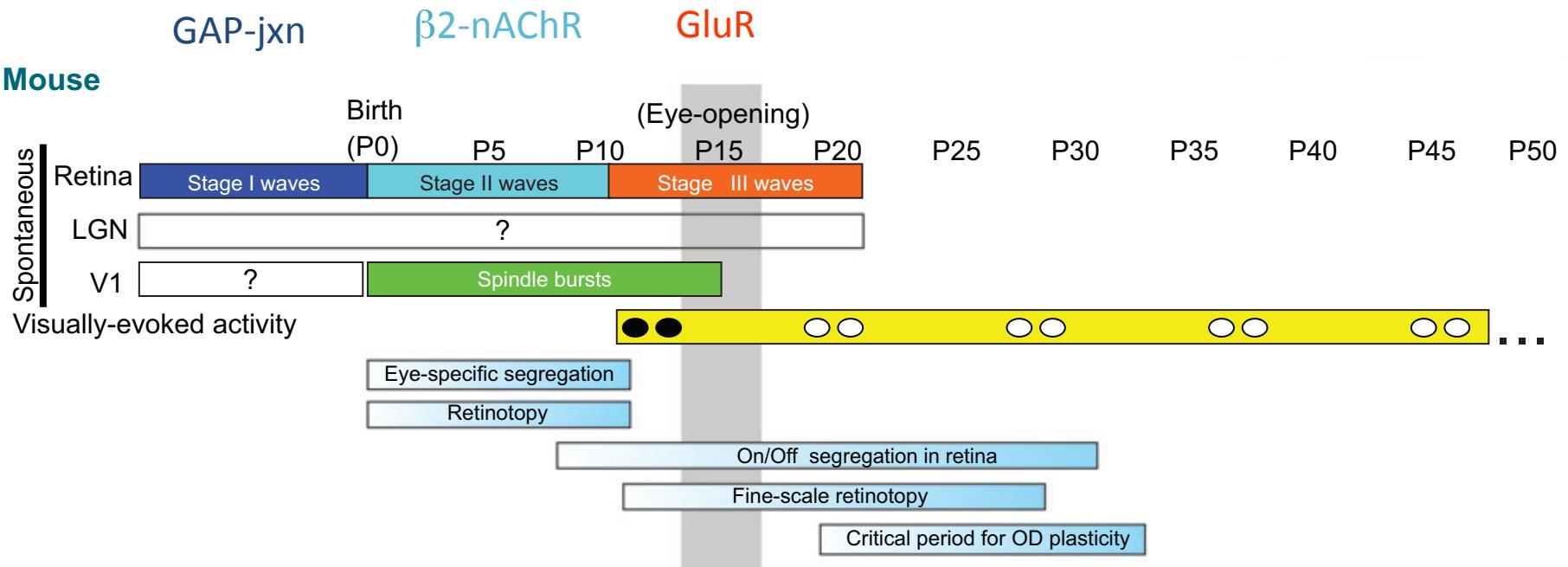
c Axon-axon recognition cues



d Sub-cellular adhesion cues



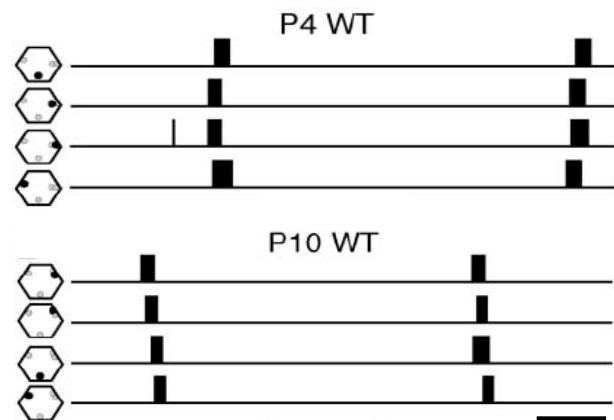
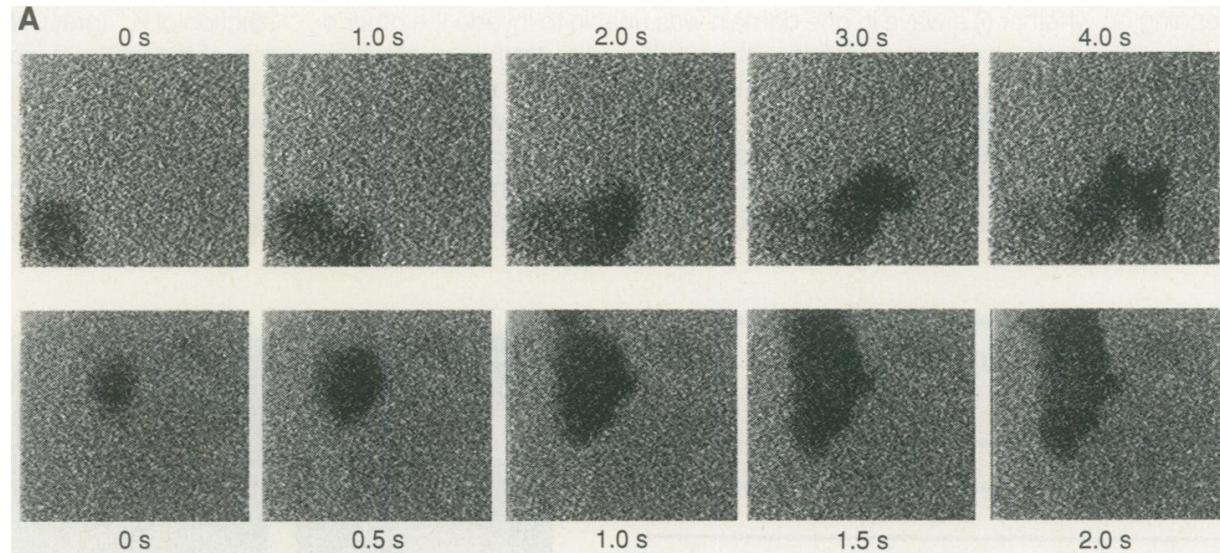
Activity and visual maps



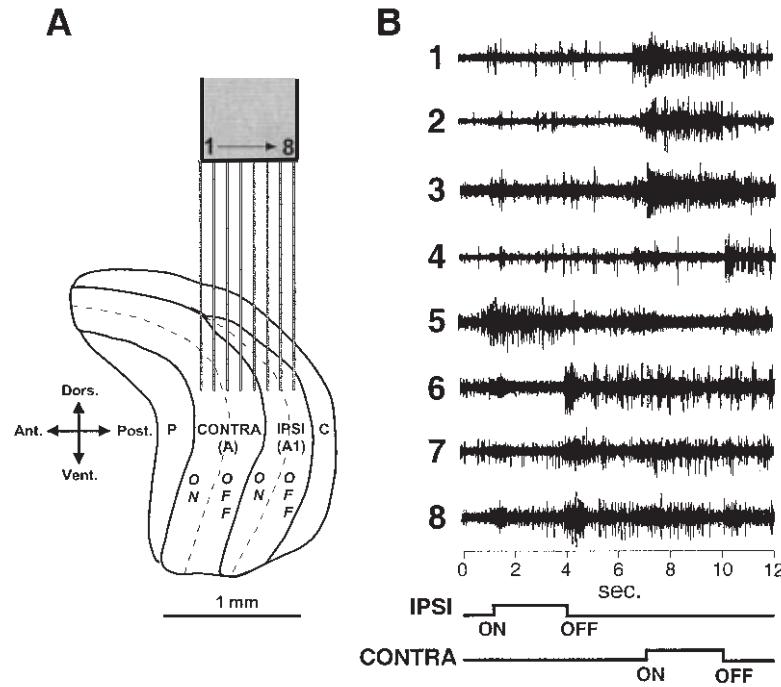
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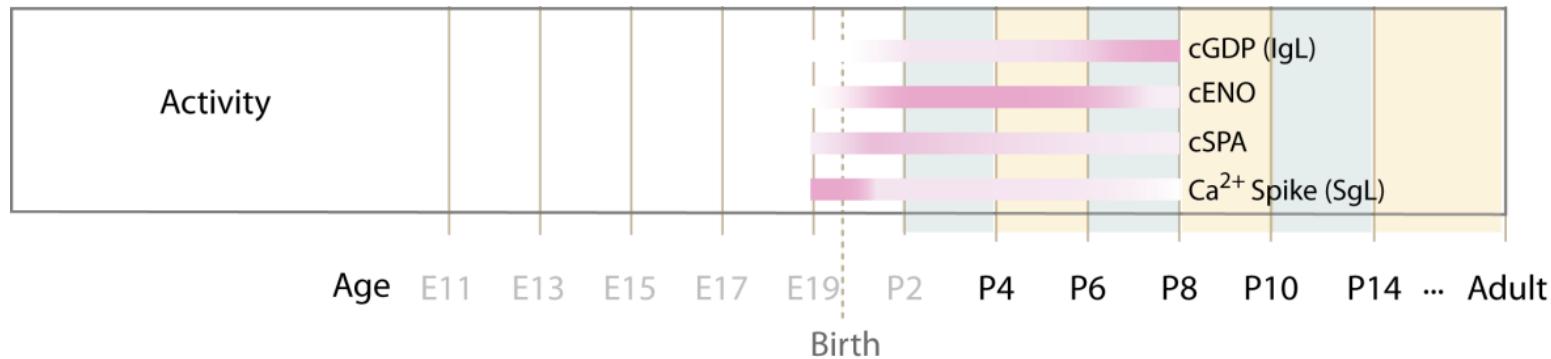
Spontaneous activity in visual system - retina



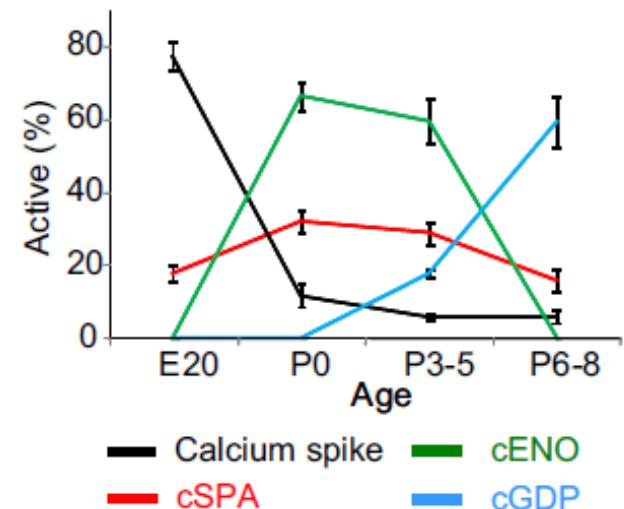
Spontaneous activity in visual system - LGN



Spontaneous activity in visual system – Visual Cortex



- cortical synchronous plateau assemblies (cSPA)
- cortical early network oscillations (cENO)
- cortical giant depolarizing potentials (cGDP)



What does activity do?

Ocular dominance columns and plasticity



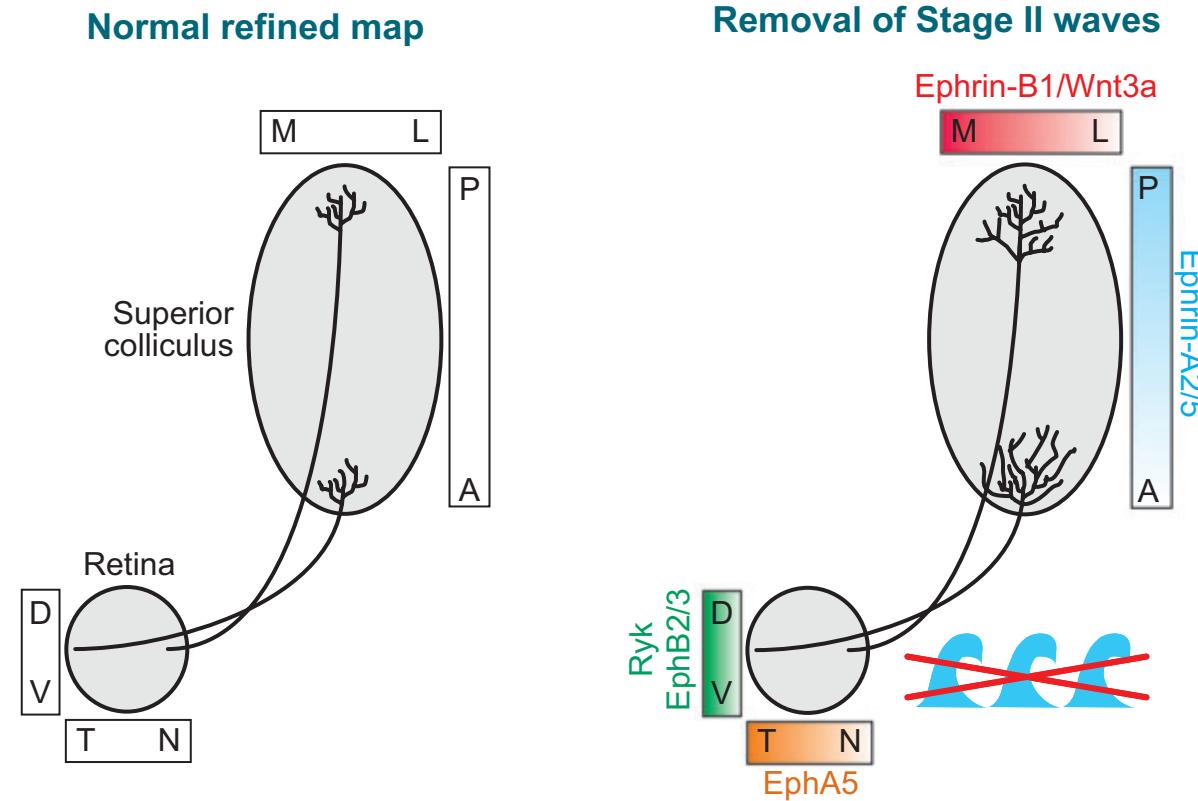
normal eye



deprived eye

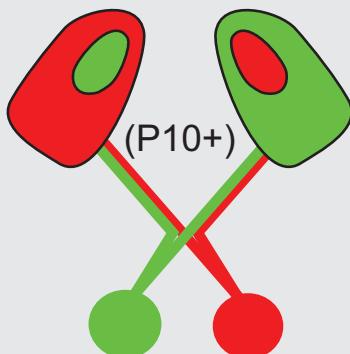
active eye

Activity on retinotopic maps

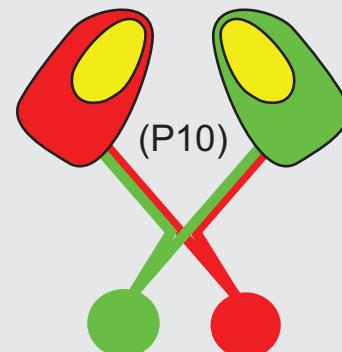


Activity on eye-specific segregation

Normal refined pattern of eye-specific segregation in the mouse LGN



Stage II waves blocked in both eyes with epibatidine



How do activity shape the maps?

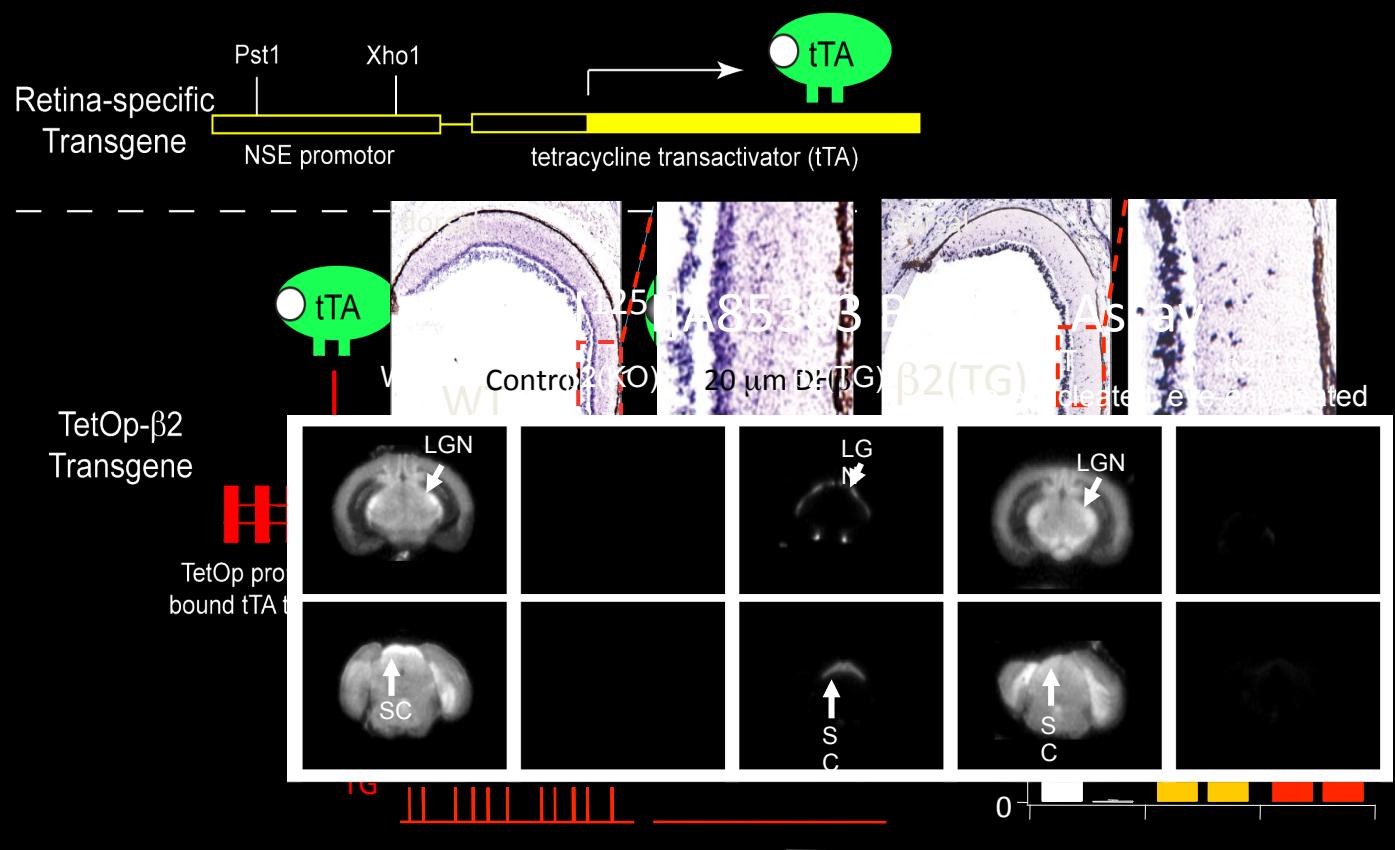
Hebbian rules may be important!

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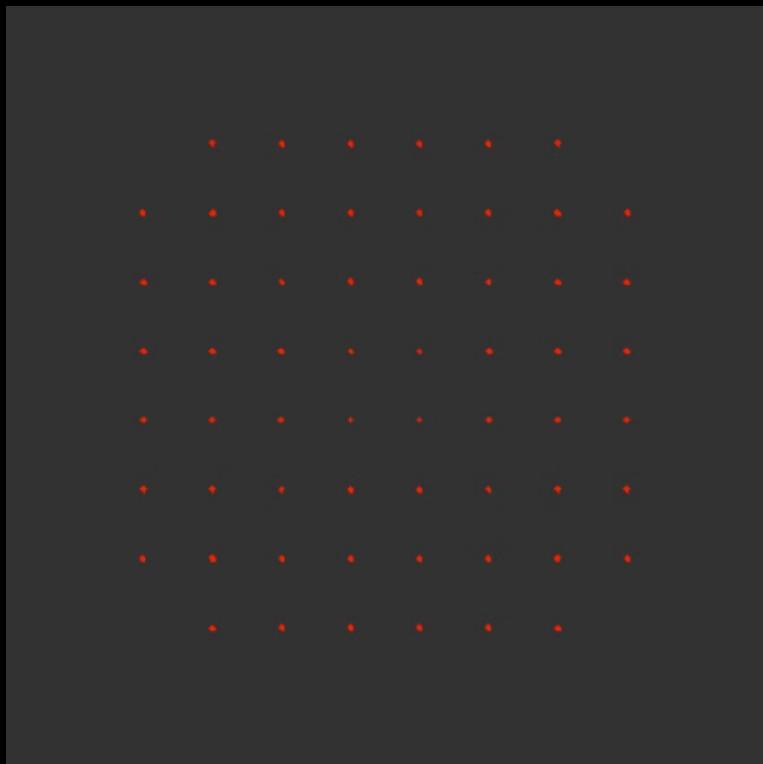
1. Size of retinal activity matters

Generation of small-wave mice

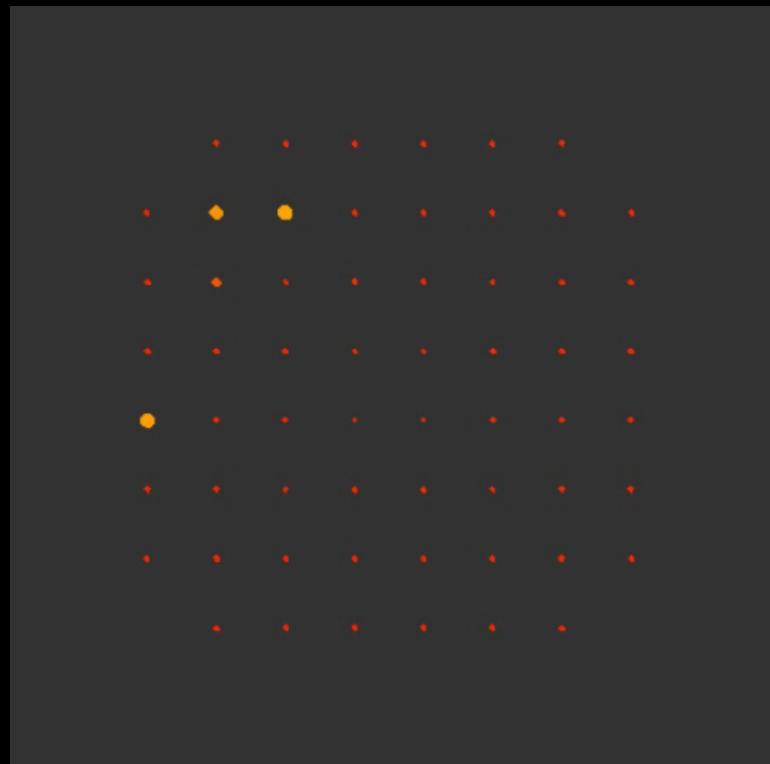


Small wave

WT

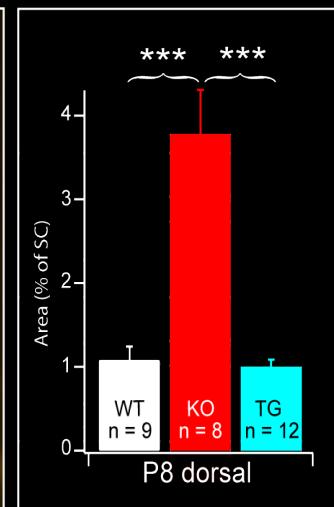
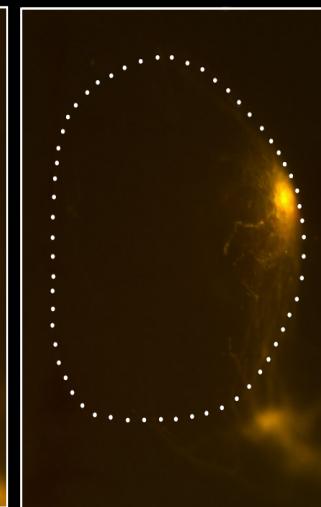
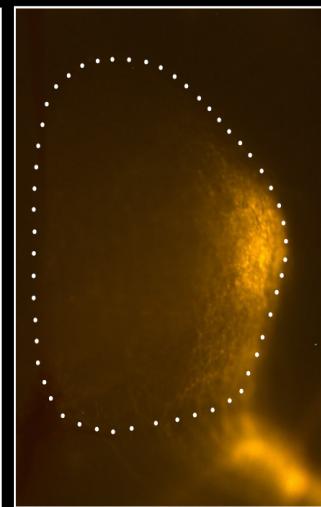
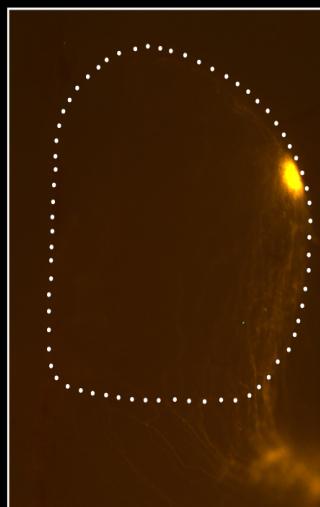
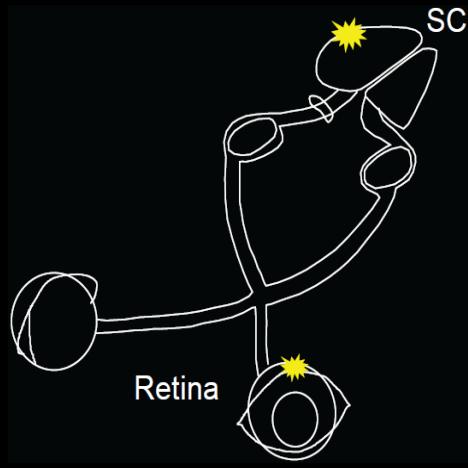


$\beta 2(TG)$

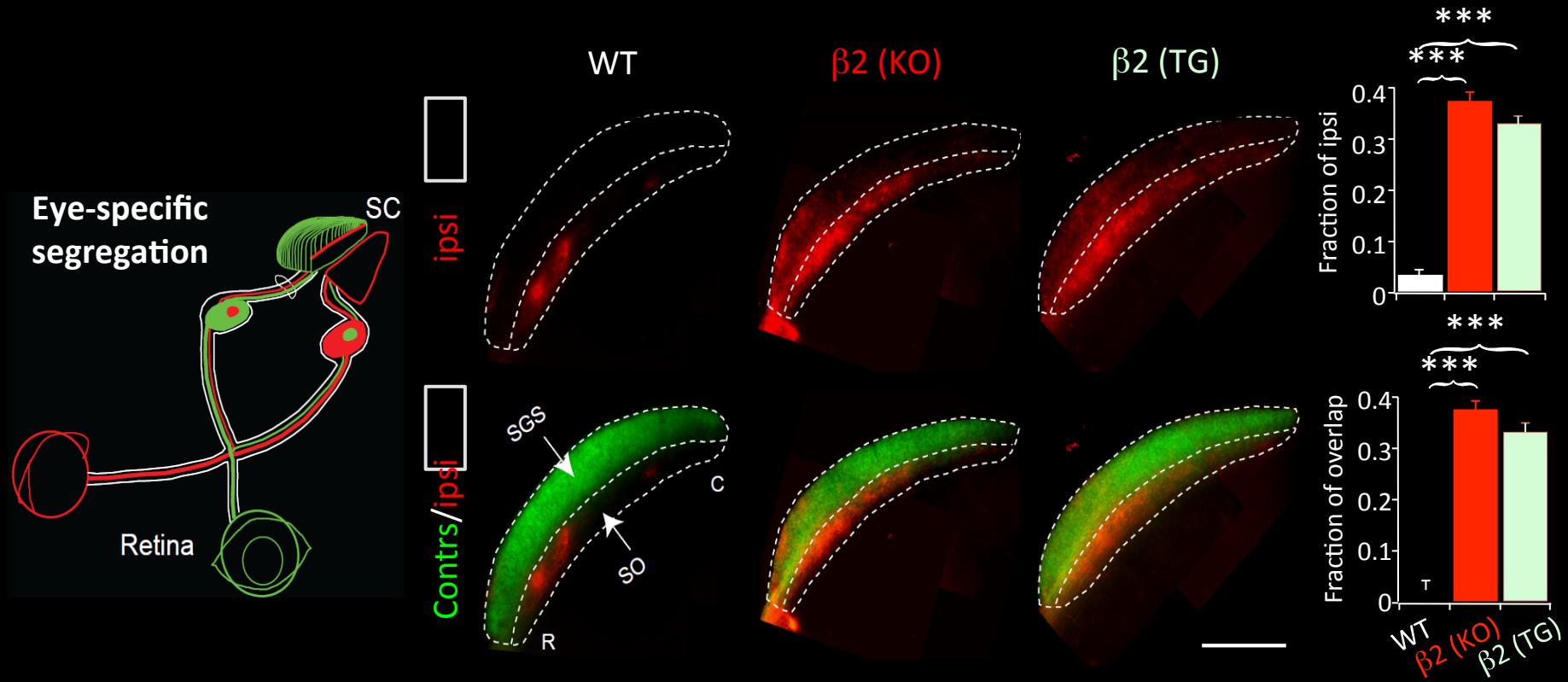


Retinotopic map is normal in small-wave mice

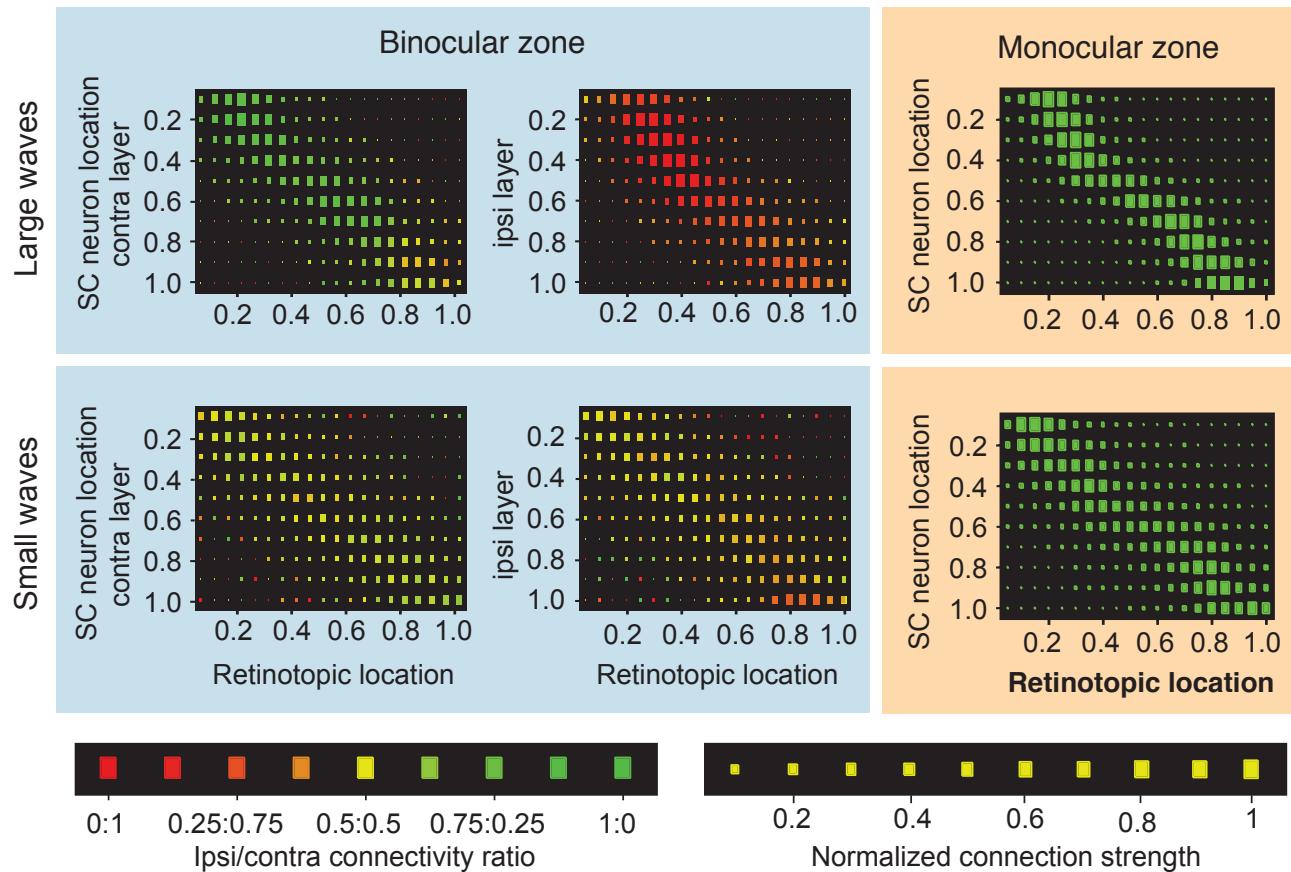
Dorsal Dil injection



Eye-Specific segregation map is disrupted in small-wave mice

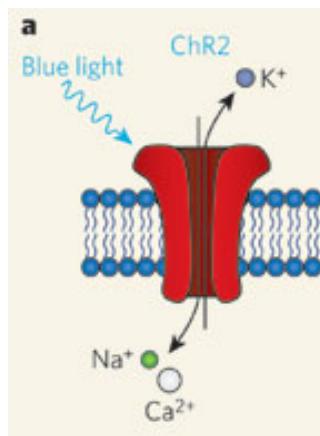


Computational modeling for small-wave mice

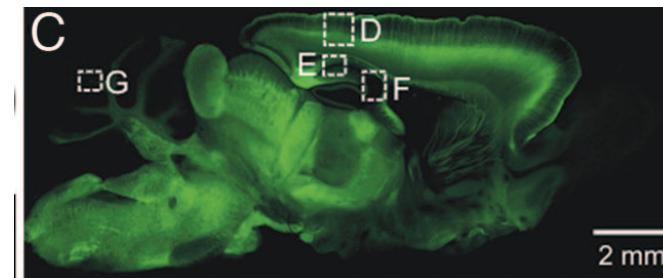


2. Timing of retinal activity
matters

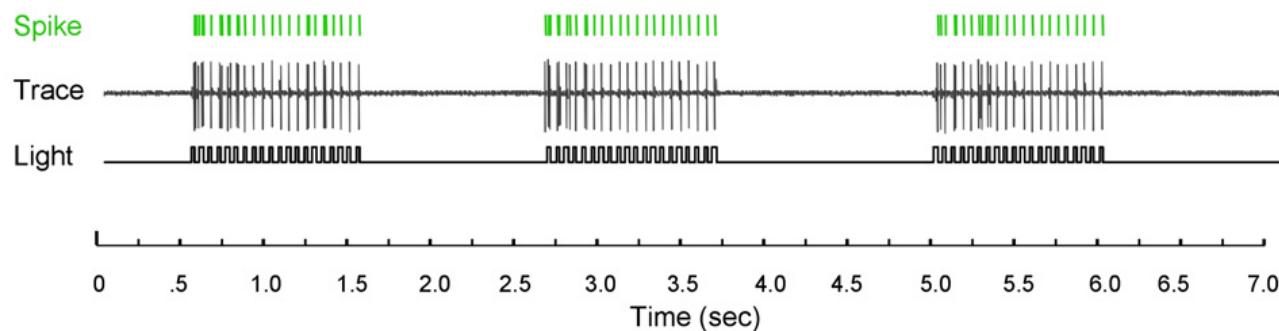
Optogenetics to control precise activity pattern *in vivo*



Thy1-ChR2-eYFP transgenic mouse

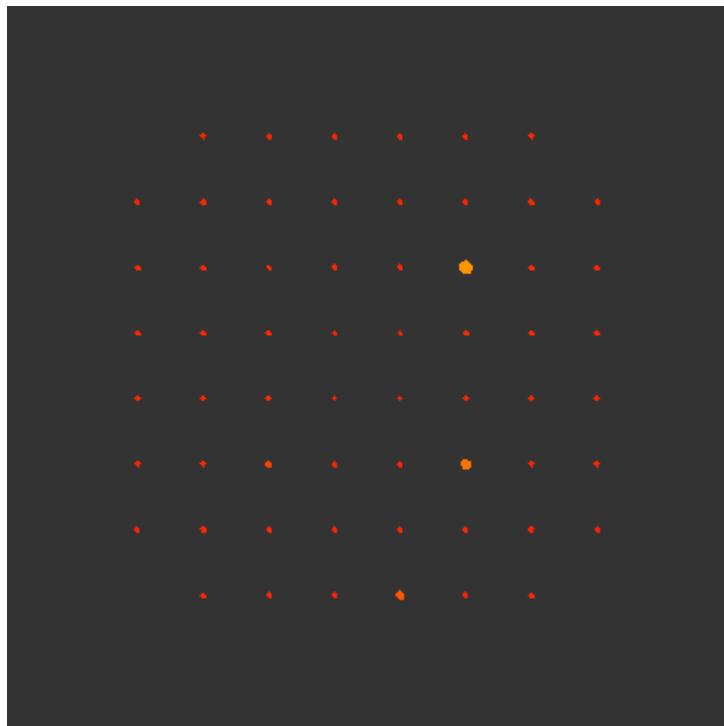


Layer V cortical neuron *in vivo*

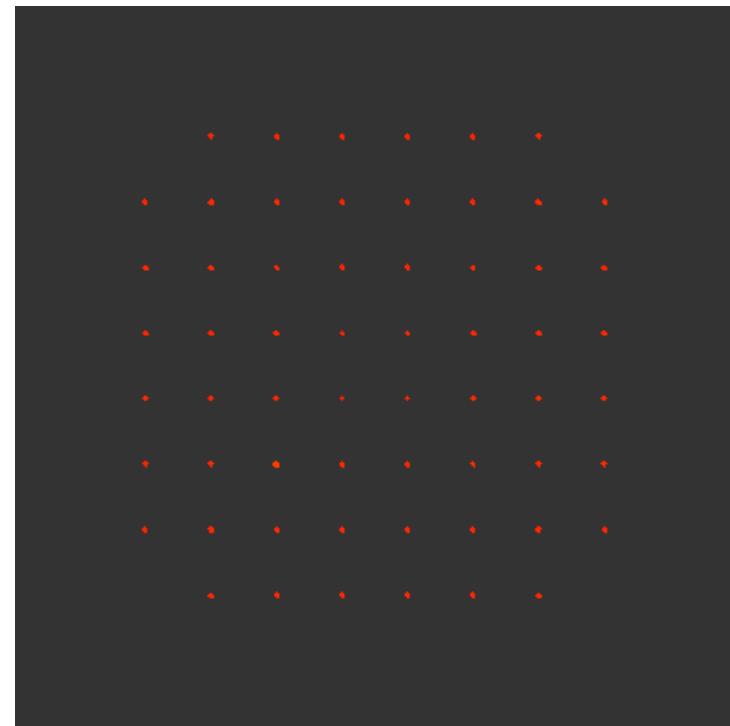


Control of retinal activity

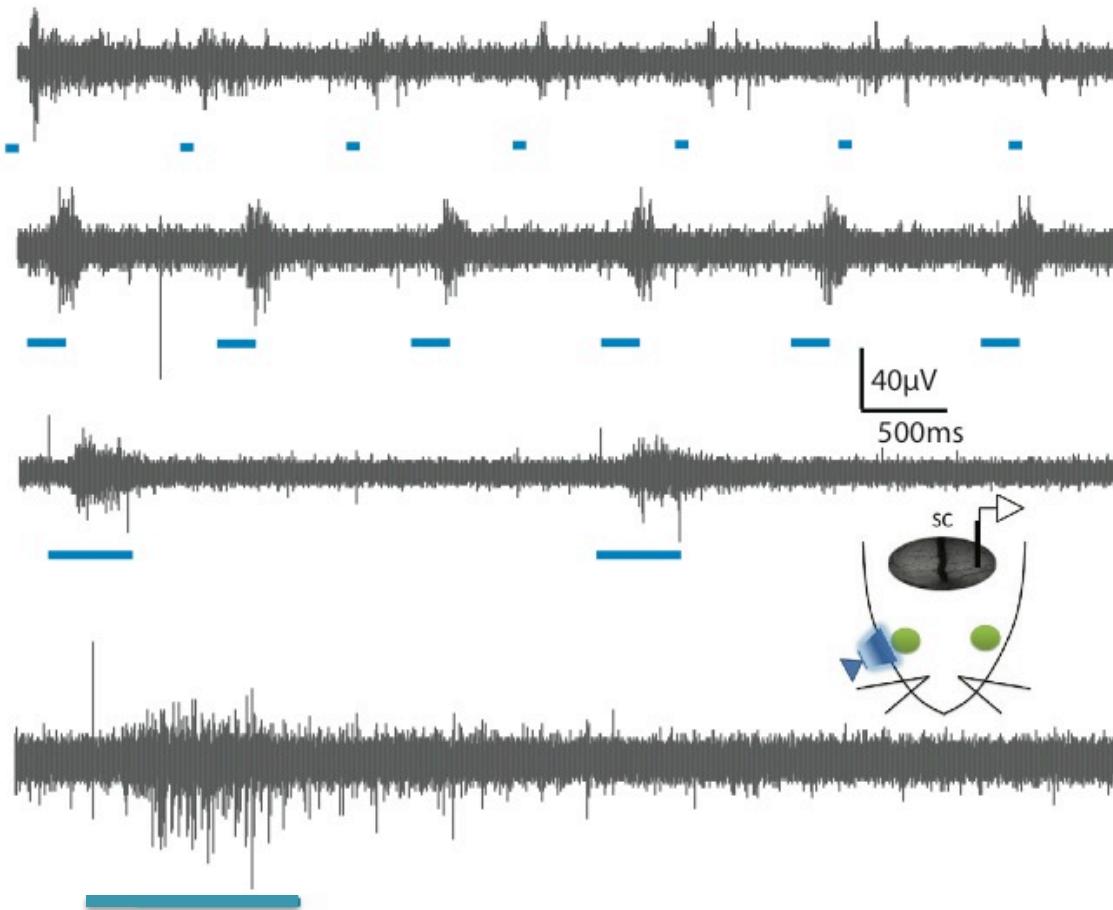
200 msec



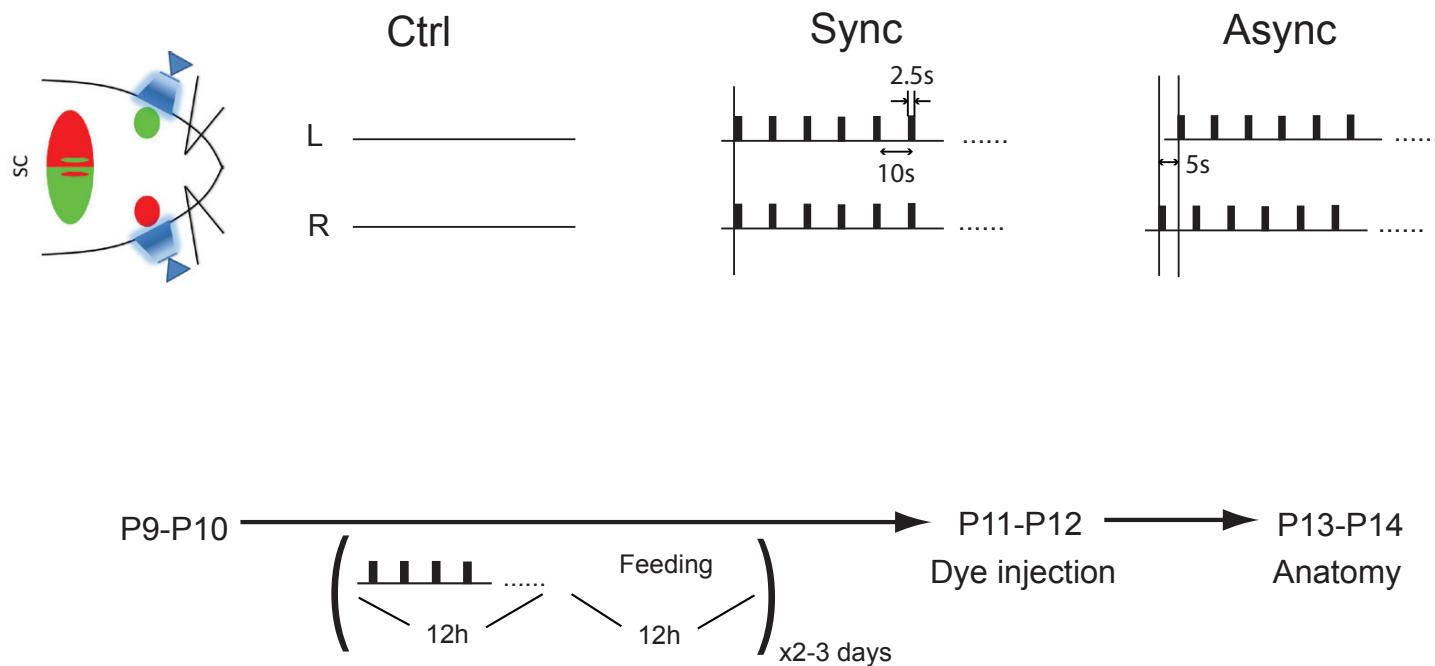
1 sec



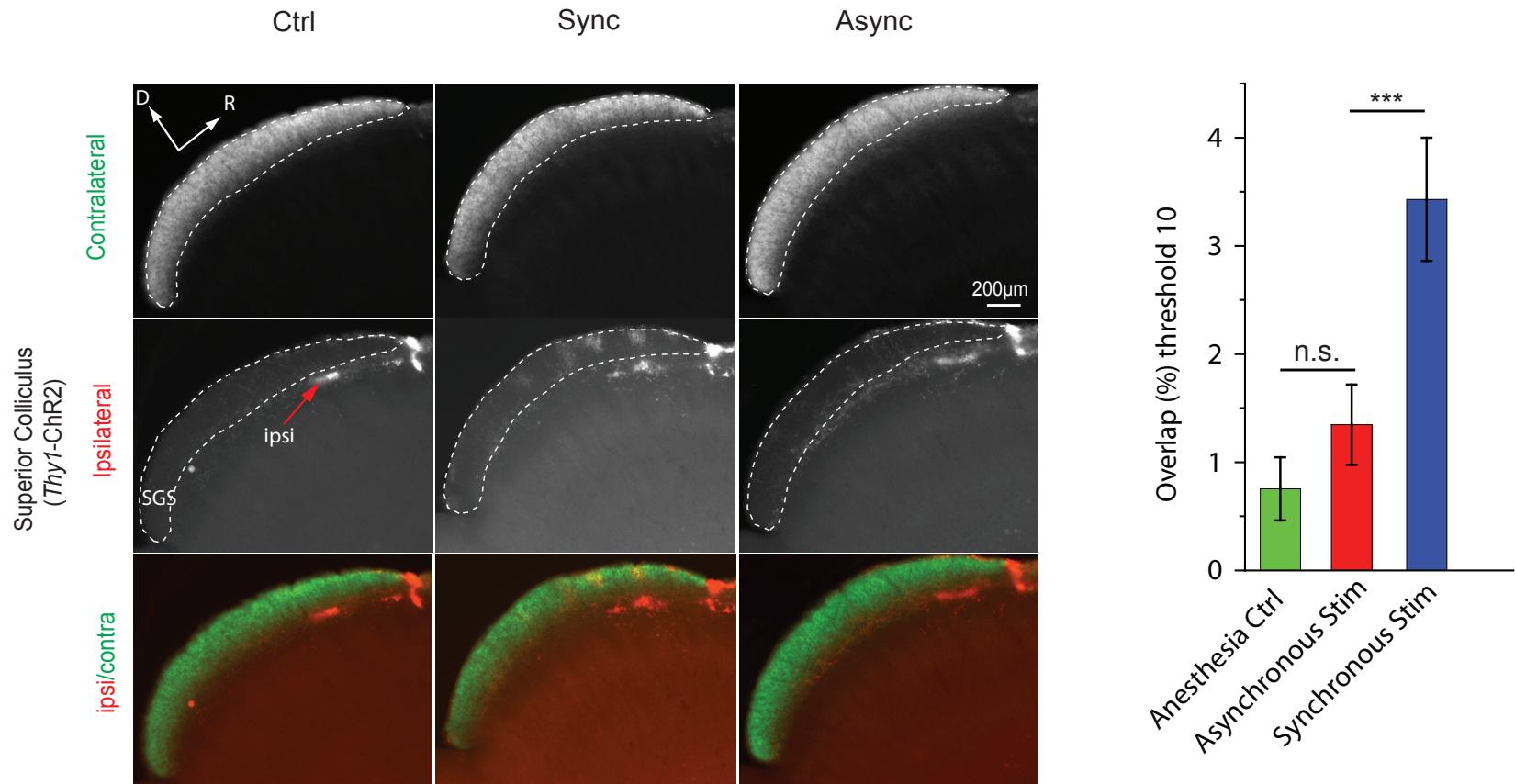
Extracellular responses of Thy1-ChR2 mice *in vivo*



Does timing in binocular activity affect eye segregation?



Synchronous but not asynchronous stimulation disturbs segregation.

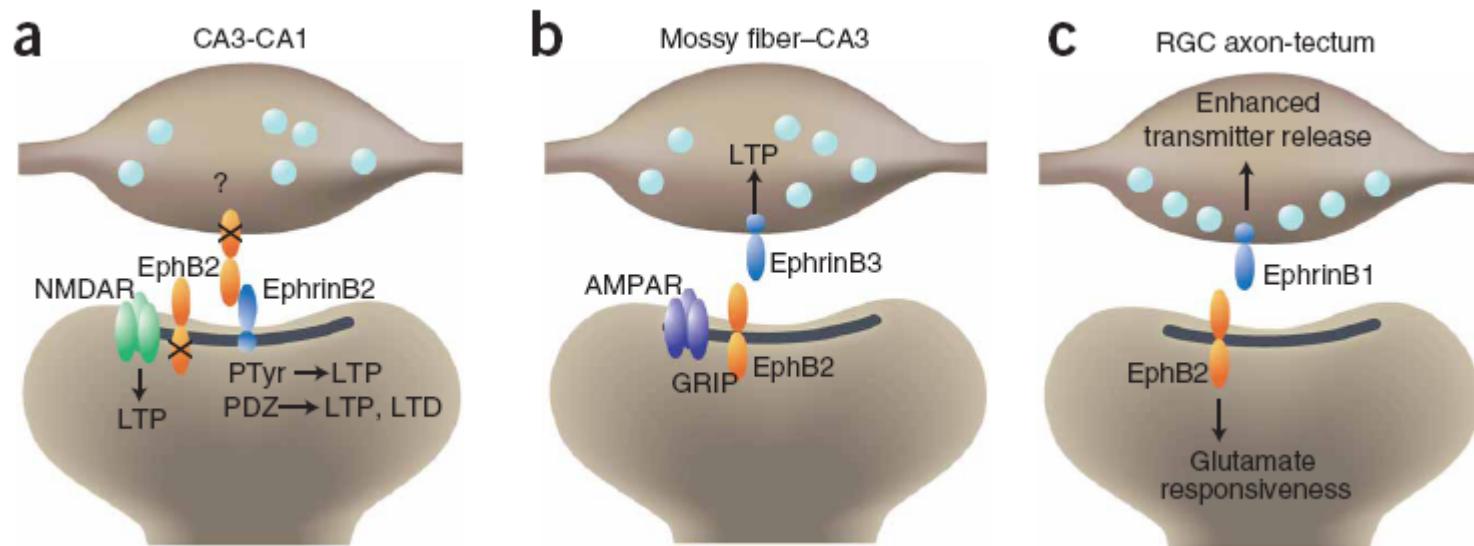


- Eye-specific segregation was disrupted by synchronous stimulation.
- Asynchronous stimulation did not affect segregation.

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Future remarks



- EphB can directly mediate LTP through tyrosine phosphorylation of NMDA receptor.
- Tyrosine phosphorylation sites in EphrinB are associated with LTP, whereas PDZ binding sites are associated with both LTP and LTD.
- EphB perfusion enhanced transmitter release and delayed enhancement of postsynaptic glutamate response.

Future remarks

- ImageNet 图像分类、定位、检测冠军 2015



method	top-5 err. (test)
VGG [41] (ILSVRC'14)	7.32
GoogLeNet [44] (ILSVRC'14)	6.66
VGG [41] (v5)	6.8
PRelu-net [13]	4.94
BN-inception [16]	4.82
ResNet (ILSVRC'15)	3.57

该挑战中第一个超越人类视觉能力 (5.1%)

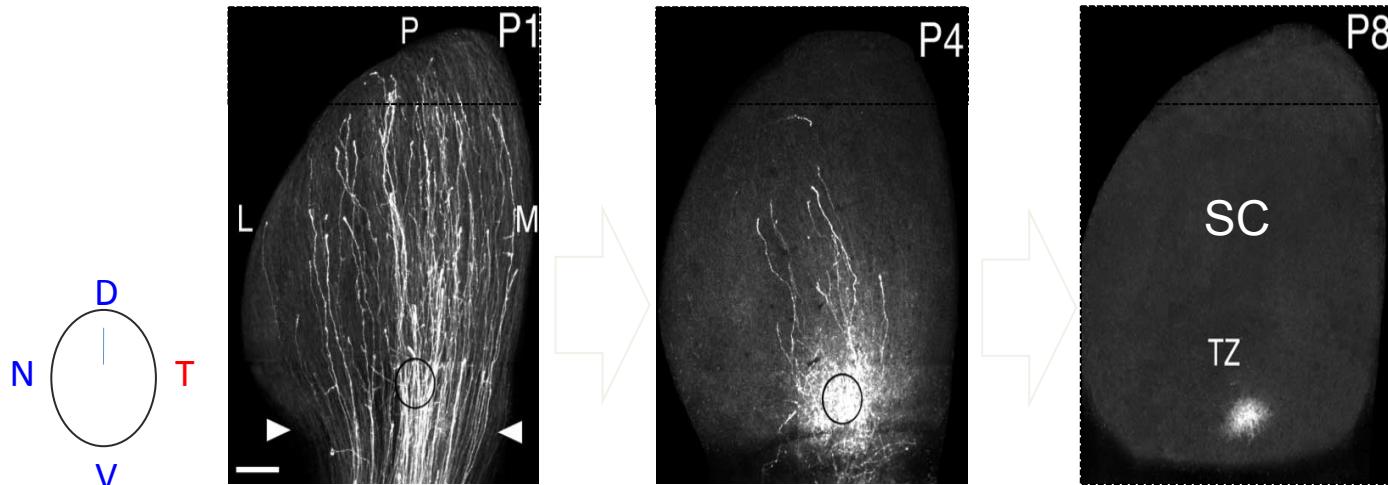
Q&A

Outline for part II: molecules

- Overview
 - Chemoaffinity hypothesis – a little bit history
 - Basic guidance function
- Retinotopic map - anterior-posterior
- Retinotopic map -medial-lateral
- Laminar-specific and axon-sorting maps
- Future remarks
- Q&A

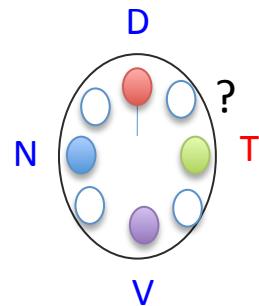
Overview

Development of retinotopic map



McLaughlin et al. (2003)

What determines the topographical map?



Genetic identity is likely to be too few for making the whole map.

Chemoaffinity hypothesis

*CHEMOAFFINITY IN THE ORDERLY GROWTH OF NERVE
FIBER PATTERNS AND CONNECTIONS**

BY R. W. SPERRY

DIVISION OF BIOLOGY, CALIFORNIA INSTITUTE OF TECHNOLOGY

Communicated July 29, 1963

Molecular tags on
projecting neurons and
their target cells
determines the
specificity of axonal
connection.

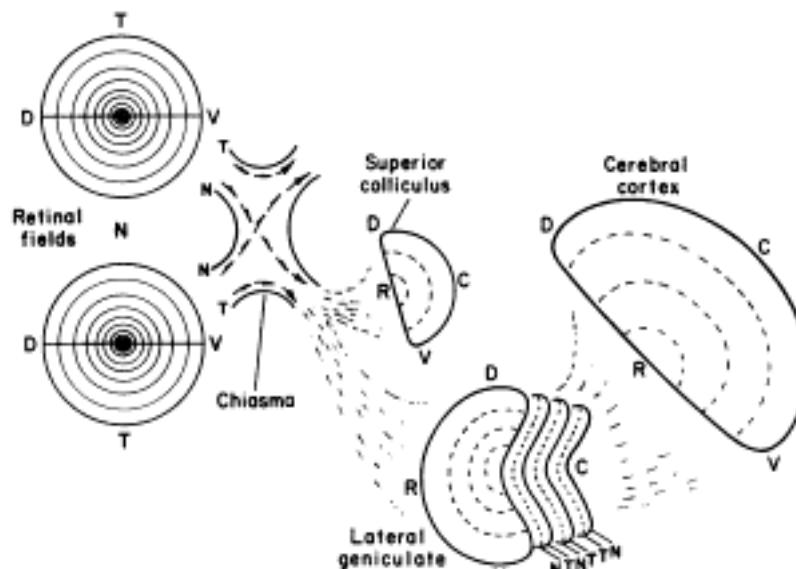
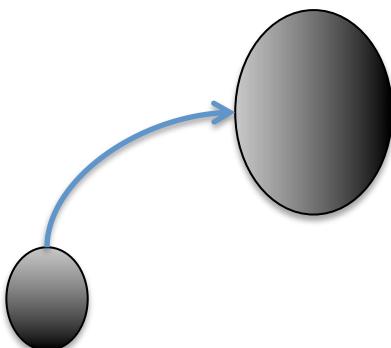
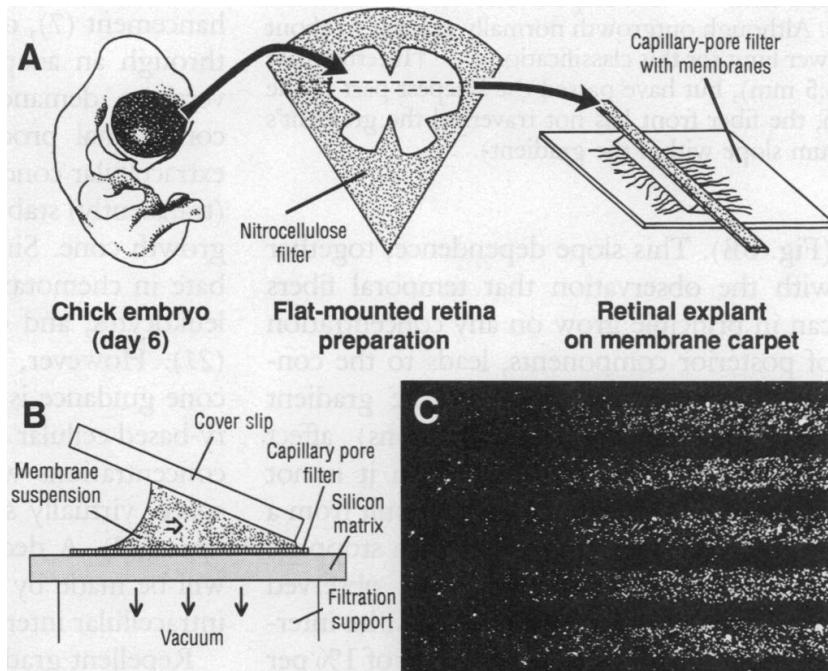


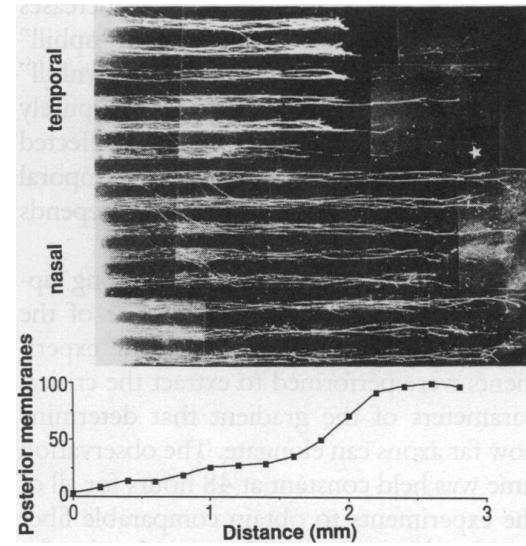
FIG. 5.—Schematic diagram indicating possible application of chemoaffinity interpretation to genesis of mammalian visual system (see text). Axial labeling of gradients for brain centers is highly tentative as the effective embryonic gradients underlying their topographic differentiation remain uncertain. D·V: dorsoventral gradient; N·T: nasotemporal; R·C: rostrocaudal.

Sperry, PNAS (1963)

Axon guidance by target gradients

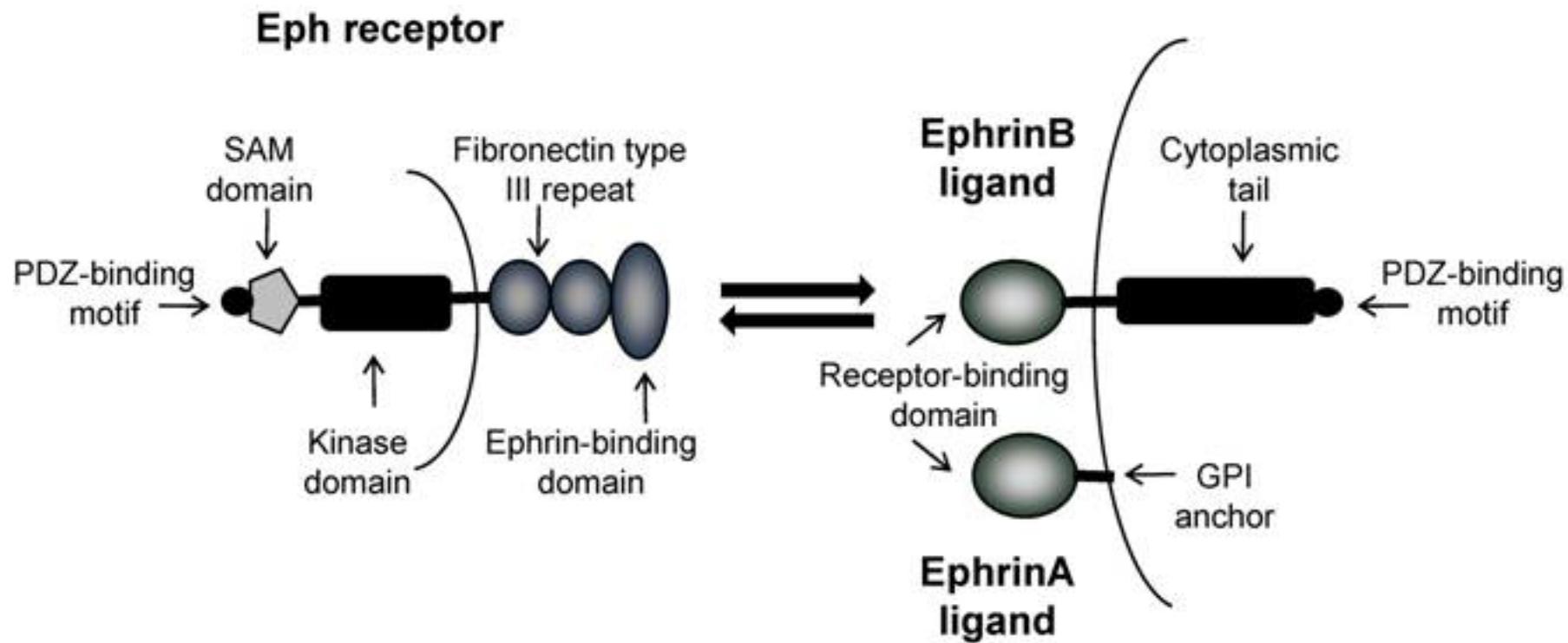


“A glycoprotein component”



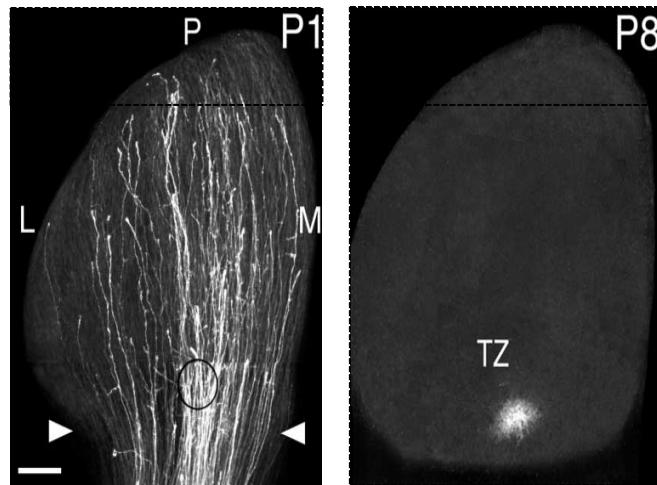
First candidate: Receptor tyrosine kinase in mice

- Receptor tyrosine kinase: high-affinity cell-surface receptors (20 classes)
- Eph class is composed of 14 Eph receptors and 8 ephrin ligands in mice
- Require direct cell-cell interactions for activation
- Involved in axon guidance, cell migration, long-term potentiation and cancer.



Anterior-posterior retinotopic map

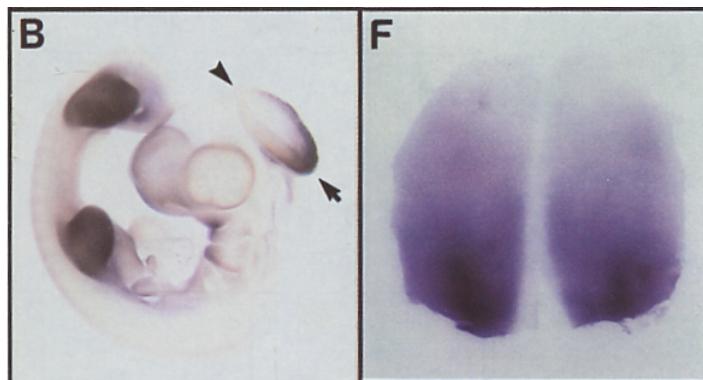
Anterior-posterior: TZ location and interstitial branching



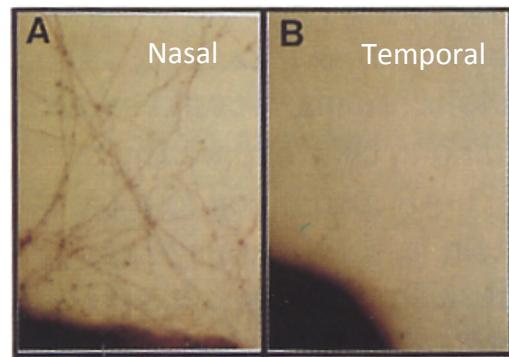
Ephrin-A2 cloned: gradients found in SC

Eph-A3 (receptor)

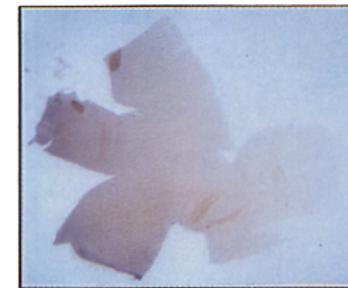
Ephrin-A2 (ligand) at *E4*



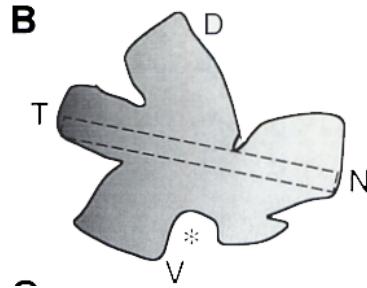
Ephrin-A2 treated culture



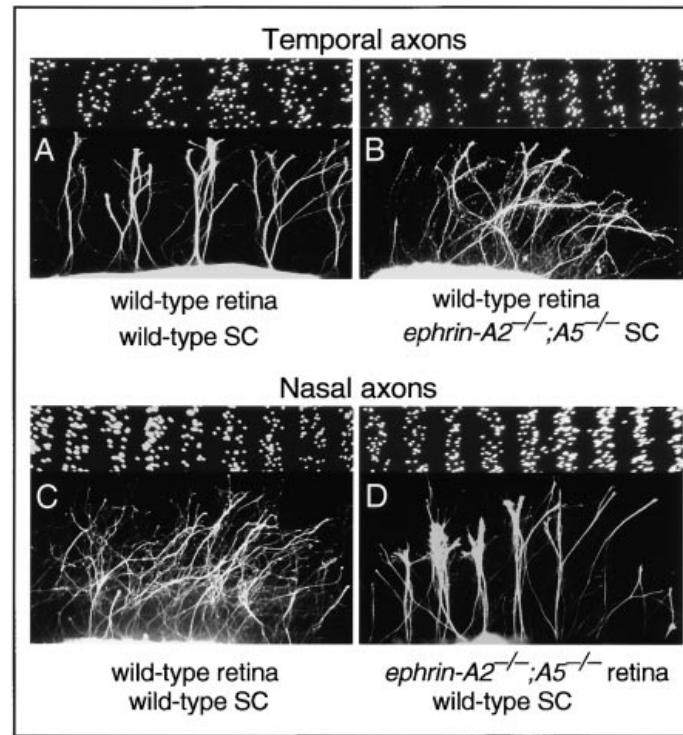
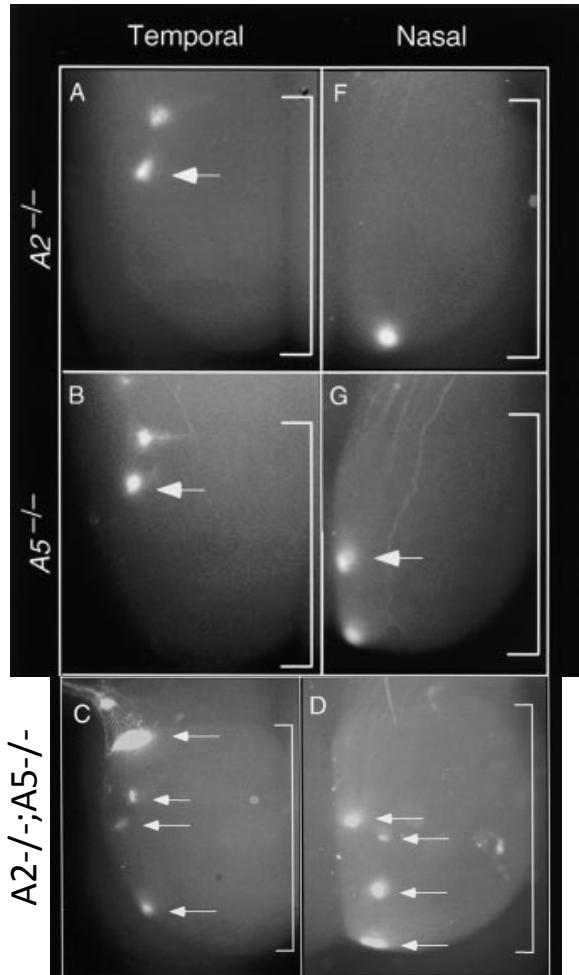
A



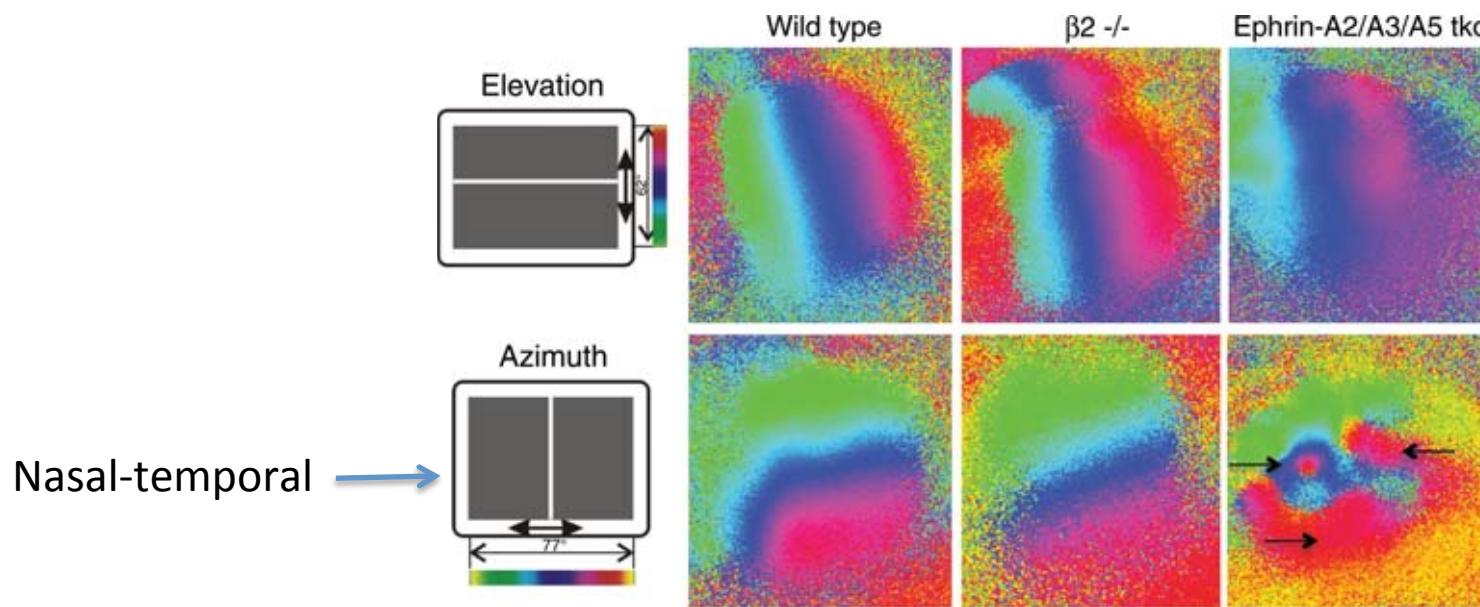
B



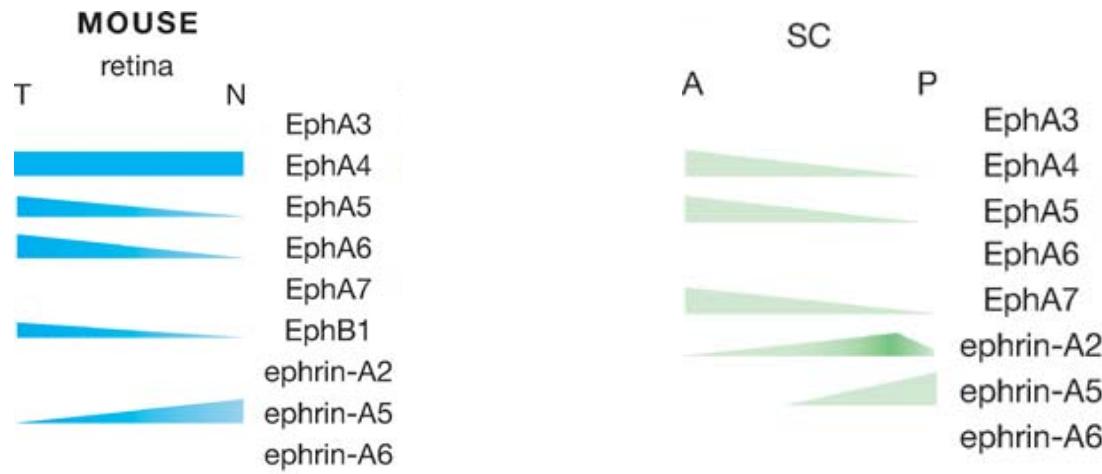
Ephrin A2 and A5 knock-out mice



Functional disruption of retinotopic map in ephrin

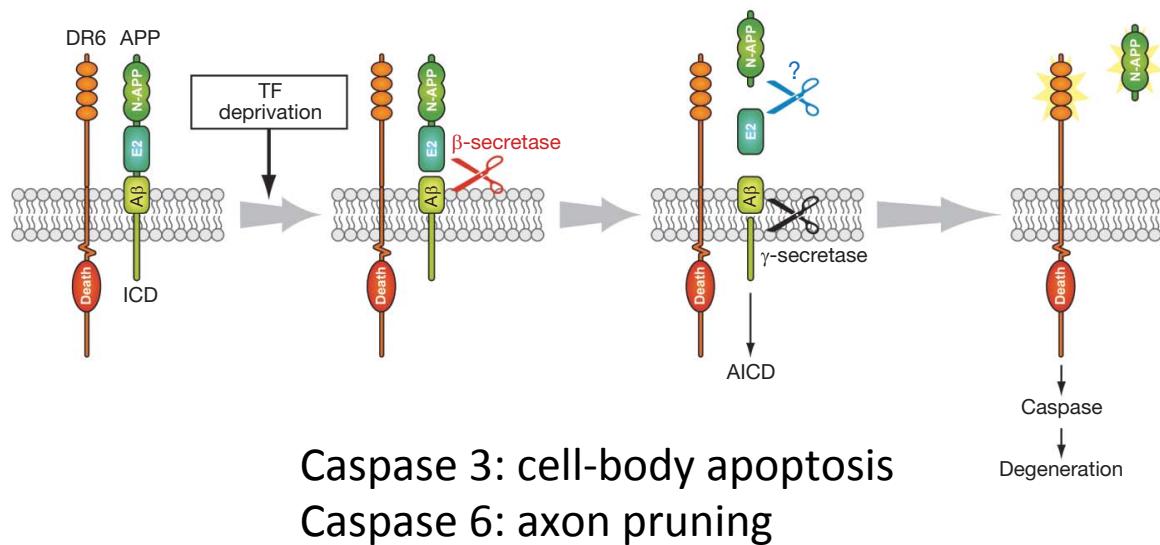
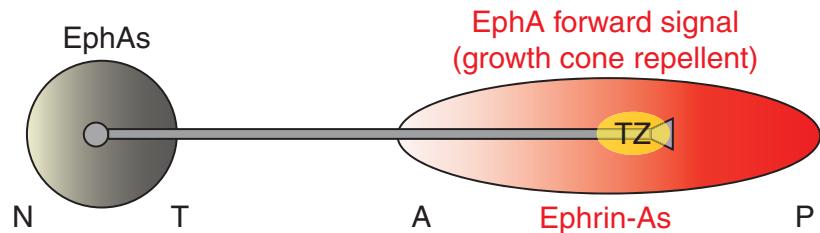


Eph distribution on anterior-posterior axis

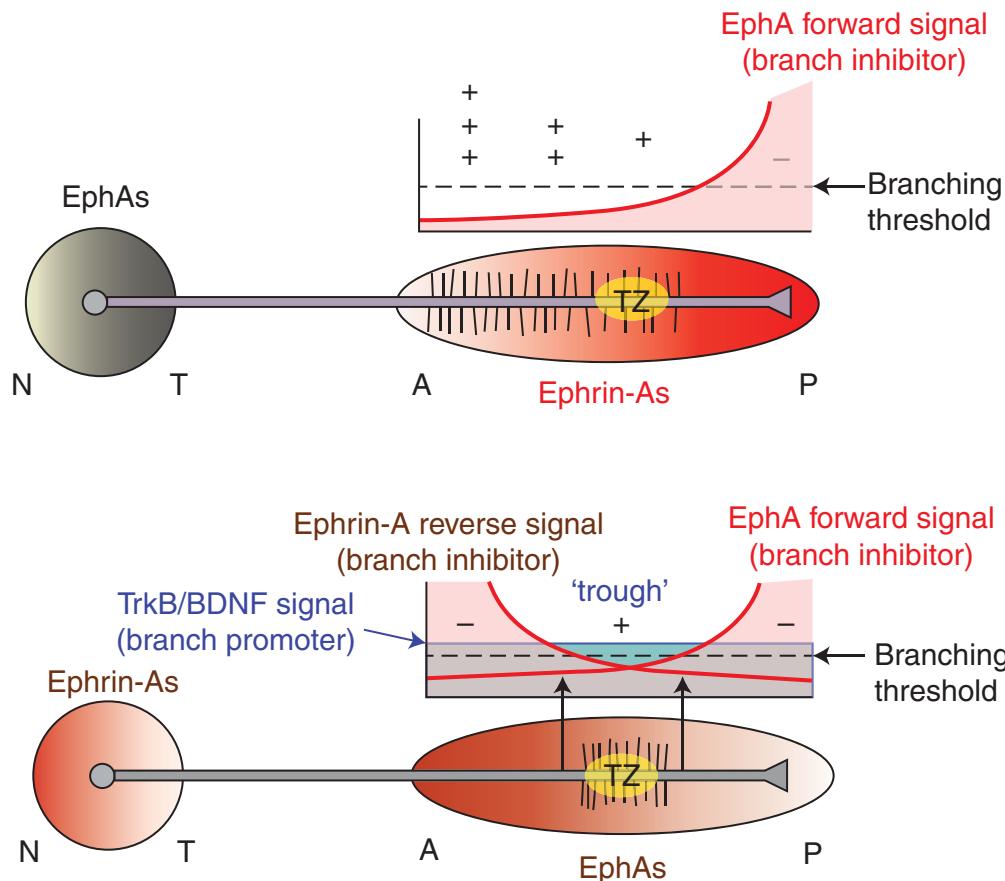


How do the gradients create anterior-posterior map?

Regulation of retinotopic map along A-P axis

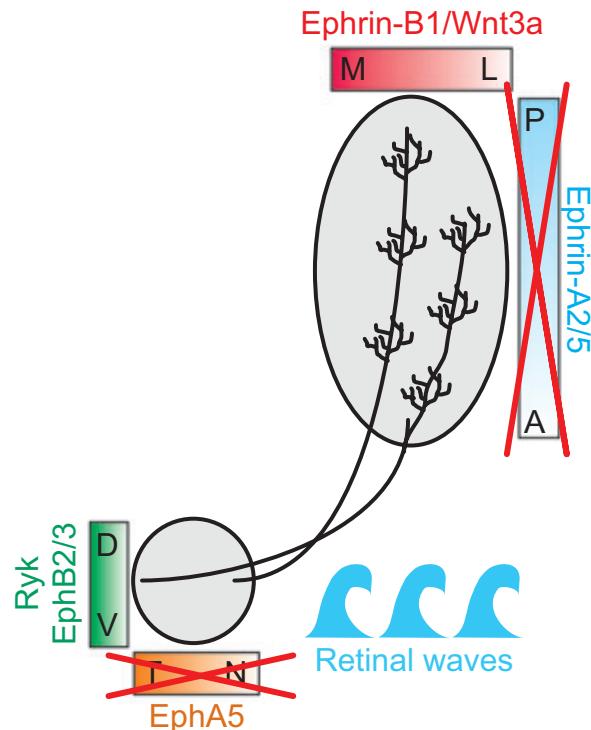


Interstitial branching along A-P axis



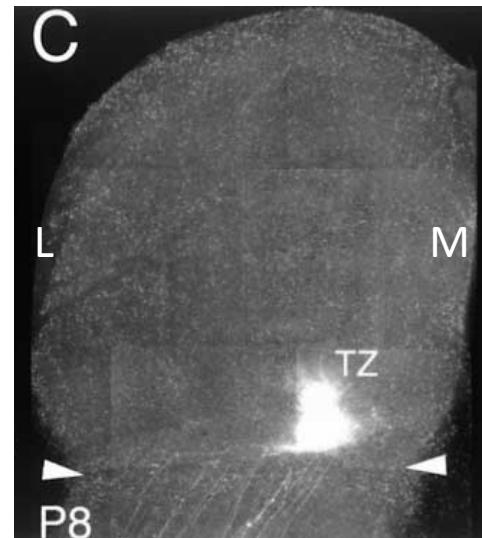
Summary for A-P retinotopy

C Removal of Eph/rin-As

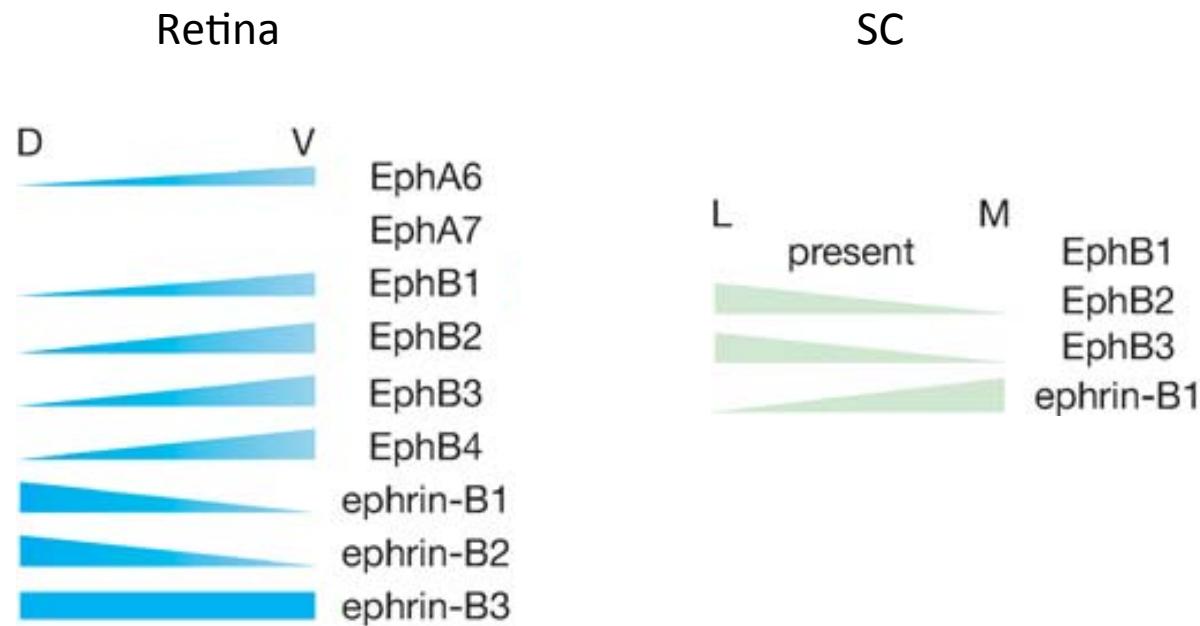


Medial-lateral retinotopic map

Broad distribution of axons along Medial-lateral axis

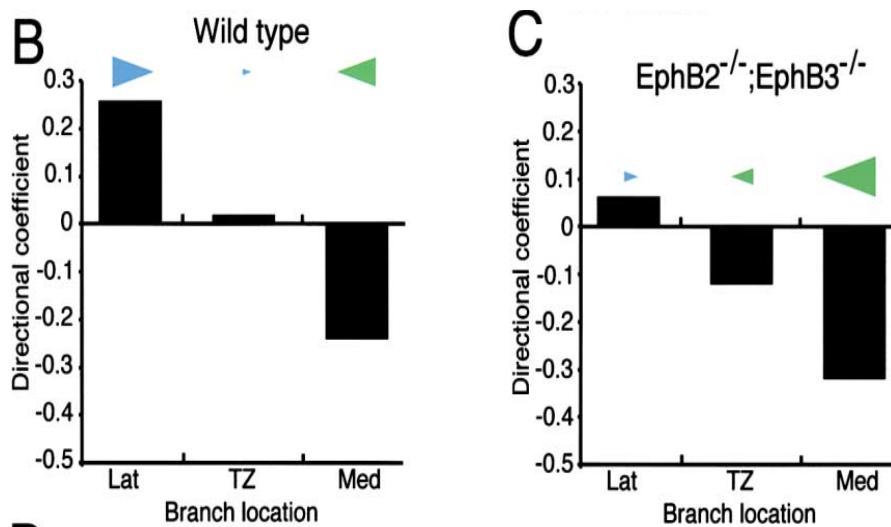


Eph distribution on medial-lateral axis

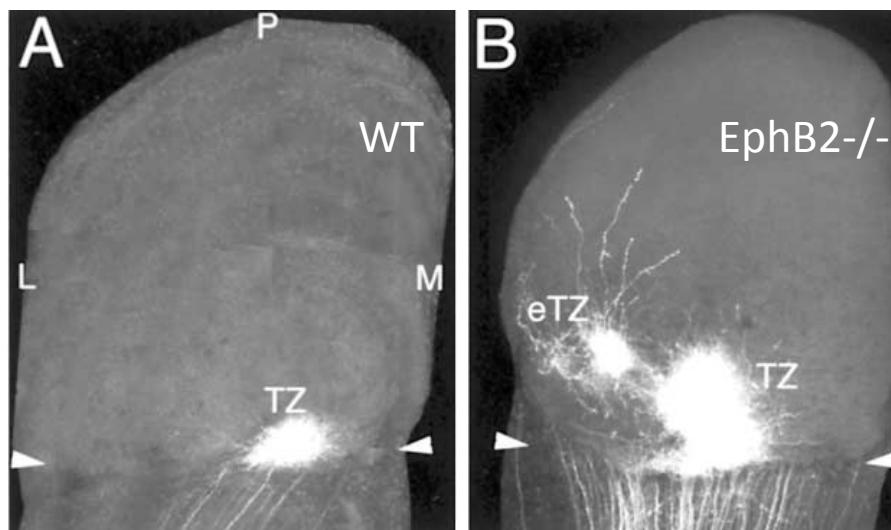


Bifunctional EphB interactions on interstitial branches

P3

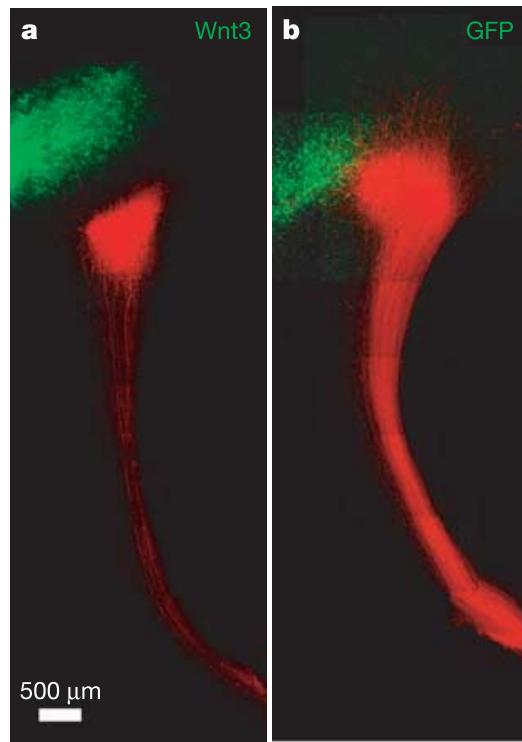


P8

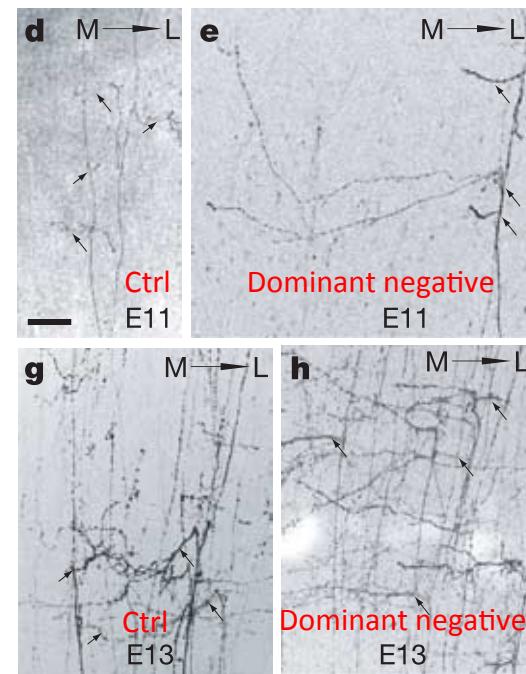


Wnt3-Ryk axon-guidance molecule

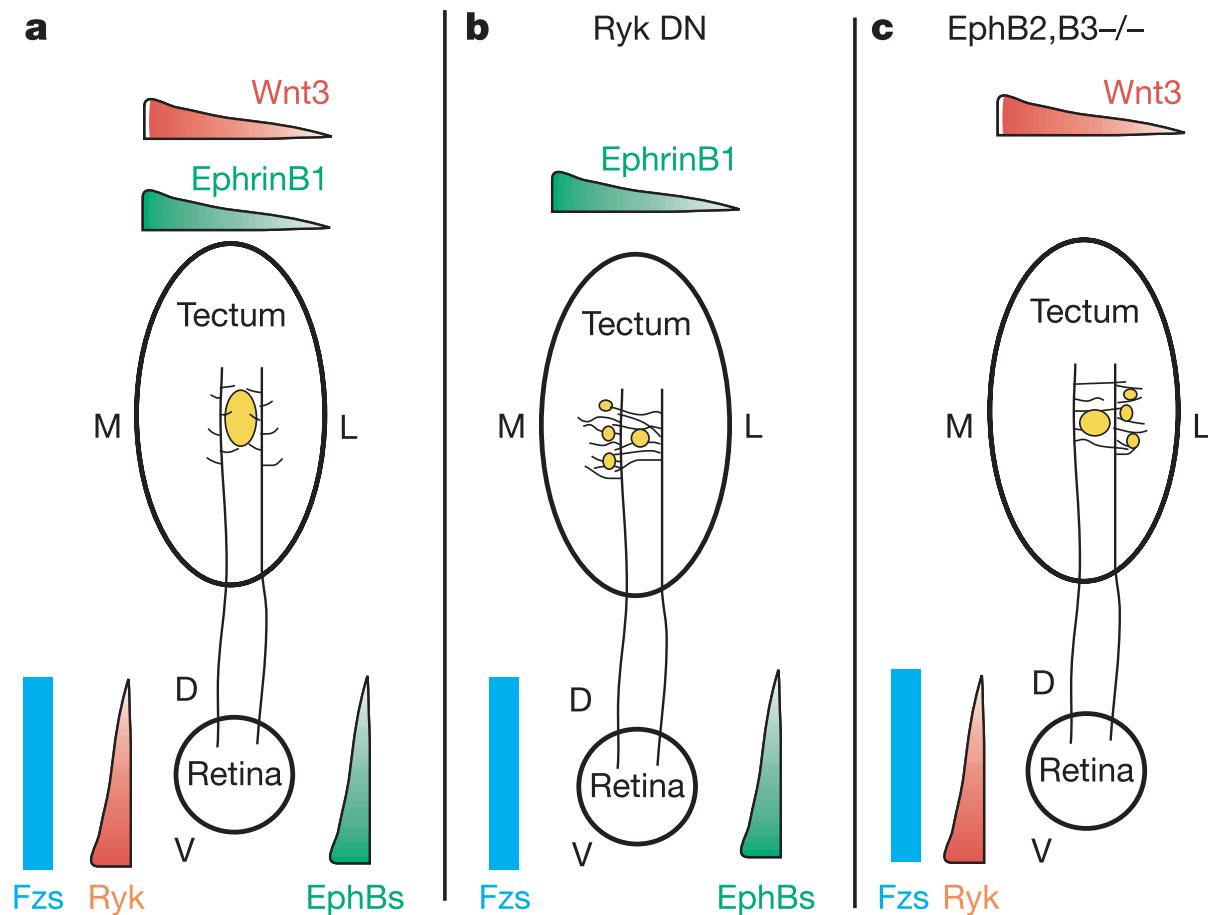
Ectopic Wnt3 expression in tectum



Dominant negative Ryk expression in RGC

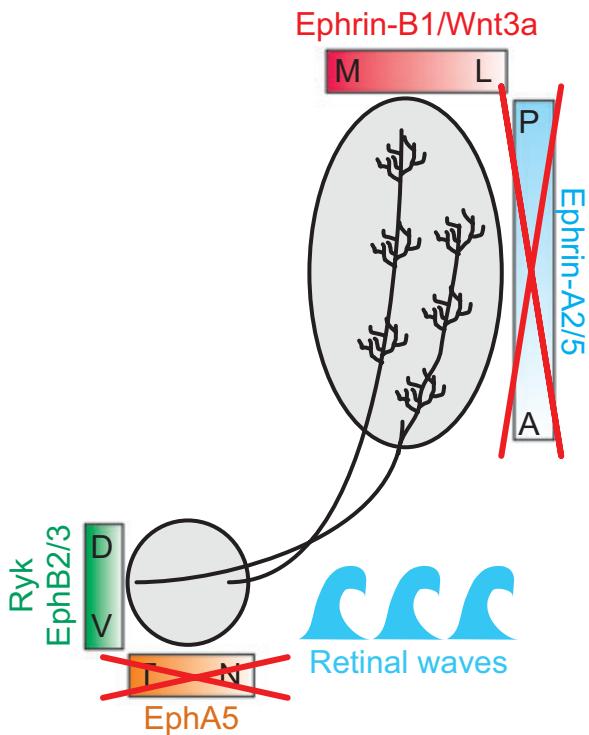


Summary for M-L retinotopy

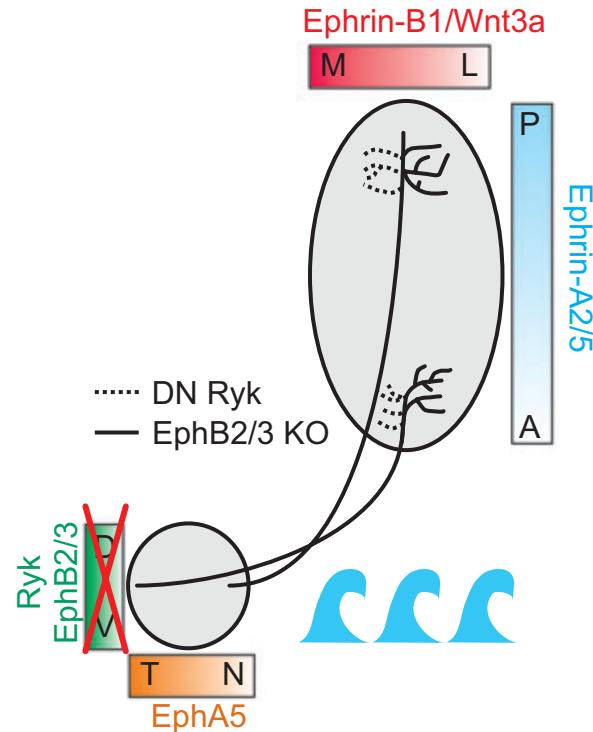


Summary for retinotopic map

c Removal of Eph/rin-As

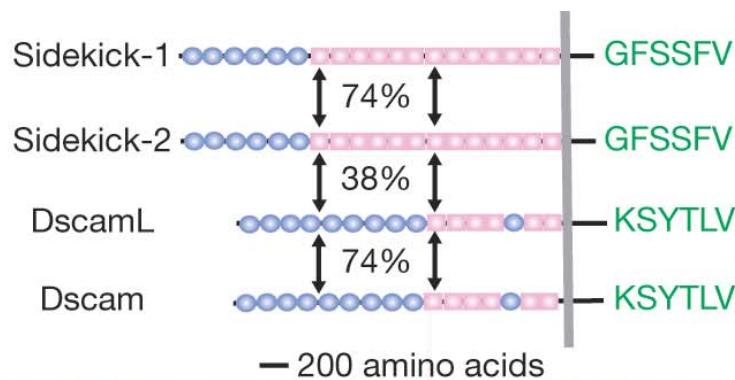


d Altering Ryk or EphB2/3

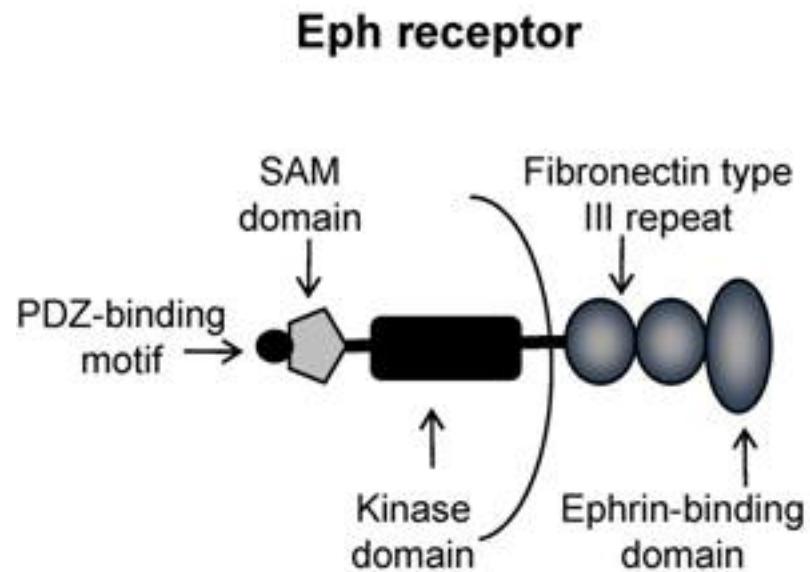


Laminar-specific guidance

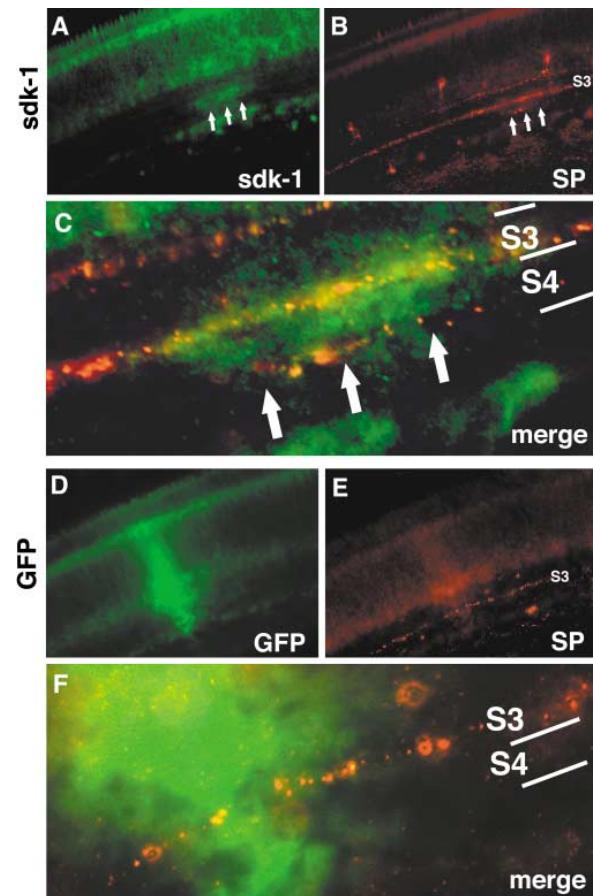
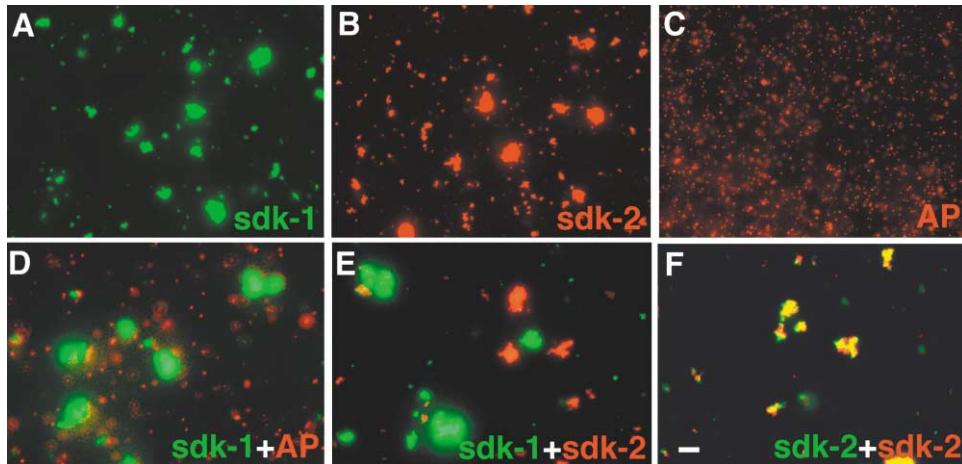
Immunoglobulin superfamily adhesion molecules – retina related



Blue: immunoglobulin domains
Pink: fibronectin type III domains
Grey: membrane
Green: Carboxy-terminal sequences
(for PDZ domain binding)

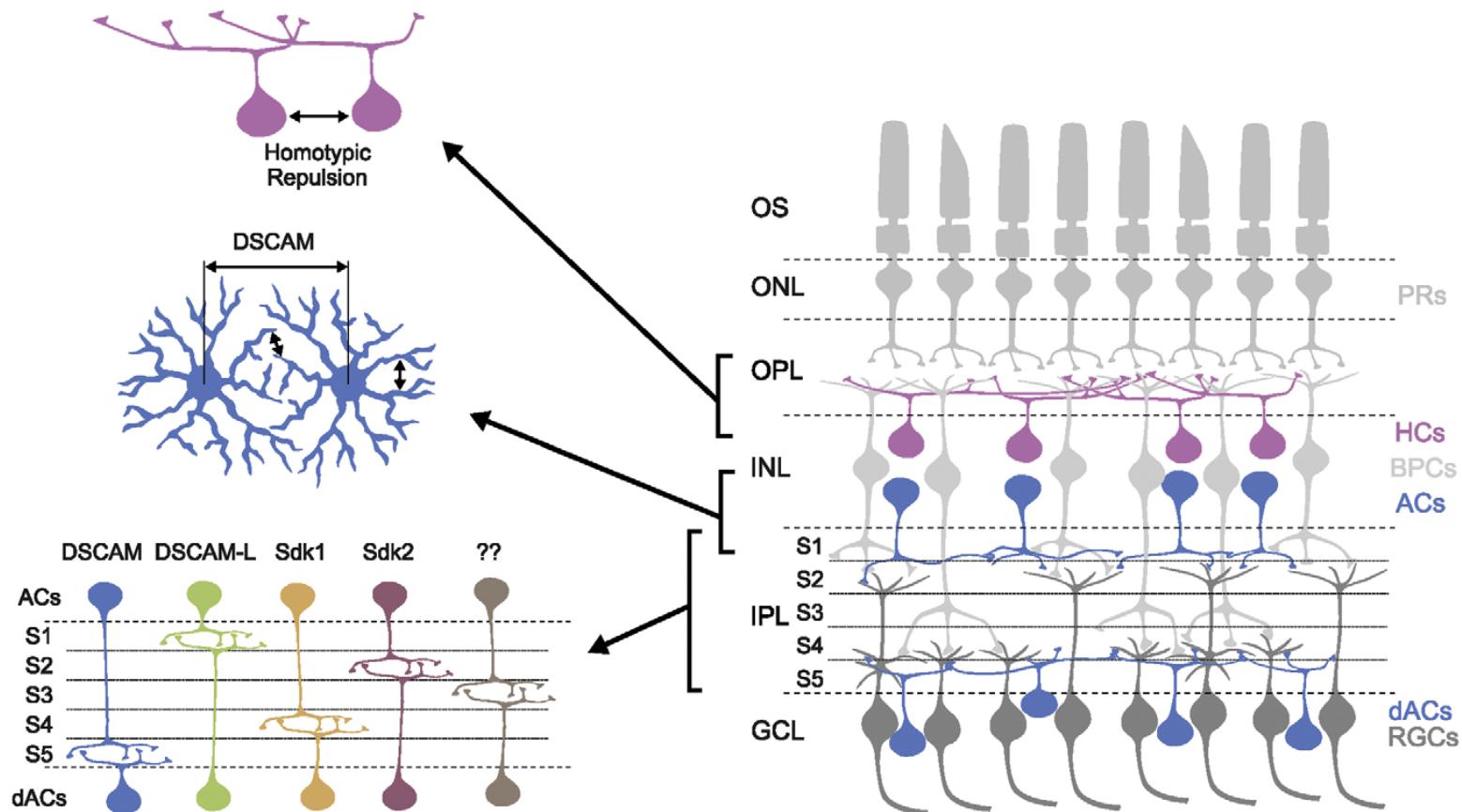


Homophilic adhesion and laminar specificity

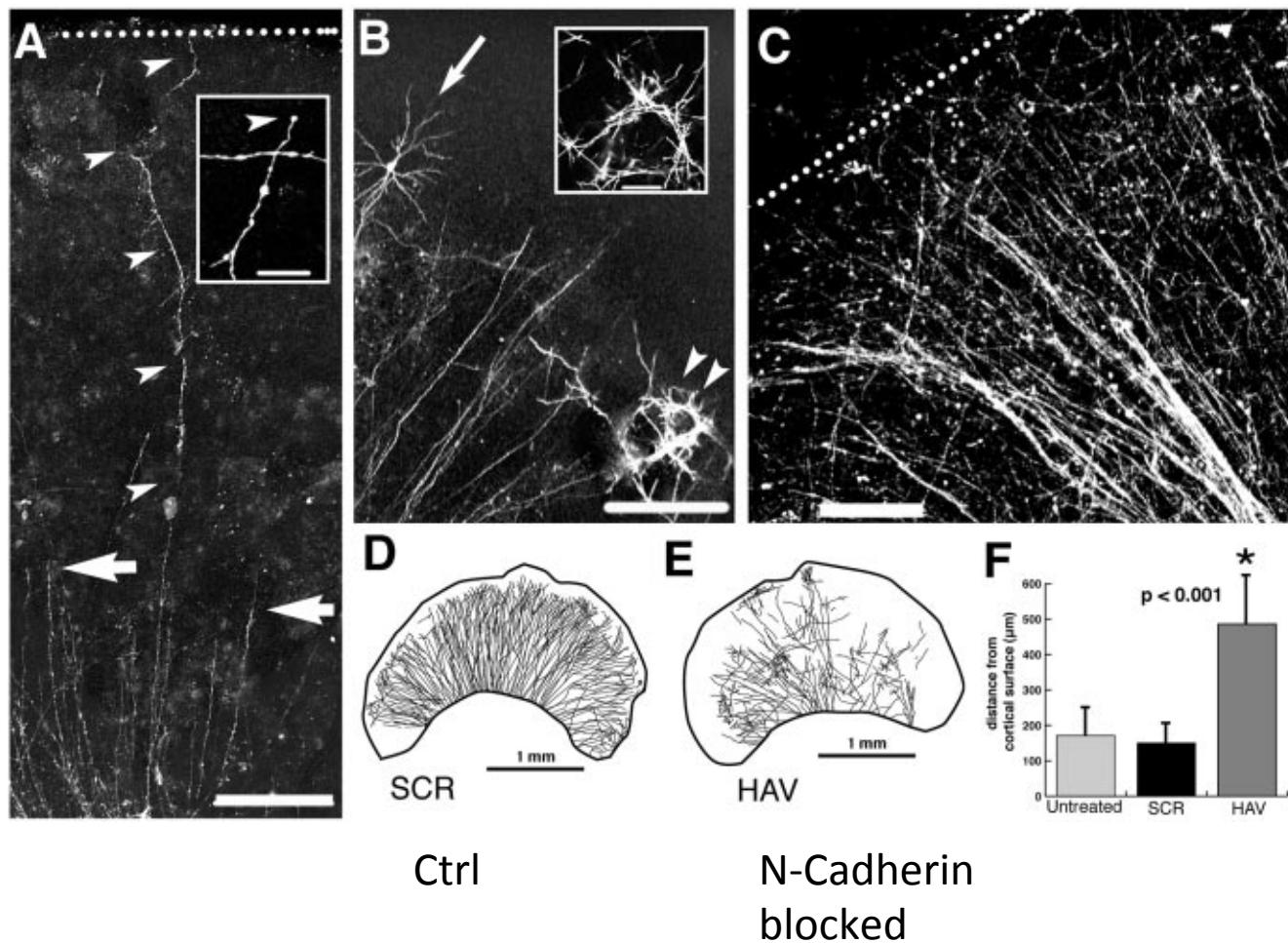


- Fluorescent polystyrene microbeads showed the homophilic adhesion of *sdk-1* and *sdk-2*.
- Ectopic expression of *sdk-1* causes terminals of SP-positive amacrine cells to be diverted to S4.

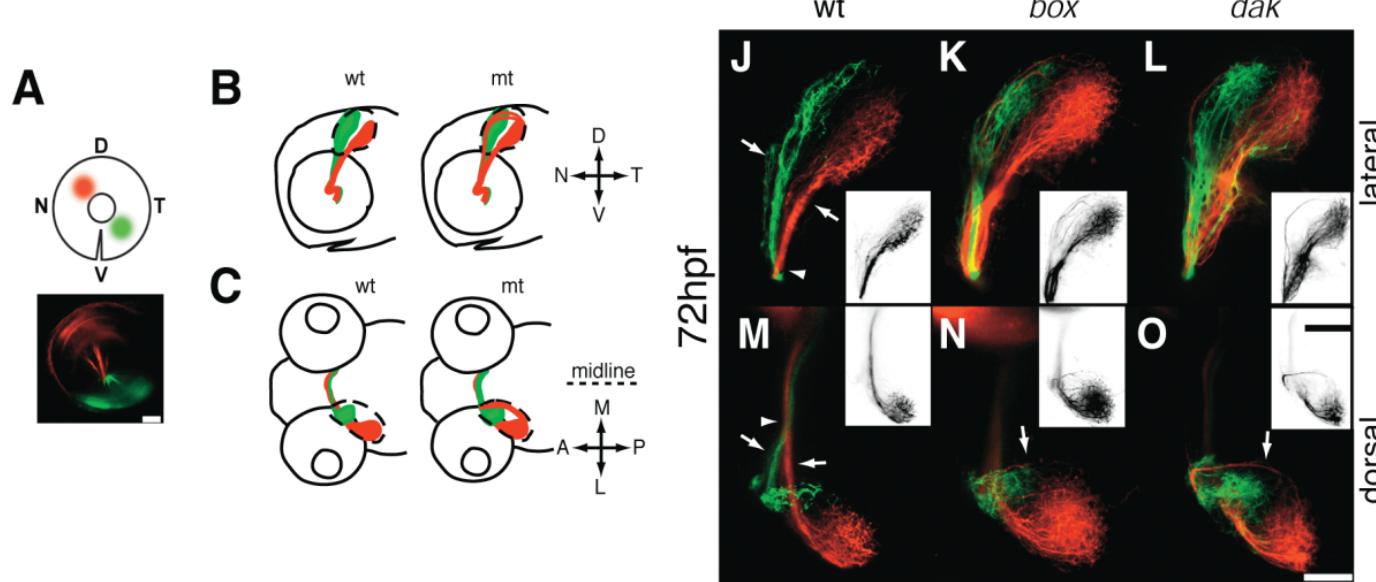
Lamination in retina



N-Cadherin regulates layer-specific targeting of thalamocortical axons

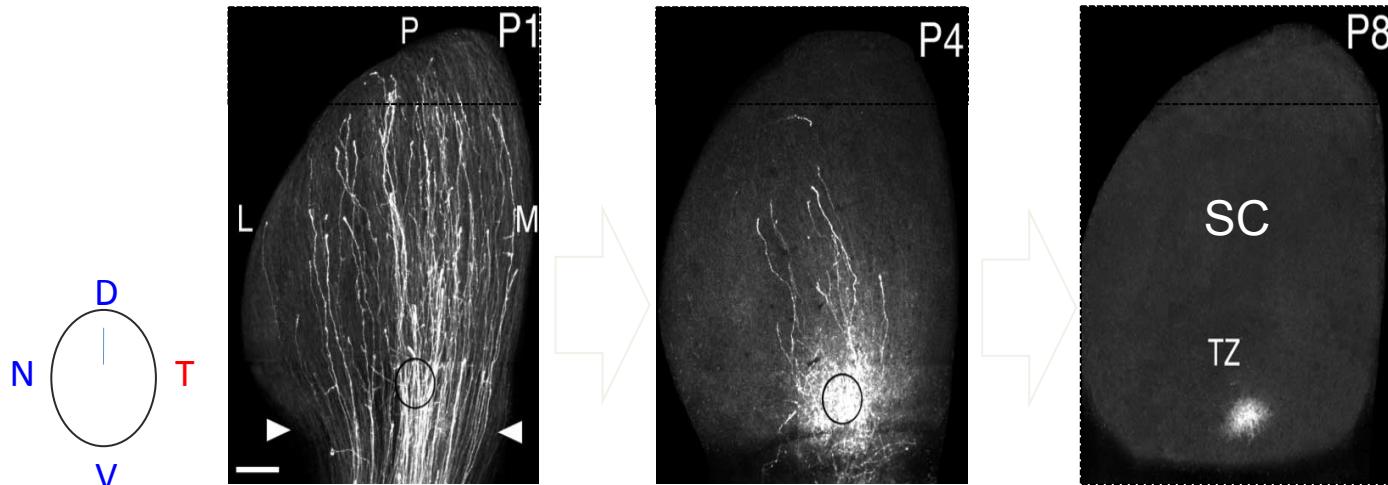


Heparan sulfate biosynthesis is necessary for axon sorting



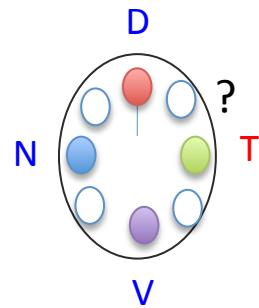
Overview

Development of retinotopic map



McLaughlin et al. (2003)

What determines the topographical map?



Genetic identity is likely to be too few for making the whole map.

Chemoaffinity hypothesis

*CHEMOAFFINITY IN THE ORDERLY GROWTH OF NERVE FIBER PATTERNS AND CONNECTIONS**

BY R. W. SPERRY

DIVISION OF BIOLOGY, CALIFORNIA INSTITUTE OF TECHNOLOGY

Communicated July 29, 1963

Molecular tags on projecting neurons and their target cells determines the specificity of axonal connection.

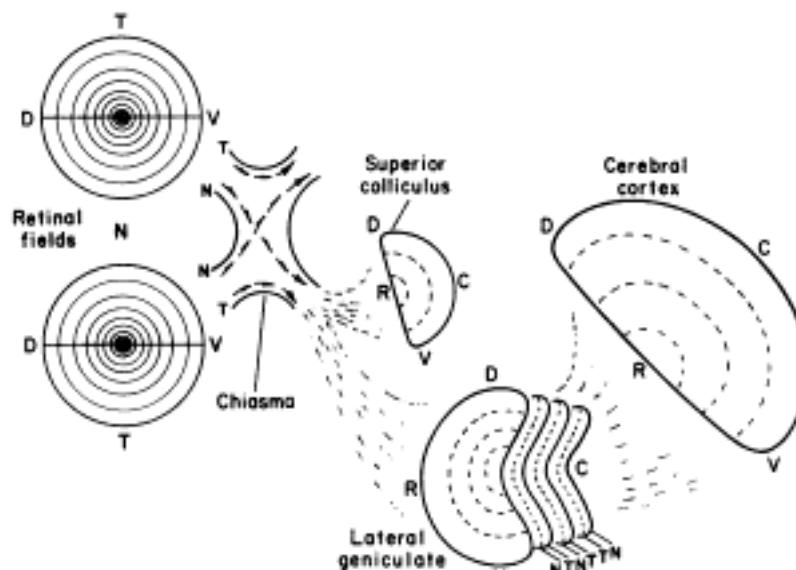
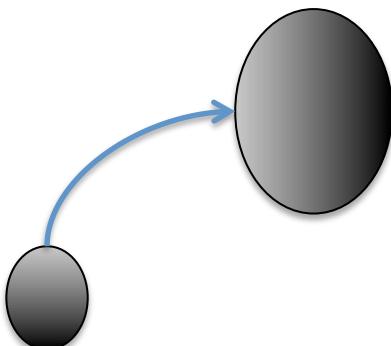
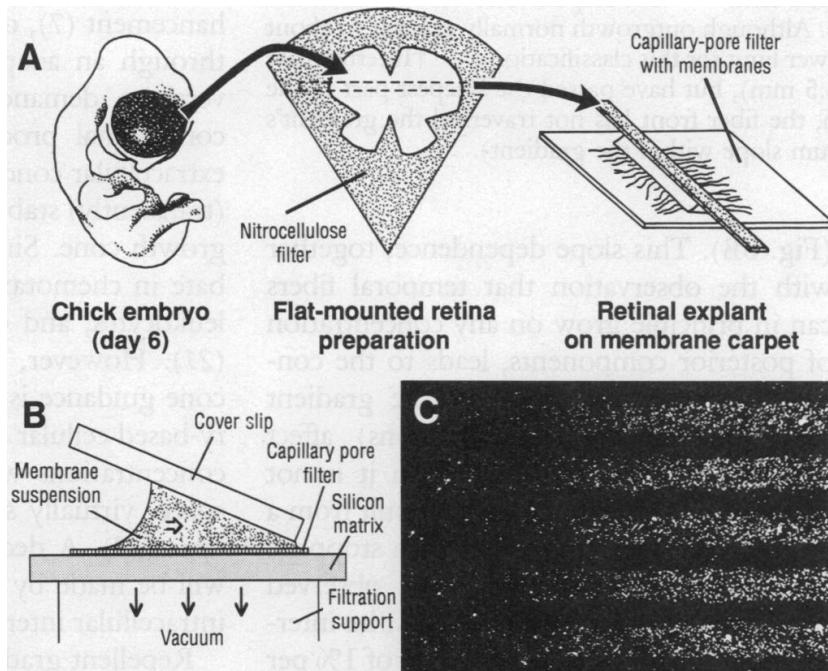


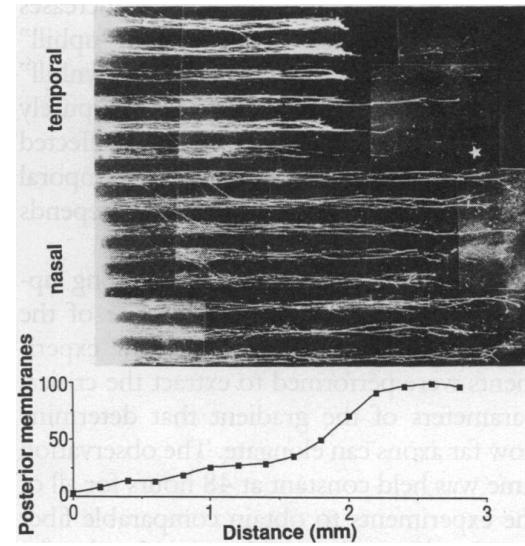
FIG. 5.—Schematic diagram indicating possible application of chemoaffinity interpretation to genesis of mammalian visual system (see text). Axial labeling of gradients for brain centers is highly tentative as the effective embryonic gradients underlying their topographic differentiation remain uncertain. D·V: dorsoventral gradient; N·T: nasotemporal; R·C: rostrocaudal.

Sperry, PNAS (1963)

Axon guidance by target gradients

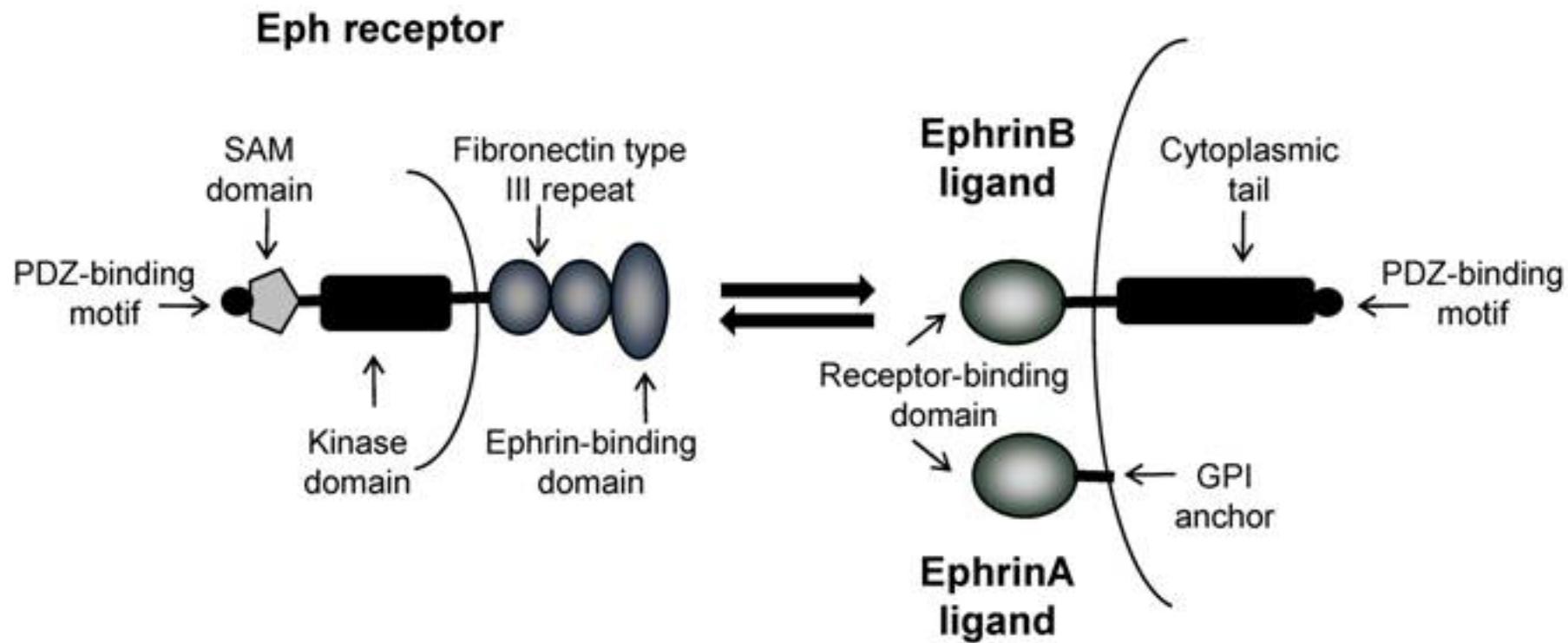


“A glycoprotein component”



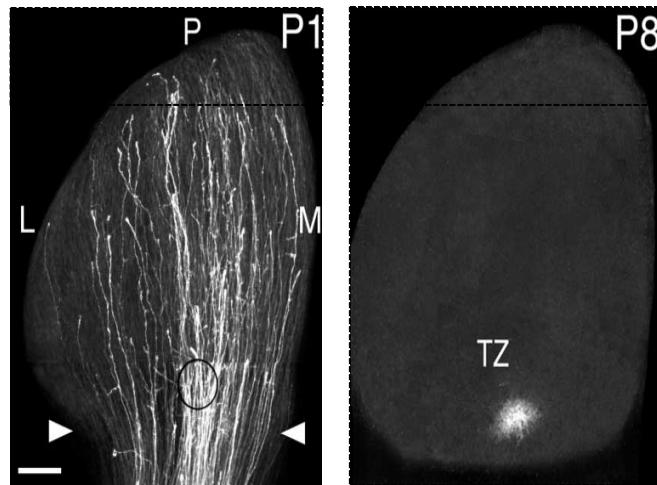
First candidate: Receptor tyrosine kinase in mice

- Receptor tyrosine kinase: high-affinity cell-surface receptors (20 classes)
- Eph class is composed of 14 Eph receptors and 8 ephrin ligands in mice
- Require direct cell-cell interactions for activation
- Involved in axon guidance, cell migration, long-term potentiation and cancer.



Anterior-posterior retinotopic map

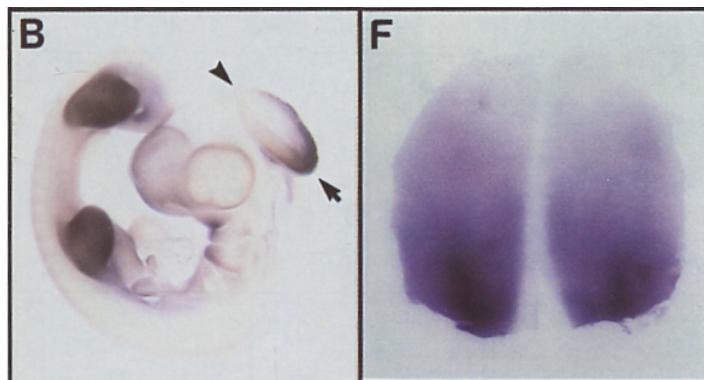
Anterior-posterior: TZ location and interstitial branching



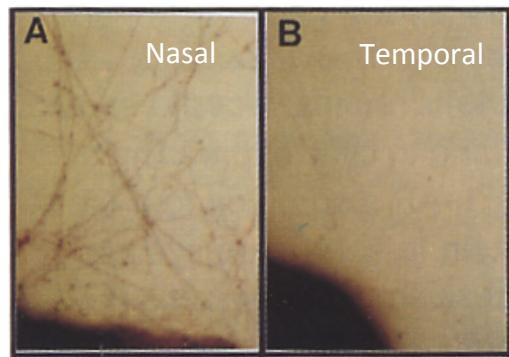
Ephrin-A2 cloned: gradients found in SC

Eph-A3 (receptor)

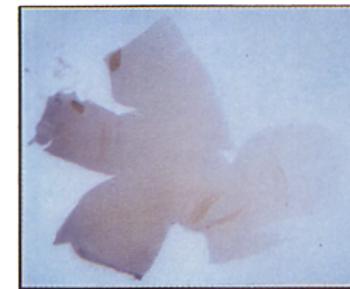
Ephrin-A2 (ligand) at *E4*



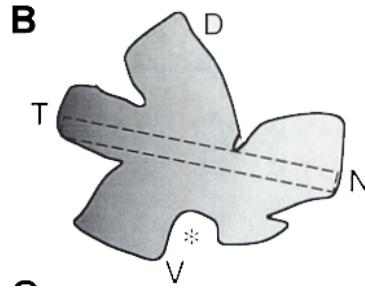
Ephrin-A2 treated culture



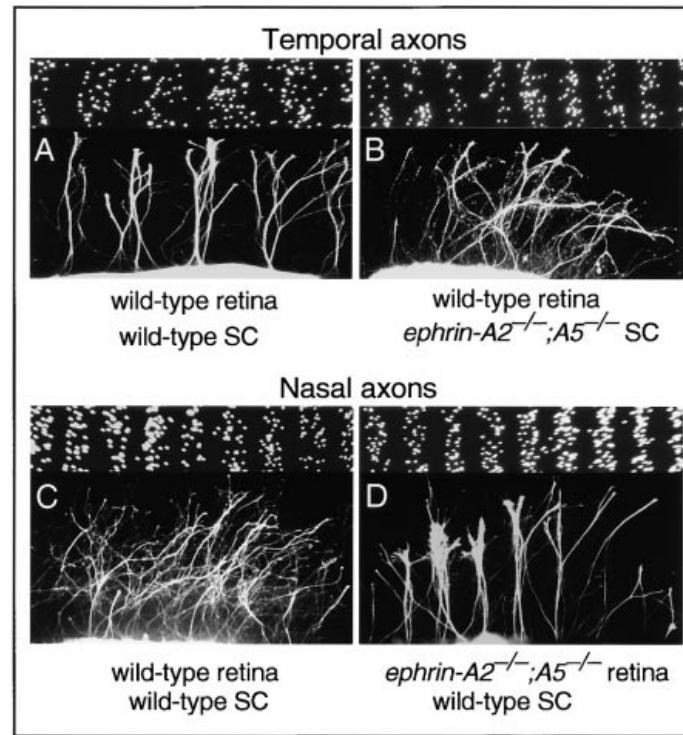
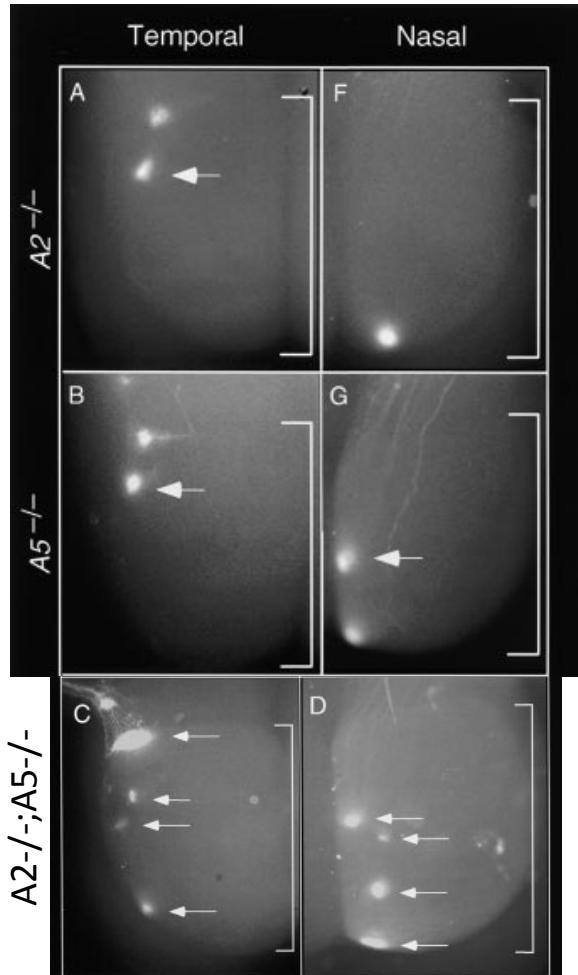
A



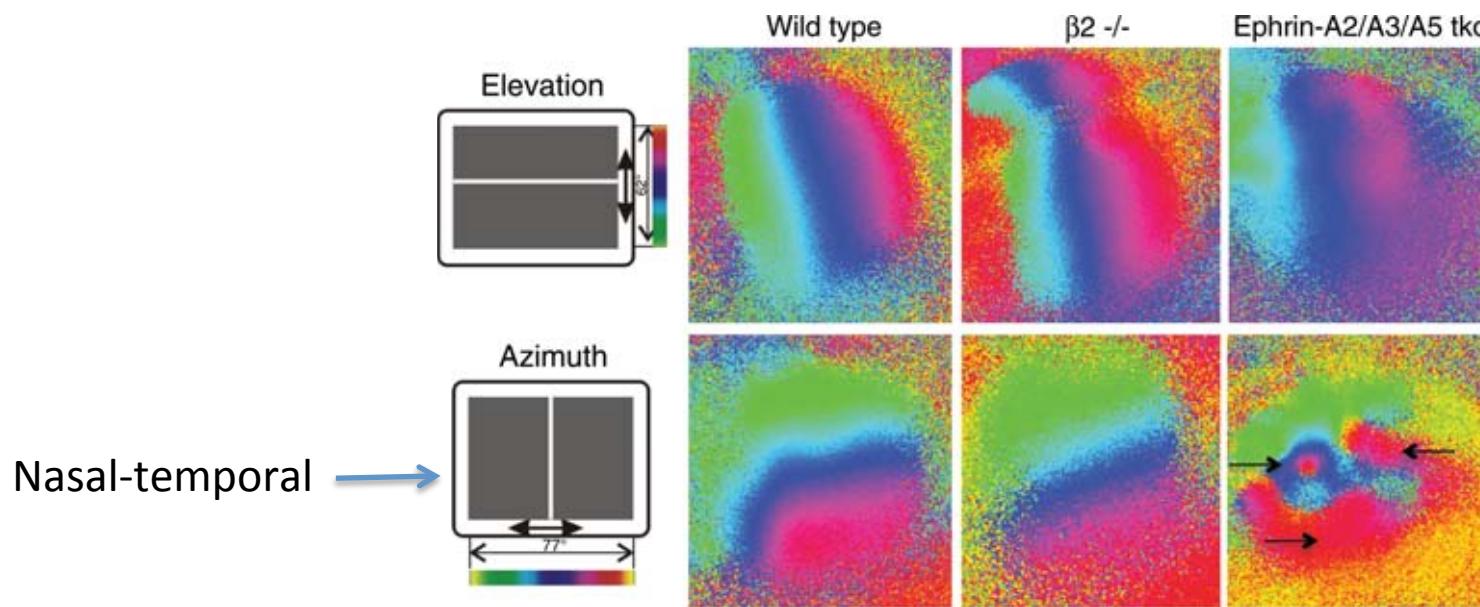
B



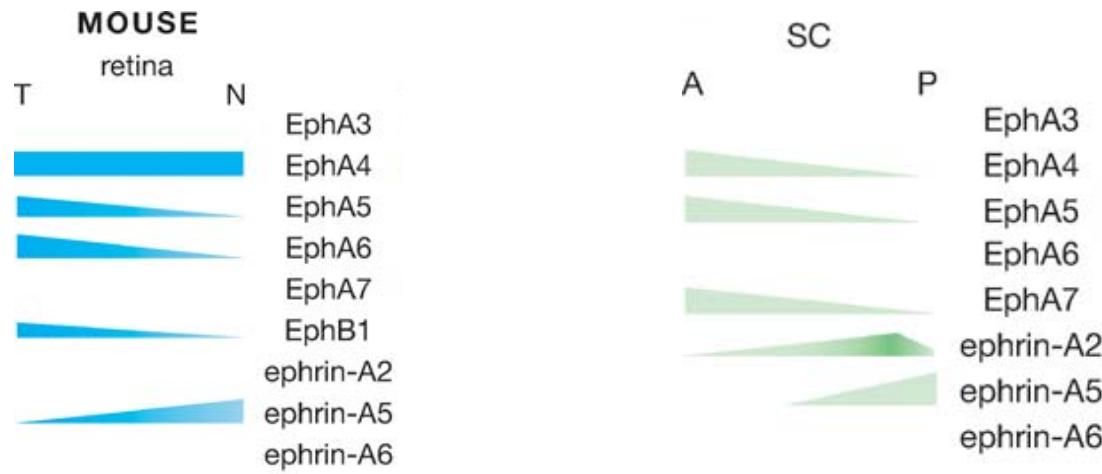
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Functional disruption of retinotopic map in ephrin

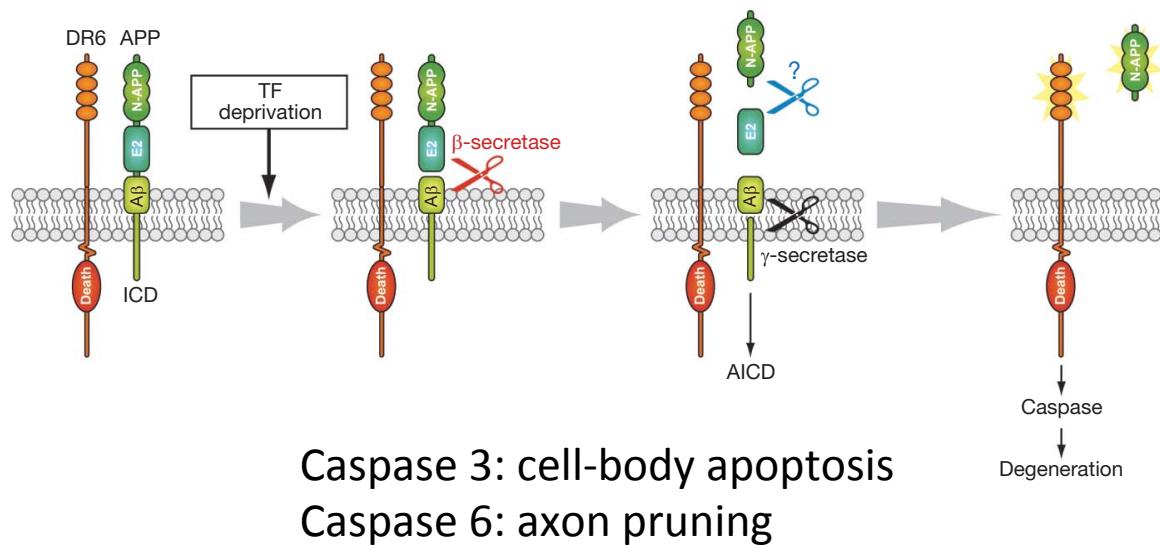
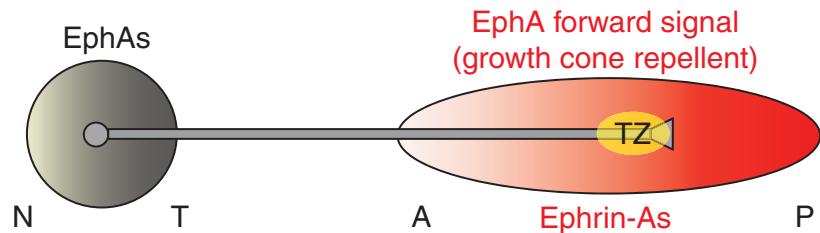


Eph distribution on anterior-posterior axis

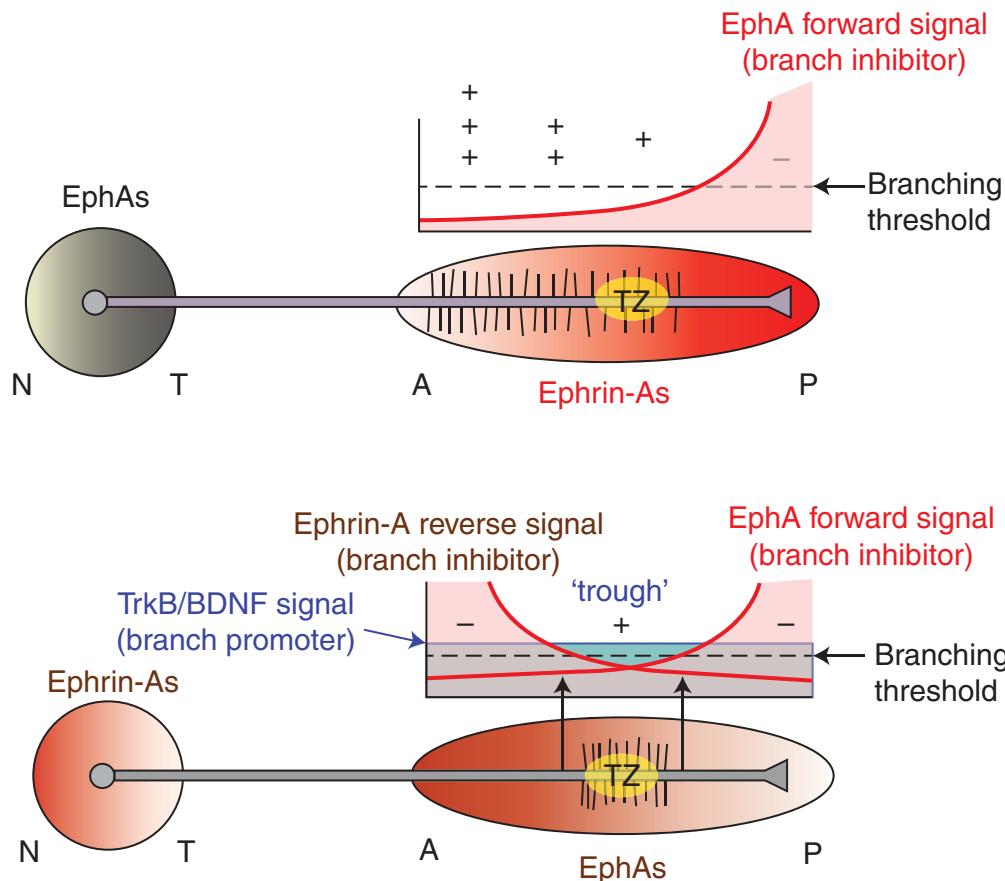


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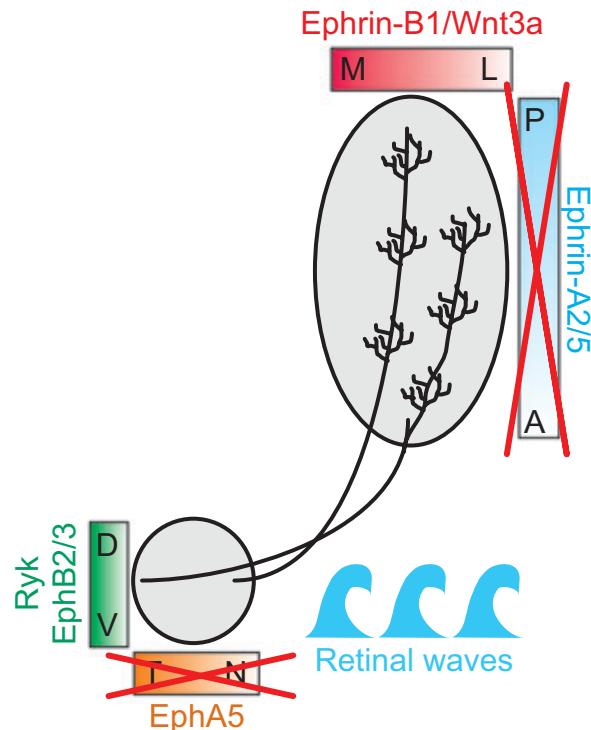


Interstitial branching along A-P axis



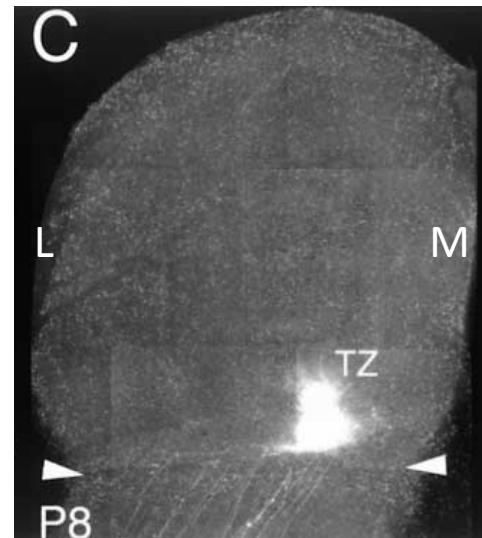
Summary for A-P retinotopy

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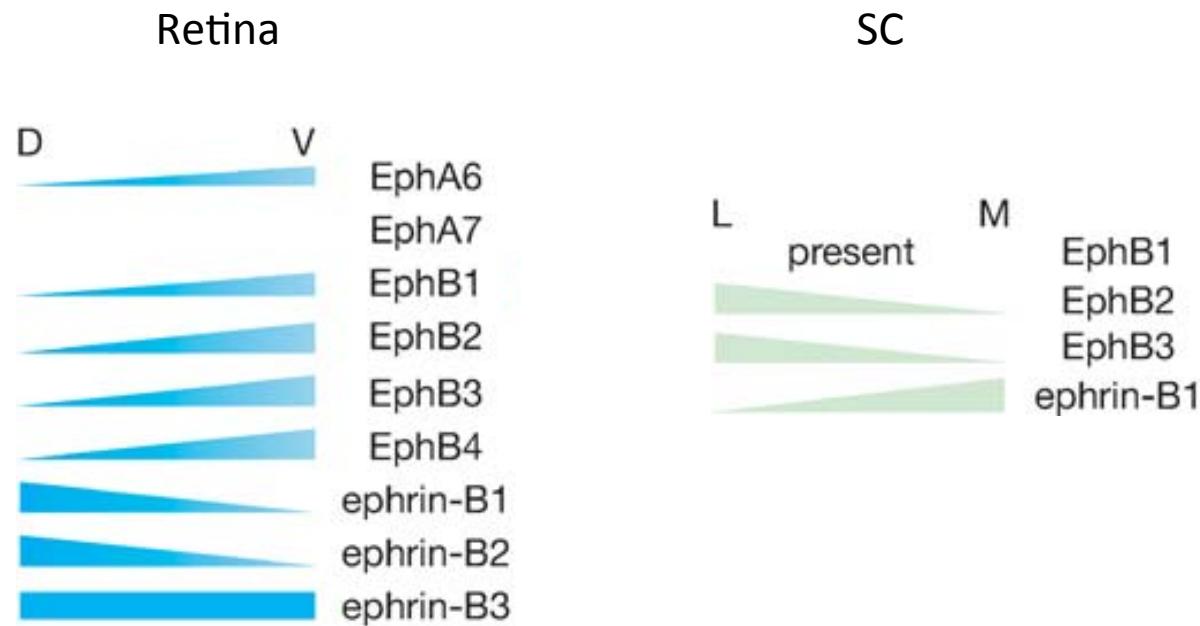


Medial-lateral retinotopic map

Broad distribution of axons along Medial-lateral axis

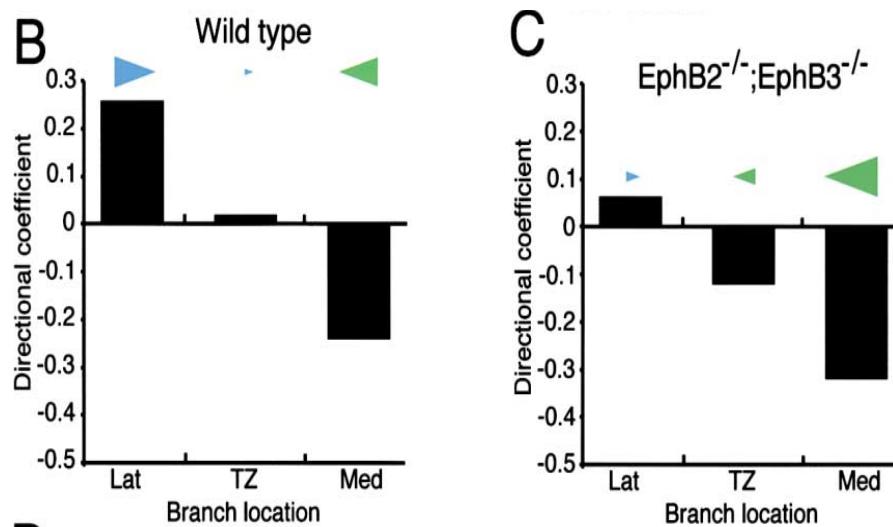


Eph distribution on medial-lateral axis

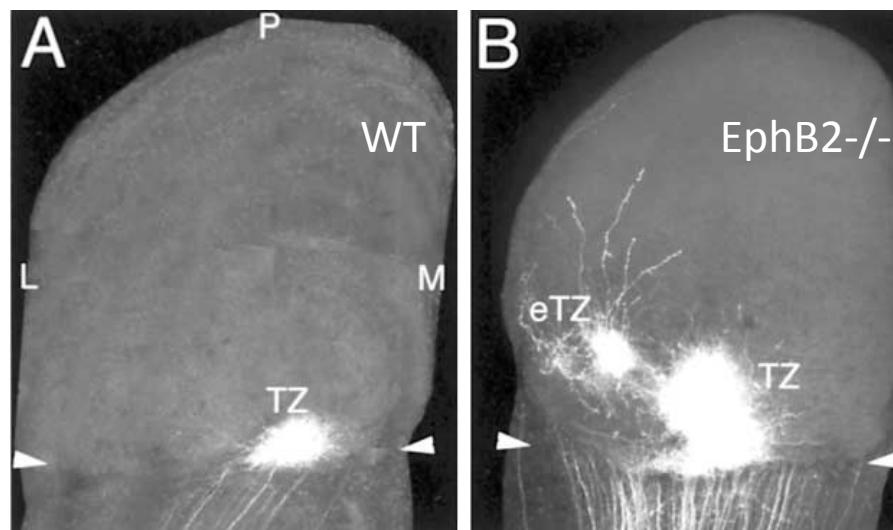


Bifunctional EphB interactions on interstitial branches

P3

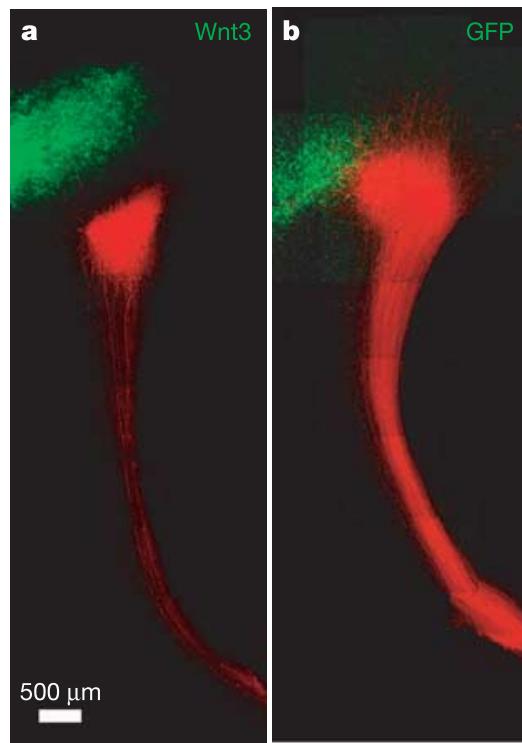


P8

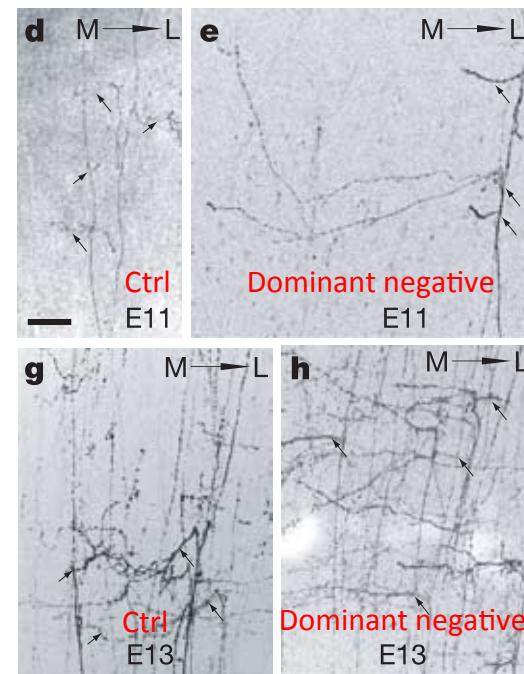


Wnt3-Ryk axon-guidance molecule

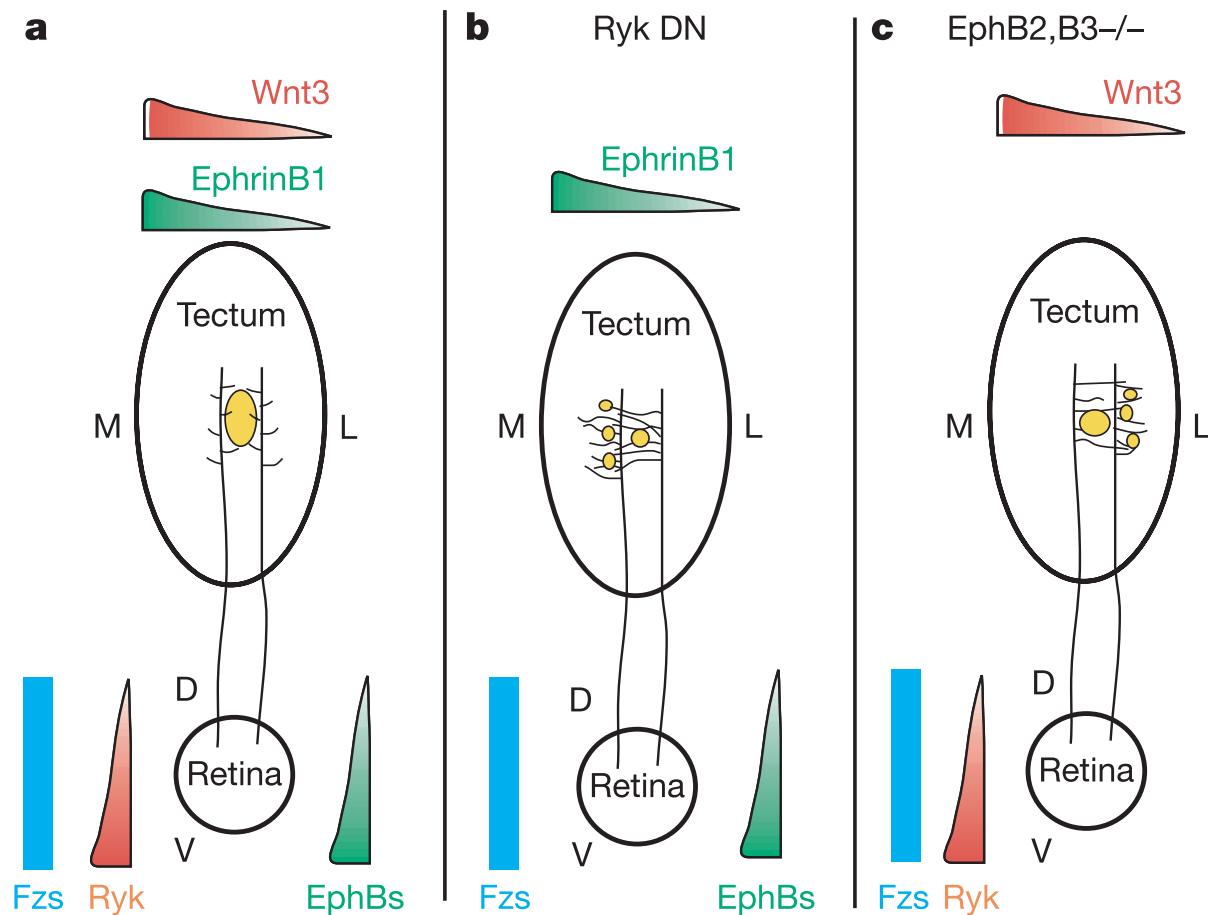
Ectopic Wnt3 expression in tectum



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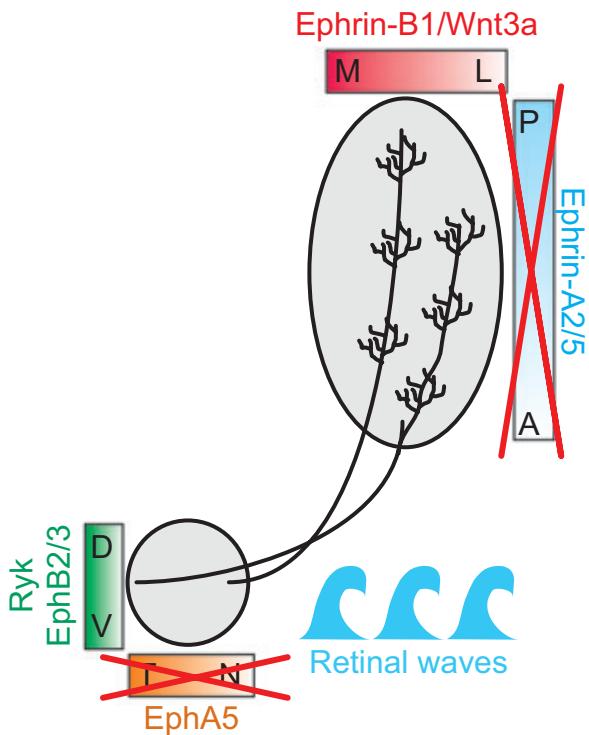


Summary for M-L retinotopy

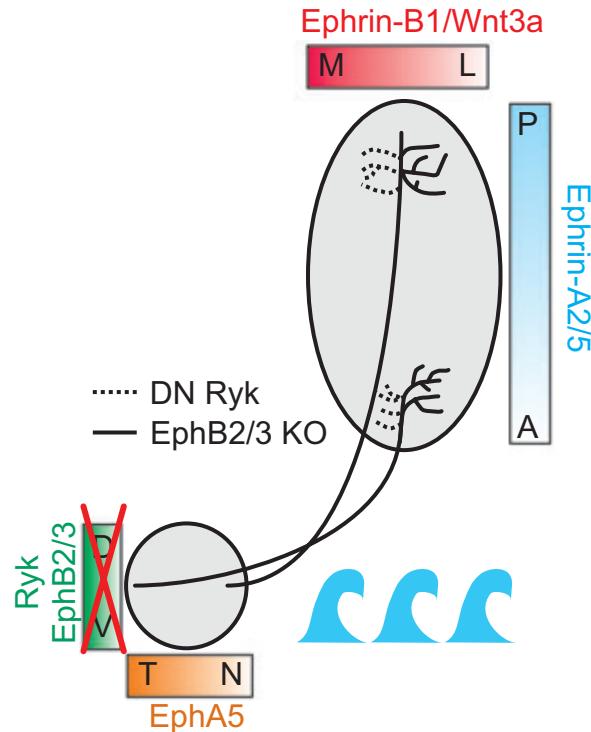


Summary for retinotopic map

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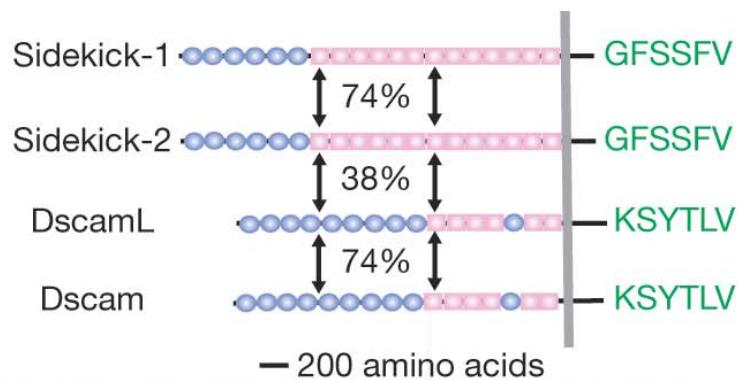


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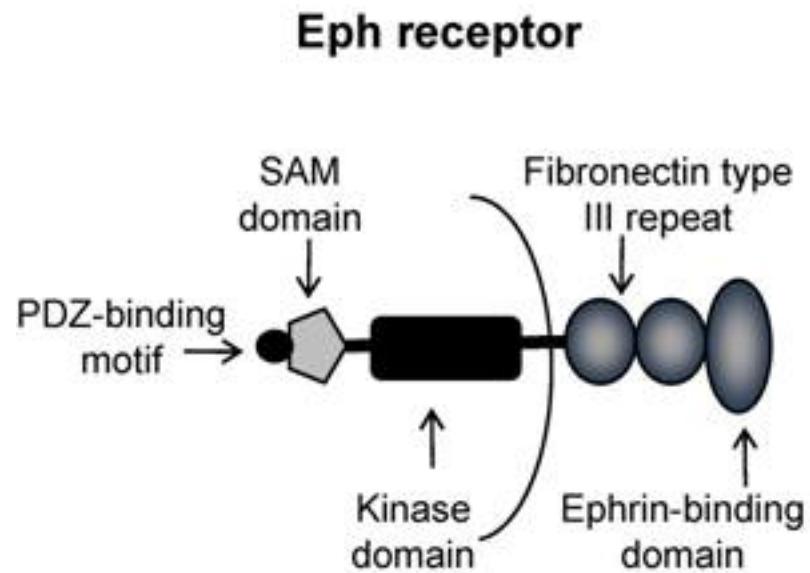


Laminar-specific guidance

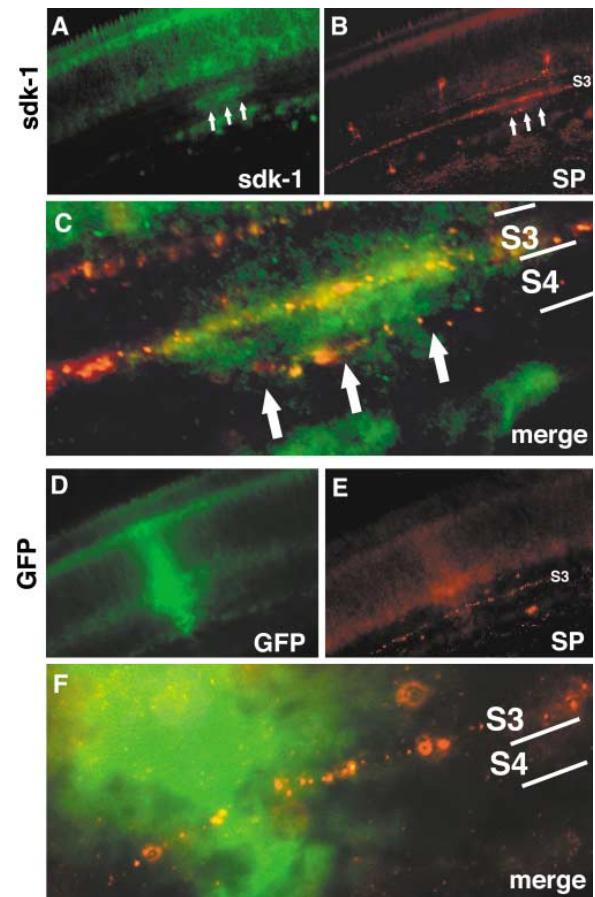
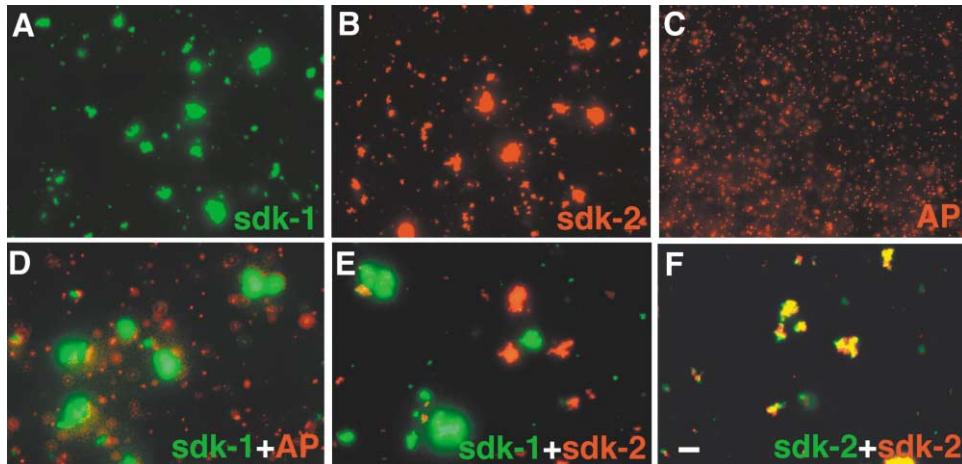
Immunoglobulin superfamily adhesion molecules – retina related



Blue: immunoglobulin domains
Pink: fibronectin type III domains
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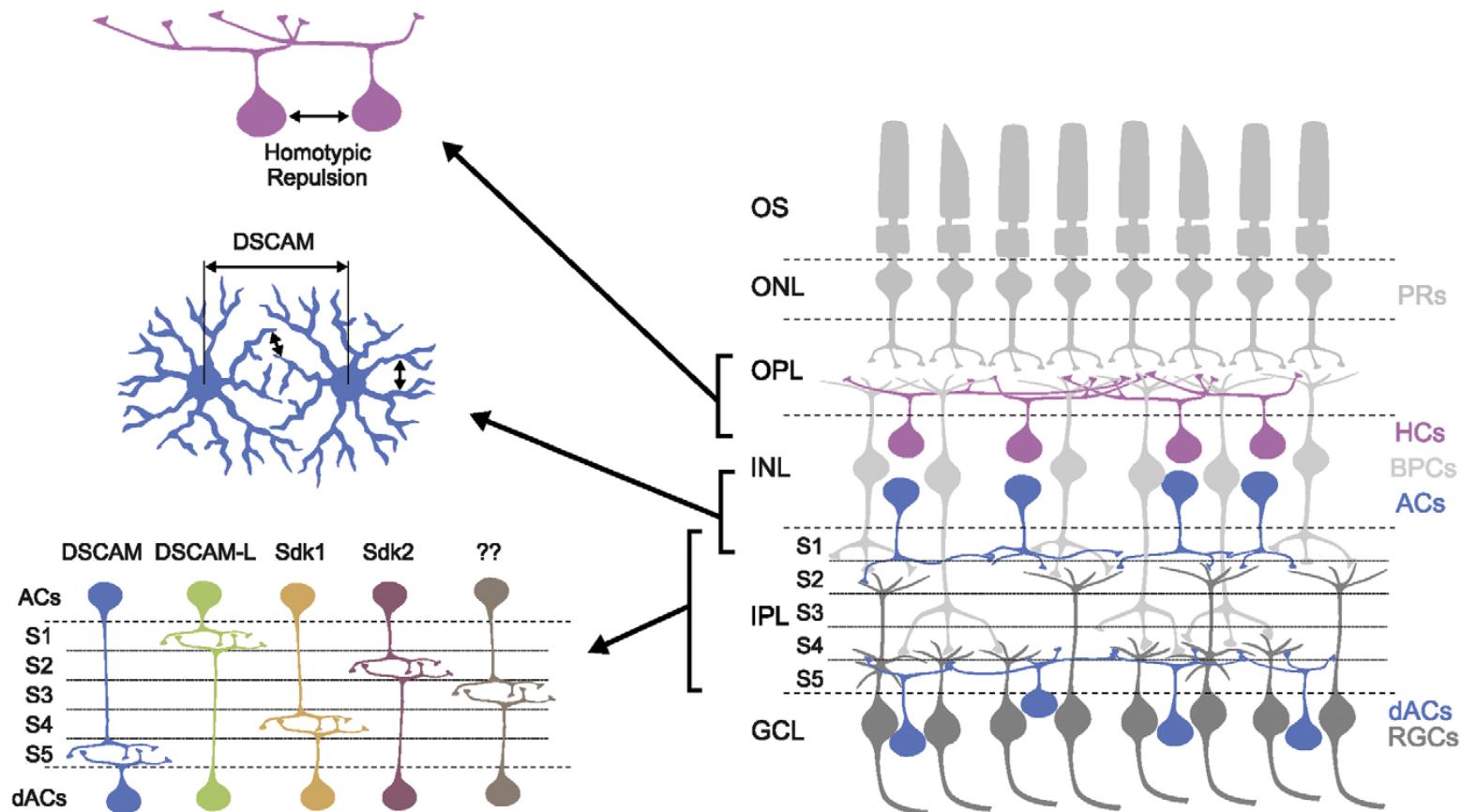


Homophilic adhesion and laminar specificity

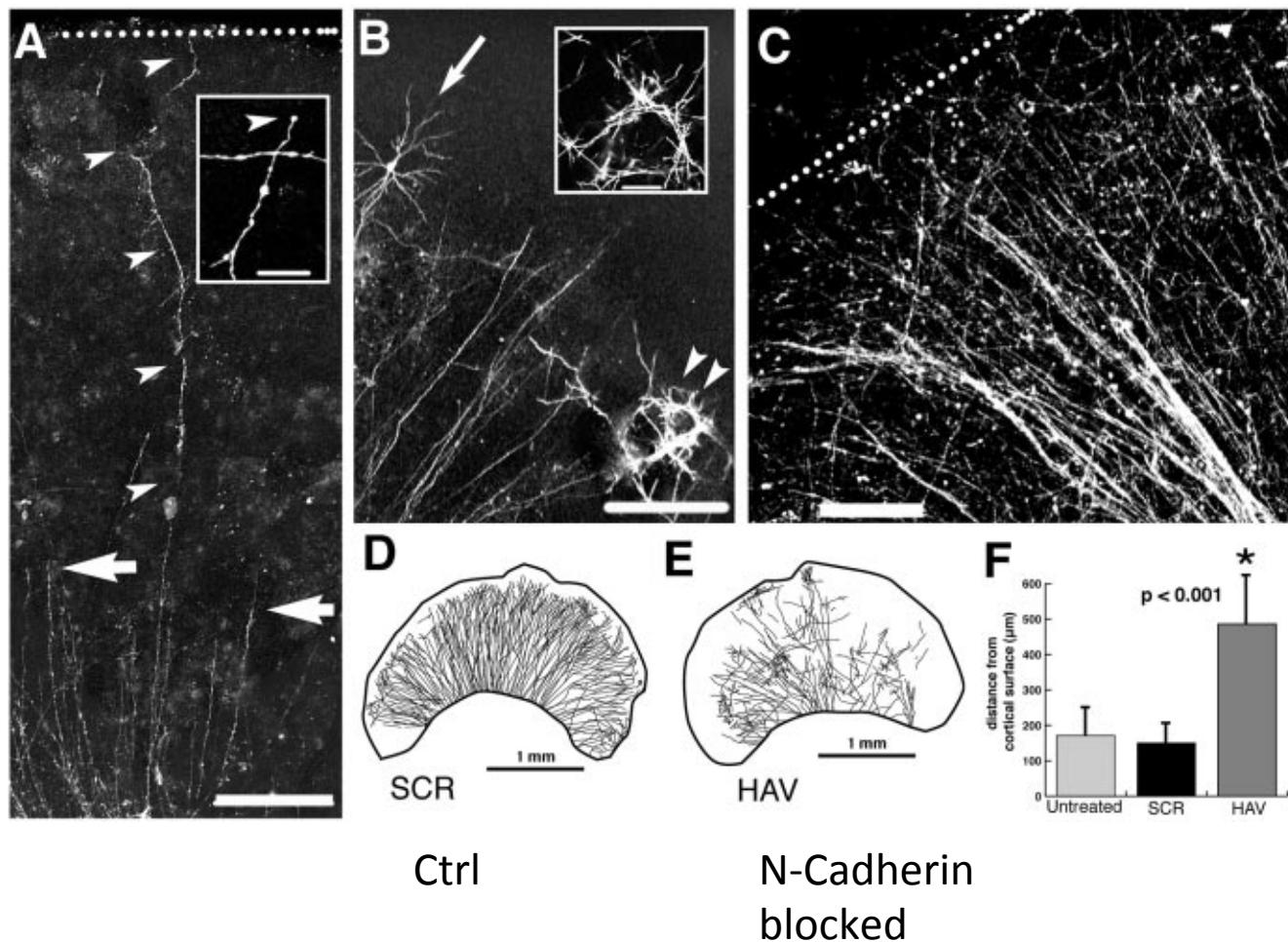


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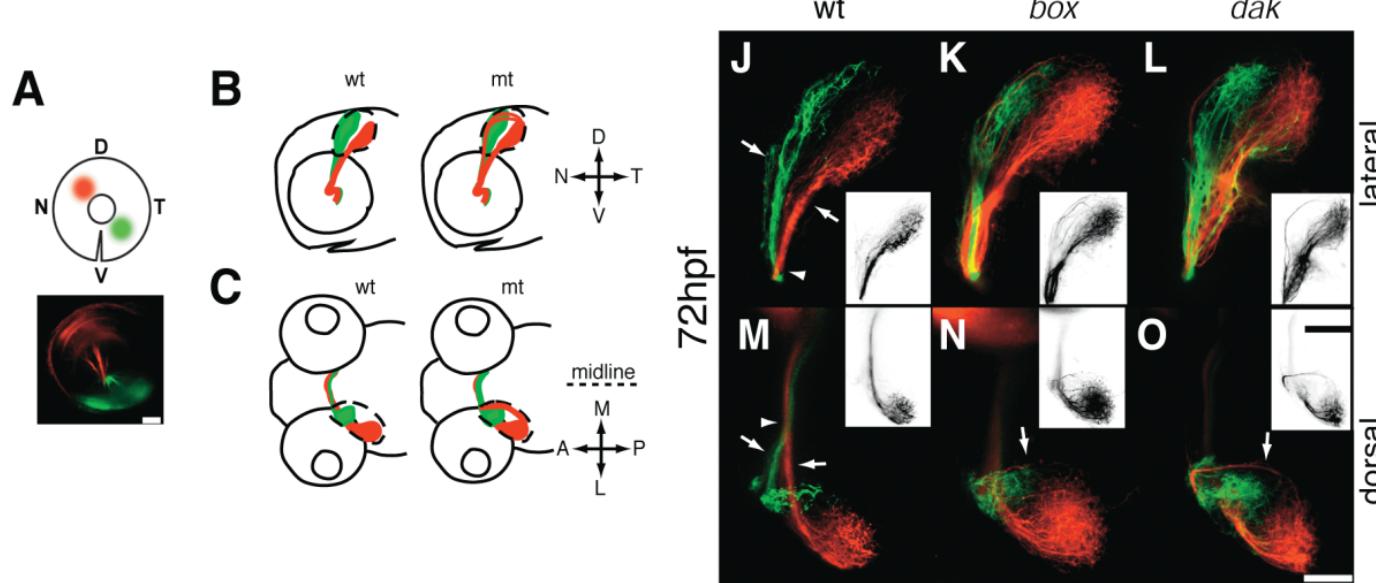
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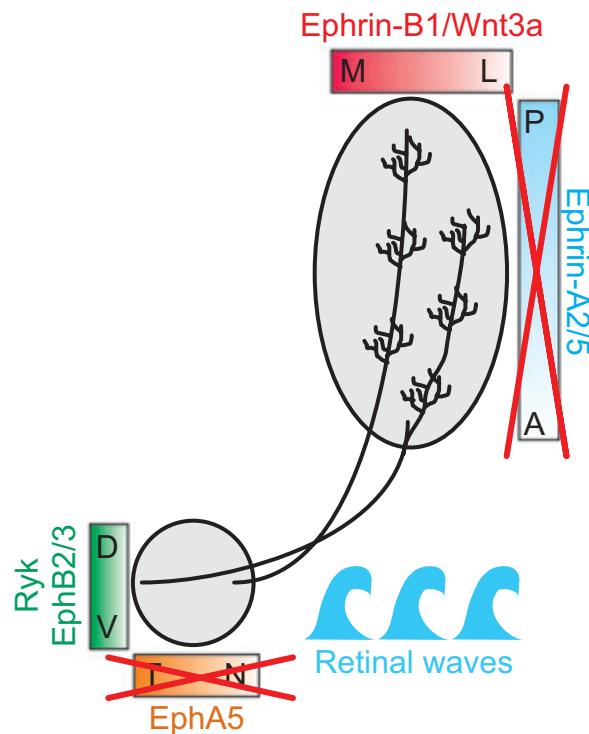
Heparan sulfate biosynthesis is necessary for axon sorting



Molecule + Activity

Molecule directs axons, activity refines arborization (?)

c Removal of Eph/rin-As



f Removal of Eph/rin-As and Stage II waves

