The role of ephrins and structured retinal activity in the development of visual map topography

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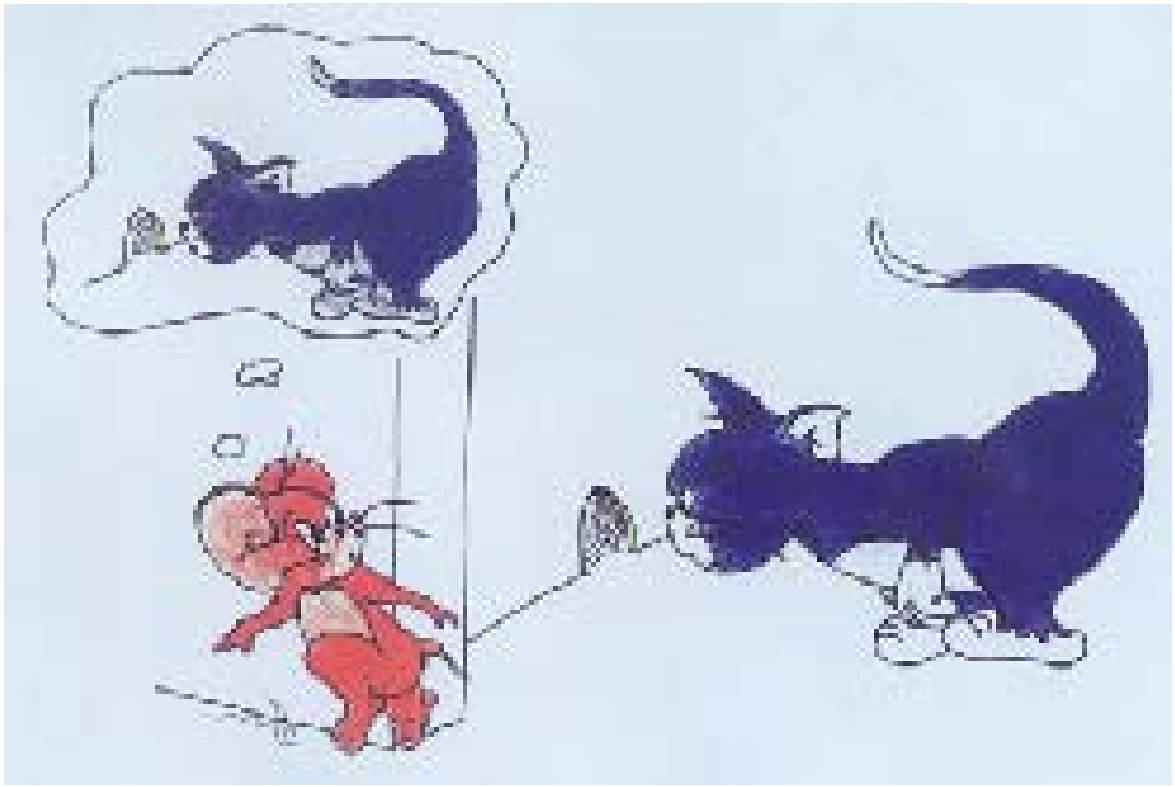
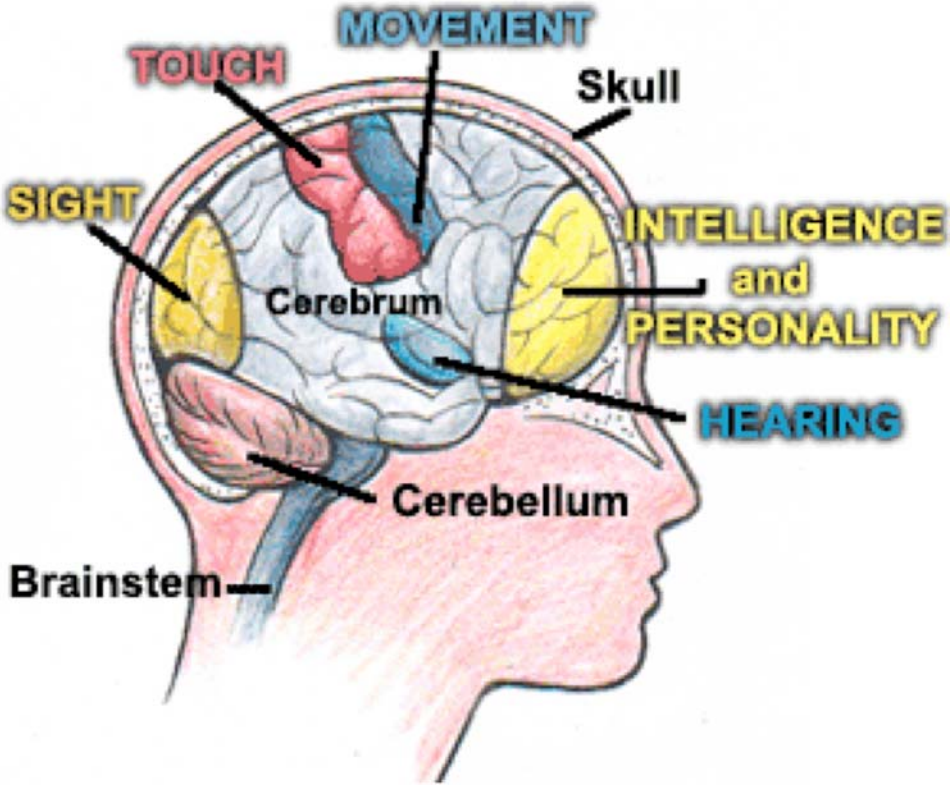
KITP Brain08 March 21, 2008

Topographic map development in the mouse visual system



The brain controls the body and mind via an intricate network of synaptic connections.



- 100 billion neurons
- Each can make multiple synaptic connections.
- Regionalized
- Parallel processing
- Sensory information eventually bound together to create "consciousness".

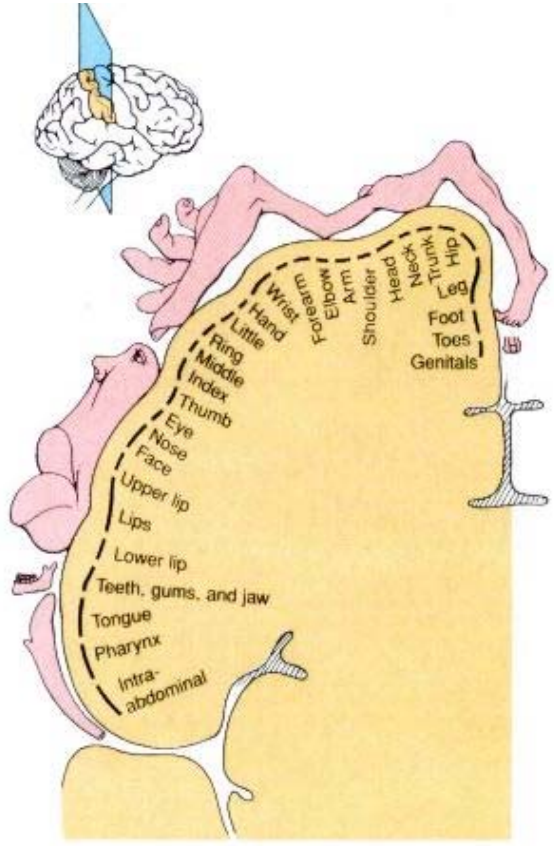
How is the brain wired up?

1. Genes (Nature)
   - brain patterning molecules
   - axon guidance cues
2. Neural activity
   - Experience-driven activity (Nurture)
   - Spontaneous activity

Somehow these two mechanisms act together. The proportion of the contributions of genetics and experience may differ between organisms, and between neural projections within the same organism.

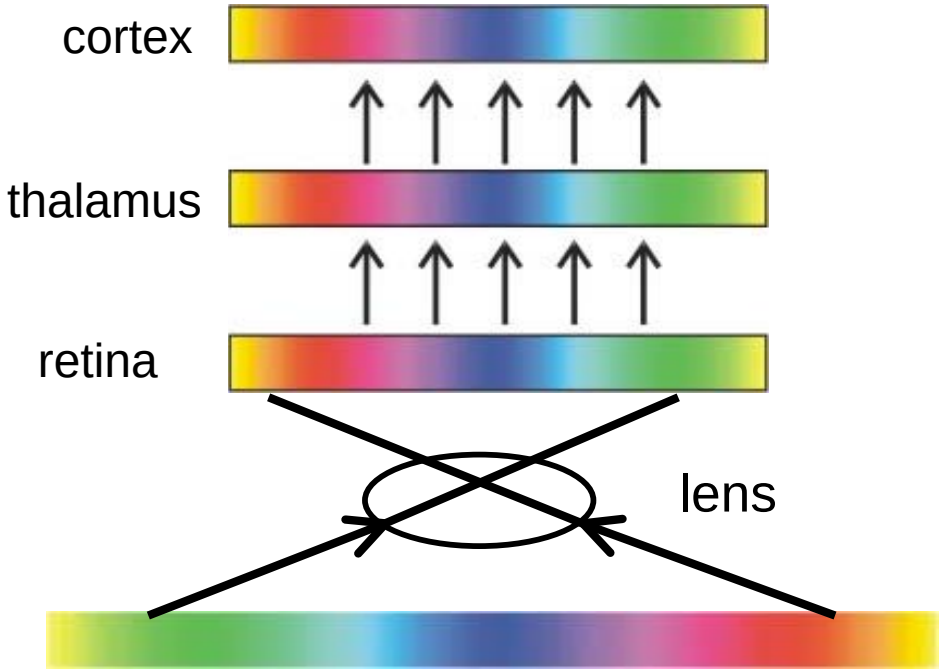
Brain connections are mapped topographically

Touch: body map



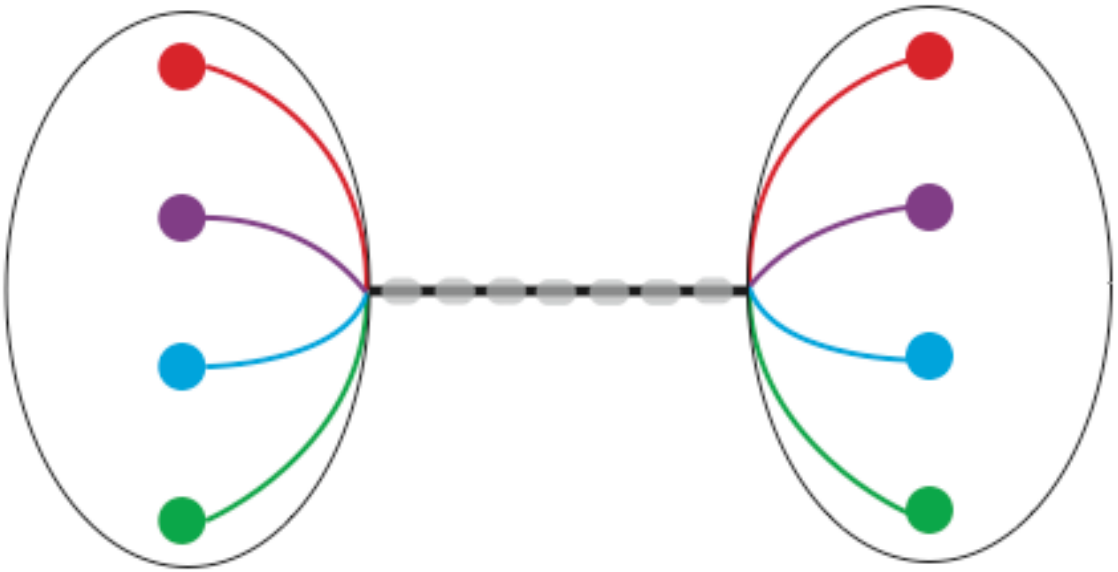
(a) Somatosensory cortex in right cerebral hemisphere

Vision: visual field map



visual field

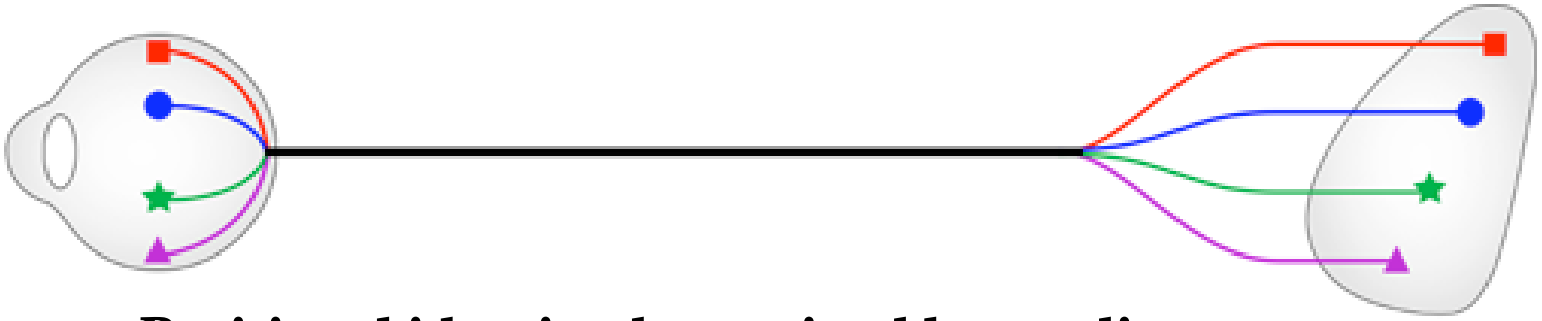
Topographic mapping



How does a neuron know its position and know where to go?

General models for topographic map formation

Positional identity determined by individual labels



Positional identity determined by gradients

Positional identity determined by neighbors

Mouse Visual System

Amenable to genetics: knockouts and transgenics

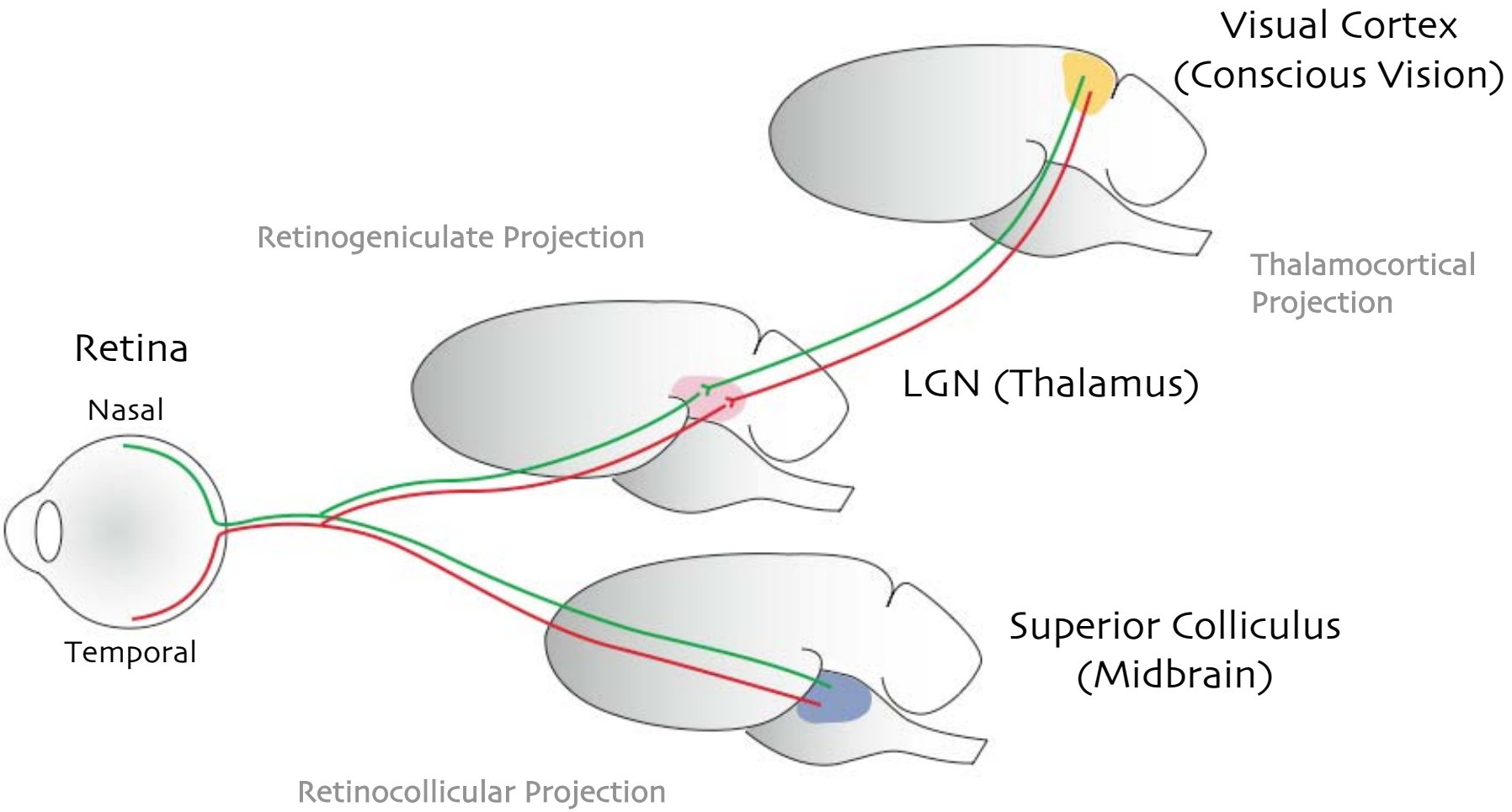
Have many of the same visual areas and connectivity patterns as humans.

Accessible to experimental manipulation.

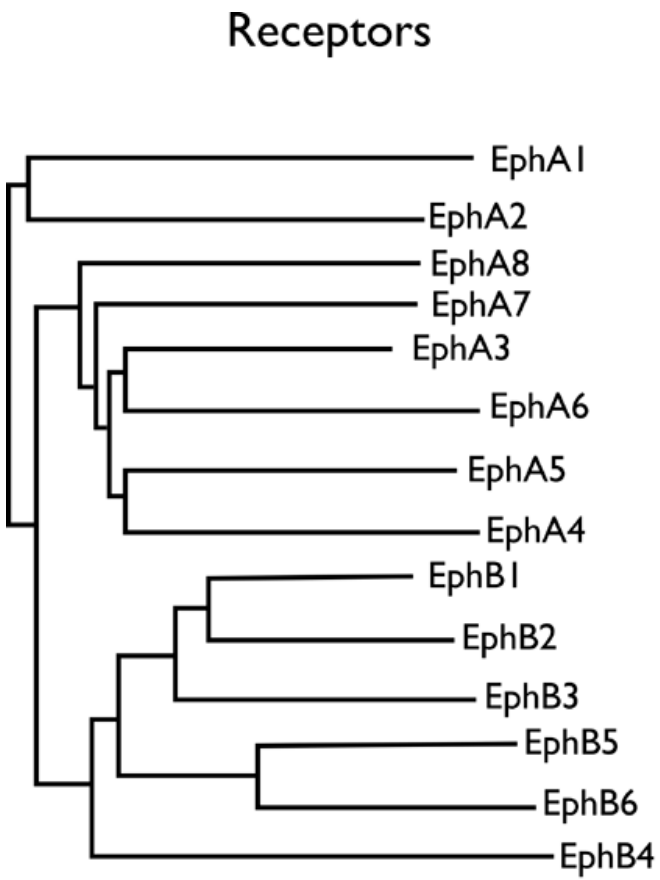
Not essential for viability.

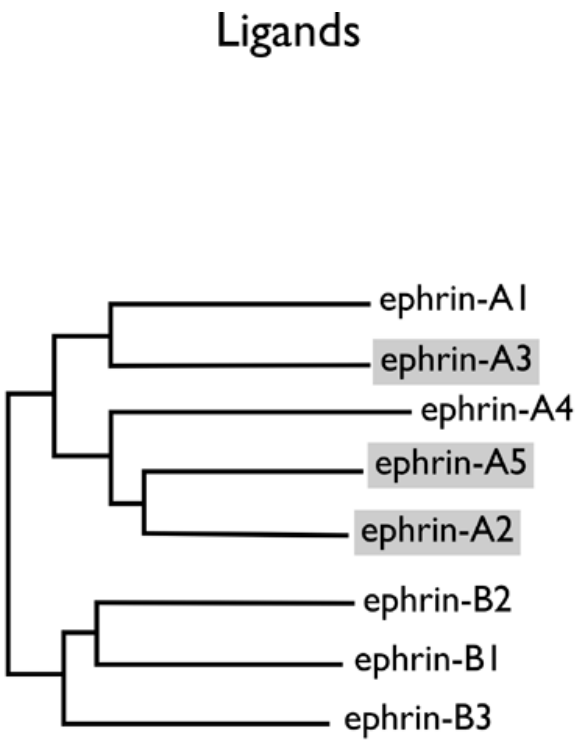
Used as a model for genetic and environmental aspects of CNS development.

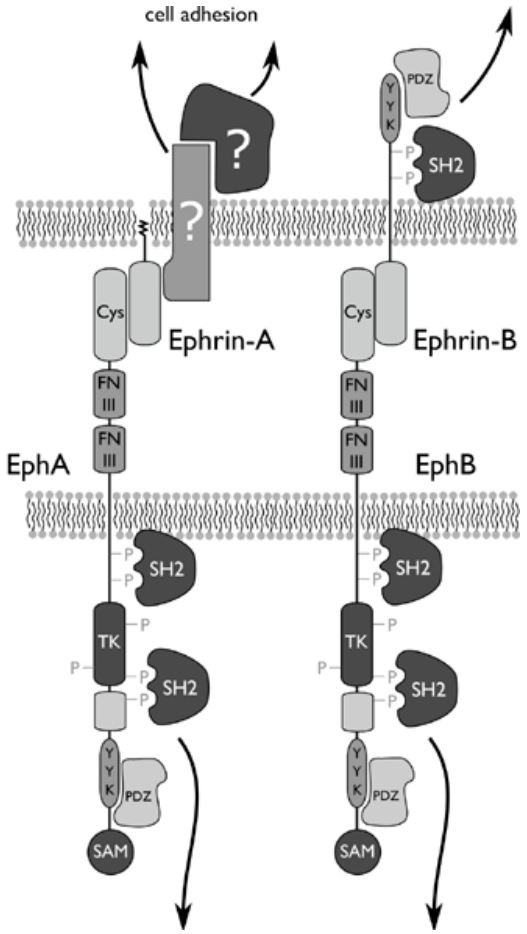
Visual Pathway in Mammals



The Eph and ephrin family of receptors and ligands







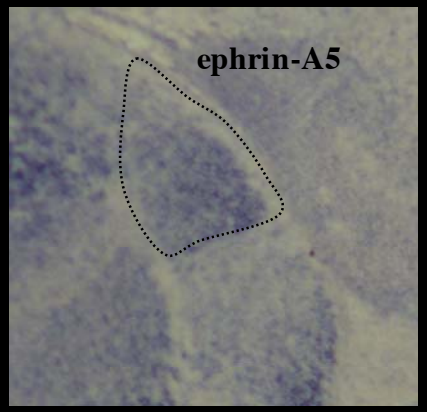
EphAs and ephrin-As in the developing mouse visual system

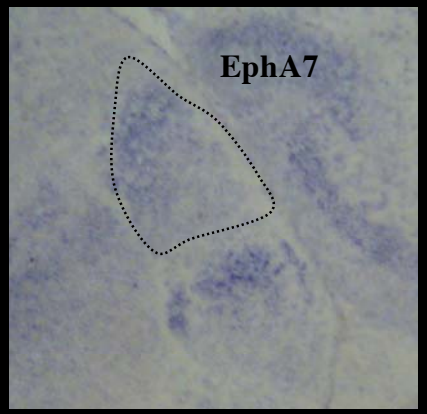
- Cell-cell contact dependent signaling molecules capable of bidirectional signaling
- Complementary gradients of expression along the N-T mapping axis in each visual area.
- Ephrin-As are target-derived repellent molecules toward EphA-bearing axons.
- Ephrin-As may also act as axon attractant molecules.
- Ephrin-As can also act as receptors for EphA bearing axons.
- Lots of redundancy

EphAs and ephrin-As are expressed in gradients within each visual area during development

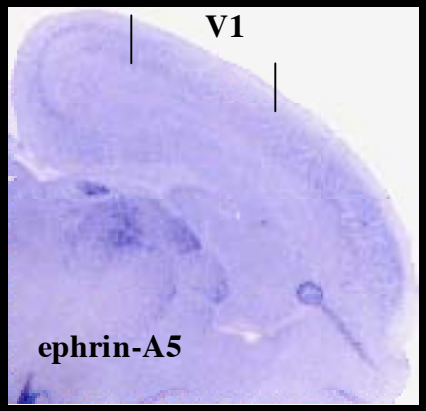
retina

LGN

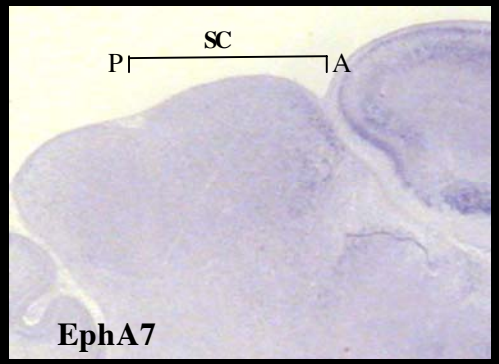


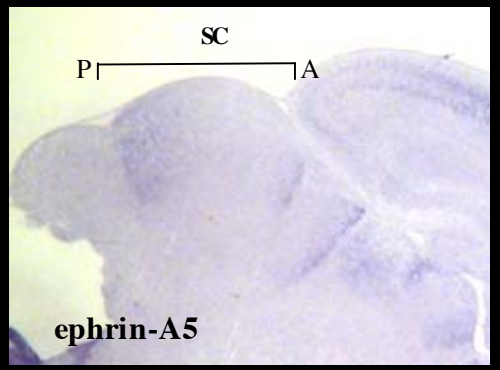


Cortex

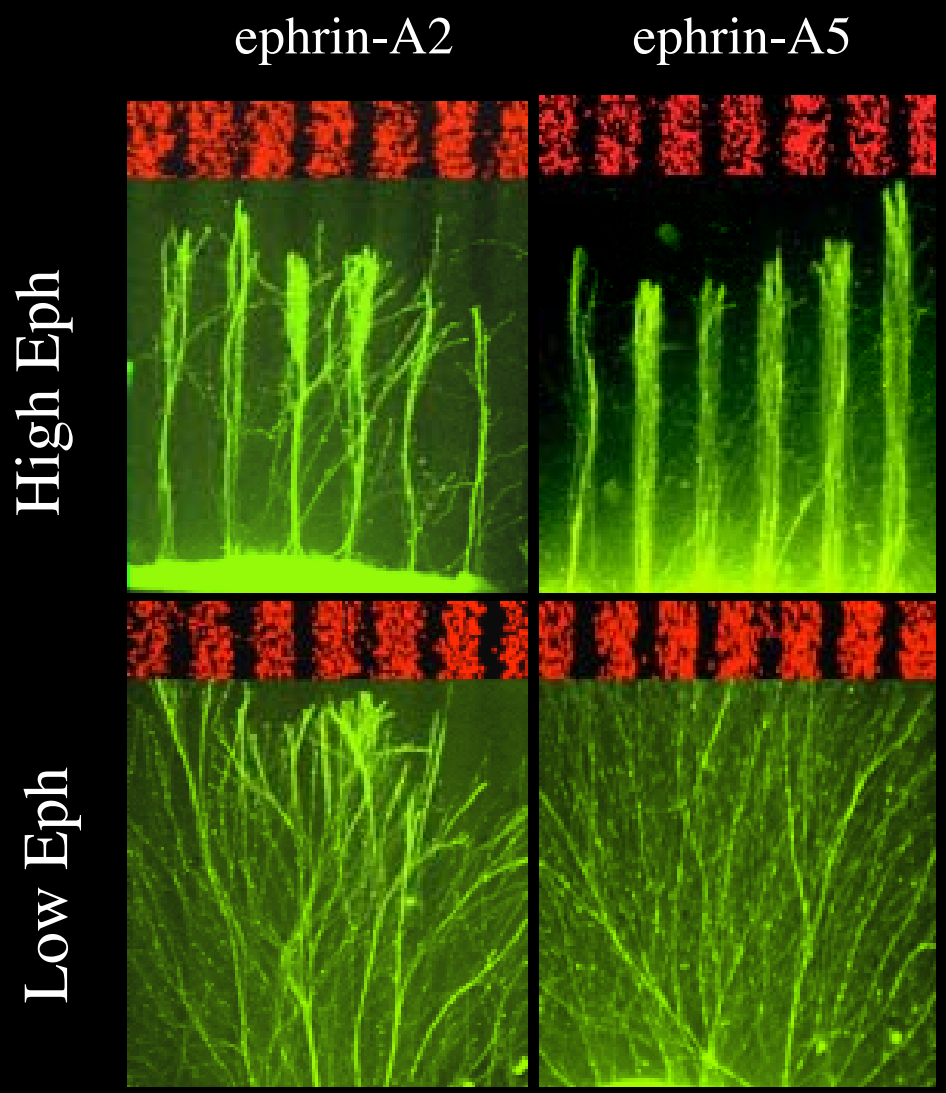


SC

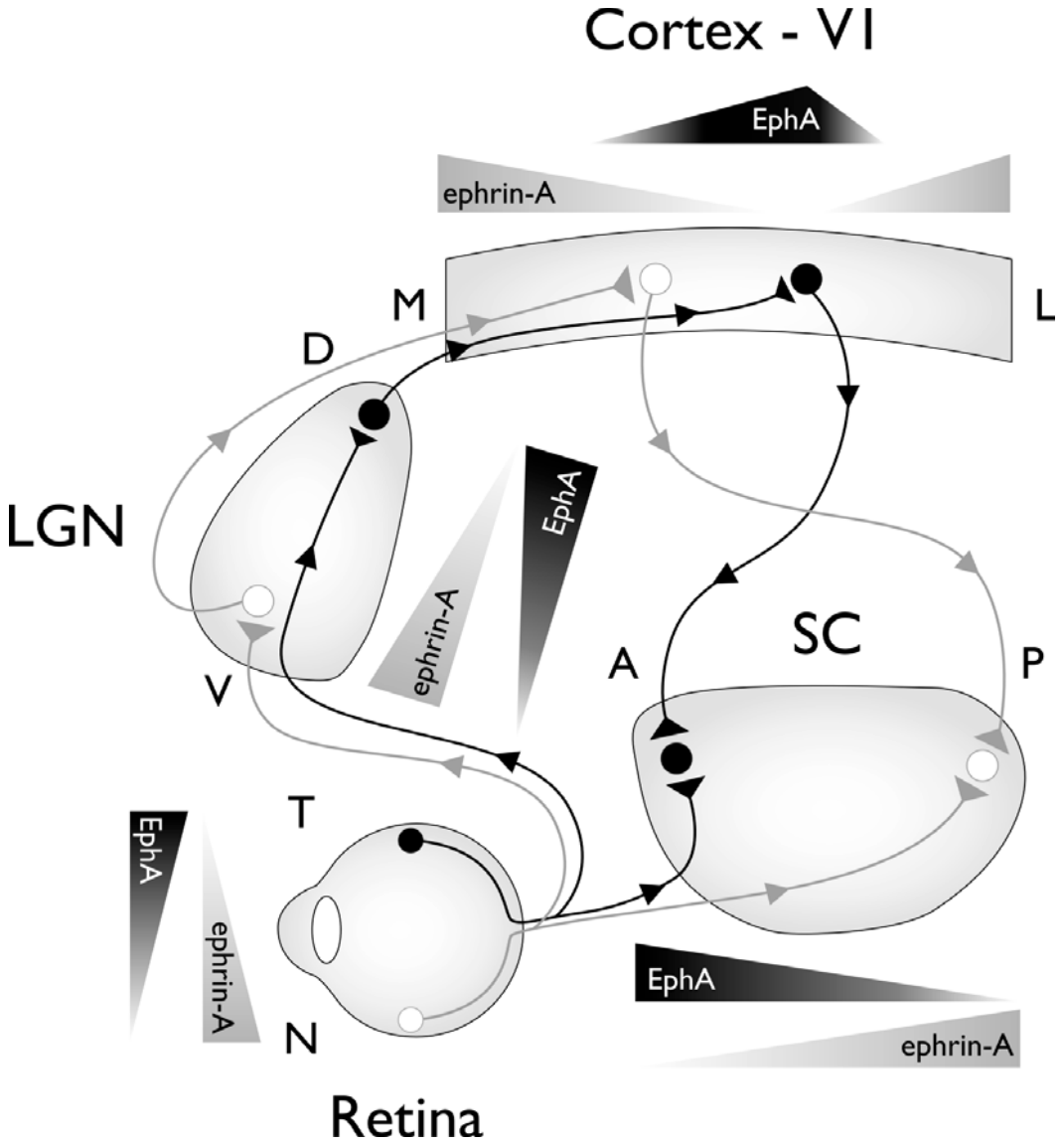




Ephrin-As are axon repellent molecules



Complementary gradients of EphAs and ephrin-As along the N-T mapping axis in the mammalian visual system.

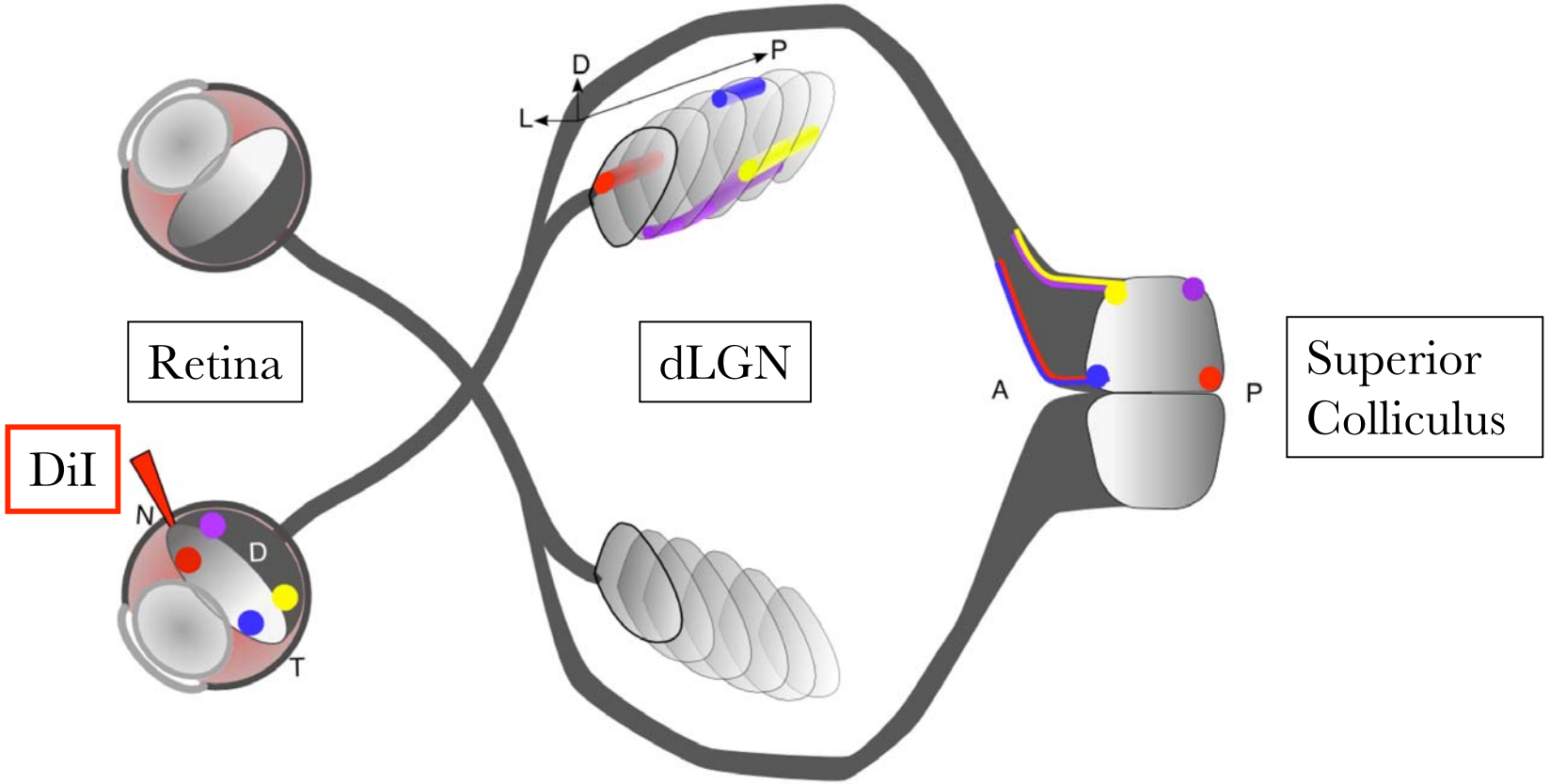


Are ephrin-As important for topographic mapping in vivo?

- Are they important for mapping at each stage of visual processing?
- Are the N-T and D-V axis mapped separately?
- Do other mapping mechanisms exist?

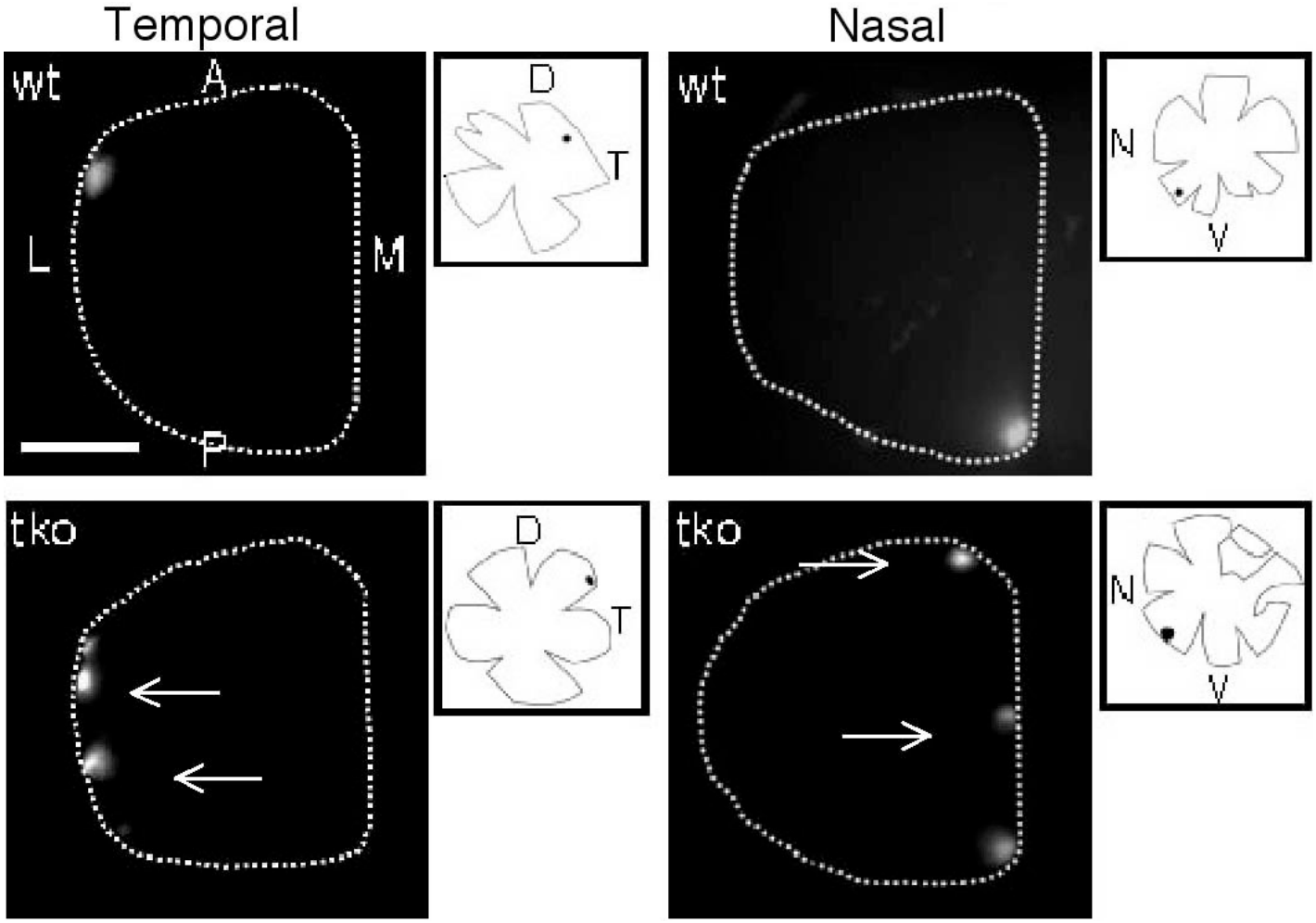
Remove them from the mouse and see what happens.

Anterograde tracing of the retinocollicular and retinogeniculate projections



- 1 DiI injection per adult mouse in 1 of 4 retinal poles.
- Single injection labels projections to the dLGN and SC (approximately 10-50 RGCs).
- Adult mice (older than P40) were analyzed to focus on mapping defects that cannot be compensated for by further development or visual experience.

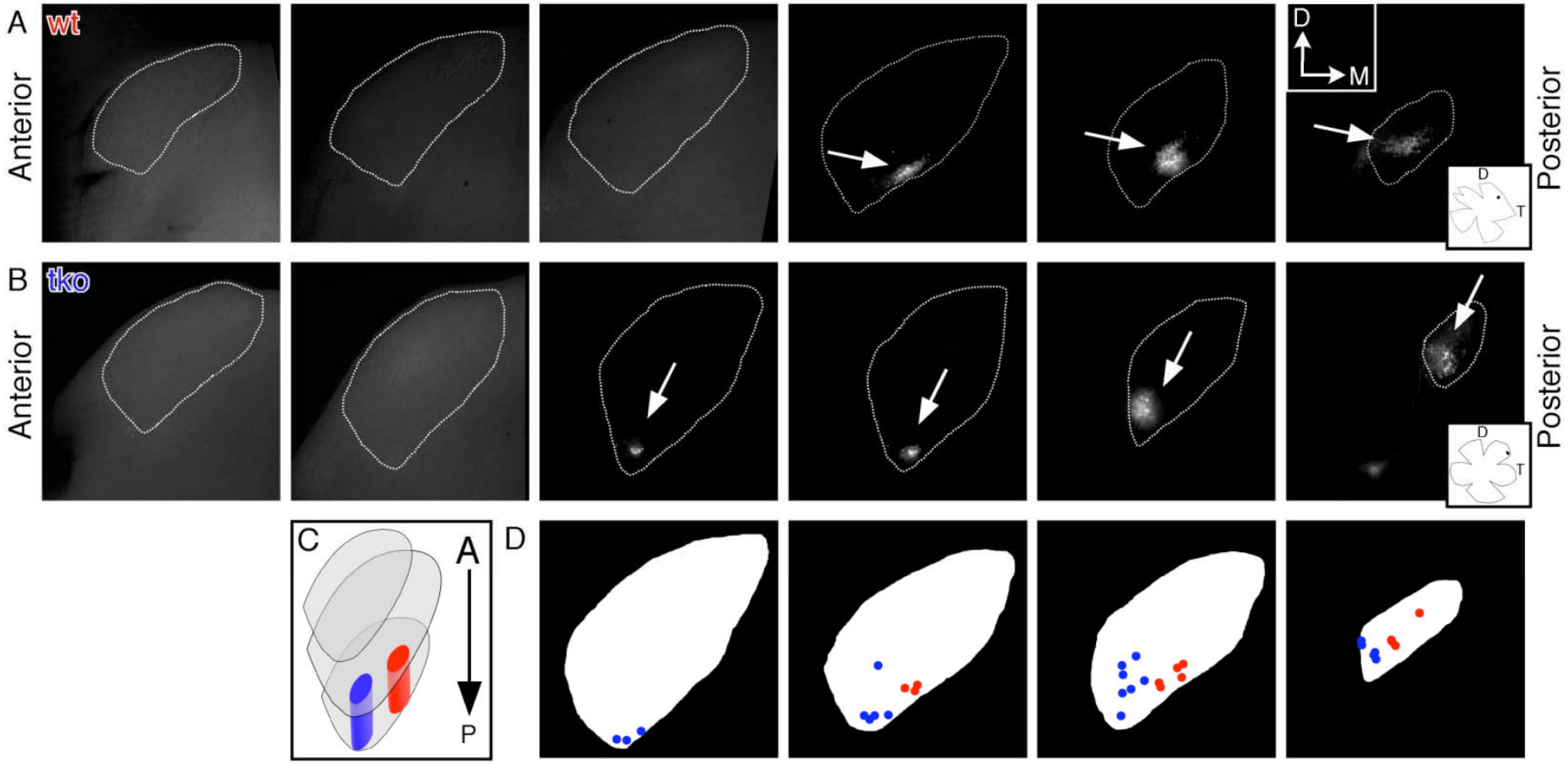
Ephrin-A2/A3/A5 tko mice have anatomical mapping defects in the retinocollicular projection.



Pfeiffenberger et al. J. Neurosci 2006

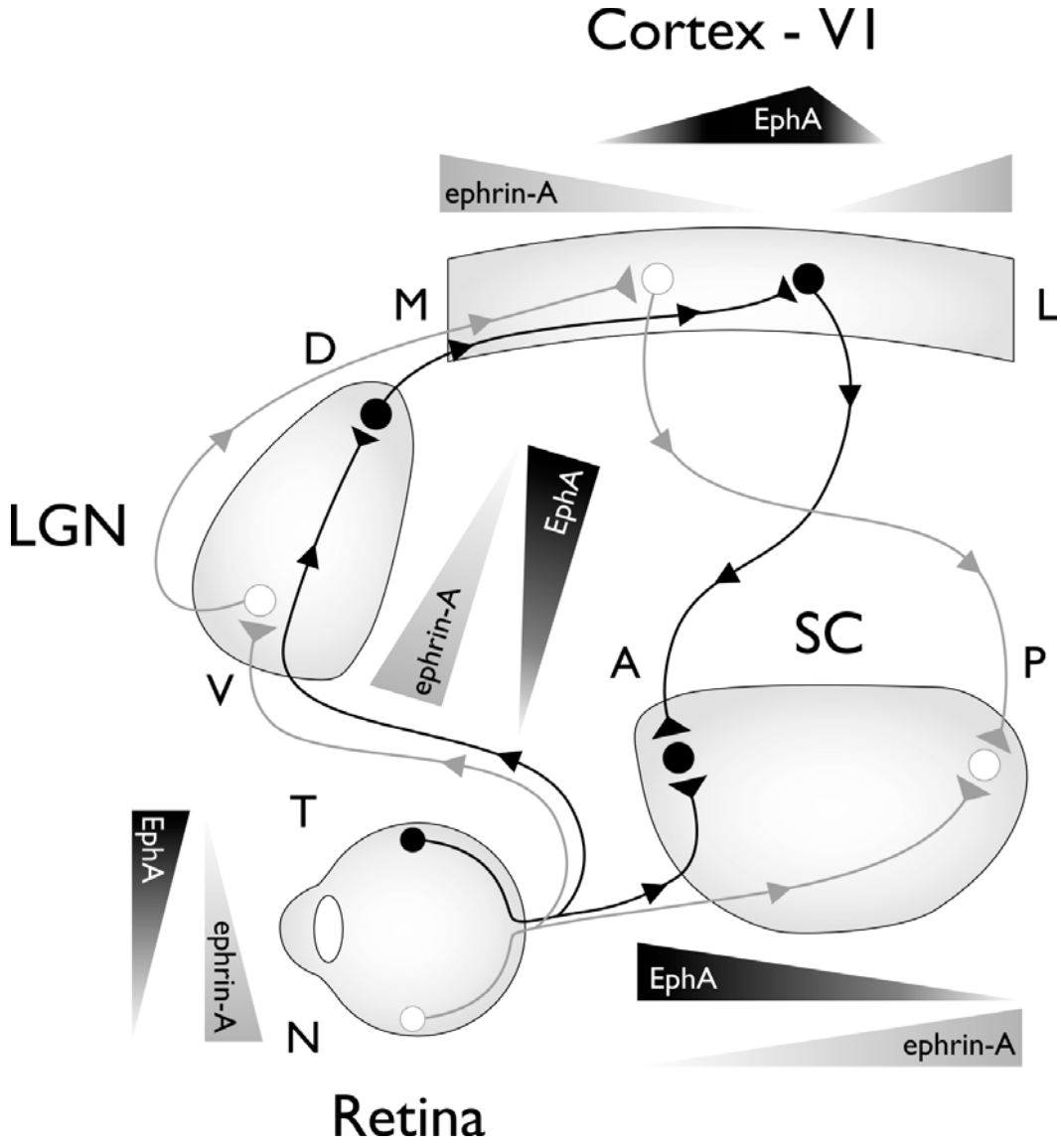
The topography of the retinogeniculate projection is disrupted in ephrin-A2/A3/A5 tko mice (but not as much as in the retinocollicular projection).

temporal retinal injection

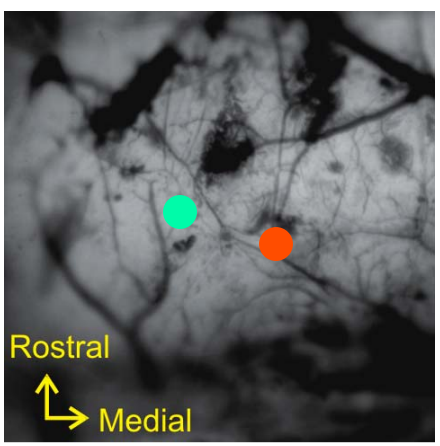


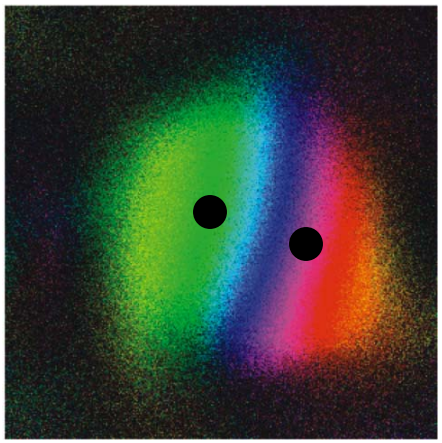
Pfeiffenberger et al. J. Neurosci 2006

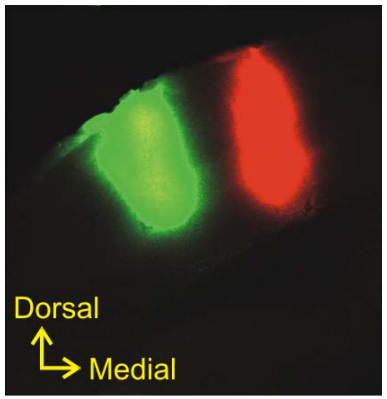
Are ephrin-As also required for the formation of topographic maps in the cortex?



Retrograde labeling of the Geniculocortical Projection

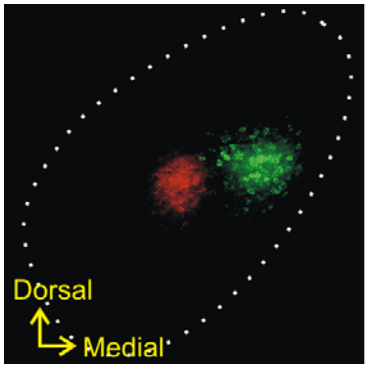


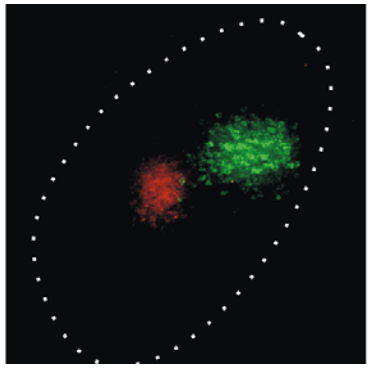


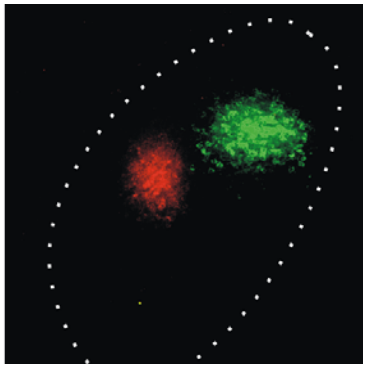


1 mm

1 mm

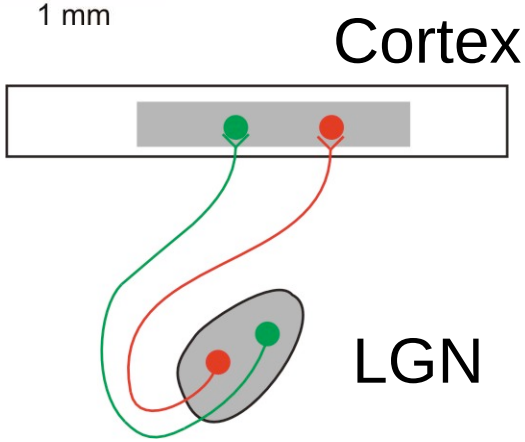






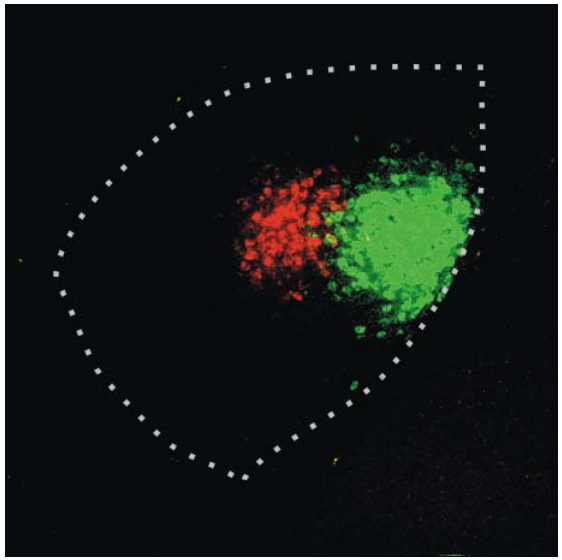
200 µm

Rostral ⟷ Caudal

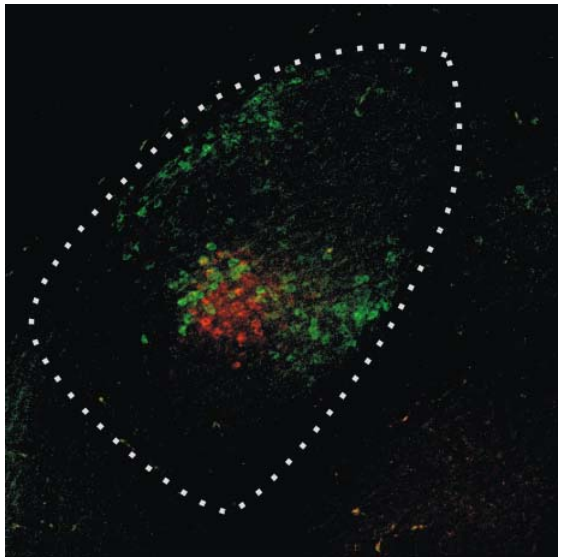


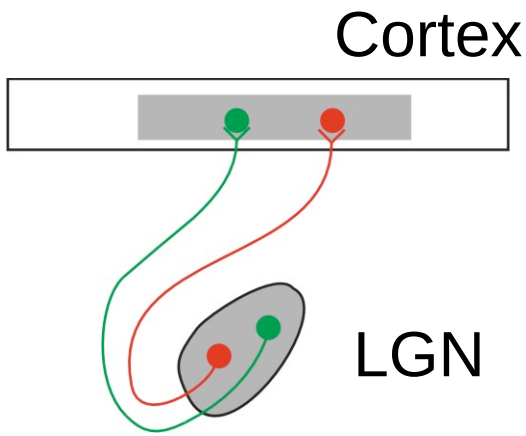
Abnormal Geniculocortical Mapping in ephrin-A2/A3/A5 TKO mice

WT



TKO





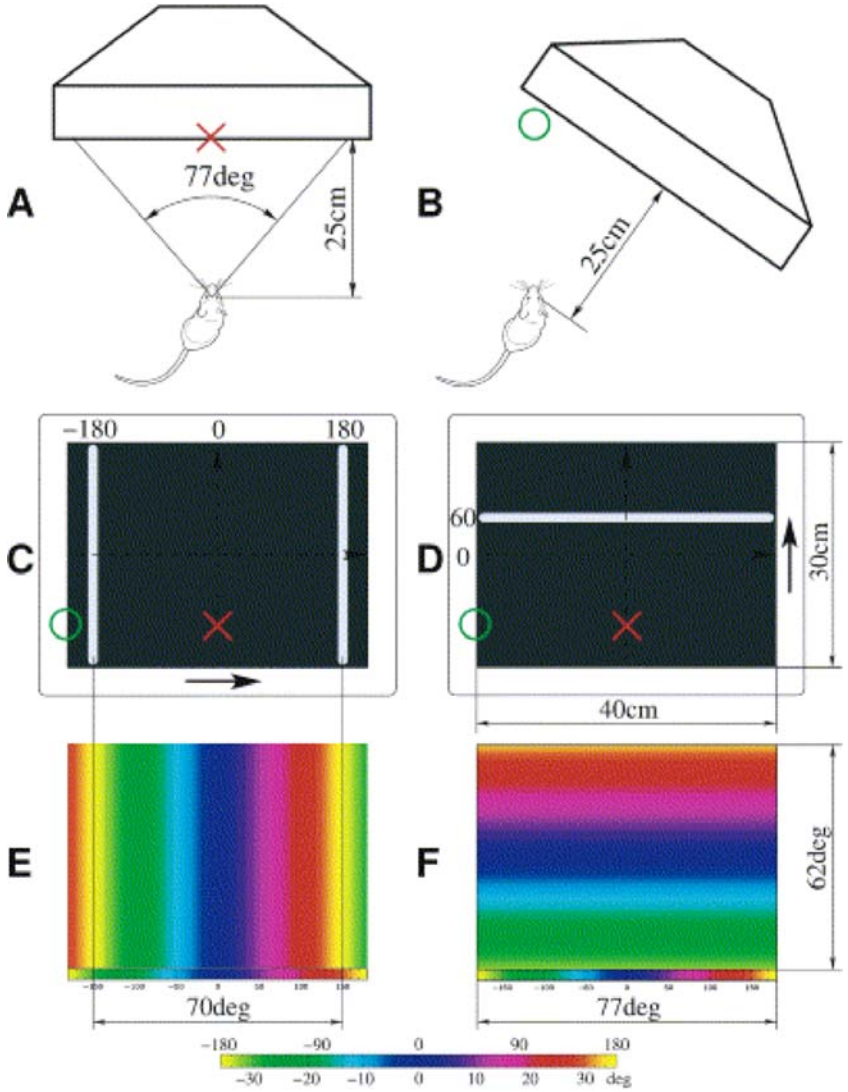
Cang et al. Neuron 2005

What do the mice see?

Neurotechnique

New Paradigm for Optical Imaging
Temporally Encoded Maps of Intrinsic Signal

Valery A. Kalatsky and Michael P. Stryker, 2003



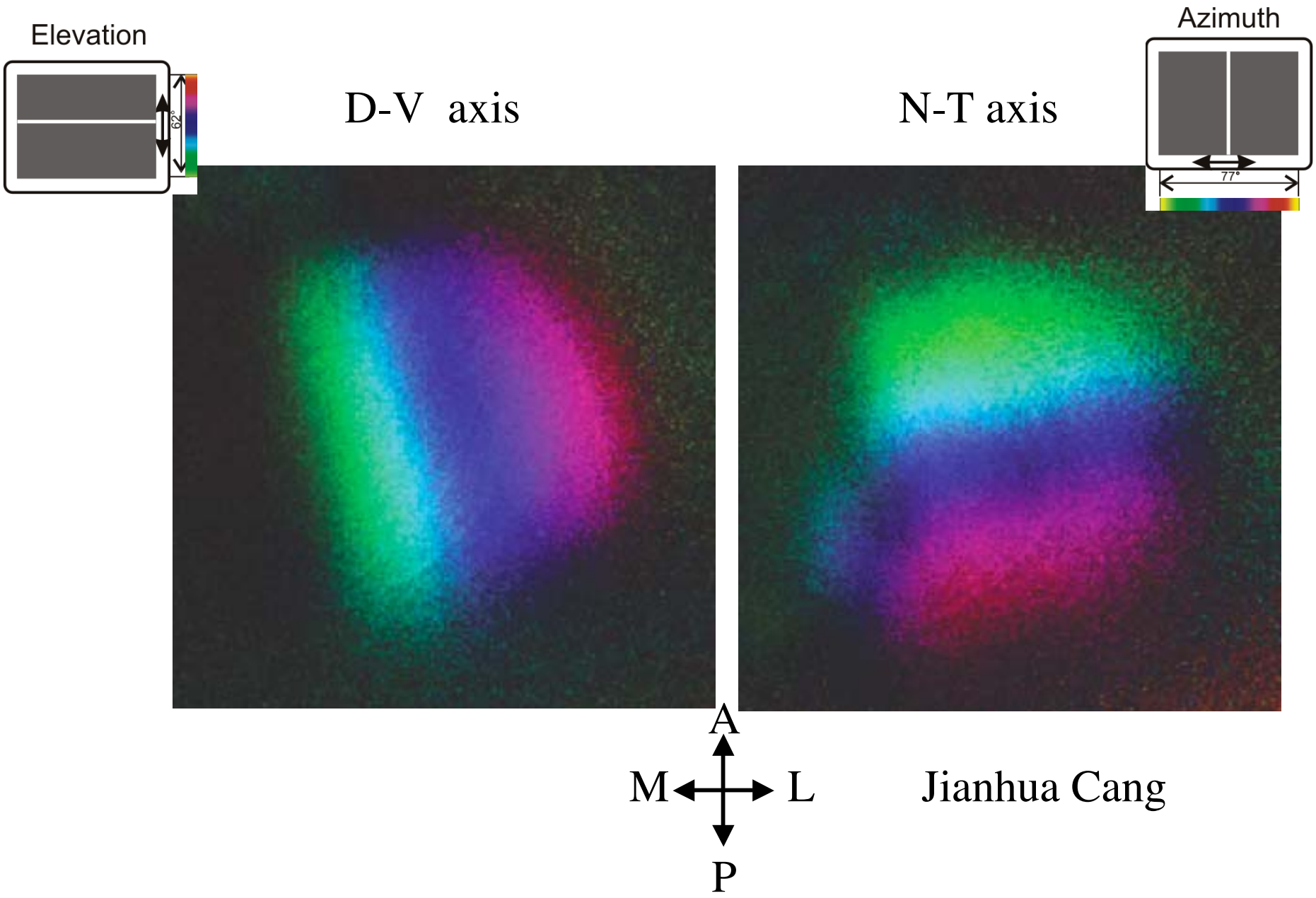
Measures changes in cortical light reflectance following local neural activation.

Reflectance changes due to changes in blood oxygenation levels.

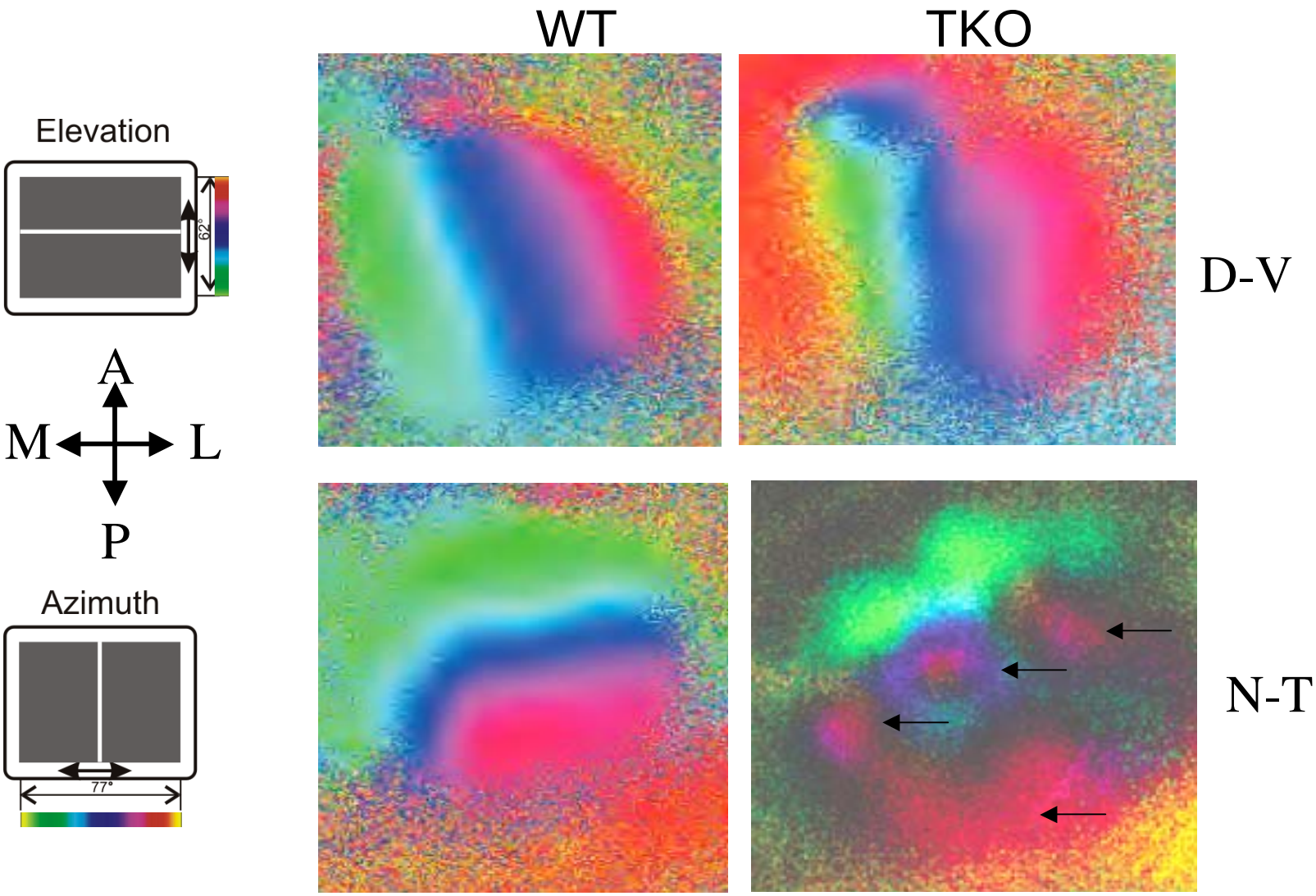
More active areas absorb more light.

Measures peak activity of large groups of neurons

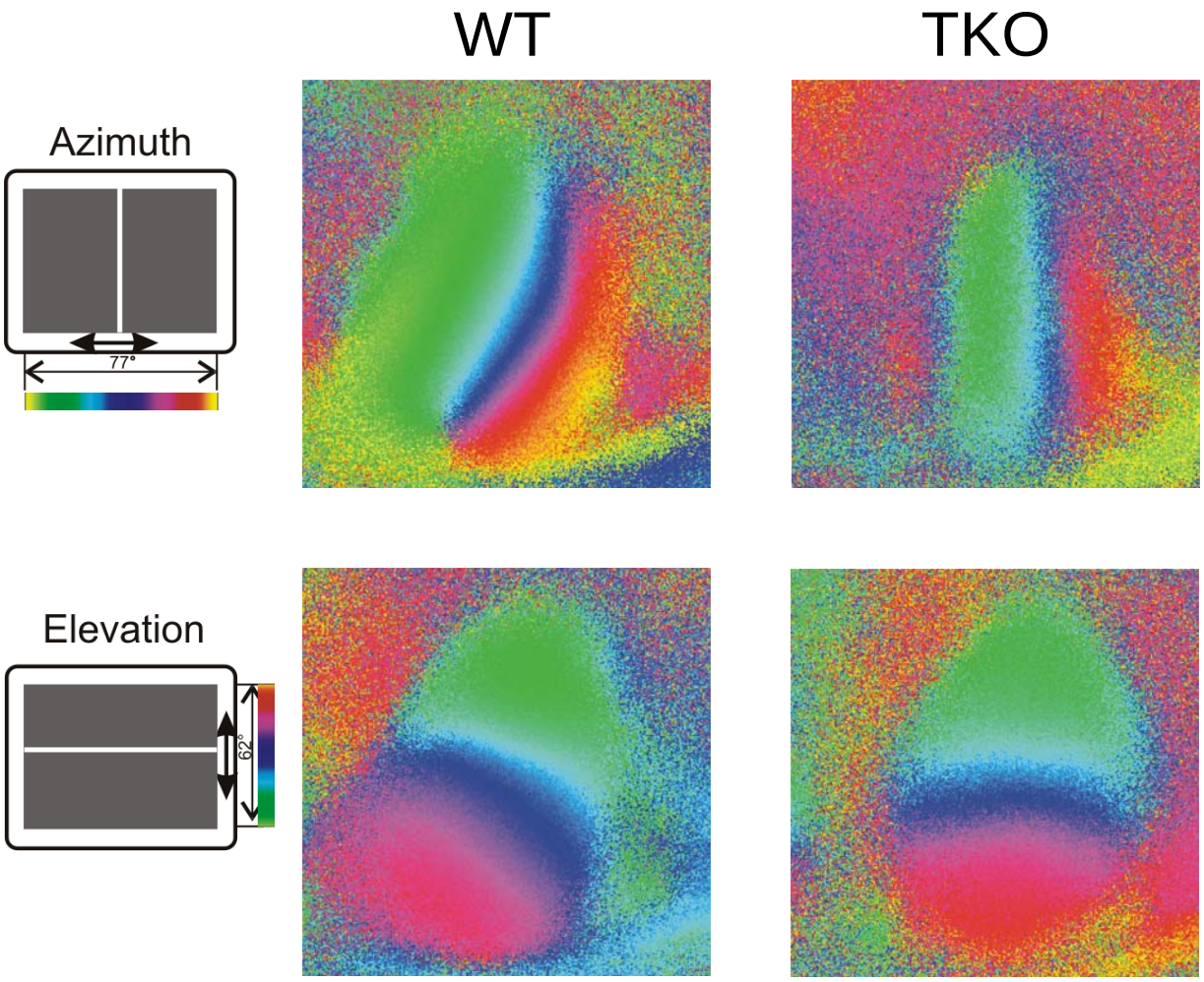
Intrinsic optical imaging of the SC map in adult mice



“Patchy” functional maps of ephrin-A2/A3/A5 tkos in the SC



Minor defects in functional cortical topography in ephrin-A2/A3/A5 tko mice

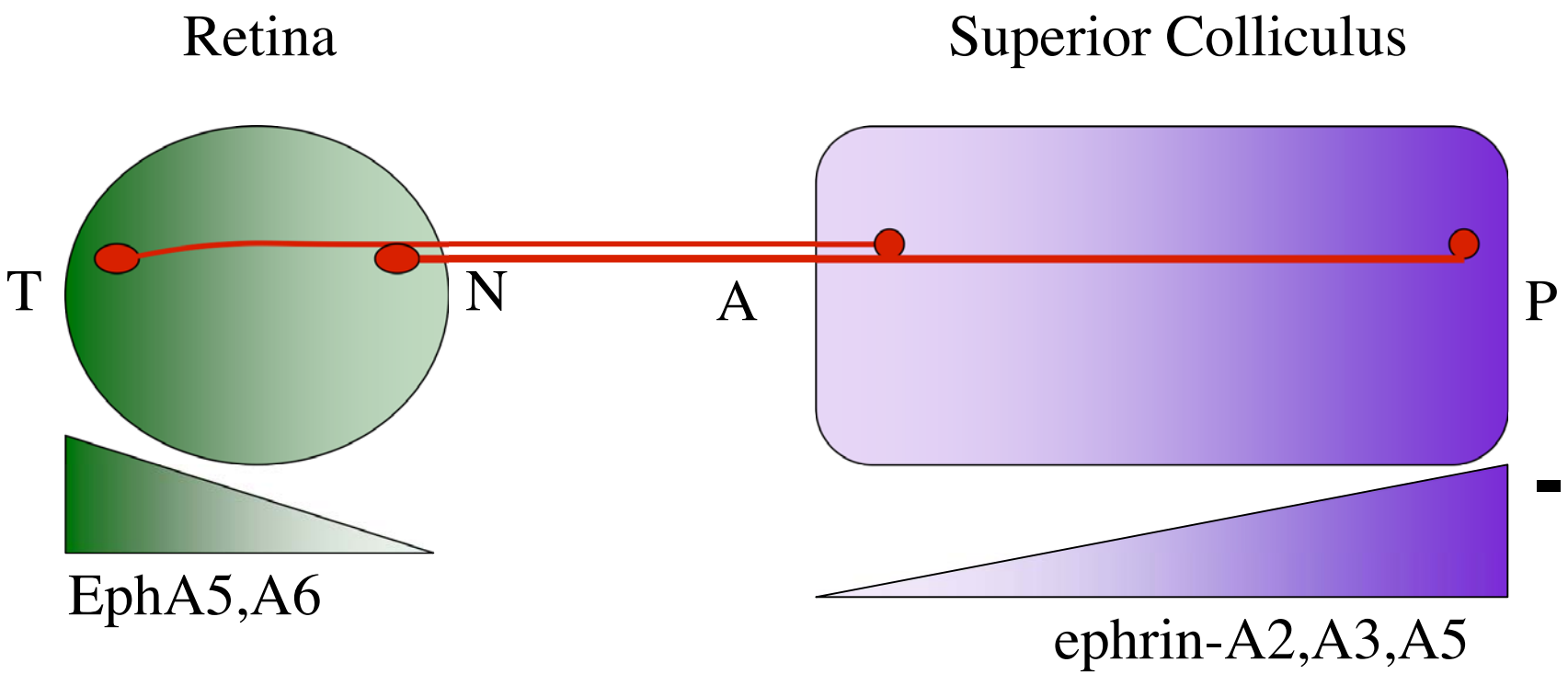


Cang et al. Neuron 2005

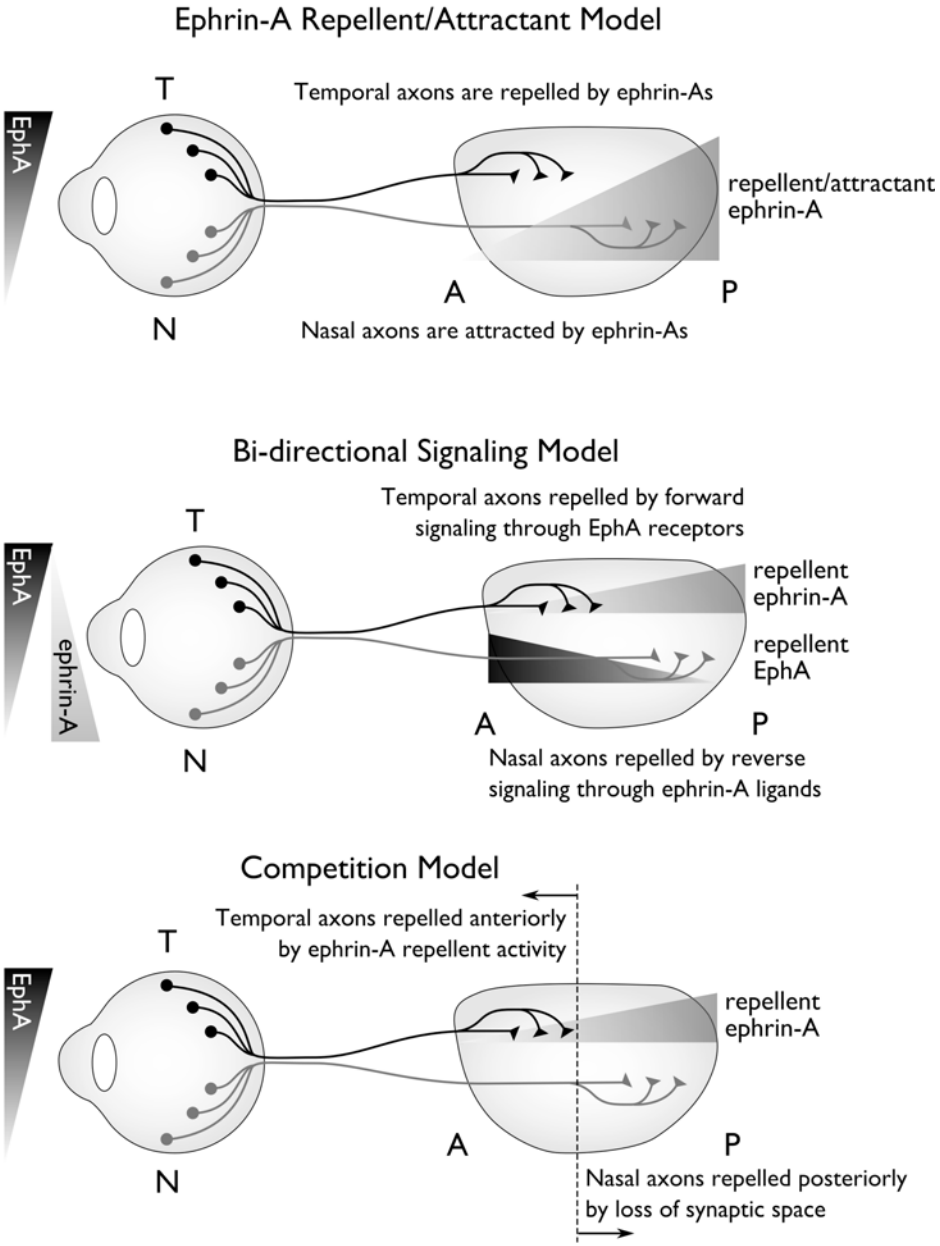
Conclusions- Part 1

- Ephrin-As are required for topographic mapping in each visual area.
- The retinal collicular map seems to require ephrin-As more than the geniculate and cortical maps.
- Some positional information remains even in ephrin-A2/A3/A5 triple mutants.

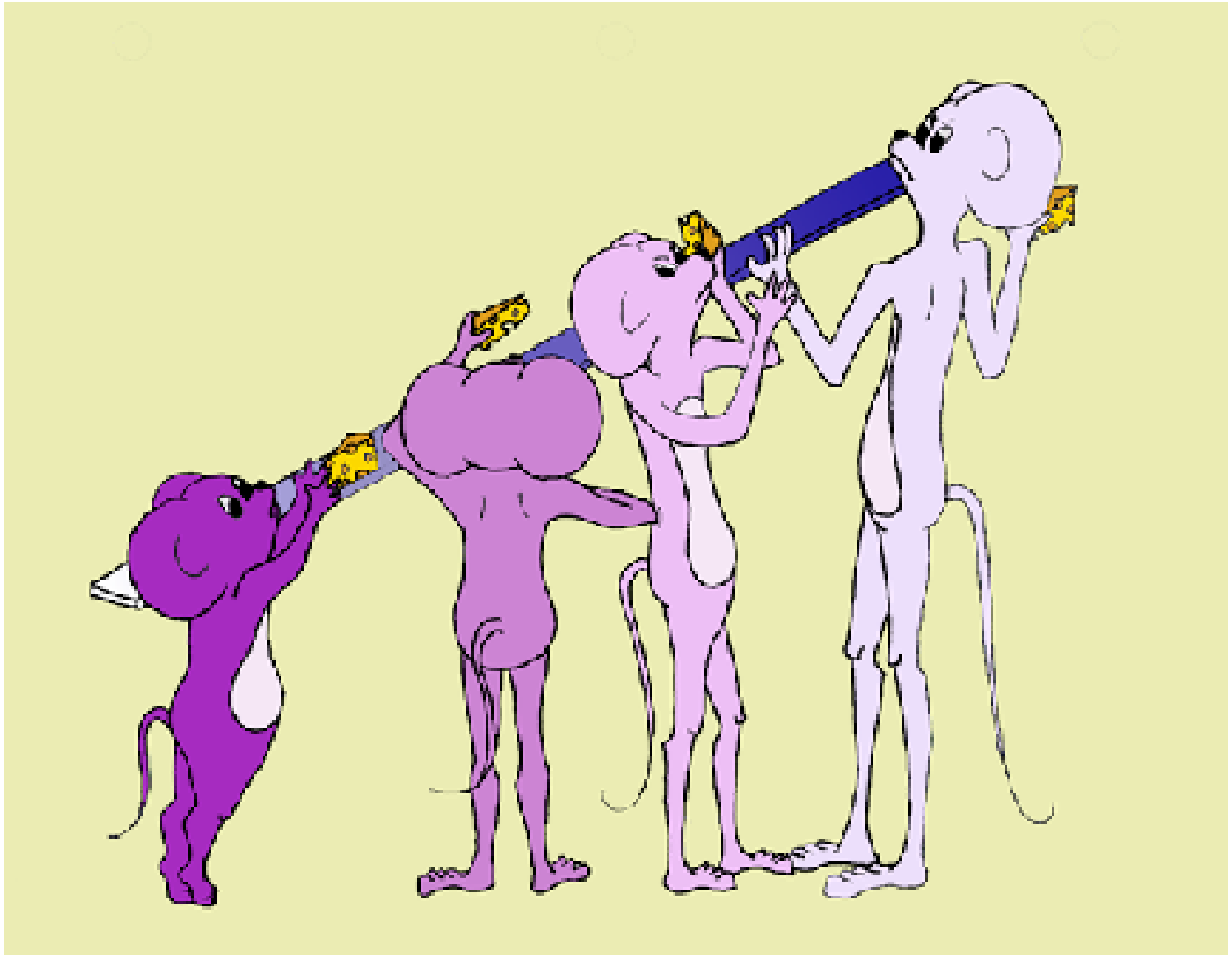
Why do nasal axons make mapping errors in ephrin-A mutants?



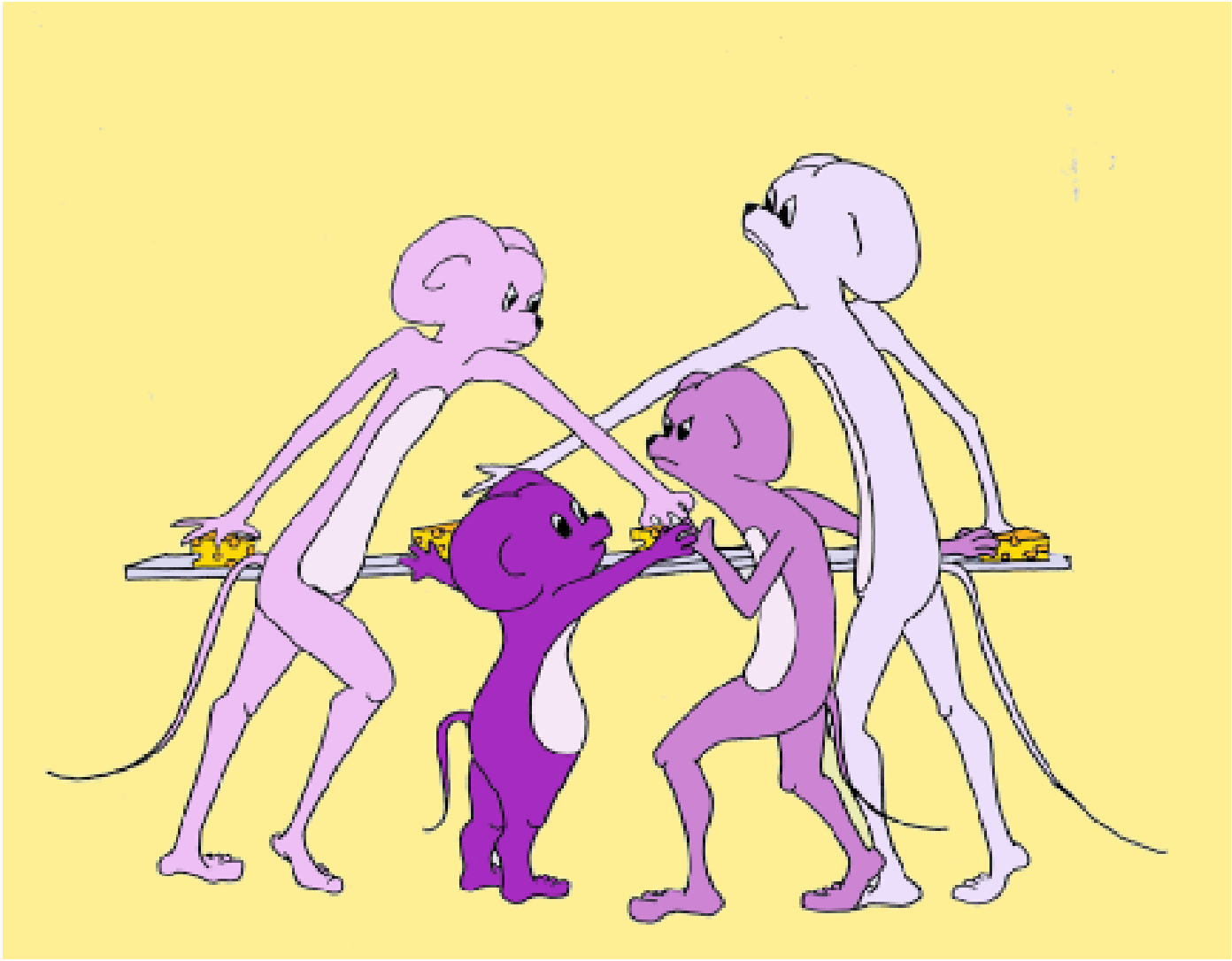
Why do nasal axons make mapping errors in ephrin-A mutants?



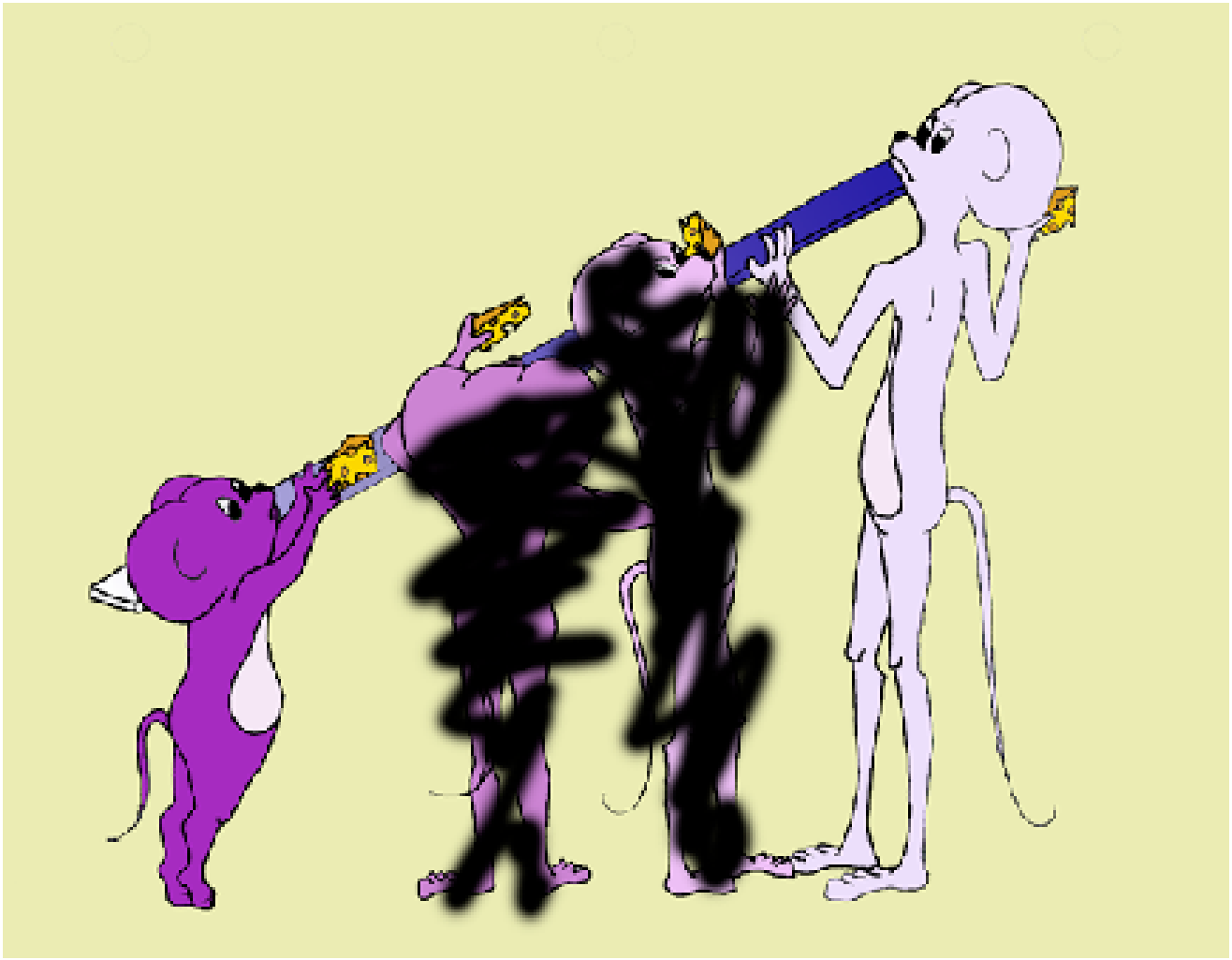
Biased competition



Competition only



Decreased competition



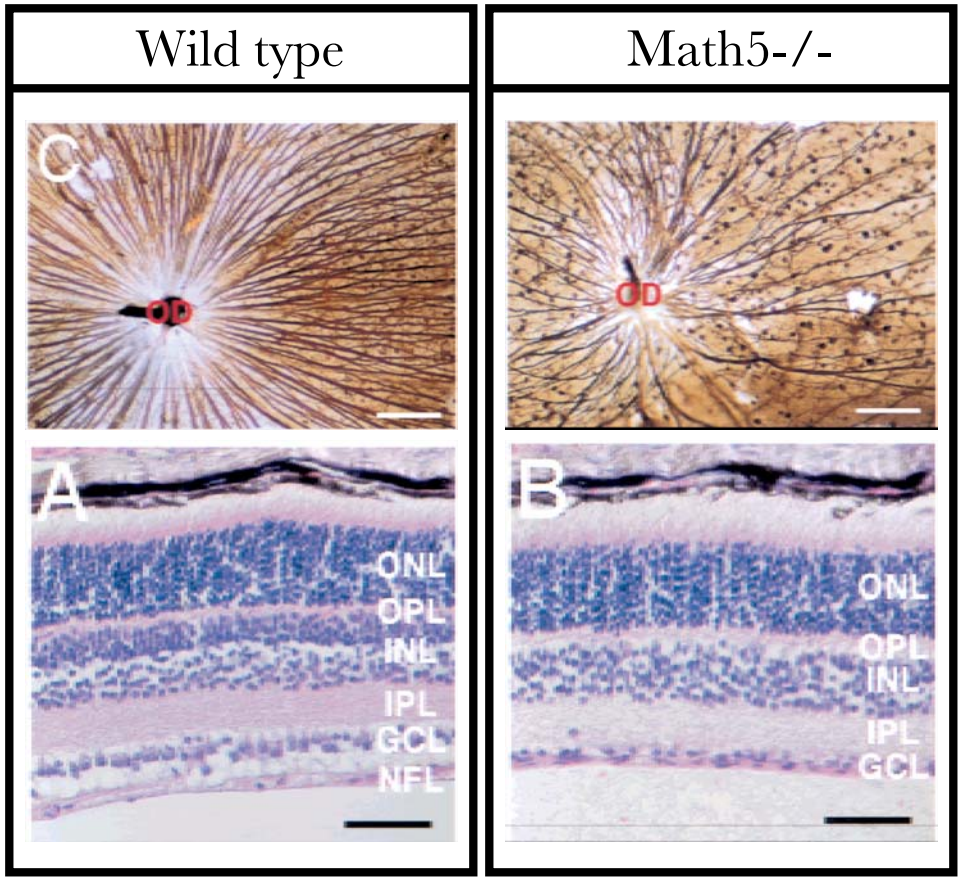
Math5 mutant mice have decreased numbers of RGCs.

- Math5 is a transcription factor required for RGC differentiation.

- Math5 knockout mice have 5-10% the normal number of RGCs.

- These RGCs are positioned throughout the retina

- Hypothesis: There will be decreased competition between RGCs in Math5 knockouts.



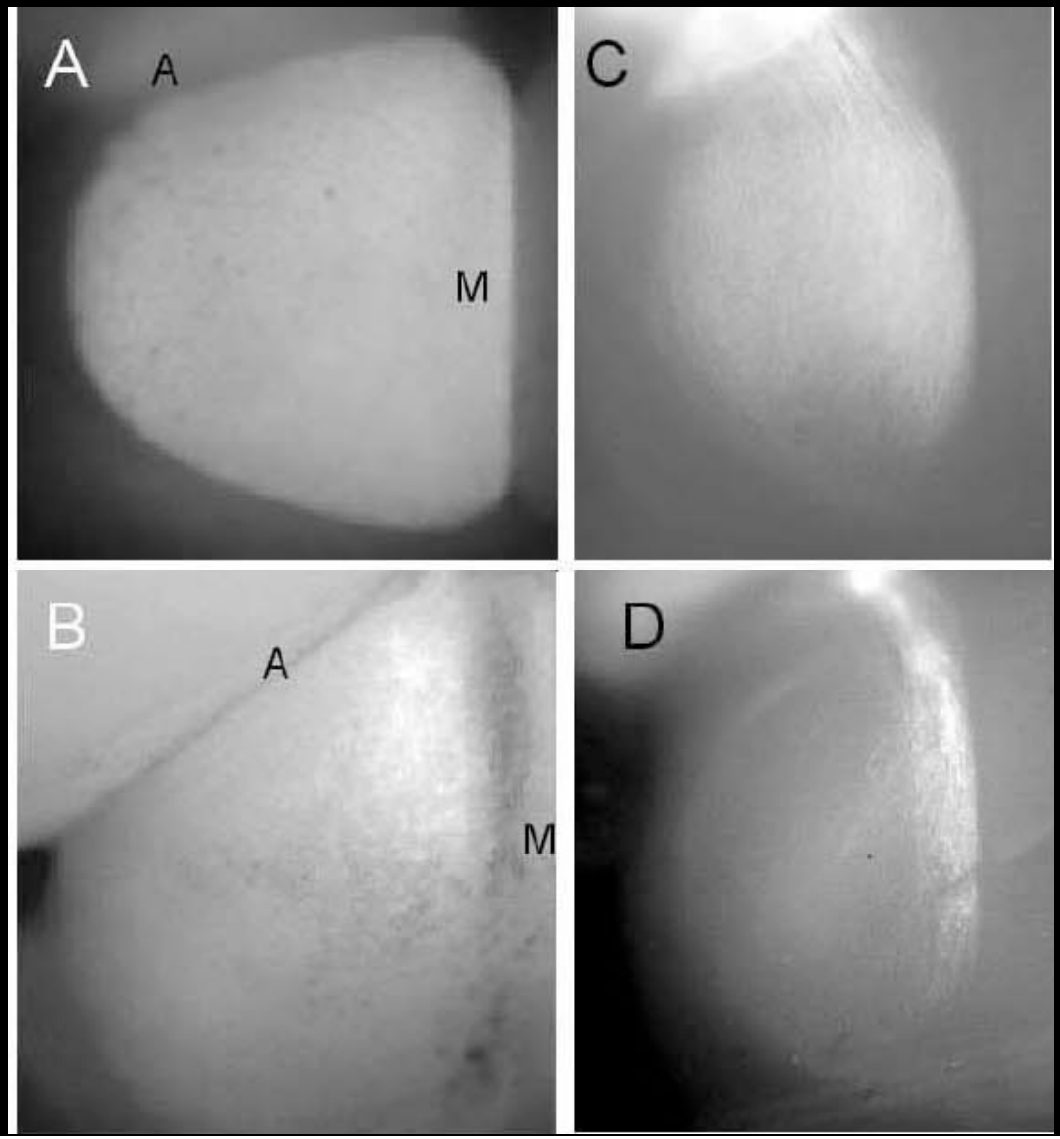
Wang et al 2001

Retinal projections in Math5 mutants do not fill the entire SC.

Adult P2

Math 5 $^{+/-}$

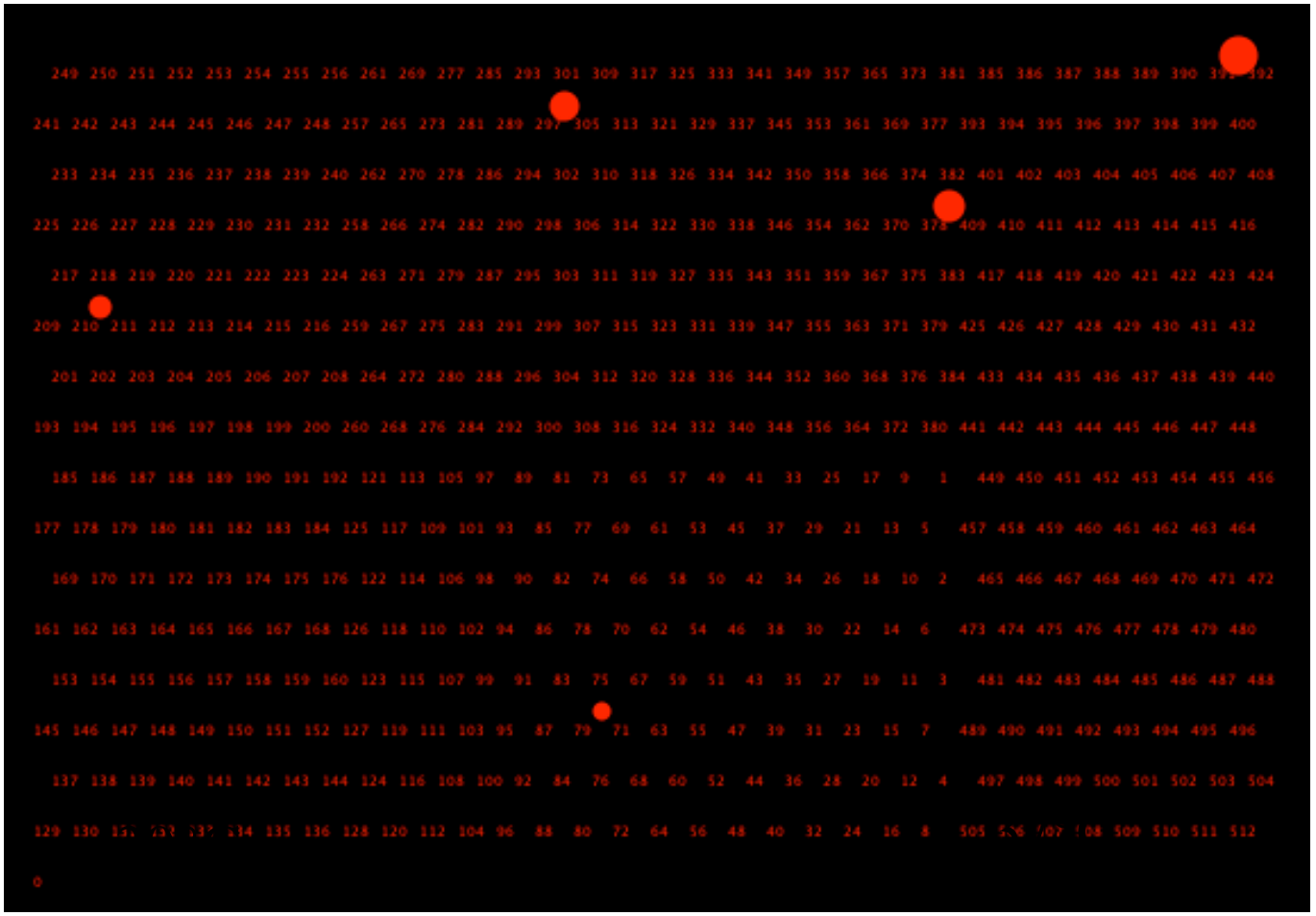
Math 5 $^{-/-}$



What accounts for the remaining mapping information in ephrin-A mutant mice?

- Hypothesis: neural activity dependent mechanisms cooperate with ephrin-As to make topographic maps
- Maps are formed before eye-opening.
- Early in development spontaneous activity in the retina is in the form of "retinal waves" (Meister, Wong, and Shatz).
- The β2 subunit of the nACh receptor is required for the normal structure of retinal waves (Feller).
- β2 mutant mice have mild defects in topographic mapping to the SC, LGN, and V1 along the N-T axis of the visual field. (Feller, O'leary, Crair, Hubener, Thompson, Stryker).

Early post-natal retina waves viewed on a multi-electrode array



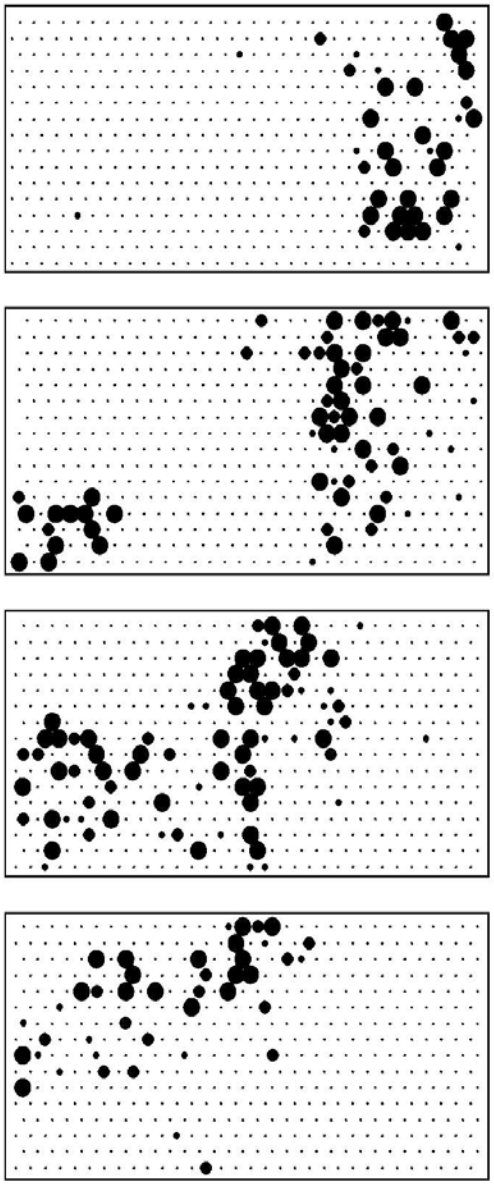
512 multielectrode array, 60um apart

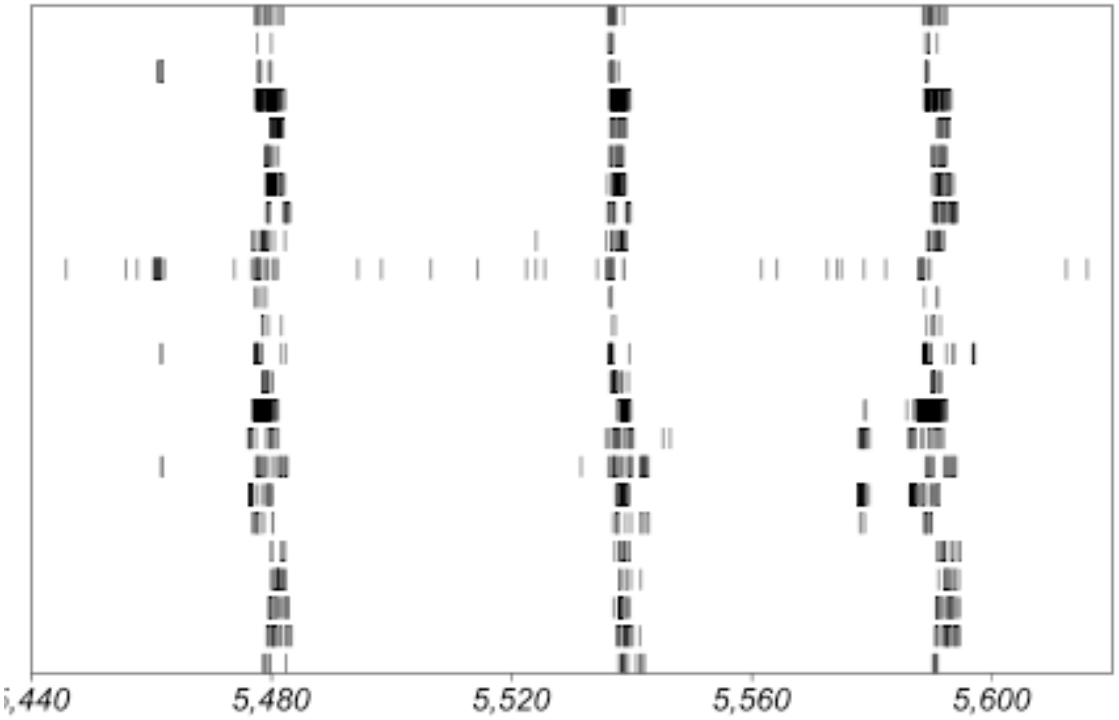
Records from approximately 1/4 of a developing retina

Measures the action potentials of hundreds of RGCs

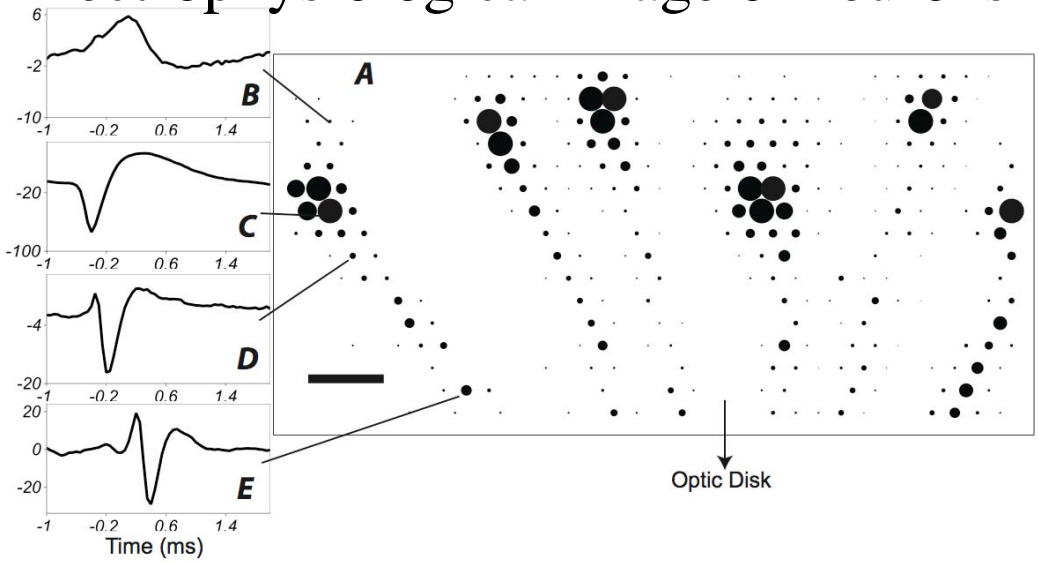
Movie is 4X time

Retinal waves correlate firing patterns of retinal neurons

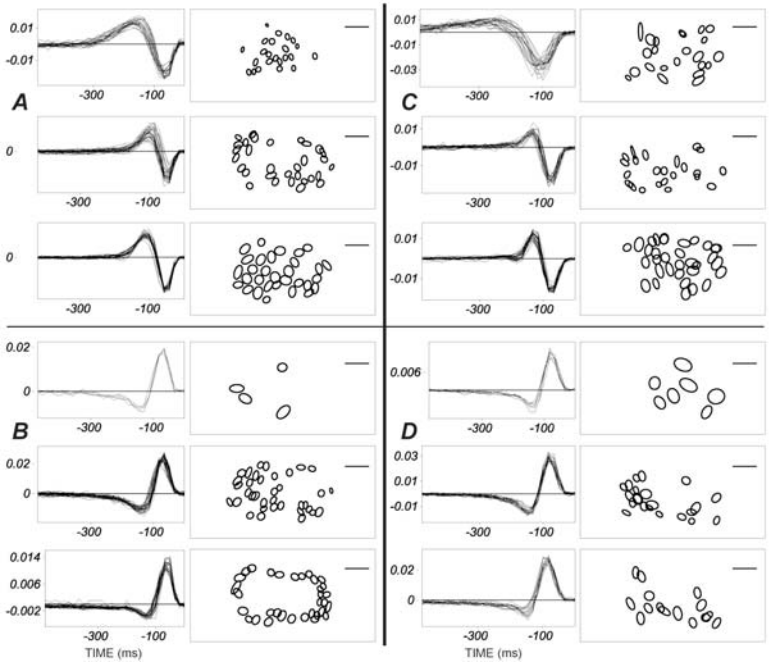




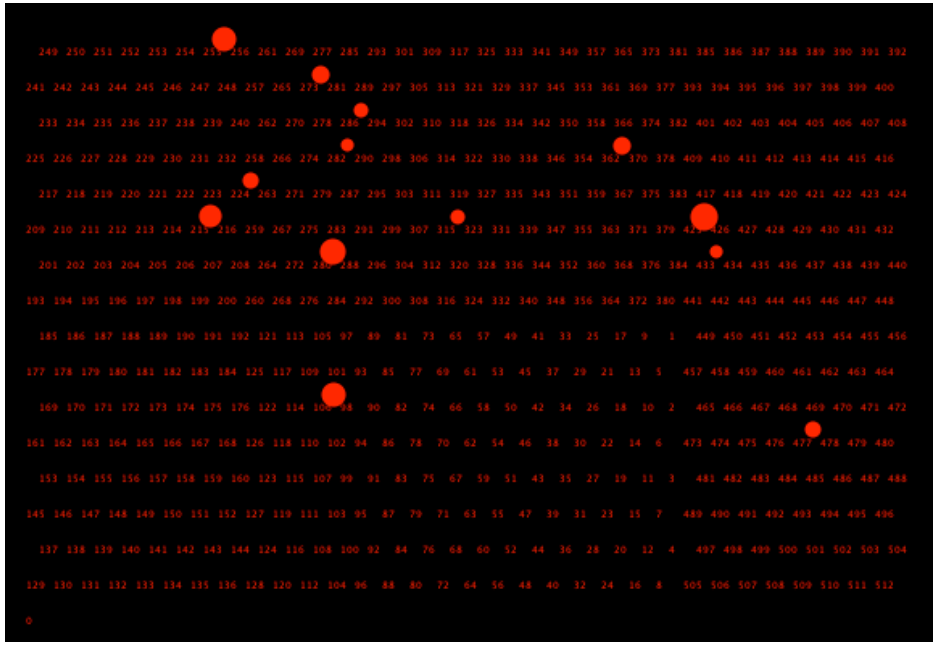
Electrophysiological image of neurons

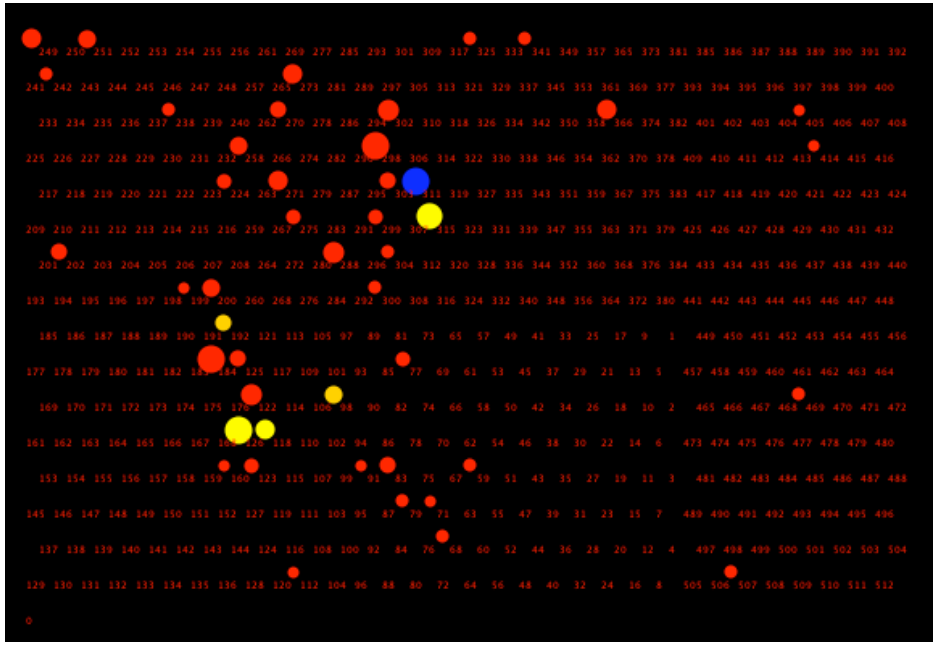


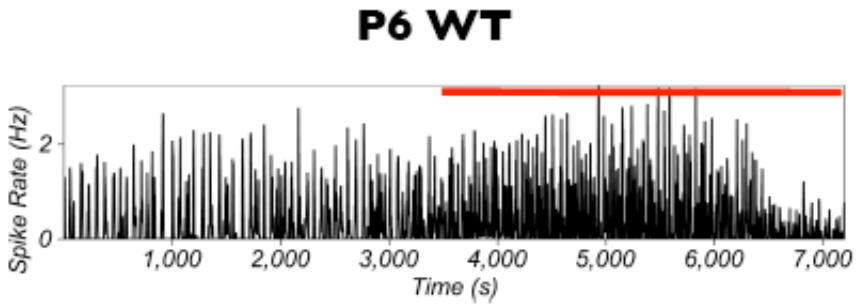
Classification of RGC subtypes

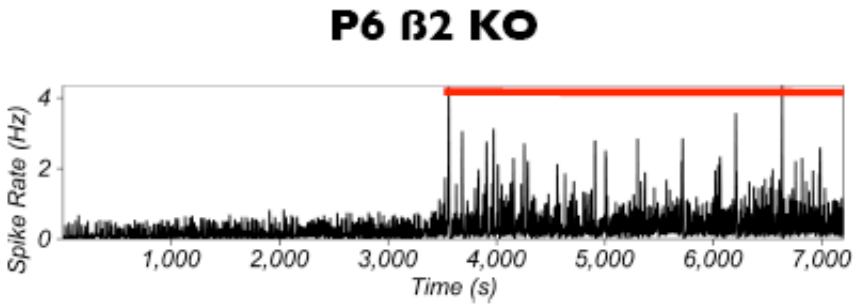


β2 mutant mice lack retinal waves at 30°C but can wave at 37°C

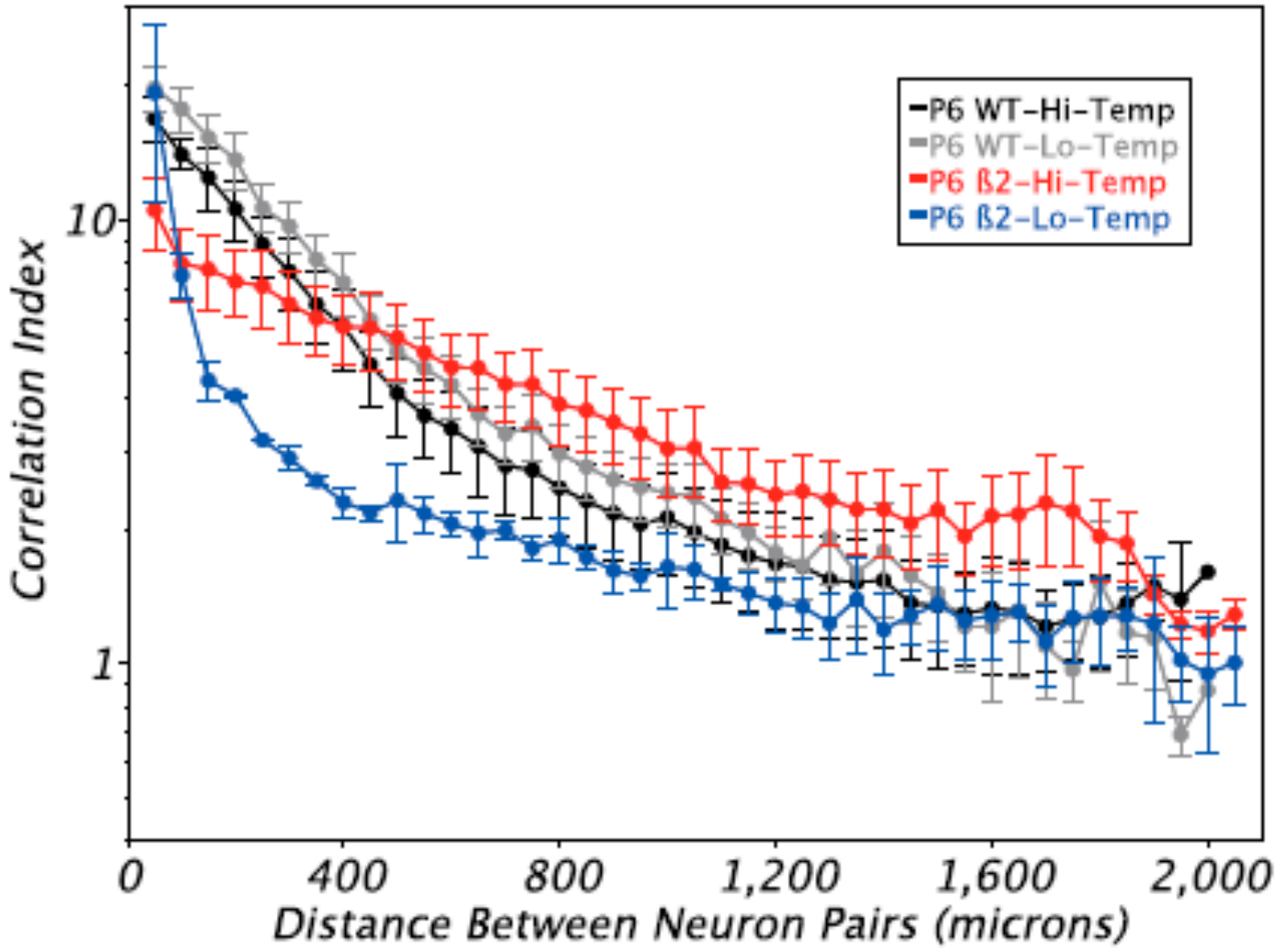




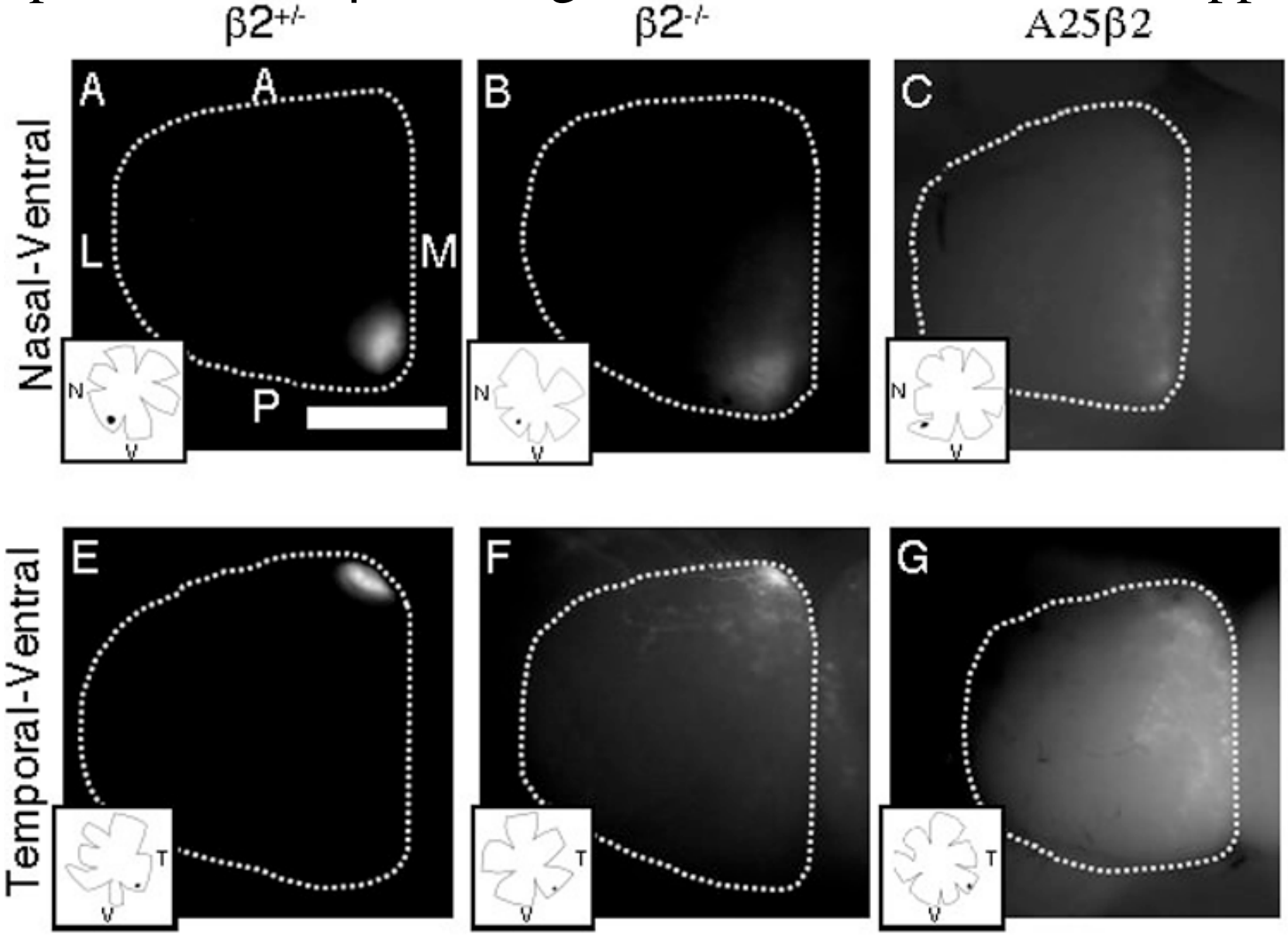




Correlated firing patterns between RGCs is altered in β2 mutant mice



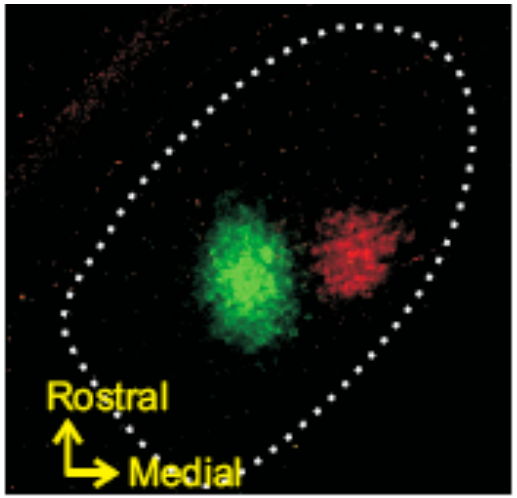
Ephrin-As and β2 act together in retinocollicular mapping



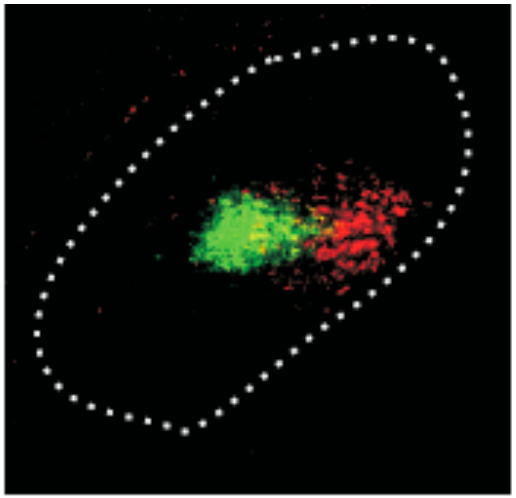
Pfeiffenberger et al. 2006

Geniculocortical topography is also severely disrupted in the absence of ephrin-As and patterned retinal activity

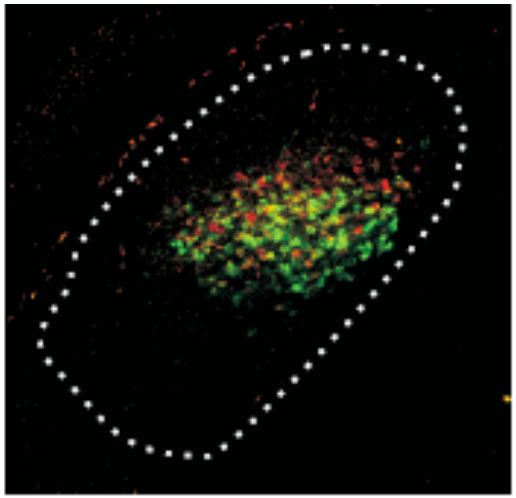
wild type

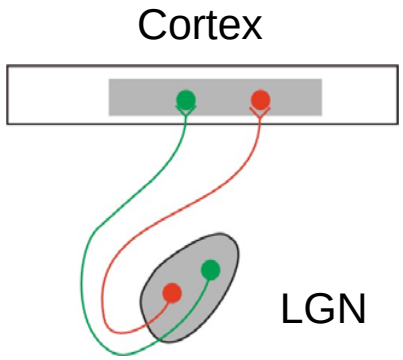


ephrin-A2/A5/β2$^{+/-}$

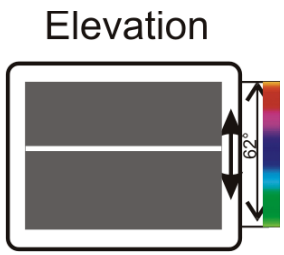


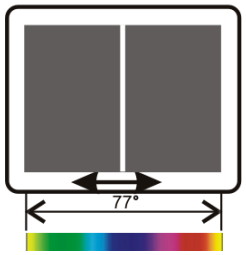
ephrin-A2/A5/β2$^{-/-}$





Ephrin-A2/A5 β2 triple mutant mice lack functional topography along the nasal-temporal mapping axis of the SC

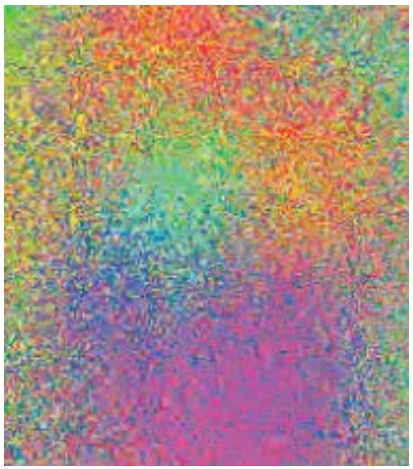




wild type

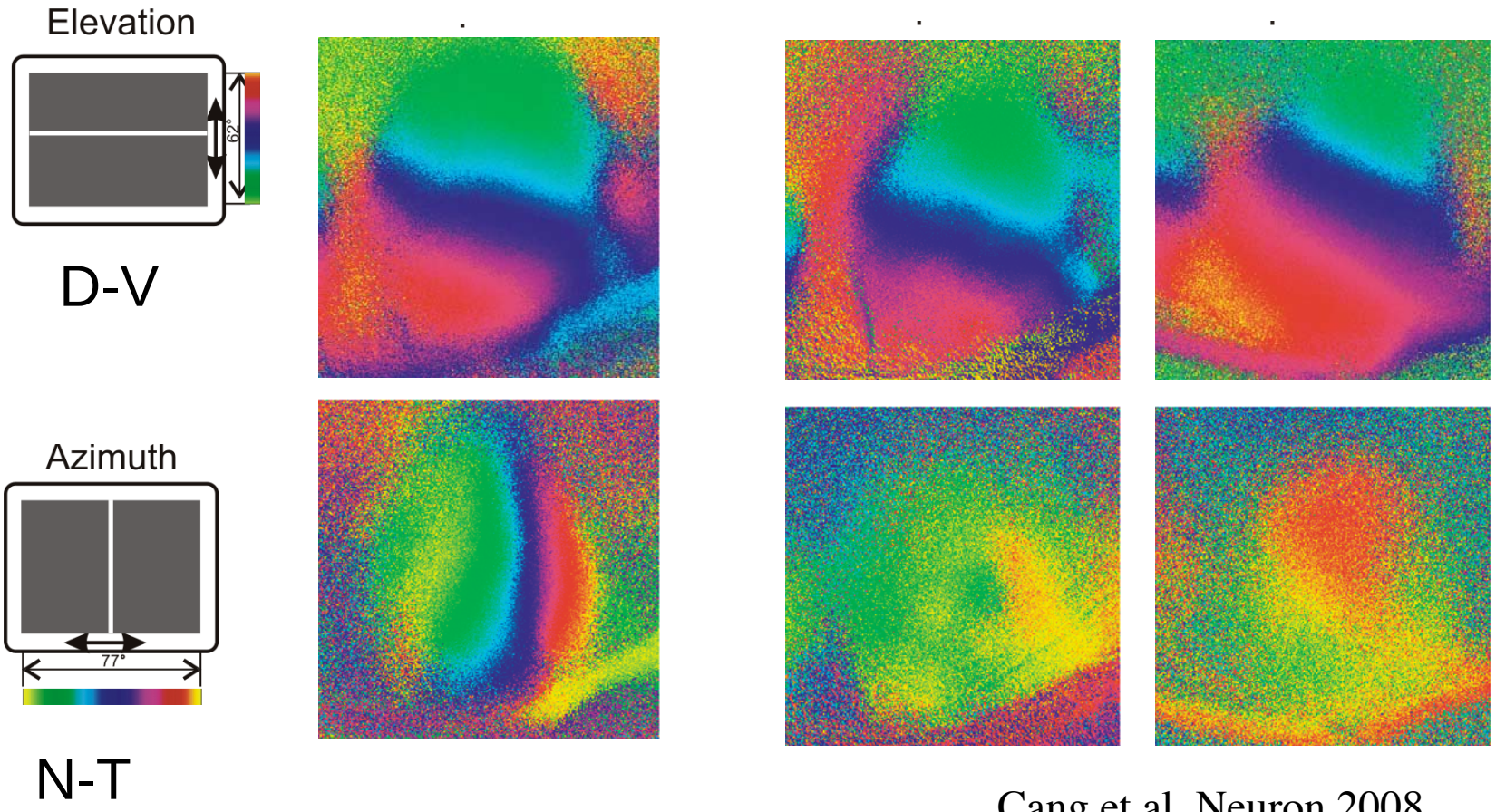
ephrin-A2/A5/β2 tko

D-V



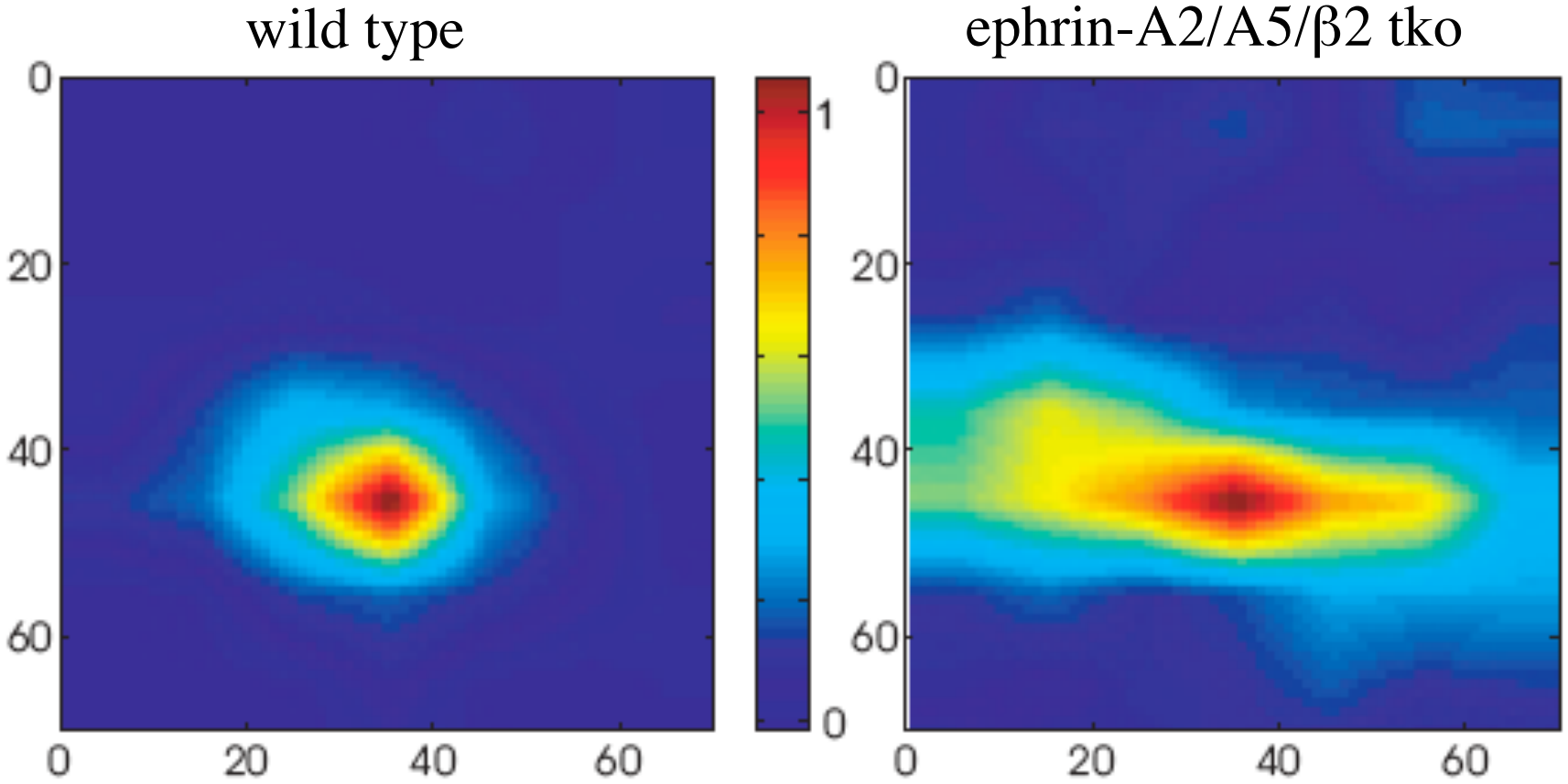
N-T

Functional cortical topography is also severely disrupted in the absence of ephrin-As and patterned retinal activity



Cang et al. Neuron 2008

Receptive fields a cortical neurons are selectively elongated along the nasal temporal axis in mice lacking ephrin-As and patterned retinal activity



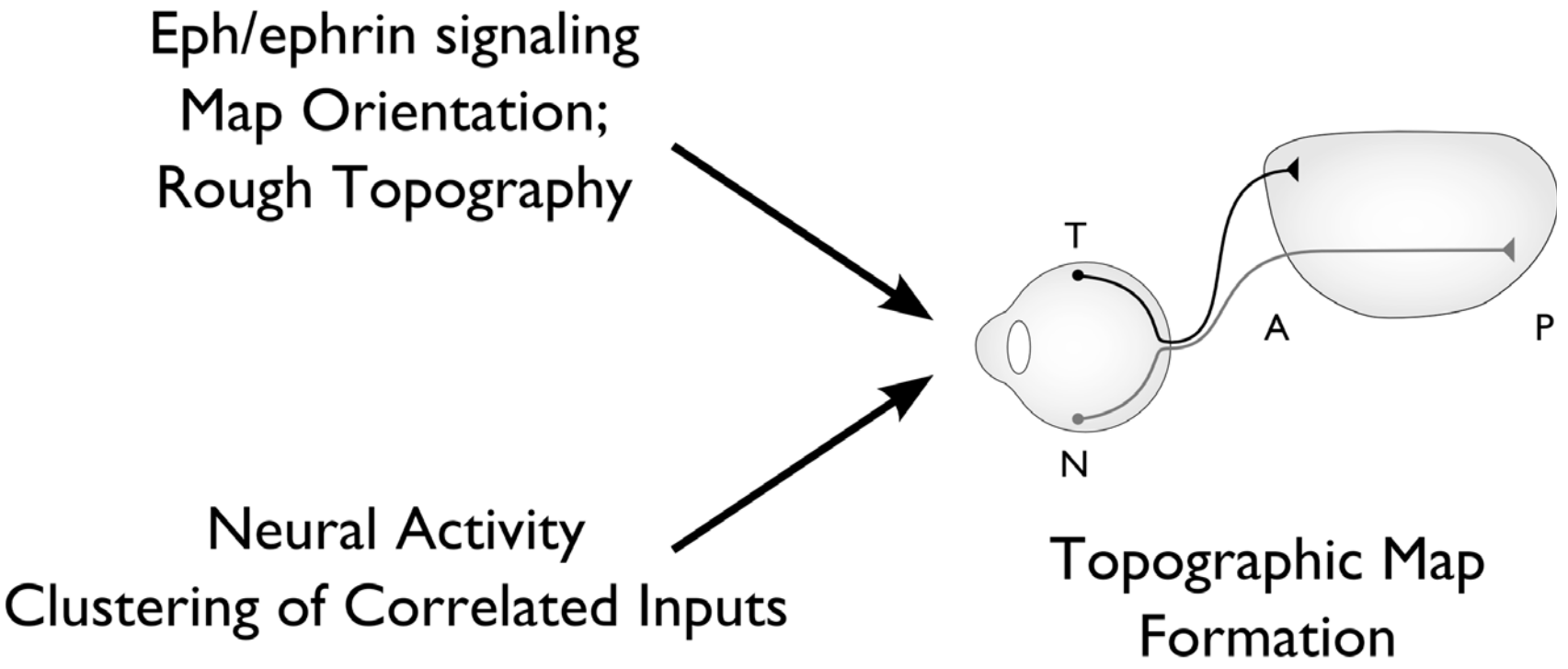
Cang et al. Neuron 2008


WELCOME

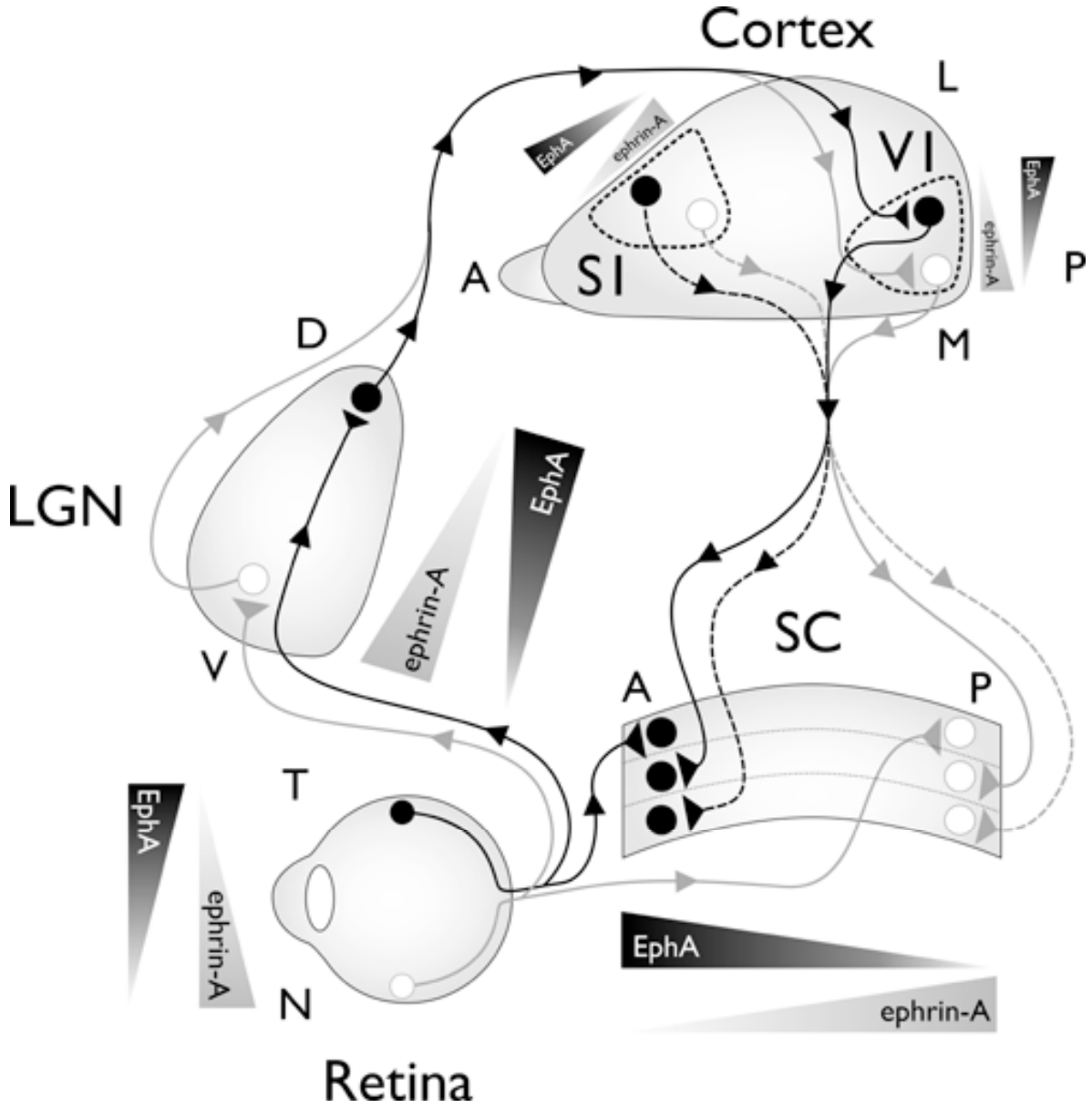
Summary Part 2:

Ephrin-As and structured retinal activity act in parallel to specify topographic maps.

The N-T and D-V maps are specified independently.



Map alignment in the Visual system

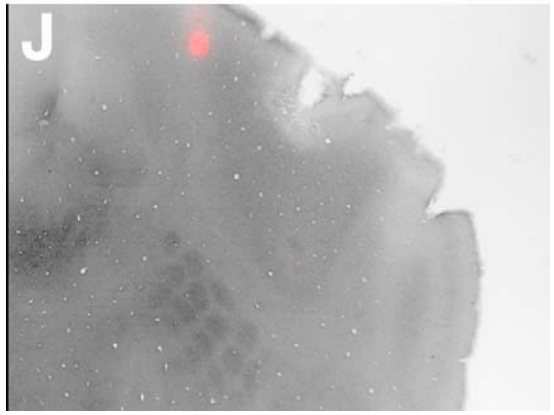


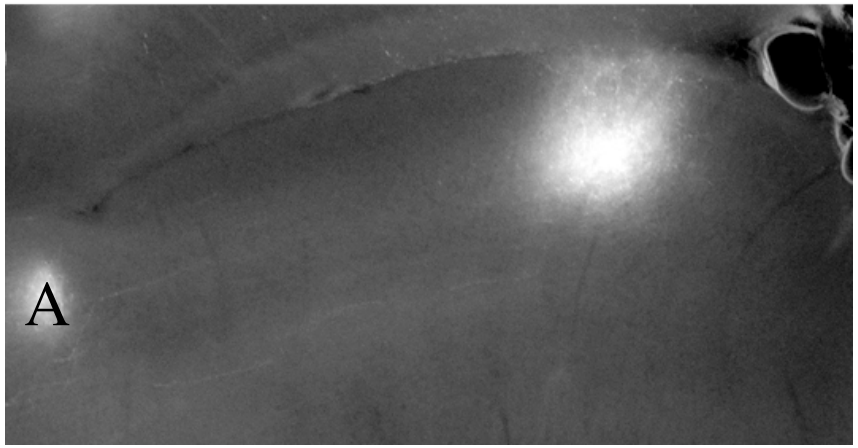
Tracing Paradigm

Drill Hole w/
25 gauge needle

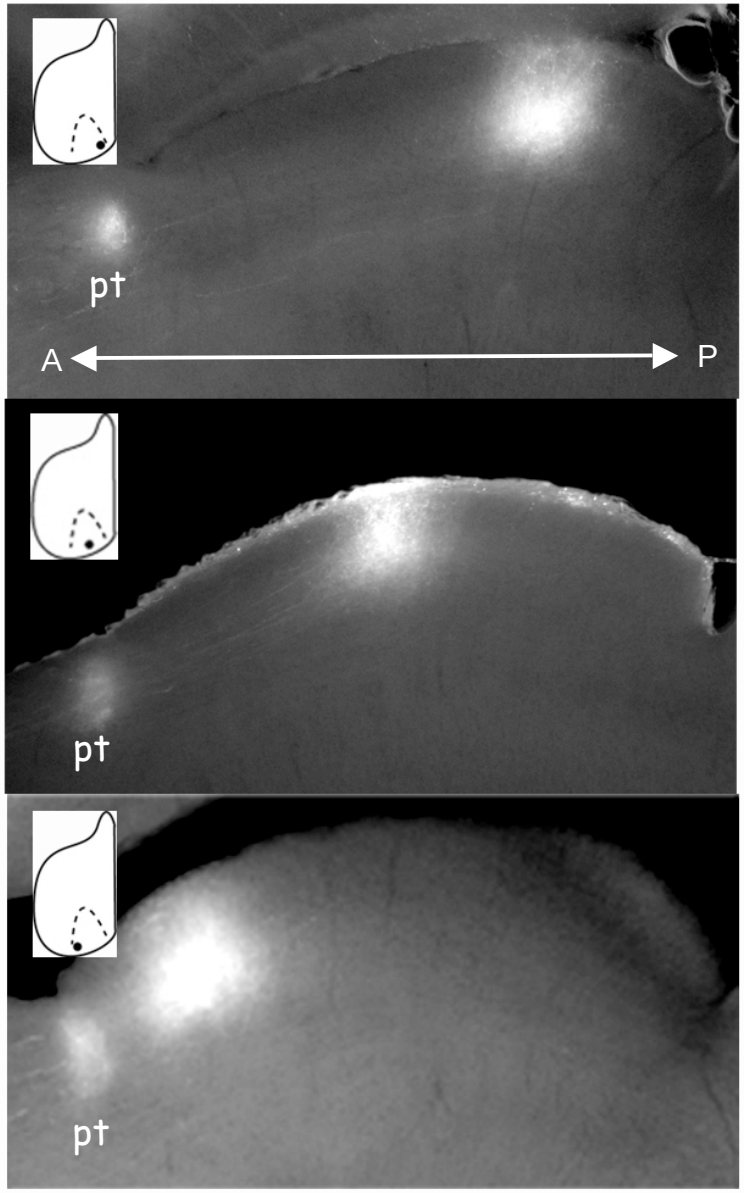
Inject DiI

After One Week:
Remove cortex for CO staining,
Section Ipsilateral SC



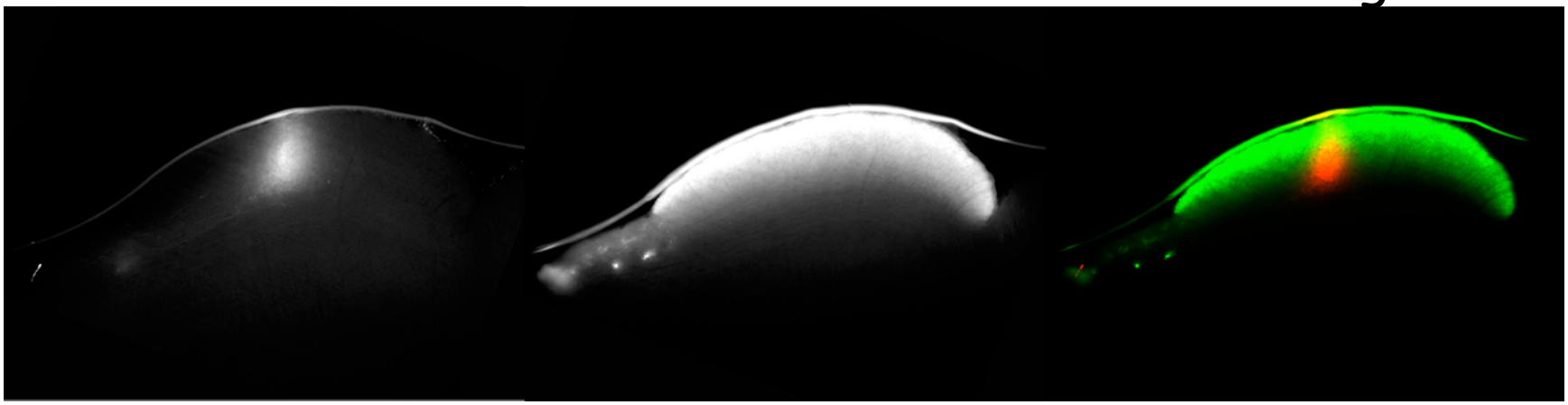


Topography of the V1-collicular Projection

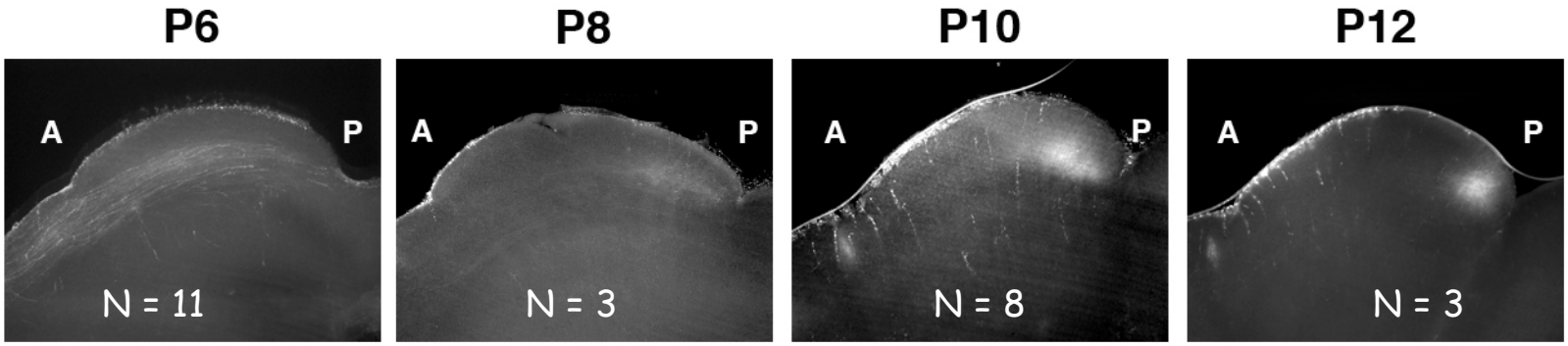


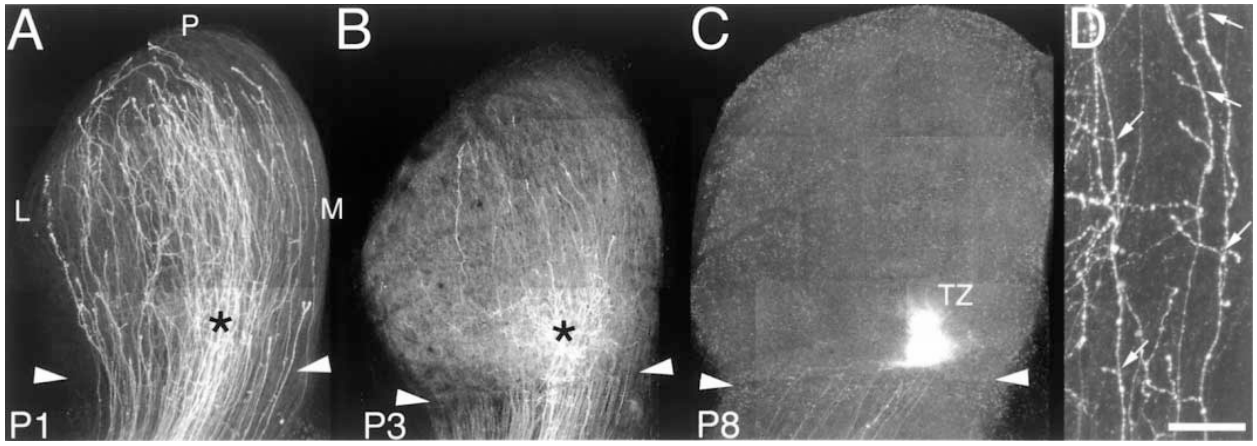
The V1-SC projection terminates in a deeper layer than the retinocollicular projection

DiI - V1 CTB-G - Retina Merge



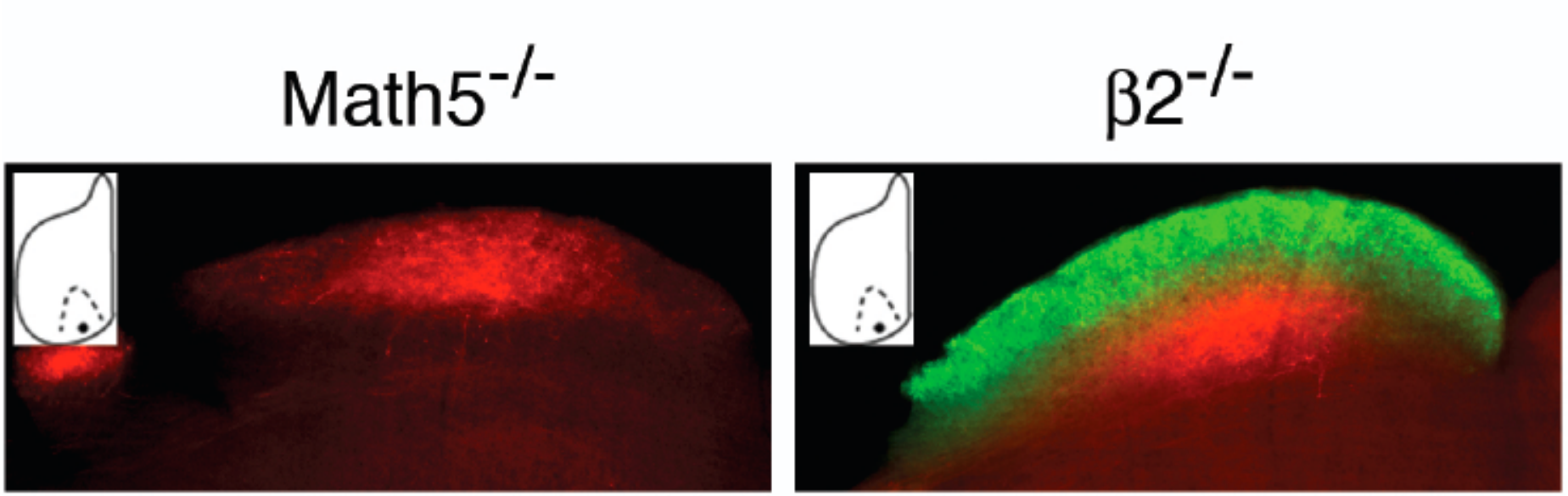
Topography of the V1-SC projection is established after the retinocollicular projection



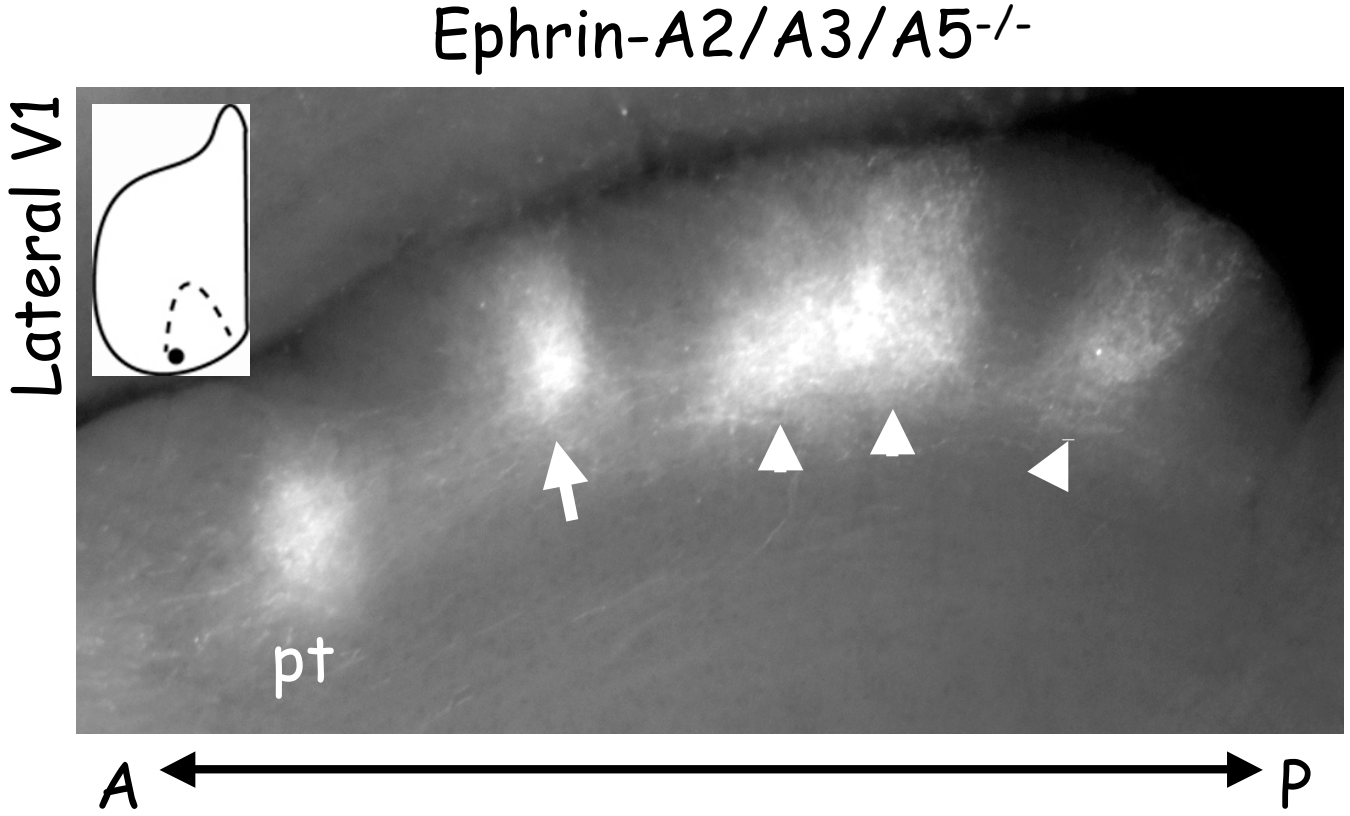


Hindges et al. Neuron 2000

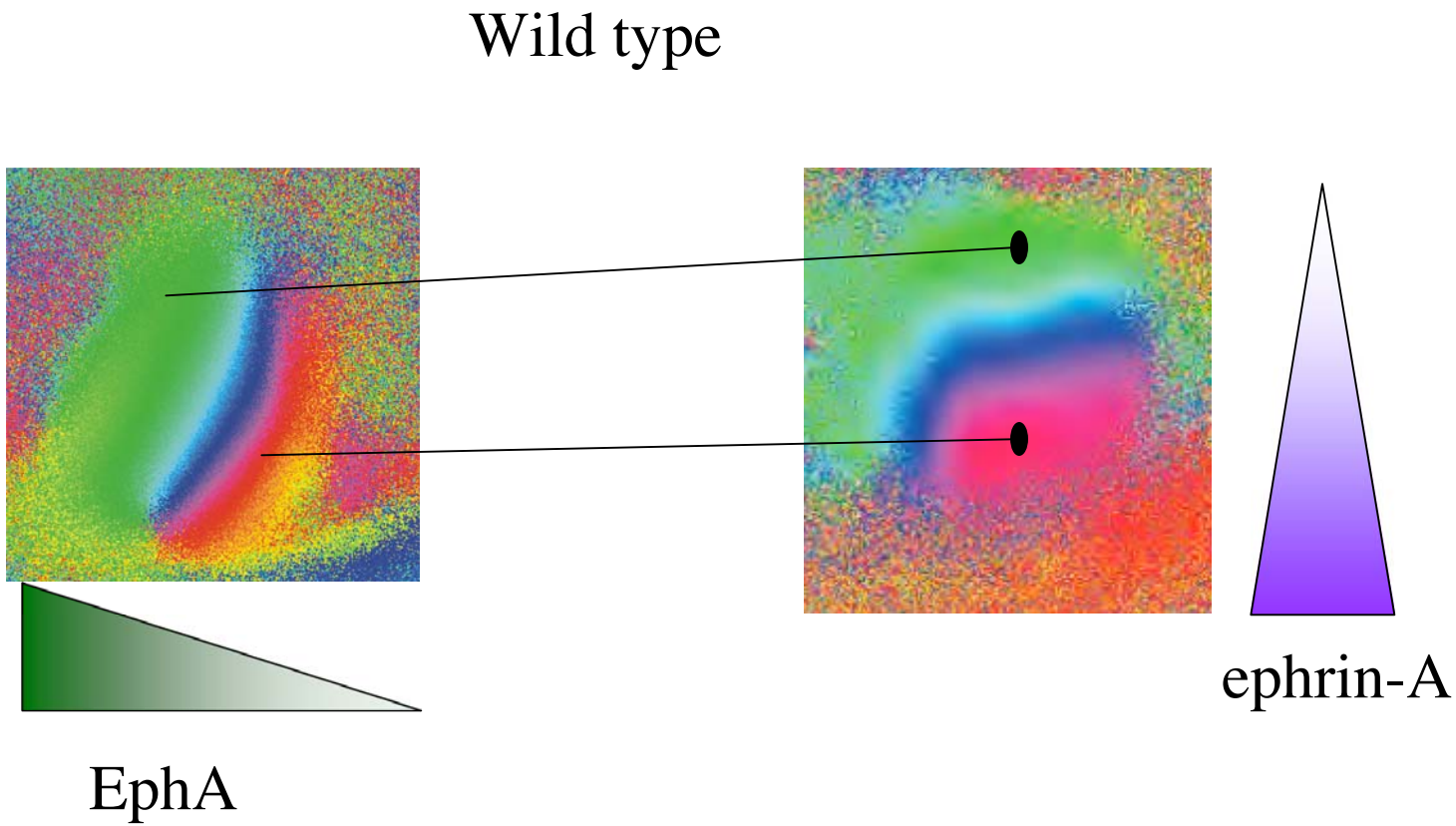
Topography of the V1-collicular projection requires retinal input and structured retinal activity.



Ephrin-As are required for V1-SC topography



Why are there V1-SC mapping errors in ephrin-A mutants?

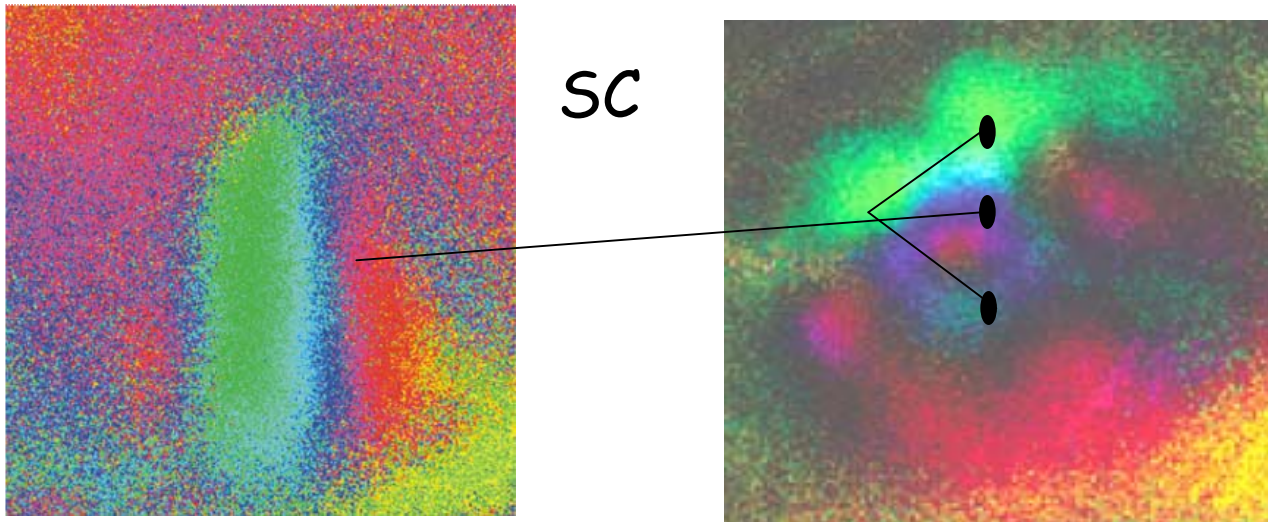


Why are there V1-SC mapping errors in ephrin-A mutants?

V1

SC

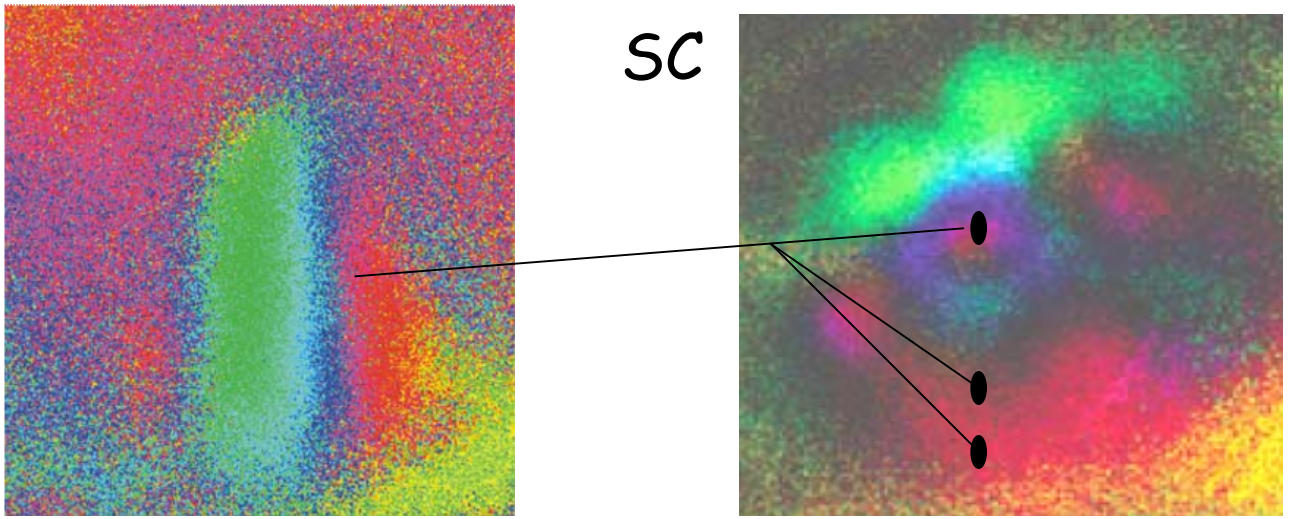
EphA/ephrin-A dependent mapping



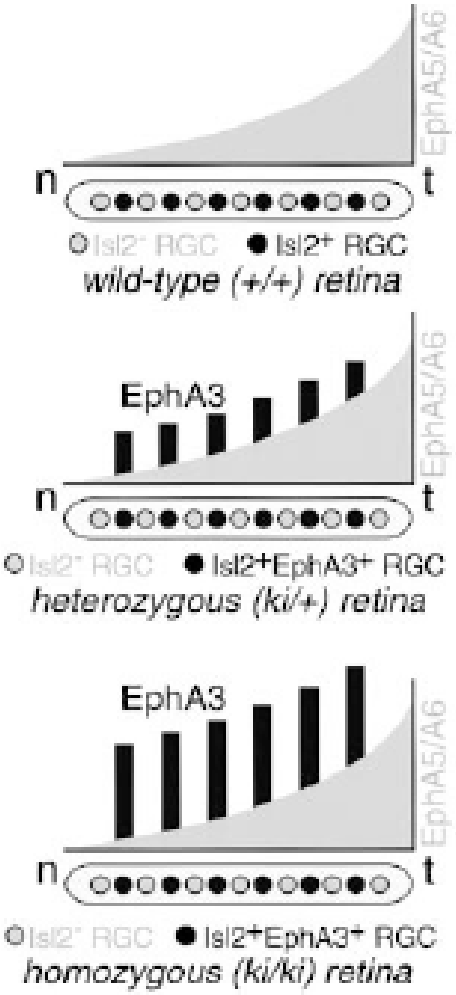
V1

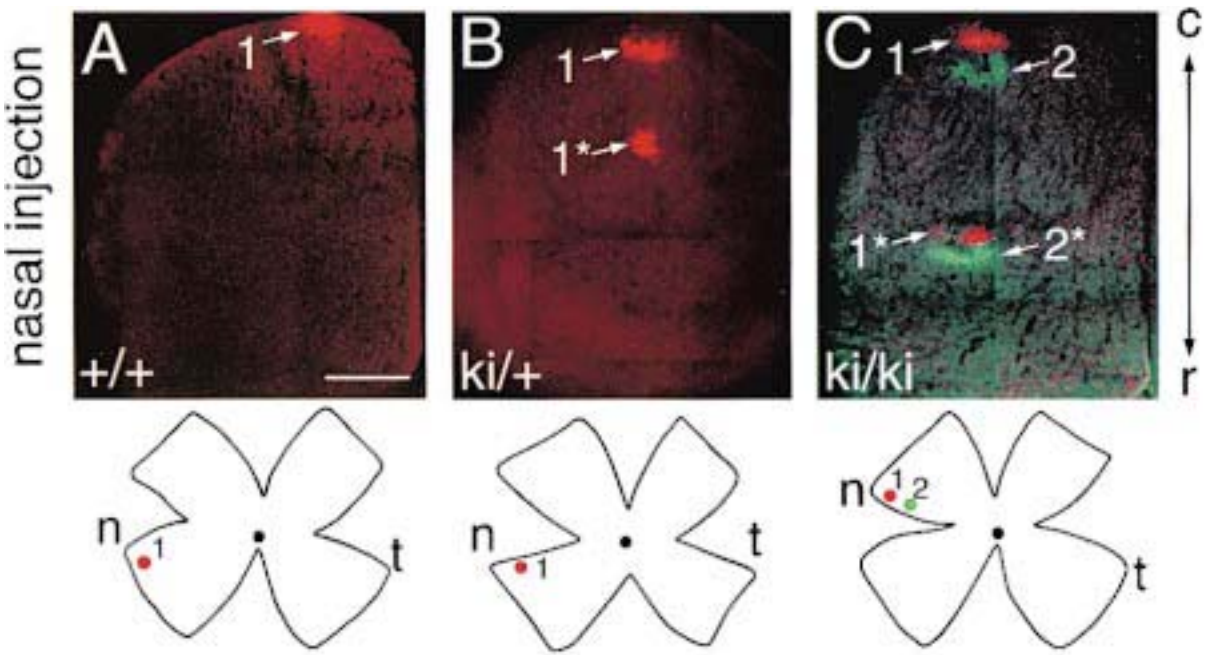
SC

Mapping by matching activity patterns



Isl2-EphA3 Knock-in Model

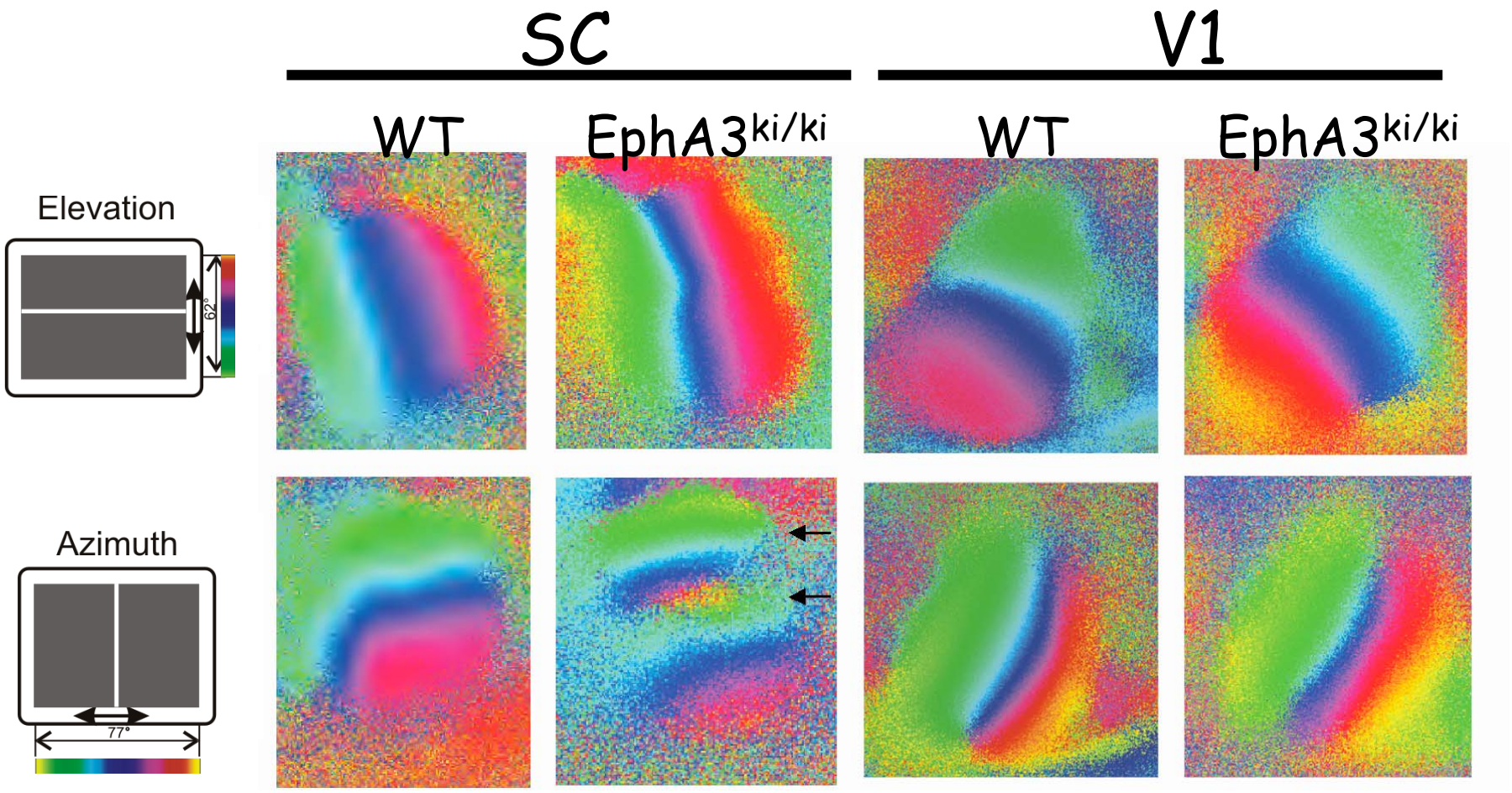




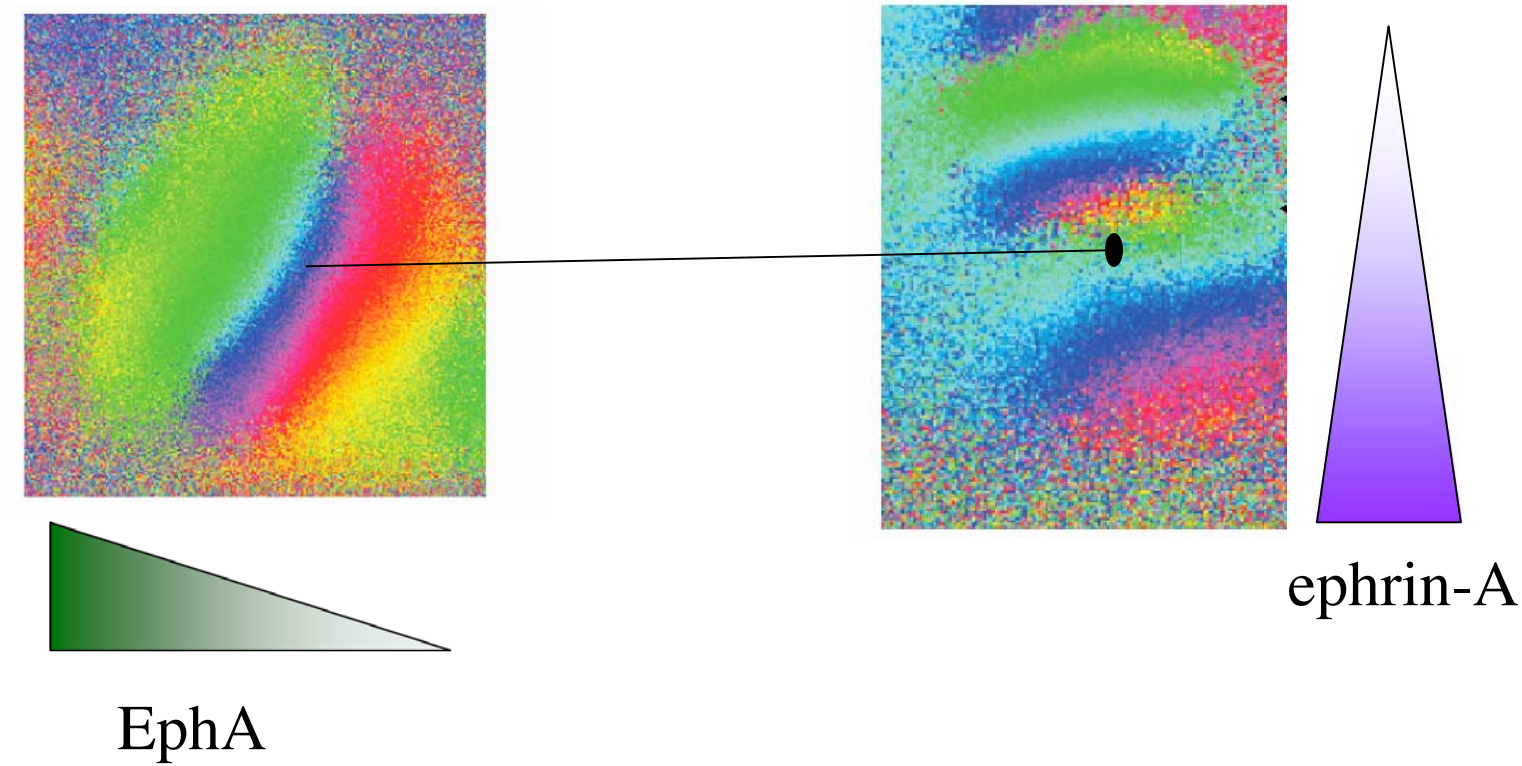
Each part of the retina projects to two locations in the SC.

Brown, et al. *Cell* 2000

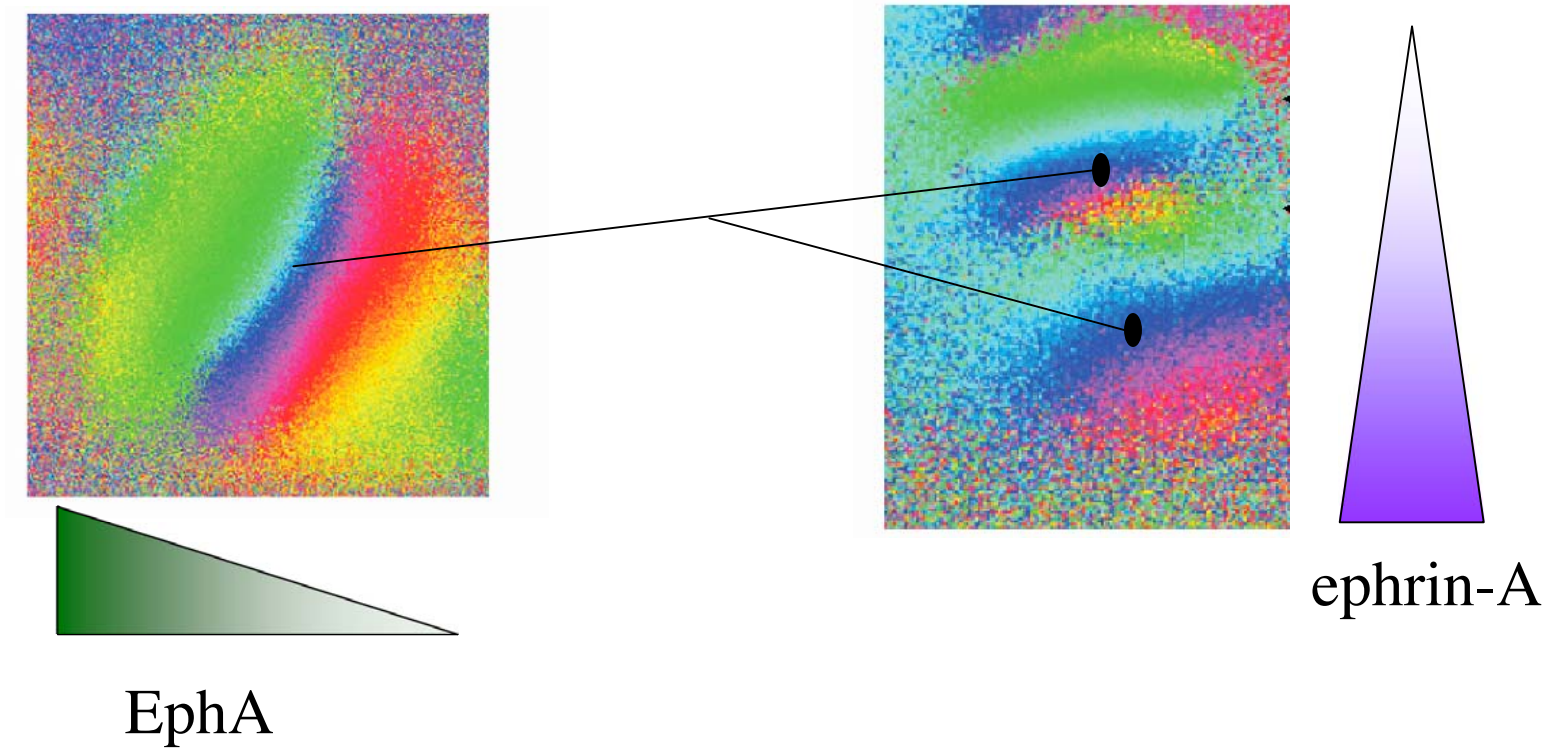
EphA3^{-}Ki mouse - Two maps in SC, One in V1



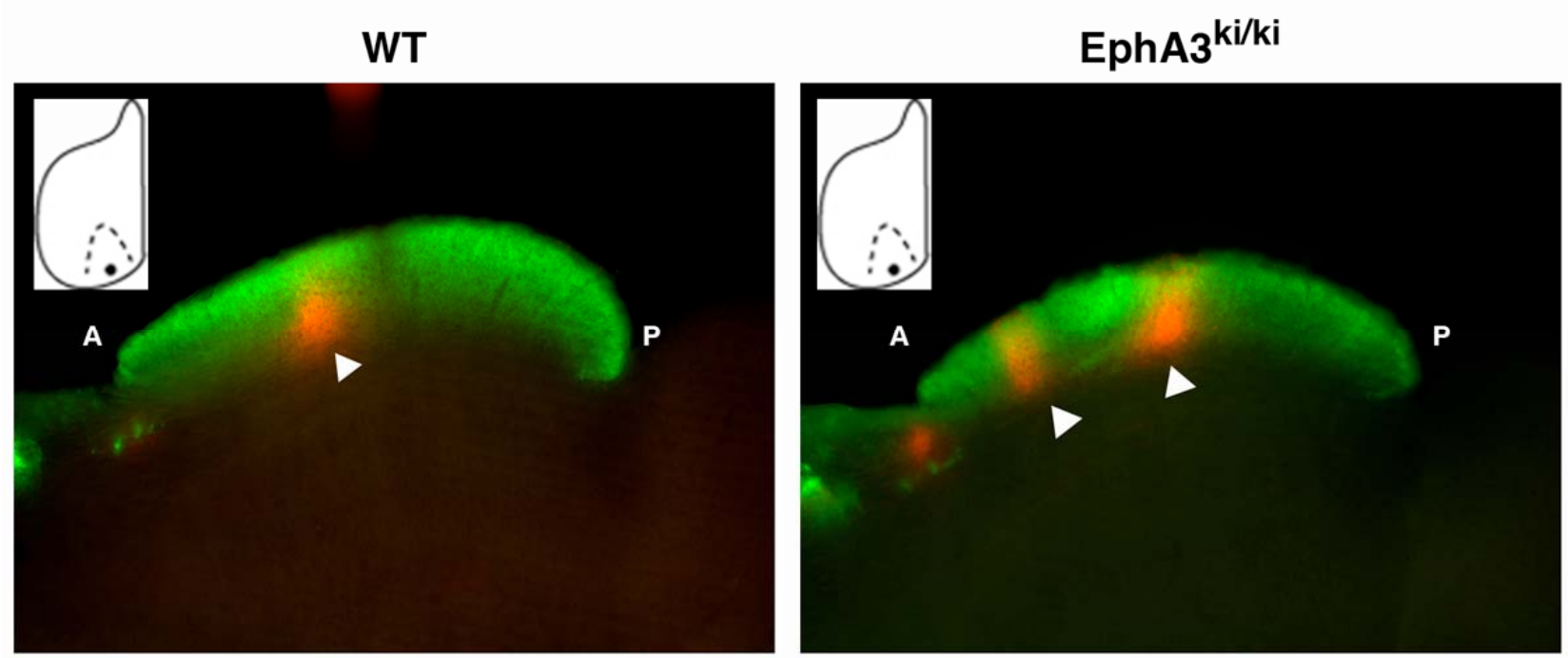
Does the V1-SC projection align with the retinocollicular projection when they are out of register?



Does the V1-SC projection align with the retinocollicular projection in EpphA3-ki mice?



The V1-SC map duplicates in EphA3$^{ki/ki}$ mice



Conclusions

- EphA/ephrin-A signaling and neural activity combine to form topographic maps during development.
- Neural activity seems to play a stronger role in forebrain mapping than in collicular mapping.
- The retinocollicular map is a template that is used to organize the V1-SC connection in order to integrate conscious vision with reflexive vision.
- May be true for the alignment of other sensory modalities with vision in the SC.

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