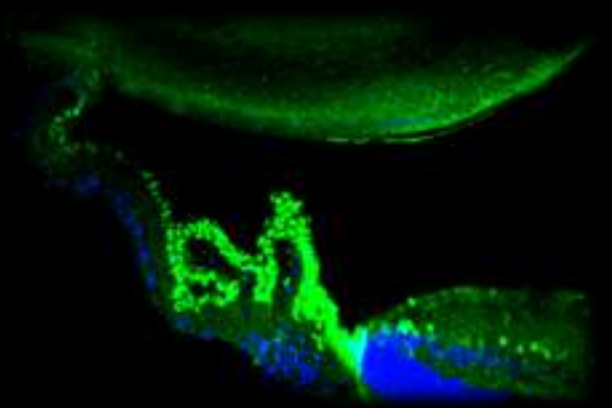
FUNDACIÓN RAMÓN ARECES

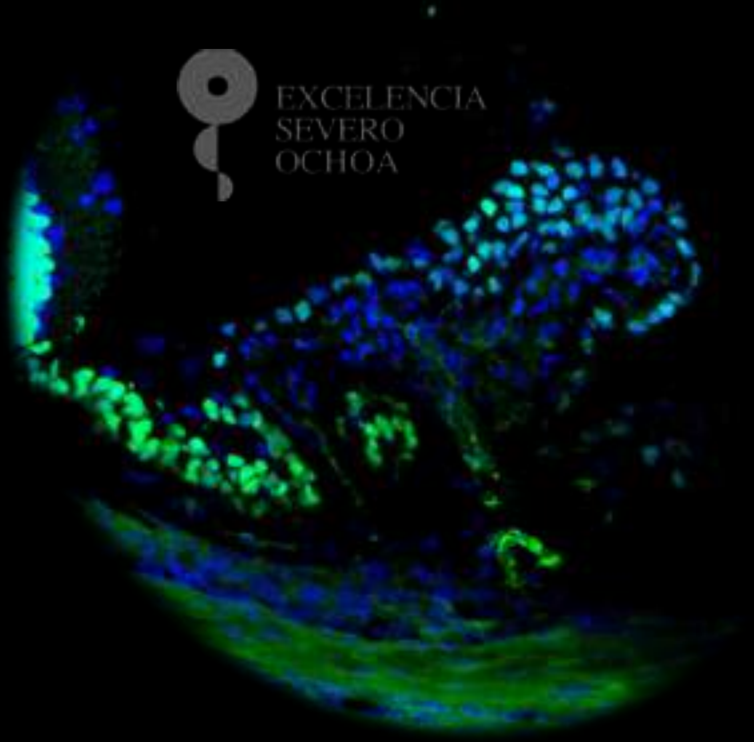
Comprender y reprogramar los trastornos visuales del desarrollo

Desde la anoftalmia hasta las deficiencias corticales

En colaboración con el Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER) y el Consejo Superior de Investigaciones Científicas (CSIC)

The peripheral eye: A neurogenic area with potential to treat retinal pathologies?





EXCELENCIA SEVERO OCHOA

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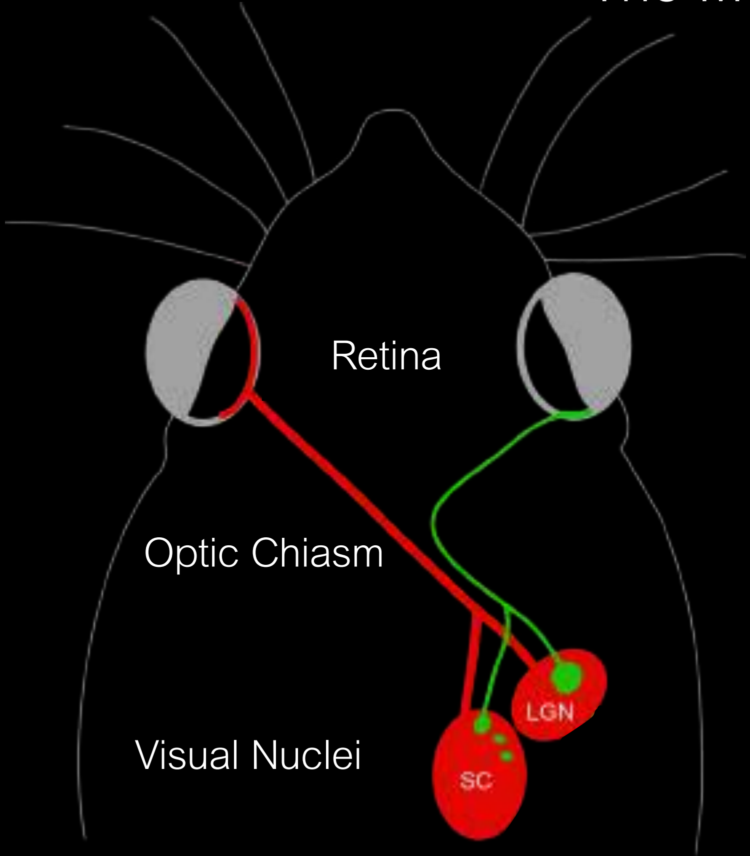
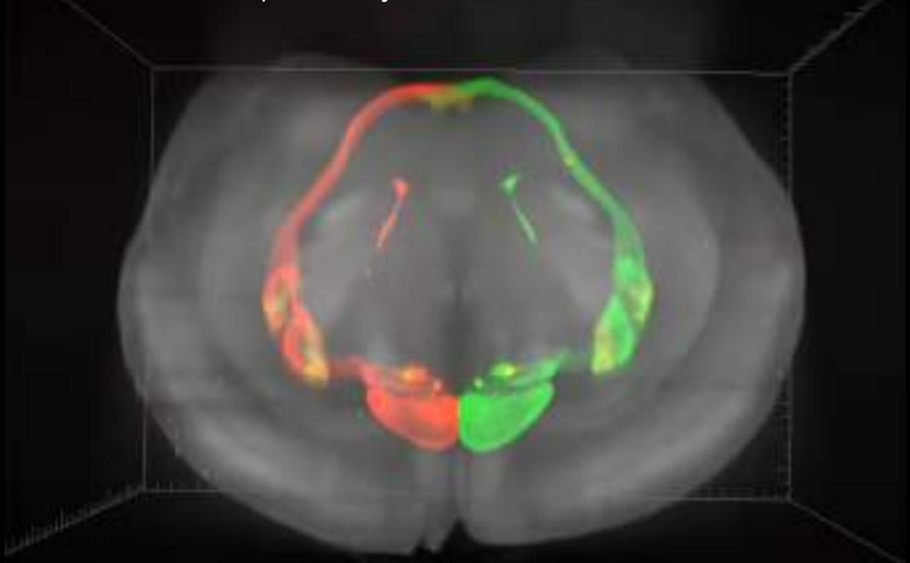
The Mouse Visual Pathway

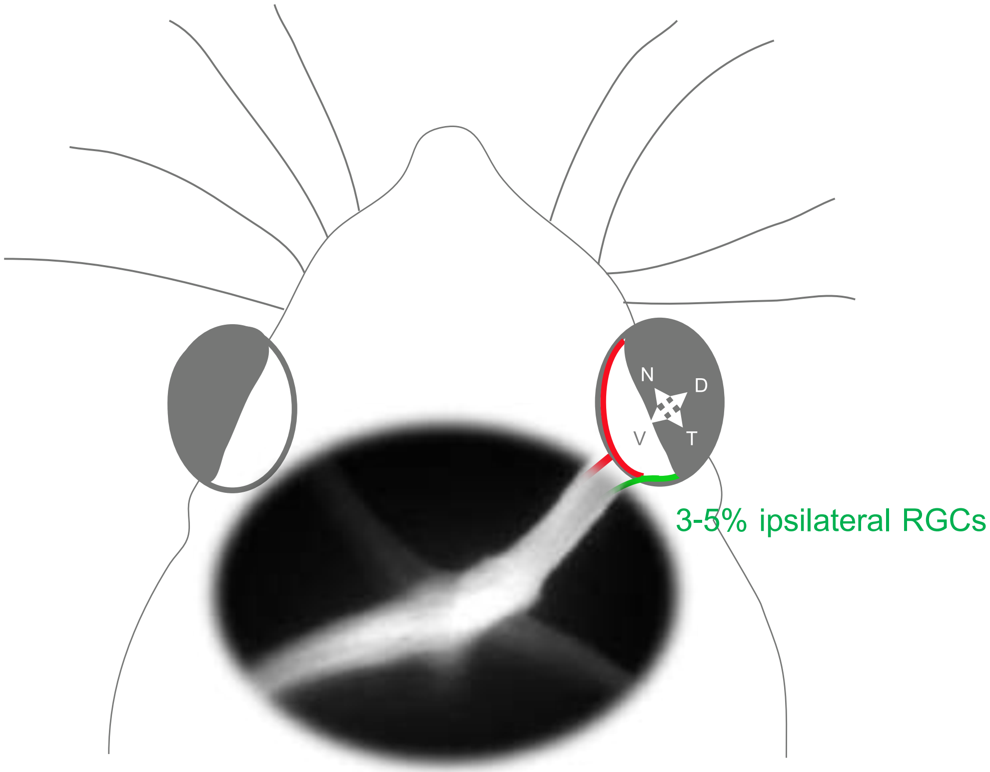


The visual pathway in a mouse clarified brain



CTB-488 right eye CTB-594 left eye

The Mouse Optic Chiasm

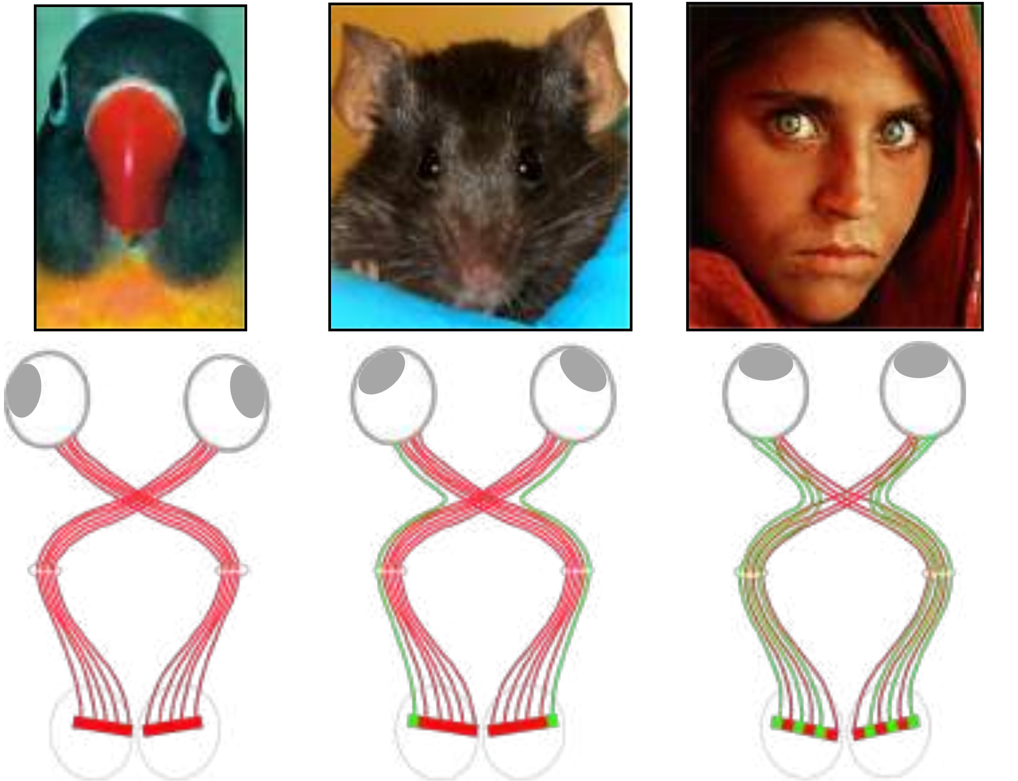


RGC axons divergence at the chiasm allows binocular

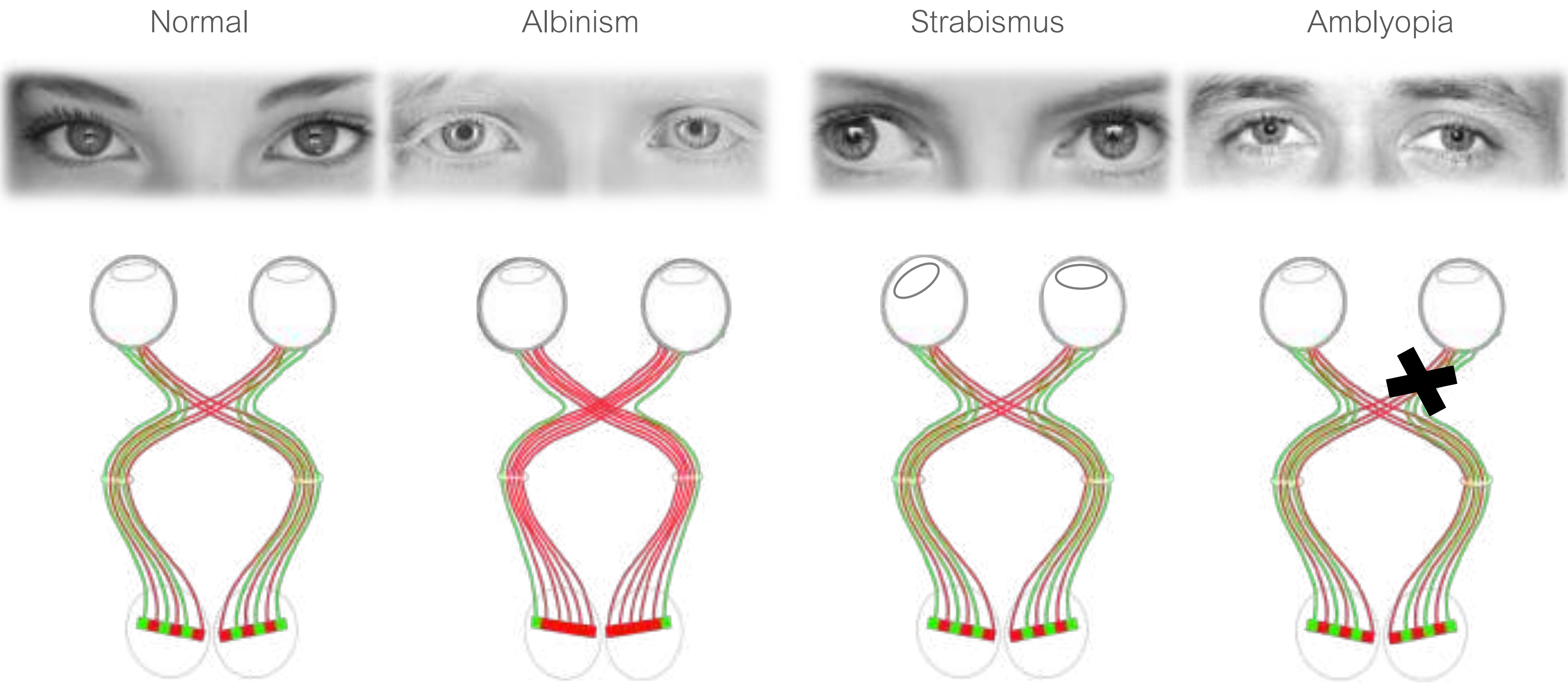
The number of ipsilateral axons correlates with the extent of binocular vision through evolution

Panoramic Vision

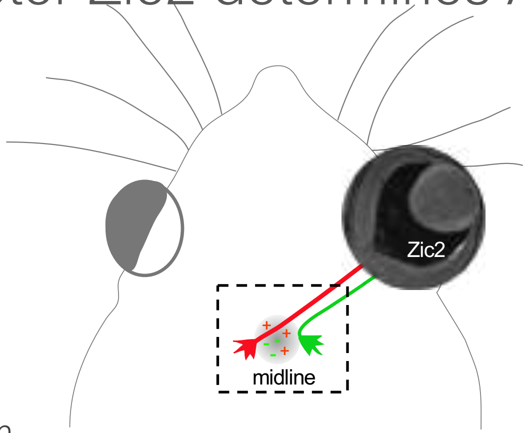
Binocular Vision



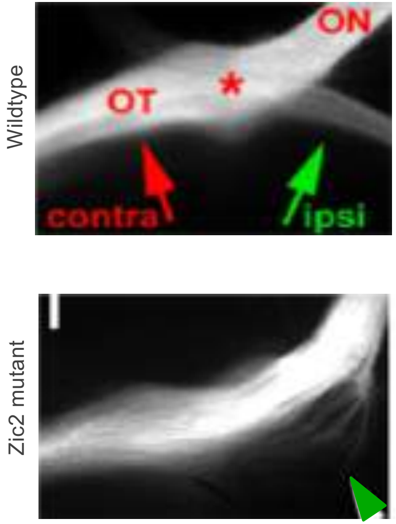
Lost of binocular vision



The transcription factor Zic2 determines Axon Midline Avoidance

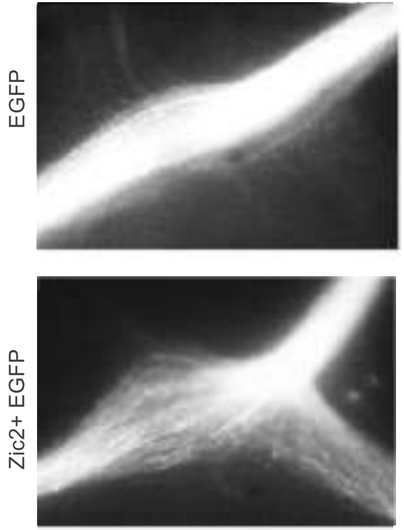


Loss of Function



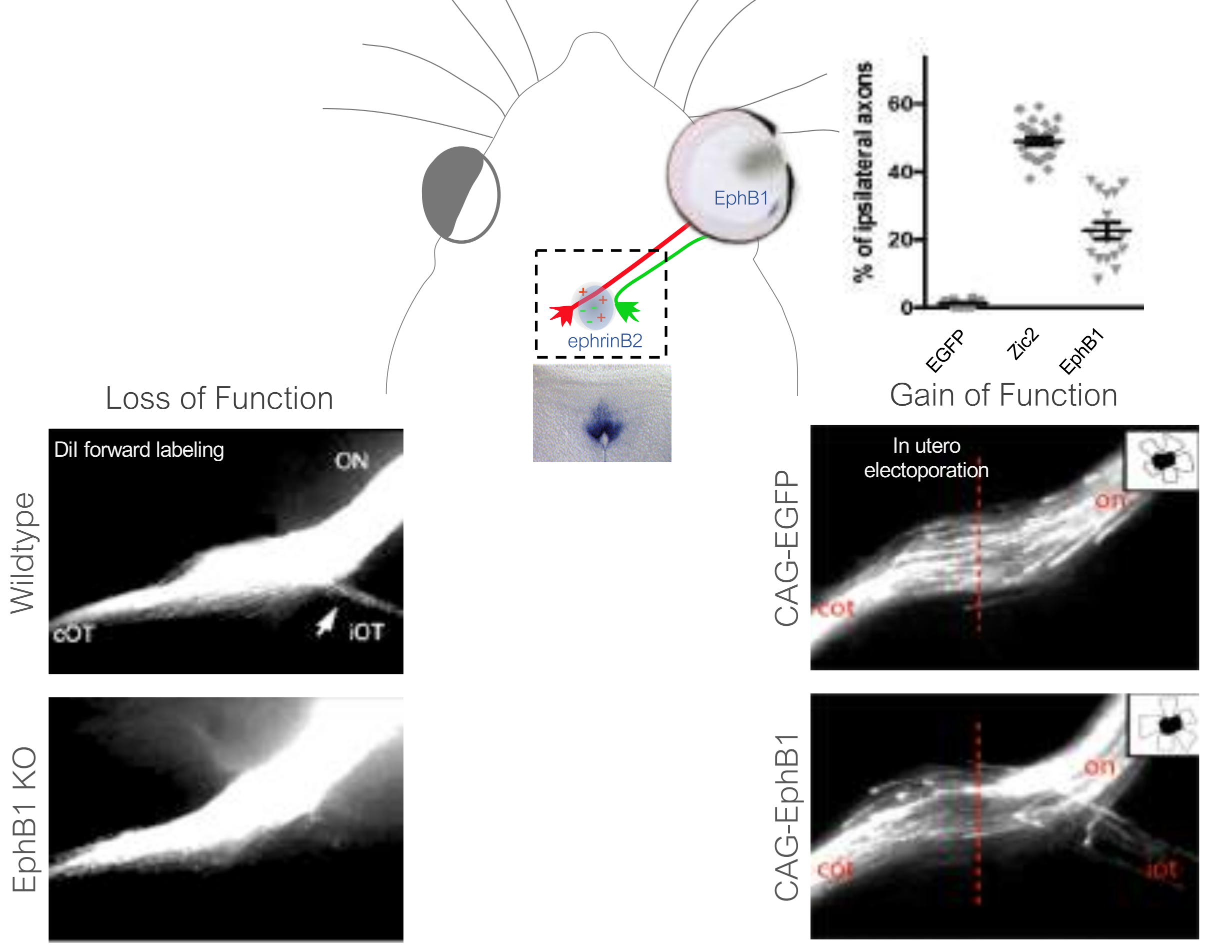
Herrera et al *Cell* (2003)

Gain of Function



García-Frigola et al *Development* (2008)

EphB1/ephrinB2 signaling induces Axon Midline Repulsion

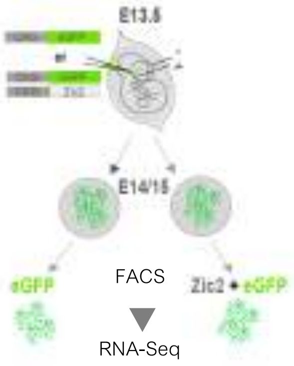


Williams et al. *Neuron* (2004)

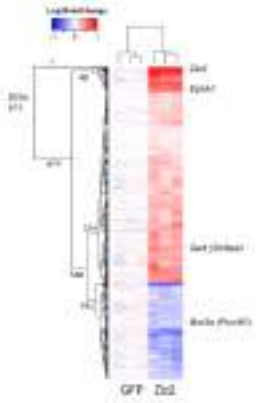
García-Frigola et al. *Development* (2008)

The genetic program triggered by Zic2

In utero electroporation

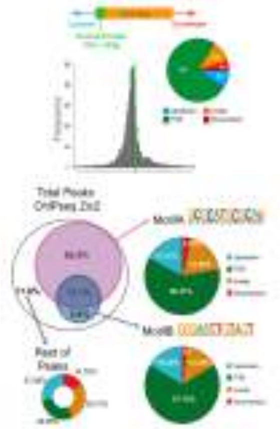


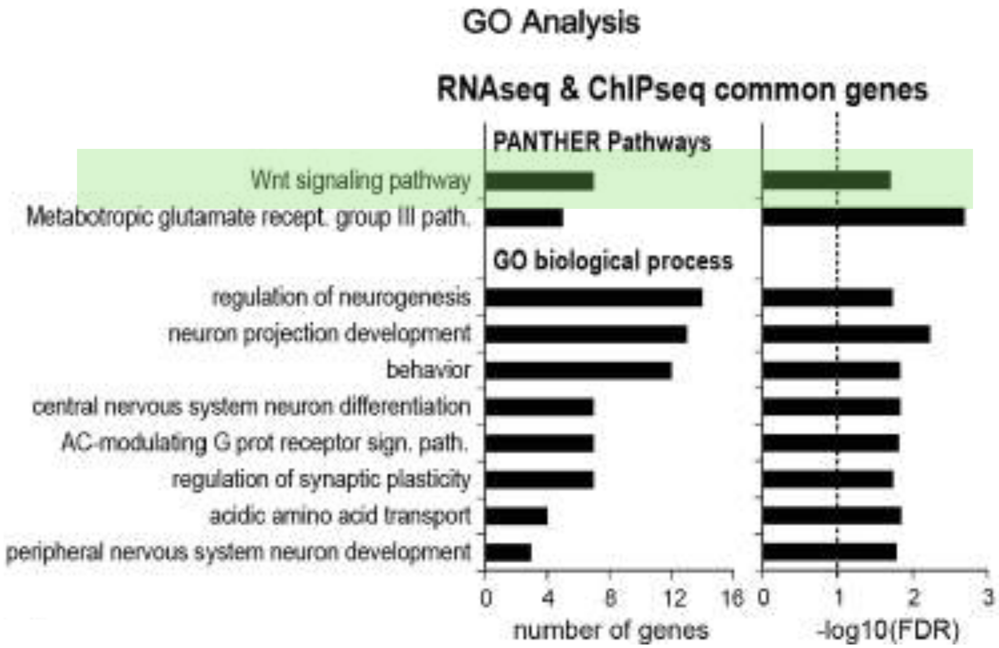
Heatmap



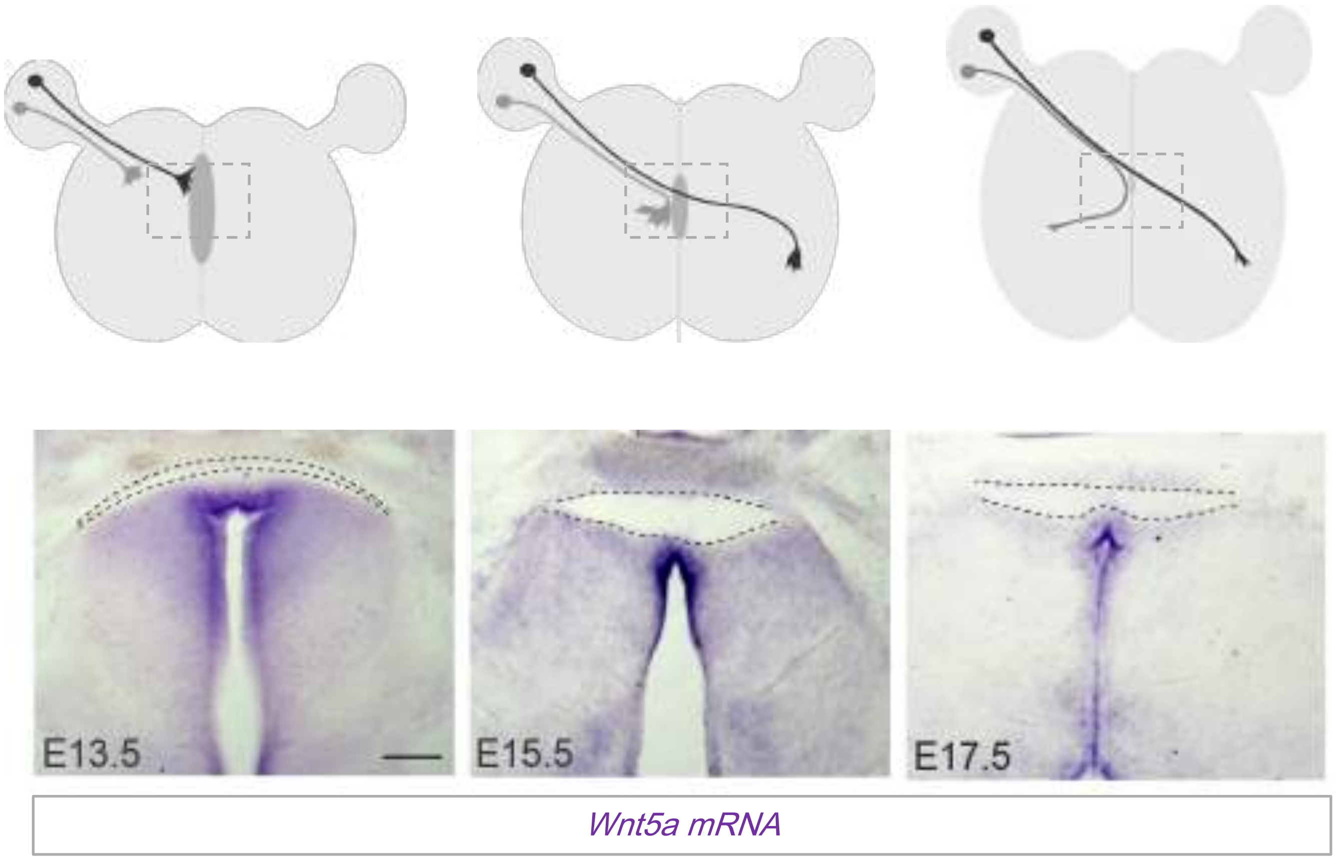
Zic2 ChIP-Seq in retinal tissue

Zic2 mainly binds to promoters

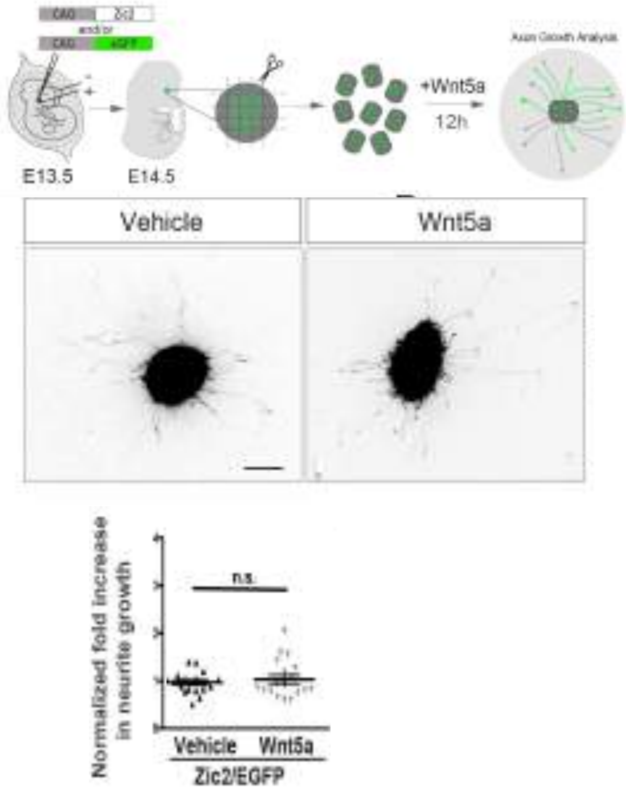


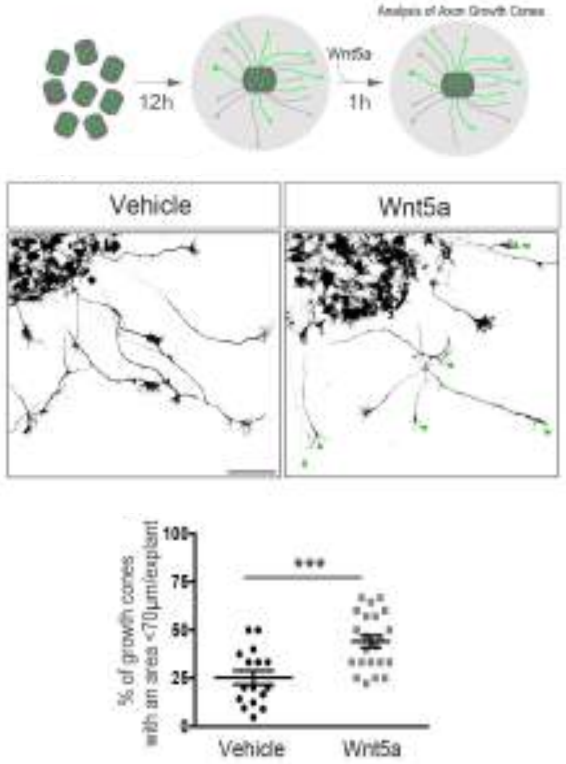


Wnt5a is highly expressed at the developing chiasmatic midline

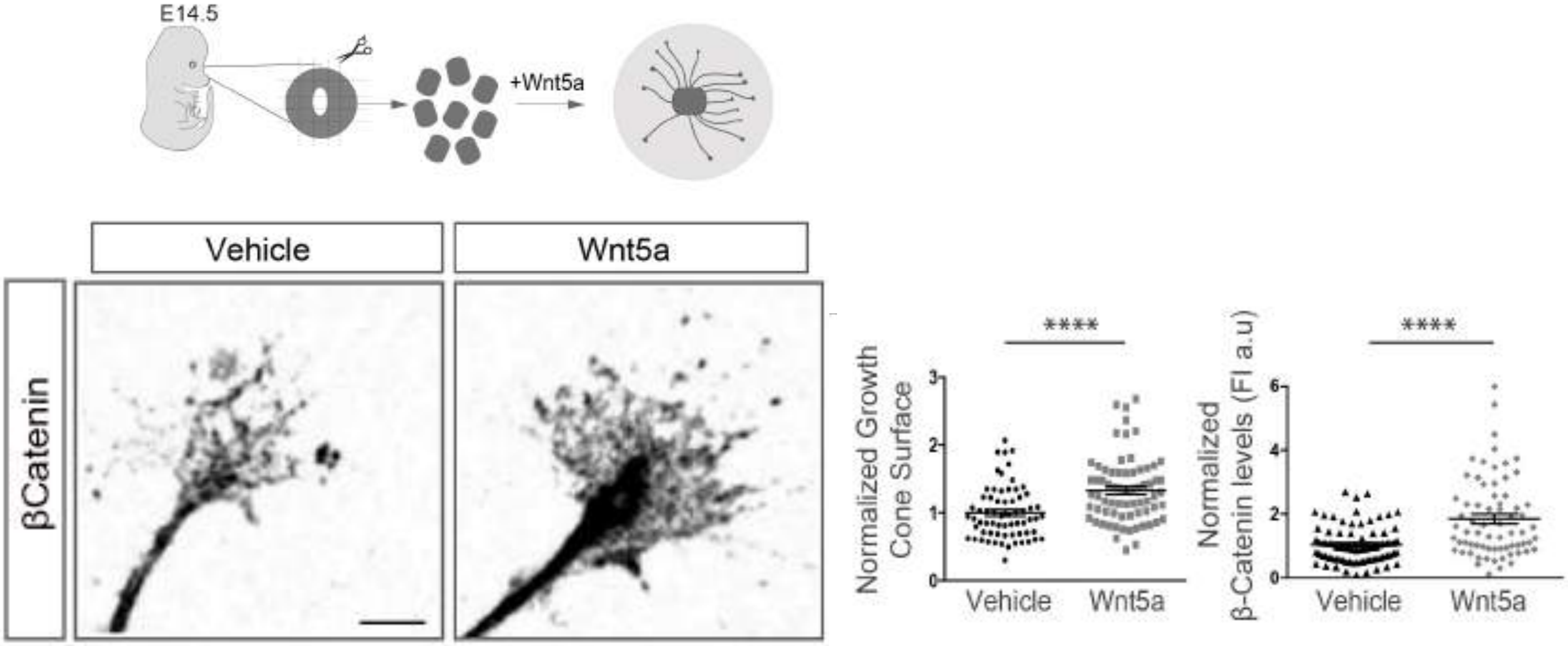


Wnt5a induces the transient collapse of ipsilateral Zic2/RGC axons

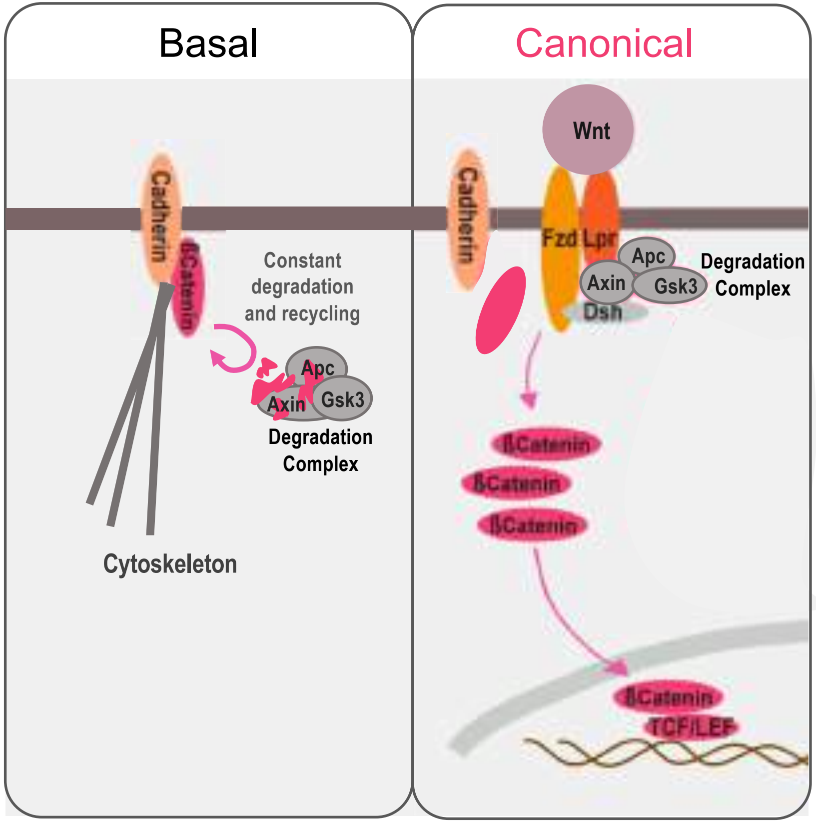




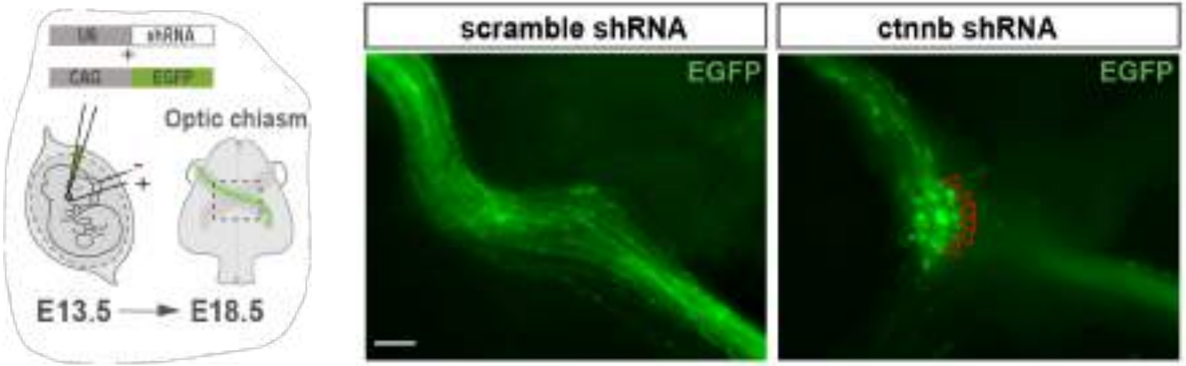
Wnt5a enhances the growth of contralateral RGC axons

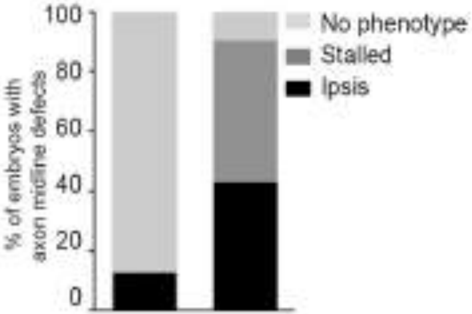


The Wnt Canonical Signaling Pathway

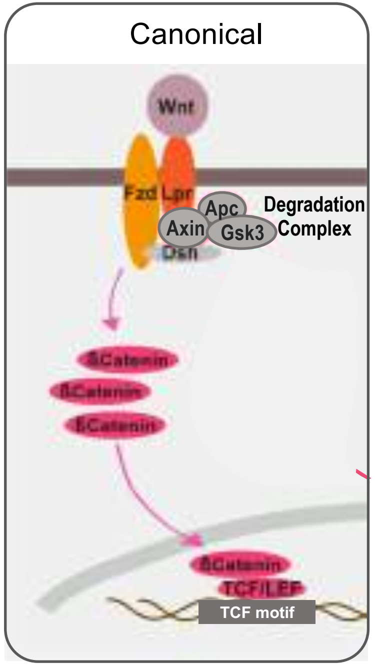


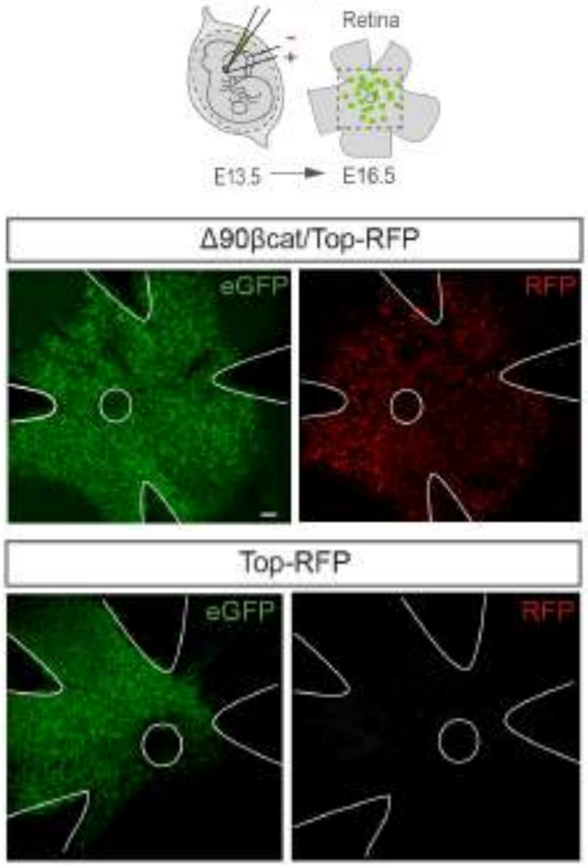
βcatenin is required for midline crossing

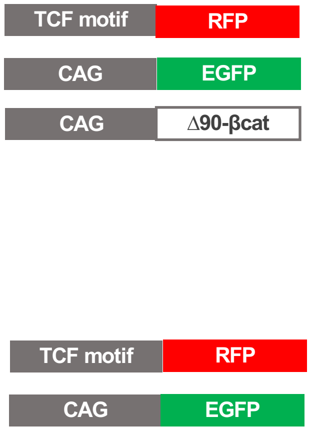




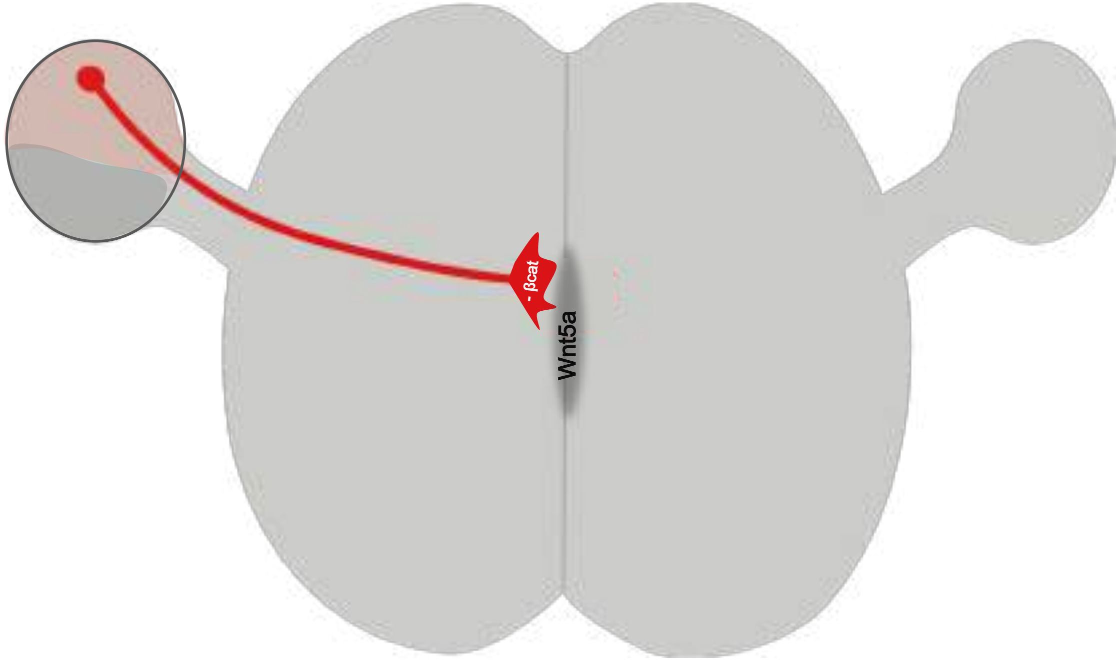
Canonical Wnt signaling is not activated during midline crossing



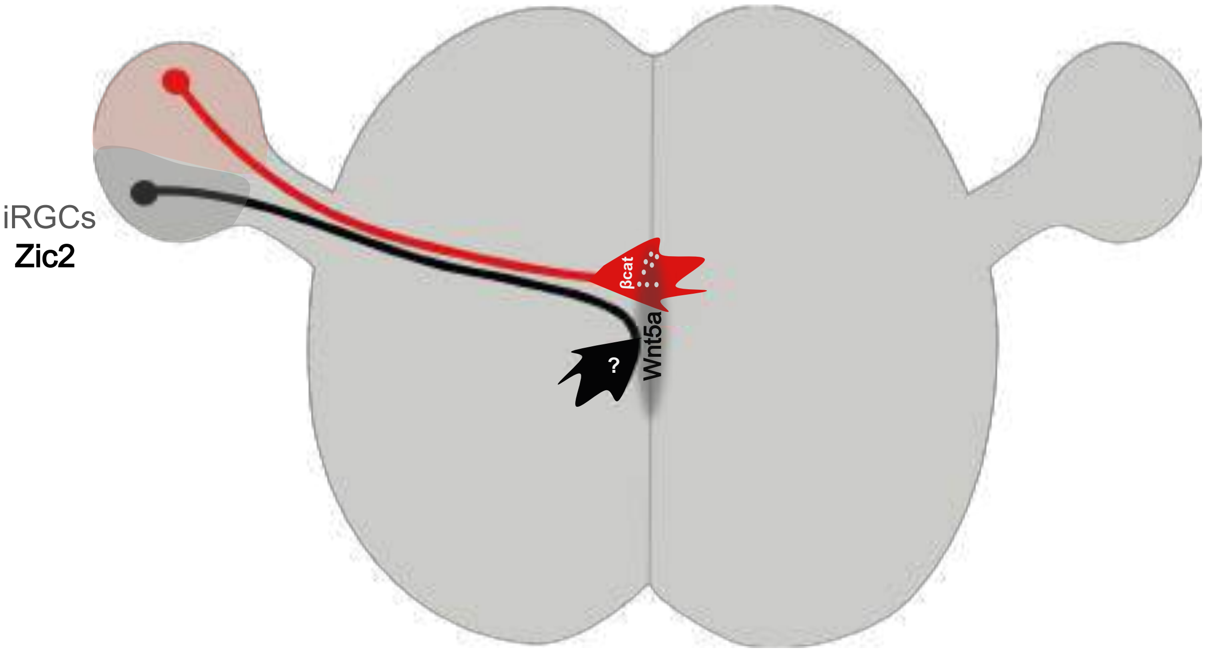




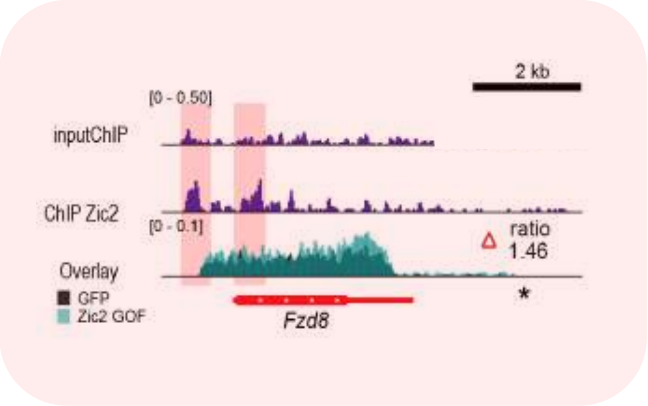
A βcatenin-dependent/not-canonical Wnt signaling is activated in contralateral RGCs to cross the midline

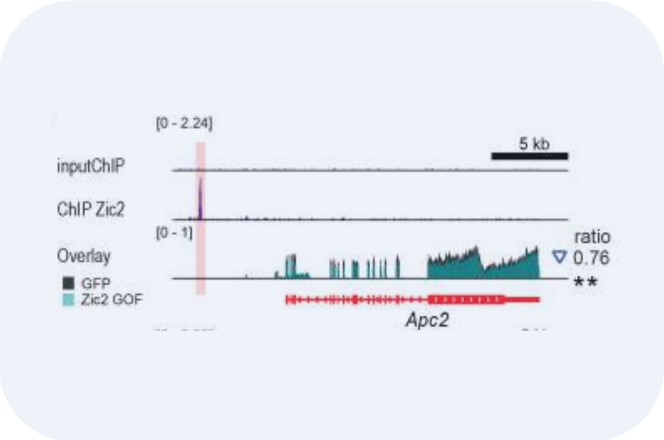


How does Zic2 affect the βcatenin-dependent/not-canonical Wnt pathway to avoid midline crossing?

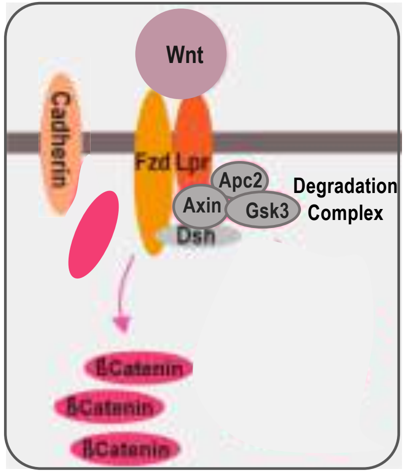


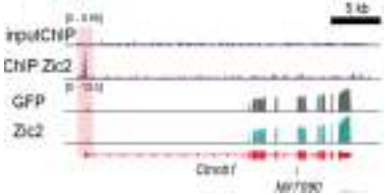
Zic2 induces a set of Wnt receptors and represes Apc2

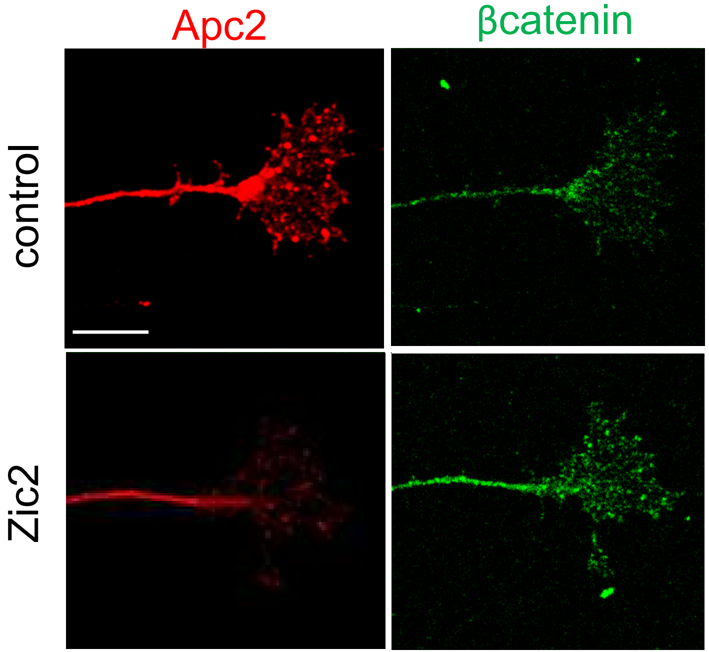


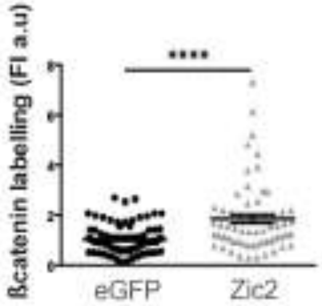


Before reaching the midline βcatenin levels are higher in iRGC than in cRGCs

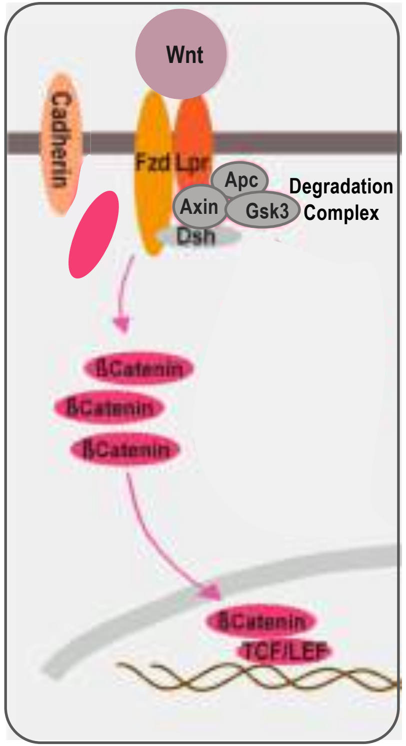


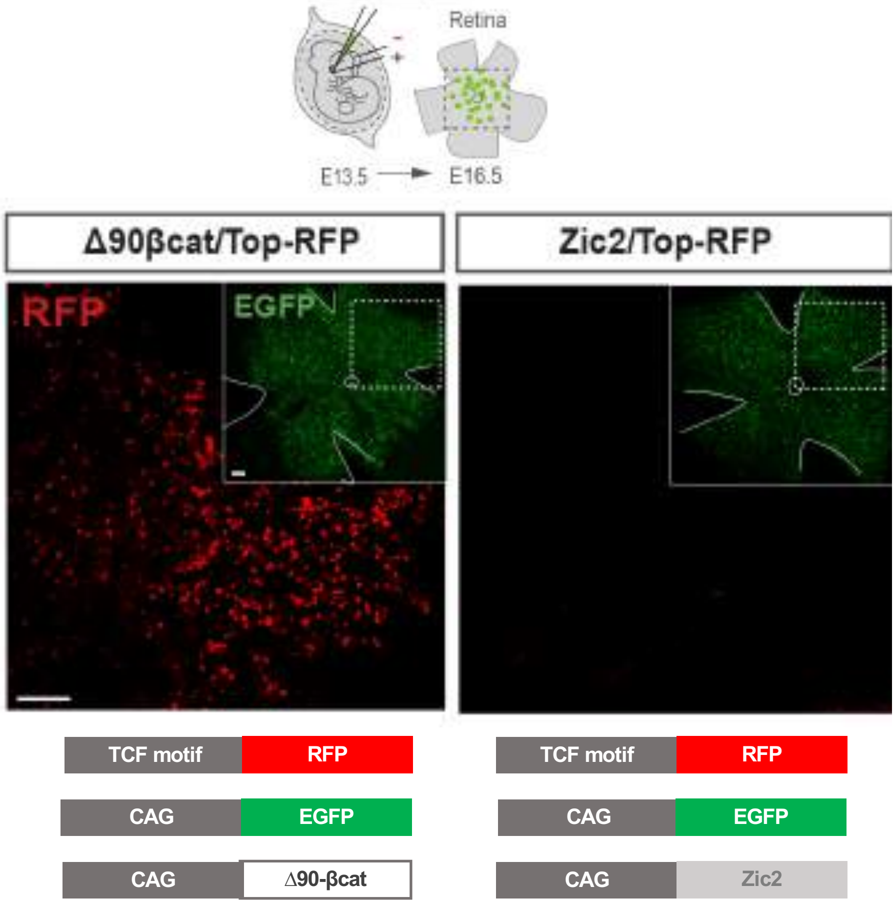




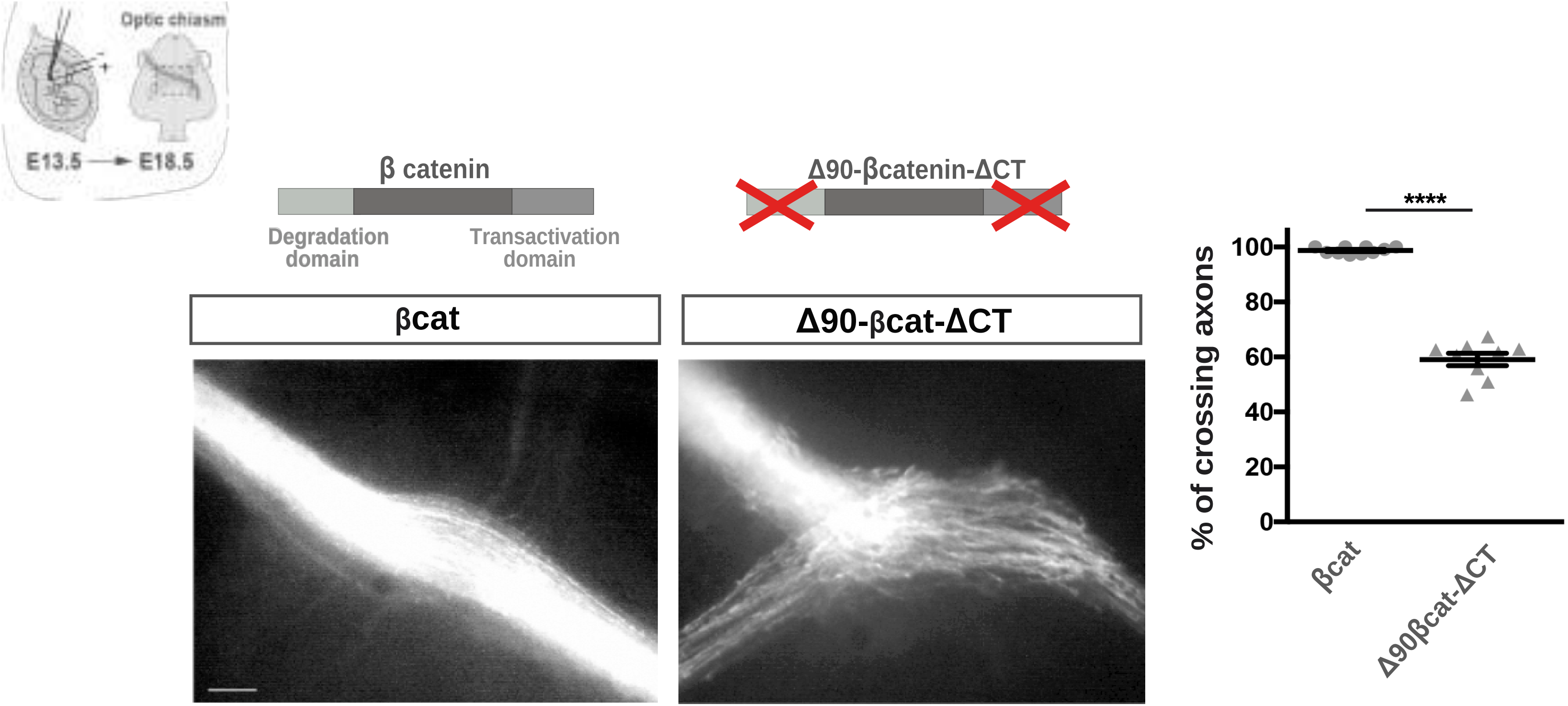


Zic2 does not activate the canonical pathway in iRGCs

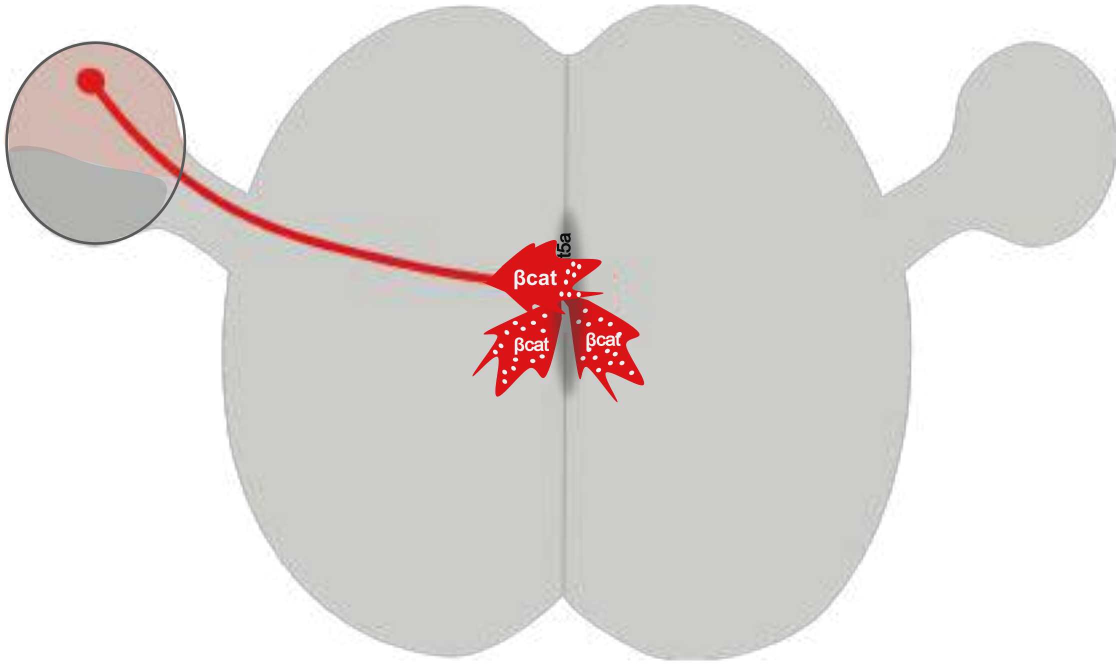




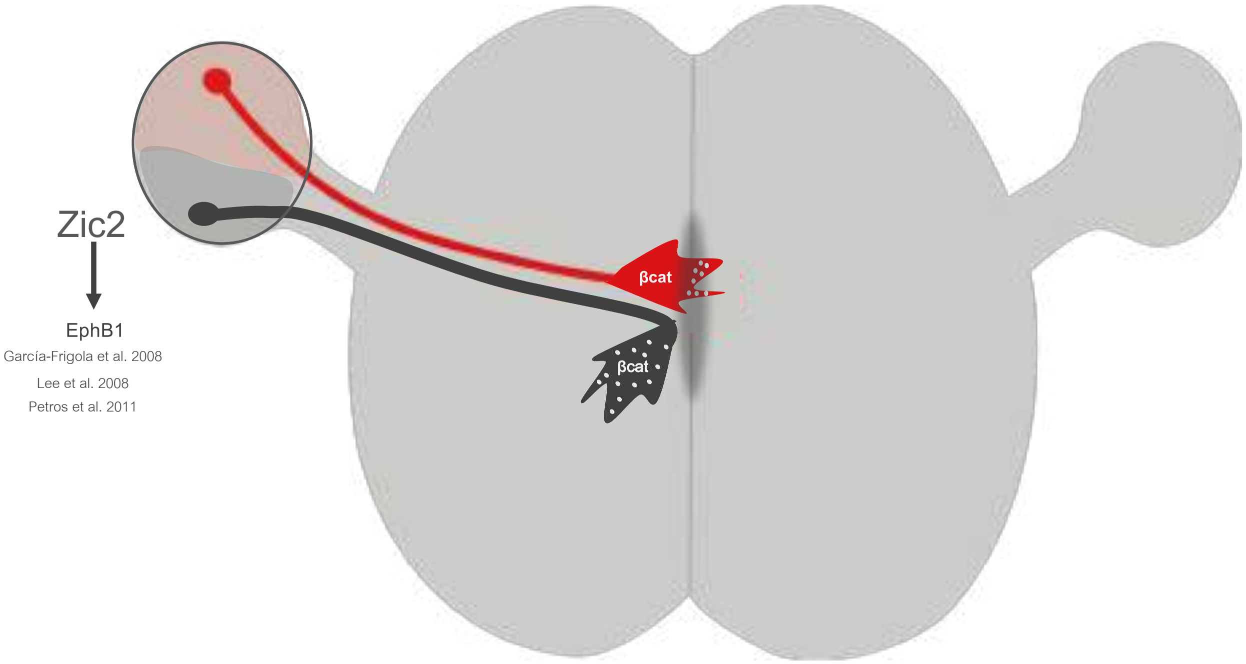
Accumulation of βcatenin in the axons produces an ectopic ipsilateral projection



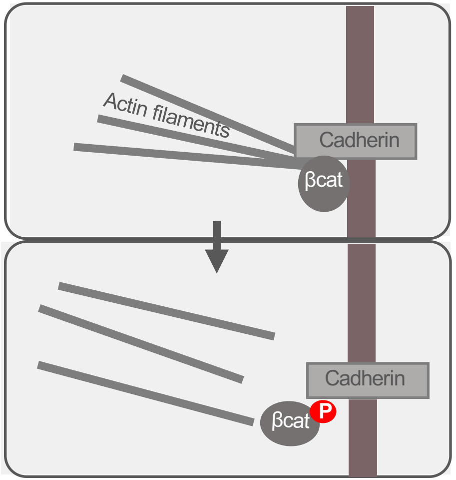
Alterations in the levels of βcatenin disrupt midline crossing



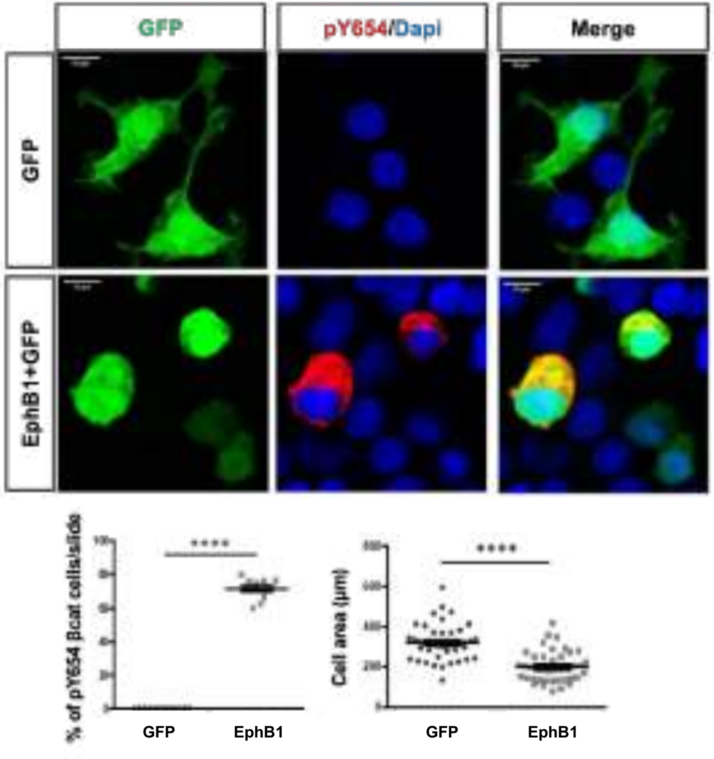
How do the iRGCs turn at the midline despite the high levels of βcatenin?



EphB1 phosphorylates βcatenin in Y645



Kwonseop and Lee (2011)



Working Model

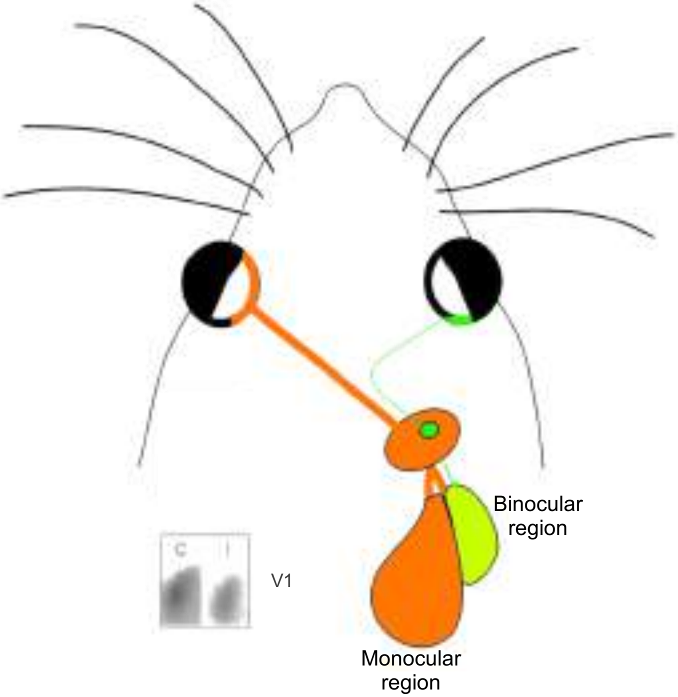
Conclusions (I)

- Contralateral and ipsilateral RGC axons respond differentially to Wnt5a
- An alternative Wnt pathway that is βcatenin-dependent but not canonical is essential for midline crossing
- Zic2 abrogates the alternative Wnt pathway to block the positive axonal response to Wnt5a
- Zic2 induces accumulation of βcatenin at the growth cone
- EphB1 phosphorylates βcatenin in Y654

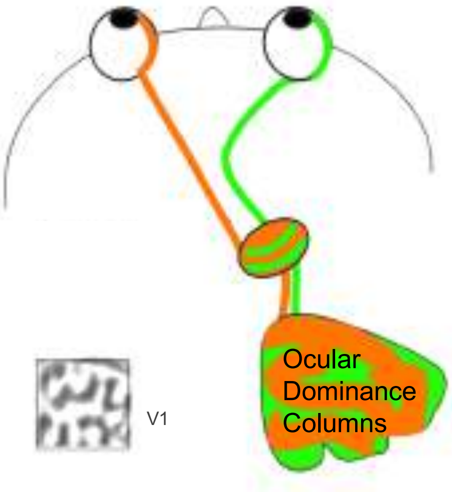
Morenilla-Palao et al. BioRxiv 2020

Mice do not have ocular dominance columns in the visual cortex

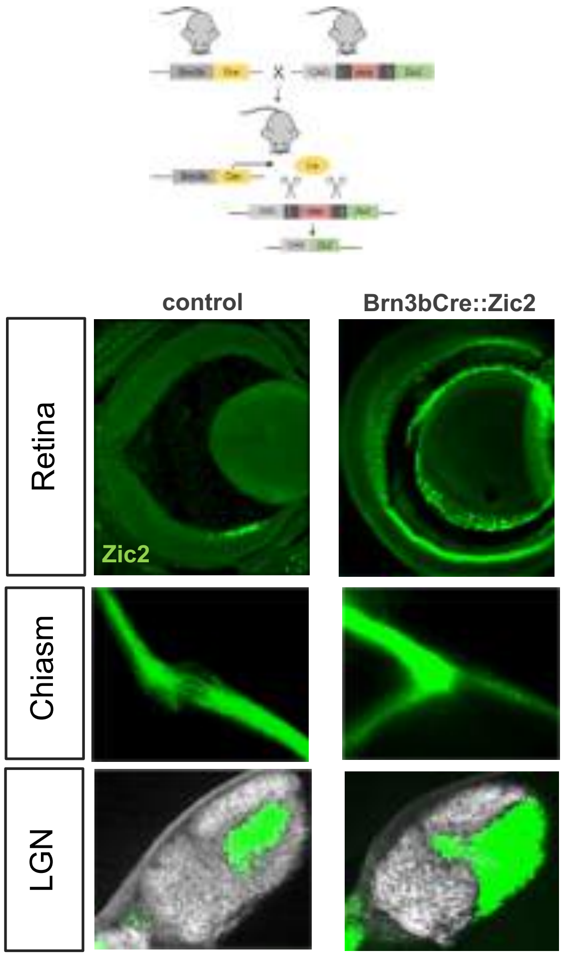
Rodents

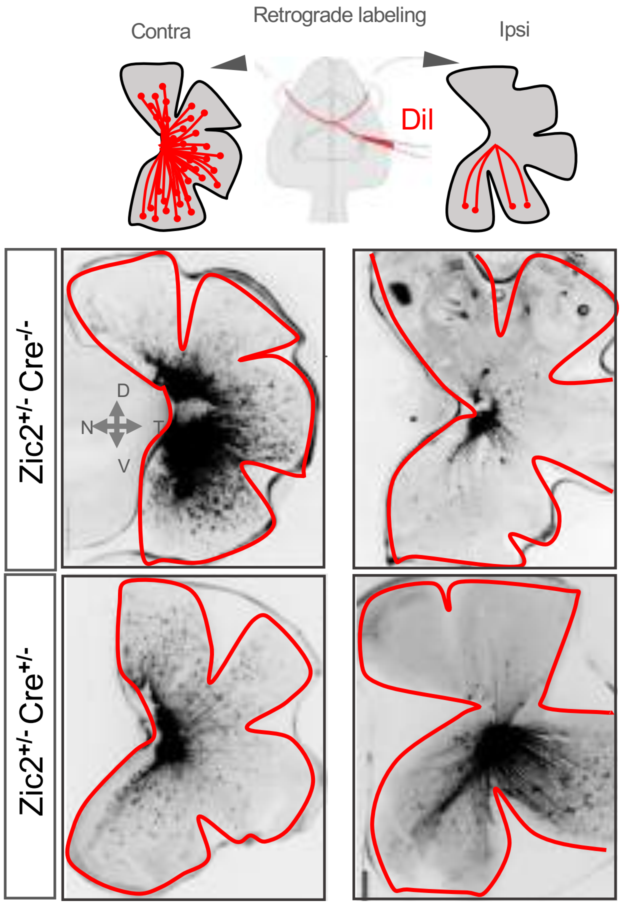


Primates

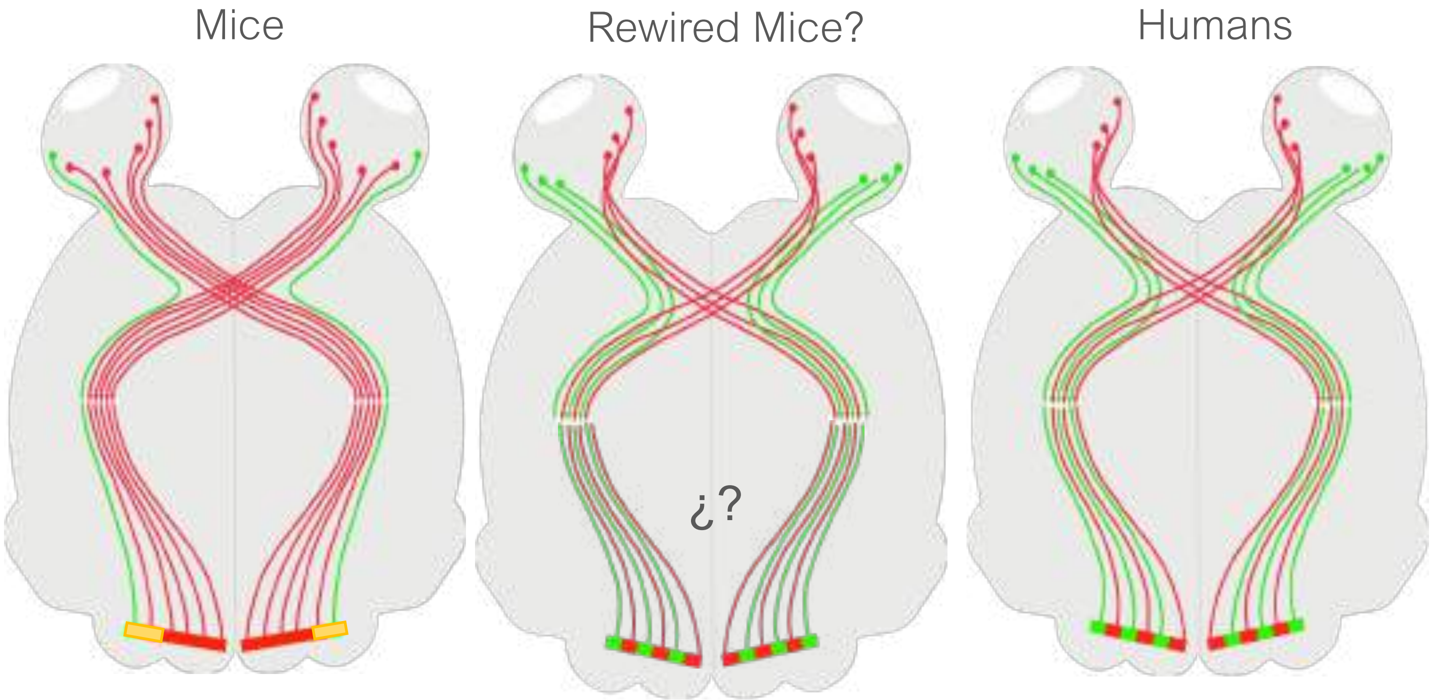


Generating a mouse line with a rewired visual system



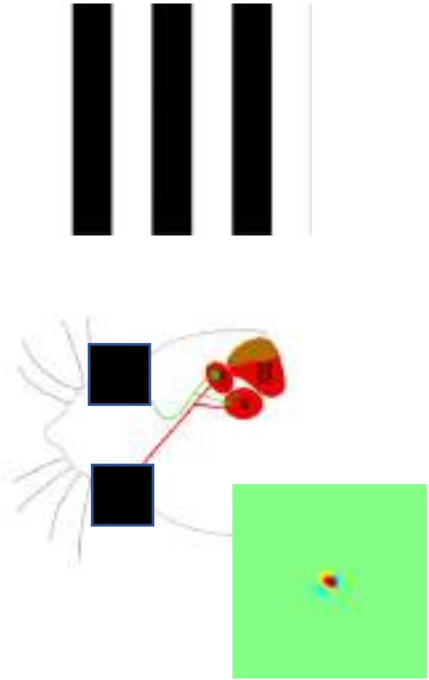


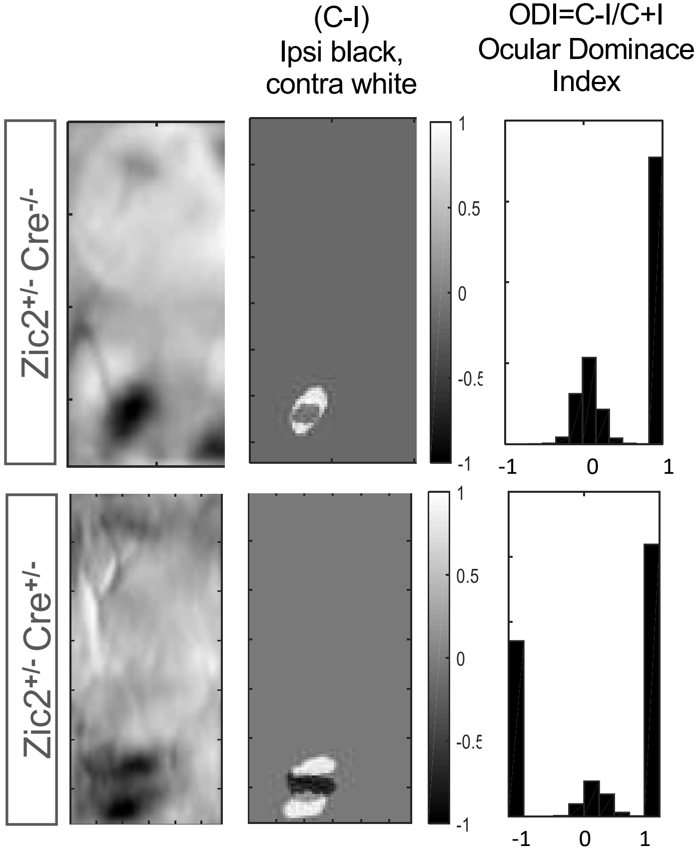
Does a change in the primary visual pathway leads to a rewiring of the secondary pathway?



Ocular dominance columns emerge in the V1 of rewired mice

Experimental Approach





Conclusions (II)

- The D-N retina is reluctant to acquire an ipsilateral RGC fate
- An increase in the number of ipsilateral retinal neurons generates a pattern of ocular dominance columns in the visual cortex similar to the observed in species with good binocular vision
- A change in the expression of a single gene that induces a rewiring of the first segment of the visual pathway leads to a functional reorganization of the circuit that may result in the emergence of binocular vision
- The rewired mice may be useful as an experimental model to understand how binocular vision emerged in evolution and to better investigate the physiological basis underlying binocular vision

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