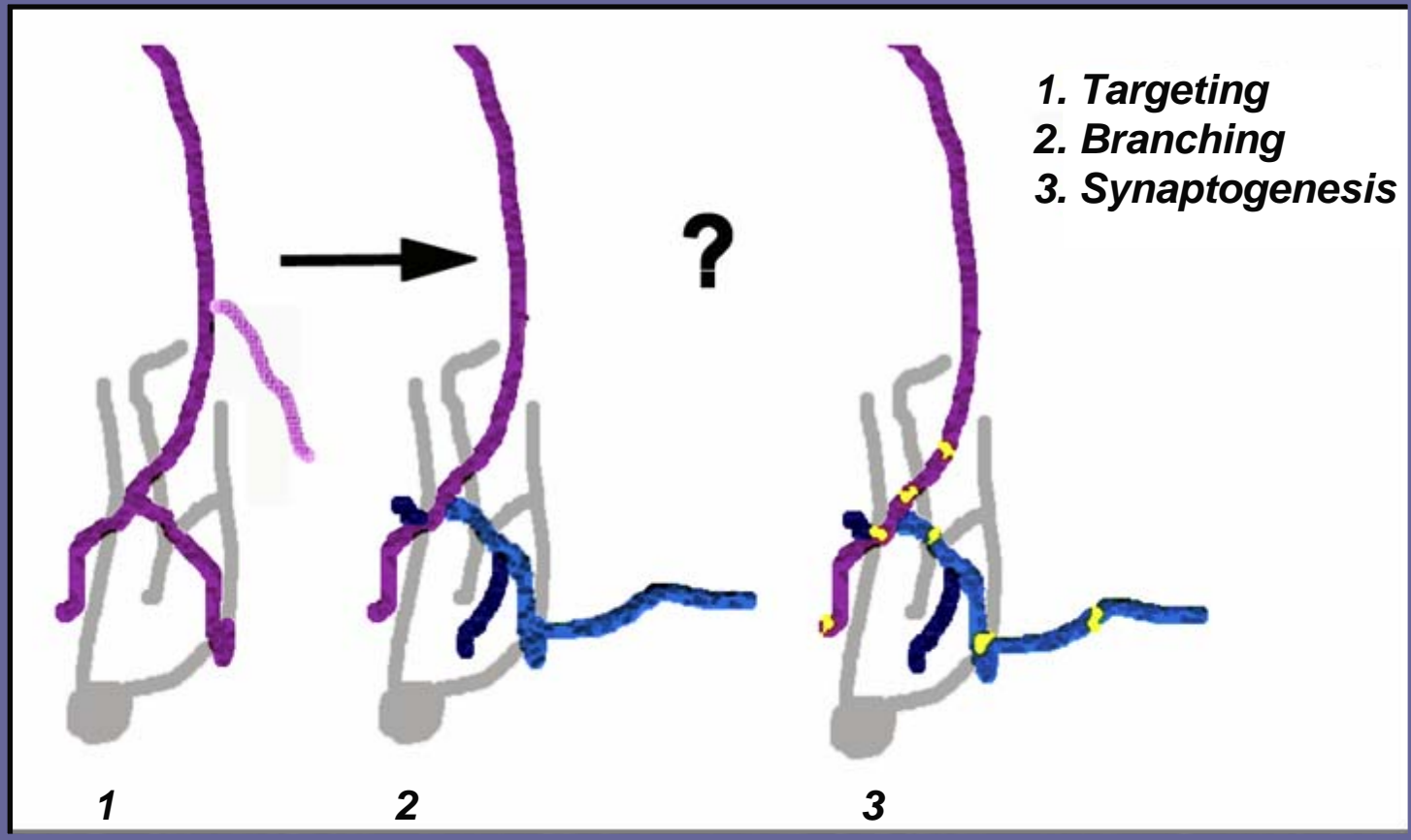
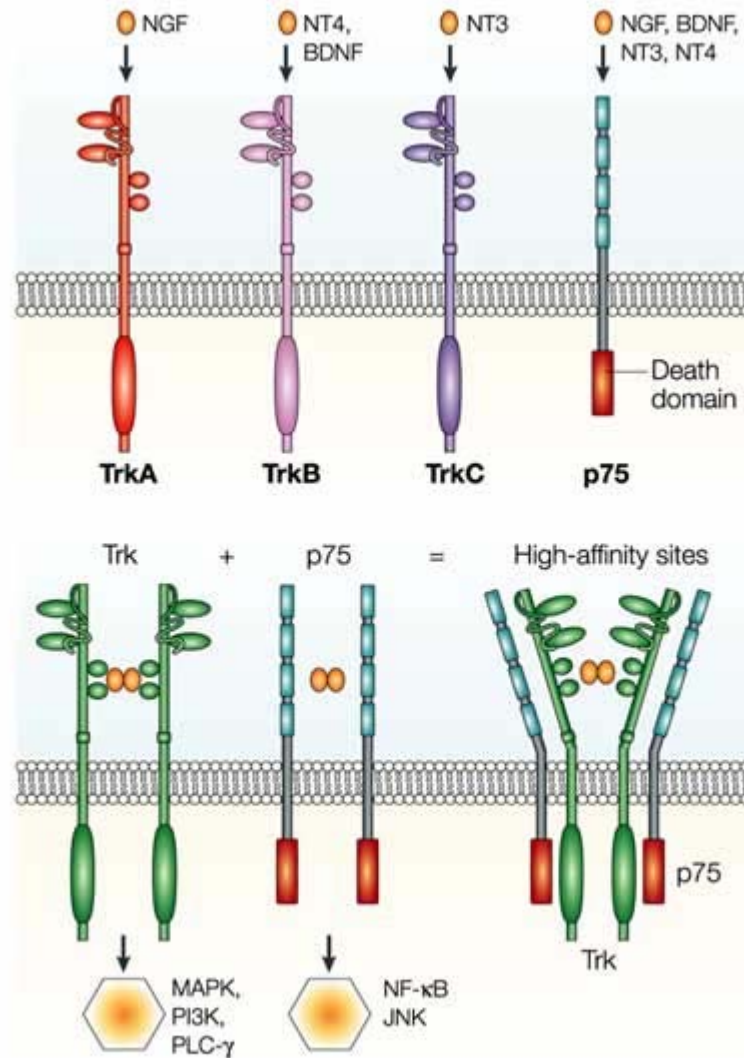


Neurotrophin-induced plasticity in the developing visual system: from axons and dendrites to synapses

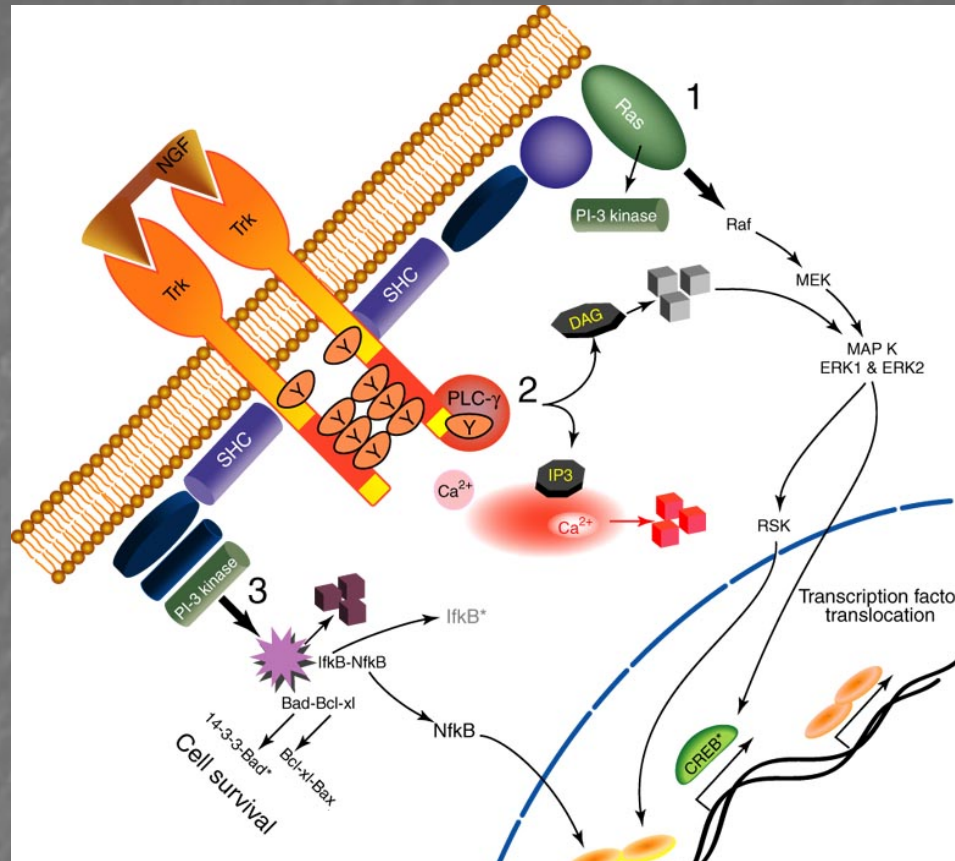


*Susana Cohen-Cory, Ph.D.
Dept. of Neurobiology and Behavior
University of California, Irvine*

Neurotrophins and their receptors

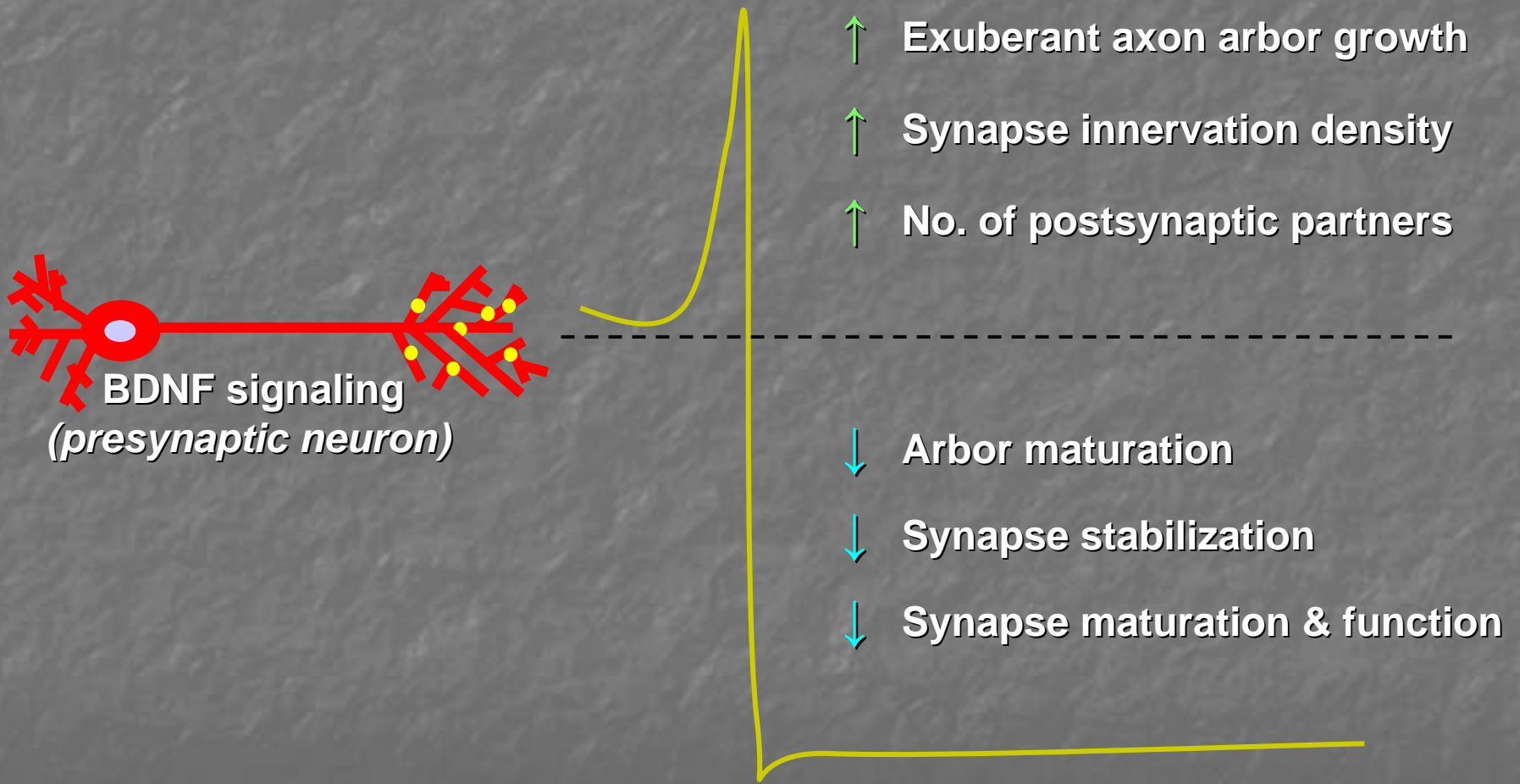


Neurotrophins can induce multiple actions and activate multiple signaling mechanisms

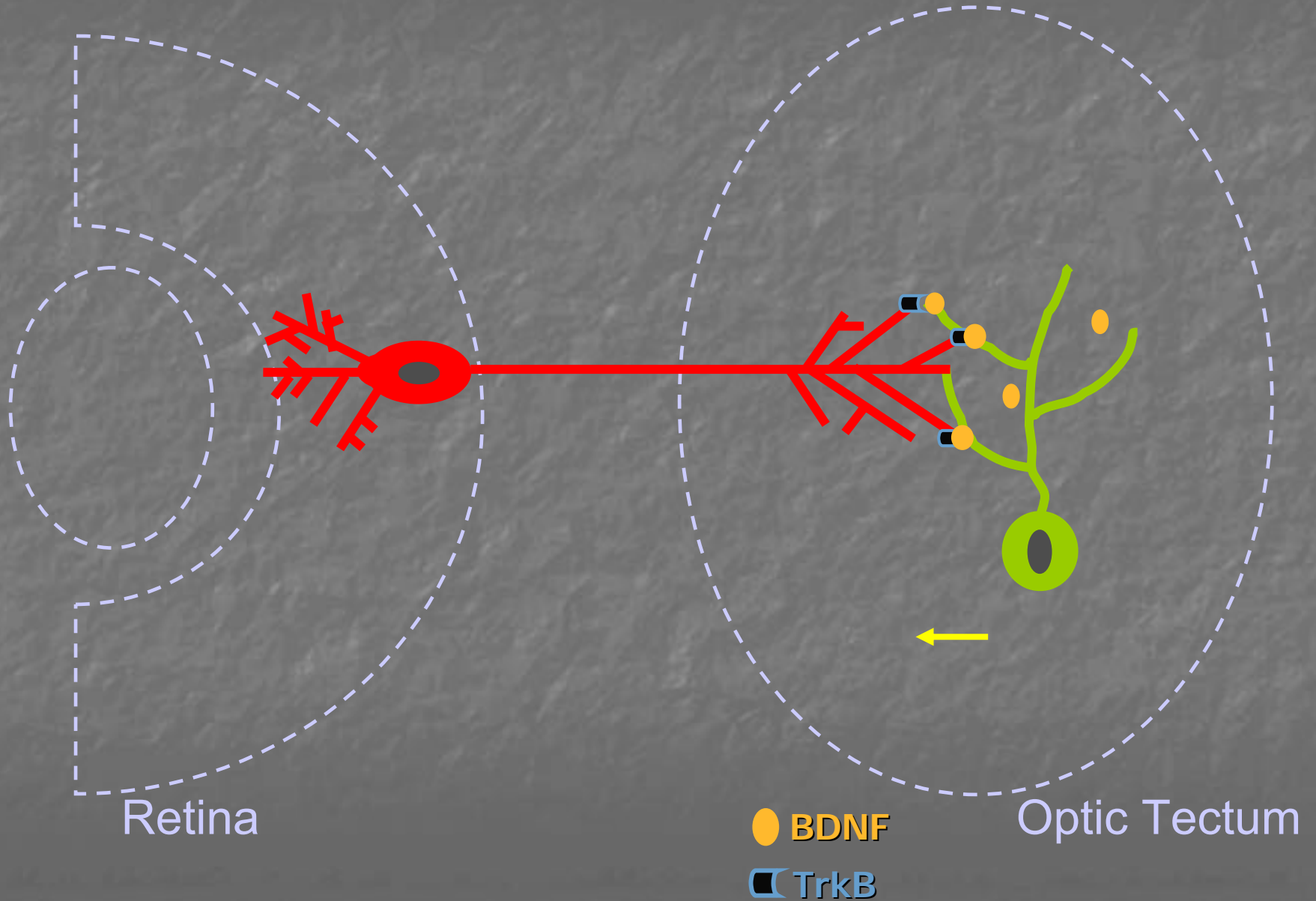


- *Neuronal survival*
- *Differentiation*
- *Axonal/dendritic growth*
- *Synaptic potentiation/plasticity*

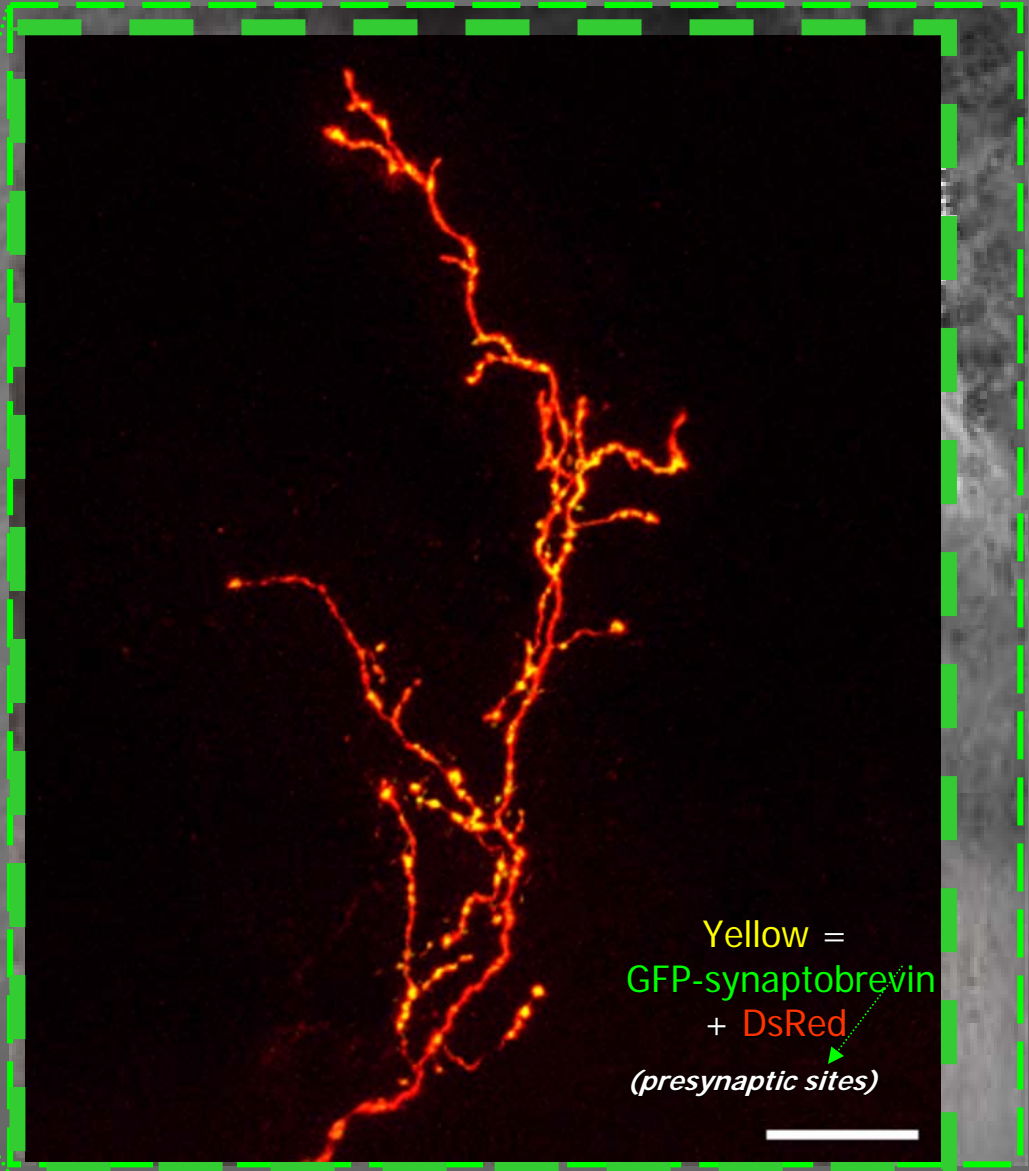
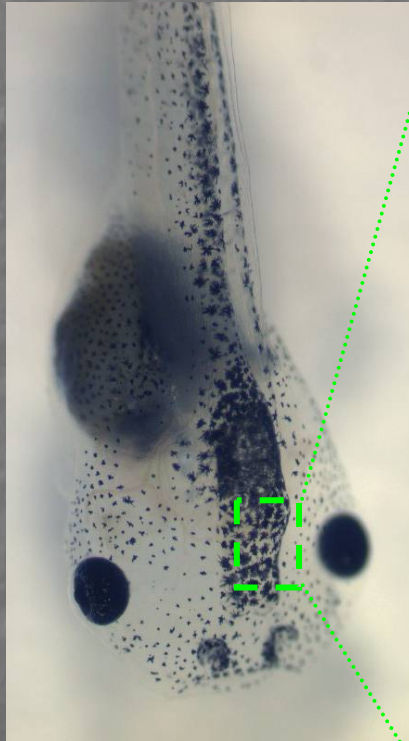
BDNF and the control of synaptic connectivity



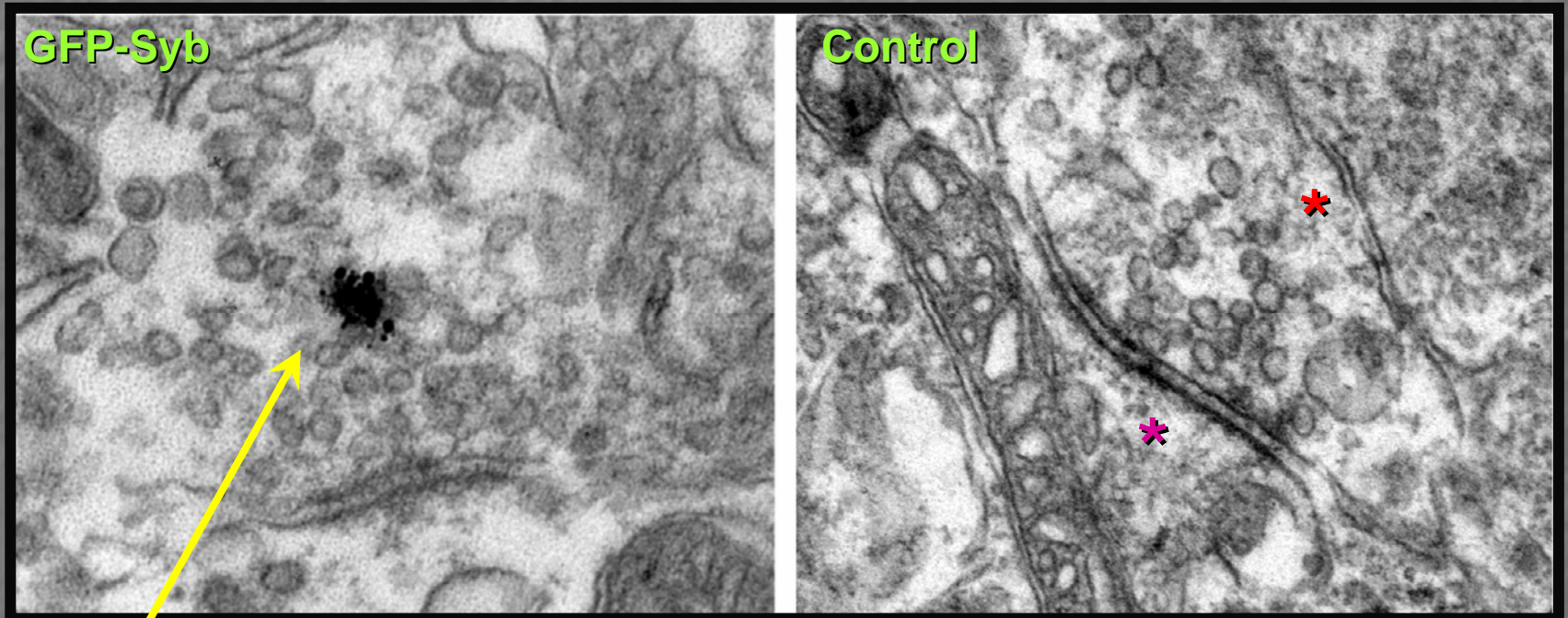
IN VIVO ROLE – ALTERING TARGET TISSUE INFLUENCE



Imaging presynaptic sites in retinal axons *in vivo*



GFP-tagged synaptic markers localize to ultrastructurally identified synapses in the tadpole optic tectum

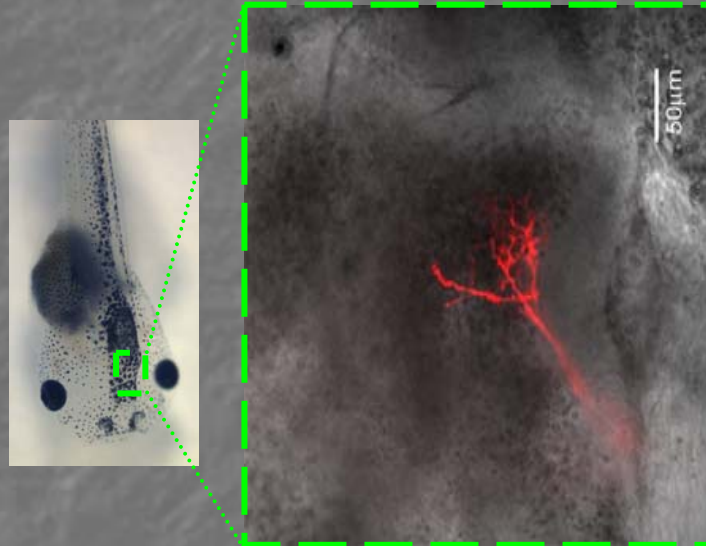


Ab-associated
gold particles

* Postsynaptic ending
* Presynaptic terminal

Manipulating BDNF levels in the optic tectum

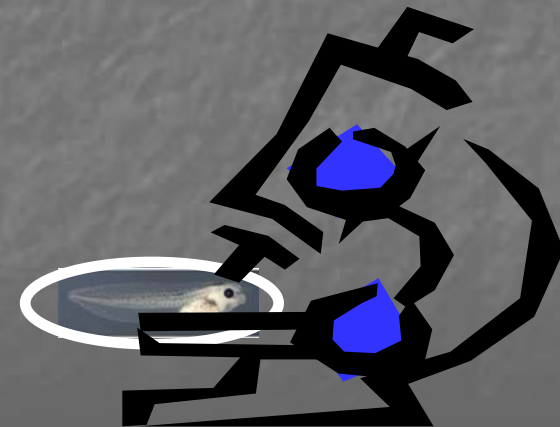
↑ *BDNF* or *blocking antibodies to BDNF* ↓



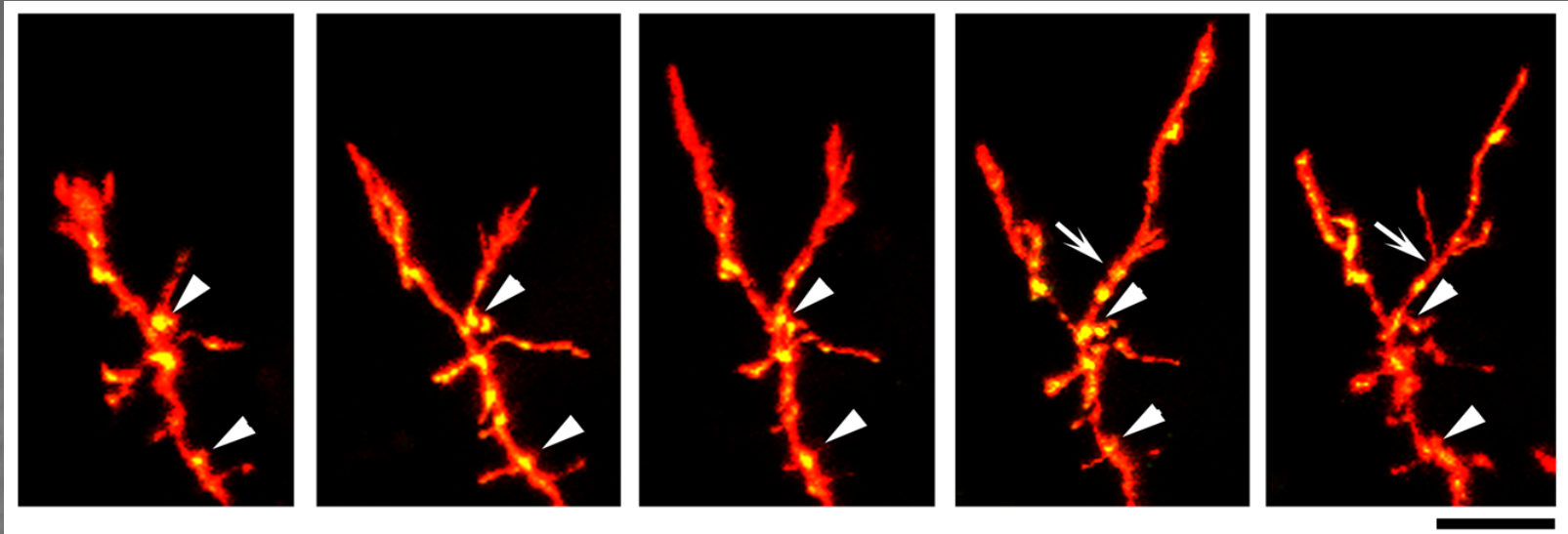
BDNF or
anti-BDNF



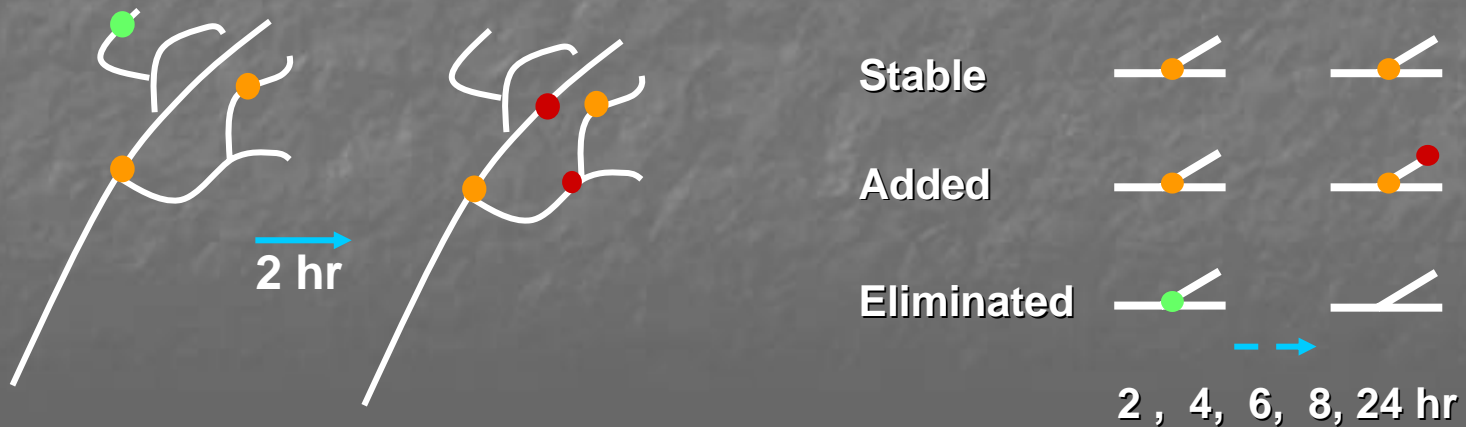
Time lapse



Synapses are formed and eliminated in actively branching axon arbors

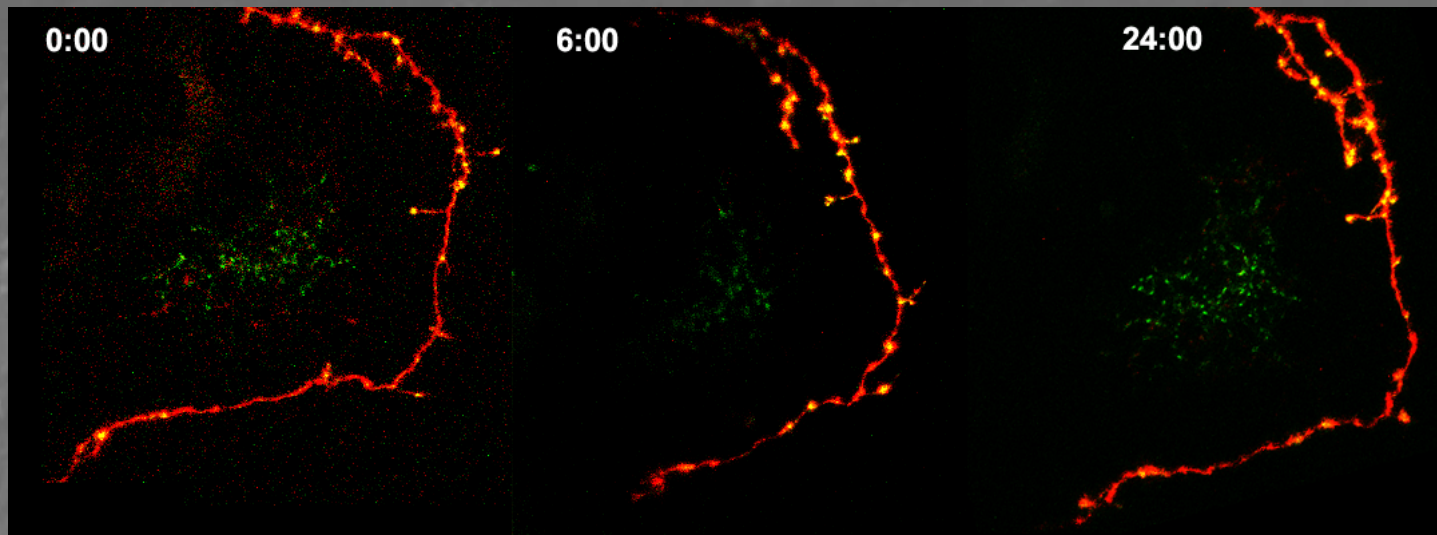


Analysis of axon branch and presynaptic site dynamics

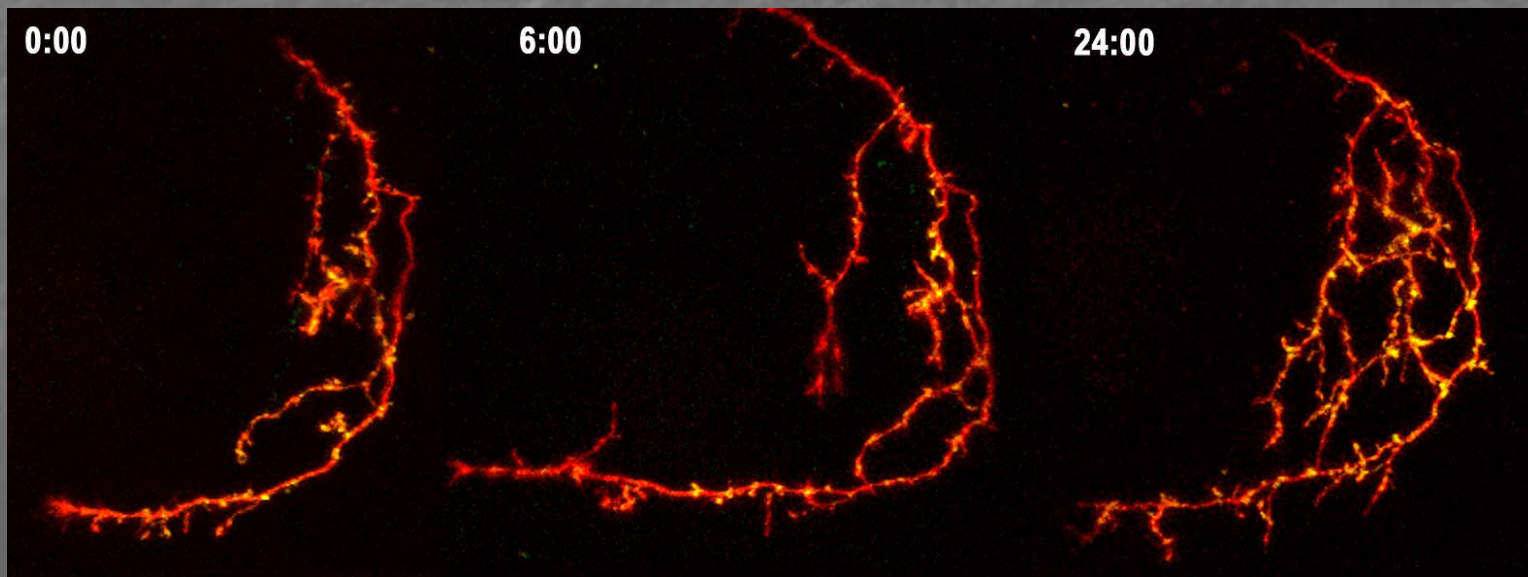


BDNF enhances RGC axon arbor complexity and synaptic number

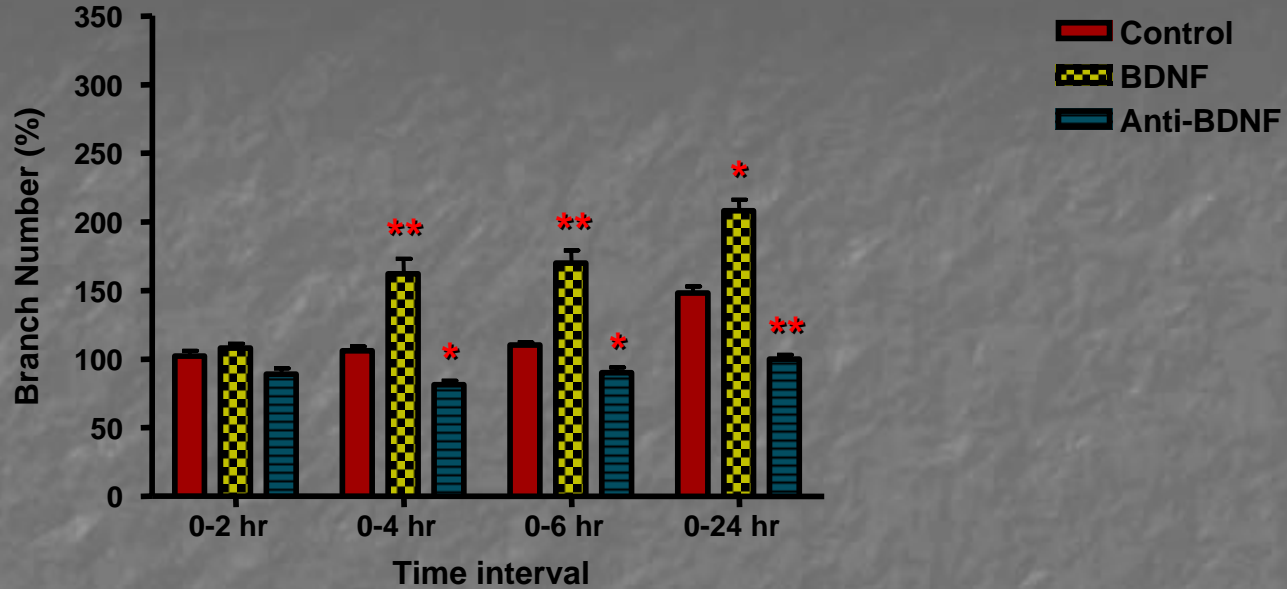
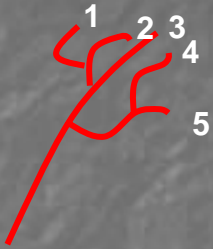
Control



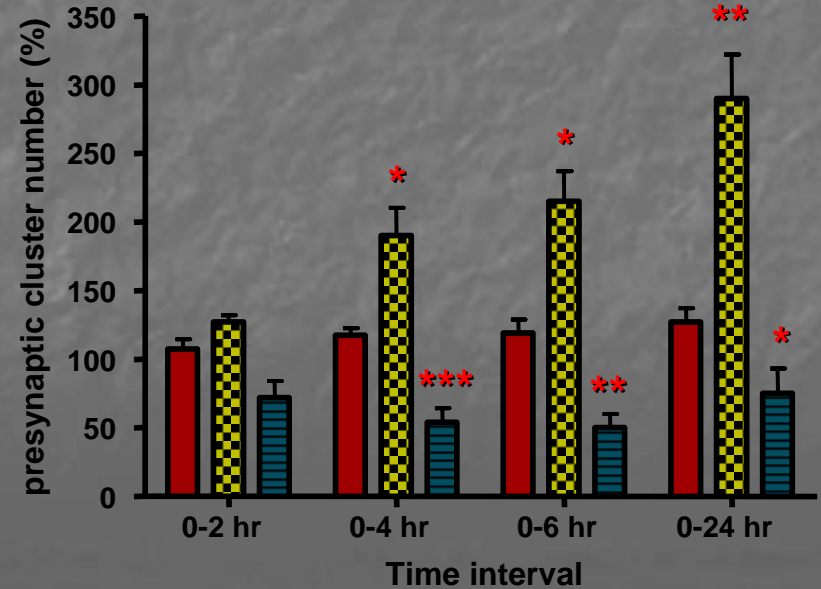
BDNF



BDNF influences axon arbor branch number...

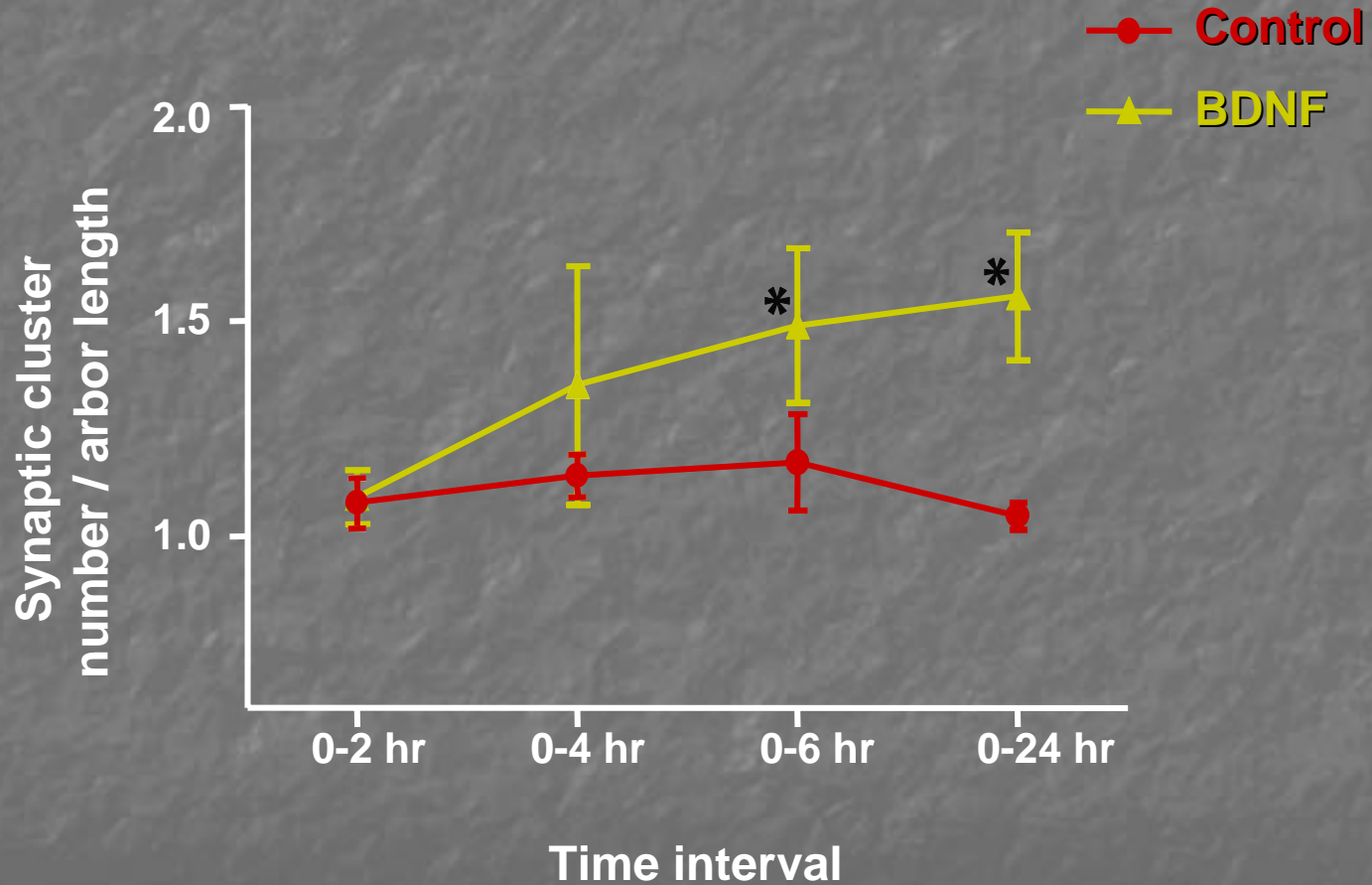


...and synapse number

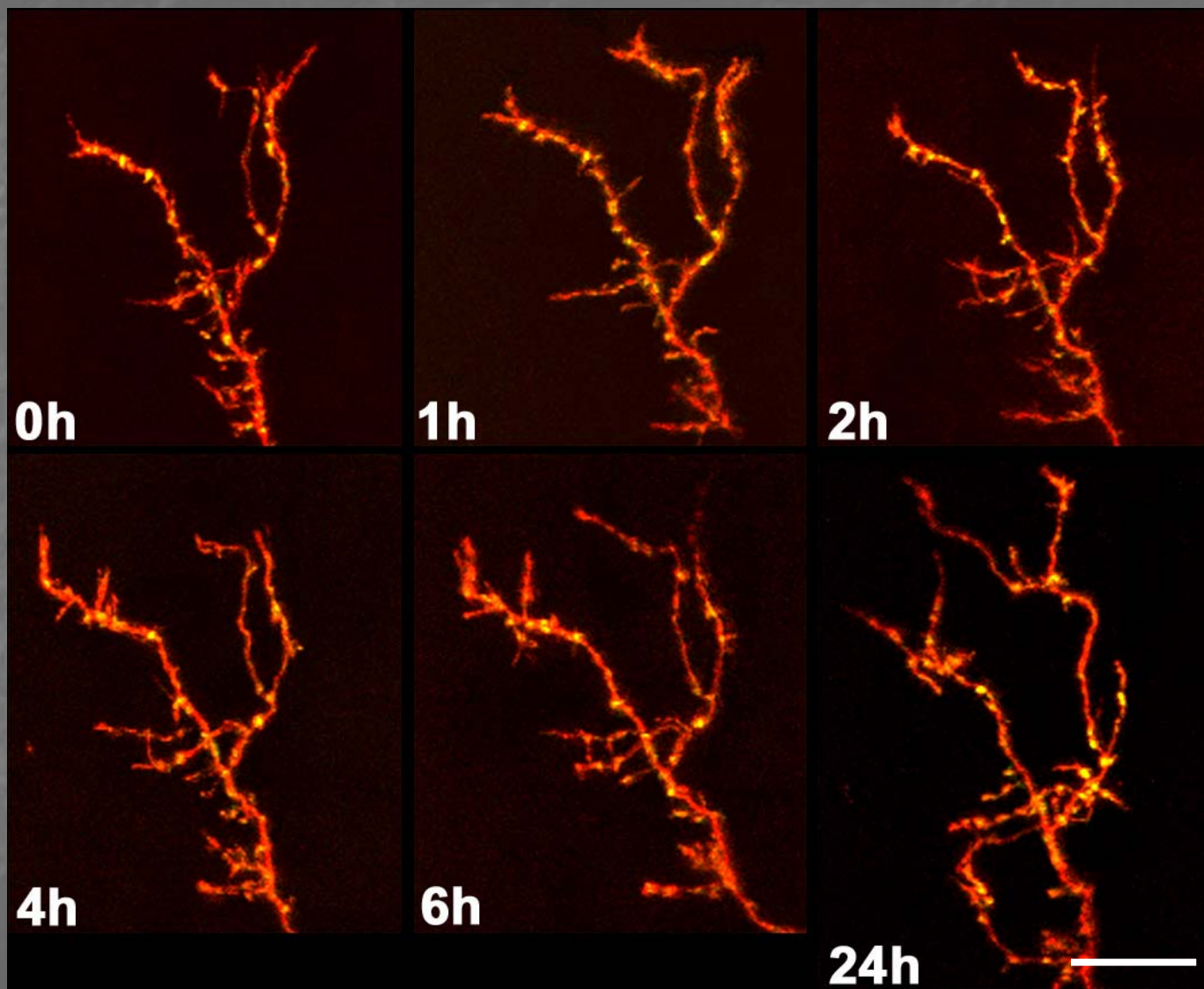


*** $p < 0.0005$
** $p < 0.005$
* $p < 0.05$

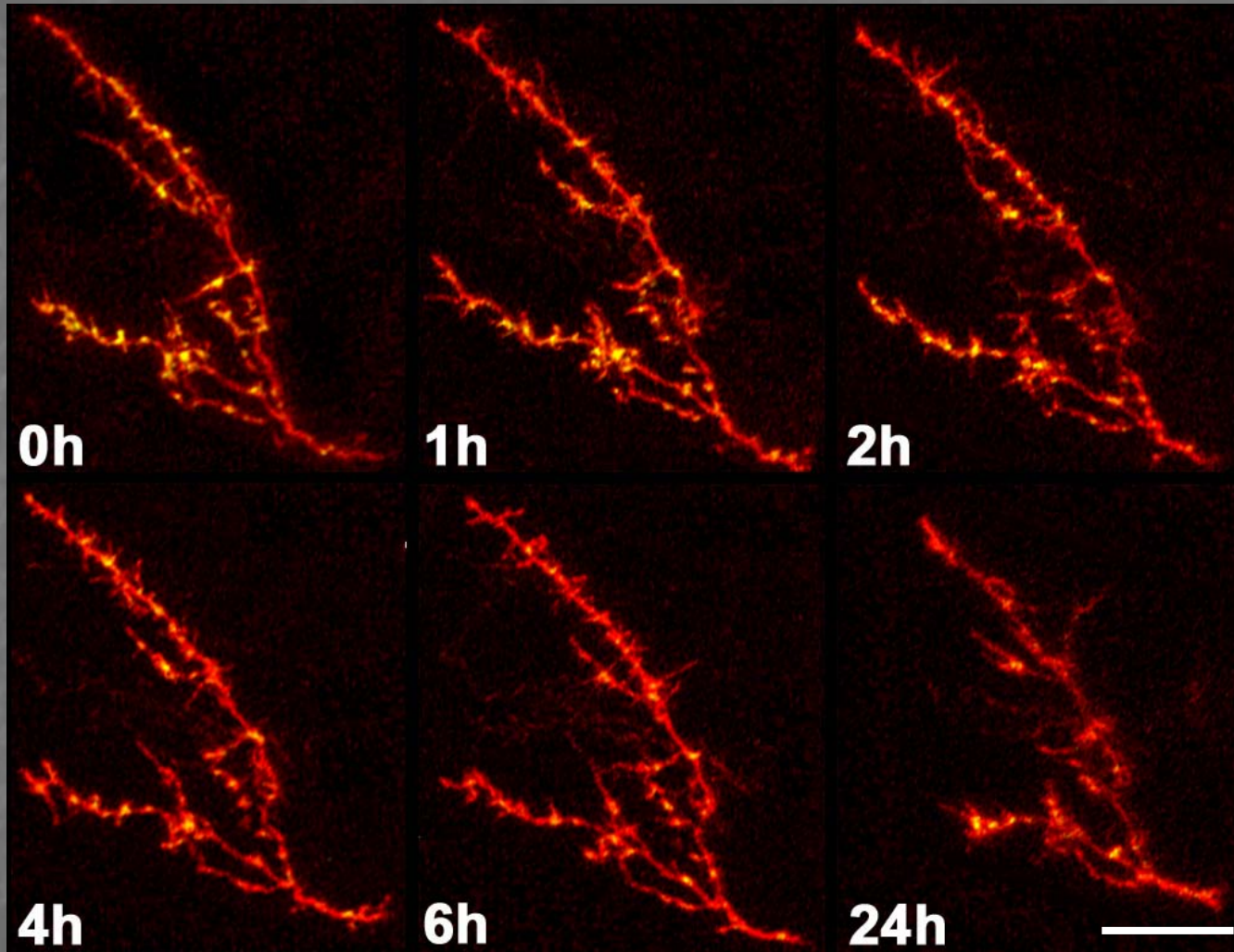
BDNF increases synaptic innervation density per axon terminal



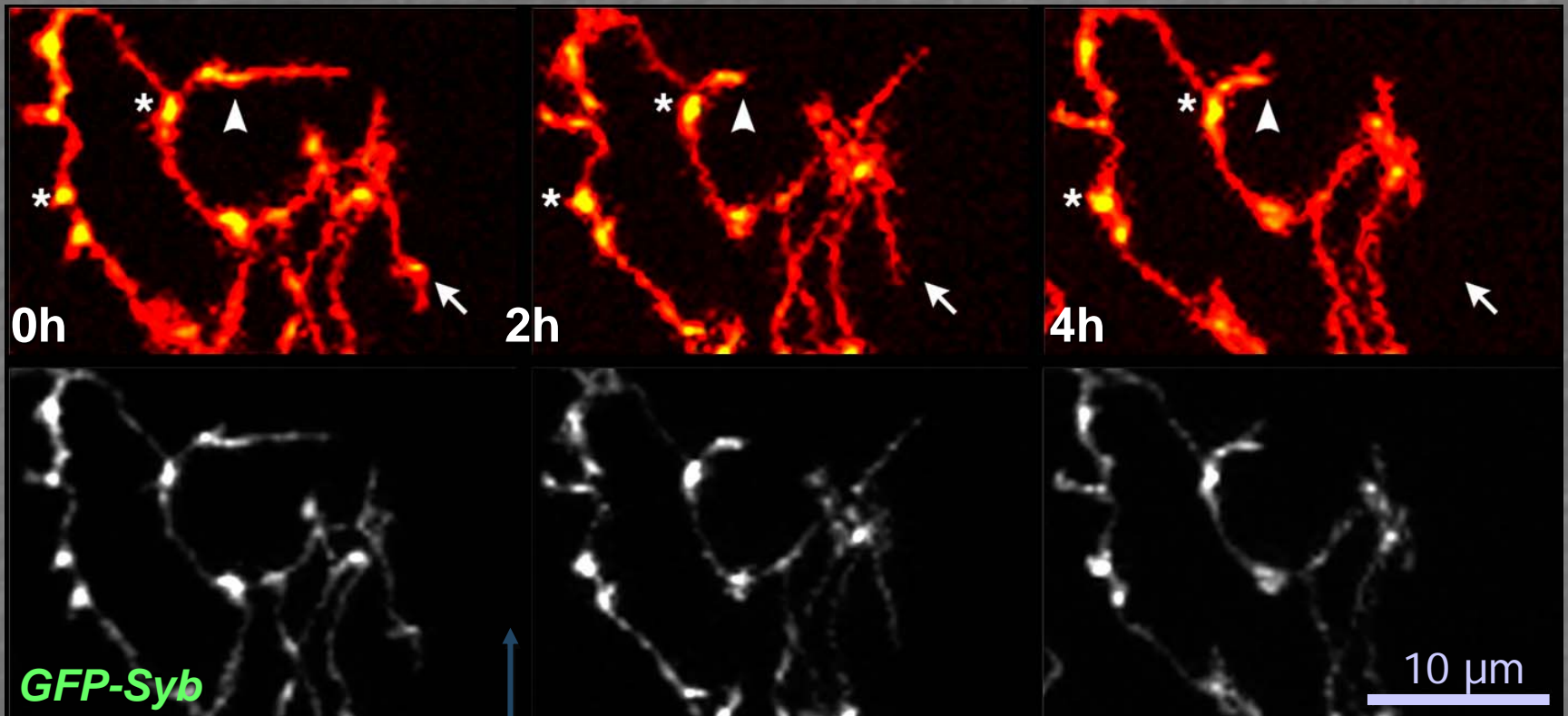
Control



Anti-BDNF



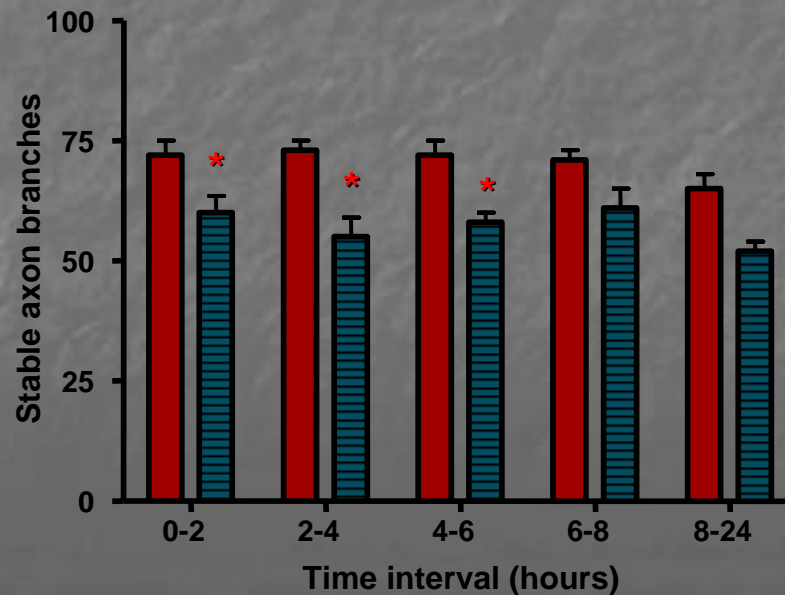
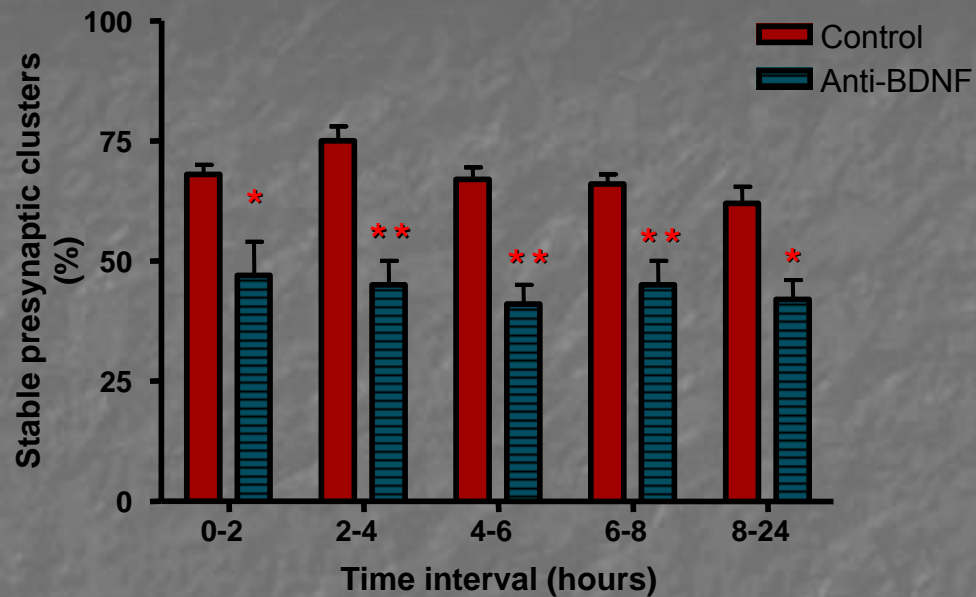
Neutralizing endogenous BDNF with blocking antibodies promotes axon branch and synapse elimination



(Hu, Nikolakopoulou and Cohen-Cory, *Development* 2005)

Anti-BDNF

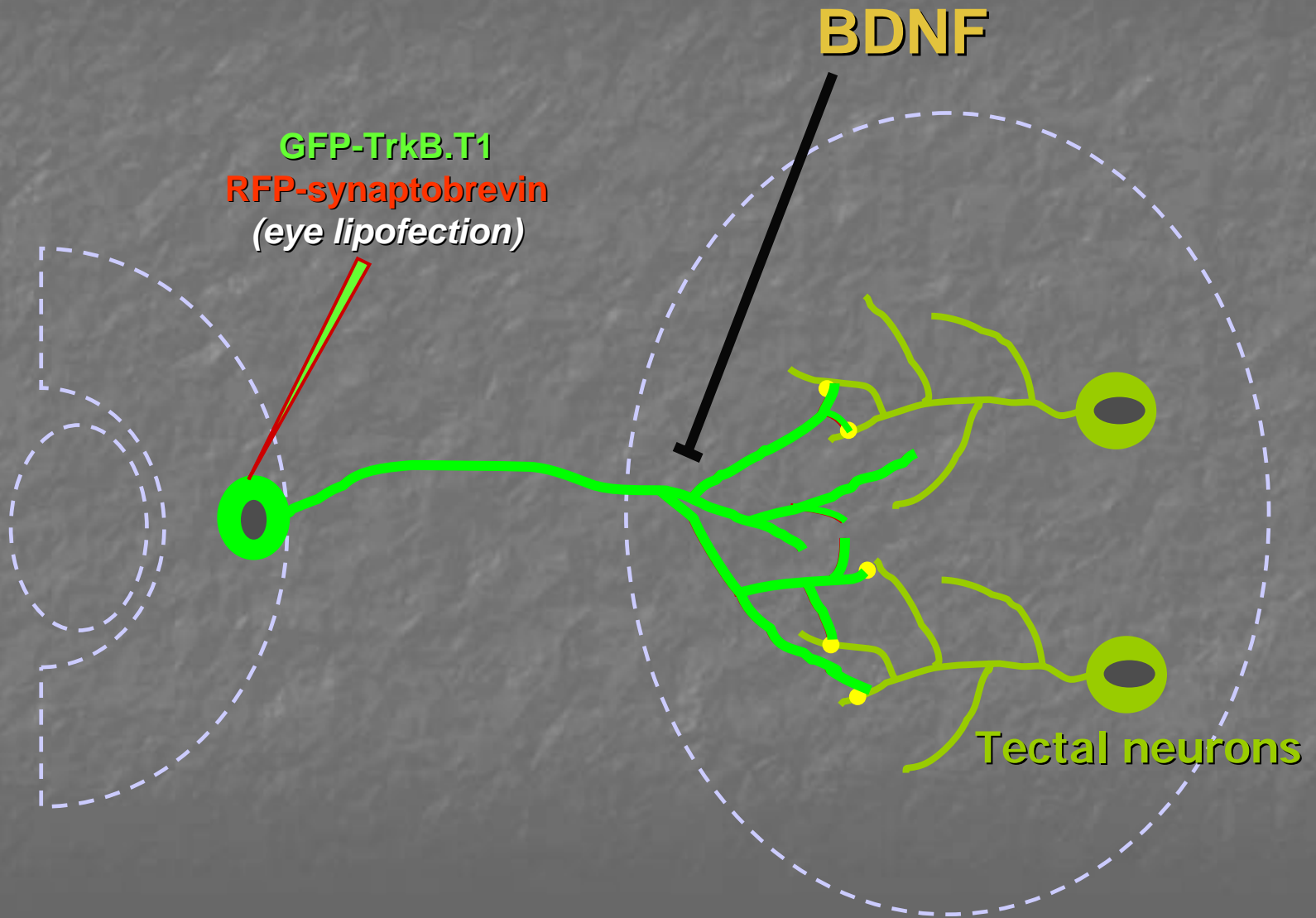
Presynaptic sites are destabilized and eliminated in the absence of BDNF



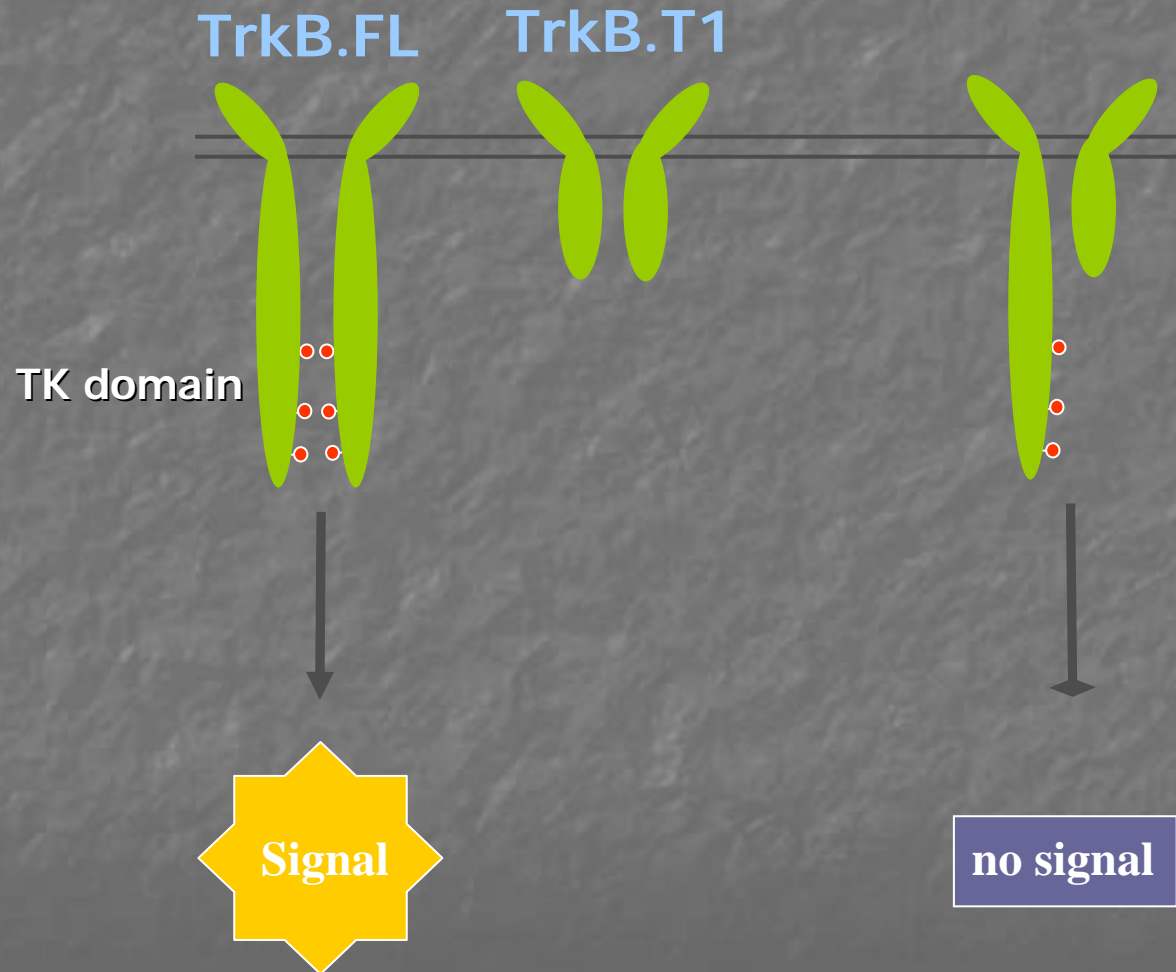
- ✓ BDNF increases axon arbor complexity by promoting branching and growth.
- ✓ BDNF increases the density of synaptic innervation per axon terminal.
- ✓ Neutralizing endogenous BDNF induces synapse disassembly and axon branch elimination.



Are the effects of BDNF direct on presynaptic terminal axons?

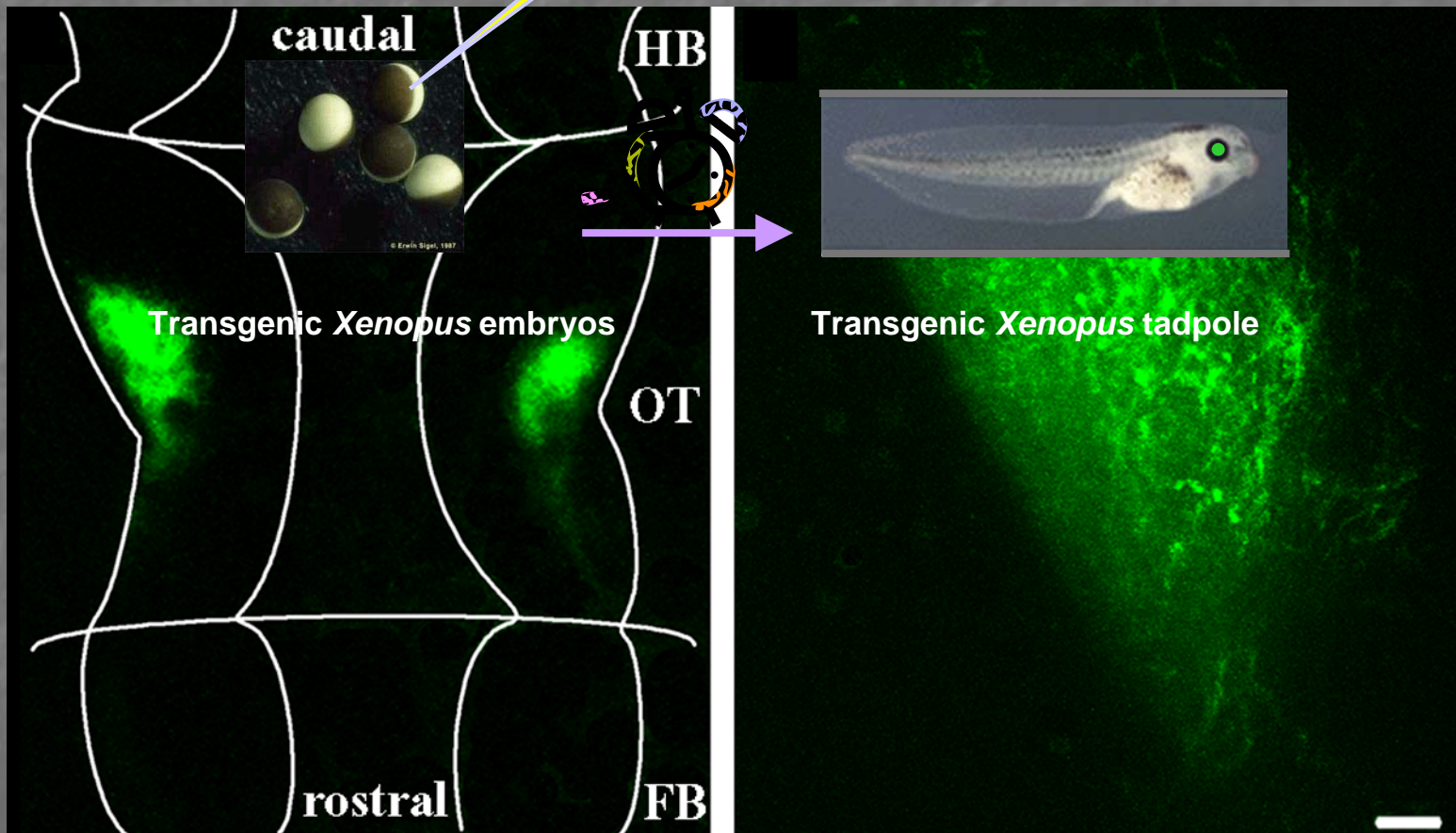


Truncated TrkB.T1 acts as a dominant negative receptor



GFP-TrkB.T1 expressing optic axons project appropriately to the optic tectum in cell-specific transgenic tadpoles

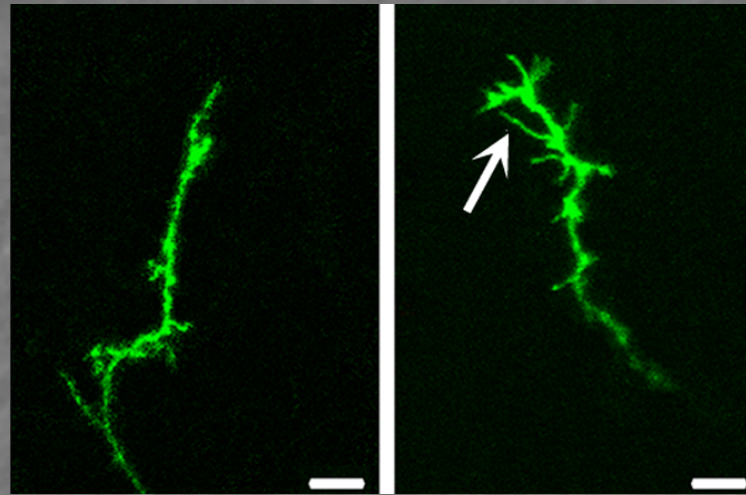
GFP-TrkB.T1
under AchR promoter



Altering TrkB signaling influences axon growth cone morphology at the target

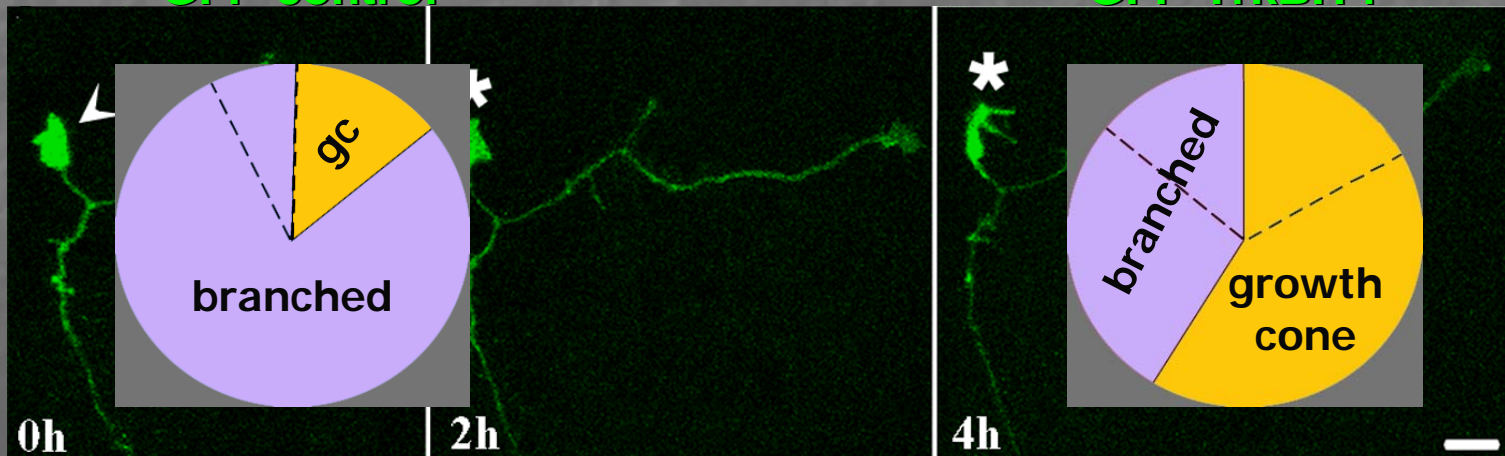
GFP-control

GFP-TrkB.T1



GFP-control

GFP-TrkB.T1



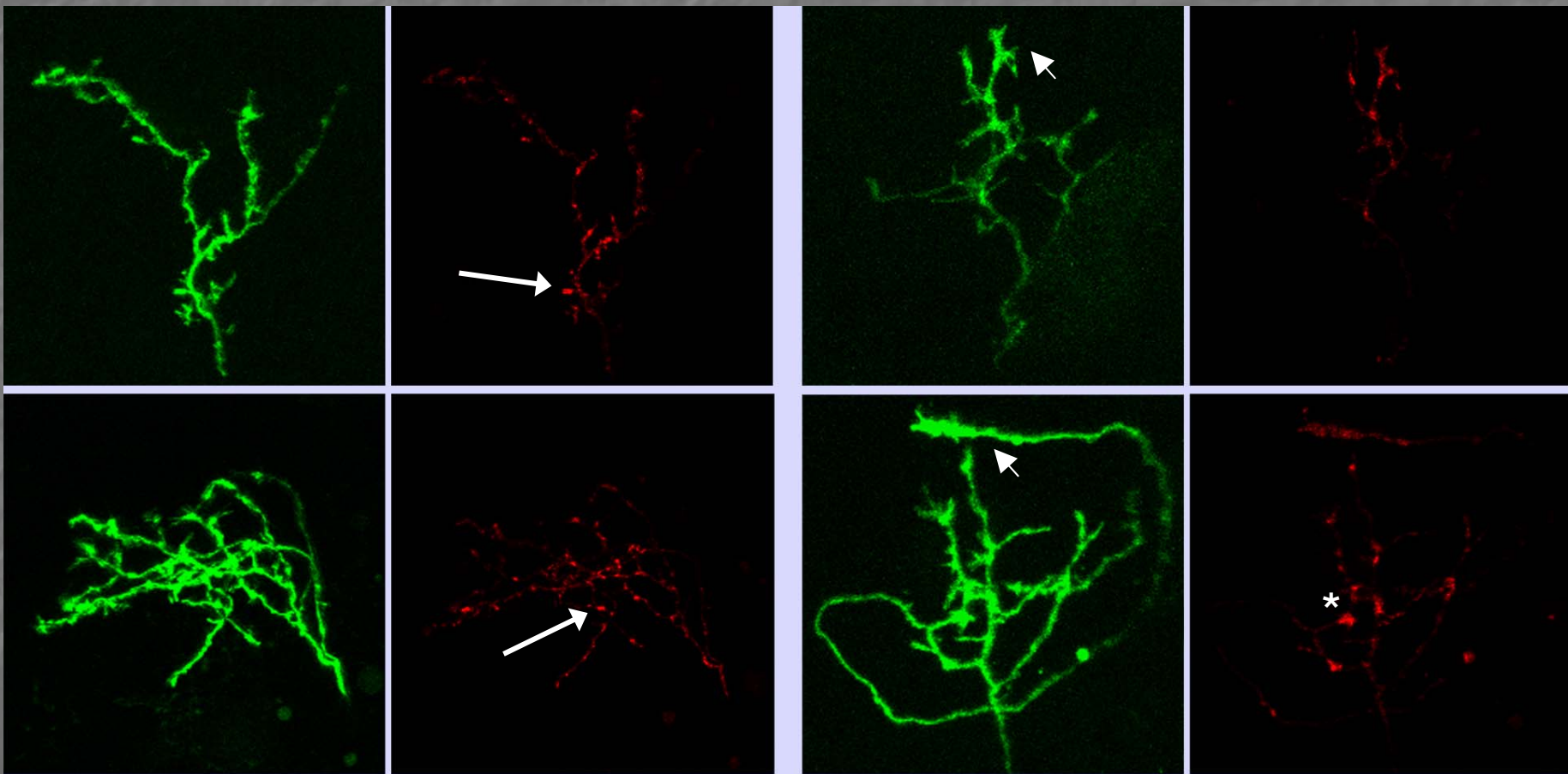
Branched RGC axons expressing GFP-TrkB.T1 retain growth cone-like structures and develop few presynaptic sites

GFP-control

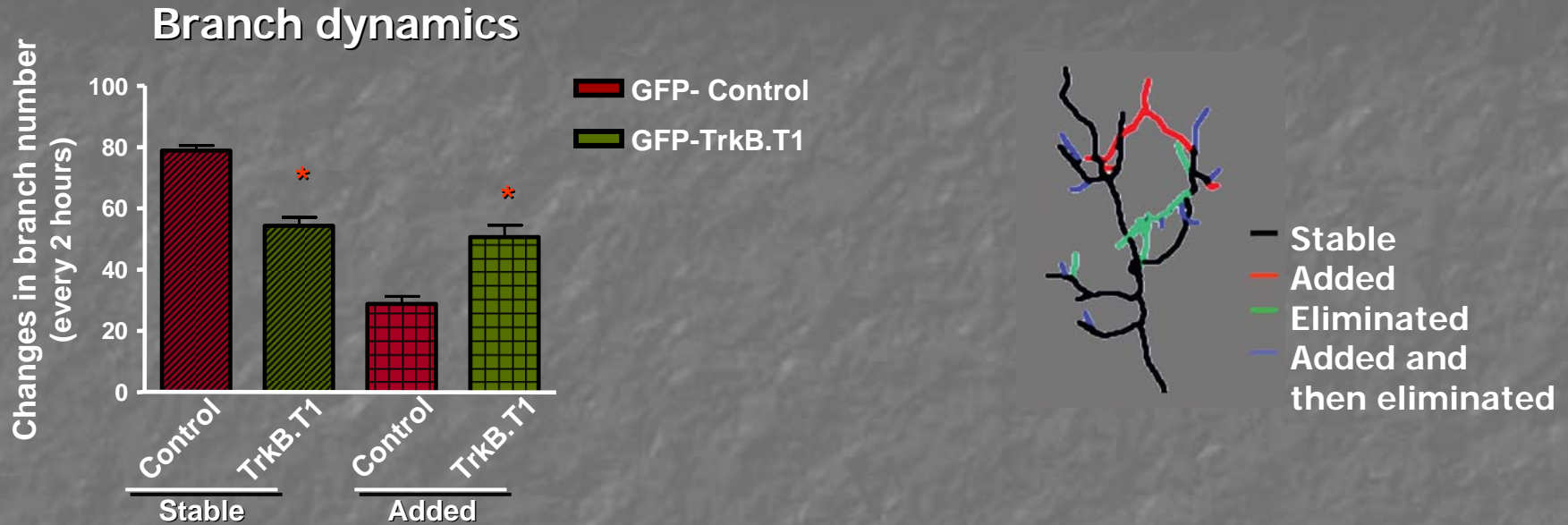
RFP-syb

GFP-TrkB.T1

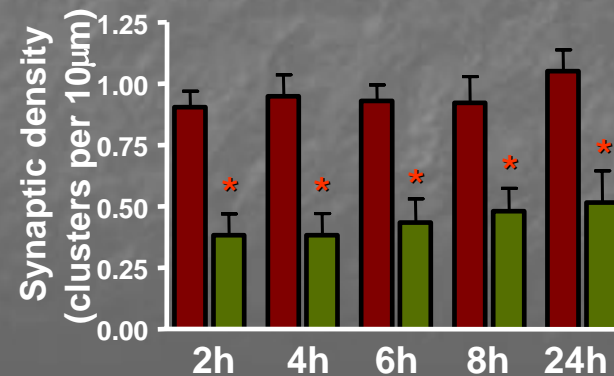
RFP-syb



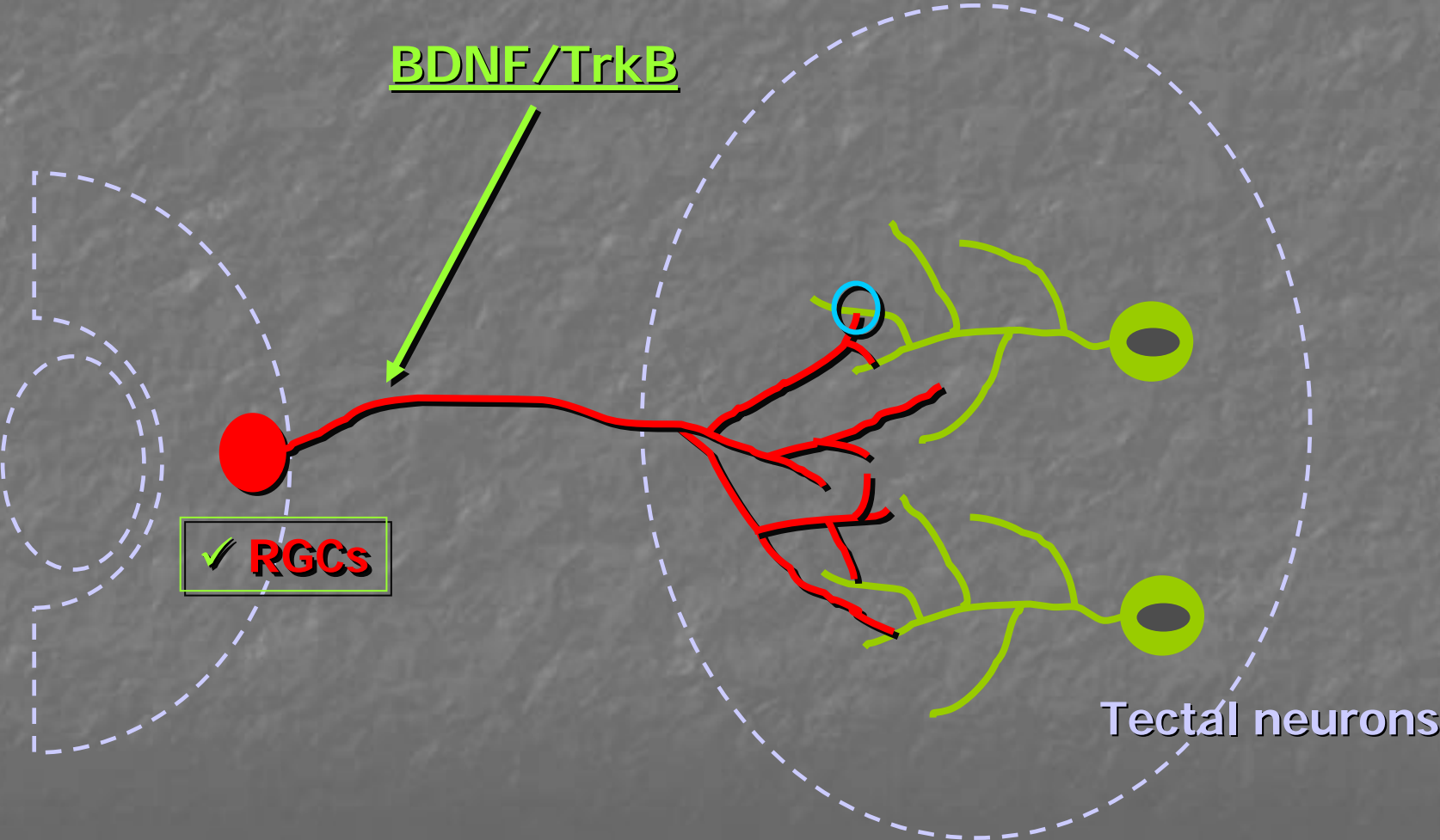
Expression of GFP-TrkB.T1 in RGCs results in simpler axon arbors with high branch turnover rates



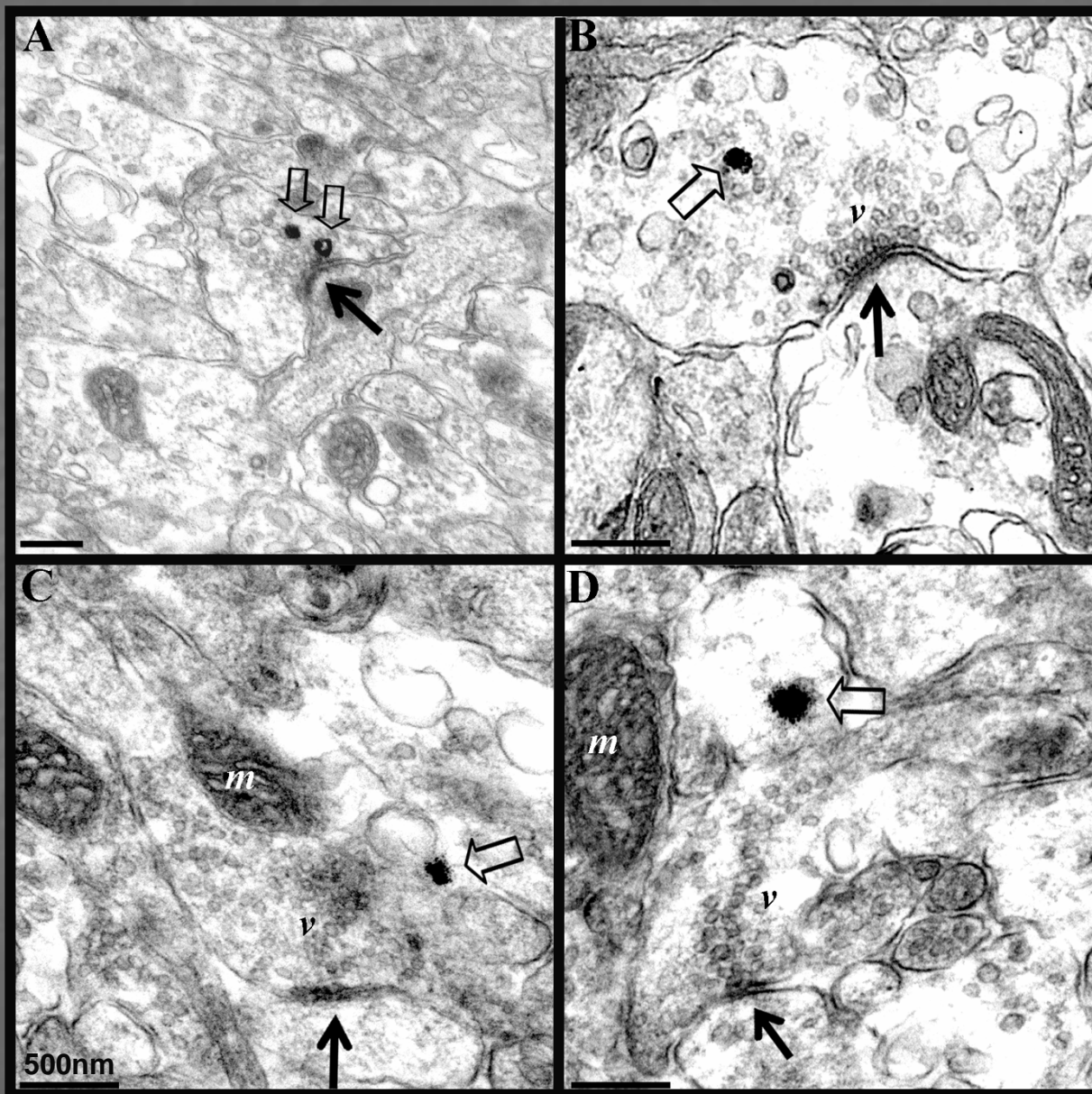
Presynaptic site density



Cell autonomous TrkB signaling in RGCs modulates the establishment of retinotectal synaptic connectivity



Expression of GFP-TrkB.T1 in single RGC axons alters synaptic vesicle number at retinotectal synapses



GFP-control

Synaptic vesicle pool

70.8 ± 6.16

Docked vesicles

6.4 ± 0.46

GFP-TrkB.T1

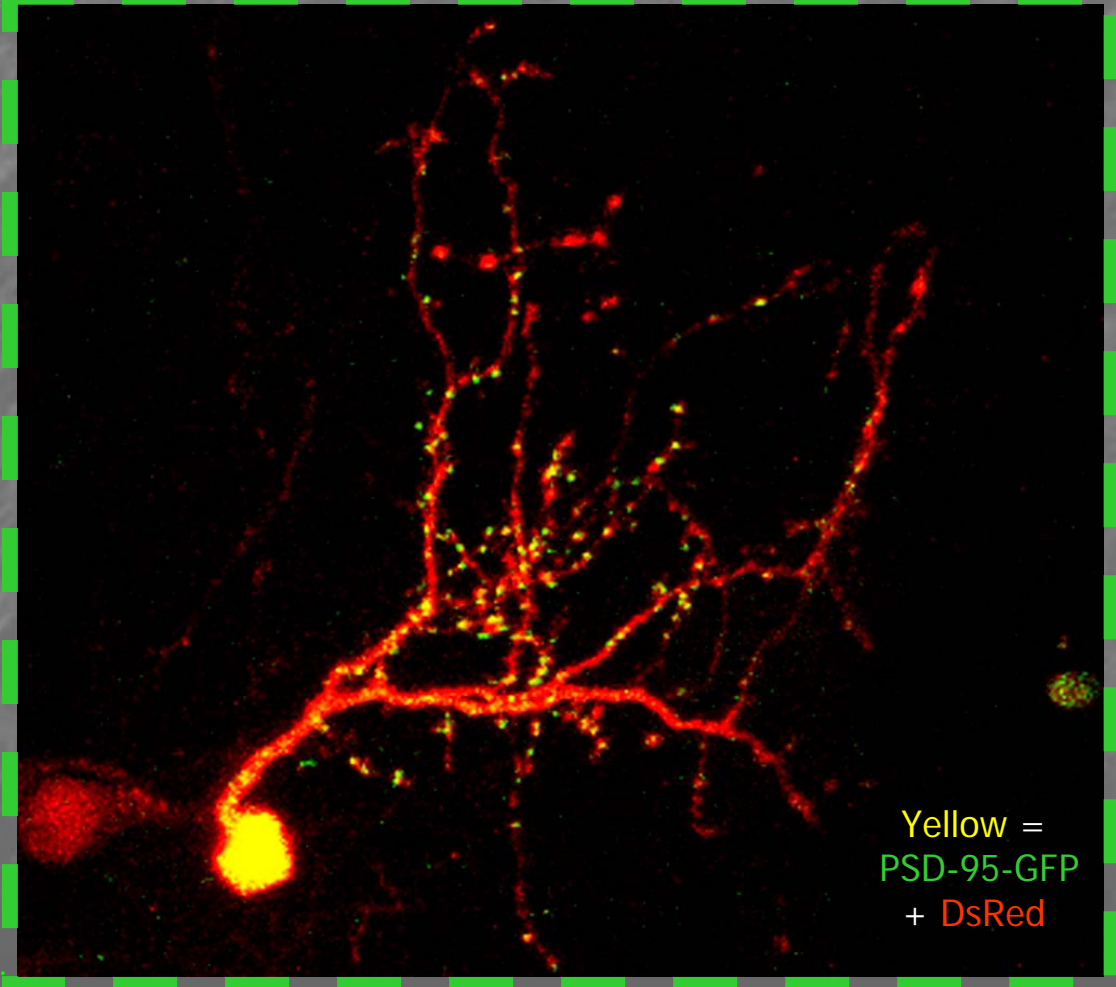
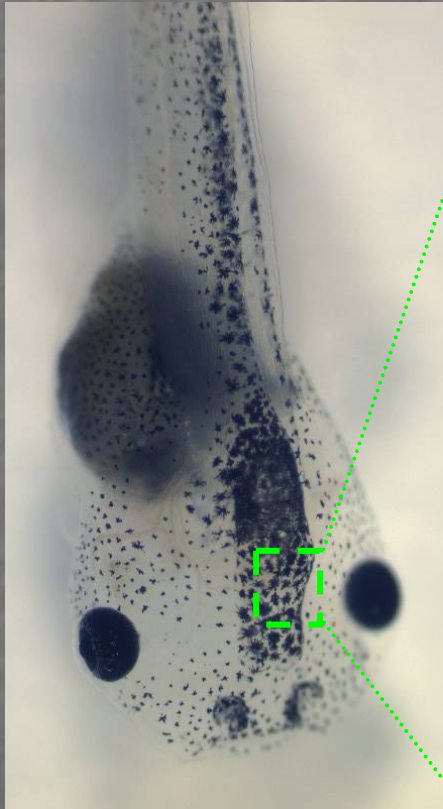
Synaptic vesicle pool

48.3 ± 5.01 *

Docked vesicles

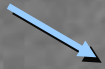
3.9 ± 0.59 *

Imaging postsynaptic sites in tectal neuron dendritic arbors *in vivo*

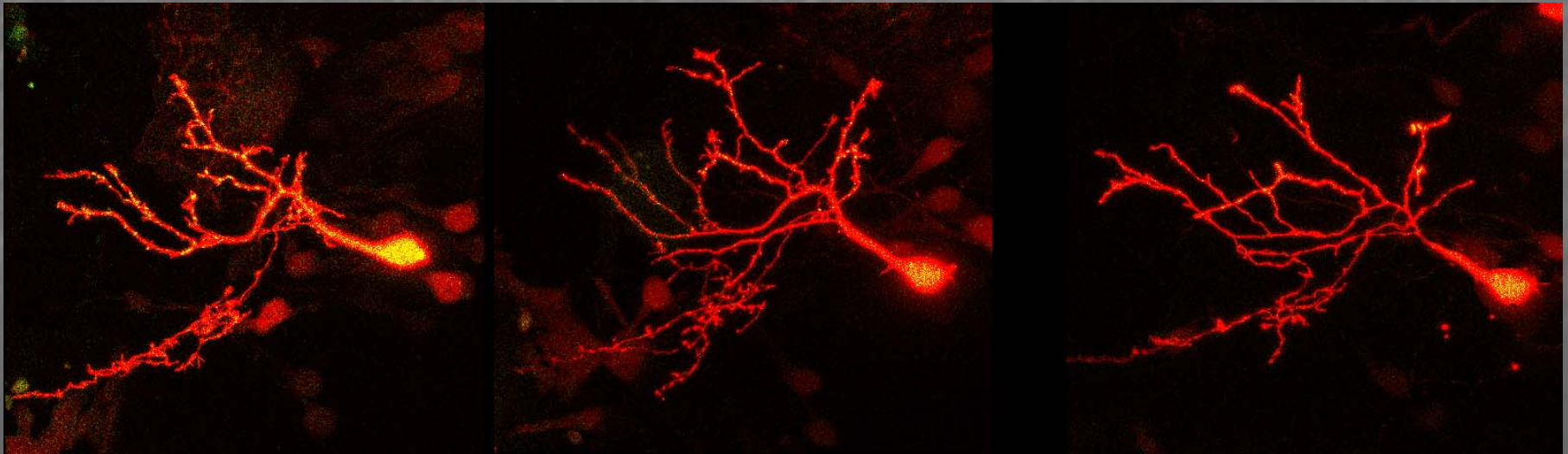
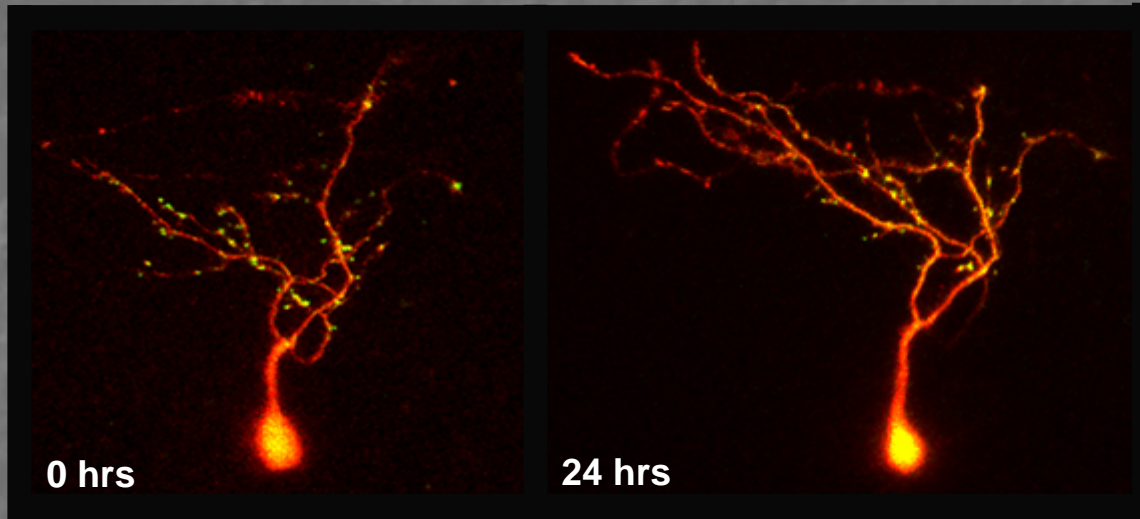


Blocking endogenous BDNF induces postsynaptic site elimination

Control

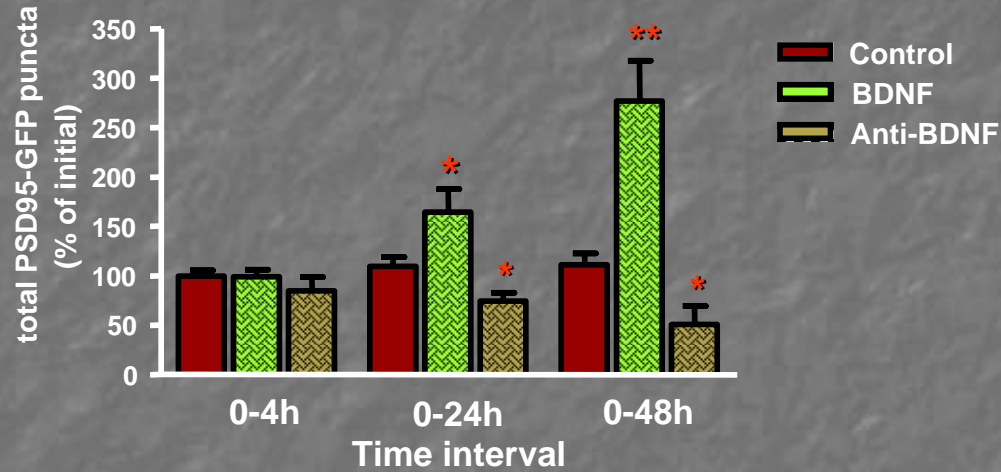


Anti-BDNF

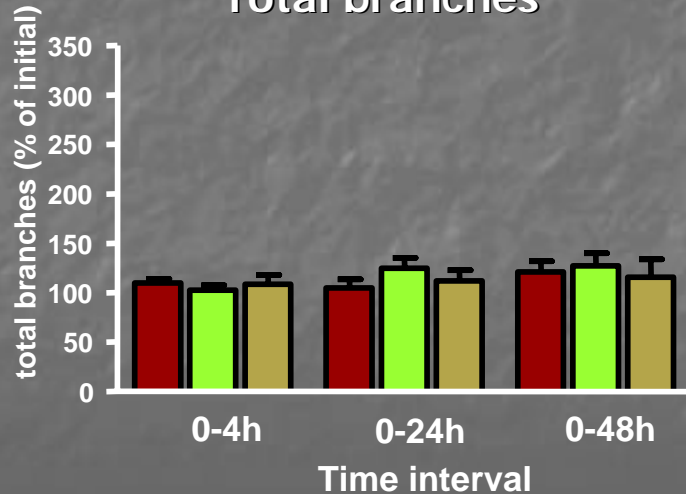


BDNF influences postsynaptic site number by 24 hours but does not alter dendritic branching

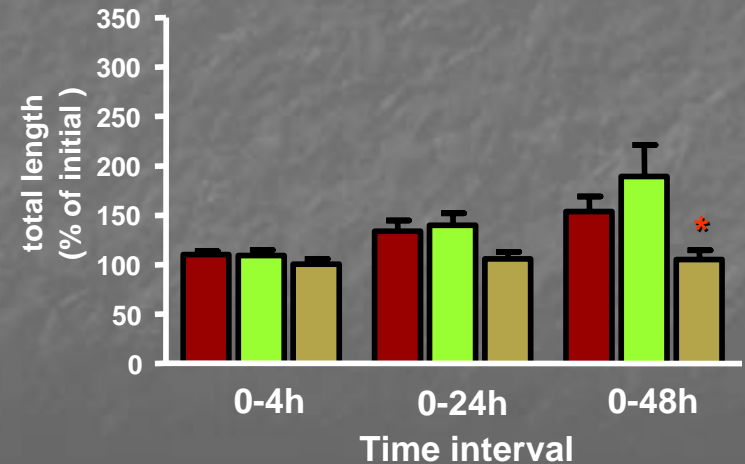
PSD-95-GFP puncta



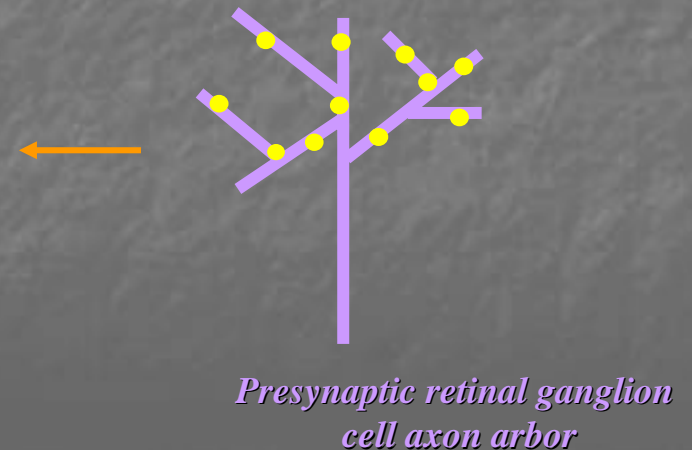
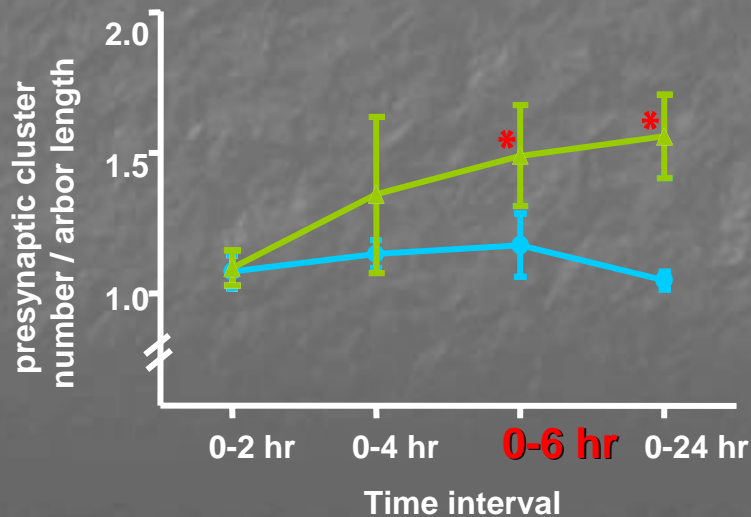
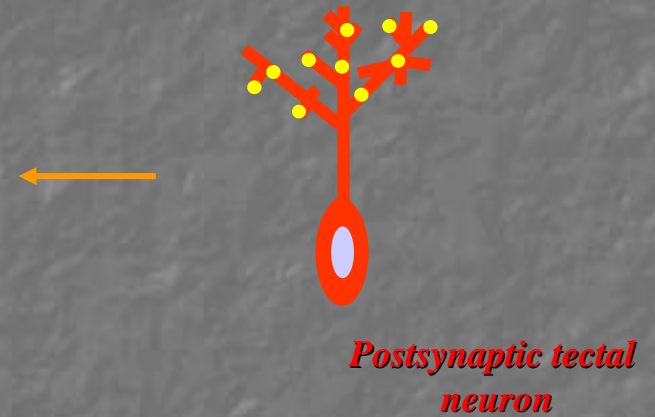
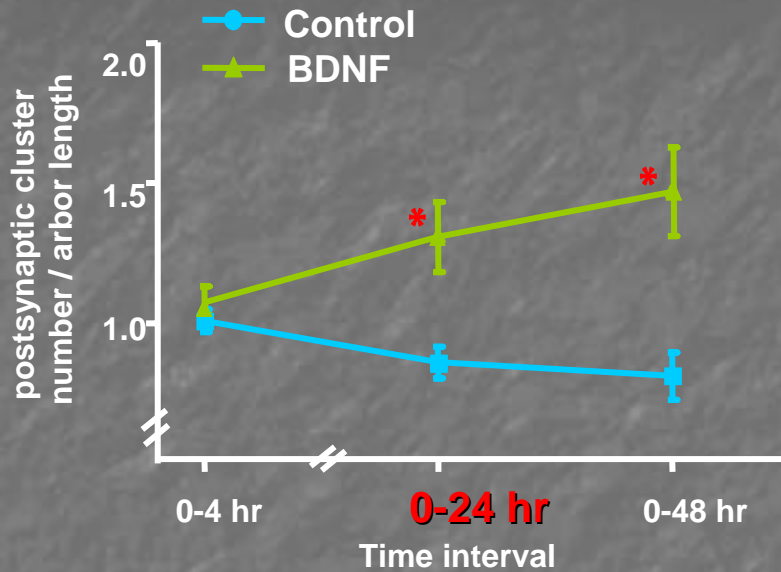
Total branches



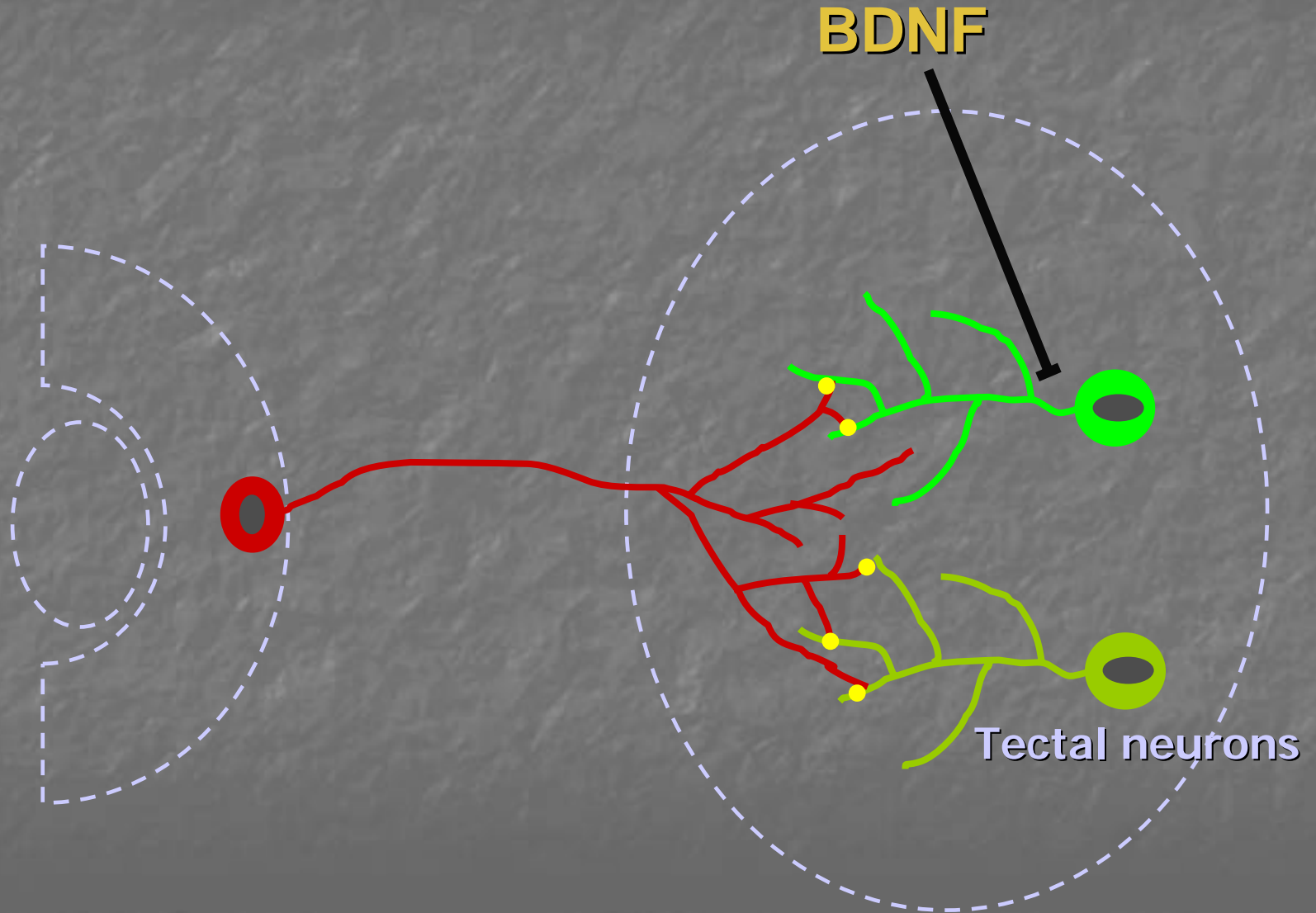
Total length



BDNF increases synaptic innervation density in tectal neuron dendritic terminals

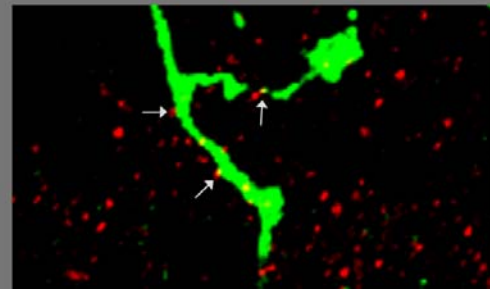
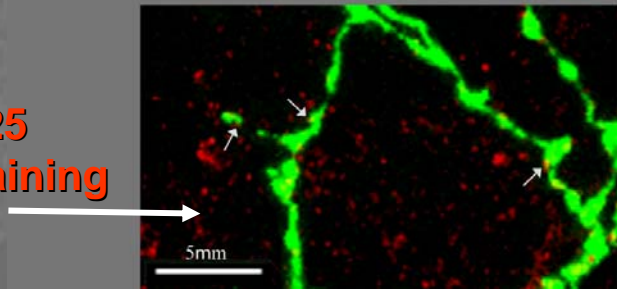
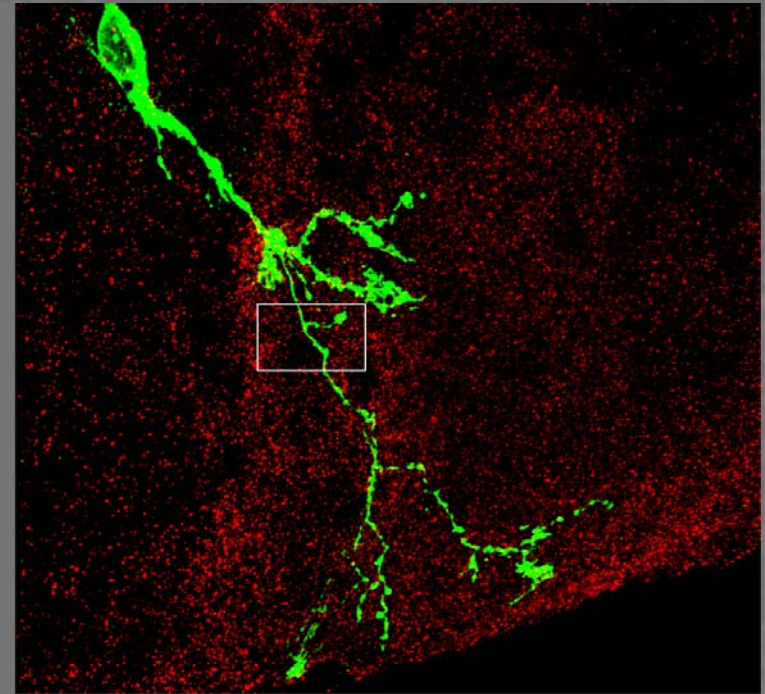
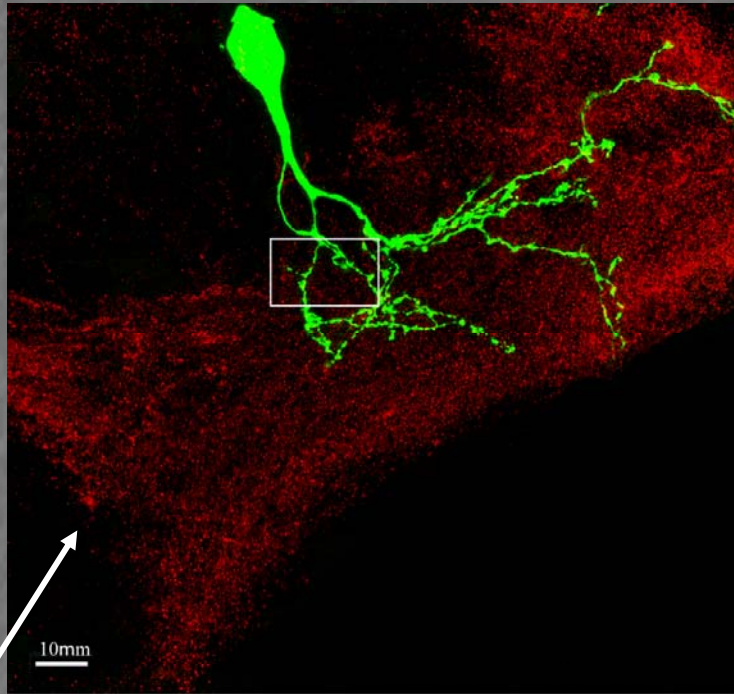


Imaging dendritic morphology and synaptic specializations in tectal neurons with altered TrkB signaling



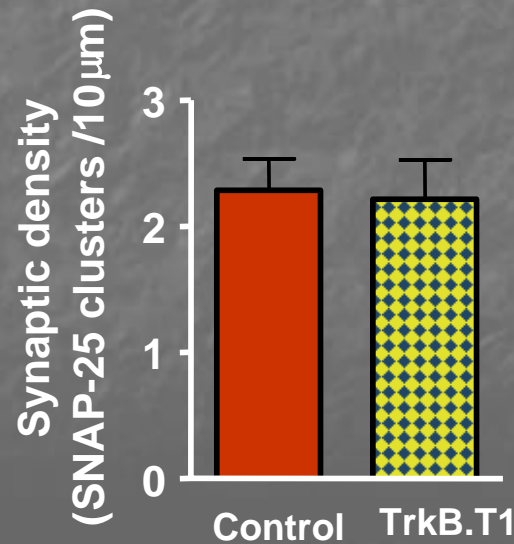
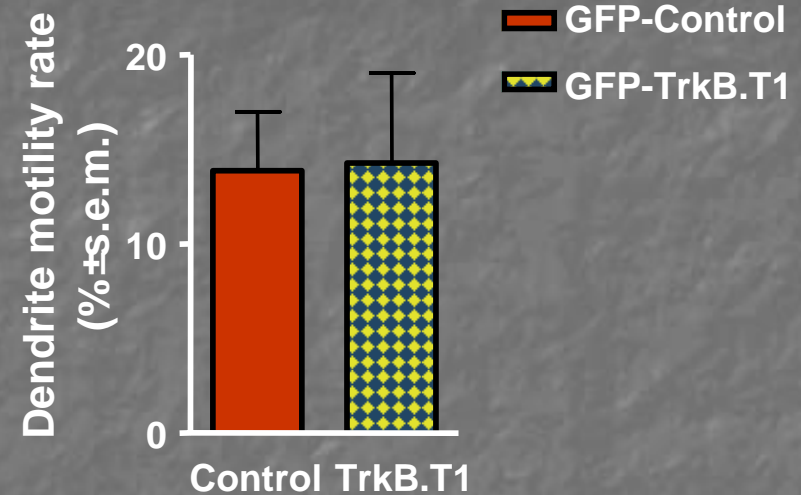
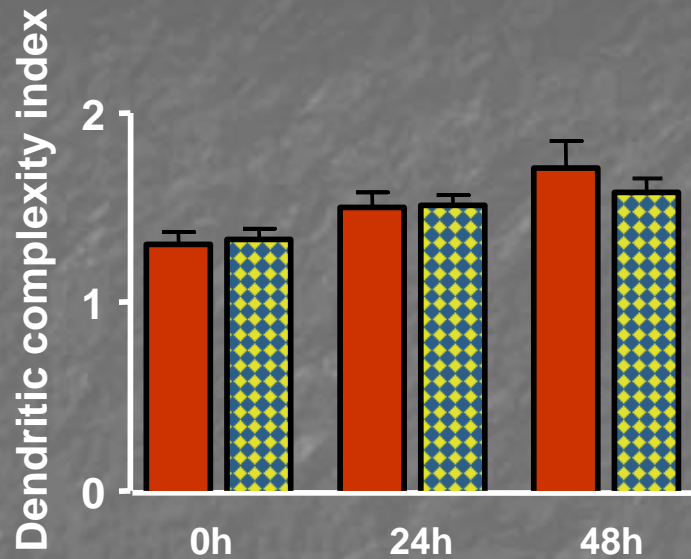
GFP-control

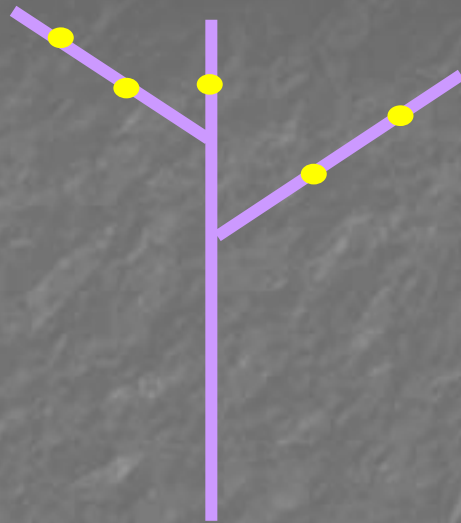
GFP-TrkB.T1



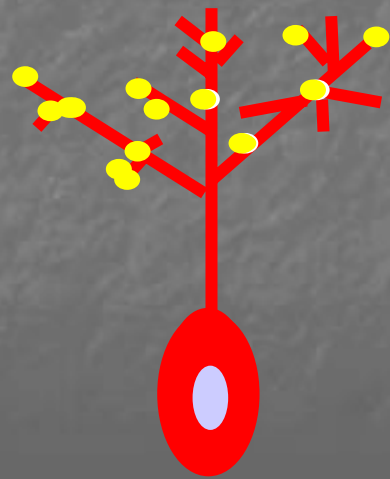
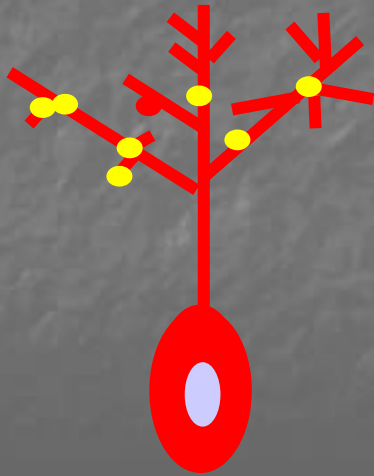
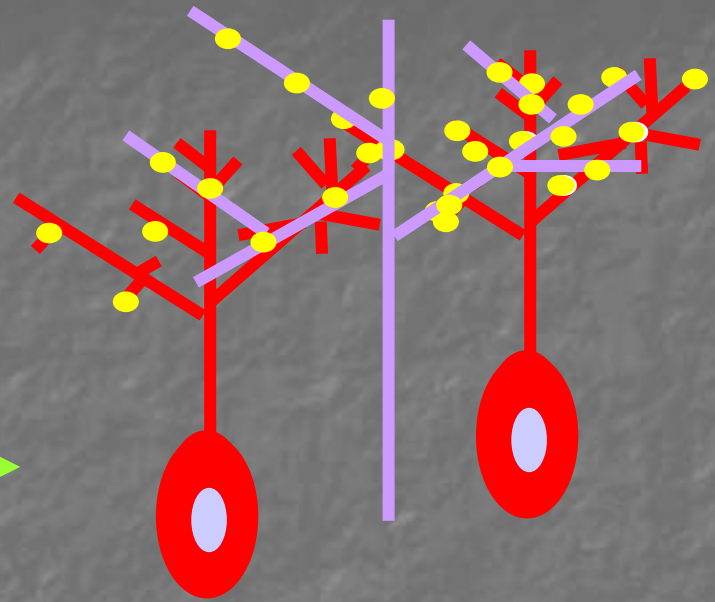
SNAP-25
immunostaining

Altering TrkB signaling in tectal neurons does not influence dendrite branch dynamics or synapse density





BDNF



Single-cell manipulations in TrkB signaling

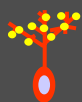
Cell-autonomous TrkB signaling influences axon arbor shape and synaptic site stability. TrkB-mediated changes at synapses can significantly affect synaptic function (EM observations – decreased synaptic vesicle number).

- ❖ ***Confirm anti-BDNF effects***
- ❖ ***Support BDNF's potential to rescue developing circuits with altered activity or after injury***





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Thuy Vu



Bing Hu

Analiza Sanchez

Sana Javed

Ben Matthews

Sonia Marshak

Margarita Meynard

Mariangela Nikolakopoulou

Supported by:

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