Refinement of Connections II

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Course News

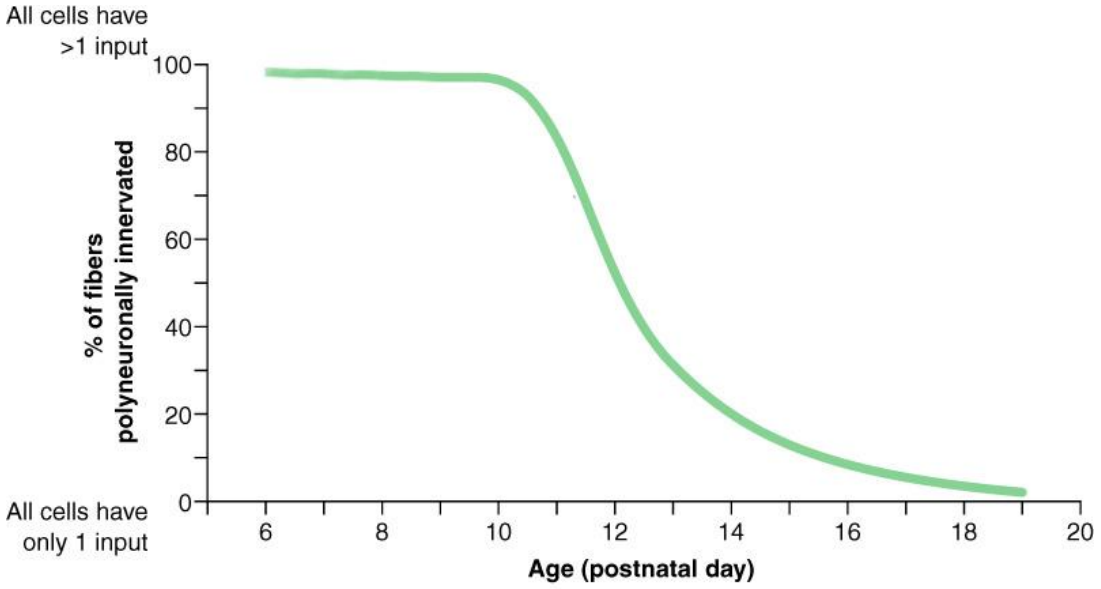
Graduate School Discussion

Wednesday, Nov 28
11:00am (right after lecture)
In Mayo 3-100

with Dr. Paul Mermelstein
(invite your friends)

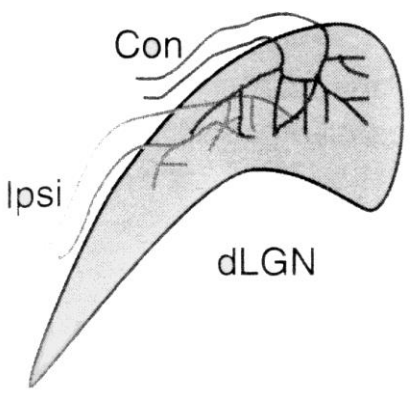
Refinement takes place during a 'critical period' of development.

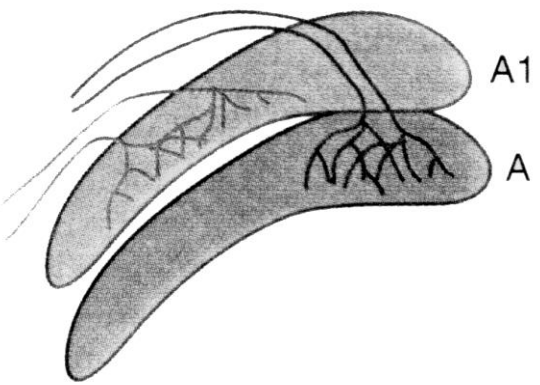
- Major sculpting of the pattern of connections takes place during a discrete period of development.
  - Most muscle fibers have multiple, functional nerve terminals through the first two postnatal weeks in rodents. During the second week, the extra synapses are eliminated resulting in muscle fibers having a single nerve terminal.
- Not known what initiates the onset of the critical period.

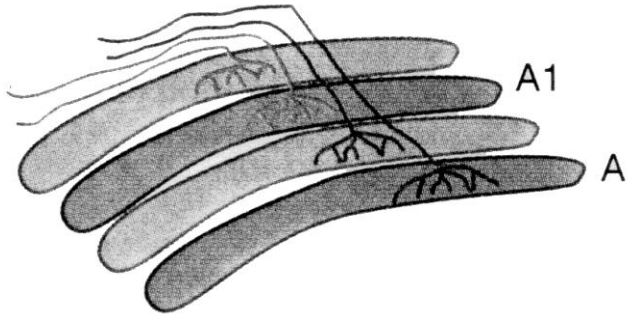


Refinement takes place during a 'critical period' of development.

- The timing of the critical period differs for different neuronal populations.
  - Retinal axons from the two eyes initially overlap in the lateral geniculate nucleus and then segregate <u>prenatally</u> in mammals.



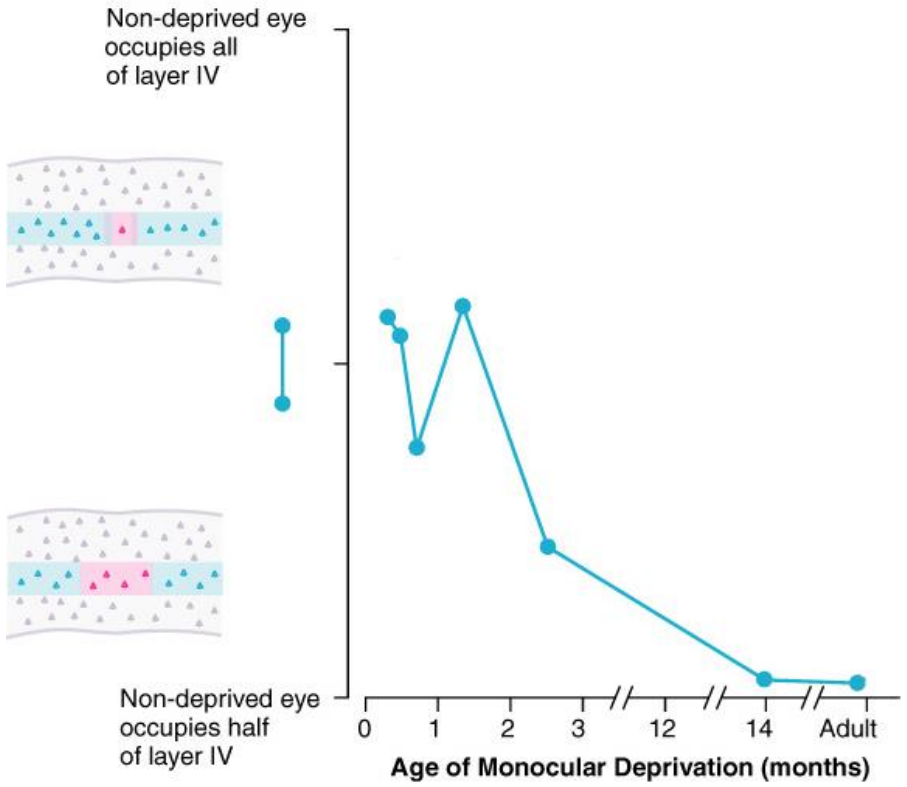




  - Geniculocortical axons carrying input from the two eyes initially overlap in layer IV of visual cortex and then segregate <u>postnatally</u> in mammals.

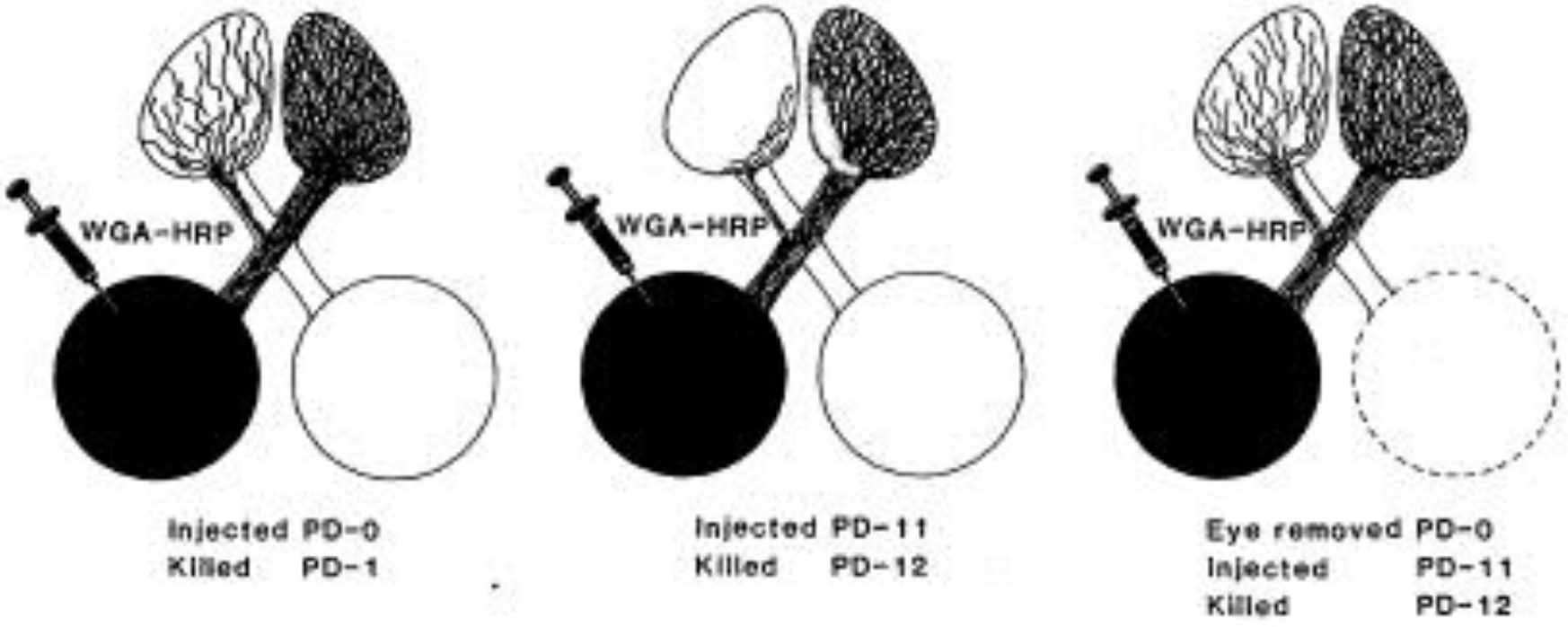
Refinement takes place during a 'critical period' of development.

- The ability of the circuitry to change significantly in response to activity gradually declines, hence the critical period.

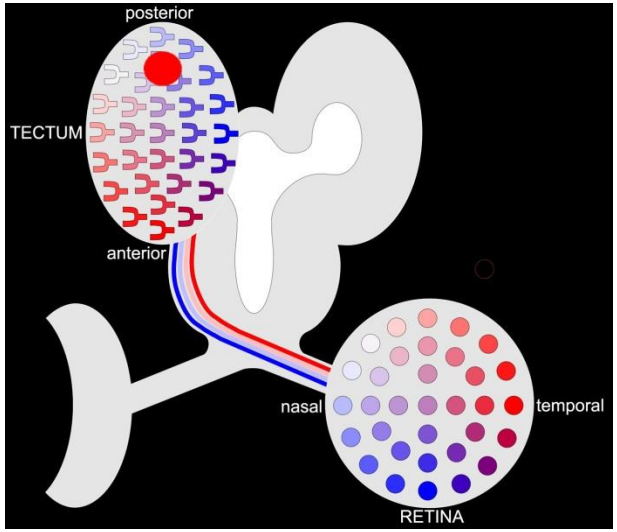


Refinement involves competition between axons for synaptic targets.

- Retinal axons from the two eyes initially overlap in the superior colliculus and then segregate into separate terminal domains.
- Axons from one eye will continue to project to the entire colliculus when the opposite eye is removed at the start of critical period.



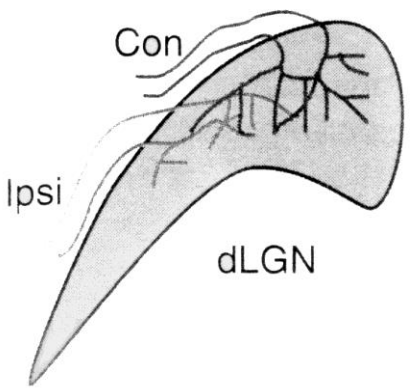
Refinement results in neighboring neurons synapsing together.

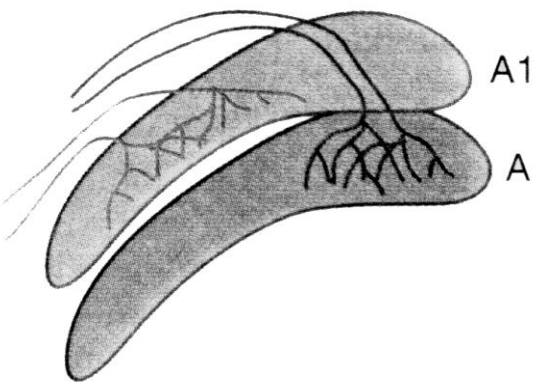


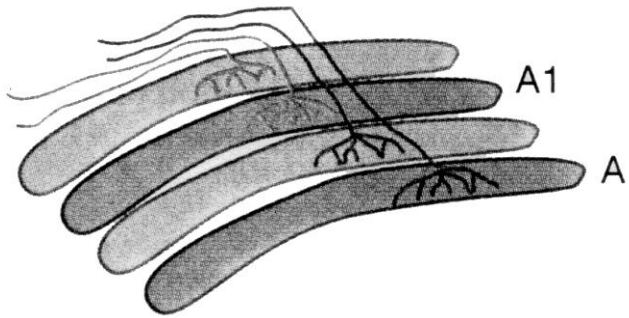
- Early in development, the topography of the projection from one eye to any visual nucleus is rough.
- After refinement only neighboring ganglion cells synapse together.

Refinement results in neighboring neurons synapsing together.

- Early in development, retinal axons from the two eyes overlap in the lateral geniculate nucleus.
- After refinement, axons from the two eyes project to eye specific layers of the LGN.

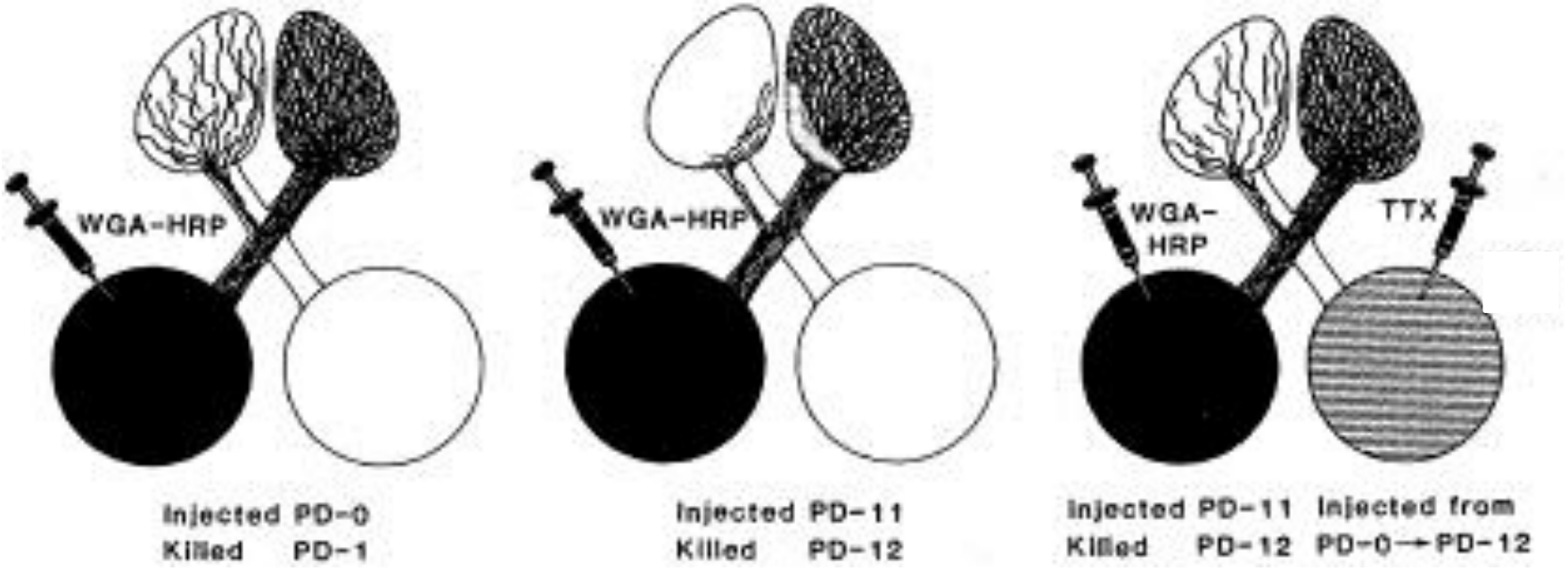






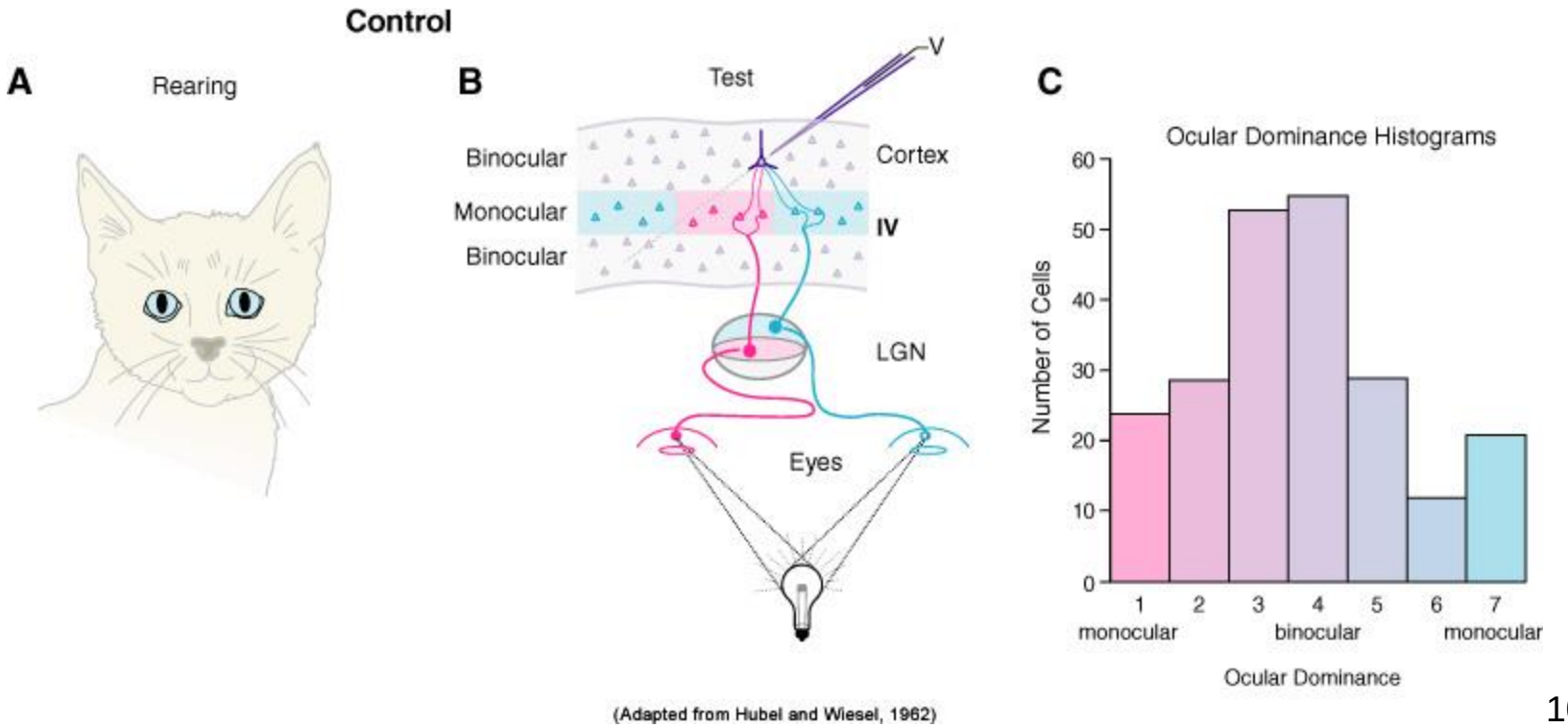
Activity is required for neighboring neurons to wire together (i.e. activity is required for competition).

- Blocking activity by administration of TTX blocks refinement in many systems.



Synchronized activity of neighboring neurons allows them to wire together.

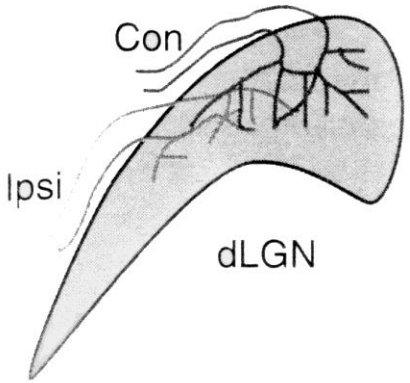
- Late in development, neighboring cells are likely to experience the same naturally evoked activity.
  - Normal formation of ocular dominance columns in the projection from the lateral geniculate nucleus to layer IV of visual cortex requires normal vision

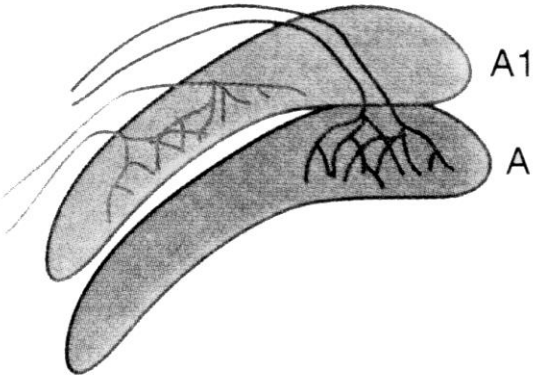


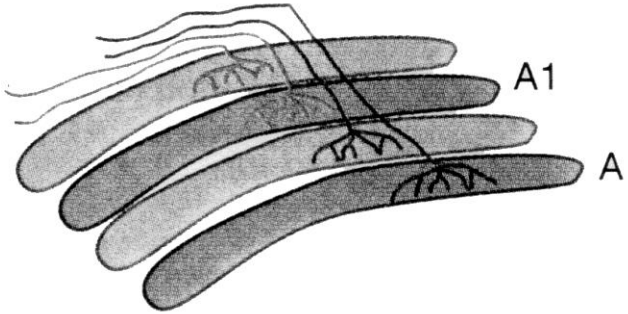
(Adapted from Hubel and Wiesel, 1962)

Synchronized activity of neighboring neurons allows them to wire together.

- Early in development, spontaneous activity of neighboring cells is synchronized.
  - Segregation of ipsilateral and contralateral retinal axons in the lateral geniculate nucleus takes place in the embryo (i.e. without vision).
  - TTX administered prenatally to the retinal axons can block this refinement, indicating that it is activity dependent.
  - Since refinement takes place without vision, the activity must be spontaneous (rather than evoked).

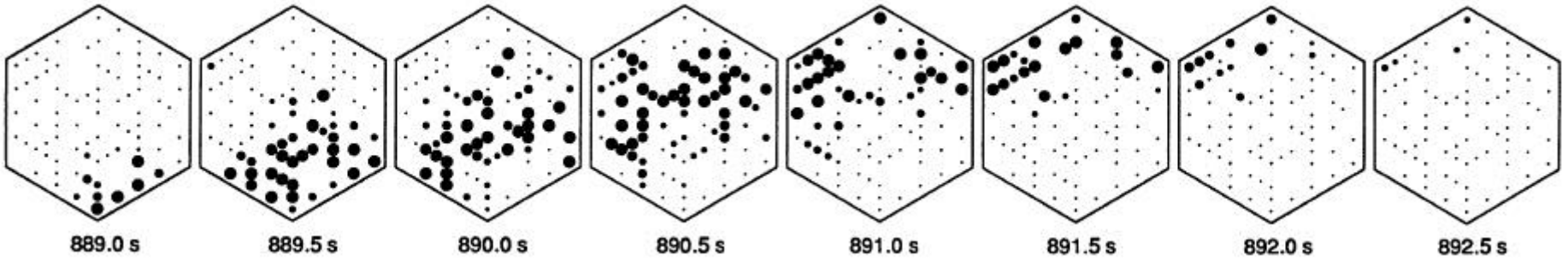






Synchronized activity of neighboring neurons allows them to wire together.

- Early in development, activity of neighboring retinal ganglion cells is synchronized.
- Waves of activity spread spontaneously across the retina.



Synchronized activity of neighboring neurons allows them to wire together.

- Starburst amacrine cells are essential for the waves of activity.
- These cholinergic cells synapse with ganglion cells and with neighboring starburst amacrine cells.
- After activation, they have a refractory period that prevents a wave from returning.

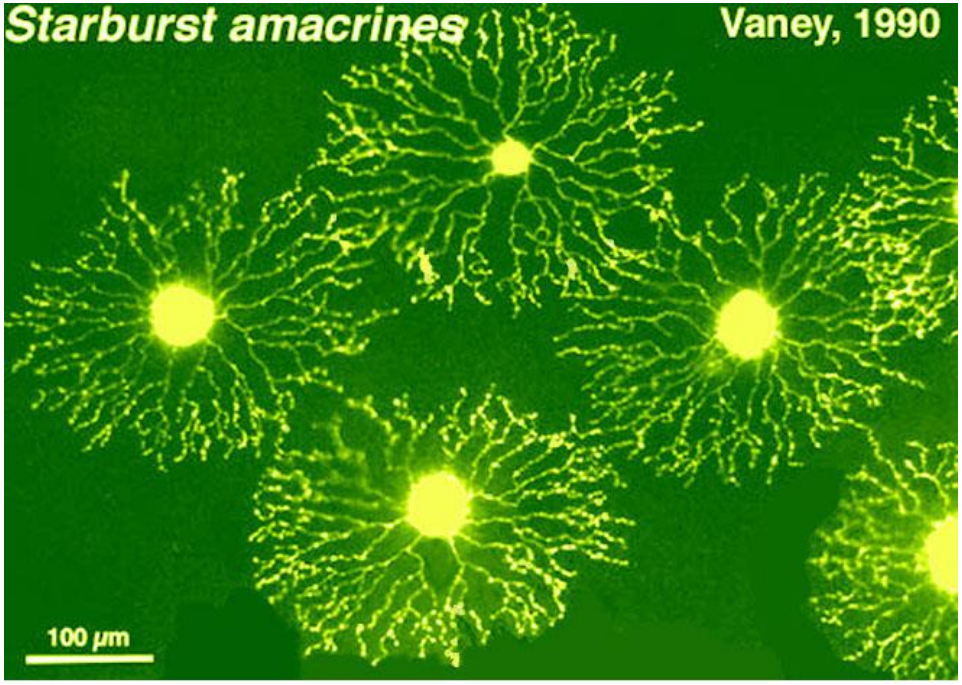


Fig.7. Starbust amacrine cells as stained with lucifer yellow in wholemount rabbit retina.

Synchronized activity of neighboring neurons allows them to wire together.

- Similar local circuits synchronize spontaneous activity in other parts of the developing nervous system.

Synchronized activity of neighboring neurons allows them to wire together.

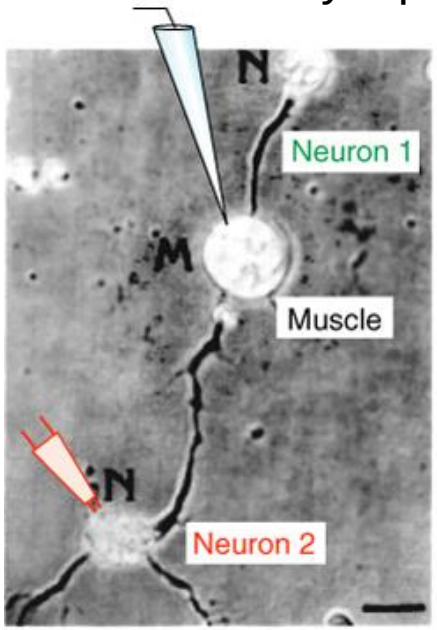
- Experimentally synchronizing the activity of two competing populations of neurons prevents the segregation of their terminals.
  - Stimulating both optic nerves of a kitten simultaneously during the critical period prevented ocular dominance columns from forming in layer IV of visual cortex.

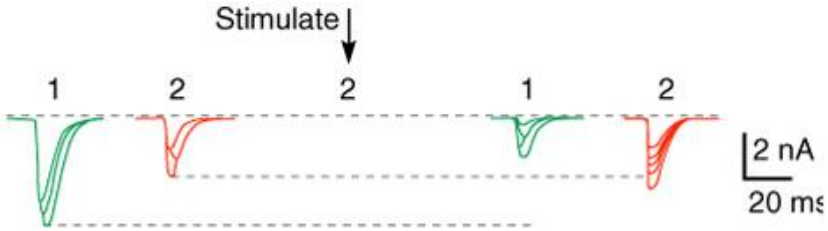
*****Axons that fire together, wire together.*****

Asynchronous activity drives synapse elimination (heterosynaptic competition).

Neuromuscular refinement:

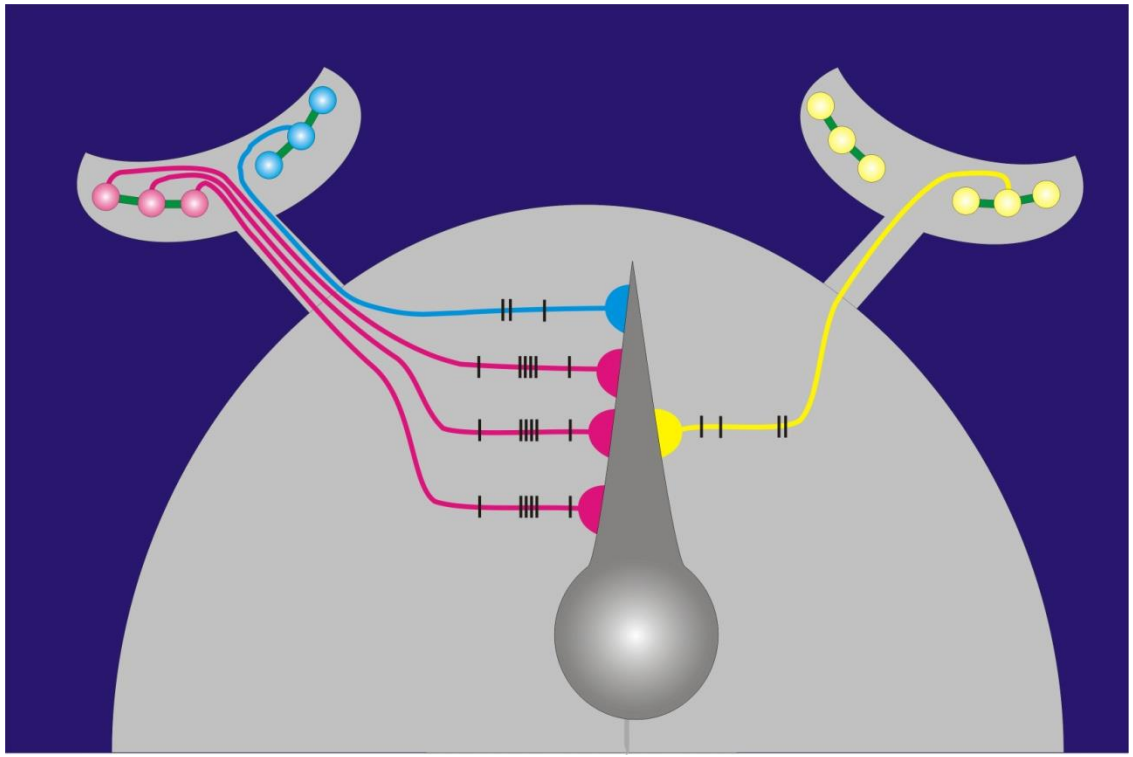
- Two neurons innervate a single muscle fiber in culture. Initially both neurons will result in similar postsynaptic responses in the muscle cell.
- Stimulate one neuron for a few seconds resulted in subsequent stimulation of the second neuron being less effective at driving activity in the muscle fiber.
- Thus, the activity of one synapse changed the efficacy of another synapse on the same target cell.

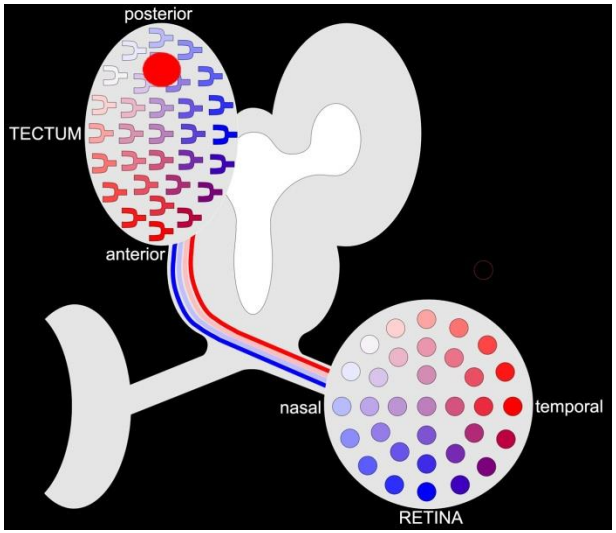




Hebb's Postulate of Learning

- Synapses are strengthened when the presynaptic activity correlates with post-synaptic activity.
- Synapses are weakened and eventually eliminated when the presynaptic activity is asynchronous with post-synaptic activity.




posterior
TECTUM
anterior
nasal
temporal
RETINA


E11
E13
E15
E17
nasal
temporal

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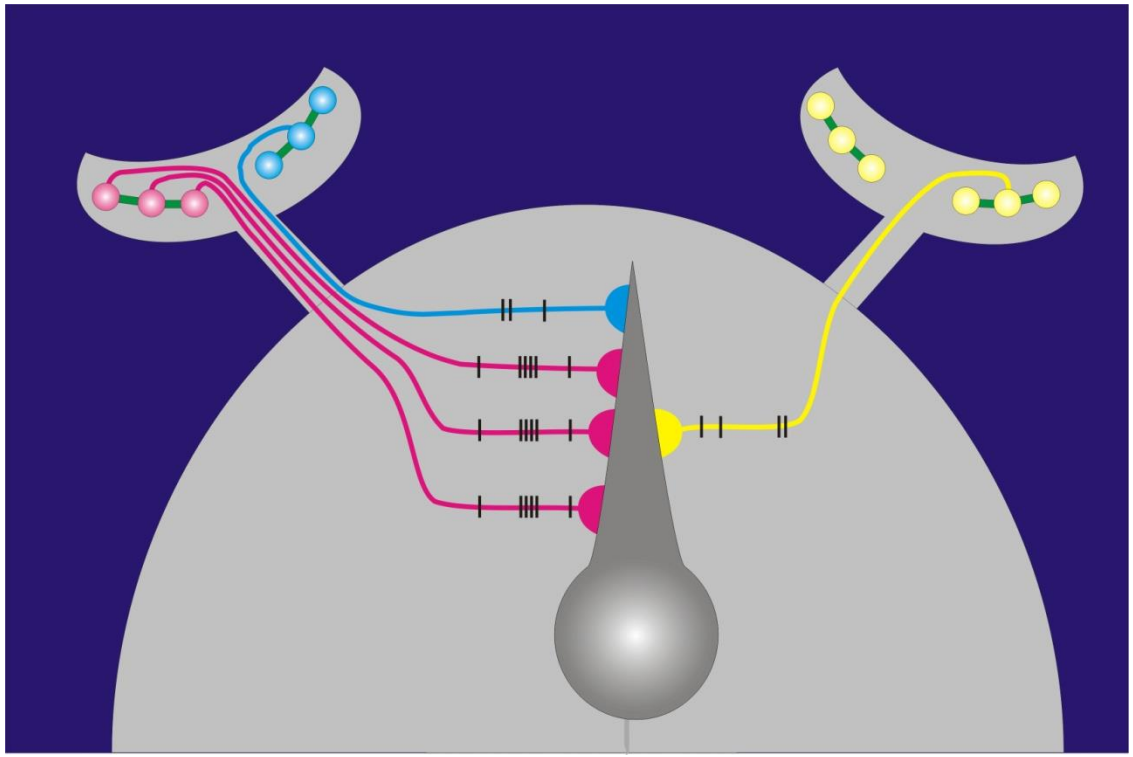
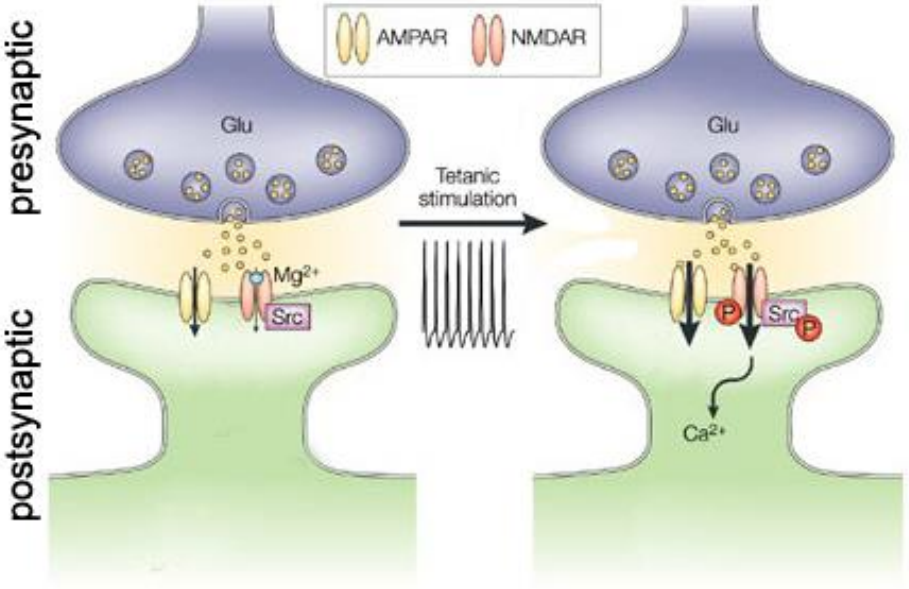


What is the cellular basis of a 'coincidence detector'? -or- How does a postsynaptic cell know that inputs are synchronous?

- NMDA glutamate receptors, being both voltage and ligand gated, are ideal for integrating the activity of multiple inputs.
- Multiple synapses need to be active simultaneously to depolarize the cell via AMPA receptors.
- This removes the Mg-block on the NMDAr, allowing the NMDAr to open.
- Calcium enters the cell via the open NMDAr.



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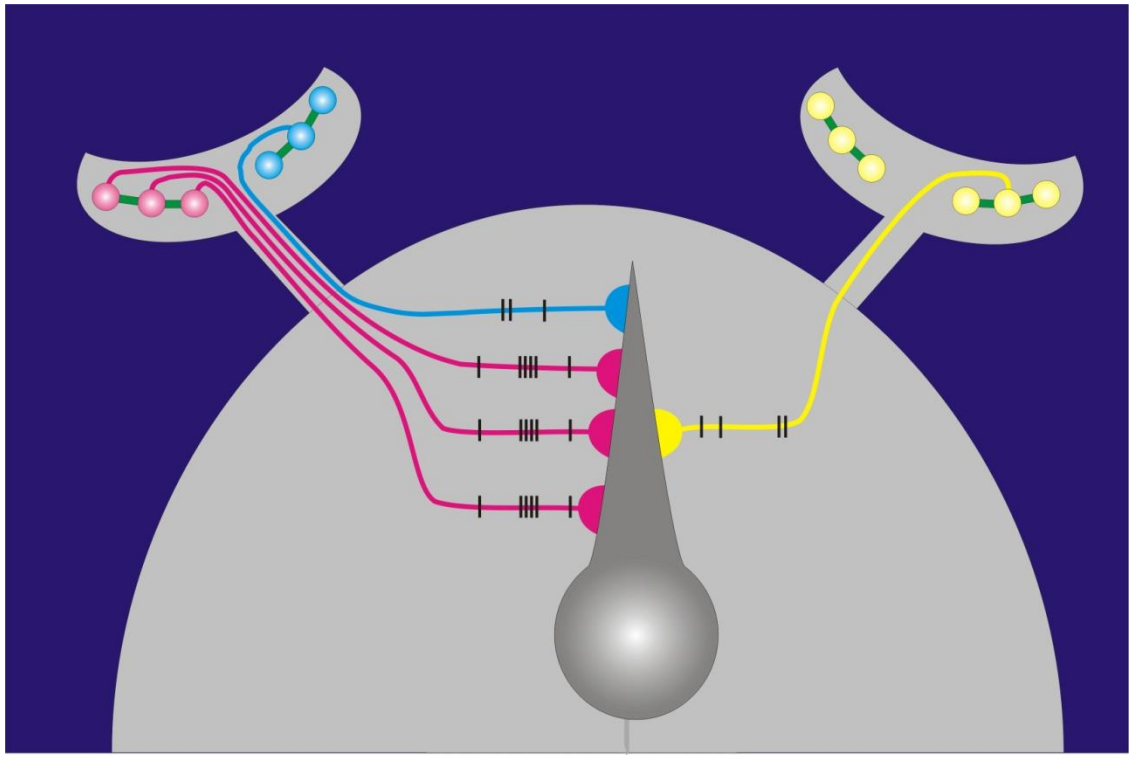
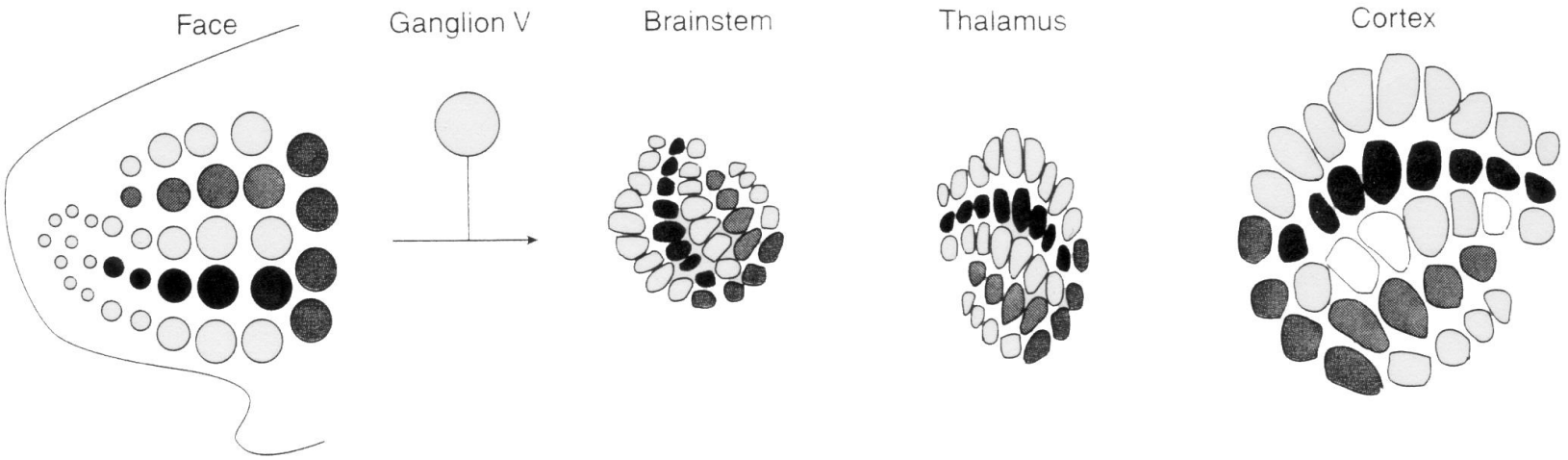
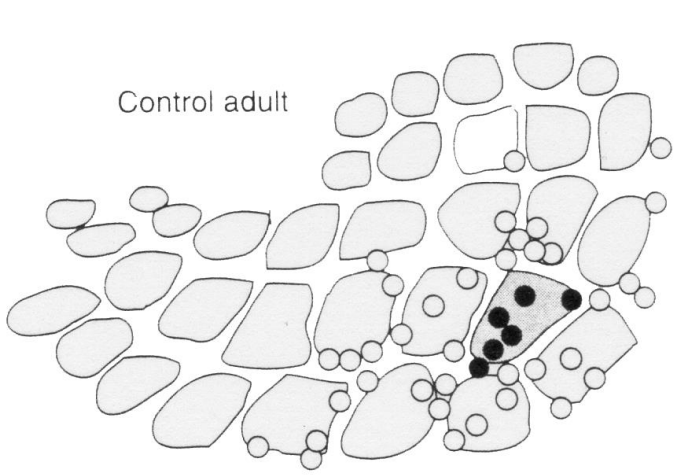
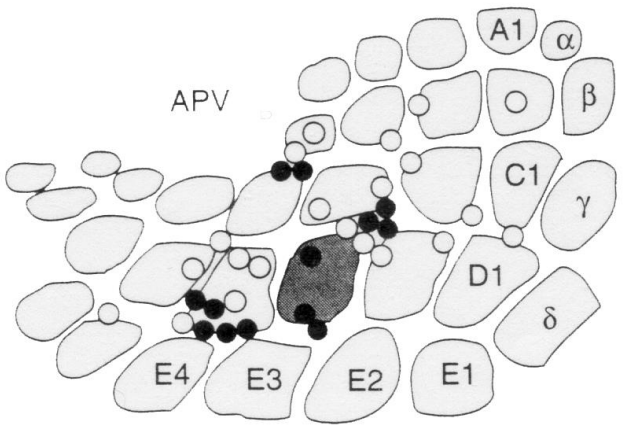


What is the cellular basis of a 'coincidence detector'? -or- How does a postsynaptic cell know that inputs are synchronous?

- Blocking NMDA receptors (i.e. administer APV or MK801) during the critical period disrupts formation of barrel fields in rodent somatosensory cortex.

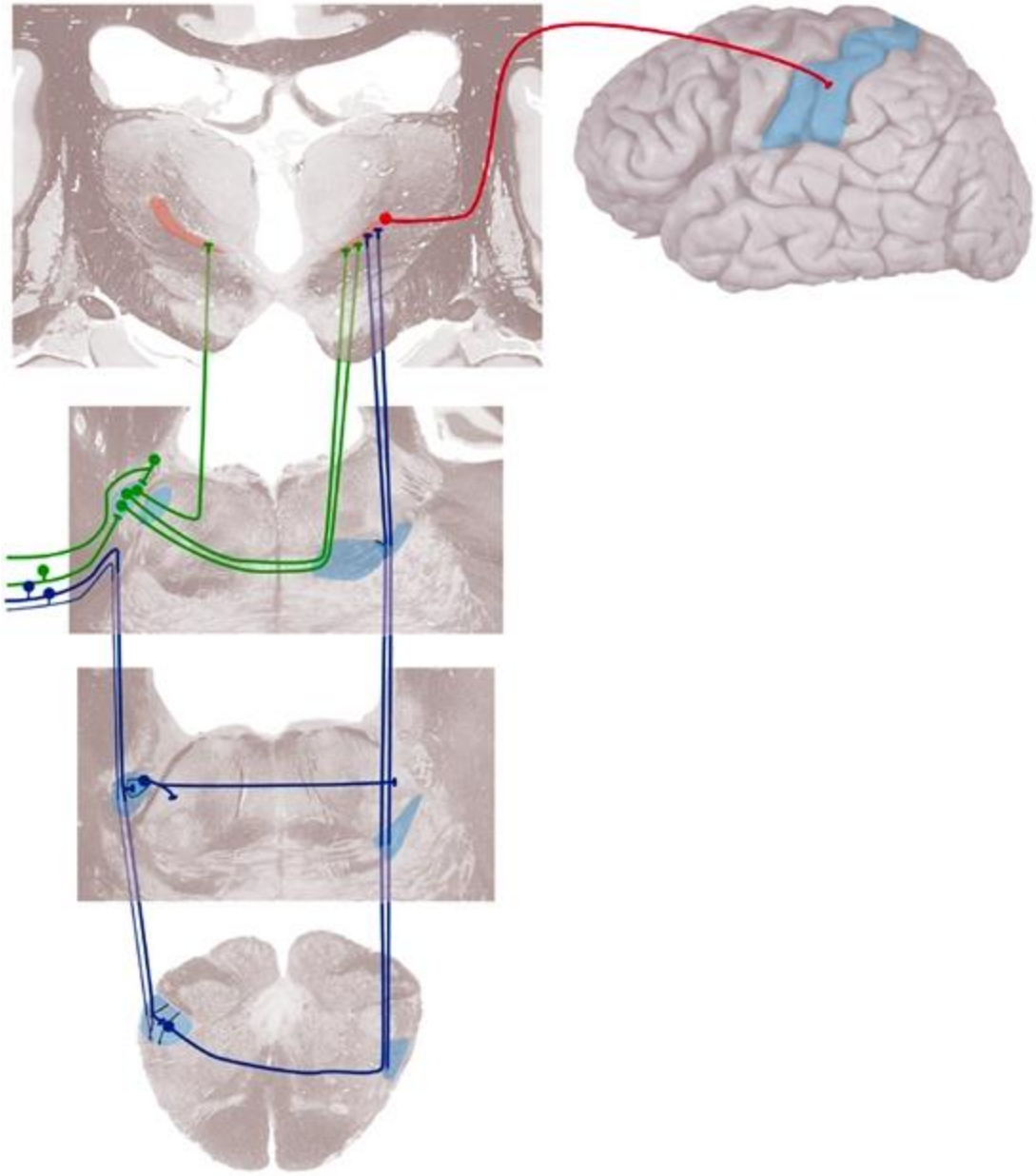






Trigeminal Nerve (CN V)

- Trigeminal sensory pathway in the brain is similar to that for the rest of the body.



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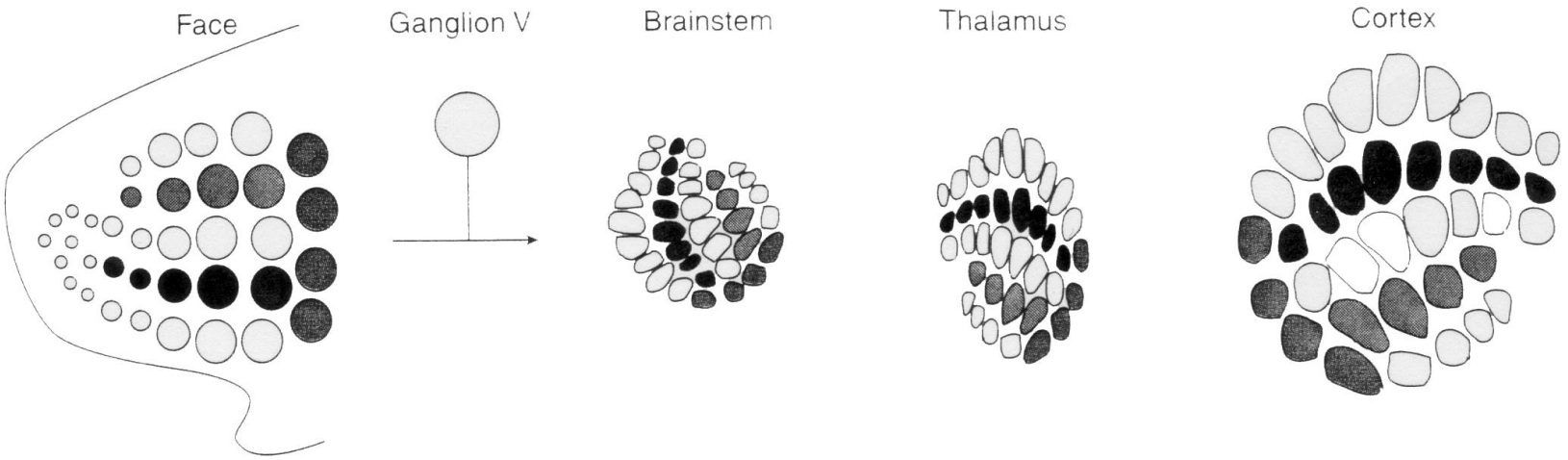
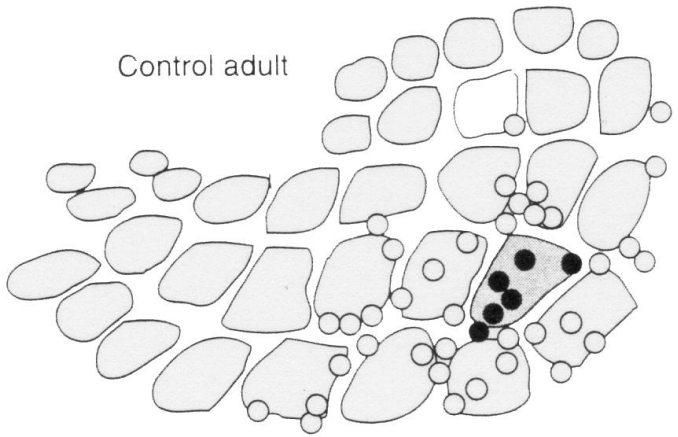
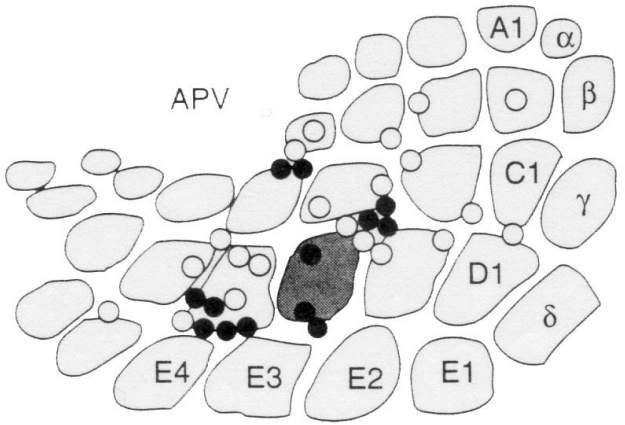




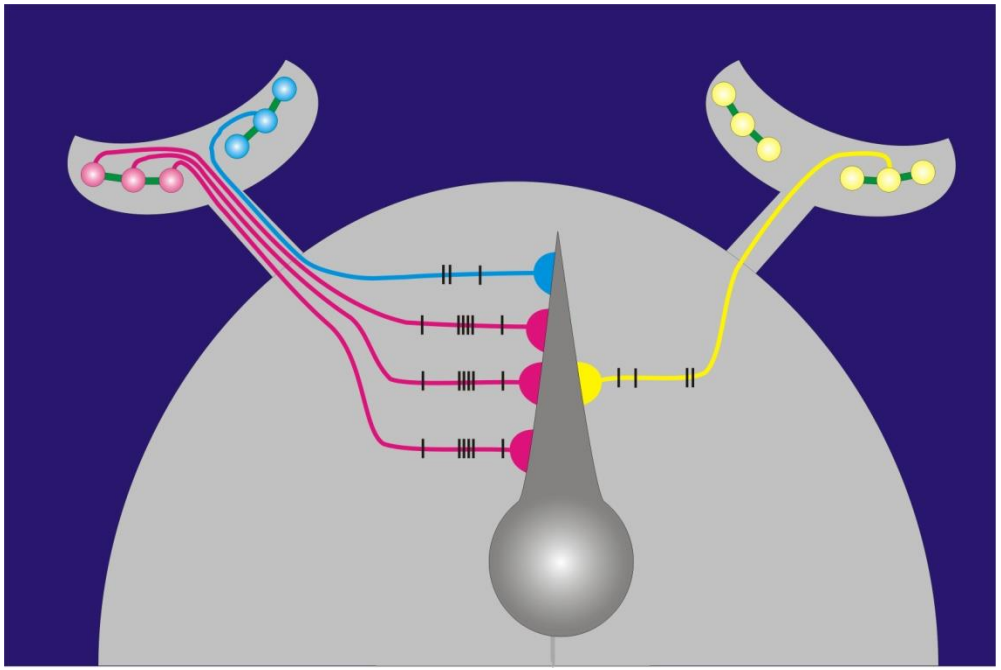


What is the cellular basis of a 'coincidence detector'? -or- How does a postsynaptic cell know that inputs are synchronous?

- Blocking NMDAr in visual cortex during the critical period blocks formation of ocular dominance columns.
- Blocking NMDAr in many systems blocks refinement.

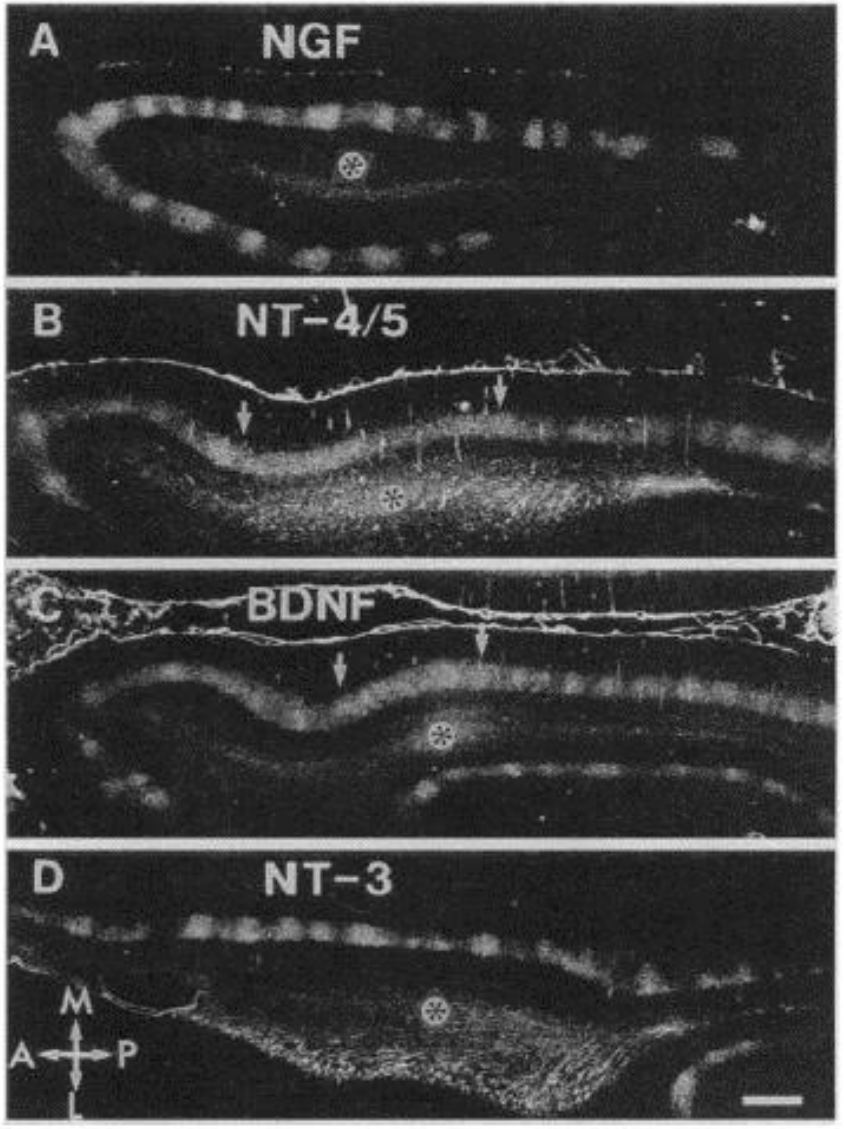
Retrograde Synapse Stabilization / Destabilization

- If NMDA receptors on a postsynaptic cell are required to initiate a change in presynaptic connections to that cell, then the postsynaptic cell must communicate back to the presynaptic axons (i.e. a retrograde signal).
- The nature of the retrograde signal:
  - stabilizing factor
  - destabilizing factor



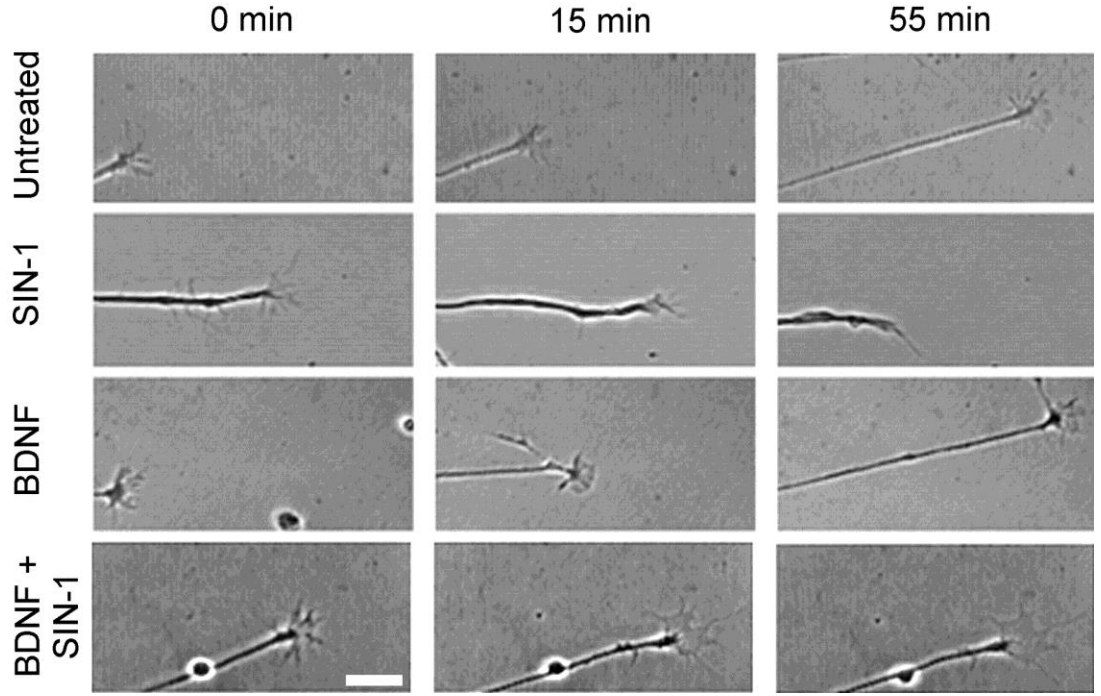
Retrograde Synapse Stabilization / Destabilization

- Neurotrophin could be a stabilizing factor:
  - Neurotrophin is synthesized by neurons following activation of their NMDA receptors.
  - Neurotrophin (NT4/5 or BDNF) administered to the cortex during the critical period prevented formation of ocular dominance columns.



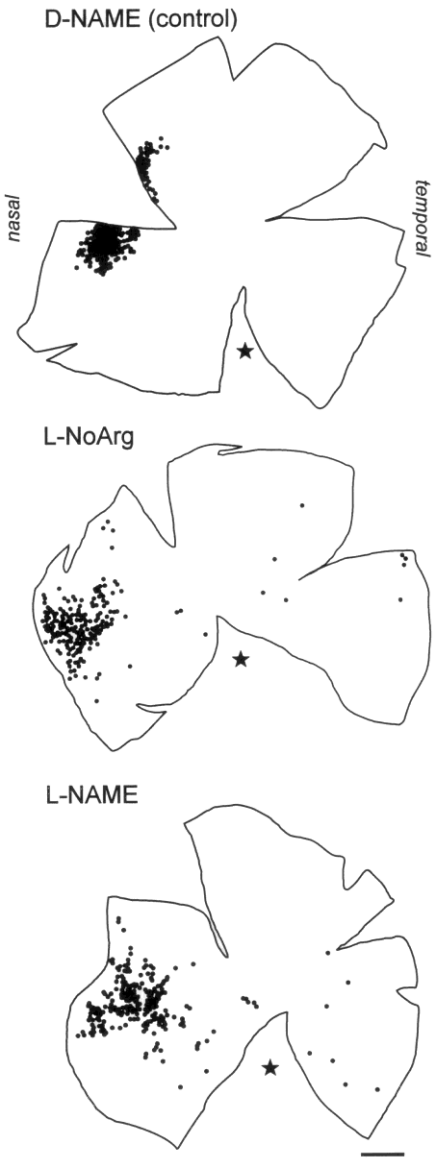
Retrograde Synapse Stabilization / Destabilization

- Nitric oxide could be a destabilizing factor:
  - Nitric oxide is synthesized following activation of NMDA receptors.
  - Nitric oxide caused retraction of retinal axons in tissue culture.



Retrograde Synapse Stabilization / Destabilization

- Nitric oxide could be a destabilizing factor:
  - Blocking nitric oxide synthesis in vivo prevented elimination of transient retinotectal projections.



Retrograde Synapse Stabilization / Destabilization

- Nitric oxide could be a destabilizing factor:
  - However, blocking nitric oxide synthesis did not effect development of ocular dominance columns in cortex.

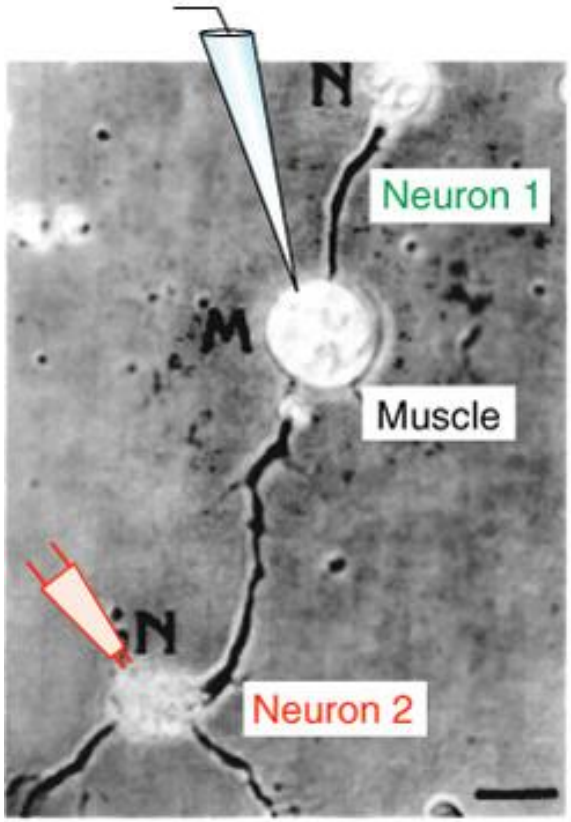
Retrograde Synapse Stabilization / Destabilization

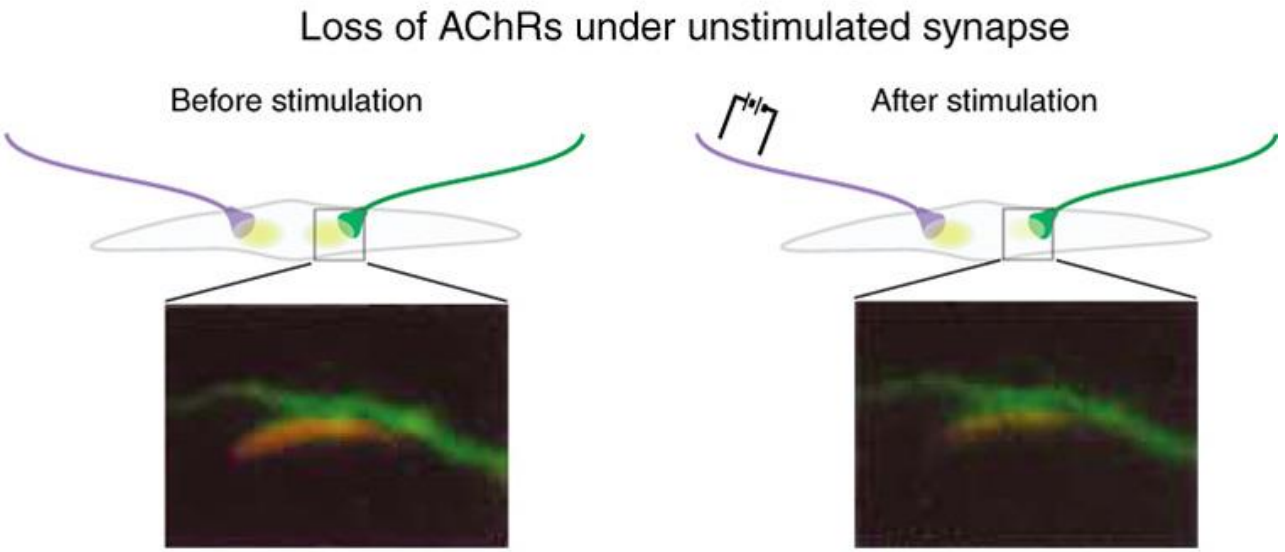
Neuromuscular refinement:

- The muscle releases proBDNF at all synapses.
- The muscle also releases a protease at the most active synapse, which cleaves proBDNF to BDNF.
- BDNF strengthens the most active synapse.
- proBDNF via $p75^{NTR}$ and sortilin causes the less active axon to retract.

Retrograde Synapse Stabilization / Destabilization

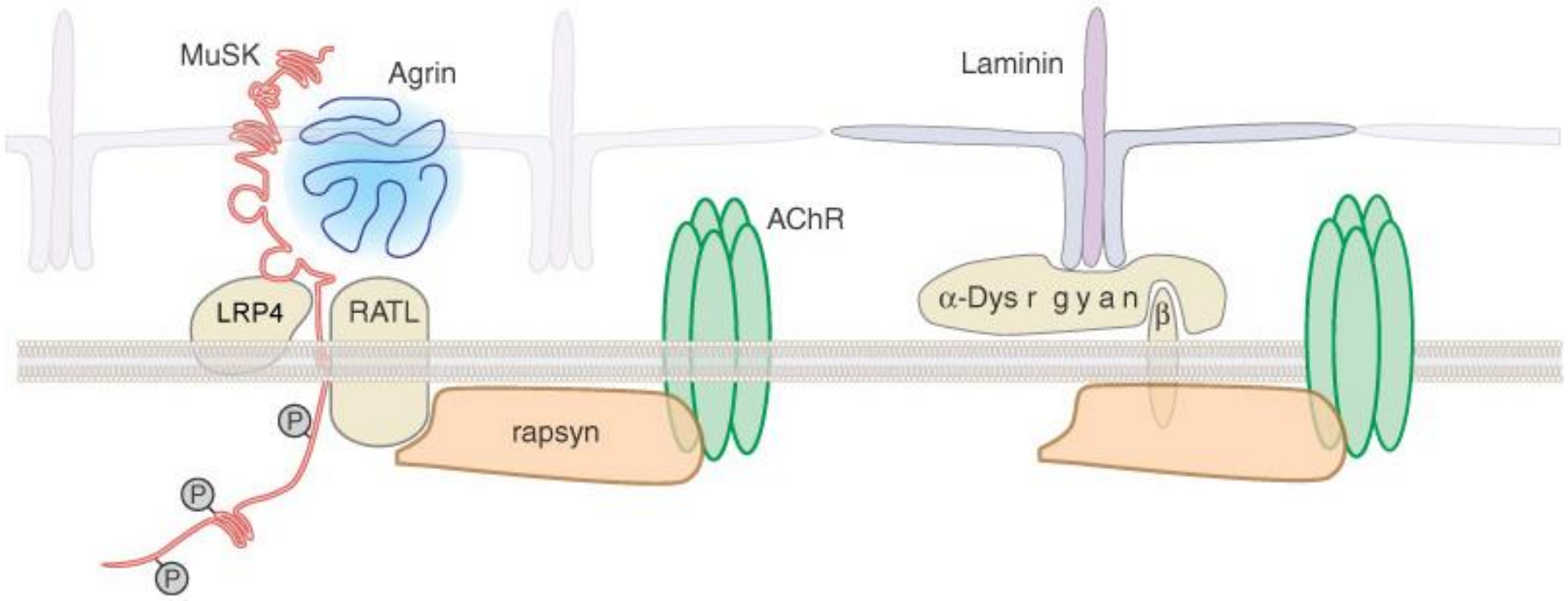
- Loss of ‘synapse anchoring’:
  - During neuromuscular competition, AChRs become unanchored under the weak terminal.





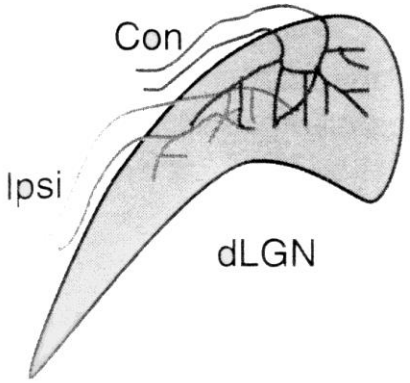
Retrograde Synapse Stabilization / Destabilization

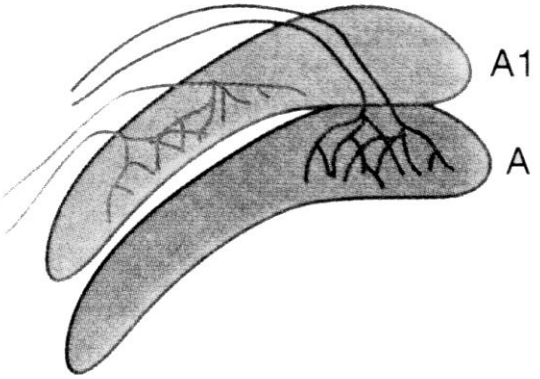
- Loss of ‘synapse anchoring’:
  - The same mechanism that anchors the Ach receptors also anchors the motor neuron terminal via s-laminin.

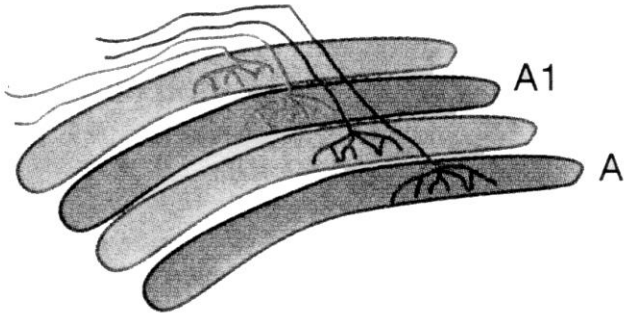


Other Mechanisms Involved in Refinement

- Not every system requires NMDAr activation for refinement.
  - There is no NMDAr in the neuromuscular junction.
  - Segregation of on-off layers in the lateral geniculate nucleus is not blocked by blocking NMDAr function.







Other Mechanisms Involved in Refinement

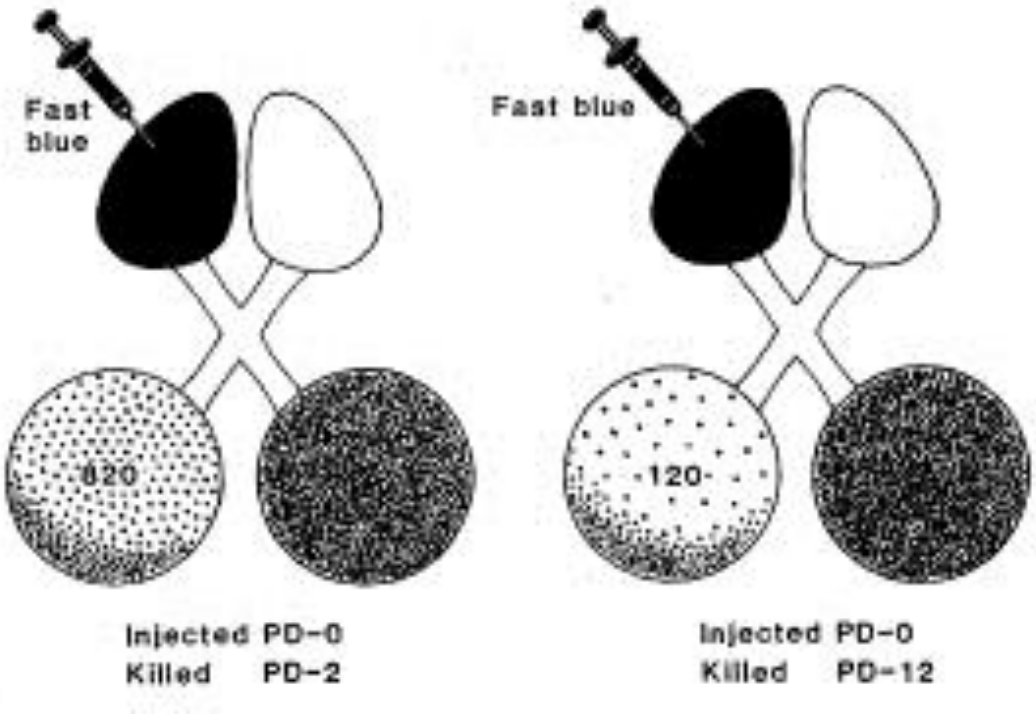
- Other signaling systems that have been implicated in refinement:
  - Class I MHC genes
  - Activity-regulated gene cpg15
  - CaMKII and CREB (activated by NMDAr activation; lead to changes in gene expression)
  - GABAergic (inhibitory) interneurons

Endpoint of Refinement

- Cell death
  - Neurons with incorrect connections appear to have an increased likelihood of being eliminated by programmed cell death compared to the population as a whole.

Endpoint of Refinement

- Cell death
  - ~85% of retinal ganglion cells projecting incorrectly to the ipsilateral side of the brain die during the refinement period compared to ~50% death of the total ganglion cell population.



Endpoint of Refinement

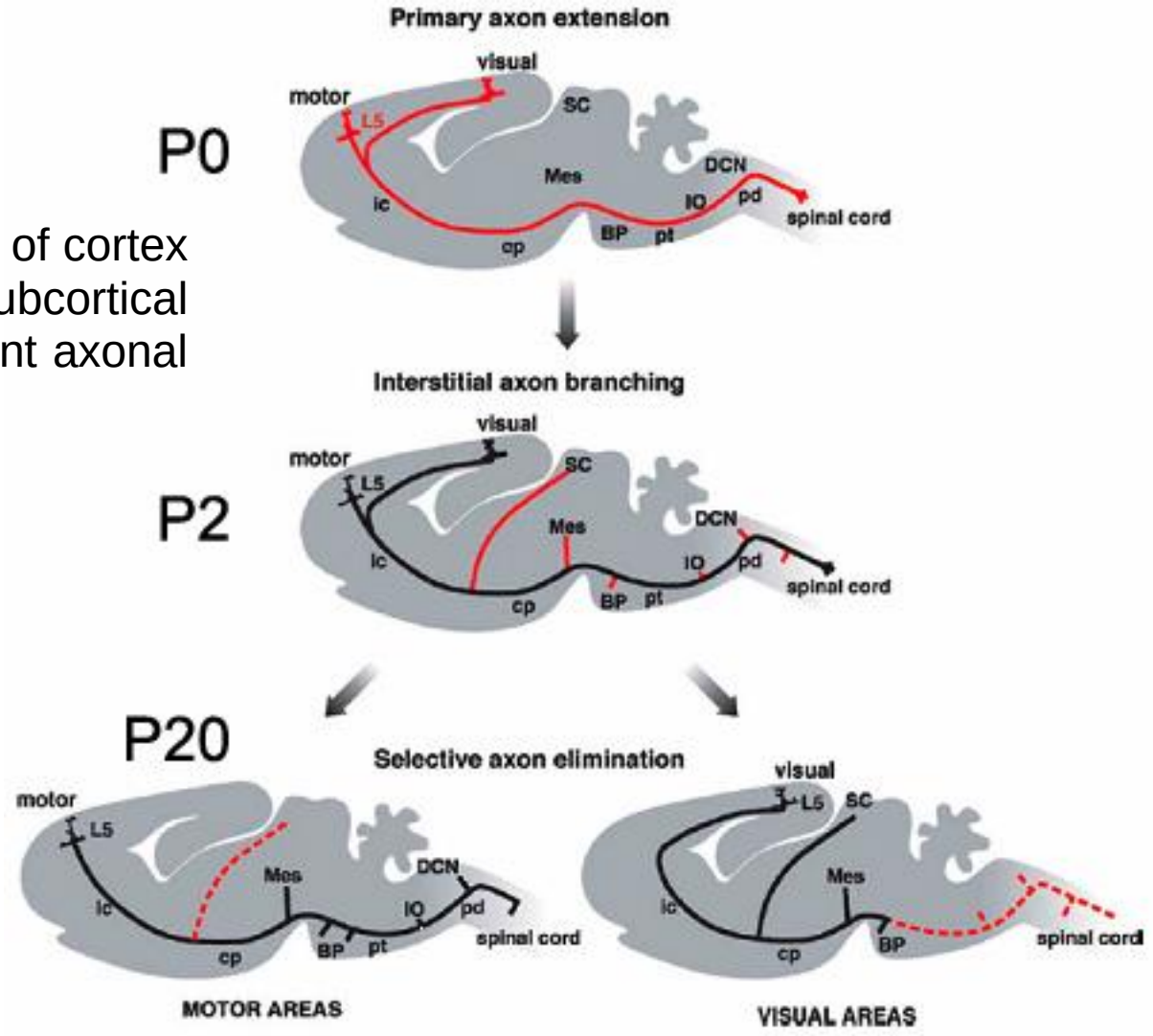
- Cell death
  - Cell death/survival is regulated by amount of neurotrophin neurons receive via synaptic connections.
  - Thus, neurons with incorrect connections do not receive sufficient neurotrophin.

Endpoint of Refinement

- Axon retraction
  - Neurons sustained by correct connections may eliminate their incorrectly projecting axon branches.

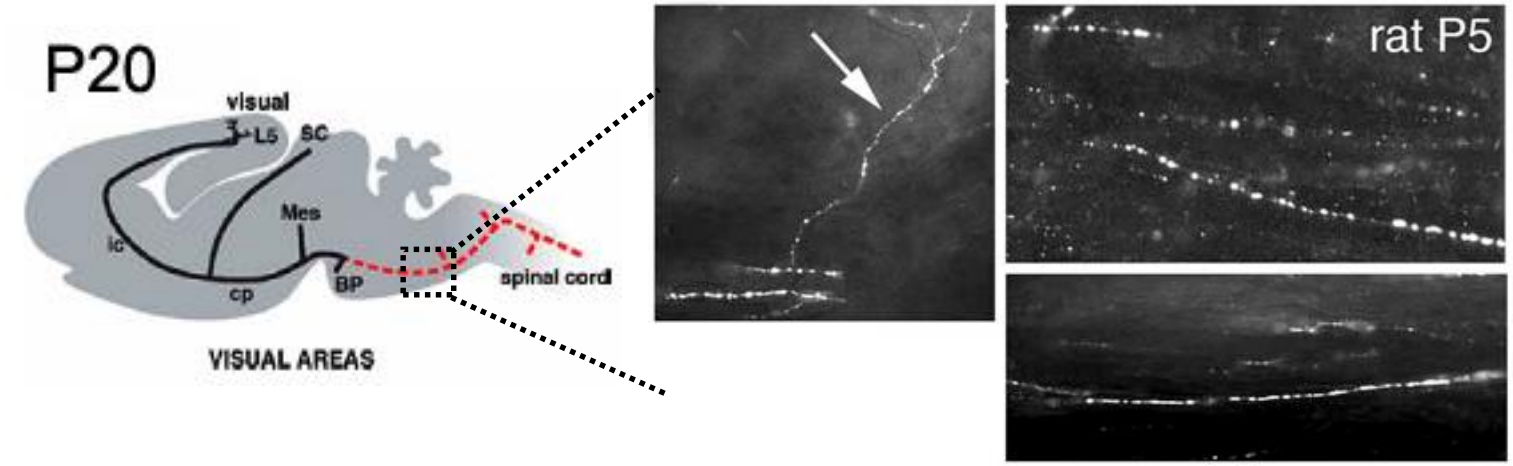
Endpoint of Refinement

- Axon retraction
  - Layer 5 pyramidal neurons of cortex that project to several subcortical targets also have a transient axonal branch to the spinal cord.



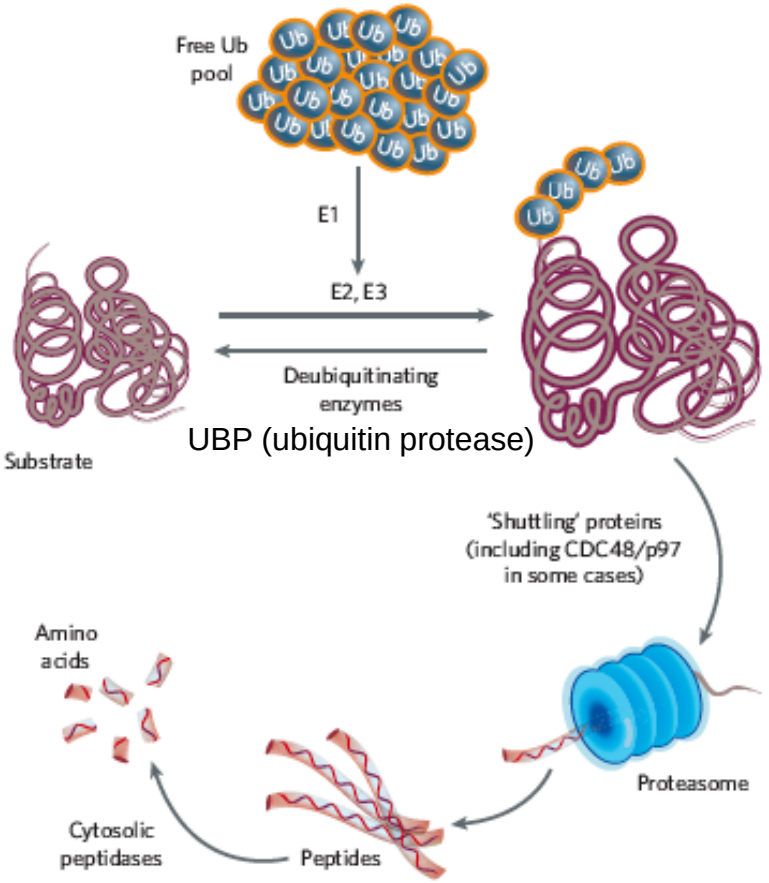
Endpoint of Refinement

- Axon retraction
  - Eliminated axons appeared to degenerate (rather than retract).



Endpoint of Refinement

- Axon retraction
  - Ubiquitin-proteasome system is involved in axon degeneration.



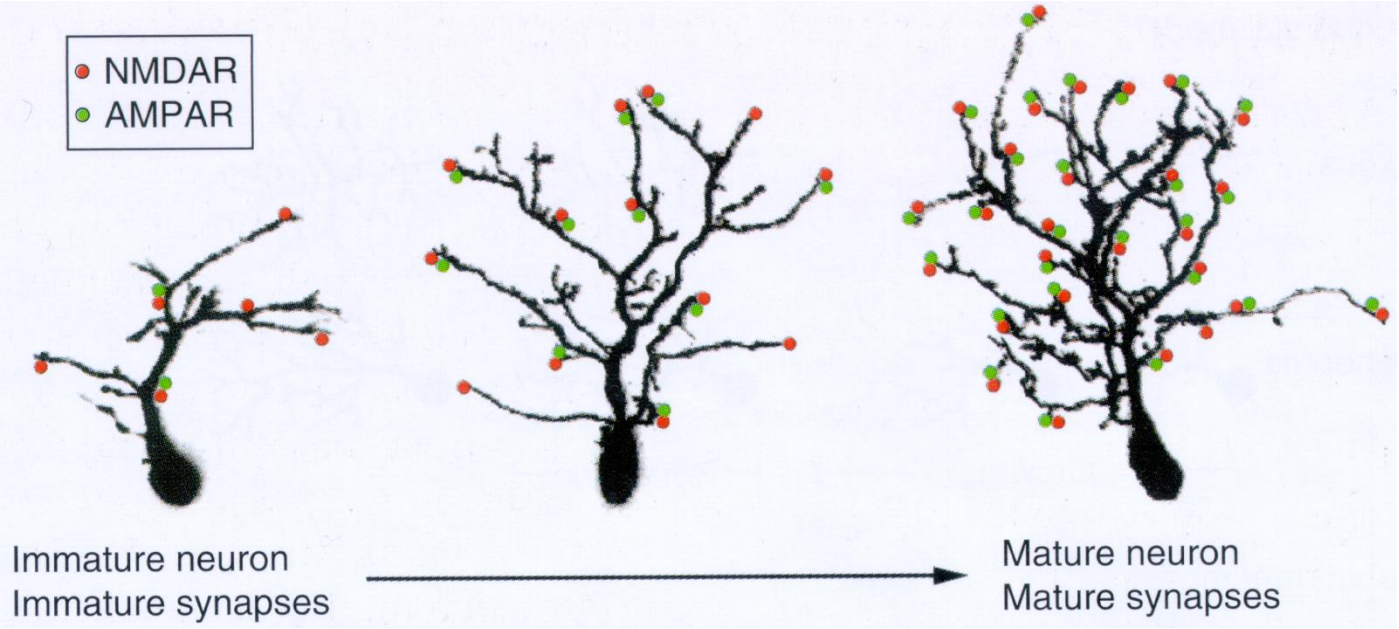
Microglia and Refinement

- Microglia phagocytize synapses in the developing brain.
- Mice without microglia (Cx3cr1 knockout) had more synapses on cortical neurons than wildtype mice.

(Paolicelli et al., 2011)

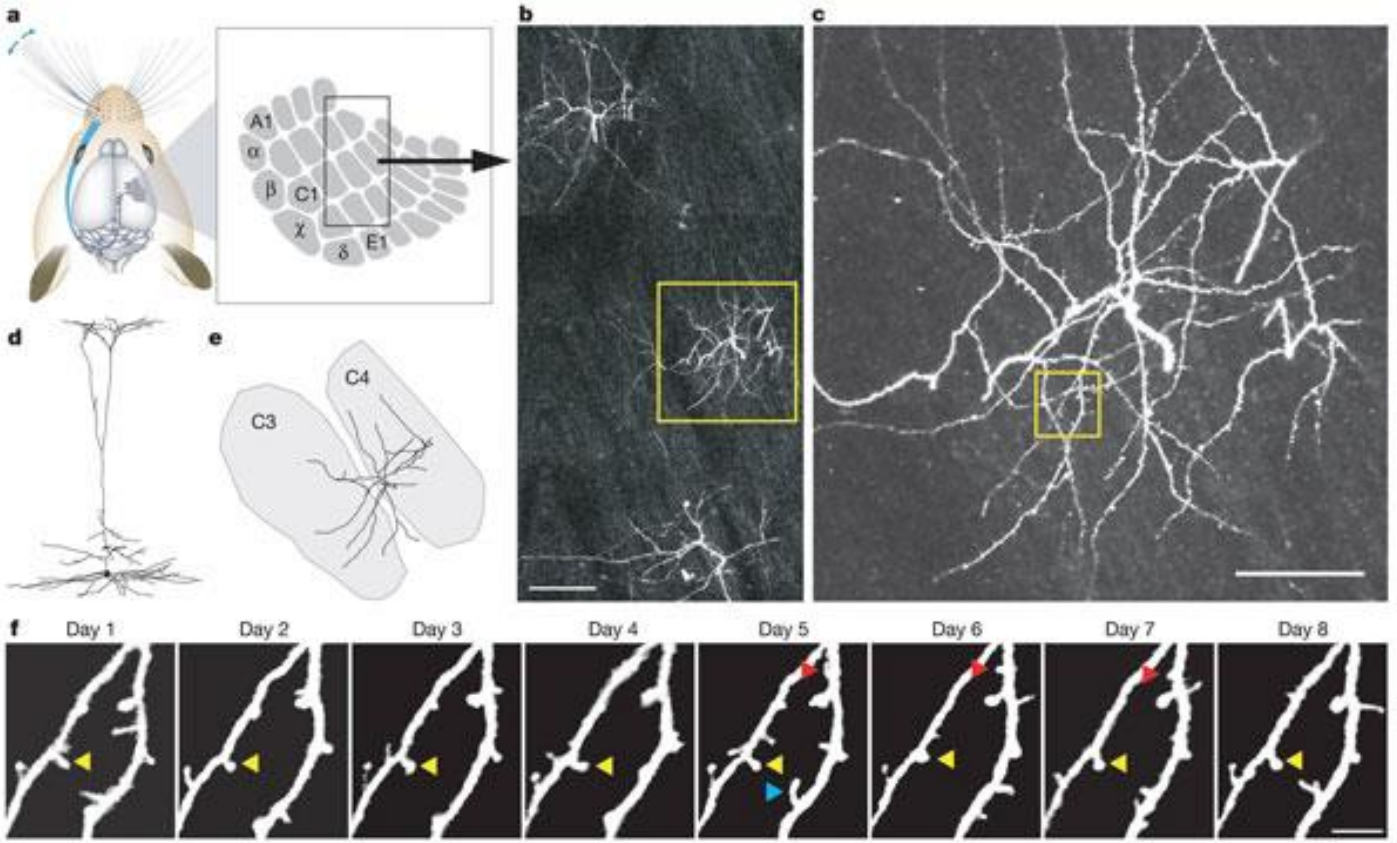
There is a net increase axonal/dendritic arbor size and in number of synapses during refinement.

- During refinement, retinal axons arborize extensively in the topographically correct location while eliminating branches in incorrect locations.
- In most systems, there is a net increase in the number of synapses.
- Refinement is not just an elimination of connections.

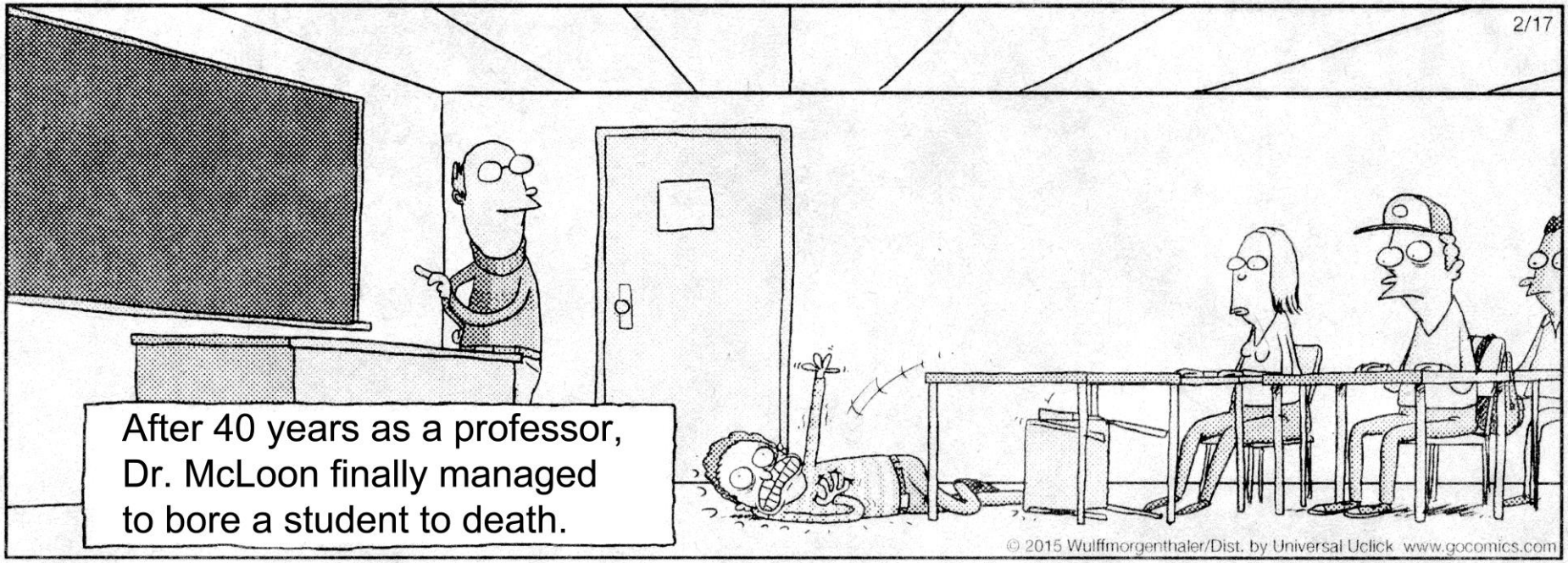


Synapses continue to remodel in the adult.

- Cortical pyramidal cells expressing GFP were imaged live daily over a month.
  - Dendrites were stable.
  - 50% of the spines were stable. The rest turned over, many within a few days.



Questions?


2/17
After 40 years as a professor, Dr. McLoon finally managed to bore a student to death.
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