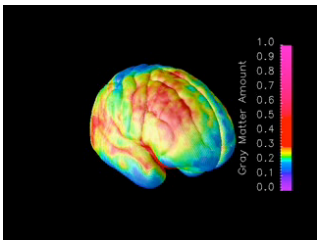
Bi/CNS/NB 150: Neuroscience

Lecture

Friday, October 2, 2015

Development



We emphasize these points from Kandel in Bi/CNS 150

Read			Lecture
1: pp 5-10	Introduction	Brains evolved All higher animals have brains Neurons across species look remarkably similar How these neurons are connected differs A hallmark of brains is complexity Human brains are large and wrinkly and have large frontal cortex	Sept 28 (today)
15: 337-344	Anatomy	The nervous system can be subdivided into regions The brain is a tube The brain floats in your skull NS = PNS + CNS ANS = PNS + CNS = sympathetic + parasympathetic Sensorimotor cortices are topographically organized	Sept 30 (Weds)
	Discussion section	Real human brains	Oct 1 (Thurs)
52: 1165-1185 53: 1187-1194 53: 1218-1227	Development	Most of the complexity of the brain comes from development It is impossible to create an adult human brain without development There are relatively simple developmental rules Development = genes + environment	Oct 2 (Fri)

Why is development interesting?

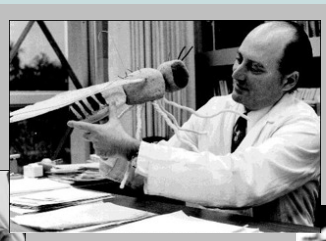
Reason 1: engineering.
"you gotta build it to understand it"
"you can't build it without development"

Reason 2: ubiquity.
"lifespan development"
phylogenetic conservation

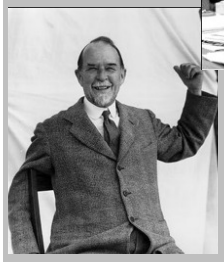
Reason 3: developmental disorders.
e.g., Autism

Reason 4: representation.
How could a brain that never developed know anything about the world?

Developmental neuroscience at Caltech



Seymour Benzer



Thomas Hunt Morgan

Drosophila melanogaster

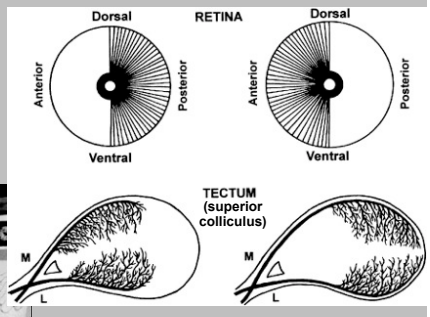
Ed Lewis

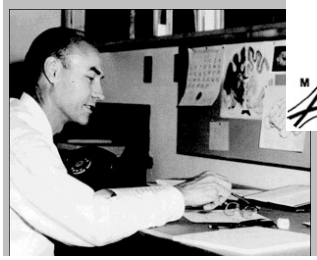
Developmental neuroscience at Caltech

Roger Sperry's famous experiments.

goldfish:

After he cut the optic nerve, individual fibers grew back to their original destination in the brain.





Sperry postulated a "chemoaffinity" between the nerves and their target cells.

THE PROBLEMS OF DEVELOPMENT

- **Cell differentiation**
  - **How do cells get different from one another?**
- **Cell determination**
  - **When do cells first "know" they are going to differentiate?**
- **Pattern formation**
  - **How are differentiated cells positioned correctly in space and time to create structure in a brain?**

Basic Mechanisms

Proliferation

Migration

Differentiation

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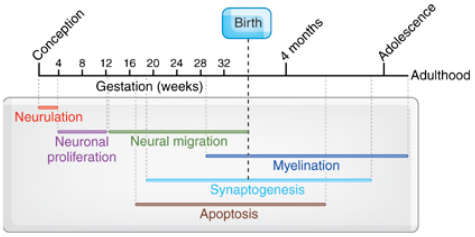

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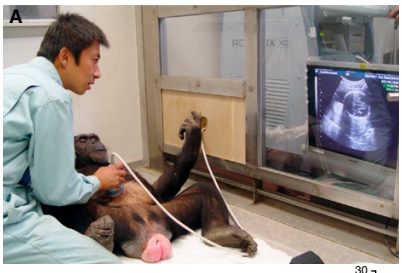
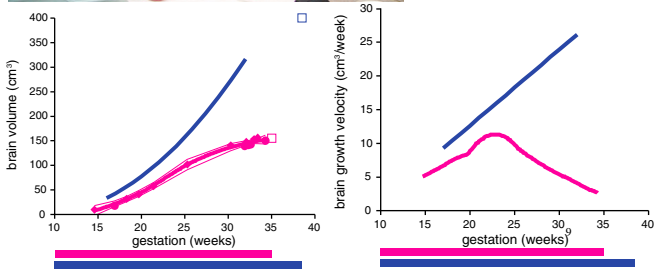


work of Tetsuro Matsuzawa

Sakai et al.,Current Biology 2012



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QUIZ

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The brain is a tube

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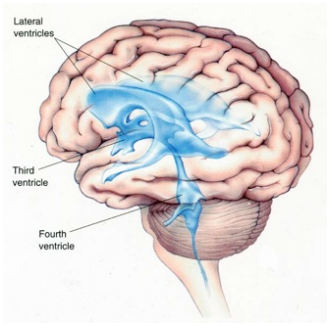
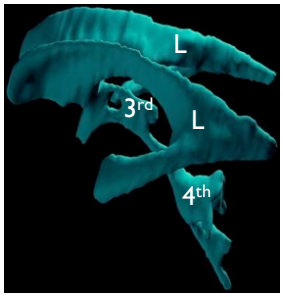
Cerebral Ventricles





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Induction of the vertebrate nervous system

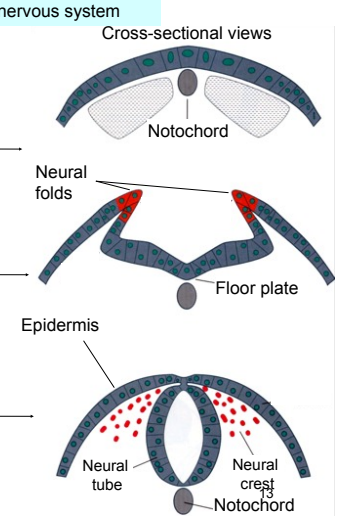
Greek, "outer"; Greek, "skin"

After gastrulation the ectodermal and mesodermal layers approach closely

Greek, "middle"

Ectoderm/mesoderm contact induces the neural plate, which folds

The neural plate rolls into a tube, and neural crest migrates away from the dorsal region of the tube



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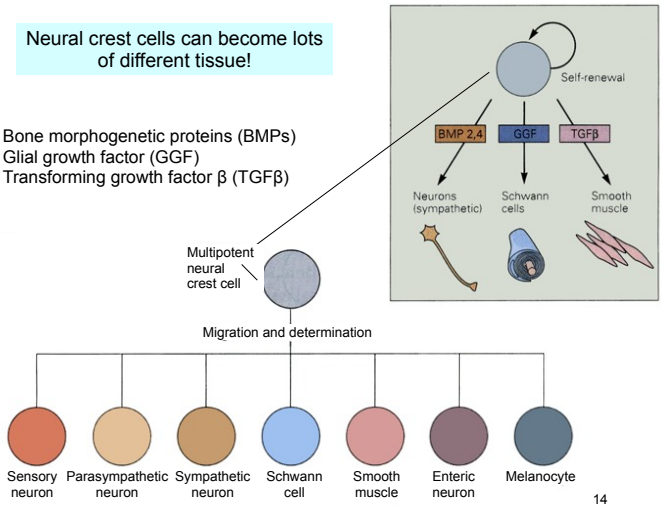
Neural crest cells can become lots of different tissue!

Bone morphogenetic proteins (BMPs)
Glial growth factor (GGF)
Transforming growth factor β (TGFβ)



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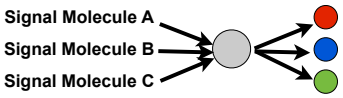
How could a cell be instructed to differentiate?

-external influence (i.e., some molecular signals)

Inducing factors



Note one consequence:
being in a different place/time = exposure to different inducing factors

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What else is needed?

COMPETENCE of the cell to respond to the signals!

- many different types of cell-surface receptors
- differentially expressed on different cells

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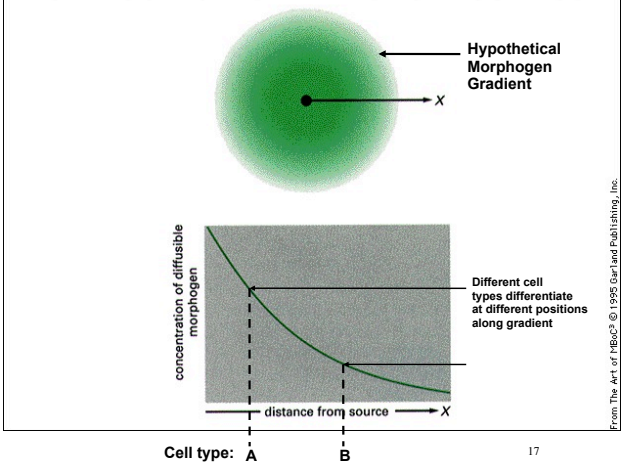
MORPHOGENS: MORE BANG FOR YOUR BUCK



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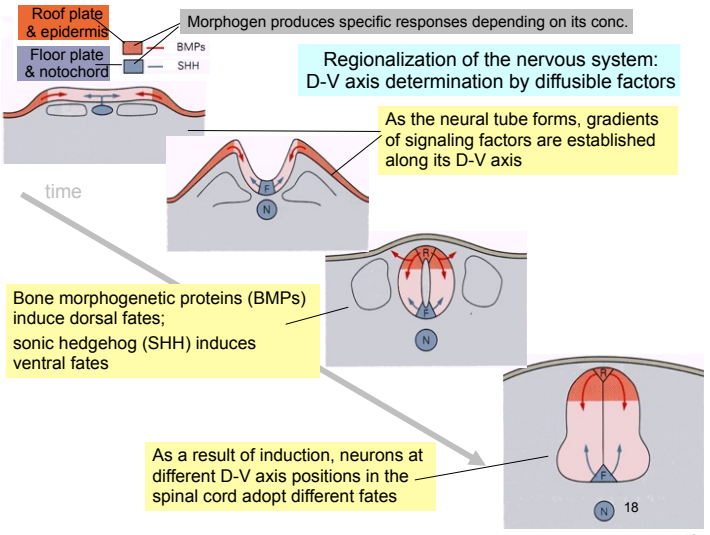

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Summary of D-V patterning:

1. Dorsal: several BMPs. These are inhibited for neural induction. (follistatin, noggin, chordin, fibroblast growth factor, retinoic acid)

2. Ventral: SHH acts as a morphogen (its gradient matters) (note this is quite precisely regulated)

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But how do inducing factors get cells to differentiate?

1. need to bind to cell surface receptors (competence)
2. to trigger intracellular processes
3. that dictate gene transcription

So genes do matter: namely, when and where they are expressed

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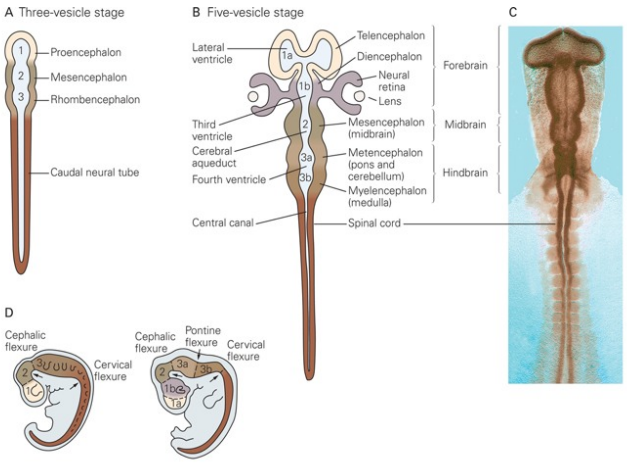

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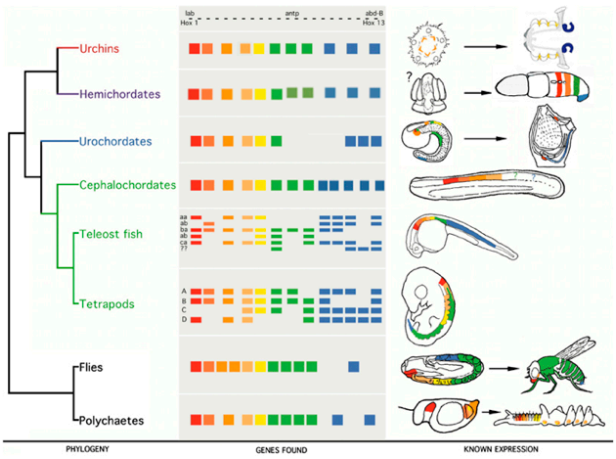

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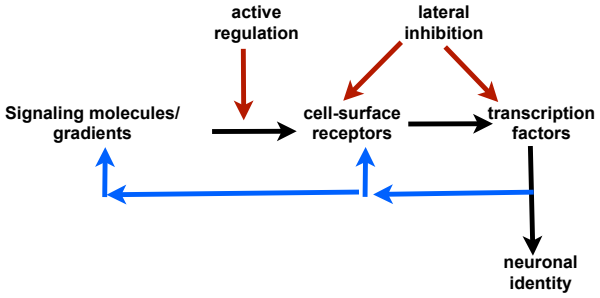
Overall scheme:



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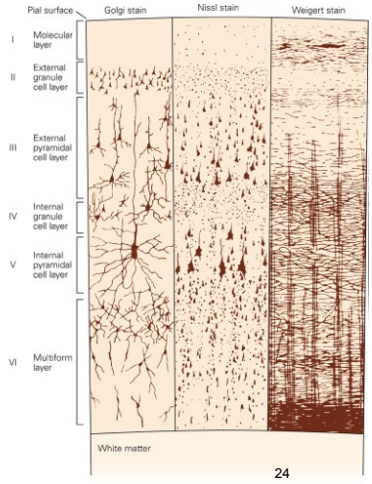

Figure 15–6 The neurons of the neocortex are arranged in distinctive layers. The appearance of the neocortex depends on what is used to stain it. The Golgi stain reveals a subset of neuronal cell bodies, axons, and dendritic trees. The Nissl method shows cell bodies and proximal dendrites. A Weigert stain reveals the pattern of myelinated fibers. (Reproduced, with permission, from Heimer 1994.)

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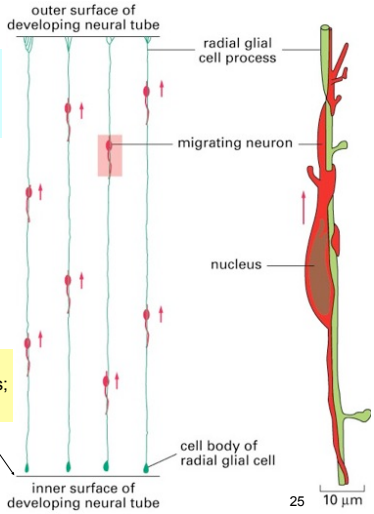
In cortical areas,
detailed cell fate is specified
during birth and migration
along radial glia

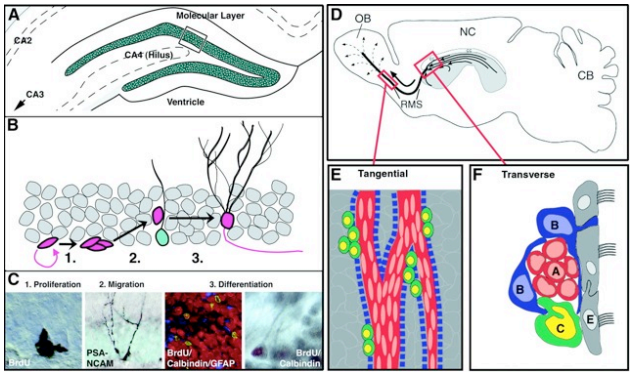
Inside-first, outside last
(newly born cells overtake older cells)

Most cells are born at the inner surface;
Vertical division plane → symmetric fates;
Horizontal plane → asymmetric fates

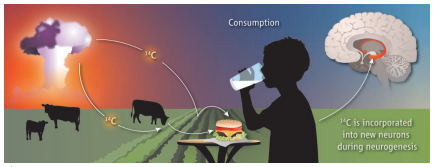


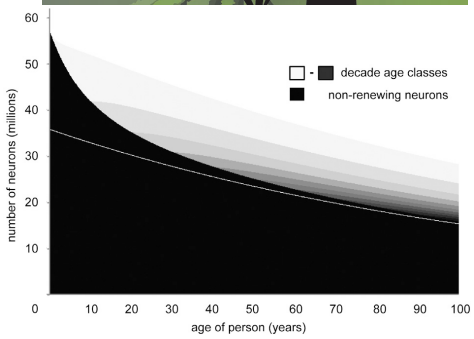
Neurogenesis: new neurons are born in the adult rodent brain
. . . and **definitely** happens in the primate brain.

Hippocampus **Olfactory Bulb**



Gage, F.H. (2000) Science *287*:1433-1438





Spalding et al., Cell 2013

Axonal guidance

once neurons have differentiated and are in the right place....

how do they make the right connections?

Debates about how axons get to their targets

-Langley: they are guided by cues (early 1900s)
- Weiss: random outgrowth and subsequent matching by "resonance" (1930s)

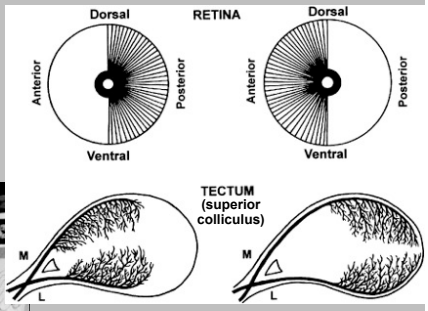
decisive experiment: Roger Sperry's frog (1940s).

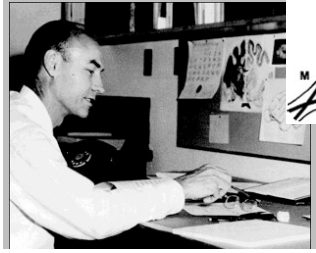
Developmental neuroscience at Caltech

Roger Sperry's famous experiments.

goldfish:

After he cut the optic nerve, individual fibers grew back to their original destination in the brain.





Sperry postulated a "chemoaffinity" between
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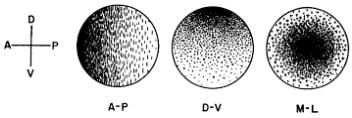

The Chemoaffinity Hypothesis:

1. **Axons have differential markers on them**
2. **Targets cells and pathways have corresponding markers**
3. **Axonal growth is actively directed by markers to establish specific connections**

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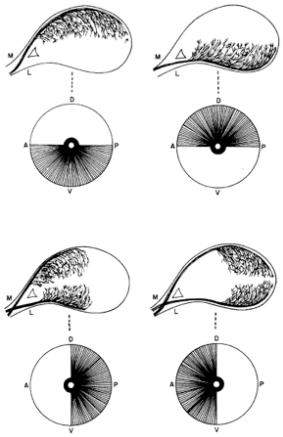

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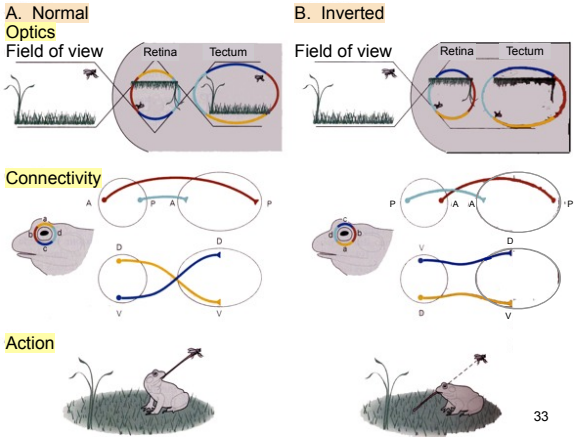
Roger Sperry's classic experiment

Sever optic nerve, Rotate the eye 180° → the frog sees an inverted world. Why?
Because the connections are appropriate for the right-side-up eye.



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Sperry's "chemoaffinity" in the retinotectal system: a 21st Century view

Ephrins: cell-surface proteins that can induce growth cone collapse.

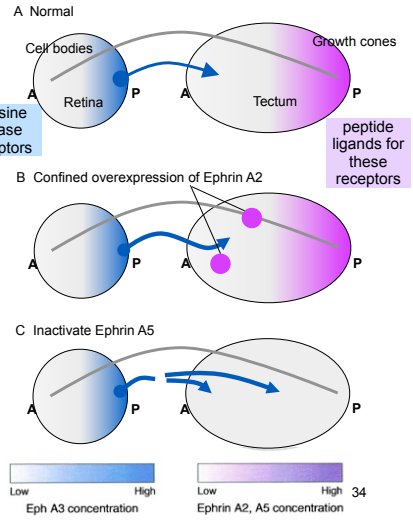
tyrosine kinase receptors

peptide ligands for these receptors

Eph kinases and Ephrins are distributed in gradients in the retina and tectum.

Eph repulsive signaling partially defines Sperry's "chemoaffinity" that sets up the retinotectal map.

Axons with high Eph kinase expression avoid tectal regions with high levels of ephrin



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GFP-actin growth cone in a hippocampal neuron

Fischer et al., *Neuron* 1998

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Once neurons have ....

-differentiated
-are in the right place
-and have made connections

... how do they form the right synapses?

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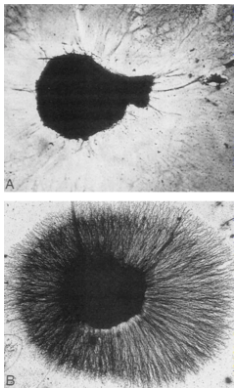
Activity
Trophic Factors



Nerve Growth Factor (effect on DRG neuron)

Hypothesized: 1930s
Isolated: 1970s

There are 4 NTs, recognized by 3 tyrosine receptor kinase subtypes, called Trks.

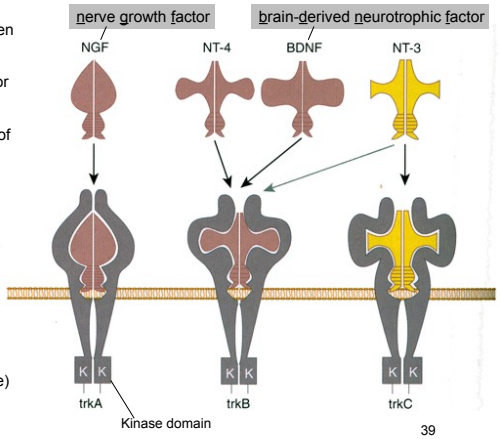
There is cross-talk between NTs in activation of TrkB.

The low MW NGF receptor (not shown) binds to all NTs and facilitates their activation of Trks.

NTs regulate:
Neuronal survival
Precursor proliferation
Neuronal differentiation
Axon growth
Axon branching
Transmitter synthesis
Synaptic efficacy
Dendritic arborization
Synaptic rearrangement

(trk is a proto-oncogene)

The Trk class of Neurotrophins and their receptors



Some themes to note:

BMP prevents dorsal neural tube cells from becoming neurons
Ephrins repel axons coming into the tectum
NGF rescues normal neuronal cell death

A lot of mechanisms have to do with stopping complex, pre-established programs, rather than initiating new ones.

Once neurons have ....

-differentiated
-are in the right place
-and have made connections
-and have formed synapses

... is development over??

Your brain is always on

Your brain is always changing

Brain changes -> behavioral changes -> environment changes