4/14/04

ephrins - short-range inhibitory molecules

pioneer neurons - different pathfinding than later neurons, establish tracts (later ones use contact attraction)
- must sense gradients
- express fasciculins (later axons follow for good distance b/f branching off)

synaptic basal lamina - holds determinants of synapse formation

- $Ca^{2+} \rightarrow$ PKC $\dashv$ nonsynaptic AChRs

- retrograde signals for nerve terminal differentiation not well understood; thought to involve wingless, TGFβ, etc

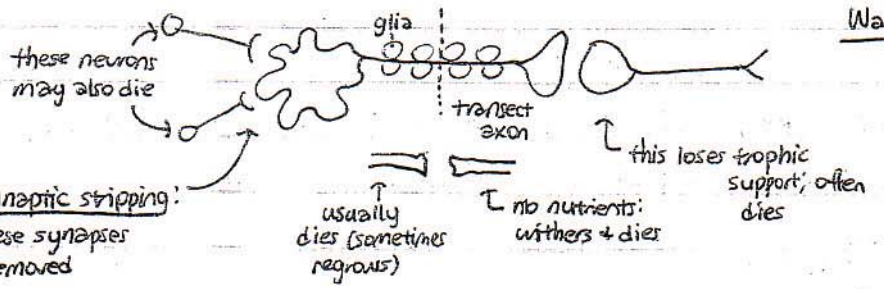
- each muscle fiber innervated by single motor neuron (but one motor neuron innervates more than one muscle fiber)

- agrins expressed in CNS, but unknown if function in clustering

NMJ: large postsynaptic area, just want muscle to contract
CNS synapse: small spine to compartmentalize synapses, so can perform computing role
↳ dendritic spine
- glutamatergic synapses use PDZ proteins instead of rapsyn for clustering
- neurexin (presynaptic) + neuroligin (postsynaptic) initiate synaptic development events

~~refinement of synaptic connections:~~

- damage in brain: neuron wrapped in glial cells, has inputs & outputs



how to fix nerve damage:

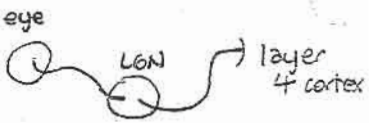
1. neurogenesis
   - ventricular zone: still making neurons in mature brain (although no new cortex)
     - try to convert developing stem cell neurons for other parts of brain

2. repair
   - PNS much better at regenerating than CNS:
     1. environment may be different, positive PNS factors
        - eg Schwann cells: put basal lamina components etc back in CNS, or Schwann cells themselves
        - some evidence: PNS nerve in CNS can sometimes grow?
     2. negative factors in CNS
        - myelination happens very late in development (after connections made)
          - myelin bad for outgrowth
            - myelin associated glycoprotein & NI-35: Abs against these give much better axonal growth in ~~to~~ culture
     3. difference inherently between CNS & PNS neurons
        - identify different factors
          - GAP-43: associated w/ cytoskeleton, thought to transduce growth signals
            - high in maturing PNS: if damage neuron, goes up even more
              in CNS, if high until connections formed, then drops; damage won't make go up again
     4. different responses to damage
        - in CNS, astrocytes multiply, also microglia (macrophage-like) come in, eat stuff, leave scar tissue, big inflammatory response so repair very difficult
          - give steroids to prevent response, eg for spinal cord injuries (kill immune cells?)

so far:

1. molecular cues (development, wiring, synapse formation)
2. activity-dependent refinement of synaptic connections: happens throughout nervous system

| | early | later |
|---|---|---|
| NMJ | 2-6 MNS | 1 |
| visual cortex layer 4 | binocular innervation | monocular innervation |
| thalamus (LGN) | binocular (20) ← axons driving neuron | monocular (1-2) |
| cerebellum climbing fiber input → | 3 CFs | 1 |

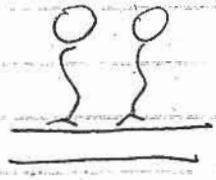


| | early | later |
|---|---|---|
| parasubmandibular | 5 | 1 |
| sympathetic NS | ~14 | ~7 |

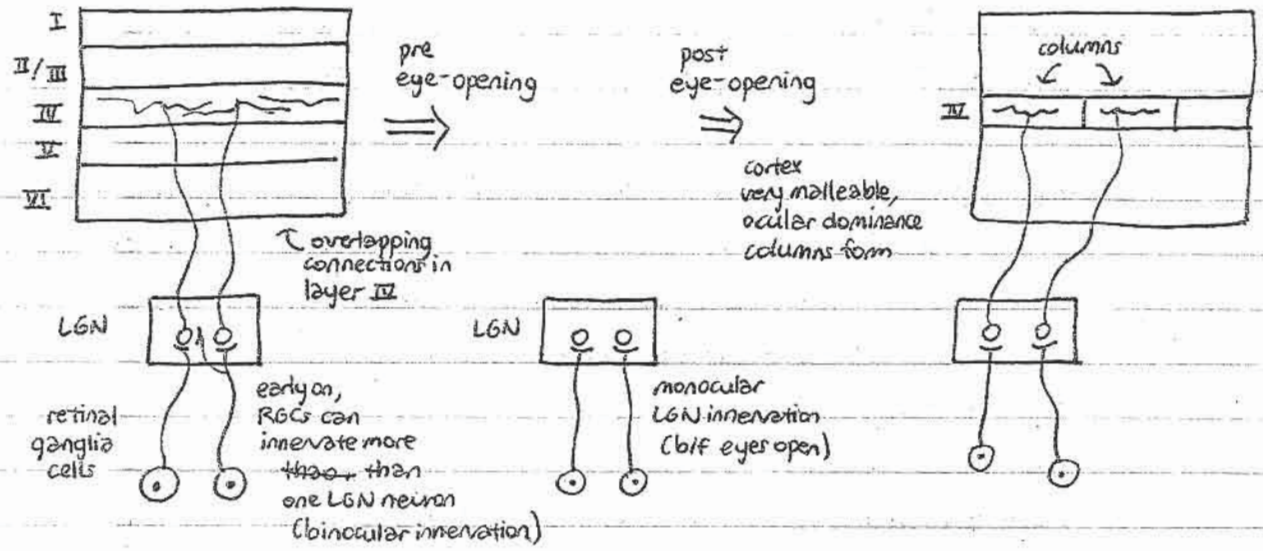
synapse elimination - start out w/ more connections than you need, prune down
- more like input elimination (remove inputs from one source)
- also strengthening remaining connections (not net loss of synapses)
- probably going on all over brain

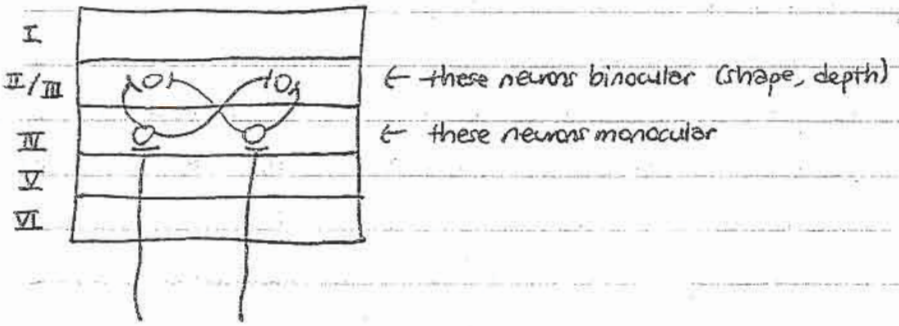
- why? 3 models:
1. get rid of errors
   - probably not true, b/c no connections "wrong", just competing for targets
2. sharpen specificity
   - especially in areas w/ topographic maps
3. duplicated neuron hypothesis
   - not widespread in ~~vertebrates~~ invertebrates: no input elimination
     - very specific populations of neurons generated, innervate muscle fibers precisely
   - invertebrates (10" neurons vs. 300): impossible to have enough molecular cues
     - have large group of duplicated neurons that innervate same cell, give modular flow of information when pruned down to 1
   - invertebrate advantage: development: born ready-wired, good for survival
   - vertebrate ~~advantage~~ disadvantage: vertebrates need to be taken care of during development
     when connection get lost, can never regain ~~it~~ them
     "can't teach old dog new tricks"

- if block APs w/ TTX, both inputs maintained throughout development
- activity drives synapse elimination
- local inhibitor of activity (eg α-bungarotoxin) can eliminate one synapse preferentially
- if stimulate both equally, no elimination
- differential activity: axons compete, one kills other



models:
- punishment - generation of punishing factor (and self-protection at same time) from postsynapti
  cell? kills other synapse (postsynaptic compartments comparing inputs)

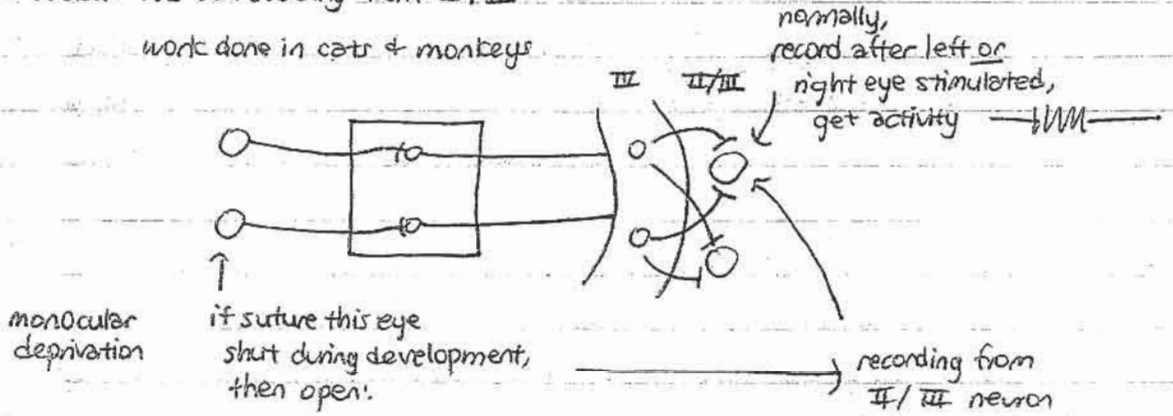



Weisel

Hubel & ~~Weisit~~: lots of recording from II/III

work done in cats & monkeys




monocular deprivation

if suture this eye shut during development, then open.

recording from II/III neuron after stimulation of deprived eye, no activity

cortical blindness (sensory information shapes function of cortex)

in vision, weeks for cats years for humans

(optic nerve, thalamic neurons, still had fine activity)

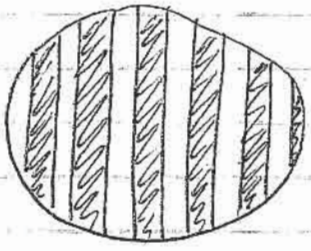
if do this to adult eye, no problems (there is critical period for cortical blindness)

4 different for different things, eg 7 years for language

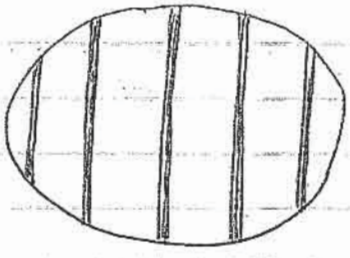
if suture both eyes shut, II/III neurons ~~both~~ still respond to both

- so idea is competition
- if suture both eyes shut but give same patterns of activity, fine II/III

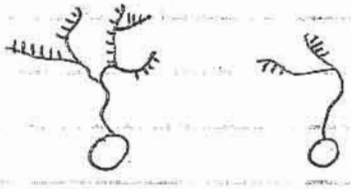
- can add radioactive label to one eye, can light connections all the way up to cortex, can then see ocular dominance columns



same width for each eye



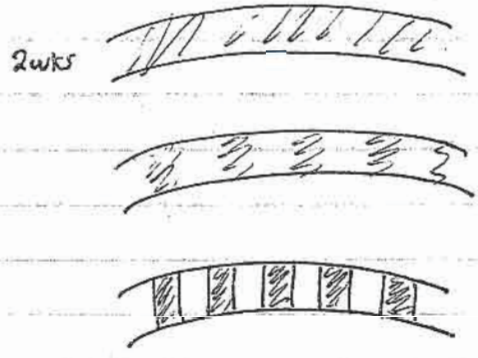
if suture one eye closed



young (extensive connections)

later (connections pruned)

w/ monocular deprivation, eye receiving input → cells like young (other eye: very few connections)

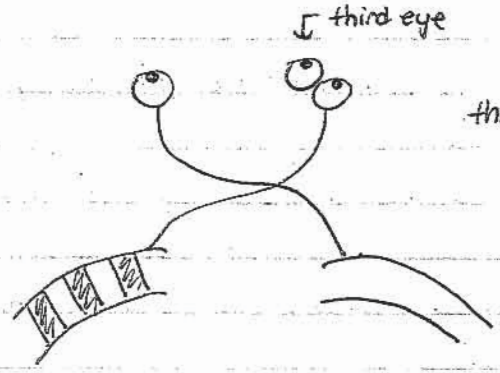



sharpening of ocular dominance columns

- if fire together, strong stimulation, lots of $Ca^{2+}$: other gets "punished" b/c not synchronous firing

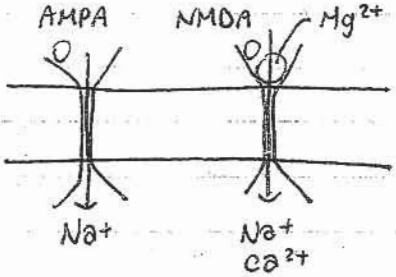
Martha Constantine-Paton:

- always monocular




three-eyed frog experiment

competition
gives stripes
like ocular dominance columns




if block NMDA function, got no segregation of inputs in three-eyed frog

if potentiate NMDA, stripes became much cleaner

- LGN neurons monocular before eyes open
  - eyes have rhythmic ~~waves~~ waves of constitutive synchronous activity, make connections monocular

# 7.29J / 9.09J Cellular Neurobiology

Spring 2012