

Neuro 80 Lecture 19

If Unigral sensory experience causes layer 2/3 cells to shift ocularity, what do you think will happen when you shut your eyes?

- Cells in layers 2/3 lose visual responsiveness
- Nothing (relative difference in activity / timing of of activity b/w inputs is unchanged)
- all cells become monocular
- all cells become binocular

If scientist alternatively patch the right eye then the left during the CP, what do you predict the OD dist to look like?

- normal (both eyes get visual input)
- normal but smaller
- shift to right (bc first patch)
- shift to ends (only monocular)

What is not a way to extend the critical period?

- ↑ attention / motivation
- incremental learning - small bit at a time
- prematurely expose animals to sensory experience
- pause, then reinstate, adolescent plasticity

When is it best to target the brain w/ a drug
to destroy/prevent Amyloid- β plaques?

- preclinical (when cognitively healthy)
- mild cognitive impairment
- when dementia present



MCB/Neuro 8o - Neurobiology of Behavior

Today's Topic:

Structural changes and aging

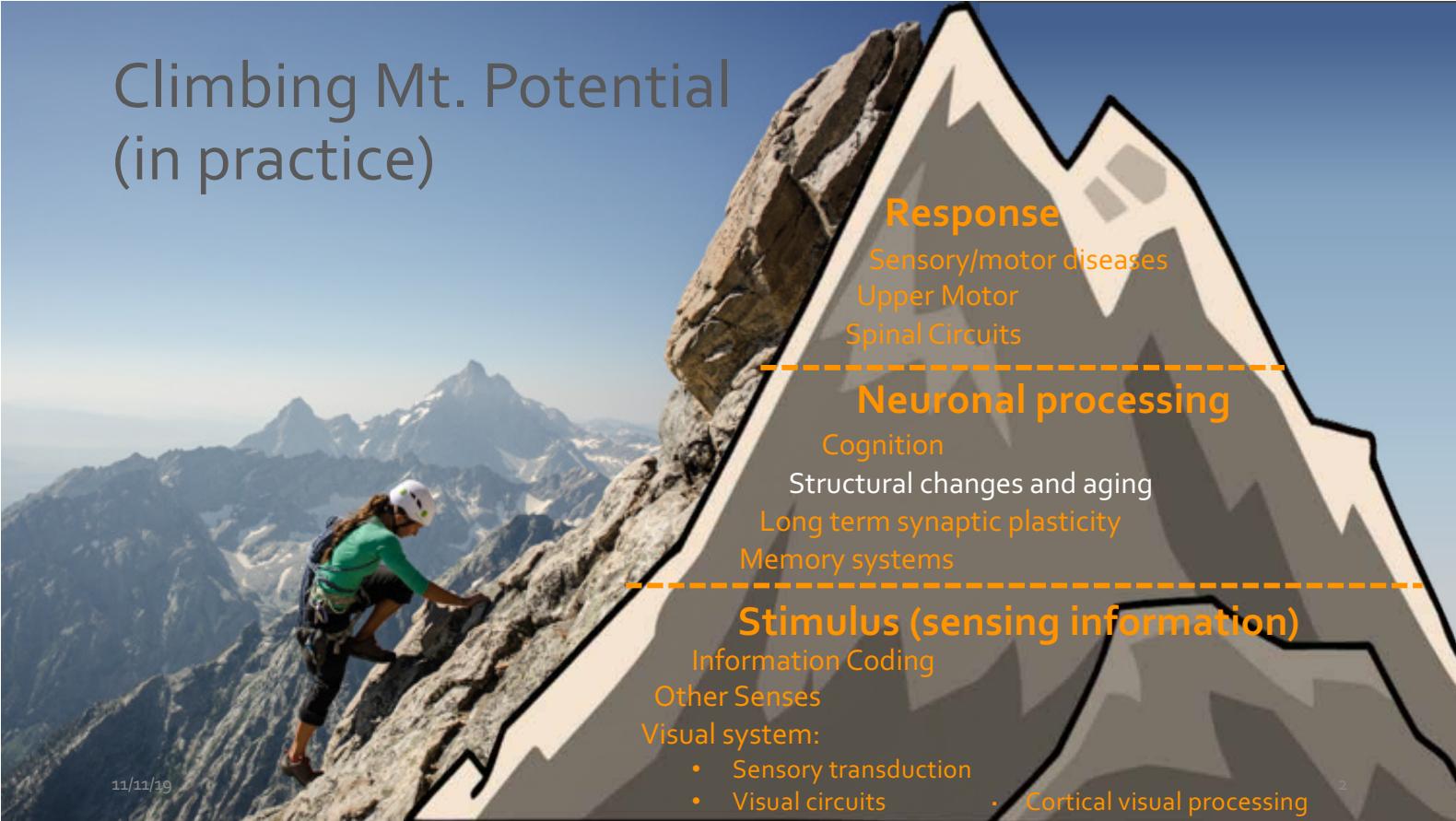
Lecture 19

Optional reading: Purves et al., Neuroscience 6th pages: 571-584, 590-592, 595-596, 694-695

Lecture notes, review questions, office hour times available at:

<https://canvas.harvard.edu/courses/59120>

Climbing Mt. Potential (in practice)



■ Which of the following mechanisms used in hippocampal LTP is not part of the hippocampal LTD mechanism?

History-dependent modification
of synaptic efficacy



NMDA receptor activation



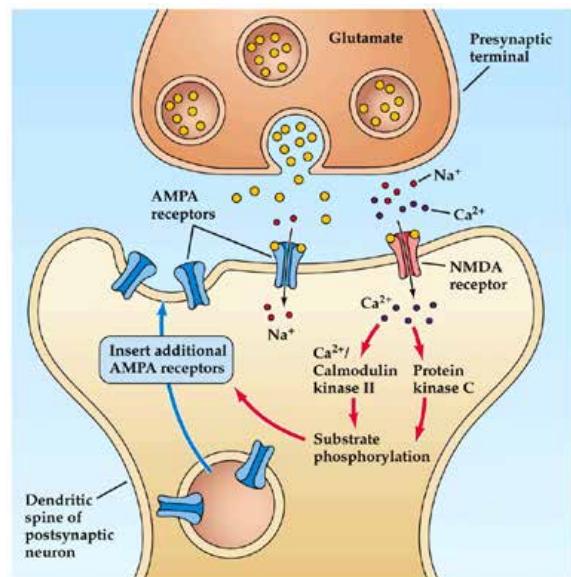
Calcium influx

Calcium-dependent activation
of protein kinase C

All of the above are used in
both LTD and LTP

Long term synaptic plasticity leads to quick and long lasting changes in synaptic strength

- LTP – strong, correlated activation
 - Coincident activation of pre- and postsynaptic neurons opens NMDARs
 - Fast, large rise in $[Ca^{++}]$
 - Activation of kinases
 - Leads to increased AMPA currents
 - Larger conductances in existing receptors
 - Insertion of additional receptors
 - Eventually, new proteins are made, and changes in gene expression lead to long lasting changes



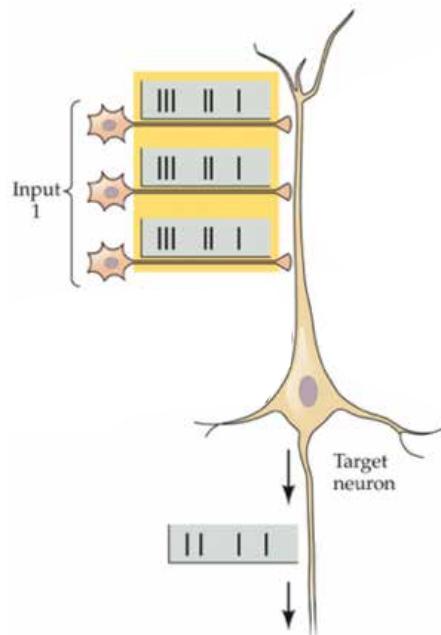
NEUROSCIENCE 5e, Figure 8.13
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Correlated neuronal activity strengthens connections while uncorrelated neuronal activity weakens connection

Hebb's postulate:

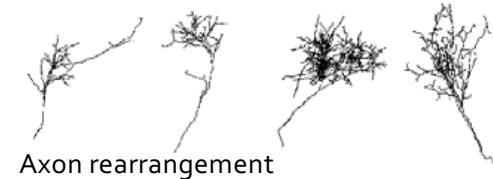
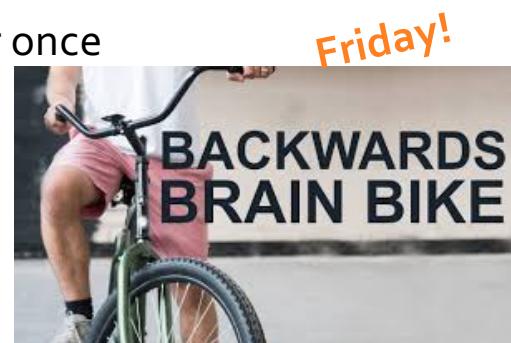
- "When a cell A repeatedly fires with cell B, A's connection to B is increased."

- *Neurons that fire together, wire together*
- *Neurons out of sync, loose their link*



Brain plasticity is not unlimited

- Often once something is learned one way, or once a developmental stage has passed, it is more difficult to learn a second method
- Synaptic Rearrangement
 - The last and longest stage of development
 - All about synaptic plasticity
 - Synaptic plasticity leads to large structural changes
 - Limited time for large changes
- Critical Periods
 - a developmental window during which the nervous system is particularly sensitive to the effects of experience



Critical periods

- Critical period is a maturational stage in the lifespan of an organism during which the nervous system is especially sensitive to certain environmental stimuli
 - More generally thought of as a period during development in which a particular skill or characteristic is believed to be most readily acquired.
 - Lots of them:

Critical period for

...imprinting in the chick
...brain sexual differentiation
...extraocular muscle development
...visual plasticity
...monocular deprivation
...addiction vulnerability
...wing pattern induction in the polyphenic tropical butterfly
...GABAergic receptor blockade for induction of a cAMP-mediated long-term depression at CA3-CA1 synapses
...methamphetamine-induced spatial deficits
...second-language acquisition
...experience-dependent Plasticity in Visual Connections in *Xenopus*
...lung cancer susceptibility
...cross-modal plasticity in blind humans
...nicotine exposure effects
...disruption of primary auditory cortex by synchronous auditory inputs
...functional vestibular development in zebrafish
...right hemisphere recruitment in American Sign Language processing
...barrel cortex critical period plasticity
...feminization in tilapia
...developmental climbing fibre plasticity
...sensory map plasticity
...sensitivity to juvenile hormone
...language acquisition
...LTP at thalamocortical synapses
...caste determination in *Bombus terrestris* and its juvenile hormone correlates
...deafferentation-induced apoptosis
...nicotine-induced disruption of synaptic development in rat auditory cortex
...activity-dependent synapse elimination in developing cerebellum
...conversion of ectodermal cells to a neural crest fate
...psychosis
...verbal language development
...reduced brain vulnerability to injury.
...chorda tympani nerve terminal field development
...the sensitivity of basal forebrain cholinergic neurones to NGF deprivation
...light-induced phase advances of the circadian locomotor activity rhythm in golden hamsters
...the influence of peripheral targets on the central projections of developing sensory neurons
...the specification of motor pools in the chick lumbosacral spinal cord
...axon regrowth through a lesion in the developing mammalian retina
...long-term potentiation in primary sensory cortex
...song learning in the zebra finch
...restoration of normal stereoacluity in acute-onset comitant esotropia
...transcription for induction of a late phase of LTP.
...regeneration capability of adult rat retinal ganglion cells after exotomy
...synaptogenesis
...experience-dependent synaptic plasticity in rat barrel cortex
...peripheral specification of dorsal root ganglion neurons
...androgenic block of neuromuscular synapse elimination

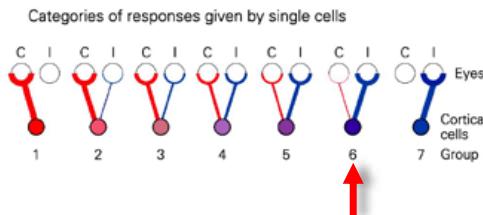
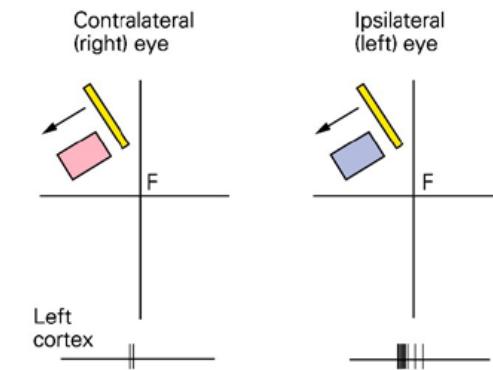
Critical periods in human development

- Language acquisition is an easily identifiable critical period in human development
- Insights have come from studies of the developing visual system
 - Strabismus(misalignment of the eyes typically due to a weakness in one or another extra-ocular muscle) is relatively common: 4% of children have this condition to varying degrees.
 - About half of children with untreated strabismus go on to develop amblyopia: a visual impairment akin to blindness but without any physical problem in the retina or lens.
 - Amblyopia can also be caused by “refractive errors”
 - One effective treatment is patching the good eye to force the use of the weaker eye

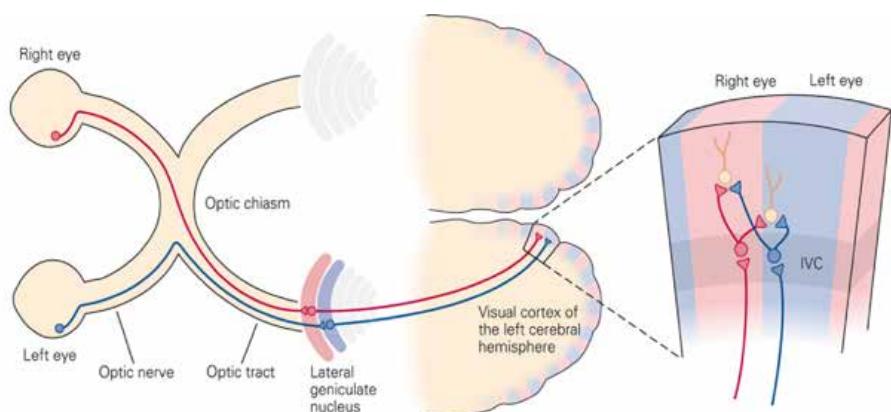


Ocular dominance and the critical period for sensory deprivation

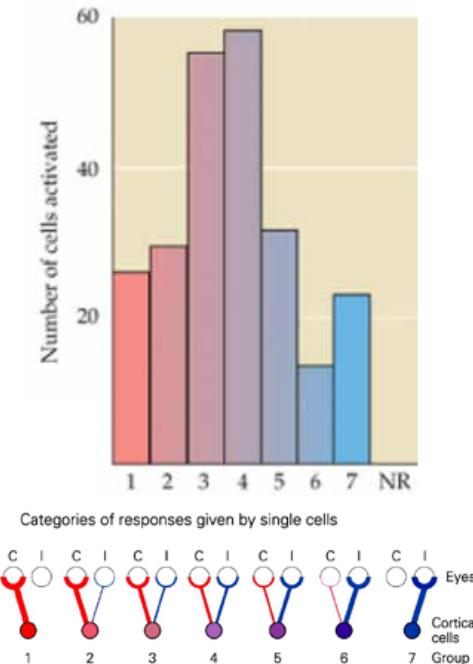
Movement across the retina



- Remember, neurons in layers 2/3 and 5 and 6 can be binocular
- Test the *ocularity* of cells in V1 by comparing the strength of the signal from the ipsi and contralateral eye

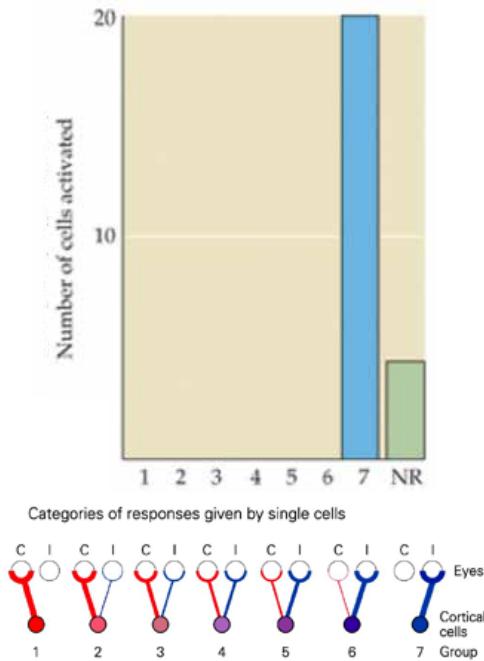


Ocular dominance and the critical period for sensory deprivation



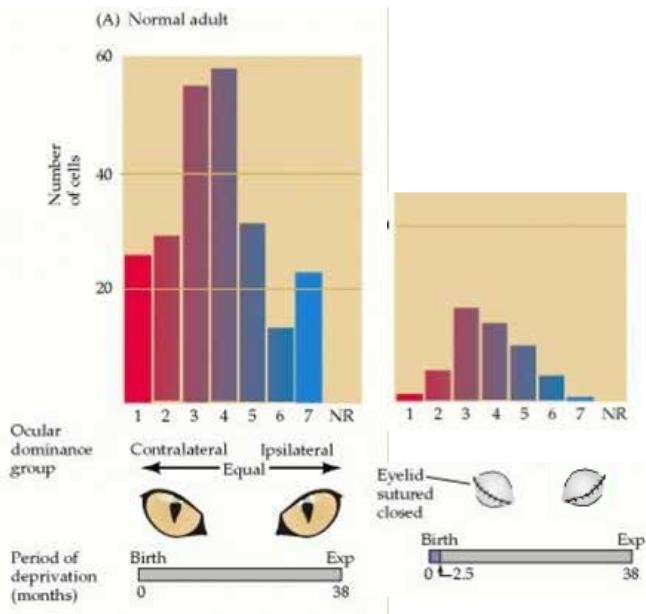
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- Test the *ocularity* of cells in V1 by comparing the strength of the signal from the ipsi and contralateral eye
- Ocular dominance histogram shows roughly equal likelihood a cortical neuron (all layers) will be activated by the ipsi- and the contralateral eye

Ocular dominance and the critical period for sensory deprivation



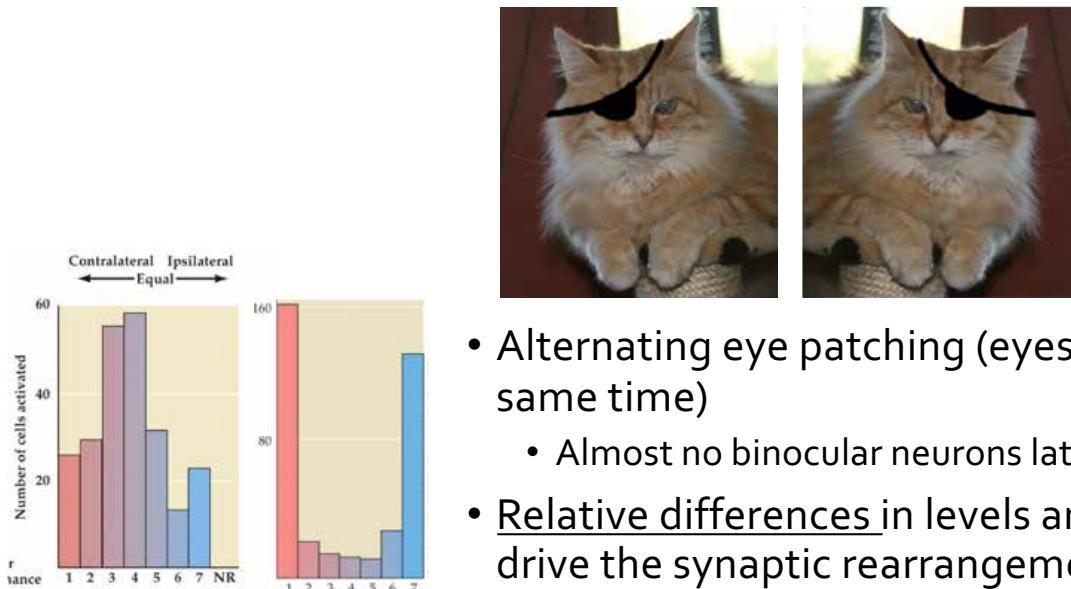
- Remember, neurons in layers 2/3 and 5 and 6 can be binocular
- Test the *ocularity* of cells in V1 by comparing the strength of the signal from the ipsi and contralateral eye
- Ocular dominance histogram shows roughly equal likelihood a cortical neuron (all layers) will be activated by the ipsi- and the contralateral eye
- However, if one eye is deprived of vision by patch in early postnatal life then the histogram is shifted in later life-in favor of the un-patched eye. Vision from the deprived eye is amblyopic
- The effect of developmental patching is permanent:
- No amount of patching of the stronger eye after the “critical period” of sensitivity is over can completely correct the imbalance

Closing both eyes has no effect on OD



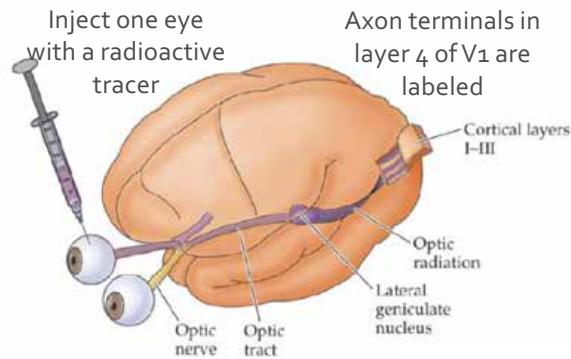
- Normal V1 binocular response
- No change in “synaptic competition”

Synaptic competition: Inputs compete to remain connected



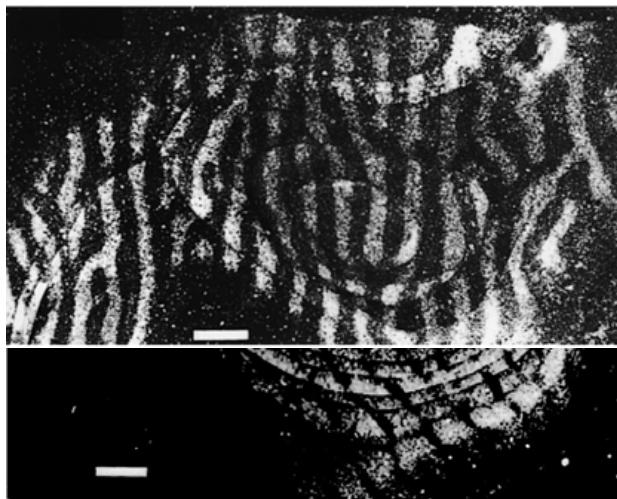
- Alternating eye patching (eyes never used at the same time)
 - Almost no binocular neurons later in life
- Relative differences in levels and timing of activity drive the synaptic rearrangements.

Radioactive labeling of ocular dominance columns



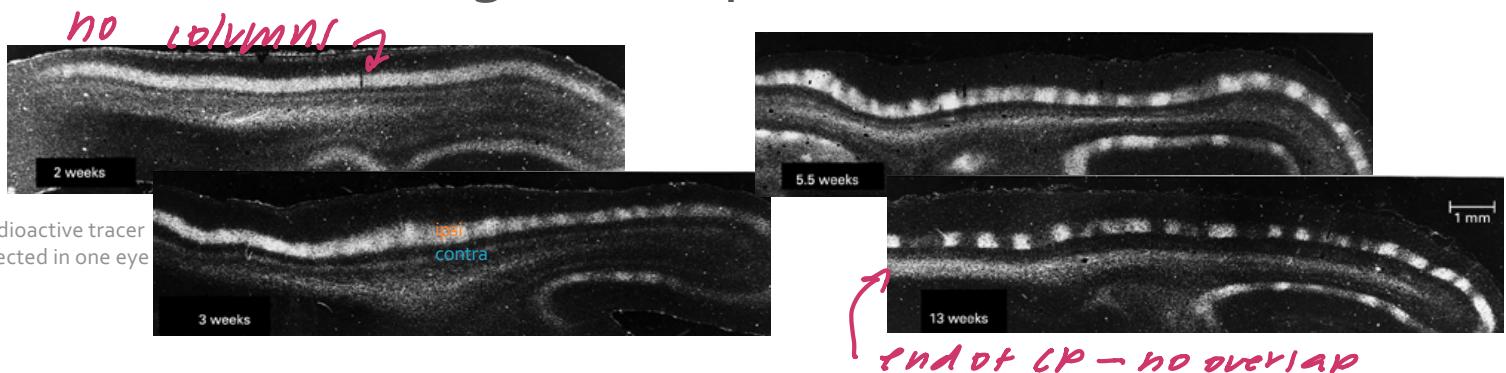
What is the basis for the shift in the ocular dominance histogram?

A Normal



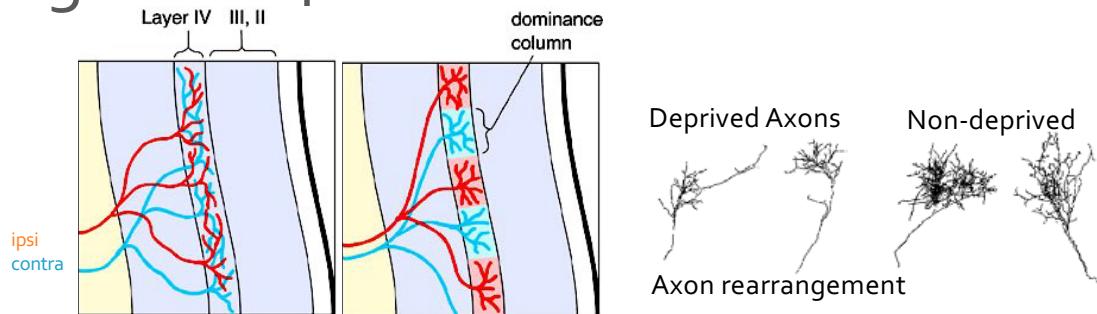
- Labeling with radioactive tracer from one eye reveals normally that the OCDs (in layer 4) are equal
- However unequal ocular dominance columns (odcs) in layer IV occur after monocular deprivation. Now the ocular dominance columns are wider for the open than the deprived eye
- This shift is due to changes in a developmental phenomenon known as ocular dominance segregation.

The segregation of ocular dominance columns (ODCs) during development



- At the same time the visual cortex is susceptible to sensory manipulations its ODCs are not fully formed- rather there appears to be considerable overlap between the regions occupied by the thalamocortical axons driven by the two eyes
- The end of the critical period coincides with the complete segregation of axons into non-overlapping ocdcs and raises the possibility that only when axons from the two eyes coincide can experience affect the outcome

The segregation of ocular dominance columns (ODCs) during development

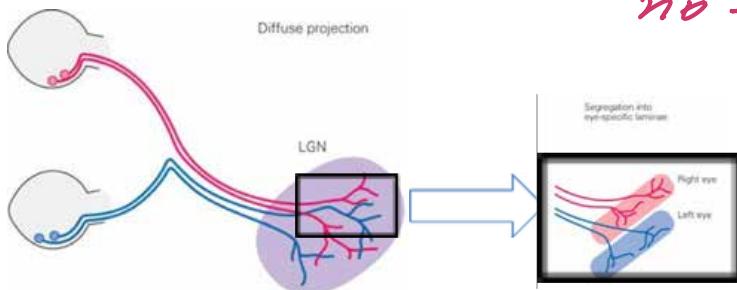


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Spontaneous activity drives some synaptic rearrangement

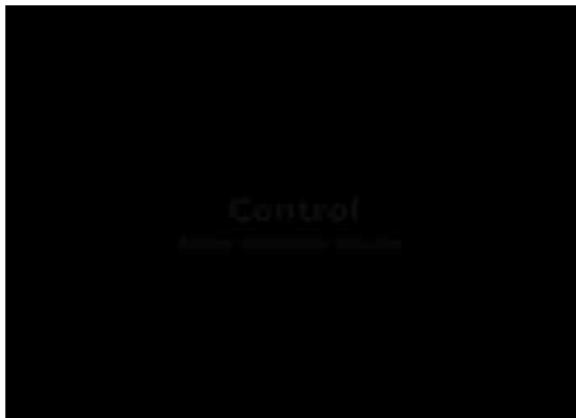
- LGN – monocular layers, center surround receptive fields
- Restricting visual experience has not effect on LGN segregation
- Although initially (in the fetus) LGN layers get input from both eyes, spontaneous activity in the retina drive segregation before visual experience.

*MONOCULAR deprivation →
no effect on LGN
segregation*

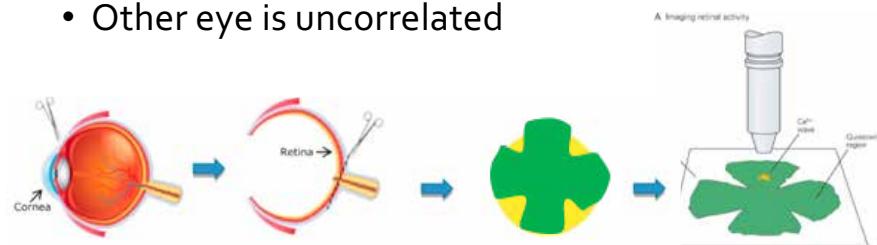


Retinal waves synchronize activity within one eye

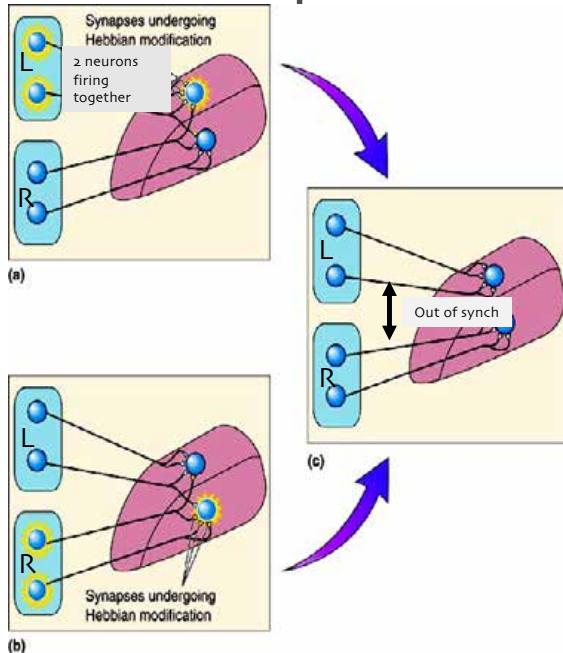
- Amacrine cells fire spontaneous action potentials
 - - Immature retinal circuits are linked by gap junctions.
• - Waves of activity spread around the retina.
 - Activity is correlated within an eye, but uncorrelated between eyes
- Hebb's Rule: cells that fire together, wire together!
 - Wave spreads across retina
 - Neurons fire within seconds of each other
 - Other eye is uncorrelated



11/11/19

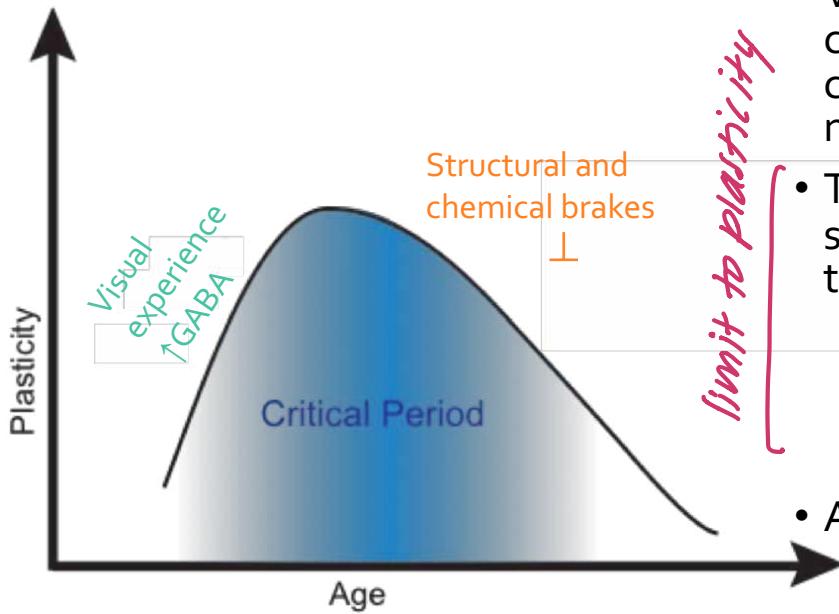


Overlapping connections provide a substrate for Hebb's postulate



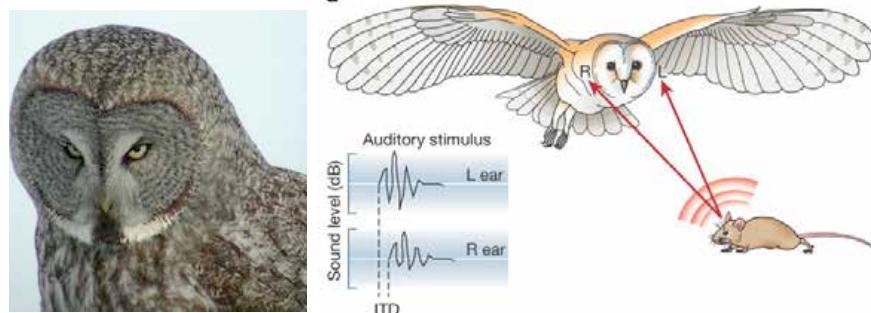
- Competition: binocular rivalry
- Activity based interaxonal competition
- Hebb's Postulate: neurons that “fire together wire together”
- Moreover, neurons that “fire out of synch, lose their link”

What limits the critical period for OD plasticity?



- Visual experience with the concurrent maturation of visual circuits, especially GABAergic neurons “opens” the critical period
- There seems to be multiple structural and chemical “brakes” that end the critical period
 - Myelination
 - Extracellular matrix (perineuronal nets)
 - Decreased cholinergic modulation
- All potential therapeutic targets

Sound localization as a model of adult plasticity



- Owls localize sounds by differences in the time at which sounds reach the two ears (interaural time difference)
- Amazing ability to detect interaural differences of just a few microseconds!
- To catch its prey, the owl needs to make sure its EARS and EYES give it the same information.

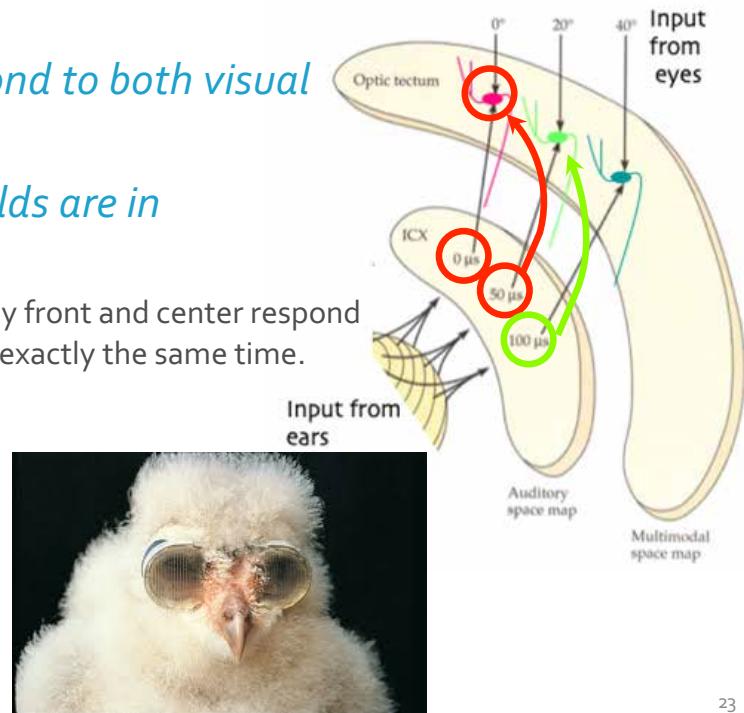
Coordinating visual and auditory space maps

- *Optic tectum has neurons that respond to both visual and auditory stimuli*
- *The visual and auditory receptive fields are in corresponding locations.*

- i.e. neurons with visual receptive fields directly front and center respond best to sounds that are heard by both ears at exactly the same time.

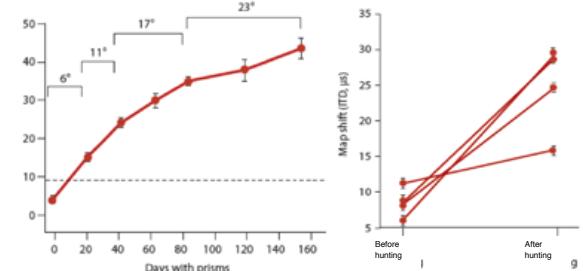
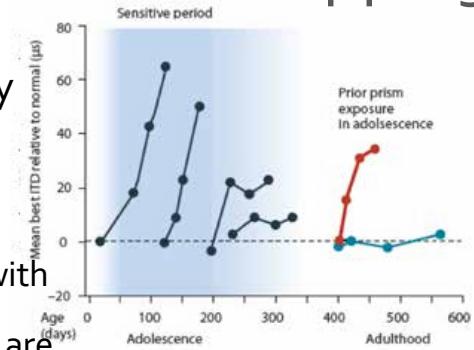
- *Fit young owl with goggles to shift its visual field right or left. Now the visual and auditory receptive fields are in different sites.*

- Yet the owl “rewires” to rematch the two fields

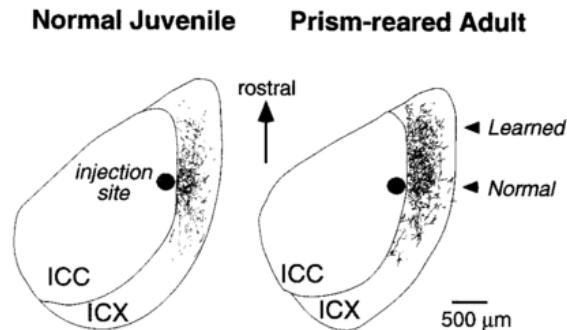


Critical period for audio-visual remapping

- In initial experiments, rewiring occurred only in young owls.
- Experimental manipulations to extend the critical period:
 - Cause plasticity in adolescence. Fit young owl with prisms during the critical period. Then remove when adjustment is complete. When the prisms are re-fit in adulthood, there is much greater remapping than if they are first fit in adulthood.
 - Incremental learning. There is much more remapping if prisms of increasing strength are fit successively than if full-strength ones fit all at once.
 - Increased motivation/attention. The initial experiments were done in a laboratory, where the owl didn't benefit from remapping. Results were different when the owl had some reason to care about the outcome...



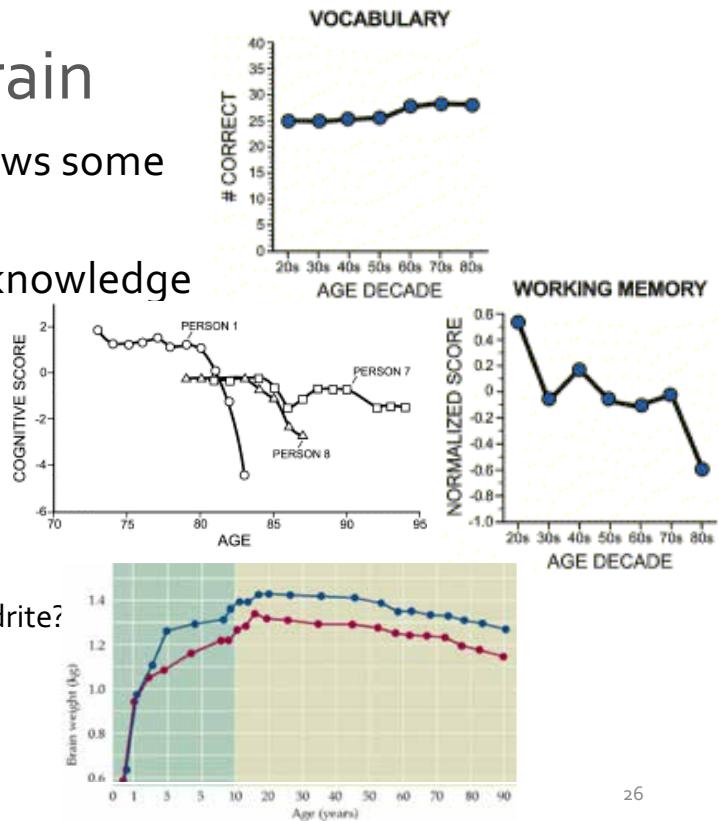
Experience can leave an anatomical “trace”



- The “normal” map was maintained even after experience shifts in this system
- Experience dependent plasticity may be different depending on the circuit
- Inhibition may drive neuronal tuning

Changes in the aging brain

- Although slower, the aging brain shows some evidence of changes
- Vocabulary and other “crystallized” knowledge increases
- Decreases in working memory and cognitive abilities (with variation)
- Brains shrink with age
 - What causes it? Loss of...
 - Glia? Myelination? Axons? Synapses? Dendrite?

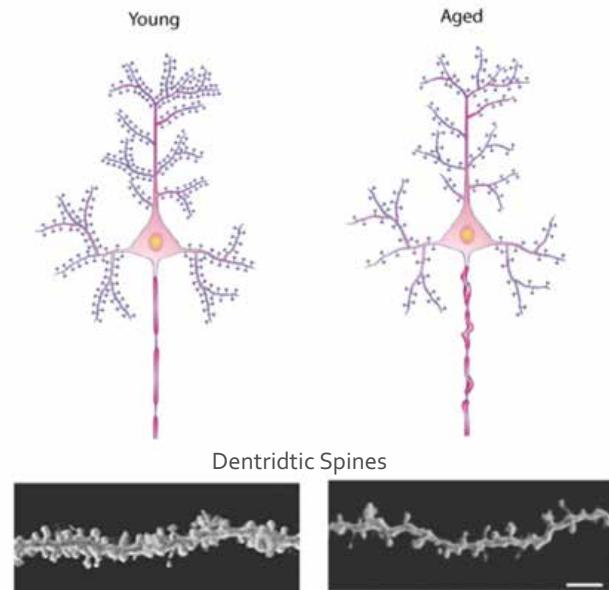


Loss of synapses

- Decreased numbers of spines and synapses
- But, reason for hope:
 - Two life style regimens that slow age-related cognitive decline in experimental animals and (probably) people.



- And for those who don't want to eat less or exercise more, there is a search for drugs that activate the same pathways (e.g., resveratrol, the anti-aging component of red wine).



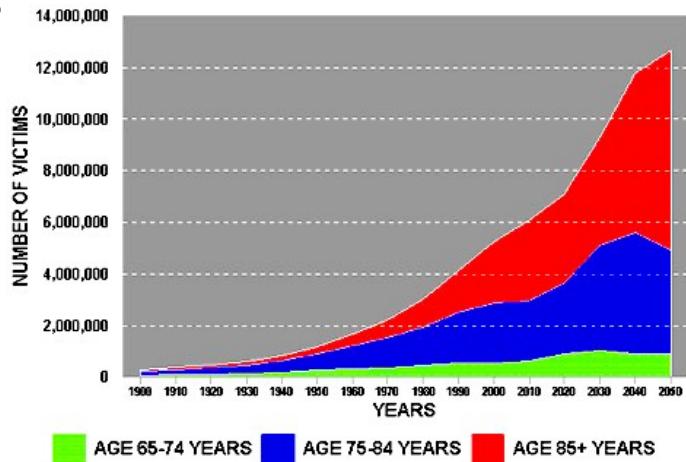
Alzheimer's disease

- Described by A. Alzheimer, late 1800s
- Form of progressive dementia.
- Memory is affected early but not exclusively.
- Slowly robs people of their most human qualities - memory, insight, judgment, abstraction, language
- Characteristic brain changes



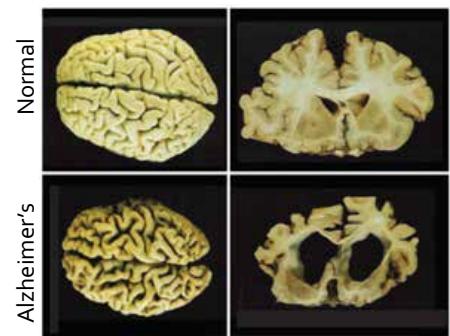
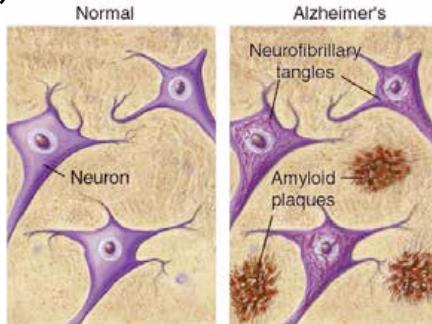
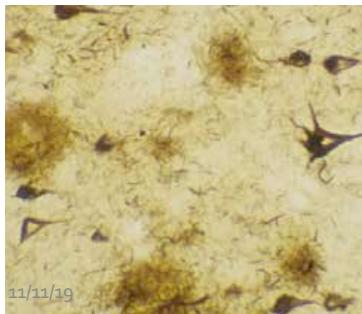
Aging is the biggest risk factor for neurodegenerative diseases

- Alzheimer's is the most common dementia affecting >1/3 of adults over 85.
- Increasing age is the biggest risk factor; family history is second.
- Number of cases in the US will increase as the population ages

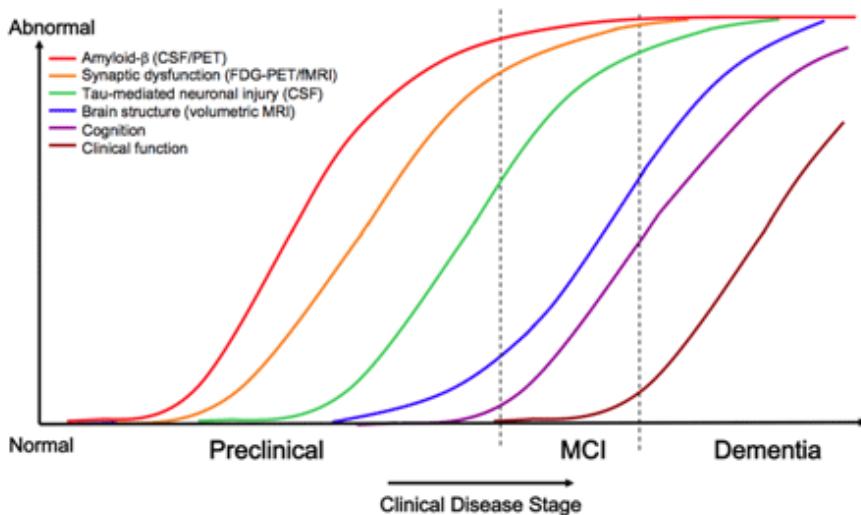


Brain changes in Alzheimer's Disease

- Amyloid plaques
 - Fragments of a protein called APP (Amyloid Precursor Protein)
 - Main component now known to be aggregates of a peptide call "A β "
- Tangles:
 - Main component now known to be aggregates of "tau," a protein normally associated with microtubules
- Progressive (gradual) degeneration



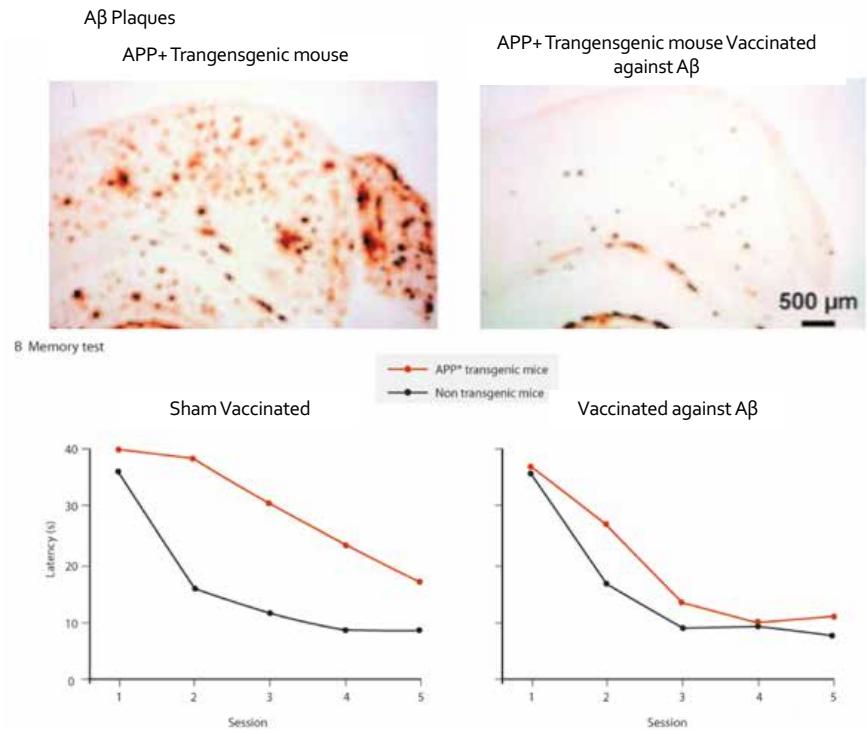
But does amyloid cause Alzheimer's?



- Most cases of Alzheimer's have no obvious genetic component. A subset, however, is clearly genetic. Different families have different genes involved.
- Three of the genes that account for the most common among this rare subset are APP, Presenilin-1 and Presenilin-2
- These results suggest ways to design drugs that prevent formation or build-up of A β

A β vaccine against Alzheimer's disease?

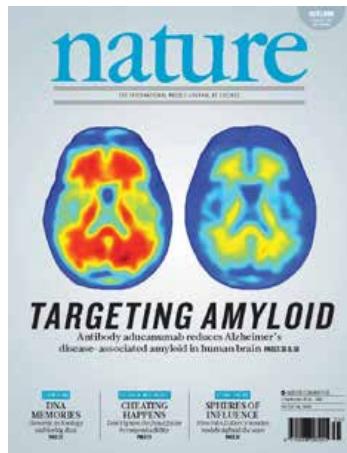
- Using genetics, researchers have created a mouse (APP+ transgenic mouse) that develops A β plaques and loses memory function
- They have created a vaccine against A β that protects against plaques and memory loss



Clinical trials of A β antibody

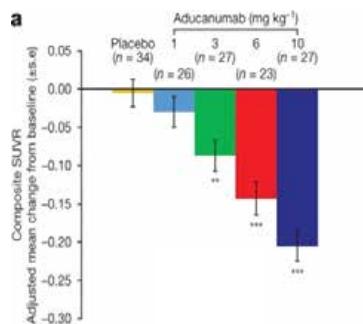
The antibody aducanumab reduces A β plaques in Alzheimer's disease

Jeff Sevigny^{1*}, Ping Chiao^{1*}, Thierry Bussière^{1*}, Paul H. Weinreb^{1*}, Leslie Williams¹, Marcel Maier², Robert Dunstan¹, Stephen Salloway³, Tianle Chen¹, Yan Ling¹, John O'Gorman¹, Fang Qian¹, Mahin Arastu¹, Mingwei Li¹, Sowmya Chollate¹, Melanie S. Brennan¹, Omar Quintero-Monzon¹, Robert H. Scannevin¹, H. Moore Arnold¹, Thomas Engber¹, Kenneth Rhodes¹, James Ferrero¹, Yaming Hang¹, Alvydas Mikulskis¹, Jan Grimm², Christoph Hock^{2,4}, Roger M. Nitsch^{2,*§} & Alfred Sandrock^{1§}

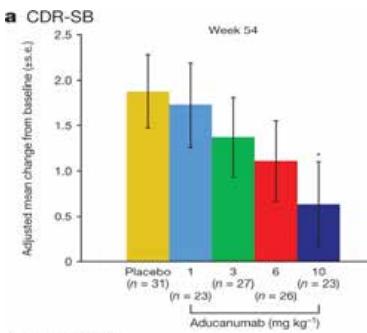


PET imaging of plaques

Alzheimer's drug resurrected, as company claims clinical benefits



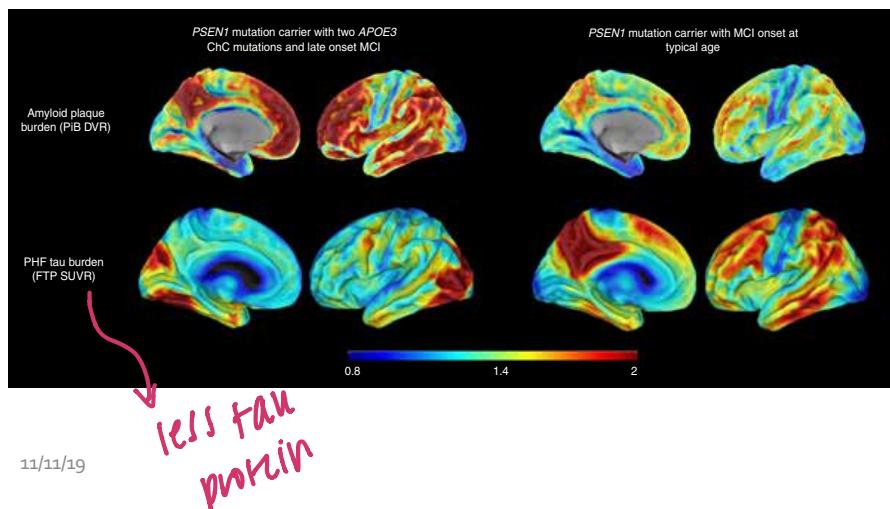
Average plaque level



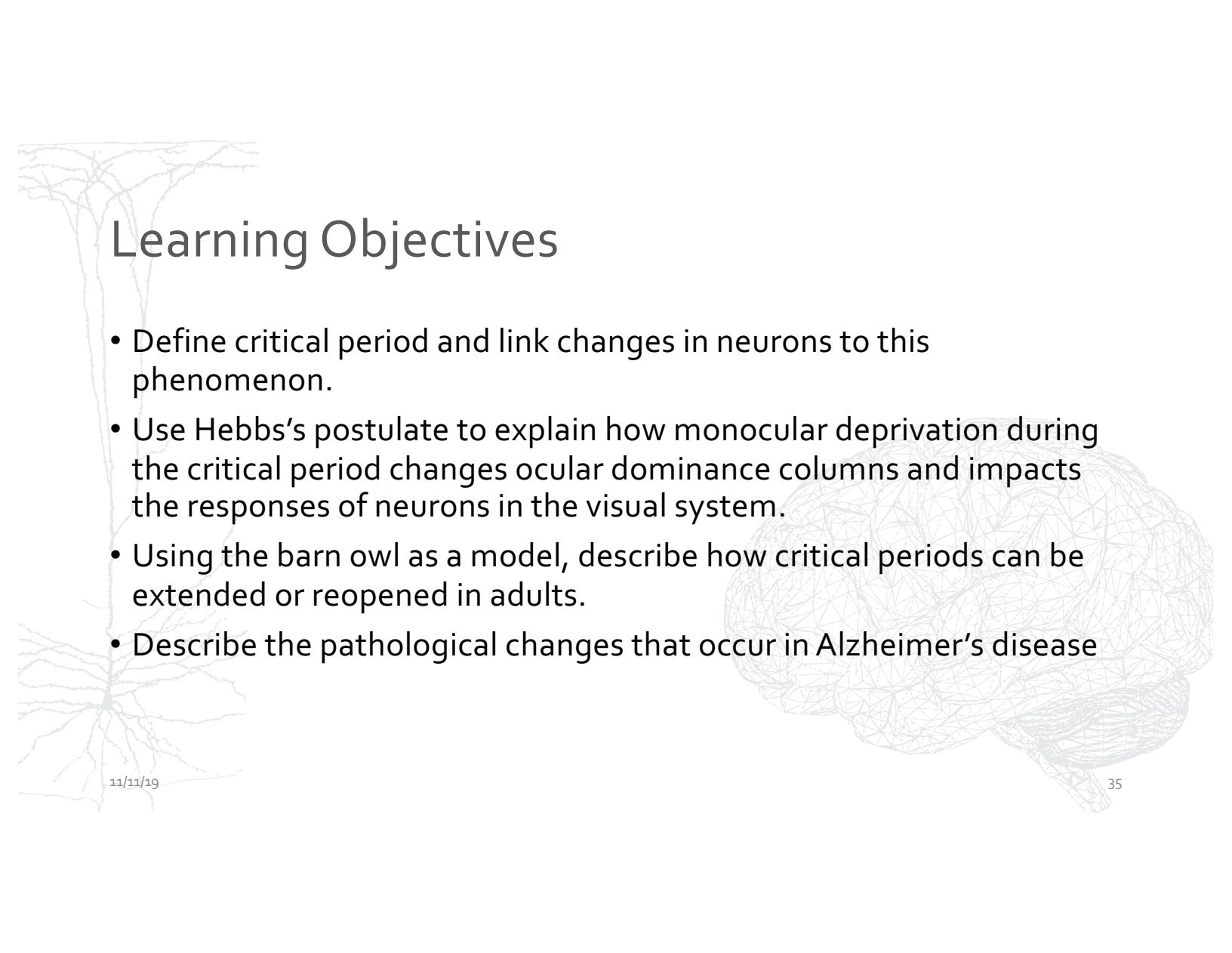
Change in "clinical dementia rating"

Amyloid may not be the entire picture

- Recent findings of a women with a gene for early onset Alzheimers was found to have another genetic mutation that may have protected her against dementia $\hookrightarrow APOE3$



- Brain scans showed heavy amyloid burden (compared to symptomatic early onset carrier)
- Less Tau**
- New treatment ideas focusing on resistance and *not destroying amyloid. Metabolism?*



Learning Objectives

- Define critical period and link changes in neurons to this phenomenon.
- Use Hebb's postulate to explain how monocular deprivation during the critical period changes ocular dominance columns and impacts the responses of neurons in the visual system.
- Using the barn owl as a model, describe how critical periods can be extended or reopened in adults.
- Describe the pathological changes that occur in Alzheimer's disease

Lecture 19 - Structural changes: critical periods and aging

Pre-class notes for November 11, 2019

Reading: *Neuroscience* ed. 6 by Purves et al., pages 571-584, 590-592, 595-596, 694-695

Plasticity - the ability of the nervous system, usually via synaptic connections, to change and adapt to new situations.

Hebb's postulate - the idea that the timing of the presynaptic and postsynaptic action potentials can alter the synaptic strength. Summarized as *Neurons that fire together, wire together* and *Neurons out of synch, loose their link*.

Critical period - a developmental period during which the nervous system is particularly sensitive to the effects of experience. Experience can permanently alter performance, behavior and /or neural circuits. The precise timing of the critical period depends on which circuit in which brain region is being altered. Usually there is little plasticity either before the beginning or after the closure of the critical period.

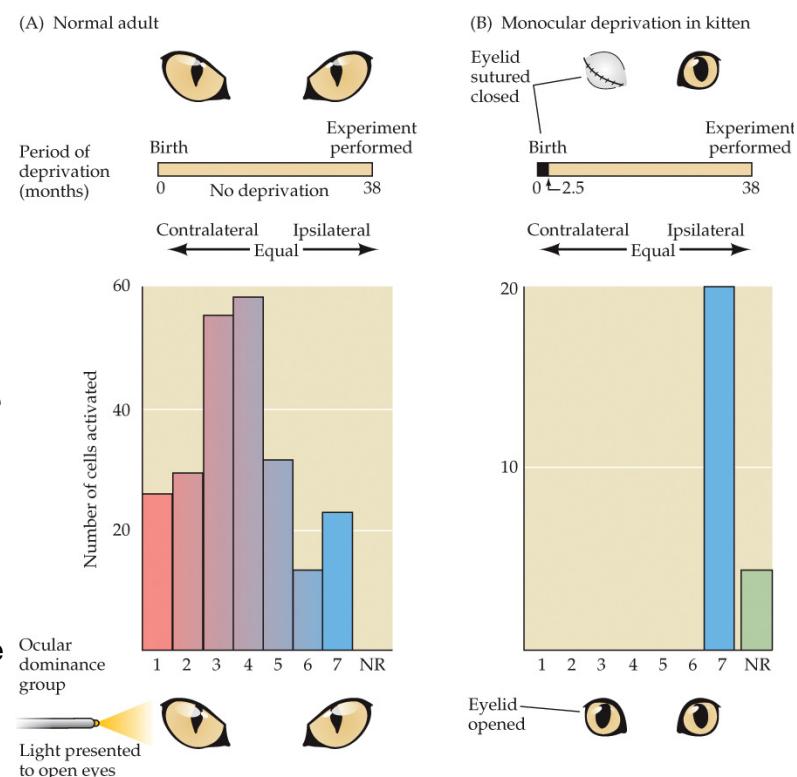
Synapse elimination (pruning) - there is an excess of synaptic connections (and even an excess of neurons) during development. Following Hebb's postulate, synapses that are more active are strengthened, and synapses that are less active are weakened and ultimately pruned. Synaptic elimination involves the removal of both the presynaptic terminal and postsynaptic density/spine.

Spontaneous neuronal activity - firing of neurons in the absences of environmental stimuli. Often occurs as oscillations or waves of activity that propagate across the brain region.

In the developing eye (before birth/eye opening), *retinal waves* of spontaneously active RGCs and amacrine cells sweep across the retina, activating nearby RGCs concurrently. By contrast, the activity of RGCs at different sides of the retina, or from the other eye, are uncorrelated. This correlated activity of the RGCs (the output neurons of the eye) helps maintain the retinotopic map in the thalamus and visual cortex, and drives the segregation of their axons so that the layers of the LGN receive input from only one eye and subsequently neurons in layer 4 of V1 are monocular.

Ocular dominance - the preference for receiving and/or representing visual input from one eye over the other eye. Neurons in layer 4 of V1 in primates, cats and some other mammals, receive input from just one eye. Neurons "beyond" layer 4, may be binocular (see *diagram to the right, of the histogram of neuronal responses in layers 2/3 of V1 in control animals on the left column*).

During the critical period for ocular dominance plasticity, the responses of neurons can shift so that following experience manipulation (closing one eye) the responses shift so more neurons respond to the open eye.

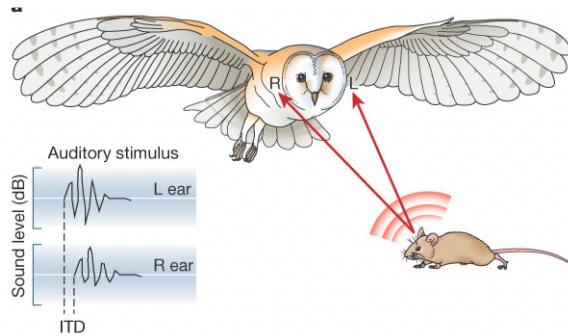


Ocular dominance columns - in primary visual cortex of primates and some other mammals, cells in the same vertical column share the same ocular dominance, thus producing ocular dominance columns.

Amblyopia - diminished visual acuity (typically just in one eye) as a result of the failure to establish appropriate visual connections during development (during the critical period). Often caused by *strabismus*, a misalignment of the two eyes, or by the inability of one eye to focus. Vision to the eye itself can be normal, but the brain favors the other eye.

Monocular deprivation - experimental procedure where one eye of an animal is patched or sutured to eliminate visual input to that eye. *Binocular deprivation* would involve either patching both eyes, or placing the animal in the dark (dark rearing).

Adult plasticity - although the large scale synaptic dynamics found during development is not found in the adult brain, there is still plenty going on at the synaptic level. One classic example comes from the *Barn owl*.



Barn owls use their visual and auditory senses for hunting and locating prey. Within the owl's brain (area called the tectum), the auditory and visual pathways converge to create a map that links sound and vision. There are cells that represent the visual/auditory space right in front of the animal - cells that respond to the center of the visual field and a 0 μ s interaural delay and cells that represent the sides (e.g. cells that respond to the left side of the visual field and a short 50-100 μ s interaural delay where the sound reaches the left ear first).

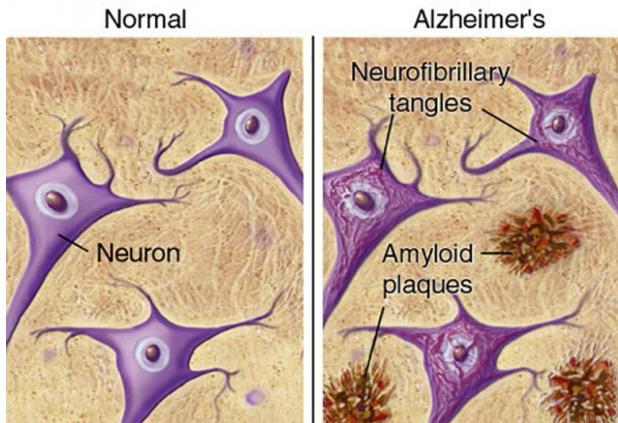
Baby barn owls fitted with prisms that shift the visual world (left or right) can rewire that map and adjust to the new visual setup (presumably an evolutionary adaptation due to variation in skull size/shape). In laboratory experiences, this rewiring becomes less and less effective as the animal ages (typical for a 'critical period'). Yet, scientists found old owls could remap – they identified three factors that helped: 1. incremental learning, 2. previous exposure and 3. increased motivation.

Neurodegenerative disorder - disorder characterized by progressive neuronal dysfunction, including loss of synapses, atrophy of dendrites and axons, and death of neurons.

Alzheimer's disease - a neurodegenerative disorder prevalent in the aging population. Initial symptoms include gradual loss of memory, impaired cognitive and intellectual capabilities, and reduced ability to cope with daily life. It is defined by the combined presence of abundant amyloid plaques and neurofibrillary tangles and eventual neuronal degeneration in postmortem brains.

Dementia - general term for a decline in memory or other thinking skills that impairs normal life.

Amyloid plaques - extracellular deposits consisting primarily of aggregates of pieces of amyloid precursor protein (APP) mostly the *amyloid β* protein, a ~40 amino acid peptide with a



strong tendency to form aggregates rich in β -pleated sheets. One theory is that the plaques cause problems for the cells: possibly disrupting synaptic transmission and eliciting an immune inflammatory response.

Neurofibrillary tangles - an intracellular tangle of cytoskeletal elements, consisting of an abnormal accumulation of hyper-hyper-phosphorylated *tau*, a microtubule-binding protein that is highly enriched in axons.

Learning Objectives: (By the end of Lecture 19 you should be able answer questions about the following)

1. Define critical periods and link changes in neurons to this phenomenon.
2. Use Hebb's postulate to explain how monocular deprivation during the critical period changes ocular dominance columns and impacts the responses of neurons in the visual system.
3. Using the barn owl as a model, describe how critical periods can be extended or reopened in adults.
4. Describe the pathological changes that occur in Alzheimer's disease