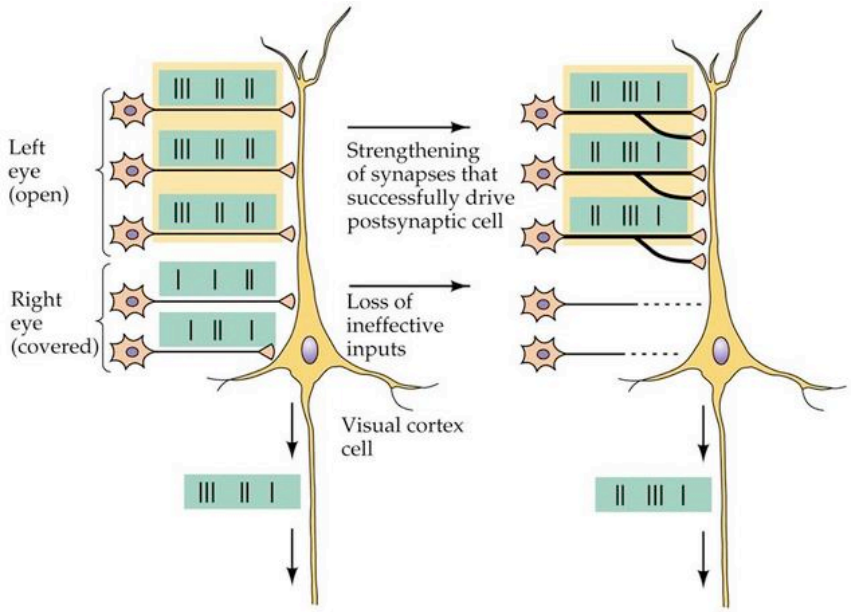
Retinal Waves and Ocular Dominance Columns

In the cat, at birth, inputs from both eyes are intermingled in the visual cortex. Ocular dominance columns start to appear a few weeks after birth. They can be visualized by injecting a radioactive amino acid (proline) into one eye, which is incorporated into proteins made by retinal ganglion cells. These proteins are transported to the LGN and then transported to layer 4C of V1. One possible theoretical framework for the formation of these columns in the LGN and V1 comes from the psychologist Donald Hebb.



Hebb's postulate (1949). "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." Hebb's postulate has been reformulated into the popular phrases:
"neurons that fire together wire together"
"neurons out of sync lose their link"

Strong co-activation of pre- and postsynaptic cells causes synapse strengthening whereas uncorrelated or lack of firing causes synapse weakening. One evidence that Hebb's postulate is relevant to ocular dominance is that eye patching during the critical period can result in the elimination of inputs from the covered eye onto V1.

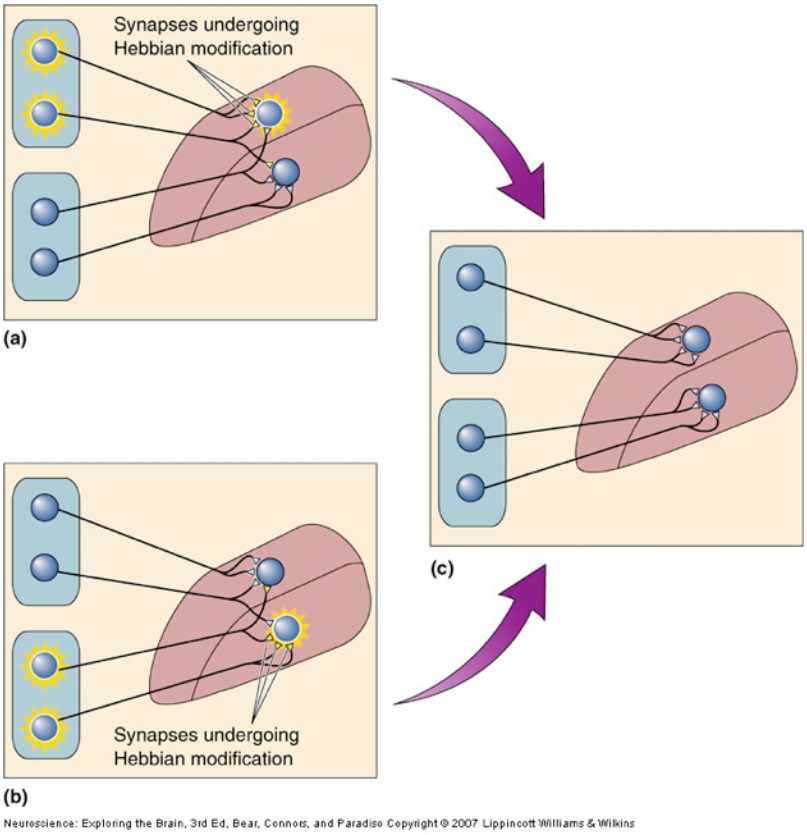


Figure 23.18: Plasticity at Hebb synapses. Two target neurons in the LGN have inputs from different eyes. Inputs from the two eyes initially overlap and then segregate under the influence of activity. **(a)** The two input neurons in one eye (top) fire at the same time. This is sufficient to cause the top LGN target neuron to fire, but not the bottom one. The active inputs onto the active target undergo Hebbian modification and become more effective. **(b)** This is the same situation as in part a, except that now the two input neurons in the other eye (bottom) are active simultaneously, causing the bottom target neuron to fire. **(c)** Over time, neurons that fire together wire together. Notice also that input cells that fire out of sync with the target lose their link.

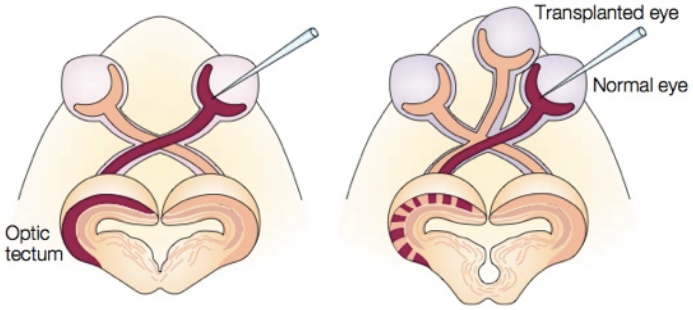
Eye input is thought to segregate because of correlated activity coming from one eye at a time. If retinal ganglion cells from one eye fire together, this can strengthen their synapses onto the LGN according to Hebb's rule. In agreement with this theory, neuronal activity appears to be required for ocular dominance columns formation: eye injections of tetrodotoxin (which selectively blocks voltage-sensitive Na+ channels) during the critical period prevent the columns from appearing. However, ocular dominance columns are observed prior to eye opening in some species, including in some monkeys, suggesting that neuronal firing takes place prior to visual input.

Indeed, retinal waves were discovered fairly recently when researchers observed patterns of highly spatially correlated spontaneous firing in the retina prior to eye opening. Waves propagate locally across the retina as retinal ganglion cells spontaneously fire bursts of action potentials. These waves might explain the formation of ocular dominance segregation even before eye opening. Whenever a wave of retinal activity drives a postynaptic LGN neuron to fire, this stabilizes the synapses between them. These waves are generated independently in the two retinas, resulting in uncorrelated inputs between the two eyes. Because of this, the inputs from the two eyes will compete on a "winner-takes-all" bases until one input is retained and the other is eliminated. Loser axons are pruned (lost) in the inappropriate LGN layer because their activity does not consistently correlate with the strongest postsynaptic response evoked by activity in the other retina.

Based on what you have learned, why would alternate eye patching during the critical period eliminate binocular neurons in the cortex?
Visual experience and correlated activity between the two eyes is required for the formation of binocular neurons in all layers of V1 except for layer 4. Eye patching eliminates correlated activity and results in "winner-take-all" scenarios, where the inputs from the two eyes segregate throughout the cortex.

What do you expect to happen to ocular dominance columns if both optic nerves are repeatedly and simultaneously stimulated?
Synchronous activation of the optic nerves prevents the formation of segregated ocular dominance columns because asynchronous activity is required for competition to take place.

What do you think would be the effect of inserting a third eye into the head of a frog on ocular dominance in the tectum? Draw your guess.

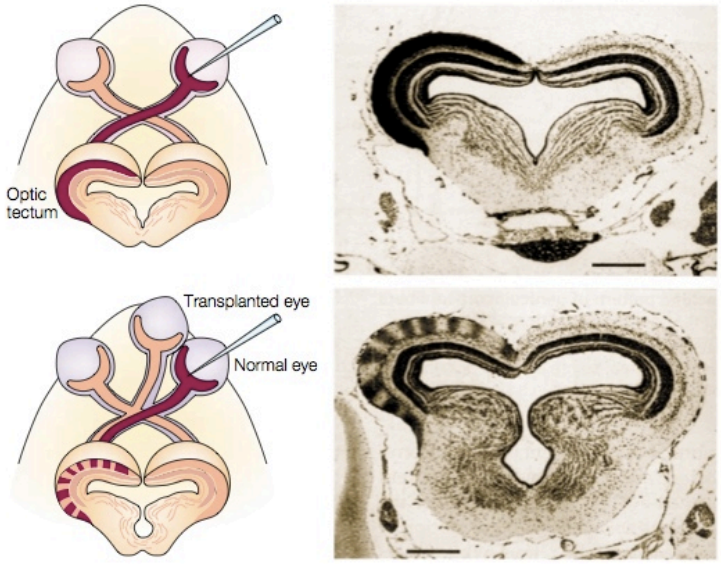


In a normal frog, the inputs from the two eyes are completely segregated in the tectum and so there is no ocular dominance to speak of. However, if a third eye is implanted, ocular dominance-like columns are observed in the tectum. This suggests that competition between two sets of retinal neurons (normal and transplanted eye) for the same population of target neurons in the tectum is sufficient to segregate the terminals of the presynaptic cells into distinct regions.

Box 1 | **Activity-dependent segregation of retinal axons**

Current evidence for activity-based competition as a generative mechanism for ocular dominance columns relies largely on analogies with pattern formation in other parts of the central nervous system, rather than direct tests in the developing visual cortex. Compelling evidence for activity-based competition in the formation of segregated patterns came from work on dually innervated optic tecta in goldfish and frogs. In a normal frog, retinal ganglion cells from each eye project to the contralateral tectum. When a third eye primordium is implanted in tadpoles, axons of retinal ganglion cells from the ectopic eye innervate an optic tectum that also receives a normal complement of innervation from its usual source. Activity-dependent competition between the two sets of retinal afferents results in segregated, eye-specific stripes with a striking visual similarity to ocular dominance columns[85] (see figure; autoradiographs reproduced with permission from REF. 86 © 1981 Massachusetts Institute of Technology).

In goldfish, regenerating axons from the two eyes, forced to grow into the same tectum, also form clear stripes[87]. Blocking retinal activity with tetrodotoxin (TTX) prevents stripes from forming and can desegregate existing stripes[51]. Significantly, blocking the NMDA (*N*-methyl-D-aspartate) glutamate receptor, which is required in mammals for the induction of long-term potentiation in the hippocampus, also induces desegregation or blocks segregation[88,89]. This points to an appealing model in which topographic cues intrinsic to retinal axons and the tectum guide axons from the two eyes to similar tectal locations, where activity-based competition sorts the two populations on the basis of correlated activity[90]. The formation of stripes represents a compromise between chemoaffinity cues guiding axons to the same locale, attractive interactions between axons with similar activity patterns (from the same eye), and repulsive interactions between axons with dissimilar activity patterns (from the other eye). In dually innervated tecta, it is extremely unlikely that an intrinsic stripe-like molecular cue in the tectum presages the segregation of stripes.



A strong case has also been made for a role of correlated activity in the specification of eye-specific layers in the cat and ferret lateral geniculate nucleus (LGN; see REF. 91 for a recent review). Early in development, axons from the two eyes form simple, sparsely branched structures that form sparse synapses throughout the undifferentiated LGN. Later, the short, spine-like branches that synapse in the inappropriate layer disappear, and there is a rapid and pronounced proliferation of branches and synapses in the appropriate eye-specific layer, leading to the formation of segregated layers[45]. This depends on retinal activity: blockade by either TTX or agents that block retinal waves[39,49] prevents axons from developing their layer-specific arborizations.

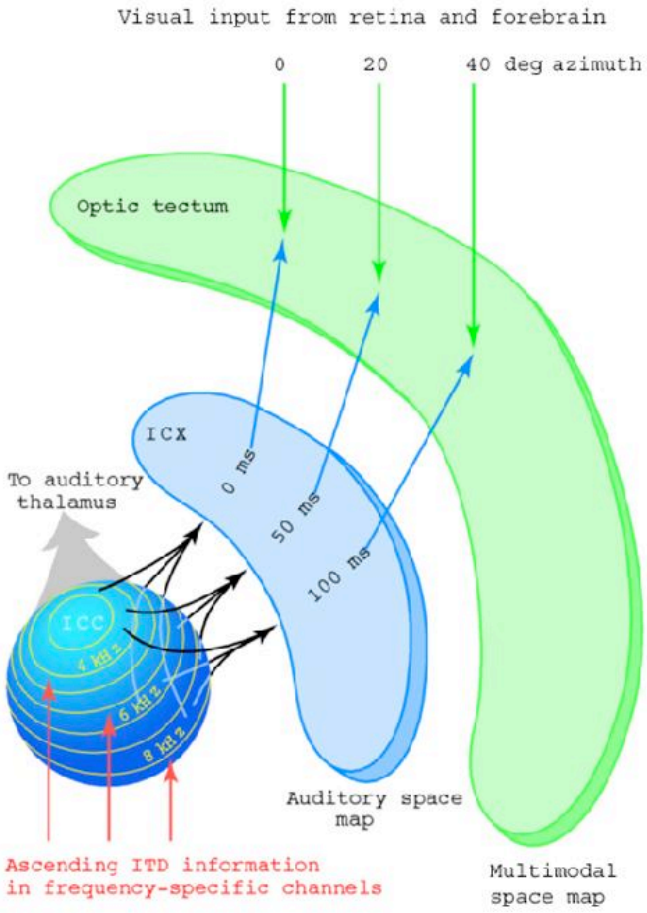
A compelling body of anatomical, electrophysiological and pharmacological experiments substantiates all of these findings. However, they are metaphors for ocular dominance column formation, rather than direct tests of the process. It will be important in future experiments to apply some of these paradigms directly to the emergence of ocular dominance columns, now that we have a better idea of when the columns emerge during development.

Katz L.C. and Crowley J.C. Development of cortical circuits: Lessons from ocular dominance columns. *Nature Reviews Neuroscience* **3**, 34-42

Imprinting describes different kinds of developmental phase-sensitive learning, which are thought to have a critical period. Certain characteristics of stimuli are imprinted onto an organism with life-long consequences.

Barn Owl, Hebbian Learning and Critical Period Plasticity:

Taken almost verbatim from: http://bbs.stardestroyer.net/viewtopic.php?t=124049

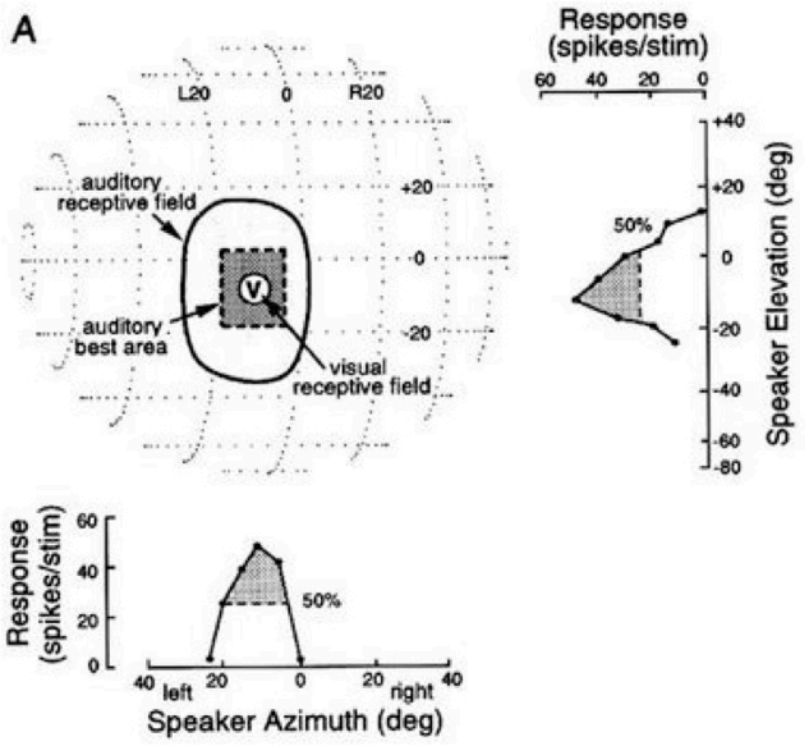


How does Hebbian learning affect behavior? The auditory and visual system of the barn owl are used to study this particular phenomenon. The barn owl is able to hunt in complete darkness by using its auditory system. Its visual system can also be used when it doesn't hunt at night. In the optic tectum of the barn owl (the second-order processing visual area in owls), there is visual input from the retinas and input from the auditory system (from the external nucleus of the inferior colliculus, or ICX.) These multimodal (= from different modalities, here auditory and visual) inputs form a topographic map in the owl's tectum. These topographic maps are reflective of the physical environment. (Azimuth = direction; ITD = interaural time difference, used to localize an auditory stimulus.)

Auditory input coming from directly ahead (0 deg azimuth) inputs into the same part of the optic tectum that is receiving visual input from straight ahead. So visual and auditory information are in alignment in the tectum. This convergence of the auditory and visual map helps the owl to cross reference visual information and auditory information in its brain to be a more effective hunter, particularly at night.

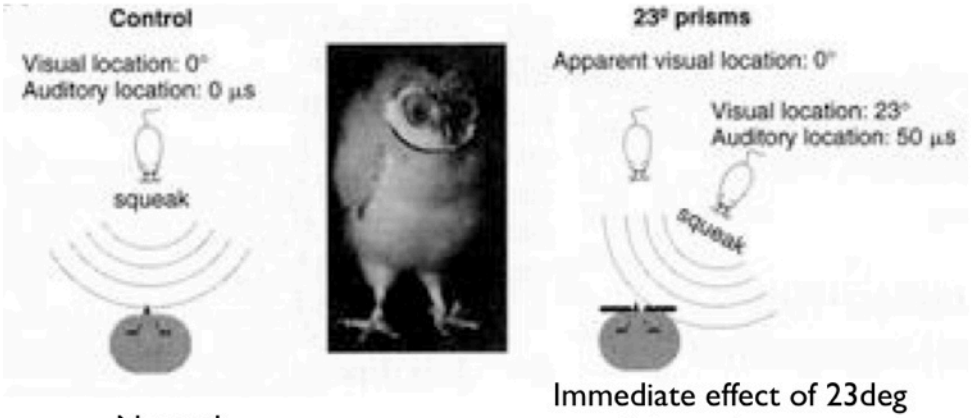
To measure receptive fields, experimenters record from neurons in the owl's brain while the owl looks ahead at a screen with light in different positions, and a speaker plays sound coming from the same location as the light on the screen. This allows the experimenters to determine the visual (shown by the V in the figure to the left) and auditory receptive fields (shown by the open circle) of the cells, that is, the part of the auditory field that excites the cells. From this, experimenters have determined that the visual and auditory maps in the tectum are in alignment.

Visual and auditory maps in the tectum are normally in alignment



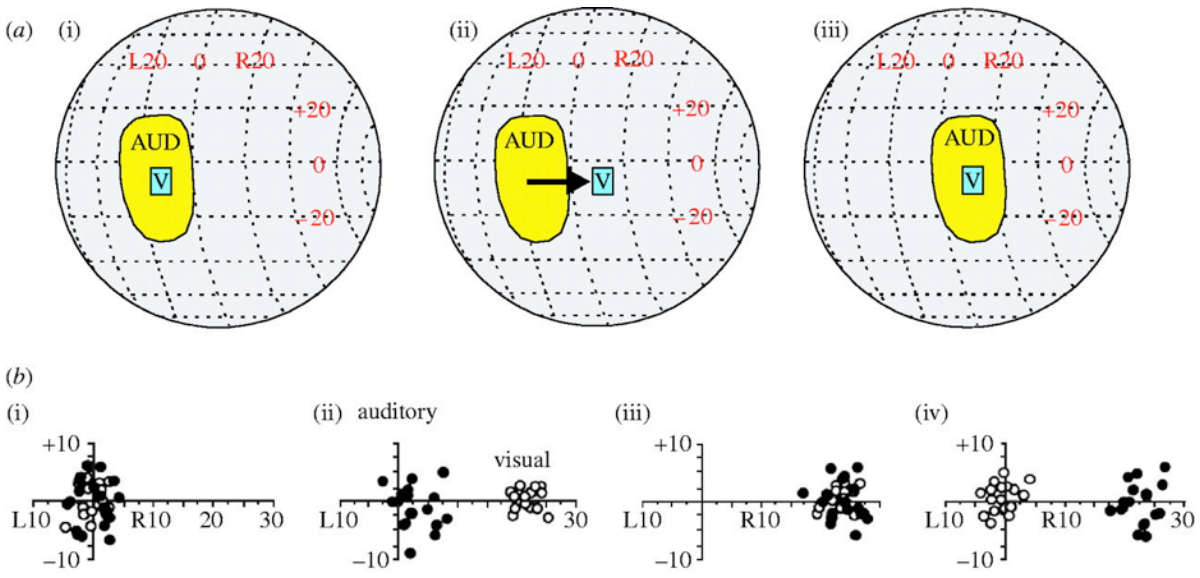
Eric Knudsen and his lab asked what happens if the visual and auditory maps are misaligned. They had young owls constantly wear prism glasses which deflect the visual field so that there would be a discrepancy between the auditory and visual fields. What happens to the behavior and brain of the owl?

Prisms glasses deviate visual field



Normal

Immediate effect of 23deg leftward prisms



Visual experience shapes the developing auditory localization pathway in the barn owl (*Tyto alba*). (*a*) Effects of prism rearing on the auditory spatial receptive fields of neurons in the optic tectum. (i) Visual (V) and auditory (AUD) receptive fields are normally in close correspondence. (ii) Placing prisms that displace the visual field to the right by 23° disrupts the alignment of these receptive fields. (iii) After young owls have worn the prisms for eight weeks, the auditory receptive field has shifted so that it becomes realigned with the visual receptive field. Adapted from Knudsen & Brainard (1991). (*b*) Adjustment of auditory orienting responses in a prism-reared owl. Head-orienting responses to visual (open circles) or auditory (filled circles) targets plotted with respect to the location of the stimulus. Owls normally make accurate head turns towards either stimulus. Prisms immediately shift the visual responses, but have no effect on the auditory responses. However, after 42 days of experience with the prisms, the auditory responses have shifted to match the optical displacement of the visual field, presumably as a consequence of the changes that take place in the optic tectum. When the prisms are removed, normal visual responses are restored, although it takes several weeks for the auditory orienting responses to recover ((i) before prisms, (ii) after 1 day with prisms, (iii) after 42 days with prisms and (iv) prisms removed). Adapted from Knudsen & Knudsen (1990).

(b) of the figure above shows successive trials of a barn owl before the prisms are put on. The owl was trained to strike at auditory and visual targets and each dot represents one trial. When the owl is not wearing the prism, it accurately detects the visual and auditory target (a look alike mouse for the visual stimulus or the sounds of a squeaking mouse for the auditory stimulus). With the 23 degree prisms on the first day, the owl's auditory targeting is fine but its visual targeting has now shifted by 23 degrees. The interesting thing is that after 42 days of training, the visual targeting is still shifted by 23 degrees to the right but now the owl's auditory targeting has shifted so that it's in alignment with its visual targeting. So even though the auditory fields are correct, in response to an auditory cue, the owl's targeting is 23 degrees off to the right. After the prisms are removed, the visual field becomes normal again and the owl is able to visually target accurately. However its auditory targeting is now off by 23 degrees to the right. This experiment indicates that "when confronted with inconsistent localization information from the auditory and visual systems, young owls use vision to calibrate associations of auditory localization cues with locations in space in an attempt to bring into alignment the perceived locations of auditory and visual stimuli emanating from a common source" (Knudsen, 1989).

To explain this behavior, the researchers measured the receptive fields during this process. They observed that during the period of adaptation to the prisms, there is a shift in the auditory receptive field towards aligning with the visual receptive field. (a) of the figure above shows a drawing of the auditory and visual receptive fields before the prisms are used, and the shift in the receptive filed occurring after 8 weeks of adaptation. This experiment suggests that a rewiring took place in the owl's brain.

What is the evidence for a critical period being involved in this process? In young owls, the adaptation occurs but in older owls, it does not occur. That is, the young owl's nervous system is able to adjust its visual or auditory fields to be in alignment but in old owls, this does not usually happen. However, if the adult owls is allowed to hunt, if they actively using their vision and audition, researchers have found that some adaptation is possible. But the adaptation is not nearly as dramatic as it is in young owls. There are two other ways to extend the critical period.

How would you interpret the finding that if adult owls have a prior experience with prisms during adolescence, there is much more adaptation to the prisms during adulthood?
Learned connections persisted and were able to reform during adulthood.

Wallerian degeneration occurs when a nerve fiber is damaged or cut and the part of the axon that is most distal (furthest) to the injury degenerates. This occurs both in the PNS and the CNS. After injury, the axonal skeleton disintegrates, and the membrane breaks apart. Then, in the CNS, the myelin sheath covering the axon breaks down and macrophages and microglia infiltrate the area to clear the axonal debris. Nissl bodies in the soma of a neuron dissolve (a process called chromatolysis). The Nissl body (or Nissl substance) is composed of rough endoplasmic reticulum -- the site of protein synthesis.

Describe the experiment by Aguayo and colleagues that demonstrated that the axon's environment, in particular the type of glia cells making up the myelin sheath, is a crucial factor in regeneration.
Aguayo and colleagues did experiments on both peripheral and central optic nerves. Cut peripheral nerves regenerate, whereas cut optic nerves do not (or do so poorly). But when the environment around the peripheral nerve (mostly Schwann cells) was grafted on the distal part of the cut optic nerve, regeneration occurred. In contrast, regeneration of the peripheral nerve did not occur when the environment around the cut optic nerves (mostly oligodendrocytes) was grafted onto the distal part of the cut peripheral nerve.

Why could an Aβ vaccine against Alzheimer's disease work?
Injecting Aβ at high dose could stimulate the immune system to produce antibodies against Aβ and attack the potential plaques later on in life.

dystrophy = wasting away

Distinguish between not remembering (hard to recall but memory still "there") and amnesia (memory absolutely gone or never formed).