Development of Behavior

Yasushi Nakagawa

Two different types of behaviors

Two distinct types of behaviors:

Innate (instinctive, inherited) behaviors

Behaviors that every individual of a given species is able to perform without first having to experience them performed by others, and without being in any way guided or instructed in them.

-children breathing, laughing, crying, walking

-a mother rat building a nest and grooming her pups even if she is raised in total isolation and has never seen other female rats engaging those acts

-caterpillars spinning a cocoon, spiders weaving a web, beavers building a dam

Acquired (learned) behaviors

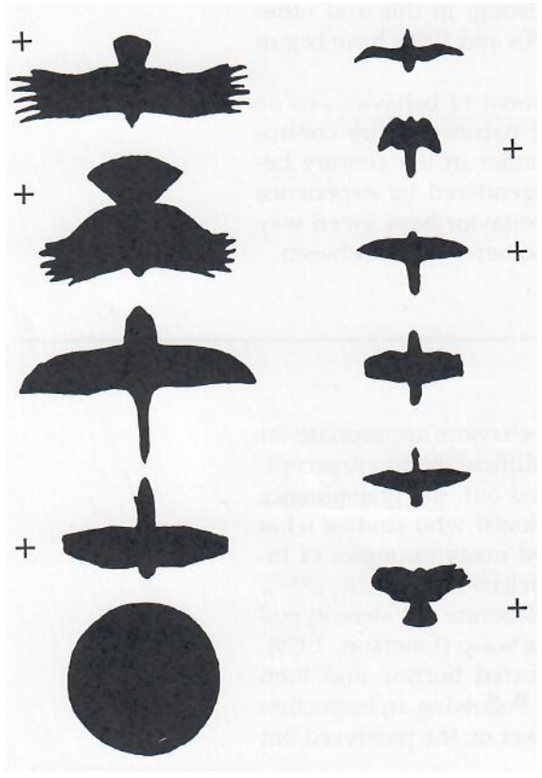
Behaviors influenced by an animal's own particular experiences, with striking differences between individuals of the same species.

-children reading, writing, playing musical instruments

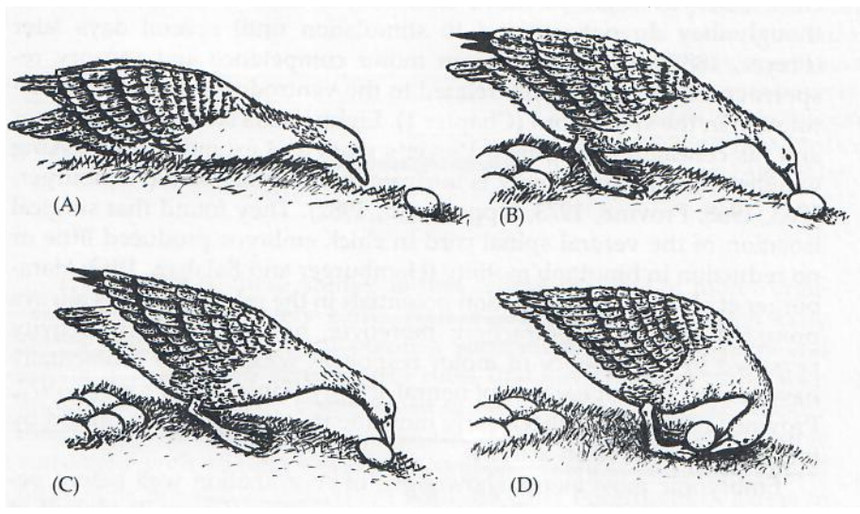
Developmental origins of behaviors

-Darwin thought the instinctive behaviors are naturally selected (consequences of the reproductive success of individuals already possessing useful habits).

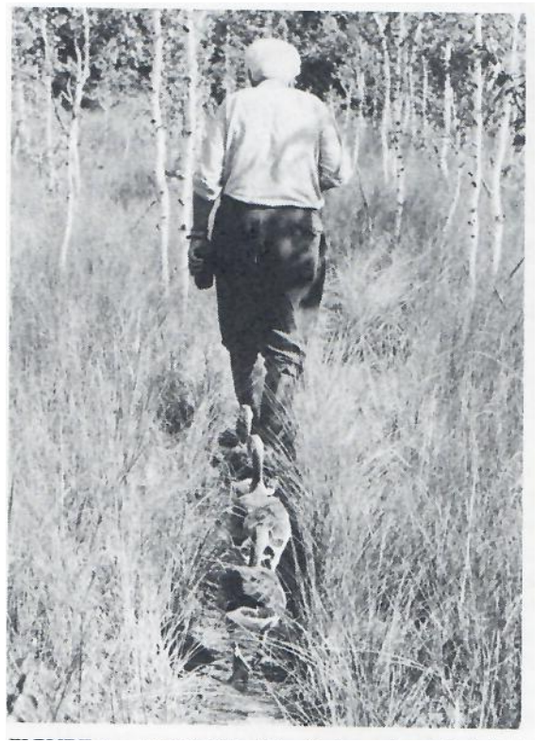
-Konrad Lorenz thought that genetics is the basis not only for complexity of biological structures but also for specific behaviors.



The shapes similar to the shadow of the bird's natural predators (+) elicited escape responses; silhouettes of songbirds and other innocuous species elicited no obvious response.



Egg-rolling behavior of greylag goose. Lorenz found this sequence of elaborate motor action is automatic; if the egg rolled away during retrieval, the goose continue to roll the now non-existent object and settled back onto the next as if successful.



Imprinting. The first moving object that goslings see after hatching is their mother.

https://www.youtube.com/watch?v=7PcteKRA3zs

Developmental mechanisms of behaviors

1. Early movements of vertebrate embryos
2. Sexually dimorphic behaviors in rodents
3. Critical period

   Ocular dominance plasticity

   Song learning in bird

Cascades of events results in the formation of neural circuits that underlies changing behaviors.

Early movements of vertebrate embryos

-First movements are the result of spontaneous activity of motor neurons.

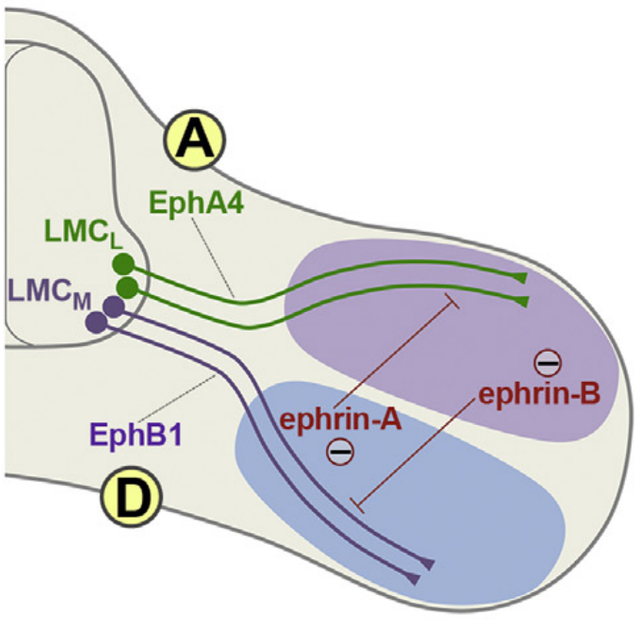
E3-4 in chick, E11.5-E12.5 in mouse

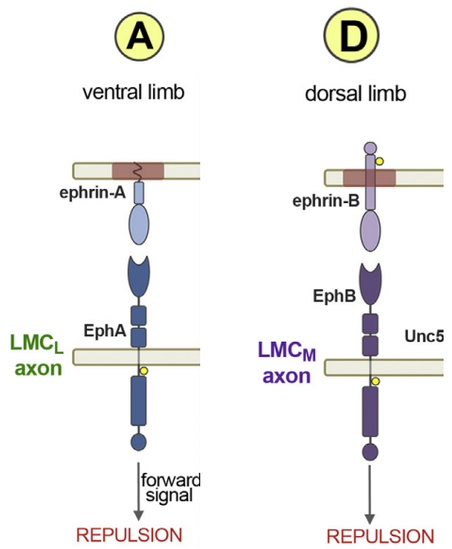
consists of propagating waves that cause near synchronous activation of most motor neurons on both sides of the cord

Acetylcholine from collaterals of motor axons provides the main drive in the absence of descending and afferent input (GABA and glycine also contribute; they are excitatory)

-The earliest activity of motor neurons helps specific innervation of limb muscles.

Blocking or slowing rhythmic bursting in chick embryos causes abnormal lateral motor column (LMC) axon fasciculation in the lumbar plexus and D/V pathfinding errors accompanied by lowering of EphA4, EphB1 and PSA-modified NCAM levels.





Bonanomi (2017)

Early movements of vertebrate embryos

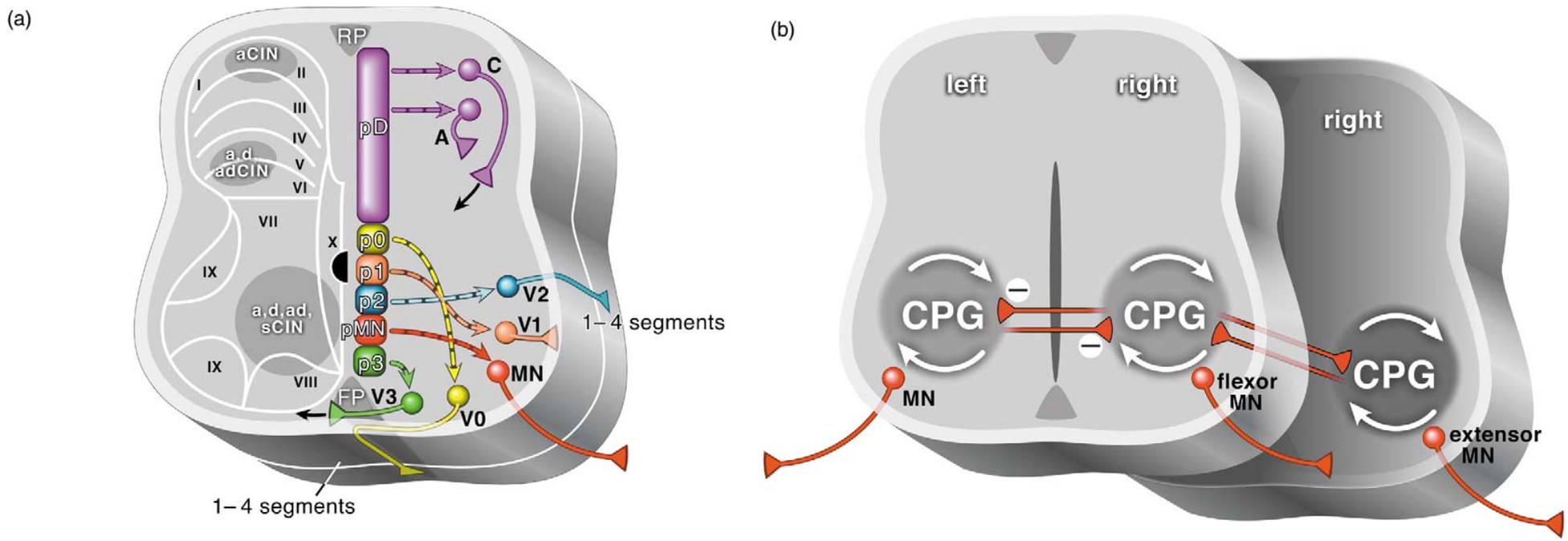
-Later, there is coordinated contraction of extensor muscles followed by flexor muscles as is typical of many adult movements.

E10 in chick, E18 in mouse

Individual motor neurons in the circuit spontaneously depolarize.

When a sufficient number are activated, threshold for activation of the entire network is reached, resulting in the generation of a wave of activity that propagates from the initiation site.

Many types of interneurons are generated and form a central pattern generating circuitry.

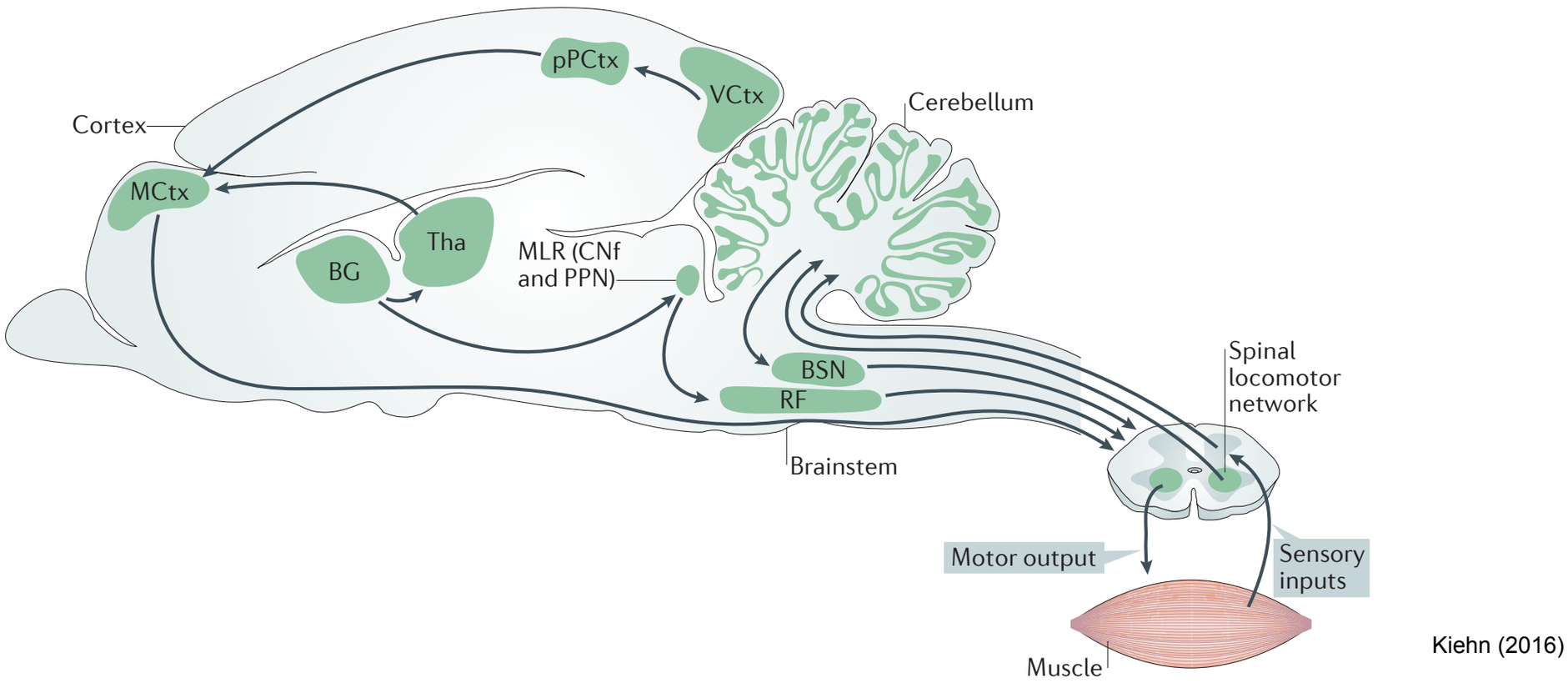


Goulding and Pfaff (2005)

Early movements of vertebrate embryos

-Central pattern-generating activity is modulated by sensory and descending inputs.

-Sensory (proprioceptive) information generated through the active movements of the limb or the bending of the body controls the activity of the central pattern generator.



Kiehn (2016)

MLR: mesencephalic locomotor region. Initiation of locomotion Is thought to be mediated by the activity of neurons in the MLR, including the cuneiform nucleus (CNf) and the pedunculopontine nucleus (PPN). MLR neurons project to neurons in the reticular formation (RF) in the hindbrain. Neurons in the RF project to locomotor networks in the spinal cord that execute locomotion.

Summary 1 (early movement)

-The first movements in vertebrate embryos are not coordinated and are caused by spontaneous activity of motor neurons that relies on acetylcholine from other motor neurons as well as glycine and GABA.

-These early activities help the guidance of motor axons to muscles.

-Central pattern-generating activity is modulated by both descending and sensory inputs.

Sexually dimorphic behaviors

-Sexual behavior is robust and often stereotyped, allowing quantitative analysis.

-Sexual behavior has strong innate component, likely to be specified by genetic programs.

-Reproductive behaviors are sexually dimorphic (differ between males and females)

-In fruit flies, sexual dimorphism in neural circuit and behavior is largely specified by cell-autonomous (intrinsic) actions of transcription factors splicing factors.

-In rodents, such dimorphism requires a combination of intrinsic and extrinsic (hormonal) controls both during development and in the adult.

Regulation of mammalian sexual behaviors

Model mammalian species (mostly rodents) show sexual and reproductive behaviors that has a large innate component.

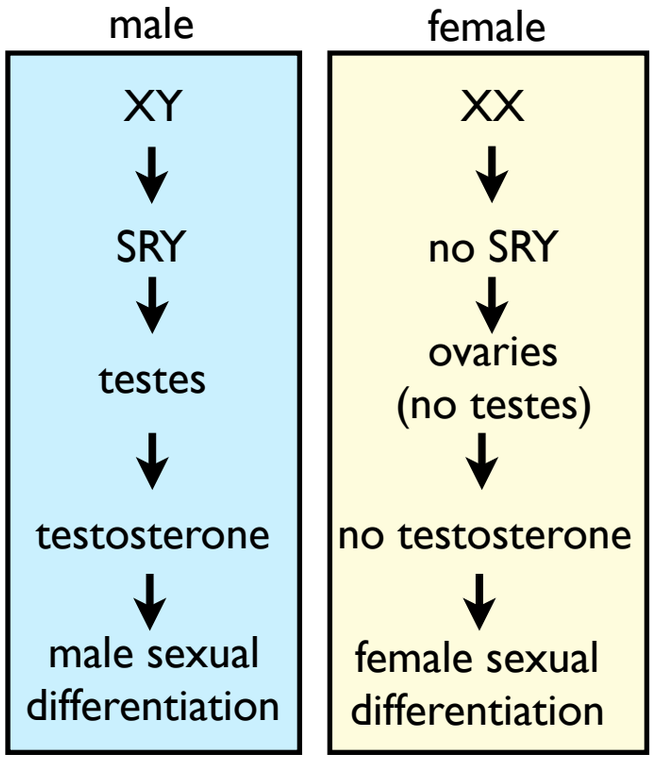
-Male rodents mount females. Female rodents exhibit lordosis .

-Males show aggressive behavior toward intruders (particularly sexually mature males).

-Females exhibit maternal behavior after giving birth to pups.

What is the developmental origin of such sexually dimorphic behaviors?

The Sry gene on the Y chromosome determines male differentiation via testosterone production



In most mammals (including mice and humans), sex is determined by the presence or absence of the Y chromosome.

-Humans with one X and no Y (XO) develop into females (Turner Syndrome).

-Humans with two X and one Y (XXY) develop into males (Kleinfelter Syndrome)

The Sry gene (encoding a transcription factor, SRY) is on the Y chromosome.

-SRY is necessary and sufficient for the development of the testis, which produces testosterone.

Testosterone is required for the brain development that leads to male sexual behavior.

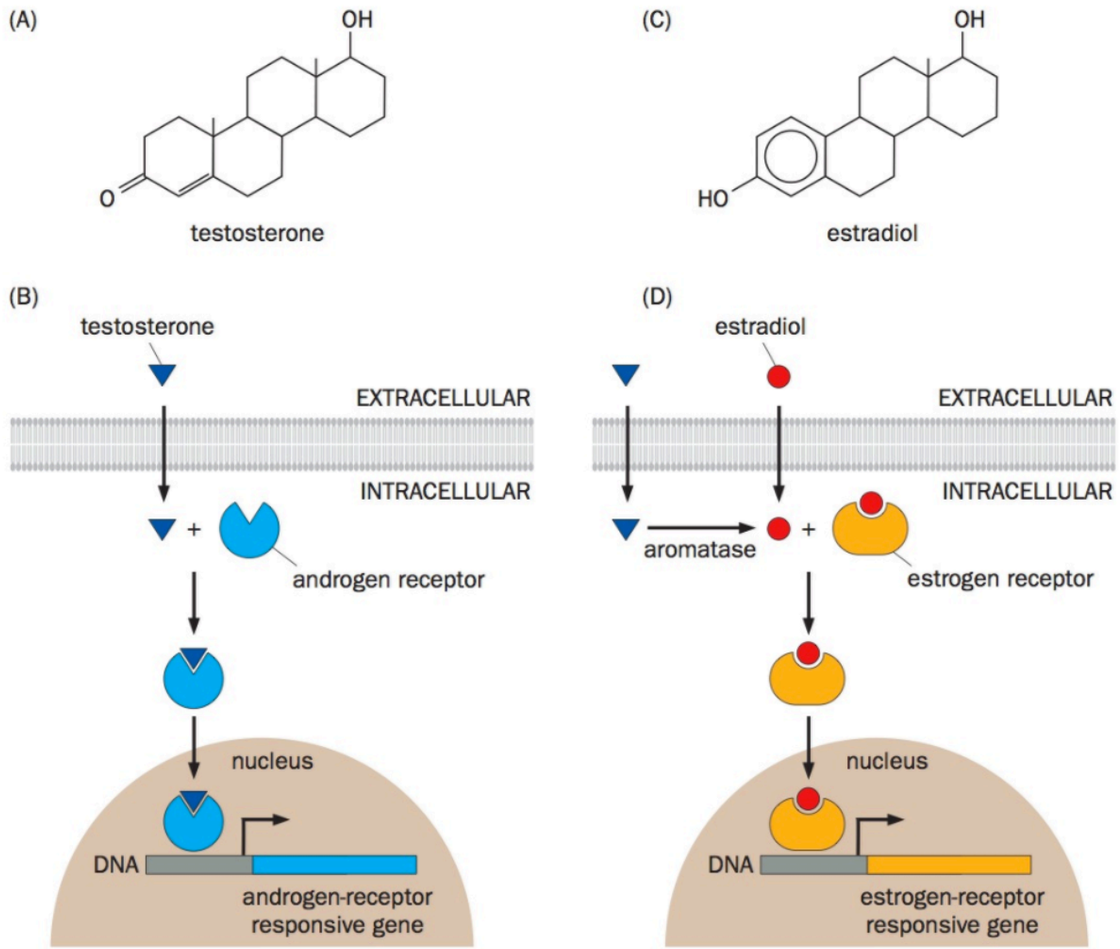
-Unlike the fruit flies in which cell-autonomous mechanisms mediate sexual differentiation, the mammalian system is more complex because of the involvement of sex hormones (testosterone, estrogen, progesterone).

Testosterone and estradiol are the major sex hormones

-Testosterone is synthesized from cholesterol in the testes and freely diffuse across the plasma membrane. Testosterone binds to androgen receptor , which are transcription factors.

-Dihydrotestosterone (DHT), a testosterone metabolite, is a more potent activator of androgen receptor than testosterone and is responsible for the development of external genital masculinization.

-Estradiol is a major estrogen (=female sex hormone) is made by the ovaries of sexually mature females. Estradiol binds to estrogen receptors (ERα and ERβ), which act as transcription factors.

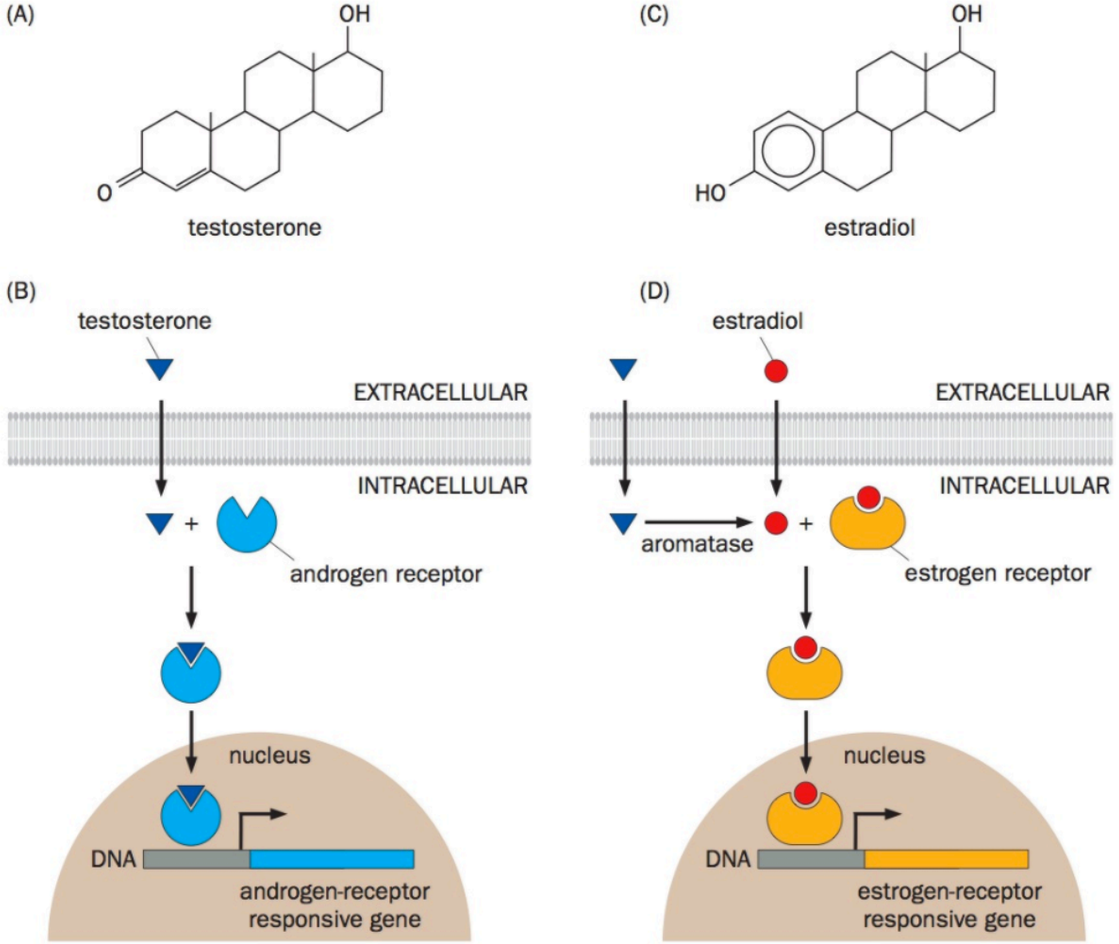


Testosterone is converted to estrogen in early developing male brains

-Cells that express the enzyme aromatase can convert testosterone to estradiol. In these cells, testosterone can exert its actions by 1) binding to an androgen receptor directly or 2) by binding to estrogen receptor after being converted to estradiol. Estradiol plays an important role in male development.

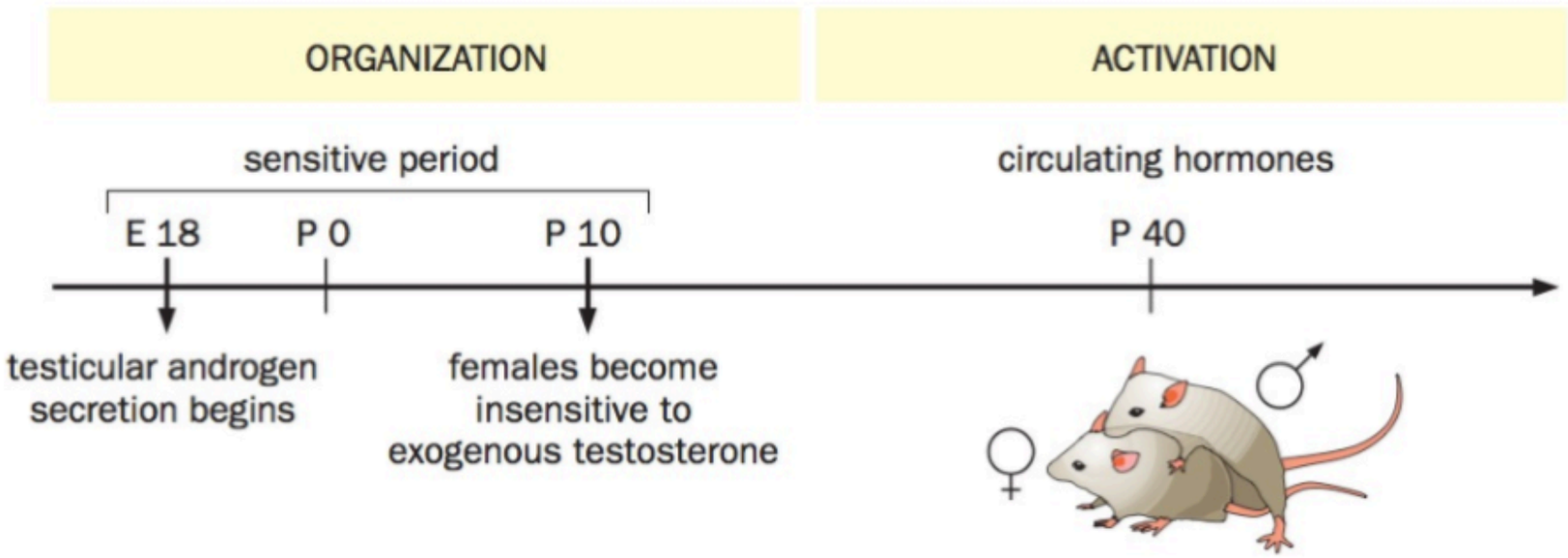
-In females, estradiol is produced by the placenta but is sequestered by α-fetoprotein and does not reach the brain in male or female.

In late embryonic to early postnatal rodent brains, estrogen is available in males but not in females.



Early exposure to testosterone causes females to exhibit male-typical sexual behavior

The organization-activation model for sex hormone action (Phoenix, 1959)



normal ♂	circulating testosterone enters brain cells and is converted to estradiol by aromatase intracellular estradiol promotes the male configuration of the brain	brain neurons are influenced by testosterone and by estradiol generated from testosterone via local action of aromatase male-typical sexual behaviors such as mounting are activated
normal ♀	no testosterone is produced, and estradiol cannot circulate to the brain in the absence of intracellular estradiol, the brain takes the default female configuration	brain neurons are influenced by estradiol and progesterone female-typical sexual behaviors such as lordosis are activated
neonatal treated ♀	when treated with testosterone or estradiol during the sensitive period, the female brain is largely masculinized, assuming a male configuration	when treated with testosterone or estradiol, females exhibit some male-typical behaviors and abnormal female-typical behaviors

Sensitive period for the organizational effect of testosterone

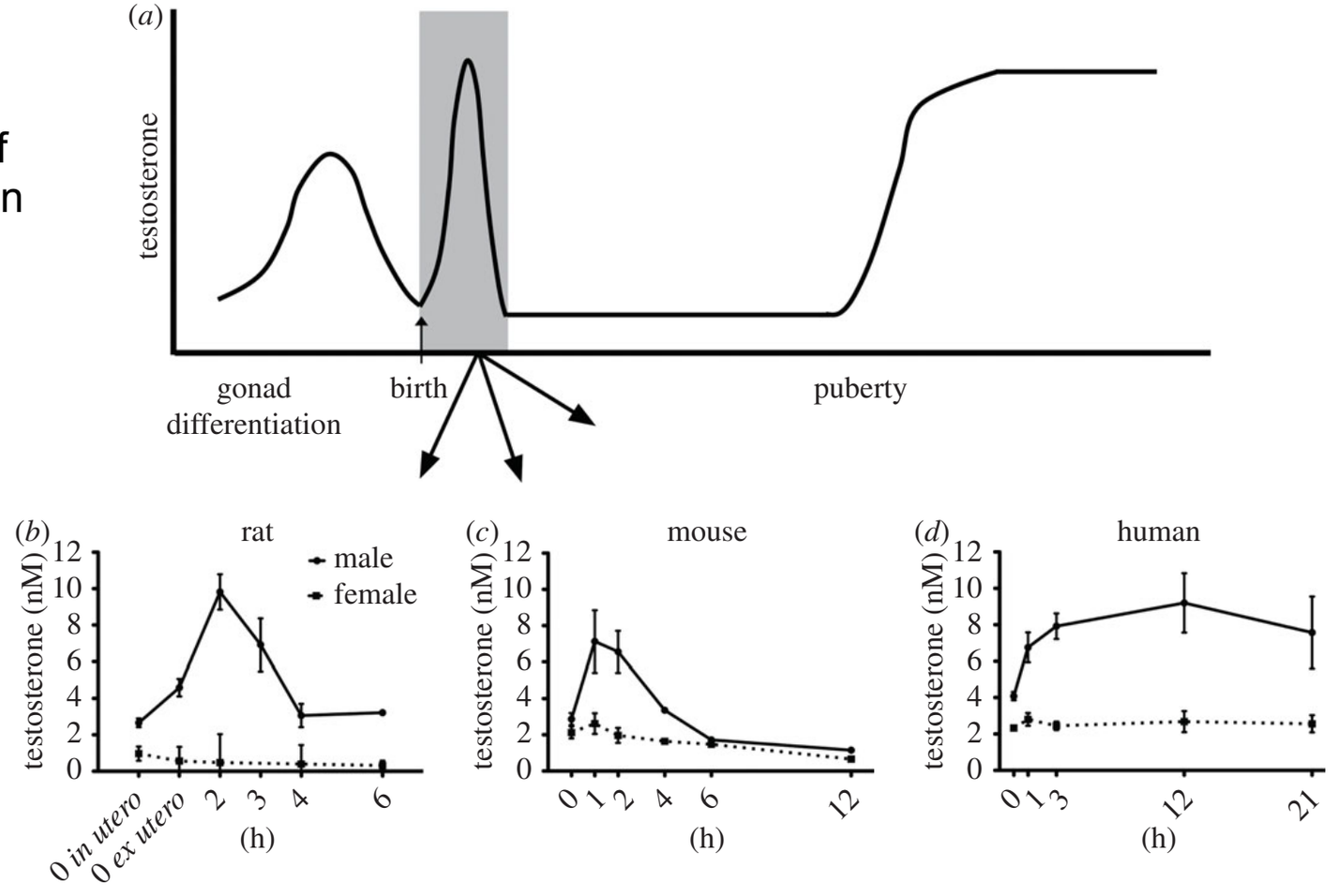
-There is a sensitive period in early development during which the brain is programmed to respond in a male or female direction when stimulated by hormones (activation) in adulthood.

-The original study by Phoenix et al. (1959) suggested the sensitive period is prenatal in guinea pig.

-In mouse and rat, the sensitive period starts shortly before birth and spans the first 10 days after birth.

-Organizational effect is mainly through estradiol rather than testosterone itself. Female mice treated with estradiol for the first 10 days after birth show male-typical behaviors. In addition, aromatase knockout mice show profound defects in male-typical behaviors.

temporal change of testosterone levels in males

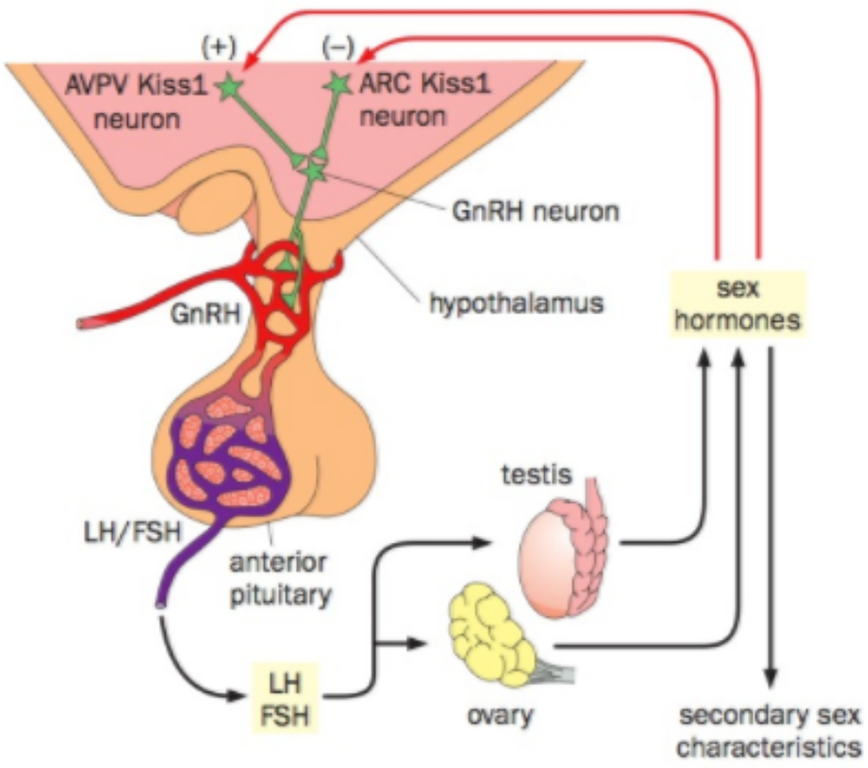


Clarkson and Herbison (2016)

Pituitary controls neonatal testosterone surge from the testes

•Male (but not female) pituitary gland has elevated LH (lutenizing hormone) concentration from E17 to E20. LH stimulates production and secretion of testosterone from male testes.

-The AV/PV (anteroventral/periventricular) nucleus of the hypothalamus contains neurons that produce the peptide Kisspeptin-1 (Kiss1). Production of these neurons require estradiol in the embryonic male brains (converted from testosterone). Kiss1 stimulates production of GnRH, which stimulates LH secretion into circulation.



Sexually dimorphic brain structures

In most sexually dimorphic nuclei, testosterone is converted to estradiol via aromatization and acts primarily through the α form of the estrogen receptor (ERα) to alter multiple aspects of brain structure and function.

Larger in male brains: MPO (medial preoptic area), principal nucleus of the bed nuclei of the stria terminalis (BSTp), medial amygdala

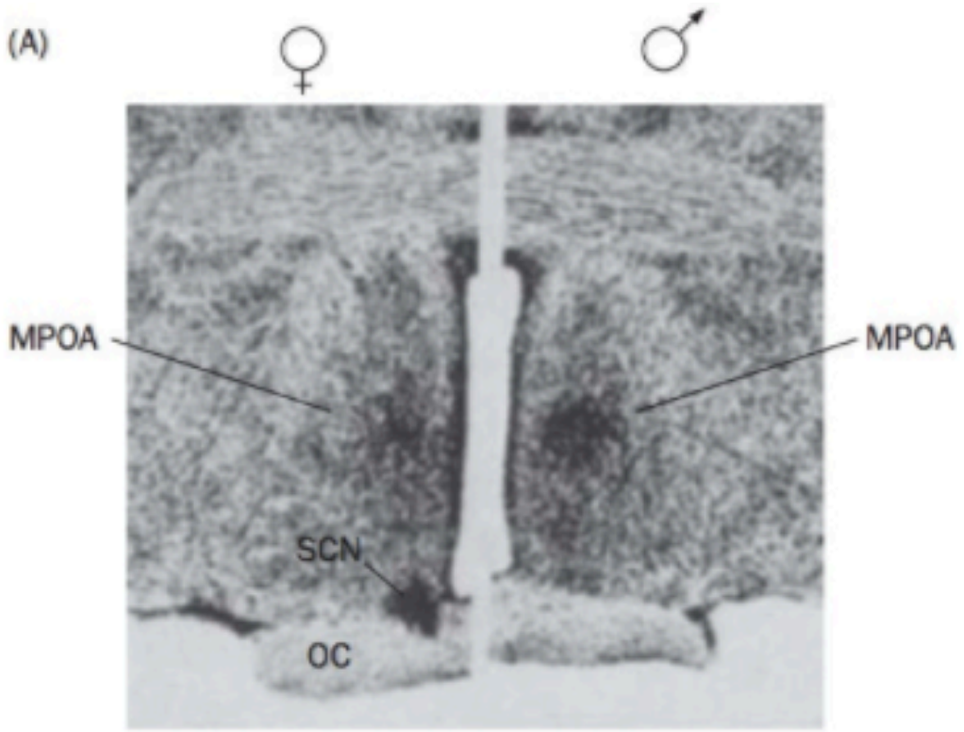
Lesion studies indicate that MPO is essential for male courtship behavior (mounting, intromission, ejaculation).

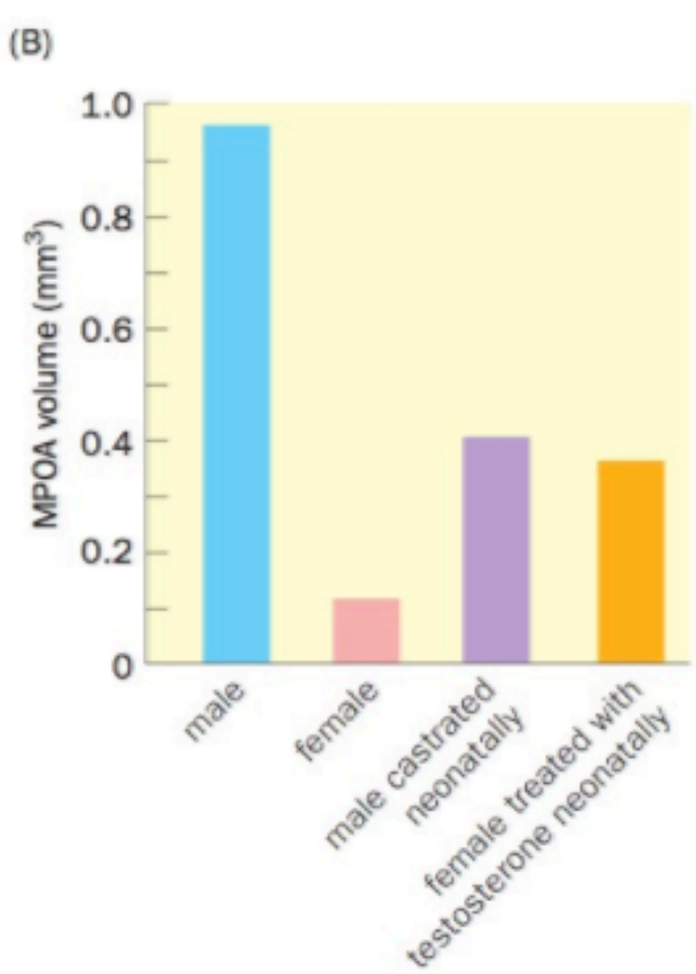
In humans, interstitial nuclei of the anterior hypothalamus (INAH1, 2, 3, 4) are larger in males.

Larger in female brains: AV/PV

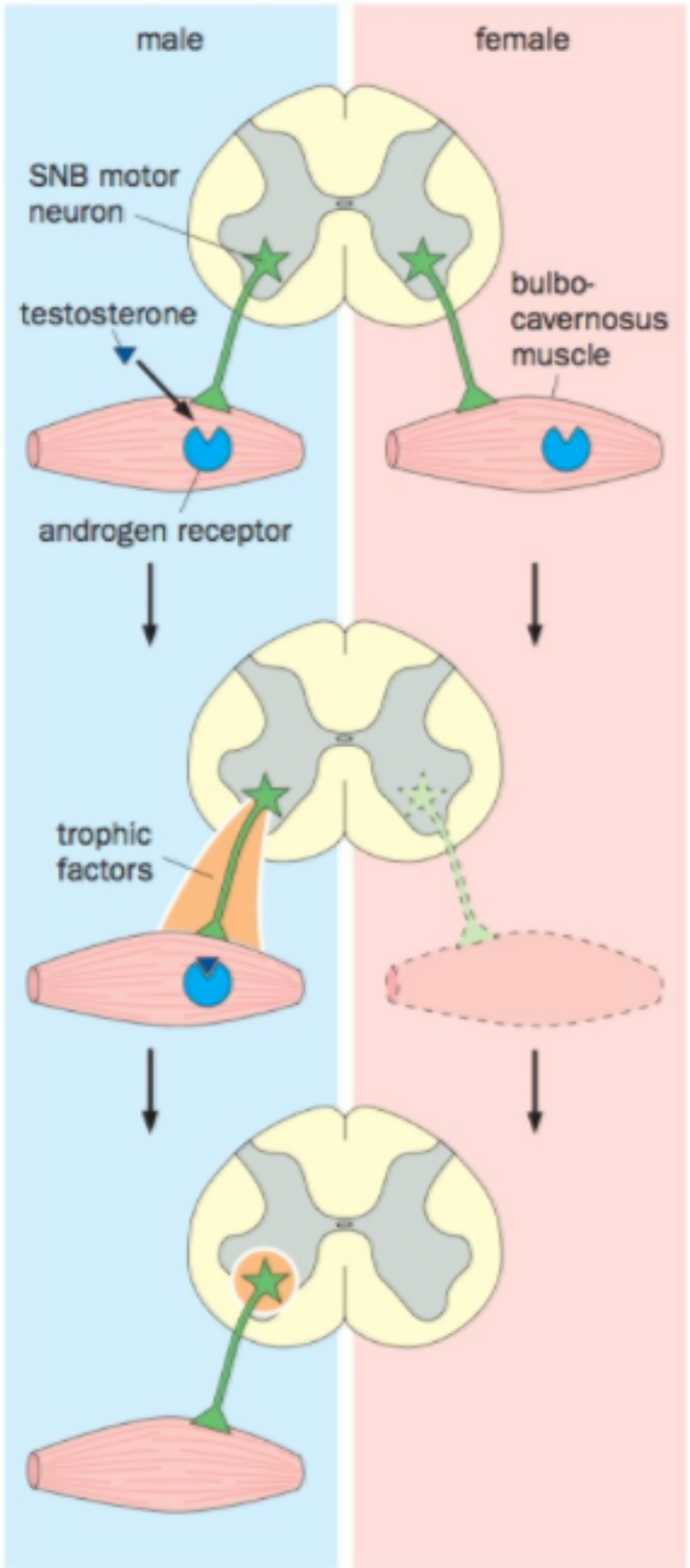
Estrogen specifies sexually dimorphic neuronal numbers by regulating programmed cell death

-More programmed cell death in females leads to the smaller size of sexually dimorphic brain structures. In males, estradiol prevents the cell death in these structures.





Sexual dimorphism of a penile muscle and its motor neurons



-Motor neurons of the spinal nucleus of the bulbocavernosus (SNB) innervate a muscle at the base of the penis.

-Both SNB neurons and their target muscle die in neonatal females but not in males.

-Dihydrotestosterone (DHT) acts via the androgen receptor to prevent programmed cell death in the muscle. The muscle provides trophic support for the survival of SNB neurons.

-Some sexually dimorphic nuclei are continually influenced by sex hormones during puberty and in the adult.

e.g., In songbird brains, testosterone promotes the survival of adult-born neurons in male song nuclei.

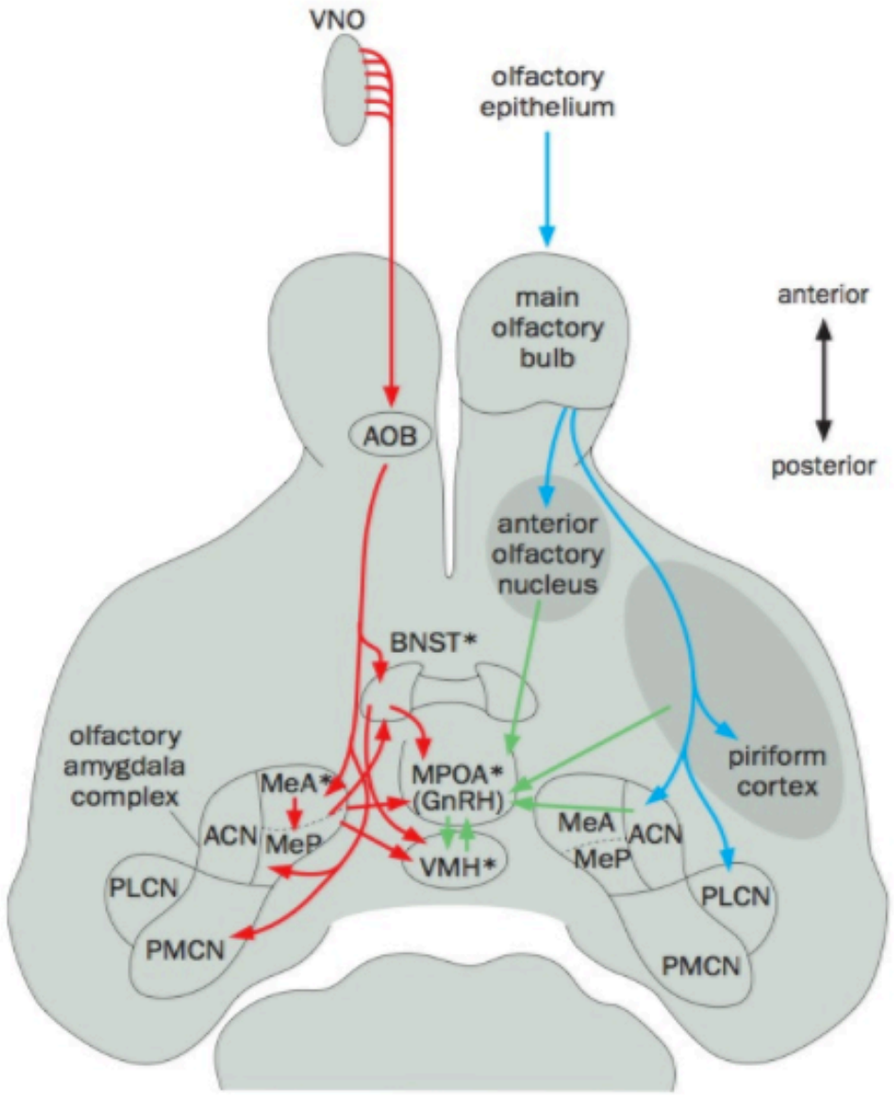
Regulation of sexual dimorphism in flies and mammals

In both flies and mammals, sexual dimorphism occurs extensively in the form of neuronal number and connections, and programmed cell death is a key mechanism in both cases.

-Deletion of *Bax* in mice eliminates sexual differences in the mouse forebrain (Forger et al., 2004). Female *Bax* knockout mice show reduced lordosis.

-In flies, transcription factors play a large role. In mammals, sex hormones play a large role.

How do sexual dimorphisms in mammalian brains regulate sexual behaviors?



Circuit-level view of sexually dimorphic structures

<u>Accessory olfactory system (discriminates sex partners)</u>

MeA (medial amygdala) and BNST both project to MPOA (medial preoptic area) and VMH (ventromedial hypothalamic nucleus)

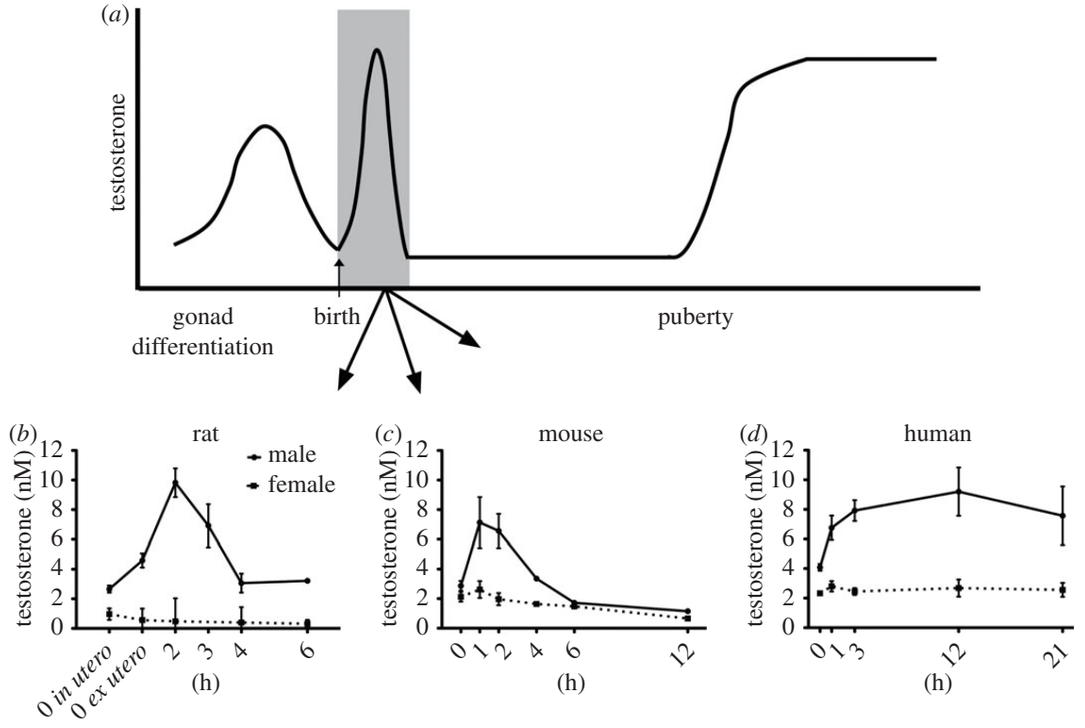
<u>Main olfactory system (essential for mating)</u>

MeA and MPOA

What regulates the sensitive period?

1. neonatal testosterone surge
2. temporal pattern of aromatase expression (down-regulated soon after birth)
3. downstream components of estrogen receptor pathway (not known?)
   -it is not known how estradiol controls apoptosis of neurons in sexually dimorphic brain structures.

temporal change of testosterone levels in males



Clarkson and Herbison (2016)

Summary 2 (sexual dimorphism)

-In mammals, sex determination is controlled by the transcription factor SRY (gene located on Y chromosome). SRY is required for the formation of the testes.

-Testes produce testosterone during male embryogenesis. This triggers neonatal surge of testosterone in males via hypothalamus-pituitary loop involving several peptide hormones.

-In developing male brains, testosterone is converted to estradiol by aromatase in developing male brains. Estradiol plays crucial roles in development of sexually dimorphic brains structures by controlling programmed cell death.

-Sexually dimorphic brain structures form brain circuitry that is critical for male sexual behaviors.

-Estrogen may play a role in brain development and function through microglia activation.

Critical (sensitive) period

-Virtually all animals can alter their behavior based on their past experiences.

The base for this ability is synaptic plasticity: strengthening, weakening, addition, removal

-The capacity for synaptic plasticity often peaks soon after birth and declines with age.

-The distinct phase of development with greatly enhanced plasticity for specific sensory experiences or sensorimotor interactions is the critical period.

Imprinting

Konrad Lorenz found that shortly after hatching in an incubator, greylag geese chicks could be imprinted on almost any moving visual object, including himself, which from then on would serve as a substitute mother for the young geese (Lorenz, 1935). The time period for imprinting was short (a day or two after hatching).

-Once imprinting occurs, the effect is permanent.

-Auditory imprinting also occurs in birds.

Language learning

Infants and young children are superior language learners compared with adults.

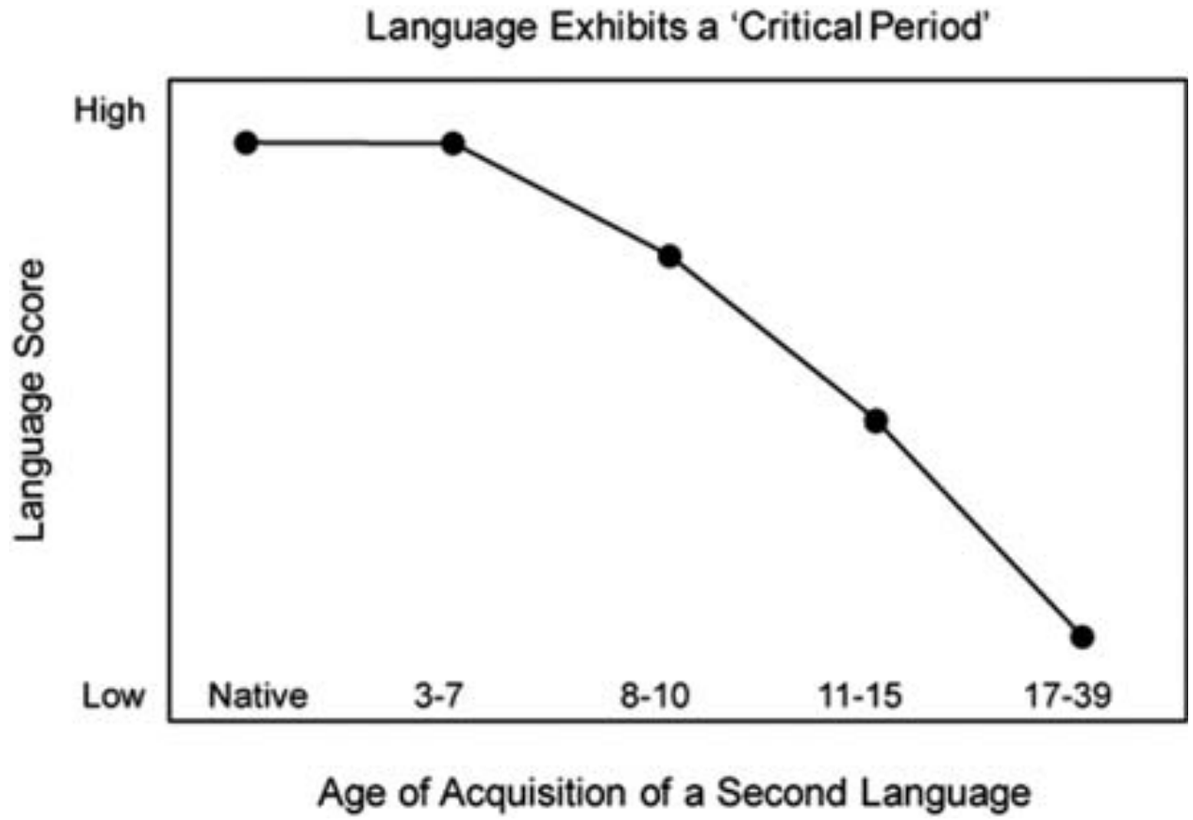


Figure 1. The relationship between age of acquisition of a second language and language skill. (Reprinted from Kuhl 2010; originally adapted from Johnson and Newport 1989, with permission from Elsevier.)

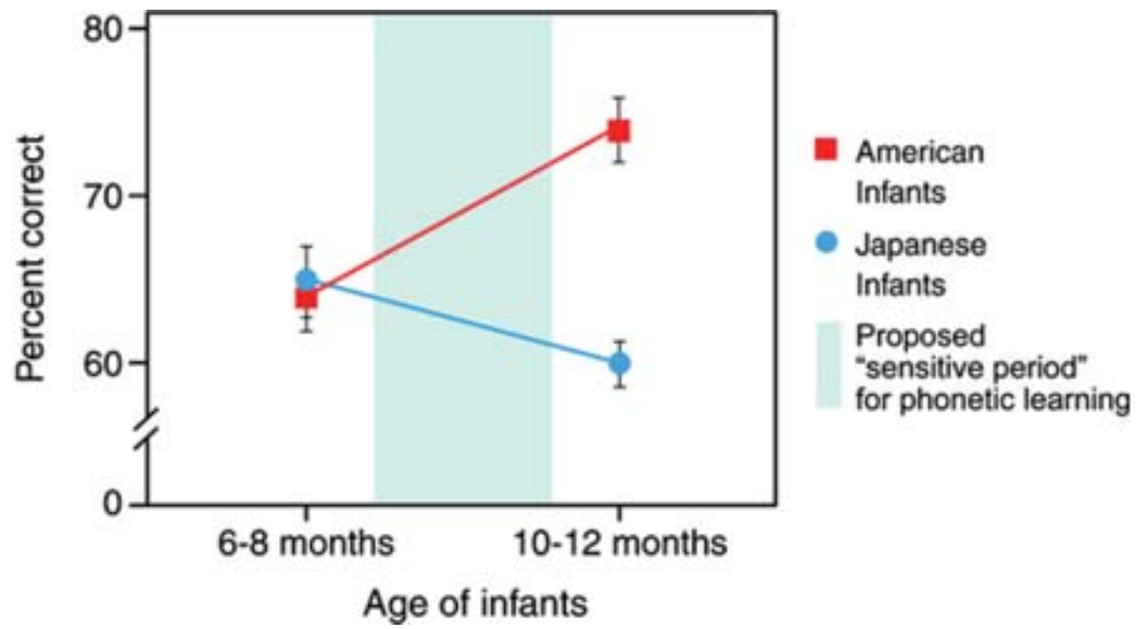


Figure 2. Effects of age on discrimination of the American English /ra-la/ phonetic contrast by American and Japanese infants at 6–8 and 10–12 mo of age. Mean percent correct scores are shown with standard errors indicated. (Reprinted from Kuhl 2010, with permission from Elsevier; originally adapted from Kuhl et al. 2006.)

Kuhl (2014)

Amblyopia

Amblyopia is an enduring loss of responsiveness (detected as reduced visual acuity) in the primary visual cortex to an eye deprived of vision during early years of life (0-7 years old)

-afflicts 2–5% of the human population

-remains without a known cure in adulthood

	Features	Unilateral or bilateral effect
Strabismus (ocular misalignment)	Each eye does not have the same image on the fovea	Unilateral
Anisometropia (difference in refractive error)	One foveal image is more blurred than the other	Unilateral
Deprivation (including ametropia—ie, large symmetric refractive errors)*	Physical obstruction of one image (eg, cataract, ptosis, or bilateral blur from uncorrected refractive error)	Either

*Amblyopia is the residual visual deficit after the physical obstruction is removed and appropriate optical correction is provided.

Table 1: **Causes of amblyopia**

Holmes and Clarke (2006)

Ocular dominance plasticity has a critical period

Temporary deprivation of vision with one eye of a kitten causes a dramatic change in the ocular dominance distribution among the neurons in its visual cortex (Hubel and Wiesel, 1963). <u>The effect is strongest between 4-8 weeks after birth in kittens.</u>

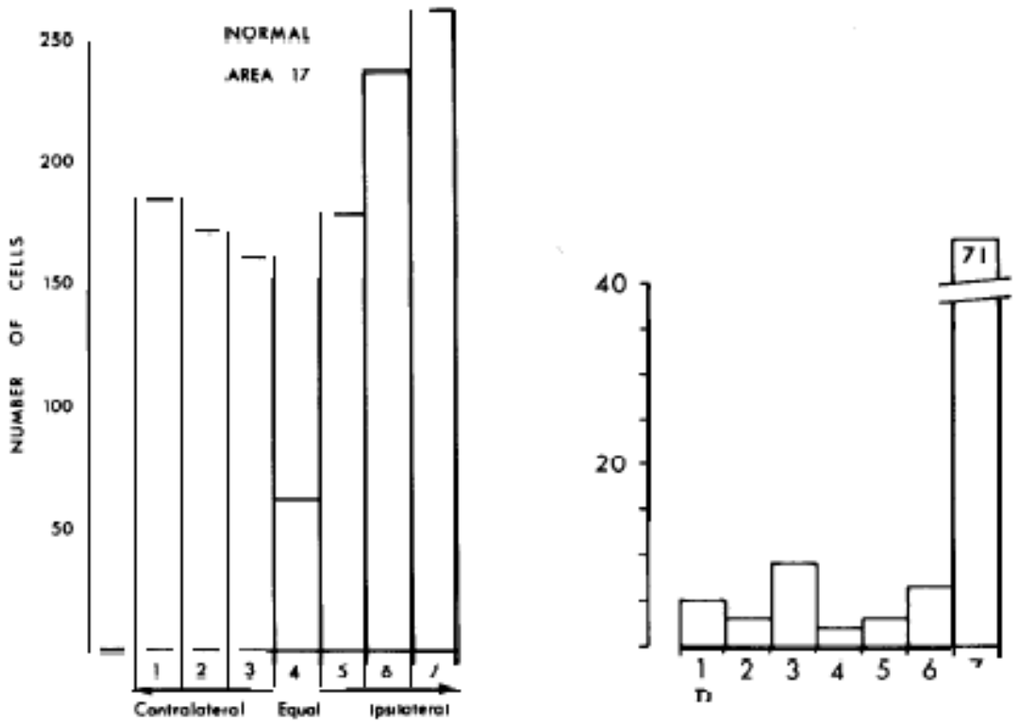


Fig. 1. Ocular dominance histograms in normal and monocularly deprived rhesus macaque monkeys.

Left histogram: 1256 cells recorded from area 17 in normal adult or juvenile rhesus monkeys.[9]

Right histogram: obtained from a monkey in which the right eye was closed at 2 weeks for 18 months.[9] It shows the relative eye preference of 100 cells recorded from the left hemisphere. The letter D indicates the side of the histogram corresponding to dominance by the deprived eye.

Cells in layer IVC are excluded in this figure and in histograms of all other figures. Cells in group 1 are driven exclusively from the contralateral eye, those in group 7 from the ipsilateral eye, group 4 cells are equally influenced, and the remaining group are intermediate.

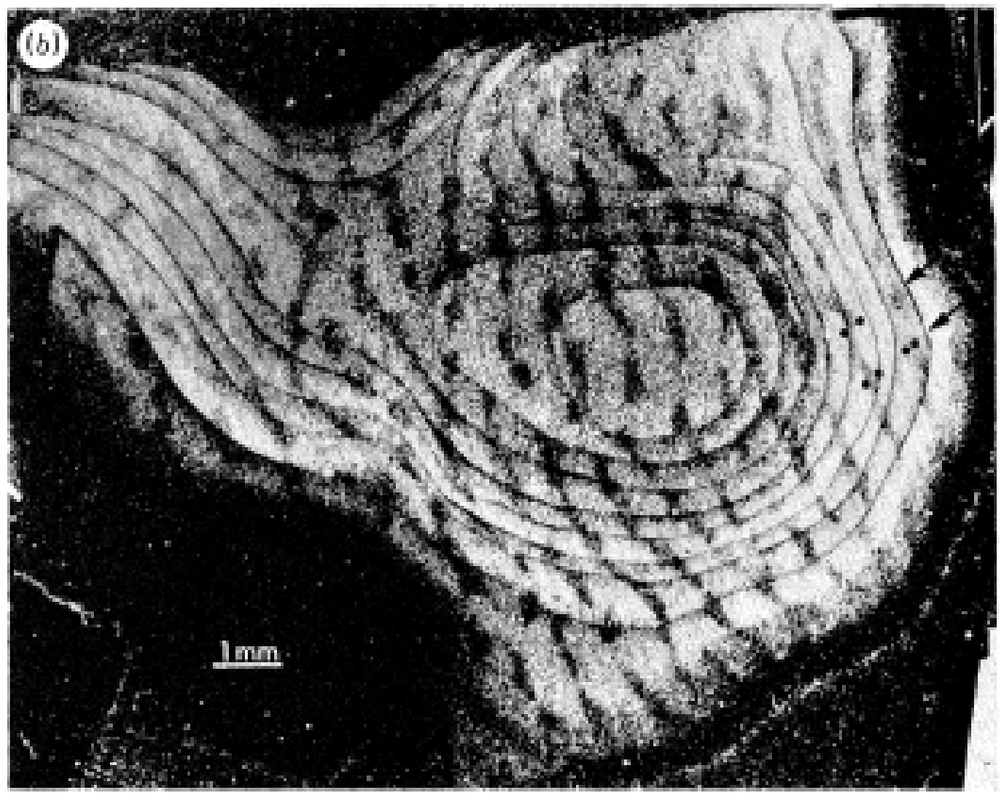


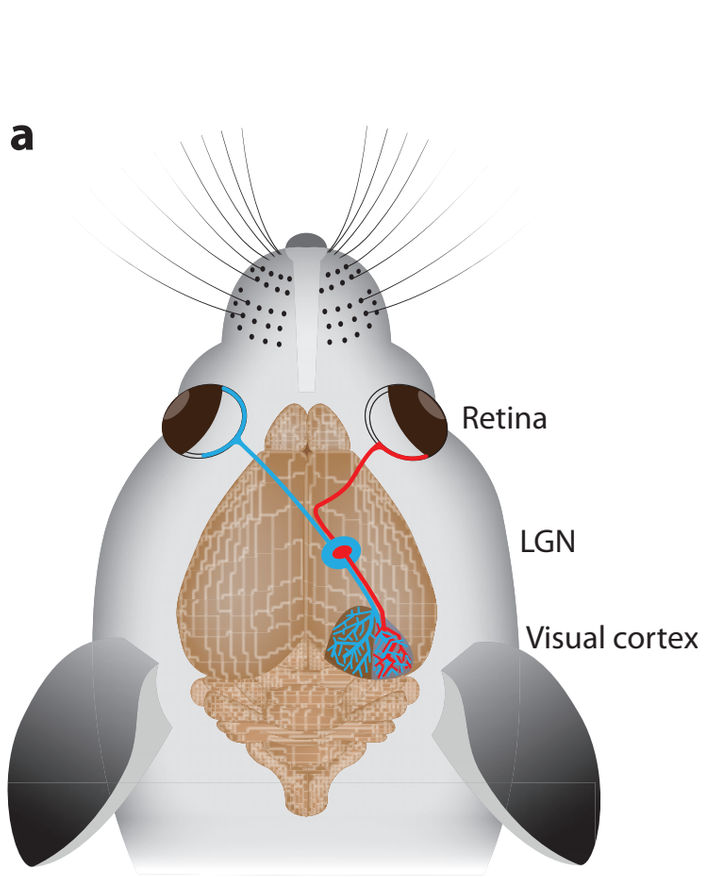
FIGURE 32. Transneuronal autoradiography of left occipital lobe of macaque monkey whose right eye was sutured closed at 2 weeks, and studied at 18 months. Left (normal) eye injected with tritiated proline-fucose mixture 2 weeks before brain was sectioned. (*a*) Section tangential to layer IVc, dark field, as in figure 23. Note expansion of labelled columns and shrinkage of the gaps. The serial reconstruction, (*b*), was made from a number of sections parallel to *a* and including *a*. The positions of six lesions, determined from neighbouring sections, are shown near the right border. These lesions were made during the electrical recordings, in two penetrations (arrows), at points of eye transition. Note how each lesion falls on a column border. (From Hubel *et al.* 1977.)

Ocular dominance plasticity in mouse V1

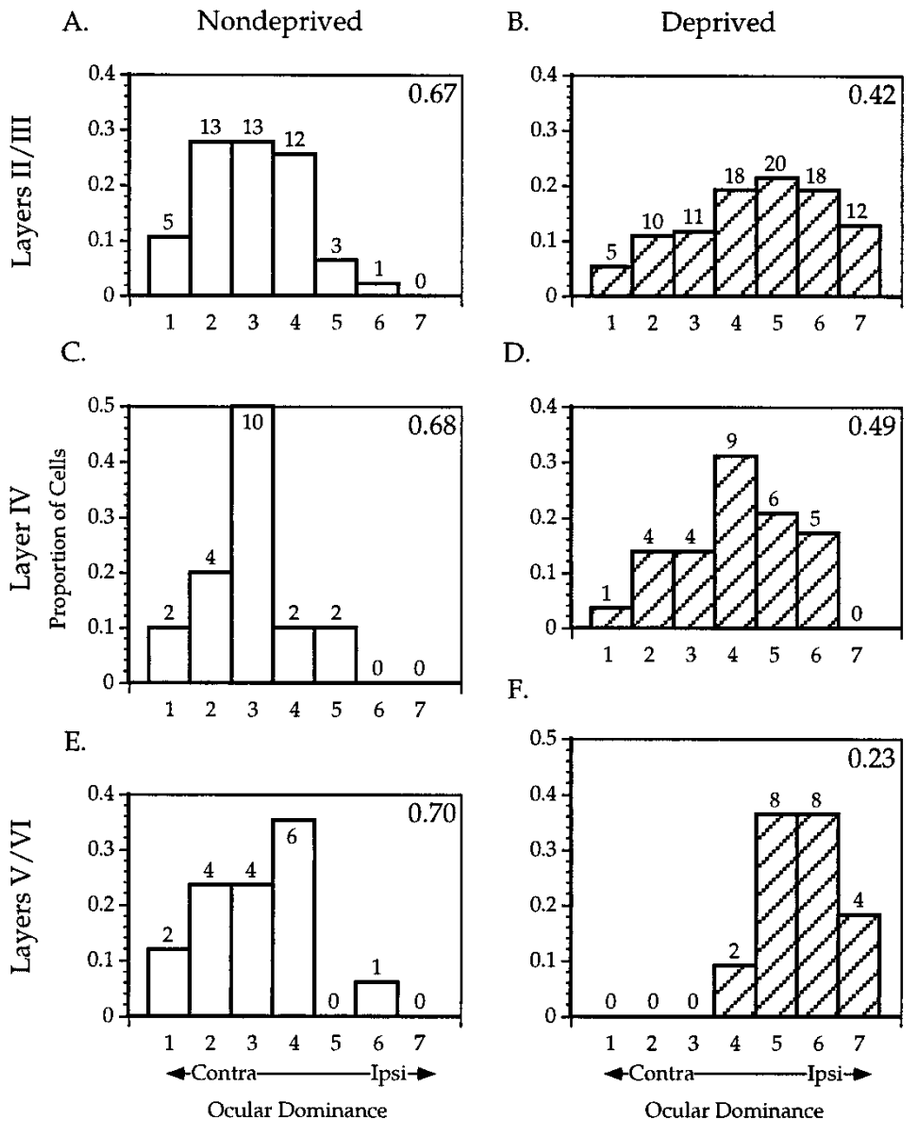
-Majority of mouse V1 (primary visual cortex) is monocular, responding only to visual input to contralateral eye.

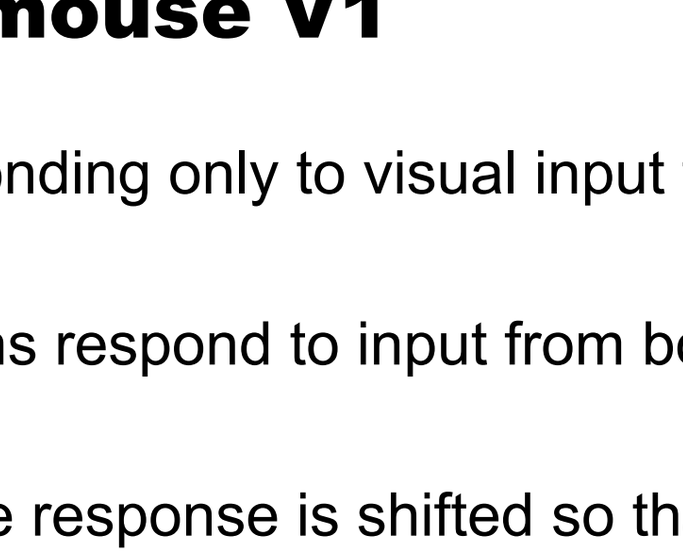
-A small patch in the lateral part of V1 is binocular, where neurons respond to input from both eyes with a contralateral dominance.

-When the contralateral eye is sutured between P28 and P32, the response is shifted so that more cells respond predominantly to ipsilateral input.



Levelt and Hübener (2012)





Gordon and Stryker (1996)

Mechanisms that control critical period

-What are the cellular events that happens during ocular dominance plasticity?

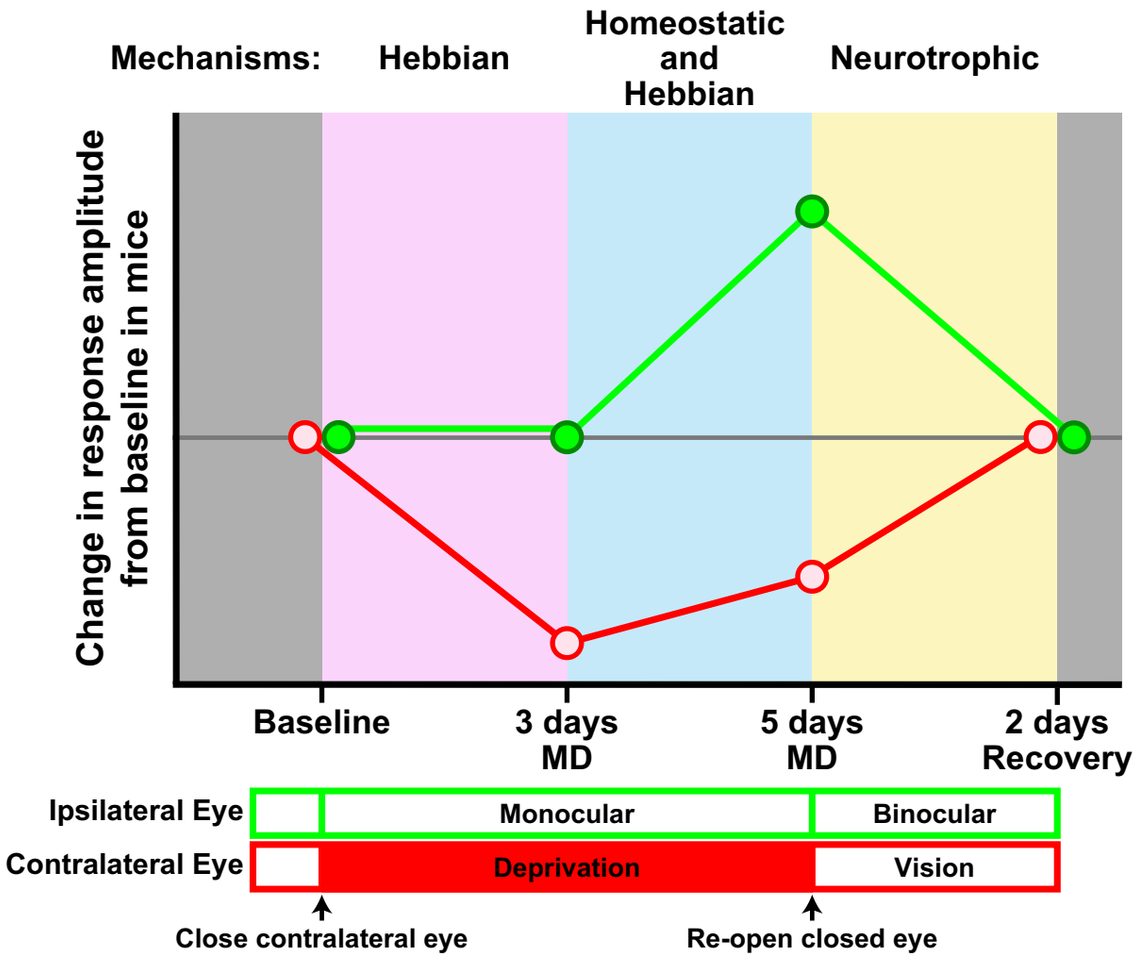
-What controls the onset of critical period?

-When control the closure of critical period?

-Can we reopen plasticity after the closure of critical period?

Stages of ocular dominance plasticity in mouse V1

-Transcranial imaging of intrinsic signals and chronic implantation of recording electrodes to measure the amplitude of visually evoked potentials allow repeated sampling from the same brain before, during and after manipulations of visual experience.



Espinosa and Stryker (2012)

[first stage] large reduction of response to deprived eye, but no change in open-eye response

[second stage] large increase of response to intact eye, small increase in deprived-eye response

[after reopening of the deprived eye during critical period] response goes back to the baseline for both eyes

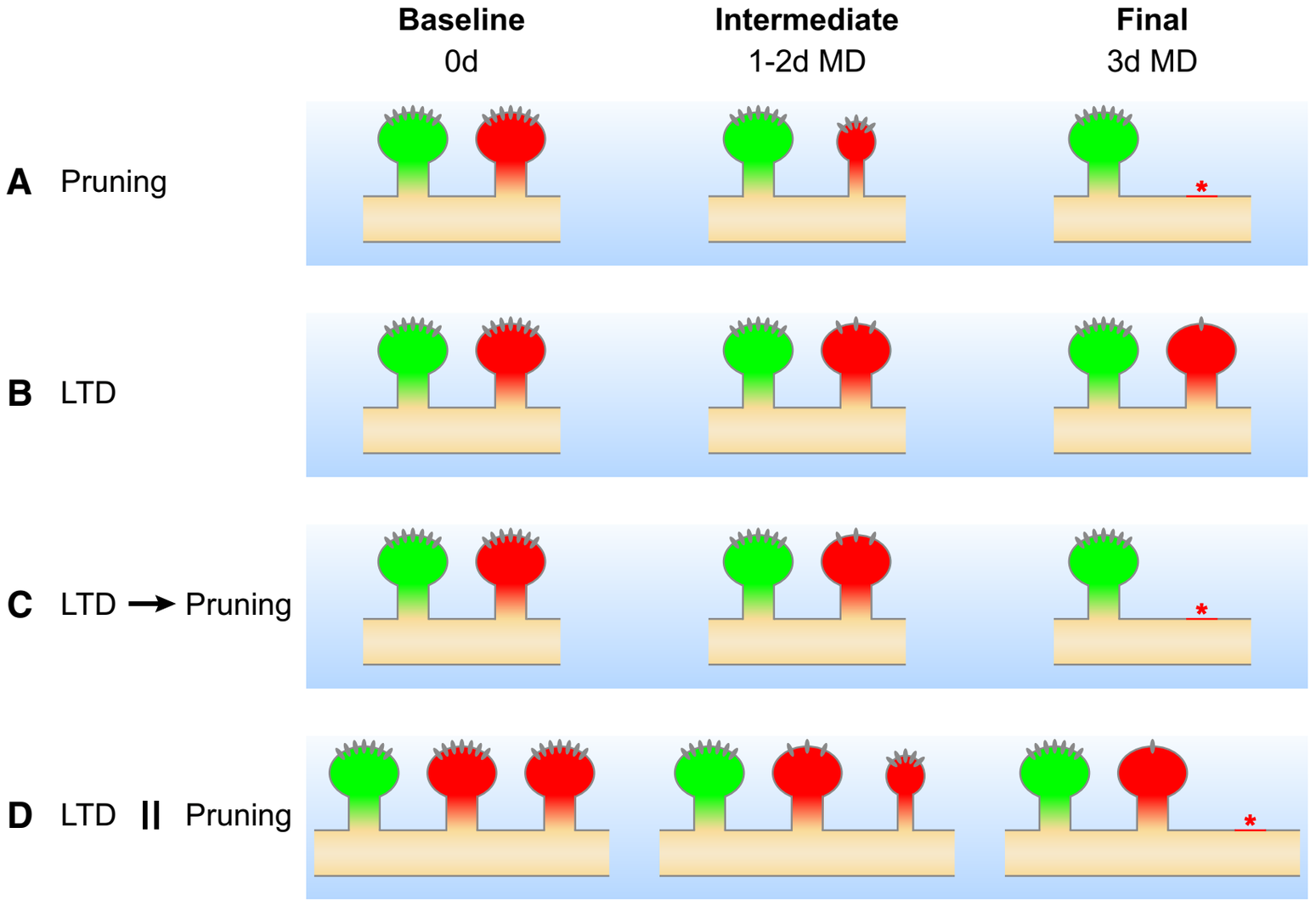
Mechanisms of ocular dominance plasticity in mouse V1

-During the first stage of ocular dominance plasticity, reduction in response to the deprived eye could be either due to selective pruning of deprived-eye connections and/or LTD-like mechanisms that reduces synaptic efficacy.

-Expression of tissue plasminogen activator (tPA) is increased during monocular deprivation.

-tPA targets many molecules including ECM proteins, growth factors, membrane proteins and cell adhesion molecules, and could be involved in pruning of inactive synapses.

-tPA knockout mice show reduction of ocular dominance plasticity.



Espinosa and Stryker (2012)

What triggers timing of the critical period?

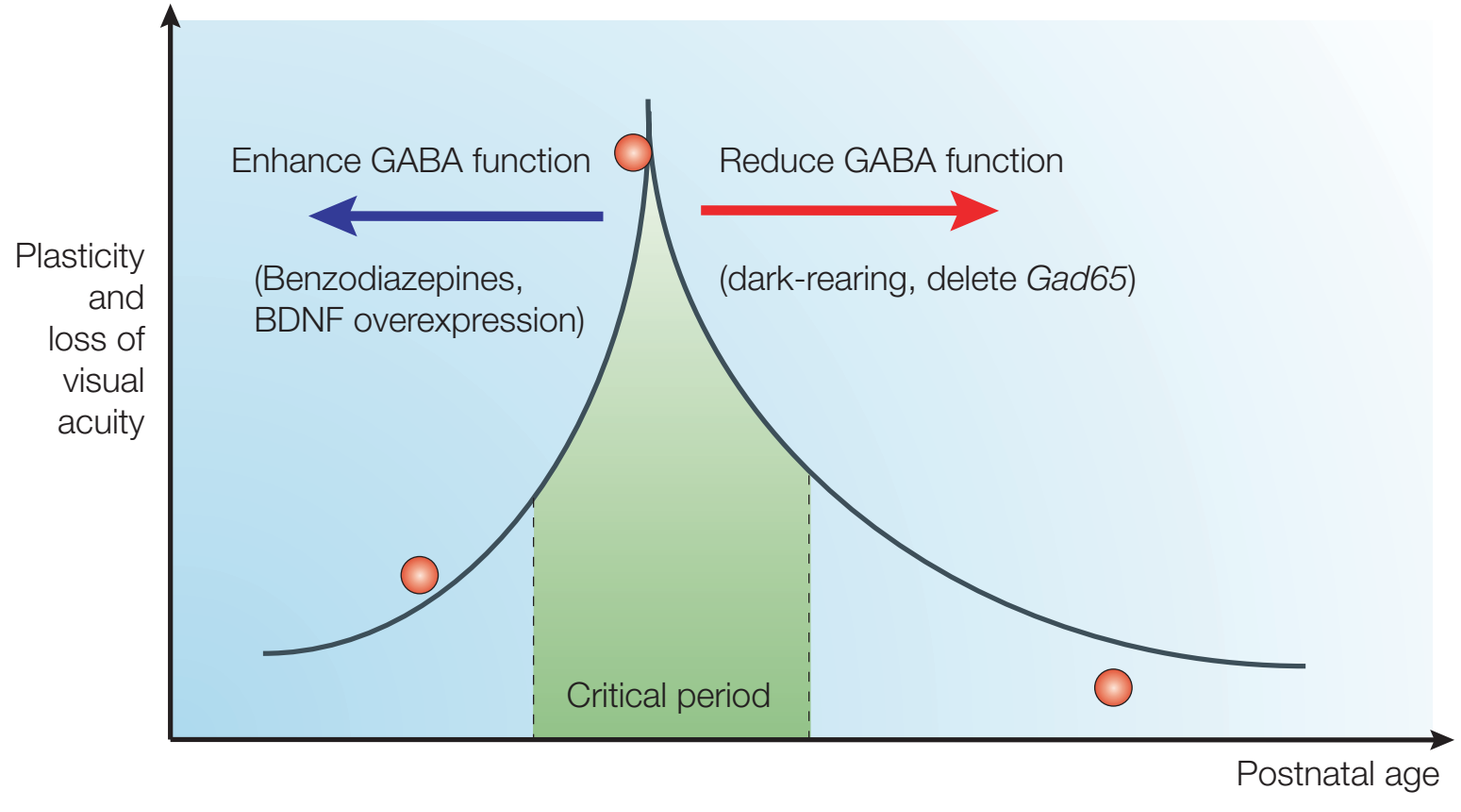
In mice with reduced GABA synthesis (glutamic acid decarboxylase (GAD65) ko mice), the critical period for ocular dominance plasticity never opened until the animals were treated with the $GABA_A$ receptor agonist, diazepam.

It is also possible to induce a precocious critical period in P19 mice by treating them with diazepam (direct infusion into V1).

Transplantation of immature inhibitory neurons into the postnatal visual cortex promotes ocular dominance plasticity even after the natural critical period

Thus, maturation of inhibitory circuit underlies the onset timing of plasticity.

Opening the critical period appears to trigger "a timer" that lead to its permanent closure 2 weeks later.

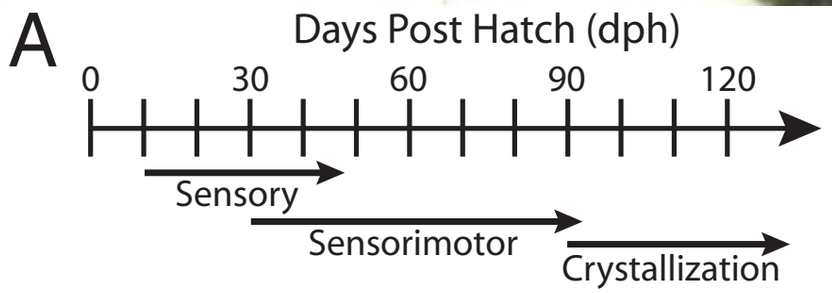


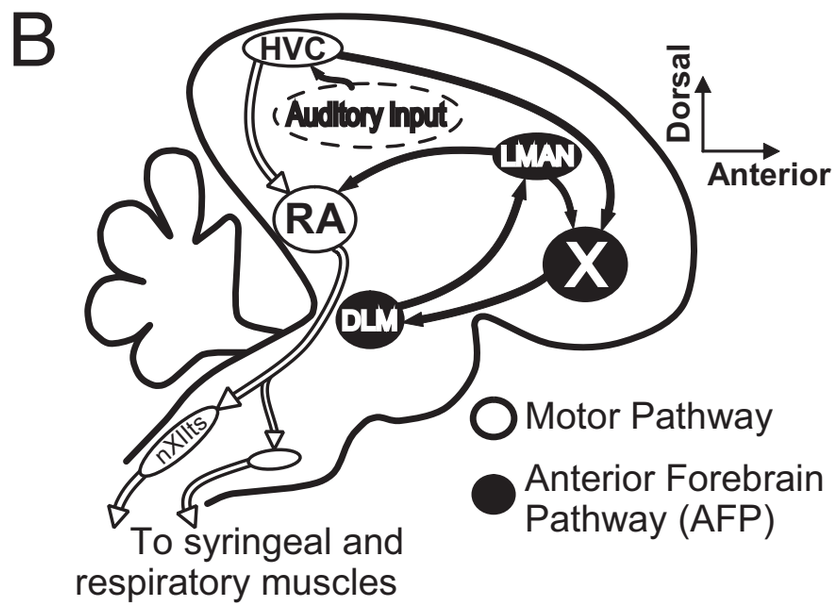
Hensch (2005)

Over-expression of brain-derived neurotrophic factor (BDNF) accelerates both GABA neuron development and critical period time course.

When neonatal mice are dark-reared, BDNF expression is down regulated and the onset of critical period is delayed.

Song learning in birds





Sizmore and Perkel (2011)

-Songbirds provide a good model for studying the neural substrate of motor learning.

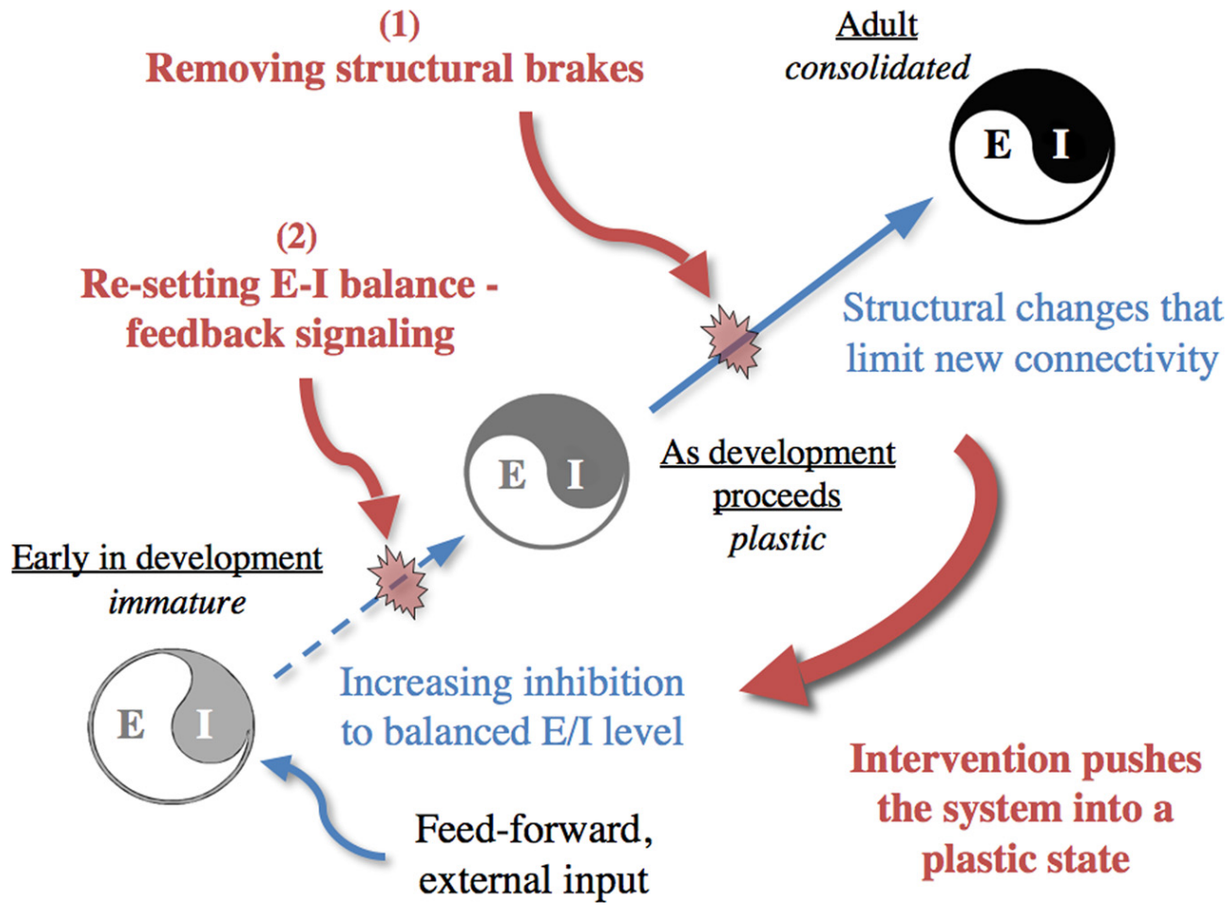
-Juvenile zebra finches learn their songs during the critical period by first listening to an adult male tutor (sensory phase), and then practicing, and listening to themselves (sensorimotor phase), until they produce a stereotyped copy of the tutor's vocalization.

-Once a stable species-specific song pattern is developed, the song structure remains unchanged throughout life ("closed-ended learner").

-Similar to the control of critical period for ocular dominance plasticity, critical period of song learning appears to be regulated by development of GABAergic neurons.

Re-introducing a critical period after its closure

-There are different ways (invasive and non-invasive) to counteract the factors that closes critical period



Intervention	Mechanism	Adult ODP	Recovery	Species
Invasive				
Astrocyte transplant	Structural	√	n.t.	Cat
NGF infusion	Structural	√	n.t.	Cat
chABC	Structural	√	√	Rat
Crtl1 KO	Structural	√	n.t.	Mouse
NgR KO	Structural	√	√	Mouse
PirB KO	Structural	√	n.t.	Mouse
dnNgR	Structural	√	n.t.	Mouse
Focal demyelination	Structural	√	√	Mouse
Locus ceruleus stimulation	E/I	√	n.t.	Cat
cAMP activation	E/I	√	n.t.	Cat
MGE transplant	E/I	√	n.t.	Mouse
Lynx1 KO	E/I	√	√	Mouse
Noninvasive				
Valproic acid/TSA	Structural	√	√	Rat/mouse
AChase inhibitor	E/I	√	√	Mouse
Fluoxetine	E/I	√	√	Rat
L-*threo*-DOPS	E/I	√	n.t.	Cat
Dark exposure	E/I	√	√	Rat
Enrichment	E/I	√	√	Rat
Perceptual learning	E/I	n.t.	√	Human
Video games	E/I	n.t.	√	Human
TMS	E/I	n.t.	√	Human

Bavelier et al. (2010)

Summary 3 (critical period)

-Animals can alter their behavior based on their past experiences via synaptic plasticity (strengthening, weakening, addition, removal).

-The capacity for synaptic plasticity often peaks soon after birth and declines with age.

-The distinct phase of development with greatly enhanced plasticity for specific sensory experiences or sensorimotor interactions is the critical period.

-Onset of ocular dominance plasticity depends on the maturation of GABAergic interneurons in the cortex. Further maturation of these neurons results in the closure of the critical period.

-Shifting the balance of excitation-inhibition as well as removing the structural constraints can reopen the critical period.

-Both animal and human studies suggest that neurodevelopment disorders such as schizophrenia and autism involve aberrant plasticity (either insufficient brakes on plasticity or hyper-mature inhibitory circuits).