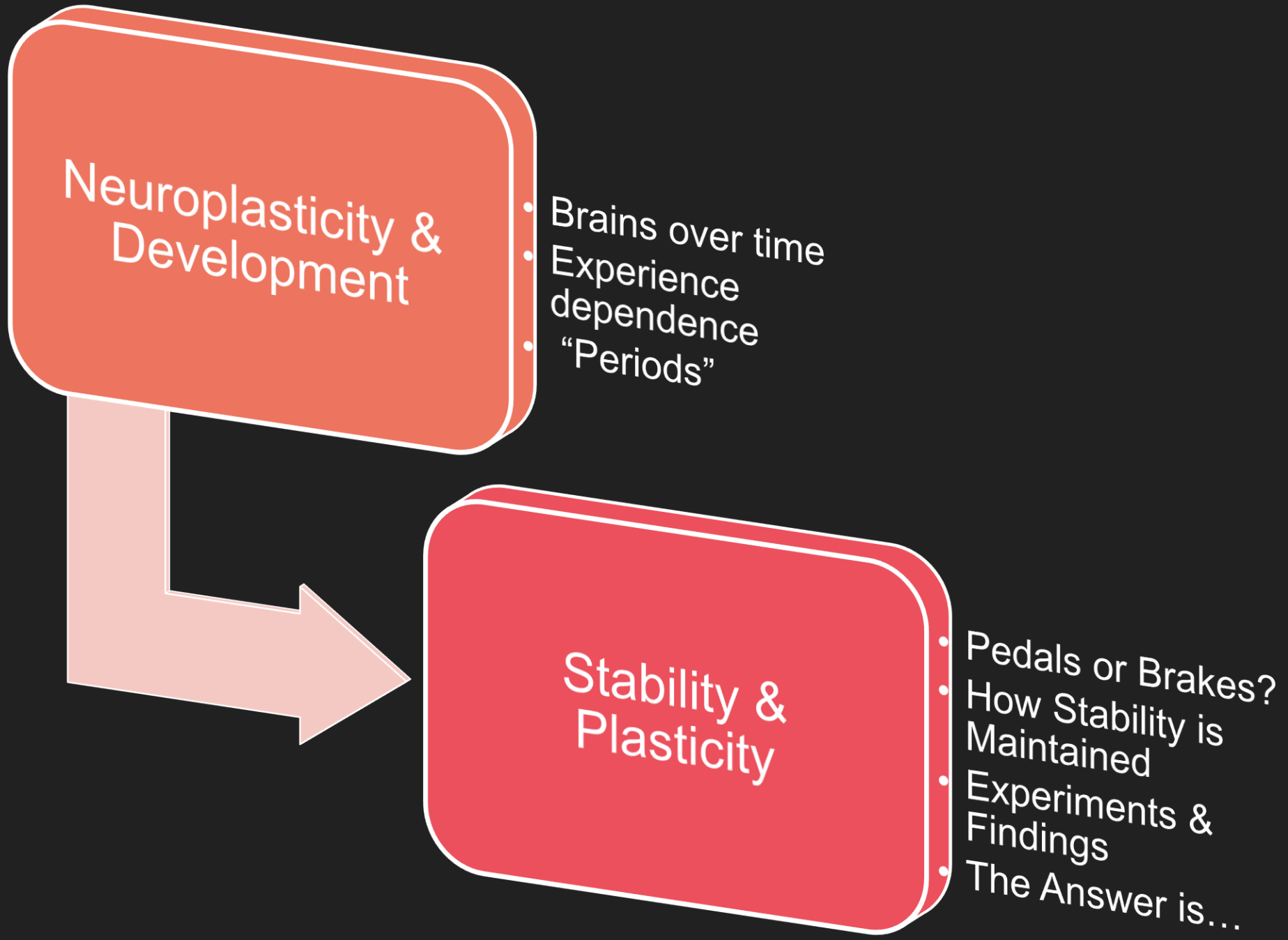
Periods in NeuroPlasticity: pedals or brakes?

Dan Ofer


Neuroplasticity & Development
Brains over time
Experience dependence
"Periods"
Stability & Plasticity
Pedals or Brakes?
How Stability is Maintained
Experiments & Findings
The Answer is…

The Early brain:

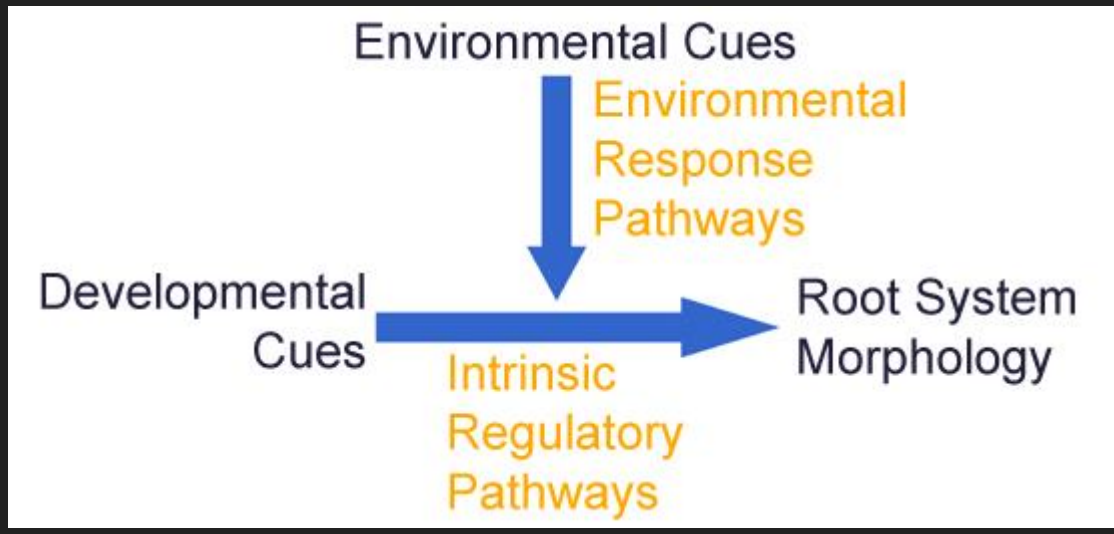
Young	Old
Learning is Easy	Learning is HARD!
Totally new abilities acquired (walking, talking..)	No new "tricks".
Most neural activity is Excitatory*	Most neural cell-cell messages are **Inhibitory**

*** Bavelier, & Hensch et al.. (2010). Removing brakes on adult brain plasticity: From molecular to behavioral interventions. Journal of Neuroscience,**

Experience and Neurodevelopment

- **Experience Dependent** Plasticity ~ Environmental input modulates.
  - Doesn't apply for all cortical circuits!
  - Different types, circuits, **periods**.
  - Depends on organism, even for the same senses ..

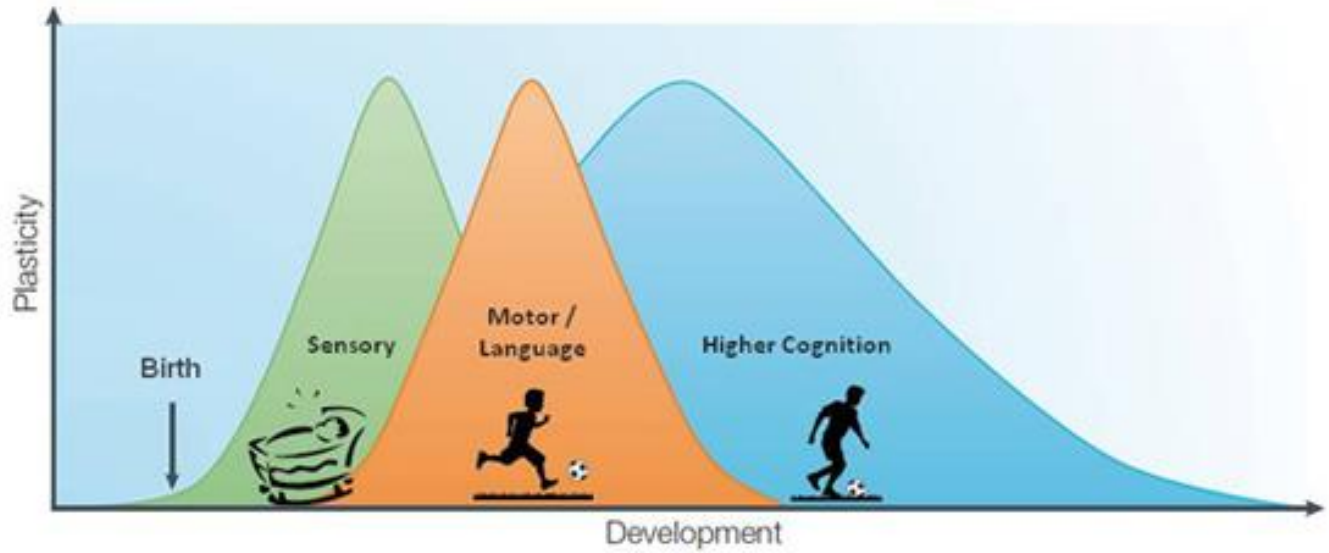
-> LET'S TALK *TIME*!



Sensitive periods

- Periods of increased sensitivity during development.
- Effects of experience are enhanced.
- **Quantitative Difference**

Fig 1: Windows of plasticity in brain development



Adapted from Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience, 6*(11), 877–888.

Sensitive periods (II)

Languages

$0 - 6+$ *Years*

Social Norms & behavior

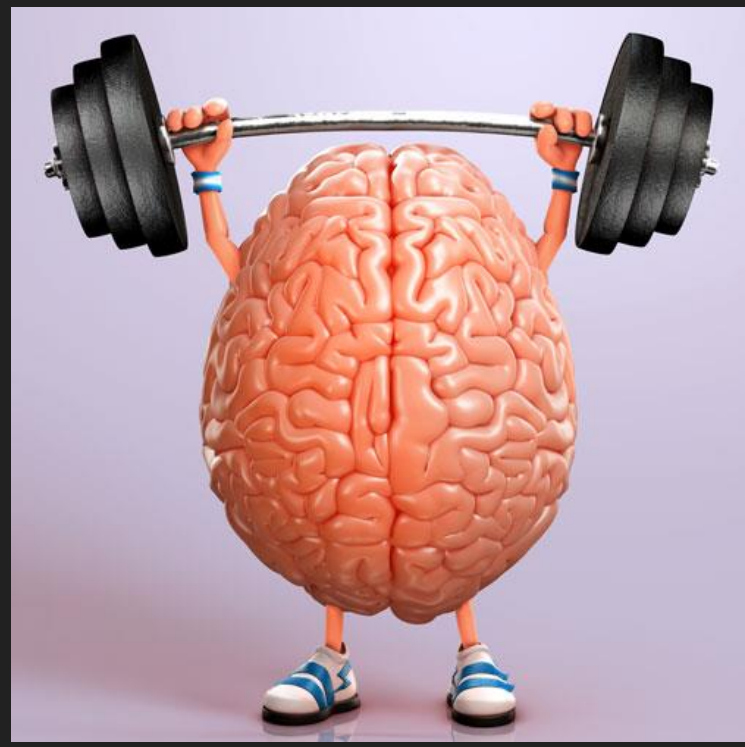
2.5 *Years* +

LeBlanc JJ, Fagiolini M. Autism: a "critical period" disorder? Neural Plast. 2011
Montessori, Maria (1949). *The Absorbent Mind*

Critical periods

A strict time window during which environmental experience provides information essential for a function's development and "fixates" it, permanently.

Qualitative Difference



CRITICAL PERIOD PLASTICITY IN LOCAL CORTICAL CIRCUITS. Hensch. NATURE REVIEWS NEUROSCIENCE. (2005)

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
…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 stereoacuity in acute-onset comitant esotropia
…transcription for induction of a late phase of LTP.
…regeneration capability of adult rat retinal ganglion cells after axotomy
..synaptogenesis
..experience-dependent synaptic plasticity in rat barrel cortex
..peripheral specification of dorsal root ganglion neurons

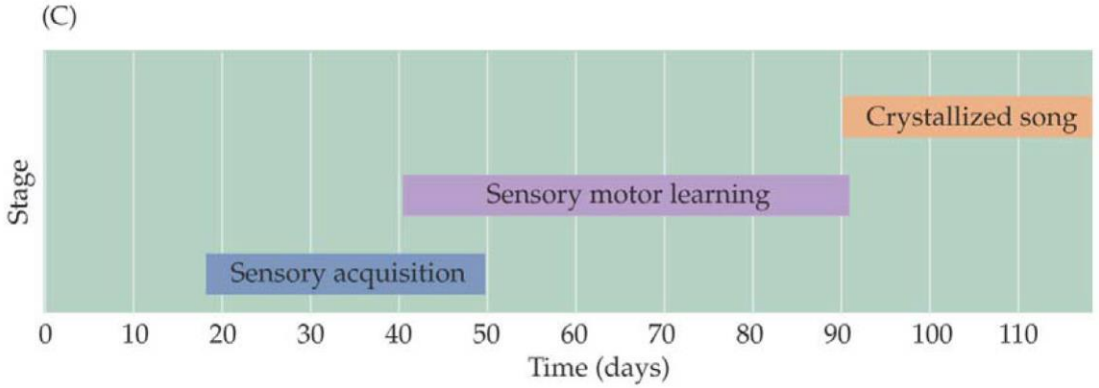
Critical period: Parental Imprinting

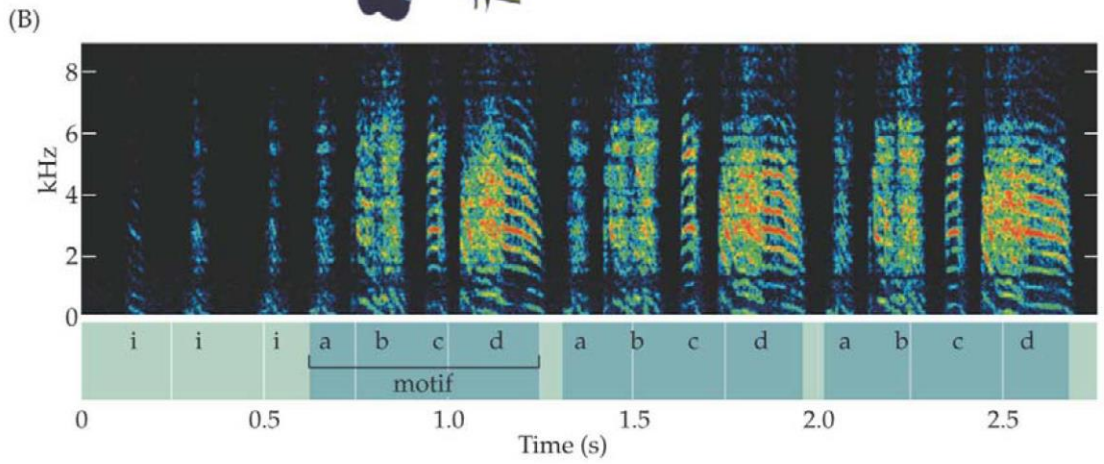
Critical Period for Song Acquisition

Selectivity for songs of own species.

In the lack of own species' song ….adaptation.

Critical period ends at puberty



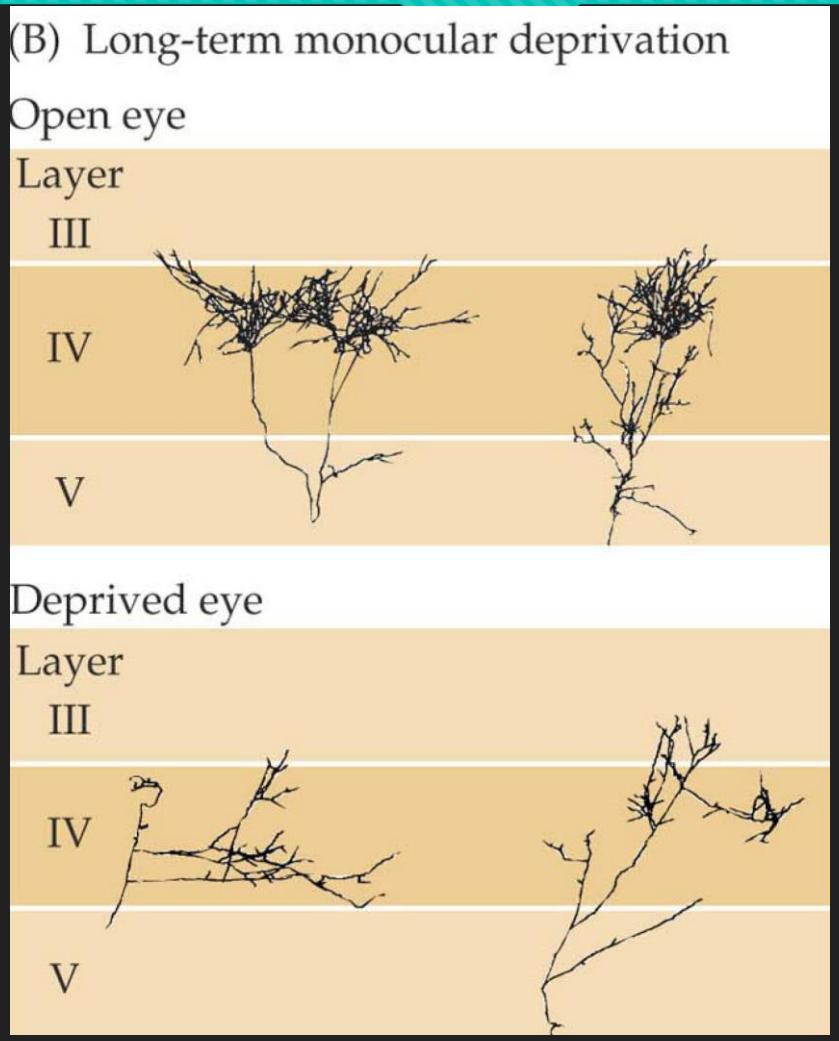


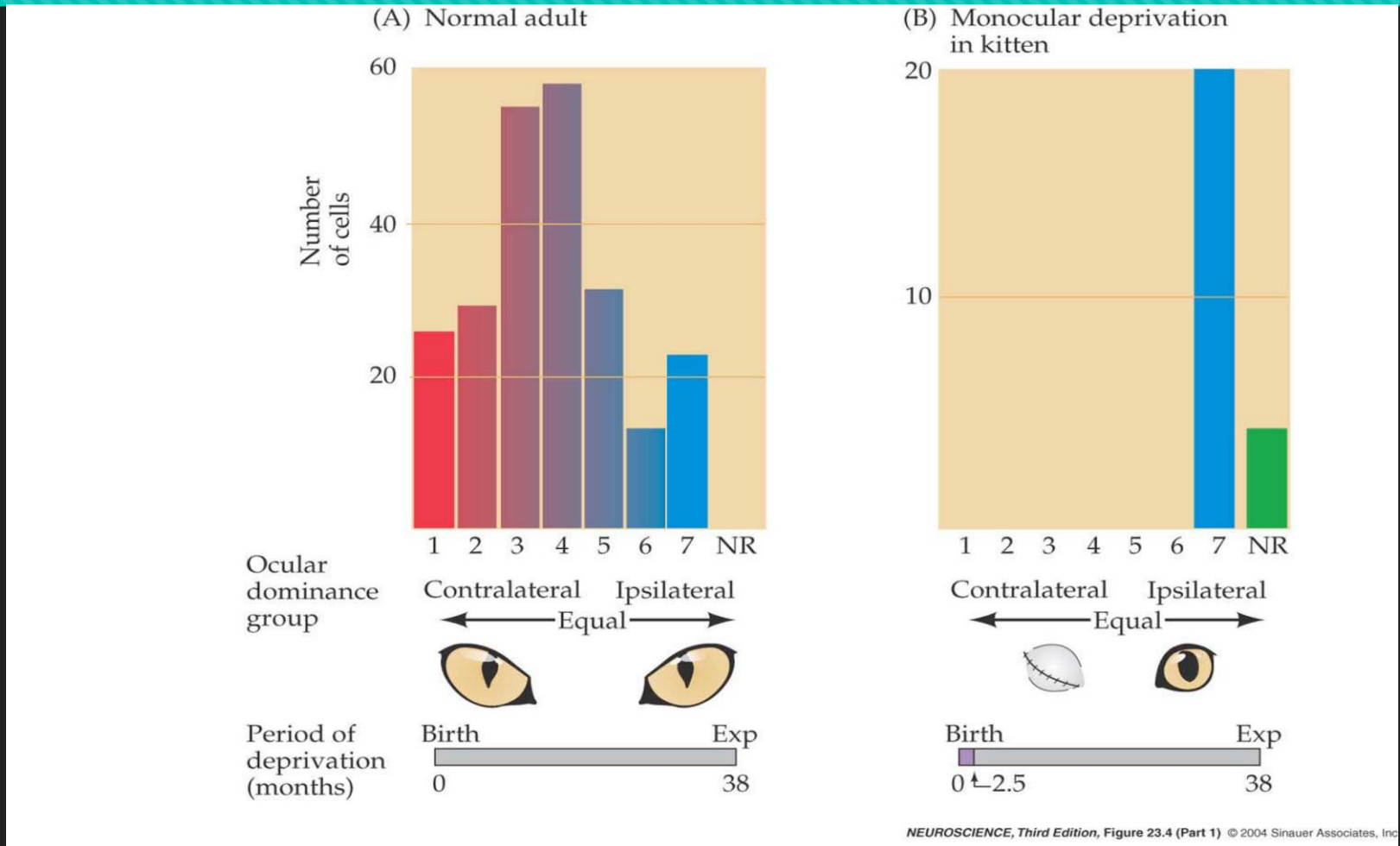
Critical period: ocular dominance monocular deprivation

- Hubel & Wiesel.
- Showed that ocular deprivation during CP causes monocular dominance, *Ambylopia*.
- Only during *critical period*.
- Common experimental system for critical period in visual system.

Wiesel, Hubel (1963). "Effects of visual deprivation on morphology and physiology of cell in the cat's lateral geniculate body". Journal of Neurophysiology

Critical period: ocular dominance



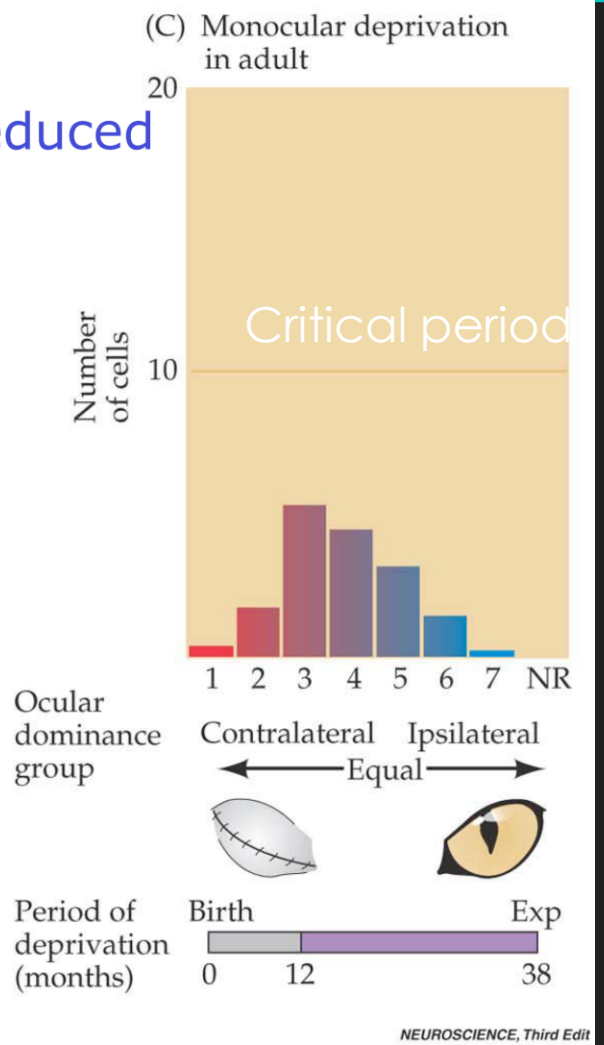


More cells in cortex become monocular

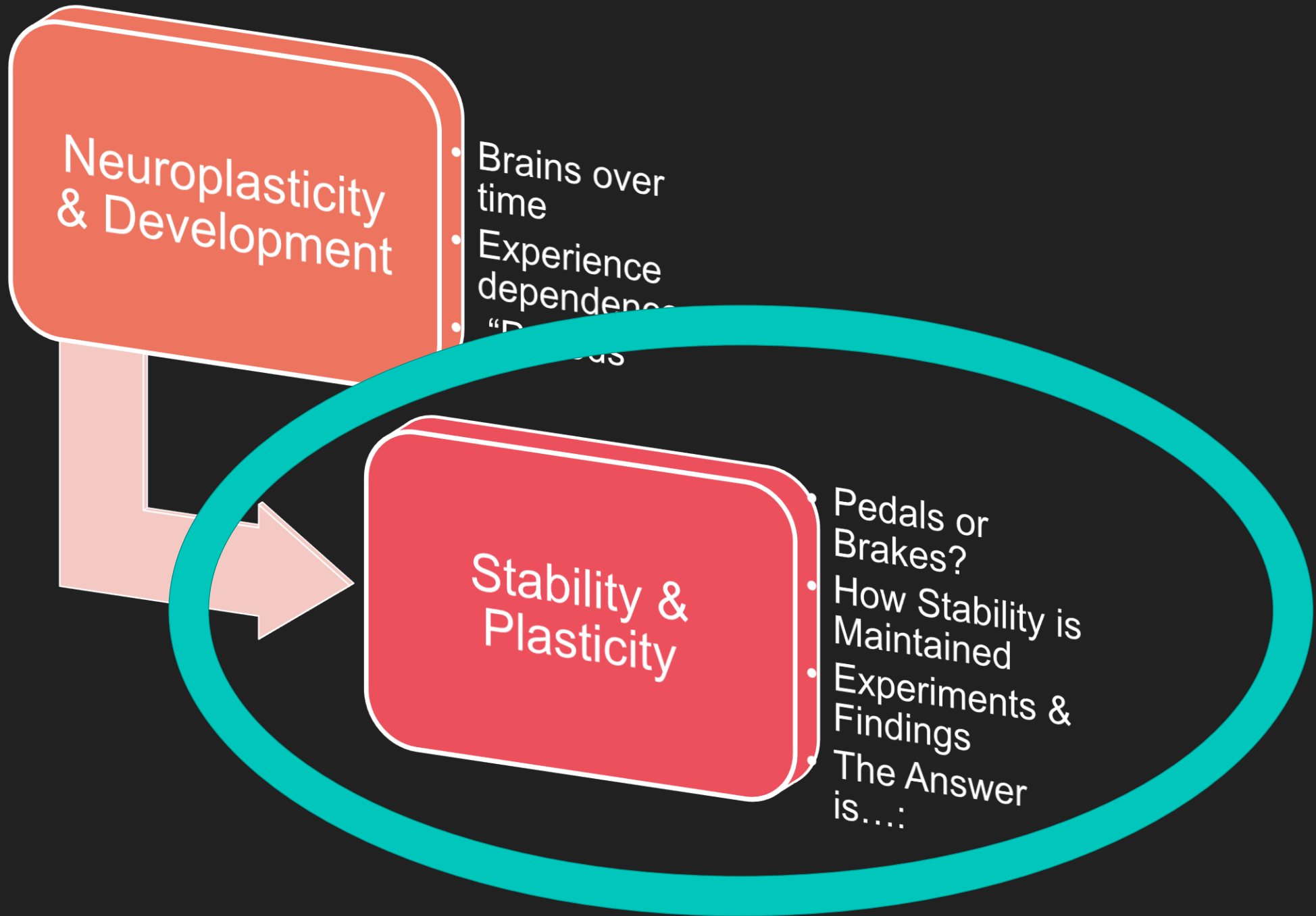
Critical period: ocular dominance

Can this be just an outcome of reduced activity from one eye?

No. Monocular deprivation in the adult does not change the physiology or the anatomy.



- Only during *critical period*.
- Common experimental system (for critical period).


Neuroplasticity & Development
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How Stability is Maintained
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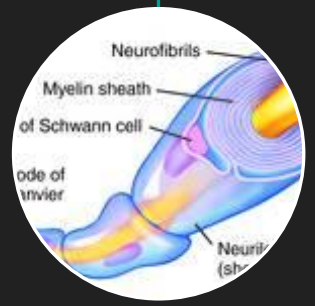
The Answer is…:

Questions:

- What is the "default" state of plasticity in the brain?
  - Plastic or stable?
- What are the factors that control or regulate cortical plasticity?
  - State "maintenance".
  - Switching between states.
- Could we make adult brains pliable & plastic?

(I) Structural Stabilization:



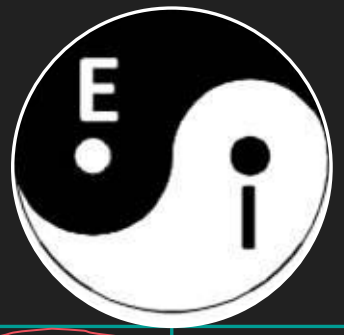
Myelinization

Glia, Astrocytes

Perineuronal nets.
Parvalbumin Interneurons

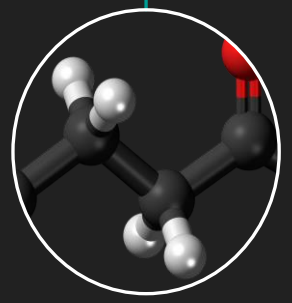
Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. Science. (2005).
Bavelier, Hensch, et'. Removing Brakes on Adult Brain Plasticity: From Molecular to Behavioral Interventions. J. Neuroscience (2010).
Bardin, J. Neurodevelopment: unlocking the brain. *Nature* **487**, 24–6 (2012).
Hensch. Critical period plasticity in local cortical circuits. *Nat. Rev. Neurosci.* (2005).

(II) Functional Stabilization:



Excitation

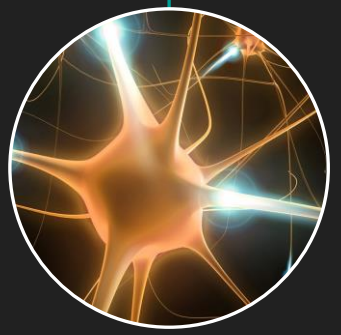
Inhibiton



GABA

Inhibitory.
Required for Crit. P!

LYNX1



More:
HDAC..

Functional Inhibition: GABA

Inhibitory threshold for critical-period activation in primary visual cortex

Michela Fagiolini & Takao K. Hensch

Laboratory for Neuronal Circuit Development, Brain Science Institute RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan

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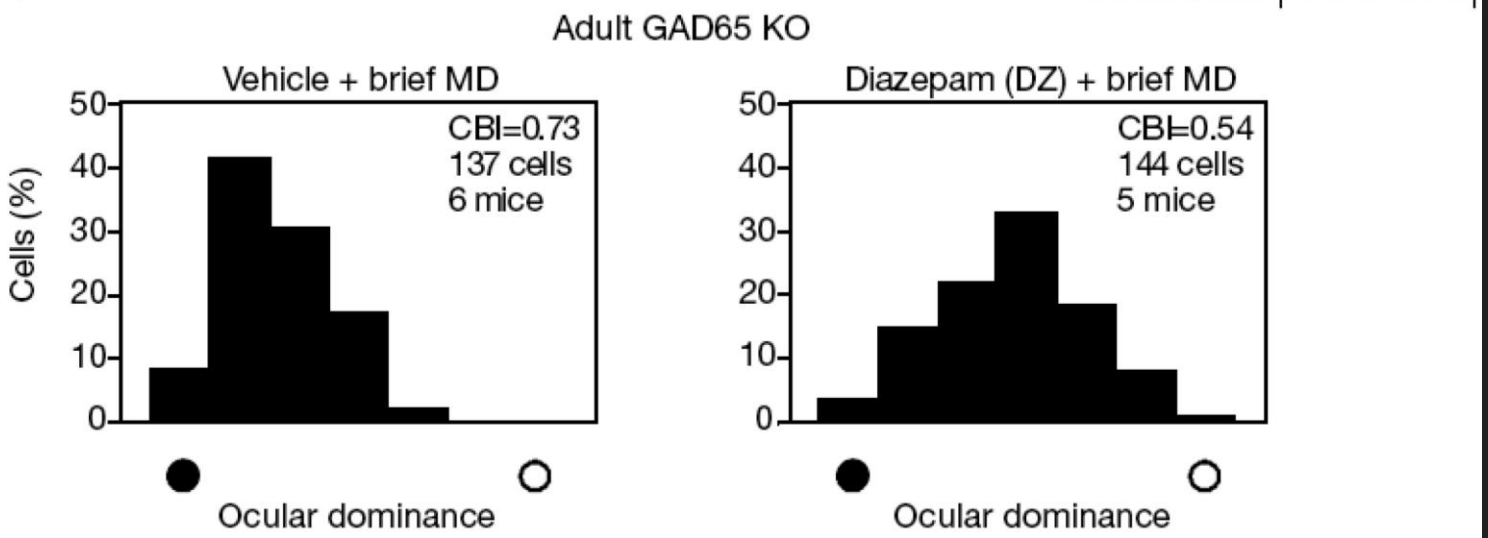


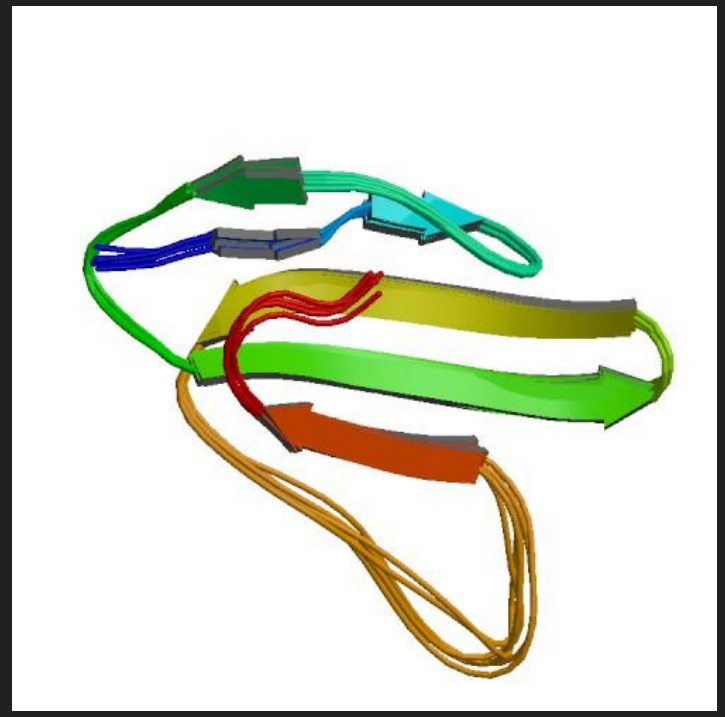
Result: When GABA is reduced, CP doesn't start. When GABA is replaced, CP starts.

Conclusion: GABA is necessary for initiation of CP.

- GABA = Inhibitory NT.
- GABA is required for Critical Period (CP), and GABAergic activity initiates CP.
- BUT! GABA +- cannot Reopen CP in adult.

Diazepam /Valium -> + GABA

Lynx1 brakes Plasticity in the Adult Cortex



Acetylcholine Antagonist.

- Binds to Ach receptors.
- ToLIP (Toxin Like Protein)

Morishita, Hensch, et al'. "Lynx1, a cholinergic brake, limits plasticity in adult visual cortex". *Science* (2010).
"Lynx for braking plasticity". *Science* (2010).

Lynx1 brakes Plasticity in the Adult Cortex

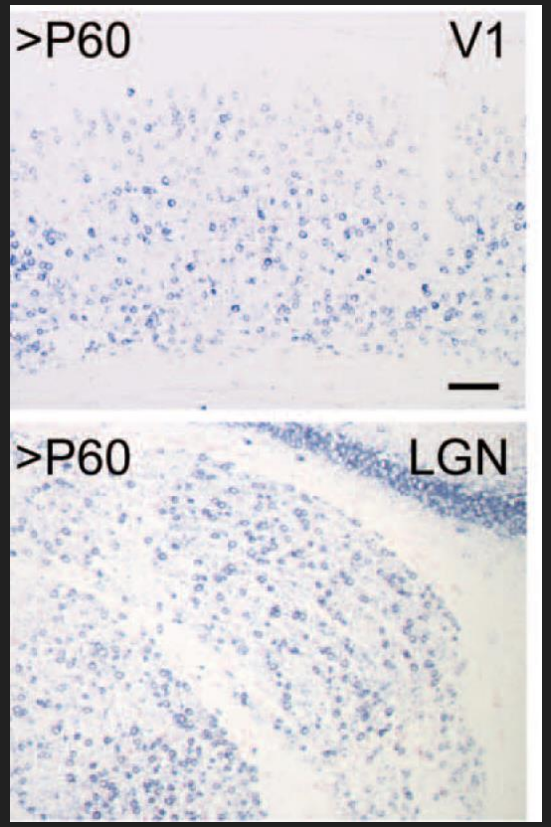
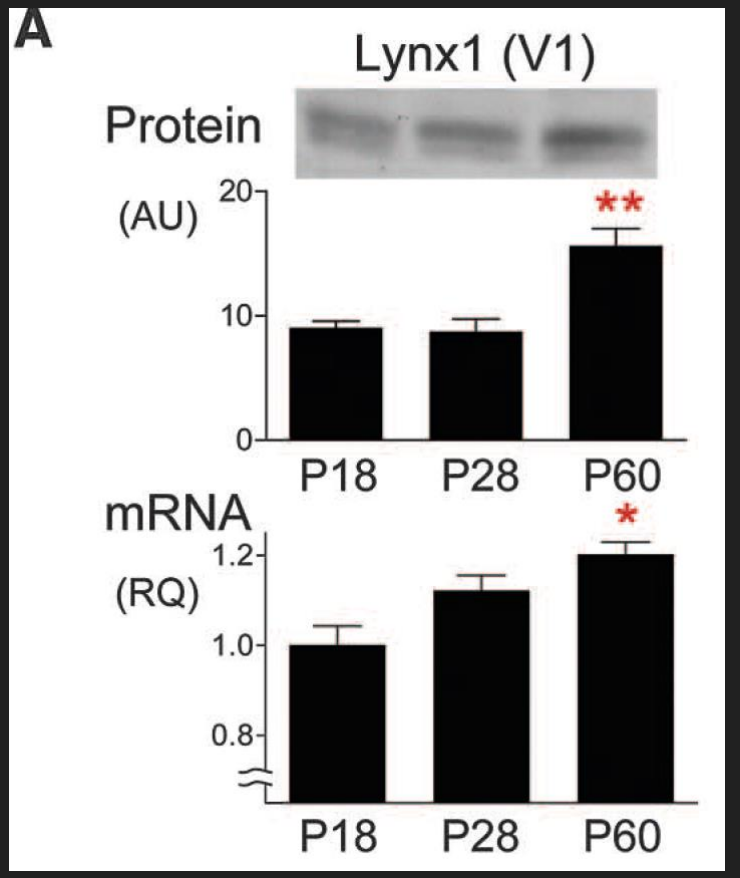


Fig. 1. Lynx1 expression increases in adulthood to limit visual plasticity. (**A**) Expression of Lynx1 protein (top) and mRNA (bottom) across the critical period (CP) (pre-CP: P18; CP: P28; post-CP: P60). $^{**}P < 0.01$, $^{*}P < 0.05$, one-way analysis of variance.



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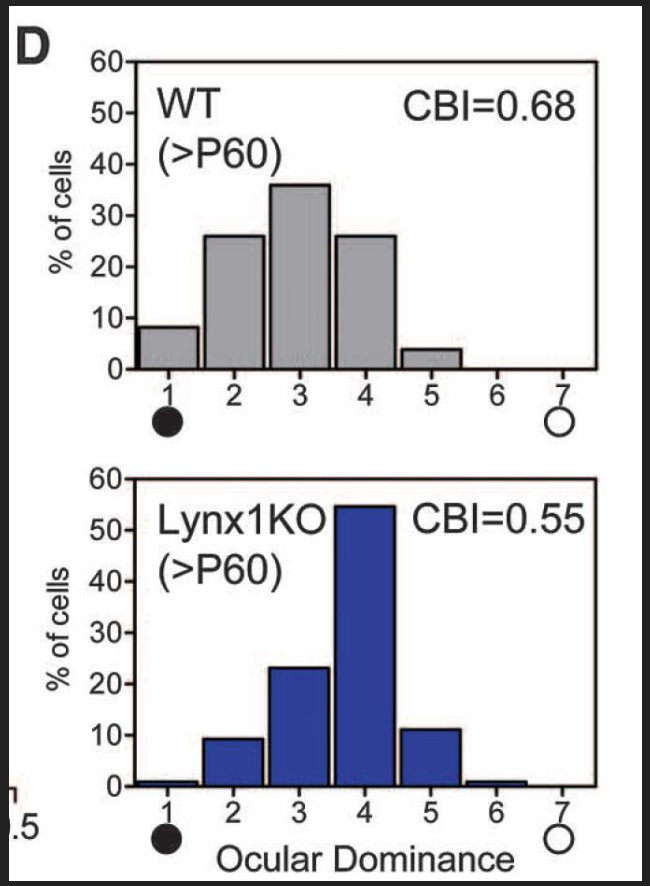
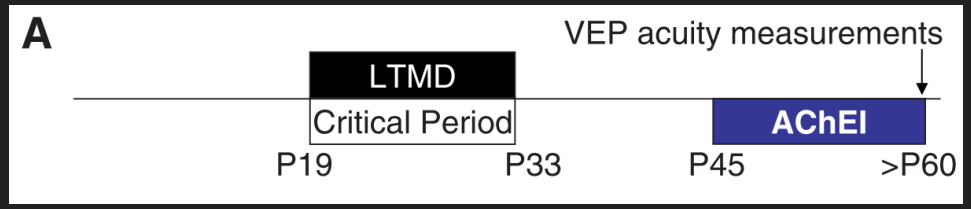
Lynx1 brakes Plasticity in the Adult Cortex

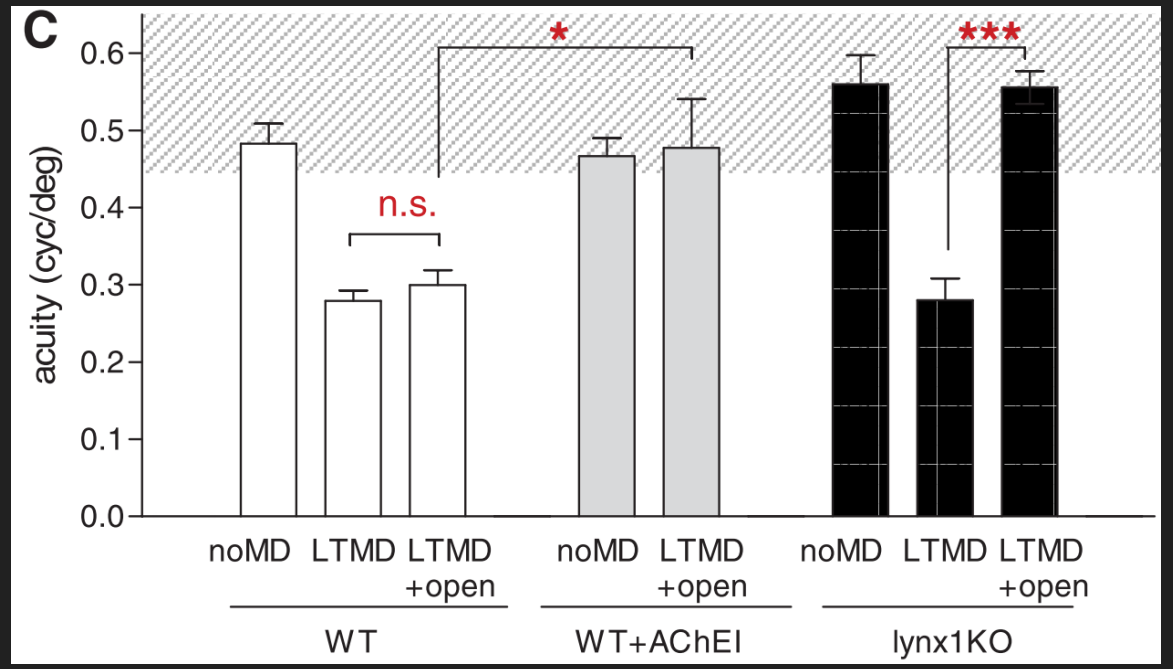


(D) Short-Term Monocular Deprivation shifts the ocular dominance distribution of Lynx1 knock-out (KO) mice [bottom], but not in wild-type (WT) mice.

Lynx1 KO reopens Critical Period Plasticity in the Adult visual Cortex

Fig. 3. Recovery from amblyopia in Lynx1 KO mice.
(A) After long-term MD (LTMD) spanning the critical period, the deprived eye was reopened & VEP (visual evoked potential) acuity was measured in V1.
(C)Visual acuity in WT mice (white) without deprivation [no MD] decreases after LTMD spanning CP and endures. Reopening the deprived eye together with Ach inhibitor (AChEI) restores vision.
Lynx1 KO mice (black bars) spontaneously recover from LTMD simply by reopening the deprived eye to reach normal levels.

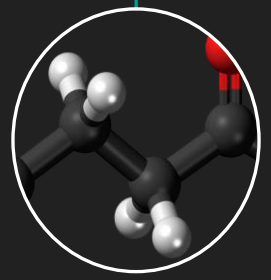




Functional Stabilization:

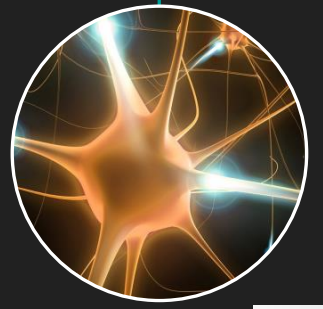
Excitation

Inhibiton



GABA

LYNX1



More Factors:

(**HDAC** – Histone-Deacetylase..)

Conclusions:

- Default state is plastic, not stable.
- Stable state is maintained by molecular brakes. (Lynx1, others).
- E/I ratio important to critical period "timer" activation.
- Don't confuse Critical and Sensitive periods!

- Many more factors to discover?
- MASSIVE clinical potential.

See You Next Time!