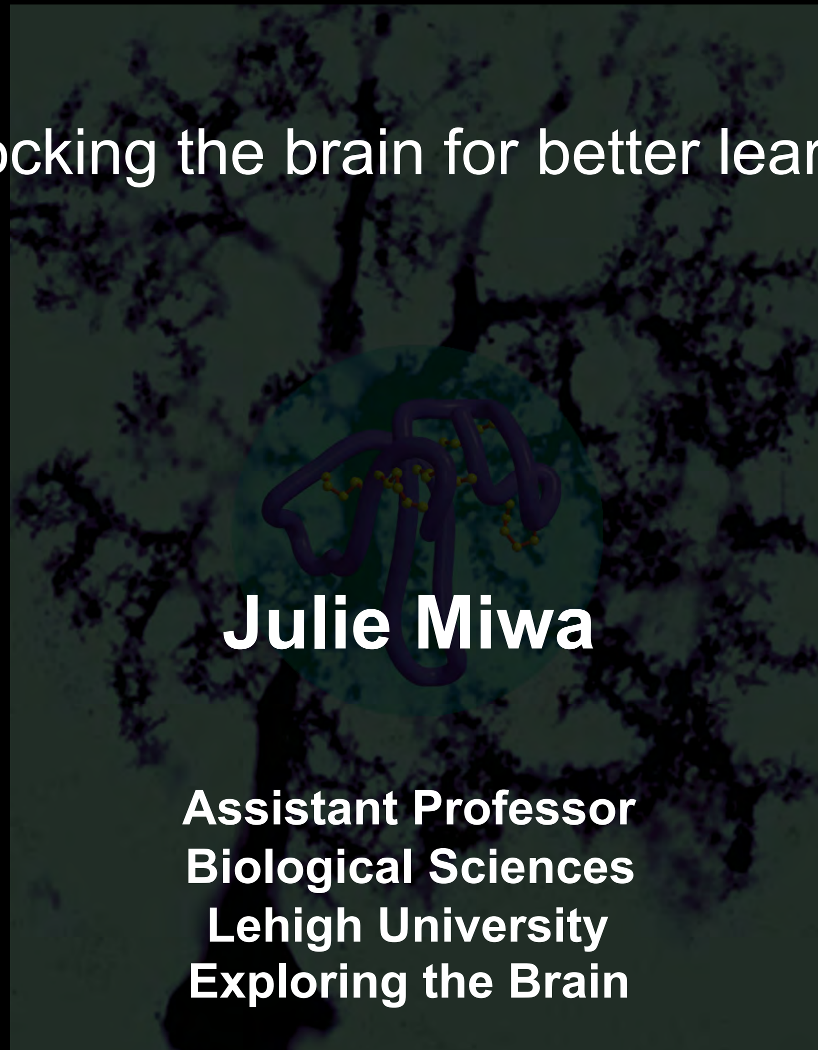
Unlocking the brain for better learning



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Exploring the Brain

November 4th, 2013

Our ability to learn changes with age

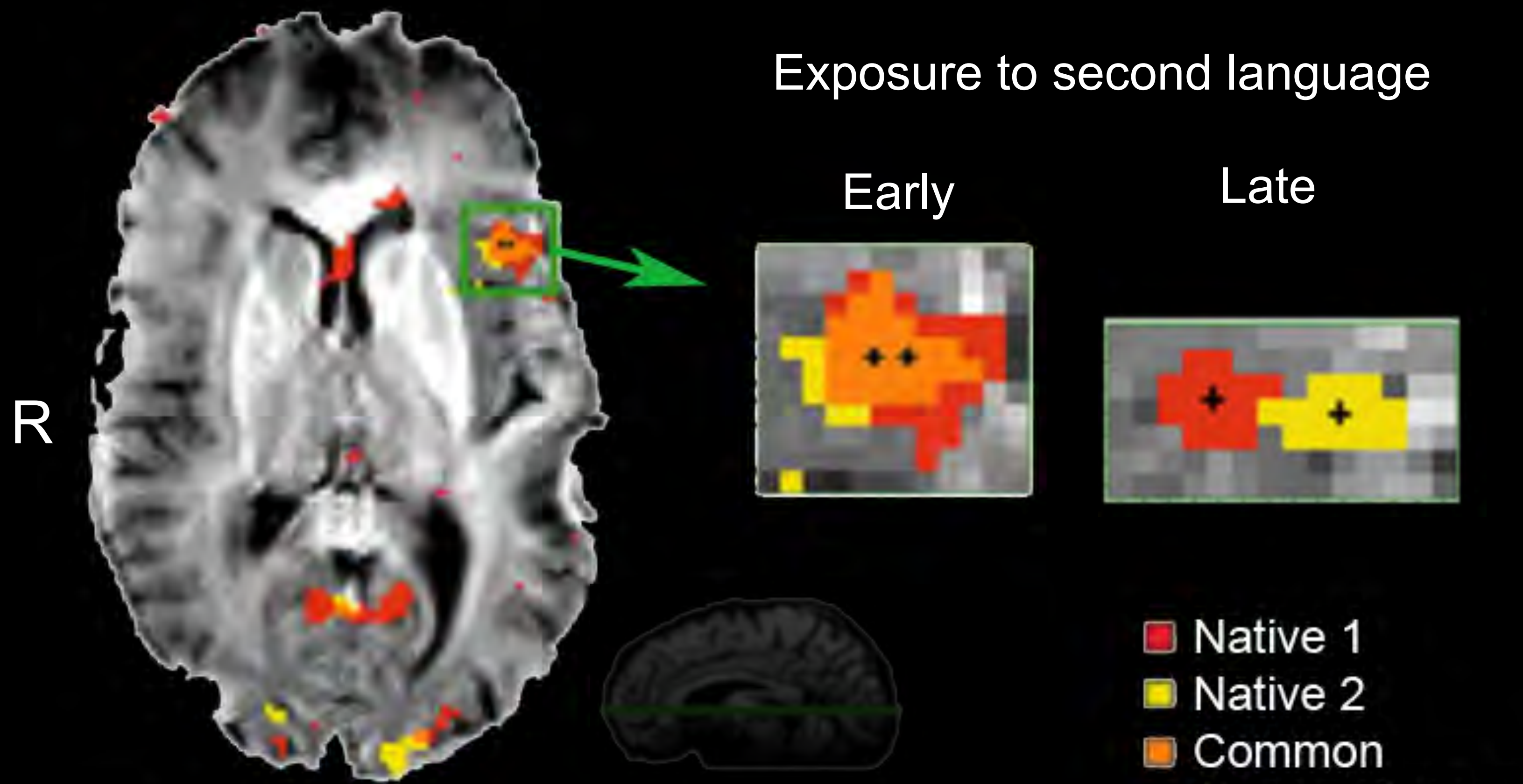
Example: language

Later in life we can learn language, but it is harder and we might retain an accent

The brain changes as it ages

Younger brains are more adaptable to new information- they have greater plasticity

Language Center “Broca’s area” activity in bilingual people



Kim, Relkin, Lee, Hirsch, Nature, 1997

Cortical Reorganization

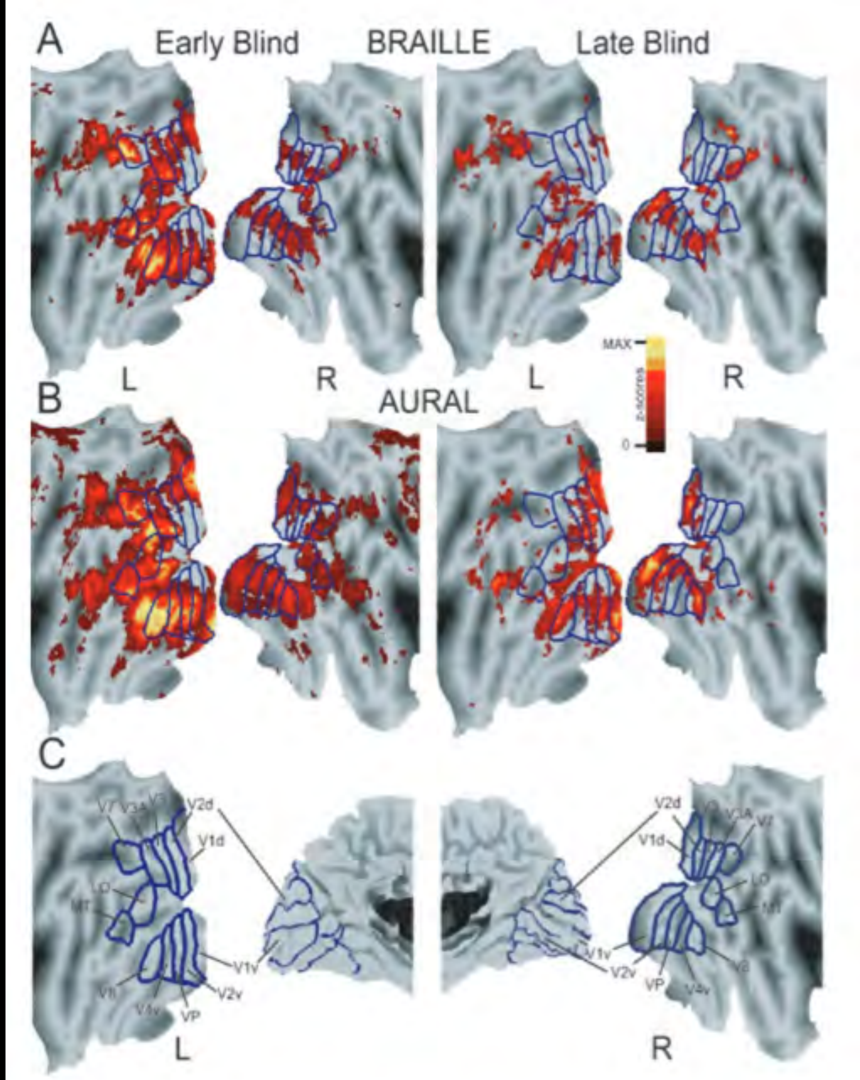


Figure 1. Two-dimensional, flattened views of *z*-score statistical parameter maps for visual cortex BOLD responses in early and late blind subjects. Maps in *A* and *B* were obtained, respectively, when subjects generated verbs to Braille read or heard nouns. A

Visual Cortex Activity in Early and Late Blind People

The Journal of Neuroscience, May 15, 2003, 23(10):4005–4011 -4005

fMRI

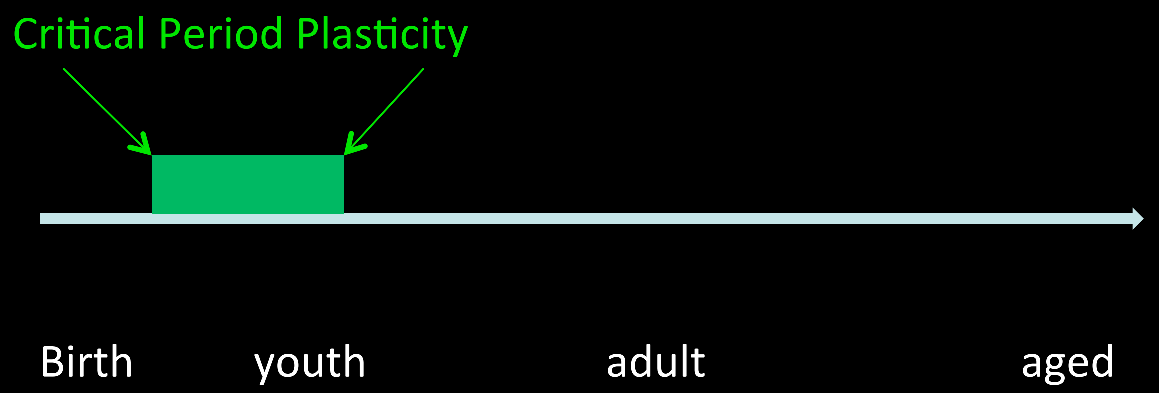
Physical changes occur in our brain as we age

The brain gets wired by early experiences

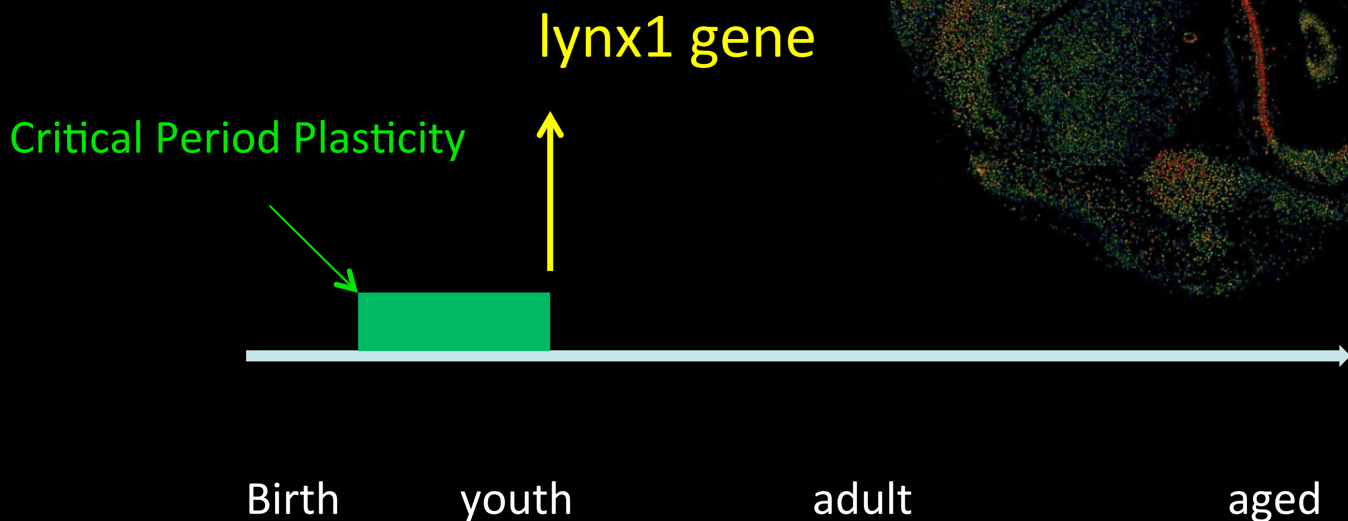
Different regions/functions have different sensitive periods

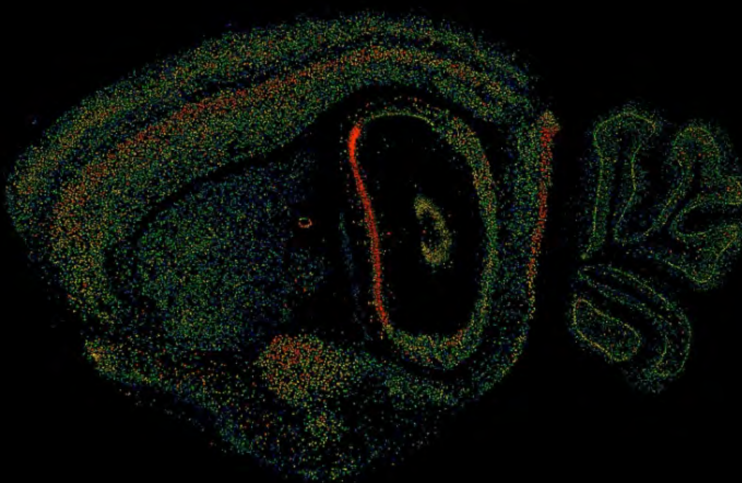
How does this happen?

It has been known that the sensitive period for robust plasticity – the "critical period closes", but the mechanism for this is unknown



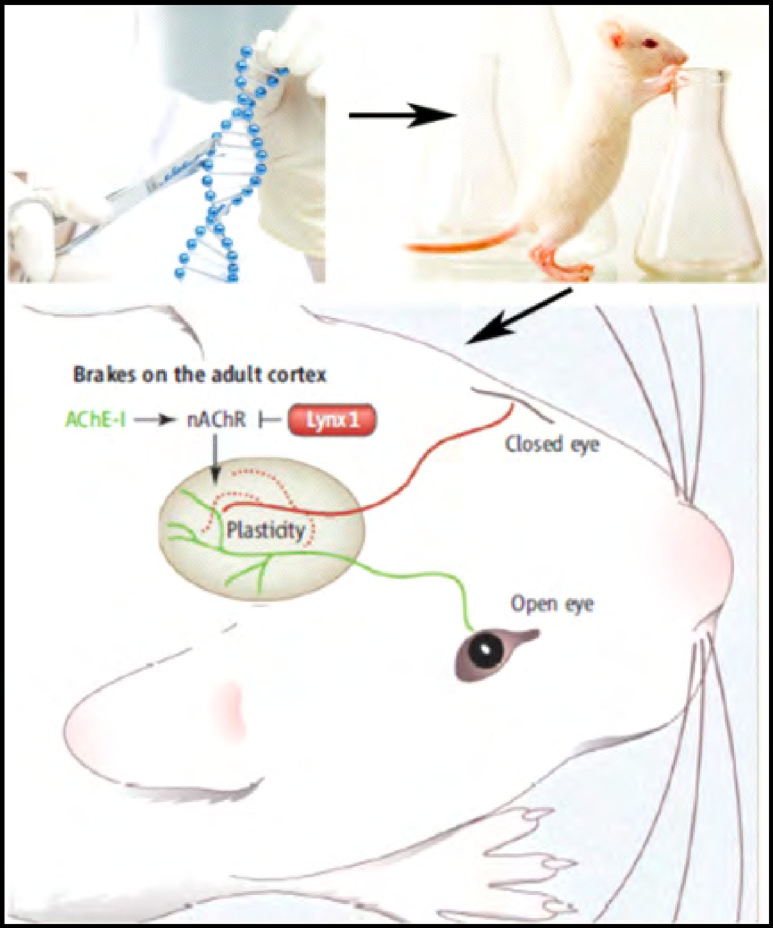
The lynx1 gene, discovered as a graduate student, up-regulates at the closing of the Critical Period in the visual cortex of mice





P19-P33 in mice

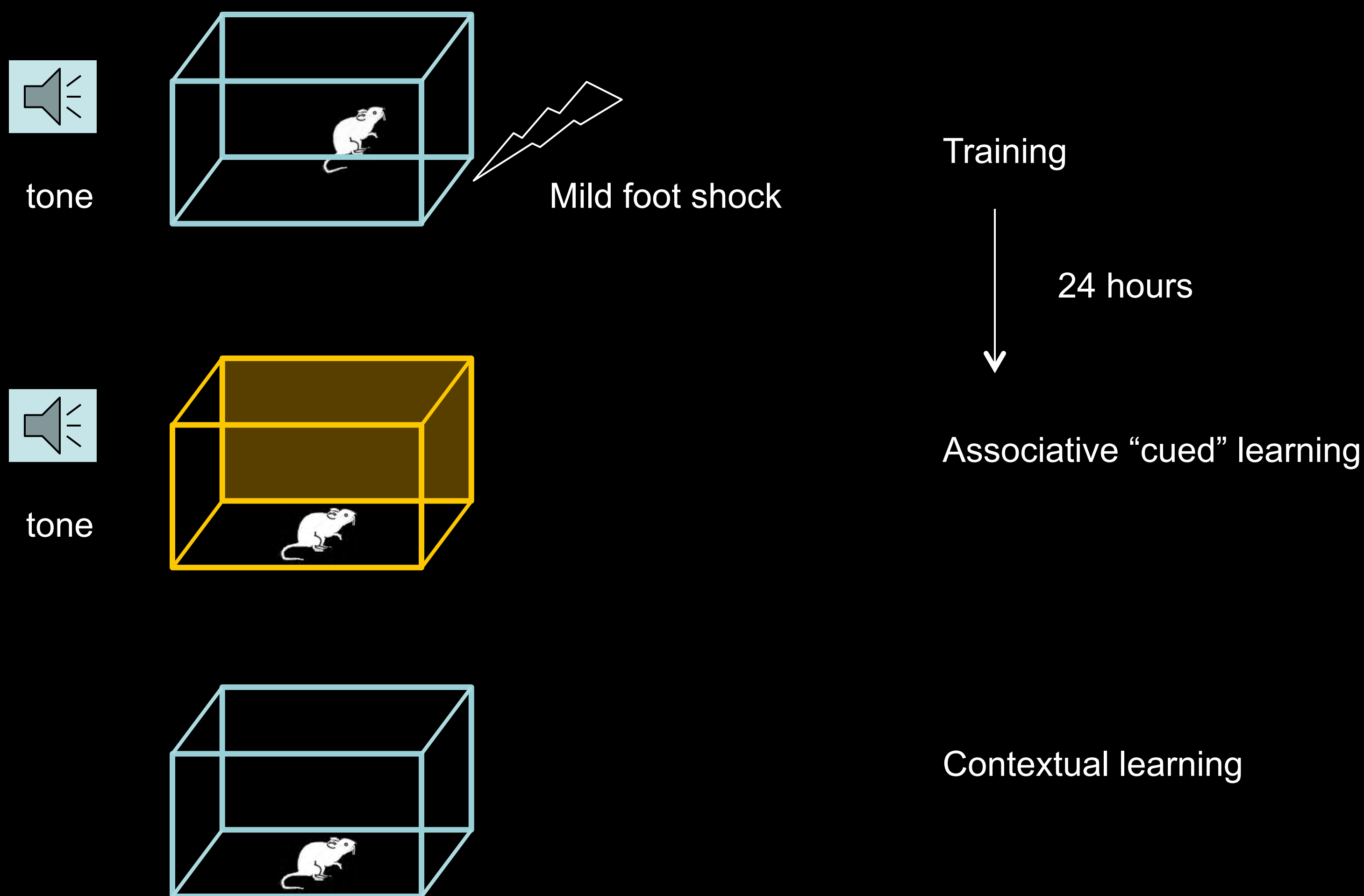
I removed the lynx1 gene through genetic engineering…



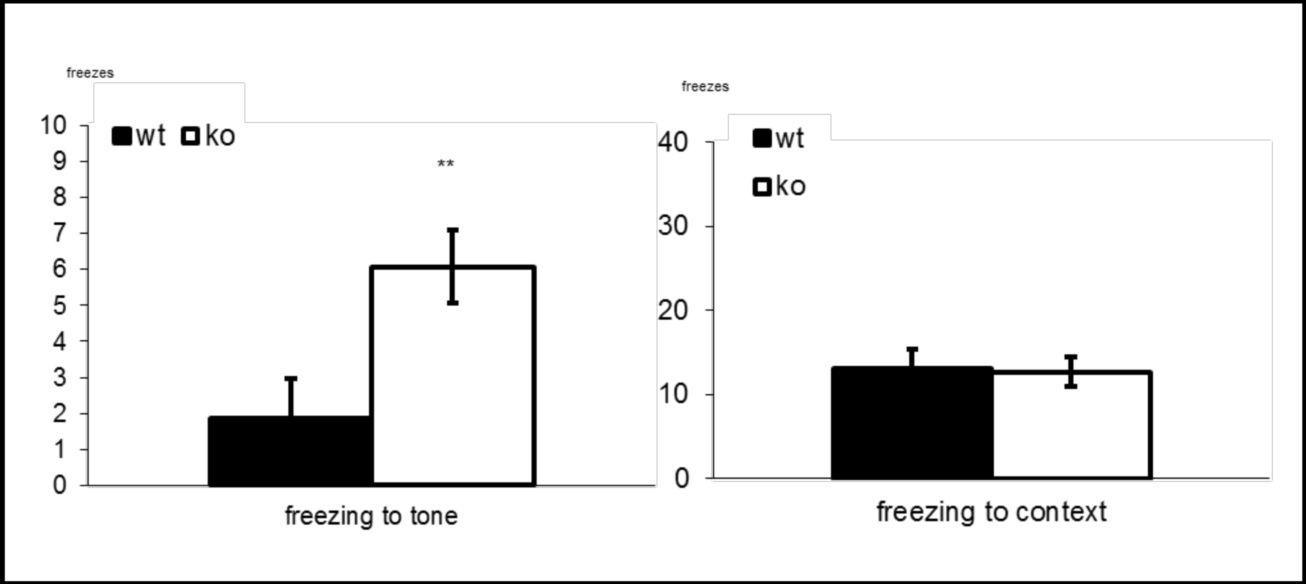
Creating lynx1KO mice

Morishita, Miwa, Heintz, Hensch, Science, 2010
Higgins, Science, (2010)

Classical Fear Conditioning (Associative Learning)



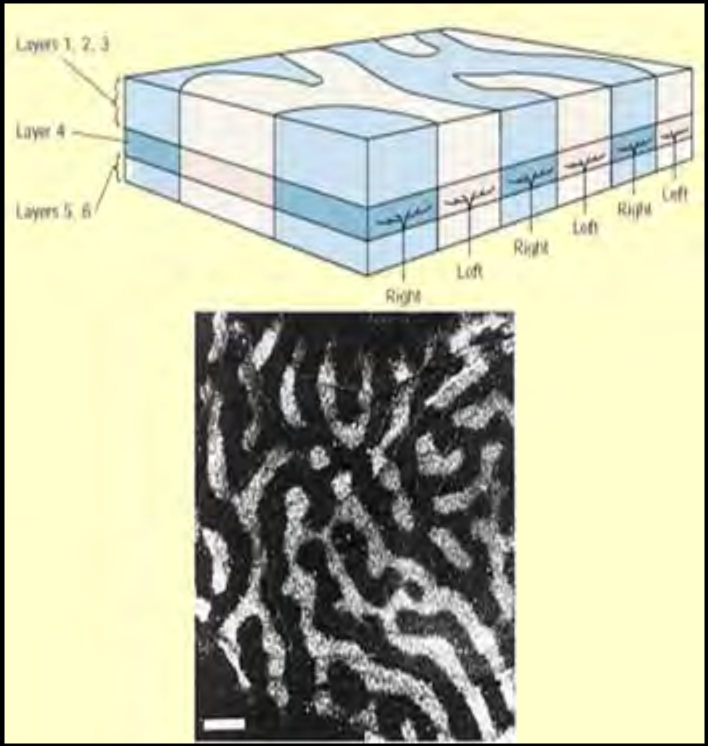
Improved Learning By Increased Cholinergic Tone



lynx1KO mice exhibit enhanced **associative** learning

Miwa et al, 51, Neuron, 2006

Another animal study- Critical Period plasticity



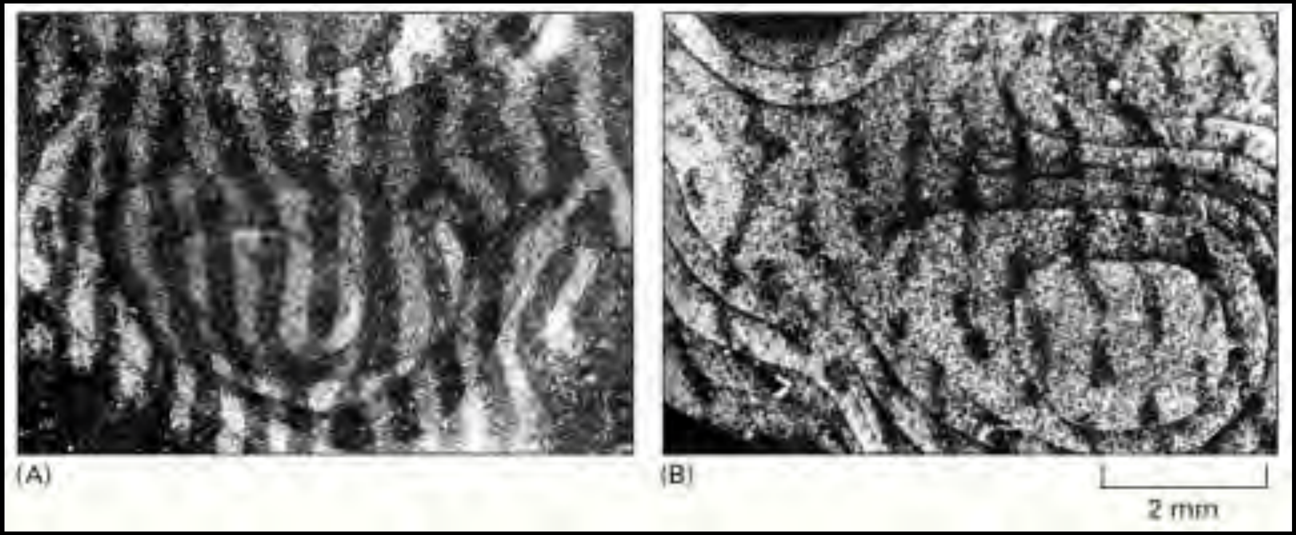
Monkey visual cortex

The visual cortex gets input from two eyes

Each eye goes to one column in the visual cortex, creating a banded pattern (right/left)

Input from two eyes compete for cortical territory in the visual cortex

Critical Period Plasticity

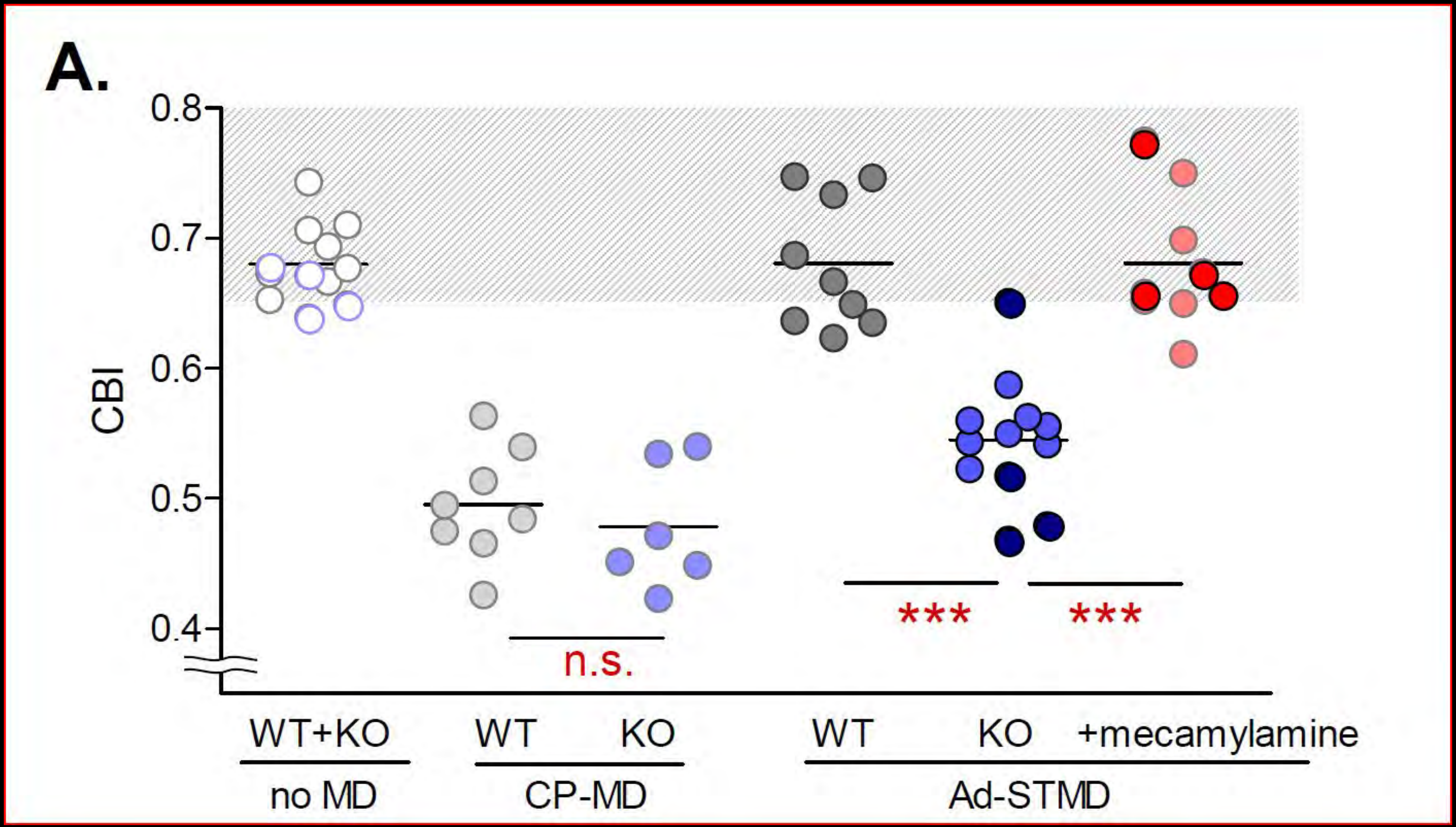


If you close one eye, monocular deprivation (MD), the cortical territory receiving more light input will expand

If you don't correct cross-eyes early in humans (one eye loses the competition), you can lose depth perception

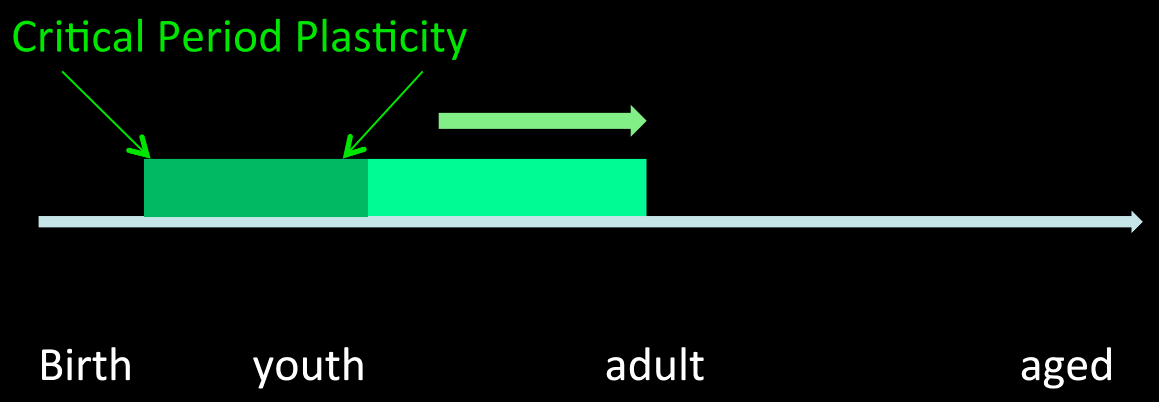
David Hubel and Torsten Wiesel received the Nobel prize for this work in 1981

The robust plasticity of the critical period was extended past the normal time frame.



P19-P33 in mice

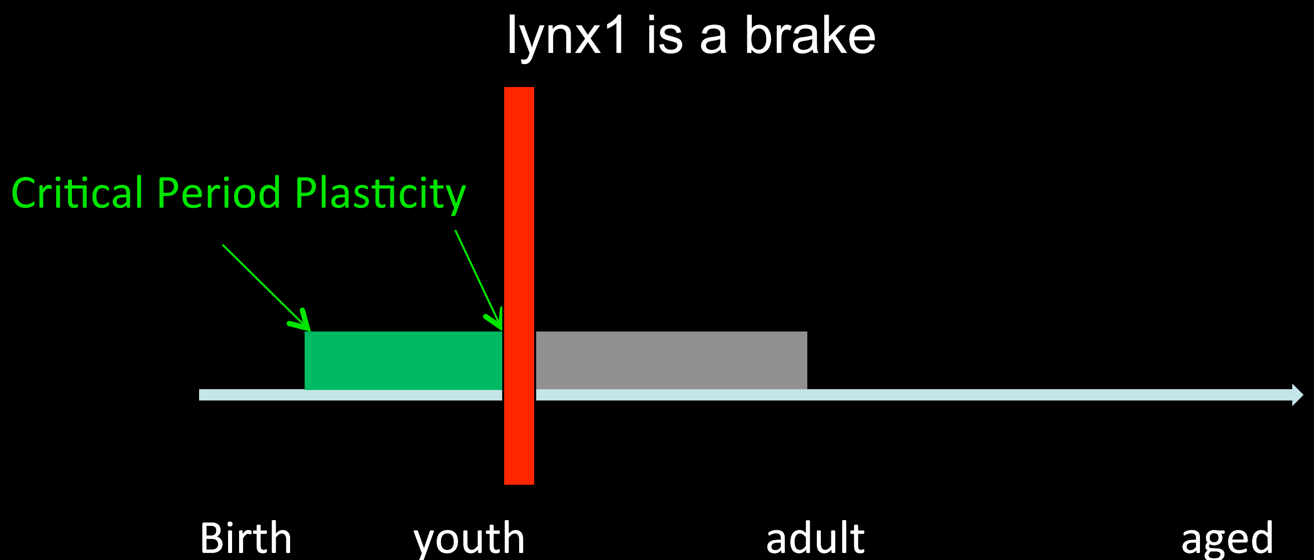
Morishita, Miwa, Heintz, Hensch, Science, (2010) The robust plasticity of the critical period was extended past the normal time frame.



Morishita, Miwa, Heintz, Hensch, Science, (2010)

P19-P33 in mice

This showed that the lynx1 gene acts as a molecular brake on Critical Period plasticity

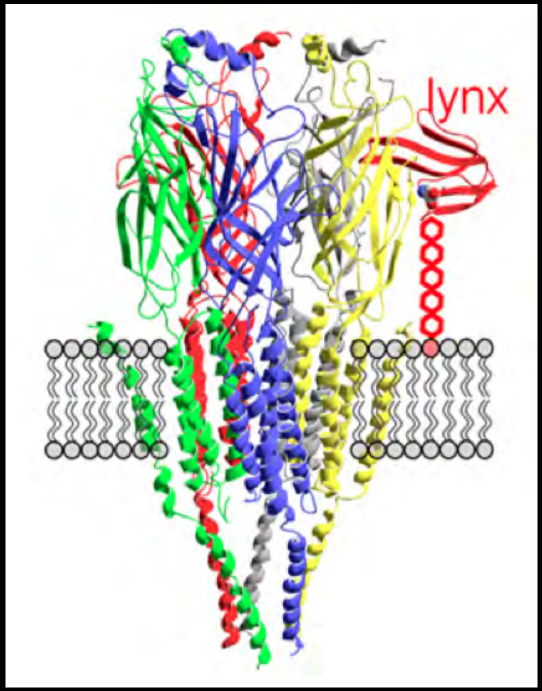


P19-P33 in mice

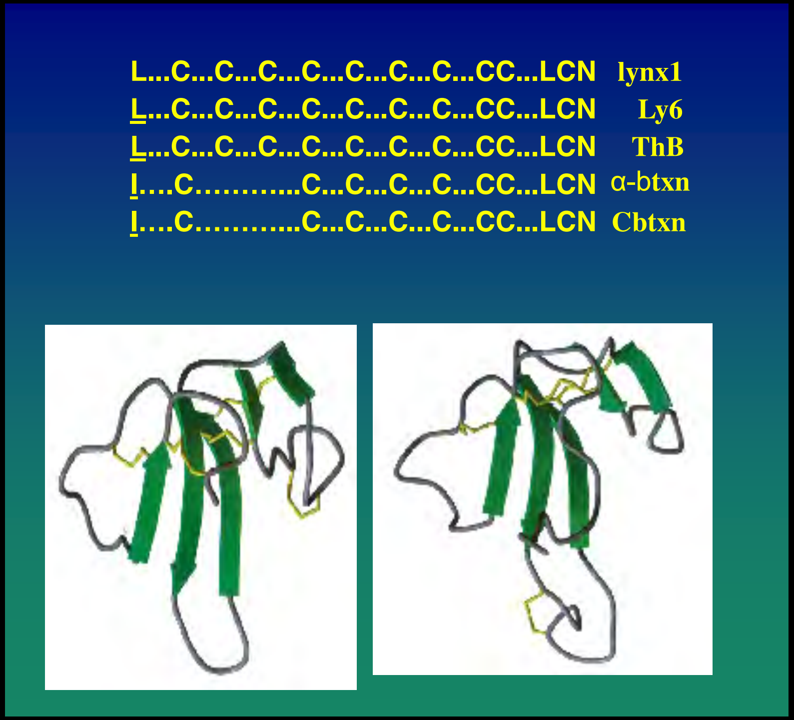
How does lynx suppress learning?

Lynx1 binds nicotinic receptors of the cholinergic system

Lynx1 is similar to snake toxin proteins, which bind on muscle and inhibit



Miwa et al., 70, Neuron 2011



Miwa et al., 23, Neuron 1999

Lynx1 modulates the cholinergic system

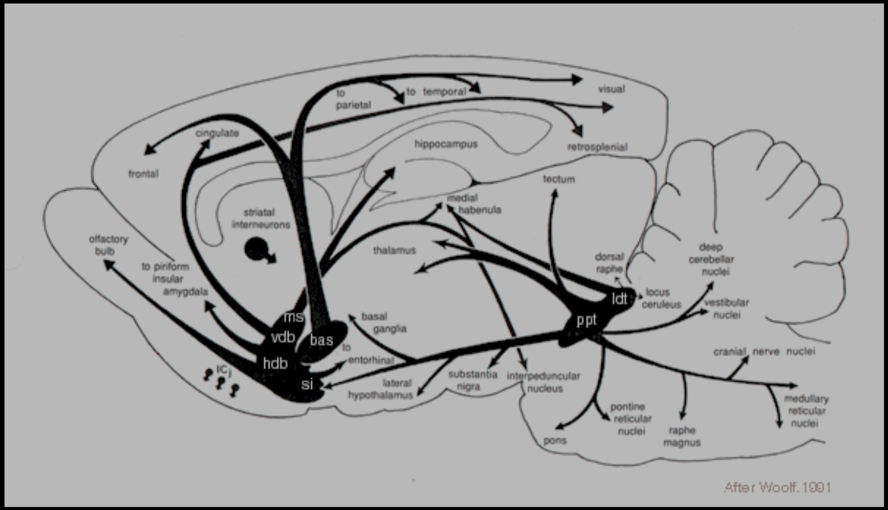
cholinergic neurons

- •localized discretely
- •project widely
- •release the neurotransmitter acetylcholine diffusely

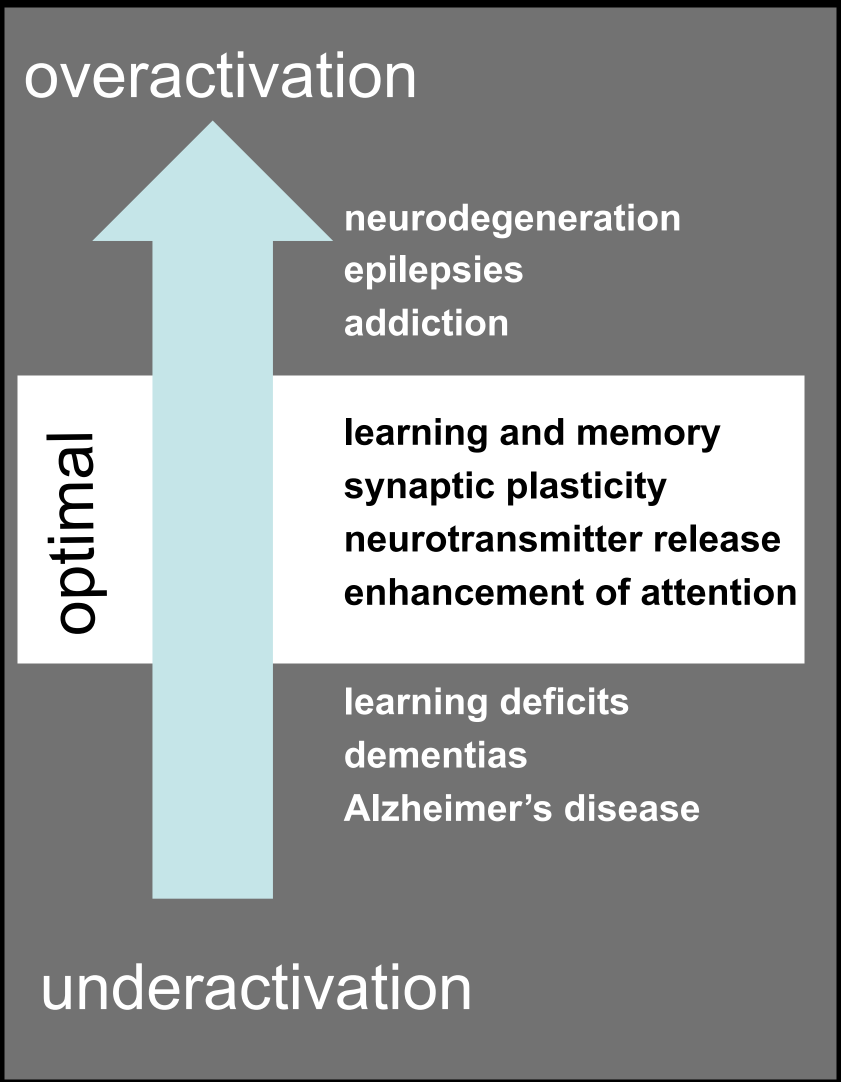
•The cholinergic system can raise brain excitability

The cholinergic system contributes to learning

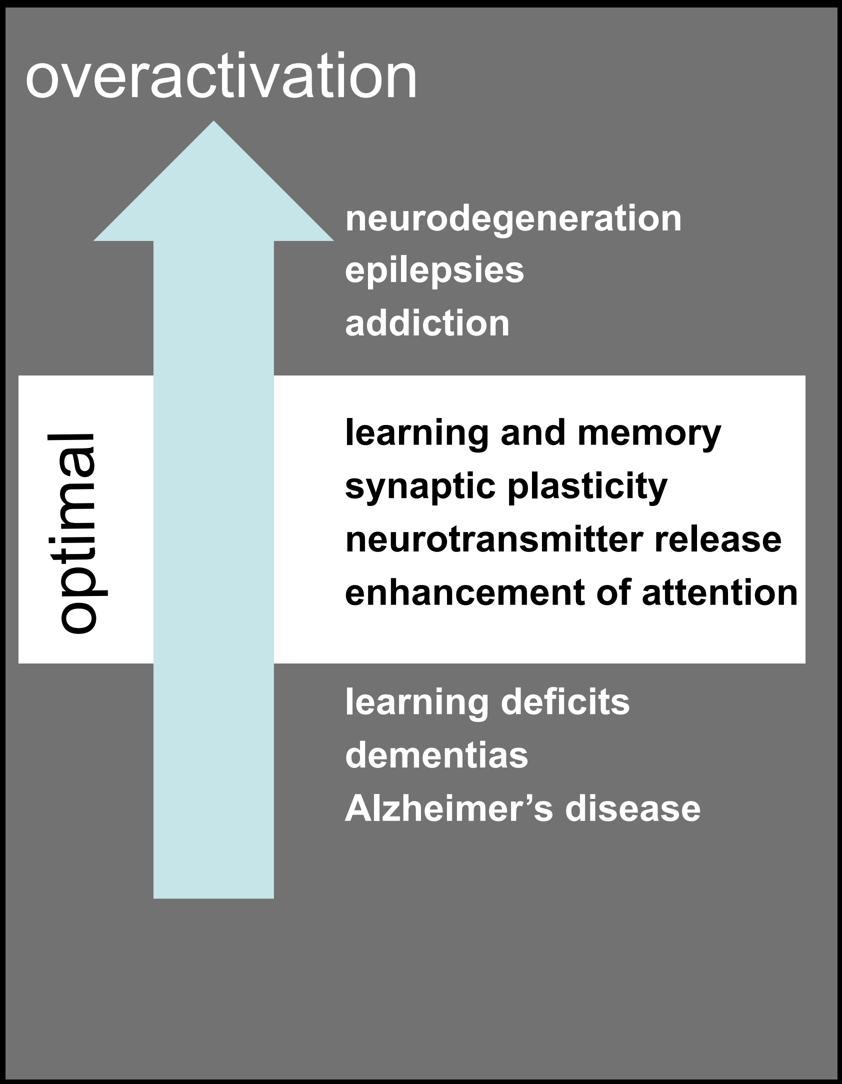
It operates on a gradient of activation



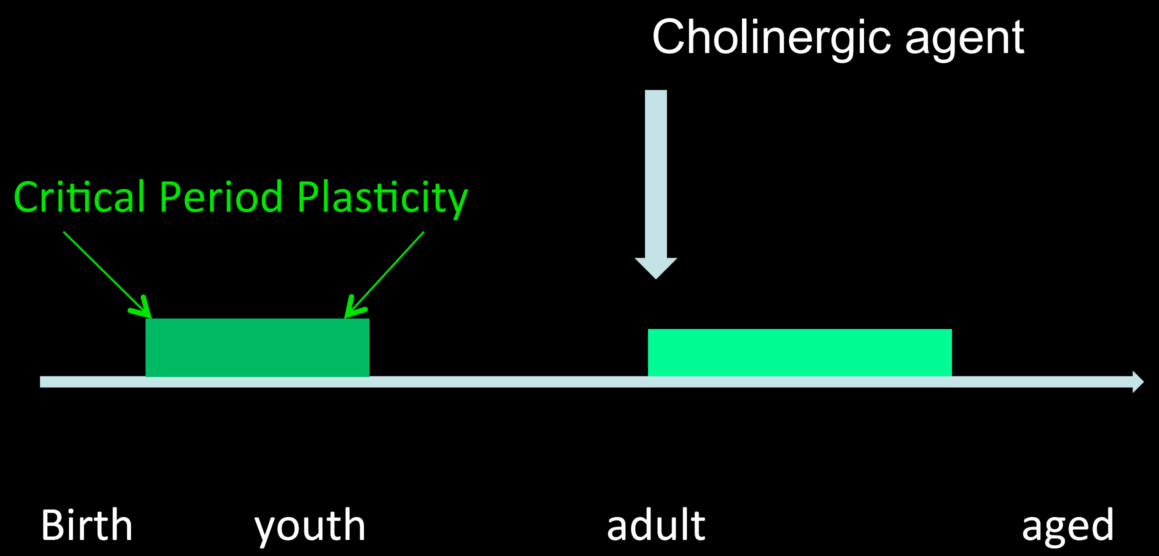
Optimized Cholinergic Tone



We can also raise cholinergic tone through pharmacology



Cholinergic agents that raise cholinergic tone can lead to enhanced critical period plasticity in normal adult mice



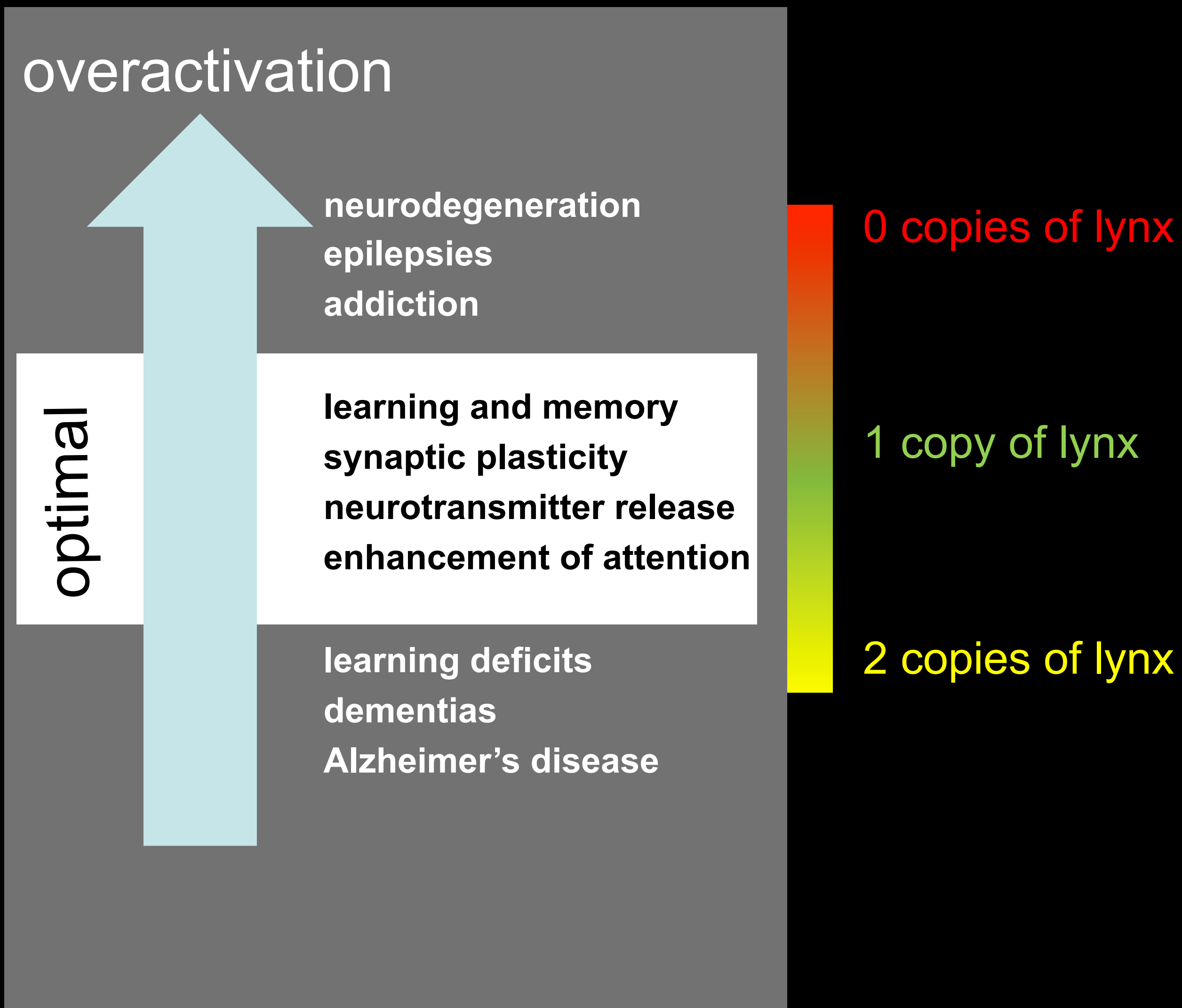
P19-P33 in mice

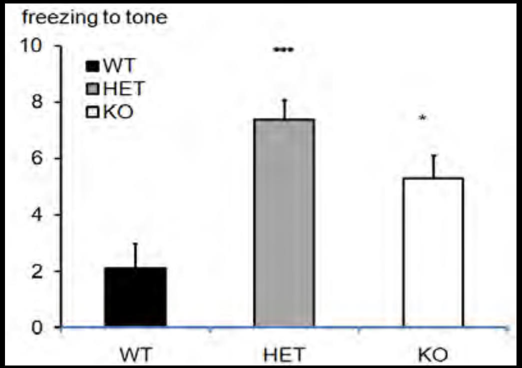
This demonstrates that the mechanisms for robust plasticity are still present in the adult brain

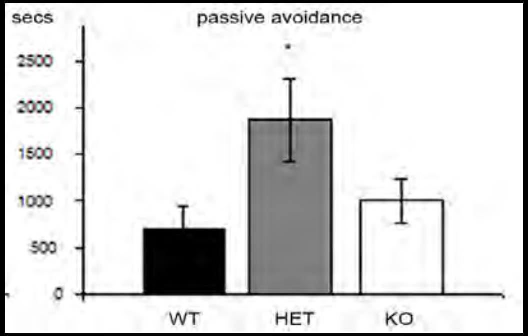
Cholinergic activation mediates this plasticity

BUT, that plasticity is suppressed by the presence of lynx modulators

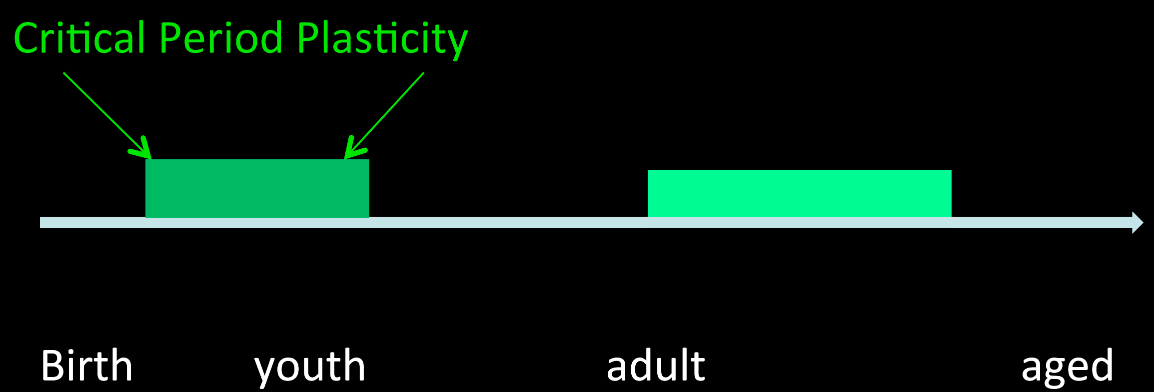
We can also raise cholinergic tone through lynx dosage







Question: Can we remove the brake (lynx1) and recapture youthful plasticity in humans?



P19-P33 in mice

WHAT

What therapeutic advantages can we achieve if so?

Language learning in stroke

Learning deficits in dementias (Alzheimer’s disease)

Traumatic brain injury

HOW

How could we manipulate the lynx1 gene or lynx1 protein for learning benefits?

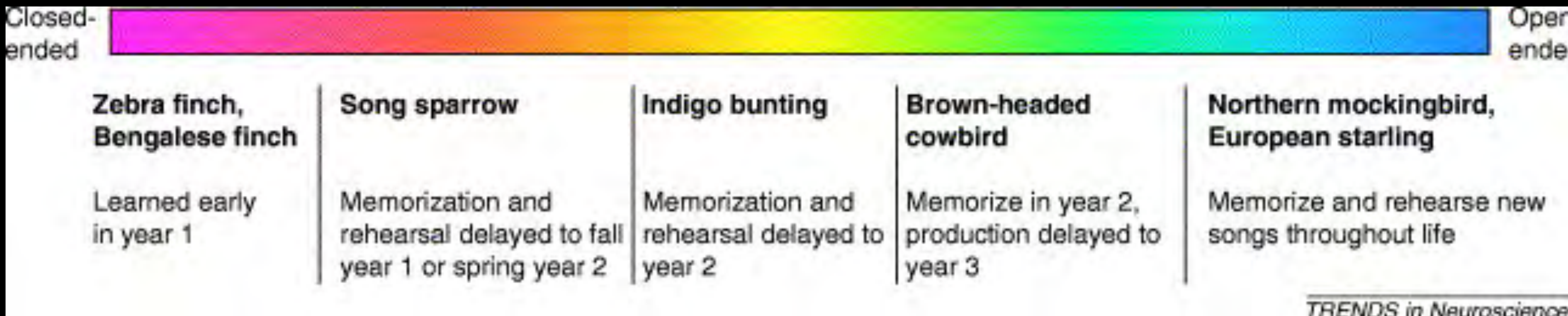
Further genetic manipulation- let animal grow up normally, and remove the lynx1 gene in adulthood

Environmental manipulations of lynx1 (Miwa et al., Physiology, 2012)

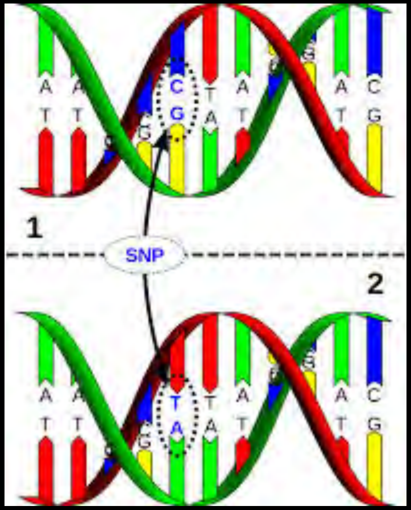
Individual variation in the lynx1 gene in the natural population

Closed ended learners

Open ended learners

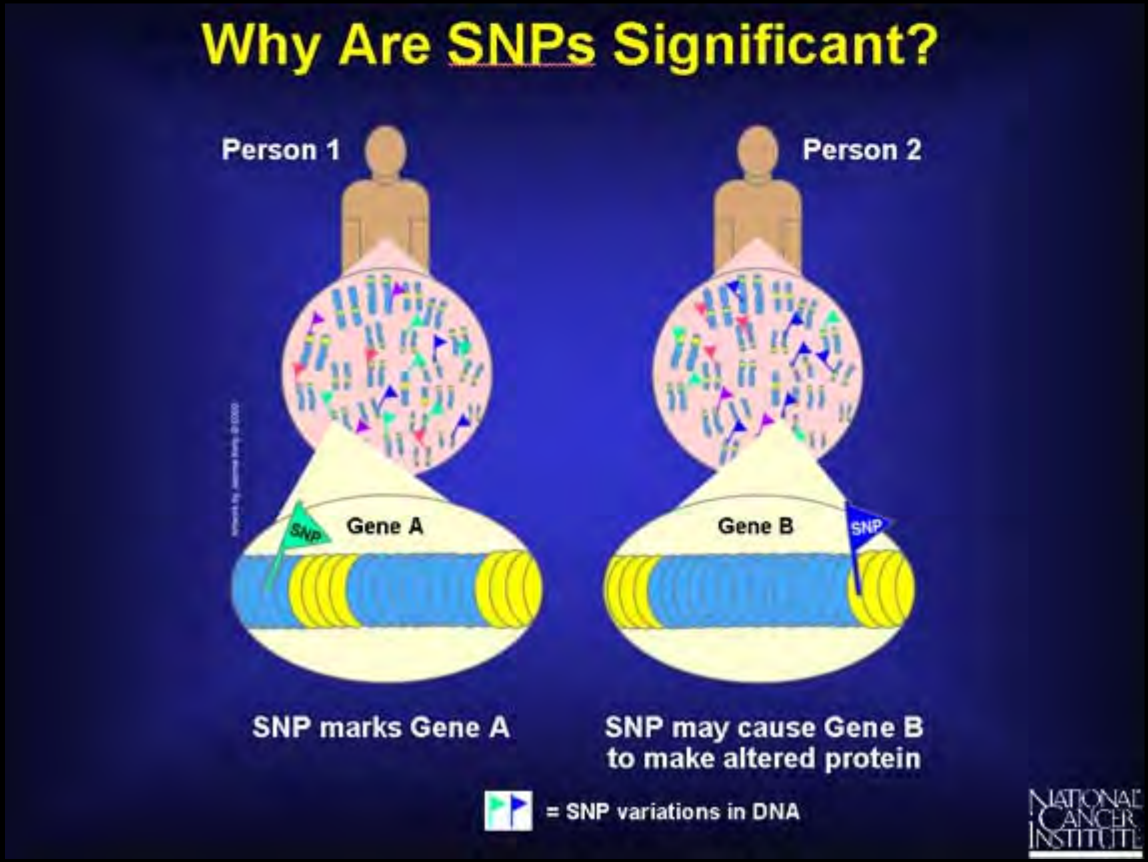


What is a SNP? Single Nucleotide Polymorphism



Sequence differences at a defined place in the person's gene
Many are scattered throughout many genes (the genome)
These are inherited mutations
They can exist in the population at different frequencies (1-49%)
They are used in forensic science to identify individuals (DNA fingerprinting)

expression levels (amount of protein)



Regulation (turn the gene on/ off more readily)

the amino acid sequence (protein function)

What if one SNP sequence made the lynx protein less effective?

Have better cognitive flexibility?

GACTTA

GAGTTA

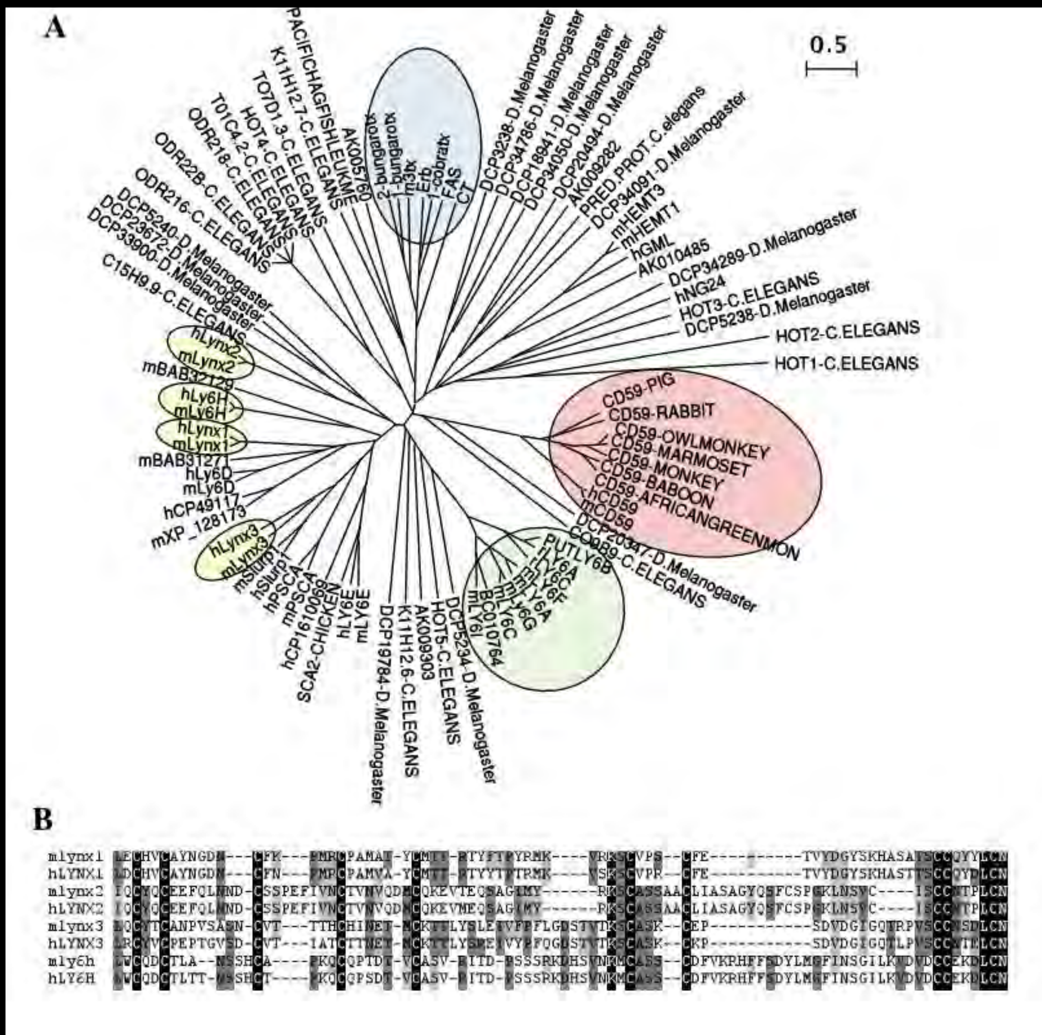
Would that person learn better?

Be more creative?

The gene superfamily arose by gene duplication and Divergence

Gave rise to snake venom toxin protein through accelerated evolution

The lynx Family

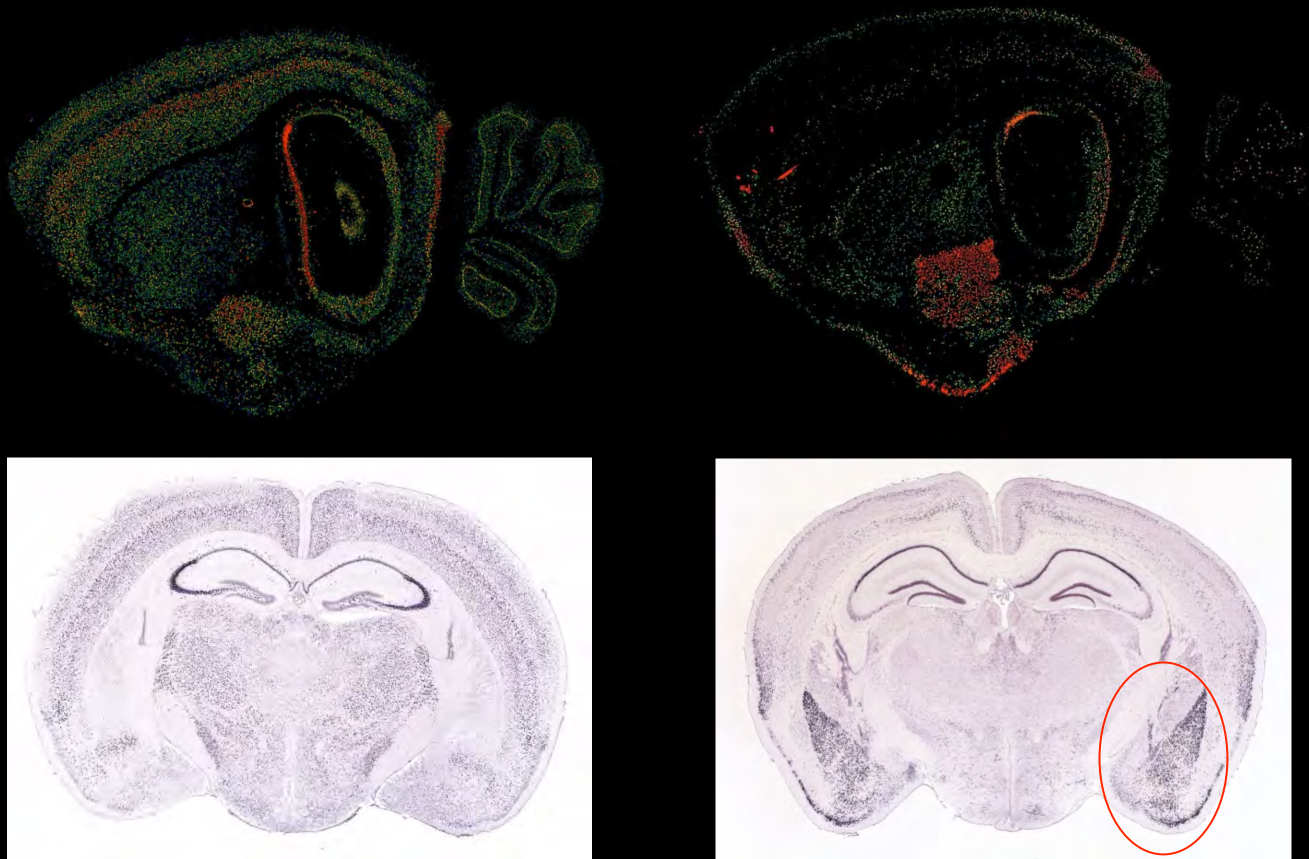


lynx genes are highly conserved

Exist in all animals from C. elegans to humans

Most bind to nicotinic receptors

lynx Expression Patterns



lynx1

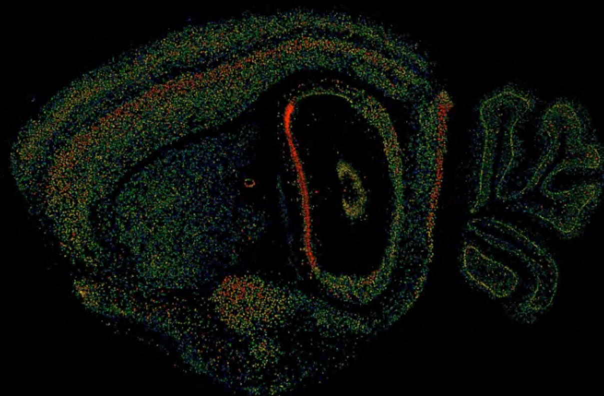
lynx2

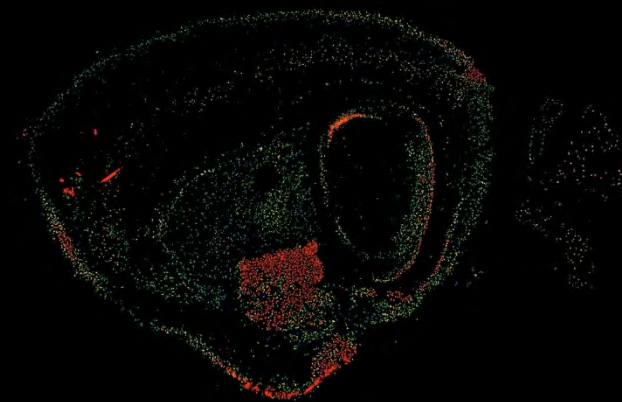
amydgala

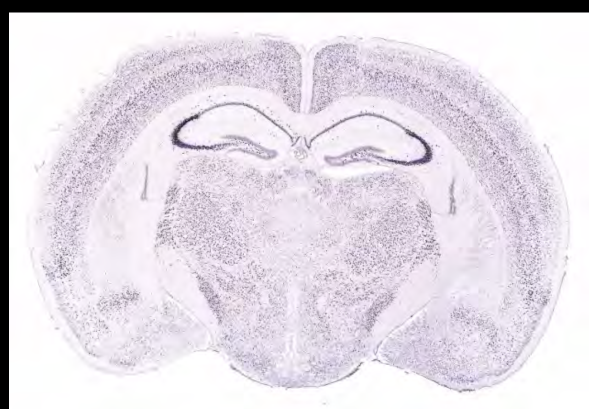
lynx Binding Specificity

	$\alpha 4\beta 2$	$\alpha 7$	muscle	$\alpha 4\beta 4$	$\alpha 3\beta 4$
lynx1	+++	+++	+	+++	-
lynx2	+++	+	+++	+++	-
lynx5	-	-	-	+	-

lynx Expression Patterns







lynx1

lynx2

Cognition and learning

fear and anxiety

WHY

If lynx1 suppresses cholinergic activity, why have it?

Control cholinergic tone in discrete areas

Acknowledgements

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Structural Modeling

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Adam Van Handel- Eckhardt scholar
Tim Yeh
Sana Ali- sophomore
Chris Hoke
Kyra Feuer- BDSI

Former students

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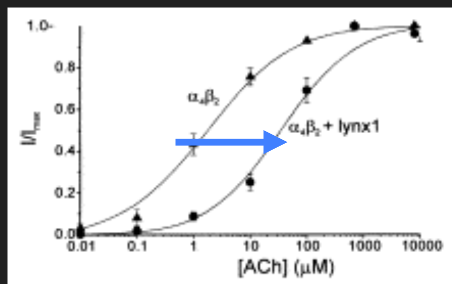
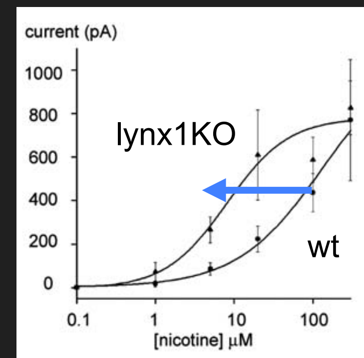
Kasarah Ackerman- graduated 2014
Courtney Meyer- President of Lehigh’s Neuroscience club
Chelsea Serrano
Jacquelin Botello

Julie Miwa
Biological Sciences

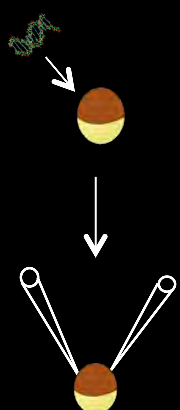
lynx Acts As A Molecular Brake



Addition of lynx shifts dose response curve to the right



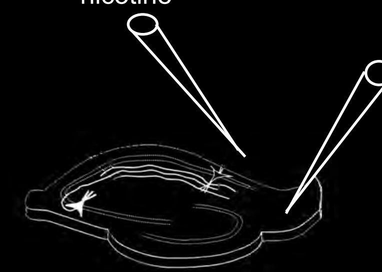
lynx1 removal shifts dose response curve to the left



Oocytes

Co-expression of lynx with α4β2 nAChRs:

- reduces sensitive to agonist
- increases desensitization kinetics
- slows recovery from desensitization



Brain slice recordings

Ibanez-Tallon et al., 33, Neuron, 2002

Miwa et al., Neuron, 51, 2006