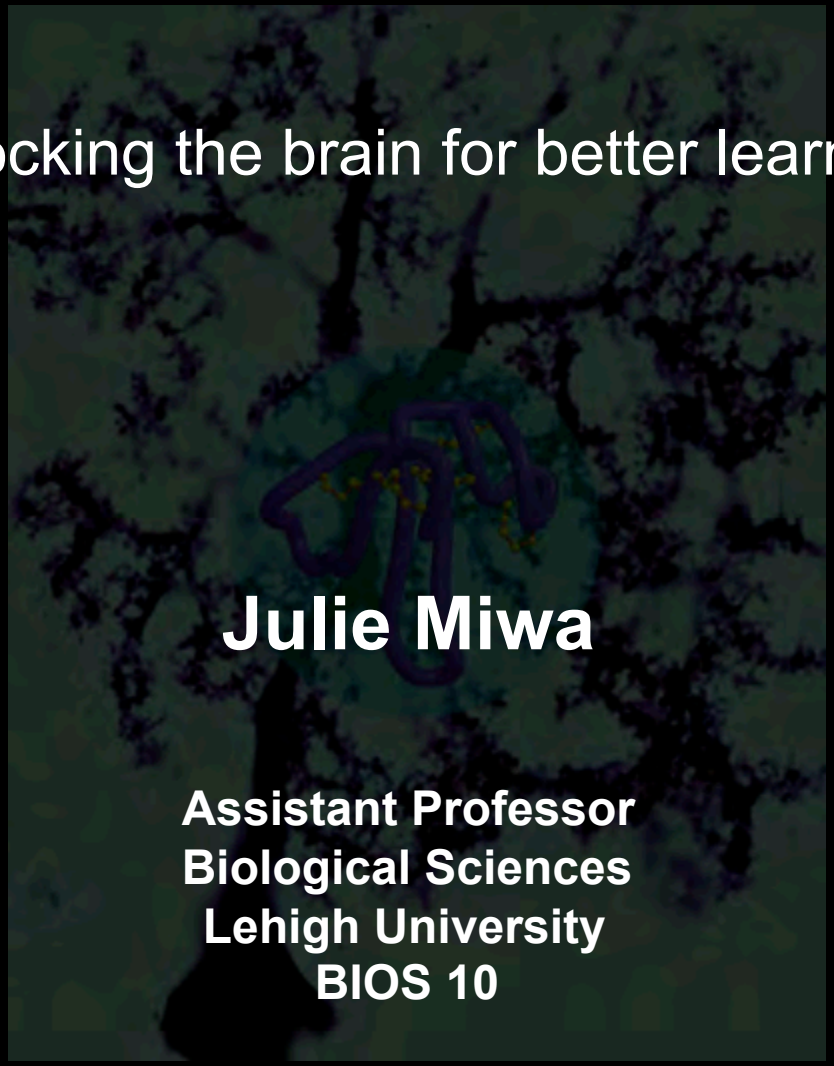
Unlocking the brain for better learning



Julie Miwa

Assistant Professor
Biological Sciences
Lehigh University
BIOS 10

October 5th, 2015

Behavioral change can be adaptive
Allows us to better navigate environmental challenges

If behavioral change is adaptive….

Why is it so difficult to change?

Why do we make the same resolutions every year?

Actually changing behavior is not easy

Our ability to learn changes with age

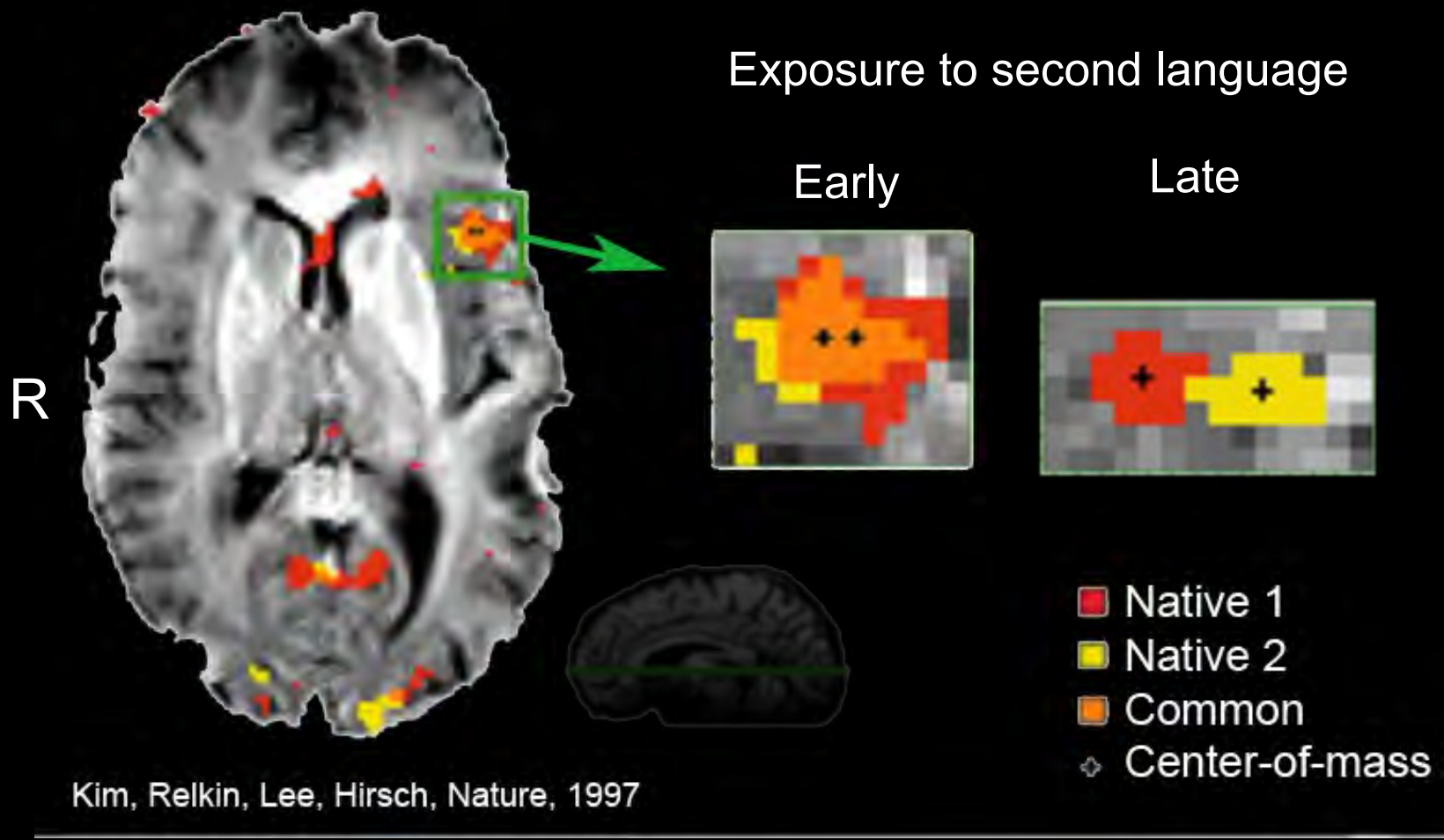
Example: language

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

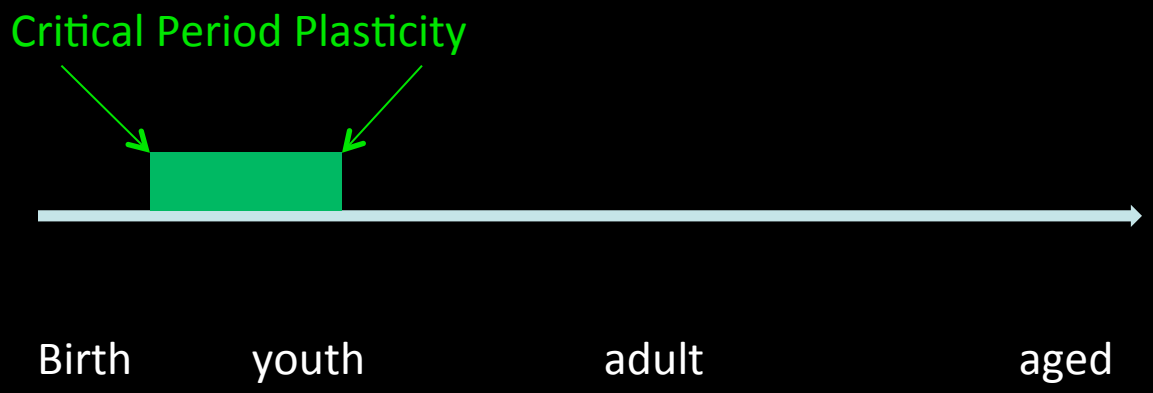
Physical changes occur in our brain as we age

The brain gets wired by early experiences

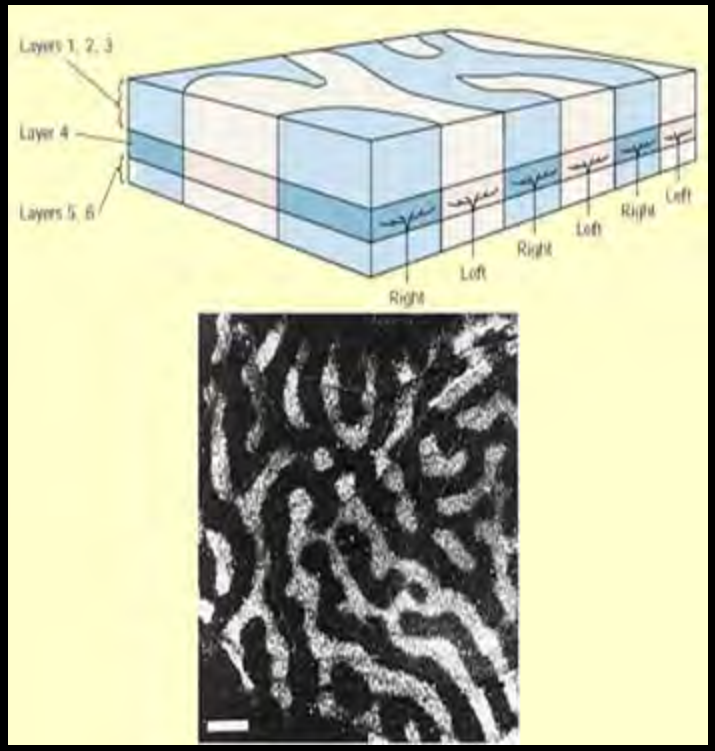
Different regions/functions have different sensitive periods

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



Critical Period plasticity



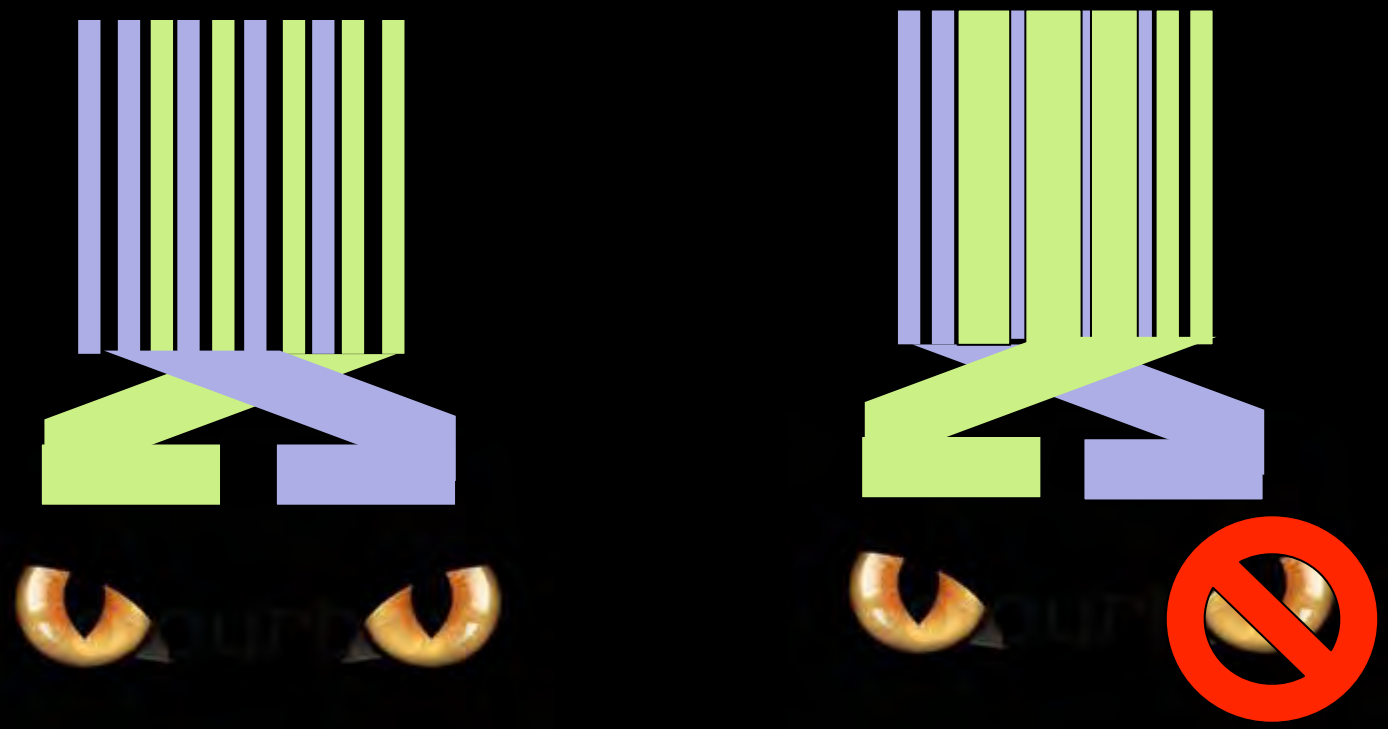
Monkey visual cortex

The visual cortex gets input from two eyes

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

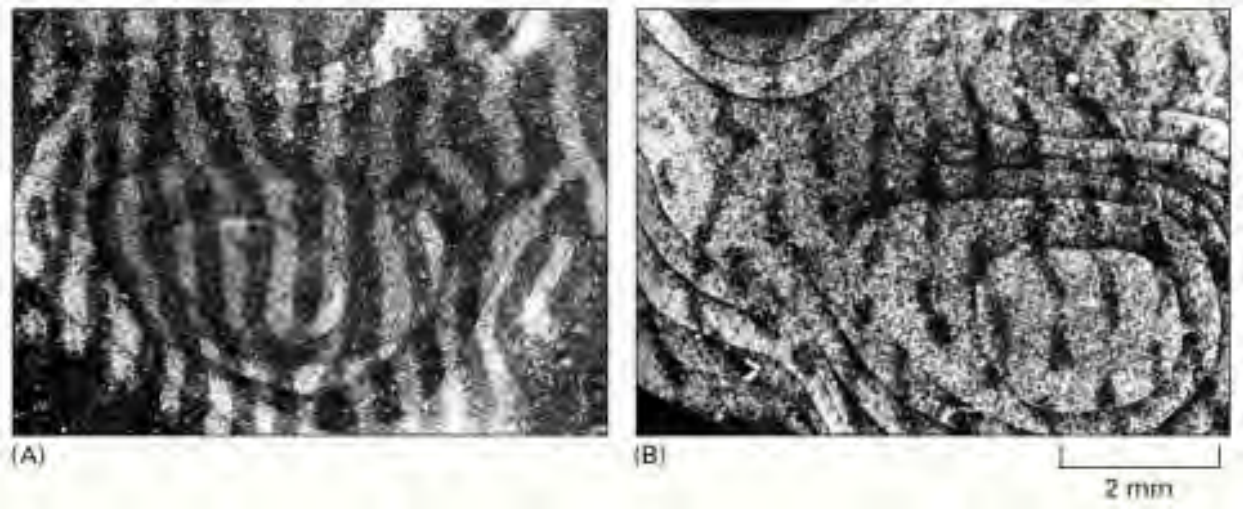
Input from two eyes compete for cortical territory in the visual cortex

Critical Period Plasticity is use-dependent



If one eye is closed, (monocular deprivation = MD), the active eye will outcompete for cortical territory and that part of the cortex will expand

Critical Period Plasticity



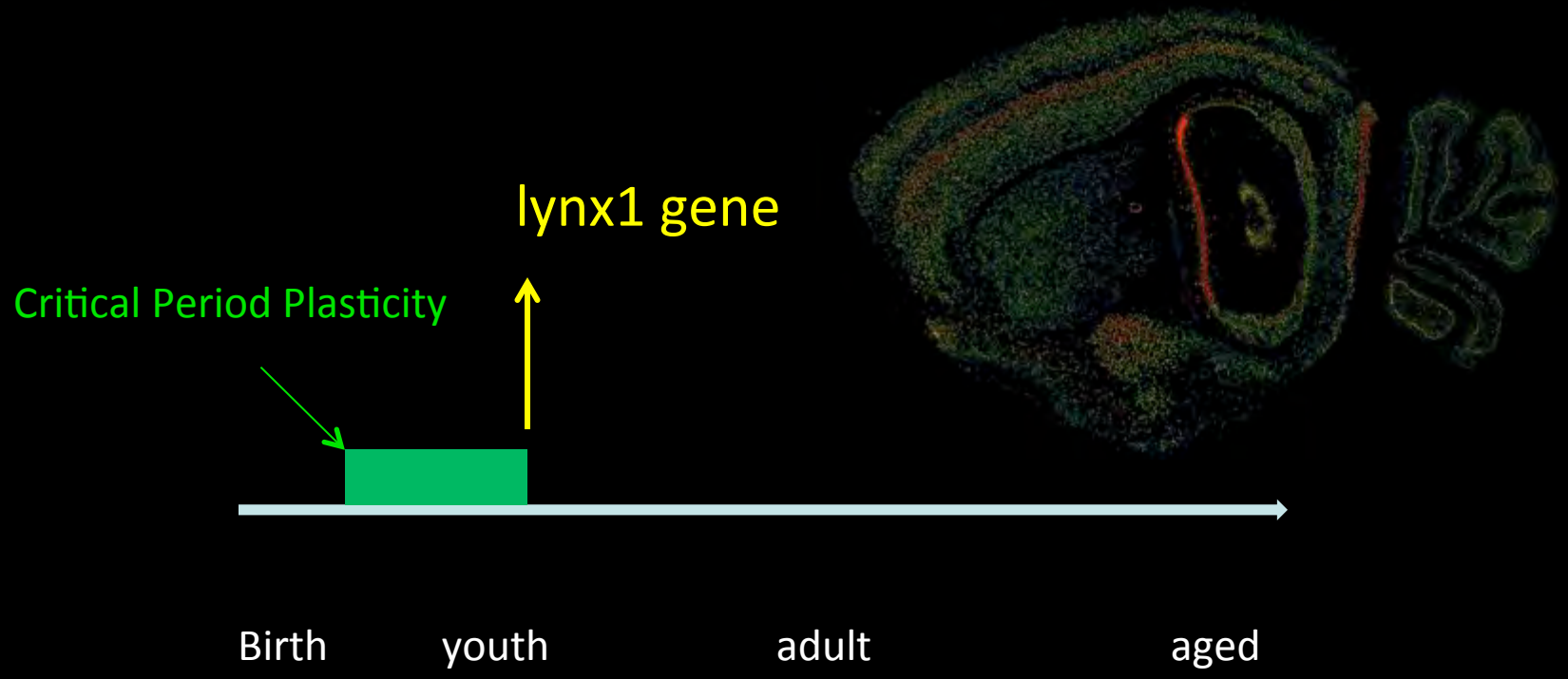
What monocular deprivation (MD) look like in the cortex if you label only one eye- the active cortical territory will expand

This change due to light input happens only during early time points

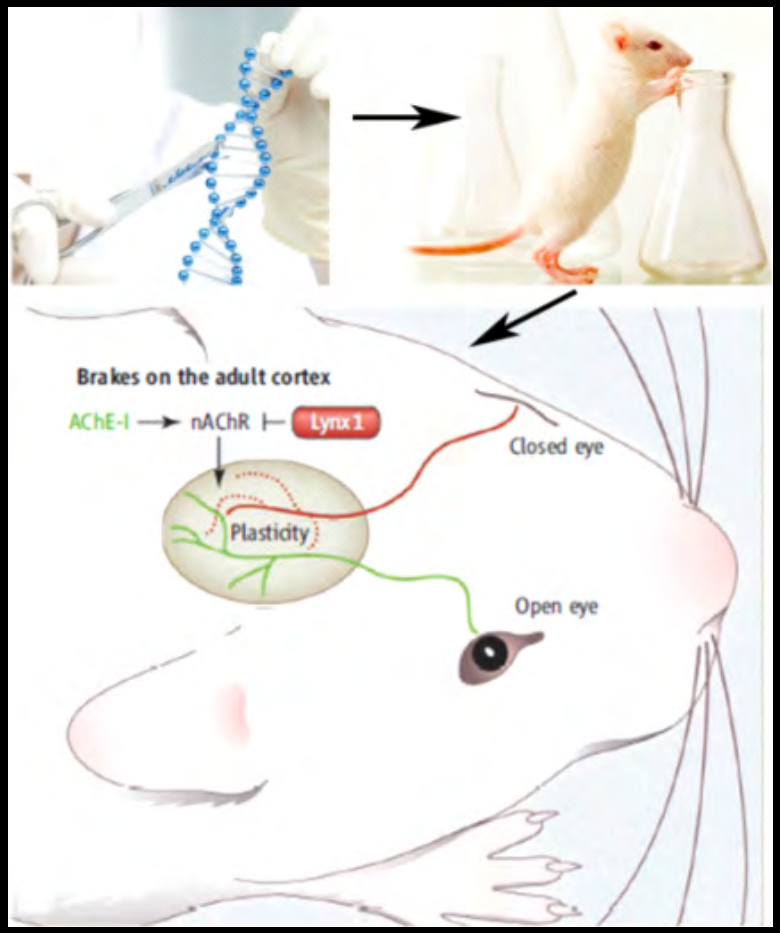
If you don't correct cross-eyes early in humans (one eye loses the competition), you can lose depth perception

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

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



I removed the lynx1 gene through genetic engineering…



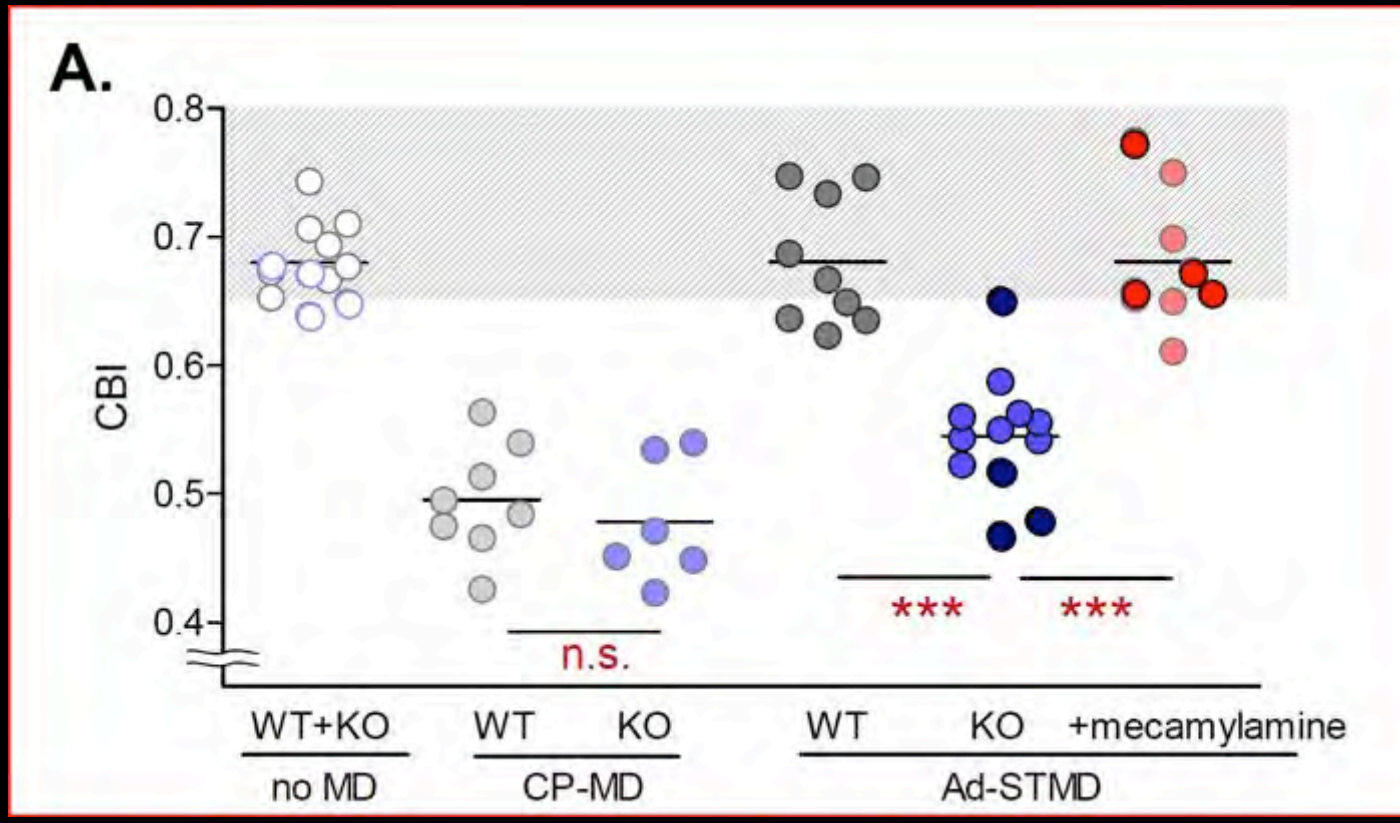
Creating lynx1KO mice

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

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

Less plasticity

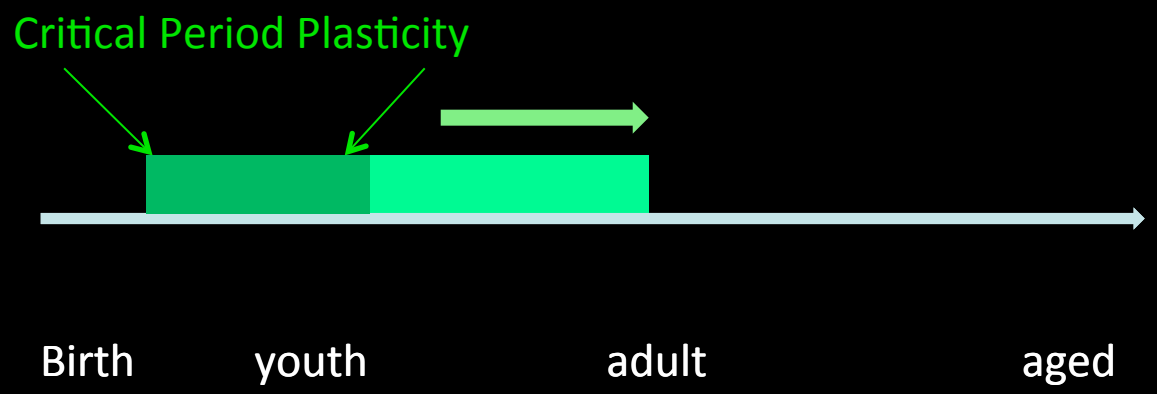
More plasticity



P19-P33 in mice

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

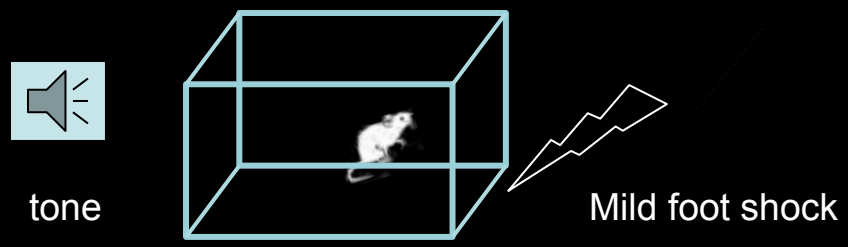
The robust plasticity of the critical period was extended past the normal time frame.



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

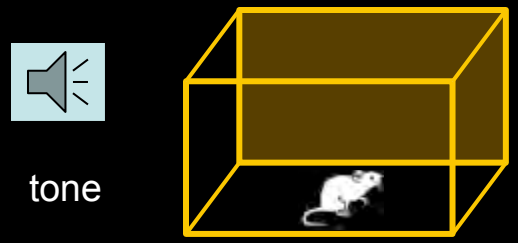
P19-P33 in mice

Classical Fear Conditioning (Associative Learning)

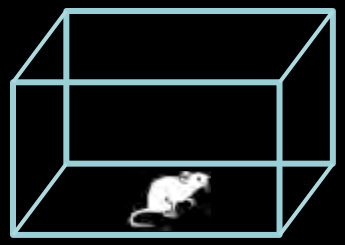


Training

24 hours

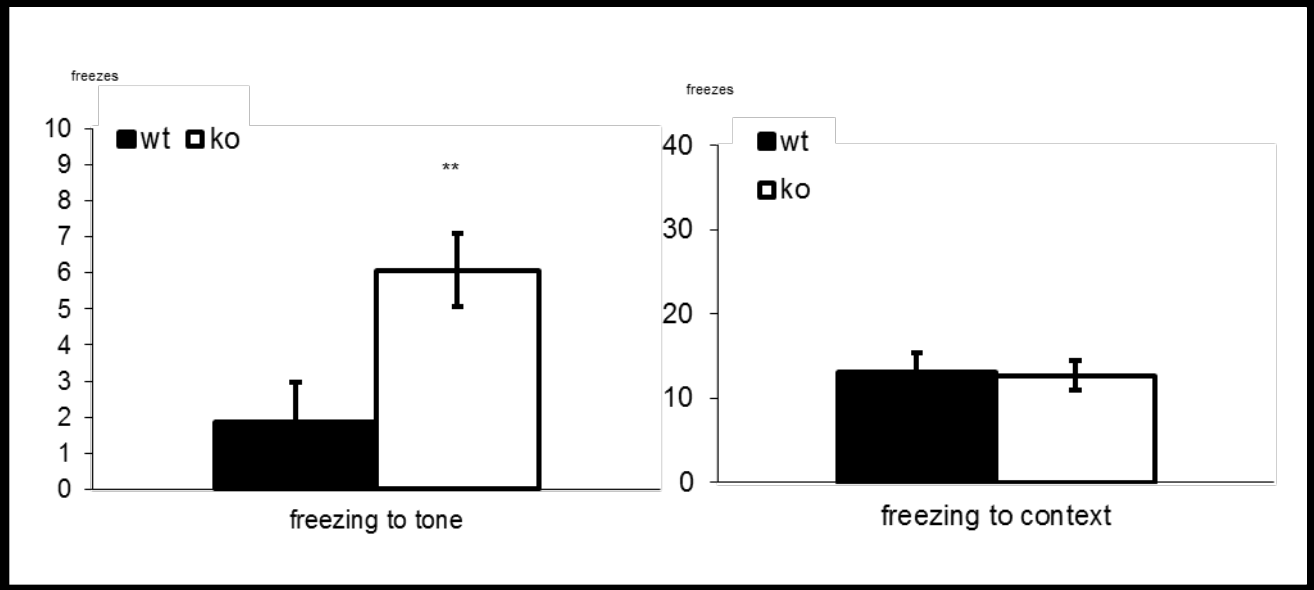


Associative “cued” learning



Contextual learning

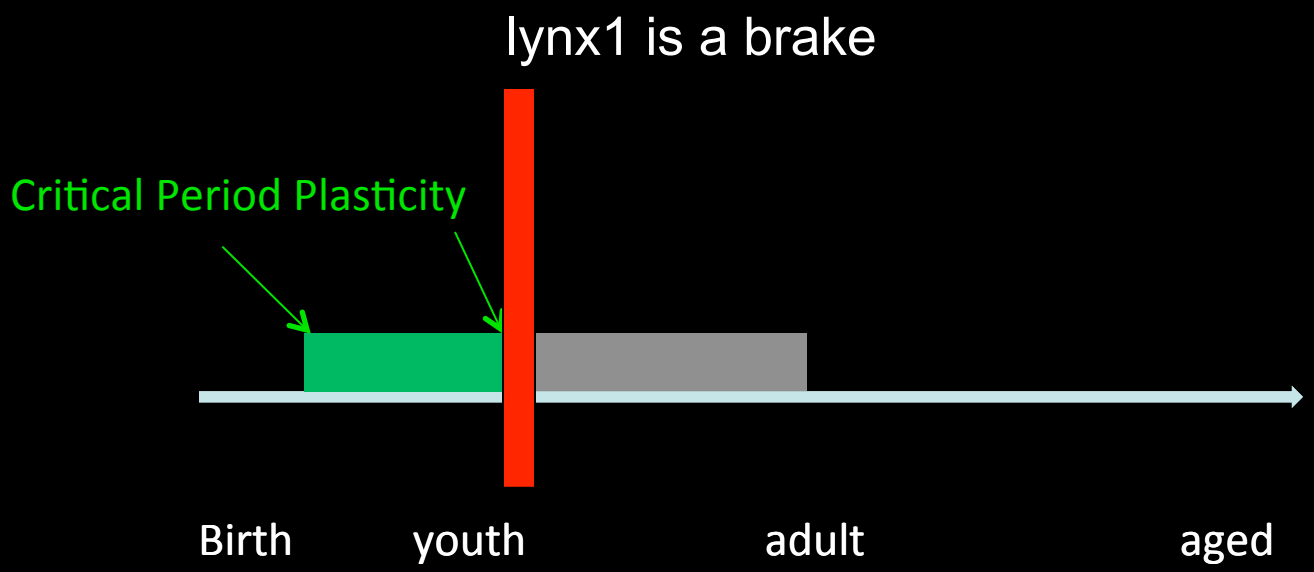
Improved Learning By Removing the Brake on Plasticity



lynx1KO mice exhibit enhanced **associative** learning

Miwa et al, 51, Neuron, 2006

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

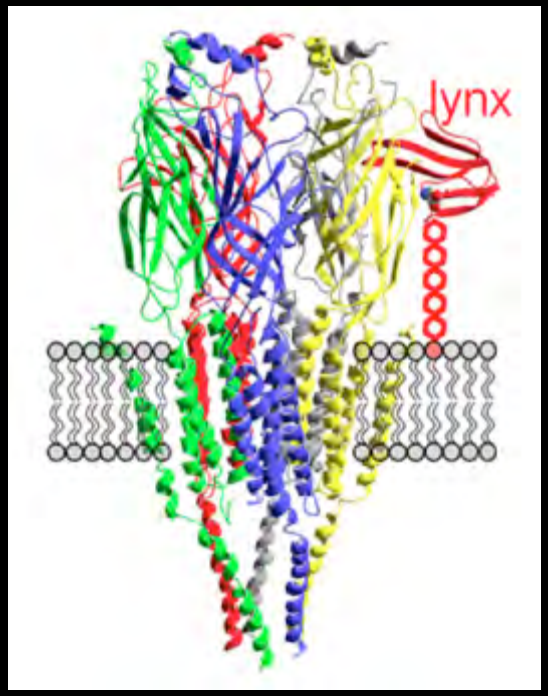


P19-P33 in mice

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

L...C...C...C...C...C...C...C...CC...LCN lynx1
L...C...C...C...C...C...C...C...CC...LCN Ly6
L...C...C...C...C...C...C...C...CC...LCN ThB
I....C.....C...C...C...C...CC...LCN α-btxn
I....C.....C...C...C...C...CC...LCN Cbtxn

Miwa et al., 23, Neuron 1999

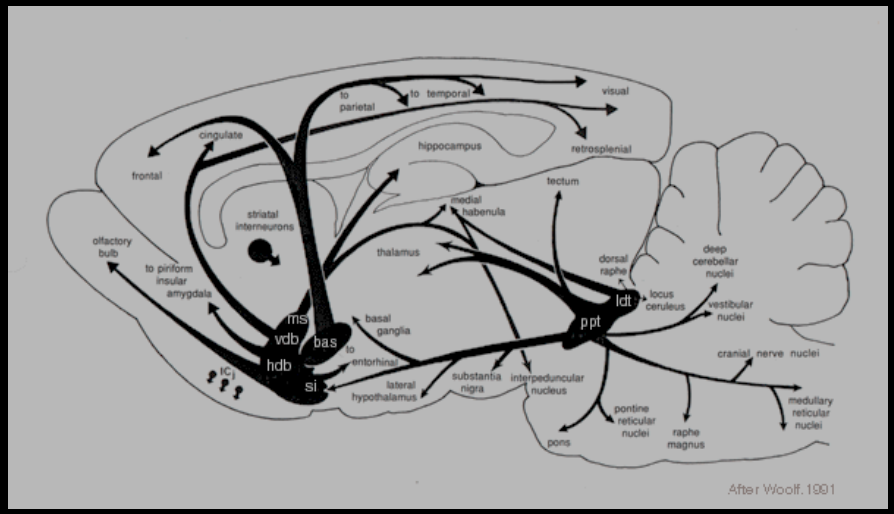
Lynx1 modulates the cholinergic system

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

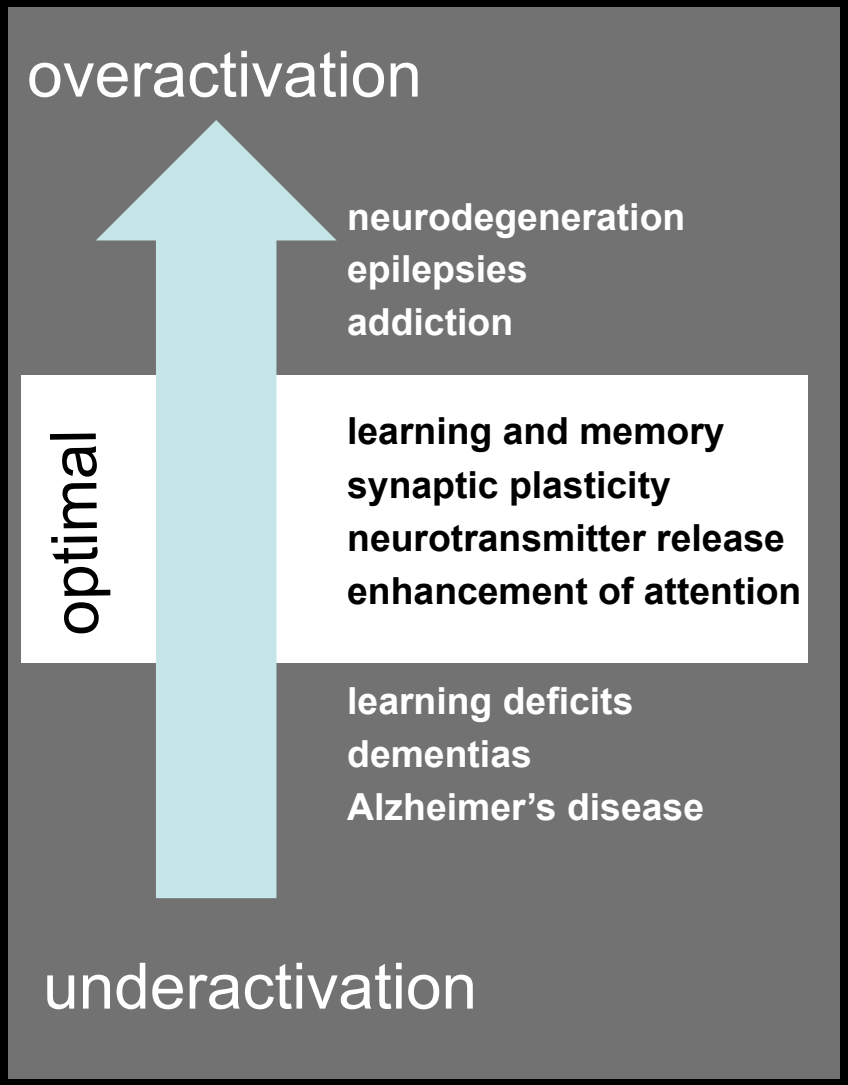
•The cholinergic system can raise brain excitability

The cholinergic system contributes to learning

It operates on a gradient of activation



Optimized Cholinergic Tone



We can also raise cholinergic tone through lynx dosage

overactivation

neurodegeneration
epilepsies
addiction

optimal

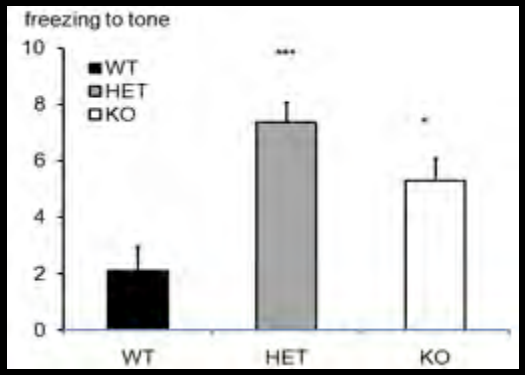
learning and memory
synaptic plasticity
neurotransmitter release
enhancement of attention

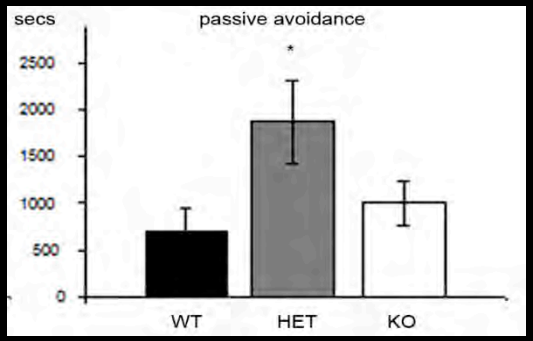
learning deficits
dementias
Alzheimer's disease

0 copies of lynx

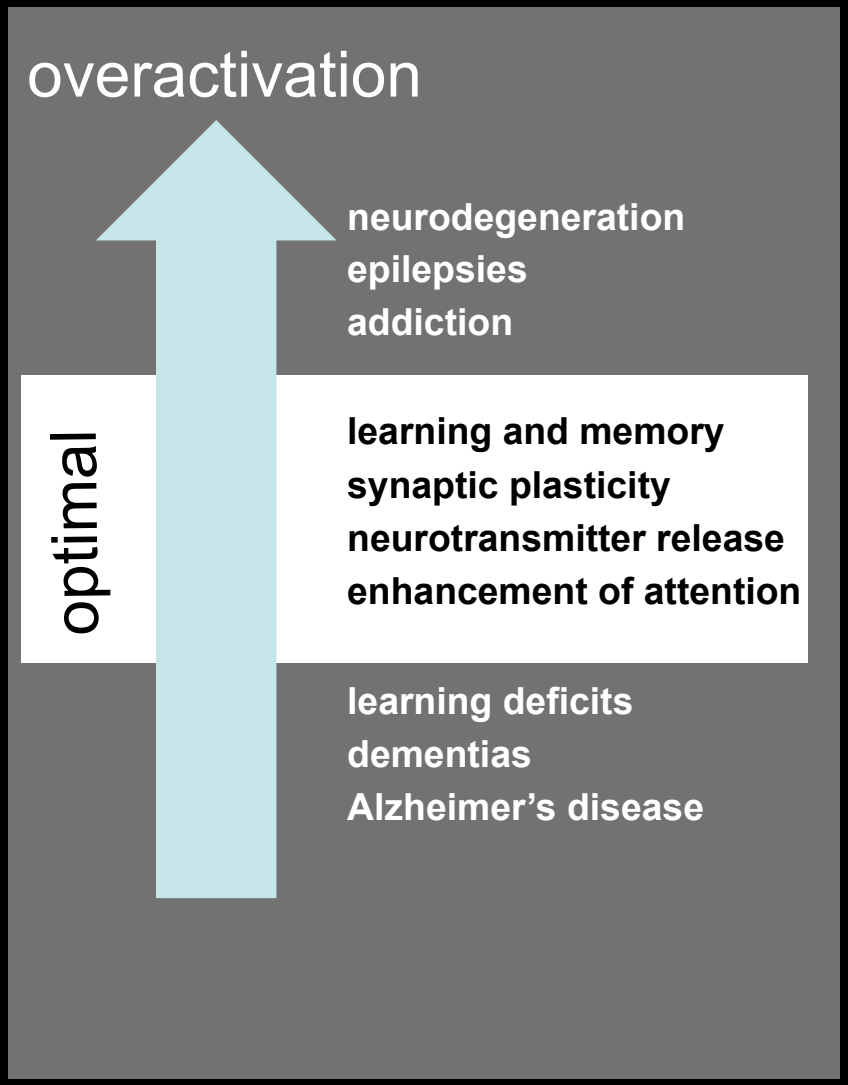
1 copy of lynx

2 copies of lynx

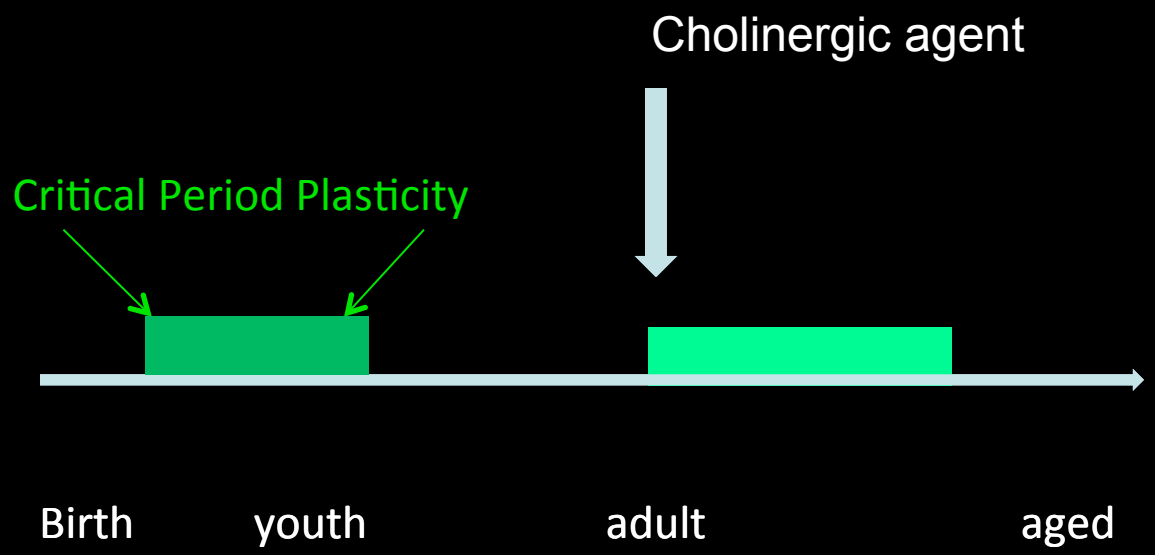




We can also raise cholinergic tone through pharmacology



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

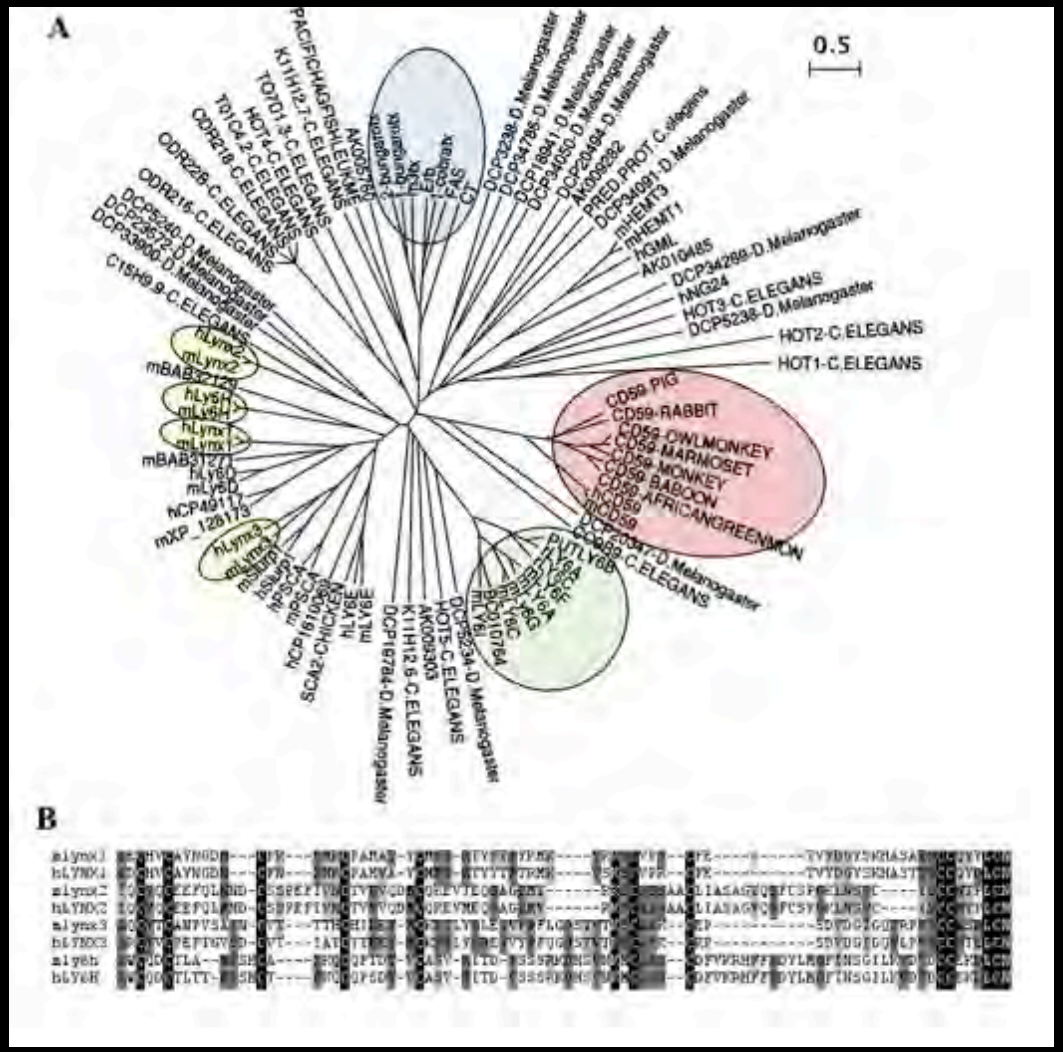
Cholinergic activation mediates this plasticity

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

If we can learning how to turn on/off lynx, this could be helpful

What would this be useful for?

The lynx Family



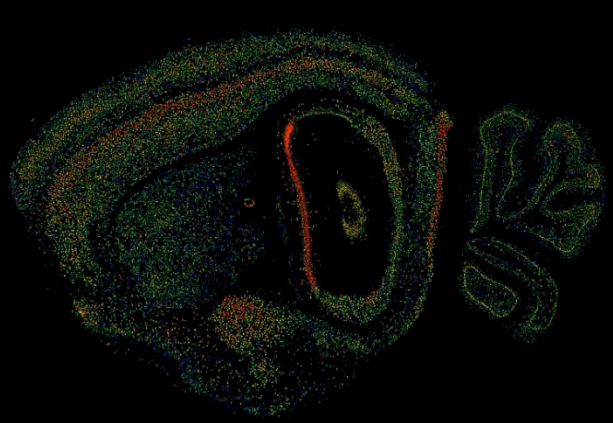
lynx genes are highly conserved

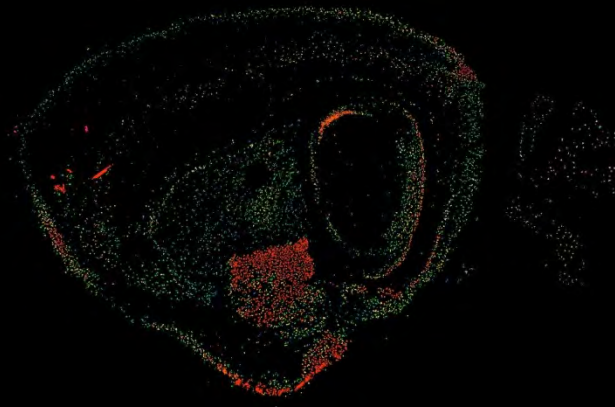
Arose by gene duplication

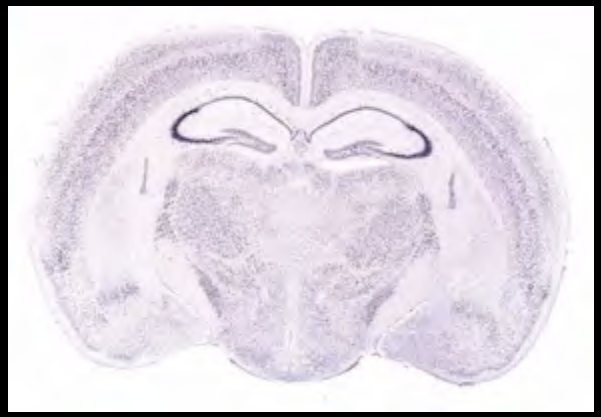
Exist in all animals from C. elegans to humans

Most bind to nicotinic receptors

lynx Expression Patterns







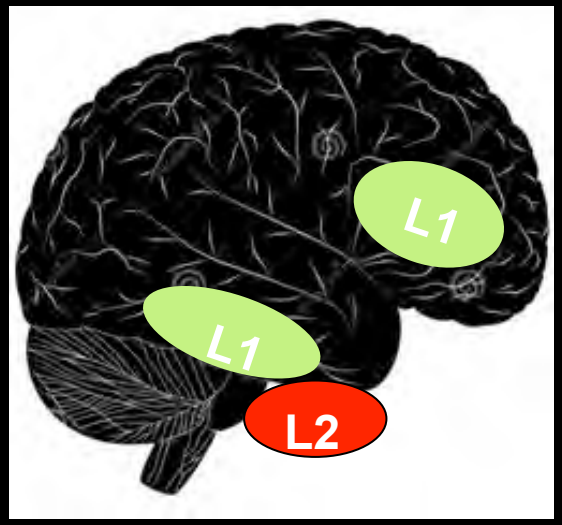
lynx1

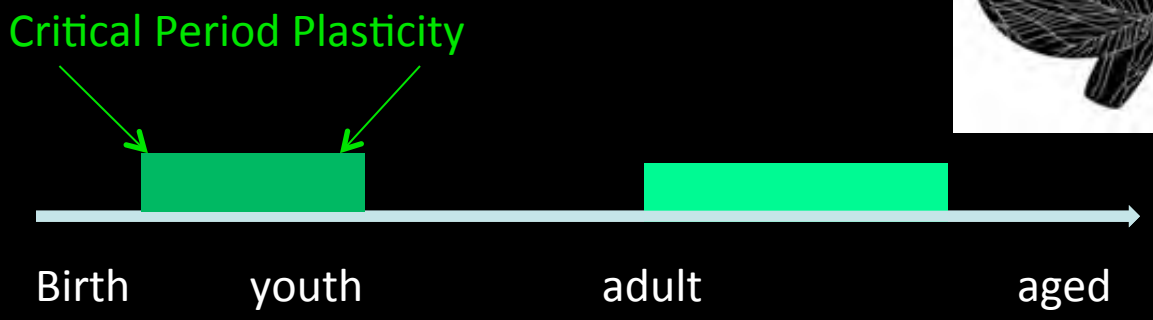
lynx2

Cognition and learning

fear and anxiety

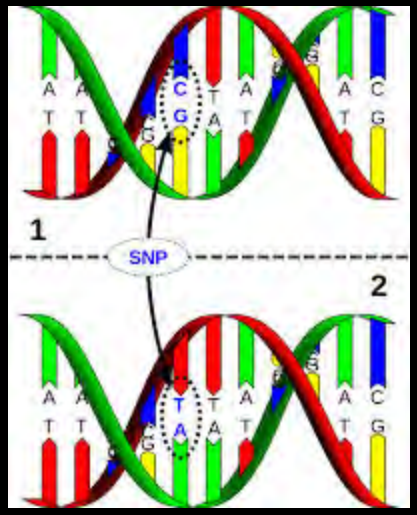
Question: Can we remove the brake and recapture youthful plasticity in humans?





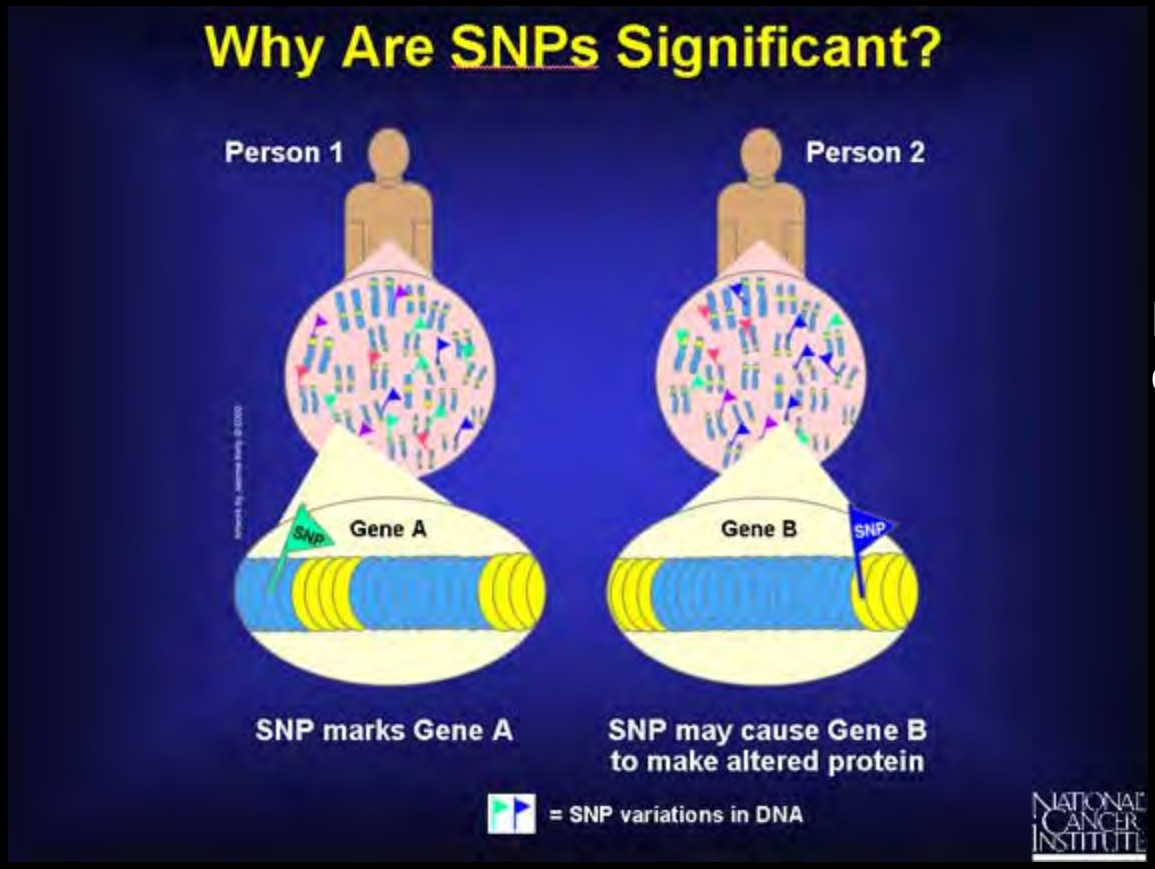
By learning how to turn on/off lynx, we can capture islands of plasticity in the brain through raising cholinergic tone selectively

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)

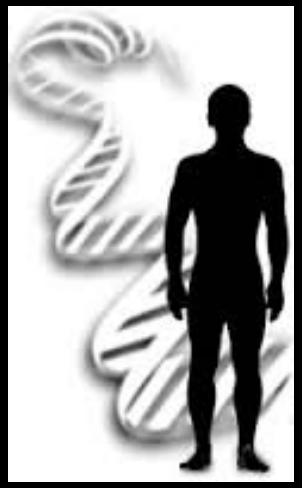
the amino acid sequence (protein function)

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

Have better cognitive flexibility?

GACTTA

GAGTTA



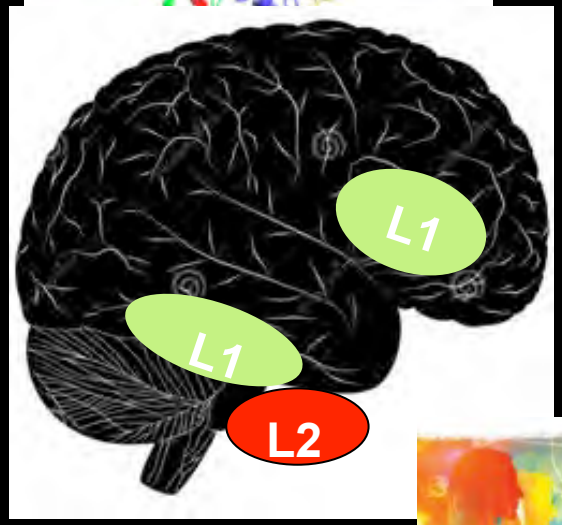
Would that person learn better?

Be more creative?

OPEN MINDSET

CLOSED MINDSET

Would people harboring mutations in lynx genes be more adaptable?



SUMMARY

Lynx acts as a molecular brake on learning and plasticity in the brain by binding nicotine receptors and dampening their function

Lynx inhibition can open up local islands of raised cholinergic tone altering complex traits- cognition through lynx1, anxiety through lynx2

Individual gene differences in humans can explain differences in complex traits
Possibly unlocking the brain for better learning and behavioral adaptation

Bardin Nature 487 2012

OUR STUDY

We collect cheek cells and saliva and extract DNA from it

This is a non-invasive test, and results are kept confidential

We give a battery of psychological tests, 2 sessions lasting 1 hour

DNA sequence is matched to psychological results

If you are interested in volunteering to best tested in our study, please sign up after the class or contact me

GOT SNPs?

What is your genotype?

Julie Miwa
Biological Sciences

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Lynx2 electrophysiology
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Chelsea Serrano
Jacquelin Botello

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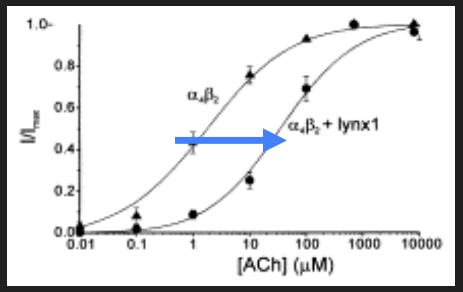
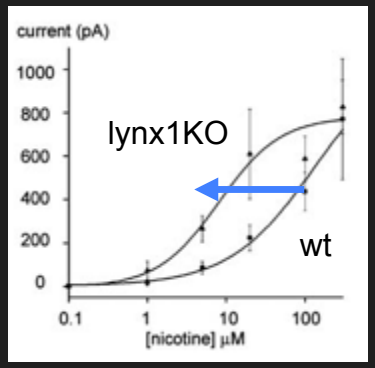
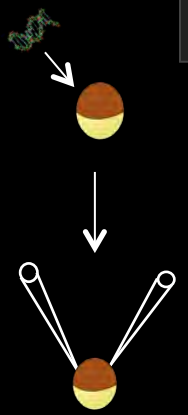
lynx Acts As A Molecular Brake



Addition of lynx shifts dose response curve to the right



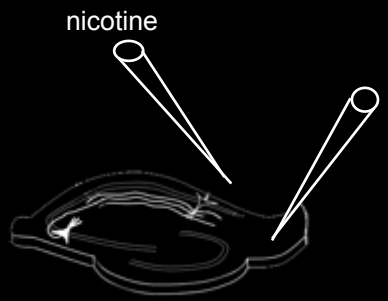
lynx1 removal shifts dose response curve to the left



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

lynx Binding Specificity

	$\alpha4\beta2$	$\alpha7$	muscle	$\alpha4\beta4$	$\alpha3\beta4$
lynx1	+++	+++	+	+++	-
lynx2	+++	+	+++	+++	-
lynx5	-	-	-	+	-