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

Exposure to second language

Early

Late

Cortical Reorganization

Visual Cortex Activity in Early and Late Blind People


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.
I removed the lynx1 gene through genetic engineering...

Creating lynx1KO mice

Morishita, Miwa, Heintz, Hensch, Science, 2010
Classical Fear Conditioning (Associative Learning)

Training

- Associative “cued” learning
- Contextual learning

Mild foot shock
Improve Learning By Increased Cholinergic Tone

Lynx1KO mice exhibit enhanced associative learning

Miwa et al, 51, Neuron, 2006
Another animal study- Critical Period plasticity

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.

Monkey 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.

![Graph showing data points and comparisons between different groups with and without interventions.](image)
The robust plasticity of the critical period was extended past the normal time frame.

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

- overactivation
  - neurodegeneration
  - epilepsies
  - addiction

- optimal
  - learning and memory
  - synaptic plasticity
  - neurotransmitter release
  - enhancement of attention

- underactivation
  - learning deficits
  - dementias
  - Alzheimer’s disease
We can also raise cholinergic tone through pharmacology.

- Overactivation
  - Neurodegeneration
  - Epilepsies
  - Addiction

- Optimal
  - Learning and memory
  - Synaptic plasticity
  - Neurotransmitter release
  - Enhancement of attention

- Learning deficits
- Dementias
- Alzheimer’s disease
Cholinergic agents that raise cholinergic tone can lead to enhanced critical period plasticity in normal adult 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

- 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
Question: Can we remove the brake (lynx1) and recapture youthful plasticity in humans?
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
<table>
<thead>
<tr>
<th>Closed ended learners</th>
<th>Open ended learners</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zebra finch, Bengalese finch</strong></td>
<td><strong>Brown-headed cowbird</strong></td>
</tr>
<tr>
<td>Learned early in year 1</td>
<td>Memorize in year 2, production delayed to year 3</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Song sparrow</strong></td>
<td><strong>Northern mockingbird, European starling</strong></td>
</tr>
<tr>
<td>Memorization and rehearsal delayed to fall year 1 or spring year 2</td>
<td>Memorize and rehearse new songs throughout life</td>
</tr>
</tbody>
</table>
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?

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

 amygdala
## lynx Binding Specificity

<table>
<thead>
<tr>
<th></th>
<th>$\alpha 4\beta 2$</th>
<th>$\alpha 7$</th>
<th>muscle</th>
<th>$\alpha 4\beta 4$</th>
<th>$\alpha 3\beta 4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>lynx1</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>lynx2</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>lynx5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
lynx Expression Patterns

Cognition and learning

fear and anxiety
WHY

If lynx1 suppresses cholinergic activity, why have it?

Control cholinergic tone in discrete areas
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Former students

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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

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