Unlocking the brain for better behavioral adaptation

Julie Miwa
Assistant Professor
Biological Sciences
Lehigh University
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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

Multiple factors drive behavioral change
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

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

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

P19-P33 in mice

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


P19-P33 in mice
Classical Fear Conditioning (Associative Learning)

Training

- Associative “cued” learning
- Contextual learning

- Tone
- Mild foot shock

24 hours
Improved Learning By Removing the Brake on Plasticity

Miwa et al, 51, Neuron, 2006

 lynx1KO mice exhibit enhanced **associative** learning
This showed that the lynx1 gene acts as a molecular brake on Critical Period plasticity.
• Lynx binds nicotine receptors
• Negative allosteric modulator
• Ly6/neurotoxin superfamily- endogenous

Lyukmanova et al., The Journal of Biological Chemistry, 2011
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

Release increases with sustained attention

It operates on a gradient of activation
Optimized Cholinergic Tone

- Overactivation:
  - Neurodegeneration
  - Epilepsies
  - Addiction

- Underactivation:
  - Learning deficits
  - Dementias
  - Alzheimer’s disease

- Optimal:
  - Learning and memory
  - Synaptic plasticity
  - Neurotransmitter release
  - Enhancement of attention
We can also raise cholinergic tone through lynx dosage

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- Epilepsies
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Overactivation:
- 0 copies of lynx
- 1 copy of lynx
- 2 copies of lynx

Optimal:

Graph showing box plots for different conditions (WT, HET, KO) with annotations.
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.
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.
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

Cognition and learning

fear and anxiety
The Amygdala

- What is the amygdala?
  - Fear and anxiety region
  - Highly conserved
  - Governs emotions
  - Anxiety and social function are related
Mice without lynx2 are more anxious

- Light/Dark Box Paradigm
  - lynx2 KO mice spend more time in dark

- Elevated Plus Maze Paradigm
  - lynx2 KO mice spend less time in open arms

Tekinay et al., Proc Natl Acad Sci U.S.A., 2009
• Social interaction Paradigm
  – lynx2 KO mice spend less time near and less time interacting with stranger mice than normal WT mice

Tekinay et al., Proc Natl Acad Sci U.S.A. 2009
Monkeys with lesions of the amygdala show less anxiety and increased social interactions

The normal monkeys demonstrated increased social affiliation towards the lesioned animals

Can genetics explain differences in people?

Whether a person socializes, seeks a support network
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.

Lynx1 for cognition and lynx2 for anxiety and sociability.
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)

Why Are SNPs Significant?

Person 1

SNP marks Gene A

Person 2

SNP may cause Gene B to make altered protein

SNP = SNP variations in DNA

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?

Have better resilience?
Can genetics explain differences in people?
WHAT DRIVES BEHAVIORAL ADAPTATION?

Success depends on an interplay of social and cognitive factors

Positive (reward) and negative (anxiety) factors drive learning

Things that support sustained attention (e.g. interest in a subject) increases cholinergic tone by release of acetylcholine
WHAT DRIVES BEHAVIORAL ADAPTATION?

The balance of intellectual and emotional can influence success and performance.

Could play a role in directing adaptation and resilience.
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.
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GOT SNPS?

What is your genotype?

Julie Miwa
Biological Sciences