Modelling impaired and enhanced learning with enhanced plasticity

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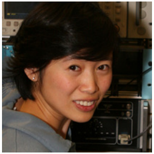
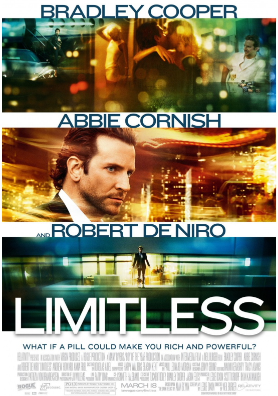
Barbara Nguyen-Vu

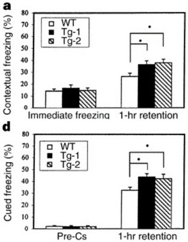


Grace Zhao

Learning requires synaptic plasticity.
Expect: enhanced plasticity $\rightarrow$ enhanced learning.



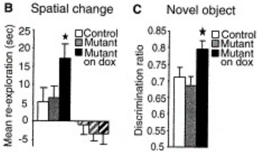
Overexpress NR2B



Fear conditioning

[Tang et al. (1999)]

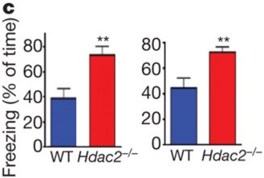
Inhibit CN



Novel object recog.

[Malleret et al. (2001)]

Knockout Hdac2

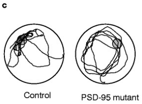


Fear conditioning

[Guan et al. (2009)]

Enhanced plasticity can *impair* learning

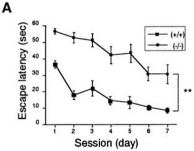
Mutate PSD-95



Water maze

[Migaud et al. (1998)]

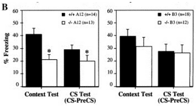
Knockout PTPδ



Water maze

[Uetani et al. (2000)]

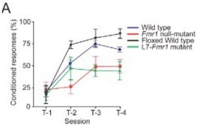
Delete Tmod2



Fear cond.

[Cox et al. (2003)]

Knockout FMR1



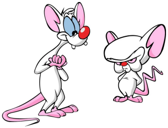
Eyeblink

[Koekkoek et al. (2005)]

also: [Hayashi et al. (2004), Rutten et al. (2008)]

Overview

Sometimes enhanced plasticity $\rightarrow$ enhanced learning.
Sometimes enhanced plasticity $\rightarrow$ impaired learning.



Why? How? When?

Overview

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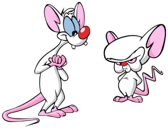
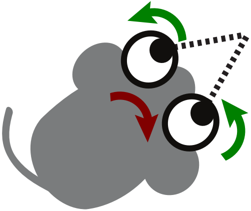


Why? How? When?

Mice with enhanced cerebellar plasticity can show both impaired and enhanced learning.

Simple synapses cannot explain behaviour. Complex synapses are required.
$\rightarrow$ predictions for synaptic physiology.

Vestibulo-Occular Reflex



Eye movements compensate for head movements
$\Longrightarrow$ stabilise image on retina.

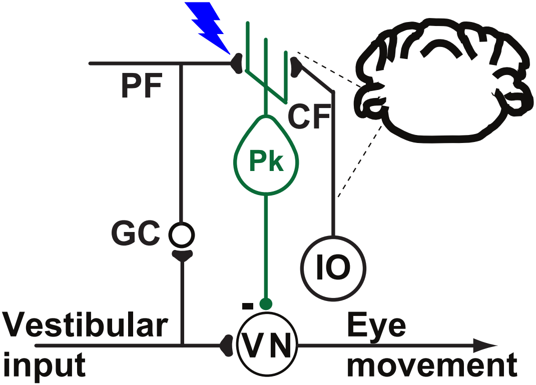
Requires control of VOR gain $= \frac{\text{eye velocity}}{\text{head velocity}}$.

Needs to be adjusted as eye muscles age, etc.

Vestibulo-Occular Reflex training

VOR Increase Training

VOR Decrease Training

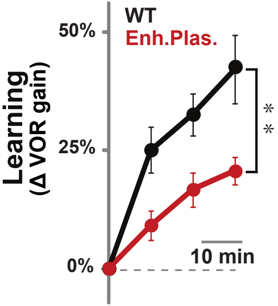


VOR increase:	LTD in PF-Pk synapses.
VOR decrease:	different mechanism, also reverses LTD in PF-Pk.

[Marr (1969), Albus (1971), Ito (1972)]

Enhanced plasticity impairs learning

Expectation: enhanced LTD → enhanced learning.

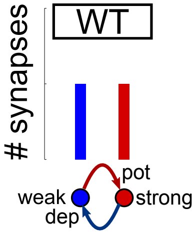


Experiment: enhanced plasticity → impaired learning.

Knockout of MHC-I K^bD^b molecules in PF-Pk synapses
→ lower threshold for LTD [McConnell et al. (2009)]

Depletion hypothesis

Learning rate $\sim$ intrinsic plasticity rate $\times$ $\#$ synapses available for LTD.



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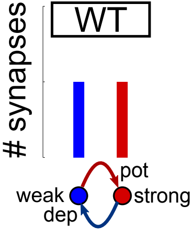
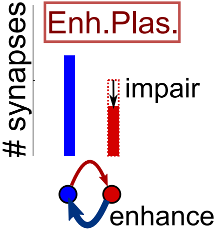
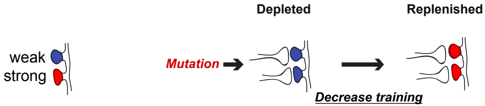




Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

Replenishment by reverse-training

Replenishment by reverse-training



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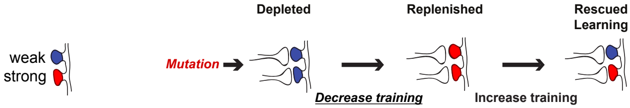

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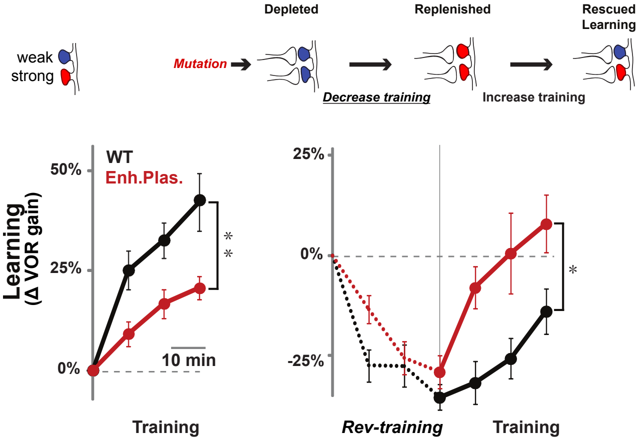

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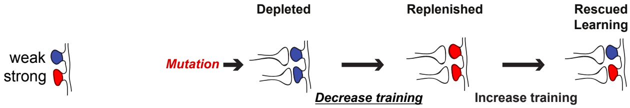
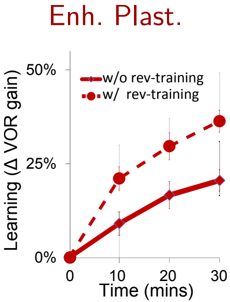
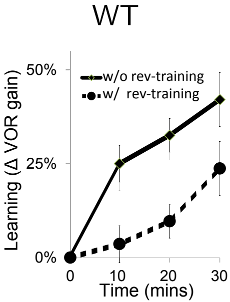
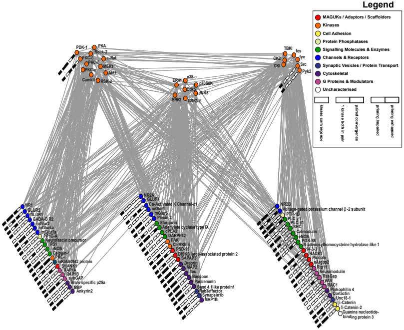




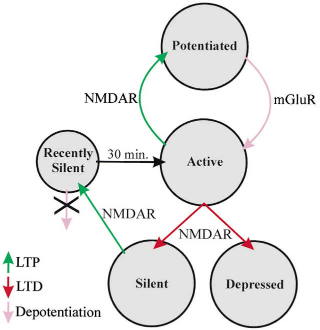


Question 2: How can replenishment *ever* impair learning?

Synapses are complex

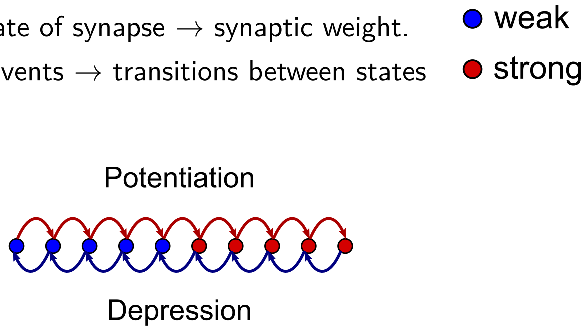


[Coba et al. (2009)]



[Montgomery and Madison (2002)]

- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states



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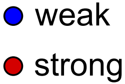

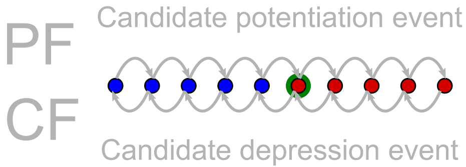

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Models of complex synaptic dynamics

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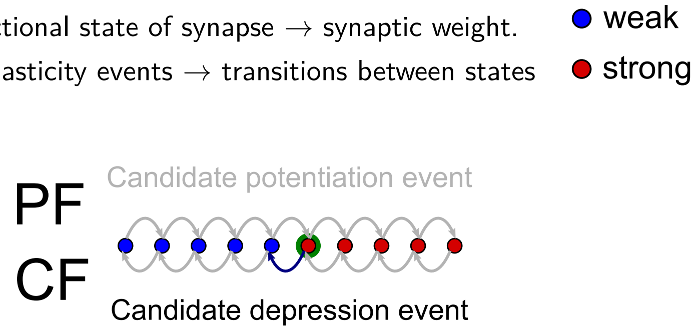

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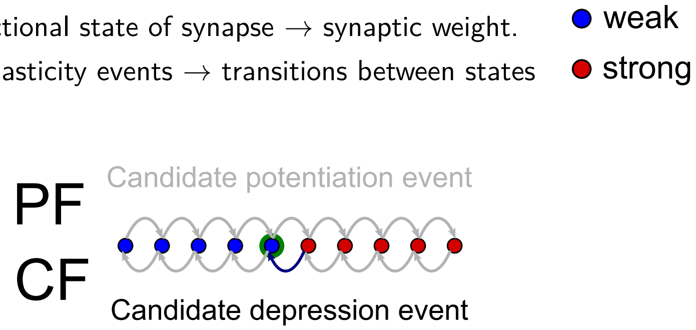

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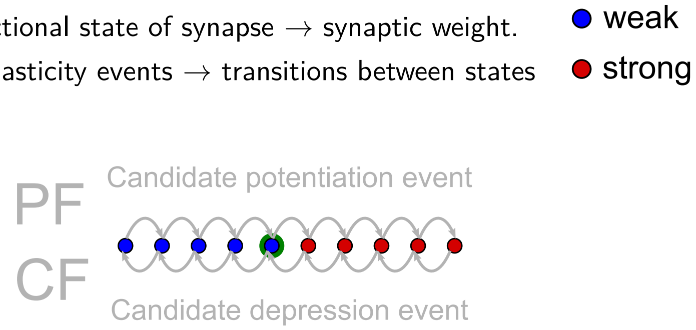

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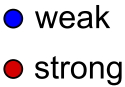

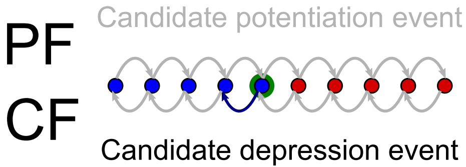

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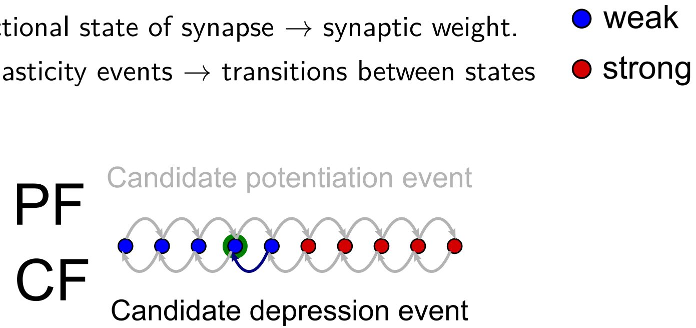

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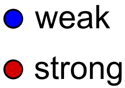

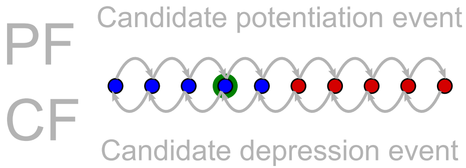

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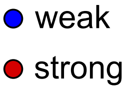

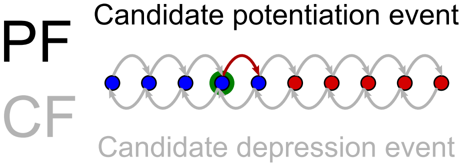

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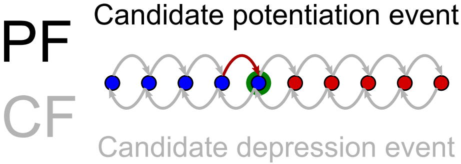
weak
strong



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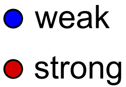

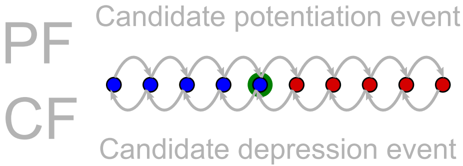

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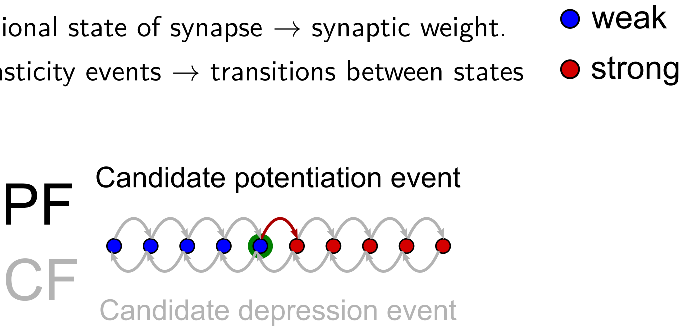

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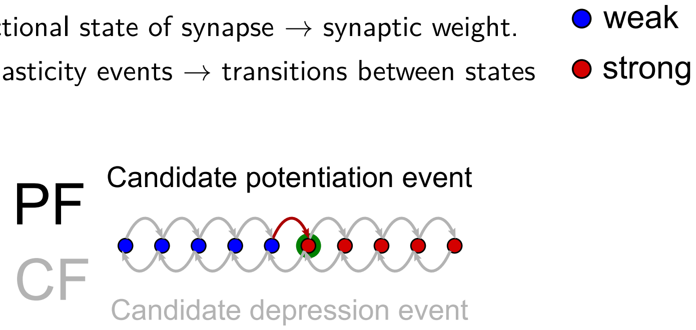

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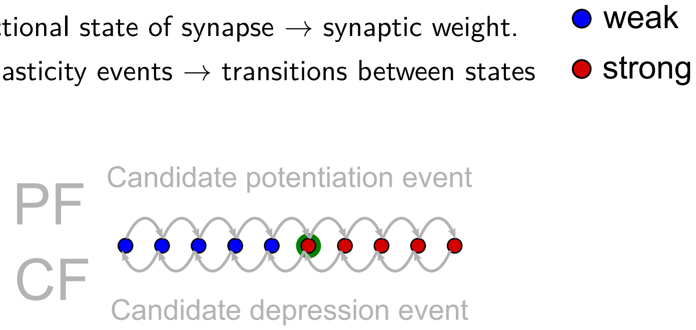

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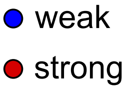

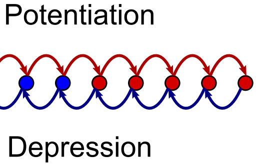

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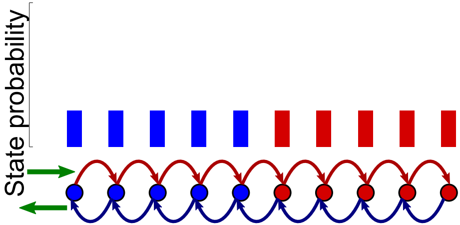
Modelling VOR experiments



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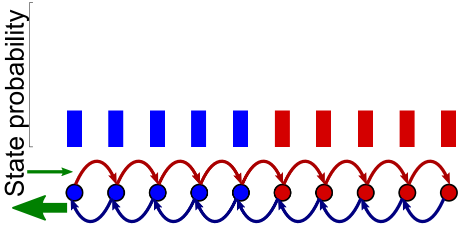
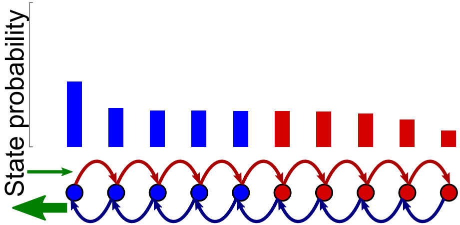


Training: different CF activity $\Longrightarrow$
change frequency of pot/dep events.

Modelling VOR experiments



Training: different CF activity $\implies$
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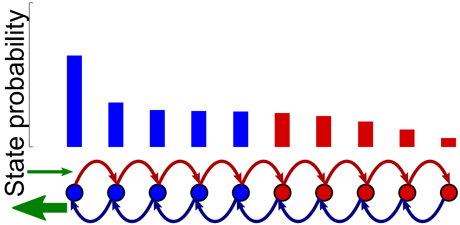
Modelling VOR experiments



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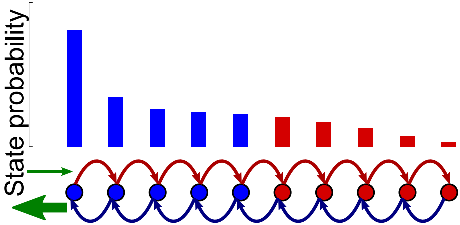

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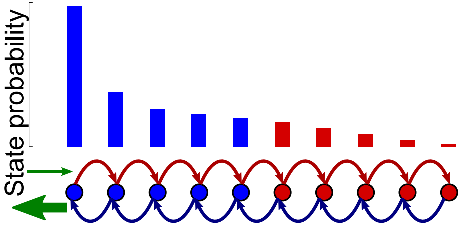

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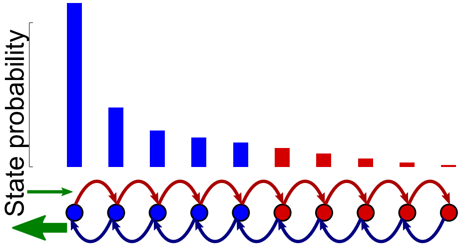

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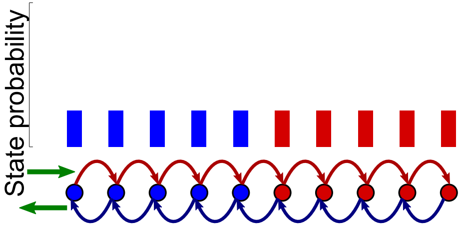
Learning: decrease in average synaptic weight.

Modelling VOR experiments



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increase transition probability for depression events.

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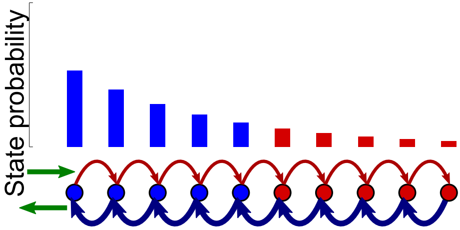


Training: different CF activity $\Longrightarrow$
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

Mutation: lower threshold for LTD $\Longrightarrow$
increase transition probability for depression events.

Questions

Depletion effect competes with enhanced intrinsic plasticity.

Question 1: When is the depletion effect stronger?

Reverse training impairs learning in wild-type.

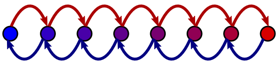
Question 2: How can replenishment *ever* impair learning?

Enhanced plasticity $\rightarrow$ enhanced/impaired learning

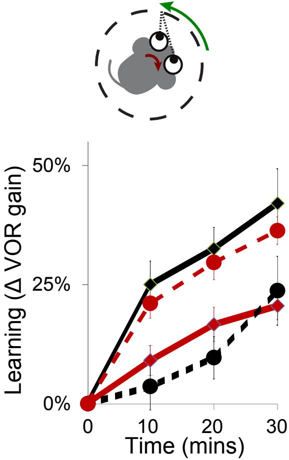
Big question: Why?

Simple synapses cannot explain the data

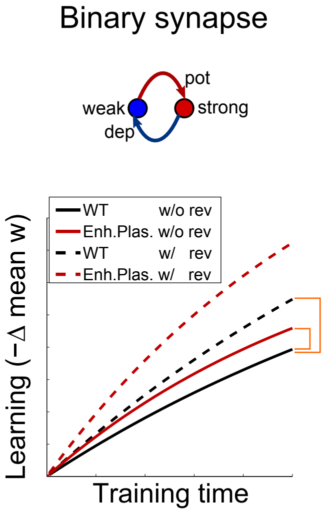
Multistate synapse

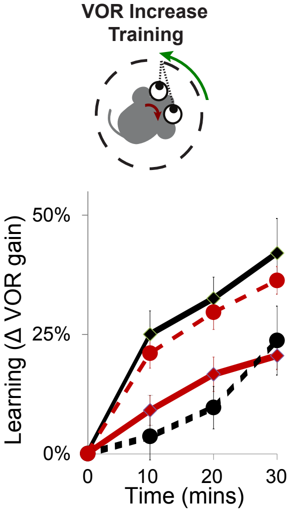


VOR Increase Training



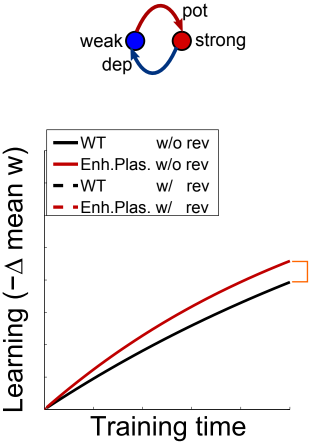
Simple synapses cannot explain the data



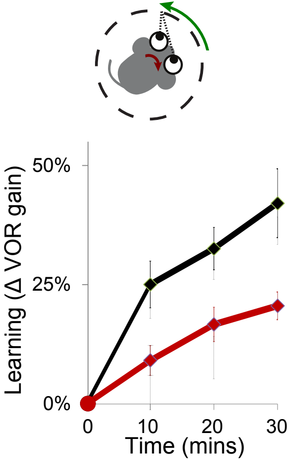


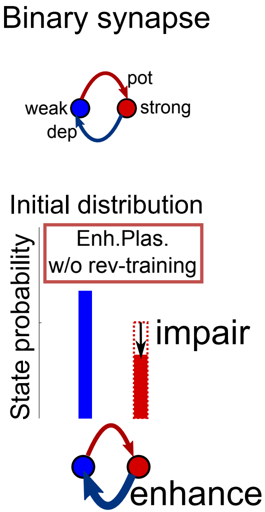
Simple synapses cannot explain the data

Binary synapse



VOR Increase Training





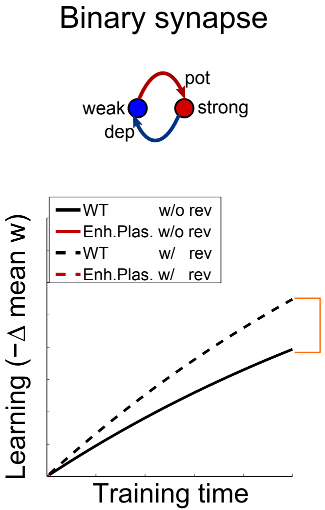
depletion effect

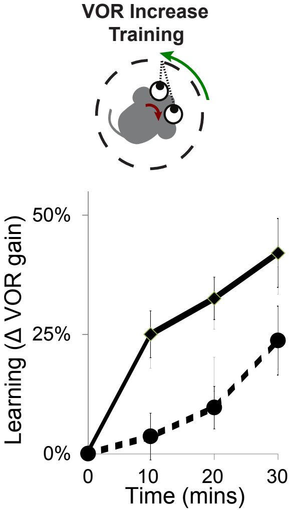
$<$

enhanced plasticity

$\Longrightarrow$ enhanced learning

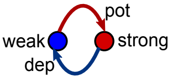
Simple synapses cannot explain the data



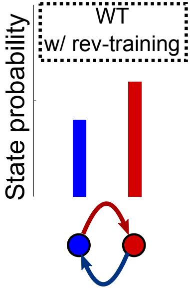


Simple synapses cannot explain the data

Binary synapse

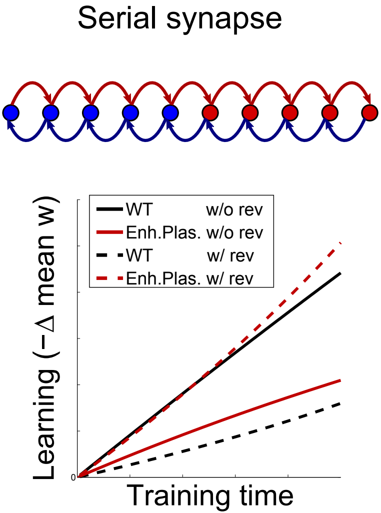


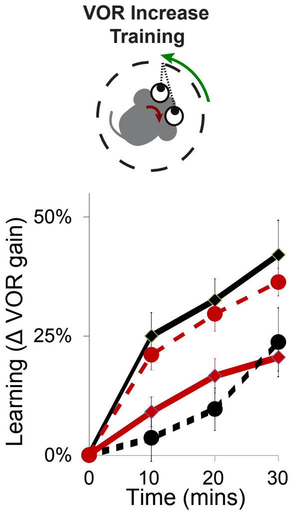
Initial distribution



reverse training
$\Longrightarrow$
replenishment
$\Longrightarrow$
enhanced learning

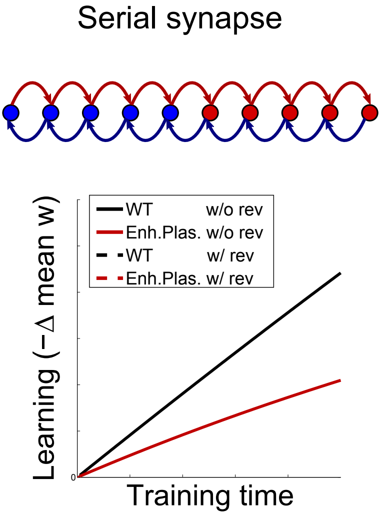
Complex metaplastic synapses can explain the data

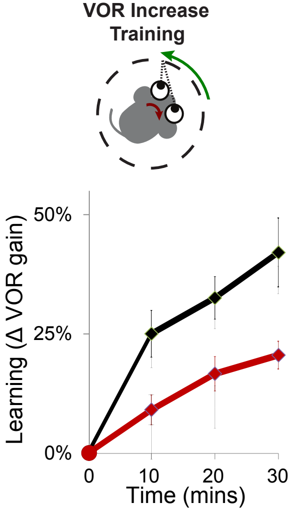




[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Complex metaplastic synapses can explain the data

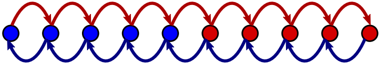


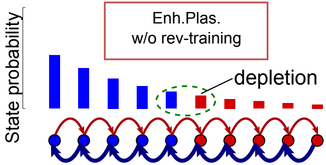


[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Complex metaplastic synapses can explain the data

Serial synapse





amplified depletion

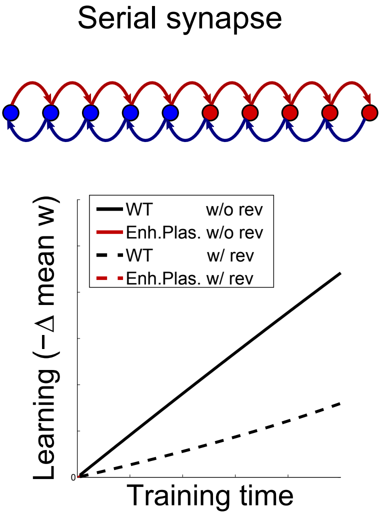
$>$

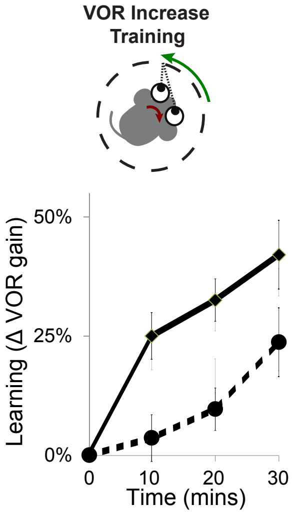
enhanced plasticity

$\Longrightarrow$ impaired learning

[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

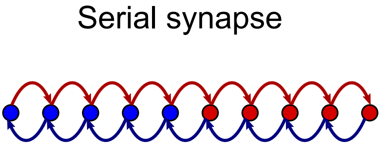
Complex metaplastic synapses can explain the data

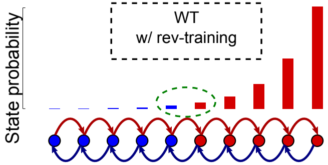




[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Complex metaplastic synapses can explain the data





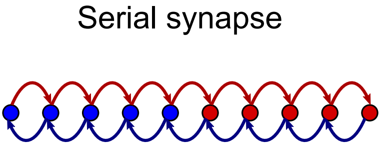
reverse training

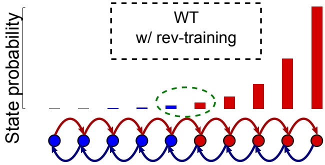
$+$

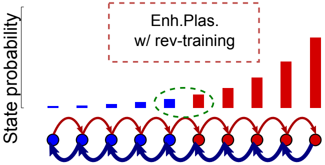
"stubborn" metaplasticity

$\Longrightarrow$ impaired learning

[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]



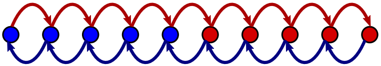




[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Complex metaplastic synapses can explain the data

Serial synapse

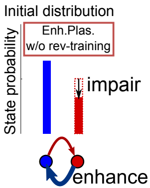


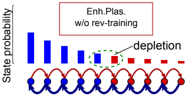
starting point:
labile states
$\downarrow$
enhanced plasticity
$\Longrightarrow$ impaired learning

starting point:
stubborn states
$\downarrow$
enhanced plasticity
$\Longrightarrow$ enhanced learning

[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Enhanced plasticity can enhance or impair learning



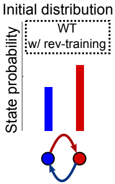


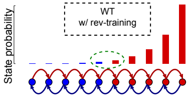
Intrinsic plasticity dominates depletion
↓
enhanced plasticity enhances learning

Depletion dominates intrinsic plasticity
↓
enhanced plasticity impairs learning

Key feature 1: Synaptic complexity that amplifies depletion effect.

Reverse-training can impair or enhance learning

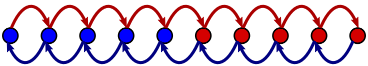




reverse-training repopulates boundary ↓ enhanced learning	reverse-training depopulates boundary ↓ impaired learning

Key feature 2: Synaptic stubbornness – metaplasticity where repeated potentiation impairs subsequent depression.

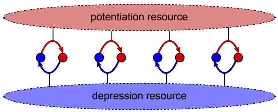
Essential features



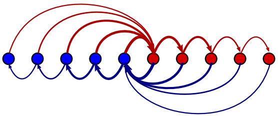
The success of the serial model relies on two features:

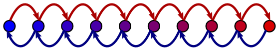
- Complexity - needed to for depletion to dominate enhanced plasticity,
- Stubbornness - repeated potentiation impairs subsequent depression.

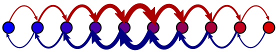
Fail:



Succeed:





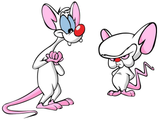


[Amit and Fusi (1994), Fusi et al. (2005)]

Conclusions

- Diverse behavioural patterns:
  Enhanced plasticity $\rightarrow$ enhance/impair learning (prior experience).
  Reverse-training $\rightarrow$ enhance/impair learning (plasticity rates).

- enhanced LTD vs. depletion $\rightarrow$ learning outcome.



- Predictions for synaptic physiology:
  Complexity: necessary to amplify depletion.
  Stubbornness: repeated potentiation impairs subsequent depression.

- We used behaviour to constrain the dynamics of synaptic plasticity.

Acknowledgements

Surya Ganguli
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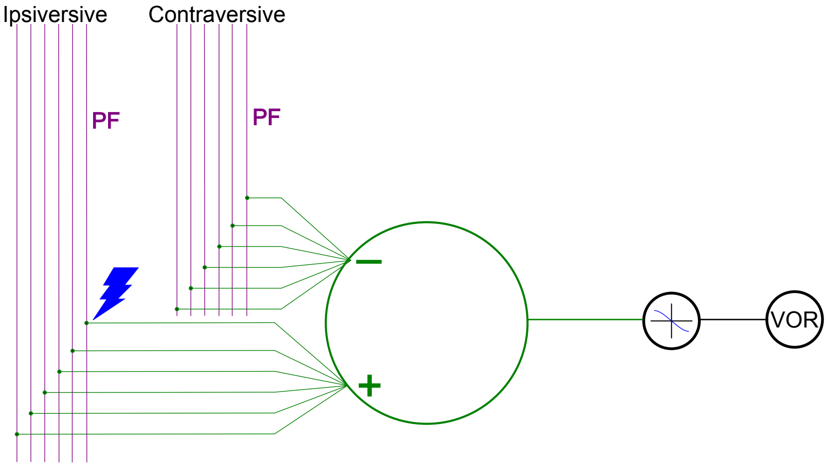
Han-Mi Lee

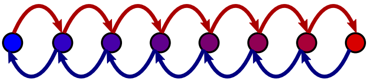
Funding: Swartz Foundation, Stanford Bio-X Genentech fellowship.

Model of circuit

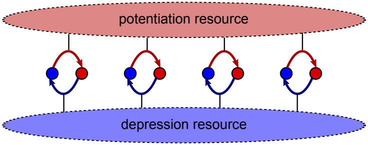


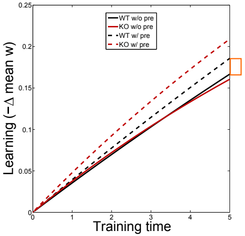
Other models that fail

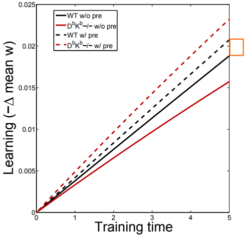
Multistate synapse



Pooled resource model



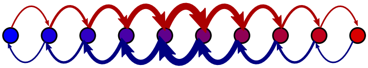


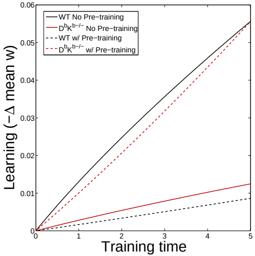


[Amit and Fusi (1994)]

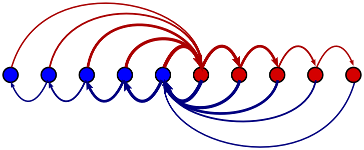
Other models that work

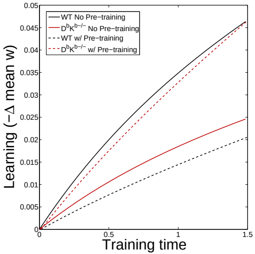
Non-uniform multistate model





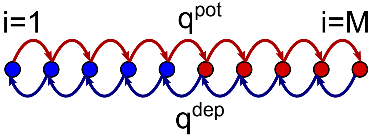
Cascade model





[Eusi et al. (2005)]

Mathematical explanation



Serial synapse: $\mathbf{p}_i^\infty \sim \mathcal{N}\left(\frac{q^{\text{pot}}}{q^{\text{dep}}}\right)^i$.

Learning rate $\sim \mathbf{p}_{M/2}^\infty \left(\frac{q^{\text{dep}}}{q^{\text{pot}}}\right) = \mathcal{N}\left(\frac{q^{\text{pot}}}{q^{\text{dep}}}\right)^{\frac{M}{2}-1}$.

For $M > 2$: larger $q^{\text{dep}} \implies$ slower learning.

For $M = 2$: larger $q^{\text{dep}} \implies$ larger $\mathcal{N} \implies$ faster learning.

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