Modelling impaired and enhanced learning with enhanced plasticity

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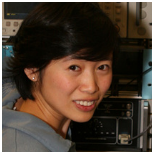
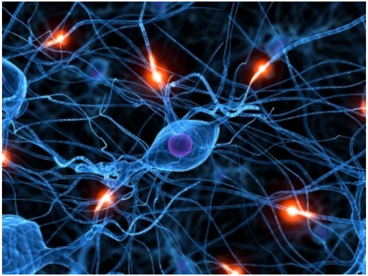
Barbara Nguyen-Vu



Grace Zhao

Introduction

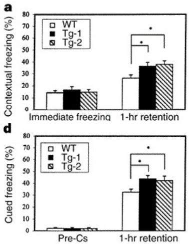
Learning requires synaptic plasticity.



Can we enhance learning by enhancing plasticity?

Enhanced plasticity *can* enhance learning

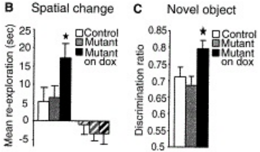
Overexpress NR2B



Fear conditioning

[Tang et al. (1999)]

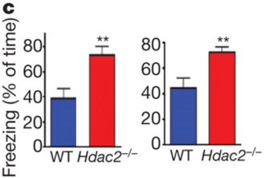
Inhibit CN



Novel object recog.

[Malleret et al. (2001)]

Knockout Hdac2

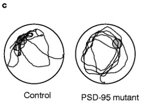


Fear conditioning

[Guan et al. (2009)]

Enhanced plasticity can *impair* learning

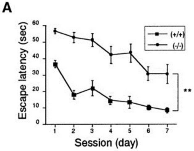
Mutate PSD-95



Water maze

[Migaud et al. (1998)]

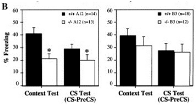
Knockout PTPδ



Water maze

[Uetani et al. (2000)]

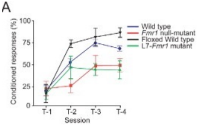
Delete Tmod2



Fear cond.

[Cox et al. (2003)]

Knockout FMR1



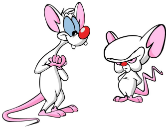
Eyeblink

[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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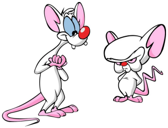
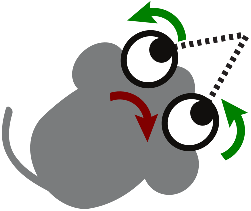


Why? How? When?

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.

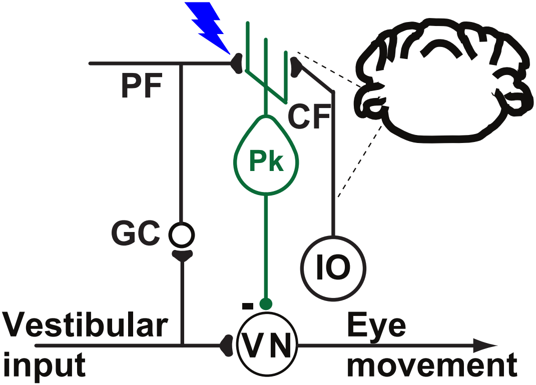
Requires control of VOR gain $= \frac{\text{eye velocity}}{\text{head velocity}}$.

Needs to be adjusted as eye muscles age, etc.

Vestibulo-Occular Reflex training

VOR Increase Training

VOR Decrease Training

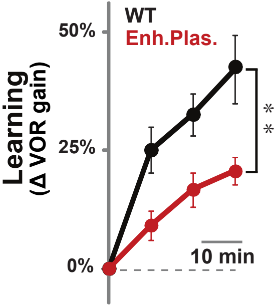


VOR increase:	LTD in PF-Pk synapses.
VOR decrease:	different mechanism, also reverses LTD in PF-Pk.

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

Enhanced plasticity impairs learning

Expectation: enhanced LTD $\rightarrow$ enhanced learning.



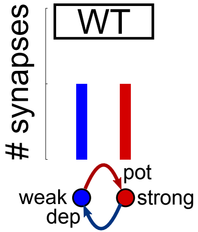
Experiment: enhanced plasticity $\rightarrow$ impaired learning.

Knockout of MHC-I K^bD^b molecules in PF-Pk synapses
$\rightarrow$ 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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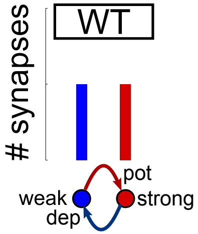
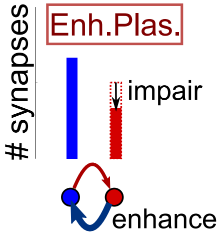
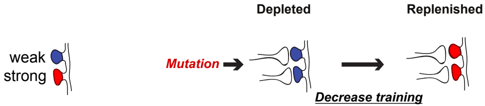




Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

Replenishment by reverse-training

Replenishment by reverse-training



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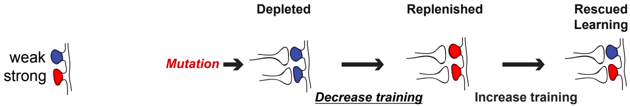

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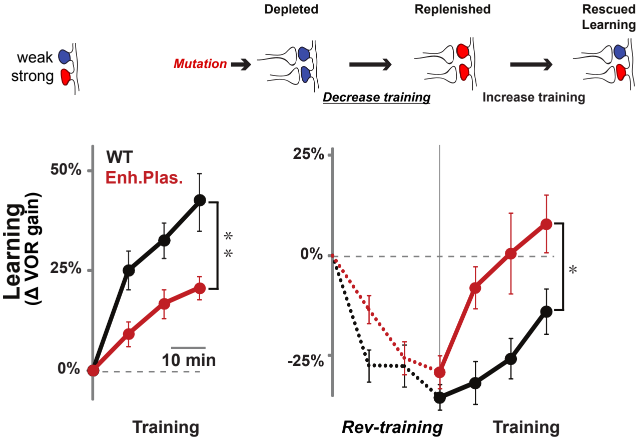

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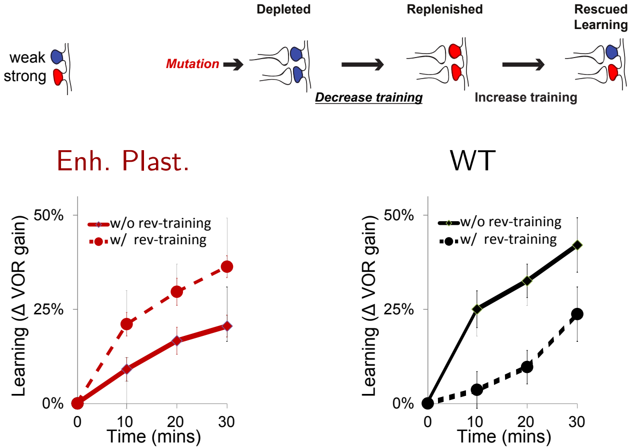
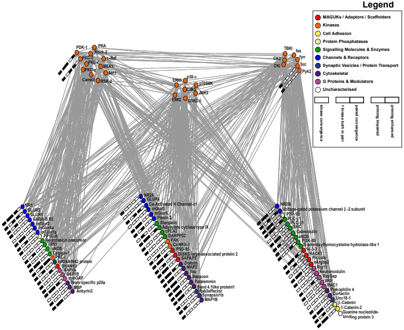
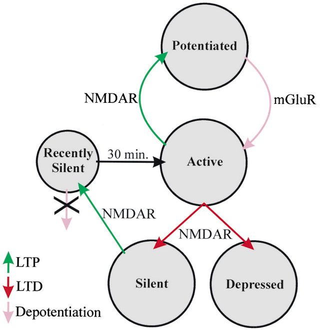


Question 2: How can replenishment *ever* impair learning?

Synapses are complex



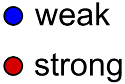
[Coba et al. (2009)]

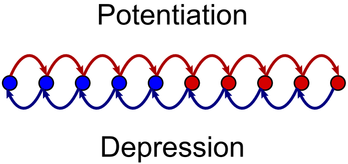


[Montgomery and Madison (2002)]

Models of complex synaptic dynamics

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





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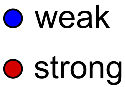

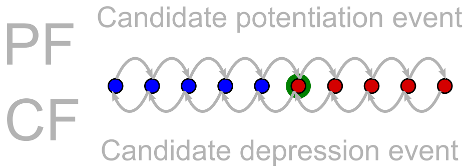

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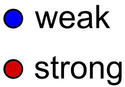

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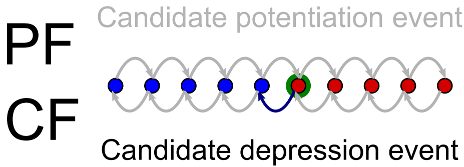

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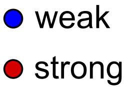

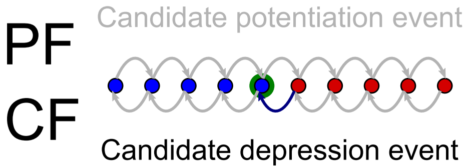

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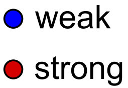

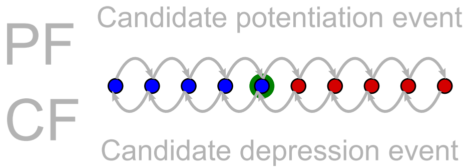

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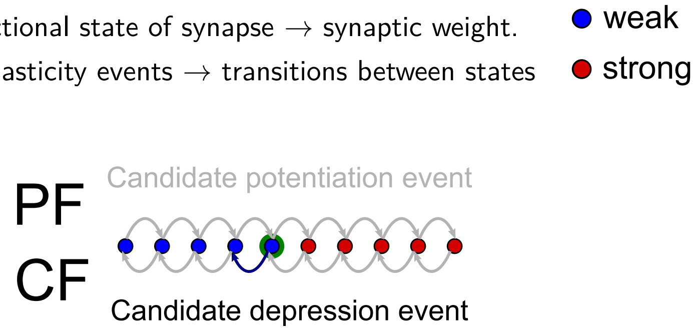

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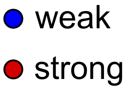

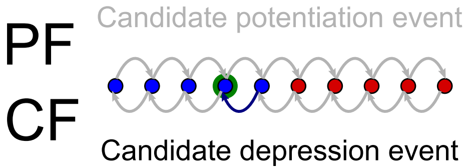

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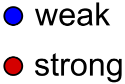

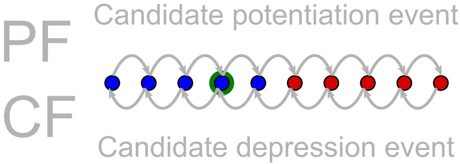

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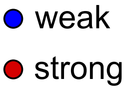

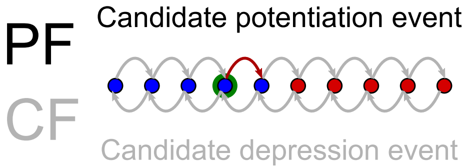

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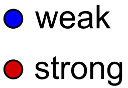

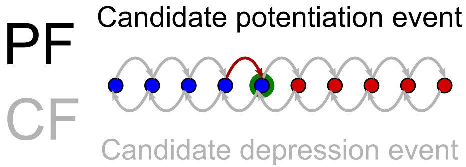

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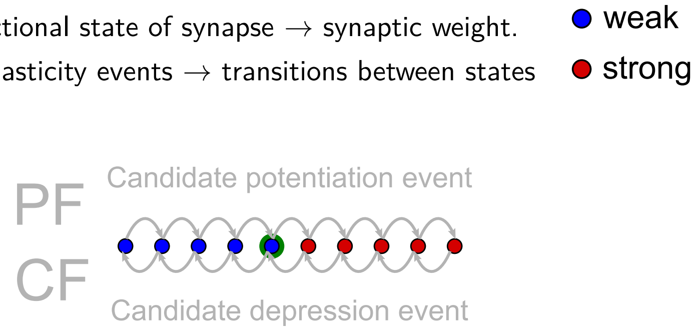

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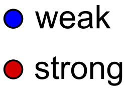

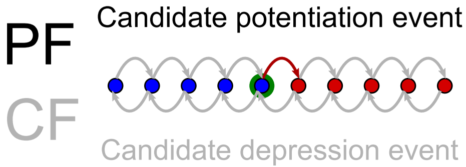

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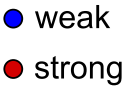

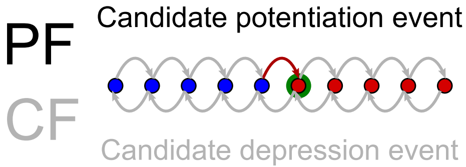

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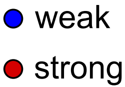

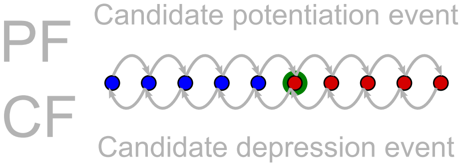

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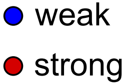

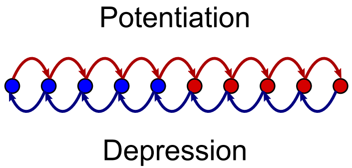

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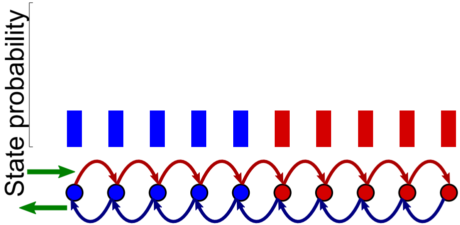
Modelling VOR experiments



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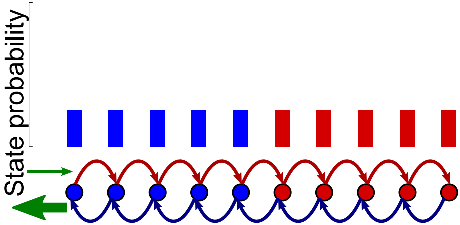
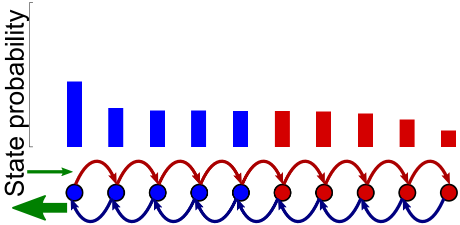


Training: different CF activity $\Longrightarrow$
change frequency of pot/dep events.

Modelling VOR experiments



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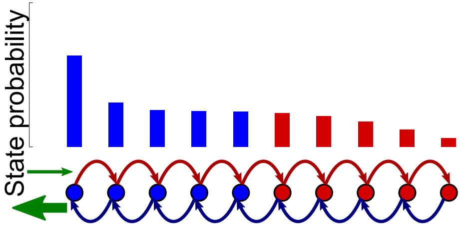

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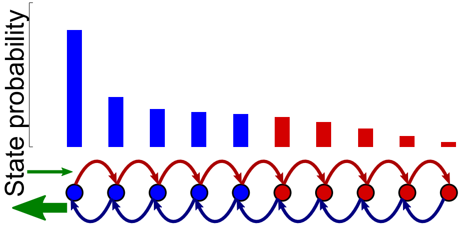

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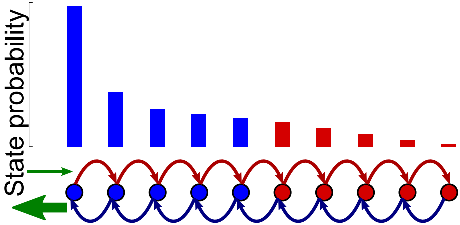

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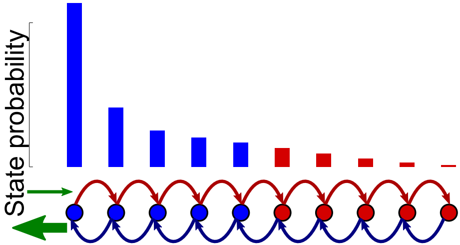

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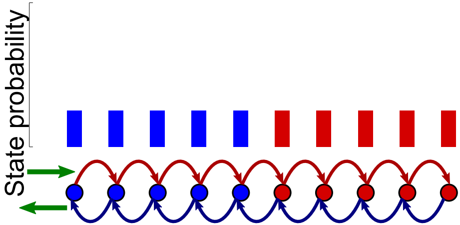
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

Modelling VOR experiments

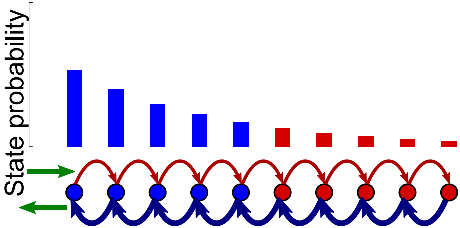


Training: different CF activity $\implies$
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

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

Modelling VOR experiments



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.

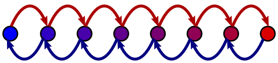
Question 2: How can replenishment *ever* impair learning?

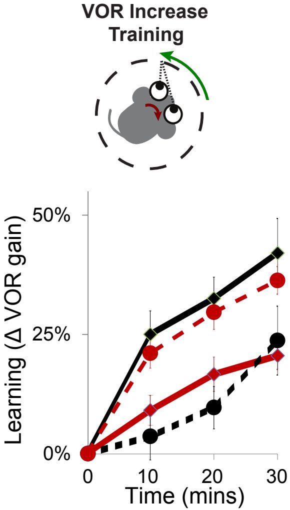
Enhanced plasticity $\rightarrow$ enhanced/impaired learning

Big question: Why?

Simple synapses cannot explain the data

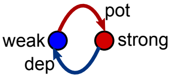
Multistate synapse

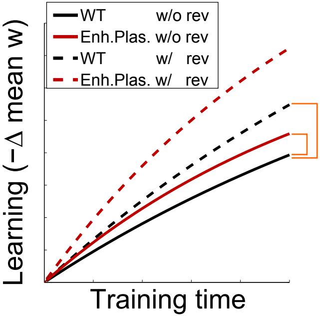




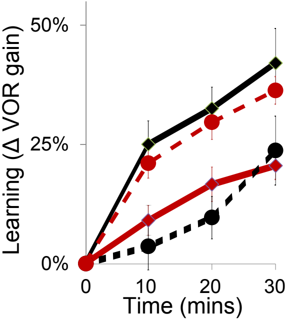
Simple synapses cannot explain the data

Binary synapse

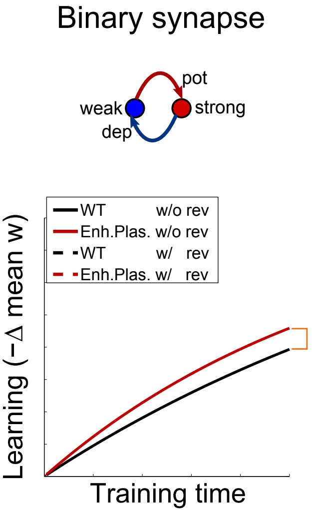


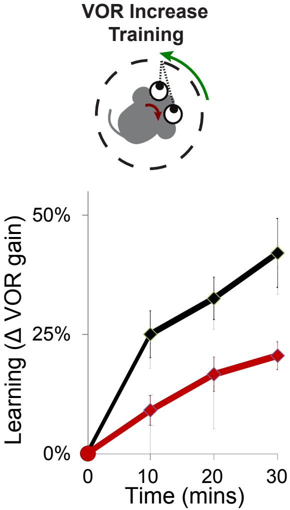


VOR Increase Training

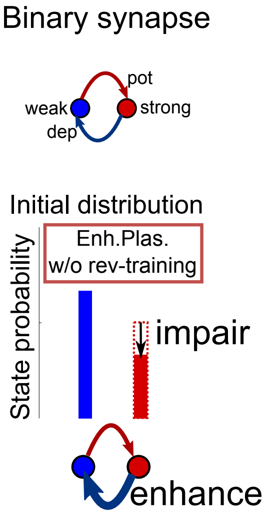


Simple synapses cannot explain the data





Simple synapses cannot explain the data



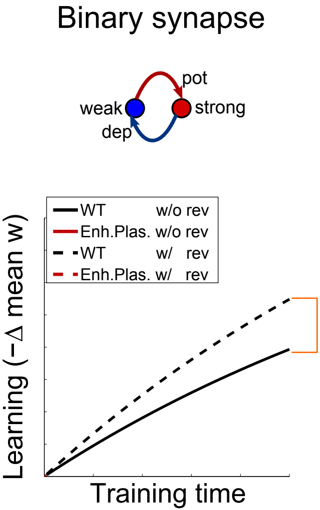
depletion effect

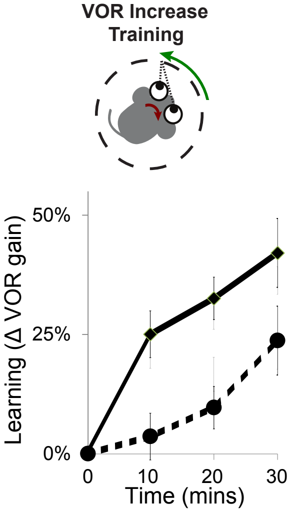
$<$

enhanced plasticity

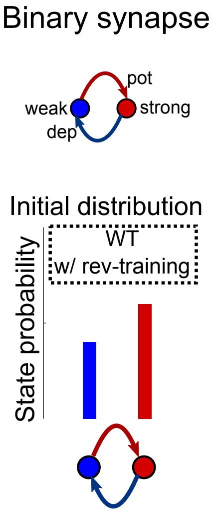
$\Longrightarrow$ enhanced learning

Simple synapses cannot explain the data





Simple synapses cannot explain the data



reverse training

$\Longrightarrow$

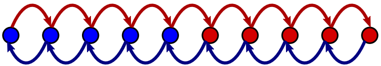
replenishment

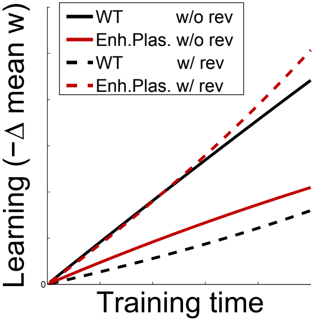
$\Longrightarrow$

enhanced learning

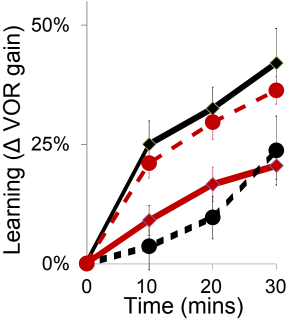
Complex metaplastic synapses can explain the data

Serial synapse





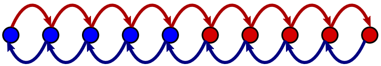
VOR Increase Training

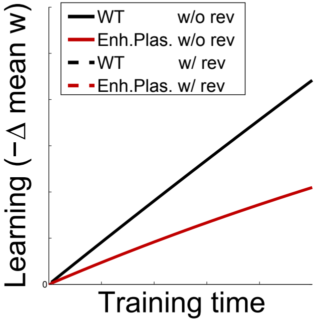


[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

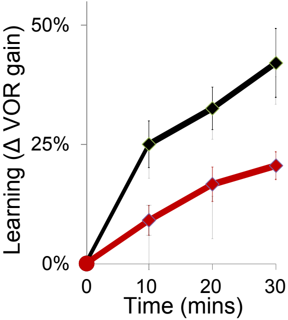
Complex metaplastic synapses can explain the data

Serial synapse





VOR Increase Training



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

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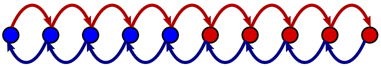
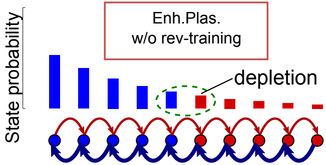




amplified depletion

$>$

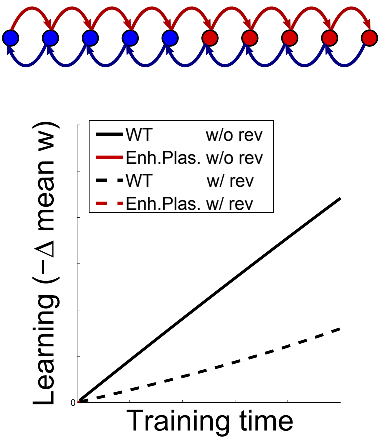
enhanced plasticity

$\Longrightarrow$ impaired learning

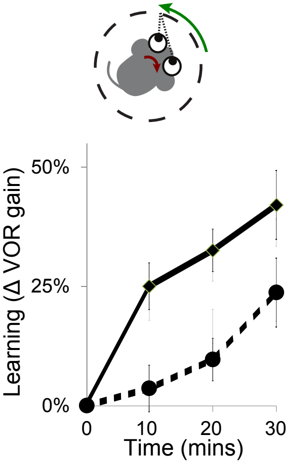
[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Complex metaplastic synapses can explain the data

Serial synapse



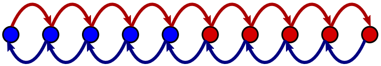
VOR Increase Training

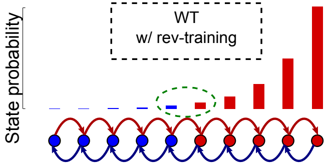


[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Complex metaplastic synapses can explain the data

Serial synapse





reverse training

$+$

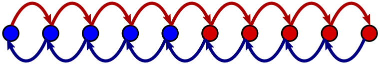
"stubborn" metaplasticity

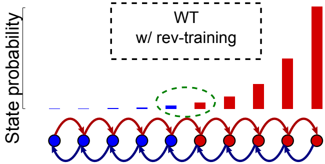
$\Longrightarrow$ impaired learning

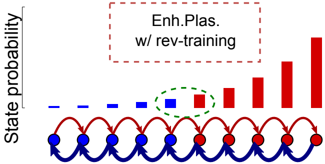
[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Complex metaplastic synapses can explain the data

Serial synapse



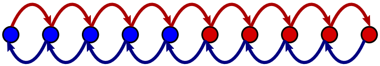




[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Complex metaplastic synapses can explain the data

Serial synapse

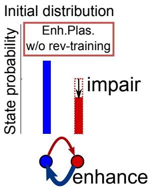


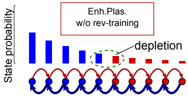
starting point:
labile states
$\downarrow$
enhanced plasticity
$\implies$ impaired learning

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

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

Enhanced plasticity can enhance or impair learning

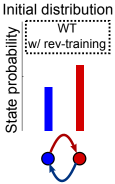


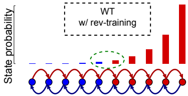


Intrinsic plasticity dominates depletion	Depletion dominates intrinsic plasticity
$\downarrow$	$\downarrow$
enhanced plasticity enhances learning	enhanced plasticity impairs learning

Key feature 1: Synaptic complexity that amplifies depletion effect.

Reverse-training can impair or enhance learning



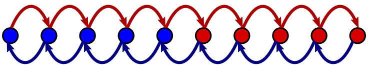


reverse-training
repopulates boundary
↓
enhanced learning

reverse-training
depopulates boundary
↓
impaired learning

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

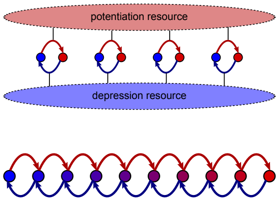
Essential features



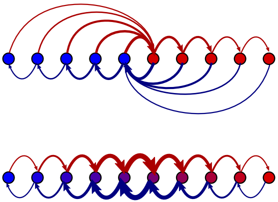
The success of the serial model relies on two features:

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

Fail:



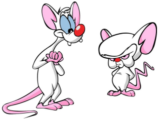
Succeed:



[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.

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Grace Zhao
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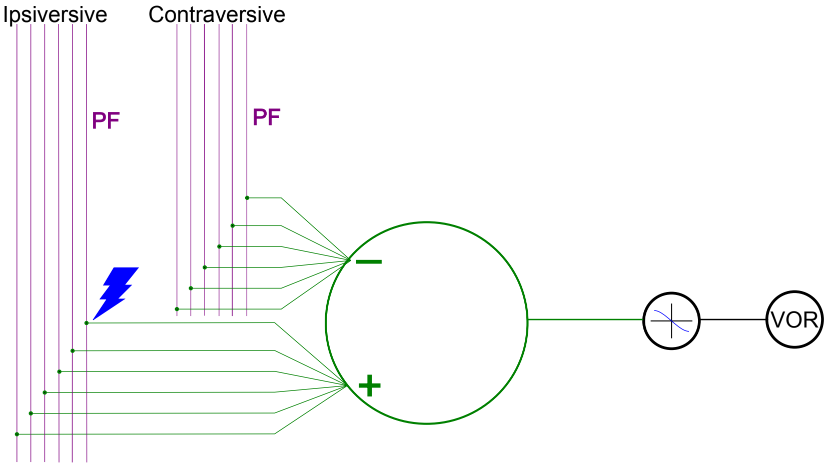
Han-Mi Lee

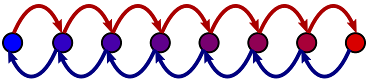
Funding: Swartz Foundation, Stanford Bio-X Genentech fellowship.

Model of circuit

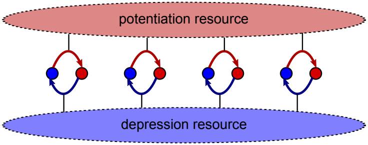


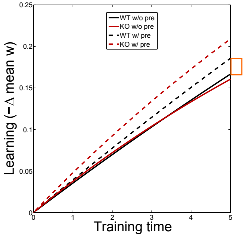
Other models that fail

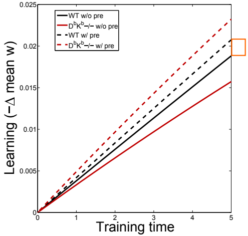
Multistate synapse



Pooled resource model



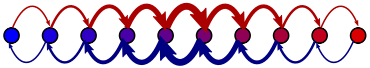


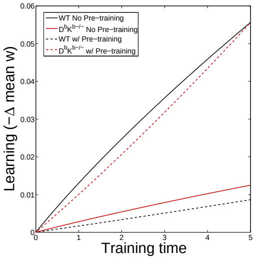


[Amit and Fusi (1994)]

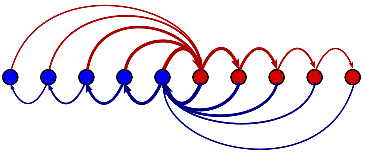
Other models that work

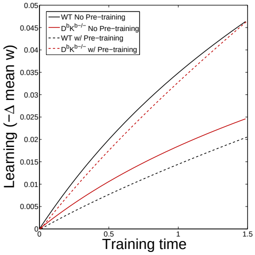
Non-uniform multistate model





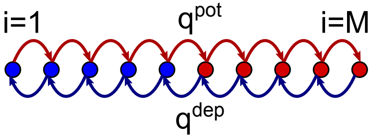
Cascade model





[Fusi 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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