

Learning and memory with complex synaptic plasticity

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Stanford University, Applied Physics

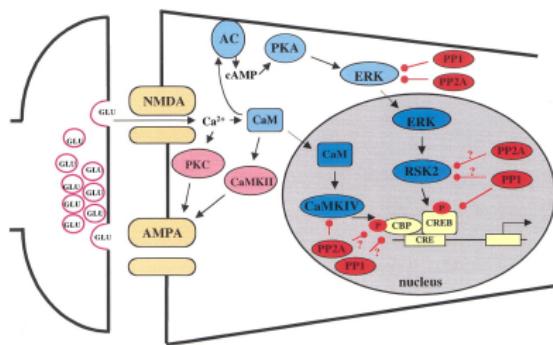
March 25, 2019

What is a synapse?

Theorists

W_{ij}

Experimentalists



[Klann (2002)]

Storage capacity of synaptic memory

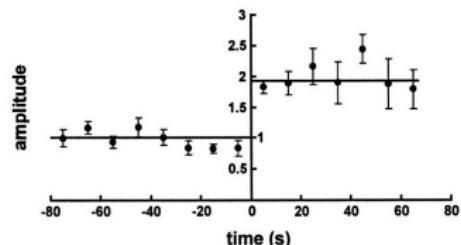
Hopfield, perceptron have capacity $\propto N$, (# synapses).

Assumes unbounded analog synapses

With discrete, finite synapses:

\implies memory capacity $\sim \mathcal{O}(\log N)$.

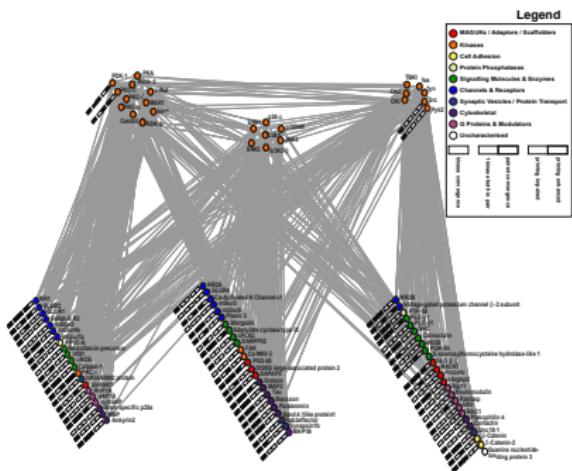
[Amit and Fusi (1992), Amit and Fusi (1994)]



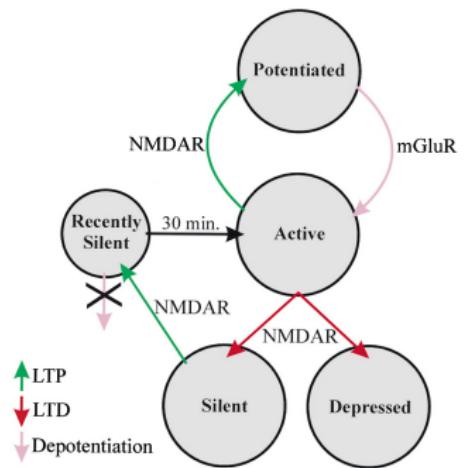
[Petersen et al. (1998), O'Connor et al. (2005)]

New memories overwrite old \implies stability-plasticity dilemma.

Synapses are complex



[Coba et al. (2009)]



[Montgomery and Madison (2002)]

Outline

1 Learning with enhanced plasticity

- Effects of enhanced plasticity on VOR learning
- Synaptic models of VOR learning
- Learning outcomes of mice and models

2 Memory over different timescales

Section 1

Learning with enhanced plasticity

Benefits of enhanced plasticity?

Learning requires synaptic plasticity.

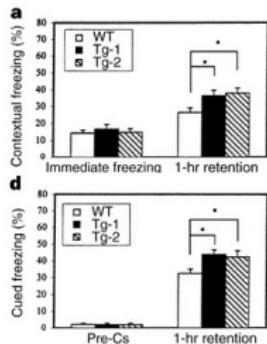


Can we enhance learning by enhancing plasticity?

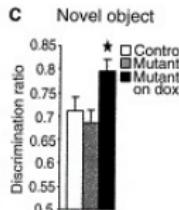
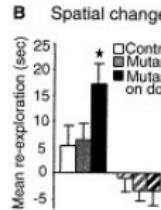


Enhanced plasticity *can* enhance learning

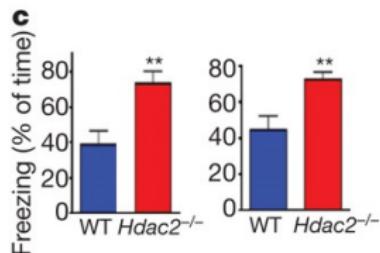
Overexpress NR2B



Inhibit CN



Knockout Hdac2



Fear conditioning

[Tang et al. (1999)]

Novel object recog.

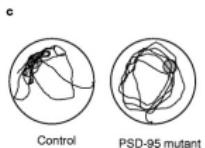
[Malleret et al. (2001)]

Fear conditioning

[Guan et al. (2009)]

Enhanced plasticity can *impair* learning

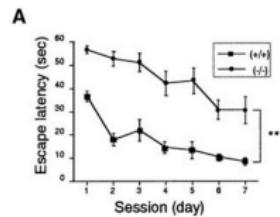
Mutate PSD-95



Water maze

[Migaud et al. (1998)]

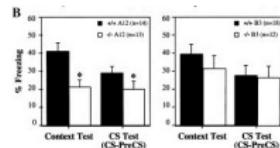
Knockout PTP δ



Water maze

[Uetani et al. (2000)]

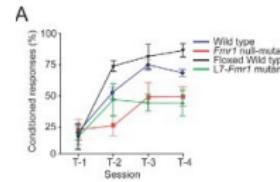
Delete Tmod2



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 → enhanced learning.
Sometimes enhanced plasticity → impaired learning.

Why? How? When?



Overview

Sometimes enhanced plasticity → enhanced learning.
Sometimes enhanced plasticity → impaired learning.



Why? How? When?

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

Simple synapses **cannot** explain behaviour. **Complex synapses** are required.
→ predictions for synaptic physiology.

Vestibulo-Occular Reflex

Eye movements compensate for head movements
⇒ 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.

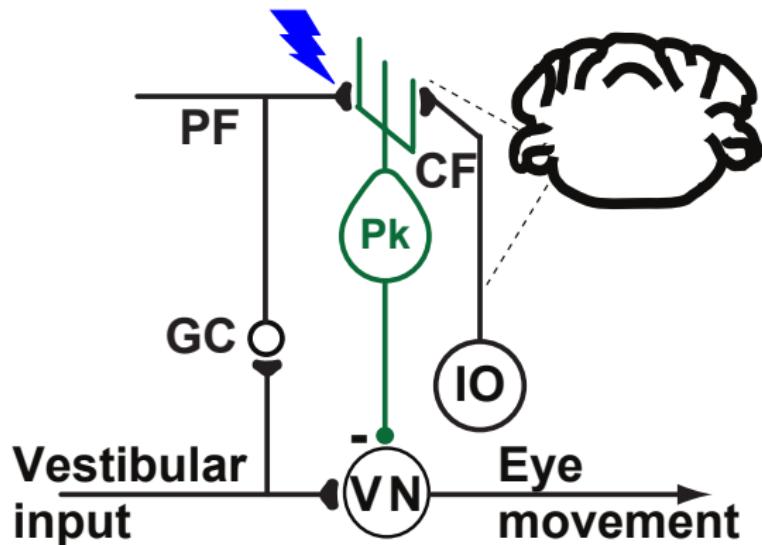


Vestibulo-Occular Reflex training

VOR Increase
Training



VOR Decrease
Training



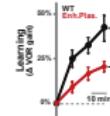
VOR increase: LTD in PF-Pk synapses.
VOR decrease: different mechanism,
also reverses LTD in PF-Pk.

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

Enhanced plasticity impairs learning

Expectation: enhanced LTD \rightarrow enhanced learning.

VOR Increase Training



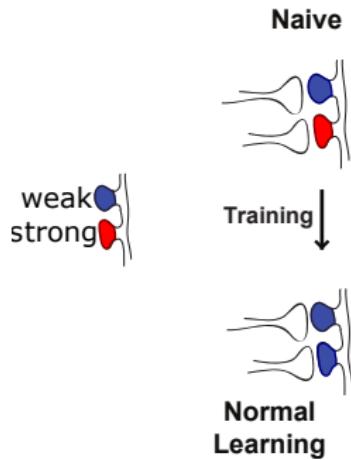
Experiment: enhanced plasticity \rightarrow impaired learning.

Knockout of MHC-I K^bD^b molecules in PF-Pk synapses
 \rightarrow lower threshold for LTD

[McConnell et al. (2009)]

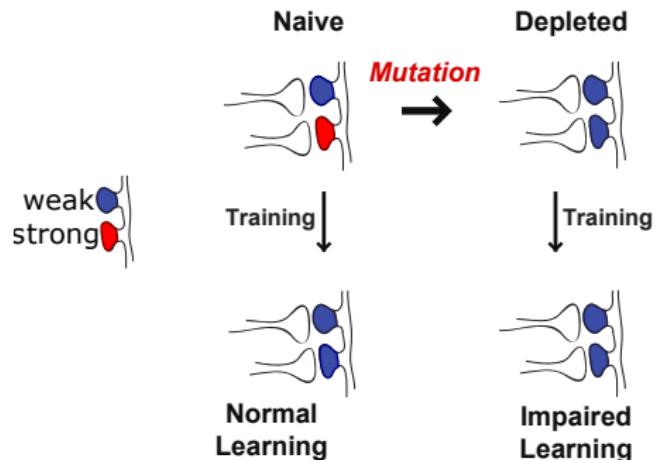
Depletion hypothesis

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



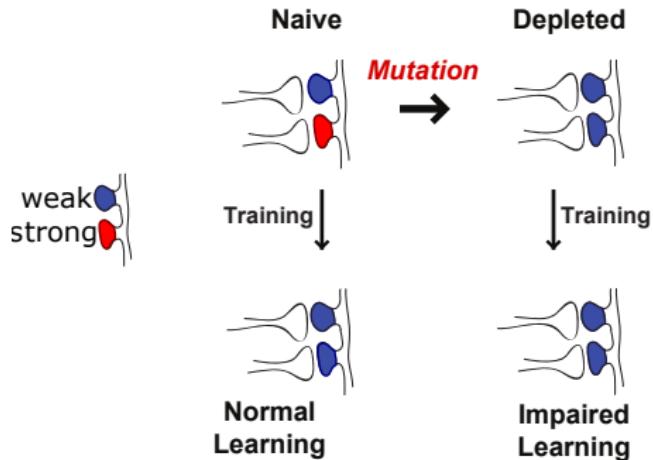
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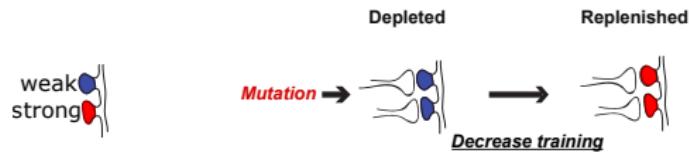


Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

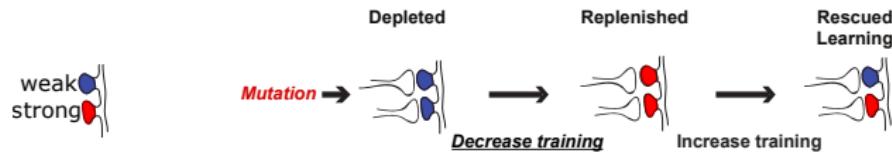
Replenishment by reverse-training



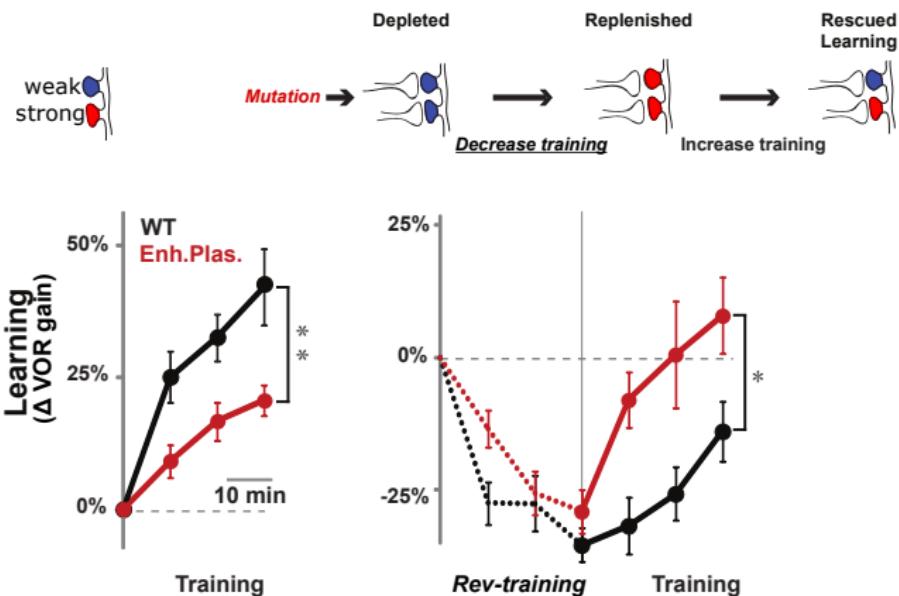
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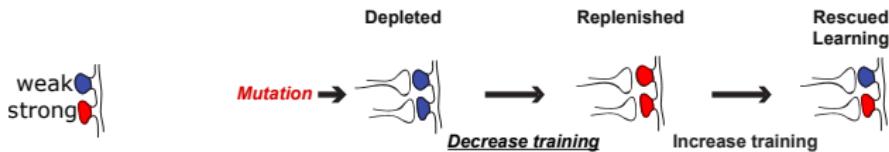
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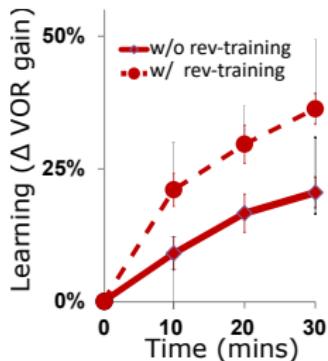
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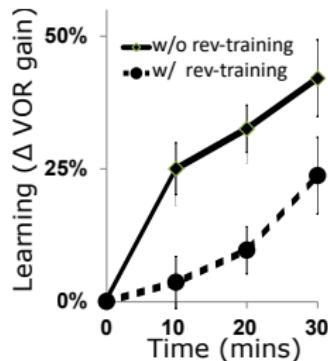
Replenishment by reverse-training



Enh. Plast.

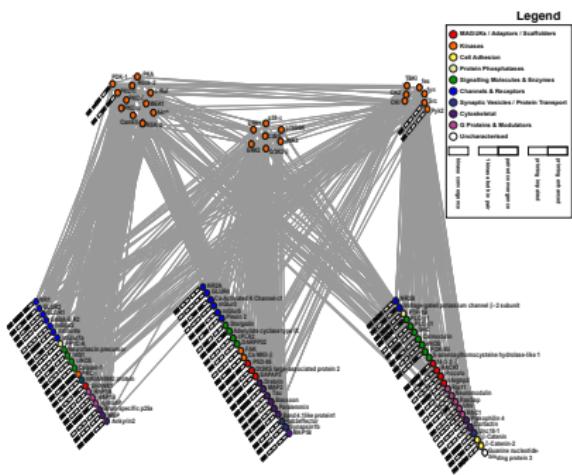


WT

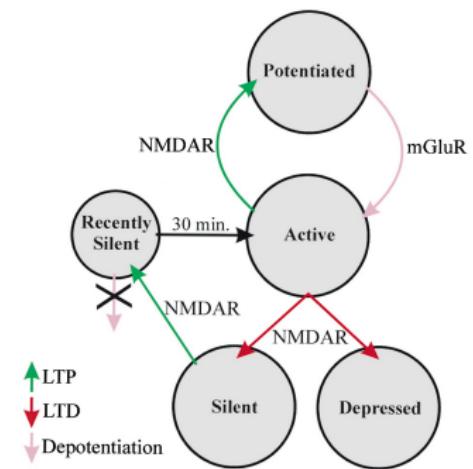


Question 2: How can replenishment ever impair learning?

Synapses are complex



[Coba et al. (2009)]



[Montgomery and Madison (2002)]

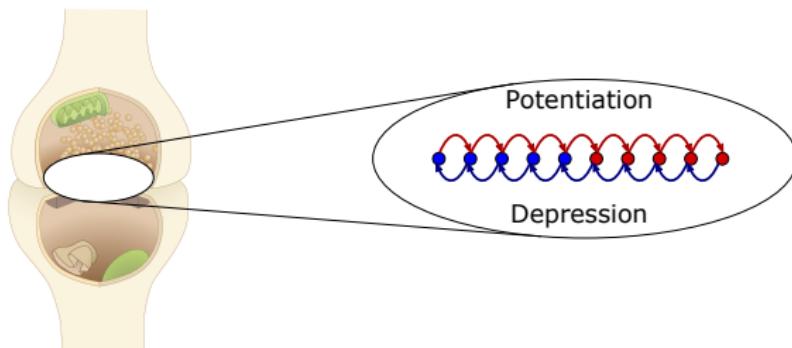
Models of complex synaptic dynamics



Models of complex synaptic dynamics

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

weak
strong



States: NMDAR subunit composition, CaMK II autophosphorylation, activating PKC, p38 MAPK,...

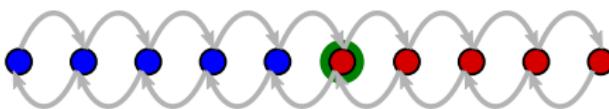
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]

[Smith et al. (2006); Lahiri and Ganguli (2013)]

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Potentiation event

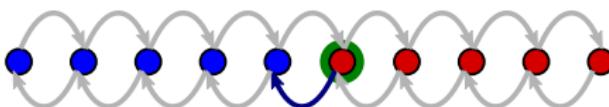


Depression event

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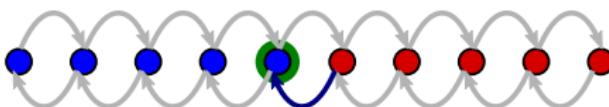


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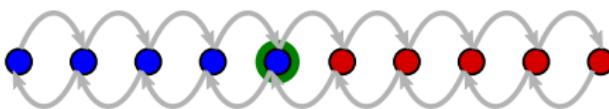


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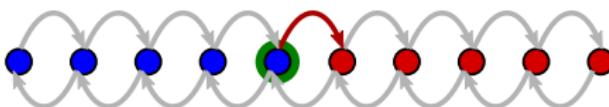


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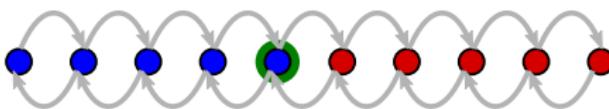


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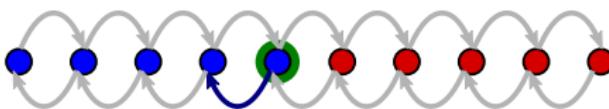


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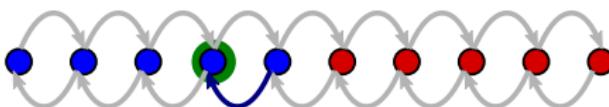
Depression event

Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

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Potentiation event



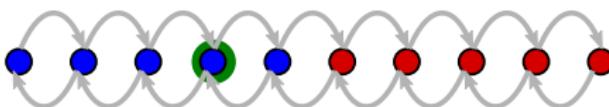
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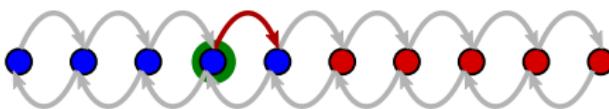
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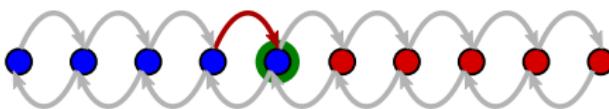
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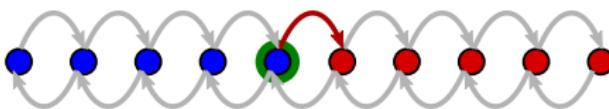
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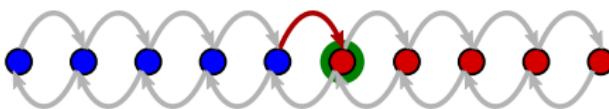
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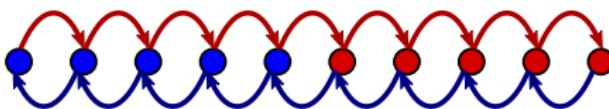
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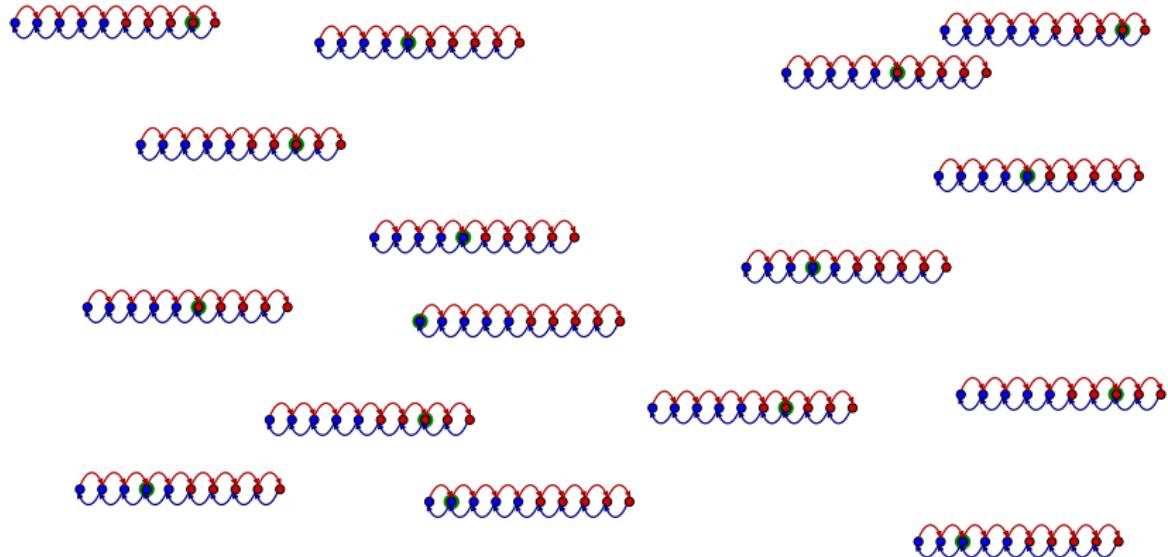
Potentiation



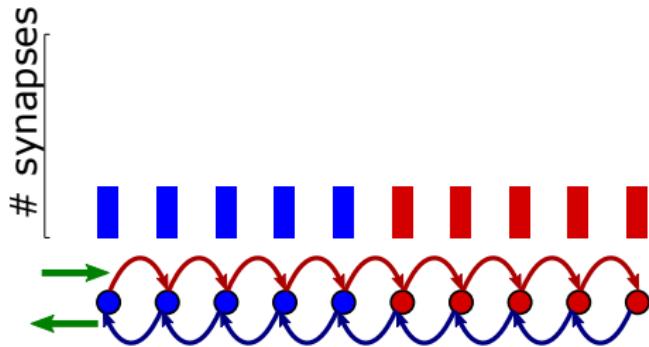
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Modelling VOR experiments

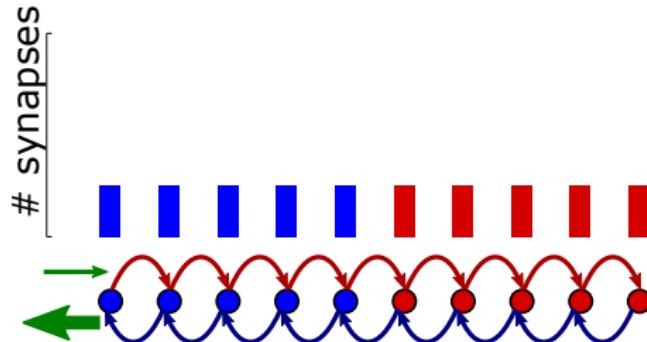


Modelling VOR experiments



Modelling VOR experiments

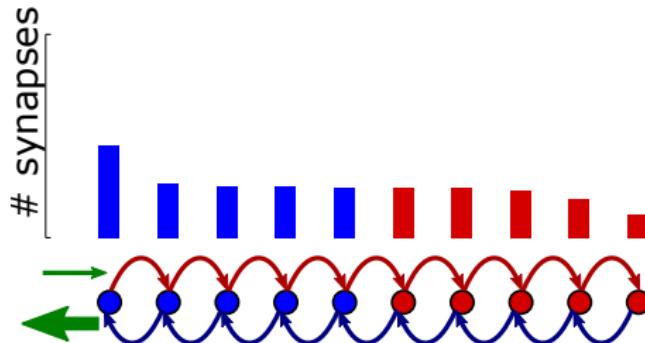
PF-Pk LTD → VOR increase



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

Modelling VOR experiments

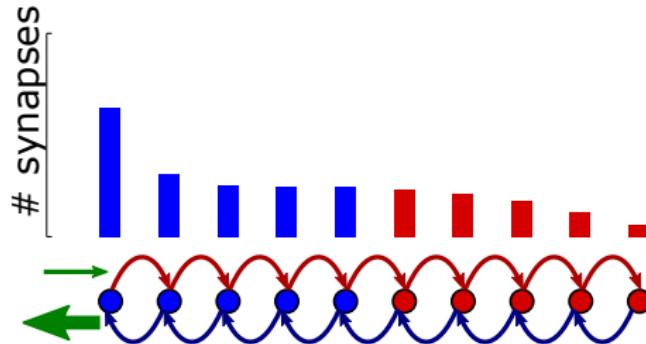
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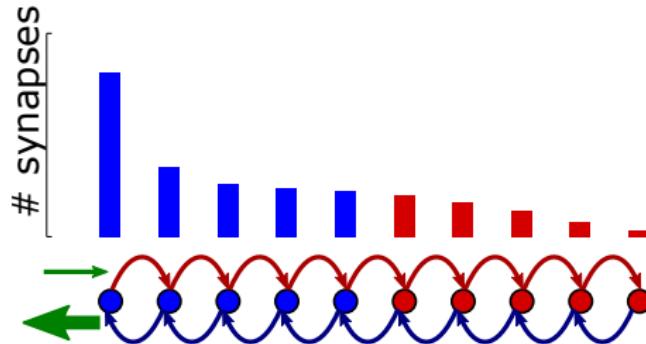
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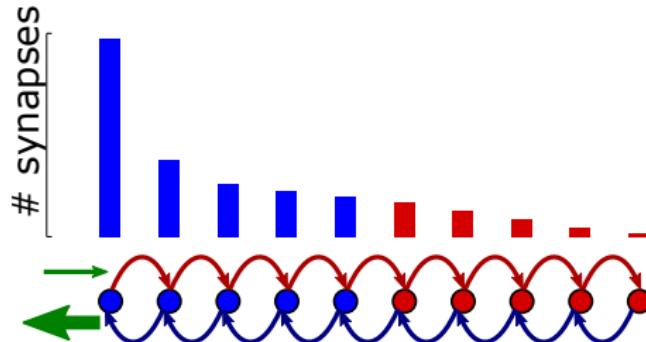
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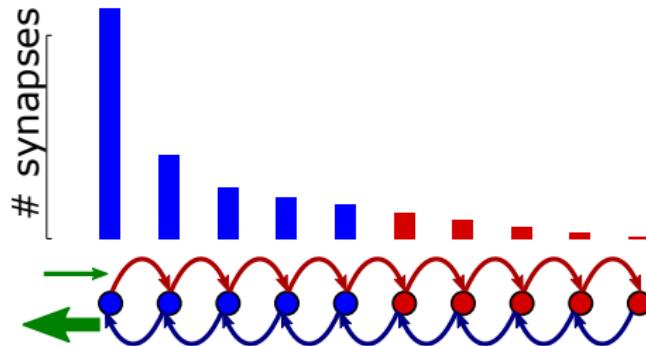
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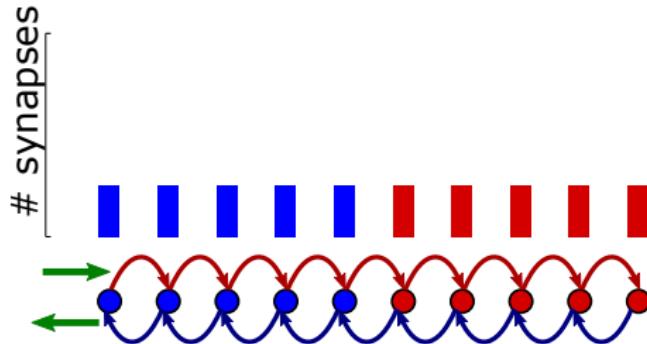


Training: different CF activity \implies
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Learning: decrease in average synaptic weight.

Modelling VOR experiments

PF-Pk LTD → VOR increase



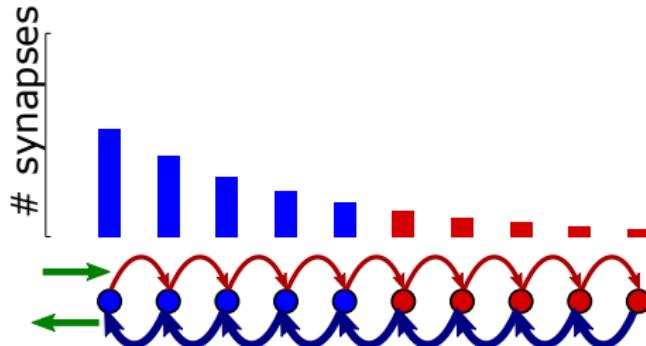
Training: different CF activity \Rightarrow
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Learning: decrease in average synaptic weight.

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

Modelling VOR experiments

PF-Pk LTD → VOR increase



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

Learning: decrease in average synaptic weight.

Mutation: lower threshold for LTD \Rightarrow
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.

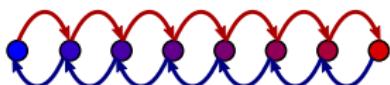
Question 2: How can replenishment ever impair learning?

Enhanced plasticity → enhanced/impaired learning

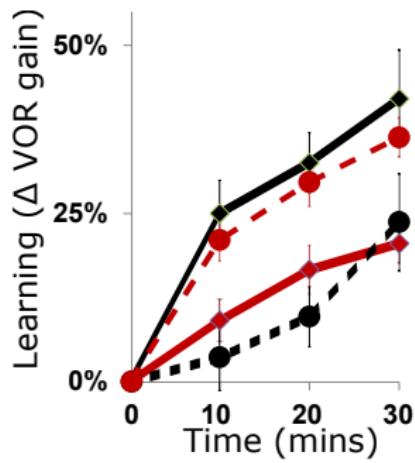
Big question: Why? When?

Simple synapses cannot explain the data

Multistate synapse

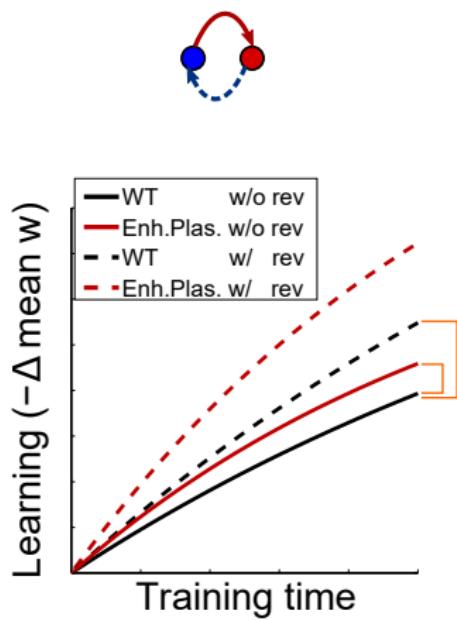


VOR Increase
Training

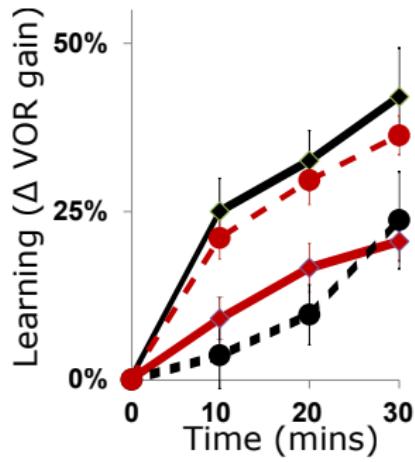


Simple synapses cannot explain the data

Two-state model

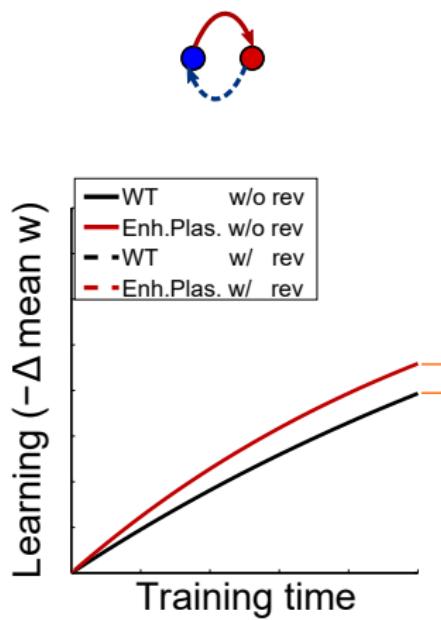


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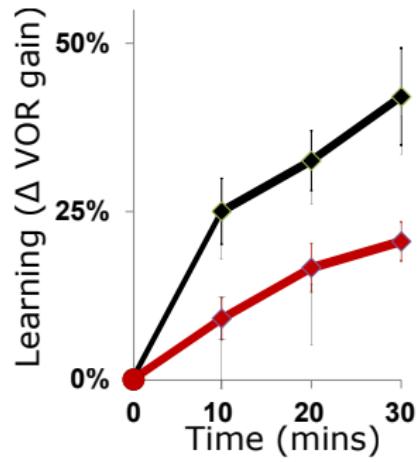


Simple synapses cannot explain the data

Two-state model



VOR Increase
Training



Simple synapses cannot explain the data

Two-state model



Initial distribution

Enh.Plas.
w/o rev-training

synapses



enhance

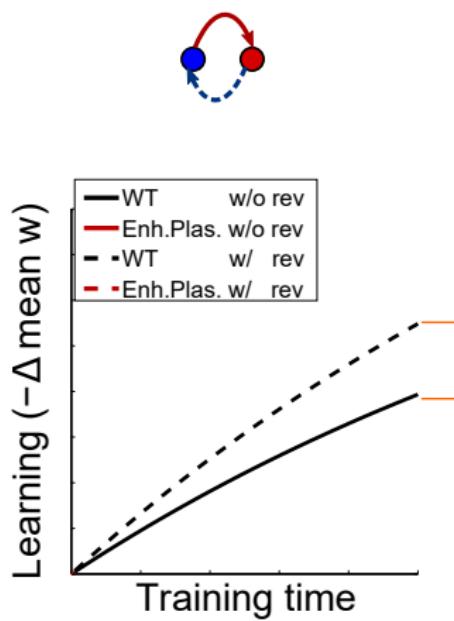
depletion effect

<
enhanced plasticity

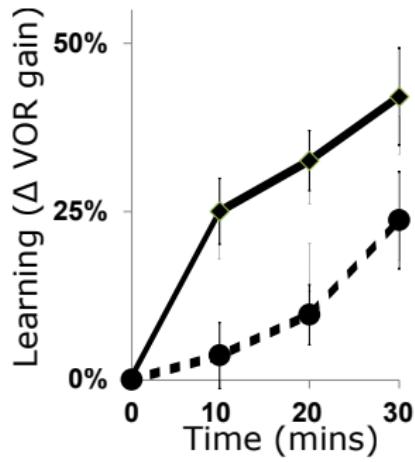
⇒ enhanced learning

Simple synapses cannot explain the data

Two-state model



VOR Increase
Training



Simple synapses cannot explain the data

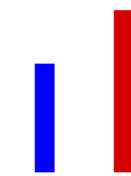
Two-state model



Initial distribution

WT
w/ rev-training

synapses



reverse training

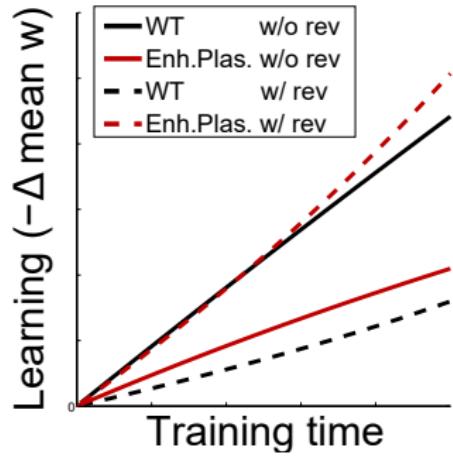
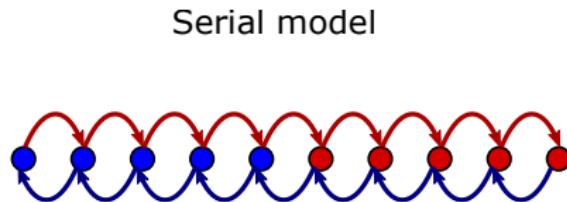


replenishment

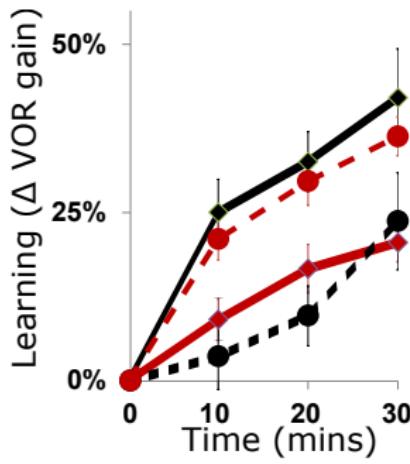


enhanced learning

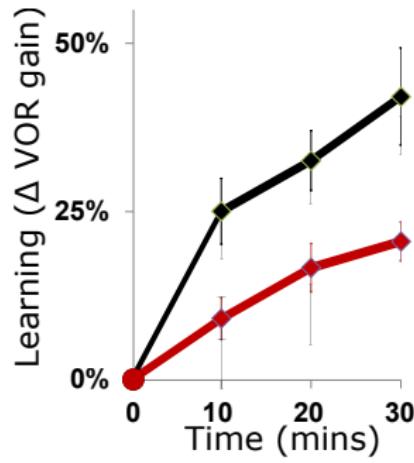
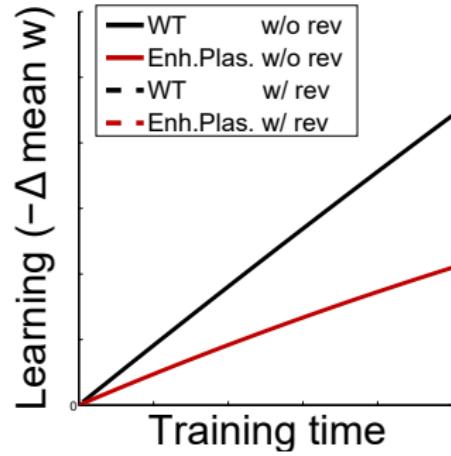
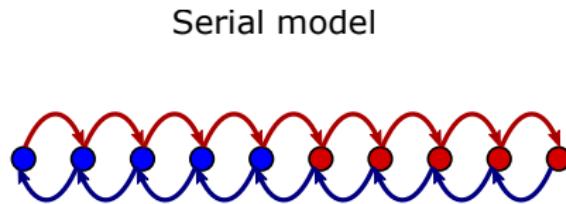
Complex metaplastic synapses can explain the data



VOR Increase
Training

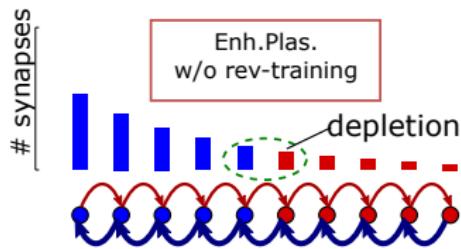
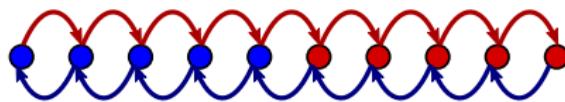


Complex metaplastic synapses can explain the data



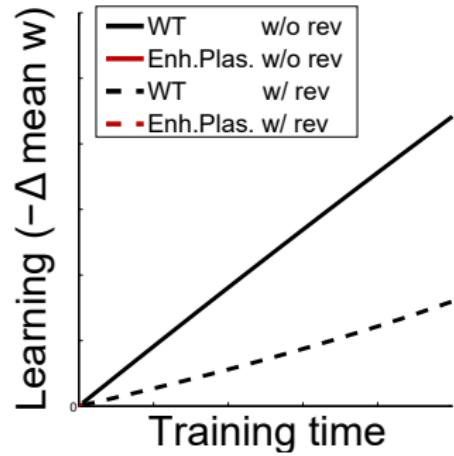
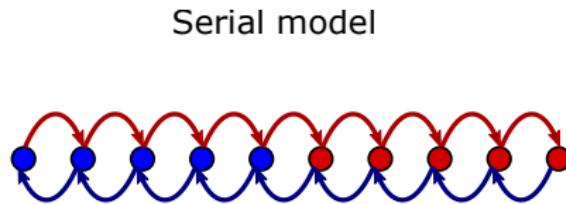
Complex metaplastic synapses can explain the data

Serial model

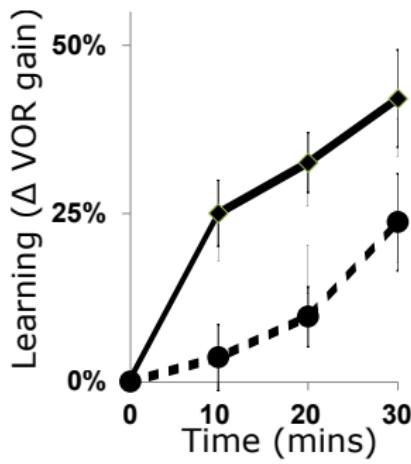


amplified depletion
>
enhanced plasticity
⇒ impaired learning

Complex metaplastic synapses can explain the data

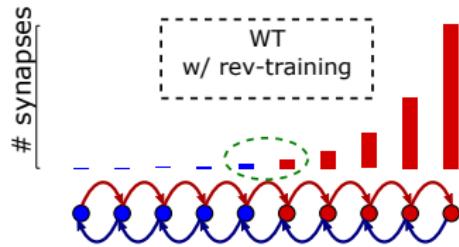
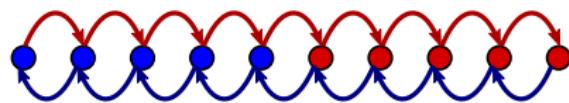


VOR Increase
Training



Complex metaplastic synapses can explain the data

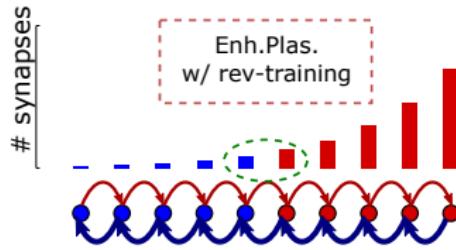
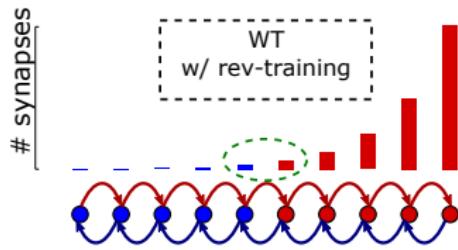
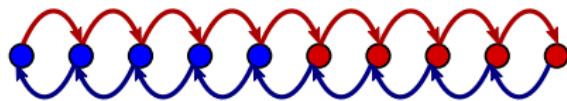
Serial model



reverse training
+
“stubborn” metaplasticity
⇒ impaired learning

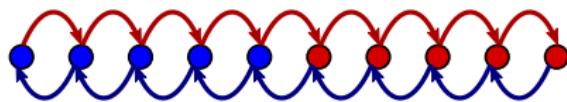
Complex metaplastic synapses can explain the data

Serial model



Complex metaplastic synapses can explain the data

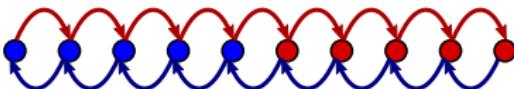
Serial model



starting point:
labile states
↓
enhanced plasticity
 \implies impaired learning

starting point:
stubborn states
↓
enhanced plasticity
 \implies enhanced learning

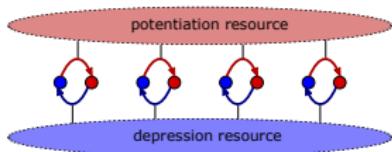
Essential features



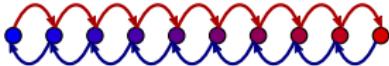
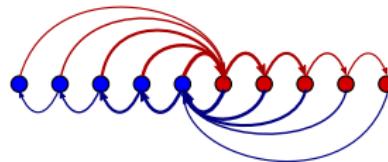
The success of the serial model relies on two features:

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

Fail:



Succeed:



Conclusions

- Diverse behavioural patterns:
Enhanced plasticity → enhance/impair learning (prior experience).
Reverse-training → enhance/impair learning (plasticity rates).
- **enhanced LTD vs. depletion** → 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.



Section 2

Memory over different timescales

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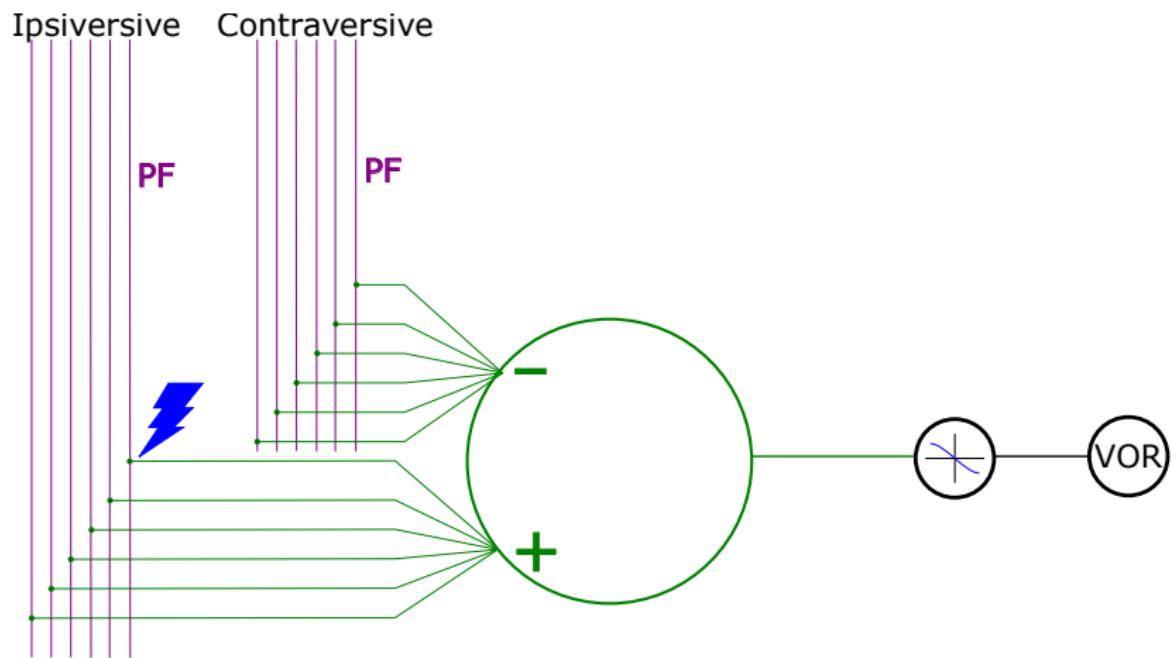
Aparna Suvrathan

Carla Shatz

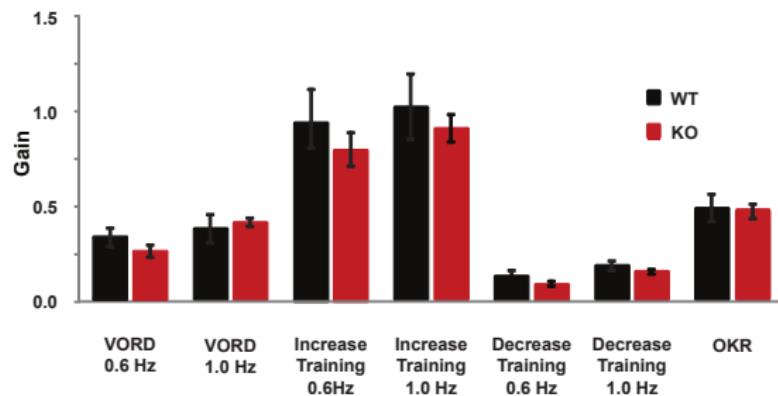
Han-Mi Lee

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

Model of circuit

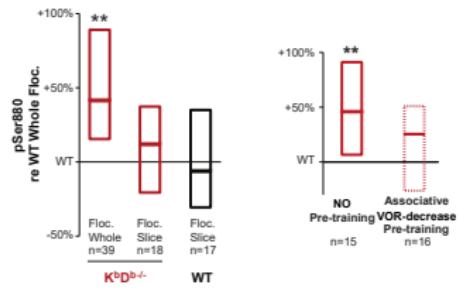


Baseline



Evidence: level of depression

Basal level of GluR2 phosphorylation at serine 880 in AMPA receptor.

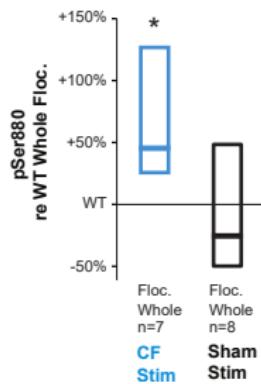
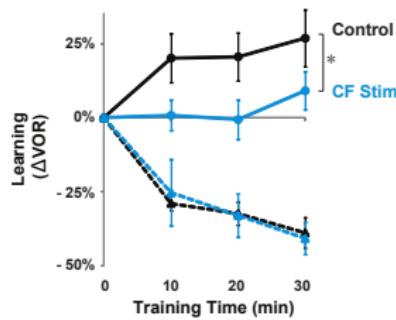
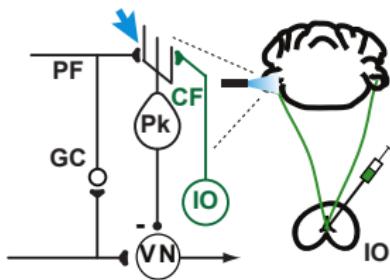


Biochemical signature of PF-Pk LTD.

Shows that # depressed synapses in flocculus is larger in KO than WT.

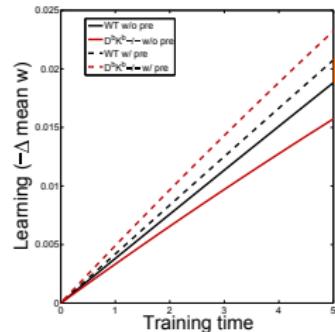
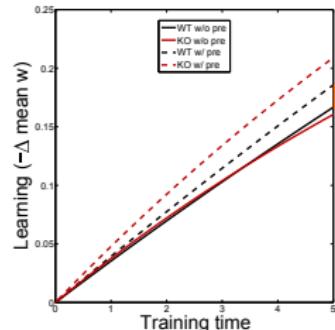
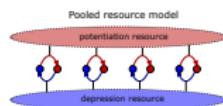
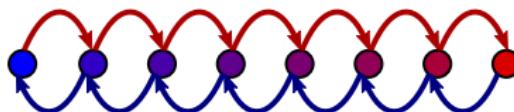
Evidence: saturation by CF stimulation

Use Channelrhodopsin to stimulate CF → increase LTD in PF-Pk synapses
→ simulate saturation in WT.



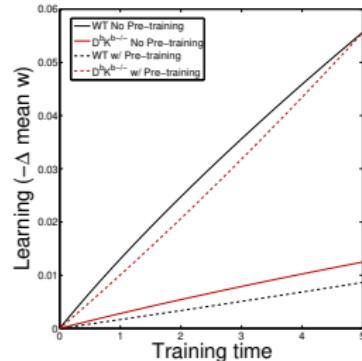
Other models that fail

Multistate synapse

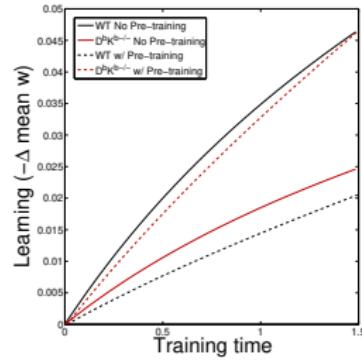
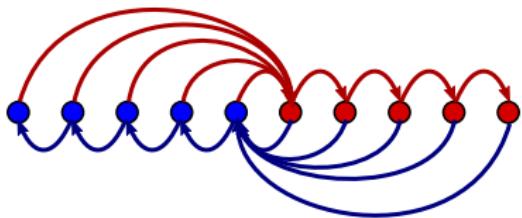


Other models that work

Non-uniform multistate model

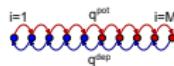


Cascade model



[Fusi et al. (2005)]

Mathematical explanation



Serial synapse: $n^\infty \sim \mathcal{N} \left(\underline{q^{\text{pot}}} \right)^i$

Subhaneil Lahiri (Stanford)

Complex synapses

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