Modelling impaired and enhanced learning with enhanced plasticity

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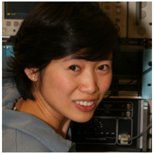
December 3, 2014

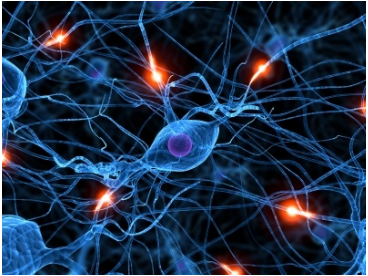
Barbara Nguyen-Vu



Grace Zhao

Introduction

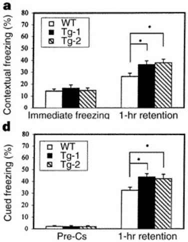
Learning requires synaptic plasticity.



Can we enhance learning by enhancing plasticity?

Enhanced plasticity *can* enhance learning

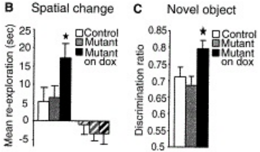
Overexpress NR2B



Fear conditioning

[Tang et al. (1999)]

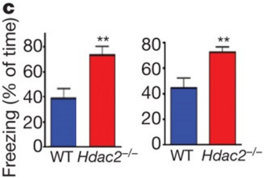
Inhibit CN



Novel object recog.

[Malleret et al. (2001)]

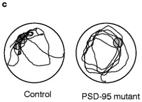
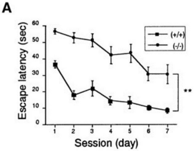
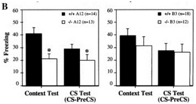
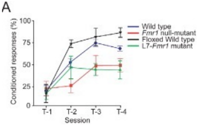
Knockout Hdac2



Fear conditioning

[Guan et al. (2009)]

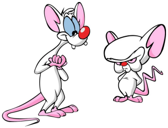
Enhanced plasticity can *impair* learning

Mutate PSD-95	Knockout PTPδ	Delete Tmod2	Knockout FMR1
			
Water maze	Water maze	Fear cond.	Eyeblink
[Migaud et al. (1998)]	[Uetani et al. (2000)]	[Cox et al. (2003)]	[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?

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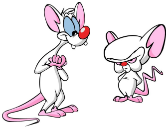
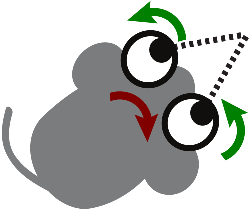


Why? How? When?

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.

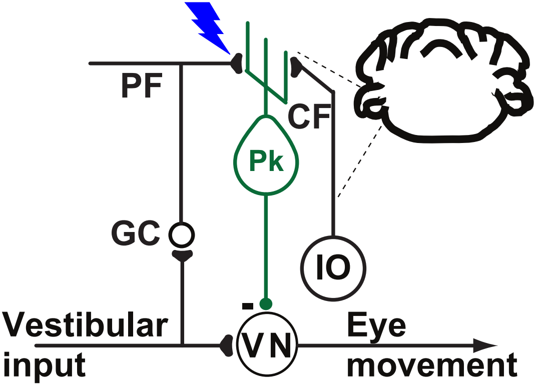
Requires control of VOR gain $= \frac{\text{eye velocity}}{\text{head velocity}}$.

Needs to be adjusted as eye muscles age, etc.

Vestibulo-Occular Reflex training

VOR Increase Training

VOR Decrease Training

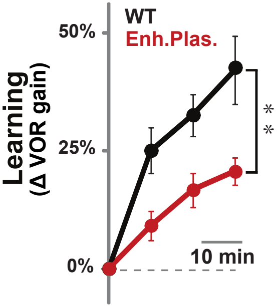


VOR increase: LTD in PF-Pk synapses.
VOR decrease: different mechanism, also reverses LTD in PF-Pk.

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

Enhanced plasticity impairs learning

Expectation: enhanced LTD → enhanced learning.

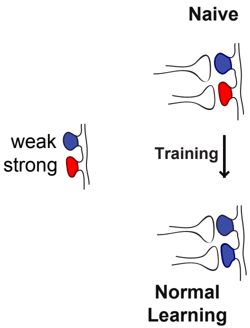


Experiment: enhanced plasticity → impaired learning.

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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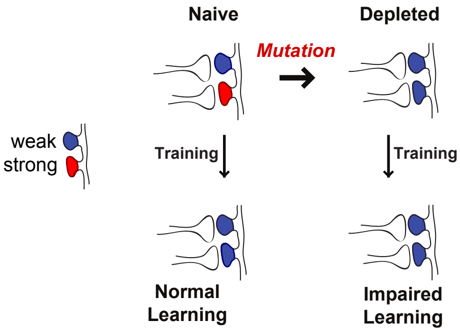

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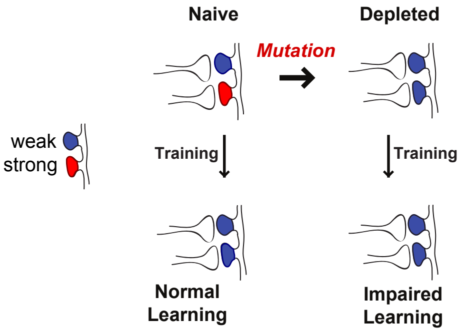

Question 1: depletion effect competes with enhanced intrinsic plasticity. When is depletion effect stronger?

Replenishment by reverse-training

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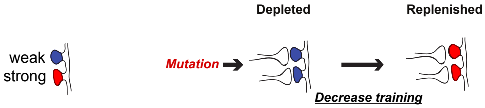

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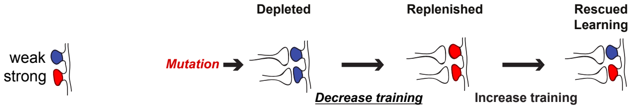

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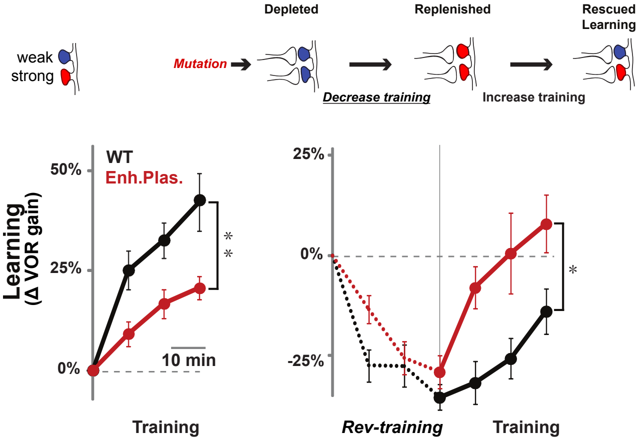

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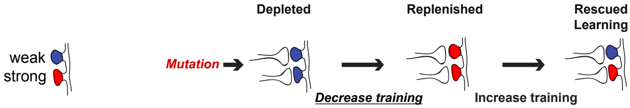
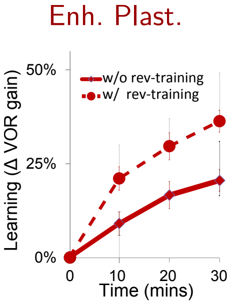
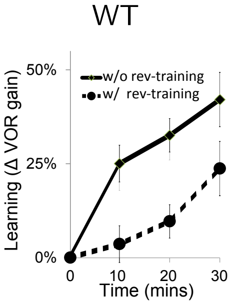
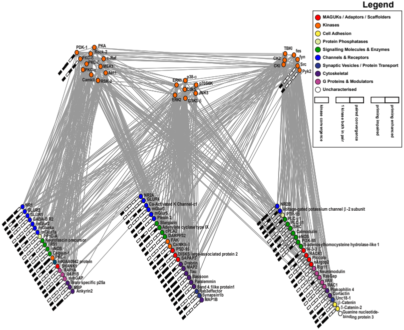




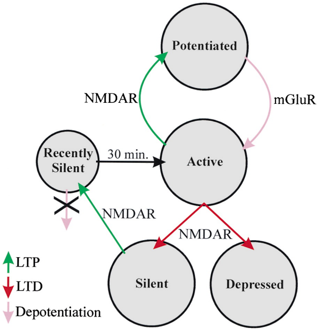


Question 2: How can replenishment *ever* impair learning?

Synapses are complex

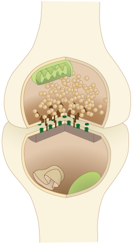


[Coba et al. (2009)]



[Montgomery and Madison (2002)]

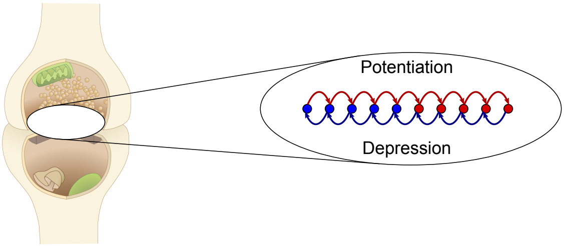
Models of complex synaptic dynamics



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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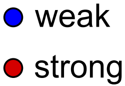

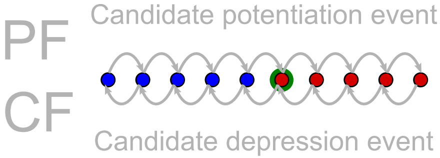

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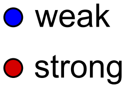

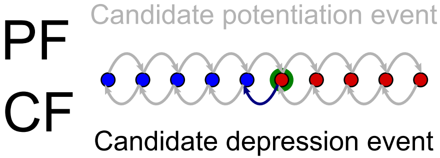

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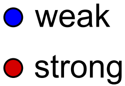

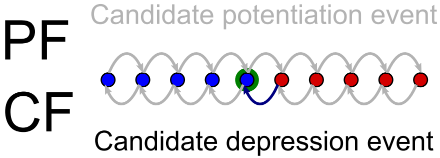

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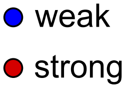

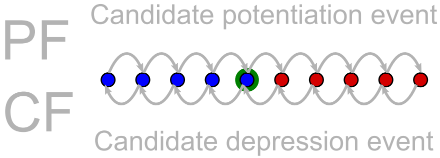

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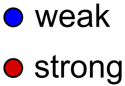

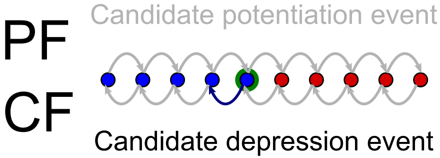

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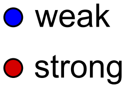

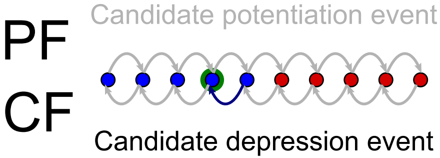

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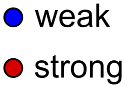

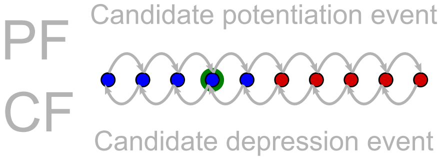

Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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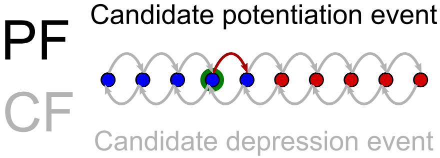
weak
strong



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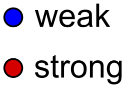

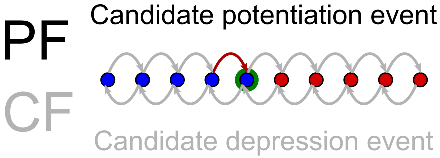

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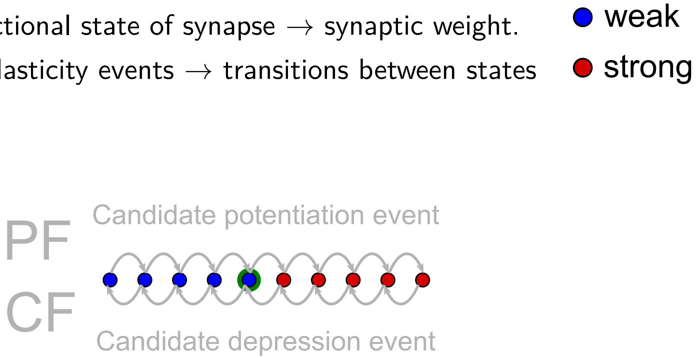

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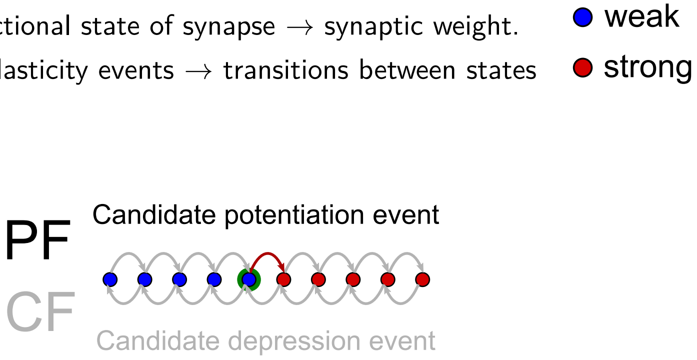

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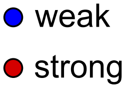

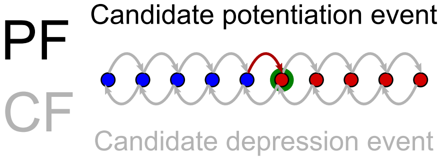

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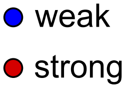

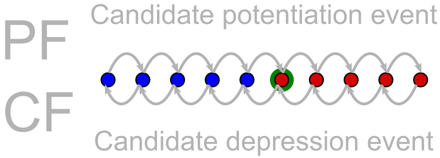

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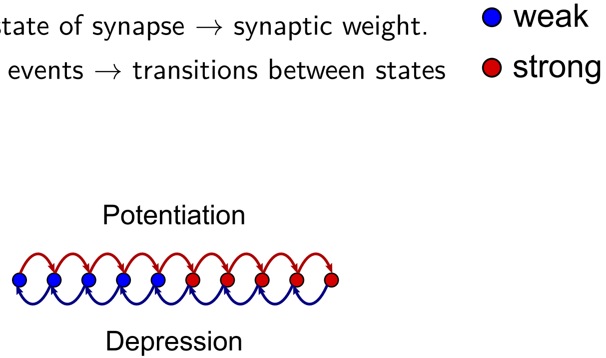

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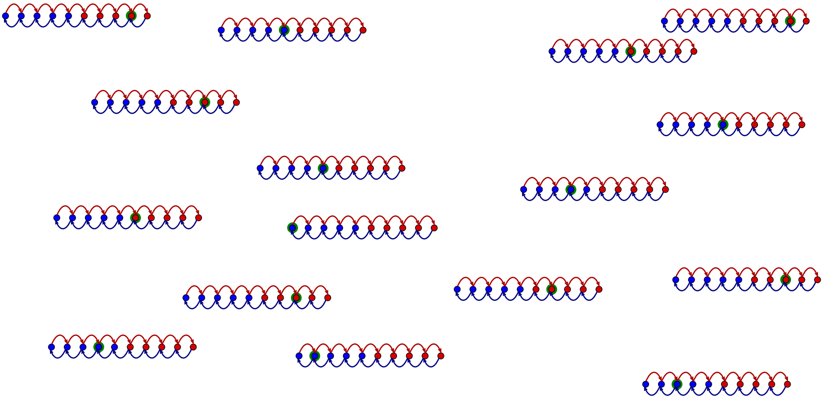
Modelling VOR experiments



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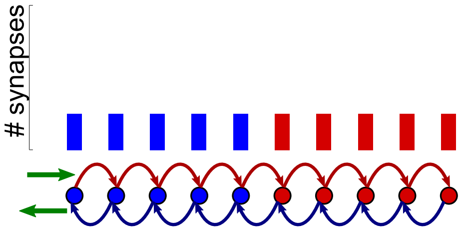
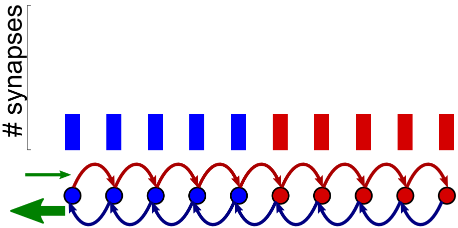


PF-Pk LTD $\rightarrow$ VOR increase



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

Modelling VOR experiments

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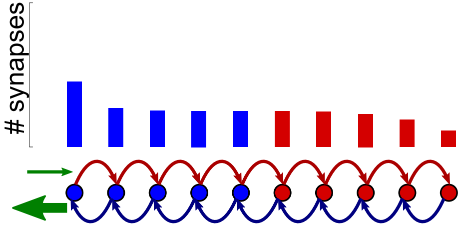

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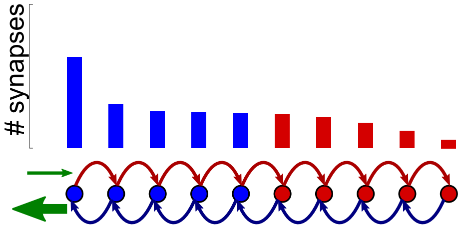

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Modelling VOR experiments

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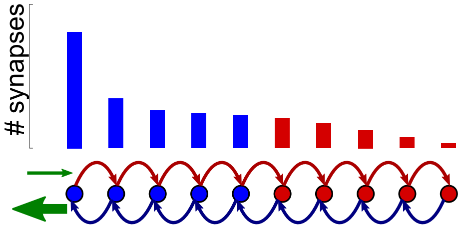

Training: different CF activity $\implies$
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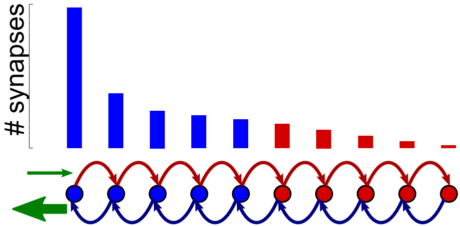
Modelling VOR experiments

PF-Pk LTD $\to$ VOR increase



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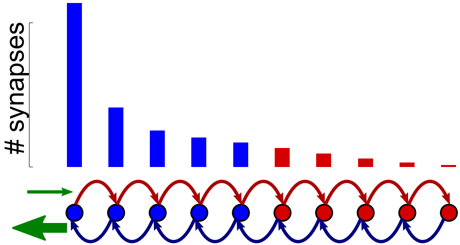

Training: different CF activity $\implies$
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Learning: decrease in average synaptic weight.

Modelling VOR experiments

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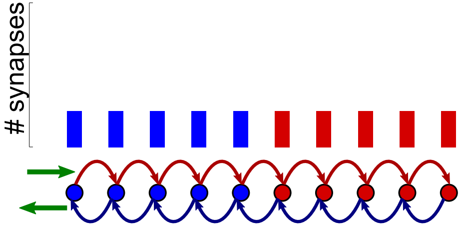
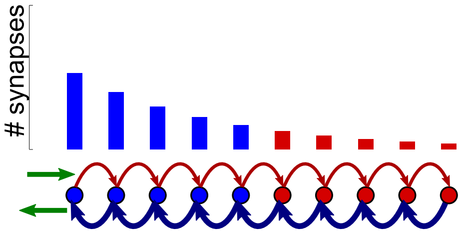


Training: different CF activity $\implies$
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

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

PF-Pk LTD $\rightarrow$ VOR increase



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.

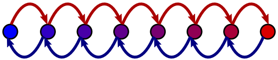
Question 2: How can replenishment *ever* impair learning?

Enhanced plasticity $\rightarrow$ enhanced/impaired learning

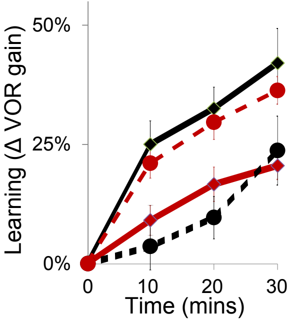
Big question: Why?

Simple synapses cannot explain the data

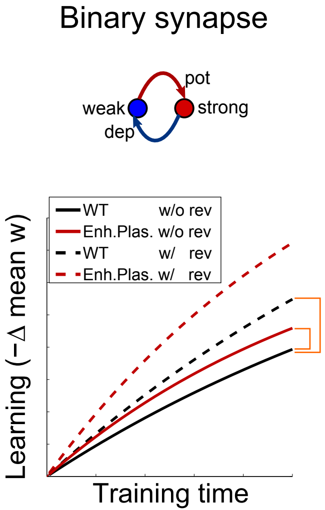
Multistate synapse

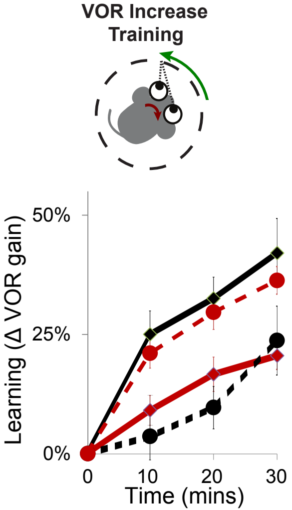


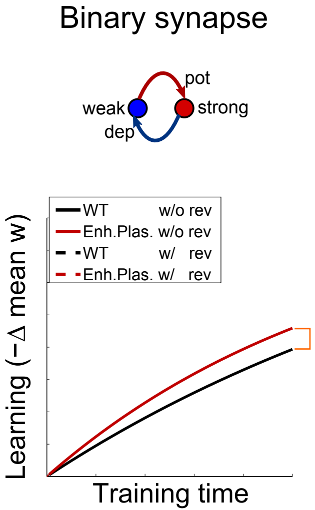
VOR Increase Training

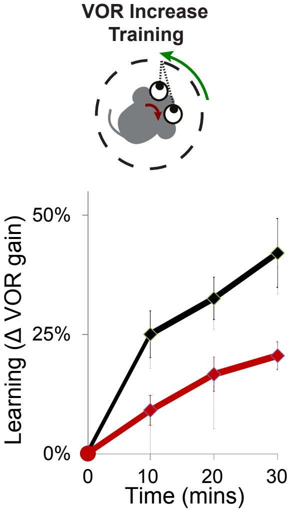


Simple synapses cannot explain the data

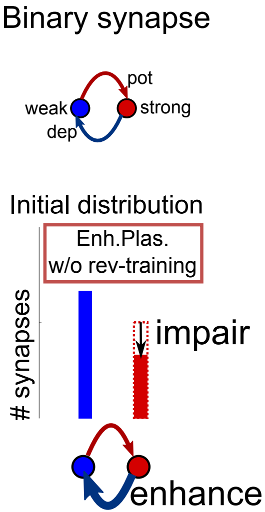





Binary synapse
pot
weak
strong
dep
WT w/o rev
Enh.Plas. w/o rev
WT w/ rev
Enh.Plas. w/ rev
Learning (−Δ mean w)
Training time


VOR Increase Training
50%
25%
0%
Learning (Δ VOR gain)
0
10
20
30
Time (mins)

Simple synapses cannot explain the data



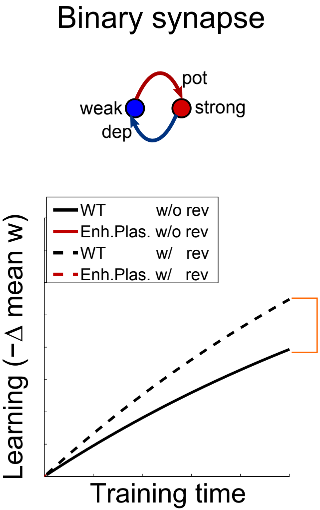
depletion effect

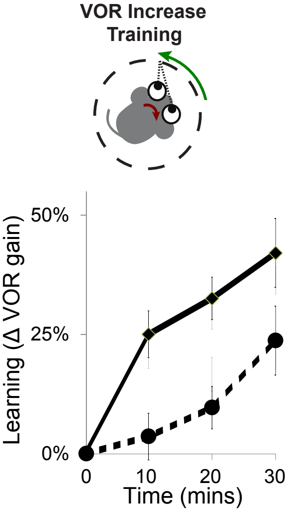
$<$

enhanced plasticity

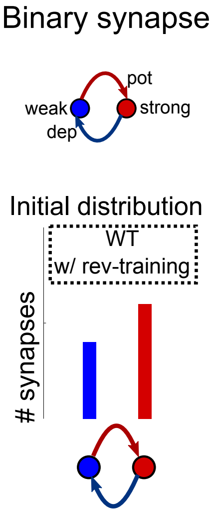
$\Longrightarrow$ enhanced learning

Simple synapses cannot explain the data





Simple synapses cannot explain the data



reverse training

$\Longrightarrow$

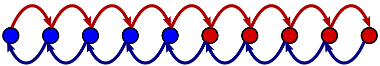
replenishment

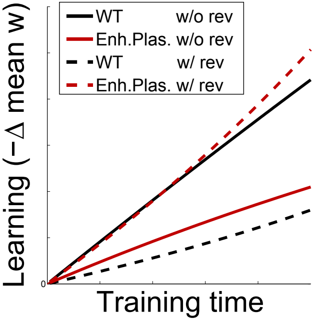
$\Longrightarrow$

enhanced learning

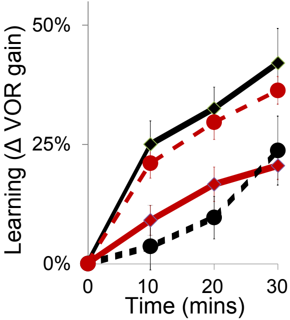
Complex metaplastic synapses can explain the data

Serial synapse

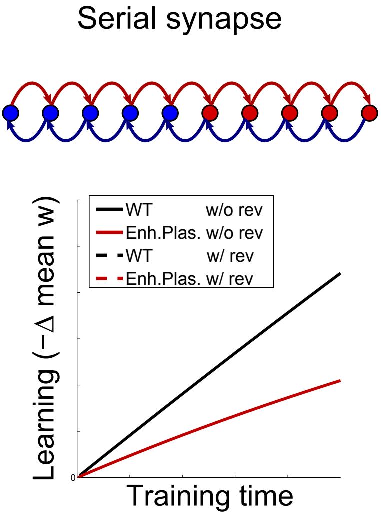


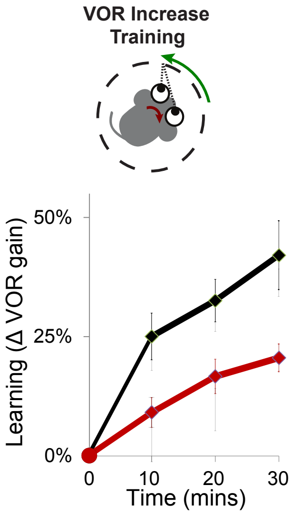


VOR Increase Training

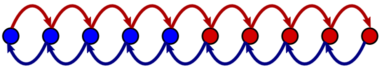


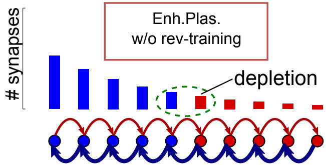
Complex metaplastic synapses can explain the data





Serial synapse



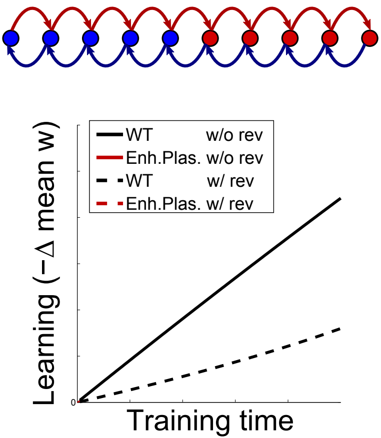


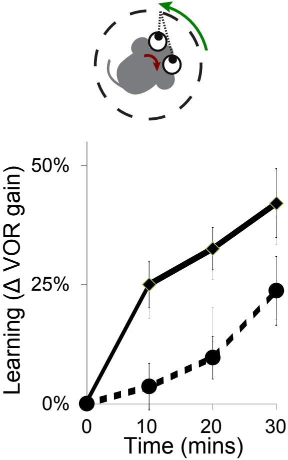
amplified depletion
$>$
enhanced plasticity

$\Longrightarrow$ impaired learning

Complex metaplastic synapses can explain the data

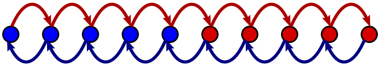
Serial synapse

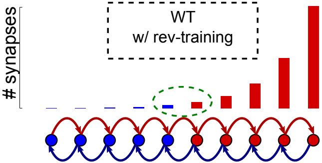




Complex metaplastic synapses can explain the data

Serial synapse





reverse training

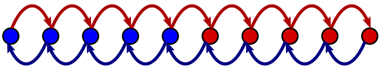
$+$

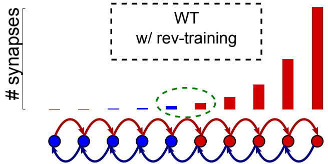
"stubborn" metaplasticity

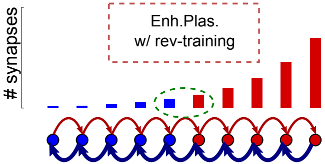
$\Longrightarrow$ impaired learning

Complex metaplastic synapses can explain the data

Serial synapse

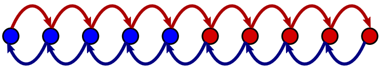






Complex metaplastic synapses can explain the data

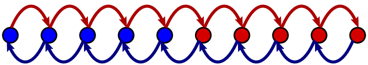
Serial synapse



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

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

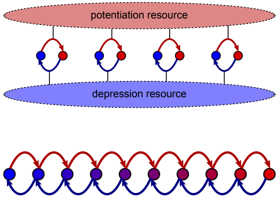
Essential features



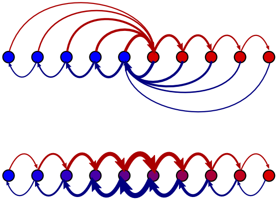
The success of the serial model relies on two features:

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

Fail:

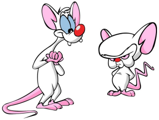


Succeed:



Conclusions

- Diverse behavioural patterns:
  Enhanced plasticity $\rightarrow$ 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

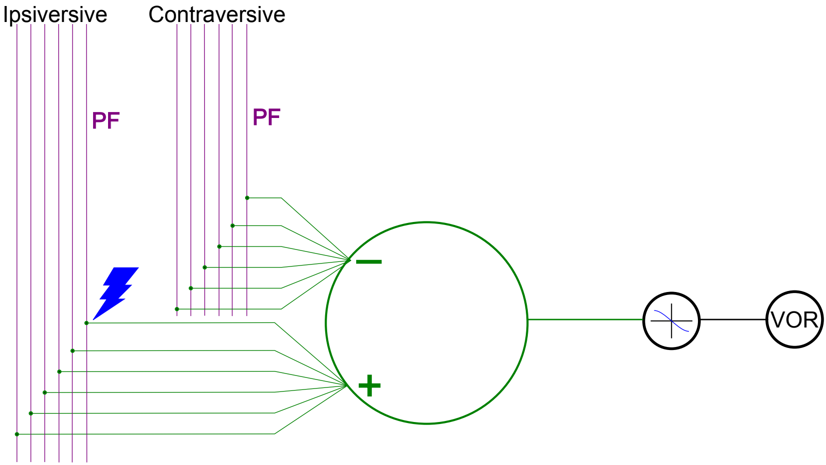
Surya Ganguli
Madhu Advani
Peiran Gao
Niru Maheswaranathan
Ben Poole
Jascha Sohl-Dickstein
Kiah Hardcastle
Jay Sarkar

Jennifer Raymond
Barbara Nguyen-Vu
Grace Zhao
Aparna Suvrathan

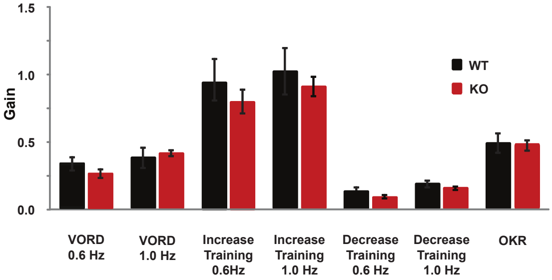
Carla Shatz
Han-Mi Lee

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

Model of circuit

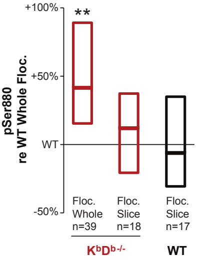


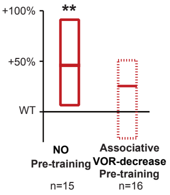
Baseline



1.5
1.0
0.5
0.0
Gain
WT
KO
VORD 0.6 Hz
VORD 1.0 Hz
Increase Training 0.6Hz
Increase Training 1.0 Hz
Decrease Training 0.6 Hz
Decrease Training 1.0 Hz
OKR

Evidence: level of depression





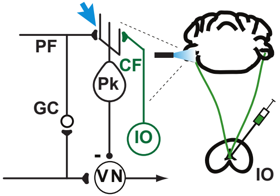
Basal level of GluR2 phosphorylation at serine 880 in AMPA receptor.

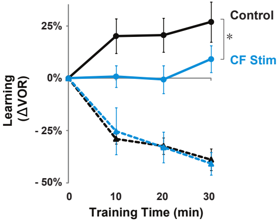
Biochemical signature of PF-Pk LTD.

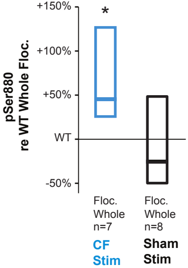
Shows that # depressed synapses in flocculus is larger in KO than WT.

Evidence: saturation by CF stimulation

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

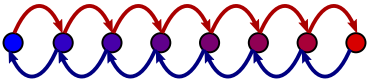




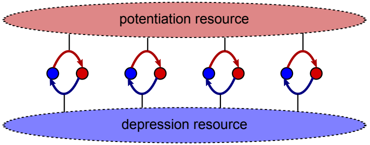


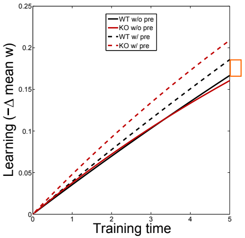
Other models that fail

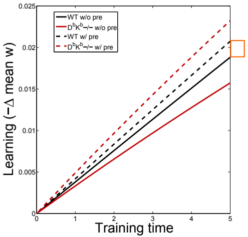
Multistate synapse



Pooled resource model



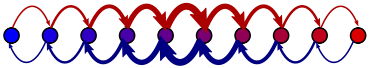


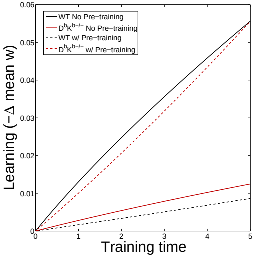


[Amit and Fusi (1994)]

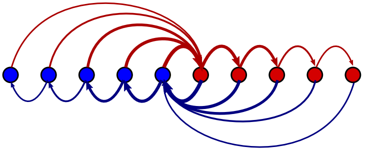
Other models that work

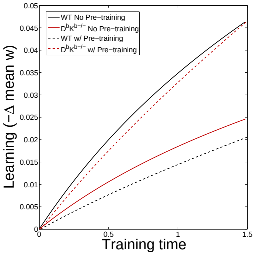
Non-uniform multistate model





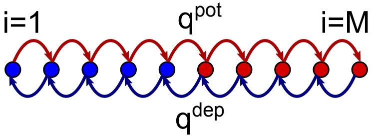
Cascade model





[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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