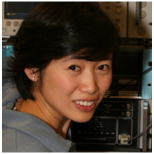
Modelling impaired and enhanced learning with enhanced plasticity

Subhaneil Lahiri
with: Barbara Nguyen-Vu, Grace Zhao, Aparna Suvrathan, Han-Mi Lee, Surya Ganguli, Carla Shatz and Jennifer Raymond

Stanford University

December 3, 2014

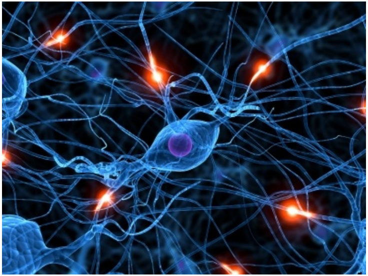
Barbara Nguyen-Vu



Grace Zhao

Introduction

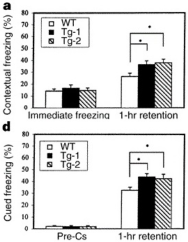
Learning requires synaptic plasticity.



Can we enhance learning by enhancing plasticity?

Enhanced plasticity *can* enhance learning

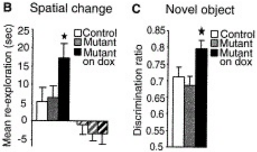
Overexpress NR2B



Fear conditioning

[Tang et al. (1999)]

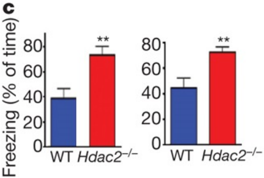
Inhibit CN



Novel object recog.

[Malleret et al. (2001)]

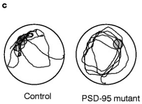
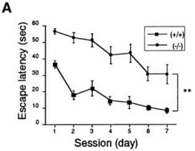
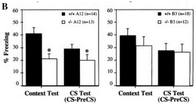
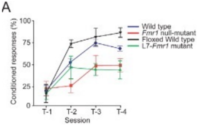
Knockout Hdac2



Fear conditioning

[Guan et al. (2009)]

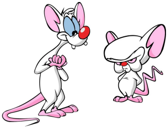
Enhanced plasticity can *impair* learning

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

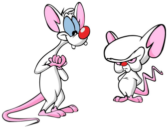
Sometimes enhanced plasticity $\rightarrow$ enhanced learning.
Sometimes enhanced plasticity $\rightarrow$ impaired learning.



Why? How? When?

Overview

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

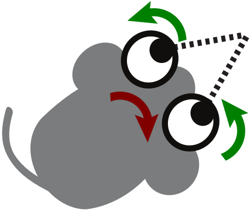


Why? How? When?

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

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

Vestibulo-Occular Reflex



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

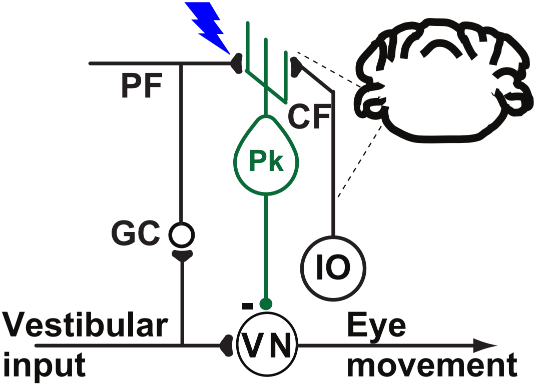
Requires control of VOR gain $= \frac{\text{eye velocity}}{\text{head velocity}}$.

Needs to be adjusted as eye muscles age, etc.

Vestibulo-Occular Reflex training

VOR Increase Training

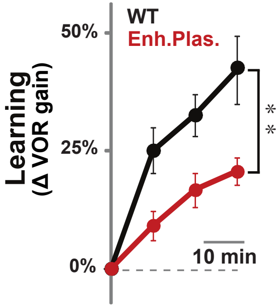
VOR Decrease Training



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

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

Expectation: enhanced LTD $\rightarrow$ enhanced learning.



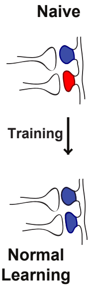
Experiment: enhanced plasticity $\rightarrow$ impaired learning.

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

[McConnell et al. (2009)]

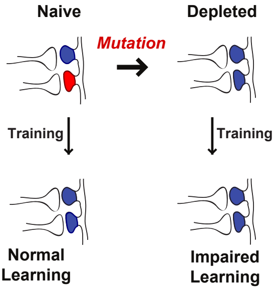
Depletion hypothesis

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



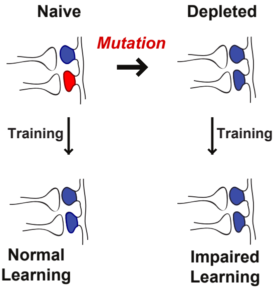
Depletion hypothesis

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



Depletion hypothesis

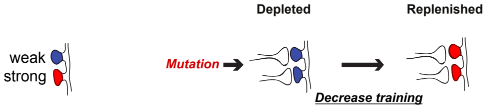
Learning rate $\sim$ intrinsic plasticity rate $\times$ # synapses available for LTD.



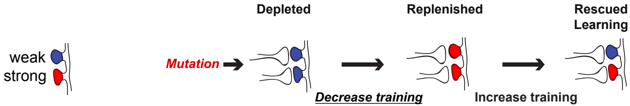
Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

Replenishment by reverse-training

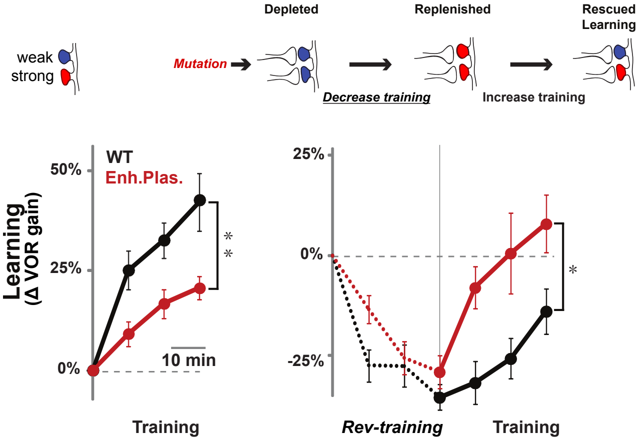
Replenishment by reverse-training



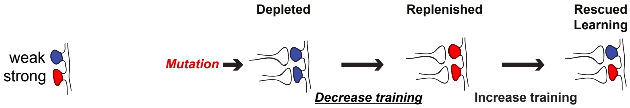
Replenishment by reverse-training



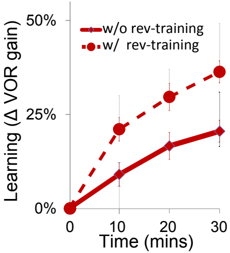
Replenishment by reverse-training



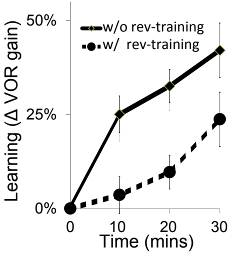
Replenishment by reverse-training



Enh. Plast.

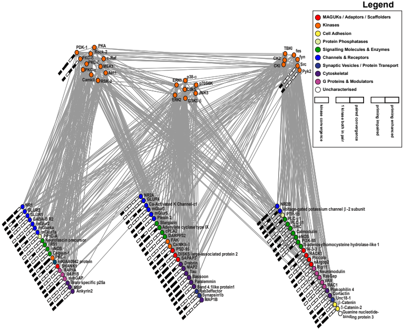


WT

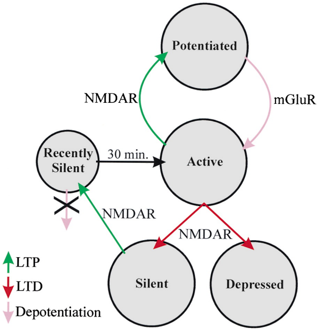


Question 2: How can replenishment *ever* impair learning?

Synapses are complex

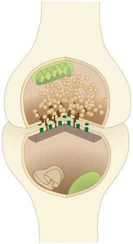


[Coba et al. (2009)]



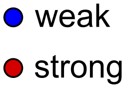
[Montgomery and Madison (2002)]

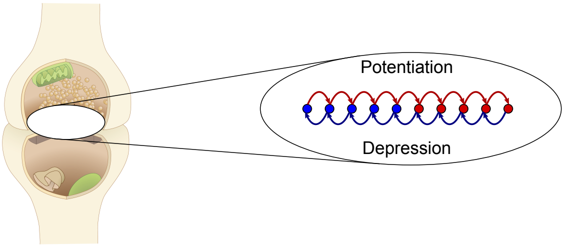
Models of complex synaptic dynamics



Models of complex synaptic dynamics

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



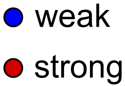


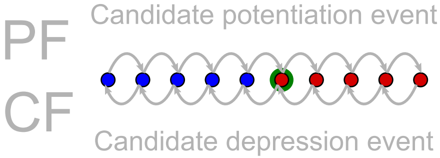
States: NMDAR subunit composition, CaMK II autophosphorylation, activating PKC, p38 MAPK,...

[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]
[Smith et al. (2006), Lahiri and Ganguli (2013)]

Models of complex synaptic dynamics

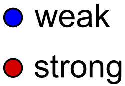
- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states

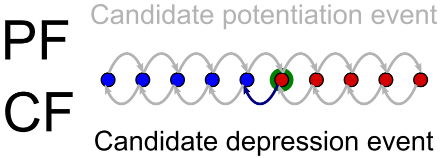




Models of complex synaptic dynamics

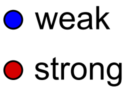
- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states

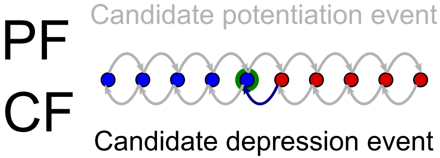




Models of complex synaptic dynamics

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



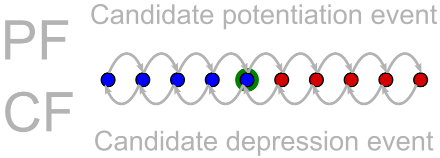


Models of complex synaptic dynamics

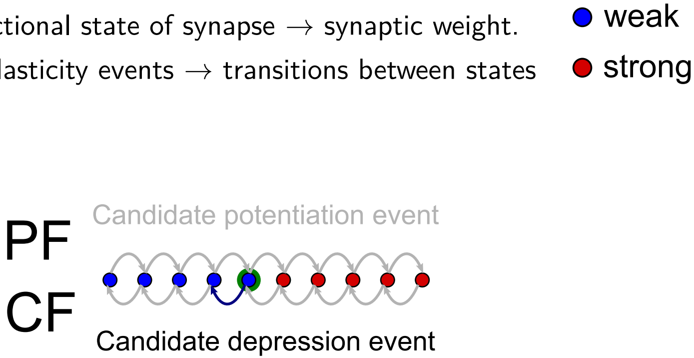
- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states

weak

strong

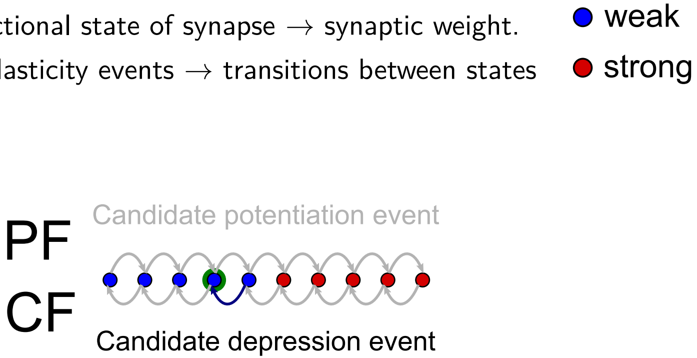


- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states



Models of complex synaptic dynamics

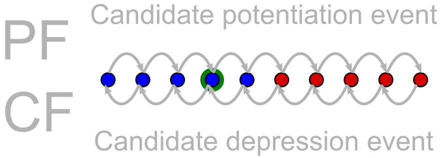
- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states



Models of complex synaptic dynamics

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

weak
strong



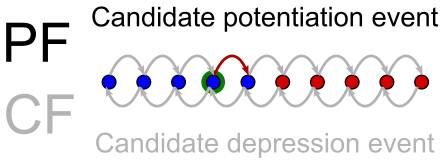
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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

weak

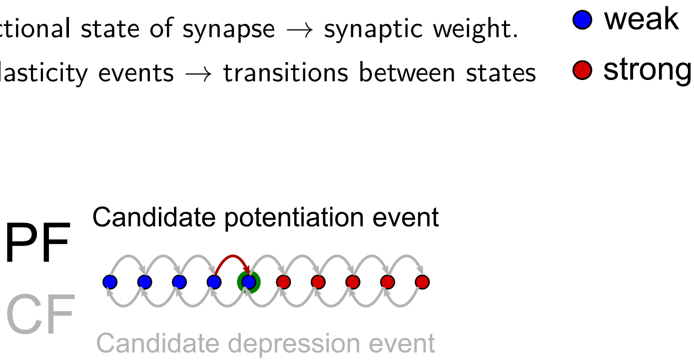
strong



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

Models of complex synaptic dynamics

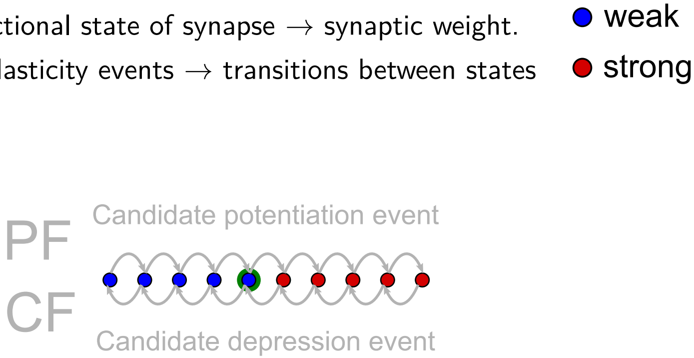
- Internal functional state of synapse $\rightarrow$ synaptic weight.
- Candidate plasticity events $\rightarrow$ transitions between states



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

Models of complex synaptic dynamics

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



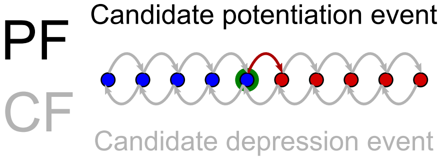
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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

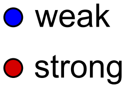
weak

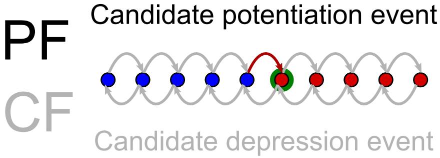
strong



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

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

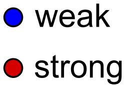


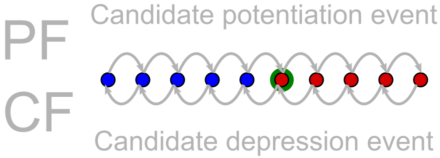


Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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

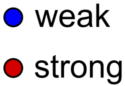


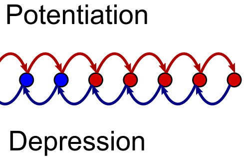


Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

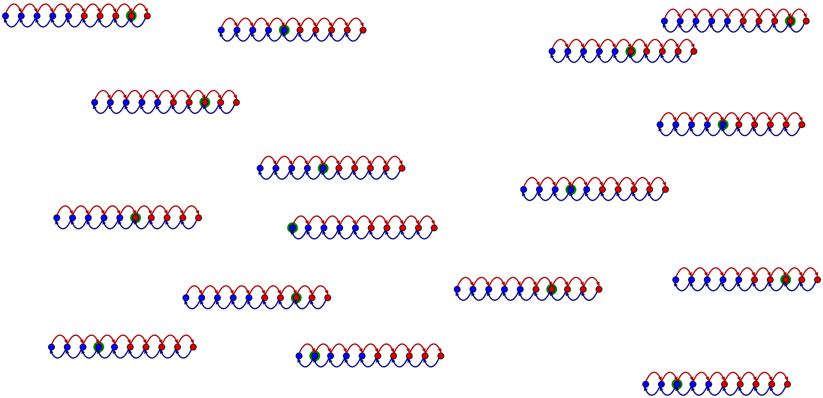
Models of complex synaptic dynamics

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

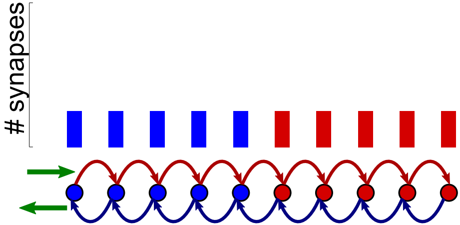




Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

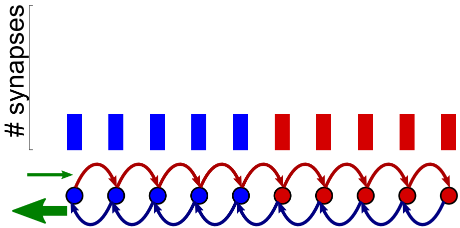


Modelling VOR experiments



Modelling VOR experiments

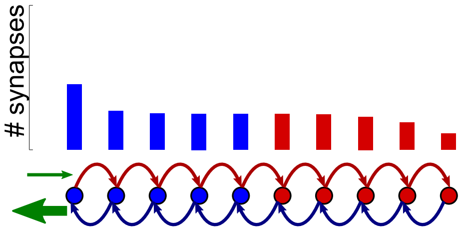
PF-Pk LTD $\to$ VOR increase



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

Modelling VOR experiments

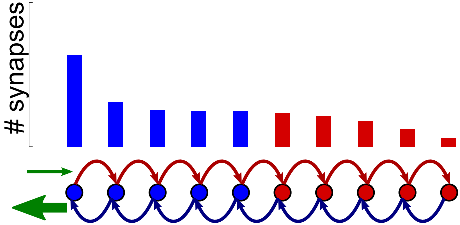
PF-Pk LTD $\rightarrow$ VOR increase



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

Modelling VOR experiments

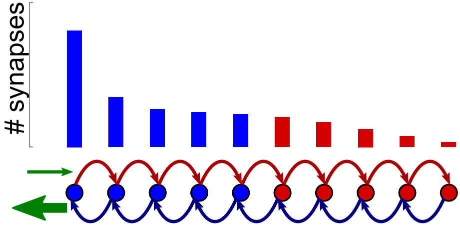
PF-Pk LTD $\rightarrow$ VOR increase



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

Modelling VOR experiments

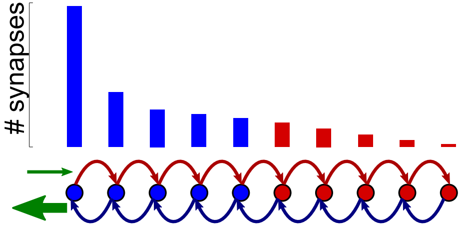
PF-Pk LTD $\rightarrow$ VOR increase



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

Modelling VOR experiments

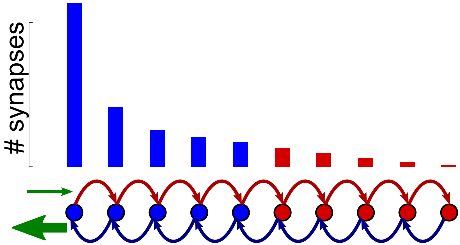
PF-Pk LTD $\rightarrow$ VOR increase



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

Modelling VOR experiments

PF-Pk LTD $\rightarrow$ VOR increase

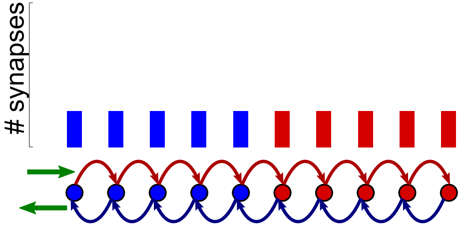


Training: different CF activity $\implies$
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

Modelling VOR experiments

PF-Pk LTD $\rightarrow$ VOR increase



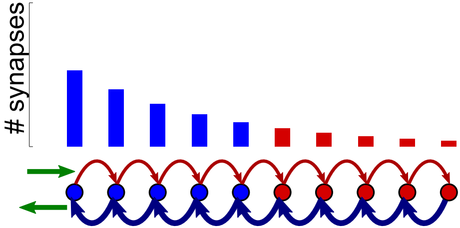
Training: different CF activity $\implies$
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

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

Modelling VOR experiments

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.

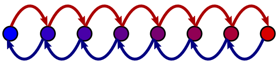
Question 2: How can replenishment *ever* impair learning?

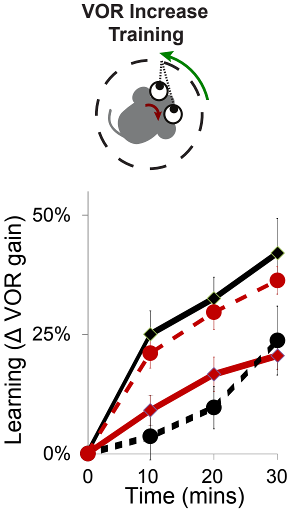
Enhanced plasticity $\rightarrow$ enhanced/impaired learning

Big question: Why?

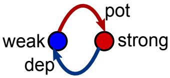
Simple synapses cannot explain the data

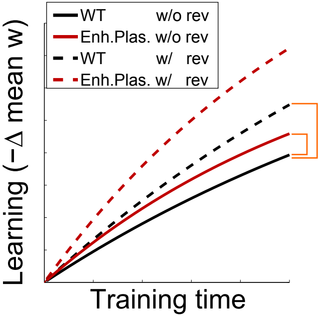
Multistate synapse



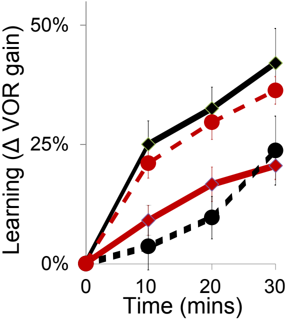


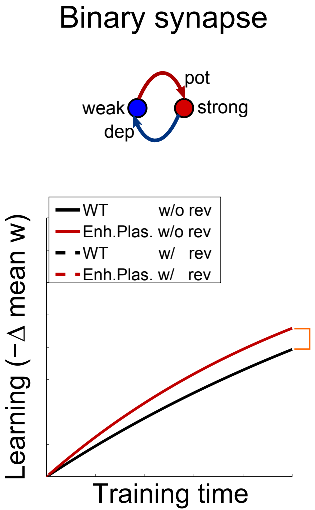
Binary synapse

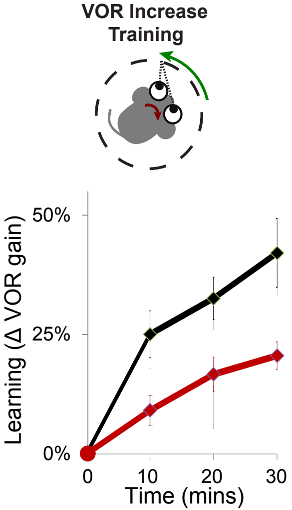




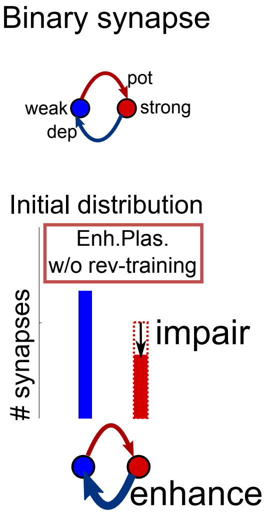
VOR Increase Training




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

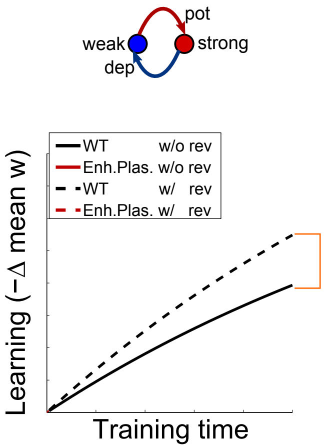
$<$

enhanced plasticity

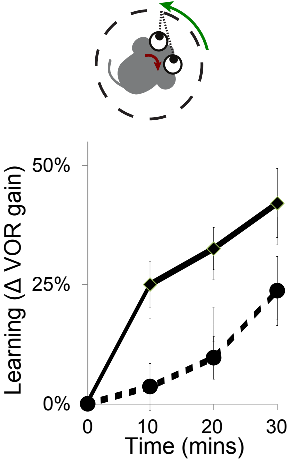
$\Longrightarrow$ enhanced learning

Simple synapses cannot explain the data

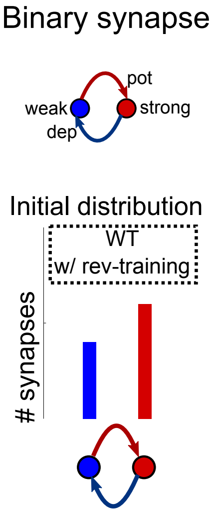
Binary synapse



VOR Increase Training



Simple synapses cannot explain the data



reverse training

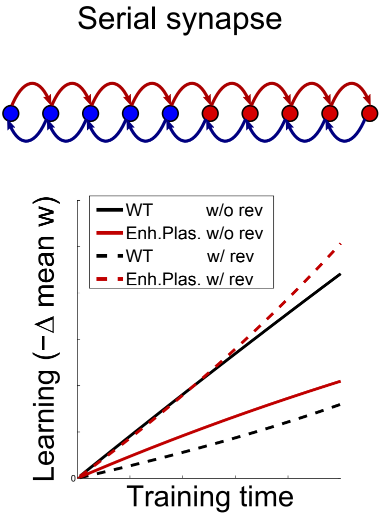
$\Longrightarrow$

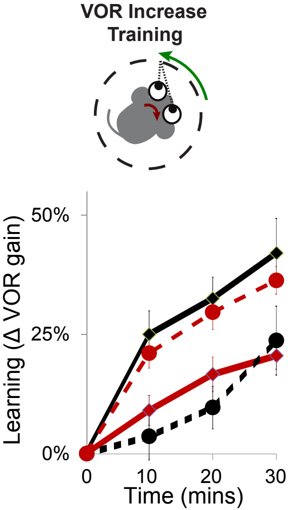
replenishment

$\Longrightarrow$

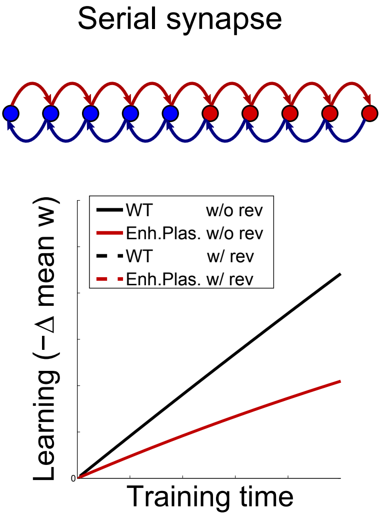
enhanced learning

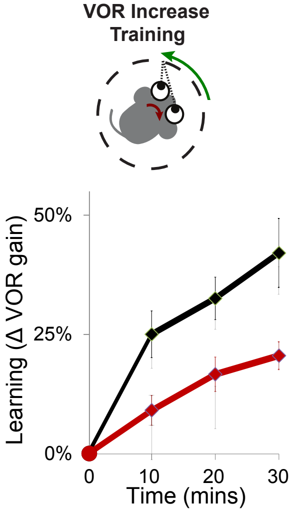
Complex metaplastic synapses can explain the data



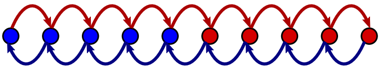


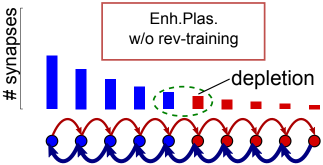
Complex metaplastic synapses can explain the data





Serial synapse





amplified depletion

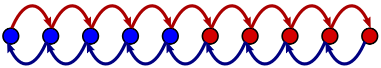
$>$

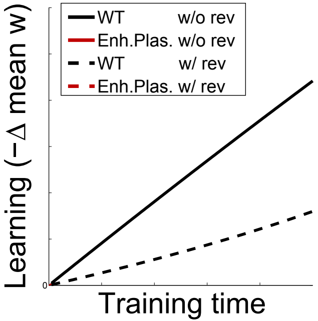
enhanced plasticity

$\Longrightarrow$ impaired learning

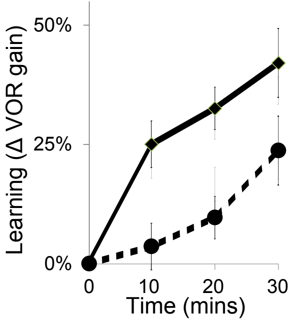
Complex metaplastic synapses can explain the data

Serial synapse



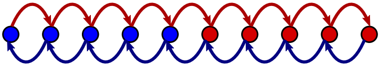


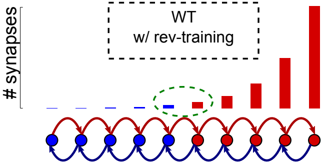
VOR Increase Training



Complex metaplastic synapses can explain the data

Serial synapse





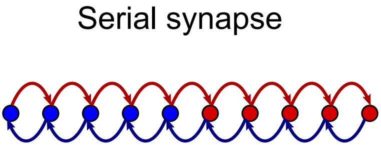
reverse training

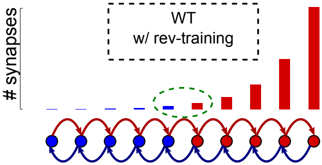
$+$

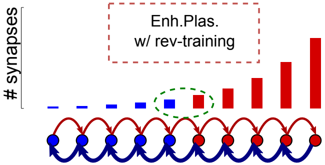
"stubborn" metaplasticity

$\Longrightarrow$ impaired learning

Complex metaplastic synapses can explain the data

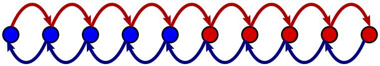






Complex metaplastic synapses can explain the data

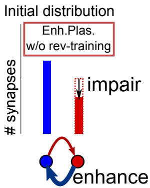
Serial synapse

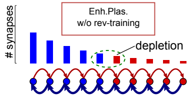


starting point:
labile states
$\downarrow$
enhanced plasticity
$\Longrightarrow$ impaired learning

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

Enhanced plasticity can enhance or impair learning

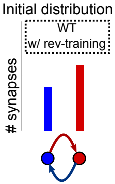


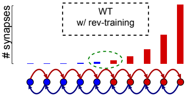


intrinsic plasticity dominates depletion
↓
enhanced plasticity enhances learning

depletion dominates intrinsic plasticity
↓
enhanced plasticity impairs learning

Key feature 1: Synaptic complexity that amplifies depletion effect.



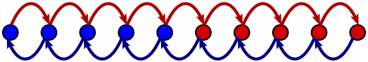


reverse-training
repopulates boundary
↓
enhanced learning

reverse-training
depopulates boundary
↓
impaired learning

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

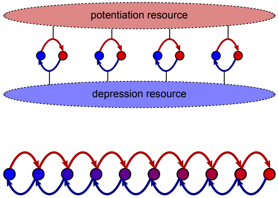
Essential features



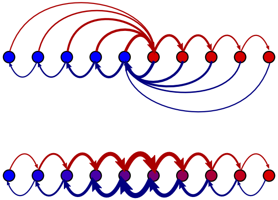
The success of the serial model relies on two features:

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

Fail:

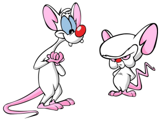


Succeed:



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

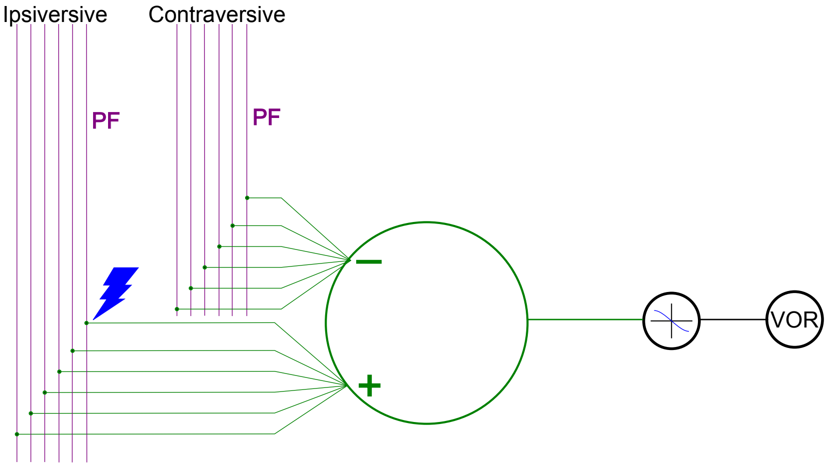
Surya Ganguli
Madhu Advani
Peiran Gao
Niru Maheswaranathan
Ben Poole
Jascha Sohl-Dickstein
Kiah Hardcastle
Jay Sarkar

Jennifer Raymond
Barbara Nguyen-Vu
Grace Zhao
Aparna Suvrathan

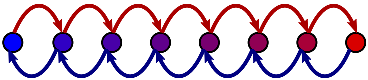
Carla Shatz
Han-Mi Lee

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

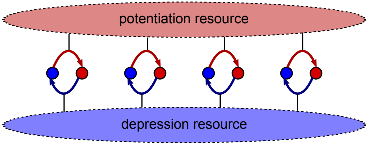
Model of circuit

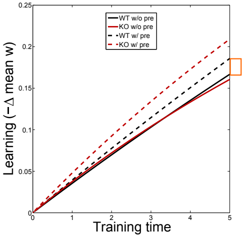


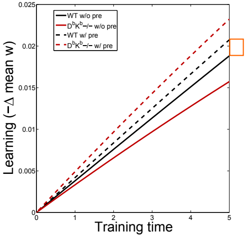
Multistate synapse



Pooled resource model



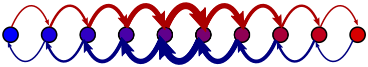


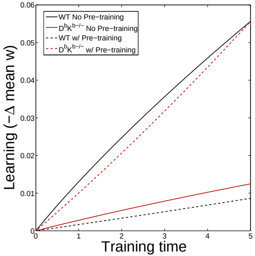


[Amit and Fusi (1994)]

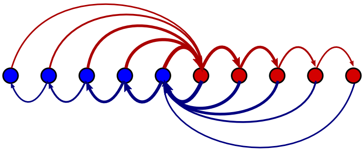
Other models that work

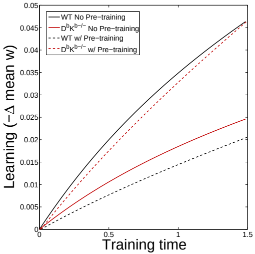
Non-uniform multistate model





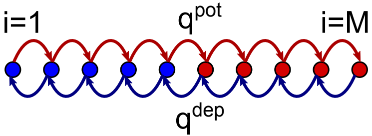
Cascade model





[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.

References I

Y. P. Tang, E. Shimizu, G. R. Dube, C. Rampon, G. A. Kerchner, M. Zhuo, G. Liu, and J. Z. Tsien.
"Genetic enhancement of learning and memory in mice".
Nature, 401(6748):63–69, (Sep, 1999) .
3

Gaël Malleret, Ursula Haditsch, David Genoux, Matthew W. Jones, Tim V.P. Bliss, Amanda M. Vanhoose, Carl Weitlauf, Eric R. Kandel, Danny G. Winder, and Isabelle M. Mansuy.
"Inducible and Reversible Enhancement of Learning, Memory, and Long-Term Potentiation by Genetic Inhibition of Calcineurin".
Cell, 104(5):675 – 686, (2001) .
3

J. S. Guan, S. J. Haggarty, E. Giacometti, J. H. Dannenberg, N. Joseph, J. Gao, T. J. Nieland, Y. Zhou, X. Wang, R. Mazitschek, J. E. Bradner, R. A. DePinho, R. Jaenisch, and L. H. Tsai.
"HDAC2 negatively regulates memory formation and synaptic plasticity".
Nature, 459(7243):55–60, (May, 2009) .
3

M. Migaud, P. Charlesworth, M. Dempster, L. C. Webster, A. M. Watabe, M. Makhinson, Y. He, M. F. Ramsay, R. G. Morris, J. H. Morrison, T. J. O'Dell, and S. G. Grant.
"Enhanced long-term potentiation and impaired learning in mice with mutant postsynaptic density-95 protein".
Nature, 396(6710):433–439, (Dec, 1998) .
4

N. Uetani, K. Kato, H. Ogura, K. Mizuno, K. Kawano, K. Mikoshiba, H. Yakura, M. Asano, and Y. Iwakura.
"Impaired learning with enhanced hippocampal long-term potentiation in PTPdelta-deficient mice".
EMBO J., 19(12):2775–2785, (Jun, 2000) .
4

References II

Patrick R Cox, Velia Fowler, Bisong Xu, J.David Sweatt, Richard Paylor, and Huda Y Zoghbi.
"Mice lacking tropomodulin-2 show enhanced long-term potentiation, hyperactivity, and deficits in learning and memory".
Molecular and Cellular Neuroscience, 23(1):1 – 12, (2003) .
4

S.K.E. Koekkoek, K. Yamaguchi, B.A. Milojkovic, B.R. Dortland, T.J.H. Ruigrok, R. Maex, W. De Graaf, A.E. Smit, F. VanderWerf, C.E. Bakker, R. Willemsen, T. Ikeda, S. Kakizawa, K. Onodera, D.L. Nelson, E. Mientjes, M. Joosten, E. De Schutter, B.A. Oostra, M. Ito, and C.I. De Zeeuw.
"Deletion of *FMR1* in Purkinje Cells Enhances Parallel Fiber LTD, Enlarges Spines, and Attenuates Cerebellar Eyelid Conditioning in Fragile X Syndrome".
Neuron, 47(3):339 – 352, (2005) .
4

Mansuo L Hayashi, Se-Young Choi, B.S.Shankaranarayana Rao, Hae-Yoon Jung, Hey-Kyoung Lee, Dawei Zhang, Sumantra Chattarji, Alfredo Kirkwood, and Susumu Tonegawa.
"Altered Cortical Synaptic Morphology and Impaired Memory Consolidation in Forebrain- Specific Dominant-Negative {PAK} Transgenic Mice".
Neuron, 42(5):773 – 787, (2004) .
4

Kris Rutten, Dinah L. Misner, Melissa Works, Arjan Blokland, Thomas J. Novak, Luca Santarelli, and Tanya L. Wallace.
"Enhanced long-term potentiation and impaired learning in phosphodiesterase 4D-knockout (PDE4D-/-) mice".
European Journal of Neuroscience, 28(3):625–632, (2008) .
4

References III

David Marr.
"A theory of cerebellar cortex".
The Journal of Physiology, 202(2):437–470, (1969) .
8

James S. Albus.
"A theory of cerebellar function".
Mathematical Biosciences, 10(1):25 – 61, (1971) .
8

Masao Ito.
"Neural design of the cerebellar motor control system".
Brain research, 40(1):81–84, (1972) .
8

Michael J. McConnell, Yanhua H. Huang, Akash Datwani, and Carla J. Shatz.
"H2-Kb and H2-Db regulate cerebellar long-term depression and limit motor learning".
Proc. Natl. Acad. Sci. U.S.A., 106(16):6784–6789, (2009) .
9

M. P. Coba, A. J. Pocklington, M. O. Collins, M. V. Kopanitsa, R. T. Uren, S. Swamy, M. D. Croning, J. S. Choudhary, and S. G. Grant.
"Neurotransmitters drive combinatorial multistate postsynaptic density networks".
Sci Signal, 2(68):ra19, (2009) .
18

References IV

Johanna M. Montgomery and Daniel V. Madison.
"State-Dependent Heterogeneity in Synaptic Depression between Pyramidal Cell Pairs".
Neuron, 33(5):765 – 777, (2002) .
18

S. Fusi, P. J. Drew, and L. F. Abbott.
"Cascade models of synaptically stored memories".
Neuron, 45(4):599–611, (Feb, 2005) .
20 66

S. Fusi and L. F. Abbott.
"Limits on the memory storage capacity of bounded synapses".
Nat. Neurosci., 10(4):485–493, (Apr, 2007) .
20

A. B. Barrett and M. C. van Rossum.
"Optimal learning rules for discrete synapses".
PLoS Comput. Biol., 4(11):e1000230, (Nov, 2008) .
20

Maurice A Smith, Ali Ghazizadeh, and Reza Shadmehr.
"Interacting Adaptive Processes with Different Timescales Underlie Short-Term Motor Learning".
PLoS Biol, 4(6):e179, (May, 2006) .
20

References V

Subhaneil Lahiri and Surya Ganguli.
"A memory frontier for complex synapses".
In C.J.C. Burges, L. Bottou, M. Welling, Z. Ghahramani, and K.Q. Weinberger, editors, *Advances in Neural Information Processing Systems 26*, pages 1034–1042. NIPS, 2013.
20

D. J. Amit and S. Fusi.
"Learning in neural networks with material synapses".
Neural Computation, 6(5):957–982, (1994) .
65