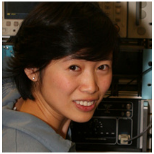
Modelling impaired and enhanced learning with enhanced plasticity

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

Stanford University

March 1, 2014

Barbara Nguyen-Vu



Grace Zhao

Introduction

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

[Tang et al. (1999), Malleret et al. (2001), Guan et al. (2009)]

Introduction

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

[Tang et al. (1999), Malleret et al. (2001), Guan et al. (2009)]

But often: enhanced plasticity $\to$ impaired learning.

[Migaud et al. (1998), Uetani et al. (2000), Hayashi et al. (2004)]
[Cox et al. (2003), Rutten et al. (2008), Koekkoek et al. (2005)]

Introduction

Learning requires synaptic plasticity.
Expect: enhanced plasticity → enhanced learning.

[Tang et al. (1999), Malleret et al. (2001), Guan et al. (2009)]

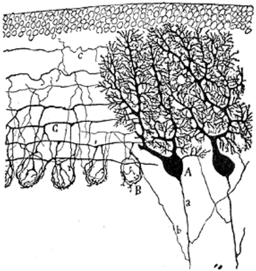
But often: enhanced plasticity → impaired learning.

[Migaud et al. (1998), Uetani et al. (2000), Hayashi et al. (2004)]
[Cox et al. (2003), Rutten et al. (2008), Koekkoek et al. (2005)]

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 training



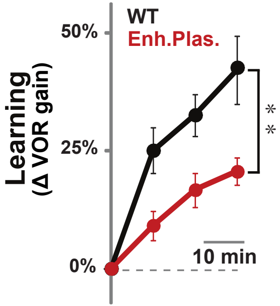
[Cajal]

VOR increase: LTD in PF-Pk synapses.

[du Lac et al. (1995), Boyden et al. (2004)]

Enhanced plasticity impairs learning

Expectation: enhanced LTD → enhanced learning.



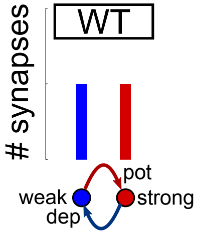
Experiment: enhanced plasticity → impaired learning.

Knockout of MHC-I D^bK^b molecules in PF-Pk synapses
→ lower threshold for LTD

[McConnell et al. (2009)]

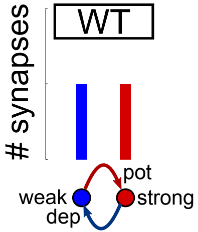
Depletion hypothesis

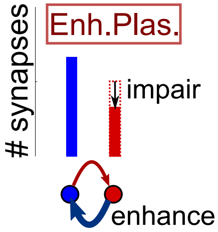
Learning rate $\sim$ intrinsic plasticity rate $\times$ # synapses available for LTD.



Depletion hypothesis

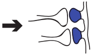
Learning rate $\sim$ intrinsic plasticity rate $\times$ # synapses available for LTD.



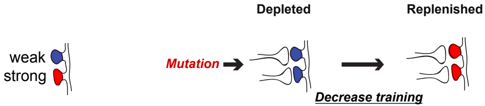


Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

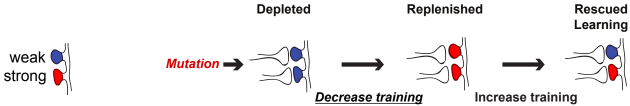
Replenishment by reverse-training



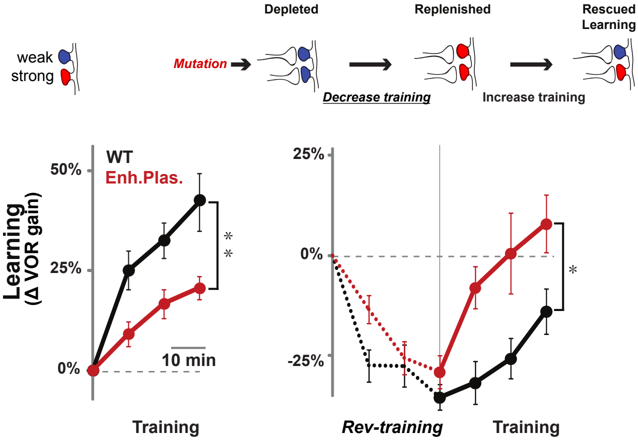
Replenishment by reverse-training



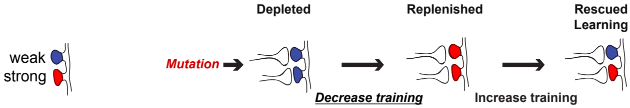
Replenishment by reverse-training

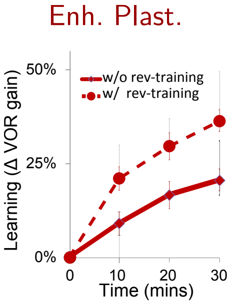


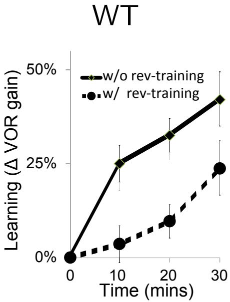
Replenishment by reverse-training



Replenishment by reverse-training

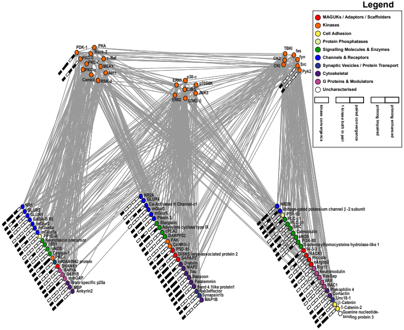




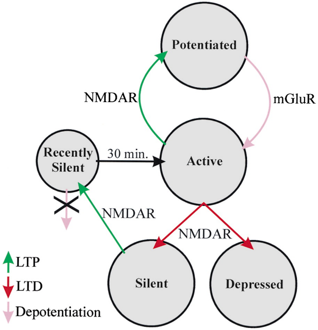


Question 2: How can replenishment *ever* impair learning?

Synapses are complex



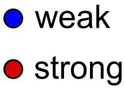
[Coba et al. (2009)]

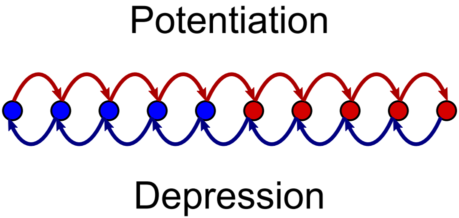


[Montgomery and Madison (2002)]

Models of complex synaptic dynamics

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

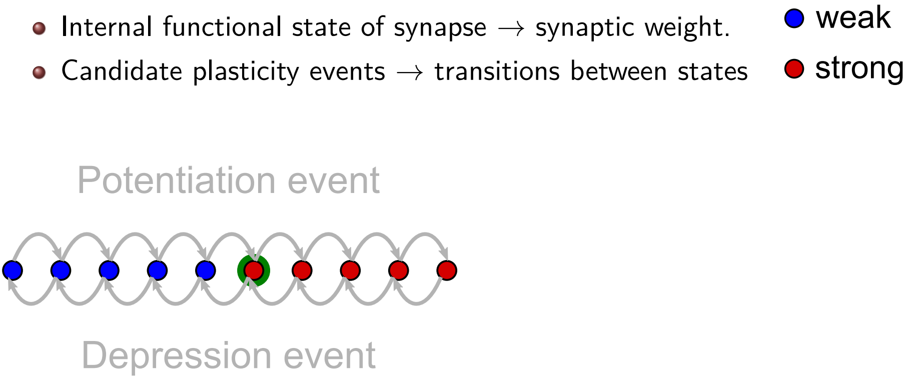




[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]
[Smith et al. (2006), Lahiri and Ganguli (2013)]

Models of complex synaptic dynamics

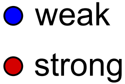
- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states



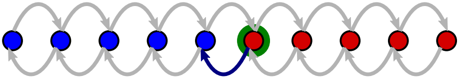
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]
[Smith et al. (2006), Lahiri and Ganguli (2013)]

Models of complex synaptic dynamics

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



Potentiation event

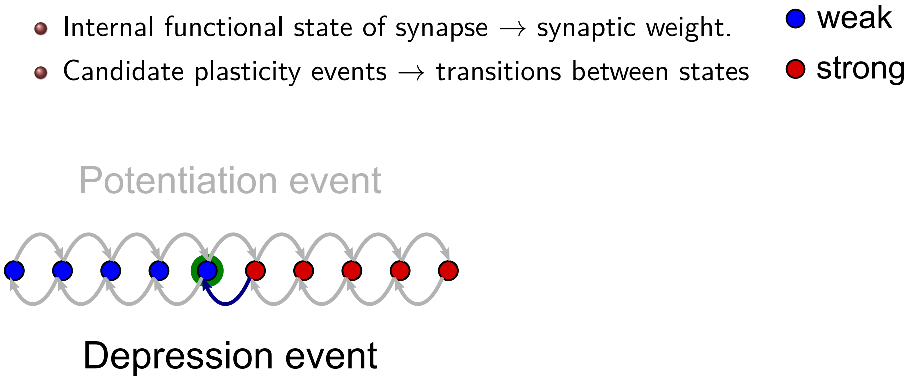


Depression event

[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



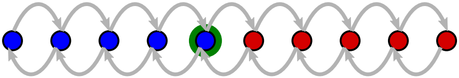
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]
[Smith et al. (2006), Lahiri and Ganguli (2013)]

Models of complex synaptic dynamics

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

weak
strong

Potentiation event

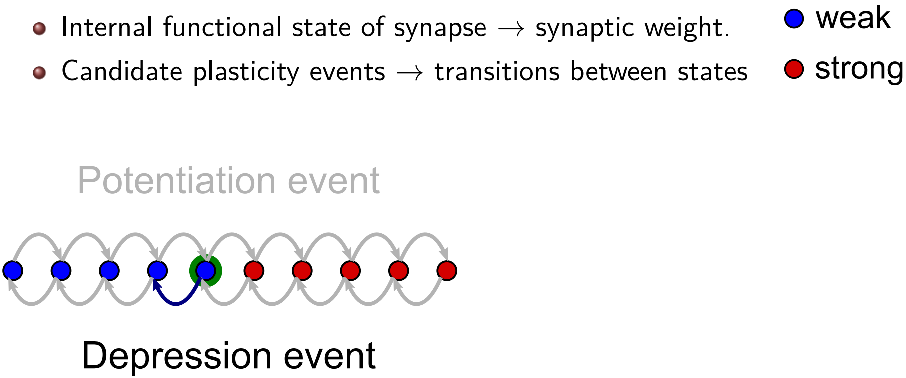


Depression event

[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

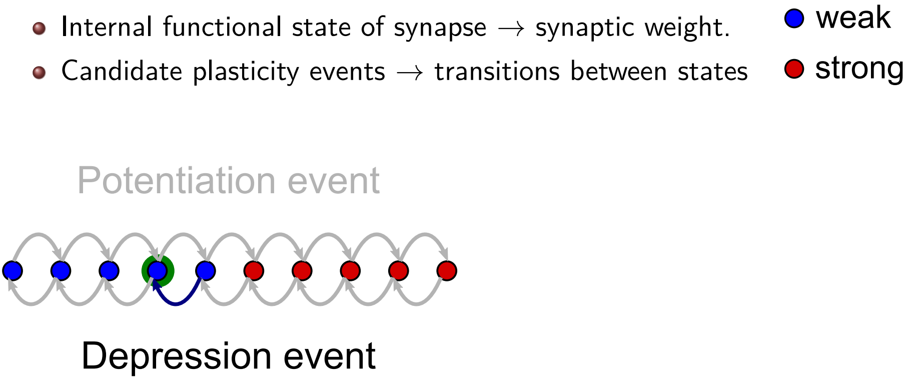
- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states



[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

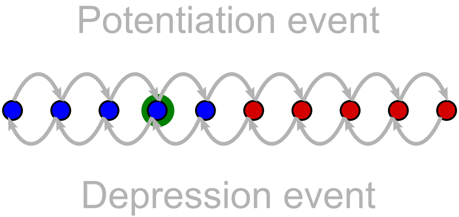
- Internal functional state of synapse $\rightarrow$ synaptic weight.
- Candidate plasticity events $\rightarrow$ transitions between states



[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



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

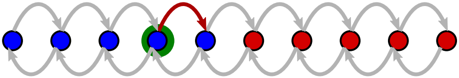
Models of complex synaptic dynamics

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

weak

strong

Potentiation event



Depression event

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

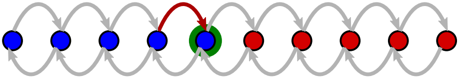
Models of complex synaptic dynamics

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

weak

strong

Potentiation event

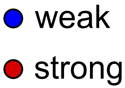


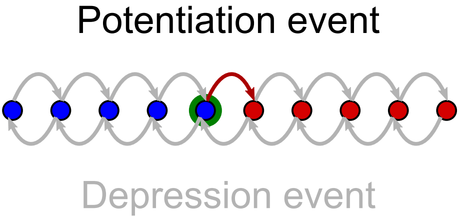
Depression event

[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

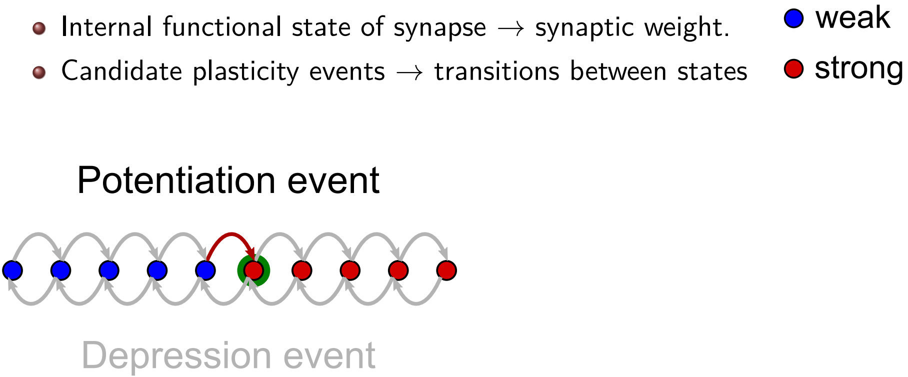




[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]
[Smith et al. (2006), Lahiri and Ganguli (2013)]

Models of complex synaptic dynamics

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



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

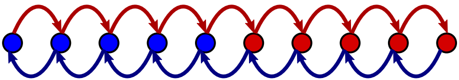
Models of complex synaptic dynamics

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

weak

strong

Potentiation



Depression

Mutation: trans. probs.

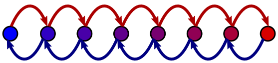
Training: freq. of pot/dep events

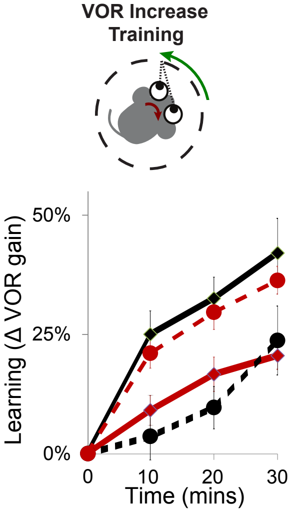
Learning: synaptic weight

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

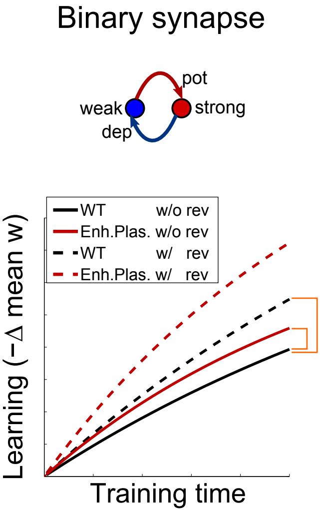
Simple synapses cannot explain the data

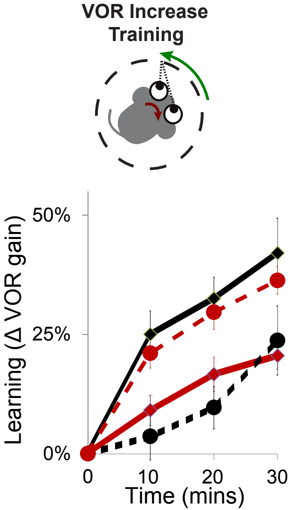
Multistate synapse



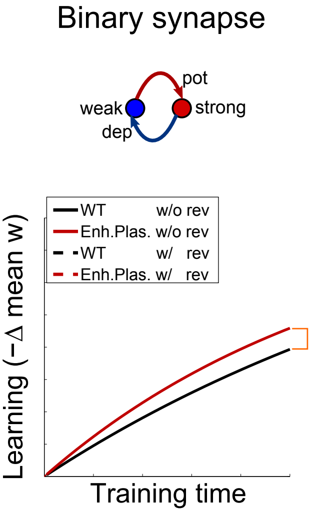


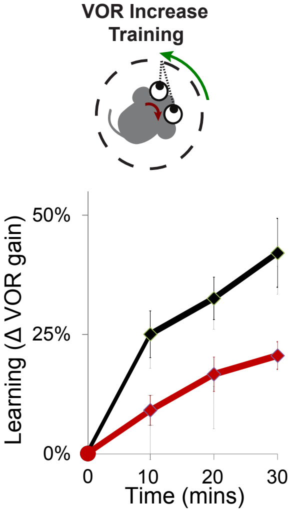
Simple synapses cannot explain the data



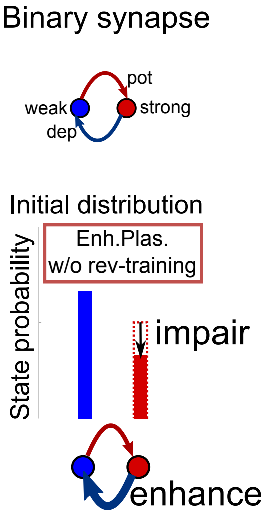


Simple synapses cannot explain the data





Simple synapses cannot explain the data



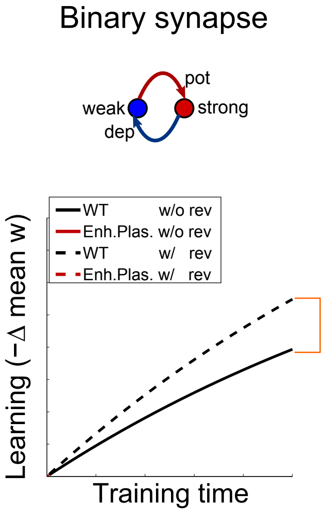
depletion effect

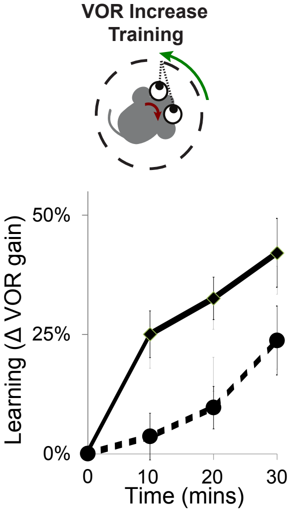
$<$

enhanced plasticity

$\Longrightarrow$ enhanced learning

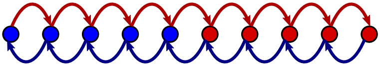
Simple synapses cannot explain the data

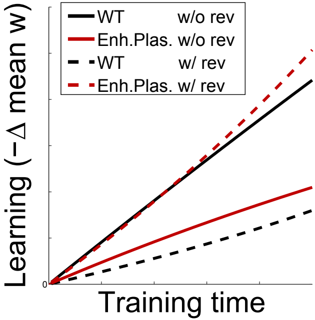




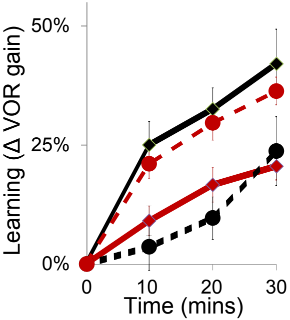
Complex metaplastic synapses can explain the data

Serial synapse



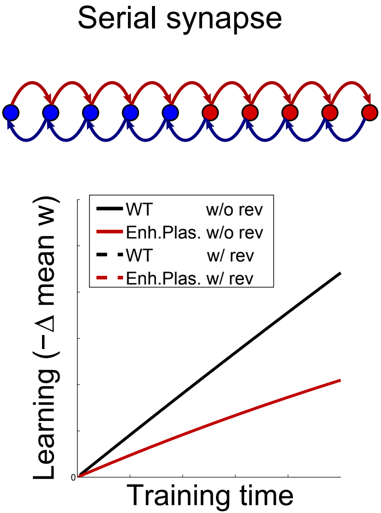


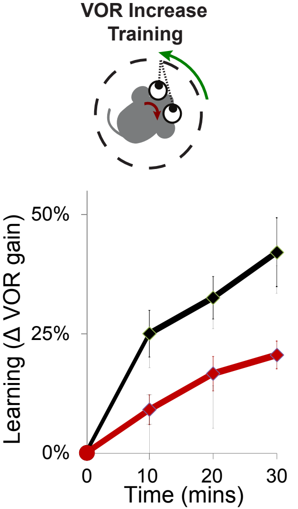
VOR Increase Training



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

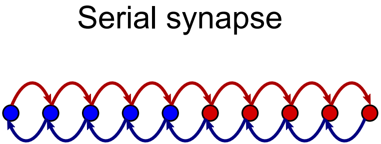
Complex metaplastic synapses can explain the data

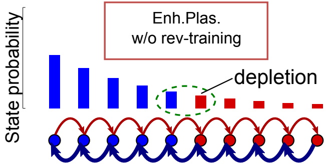




[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]

Complex metaplastic synapses can explain the data





amplified depletion

$>$

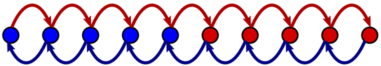
enhanced plasticity

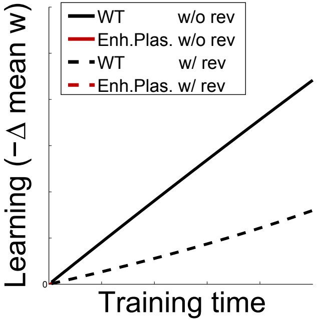
$\Longrightarrow$ impaired learning

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

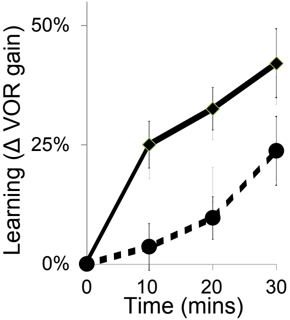
Complex metaplastic synapses can explain the data

Serial synapse



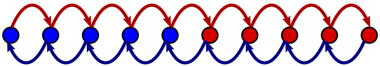


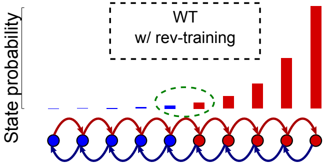
VOR Increase Training



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

Serial synapse





reverse training

$+$

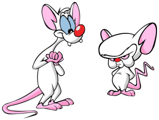
"stubborn" metaplasticity

$\Longrightarrow$ impaired learning

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

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:
  Synaptic complexity: necessary to amplify depletion.
  Synaptic stubbornness: repeated potentiation makes subsequent depression harder.

- 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.

Travel grant: Gatsby Charitable Foundation, Qualcomm Incorporated, Brain Corporation, Evolved Machines.

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) .
2 3 4

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) .
2 3 4

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) .
2 3 4

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) .
2 3 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) .
2 3 4

References II

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) .
2 3 4

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) .
2 3 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) .
2 3 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) .
2 3 4

S du Lac, J L Raymond, T J Sejnowski, and S G Lisberger.
"Learning and Memory in the Vestibulo-Ocular Reflex".
Annual Review of Neuroscience, 18(1):409–441, (1995) .
5

Edward S. Boyden, Akira Katoh, and Jennifer L. Raymond.
"CEREBELLUM-DEPENDENT LEARNING: The Role of Multiple Plasticity Mechanisms".
Annual Review of Neuroscience, 27(1):581–609, (2004) .
5

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) .
6

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) .
14

Johanna M. Montgomery and Daniel V. Madison.
"State-Dependent Heterogeneity in Synaptic Depression between Pyramidal Cell Pairs".
Neuron, 33(5):765 – 777, (2002) .
14

References IV

S. Fusi, P. J. Drew, and L. F. Abbott.
"Cascade models of synaptically stored memories".
Neuron, 45(4):599–611, (Feb, 2005) .
15 16 17 18 19 20 21 22 23 24 25 26 27 47

S. Fusi and L. F. Abbott.
"Limits on the memory storage capacity of bounded synapses".
Nat. Neurosci., 10(4):485–493, (Apr, 2007) .
15 16 17 18 19 20 21 22 23 24 25 26 27

A. B. Barrett and M. C. van Rossum.
"Optimal learning rules for discrete synapses".
PLoS Comput. Biol., 4(11):e1000230, (Nov, 2008) .
15 16 17 18 19 20 21 22 23 24 25 26 27

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) .
15 16 17 18 19 20 21 22 23 24 25 26 27

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. 2013.
15 16 17 18 19 20 21 22 23 24 25 26 27

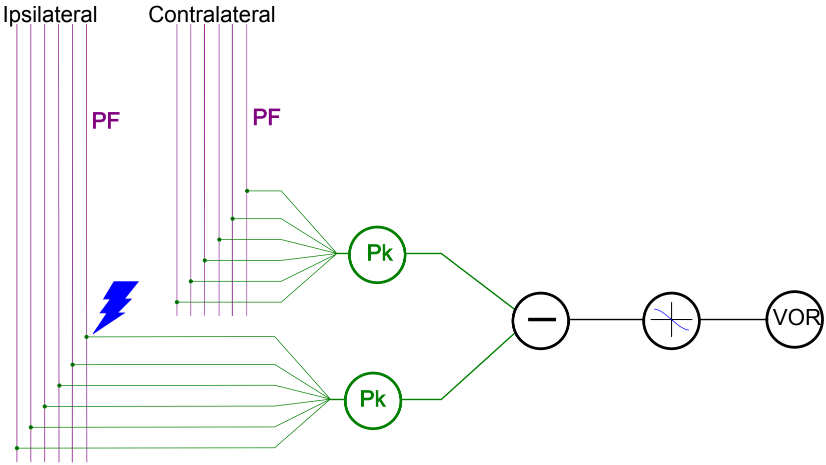
References V

Christian Leibold and Richard Kempter.
"Sparseness Constrains the Prolongation of Memory Lifetime via Synaptic Metaplasticity".
Cerebral Cortex, 18(1):67–77, (2008) .
33 34 35 36 37

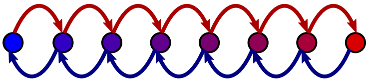
Daniel D Ben-Dayan Rubin and Stefano Fusi.
"Long memory lifetimes require complex synapses and limited sparseness".
Frontiers in computational neuroscience, 1(November):1–14, (2007) .
33 34 35 36 37

D. J. Amit and S. Fusi.
"Learning in neural networks with material synapses".
Neural Computation, 6(5):957–982, (1994) .
46

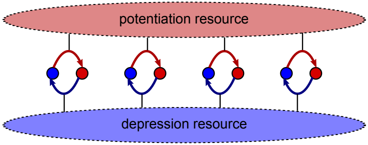
Model of circuit

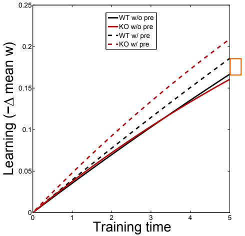


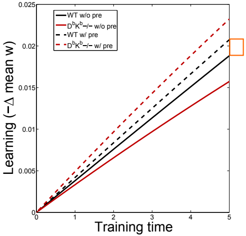
Multistate synapse



Pooled resource model



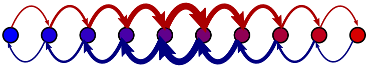


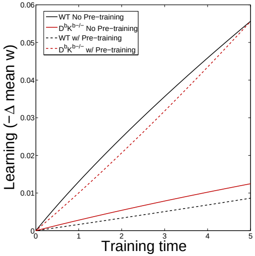


[Amit and Fusi (1994)]

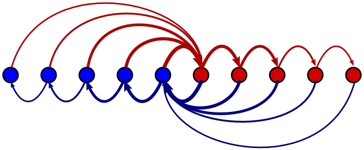
Other models that work

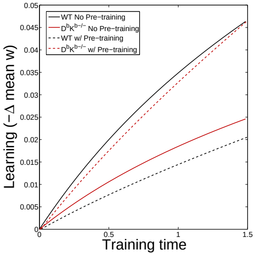
Non-uniform multistate model





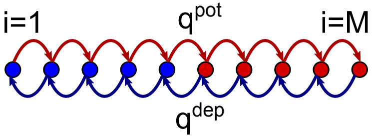
Cascade model





[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.