Understanding impaired learning with enhanced plasticity

based on work in preparation with: T.D. Barbara Nguyen-Vu, Grace Q. Zhao, Aparna Suvrathan, Han-Mi Lee, Surya Ganguli, Carla J. Shatz, Jennifer L. Raymond

Subhaneil Lahiri

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1. Acknowledge Barbara and Grace

Introduction

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

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2. Want to understand when and why
3. Depends on circumstance. Rich pattern of behaviour
4. Develop understanding of when and why learning is enhanced/impaired

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

Simple synapses cannot explain behaviour.
$\rightarrow$ Necessary & sufficient conditions on complex synapses to replicate this.

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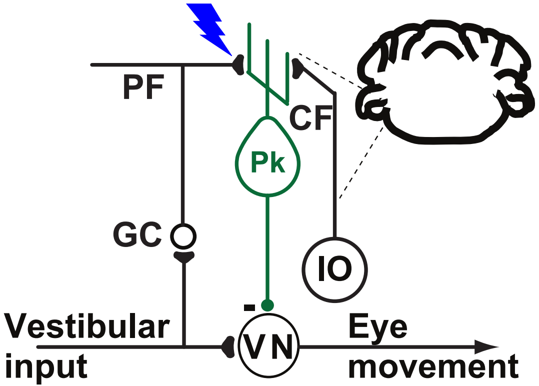
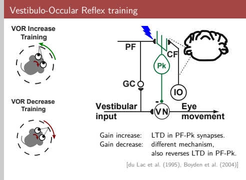
VOR Increase Training

VOR Decrease Training



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

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



1. Explain what VOR gain is
2. trick brain into thinking VOR gain needs adjusting my moving visual stimulu
3. anti-phase → increase gain
4. in phase → decrease gain
5. Gain change involves cerebellum
6. If we enhanced plasticity here: expect enhanced learning

Knockout of MHC-I D^bK^b molecules in PF-Pk synapses

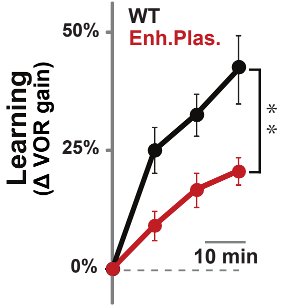
[McConnell et al. (2009)]

$\rightarrow$ lower threshold for LTD $\rightarrow$ enhanced plasticity

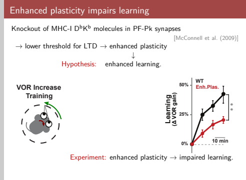
$\downarrow$

Hypothesis: enhanced learning.

VOR Increase Training



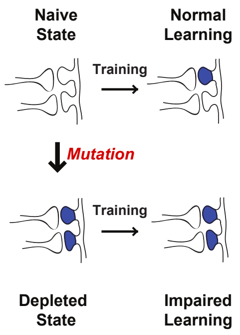
Experiment: enhanced plasticity $\rightarrow$ impaired learning.



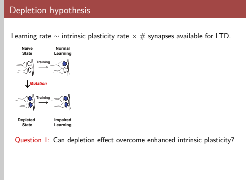
1. Major Histocompatibility Complex - involved in synaptic plasticity (Carla Shatz lab)
2. Easier LTD $\rightarrow$ expect better learning
3. Impairment of learning
4. Looking at change of VOR gain during gain-up training

Depletion hypothesis

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



Question 1: Can depletion effect overcome enhanced intrinsic plasticity?



1. Our model: baseline activity $\to$ saturation $\to$ less depression possible
2. Saturation has to compete with enhanced plsaticity. Which will win?

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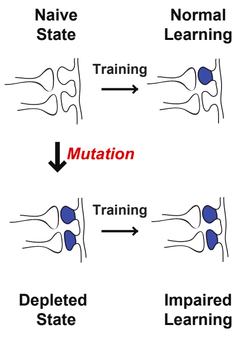
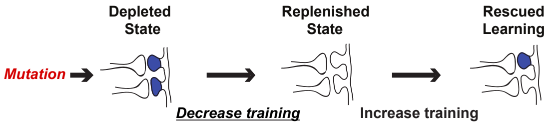


- Mimic depletion with ChR2 stim of CF
- Biochemical marker of LTD



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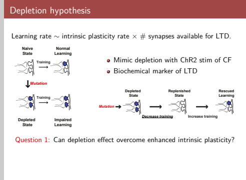
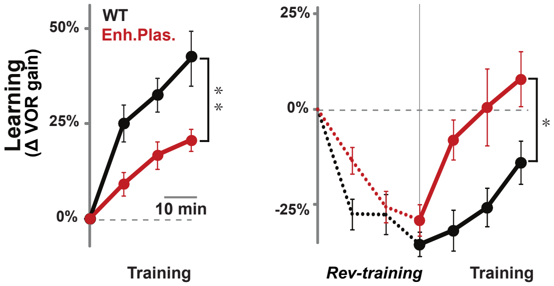
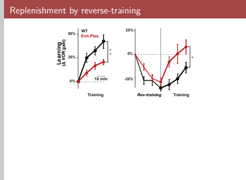


1. Our model: baseline activity $\to$ saturation $\to$ less depression possible
2. Saturation has to compete with enhanced plsaticity. Which will win?
3. Prediction: replenish with rev-training $\to$ rescue

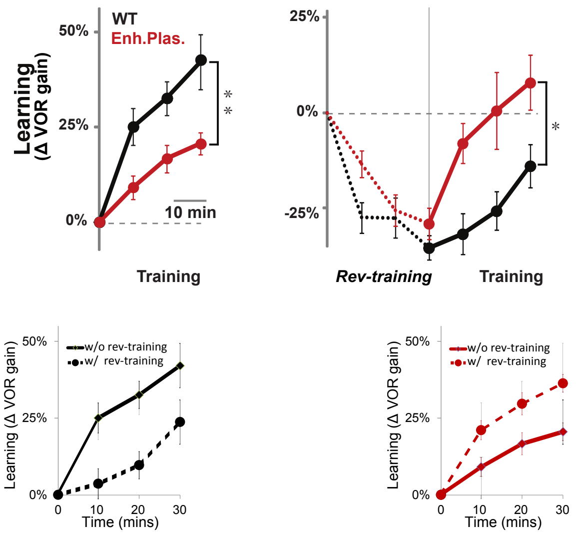
Replenishment by reverse-training



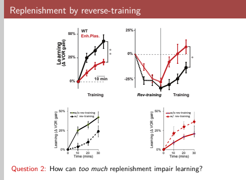


1. precede gain inc training w/ gain dec rev-training: reverses LTD
2. but behaviour from elsewhere → not modelled
3. Focus on gain inc part

Replenishment by reverse-training



Question 2: How can *too much* replenishment impair learning?



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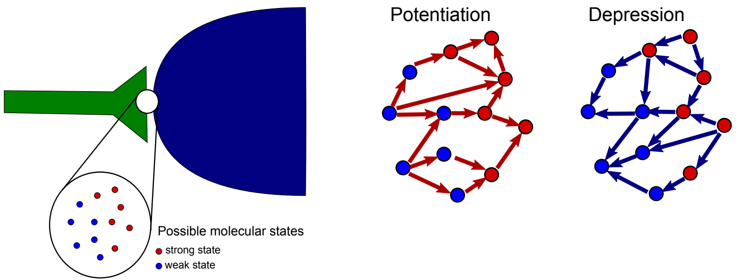
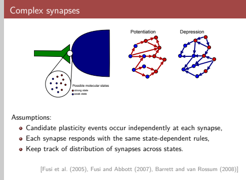
Complex synapses



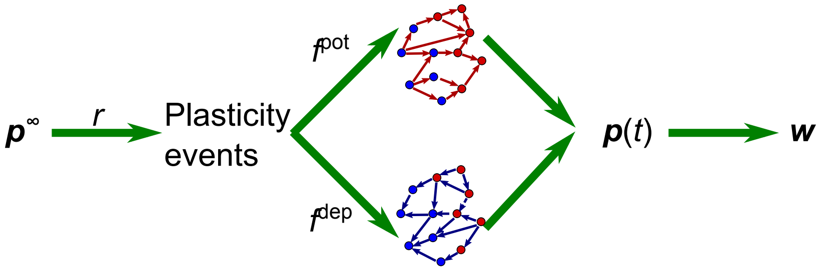
Assumptions:

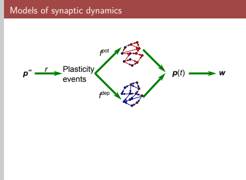
- Candidate plasticity events occur independently at each synapse,
- Each synapse responds with the same state-dependent rules,
- Keep track of distribution of synapses across states.

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



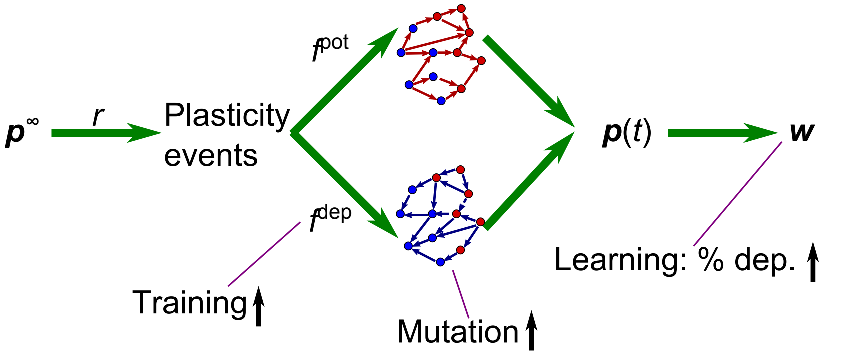
1. Not just synaptic weight, internal dynamical system
2. Important for memory: simple synapses – terrible storage, rescued by complexity
3. Multiple functional states w/ different weights
4. Stochastic transitions between states
5. allows us to concentrate on synapse, not neuron/network
6. This is a question about synaptic populations after all.





1. stoch process has steady state distribution.
2. Prior activity puts it in this state. row vec.
3. plasticity events at rate r
4. fraction pot/dep
5. probs changed by Markov matrices, prob $i \to j$
6. Readout: synaptic weight vec when in each state.

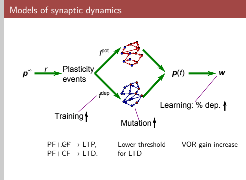
Models of synaptic dynamics



PF+$\cancel{\text{CF}}$ → LTP,
PF+CF → LTD.

Lower threshold for LTD

VOR gain increase



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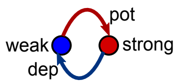
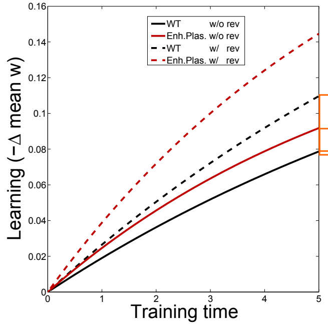
5. probs changed by Markov matrices, prob $i \to j$
6. Readout: synaptic weight vec when in each state.
7. Mutation: lower threshold → increase transition probs
8. Training: Changes statistics of LTP/LTD. Only parameters we have. Don't care about r.
9. Learning: Only output we have. Don't keep track of synaptic identity.

Binary synapse





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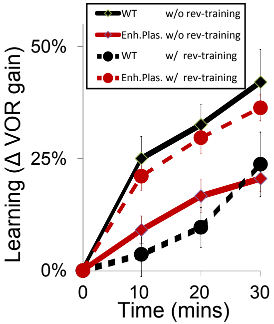
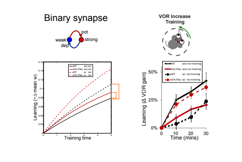
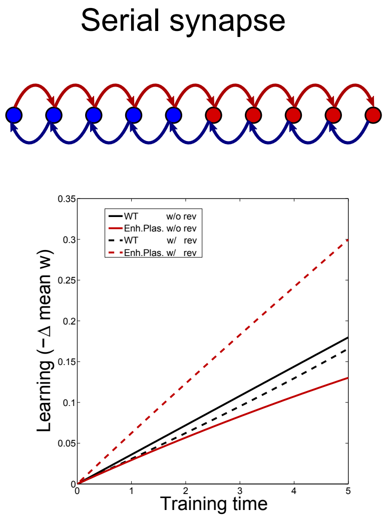
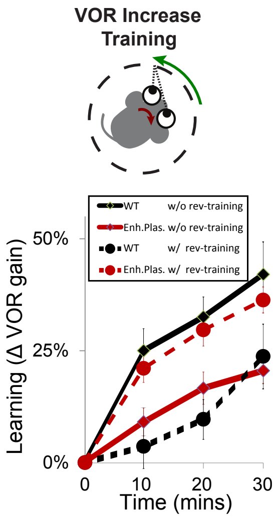




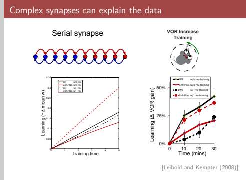
1. Binary fails – mathematical proof for any params
2. Enh.Plas: faster depression wins over bias
3. pre: reduces/reverses bias. always helps.

Complex synapses can explain the data



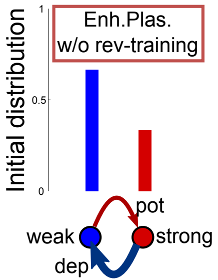


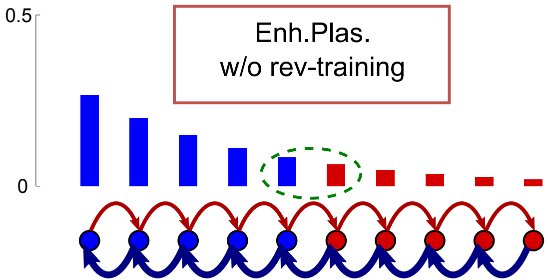
[Leibold and Kempter (2008)]



1. Serial: still only two weights. Works.
2. Understand by looking at distributions before training

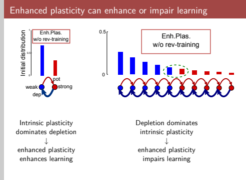
Enhanced plasticity can enhance or impair learning





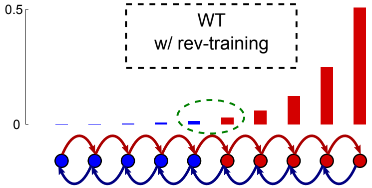
Intrinsic plasticity dominates depletion
↓
enhanced plasticity enhances learning

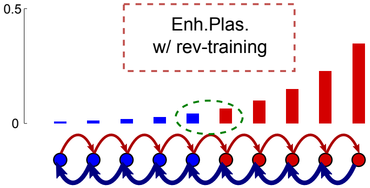
Depletion dominates intrinsic plasticity
↓
enhanced plasticity impairs learning



1. Binary: enhanced plasticity $\to$ bias
2. Not enough to overcome faster depression
3. Serial: Only get signal from boundary
4. Exponential decay depopulates boundary, enhances effect of bias

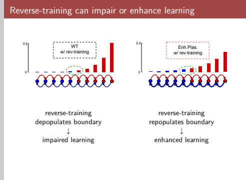
Reverse-training can impair or enhance learning





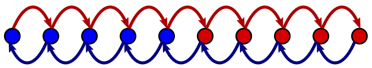
reverse-training
depopulates boundary
↓
impaired learning

reverse-training
repopulates boundary
↓
enhanced learning



1. rev-training: little repopulates boundary
2. Too much pushes to other side, depopulates boundary
3. this effect is absent in any simple synapse

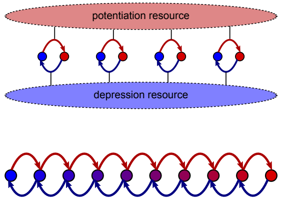
Essential features



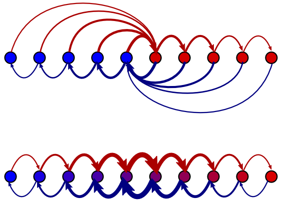
The success of the serial model relies on two features:

- Complexity - needed to amplify the effect of depletion,
- Metaplasticity – repeated potentiation makes subsequent depression harder.

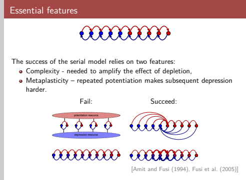
Fail:



Succeed:



[Amit and Fusi (1994), Fusi et al. (2005)]



1. due to exponential decay
2. push away from boundary where signal generated
3. borne out by other models that fail/succeed

Conclusions

- We find diverse behavioural patterns in these mutant mice:
  Enhanced plasticity $\rightarrow$ enhance/impair learning depending on prior experience.
  Reverse-training $\rightarrow$ enhance/impair learning depending on plasticity rates.
- We can explain these behavioural patterns using synaptic models.
- Key required synaptic properties are:
  Synaptic complexity: necessary to amplify depletion.
  Synaptic stubbornness: repeated potentiation makes subsequent depression harder.
- We used behaviour to constrain the dynamics of synaptic plasticity

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