Doctoral Class in Neurophysics
EPFL, June 12-16, 2023 – Lausanne, Switzerland

Synaptic Volatility, Inhibitory Plasticity and the Synaptic Trace Theory of Memory

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Plan of the Lecture

First 2 hours (talk + blackboard):

G Mongillo, **S Rumpel**, **Y Loewenstein** (2017).
Intrinsic volatility of synaptic connections -- a challenge to the synaptic trace theory of memory.
Current Opinion in Neurobiology **46**:7-13.

G Mongillo, **S Rumpel**, **Y Loewenstein** (2018).
Inhibitory connectivity defines the realm of excitatory plasticity.
Nature Neuroscience **21**:1463-1470.

Last hour – Implications of the balanced regime for memory function (talk):

G Mongillo & **M Tsodyks** (2023).
Balance of excitation and inhibition is necessary for robust memory storage and retrieval in cortical networks. (unpublished results).

Outline

- **Synaptic dynamics *in vivo*: chronic spine imaging**

- **Implications for learning (*and memory storage*)**

- **Conclusions**

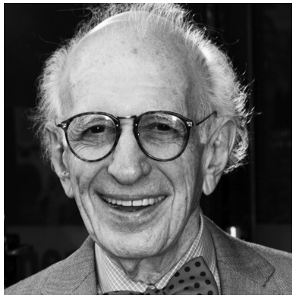
Memory, or Stabilization of Synaptic Changes

«[…] les esprits qui sortent de la glande […] ont la force […] de plier et disposer diversement les petits filets qu'ils rencontrent […] en sorte qu'ils y tracent aussi des figures, qui se rapportent à celles des objets; non pas toutefois si aisément du premier coup […] mais peu à peu de mieux en mieux, selon que leur action […] est plus de fois réitérée. Ce qui est cause que ces figures ne s'effacent pas non plus si aisément […]. Et c'est en quoi consiste la mémoire. »

René Descartes (1664)

"*The first step in this neural schematizing is a bald assumptions about the structural changes that make lasting memories possible. […] The assumption, in brief, is that a growth process accompanying synaptic activity makes the synapse more readily traversed. […] To account for the permanence [of the memory] some structural change seems necessary […]*"**.**

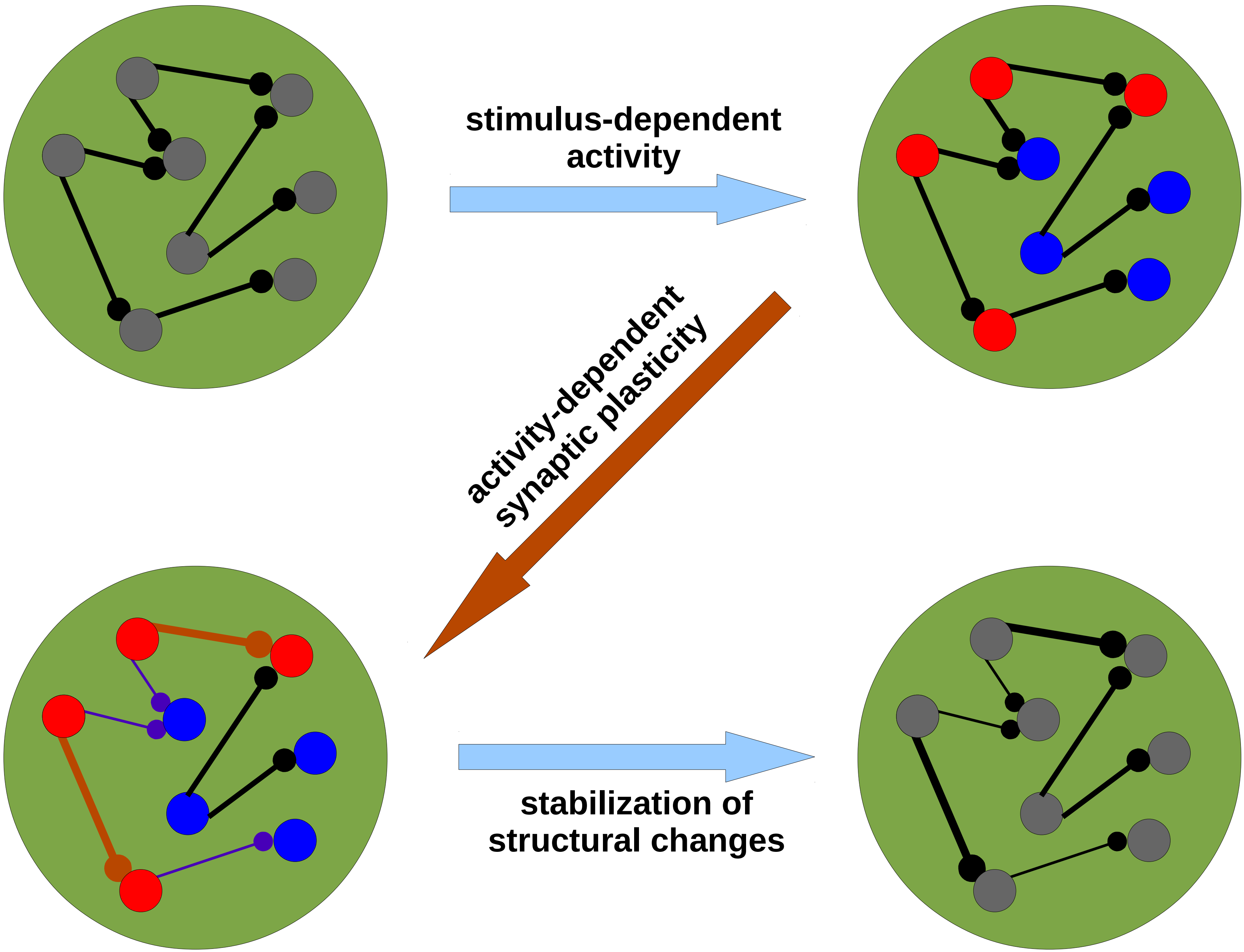
Donald O. Hebb (1949)



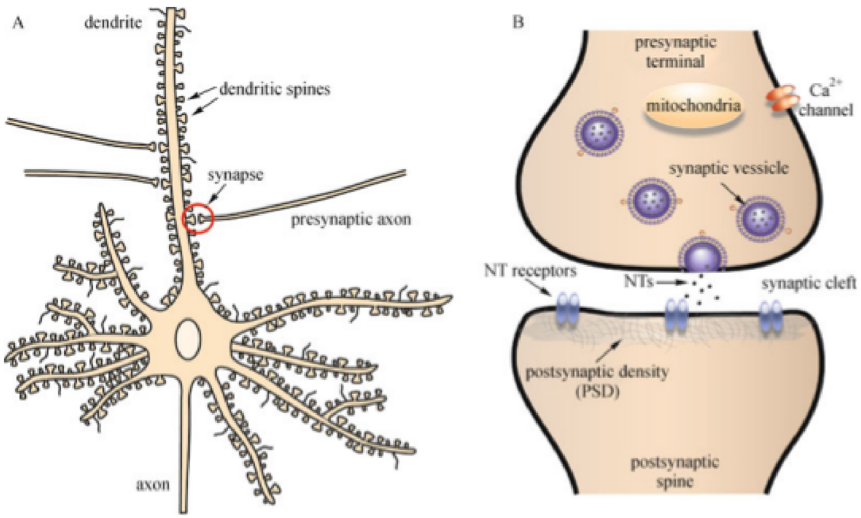
"*With both explicit and implicit memory there are stages in memory that are encoded as changes in synaptic strength and that correlate with the behavioral phases of short- and long-term memory […] whereas the long-term synaptic changes involve activation of gene expression, new protein synthesis, and the formation of new connections*"**.**

Eric R. Kandel (2001)

Synaptic Ghosts of Things Past



Spines: Basic Facts

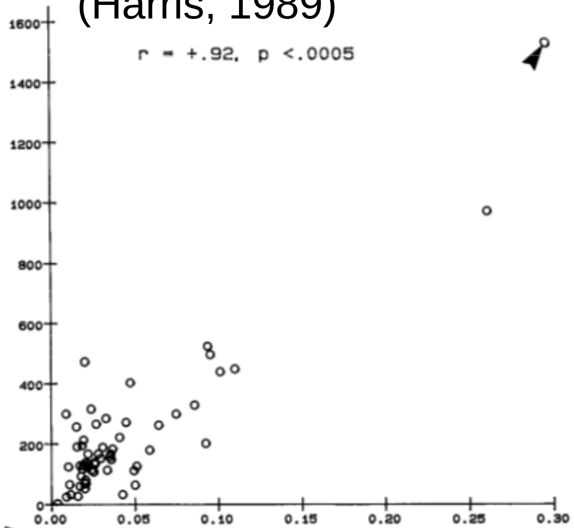


(Smrt & Zhao, 2010)

- >90% of excitatory synapses terminate on spines
- Spine volume is a proxy of the synaptic efficacy

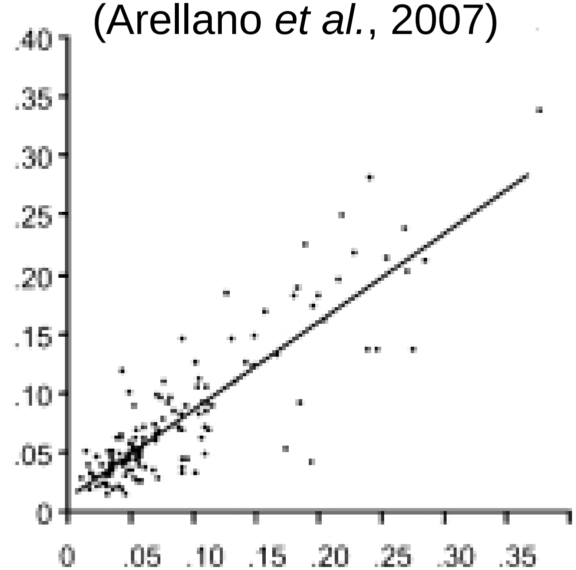
(Harris, 1989)

vesicles



(Arellano *et al.*, 2007)

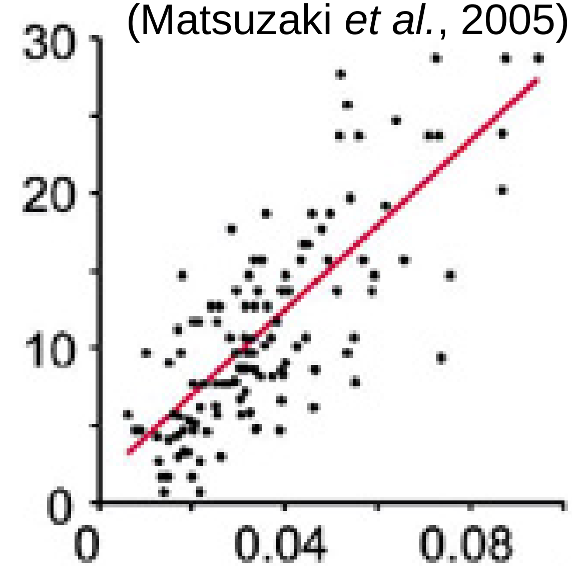
PSD area



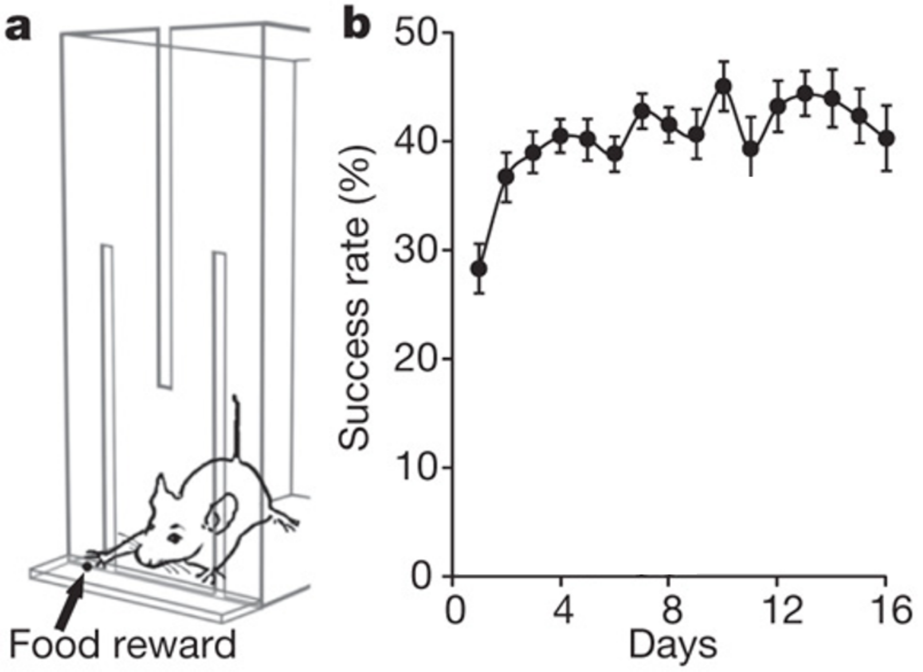
spine volume

(Matsuzaki *et al.*, 2005)

EPSC



Spines: Experience-driven Dynamics



(Xu *et al.*, 2009)

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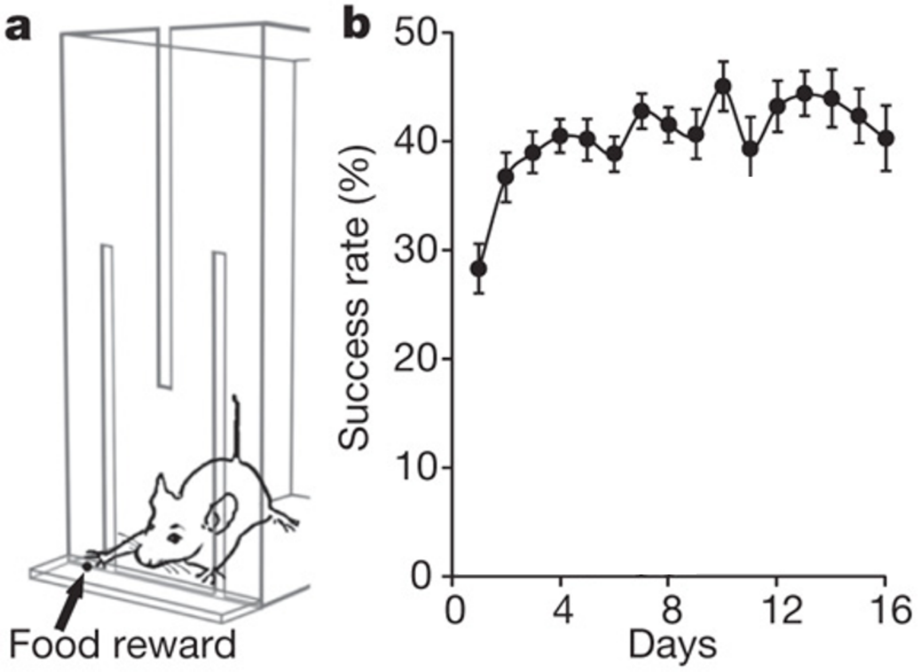

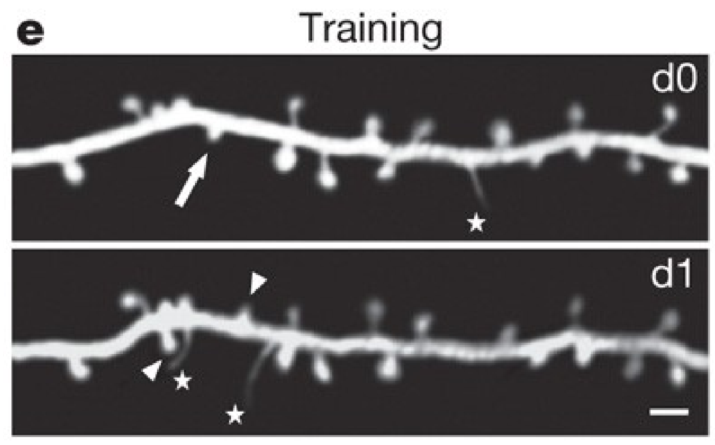

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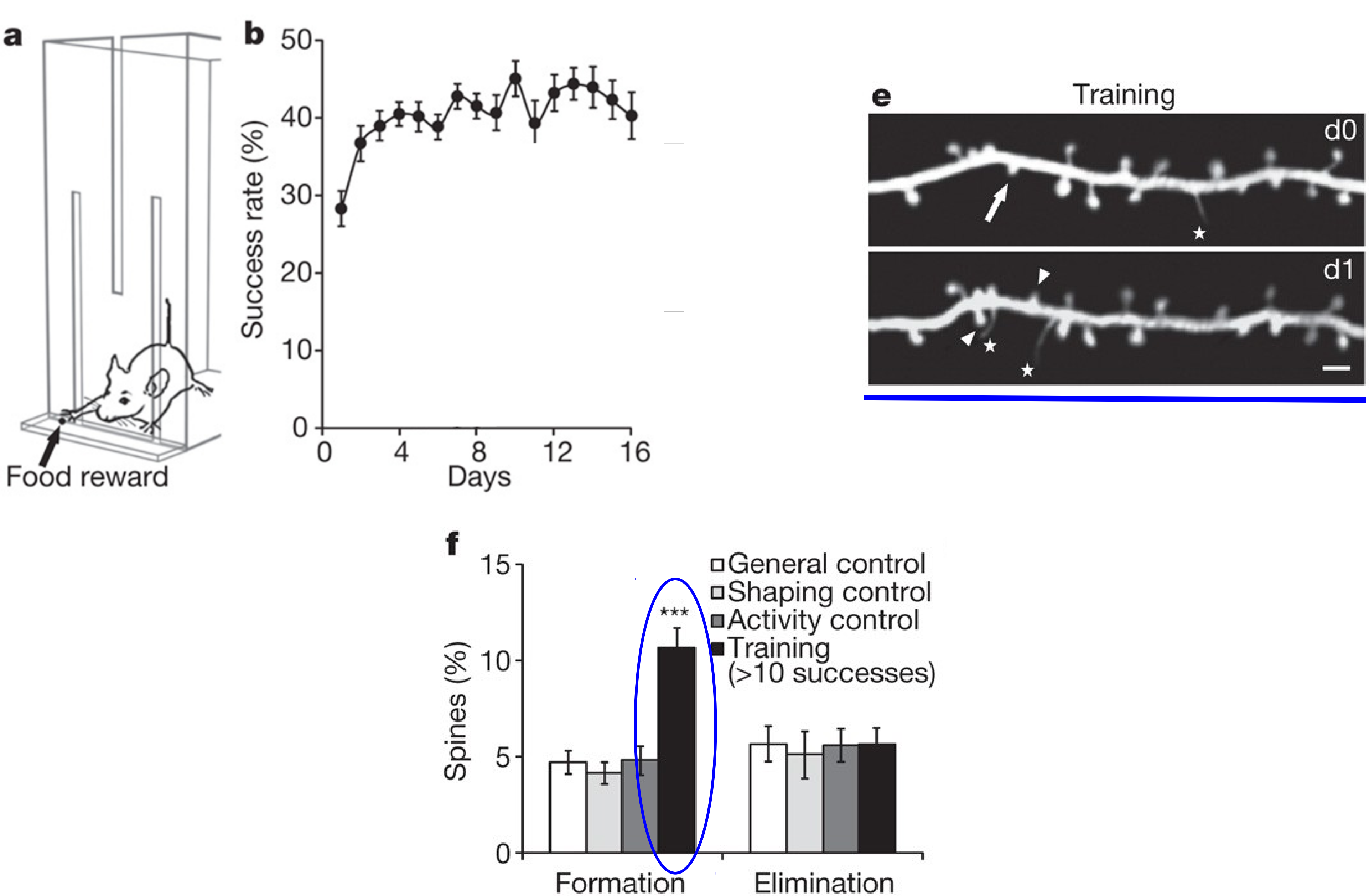

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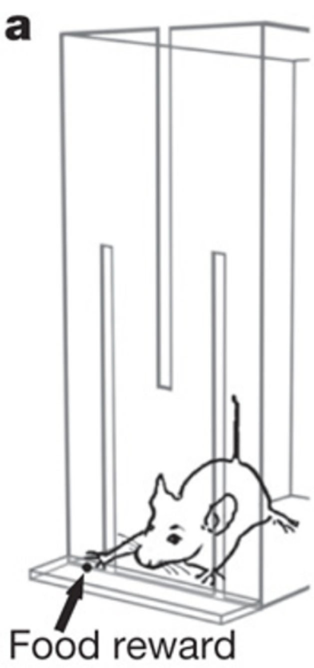
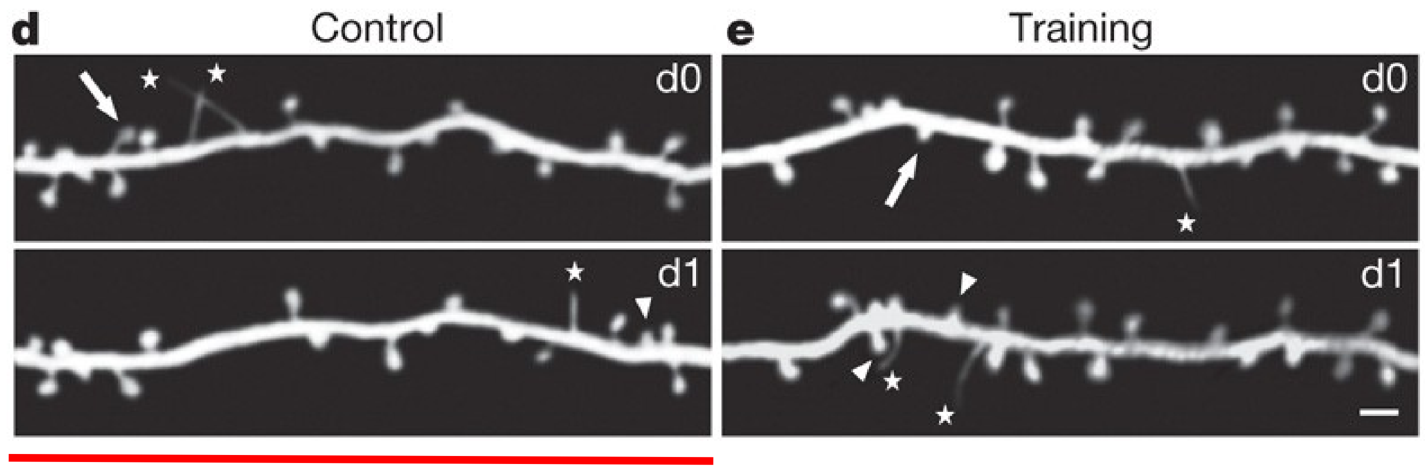
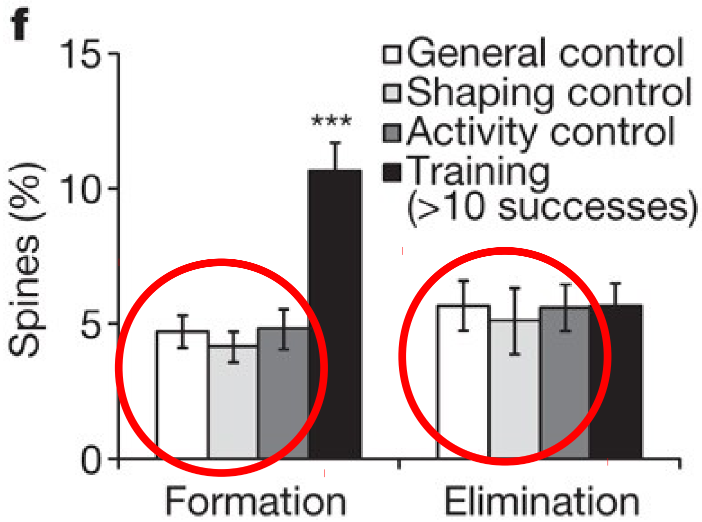
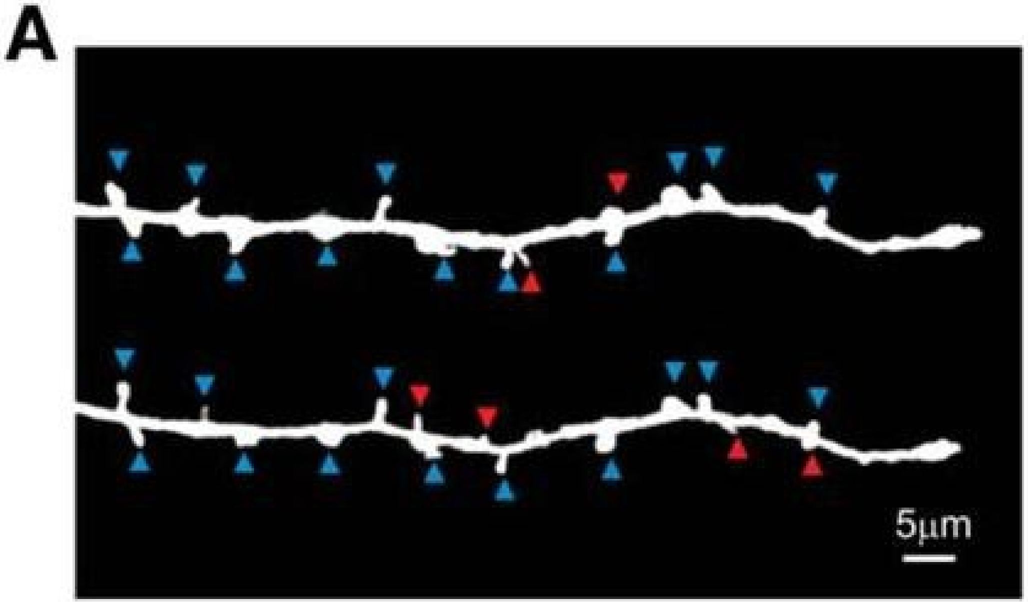






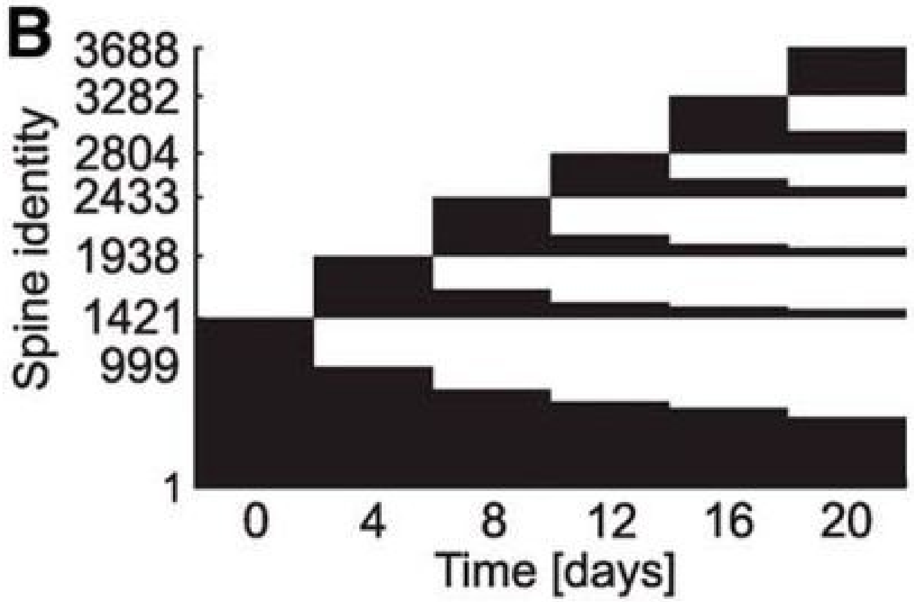
(Xu *et al.*, 2009)

Spines: 'Ongoing' Dynamics



The Dataset

6 mice
8 neurons
3688 spines
6 time points (4-days interval)



(Loewenstein *et al.*, 2011; Loewenstein *et al.*, 2015)

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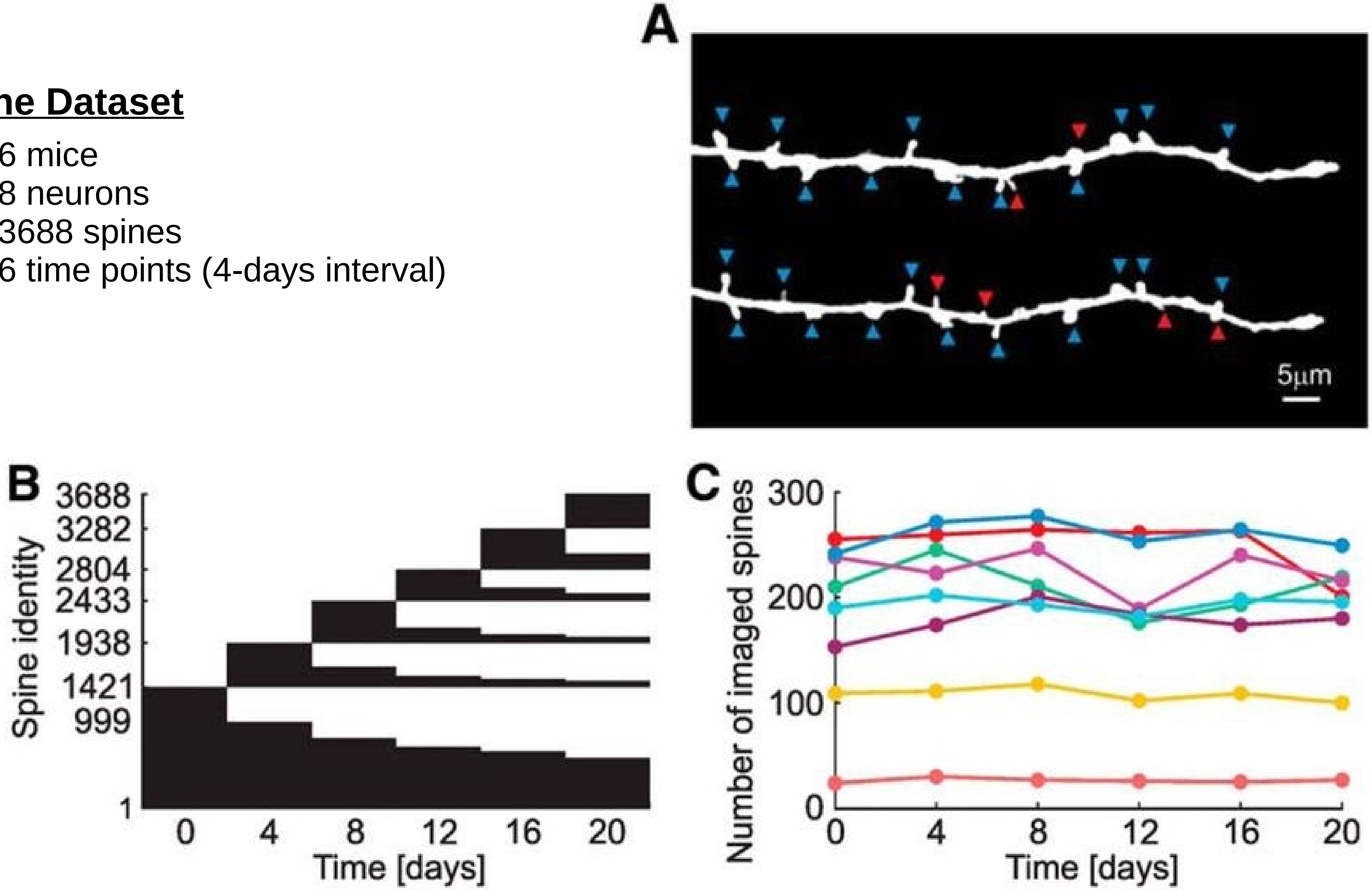

(Loewenstein *et al.*, 2011; Loewenstein *et al.*, 2015)

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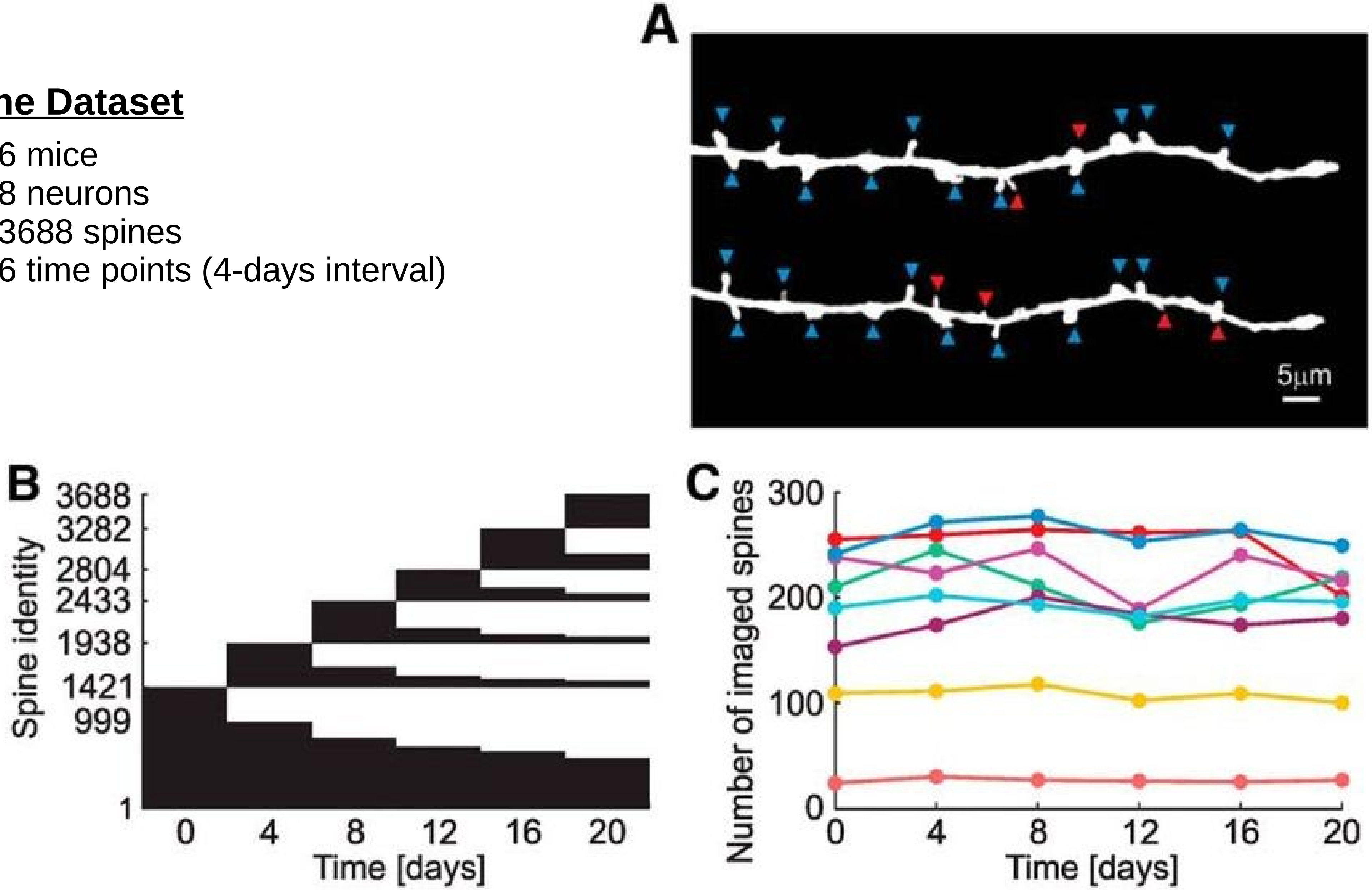
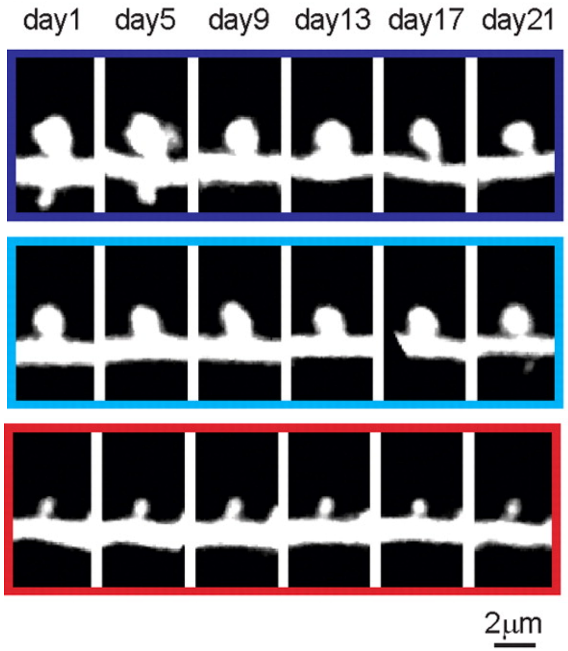


# of spines (on a given neuron) is approximately constant across sessions

(Loewenstein *et al.*, 2011; Loewenstein *et al.*, 2015)

Spines: 'Ongoing' Dynamics



(Loewenstein *et al.*, 2011)

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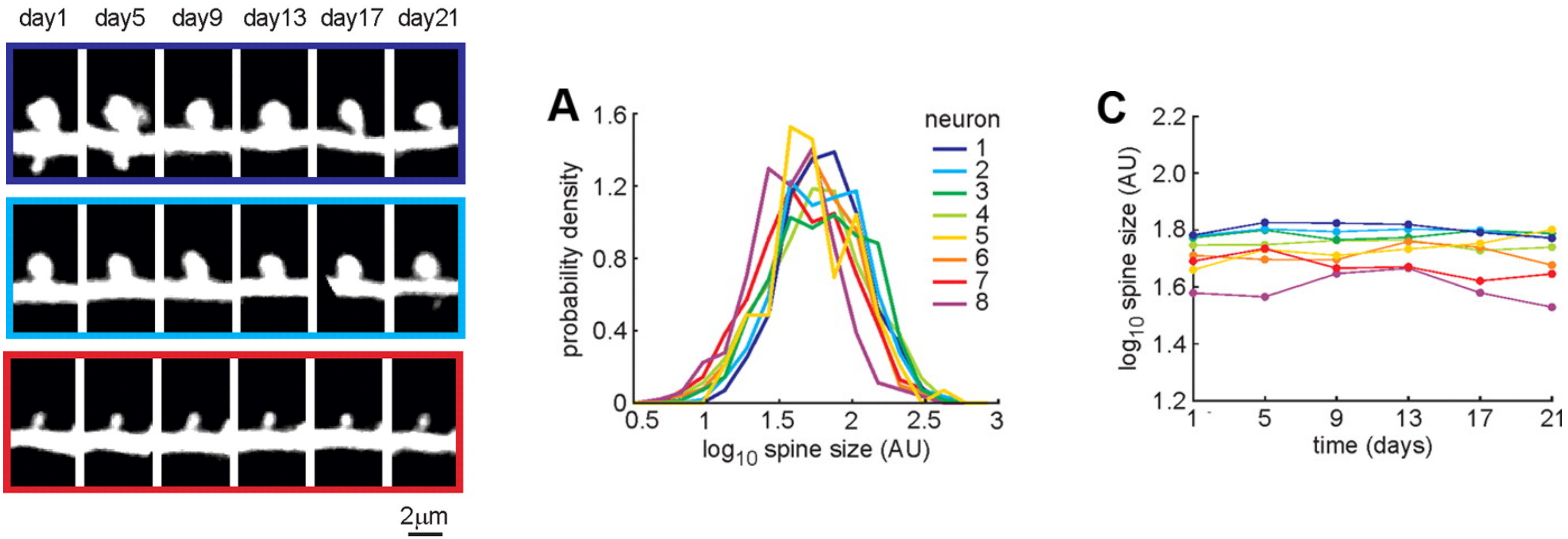
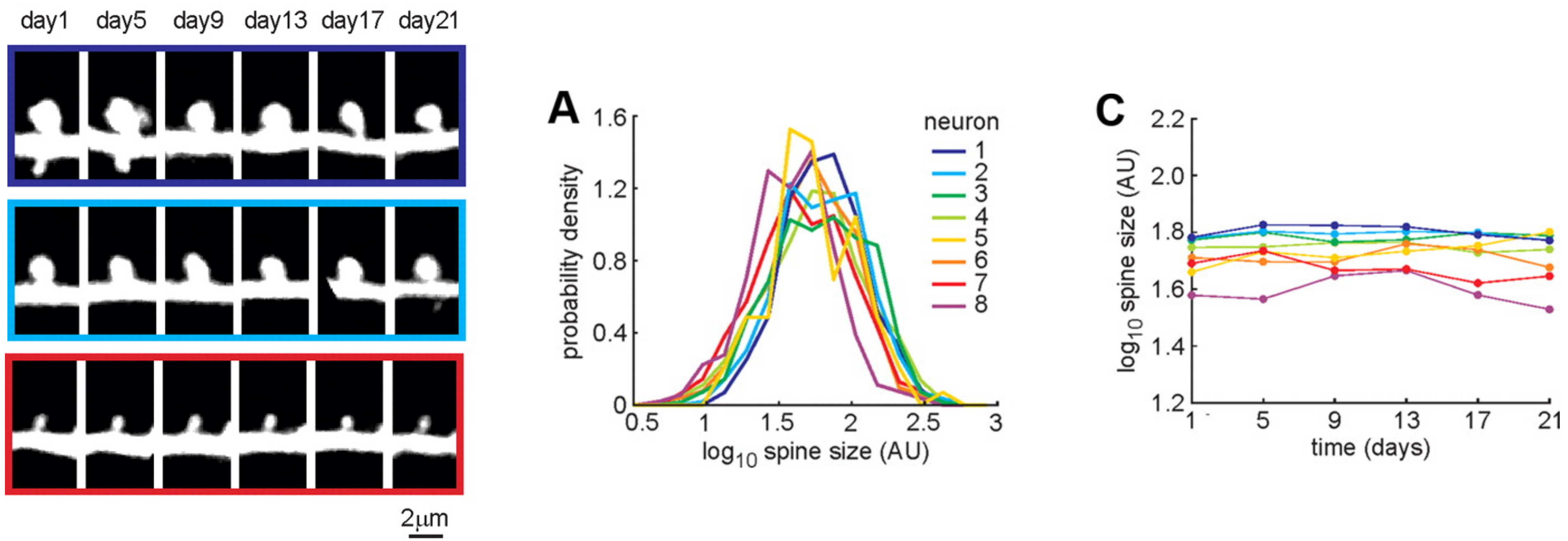


- spines' size distribution is well fitted by a log-normal distribution, and approximately constant across sessions
- spines' size distribution is approximately constant across neurons

(Loewenstein *et al.*, 2011)

Spines: 'Ongoing' Dynamics



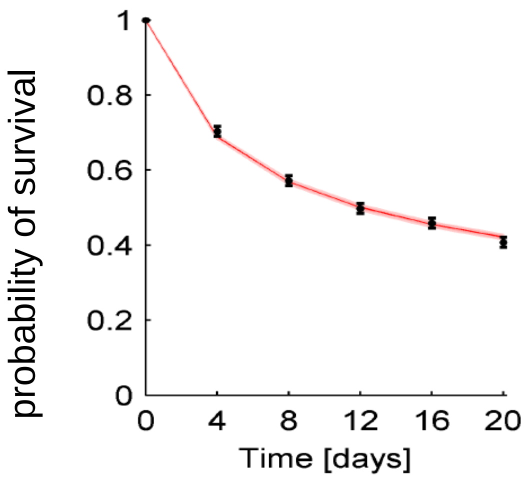
- spines' size distribution is well fitted by a log-normal distribution, and approximately constant across sessions
- spines' size distribution is approximately constant across neurons

<u>Ongoing spine dynamics preserve the gross statistical features of synaptic connectivity (E→E)</u>

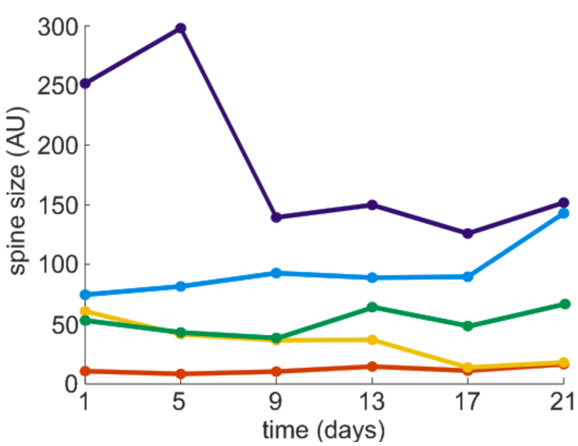
(Loewenstein *et al.*, 2011)

***Ephemeral* Cortical Circuits**

..the fine structure, however, appears to undergo dramatic changes..



Most spines present in the first imaging day are no longer present after 20 days (Loewenstein *et al*., 2015)



70% of the *stable* spines changed their size by at least a factor 2 within 20 days (Loewenstein *et al*., 2011)

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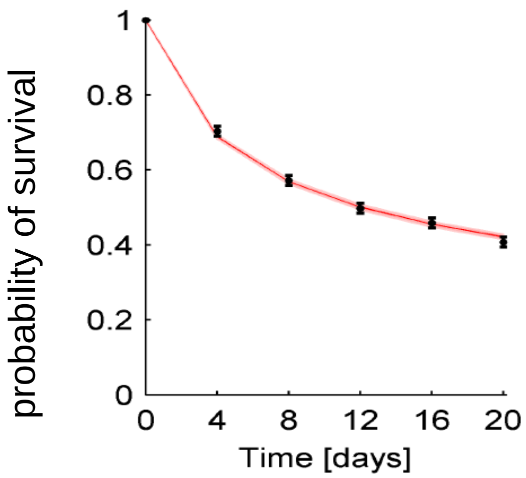

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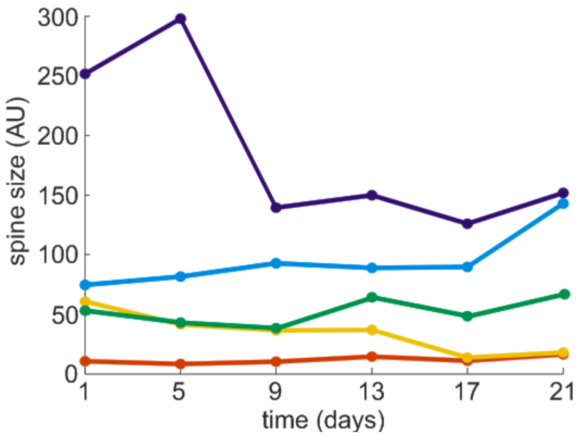
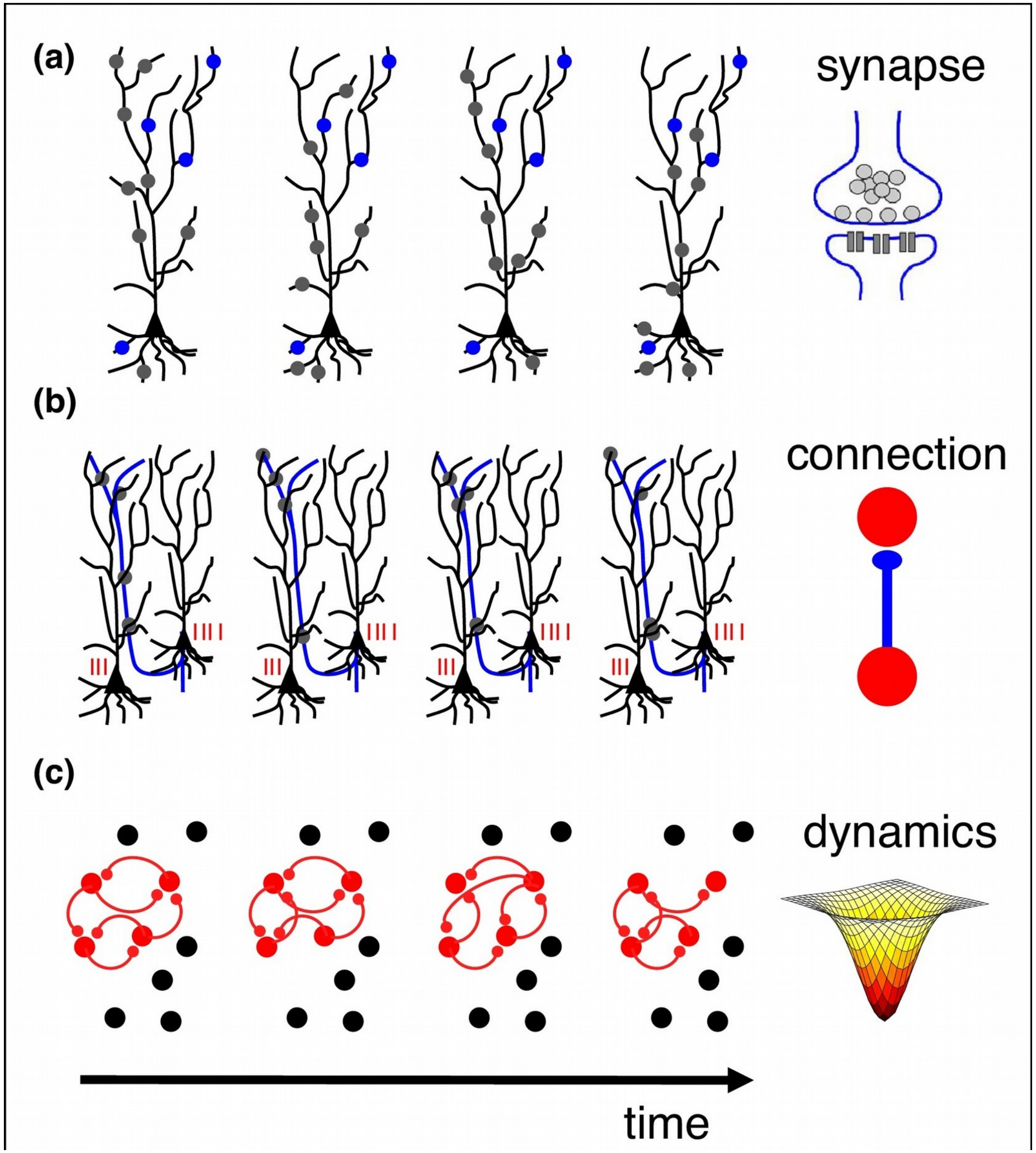


70% of the *stable* spines changed their size by at least a factor 2 within 20 days (Loewenstein *et al*., 2011)

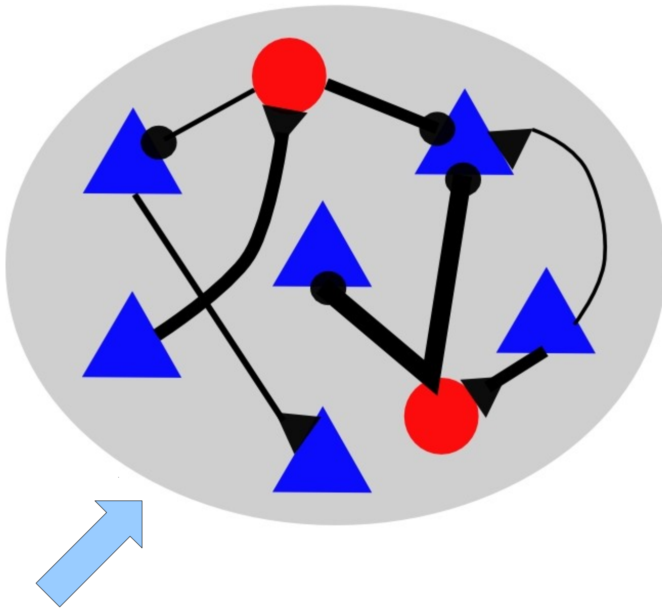
What is the effect of such a massive structural re-organization on the patterns of neuronal activity exhibited by the network?

Mechanisms for Stability of Long-term Memories



Mongillo, Rumpel & Loewenstein, *Curr. Opin. Neurobiol.* (2017)

A Biologically-Constrained Model Network



N=40.000 (80% E – 20% I) LIF Neurons

Random connectivity

Log-normal distribution of synaptic efficacies

E→E connectivity from spine data

External inputs were adjusted to reproduce experimentally observed firing rates:

Exc: ~1Hz – Inh: ~5Hz

Experimentally observed spine data were used to simulate network re-organization

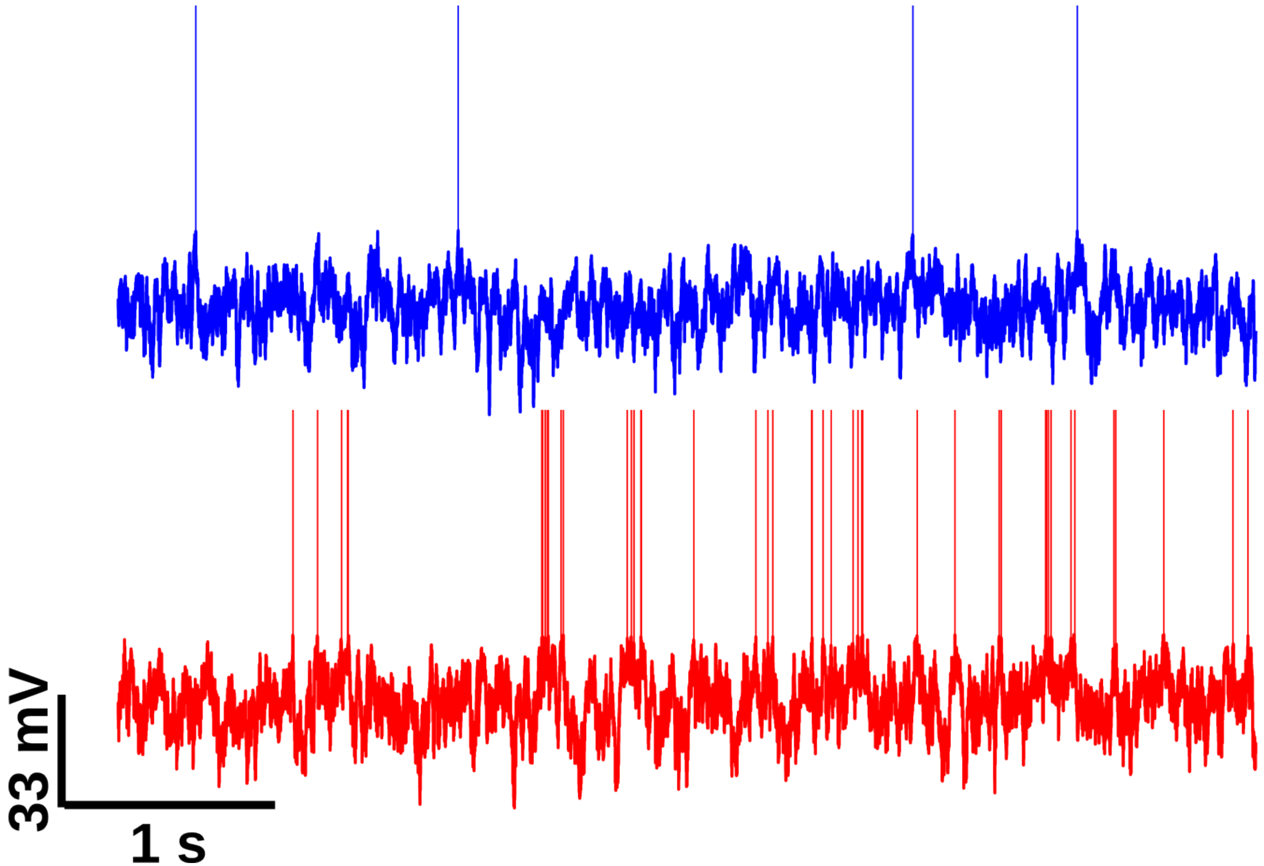
Table 2. *Synaptic connectivity and uPSP amplitudes in L2/3 of mouse barrel cortex*

Postsynaptic	Presynaptic EXC	Presynaptic FS	Presynaptic NFS
EXC			
P, % (found/tested)	16.8% (16/95)	60.0% (21/35)	46.5% (20/43)
Mean ± SE, mV	0.37 ± 0.10	−0.52 ± 0.11	−0.49 ± 0.11
Median, mV	0.20	−0.29	−0.30
Range, mV	0.06–1.42	−0.10 to −1.55	−0.10 to −2.00
FS			
P, % (found/tested)	57.5% (23/40)	55.0% (11/20)	37.9% (11/29)
Mean ± SE, mV	0.82 ± 0.10	−0.56 ± 0.14	−0.37 ± 0.10
Median, mV	0.68	−0.44	−0.23
Range, mV	0.16–1.94	−0.07 to −1.46	−0.12 to −0.99
NFS			
P, % (found/tested)	24.4% (11/45)	24.1% (7/29)	38.1% (8/21)
Mean ± SE, mV	0.39 ± 0.11	−0.83 ± 0.25	−0.49 ± 0.20
Median, mV	0.19	−0.60	−0.15
Range, mV	0.12–1.21	−0.09 to −1.85	−0.07 to −1.47

(Avermann *et al.*, 2012)

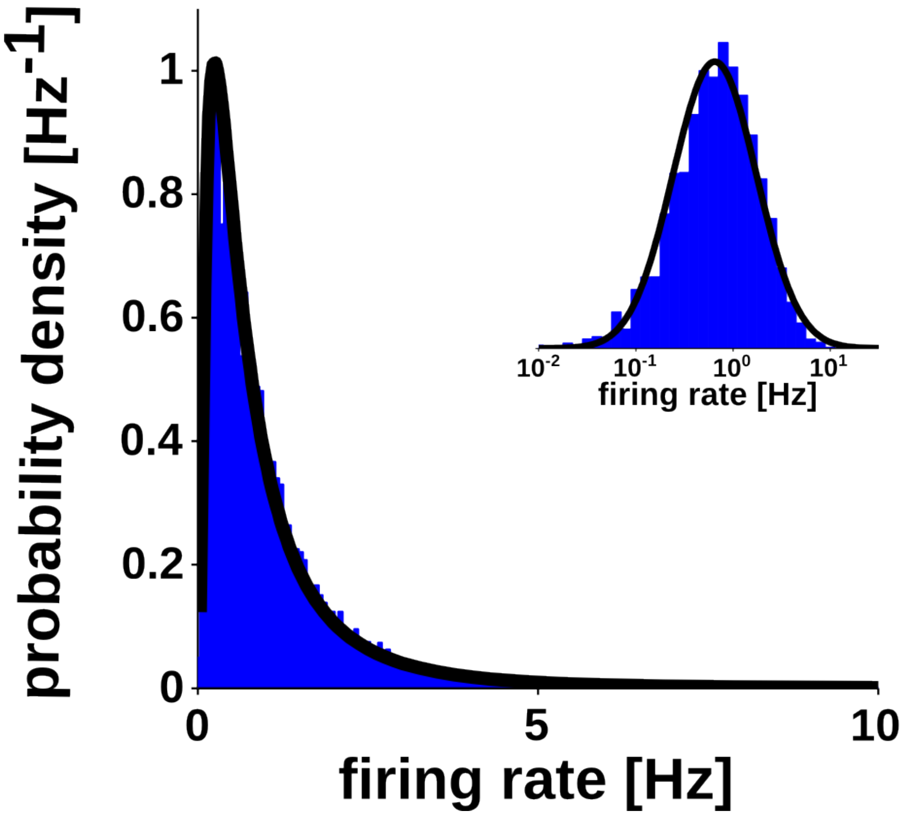
A Biologically-Constrained Model Network

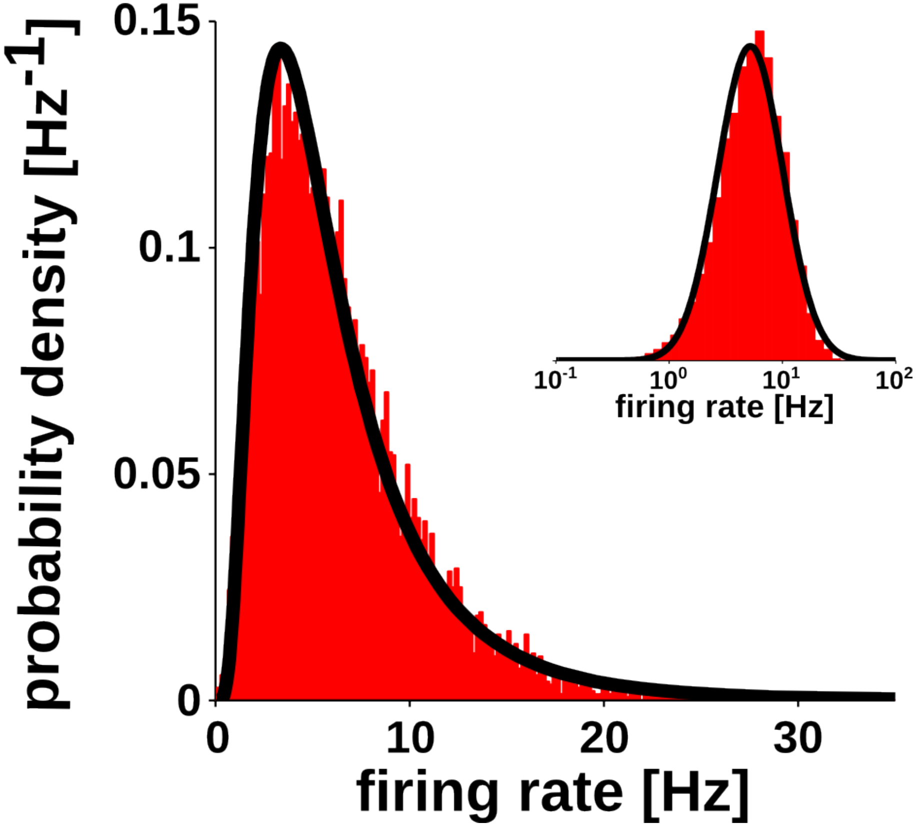
- Temporally irregular spiking resembling Poisson process.



A Biologically-Constrained Model Network

- Temporally irregular spiking resembling Poisson process.
- **Right-skewed, long-tailed distributions of average rates.**

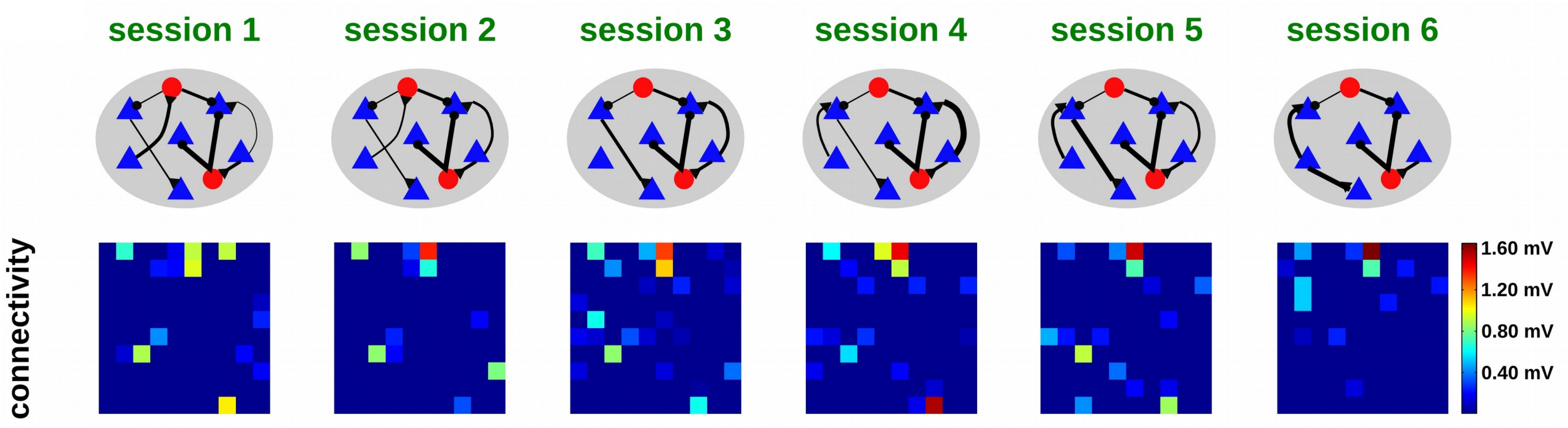




(Roxin *et al.*, 2011)

Effects of E→E Volatility

Experimentally observed spine data were used to simulate network reorganization



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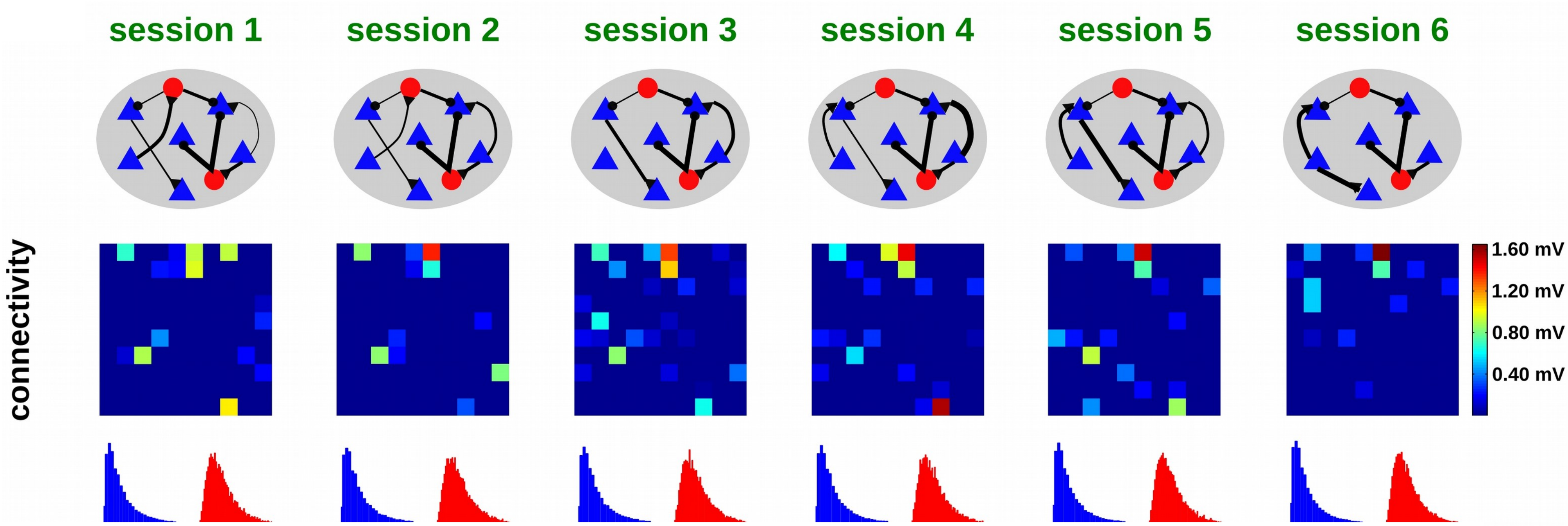

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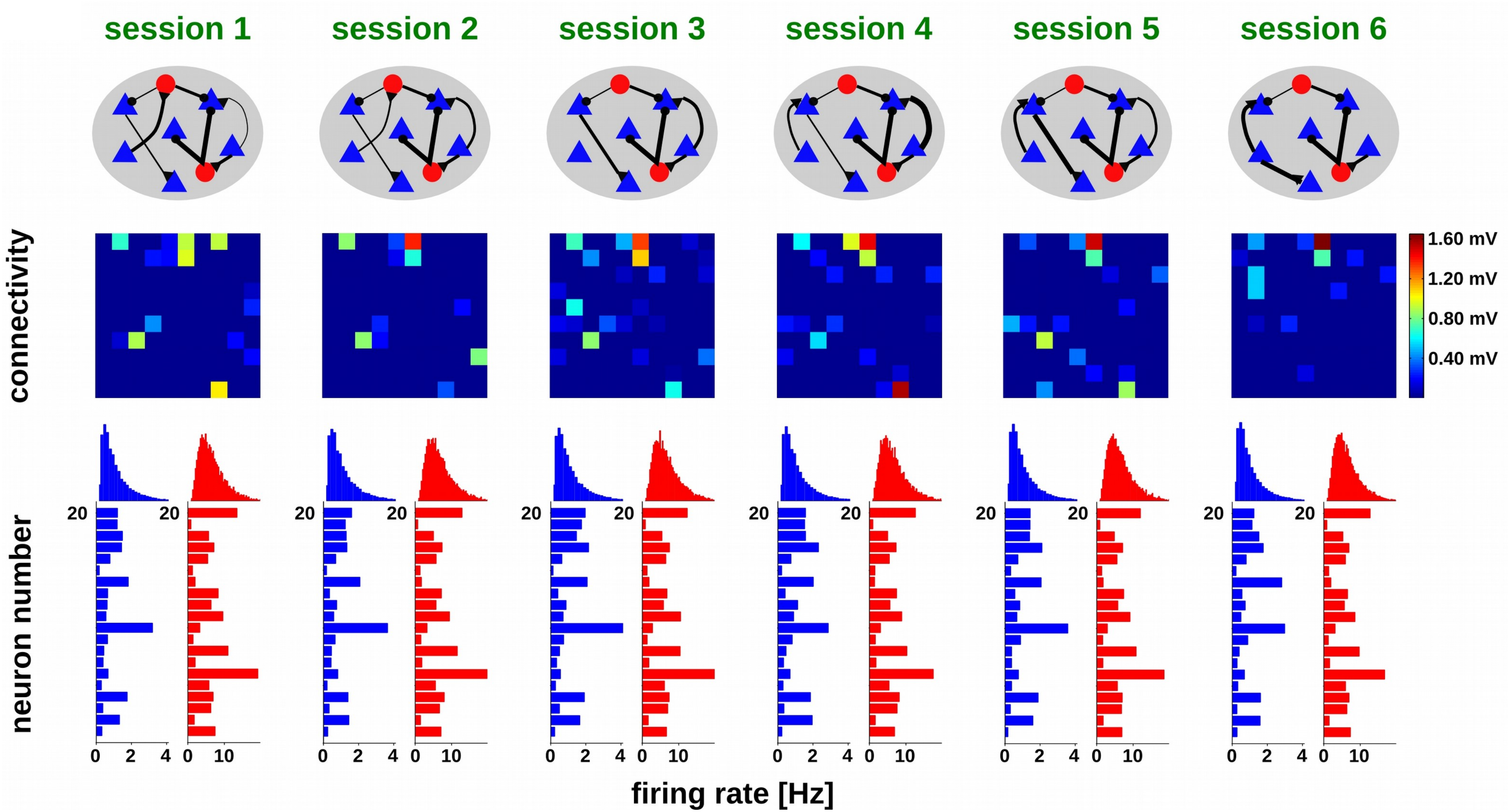

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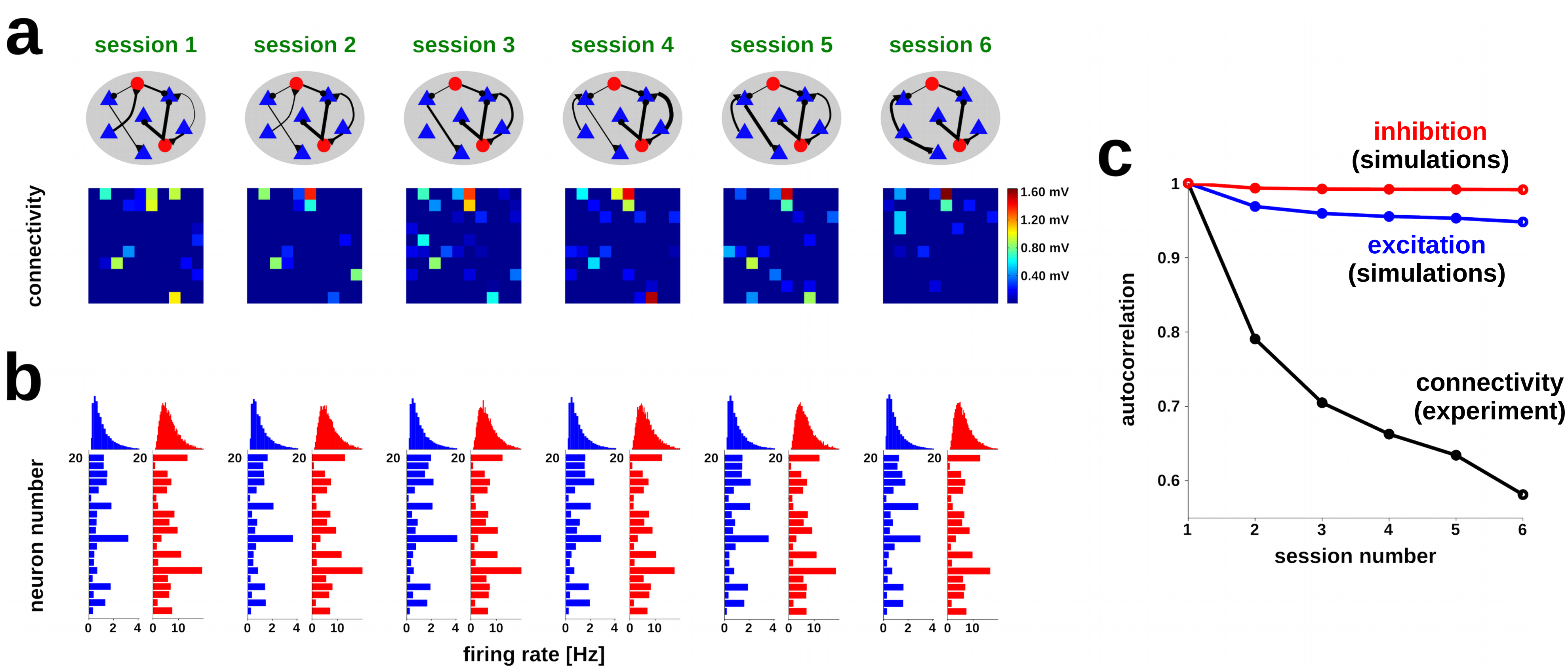
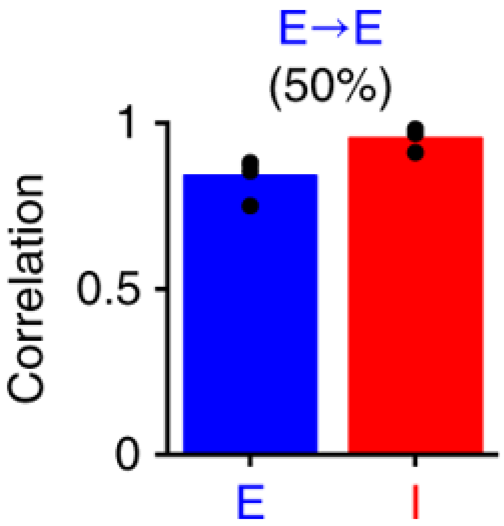


Rewiring



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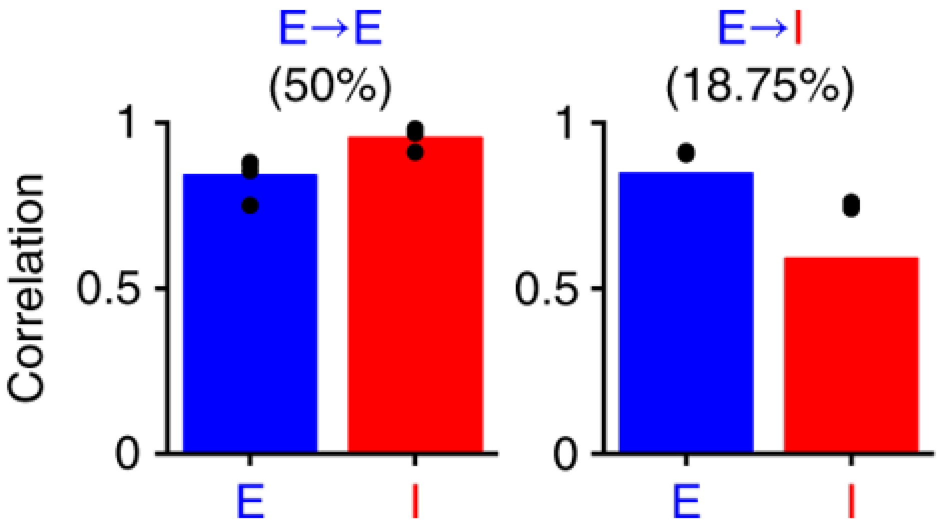

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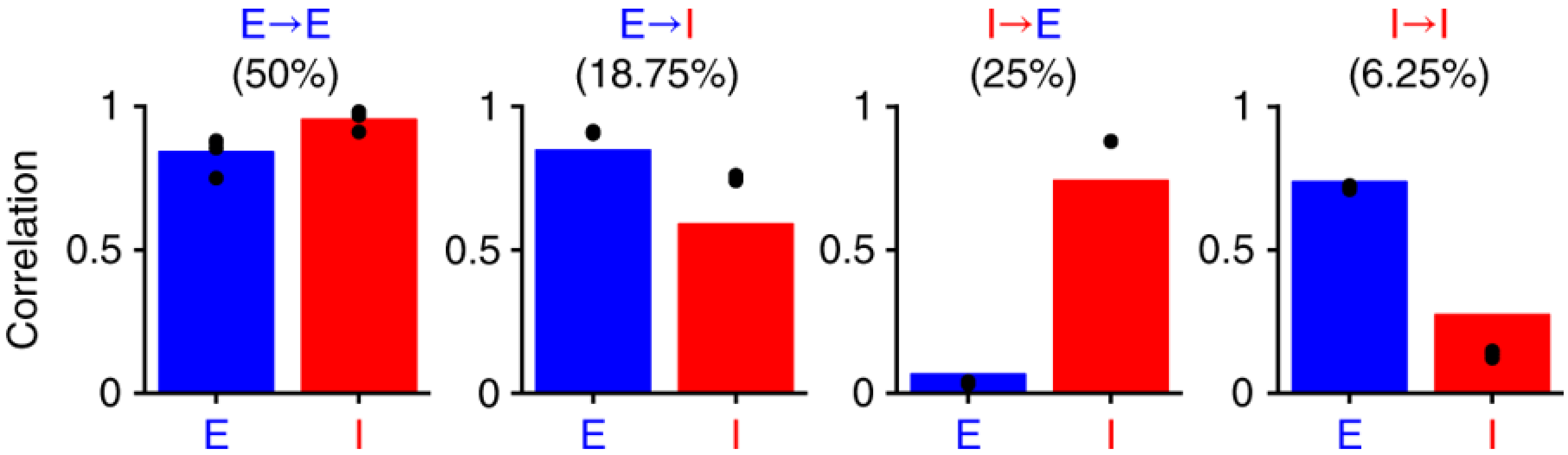

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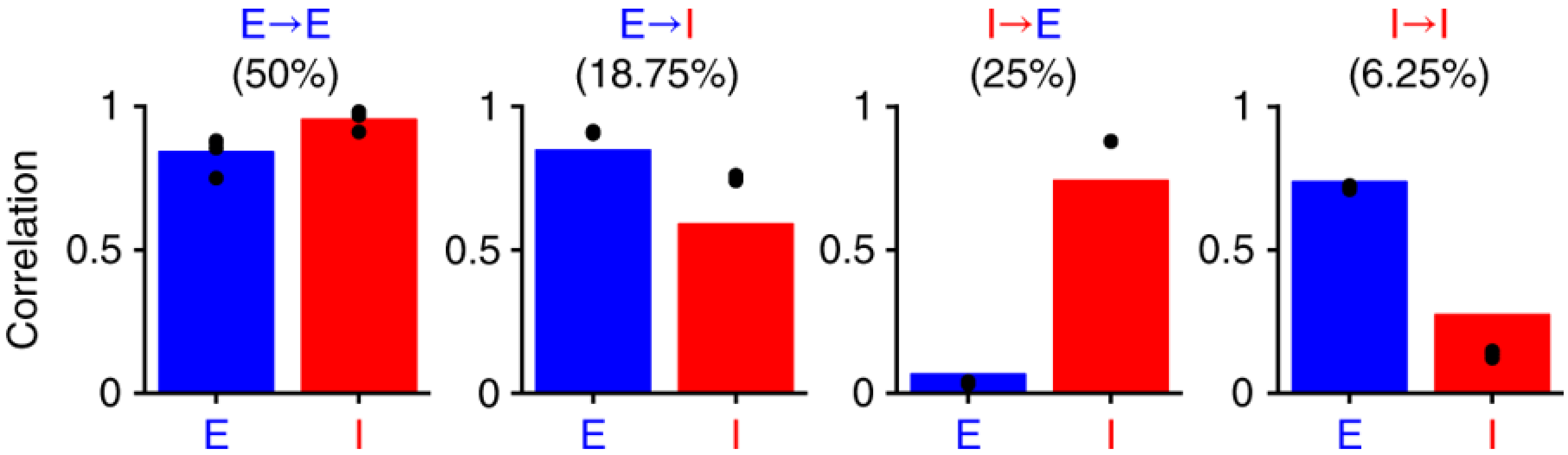
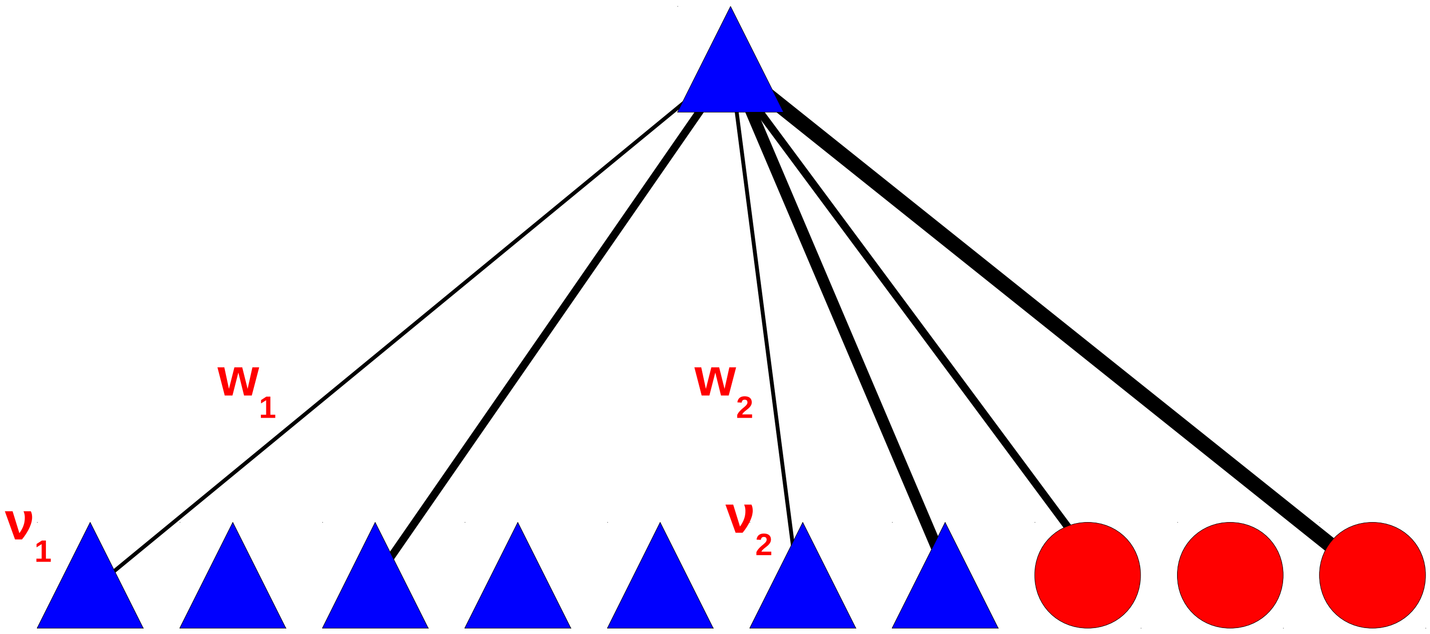


<u>Patterns of ongoing activity are robust against changes in excitatory synapses while being very sensitive to changes in inhibitory synapses</u>

A Simple Intuitive Explanation



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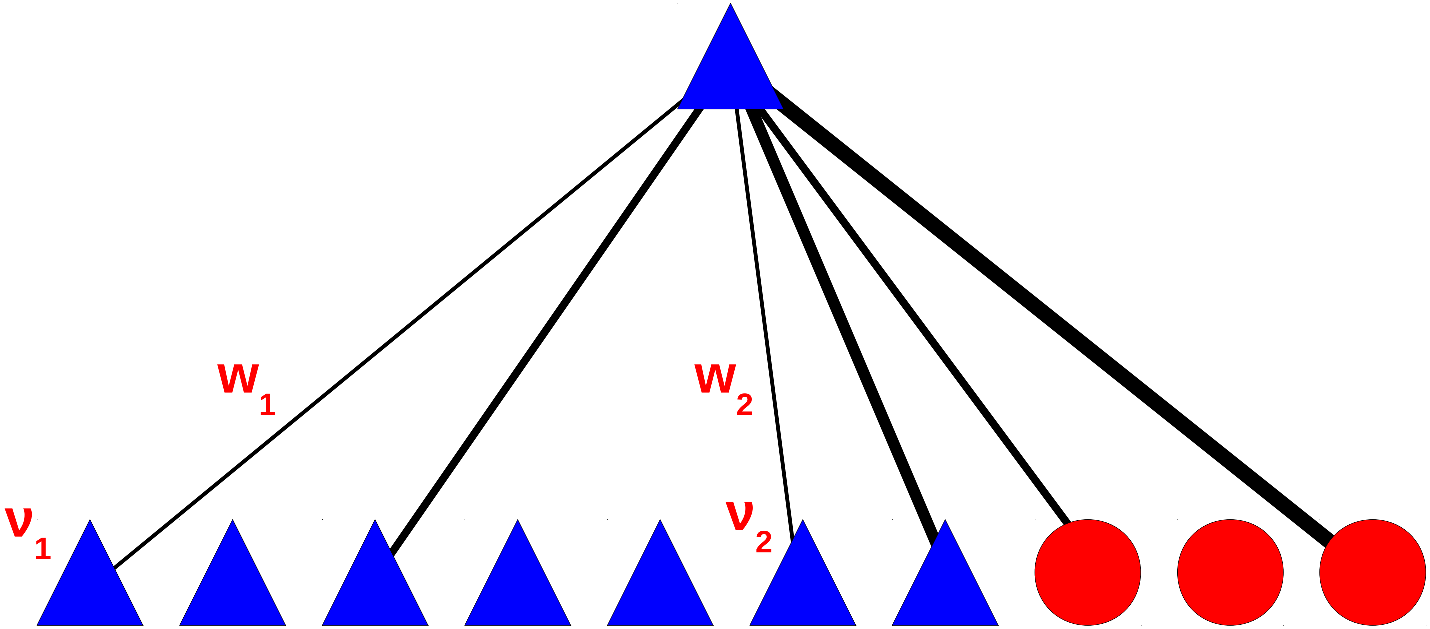

The activity will NOT change if $w_1 = w_2$ or $\nu_1 = \nu_2$

$$w_1 \nu_2 = w_2 \nu_1$$

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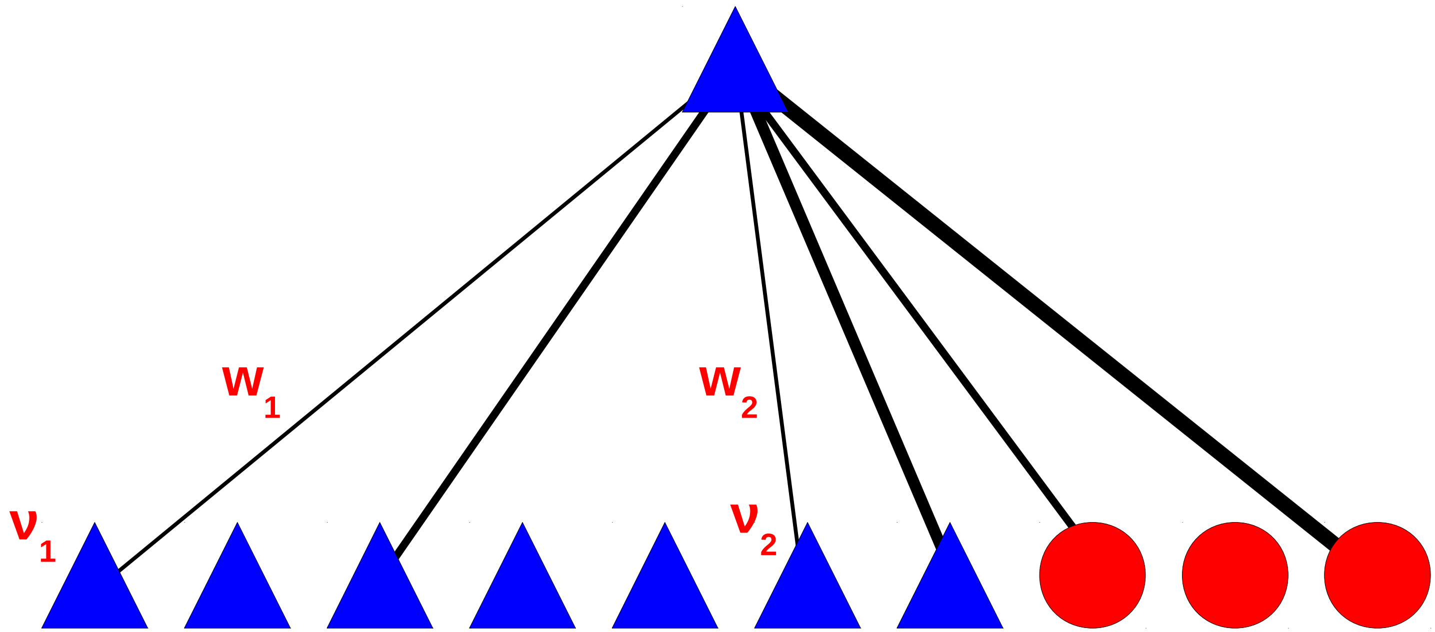

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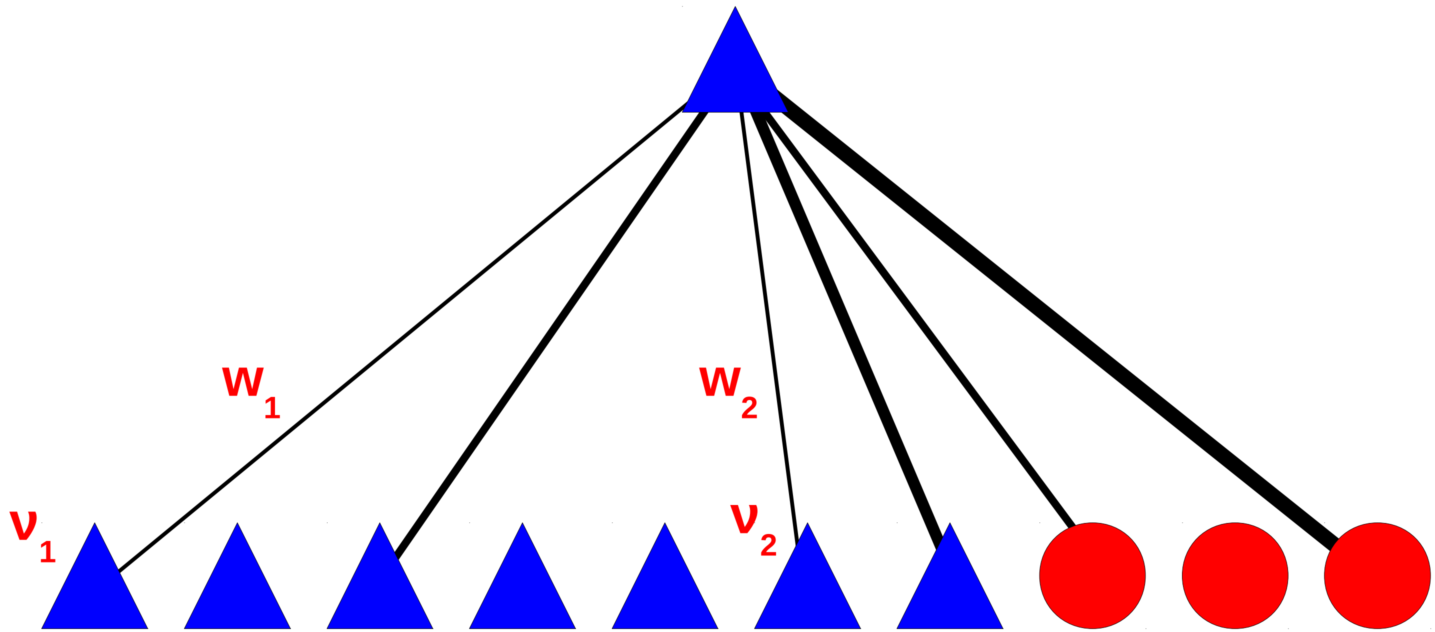
$$\sigma^2_{EE} = c_{EE} \cdot N_E \left(\langle w^2_{EE} \rangle \langle \nu^2_E \rangle - c_{EE} \langle w_{EE} \rangle^2 \langle \nu_E \rangle^2 \right)$$

$$\sigma^2_{EI} = c_{EI} \cdot N_I \left(\langle w^2_{EI} \rangle \langle \nu^2_I \rangle - c_{EI} \langle w_{EI} \rangle^2 \langle \nu_I \rangle^2 \right)$$

$$\frac{\sigma^2_{EE}}{\sigma^2_{EI}} \simeq \underline{0.04}$$

(Gentet *et al.*, 2010; Avermann *et al.*, 2012)

A Simple Intuitive Explanation



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$w_1 \nu_2 = w_2 \nu_1$

4 Hz²

$$\sigma_{EE}^2 = c_{EE} \cdot N_E \left(\langle w_{EE}^2 \rangle \langle \nu_E^2 \rangle - c_{EE} \langle w_{EE} \rangle^2 \langle \nu_E \rangle^2 \right)$$

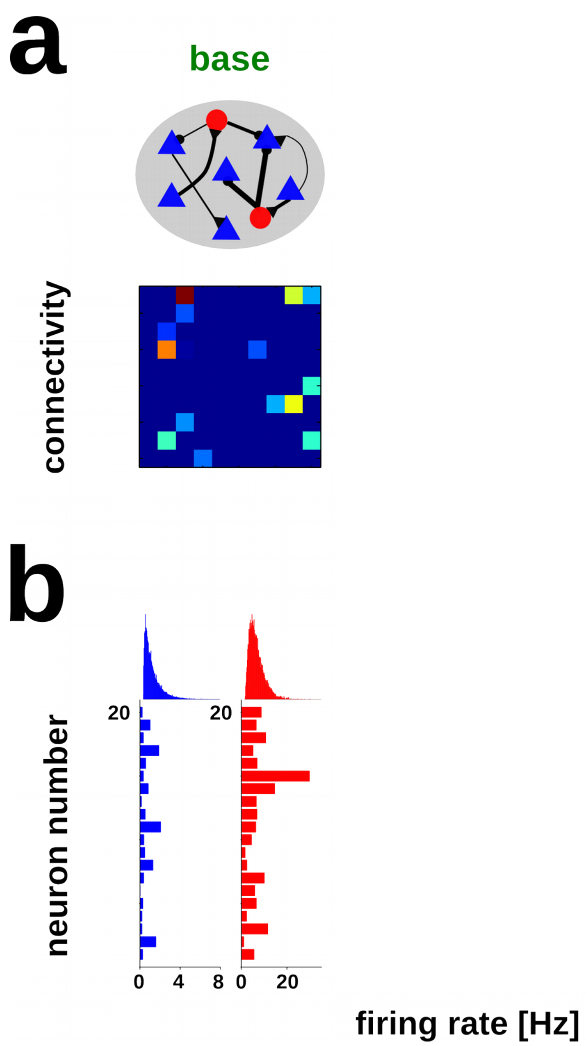
$$\sigma_{EI}^2 = c_{EI} \cdot N_I \left(\langle w_{EI}^2 \rangle \langle \nu_I^2 \rangle - c_{EI} \langle w_{EI} \rangle^2 \langle \nu_I \rangle^2 \right)$$

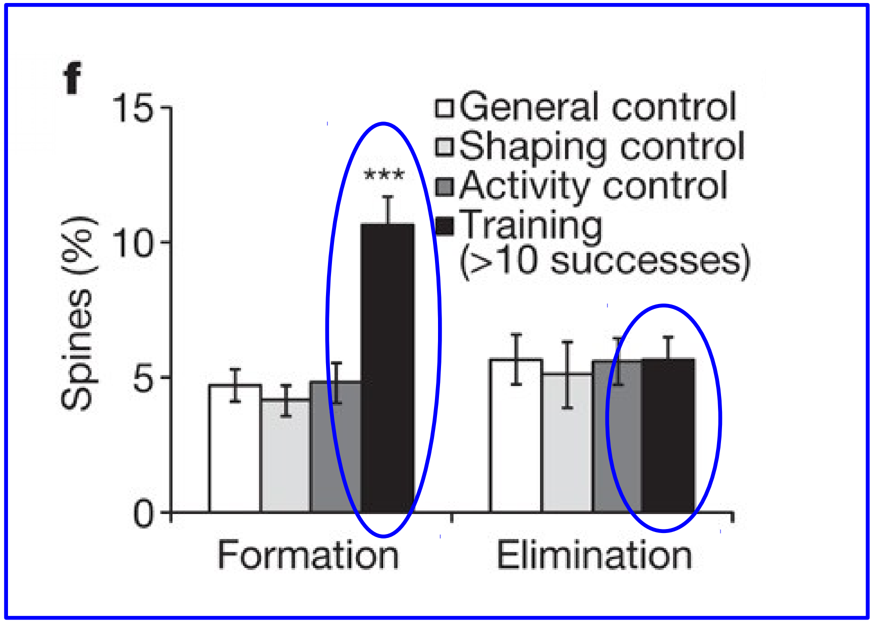
80 Hz²

$$\Rightarrow \quad \frac{\sigma_{EE}^2}{\sigma_{EI}^2} \simeq \underline{0.04}$$

(Gentet *et al.*, 2010; Avermann *et al.*, 2012)

A Possible Mechanism for Learning





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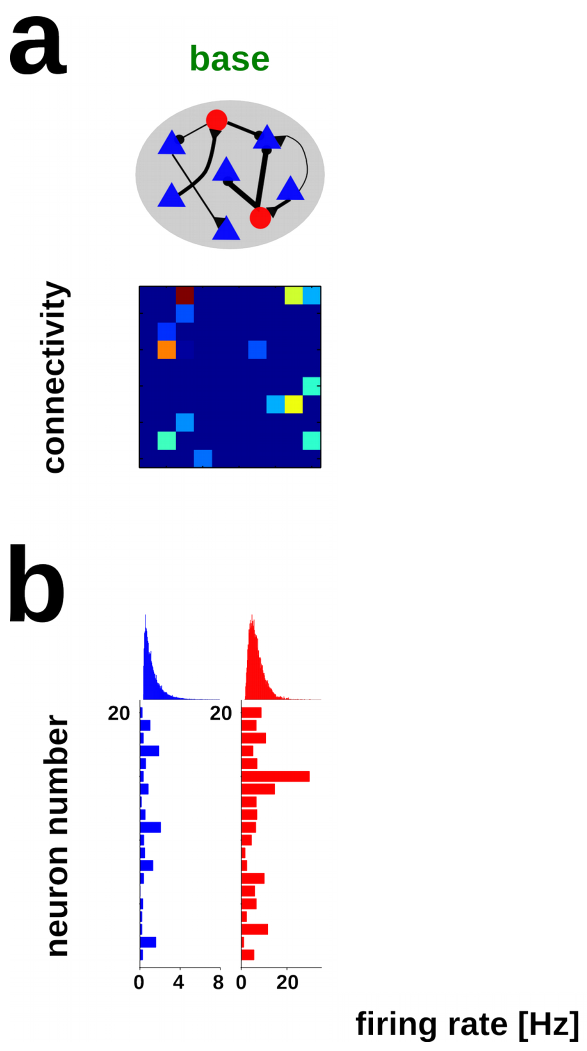

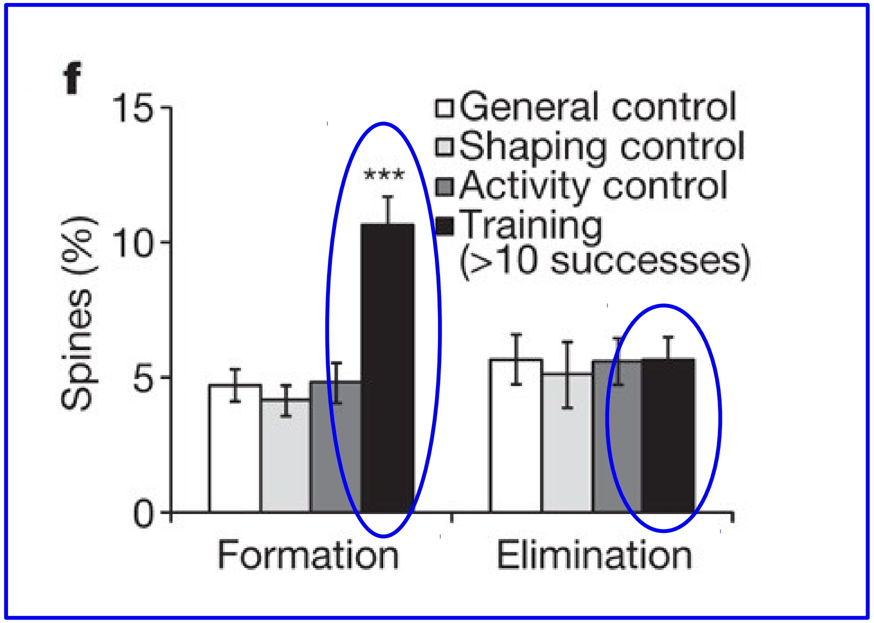

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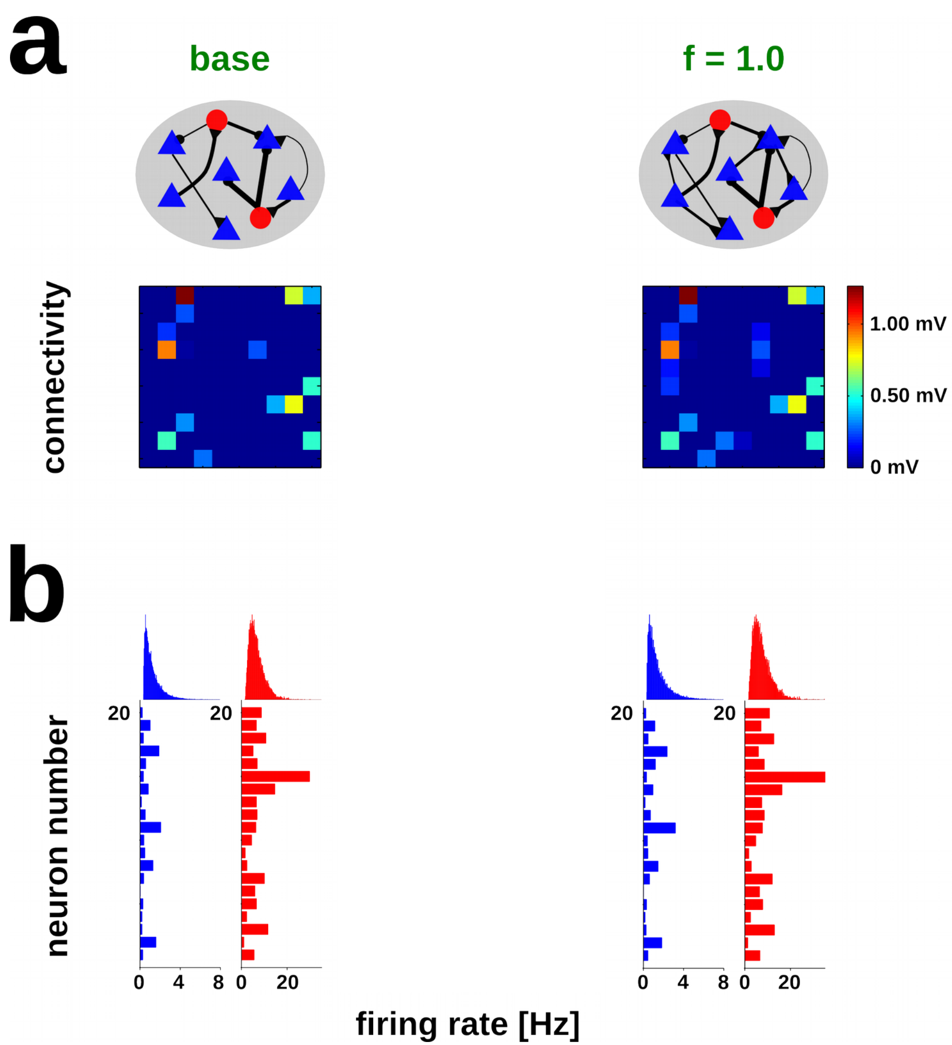

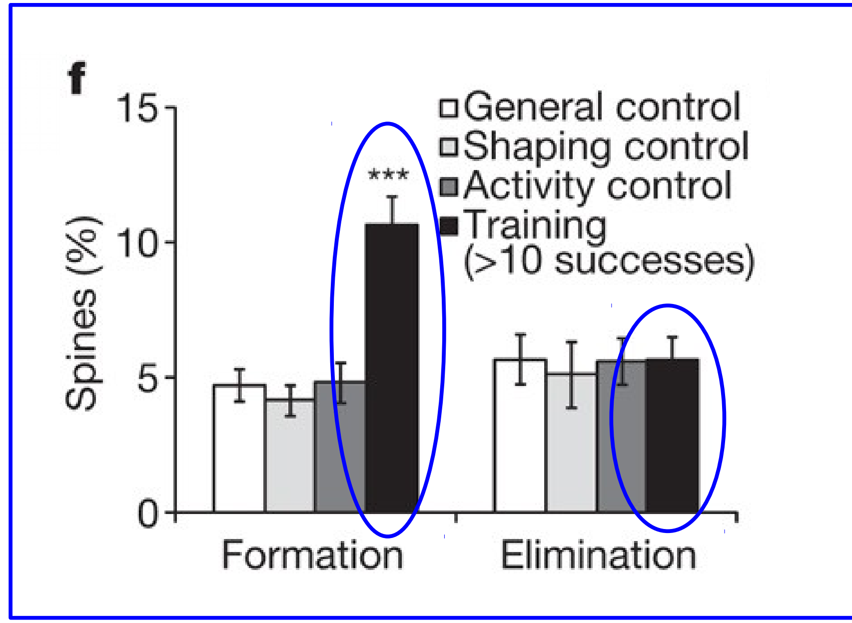

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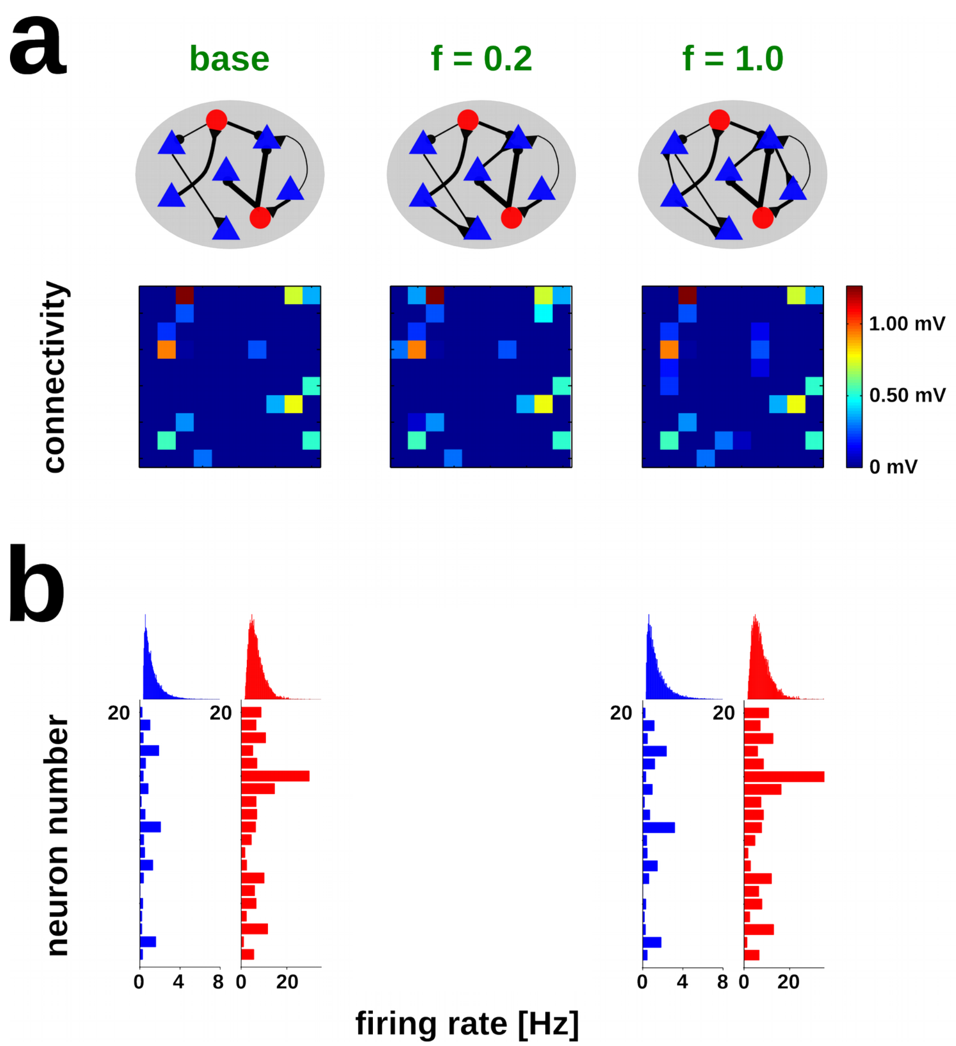

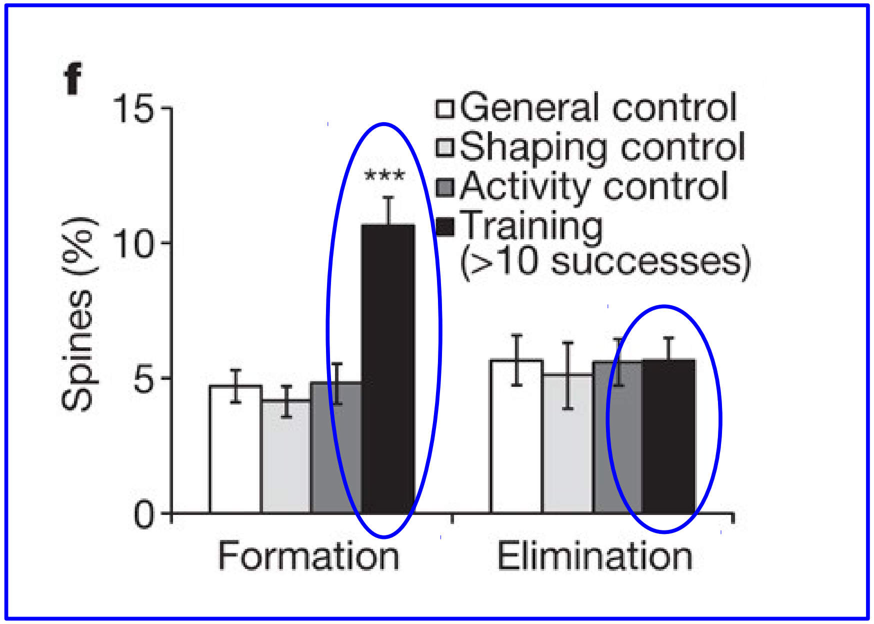

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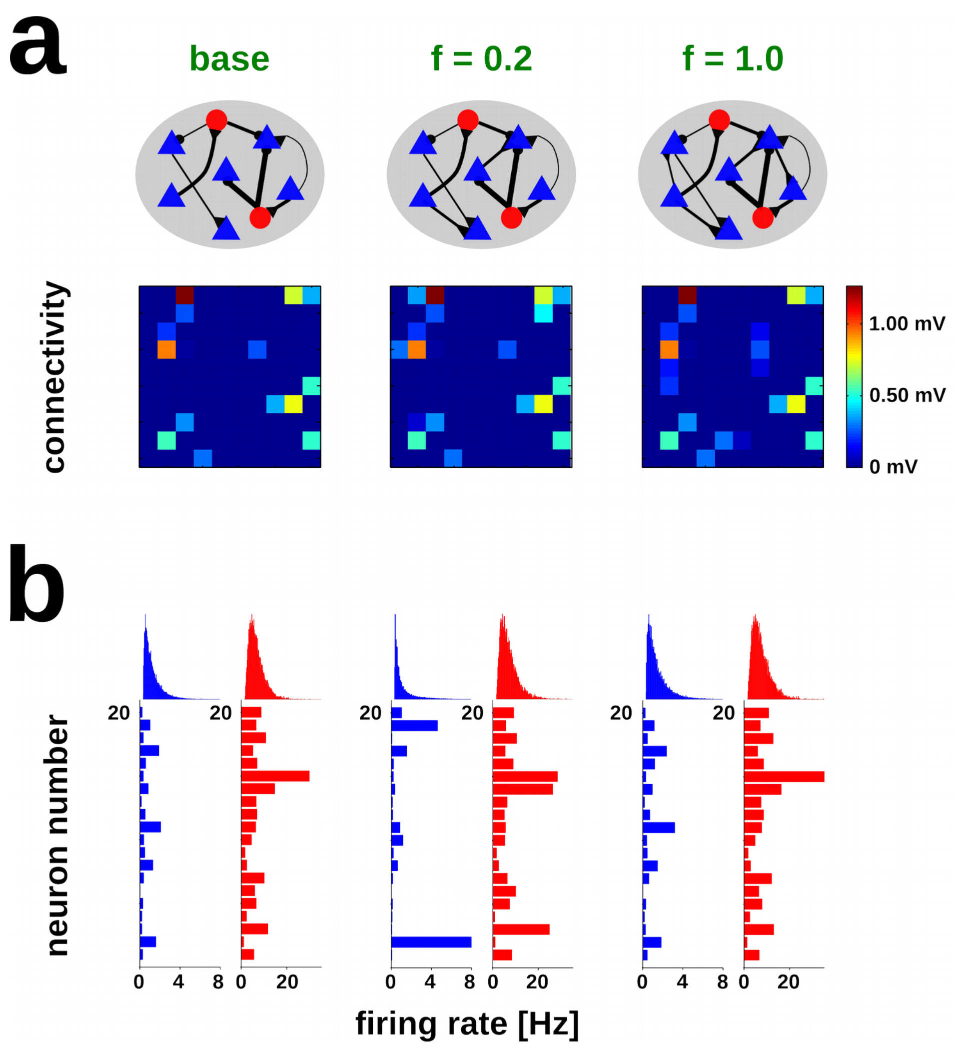
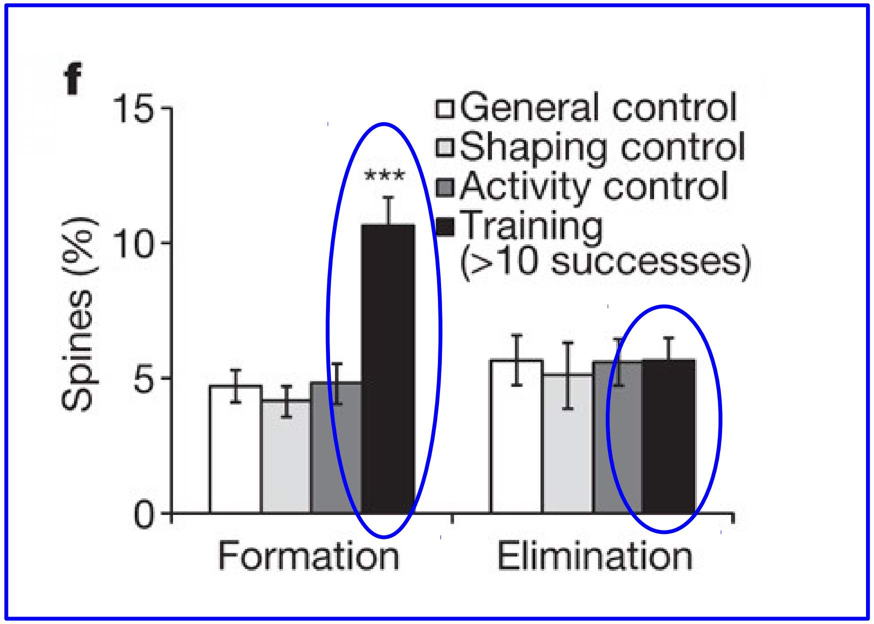
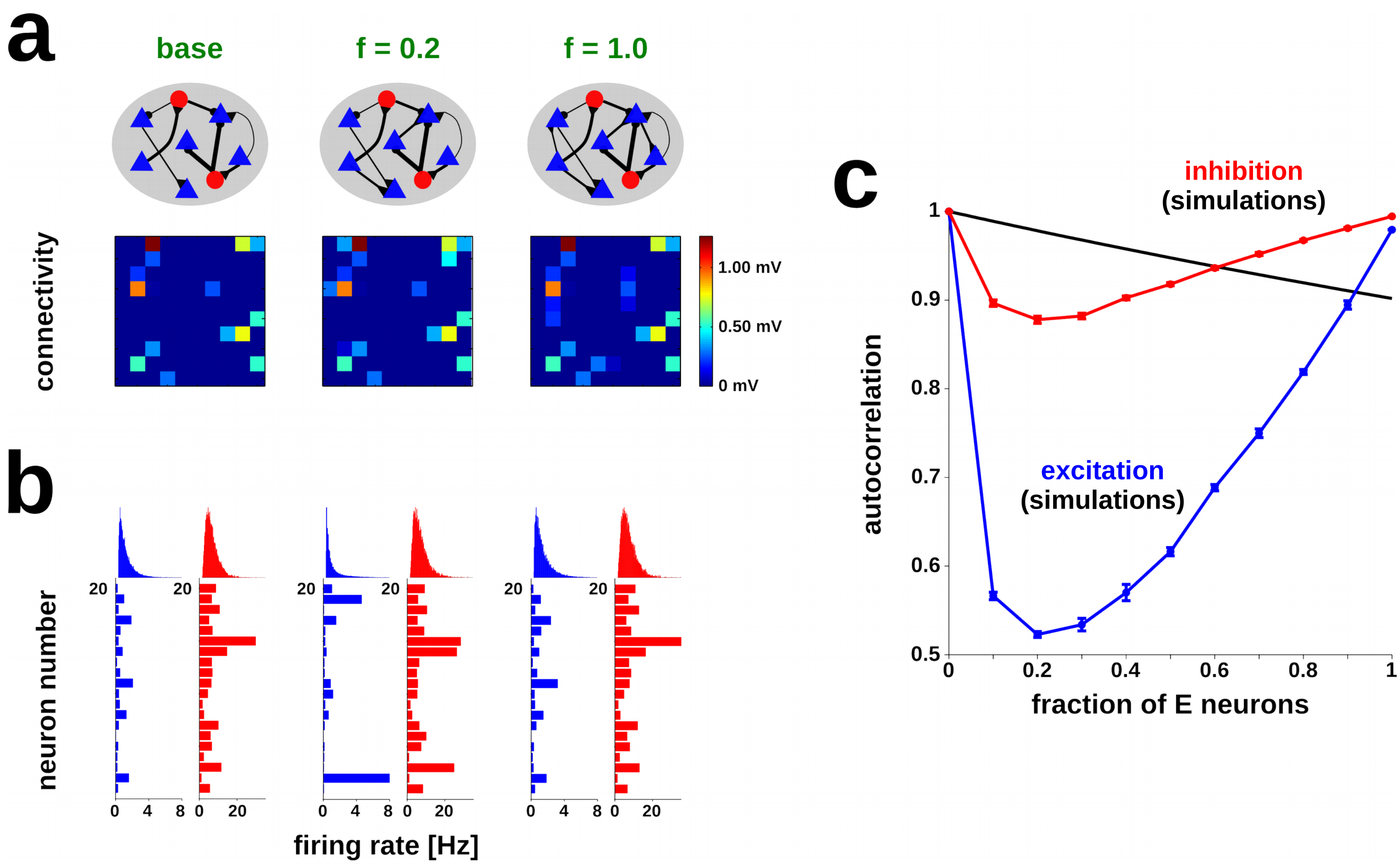


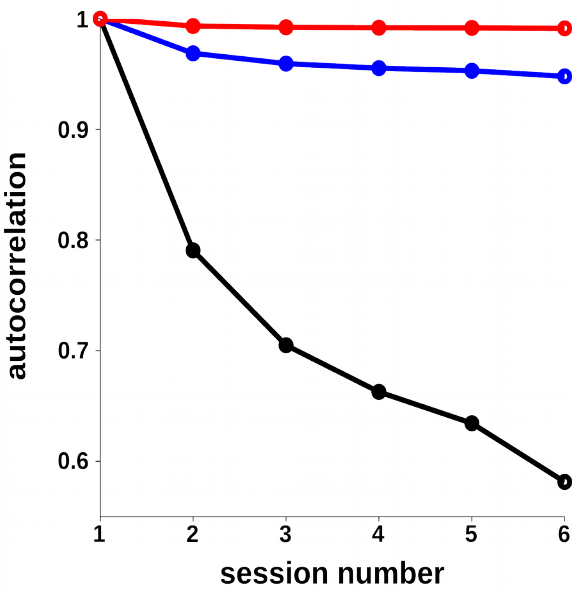


A Possible Mechanism for Learning

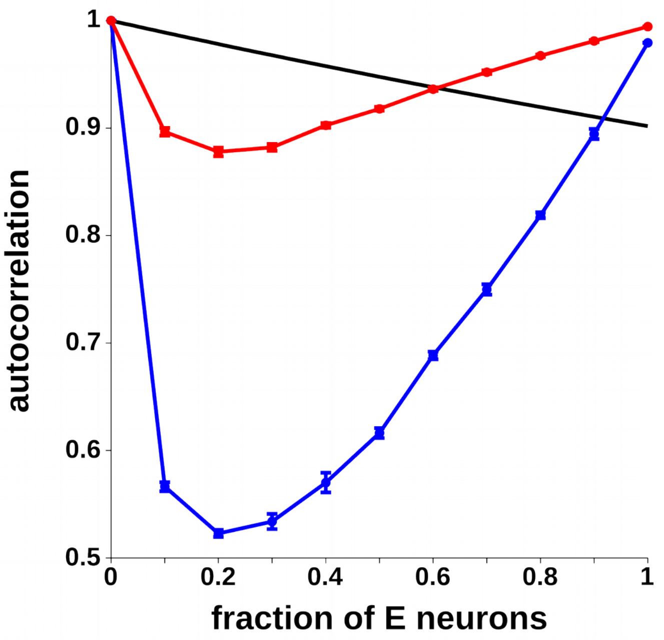


A Possible Mechanism for Learning

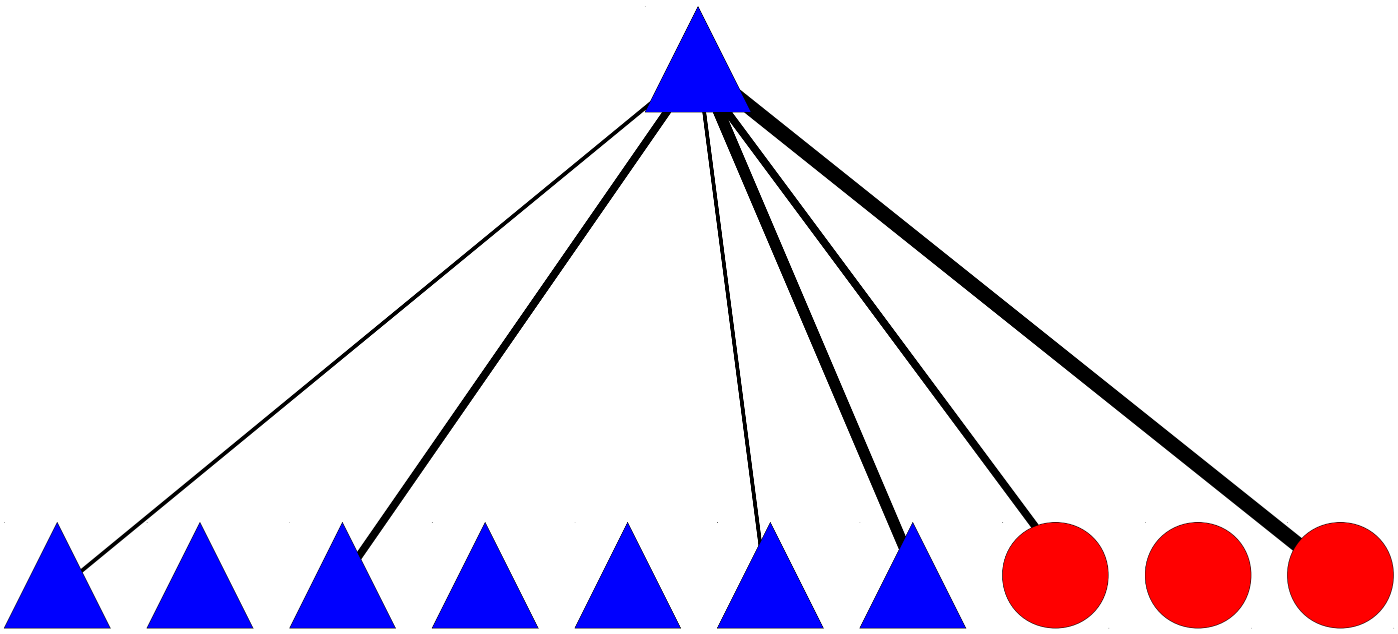
ongoing plasticity



learning-like plasticity

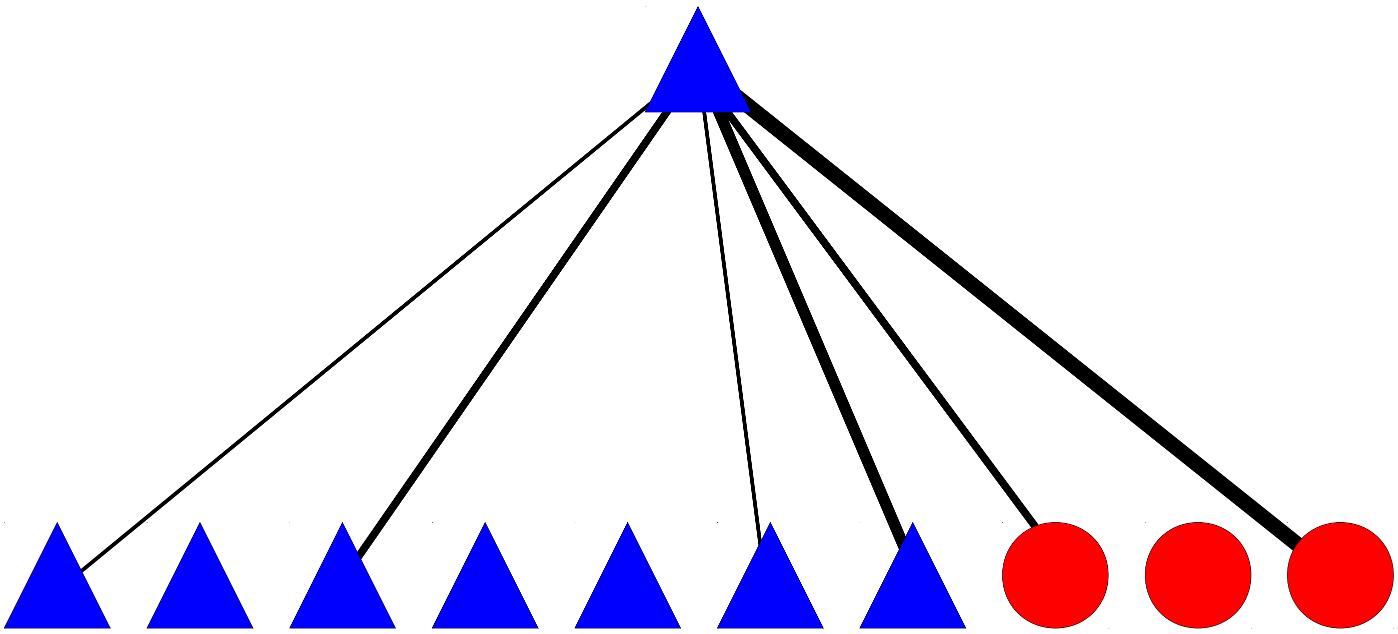


The *Balanced* State



$$
\begin{cases}
\mu_E = N \cdot \left[\mu_E^{(ext)} + \langle w_{EE} \rangle \langle \nu_E \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right] \\
\sigma_E^2 = \sigma_{EE}^2 + \sigma_{EI}^2 = N \cdot O(1)
\end{cases}
$$

The *Balanced* State



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$$\Rightarrow \quad \frac{\sigma_E}{\mu_E} = O\left(\frac{1}{\sqrt{N}}\right)$$

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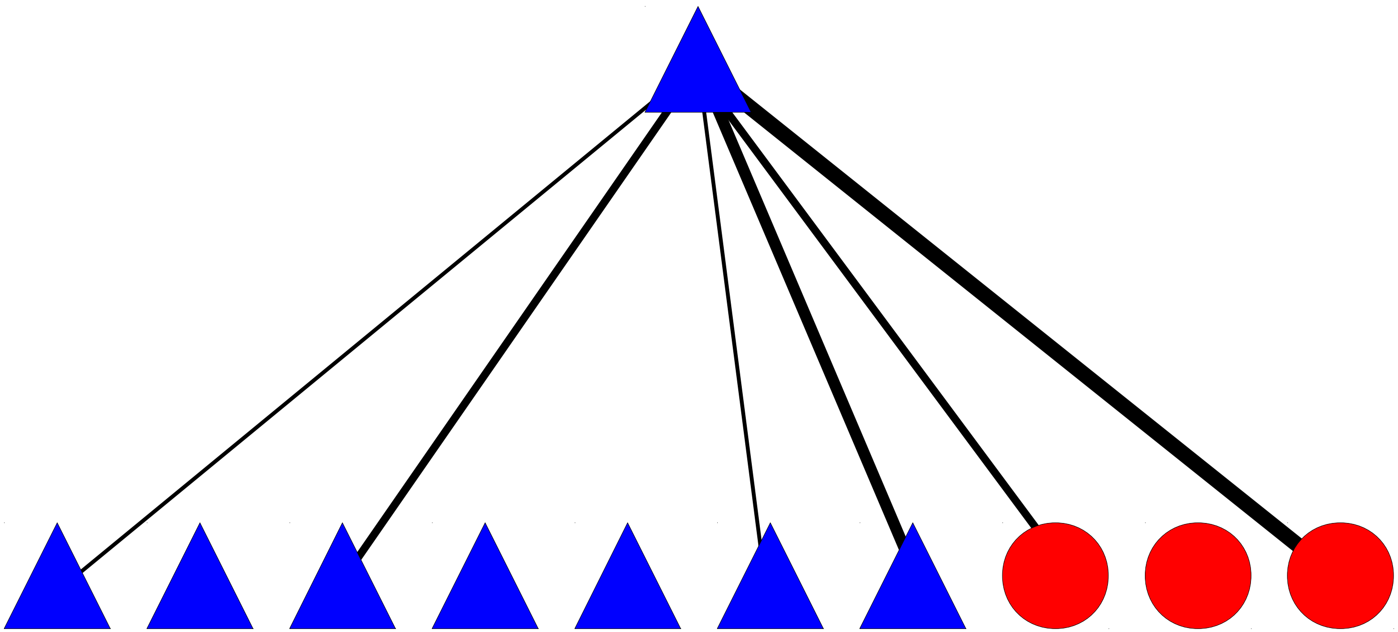

$$O\left(\frac{1}{\sqrt{N}}\right)$$

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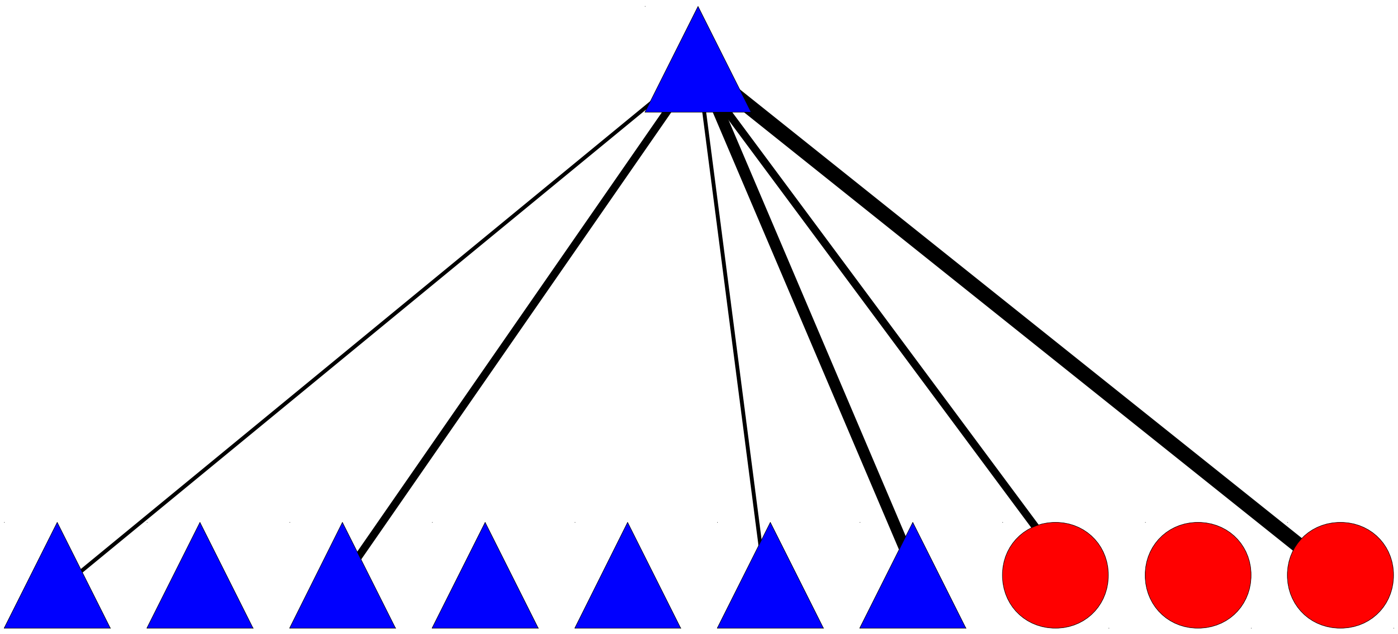

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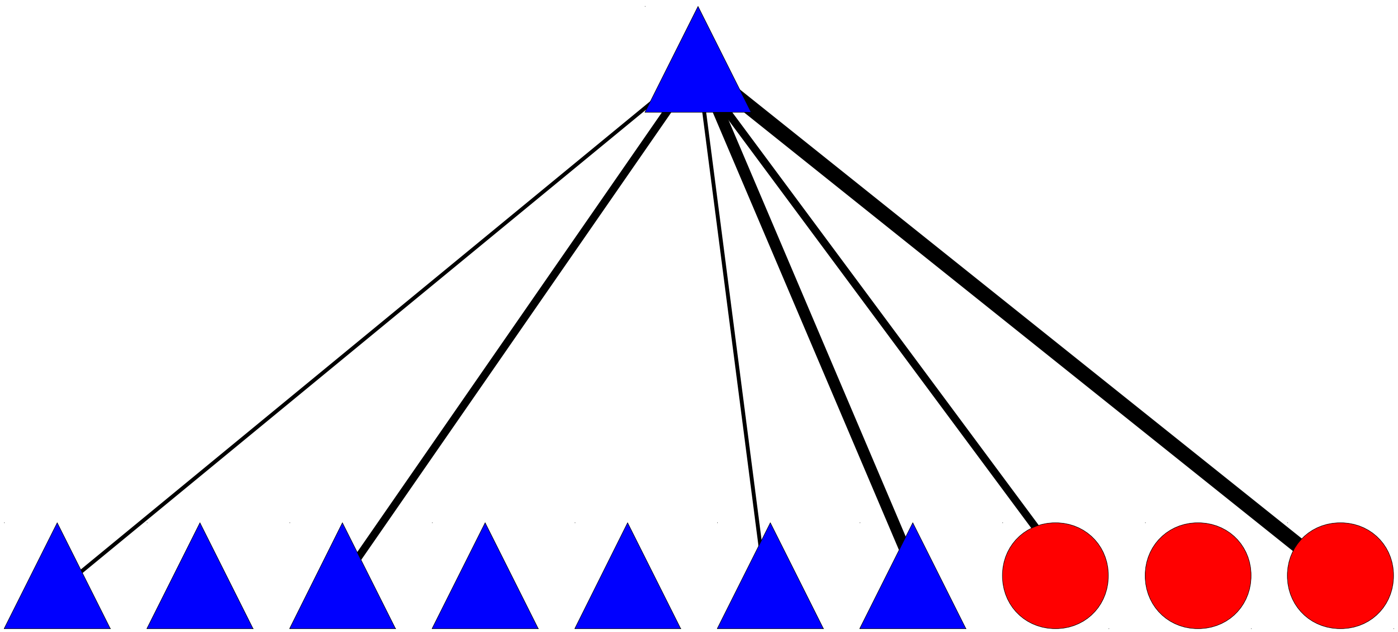

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$$\frac{\sigma_E}{\mu_E} = O(1)$$

Under very general conditions, activity will evolve to a steady state where the total excitation and inhibition nearly cancel each other (balanced state)

(van Vreeswijk & Sompolinsky, 1996; 1998)

Transiently Unbalanced Networks

$$\mu_E = N \cdot \left[\mu_E^{(ext)} + \langle w_{EE} \rangle \langle \nu_E \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right]$$

$$\mu_I = N \cdot \left[\mu_I^{(ext)} + \langle w_{IE} \rangle \langle \nu_E \rangle - \langle w_{II} \rangle \langle \nu_I \rangle \right]$$

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$$\mu_E^{(p)} = N \cdot \left[\mu_E^{(ext)} + \underline{f \gamma \langle w_{EE} \rangle \langle \nu_E^{(p)} \rangle} + (1-f) \langle w_{EE} \rangle \langle \nu_E^{(0)} \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right]$$

$$\mu_E^{(0)} = N \cdot \left[\mu_E^{(ext)} + \underline{f \langle w_{EE} \rangle \langle \nu_E^{(p)} \rangle} + (1-f) \langle w_{EE} \rangle \langle \nu_E^{(0)} \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right]$$

Transiently Unbalanced Networks

$$\mu_E = N \cdot \left[\mu_E^{(ext)} + \langle w_{EE} \rangle \langle \nu_E \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right]$$

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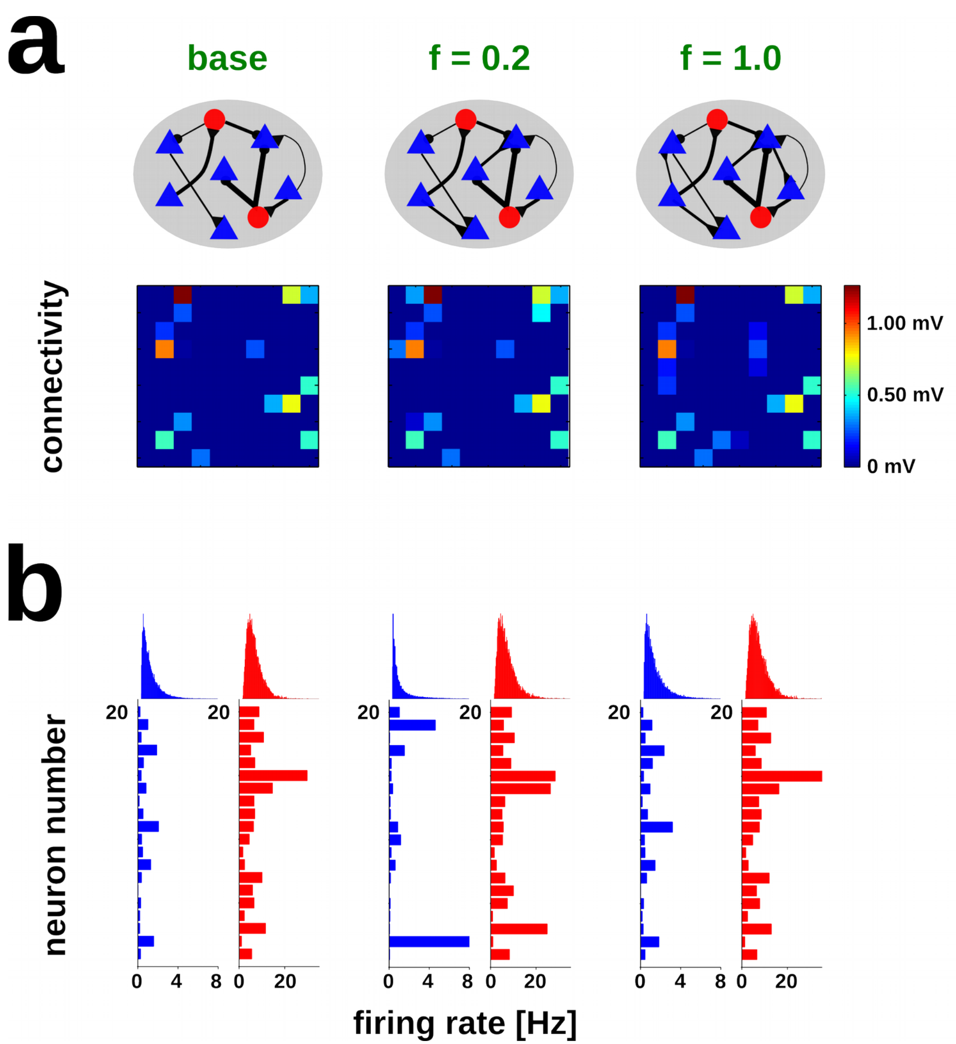
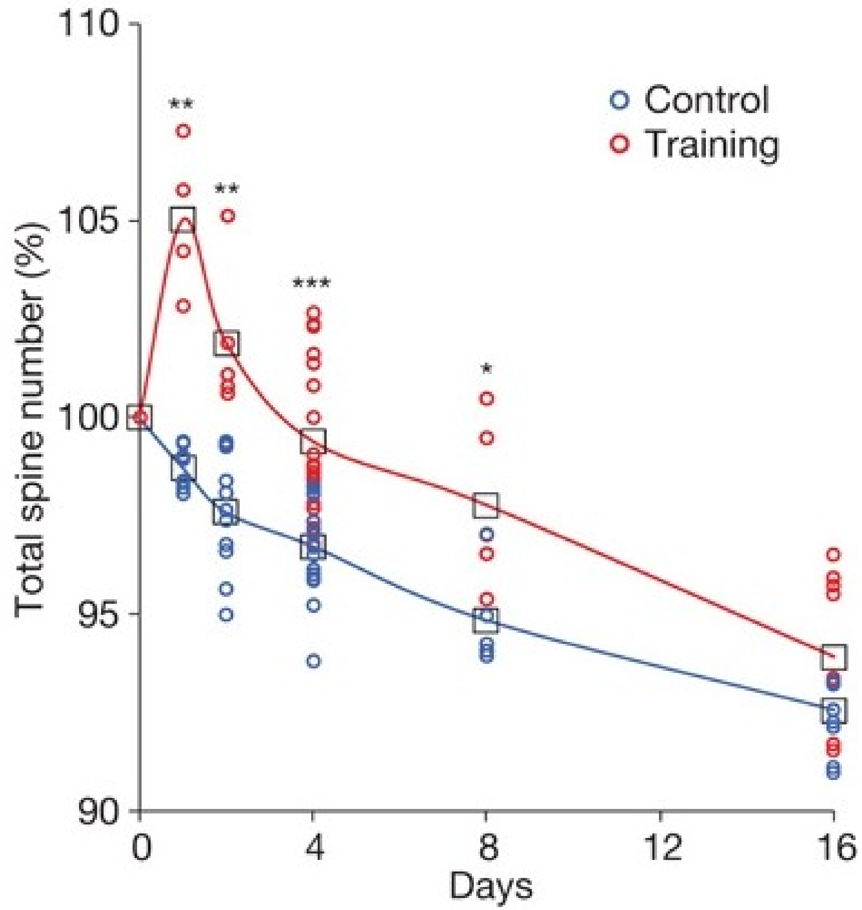
$$\mu_E^{(p)} - \mu_E^{(0)} = N \cdot \left[(\gamma - 1) f \langle w_{EE} \rangle \langle \nu_E^{(p)} \rangle \right] = O(N)$$

Transiently Unbalanced Networks



Where Is Learned Information Stored?



(Xu *et al.*, 2009)

Conclusions

- **Quantitative theory relating changes in synaptic connectivity to changes in patterns of ongoing activity.**
  (stability of neuronal representations?)

- **Considering changes that preserve the overall distribution of connections, inhibitory plasticity is both necessary and sufficient for large-scale changes in network activity.**
  (functional role of synaptic volatility?)

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Next (on the blackboard)

Storing a large number of memories in biologically-constrained model Networks – Mean-field analysis and estimate of the storage capacity