Pathway specific TNF-mediated metaplasticity in the hippocampus

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Activity-Dependent Neural Plasticity: Plasticity vs Stability

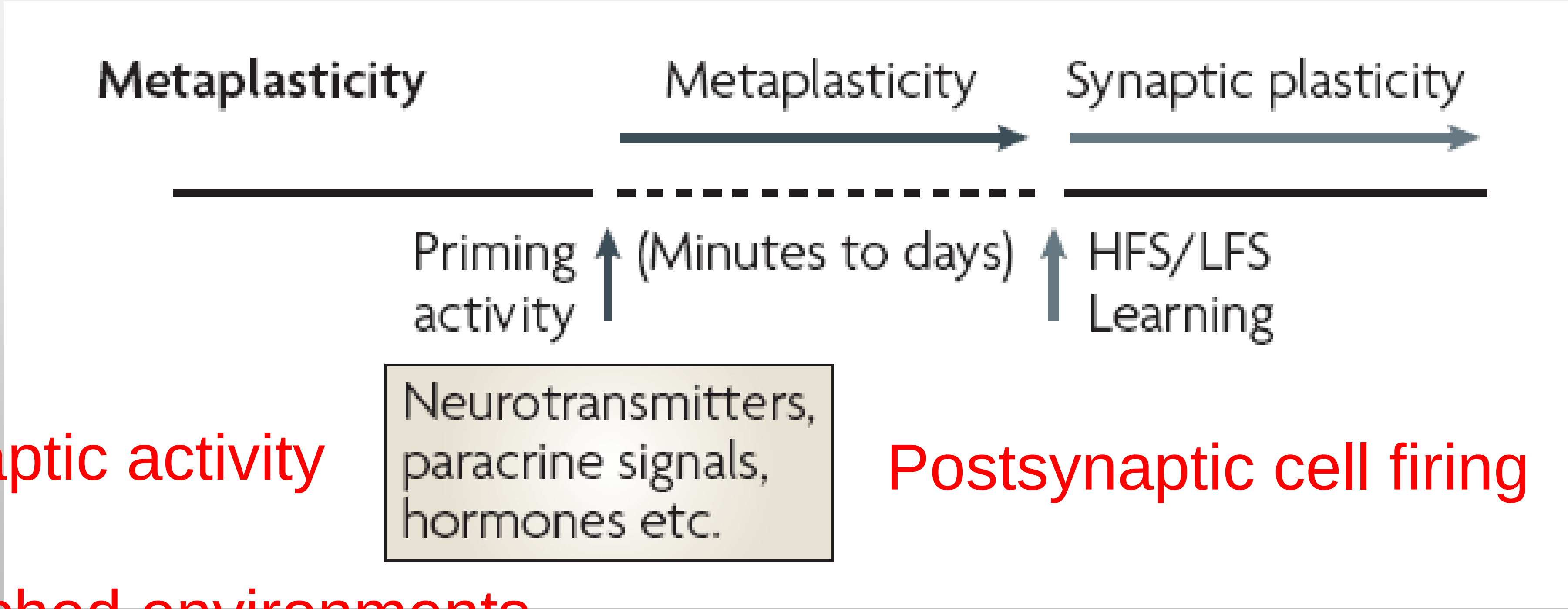
(Abraham & Robins, *TINS*, 2005)

Courtesy of Kristen Harris, Univ Texas Austin

- Synaptic Plasticity (LTP/LTD)
- Intrinsic Plasticity
- Structural plasticity
- Homeostatic Plasticity
- Regeneration
- Neurogenesis
- Epigenetic adaptations
- **Metaplasticity: Plasticity of the neural "state"**

Metaplasticity

Prior neural activity alters persistently the tonic state (forms a subthreshold memory), regulating future synaptic plasticity (and learning)



Synaptic activity

Postsynaptic cell firing

Enriched environments

Learning

Stress

Abraham & Bear, *TINS*, 1996
Abraham & Tate, *Prog Neurobiol*, 1997
Abraham, *Nat Rev Neurosci*, 2008

Instantaneous “state” variables regulating synaptic plasticity (LTP / LTD)

- NMDA receptor (subunit) complement
- Degree of postsynaptic cell excitability
- Degree of GABAergic synaptic inhibition
- Modulatory neurotransmitters, cytokines, hormones
- Recent history of synaptic or neural activity

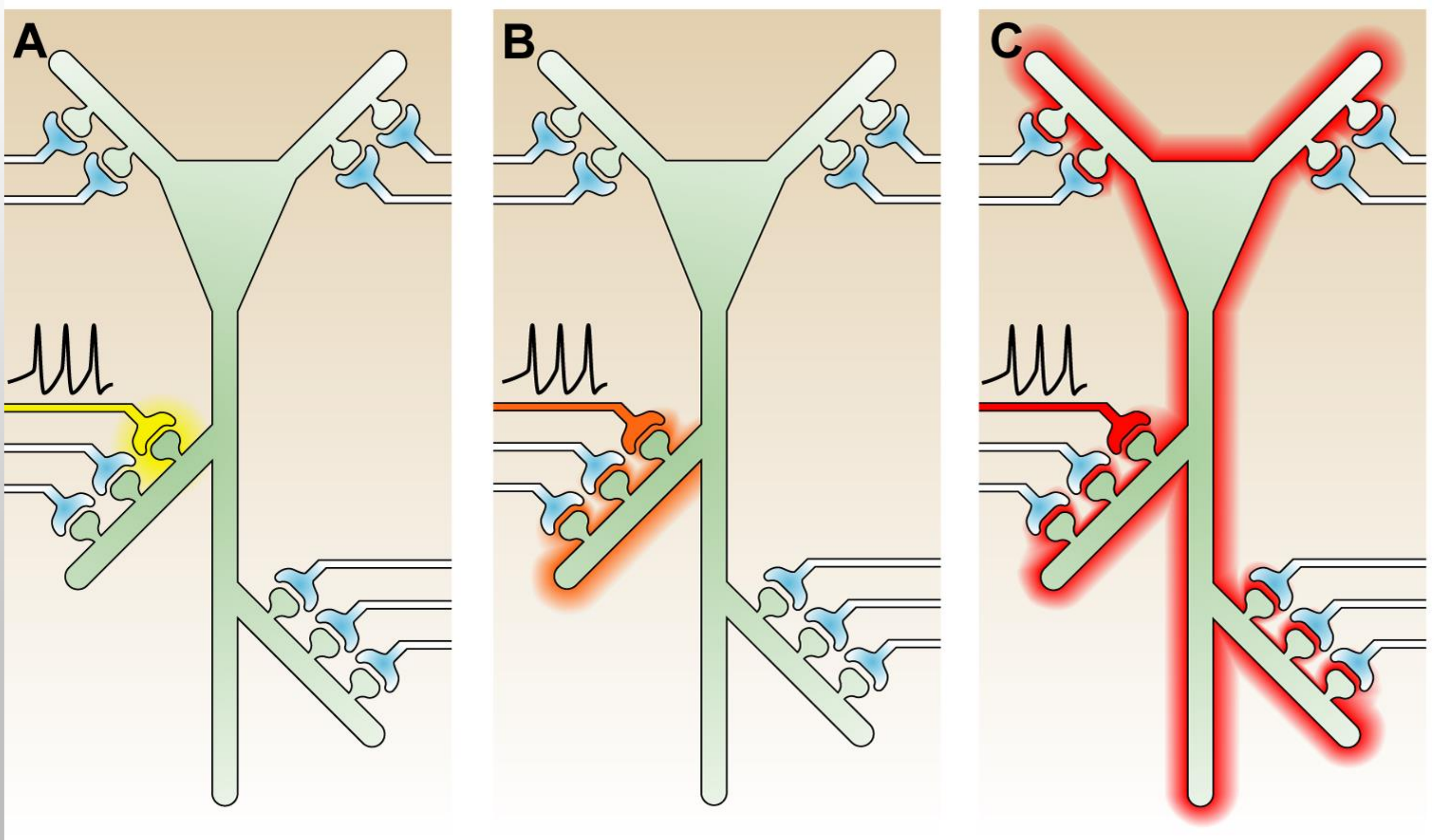
“Metaplasticity” (Abraham & Bear, *TINS*, 1996)

(Metacognition, Meta-analysis, Meta-Learning, Metaphysics)

Local state change

Global state change
i.e., Heterosynaptic metaplasticity

Synapse-specific | Compartment-specific | Cell-wide



Hulme et al, *TINS*, 2013

Computational models of memory are optimized by metaplasticity rules

Cascade models of synaptically stored memories.
Fusi S, Drew PJ, Abbott LF. *Neuron,* 2005, 45, 599-611

On the biological plausibility of artificial metaplasticity learning algorithm.
Diego Andina D, Ropero-Pelaez, F.J. *Neurocomputing*, 2013, 114, 32–35

Metaplasticity as a neural substrate for adaptive learning and choice under uncertainty.
Farashahi S, Donahue CH, Khorsand P, Seo H, Lee D, Soltani A. *Neuron,* 2017, 94, 401-414.e6.

Artificial neural networks utilize metaplasticity principles to combat catastrophic forgetting during continual learning

Contributions by metaplasticity to solving the Catastrophic Forgetting Problem.
Jedlicka P, Tomko M, Robins A, Abraham WC. *Trends in Neurosciences*. 2022 Sep;45(9):656-666.

e.g. “Regularisation”; Learning rate changes

Computational modelling suggests that cell-wide metaplasticity is needed for maintaining stability of the net strength of synaptic inputs to a cell.

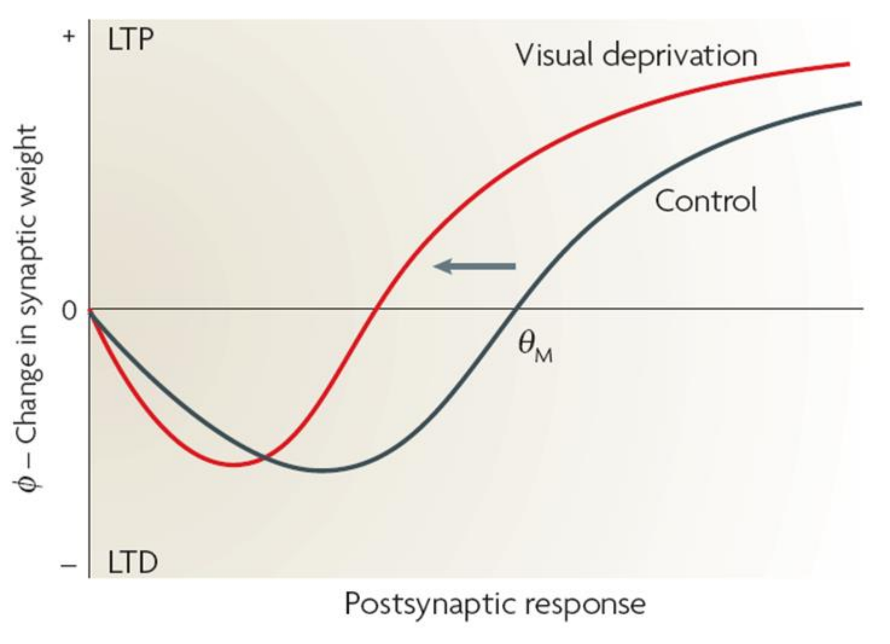
Connectivity reflects coding: a model of voltage-based STDP with homeostasis.
Clopath C, Büsing L, Vasilaki E, Gerstner W. *Nature Neuroscience,* 2010, 13, 344-52.

A voltage-based STDP rule combined with fast BCM-like metaplasticity accounts for LTP and concurrent "Heterosynaptic" LTD in the dentate gyrus in vivo.
Jedlicka P, Benuskova L, Abraham WC. *PLoS Computational Biology,* 2015, 11, e1004588.

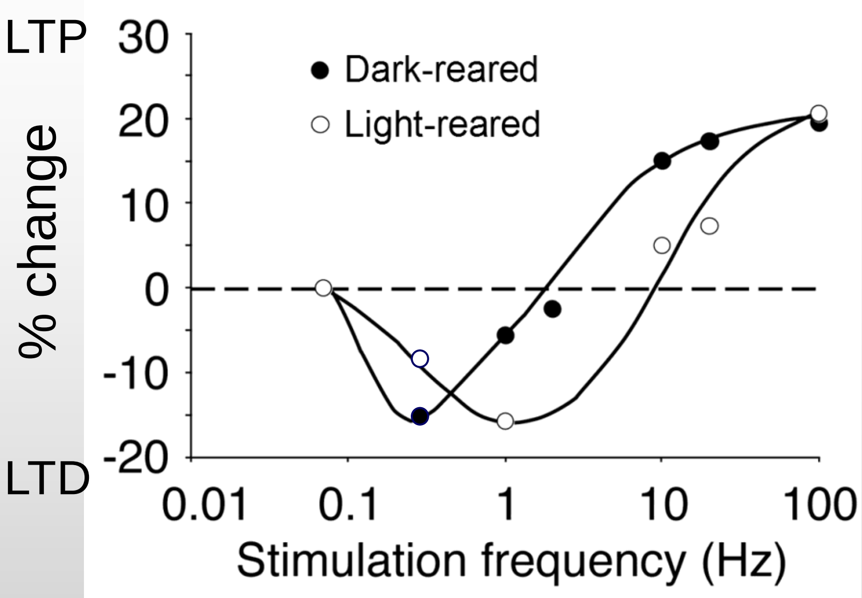
Hebbian plasticity requires compensatory processes on multiple timescales.
Zenke F, Gerstner W.
Philosophical Transactions of the Royal Society of London B, Biological Sciences, 2017, 372 (1715).

Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions
Keck, T. et al
Philosophical Transactions of the Royal Society of London B, Biological Sciences, 2017, 372 (1715).

Homeostatic Metaplasticity
Bienenstock, Cooper, Munro (BCM) theory
J Neurophysiology, 1982



adapted from Philpot et al,
J Neuroscience, 2003



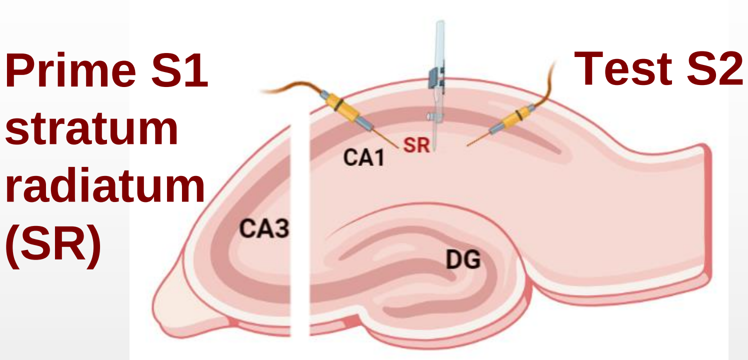
<u>BCM Postulates</u>

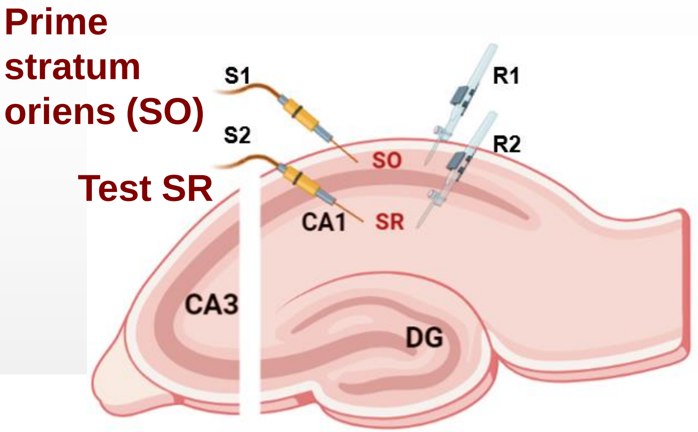
1. θ_M varies for **all excitatory synapses on the postsynaptic cell (i.e. is heterosynaptic)…**

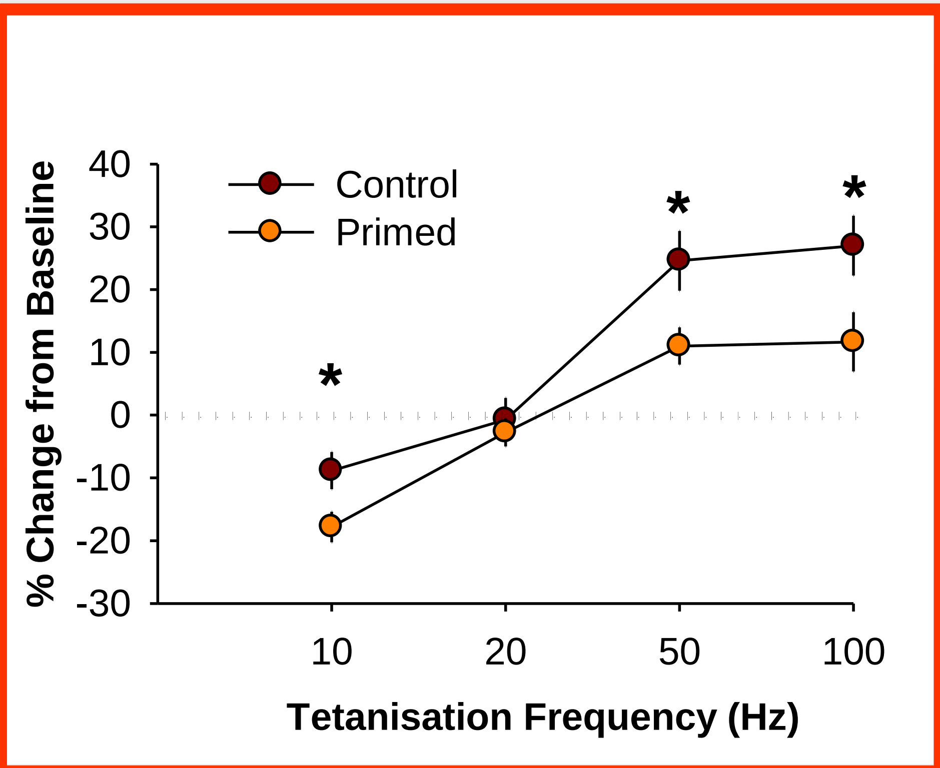
2. θ_M varies as **a function of prior time-averaged postsynaptic cell firing…**

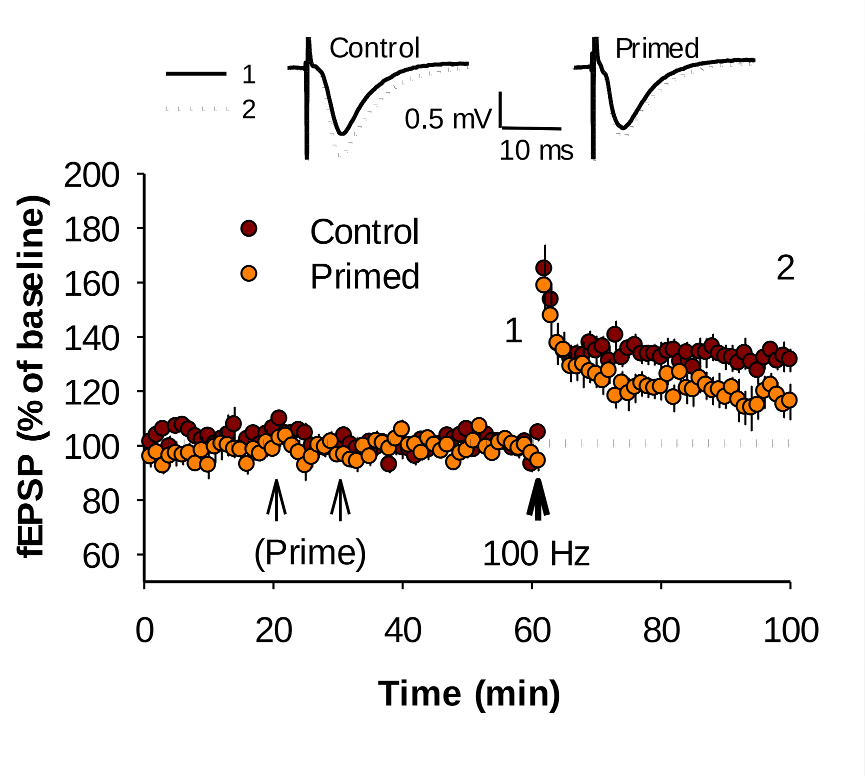
What are the mechanisms underpinning BCM-like metaplasticity?

BCM-like metaplasticity in the hippocampus









Hulme et al, *J Neurosci*, 2012

What is the “Activity Integrator” during priming?

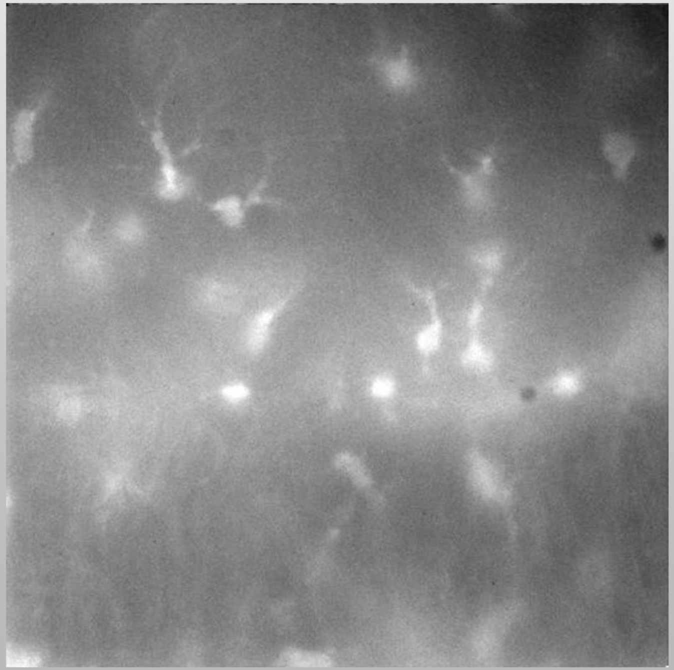
X Postsynaptic spiking / depolarization (so not BCM)

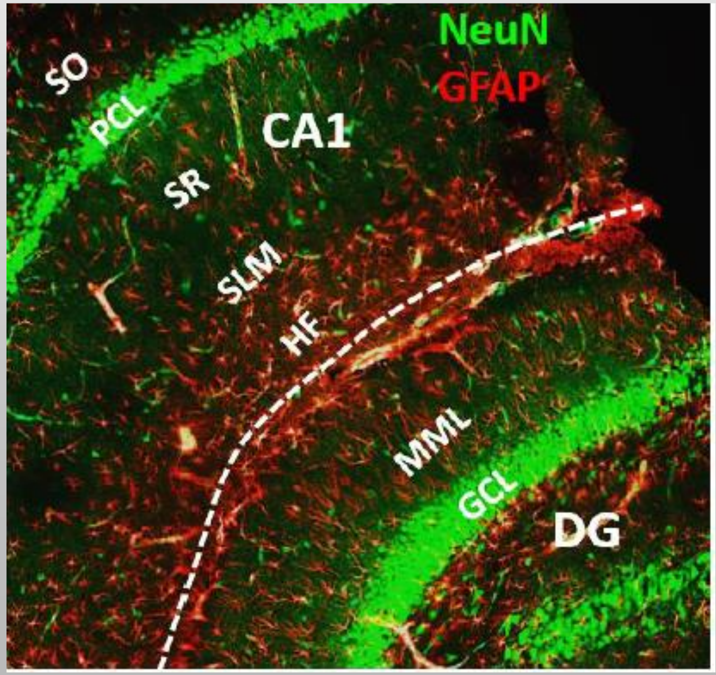
X NMDA receptors

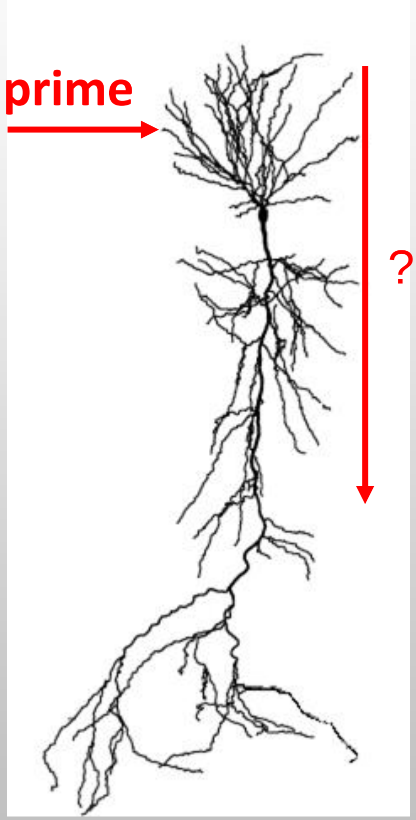
X L-Type VDCCs

✓ Calcium release from intracellular stores via IP_3 receptors

SR101-labelled astrocytes





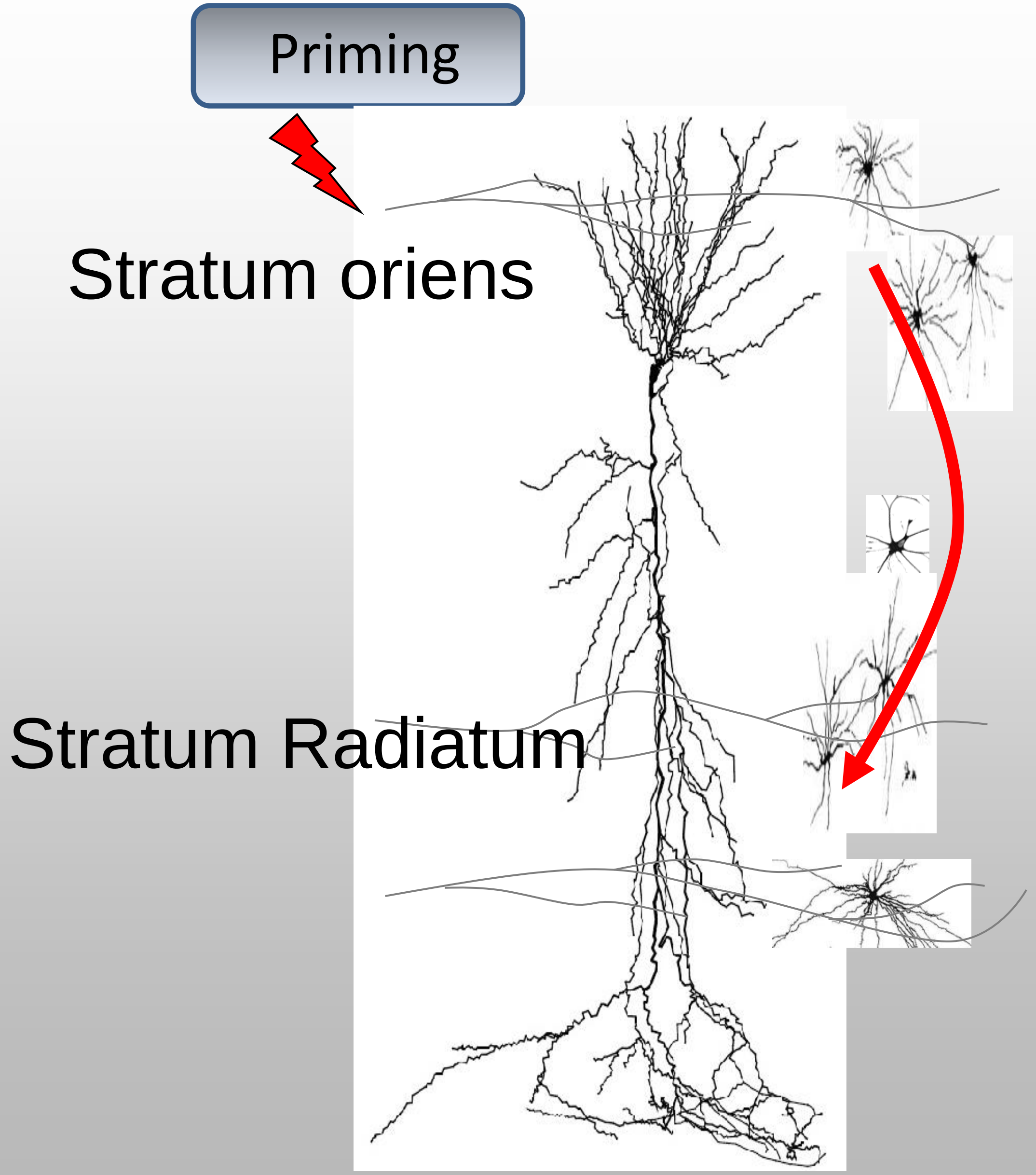


Working hypothesis

Astrocytes sense neural activity and adjust thresholds for future synaptic plasticity in the network.

Network Metaplasticity

Astrocytic Network – adding **space** to time for metaplasticity

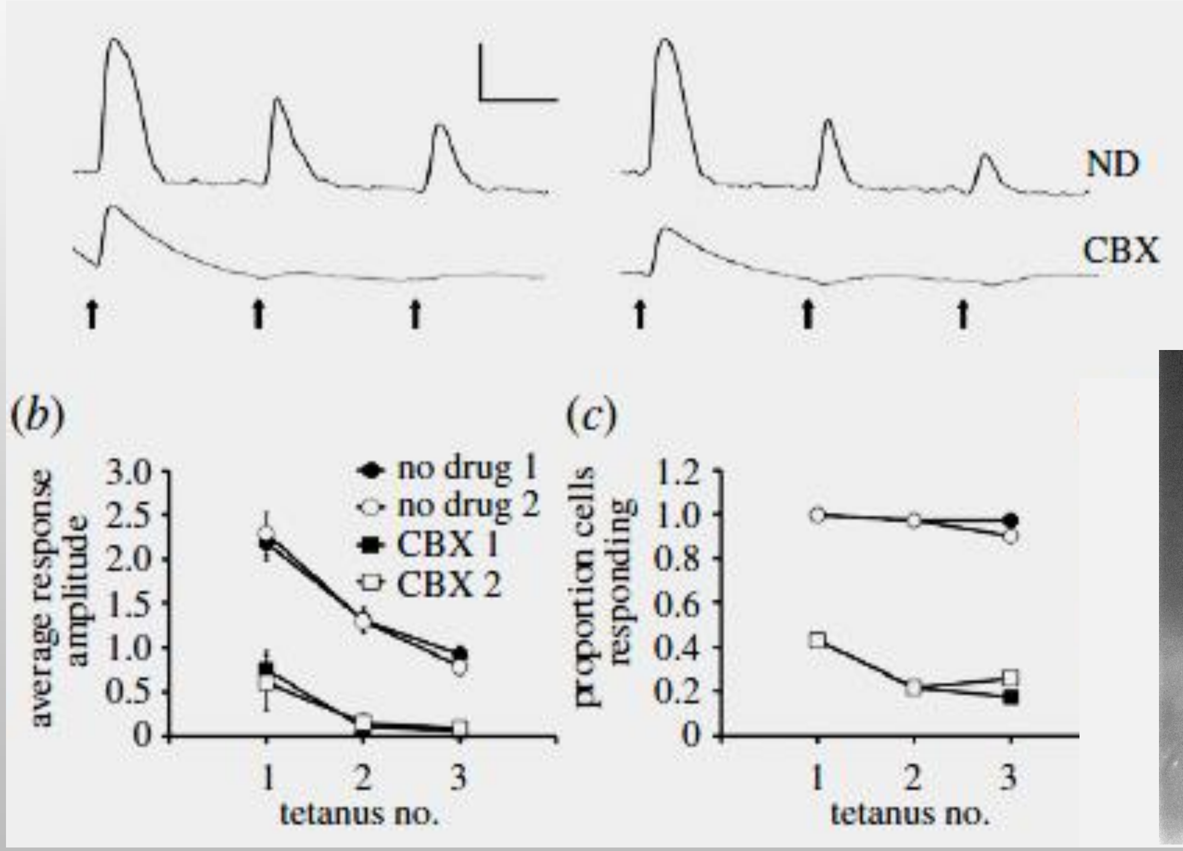


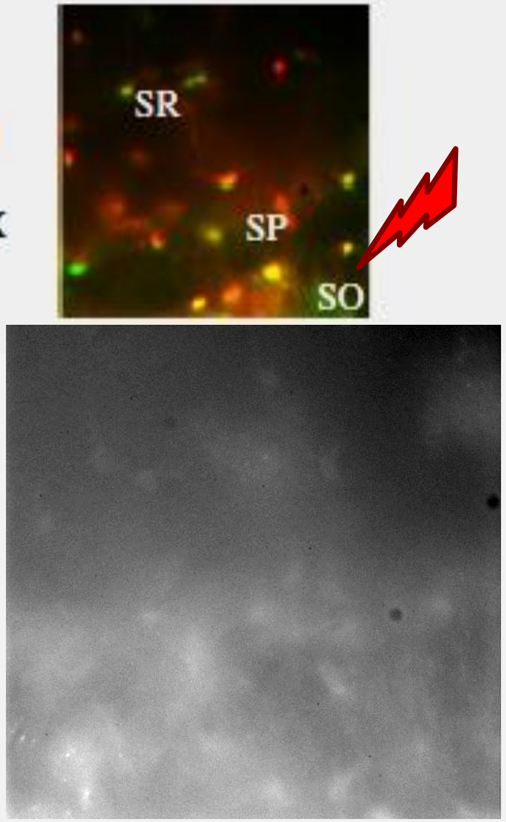
- Express neurotransmitter metabotropic receptors coupled to IP_3R signalling (e.g., **mGluRs**, **mAChRs, P2YRs**)
- Widespread, interconnected network communicating via gap junctions, hemichannels, release of ATP, etc
- Gliotransmitters released following rise in $[Ca^{2+}]_i$
  - ATP, adenosine
  - **Glutamate**, **serine**, **TNFα**

Radiatum astrocyte calcium responses to Oriens priming

Fluo-4 AM
Sulforhodamine 101

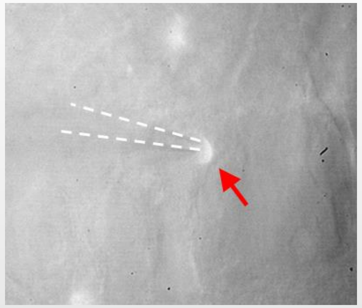
HFS (100 Hz, 1 s)

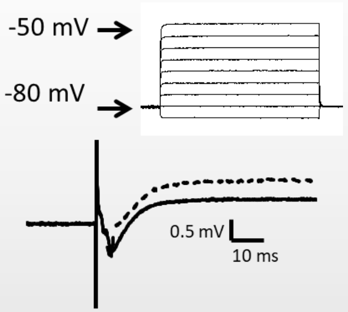




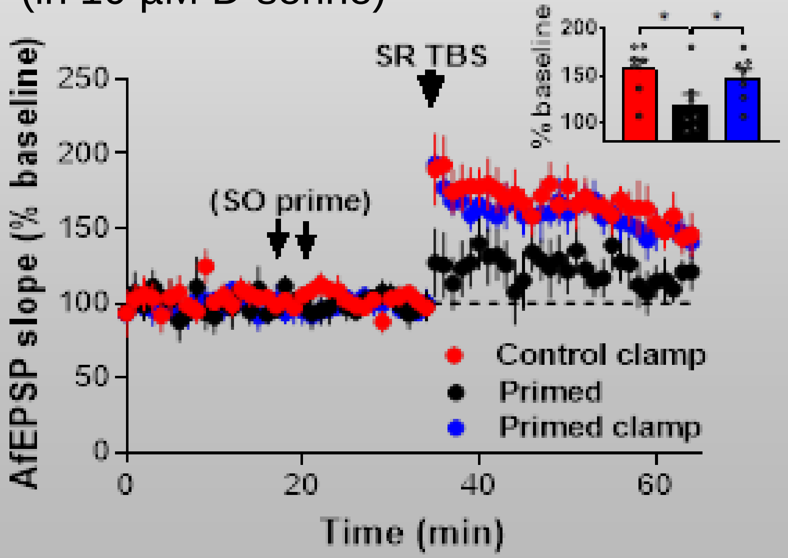
Hulme et al, *Phil Trans Royal Soc B*, 2013

Priming is blocked by astrocyte calcium control

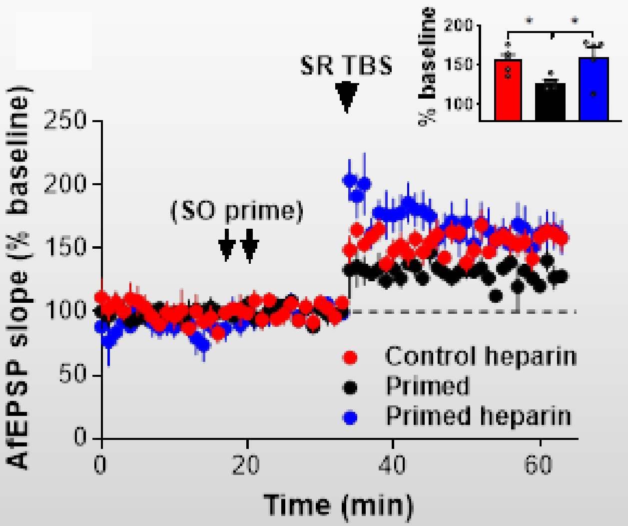




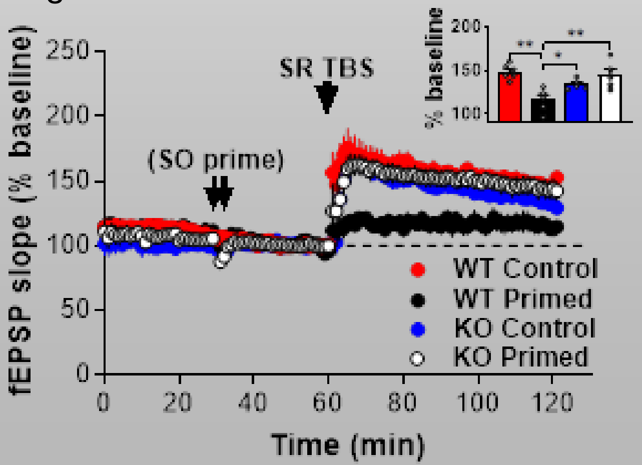
SR Astrocyte, intracellular EGTA
(in 10 µM D-serine)



SR Astrocyte intracellular heparin



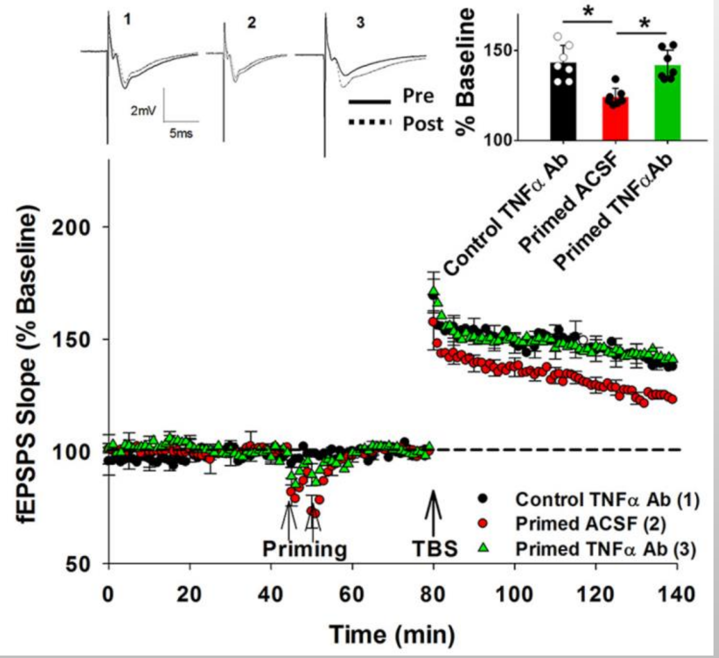
$IP_3R2^{-/-}$ mice



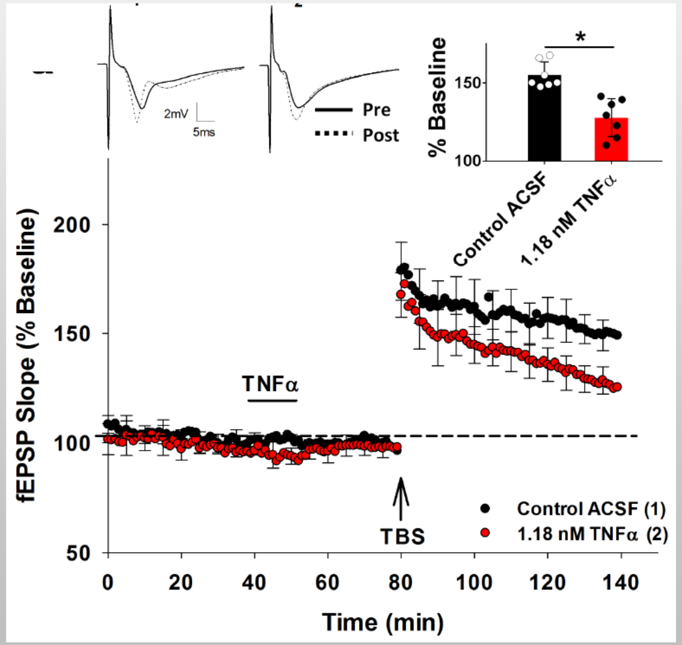
Jones et al, BioRxiv 2023

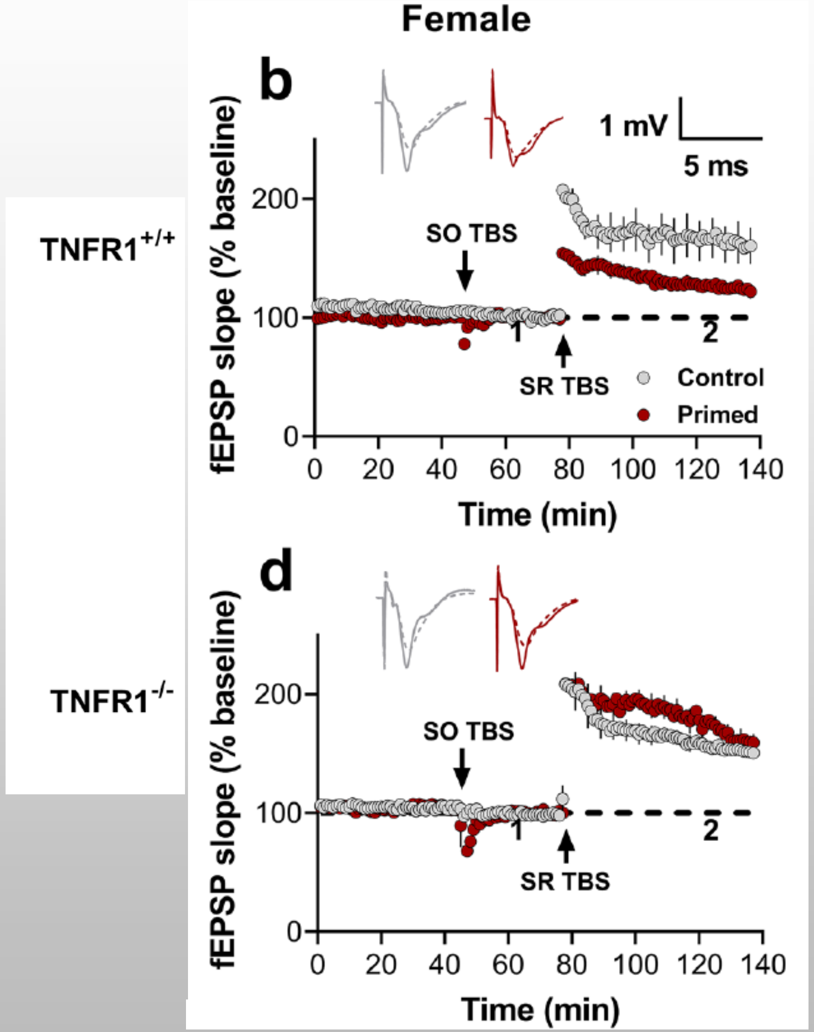
Tumor necrosis factor-α (TNFα) – TNFR1 contributes to the priming effect

TNFα antibody blocks priming



TNFα can cause priming



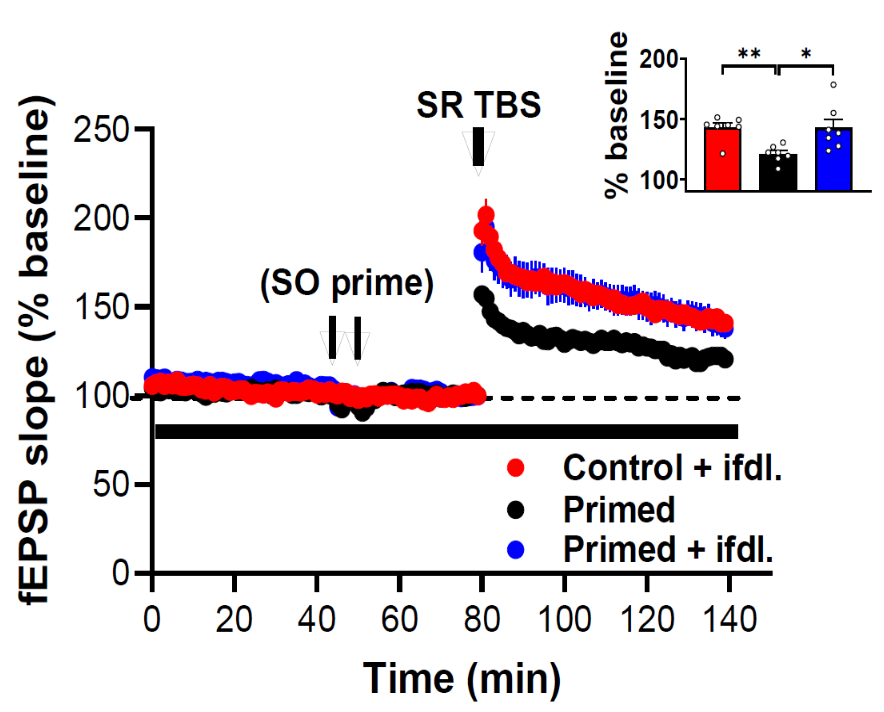


Singh et al, *J Neurosci*, 2019

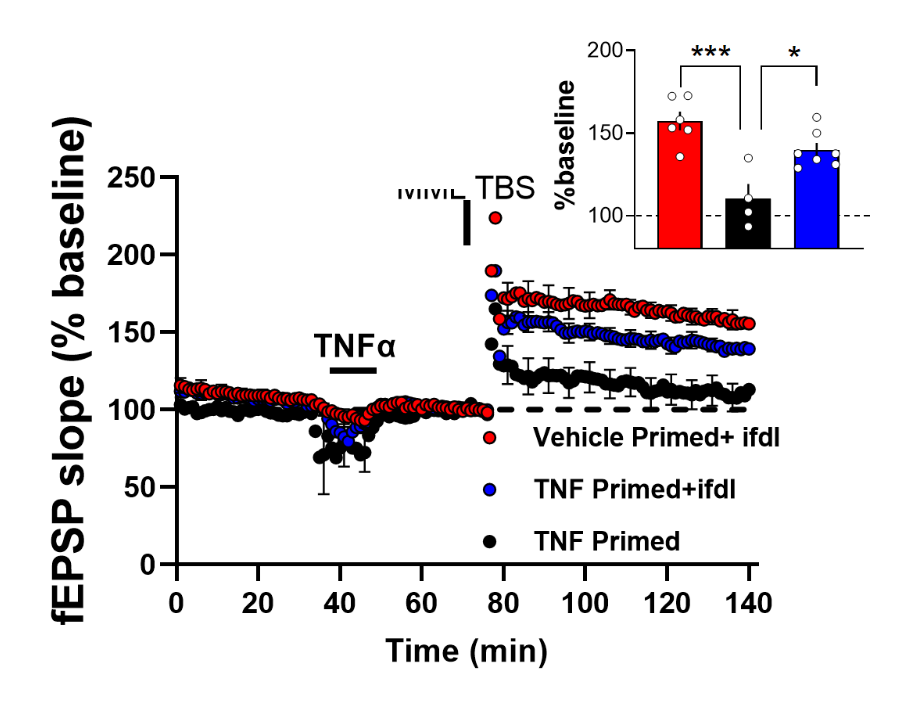
Singh, Sateesh et al, *Scientific Reports, 2022*

TNFα primes via GluN2B-containing NMDARs

Electrical priming + Ifenprodil

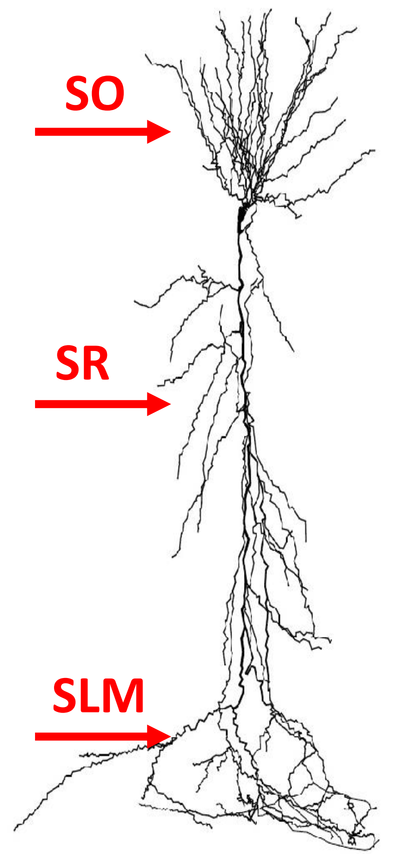


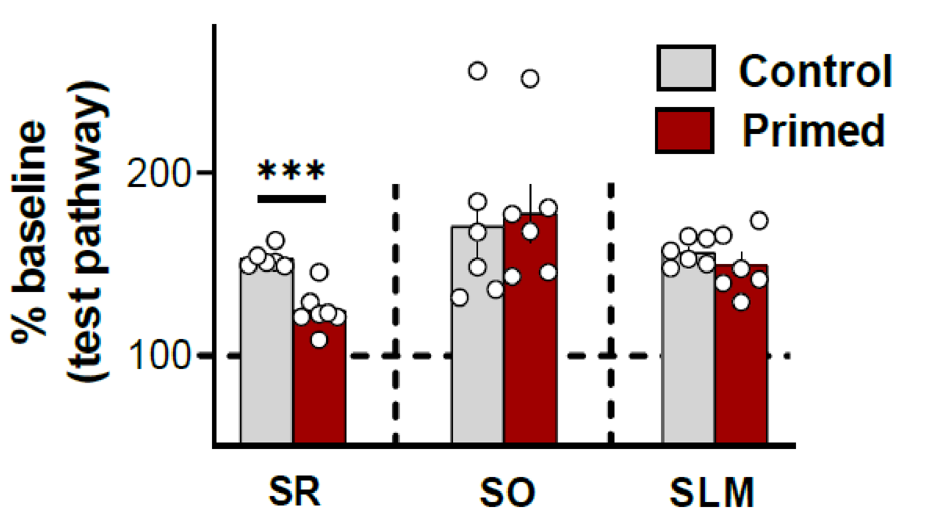
TNF priming + Ifenprodil

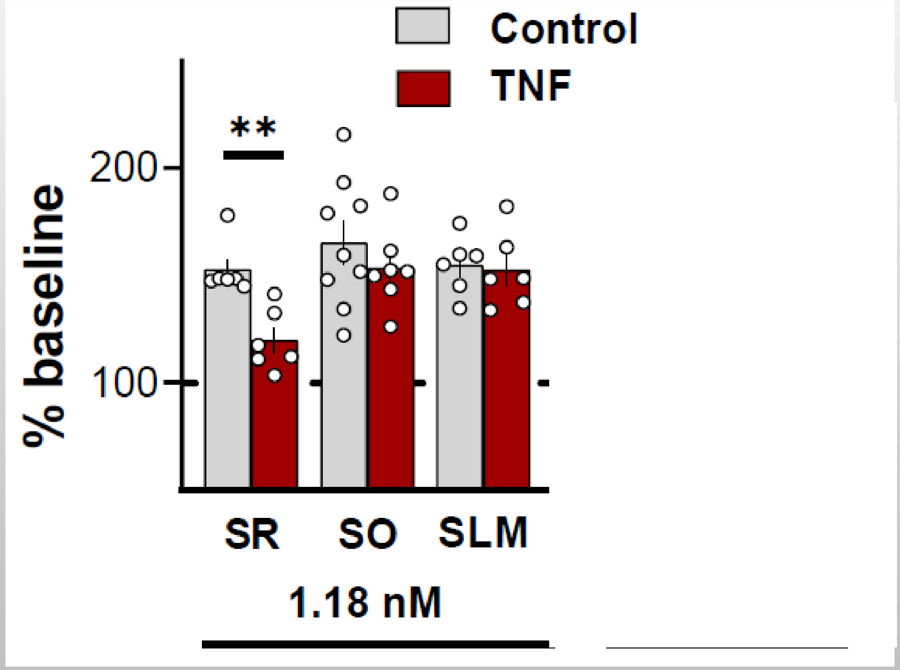


Jones et al, BioRxiv 2023

The priming effect is pathway-specific, not cell-wide







Singh, Sateesh et al, *Scientific Reports,* 2022

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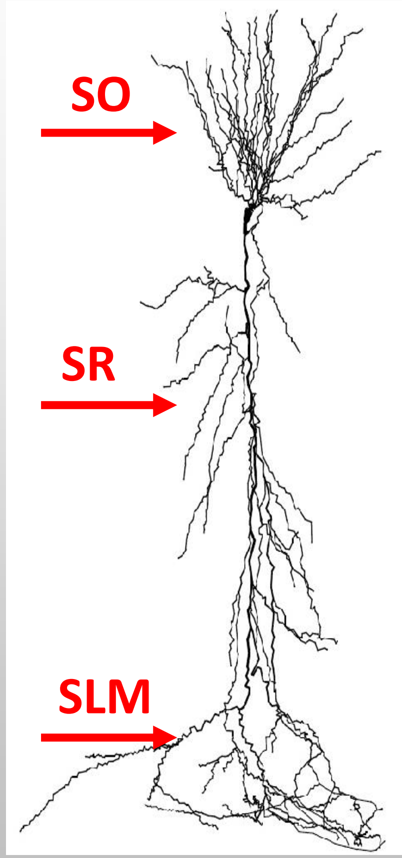
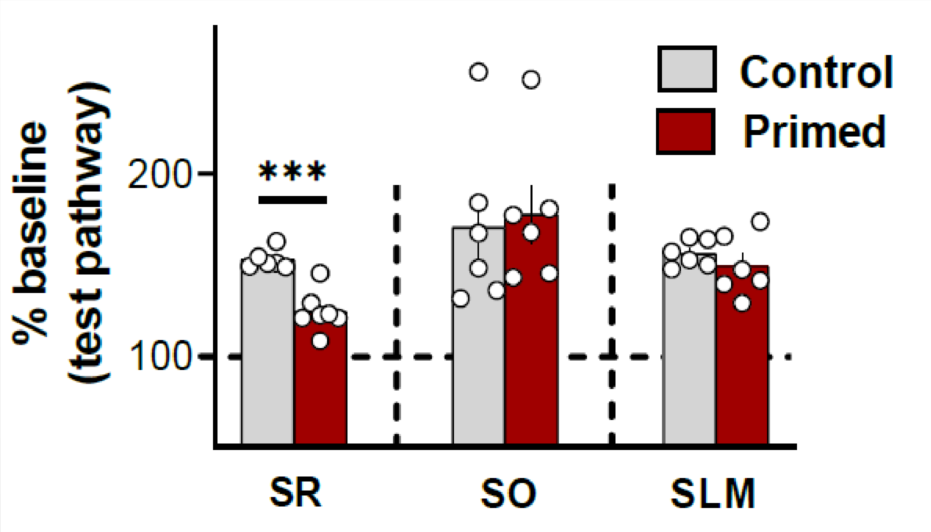
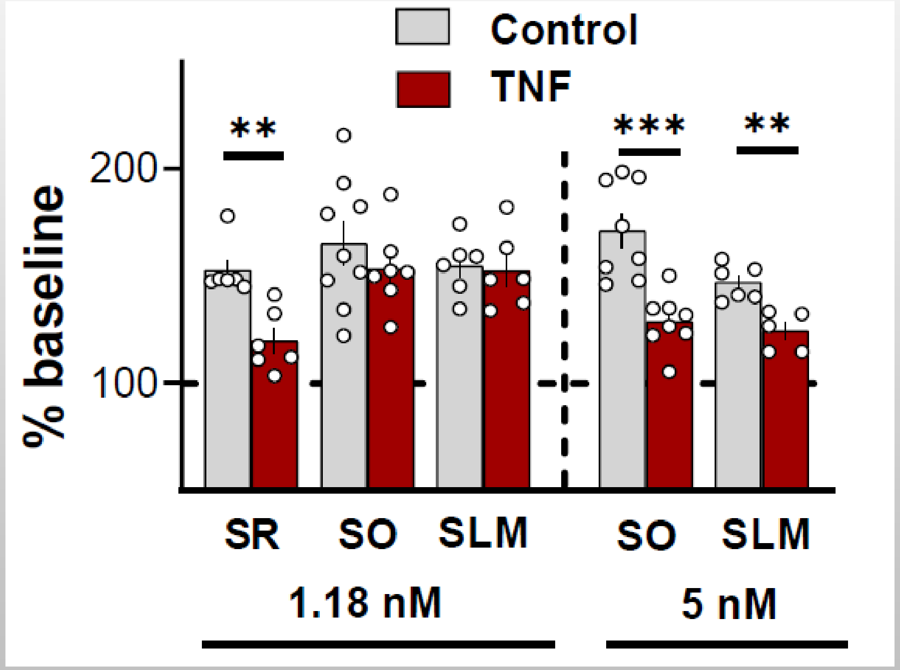


Electrical priming

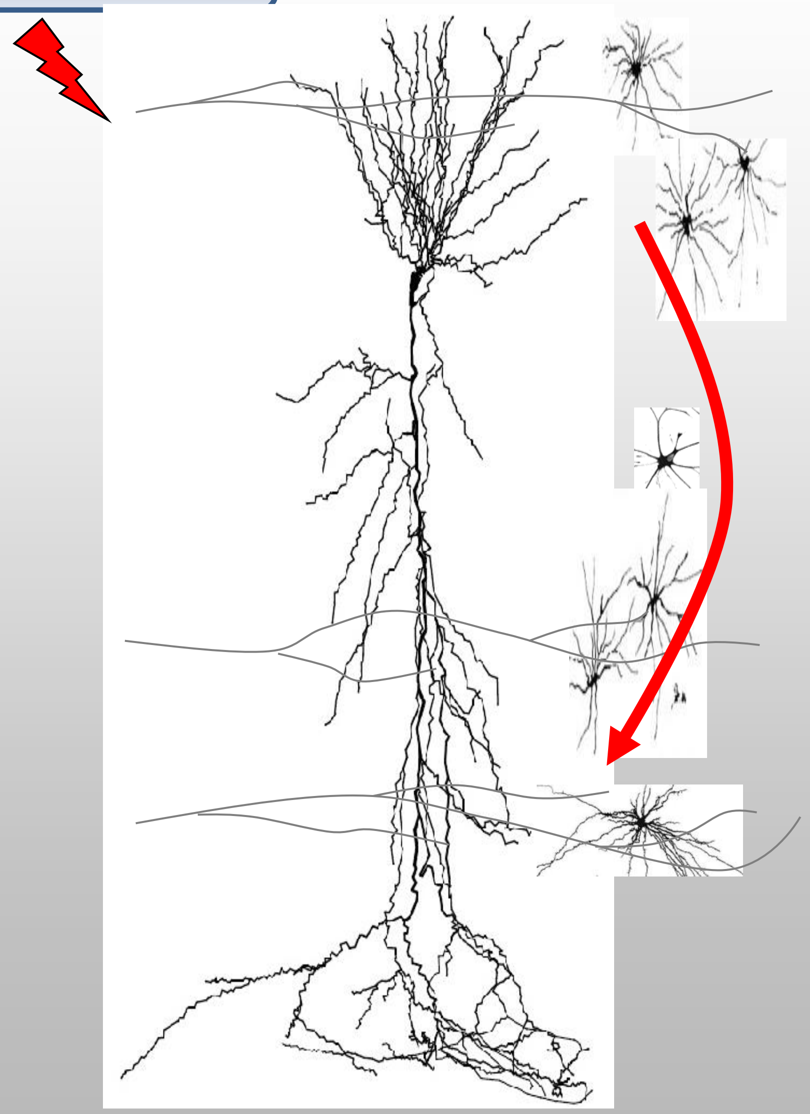


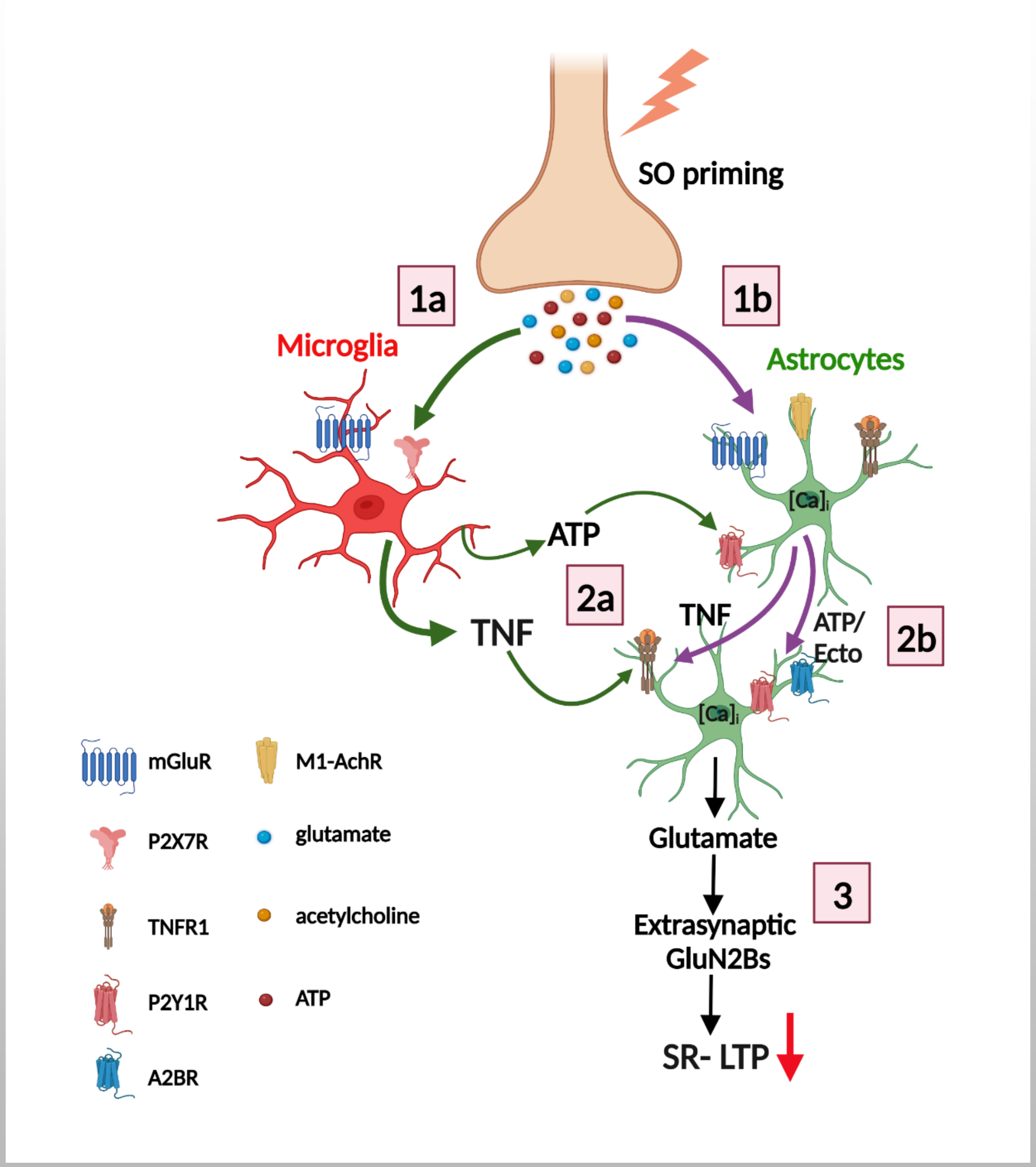
TNF priming



Singh, Sateesh et al, *Scientific Reports,* 2022

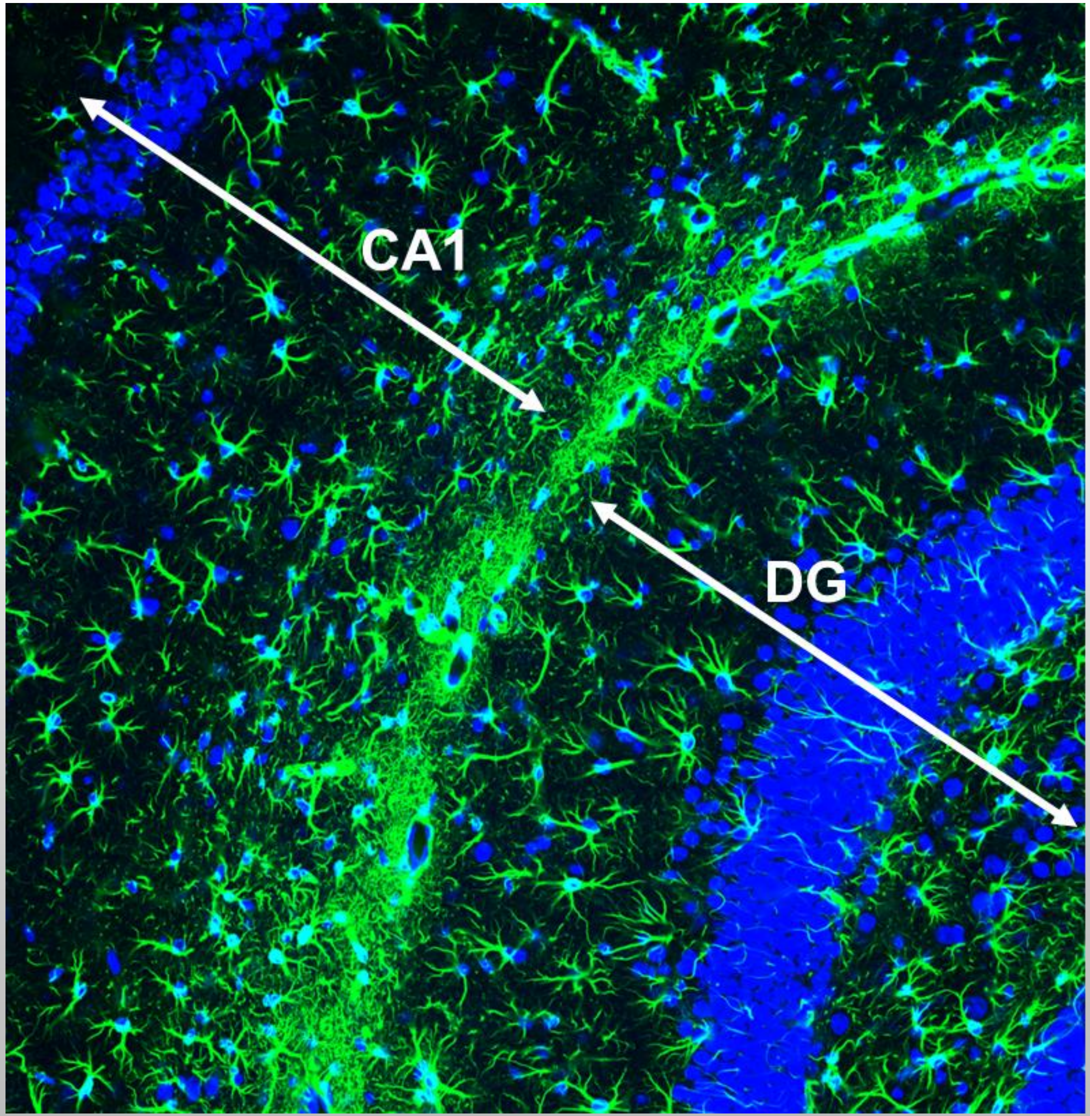
Priming



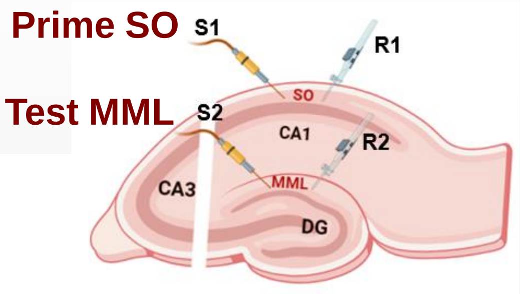


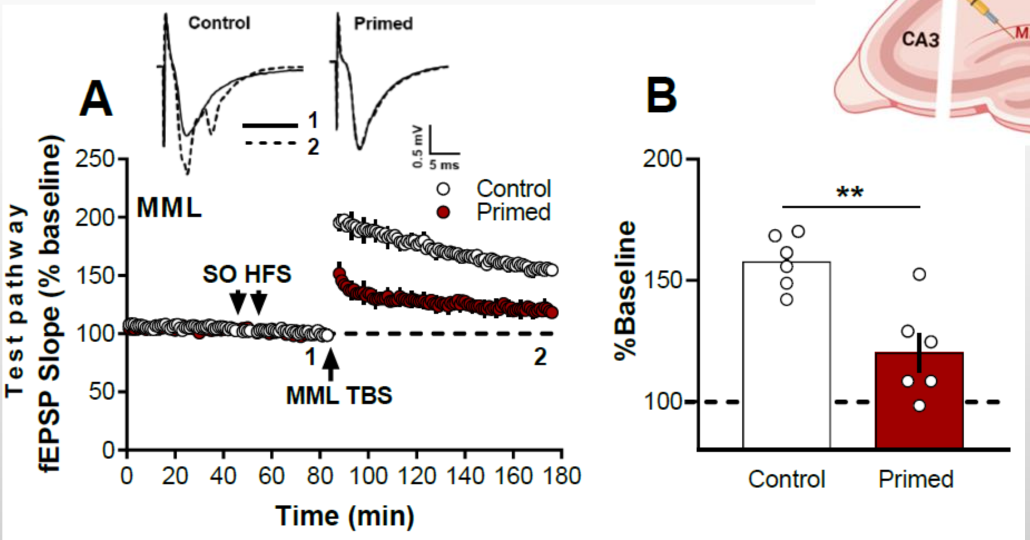
SO priming
1a
1b
Microglia
Astrocytes
[Ca]i
ATP
2a
TNF
TNF
ATP/
Ecto
2b
[Ca]i
Glutamate
3
Extrasynaptic
GluN2Bs
SR- LTP
mGluR
M1-AchR
P2X7R
glutamate
TNFR1
acetylcholine
P2Y1R
ATP
A2BR

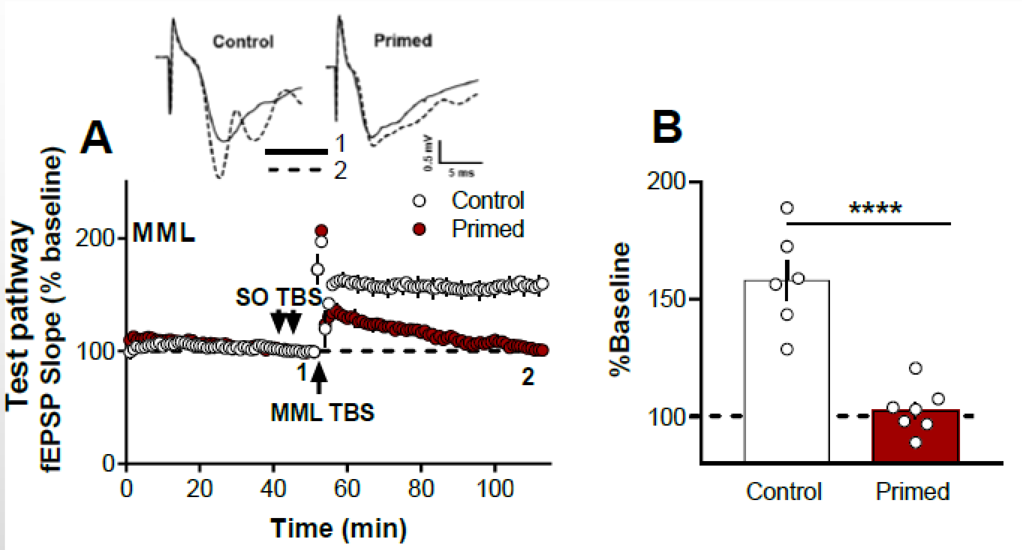
GFAP DAPI

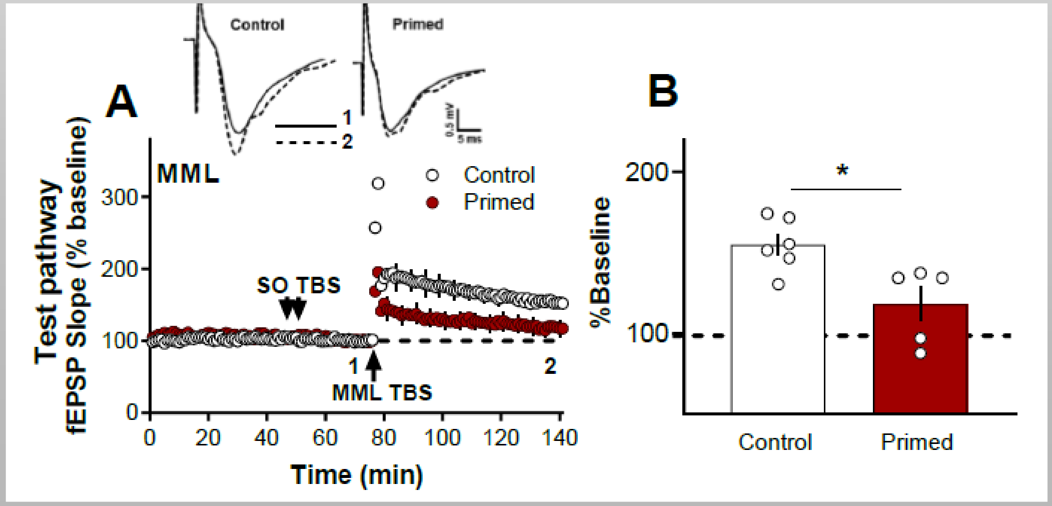


Priming in SO also inhibits LTP in the dentate gyrus middle molecular layer (MML)

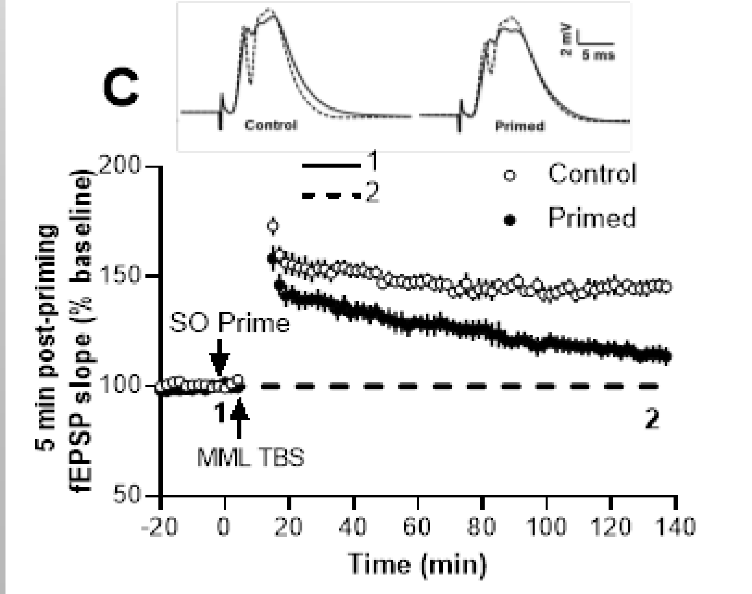






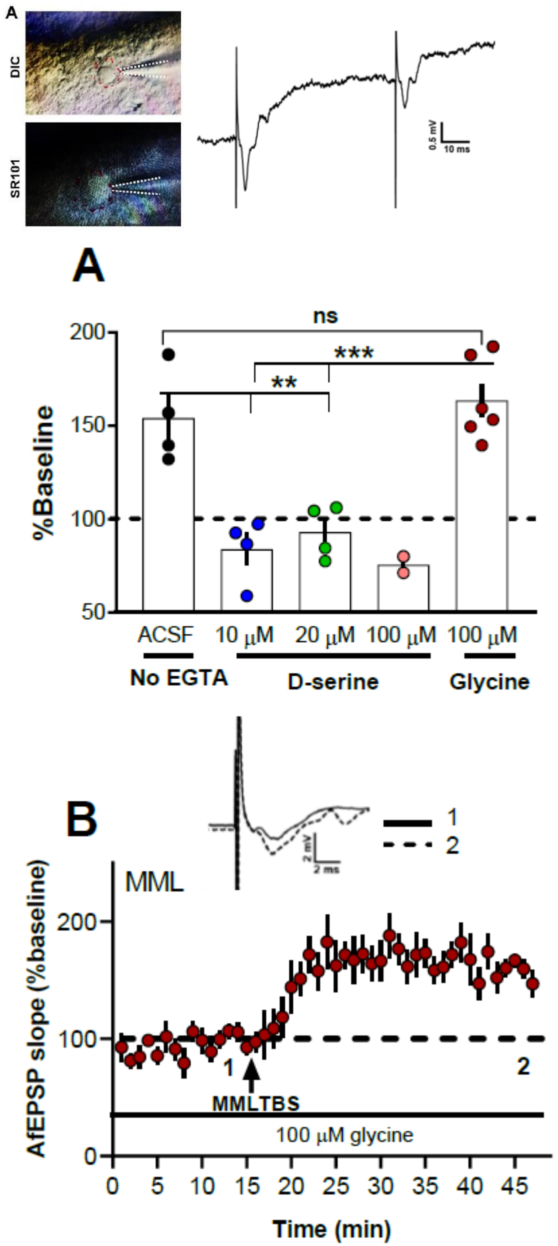


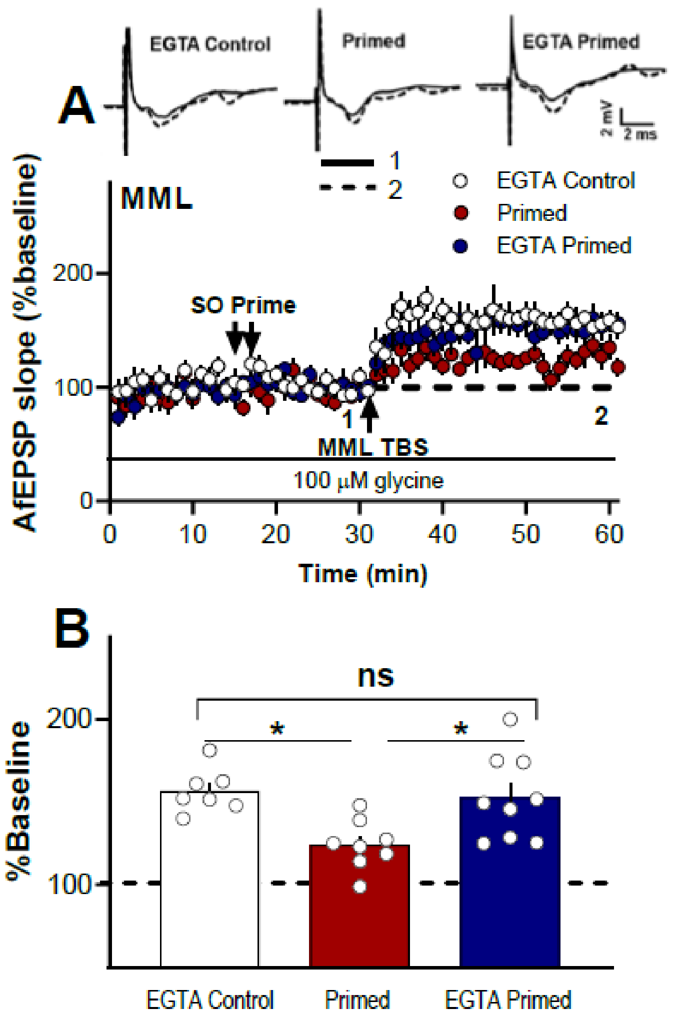
In vivo

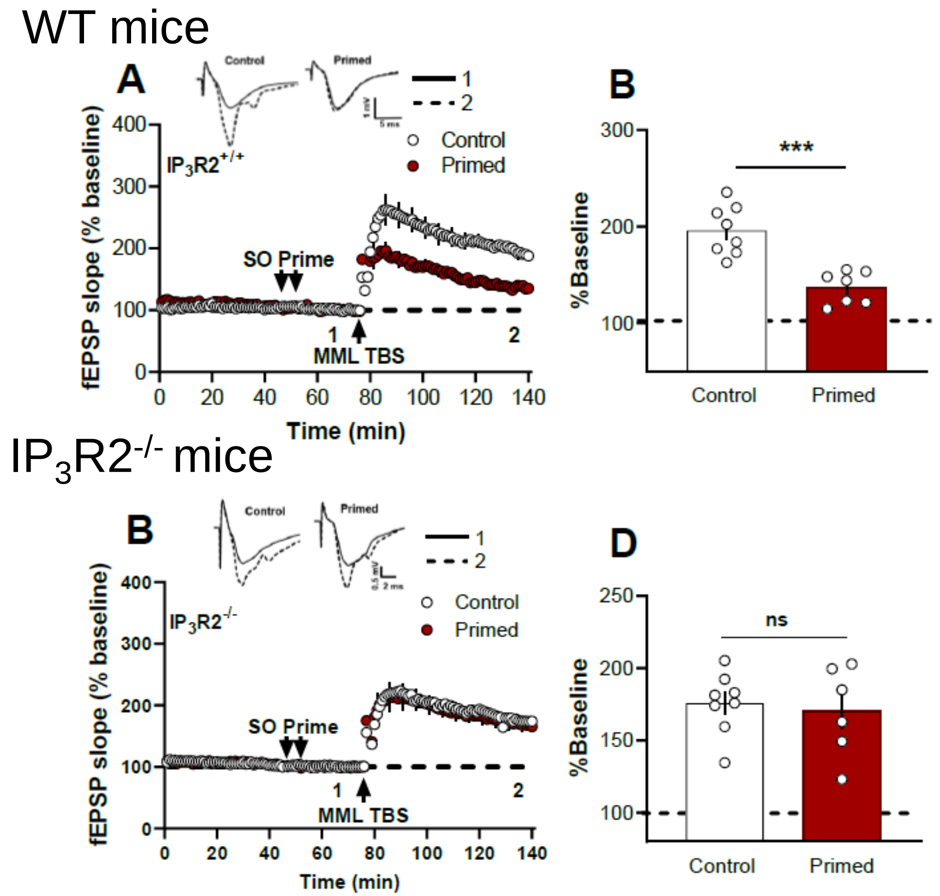


Sateesh, Suzuki et al, unpub.

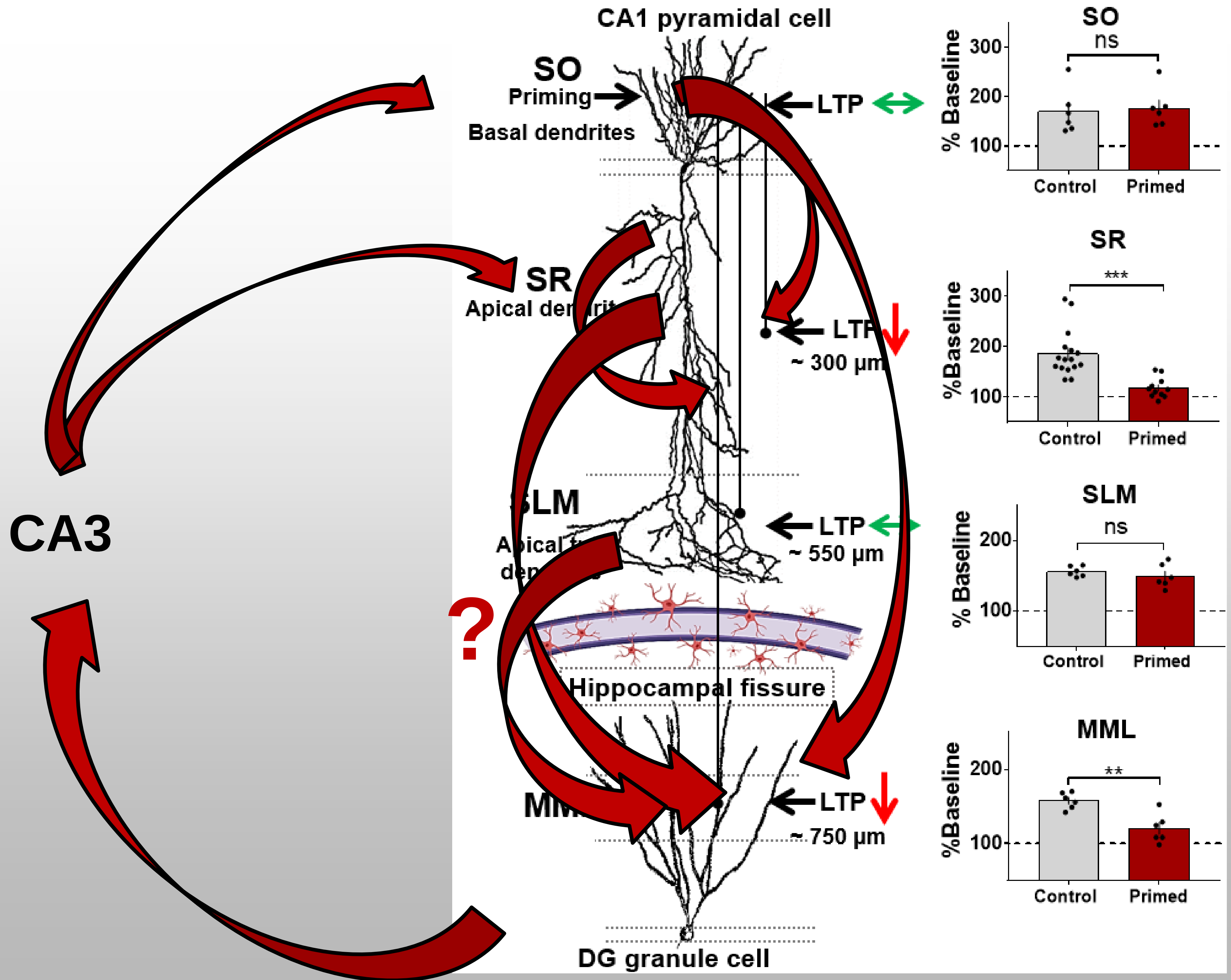
The spatial spread to the dentate gyrus is also astrocyte-mediated





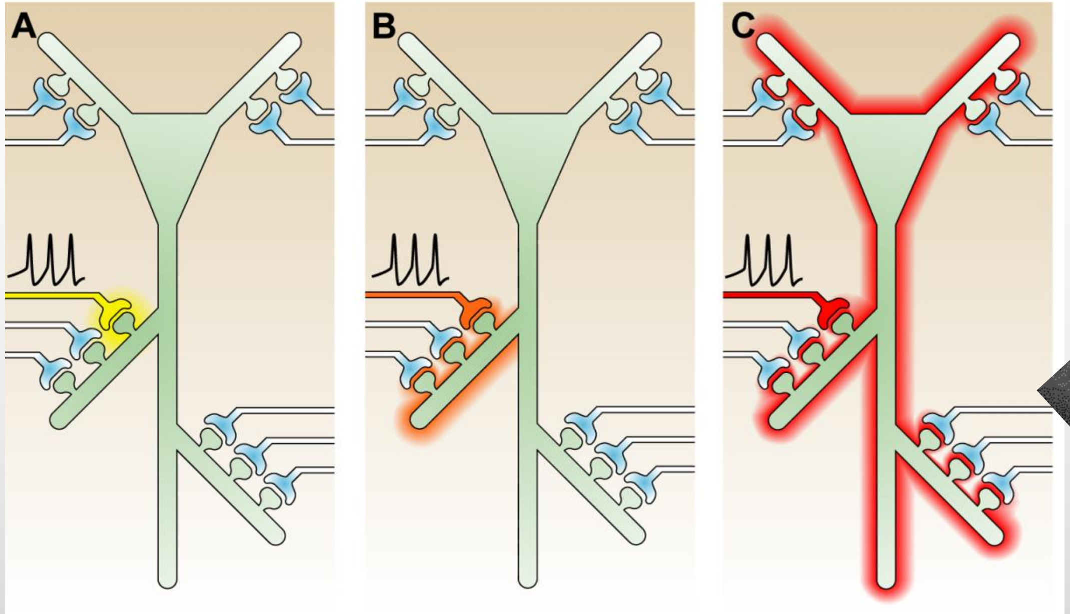


Sateesh & Abraham, unpub.


CA1 pyramidal cell
SO
Priming
Basal dendrites
LTP
SR
Apical dendrites
LTP
~ 300 µm
SLM
LTP
~ 550 µm
?
Hippocampal fissure
MML
LTP
~ 750 µm
DG granule cell
CA3
SO
ns
% Baseline
300
200
100
Control
Primed
SR
***
%Baseline
300
200
100
Control
Primed
SLM
ns
% Baseline
200
100
Control
Primed
MML
**
%Baseline
200
100
Control
Primed

Metaplasticity

Synapse-specific Compartment-specific Cell-wide



Network-wide (= ANN learning rate change?)

Astrocytes and (meta)plasticity

- Online local regulation of LTP via D-serine and glycine
- Network level metaplastic regulation of LTP/LTD across space and time through the hippocampus via TNF signalling
    - Homeostasis?
    - Biasing of storage vs retrieval pathways in the hippocampus?

Summary

1. Rapid, BCM-like metaplasticity may help stabilize synaptic drive following LTP events by facilitating ongoing activity to drive the balancing of synaptic weights.

2. But a different form of metaplasticity also exists via activation of the astrocytic network, involving TNF acting at TNF-R1s followed by glutamate acting at GluN2B-NMDARs.

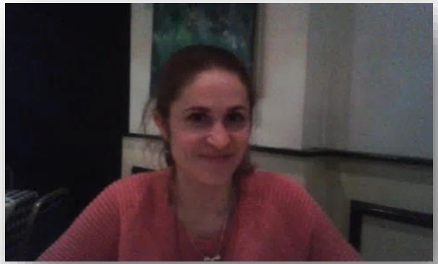
3. The effect is pathway-specific and extending even to a different subregion, revealing a novel “backward” communication from CA1 to the DG.

4. This effect is curiously opposite in direction to Synaptic Tag & Capture.

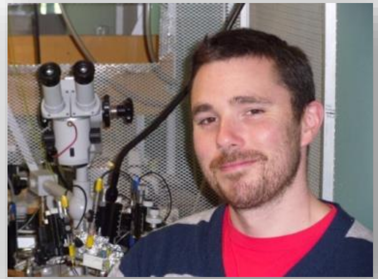
5. In normal tissue, this could be a consolidation mechanism by temporarily preventing interference from new learning via the trisynaptic circuit.
   (IP3R2-KO mice have impaired LTD and remote memory.)

6. Its aberrant engagement in neuroinflammatory disorders, e.g. AD models, appears to contribute to impairments in LTP and cognition.

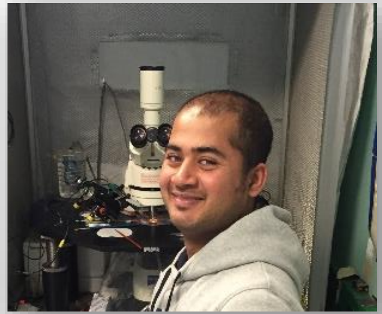
Sarah Hulme



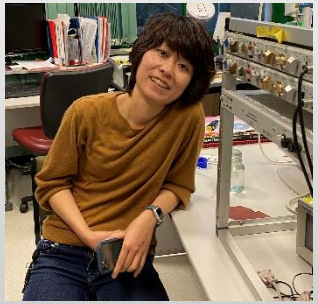
Owen Jones



Anurag Singh



Shruthi Sateesh



Miki Suzuki, Shizuoka
Clarke Raymond, ANU, Canberra
Pankaj Sah, QBI, Brisbane

Ju Chen, San Diego

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