Synaptic Plasticity

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Computational Neuroscience (Lecture 13, 2023/2024)

Outline of Lecture

- Adaptation in the brain
- Short and long term plasticity
- Long term potentiation and long term depression
- Spike time dependent plasticity
- Role of plasticity in learning and memory

Adaptation in the Brain

- Single-Neuron:

Short timescale: spike rate adaptation

Long timescale: changes in distribution/properties of ion channels (intrinsic plasticity)

- Synaptic:

Short timescale: short term plasticity

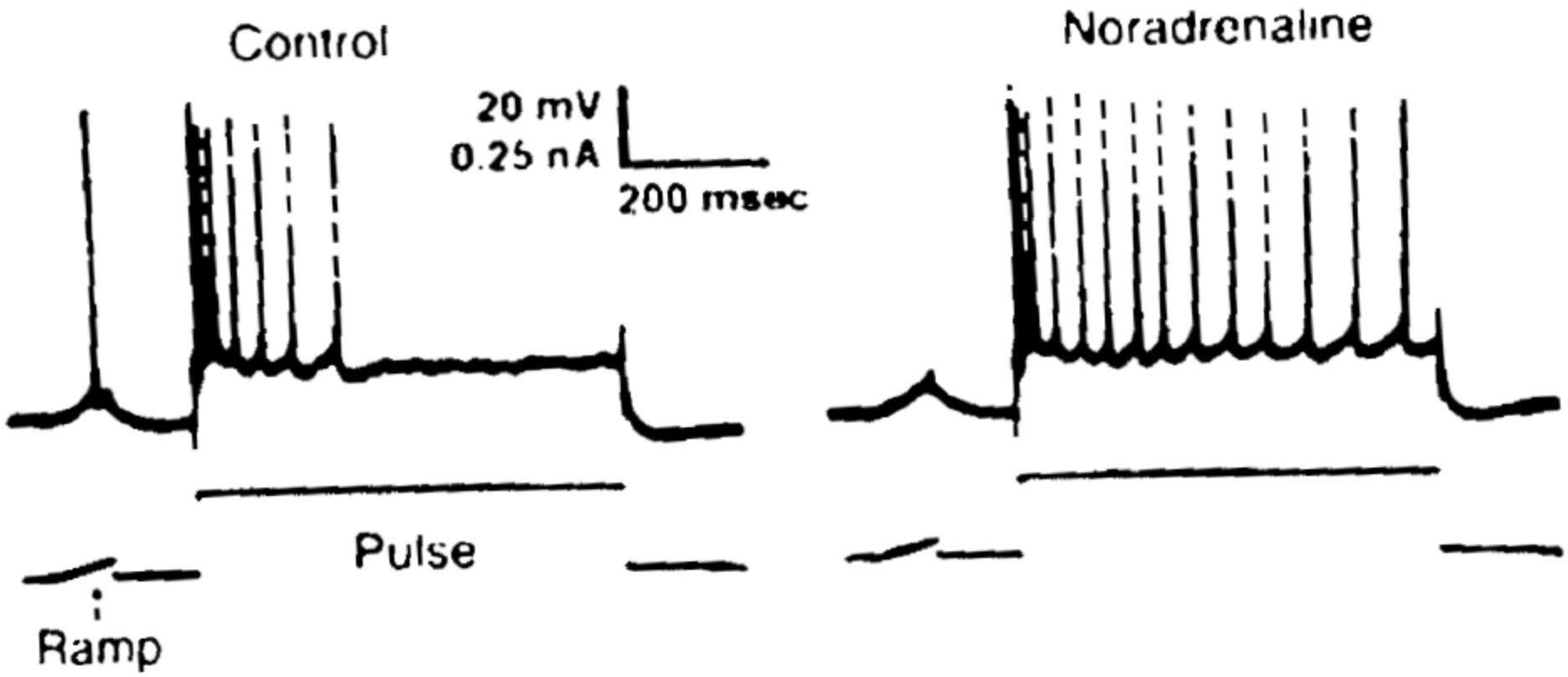
Long timescale: long term plasticity

Others: glia, genetic, neuromodulation, myelination, morphology, cell birth/death, etc.

What is adaptation for?

- Computation – e.g., spike rate adaptation and short term plasticity affect network dynamics and coding
- Learning and memory – mainly using long term synaptic changes
- Homeostasis – keep system in a correct operating regime despite environmental/internal changes
- Efficiency/robustness – minimising number of spikes required to efficiently encode sensory input with non-stationary statistics

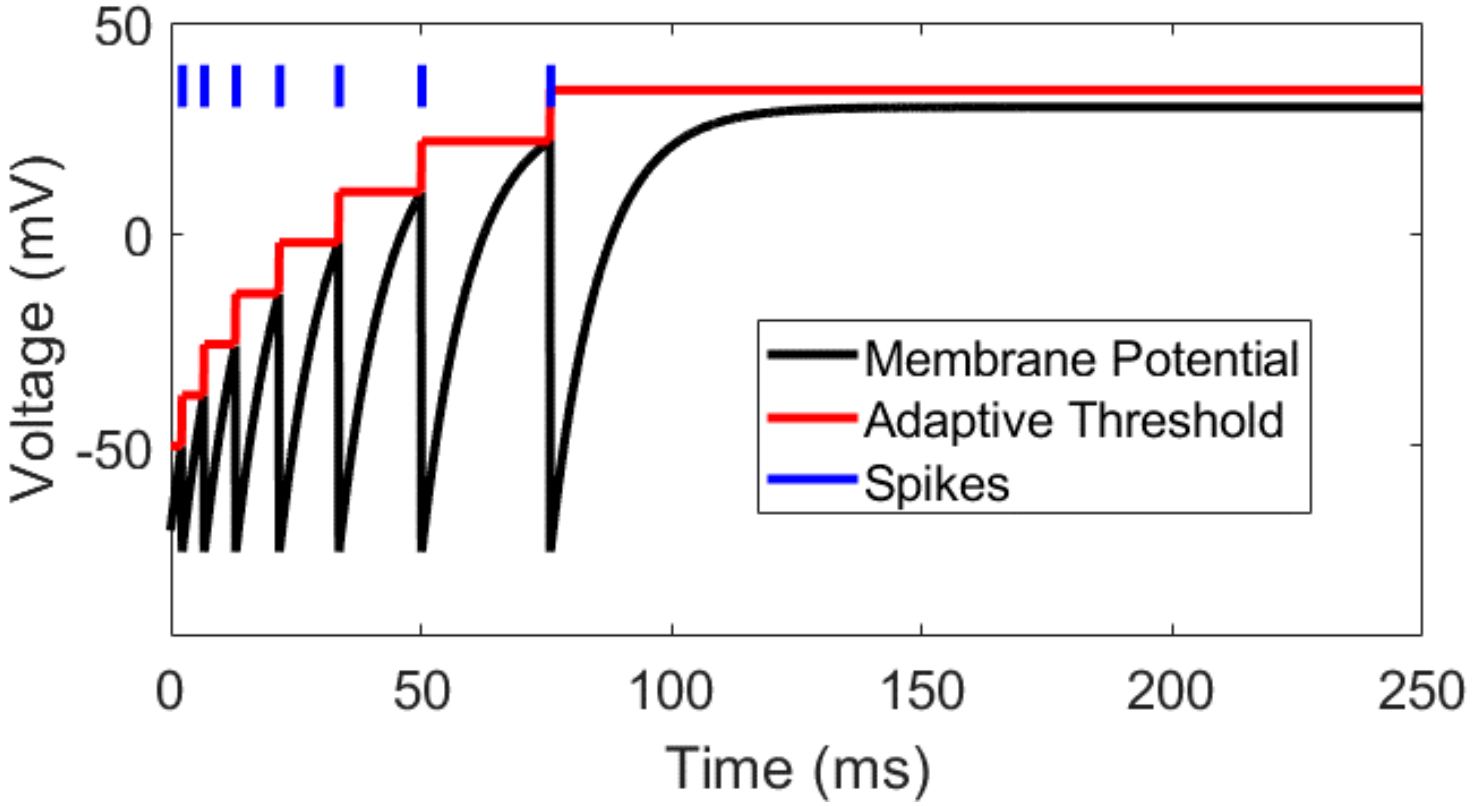
Spike Rate Adaptation



- Spiking slows down under constant current input, and can eventually stop entirely (right: noradrenaline partially blocks SRA)

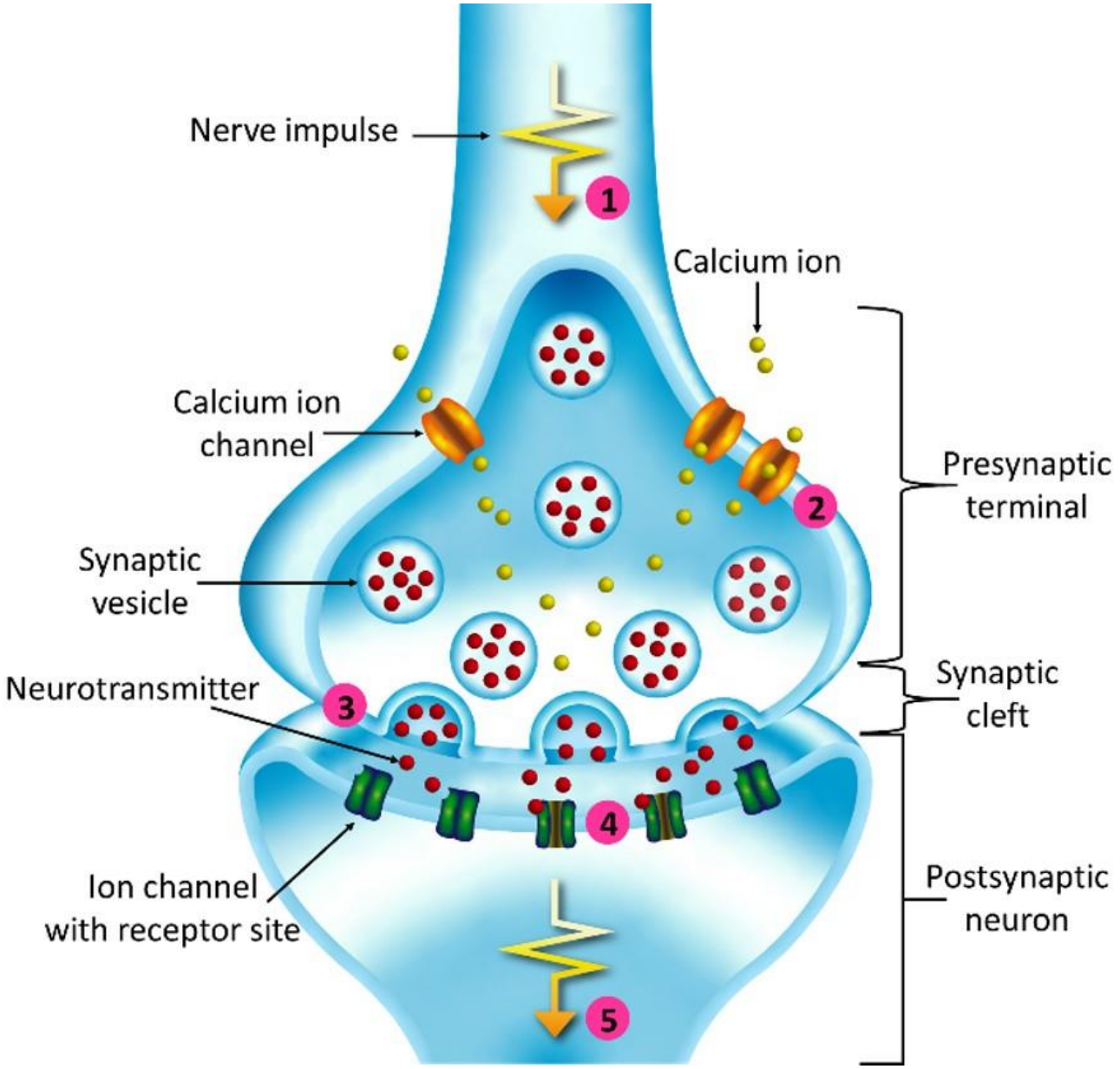
Modelling Spike Rate Adaptation

- SRA relies on a *calcium-activated potassium channel* – calcium flows into cell when it spikes, opening these channels and causing outward potassium flow
- Can model this process biophysically, or use an adaptive threshold instead:



Synapses - Recap

- Spike arrives at presynaptic side
- Voltage-gated calcium channels open
- Calcium flows in, causing vesicles to bind to cell membrane and release neurotransmitter
- Neurotransmitter diffuses across cleft and binds to receptors on postsynaptic membrane
- Receptors open ion channels and let current flow through



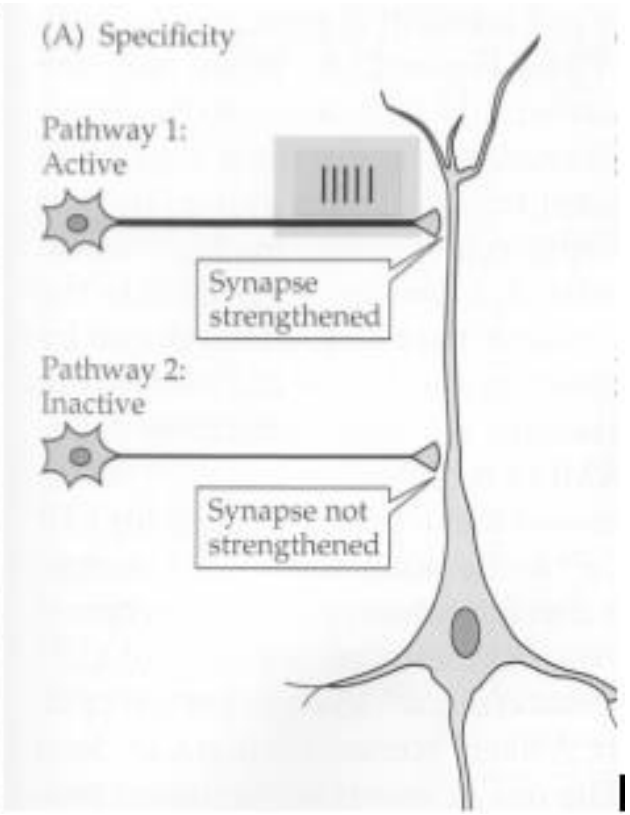
Synaptic Plasticity

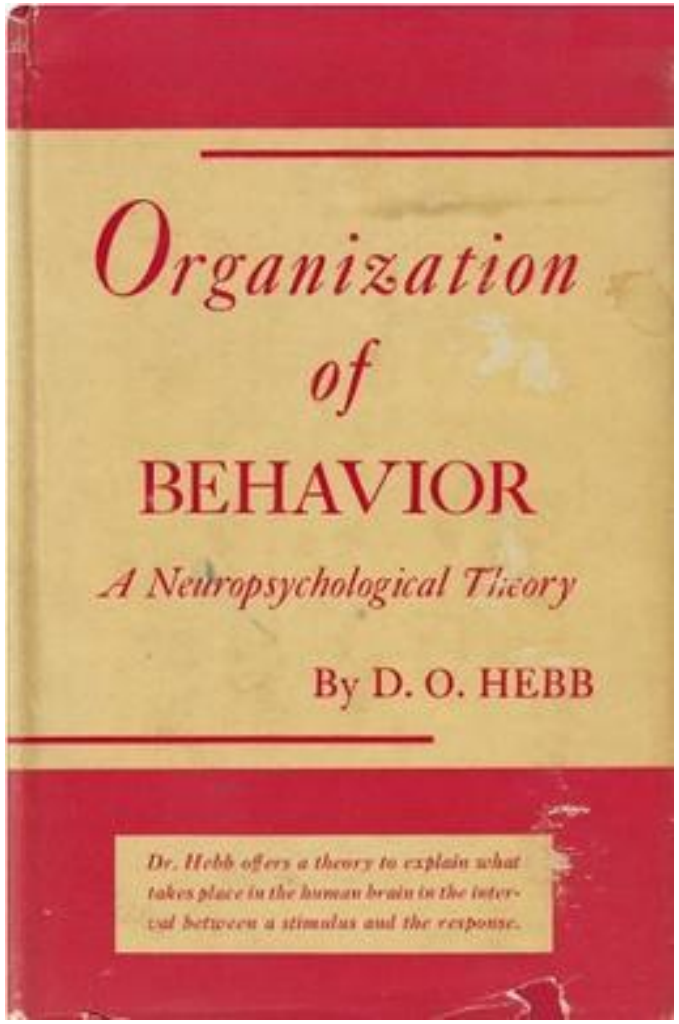
- Most plasticity involves modification of synapses
- Many possibilities: number of ion channels, properties of ion channels, number/size of vesicles, pre or post synaptic side, etc.
- Excitatory synapses have AMPA and NMDA receptors, which play different roles in plasticity
- Inhibitory synapses also undergo plasticity, but this is less well understood

Donald Hebb – Hebbian Learning and Cell Assemblies (1948)

- *"When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased"*

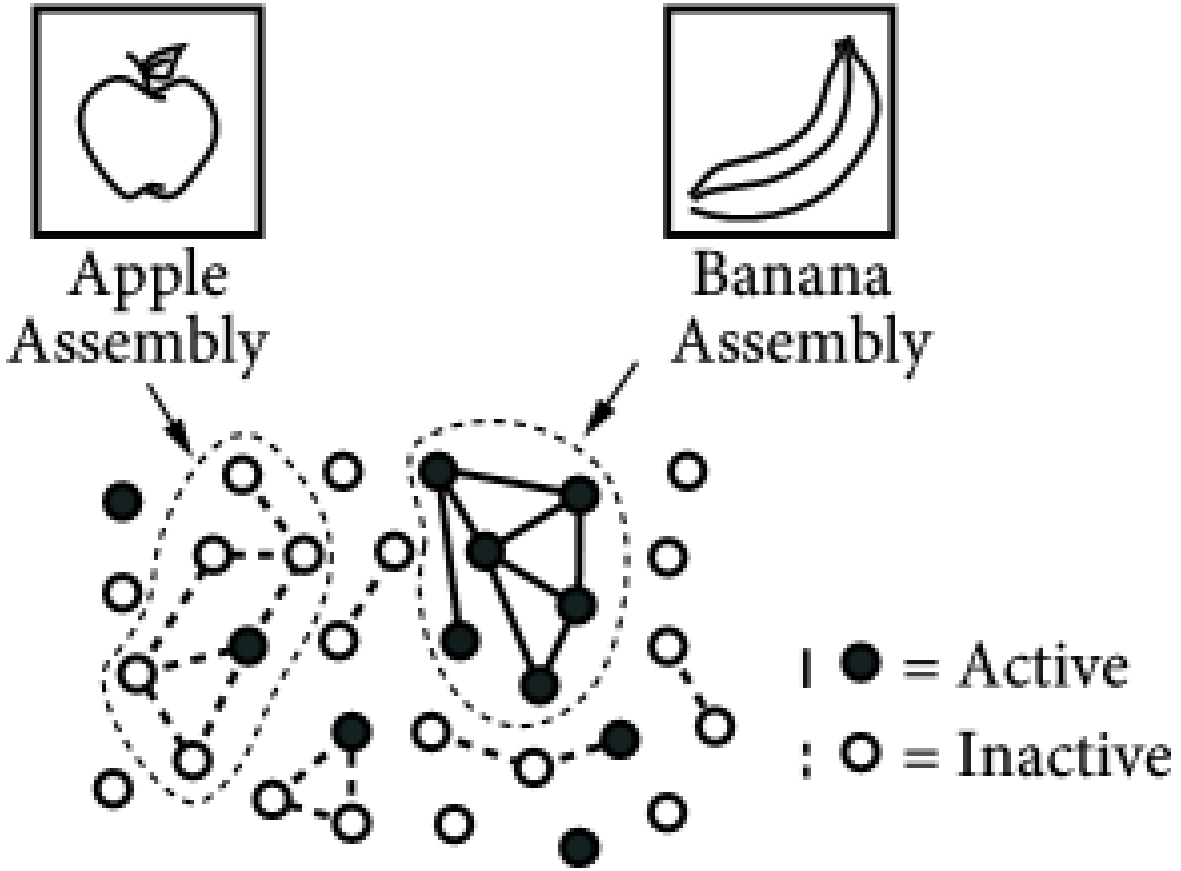
- More commonly put: *"Cells which fire together, wire together"*





Donald Hebb – Hebbian Learning and Cell Assemblies (1948)

- Coactivation of a group of cells causes connections to form/strengthen (Hebbian learning)
- Subsequent activation of a subset of those cells will reactivate the whole group (a "cell assembly")
- A mechanism for forming and retrieving associations/memories



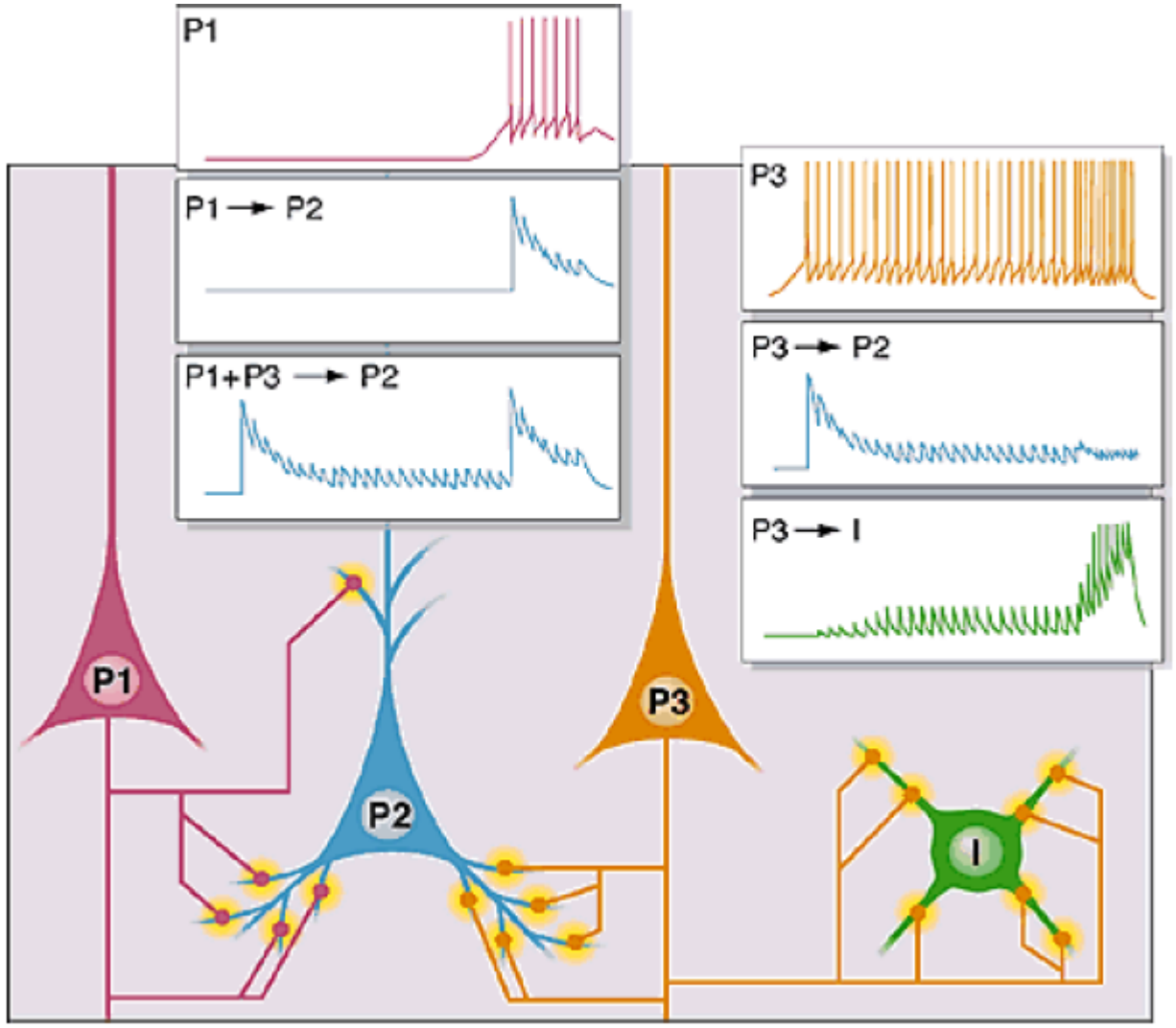
Short and Long Term Plasticity

- Synapses vary in an activity-dependent manner over short and long timescales
- Short term plasticity lasts seconds or minutes, and includes both facilitation and depression
- Long term plasticity can last a lifetime, and includes long term potentiation and long term depression (LTP and LTD)
- These two forms of plasticity rely on different biological processes

Short Term Plasticity

- Synaptic facilitation:
- calcium in presynaptic side builds up over time, increasing the probability of vesicle release
- synaptic currents increase with repeated firing

- Synaptic depression:
- pool of vesicles is depleted, release probability decreases
- synaptic currents decrease with repeated firing



Modelling Short Term Plasticity

- When spike arrives at synapse, the evoked post-synaptic conductance/current depends on number of vesicles released, size of vesicles, etc.

- Treat vesicles as identical and independent, assume when spike arrives each vesicle is released with probability *prel*

- If there are *n* vesicles in the synapse, the probability that *k* are released is:

$$P(N_{\text{vesicles}} = k) = \binom{n}{k} p_{\text{rel}}^{k} (1 - p_{\text{rel}})^{(n-k)}$$

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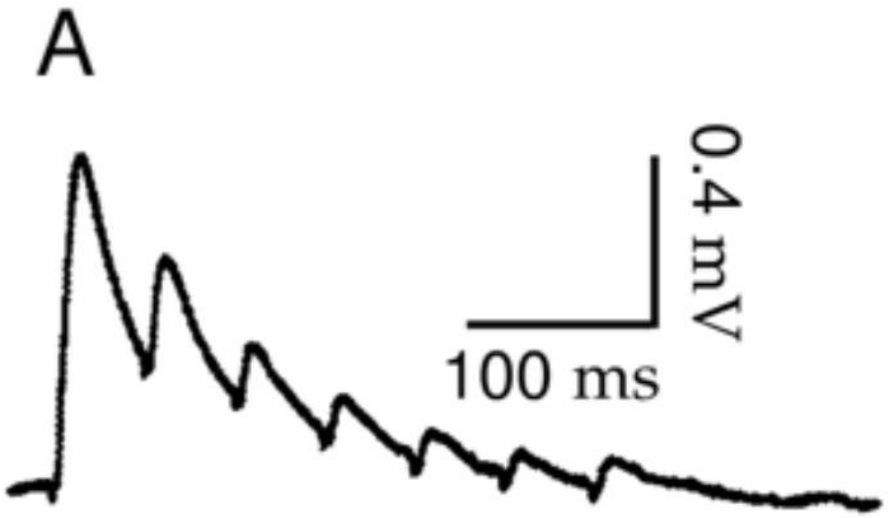
- But for large *n* and finite *n*prel* this becomes a Poisson distribution:

$$P(N_{\text{vesicles}} = k) = (np_{\text{rel}})^{k} e^{-np_{\text{rel}}} / k!$$

Modelling Short Term Plasticity

- Can model as changes in probability of vesicle release p_{rel} as a function of time and activity



Synaptic Depression

$$\tau_{depress}\frac{dp_{rel}(t)}{dt} = p_{rel}^{\infty} - p_{rel}(t)$$

$$\text{if release } p_{rel} = [p_{rel} - \alpha]_{+}$$

Modelling Short Term Plasticity

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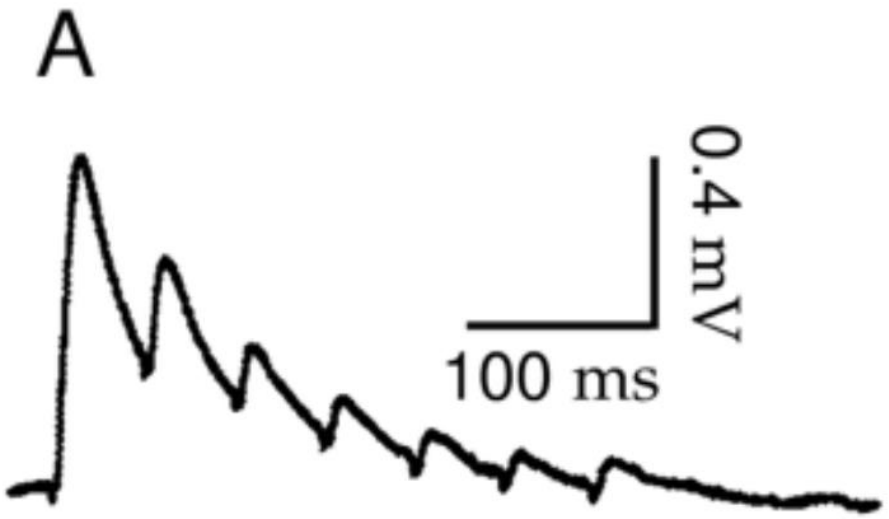


Synaptic Depression

$$\tau_{depress}\frac{dp_{rel}(t)}{dt} = p_{rel}^{\infty} - p_{rel}(t)$$

$$\text{if release } p_{rel} = [p_{rel} - \alpha]_{+}$$

Synaptic Facilitation

$$\tau_{facilitate}\frac{dp_{rel}}{dt} = p_{rel}^{\infty} - p_{rel}(t)$$

$$\text{if spike } p_{rel} = \min(p_{rel} + \beta, 1)$$

Effects of SRA and STD on Input Coding

- Both SRA and STD cause the neuron to respond to relative changes in input rather than absolute magnitude of input
- For example, high frequency synaptic inputs cause stronger depression, decreasing their effect on the neuron
- The synapse will therefore respond strongly to transient increases in input, but less so to sustained ones, and similarly for the neuron as a whole
- We see that the brain likes change: retinal ganglion cells report local difference in luminance, synapses report relative changes in input over time, and neurons adapt their spiking output over time as inputs change magnitude

Summary: Short Term Plasticity

- Synapses adapt based on recent history of synaptic input
- Both short term facilitation and short term depression occur
- Different mechanisms: STF involves build-up of calcium, STD involves depletion of vesicles/neurotransmitter
- Likely to be important for computation, e.g. could be useful for efficiently encoding stimuli with non-stationary statistics
- Perhaps for this reason, short term adaptation tends to be stronger in early sensory areas

Long Term Potentiation vs Long Term Depression

- Long term synaptic changes are thought to store memory

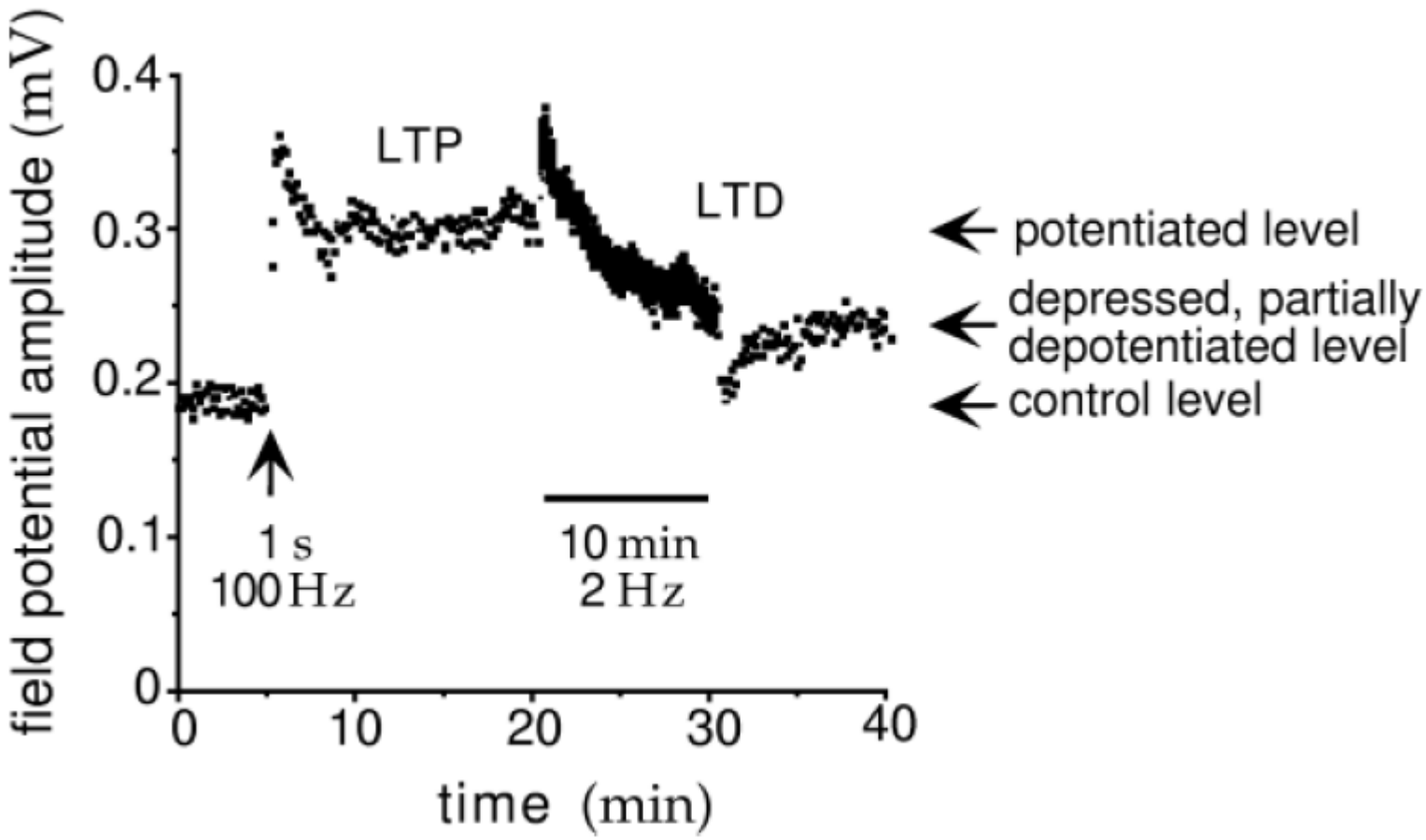
- Two main forms – long term potentiation and long term depression

- There are actually multiple forms of LTP and LTD, relying on distinct mechanisms and having different effects

- Synaptic changes depend on:

- synapse type (excitatory or inhibitory, brain region, etc.)
- stimulation protocol (high vs low frequency paired pulses)
- age of the animal/developmental stage
- many more…

Long Term Potentiation vs Long Term Depression



- Paired stimulation of pre- and post-synaptic neuron at 100 Hz strengthens synapse (LTP)
- Paired stimulation at 2 Hz weakens synapse (LTD)

AMPA and NMDA Receptors - Recap

- AMPA and NMDA are both excitatory receptors

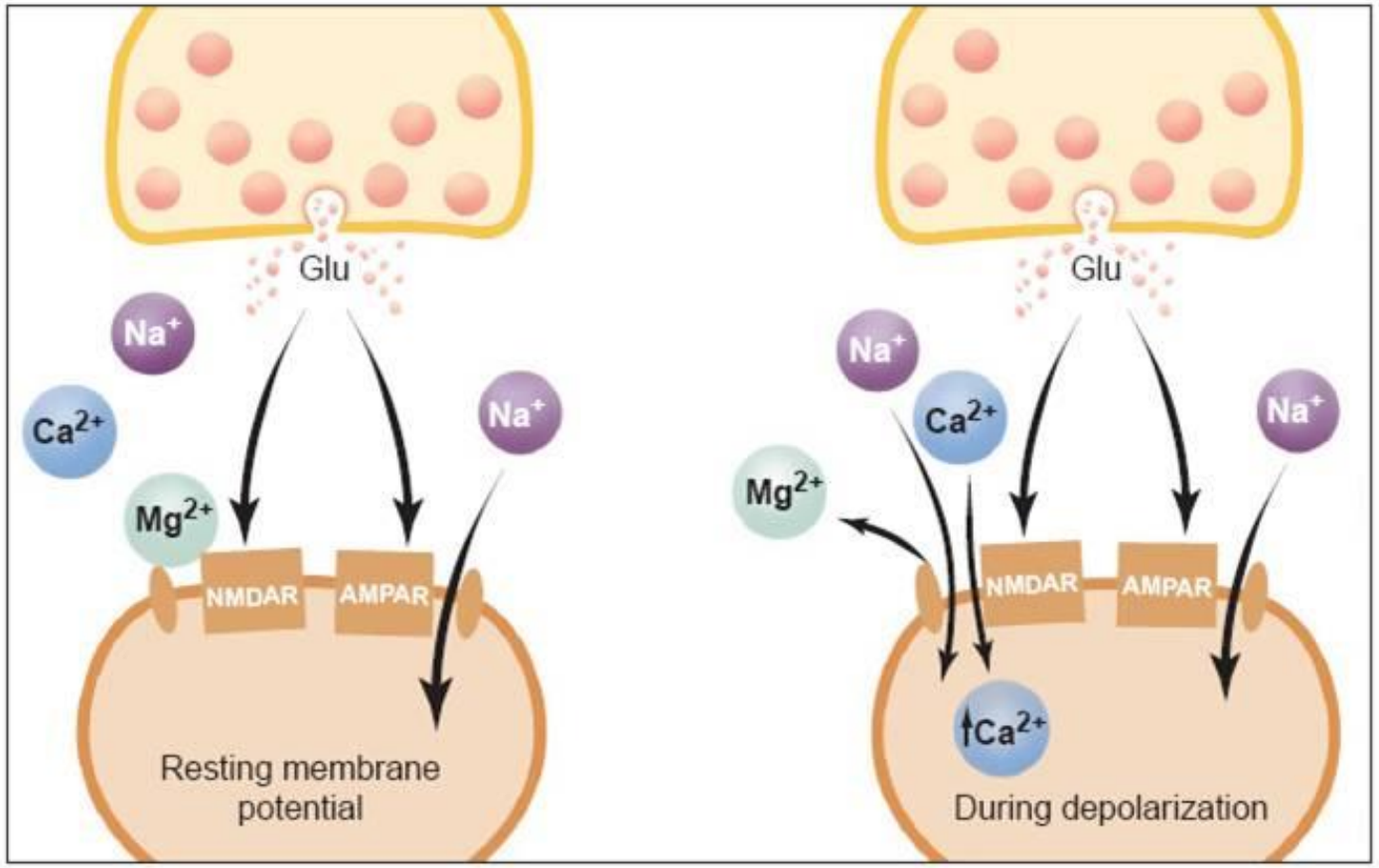
- They both open when glutamate binds to them

- But they are quite different in their properties

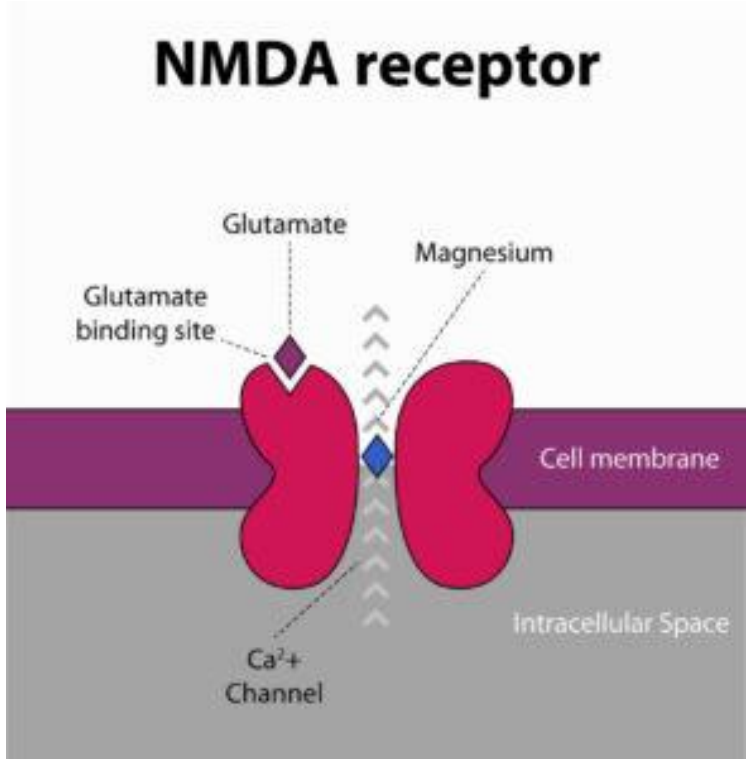
- AMPA are fast, NMDA are slow

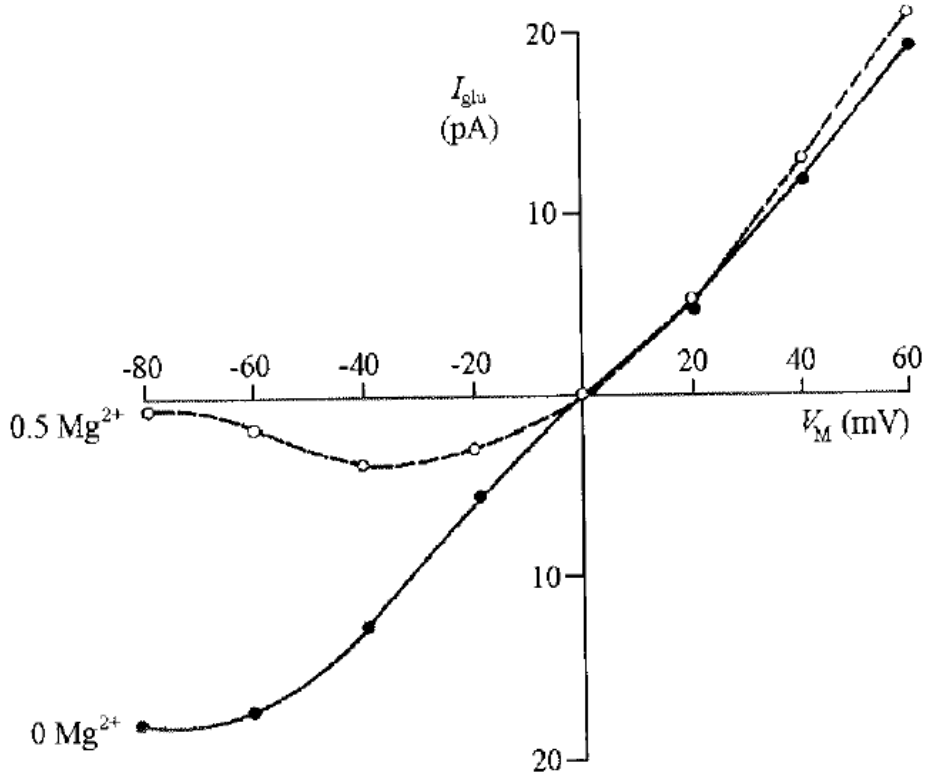
- NMDA lets calcium through, AMPDA doesn't

- AMPA opens whenever glutamate binds, NMDA requires depolarisation of post-synapse



NMDA Receptors

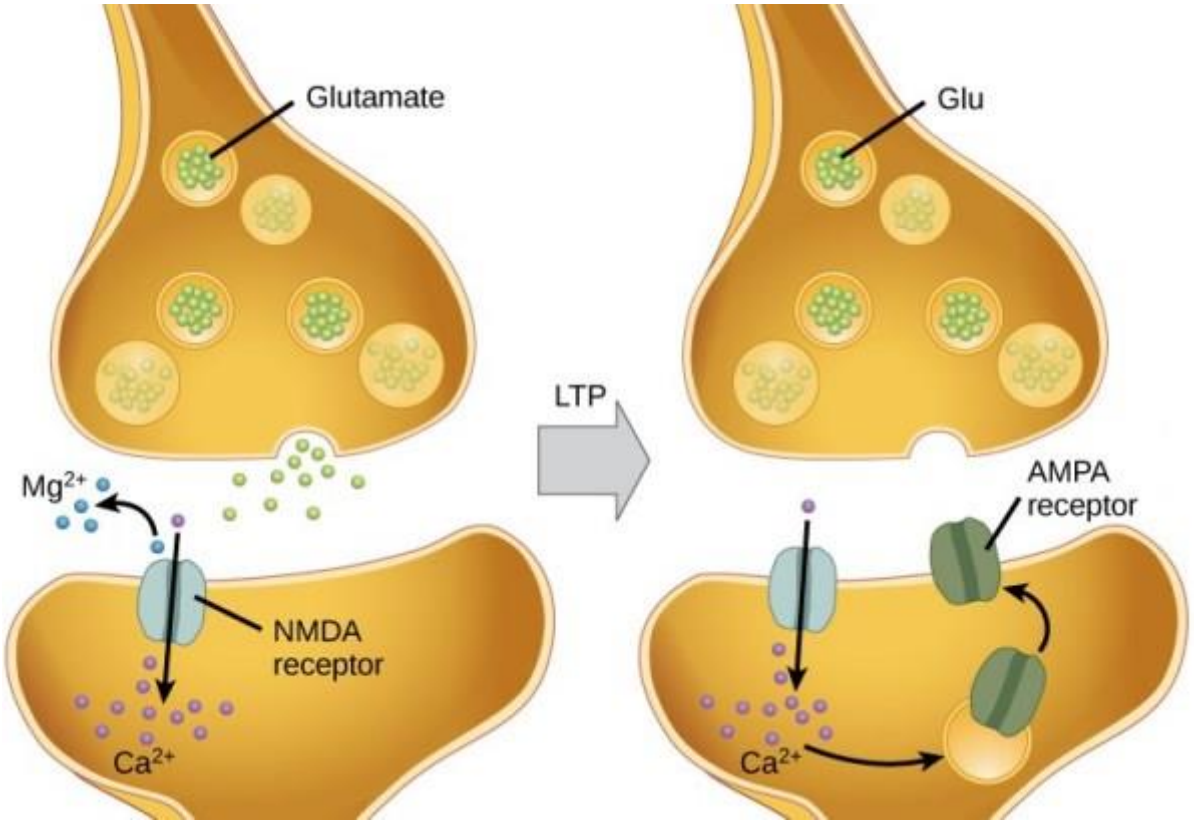




- NMDA receptors are blocked by magnesium unless the postsynaptic neuron is depolarised above resting potential – they only let current flow when both pre and post are simultaneously active!
- When open they let calcium flow in, which is a signal used by the cell for plasticity

Mechanisms of LTP

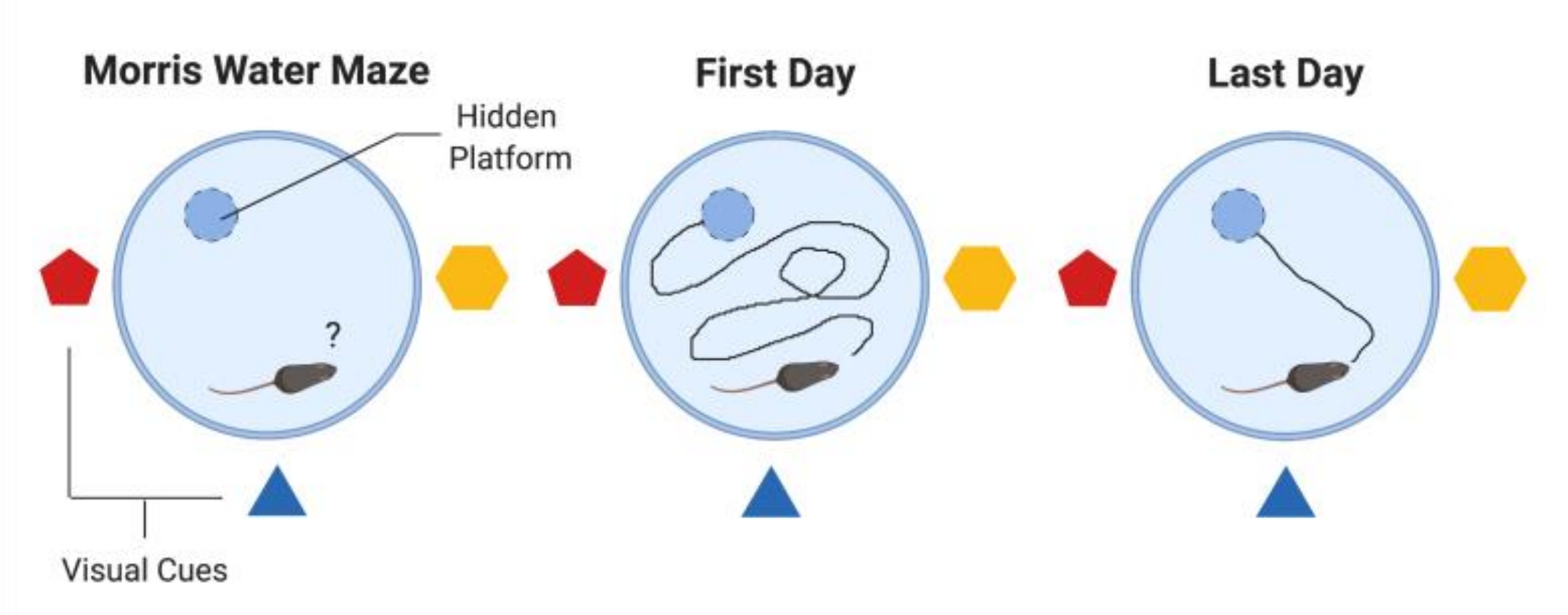
- Magnesium ion blocks the NMDA receptor, but is unblocked when the cell is depolarised
- AMPA only requires glutamate binding to open, causing depolarisation of the cell
- NMDA opening requires high-frequency firing of the presynaptic neuron (or input from other neurons/nearby synapses)
- When the postsynaptic neuron spikes, the voltage “backpropagates” from the soma down the dendrites, causing NMDA channels to open



Mechanisms of LTP

- LTP depends on NMDA receptor (usually - there are also other forms of LTP…)
- NMDA doesn't open unless glutamate binds and postsynaptic neuron is depolarised
- This makes it a coincidence detector, as required for Hebbian plasticity
- When NMDA opens, calcium flows into the postsynaptic cell
- Calcium then sets off a cascade of events, ultimately causing AMPA receptors to be inserted into the cell membrane (or new AMPA receptors to be created)
- Early vs late LTP – blocking protein synthesis ablates late but not early LTP

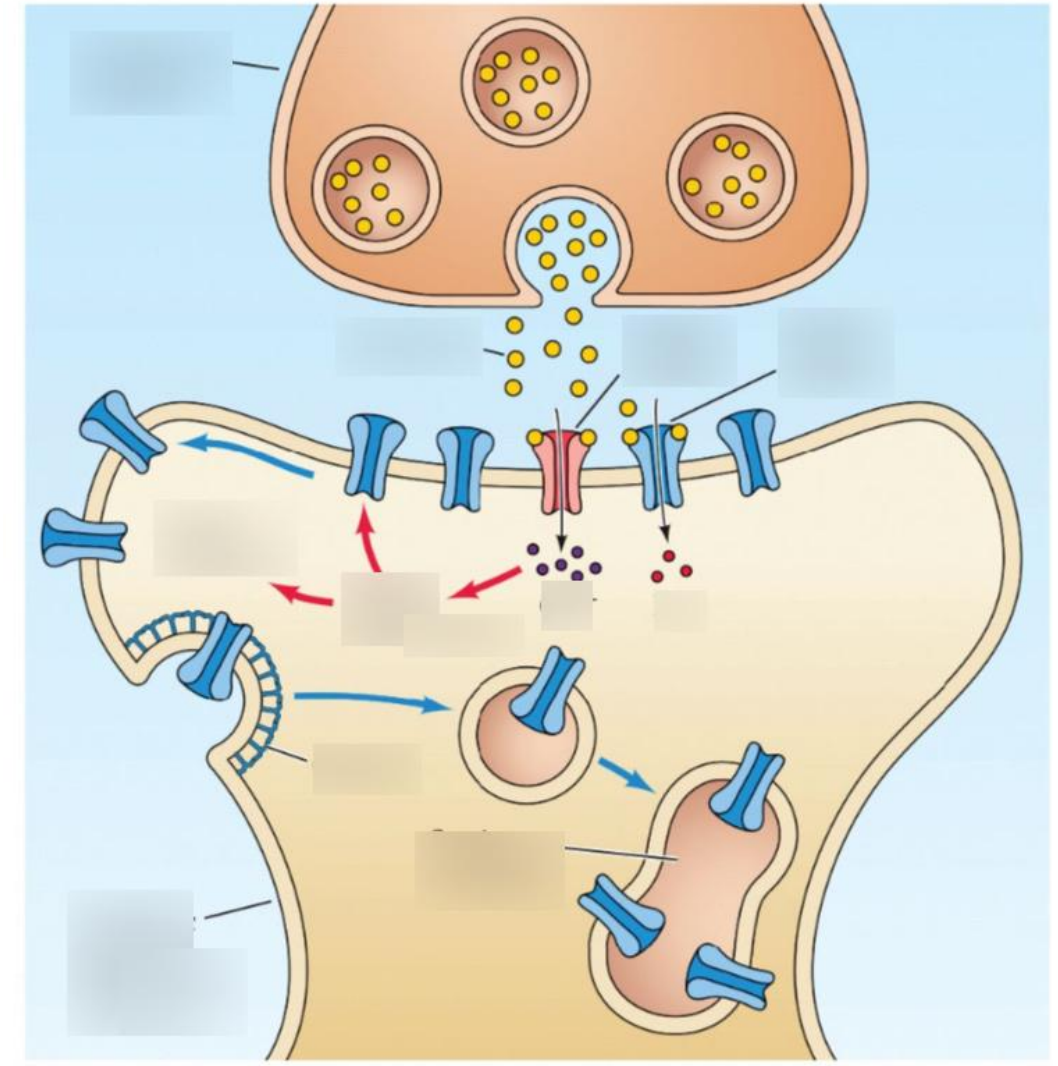
Role of LTP in Learning and Memory



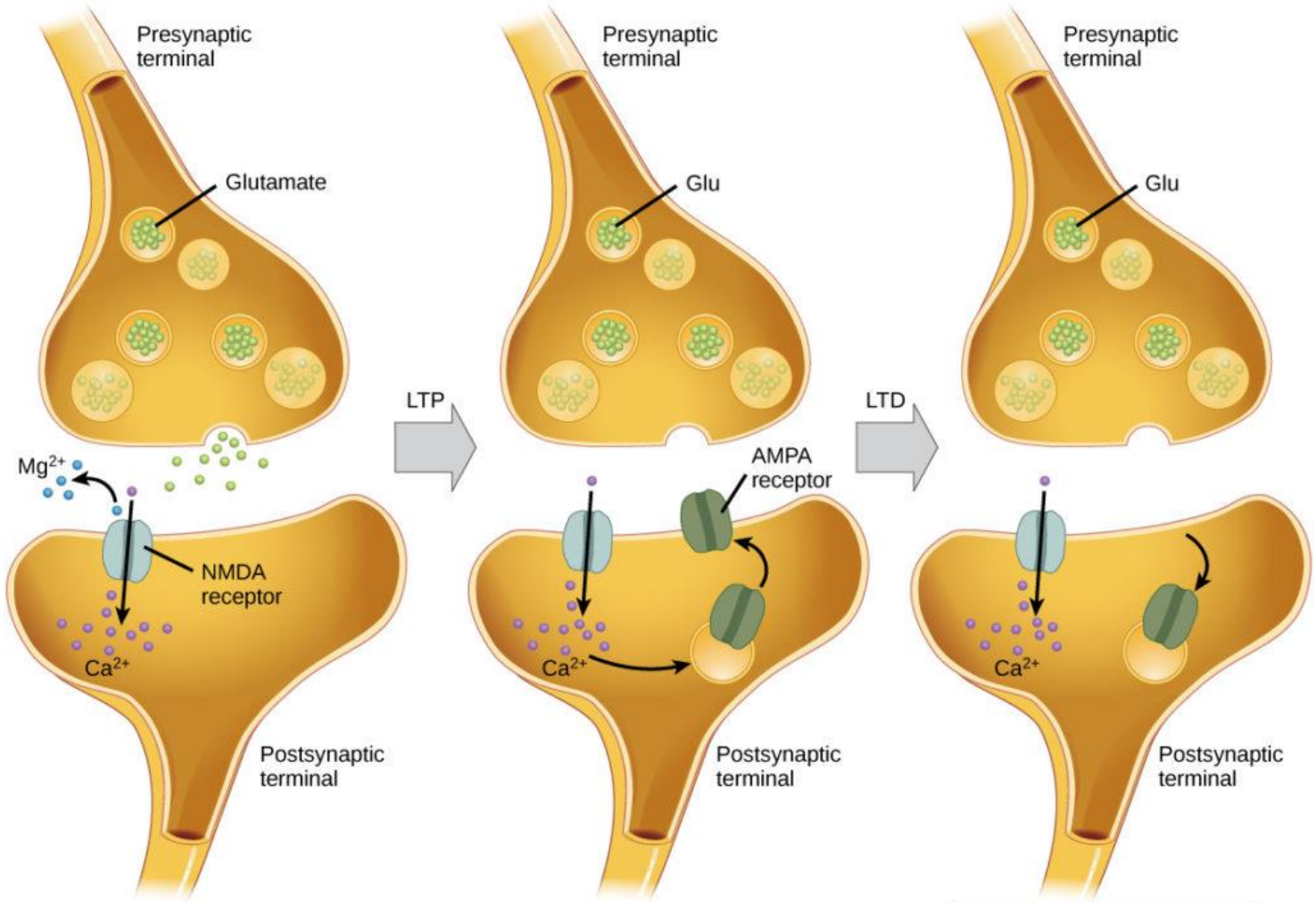
- Morris water maze is used to test for memory/learning
- Rat has to swim to hidden platform underwater, learns/remembers location of platform
- Blocking LTP interferes with rat's ability to learn the task/remember the platform location (Riedel et al., 1999)

Mechanisms of LTD

- Long term depression (LTD) typically occurs during low frequency stimulation
- Most NMDA receptors remain blocked, so calcium concentration in postsynaptic cell remains low
- Low calcium concentration causes a cascade of biochemical events, leading to removal of AMPA receptors from the cell membrane
- Thus, calcium concentration is extremely important for plasticity!



Mechanisms of LTD

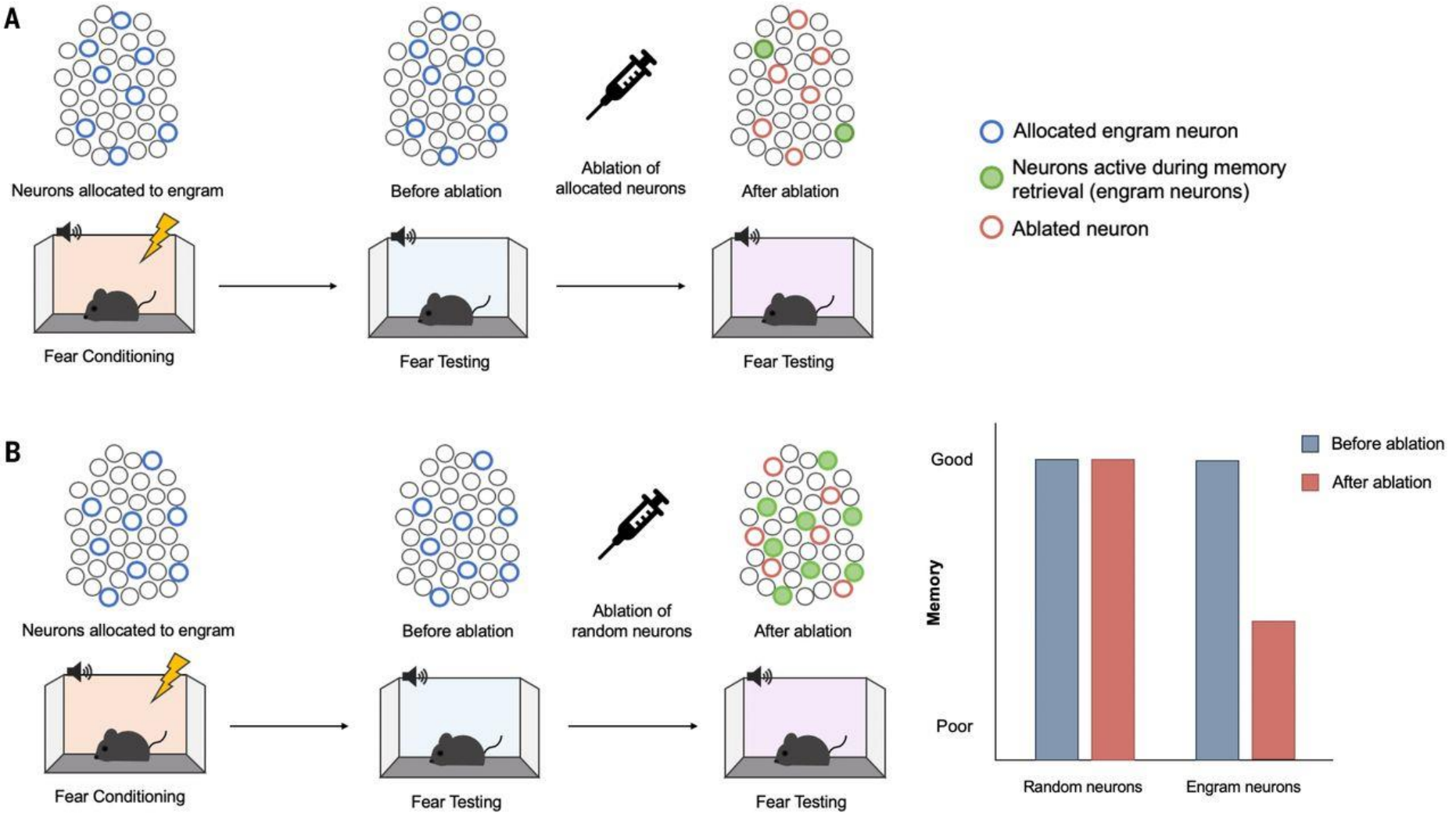


The NMDA receptor is activated by glutamate binding, but only after depolarization removes inhibitory Mg^{2+}. Once the Mg^{2+} is removed, Ca^{2+} can enter the cell.

Some AMPA receptors are present in the membrane initially. In response to an increase in intracellular $Ca2^{+}$, more are inserted.

Low-frequency stimulation results in a different Ca^{2+} -signaling cascade. AMPA receptor is removed from the membrane, and as a result, the nerve cell becomes less responsive to glutamate.

Reading and Writing Memories in Neural Circuits



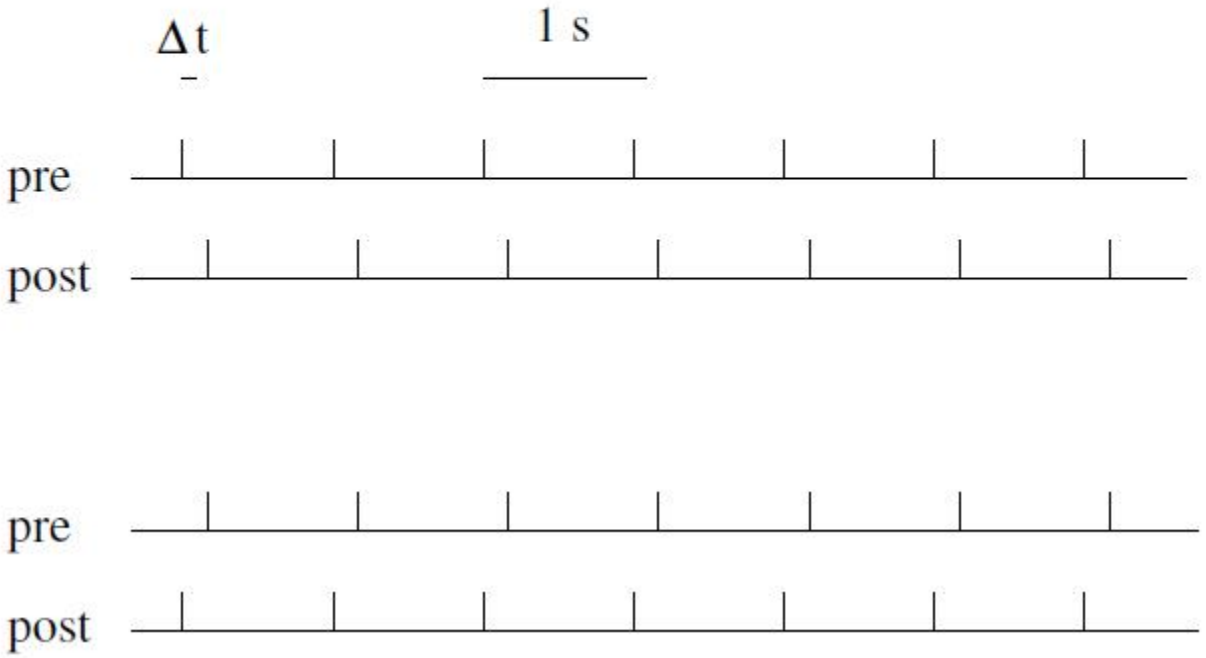
- It is possible to create or destroy memories by imprinting or ablating patterns of synaptic connections

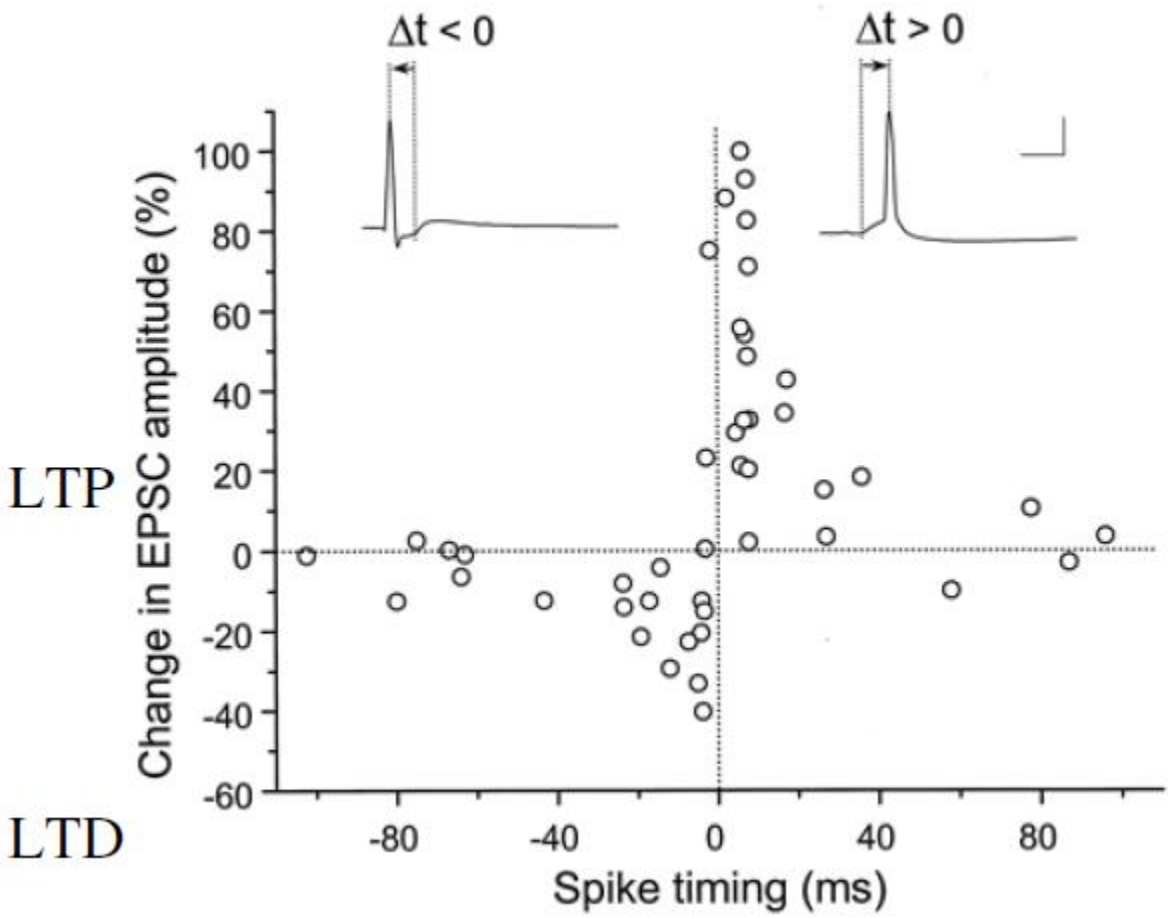
Josselyn and Tonegawa (2020)

Summary: LTP and LTD

- LTP and LTD are long term changes in the strength of a synapse
- Depends on NMDA receptor to activate, and AMPA receptor to express
- A short induction protocol can induce changes that last months (or a lifetime)
- Thought to underlie learning and memory
- There are multiple forms of LTP/LTD, and their role in learning and memory is not well understood

Spike Time Dependent Plasticity

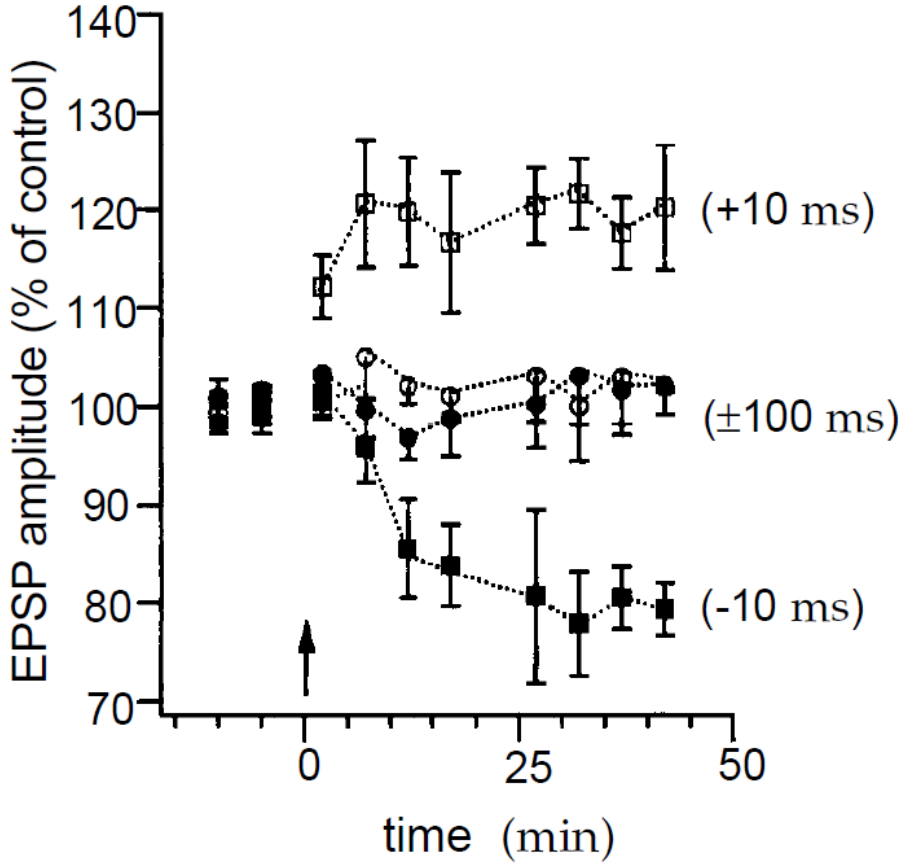




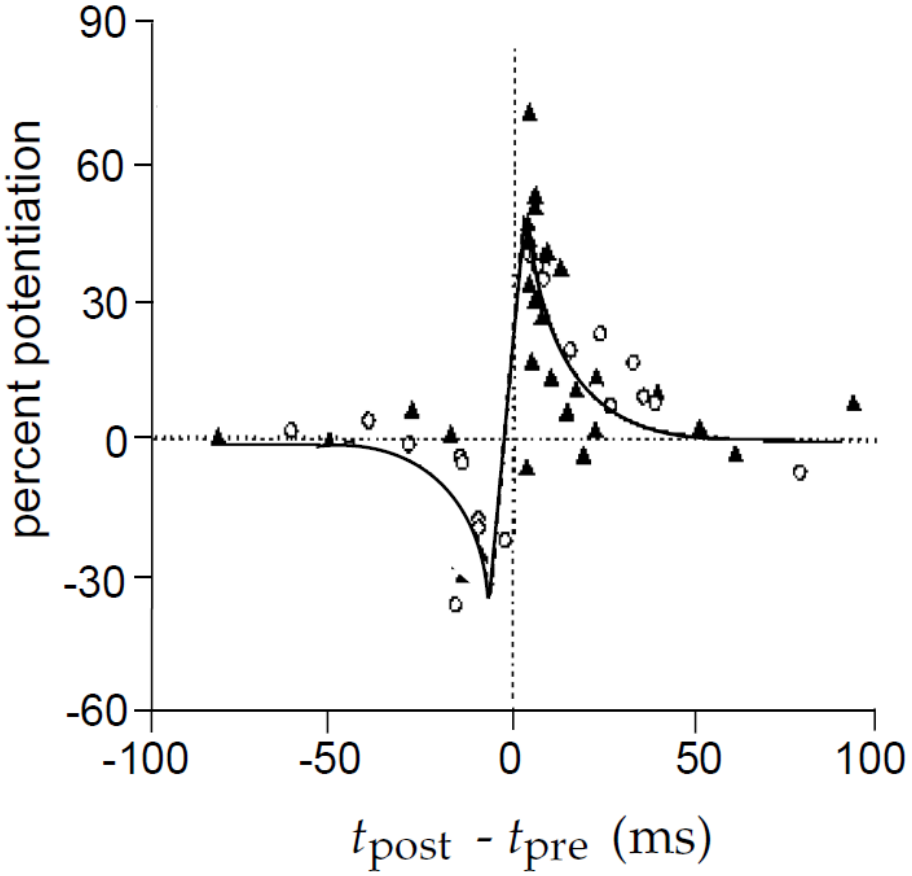
- Potentiation or depression of synapse also depends on timing of pre and post spikes

Spike Time Dependent Plasticity

Synaptic weight changes for different spike timings



STDP curve
(weight change vs spike timing)



Spike Time Dependent Plasticity

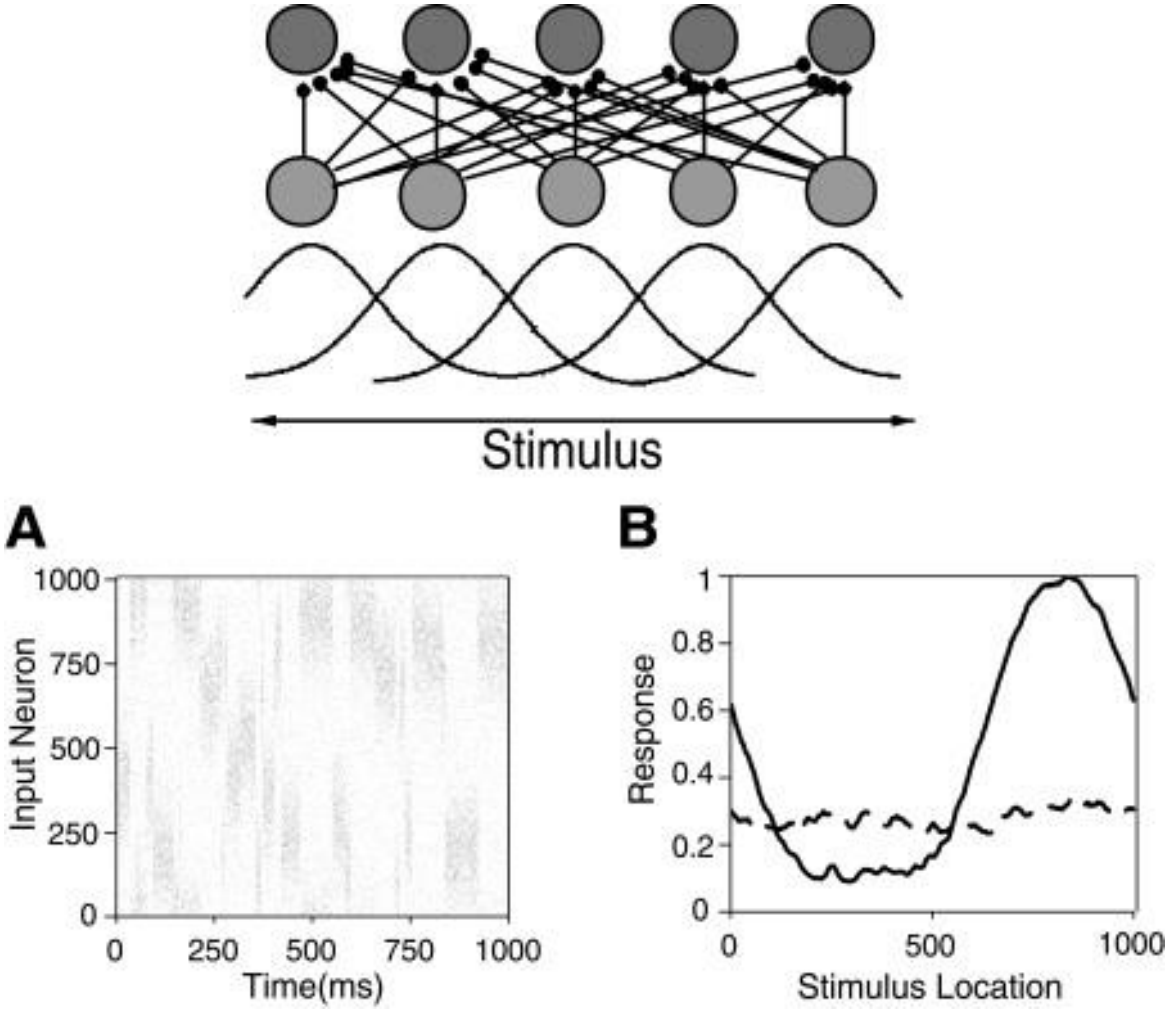
- STDP is more causal in nature – potentiation requires pre before post
- Strongly Hebbian in flavour ("when cell A causes cell B to fire…")
- Causes synapse to learn temporal correlations in spike patterns
- Can model weight updates using a simple equation:

$$\begin{aligned} \Delta w_{ij} &= A_+ \exp(-|t_i - t_j|/\tau_+) \quad (\text{if } t_i < t_j) \\ &= A_- \exp(-|t_i - t_j|/\tau_-) \quad (\text{if } t_j < t_i) \end{aligned}$$

- Or, can try to come up with a more biophysical model (dependence on voltage, calcium, etc.)

Learning via STDP

- Feedforward network with two layers, input and output layer
- Input layer has orientation tuning curves, firings with Poisson rate with randomly moving stimulus orientation (panel A)
- STDP causes output layer to learn orientation tuning curves (dashed before learning, solid after)

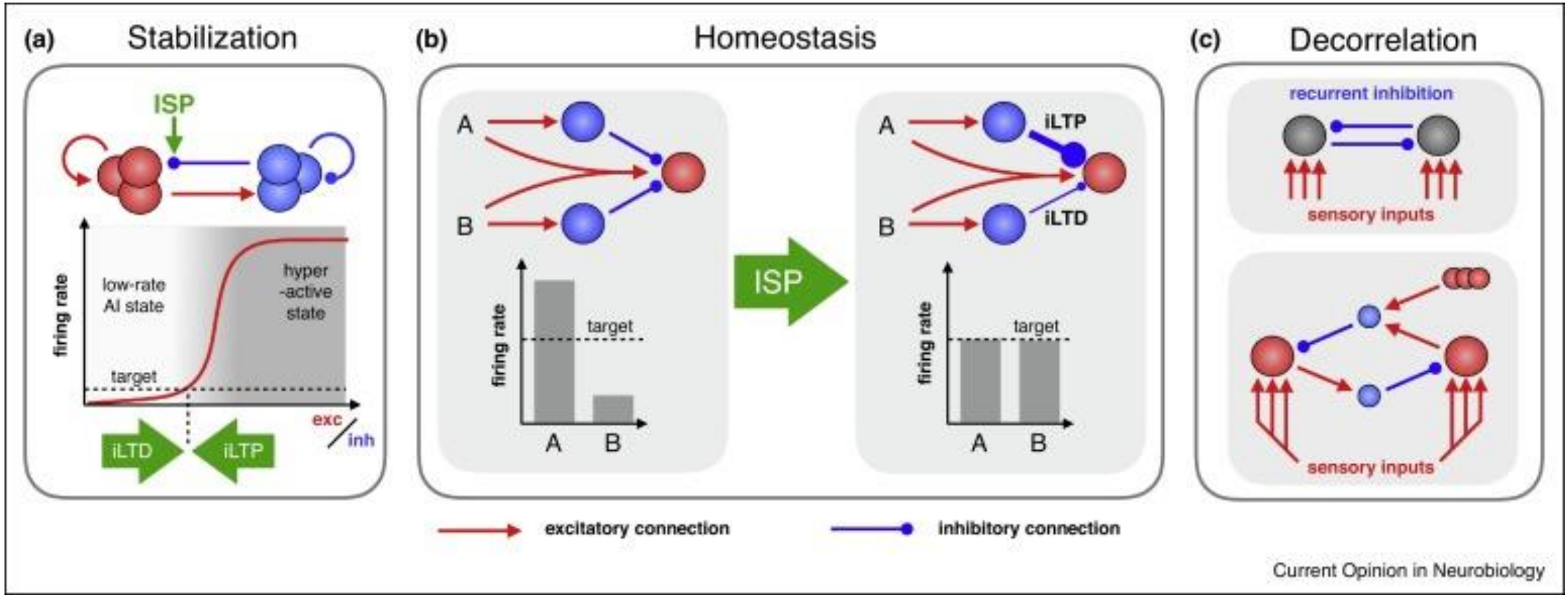


Song and Abbott (2001)

Inhibitory Plasticity

- So far we have only discussed excitatory plasticity (involving AMPA and NMDA receptors)
- What about inhibitory synapses (involving GABA)?
- This has only recently been studied – inhibitory plasticity seems to be very important in the brain
- Inhibitory synapses change their strength in an activity-dependent manner
- There is much theoretical work on the subject but not much experimental knowledge of inhibitory plasticity rules

Functional Roles of Inhibitory Plasticity



Sprekeler (2017)

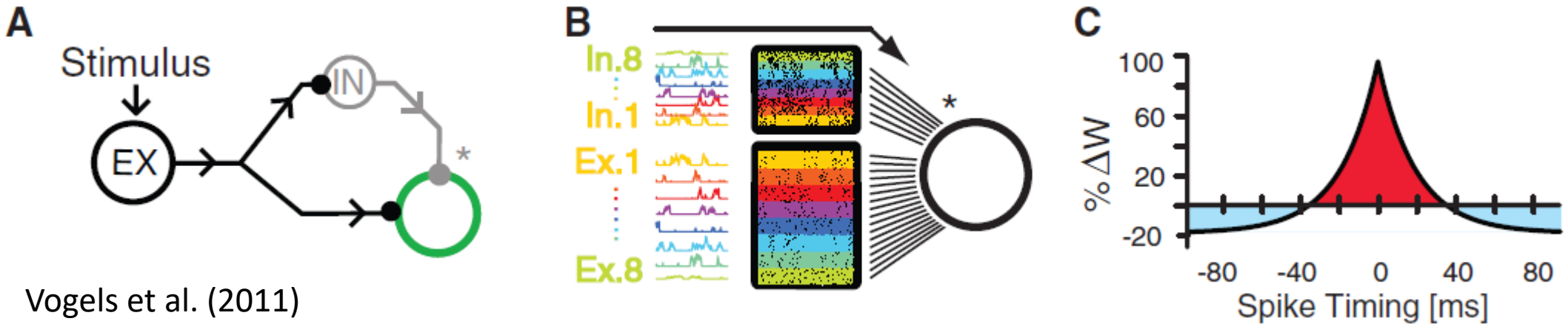
Inhibitory Plasticity and E-I Balance

Inhibitory Plasticity Balances Excitation and Inhibition in Sensory Pathways and Memory Networks

T. P. Vogels,[1]*† H. Sprekeler,[1]* F. Zenke,[1] C. Clopath,[1,2] W. Gerstner[1]

Cortical neurons receive balanced excitatory and inhibitory synaptic currents. Such a balance could be established and maintained in an experience-dependent manner by synaptic plasticity at inhibitory synapses. We show that this mechanism provides an explanation for the sparse firing patterns observed in response to natural stimuli and fits well with a recently observed interaction of excitatory and inhibitory receptive field plasticity. The introduction of inhibitory plasticity in suitable recurrent networks provides a homeostatic mechanism that leads to asynchronous irregular network states. Further, it can accommodate synaptic memories with activity patterns that become indiscernible from the background state but can be reactivated by external stimuli. Our results suggest an essential role of inhibitory plasticity in the formation and maintenance of functional cortical circuitry.

Inhibitory Plasticity and E-I Balance



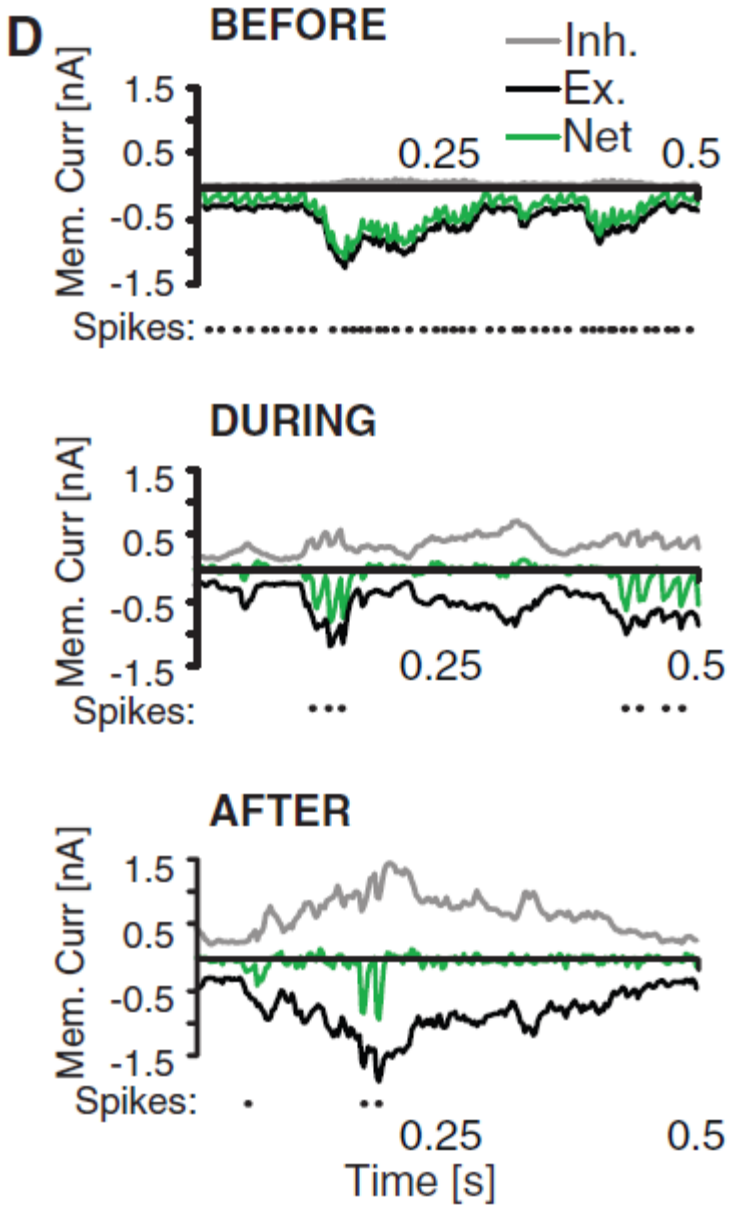
Vogels et al. (2011)

- A model of inhibitory plasticity – a neuron receives feedforward input from a stimulus via both excitatory and inhibitory synapses
- There can be many stimuli, each represented by a different set of synapses (colours in B)
- Inhibitory STDP is assumed to be a symmetric function of the spike times

Inhibitory Plasticity and E-I Balance

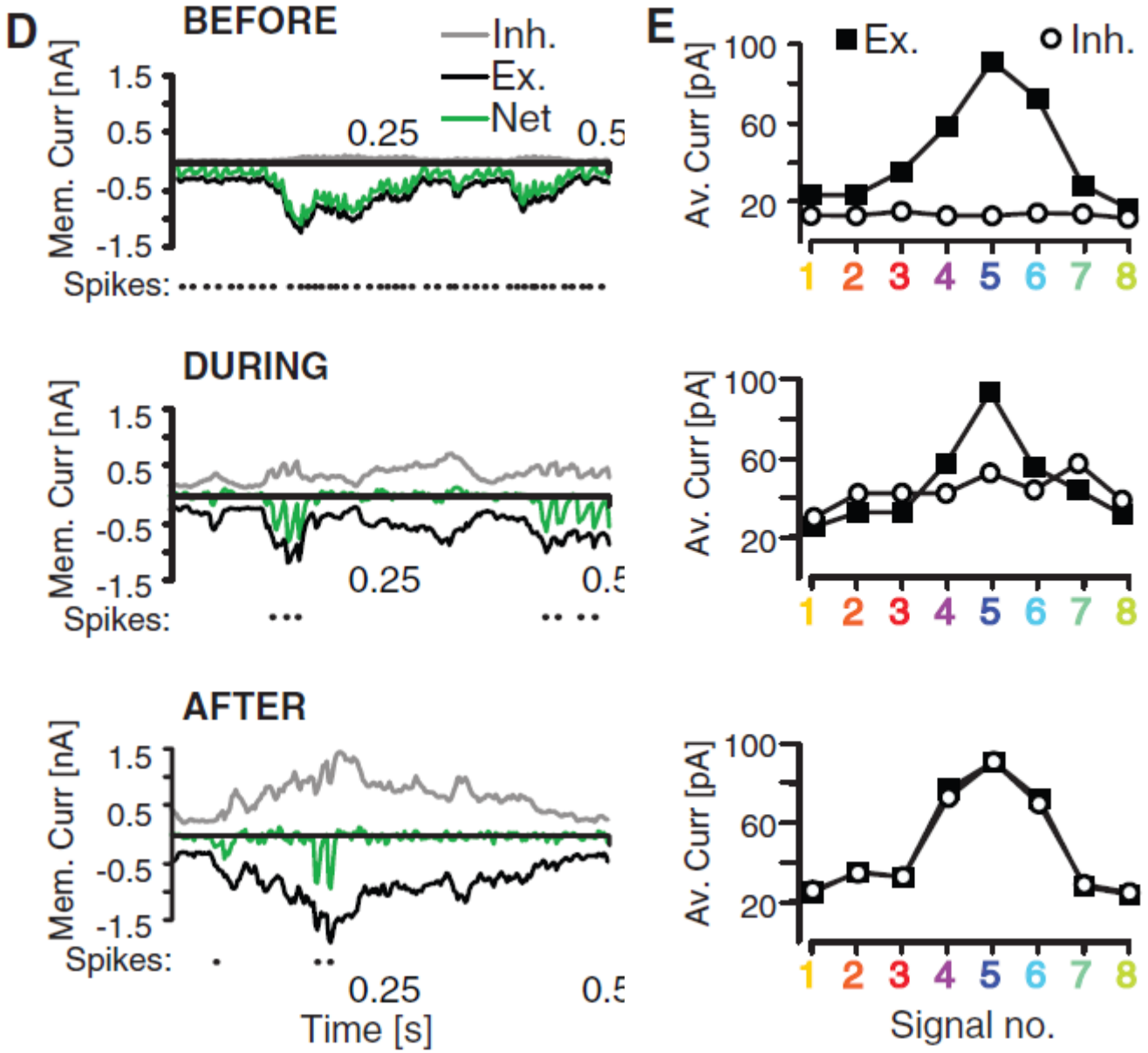
- Inhibitory plasticity causes excitatory and inhibitory synaptic input to be tightly balanced in time (D)

- Causes spiking to become sparse and asynchronous

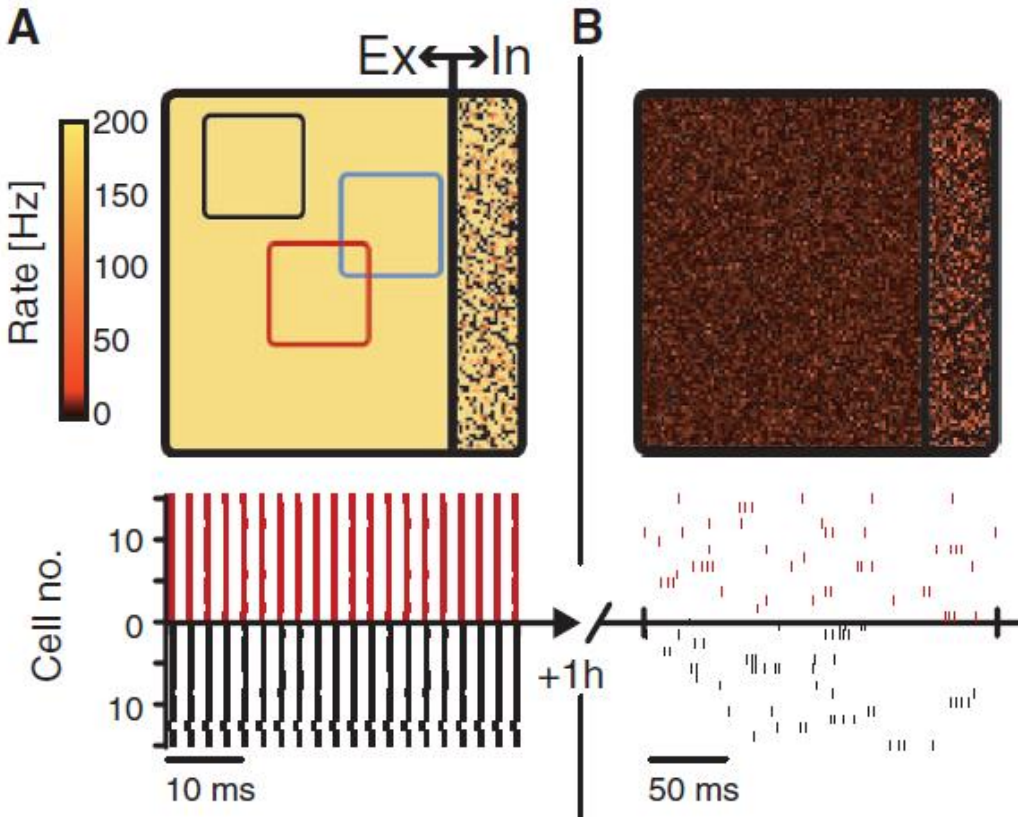


Inhibitory Plasticity and E-I Balance

- Inhibitory plasticity causes excitatory and inhibitory synaptic input to be tightly balanced in time (D)
- Causes spiking to become sparse and asynchronous
- Also causes excitatory-inhibitory balance across stimuli (E)



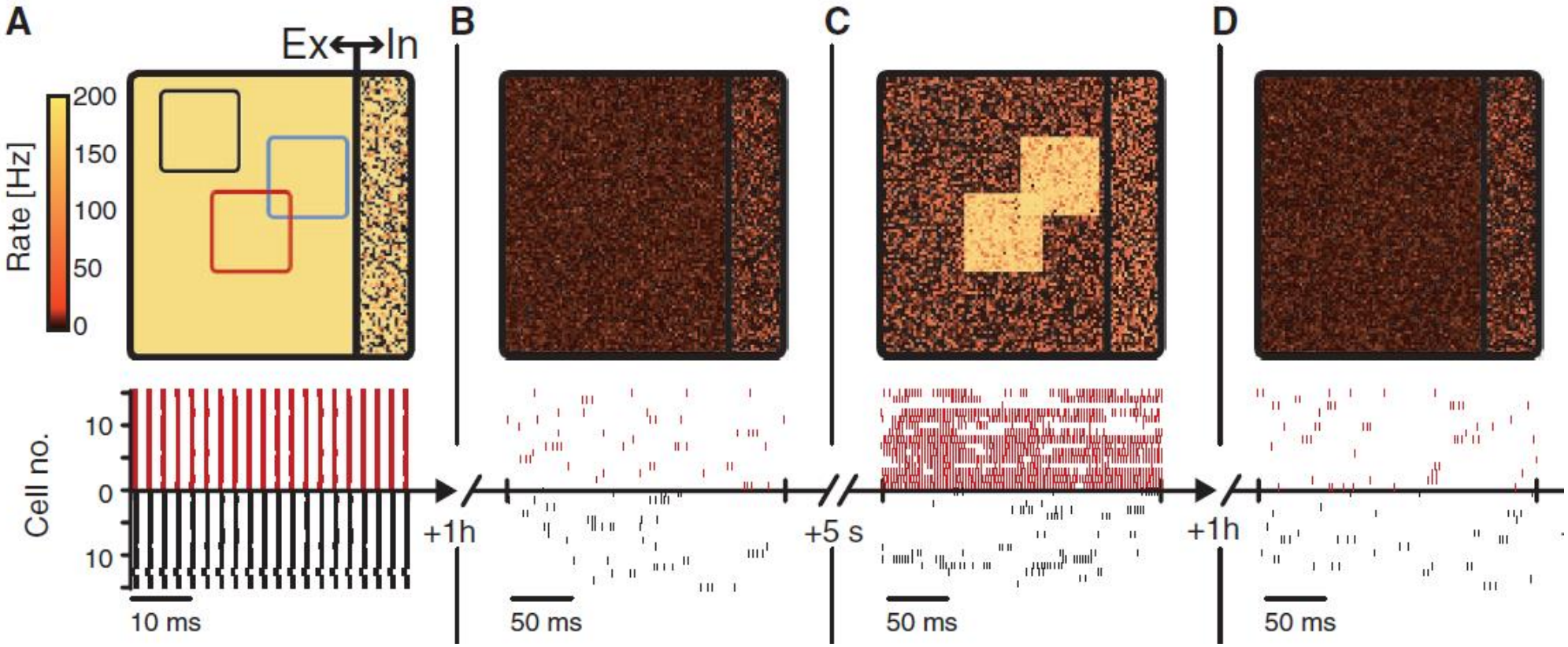
Inhibitory Plasticity in a Recurrent Network



Vogels et al. (2011)

- Inhibitory plasticity causes activity to enter asynchronous irregular regime (A->B)

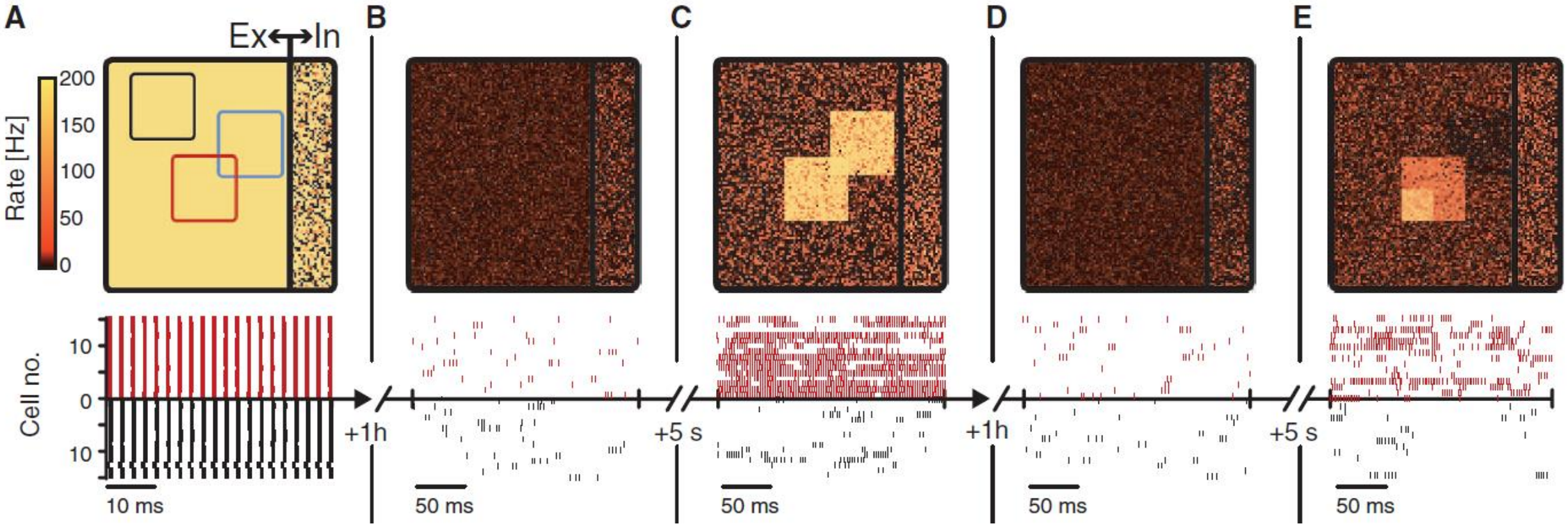
Inhibitory Plasticity in a Recurrent Network



Vogels et al. (2011)

- Inhibitory plasticity causes activity to enter asynchronous irregular regime (A->B)
- When a memory is imprinted in excitatory weights, inhibitory weights mask it (C->D)

Inhibitory Plasticity in a Recurrent Network



Vogels et al. (2011)

- Inhibitory plasticity causes activity to enter asynchronous irregular regime (A->B)
- When a memory is imprinted in excitatory weights, inhibitory weights mask it (C->D)
- But the memory can still be retrieved by activating a subset of the memory cells (E)

Anti-Memories

Researchers believe they've discovered 'anti-memories'

They could work to maintain your brain's delicate electrical balance.

A. Tarantola
@terrortola
March 31, 2016
8:56 PM

In this article: medicine, memory, neuron, neuroscience, oxford, science

According to new research out of Oxford University, and published in the journal *Neuron*, a team of scientists believe that they've found the neurological equivalent of anti-matter. Just as anti-matter acts as the mirror image of subatomic particles, these "anti-memories" may exist as the bizarro versions of our memories.

Anti-Memories

Unmasking Latent Inhibitory Connections in Human Cortex to Reveal Dormant Cortical Memories

H.C. Barron,[1,2,*] T.P. Vogels,[3] U.E. Emir,[2] T.R. Makin,[2] J. O'Shea,[2] S. Clare,[2] S. Jbabdi,[2] R.J. Dolan,[1] and T.E.J. Behrens[1,2,*]
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http://dx.doi.org/10.1016/j.neuron.2016.02.031

- Humans learned associations, and an fMRI signal was observed that decayed over time, just like in the inhibitory STDP model
- Applied transcranial current stimulation to humans (thought to influence GABA)
- Stored memories were "unmasked"
- Evidence for storage of memories in balanced E-I subnetworks

Summary: Inhibitory Plasticity

- Inhibitory plasticity typically involves strengthening of inhibitory weights to balance increases in excitation
- Can help to establish balanced E-I networks with asynchronous spiking activity
- Theories show how it can be used to stabilise increases in excitation caused by learning/memory formation
- Much of this work is theoretical/speculative – it is hard to get firm experimental data on inhibitory plasticity in the brain

Summary of Synaptic Plasticity

- Many types of plasticity and adaptation, including both intrinsic and synaptic plasticity
- Short and long term plasticity, facilitation/potentiation and depression
- Excitatory and inhibitory plasticity
- Spike time dependent plasticity
- Next time: functional models of plasticity and learning

Bibliography

- Lecture notes Ch. 4, 12, 13
- Dayan and Abbott Ch. 9
- Song and Abbott (2001)
- Vogels et al. (2011)
- Barron et al. (2016)