# Co-dependent excitatory and inhibitory plasticity accounts for quick, stable and long-lasting memories in biological networks

**Authors**: Agnes, E. J. and Vogels, T. P.

Speaker: Ziyuan Ye

Monday, November 18, 2024

Agnes, E. J., & Vogels, T. P. (2024). Co-dependent excitatory and inhibitory plasticity accounts for quick, stable and long-lasting memories in biological networks. *Nature Neuroscience*, *27*(5), 964-974.

# Overview

1. Background
2. Motivation
3. Method
4. Results
5. Take-away Message

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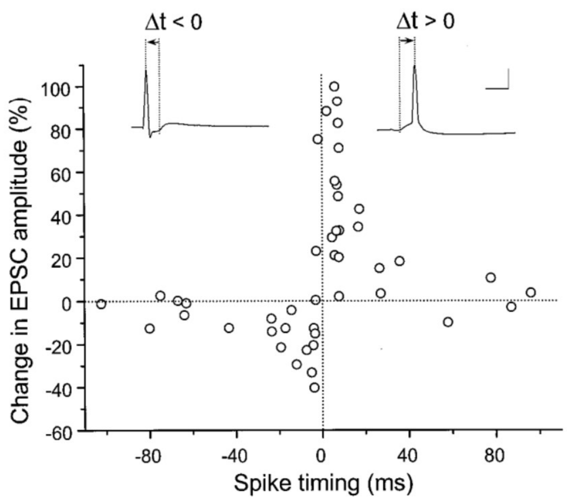
# Background

**Hebbian Learning**: Firing together, wiring together

**STDP rule**: Excitatory neurons

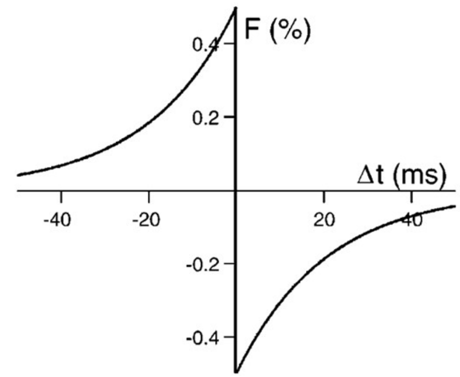
Δt=post-pre




Bi, G. Q., & Poo, M. M. (1998).

Experiments

Δt=pre-post




$$F(\Delta t) = \begin{cases} A_+ \exp(\Delta t/\tau_+) & \text{if } \Delta t < 0 \\ -A_- \exp(-\Delta t/\tau_-) & \text{if } \Delta t \geq 0 \end{cases}$$

Song, S., Miller, K. D., & Abbott, L. F. (2000).

Computation model

EPSC: Excitatory Postsynaptic Current

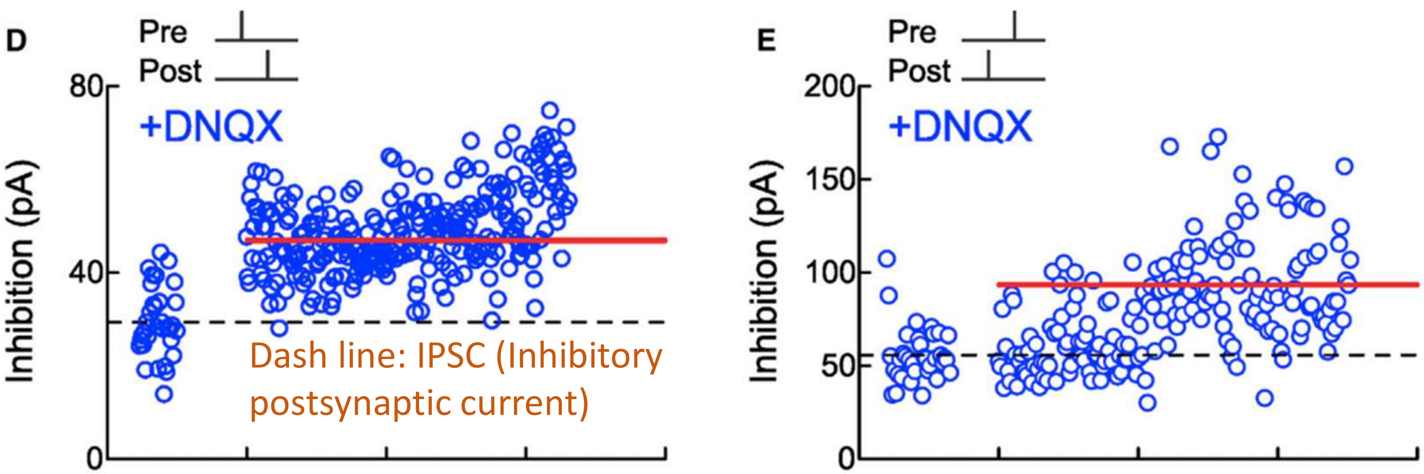

Bi, G. Q., & Poo, M. M. (1998). Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *Journal of neuroscience*, 18(24), 10464-10472.

Song, S., Miller, K. D., & Abbott, L. F. (2000). Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nature neuroscience, 3(9), 919-926.

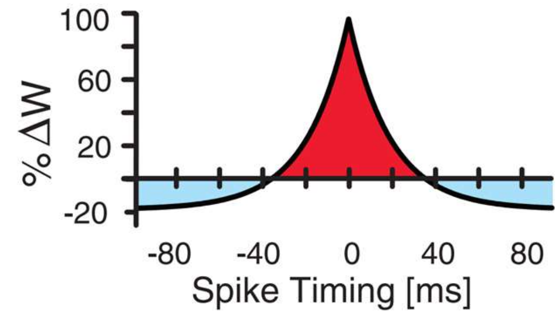
# Background

**Hebbian Learning**: Firing together, wiring together

**STDP rule**: Inhibitory neurons




D'amour, J. A., & Froemke, R. C. (2015).
Experiments



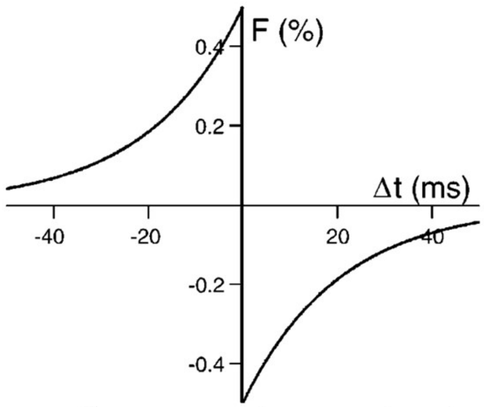

Vogels, T. P. et. al. (2011)
Computation model

The inhibitory STDP rule is in contrast to excitatory one, which displayed an asymmetrical STDP time window.

D'amour, J. A., & Froemke, R. C. (2015). Inhibitory and excitatory spike-timing-dependent plasticity in the auditory cortex. Neuron, 86(2), 514-528.
Vogels, T. P., Sprekeler, H., Zenke, F., Clopath, C., & Gerstner, W. (2011). Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. Science, 334(6062), 1569-1573.

# Background

**STDP rule**




$$F(\Delta t) = \begin{cases} A_+ \exp(\Delta t/\tau_+) & \text{if } \Delta t < 0 \\ -A_- \exp(-\Delta t/\tau_-) & \text{if } \Delta t \geq 0 \end{cases}$$

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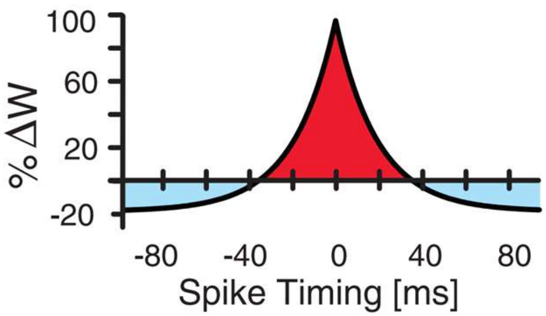


Vogels, T. P. et. al. (2011)

**Synaptic plasticity**: synapses change based solely on the activity of their **presynaptic** and **postsynaptic** counterpart (synapse-specific process)

Song, S., Miller, K. D., & Abbott, L. F. (2000). Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nature neuroscience, 3(9), 919-926.

Vogels, T. P., Sprekeler, H., Zenke, F., Clopath, C., & Gerstner, W. (2011). Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. Science, 334(6062), 1569-1573.

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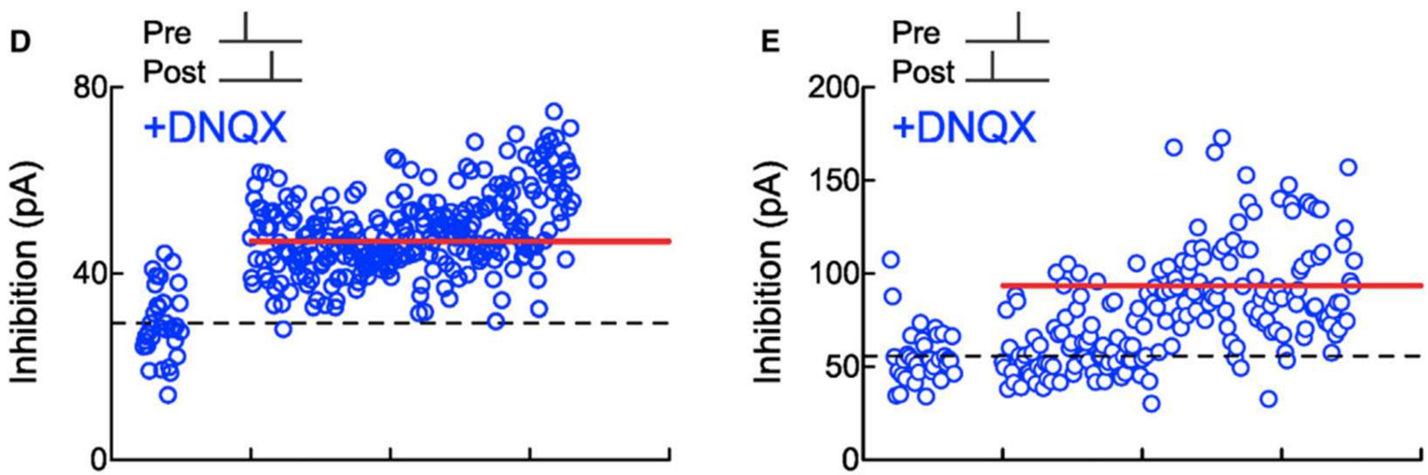
# Motivation

**Is synaptic plasticity rule a <u>synapse-specific process</u>?**




D'amour, J. A., & Froemke, R. C. (2015).

Experiments

D'amour, J. A., & Froemke, R. C. (2015). Inhibitory and excitatory spike-timing-dependent plasticity in the auditory cortex. Neuron, 86(2), 514-528.

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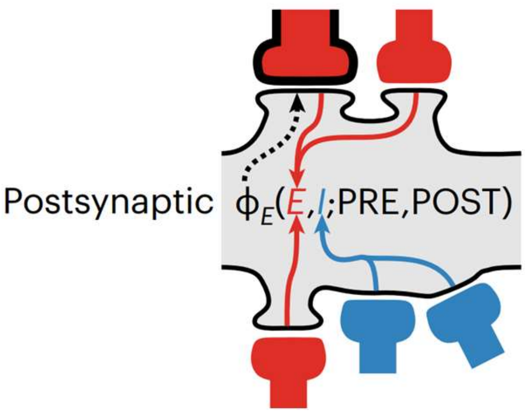
# Methods

Co-dependent excitatory plasticity




$$\Delta w_E = \phi_E(E, I; PRE, POST)$$

$$= [A_{LTP}\,(PRE_{LTP})\,(POST_{spike})\,E \quad \text{LTP (pre-before-post)}$$

$$-A_{het}\,(POST_{het})\,(POST_{spike})\,E^2 \quad \text{heterosynaptic}$$

$$-A_{LTD}\,(POST_{LTD})\,(PRE_{spike})\,w_E] \quad \text{LTD (post-before-pre)}$$

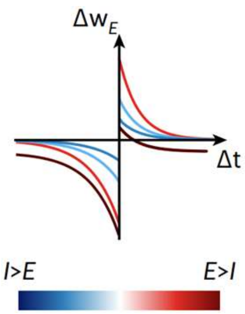
$$\times \exp\left[-\left(\frac{I}{I^*}\right)^{\gamma}\right] \quad \text{inhibitory control,}$$

$PRE_{LTP}, POST_{het}, POST_{LTD}$: eligibility trace (firing rate estimates)

$A_{LTP}$, $A_{het}$, $A_{LTD}$: learning rate (strictly positive)

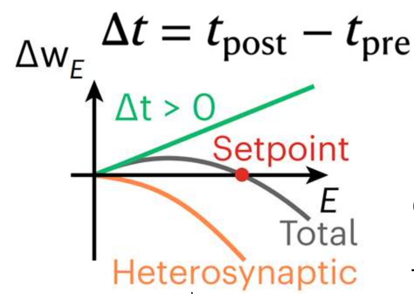
$PRE_{spike}, POST_{spike}$: firing time

$$\frac{dy_{post}(t)}{dt} = -\frac{y_{post}(t)}{\tau_{iSTDP}} + S_{post}(t)$$




Post-pre>0 → excitation

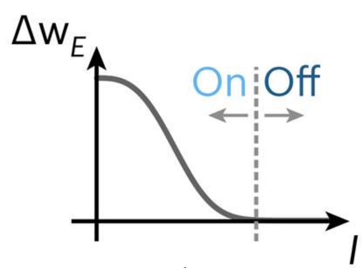
Post-pre<0 → inhibition




**Experimentally evidence**: heterosynaptic weakening of excitatory synapses <u>neighboring other synapses undergoing LTP</u>

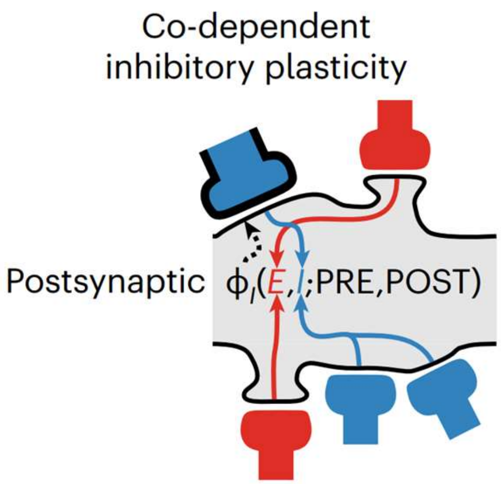
Excitatory input, E, controls:

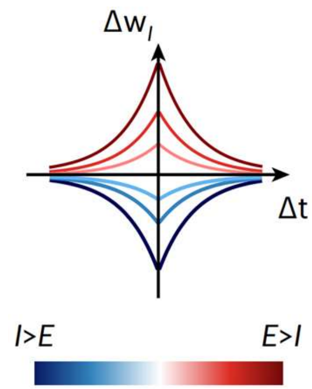
1. Hebbian LTP
2. Heterosynaptic plasticity




Inhibitory inputs, I, gate excitatory plasticity

# Methods

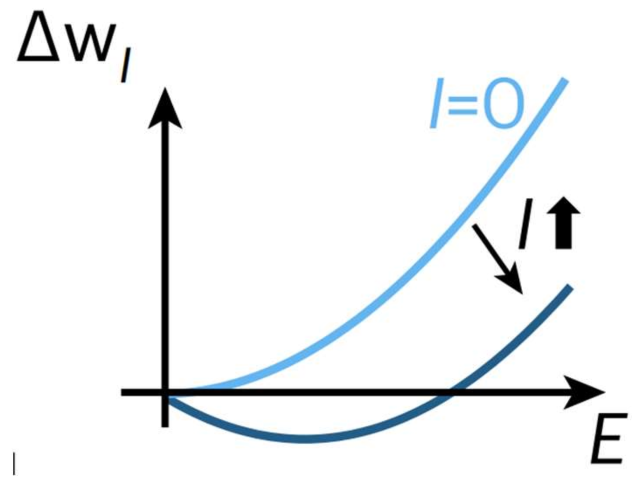


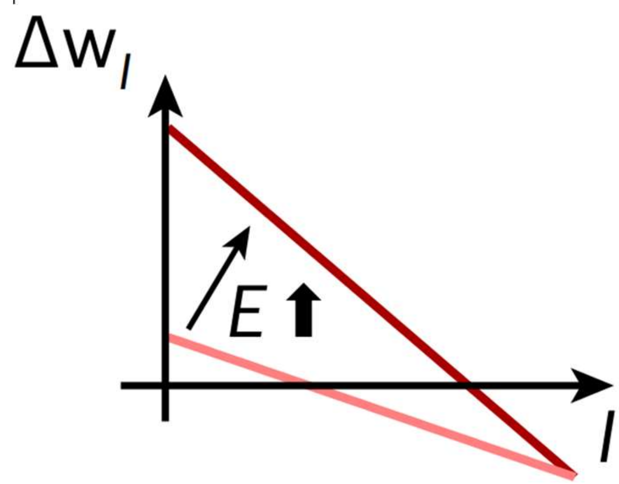




I>E→ inhibitory
E>I→ excitation

$$\Delta w_I = \phi_I(E, I; PRE, POST)$$
$$= A_{ISP} E (E - \alpha I) \quad \text{codependency}$$
$$\times [(PRE_{inh})(POST_{spike}) \quad \text{pre-before-post}$$
$$+ (POST_{inh})(PRE_{spike})] \quad \text{post-before-pre,}$$

$PRE_{inh}, POST_{inh}$ : eligibility trace (firing rate estimates)
$A_{ISP}$: learning rate (strictly positive)
$PRE_{spike}, POST_{spike}$: firing time



# Methods

**Consider influence of distance between synapses**

$$f^{\mathrm{E}}_{\Delta x}(i,j) = \exp\left[-\frac{1}{2}\left(\frac{\Delta x(i,j)}{\sigma}\right)^2\right]\left\{\frac{1}{N_{\mathrm{E}}}\sum_{k\in E}\exp\left[-\frac{1}{2}\left(\frac{\Delta x(i,k)}{\sigma}\right)^2\right]\right\}^{-1}$$

**i**: Undergoing synapse
**j**: Neighboring synapse

$\boldsymbol{N_E}$: number of excitatory synapse

$$\sum_{i\in E} E_i(t) = \sum_{i\in E}\sum_{j\in E}\tilde{E}_j(t)\exp\left[-\frac{1}{2}\left(\frac{\Delta x(i,j)}{\sigma}\right)^2\right]\left\{\frac{1}{N_{\mathrm{E}}}\sum_{k\in E}\exp\left[-\frac{1}{2}\left(\frac{\Delta x(i,k)}{\sigma}\right)^2\right]\right\}^{-1}$$

$$= \sum_{j\in E}\tilde{E}_j(t)\sum_{i\in E}\exp\left[-\frac{1}{2}\left(\frac{\Delta x(i,j)}{\sigma}\right)^2\right]\left\{\frac{1}{N_{\mathrm{E}}}\sum_{k\in E}\exp\left[-\frac{1}{2}\left(\frac{\Delta x(i,k)}{\sigma}\right)^2\right]\right\}^{-1}$$

$$\approx N_{\mathrm{E}}\sum_{j\in E}\tilde{E}_j(t), \text{ for } N_{\mathrm{E}} \gg 1.$$

Synapse-specific filtered **NMDA** **current**

$$\tau_{\mathrm{E}}\frac{d\tilde{E}_j(t)}{dt} = -\tilde{E}_j(t) - g_{\mathrm{NMDA},j}(t)H_{\mathrm{NMDA}}(u(t))\,[u(t) - E_{\mathrm{NMDA}}]$$

**Excitatory input, E**

$$E_j(t) = \sum_{k\in E} f^{\mathrm{E}}_{\Delta x}(j,k)\tilde{E}_k(t)$$

$$\frac{dw_j(t)}{dt} = \phi_{\mathrm{E}}(E_j(t), I(t); S_j(t), S_{\mathrm{post}}(t))$$
$$= \left\{\left[A_{\mathrm{LTP}}x_j^{+}(t)E_j(t) - A_{\mathrm{het}}y^{E}_{\mathrm{post}}(t)(E_j(t))^2\right]S_{\mathrm{post}}(t) - A_{\mathrm{LTD}}y^{-}_{\mathrm{post}}(t)S_j(t)w_j(t)\right\}\exp\left[-\left(\frac{I(t)}{I^{*}}\right)^{\gamma}\right],$$

Excitatory synapse update
with distance consideration

$$\Delta w_{\mathrm{E}} = \phi_{\mathrm{E}}(E, I; PRE, POST)$$
$$= [A_{\mathrm{LTP}}\,(PRE_{\mathrm{LTP}})(POST_{\mathrm{spike}})\,E \quad \text{LTP (pre-before-post)}$$
$$-A_{\mathrm{het}}\,(POST_{\mathrm{het}})(POST_{\mathrm{spike}})\,E^2 \quad \text{heterosynaptic}$$
$$-A_{\mathrm{LTD}}\,(POST_{\mathrm{LTD}})(PRE_{\mathrm{spike}})\,w_{\mathrm{E}}] \quad \text{LTD (post-before-pre)}$$
$$\times\exp\left[-\left(\frac{I}{I^{*}}\right)^{\gamma}\right] \quad \text{inhibitory control,}$$

Original excitatory synapse
update

$PRE_{LTP}, POST_{het}, POST_{LTD}$: eligibility trace (firing rate estimates)
$A_{LTP}$, $A_{het}$, $A_{LTD}$: learning rate (strictly positive)
$PRE_{spike}, POST_{spike}$: firing time

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$$\approx N_{\mathrm{E}}\sum_{j\in E}\tilde{E}_j(t), \text{ for } N_{\mathrm{E}} \gg 1.$$

Synapse-specific filtered **NMDA current**

$$\tau_{\mathrm{E}}\frac{\mathrm{d}\tilde{E}_j(t)}{\mathrm{d}t} = -\tilde{E}_j(t) - g_{\mathrm{NMDA},j}(t)H_{\mathrm{NMDA}}(u(t))\,[u(t) - E_{\mathrm{NMDA}}]$$

**Excitatory input, E** $\quad E_j(t) = \sum_{k\in E} f^{\mathrm{E}}_{\Delta x}(j,k)\tilde{E}_k(t)$

$PRE_{LTP}, POST_{het}, POST_{LTD}$: eligibility trace (firing rate estimates)

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$$\frac{\mathrm{d}w_j(t)}{\mathrm{d}t} = \phi_{\mathrm{I}}(E_j(t), I(t); S_j(t), S_{\mathrm{post}}(t))$$
$$= A_{\mathrm{ISP}}E_j(t)\,[E_j(t) - \alpha I(t)]\,[y_{\mathrm{post}}(t)S_j(t) + x_j(t)S_{\mathrm{post}}(t)]$$

Inhibitory synapse update with distance consideration

$$\Delta w_{\mathrm{I}} = \phi_{\mathrm{I}}(E, I; PRE, POST)$$
$$= A_{\mathrm{ISP}}E\,(E - \alpha I) \quad \text{codependency}$$
$$\times\left[(PRE_{\mathrm{inh}})\,(POST_{\mathrm{spike}})\right. \quad \text{pre-before-post}$$
$$\left.+ (POST_{\mathrm{inh}})\,(PRE_{\mathrm{spike}})\right] \quad \text{post-before-pre,}$$

Original inhibitory synapse update

# Methods

**Point-neuron:** LIF neuron with after-hyperpolarization (AHP) current and conductance-based synapses

$$\tau_m \frac{du(t)}{dt} = -[u(t) - u_{rest}] - g_{AHP}(t)[u(t) - E_{AHP}] + RI_{ext}(t)$$
$$- g_{AMPA}(t)[u(t) - E_{AMPA}] - g_{GABA_A}(t)[u(t) - E_{GABA_A}]$$
$$- g_{NMDA}(t) H_{NMDA}(u(t))[u(t) - E_{NMDA}],$$

$$H_{NMDA}(u) = \left(1 + a_{NMDA} \exp[b_{NMDA}(u - E_{NMDA})]\right)^{-1}$$

**Mg+ block**
Effect decay during the depolarization

$$\frac{dg_{AHP}(t)}{dt} = -\frac{g_{AHP}(t)}{\tau_{AHP}} + A_{AHP} S_{post}(t)$$
$$S_{post}(t) = \sum_k \delta(t - t^*_{k,post})$$

$$\frac{dg_X(t)}{dt} = -\frac{g_X(t)}{\tau_X} + \sum_{j \in X} w_j(t) S_j(t)$$
$$S_j(t) = \sum_k \delta\left(t - t^*_{k,j}\right)$$

$E_x$: reverse potential
δ: Dirac's delta, 1 when firing occur
$g_x$: conductance

# Methods

**Two-layer neuron:** LIF neuron and the dendrite as a leaky integrator

$$\tau_m \frac{du_{soma}(t)}{dt} = -[u_{soma}(t) - u_{rest}] - g_{AHP}(t)[u_{soma}(t) - E_{AHP}] - \sum_{i=1}^{N_B} J_i[u_{soma}(t) - u_i(t)].$$

$$\tau_m \frac{du_i(t)}{dt} = -[u_i(t) - u_{rest}] - J_i[u_i(t) - u_{soma}(t)] - g_{AMPA,i}(t)[u_i(t) - E_{AMPA}] - g_{GABA_A,i}(t)[u_i(t) - E_{GABA_A}] - g_{NMDA,i}(t)H_{NMDA}(u_i(t))[u_i(t) - E_{NMDA}]$$

**Soma-dendrite coupling strength**

$$J_i = \frac{a_i}{1 - a_i}, \quad (13)$$

where $a_i$ is the passive dendritic attenuation of the dendritic compartment $i$,

$$a_i = \frac{\bar{u}_i - u_{rest}}{\bar{u}_{soma} - u_{rest}}, \quad (14)$$

with $\bar{u}_{soma}$ being a constant steady state held at the soma and $\bar{u}_i$ being the resulting steady state at the dendritic compartment i. The coupling between soma and the dendritic compartment $i$ is a function of distance as follows:

$$J_i = f_a(d) = \frac{d_*^2}{d^2}, \quad (15)$$

where $d_*$ is a parameter that we fitted from experimental data from ref. 45 (Fig. 6c). We used this fitted parameter to approximate the distance to the soma in Fig. 6f and Extended Data Figs. 6 and 7 according to the soma–dendrite coupling strength used in our simulations.

$N_B$: N branch dendritic
$u_i$: membrane potential of dendritic branch

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$$- g_{AMPA}(t)[u(t) - E_{AMPA}] - g_{GABA_A}(t)[u(t) - E_{GABA_A}]$$
$$- g_{NMDA}(t) H_{NMDA}(u(t))[u(t) - E_{NMDA}],$$

$$H_{NMDA}(u) = \left(1 + a_{NMDA} \exp[b_{NMDA}(u - E_{NMDA})]\right)^{-1}$$

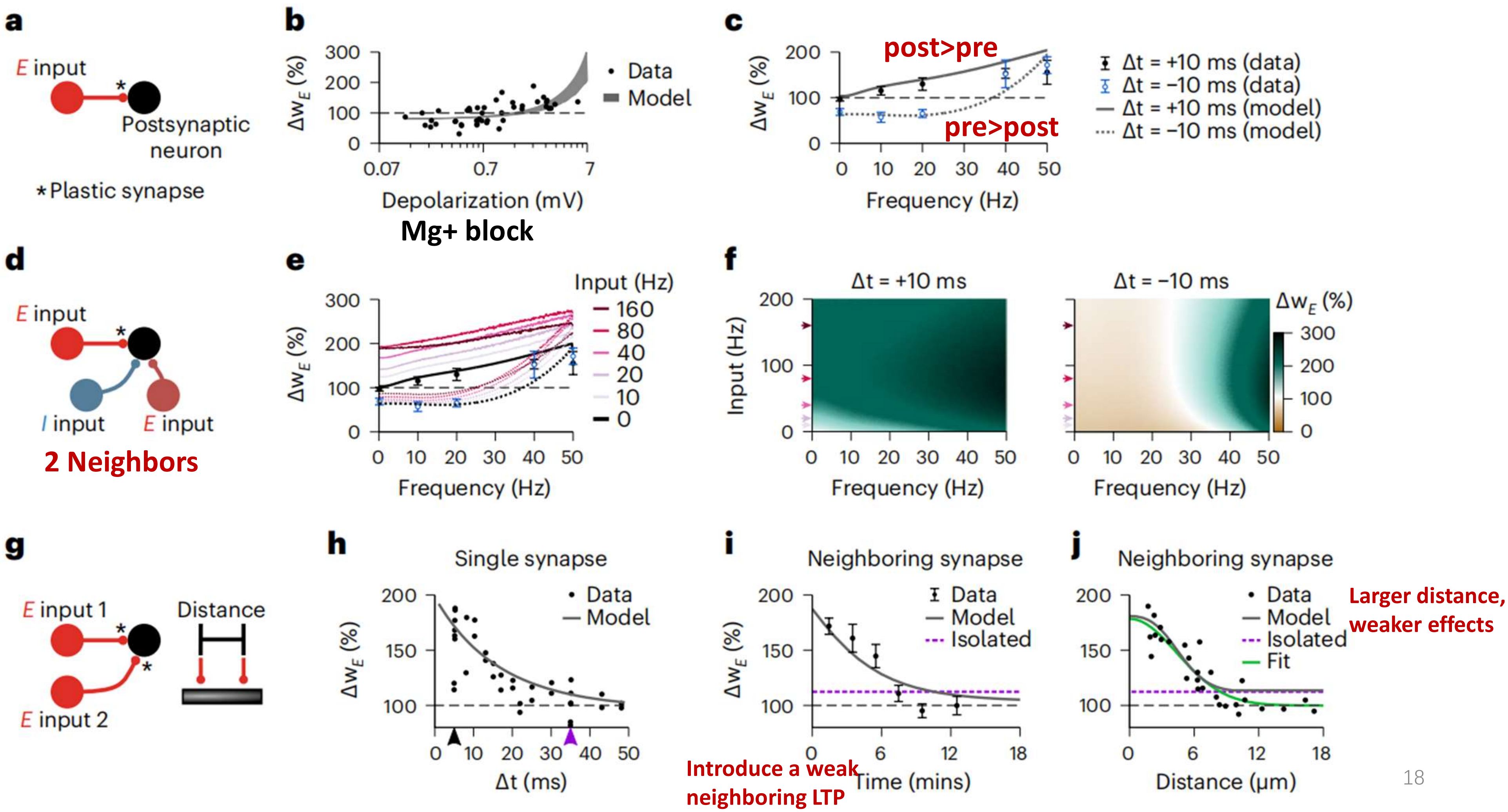
**Mg+ block**
Effect decay during the depolarization

$$\frac{dg_{AHP}(t)}{dt} = -\frac{g_{AHP}(t)}{\tau_{AHP}} + A_{AHP} S_{post}(t)$$
$$S_{post}(t) = \sum_k \delta(t - t^*_{k,post})$$

$$\frac{dg_X(t)}{dt} = -\frac{g_X(t)}{\tau_X} + \sum_{j \in X} w_j(t) S_j(t)$$
$$S_j(t) = \sum_k \delta\left(t - t^*_{k,j}\right)$$

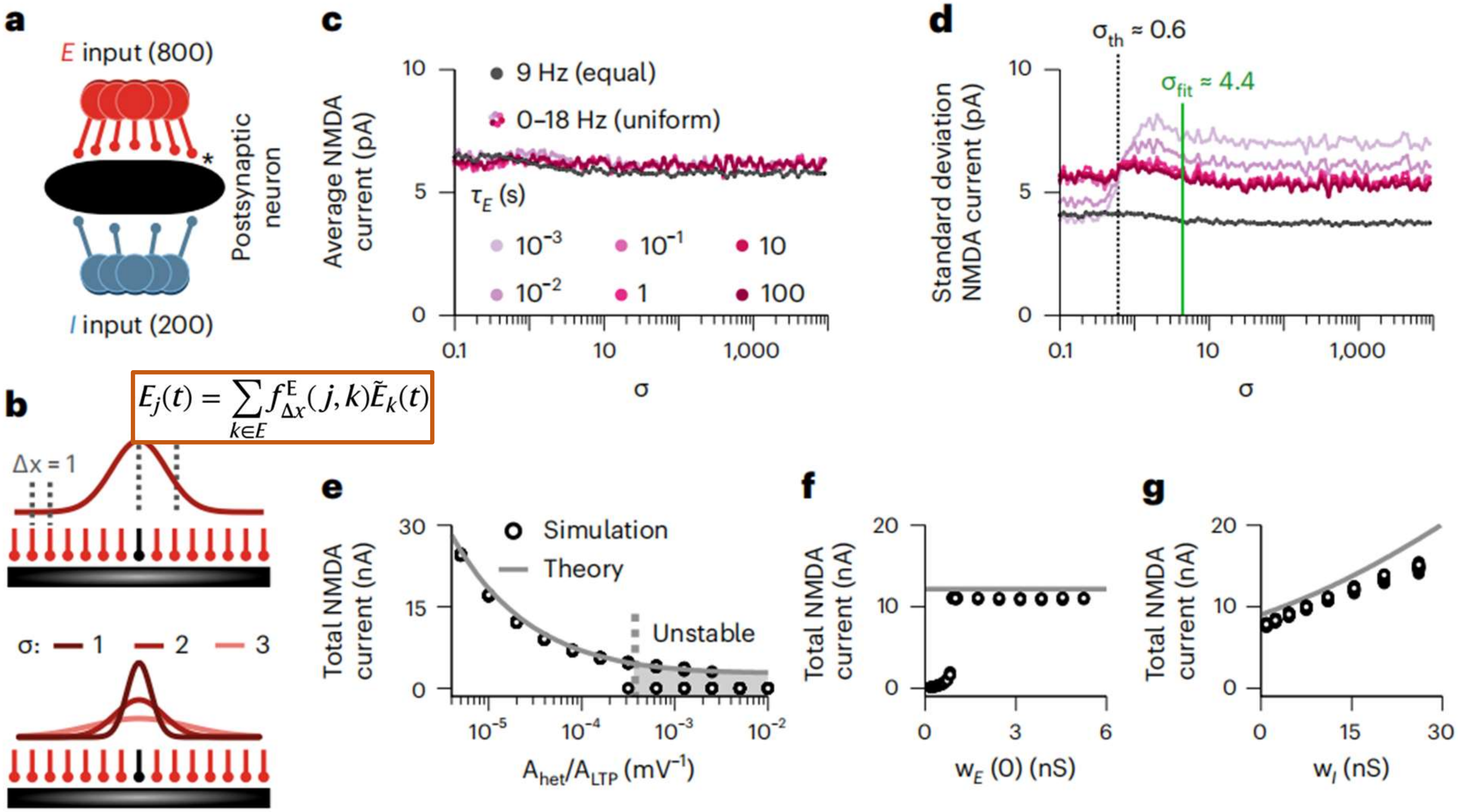
$E_x$: reverse potential
δ: Dirac's delta, 1 when firing occur
$g_x$: conductance

# Results



a
E input
Postsynaptic neuron
* Plastic synapse
b
ΔwE (%)
Data
Model
Depolarization (mV)
Mg+ block
c
post>pre
pre>post
Δt = +10 ms (data)
Δt = −10 ms (data)
Δt = +10 ms (model)
Δt = −10 ms (model)
Frequency (Hz)
d
E input
I input
E input
2 Neighbors
e
Input (Hz)
160
80
40
20
10
0
Frequency (Hz)
f
Δt = +10 ms
Δt = −10 ms
Input (Hz)
ΔwE (%)
Frequency (Hz)
g
E input 1
E input 2
Distance
h
Single synapse
Data
Model
Δt (ms)
i
Neighboring synapse
Data
Model
Isolated
Time (mins)
Introduce a weak neighboring LTP
j
Neighboring synapse
Data
Model
Isolated
Fit
Distance (μm)
Larger distance, weaker effects

# Results



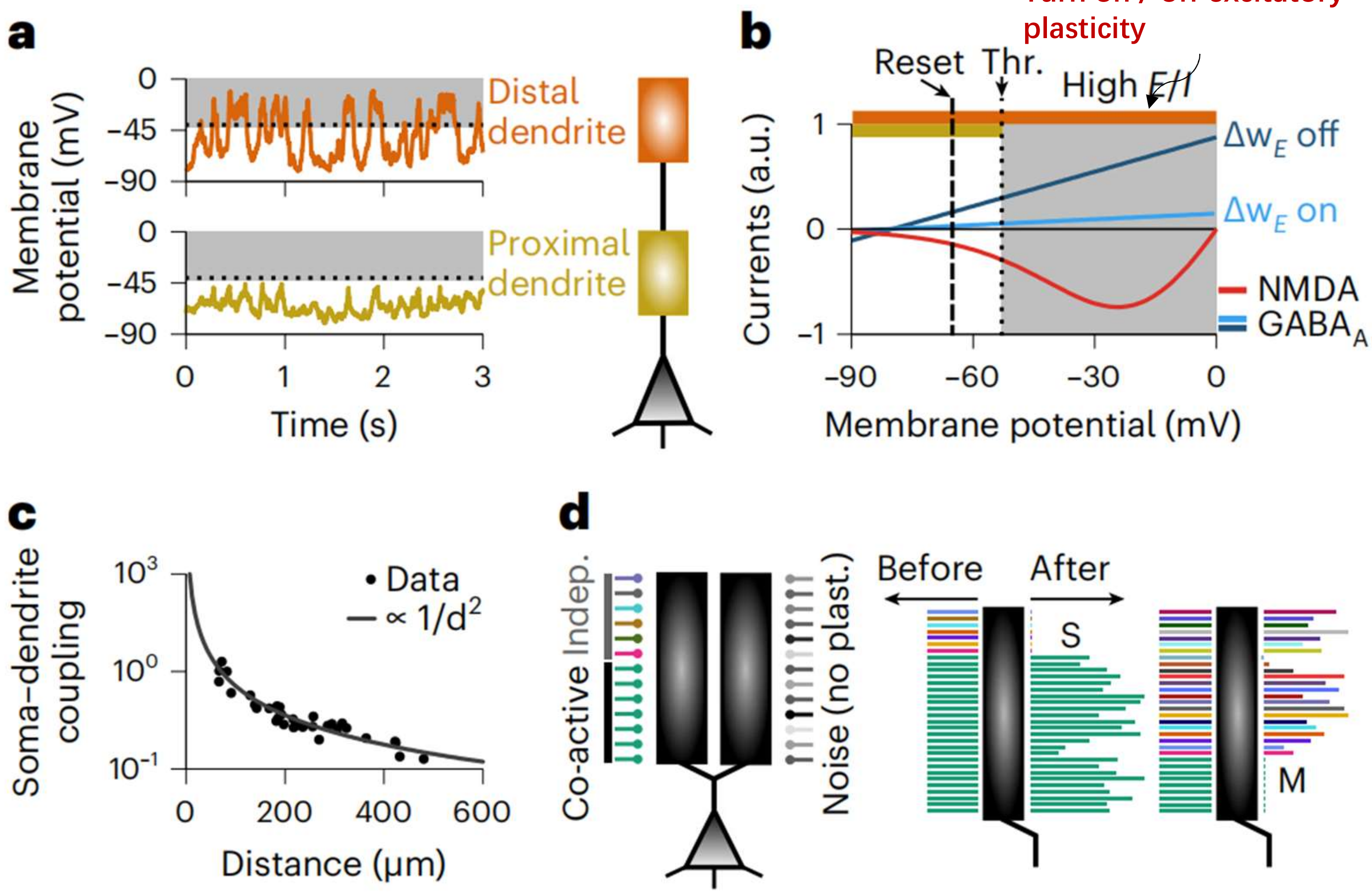

$$E_j(t) = \sum_{k \in E} f^{E}_{\Delta x}(j,k)\tilde{E}_k(t)$$

$$\tau_E \frac{d\tilde{E}_j(t)}{dt} = -\tilde{E}_j(t) - g_{NMDA,j}(t) H_{NMDA}(u(t)) \left[u(t) - E_{NMDA}\right]$$

$$f^{E}_{\Delta x}(i,j) = \exp\left[-\frac{1}{2}\left(\frac{\Delta x(i,j)}{\sigma}\right)^2\right]\left\{\frac{1}{N_E}\sum_{k \in E}\exp\left[-\frac{1}{2}\left(\frac{\Delta x(i,k)}{\sigma}\right)^2\right]\right\}^{-1}$$

# Results

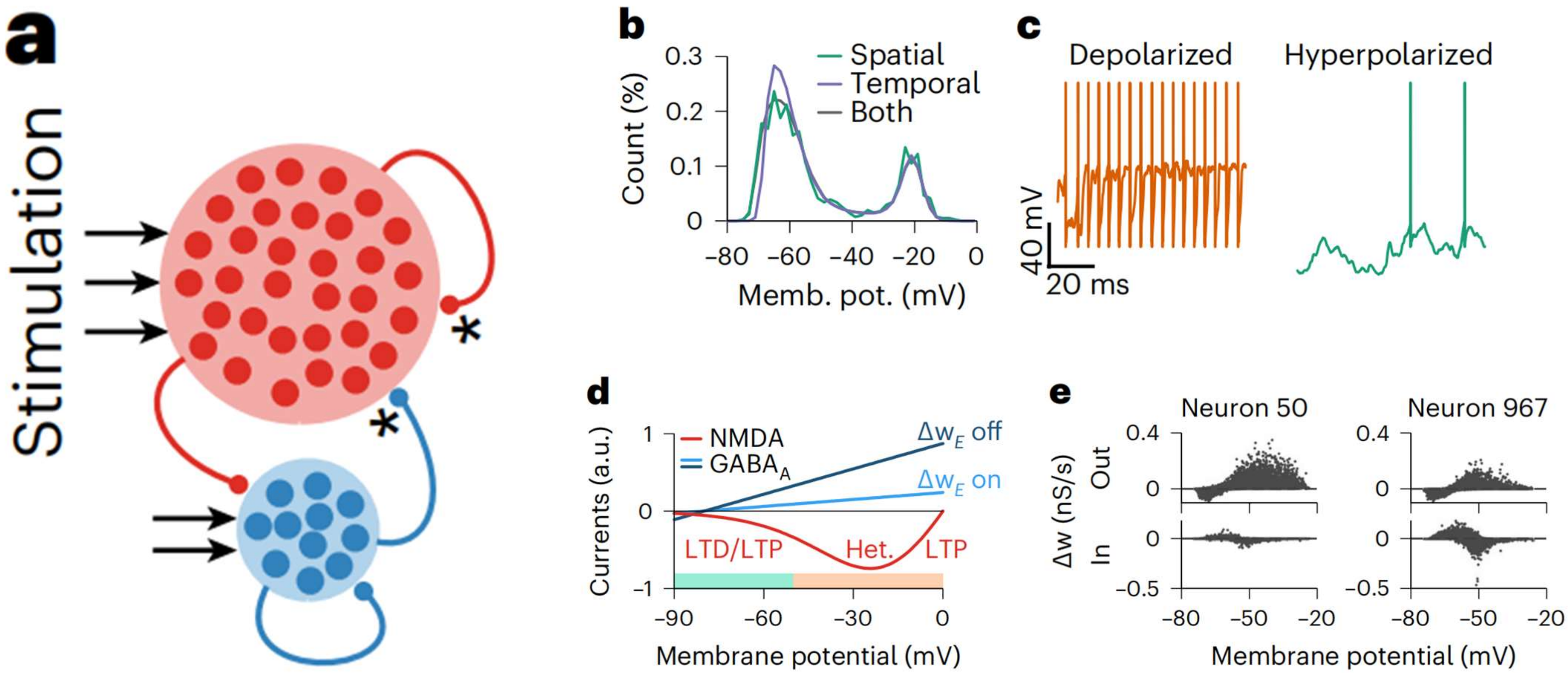
**Turn on / off excitatory plasticity**



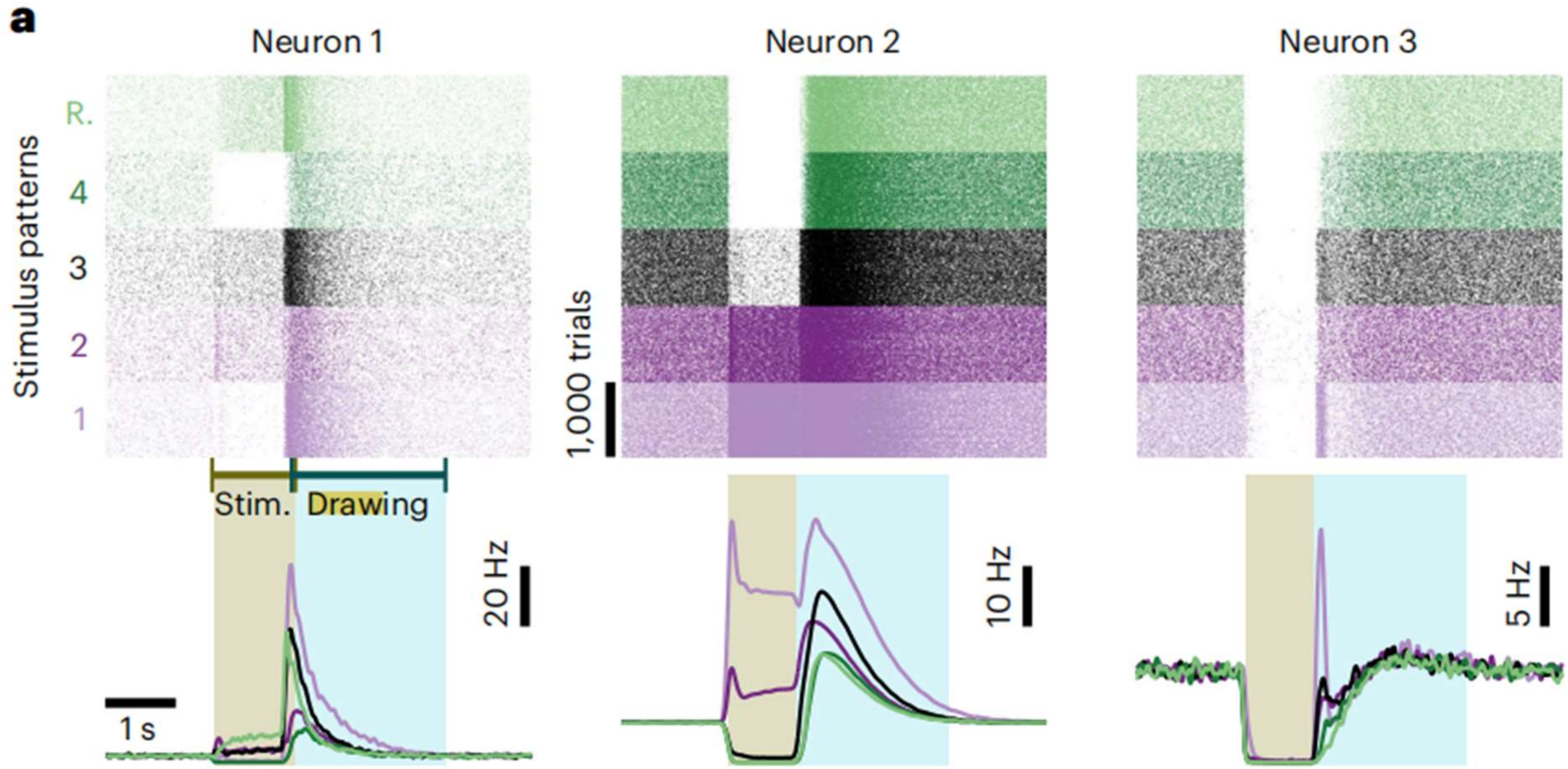

S
↓
Single feature selectivity

M
↓
Mixed feature selectivity

# Results


a
Stimulation
b
Count (%)
Spatial
Temporal
Both
Memb. pot. (mV)
c
Depolarized
Hyperpolarized
40 mV
20 ms
d
Currents (a.u.)
NMDA
GABA$_A$
$\Delta w_E$ off
$\Delta w_E$ on
LTD/LTP
Het.
LTP
Membrane potential (mV)
e
Neuron 50
Neuron 967
Δw (nS/s)
Out
In
Membrane potential (mV)

# Results




- Individual neuron responses ranged from <u>small firing rate deflections to large</u>, <u>transient events during</u> or <u>after the delivery of the stimulus</u> that could <u>last several seconds</u>
- **Similar** to real neural recordings of <u>sensory activity and motor production in mammals</u>

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# Take-away Message

**Motivation:**
Analyzing co-dependency between different connection types.

**Results:**
1. The resulting model explains how inhibition can gate excitatory plasticity while neighboring excitatory–excitatory interactions determine the strength of long-term potentiation.

2. The interplay between excitatory and inhibitory synapses can account for the quick rise and long-term stability of a variety of synaptic weight profiles, such as dendritic clustering of co-active synapses.

3. In recurrent neuronal networks, co-dependent plasticity produces rich and stable motor cortex-like dynamics with high input sensitivity.

# Thanks for your attention!

# Supplementary

The pair-based STDP rule of 19.10 can be implemented with two local variables, i.e., one for a low-pass filtered version of the presynaptic spike train and one for the postsynaptic spikes. Suppose that each presynaptic spike at synapse $j$ leaves a trace $x_j$, i.e., its update rule is

$$\frac{dx_j}{dt} = -\frac{x_j}{\tau_+} + \sum_f \delta(t - t_j^f), \tag{19.12}$$

where $t_j^f$ is the firing time of the presynaptic neuron. In other words, the variable is increased by an amount of one at the moment of a presynaptic spike and decreases exponentially with time constant $\tau_+$ afterward. Similarly, each postsynaptic spike leaves a trace $y_i$

$$\frac{dy_i}{dt} = -\frac{y_i}{\tau_-} + \sum_f \delta(t - t_i^f). \tag{19.13}$$

The traces $x_j$ and $y_i$ play an important role during the weight update. At the moment of a presynaptic spike, a decrease of the weight is induced proportional to the value of the postsynaptic trace $y_i$. Analogously, potentiation of the weight occurs at the moment of a postsynaptic spike proportional to the trace $x_j$ left by a previous presynaptic spike,

$$dw_{ij}/dt = -A_-(w_{ij})y_i(t) \sum_f \delta(t - t_j^f) + A_+(w_{ij})x_j(t) \sum_f \delta(t - t_i^f). \tag{19.14}$$

The traces $x_j$ and $y_i$ correspond here to the factors $\exp(-|\Delta t|/\tau_\pm)$ in 19.10. For the weight dependence of the factors $A_-$ and $A_+$, one can use either hard bounds or soft bounds; see Eq. (19.4).

Gerstner, W.,et. al. (2014). *Neuronal dynamics*