

The timing of external input controls the sign of plasticity at local synapses

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The method by which local networks in the brain store information from extrinsic afferent inputs is not well understood. We found that the timing of afferent input can bidirectionally control the sign of spike timing-dependent plasticity at local synapses in rat hippocampus. This mechanism provides a means by which temporal information in external input can be encoded in the local matrix of synaptic weights.

Spike timing-dependent plasticity (STDP) is a ubiquitous Hebbian learning rule¹ in which synaptic modification depends on the order of pre- and postsynaptic spiking in time windows of a few tens of milliseconds. If the presynaptic input is active before the postsynaptic spike, then potentiation occurs, as was originally predicted by Hebb²,

whereas synaptic depression is induced if this order is reversed^{3–5}. The computational consequences of this local learning rule depends on the architecture and circuit dynamics of the network in which the synapses are embedded. The hippocampus, which has an established role in memory, is an attractive experimental system in which to study such interactions, as both the network architecture and circuit dynamics are well characterized^{6,7}. CA1 pyramidal neurons receive local input via the Schaffer collaterals from CA3 and external input from the entorhinal cortex via perforant path fibers (the ‘direct’ temporo-ammonic pathway)⁸. During spatial learning, the hippocampal network engages in rhythmic theta activity, during which hippocampal principal neurons receive rhythmic perisomatic inhibition at 4–6 Hz⁹.

To mimic this network state, we subjected individual CA1 pyramidal neurons to a rhythmic inhibitory conductance using dynamic clamp while depolarizing the cell to fire a single action potential at the peak of each theta cycle (Fig. 1a,b; see Supplementary Methods). To test how the external temporo-ammonic input controls spike timing in CA1 pyramidal cells during theta oscillations, we stimulated the temporo-ammonic input at different theta phases and recorded the effects on postsynaptic spike timing. We found that, depending on the timing of the temporo-ammonic input, the spike times

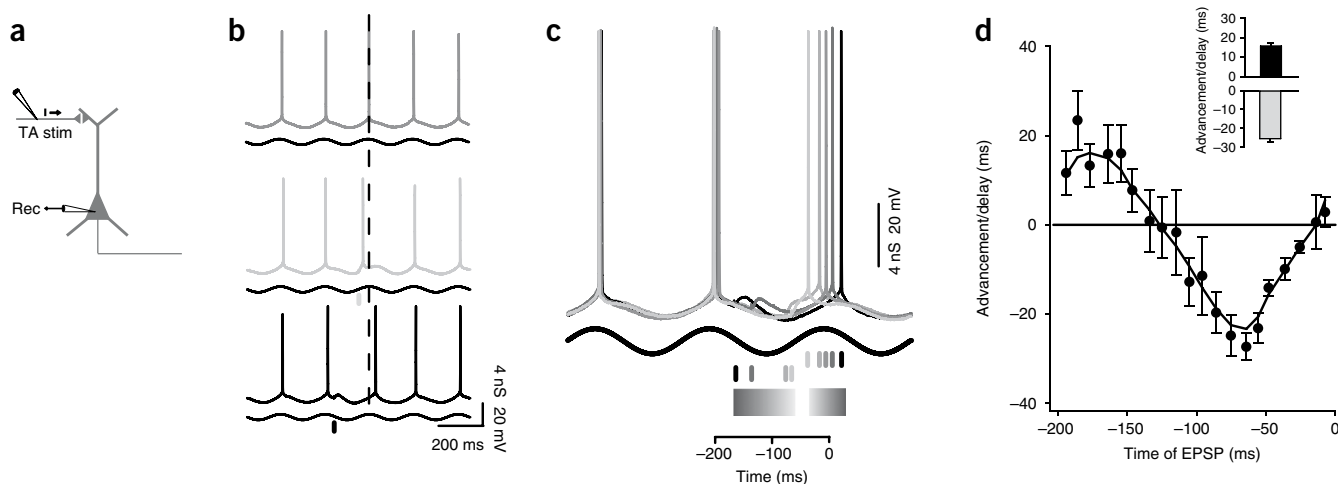


Figure 1 Temporo-ammonic input controls postsynaptic spike timing of CA1 pyramidal neurons during theta oscillation. **(a)** Experimental set-up. A CA1 neuron with a recording electrode at the soma (Rec) and an extracellular electrode stimulating temporo-ammonic input (TA stim) is shown. **(b)** Example voltage traces during theta oscillation produced by conductance clamp (black trace, minimum inhibitory conductance upwards). Without synaptic perturbation, neuron spiked near the peak of oscillation (gray, dashed line). Temporo-ammonic input stimulation on the ascending phase of oscillation (light gray bar) advanced postsynaptic spikes (light gray trace). Temporo-ammonic input stimulation on the descending phase of oscillation (black bar) delayed postsynaptic spikes (black trace). **(c)** Superimposed voltage traces of postsynaptic spikes (light gray to black bars, time of postsynaptic spike) with temporo-ammonic input stimulation at different times during theta oscillation (black to light gray bars). Note the reversal and time compression of output relative to input (gray scale). **(d)** Plot of spike time advancement and delay as a function of time of temporo-ammonic stimulation for the cell shown in **b** and **c**. Data are mean \pm s.d. of ten postsynaptic spike times for each temporo-ammonic stimulation time. Inset, maximum spike time delay (black bar) and advancement (light gray bar) induced by temporo-ammonic stimulation ($n = 7$). EPSP, excitatory postsynaptic potential.

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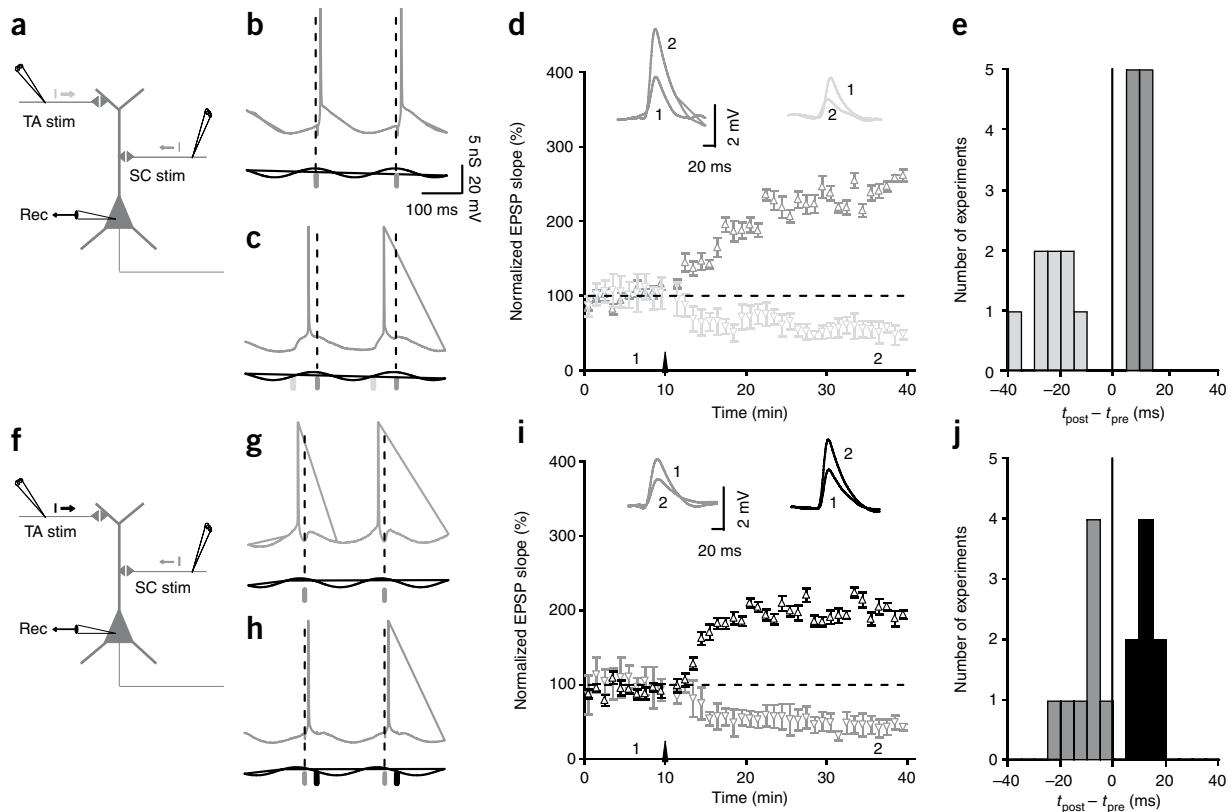
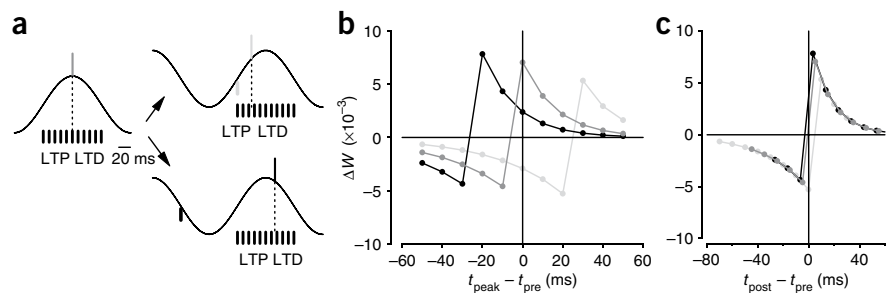


Figure 2 Tempero-ammonic input modulates the sign of STDP at hippocampal Schaffer collateral-CA1 synapses during theta oscillation. (a) Experimental setup. Extracellular electrodes stimulating tempero-ammonic (TA stim, light gray) and Schaffer collateral input (SC stim, gray). (b) Oscillatory conductance (black, minimum inhibitory conductance upwards) and voltage response (gray) during pre-before-post pairing, Schaffer collateral stimulation is indicated with the gray bar and dashed line. (c) Adding tempero-ammonic stimulation on the ascending phase of oscillation (light gray bar) advanced the postsynaptic spike time (t_{post}), changing pairing order to post-before-pre pairing. (d) The time course of the normalized Schaffer collateral EPSP slope. The induction protocol in b (arrowhead) resulted in LTP (gray symbols, $n = 10$) and the protocol in c led to LTD (light gray symbols, $n = 8$). Data are mean \pm s.e.m. Insets, example Schaffer collateral EPSP traces before (1) and after pairing (2). (e) Histogram of mean spike time difference ($t_{post} - t_{pre}$) for pairing protocol in b (gray) and c (light gray) for all cells. (f) Experimental setup as in a, with tempero-ammonic stimulation (black) on descending phase of oscillation. (g) Schaffer collateral input (gray bar) and postsynaptic spikes during post-before-pre pairing, Schaffer collateral stimulation is indicated with the gray bar and dashed line. (h) Adding tempero-ammonic stimulation on the descending phase of oscillation (black bar) delayed the postsynaptic spike, changing pairing order to pre-before-post pairing. (i) Time course of Schaffer collateral EPSP slope. The induction protocol in g (arrowhead) resulted in LTD (gray symbols, $n = 8$) and that in h led to LTP (black symbols, $n = 8$). (j) Histogram of spike time difference ($t_{post} - t_{pre}$) for pairing protocol in g (gray) and h (black) for all cells.

of CA1 pyramidal neurons could be either advanced or delayed. Stimulation of tempero-ammonic input on the ascending phase of the oscillation advanced postsynaptic spike timing (Fig. 1b), whereas stimulation on the descending phase delayed postsynaptic spike timing (Fig. 1b). That is, depending on the timing of the stimulation of tempero-ammonic input, it could either advance or delay the postsynaptic spike time relative to the oscillation (Fig. 1c,d). The maximum spike

time advancement and delay that we observed, without altering firing rate, were -25.8 ± 1.8 ms and 16.0 ± 1.5 ms, respectively (mean \pm s.e.m., $n = 10$; Fig. 1d). The spike time delay was more prominent with distal tempero-ammonic input compared with Schaffer collateral input, which could be attributed to the preferential recruitment of GABA_B receptor-mediated inhibition by tempero-ammonic stimulation⁸ (Supplementary Fig. 1).

Figure 3 Enforcement of potentiation and depression by external input during theta oscillation. (a) Schematic of Schaffer collateral inputs (black bars) near the peak of theta oscillation and effect of external tempero-ammonic input on postsynaptic spike time (dashed line) and sign of STDP. Without tempero-ammonic input, postsynaptic spikes occurred near the peak (gray line). Advancing the postsynaptic spike (light gray line) by tempero-ammonic input enforced LTD. Delaying the postsynaptic spike (black line) enforced LTP. (b,c) Synaptic weight change against time of Schaffer collateral input relative to theta peak ($t_{peak} - t_{pre}$) (b) and relative to the postsynaptic spike ($t_{post} - t_{pre}$) (c) without tempero-ammonic input (gray), with tempero-ammonic input advancing the spike (light gray) and with tempero-ammonic input delaying the spike (black).



The similarity of the range of spike time advancement and delay to spike time windows reported for STDP at hippocampal synapses⁴ prompted us to investigate whether the timing of tempero-ammonic input can control STDP at Schaffer collateral–CA1 synapses. Indeed, we found that, depending on the timing, stimulation of tempero-ammonic input could convert potentiation at the Schaffer collateral–CA1 synapse into depression or vice versa (Fig. 2). After 10 min of stable baseline recording, 200 pairings of presynaptic Schaffer collateral input stimulation ~10 ms before the postsynaptic spike during theta oscillation (pre-before-post pairing; Fig. 2a,b) induced long-term potentiation (LTP, $+154.1 \pm 4.3\%$, $P < 0.05$, $n = 10$; Fig. 2d). However, prior stimulation of tempero-ammonic input on the ascending phase of oscillation converted synaptic potentiation into depression ($-49.6 \pm 1.7\%$, $P < 0.05$, $n = 8$; Fig. 2c,d). Conversely, stimulation of presynaptic Schaffer collateral input ~15 ms after the postsynaptic spike (post-before-pre pairing; Fig. 2f,g) induced long-term depression (LTD) in the control condition ($-53.9 \pm 2.1\%$, $P < 0.05$, $n = 8$; Fig. 2i). However, prior stimulation of tempero-ammonic input on the descending phase of oscillation converted synaptic depression into potentiation ($+100.6 \pm 3.9\%$, $P < 0.05$, $n = 8$; Fig. 2h,i).

The reversal of the sign of plasticity was associated with a reversal of the order of pre- and postsynaptic spike times during pairing (Fig. 2e,j). Thus, stimulation of tempero-ammonic input on the ascending phase of oscillation advanced the postsynaptic spike and the spike order during pairing became post-before-pre pairing (Fig. 2e), whereas stimulation of tempero-ammonic input on the descending phase of oscillation delayed the postsynaptic spike, reversing the spike order to pre-before-post pairing (Fig. 2j).

Reversal of the sign of STDP by tempero-ammonic input was also observed with 60 pairings (see Supplementary Fig. 2), under intact inhibition (Supplementary Fig. 3) and required activation of NMDA receptors (Supplementary Fig. 4). A simple spike timing-based learning model (Supplementary Methods) showed that, for randomly activated Schaffer collateral inputs across the theta cycle, tempero-ammonic input could enforce either LTP or LTD on the network depending on the timing of tempero-ammonic activation relative to theta oscillation (Fig. 3). These results indicate that activation of tempero-ammonic input can reverse the sign of plasticity and enforce either LTP or LTD at the Schaffer collateral–CA1 synapse by prospectively controlling postsynaptic spike time. As few as ten pairing events could induce tempero-ammonic–enforced LTP in young adult tissue, making it likely that similar mechanisms operate *in vivo*

(Supplementary Fig. 5). Notably, activation of Schaffer collateral input instead of tempero-ammonic input primarily enforced LTD (Supplementary Fig. 6).

The control of sign of plasticity by external input strengthens earlier experimental links between synaptic plasticity and network oscillations in the hippocampus¹⁰ and emphasizes the importance of interaction between different inputs in controlling synaptic plasticity¹¹. Thus, firing correlations between local neurons determine whether plasticity will occur, whereas the sign of that plasticity can be determined by information encoded in the timing of an external input relative to the local network dynamics. Because there is a time-varying difference in the phase of synaptic input from the Schaffer collateral and tempero-ammonic input during physiological theta oscillations^{12,13}, and because these inputs are under differential neuromodulatory control¹⁴, this neurocomputational principle is likely to contribute to hippocampal memory processing *in vivo*. Notably, STDP during oscillation in mushroom bodies in the locust has recently been implicated in odor learning¹⁵, suggesting that oscillatory control of STDP is a fundamental facet of neural network operations in many species.

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

J.K. conducted the experiments and analyzed the data. J.K. and O.P. designed the experiments and wrote the manuscript.

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