SUPPLEMENTAL FIGURES LEGENDS

Figure S1: Eligibility traces are not affected by cholinergic receptors and can be induced by standard depolarization pairing paradigms. Related to Figure 1.

(A) 5 min puff of 250 μM CCh following post-pre conditioning did not alter synaptic strength (CCh only: 91.5 ± 13.8%; Pairing + CCH: 104.0 ± 5.6%). **(B)** Puffing CCh (250 μM) for 5 min before the post-pre pairing promoted LTD (CCh only: 108.0 ± 10.0%; CCh + Pairing: 68.4 ± 4.4%, p = 0.008 compared to baseline). **(C)** NE (50μM, 10 sec) puffed after low frequency stimulation (200 pulses at 10Hz) paired with postsynaptic depolarization to -10 mV, but not pairing alone, allows LTP induction in slices from mice treated with reserpine to deplete monoamines (see Methods) (paired+puff: 131.3 ± 7.1%, p = 0.006; paired only: 101.4 ± 4.6%). **(D)** Similarly, pairing low frequency stimulation (200 pulses at 10Hz) with postsynaptic depolarization to -40 mV in slices from mice treated with reserpine did not induce LTD (paired only: 106.3 ± 7.0%), but 5-HT (50μM, 10 sec) puffed after pairing promoted significant LTD (paired+puff: 78.2 ± 6.8%, p = 0.03).

Figure S2: Specific expression of ChR2 in LC noradrenergic neurons in TH-ChR2 mice. Related to Figure 2.

(A) Image from a mouse brain atlas showing the coronal slice containing the locus coeruleus (LC, highlighted with a white box). **(B)** Fluorescent image of TH-ChR2 mouse LC. YFP is specifically expressed (green) in noradrenergic neurons (yellow arrowhead). The 4th ventricle (right upper corner) was used as the landmark. **(C)** Primary visual cortical slice under low magnification (10X, tile image). Noradrenergic fibers are shown in green, and the recorded L2/3 neuron labeled with biocytin and secondary antibody are shown in red. (D) Biocytin-labeled V1 L2/3 neuron from a TH-ChR2 brain slice (40X).

Figure S3. Transformation of LTP eligibility traces is mediated by βAR activation and intracellular cAMP. Related to Figure 5.

(A) βAR activation by Iso (50 μM, 10 s) mimicked the transformation of the LTP eligibility trace by NE (pre-post: 129.1 ± 6.7%, p = 0.003; post-pre: 104.5 ± 4.6%; p = 0.008 between p1 and p2). **(B)** Iso alone (50 μM 10 s, triangle: 97.7 ± 5.0%) or following presynaptic stimulations (200 pulses at 10 Hz, circle: 97.3 ± 9.0%) did not change synaptic strength. **(C)** Experimental design for elevating intracellular cAMP by uncaging. **(D)** Elevation of intracellular cAMP alone did not significantly affect synaptic transmission (light only: 91.8 ± 4.4%), but consolidated the LTP

eligibility trace induced by pre-post conditioning (magenta dot, Pairing + light: 117.8 ± 5.5%, p = 0.008. p = 0.004 between two pathways).

Figure S4. Normal expression of paired LTP/D with the C-terminus peptide of β2AR/5-HT2CR. Related to Figure 5.

(A) LTP was induced by pairing low-frequency stimulation with membrane depolarization to 0 mV (pairing protocol shown in upper panel) with 50 μM DSPL in the internal pipette solution (185.8 ± 36.8%, p= 0.046, paired t-test). **(B)** Paired LTD was successfully induced (LFS paired with depolarization to -40 mV, upper panel) with 50 μM 2C-ct peptide in the internal pipette solution (75.0 ± 0.9%, p= 0.0005, paired t-test).

Figure S5. Properties of network training, raster plots, reversal of reward times, and sensitivity to parameters. Related to Figure 7.

Training a network of 100 neurons with different reward timing. Network activity was initiated by a 100 ms stimulus of feed-forward drive from LGN (dashed vertical magenta line). Panels **A1**-**A3** show raster plots of the complete network for three instances during training, corresponding to those shown in Fig. 7. Here, the reward is delivered 1000 ms after the stimulus offset (vertical magenta line). **(A1)** Network before, **(A2)** during (18 trials), and **(A3)** after training (50 trials). (**B**) Subsequently, reward delivery was delayed by an extra 500ms. **(B1)** Starting point (identical to **A3**), **(B2)** after another 23 training trials, and **(B3)** after an additional 65 trails. (**C**) Next, the reward was shifted back to the original delay (1000 ms). **(C1)** Initial condition (identical to **B3**), **(C2)** after training for 2 more trials, **(C3)** after the network converges back to the original reward time (compare with A3). At the end of training, the network activity decays before the reward is delivered, as seen in the raster plots. **(D)** Three examples with different parameters show that network activity after training decays prior to the reward, and that the timing of the decay is parameter-dependent. The interval between reward time (R) and decay of network activity (defined by crossing a threshold from above, as shown by horizontal dashed line), defined as D, is parameter-dependent. **(E)** Examples of how the interval, D, depends on the parameters of the learning rule (+ symbols, colors denote the values of the τ_d parameter). These are compared to an analytical approximation of D (colored dashed lines), which has the form:

$$D = log(T^p_{max}/T^d_{max})\tau_d\tau_p/(\tau_p - \tau_d)$$

(see Mathematical Model in the Experimental Procedures section for derivation).

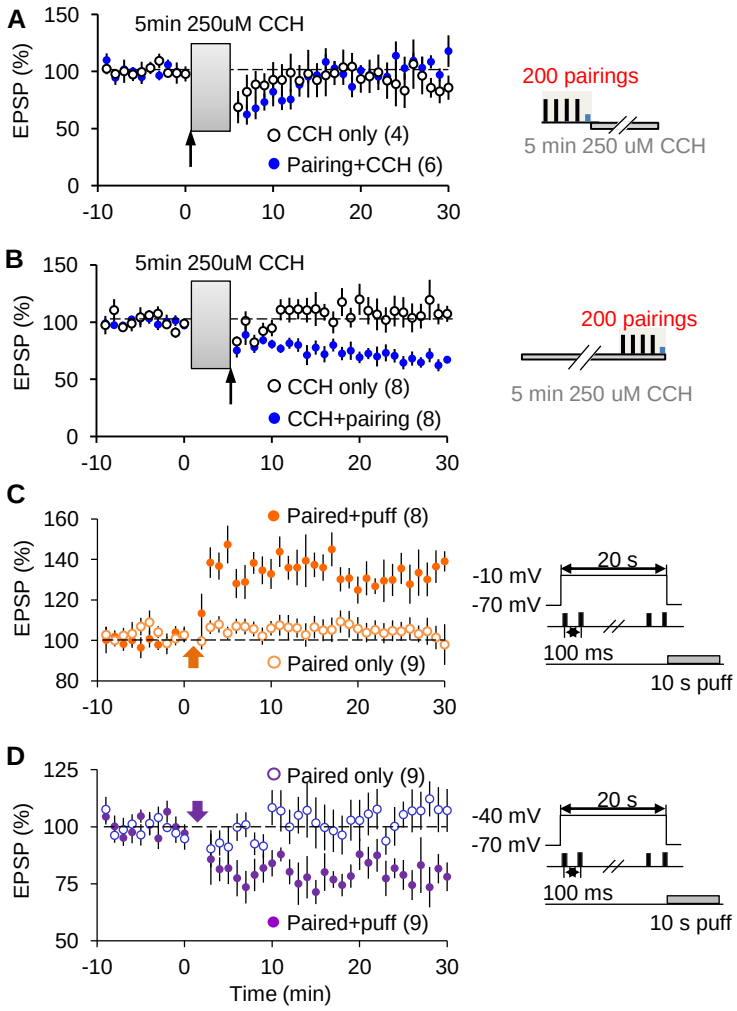

A
5min 250uM CCH
EPSP (%)
150
100
50
0
-10
0
10
20
30
CCH only (4)
Pairing+CCH (6)
200 pairings
5 min 250 uM CCH
B
5min 250uM CCH
EPSP (%)
CCH only (8)
CCH+pairing (8)
200 pairings
5 min 250 uM CCH
C
EPSP (%)
160
140
120
100
80
Paired+puff (8)
Paired only (9)
20 s
-10 mV
-70 mV
100 ms
10 s puff
D
EPSP (%)
125
100
75
50
Paired only (9)
Paired+puff (9)
20 s
-40 mV
-70 mV
100 ms
10 s puff
Time (min)

Fig S1

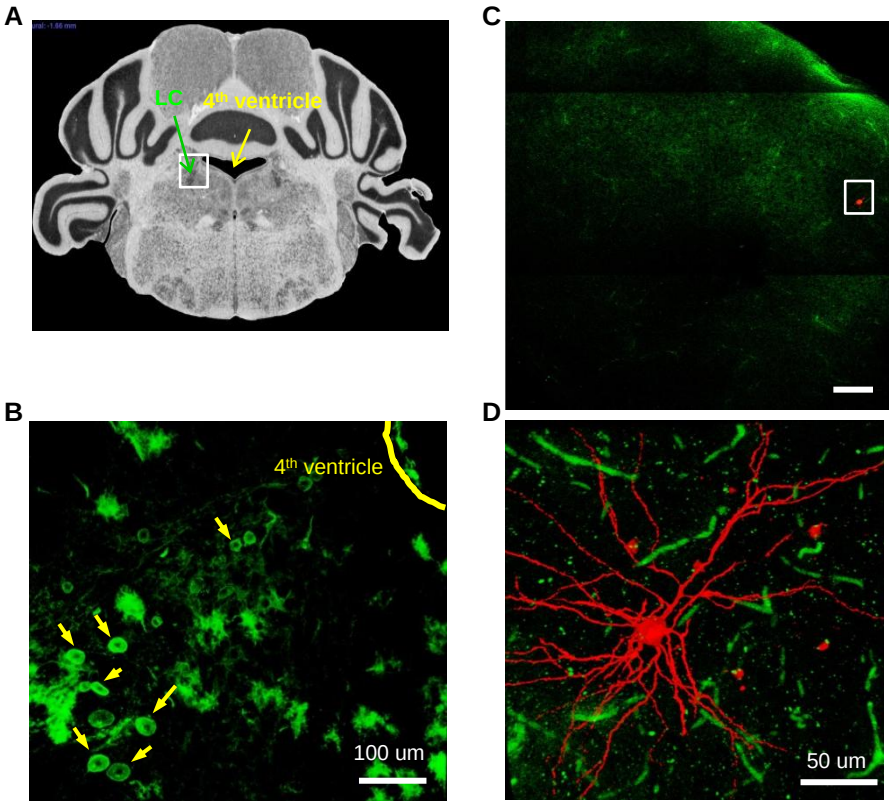


Fig S2

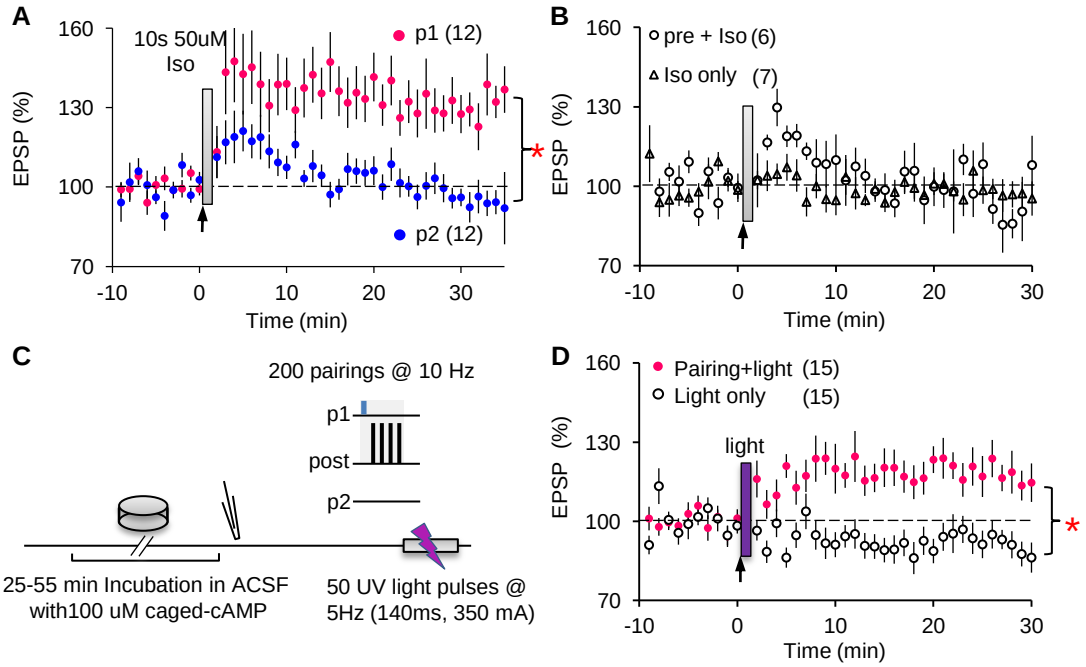

A
160
130
100
70
EPSP (%)
10s 50uM
Iso
p1 (12)
p2 (12)
*
-10
0
10
20
30
Time (min)
B
pre + Iso (6)
Iso only (7)
C
200 pairings @ 10 Hz
p1
post
p2
25-55 min Incubation in ACSF
with100 uM caged-cAMP
50 UV light pulses @
5Hz (140ms, 350 mA)
D
Pairing+light (15)
Light only (15)
light

Fig S3

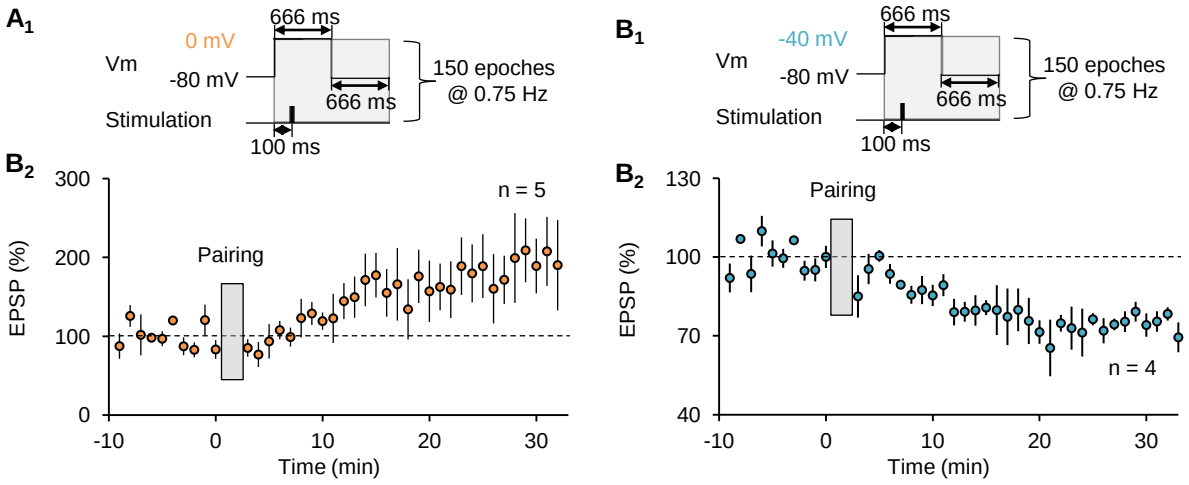
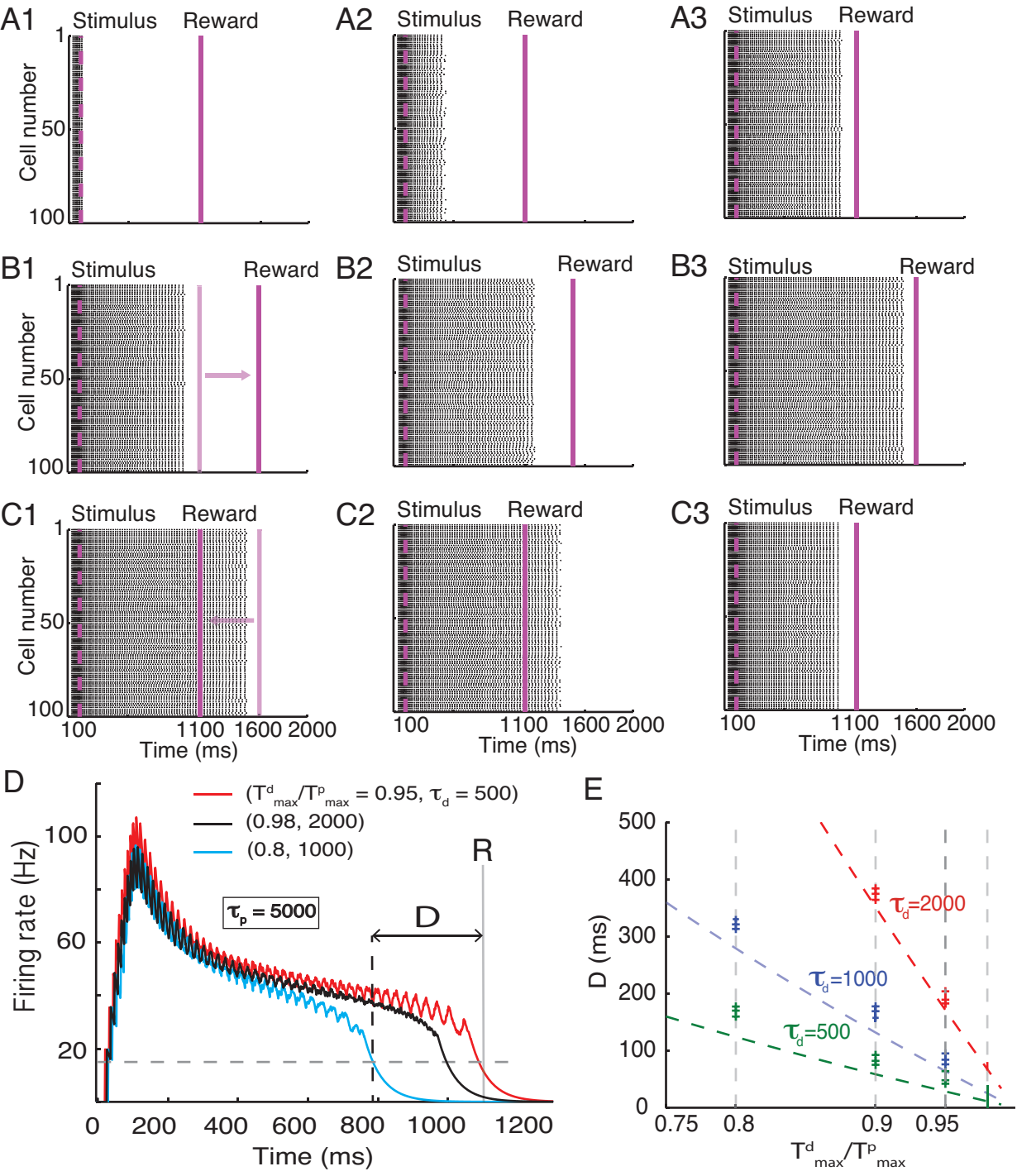

A1
666 ms
0 mV
Vm
-80 mV
666 ms
150 epoches
@ 0.75 Hz
Stimulation
100 ms
B1
666 ms
-40 mV
Vm
-80 mV
666 ms
150 epoches
@ 0.75 Hz
Stimulation
100 ms
B2
EPSP (%)
300
200
100
0
n = 5
Pairing
-10
0
10
20
30
Time (min)
B2
EPSP (%)
130
100
70
40
Pairing
n = 4
-10
0
10
20
30
Time (min)

Fig S4


A1
Stimulus
Reward
Cell number
1
50
100
A2
Stimulus
Reward
A3
Stimulus
Reward
B1
Stimulus
Reward
Cell number
1
50
100
B2
Stimulus
Reward
B3
Stimulus
Reward
C1
Stimulus
Reward
Cell number
1
50
100
100
1100
1600
2000
Time (ms)
C2
Stimulus
Reward
100
1100
1600
2000
Time (ms)
C3
Stimulus
Reward
100
1100
1600
2000
Time (ms)
D
(T^d_max/T^p_max = 0.95, τ_d = 500)
(0.98, 2000)
(0.8, 1000)
R
τ_p = 5000
D
Firing rate (Hz)
100
60
20
0
200
400
600
800
1000
1200
Time (ms)
E
D (ms)
500
400
300
200
100
0
τ_d=2000
τ_d=1000
τ_d=500
0.75
0.8
0.9
0.95
T^d_max/T^p_max