Testing Error-driven learning in the hippocampus

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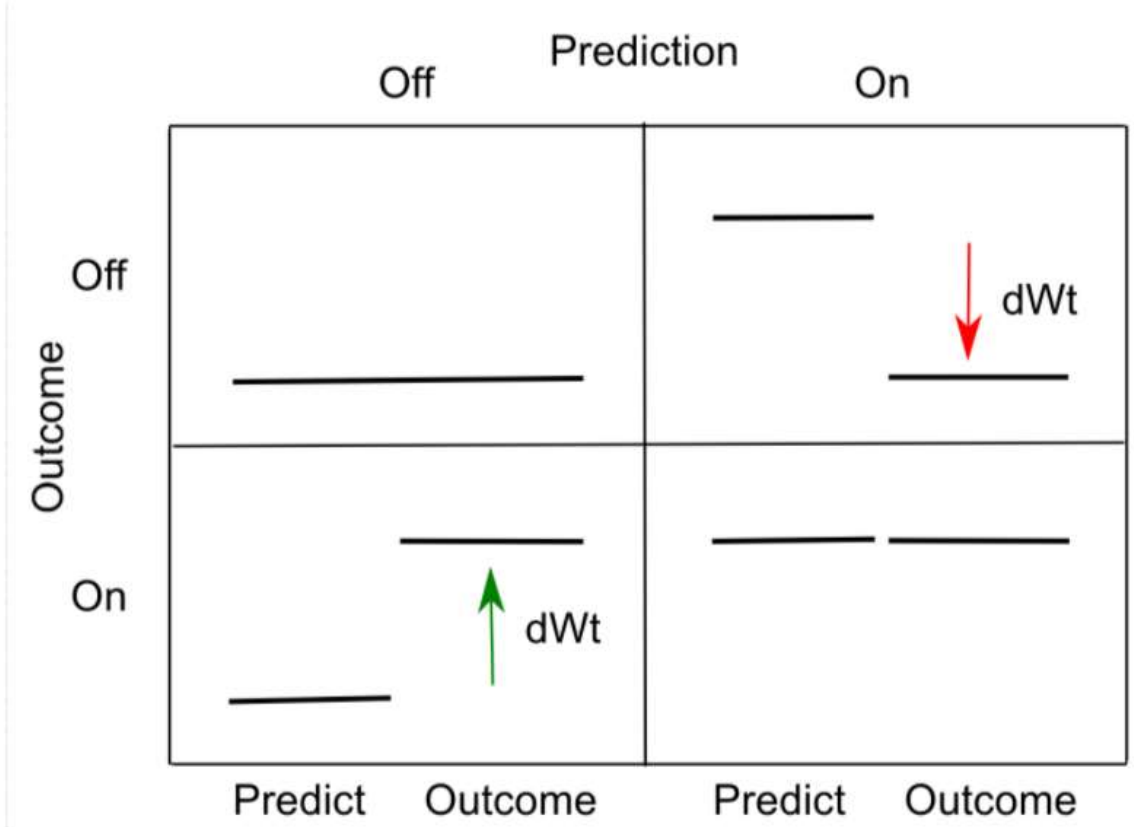
Thanks to the Astera Institute for funding this project!

Temporal Error Prediction



Prediction -then- Outcome

Error on mismatch

Two qualitative cases:

- On -then- Off = LTD
- Off -then- On = LTP

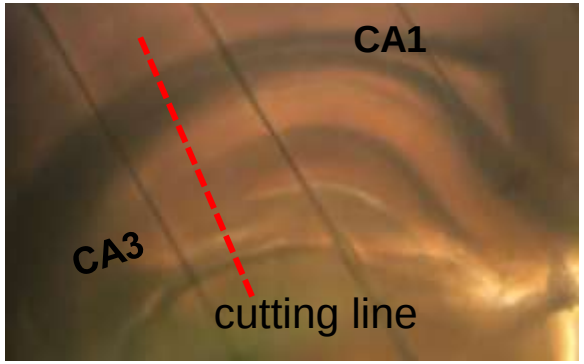
Methods

C57BL/6

17-23 day-old mice

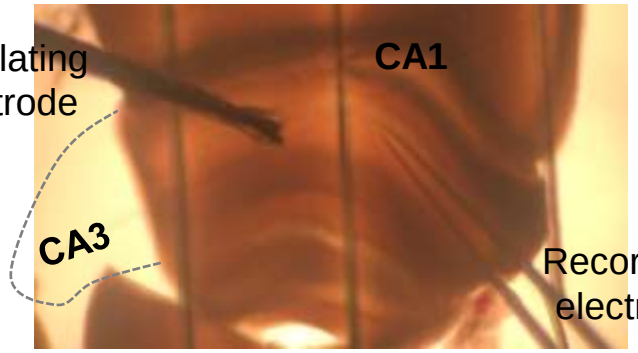
Acute slice
(350 μm)

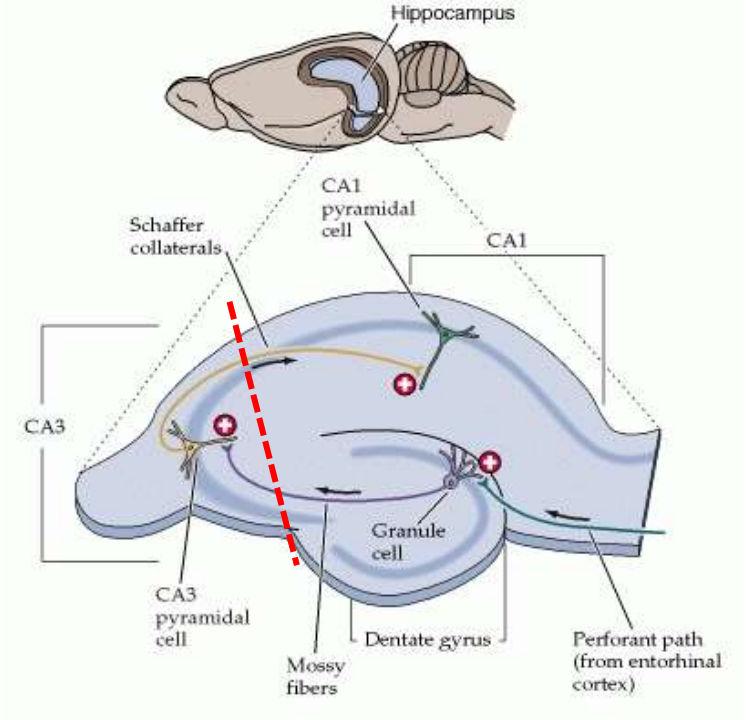
Intact hippocampal slice



Remove CA3 area
before recording

CA3 removed slice





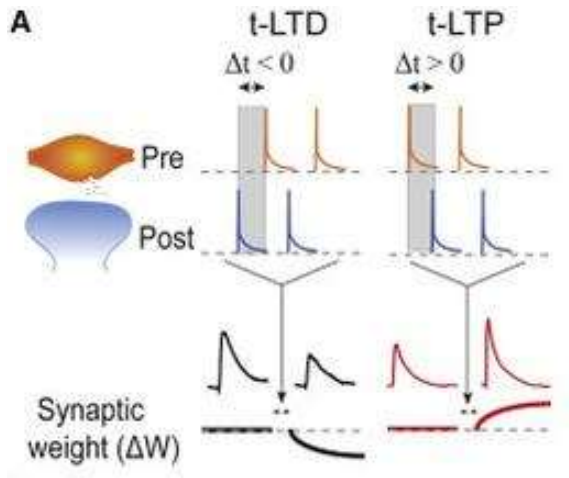
Whole-cell recording solution (in mM):
135 K^+ gluconate, 5 NaCl, 2 $MgCl_2$, 10 HEPES, 0.6 EGTA, 4 NaATP, 0.4 NaGTP, pH 7.3, 290 mOsm.

aCSF (in mM):
127 NaCl, 25 $NaHCO_3$, 1.2 NaH_2PO_4, 2.5 KCl, 25 D-glucose, 2 $CaCl_2$, 1 $MgCl_2$ pH 7.2, 310 mOsm. Aerated with 95%O2/5%CO2.

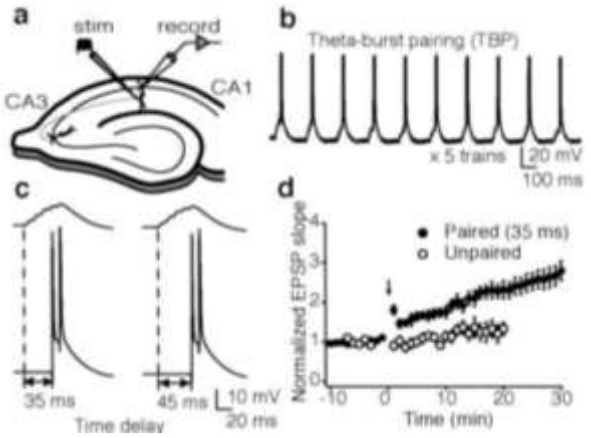
Stimulus intensity was adjusted to produce EPSPs 4–6 mV in amplitude.

Created Error-driven learning induction protocol

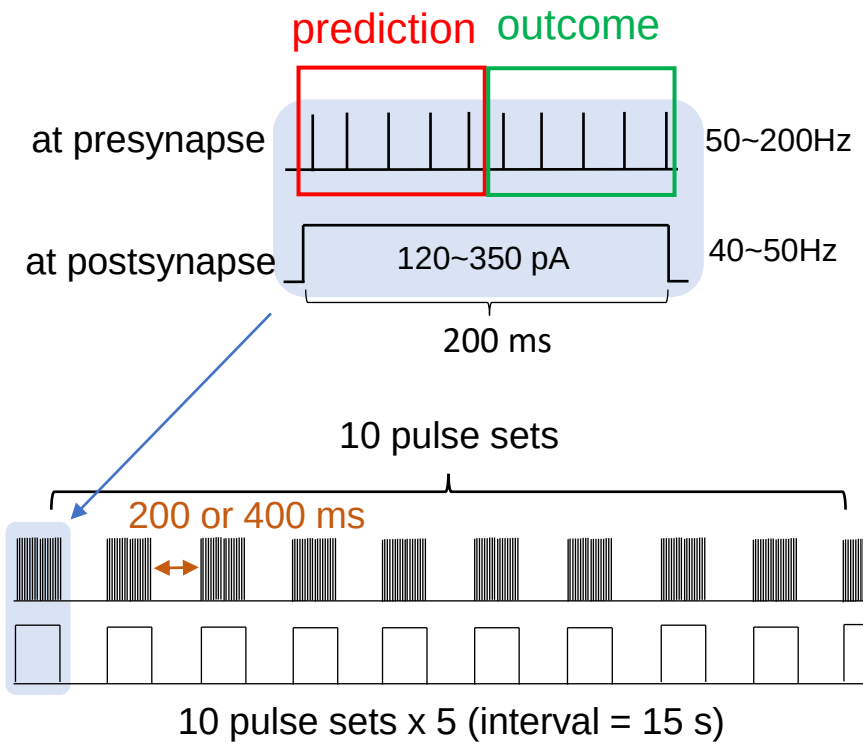
Typical STDP stimulus paradigm

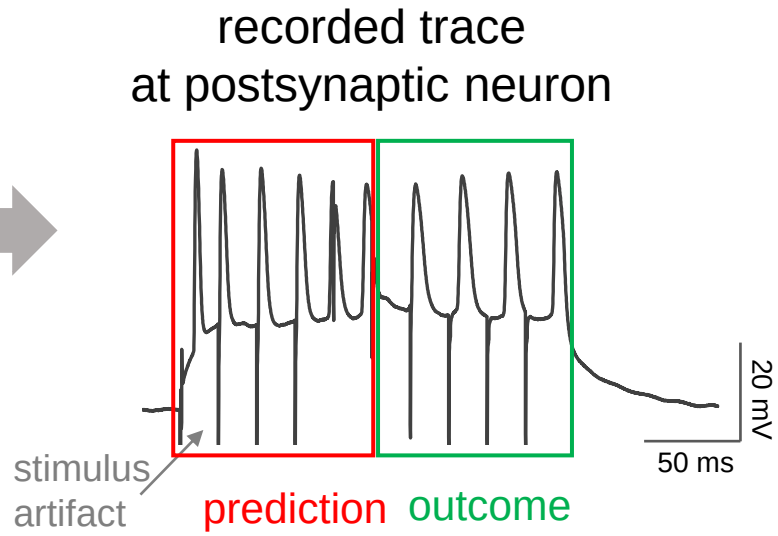


Zuzanna Brzosko et al(2019)

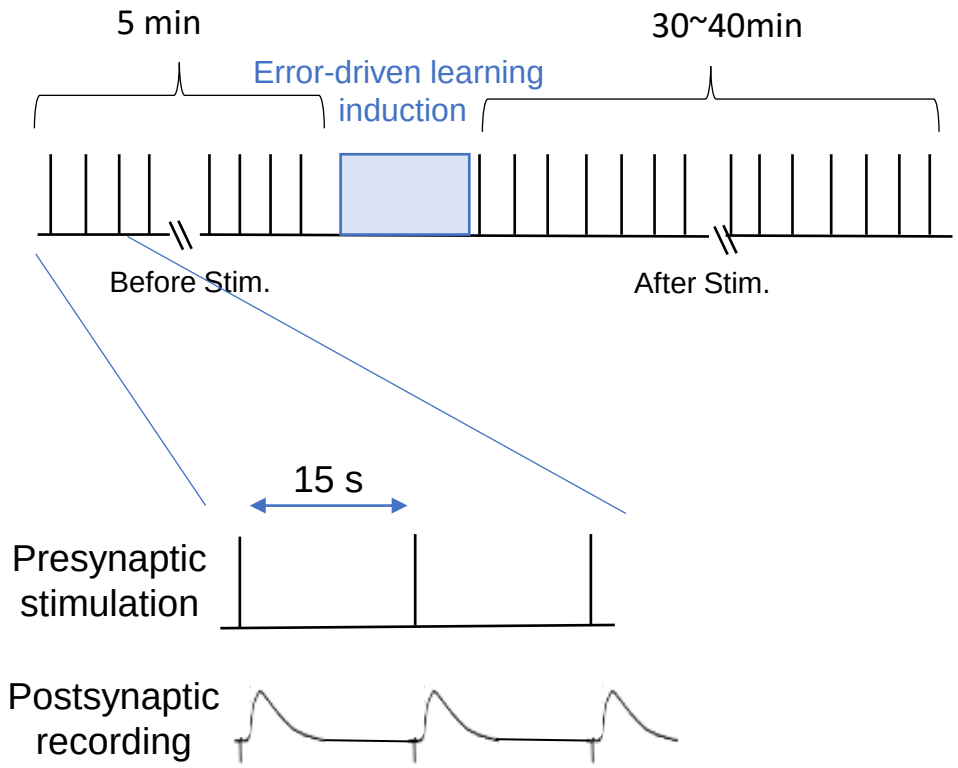


Watanabe S et al. 2002 PNAS

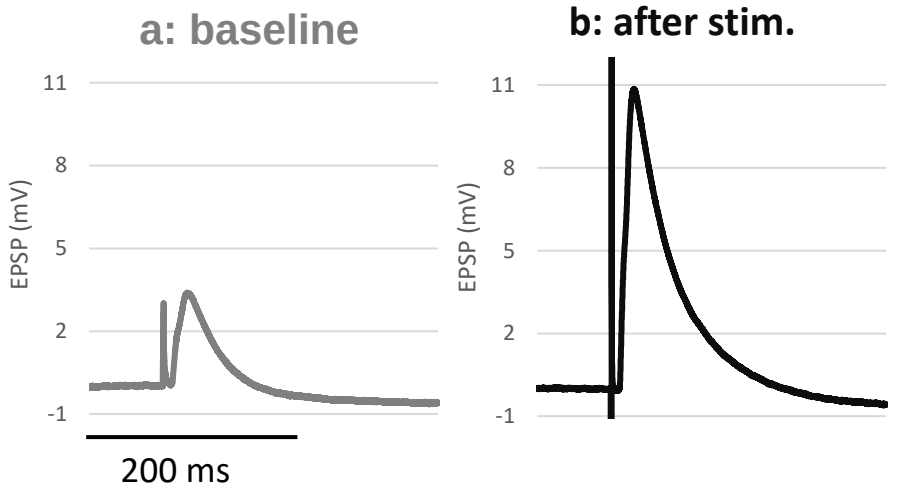




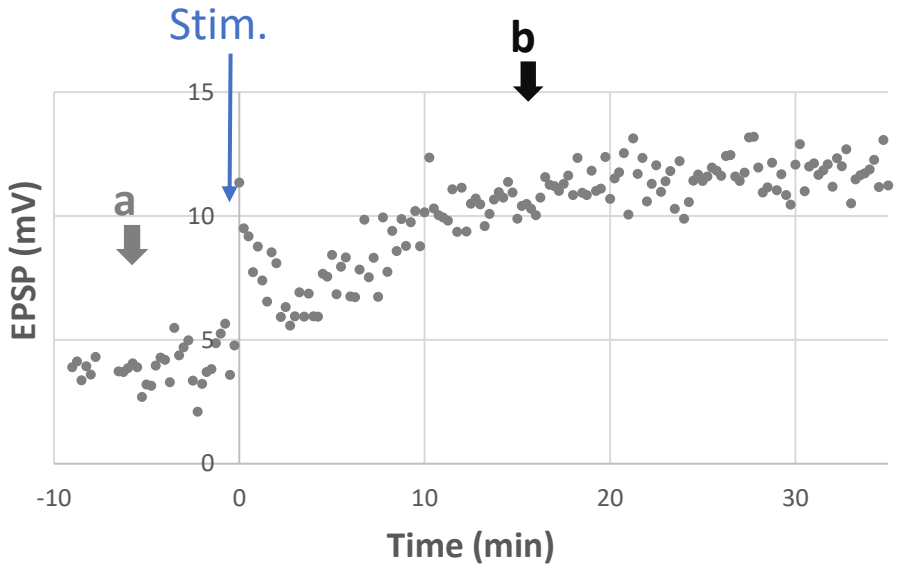
Synaptic activity recording



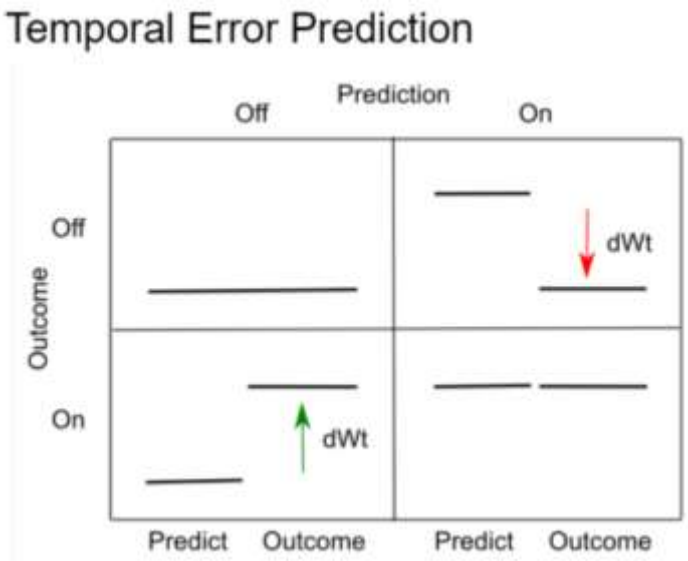
Recorded EPSPs

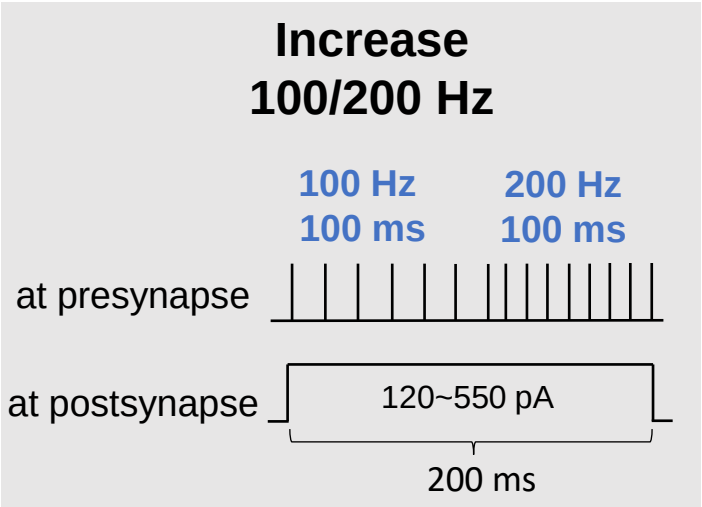


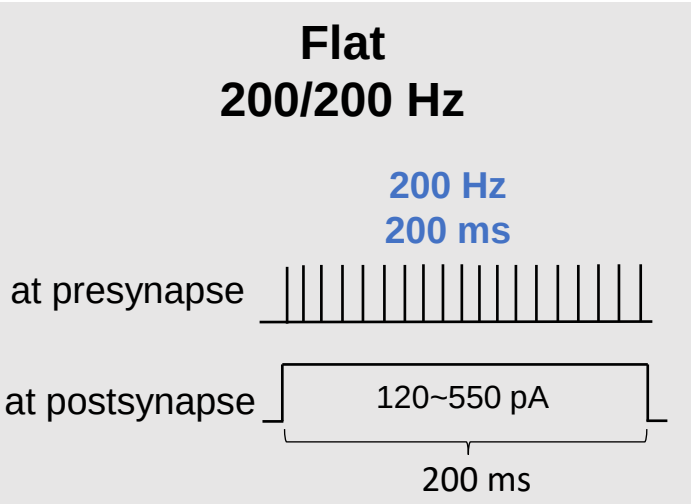
Measure amplitude of EPSPs and plot



Experiment protocols

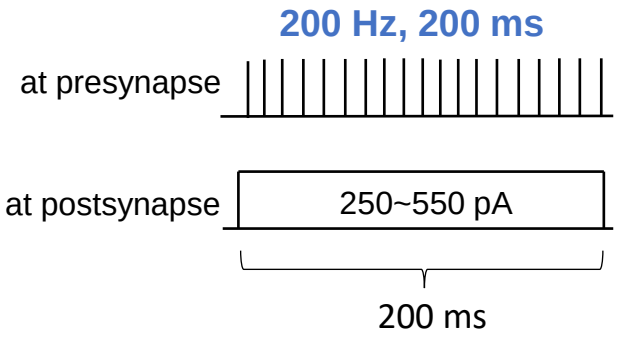


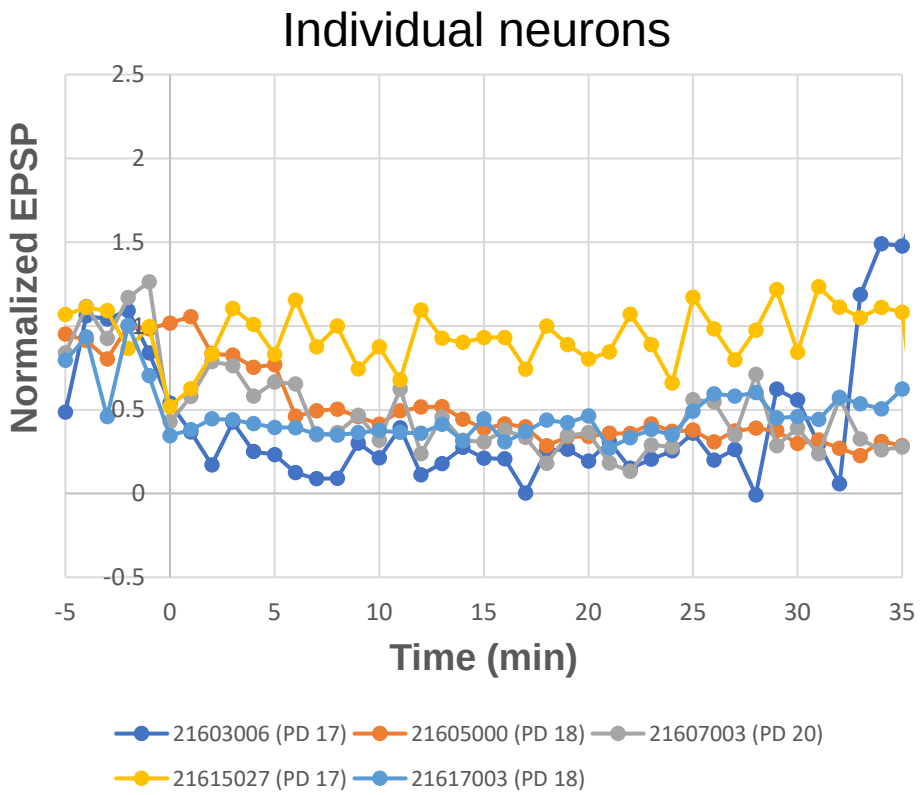


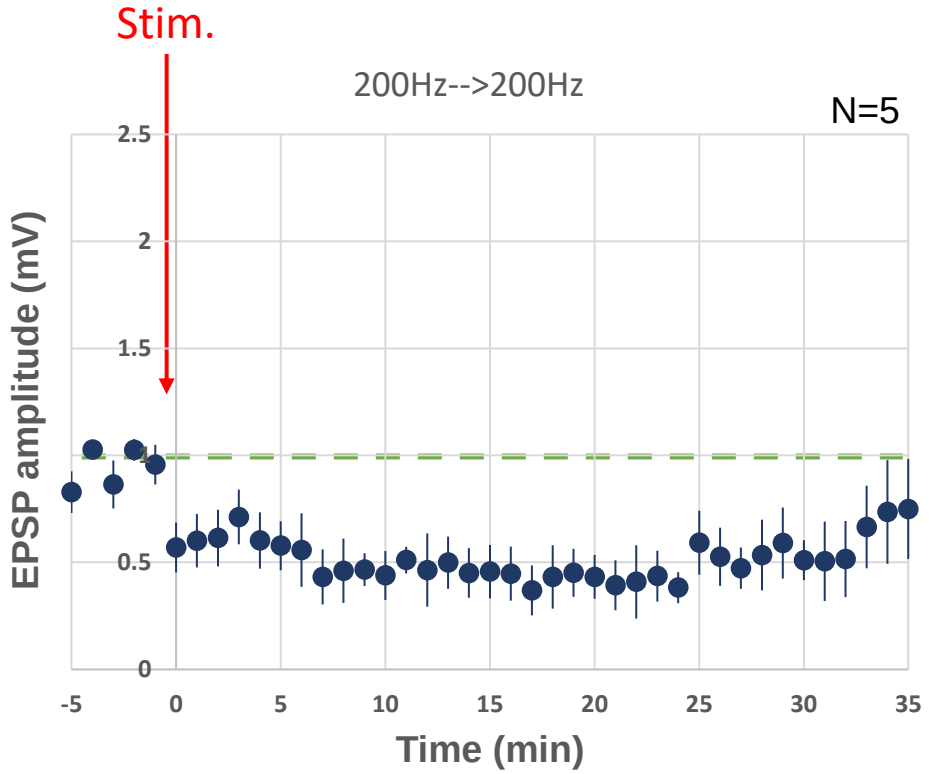


Results

Flat
200/200 Hz
200ms ISI

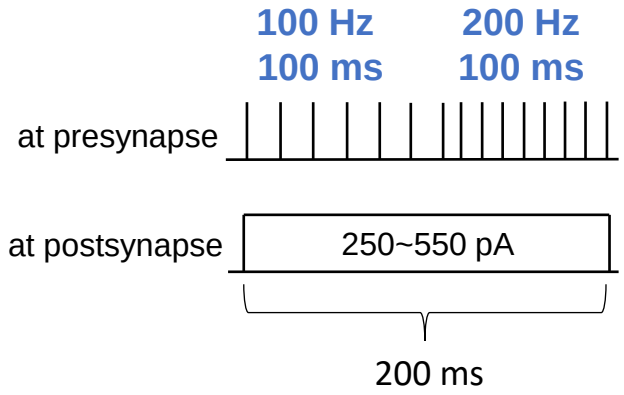


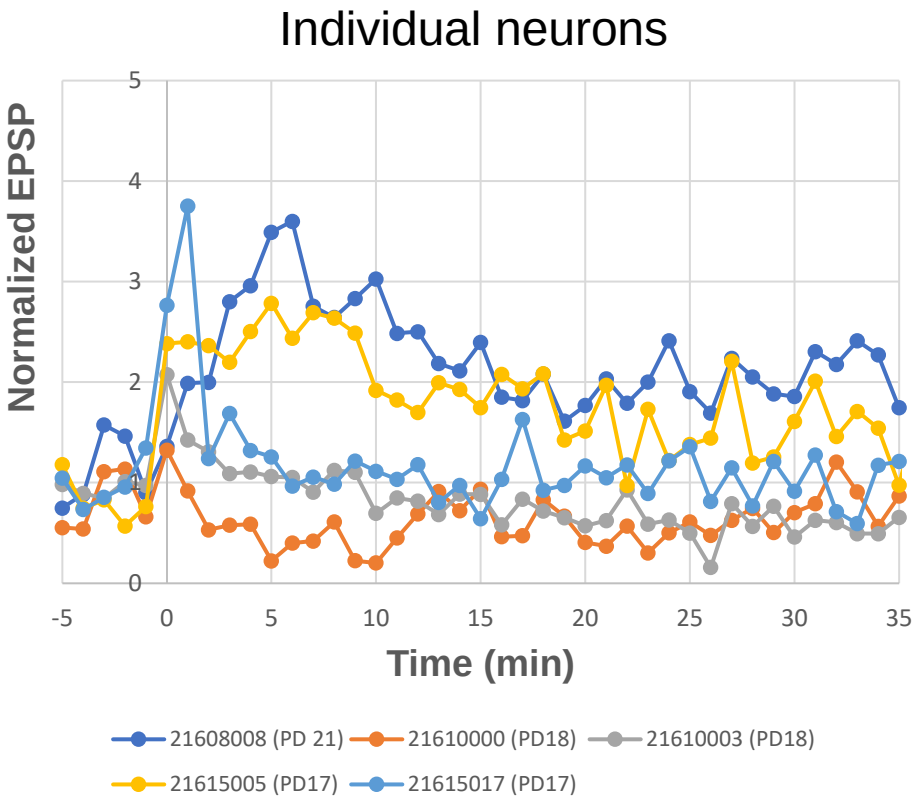


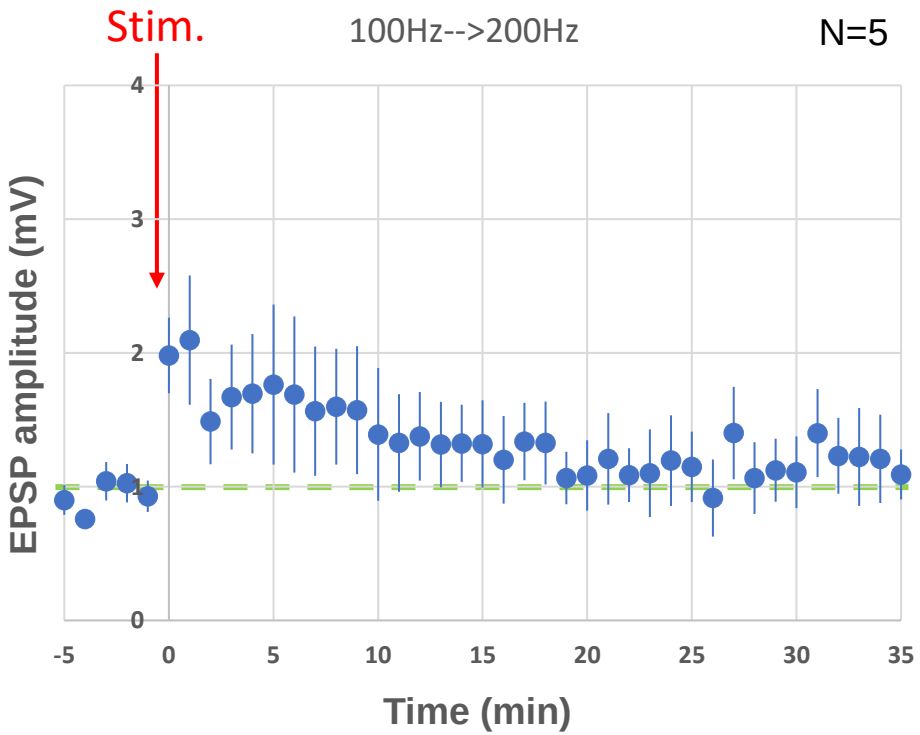


Results

Increase 100/200 Hz
200ms ISI

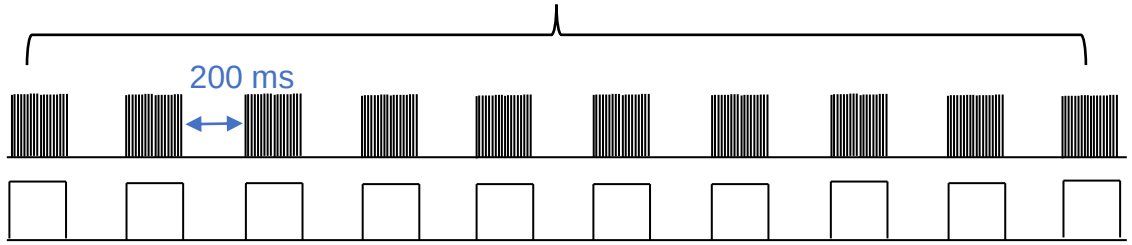




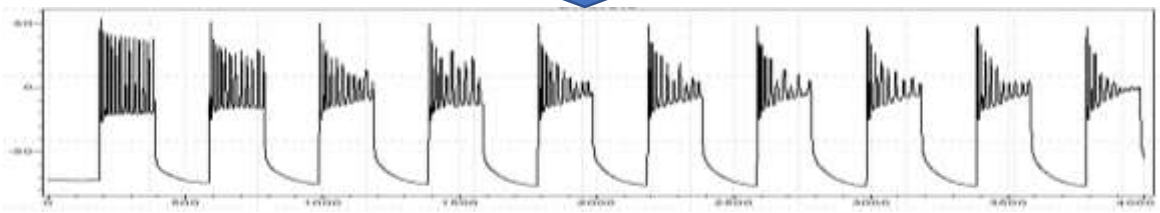


Adjust inter-set-interval of induction protocols

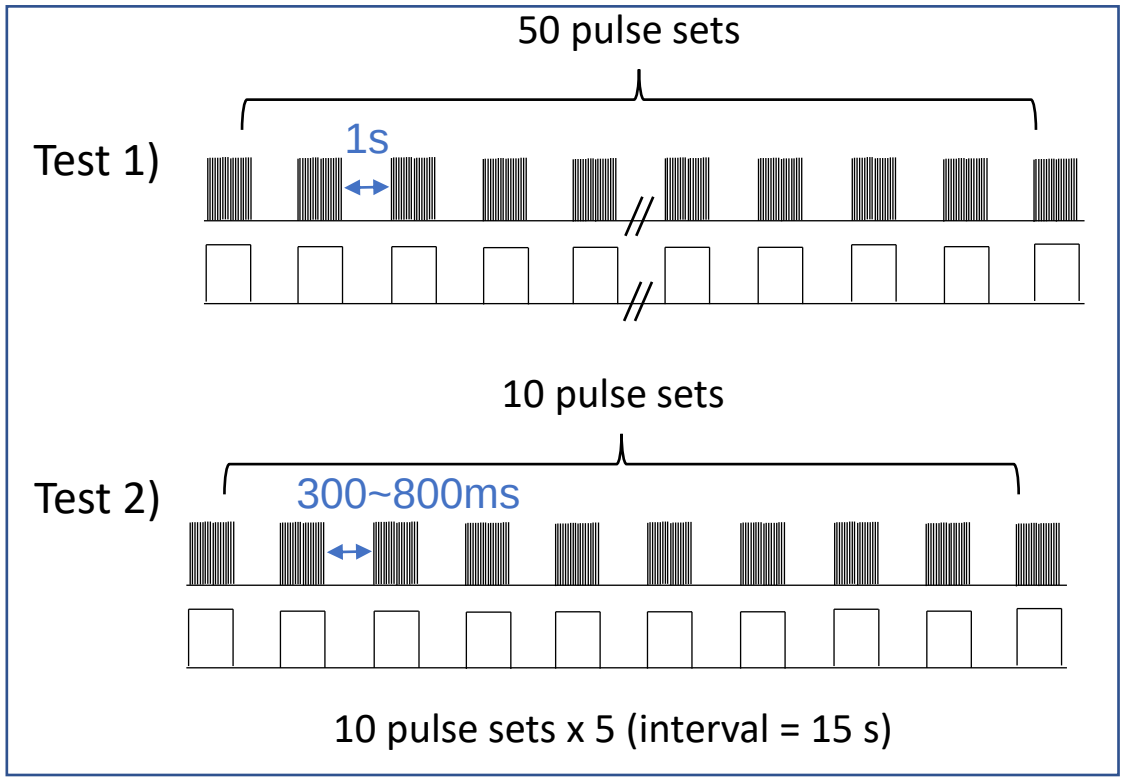
10 pulse sets



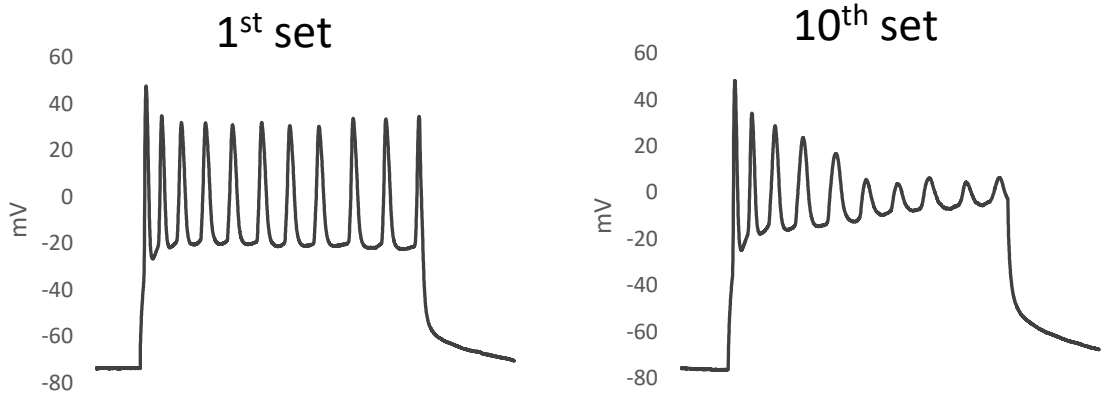
10 pulse sets x 5 (interval = 15 s)



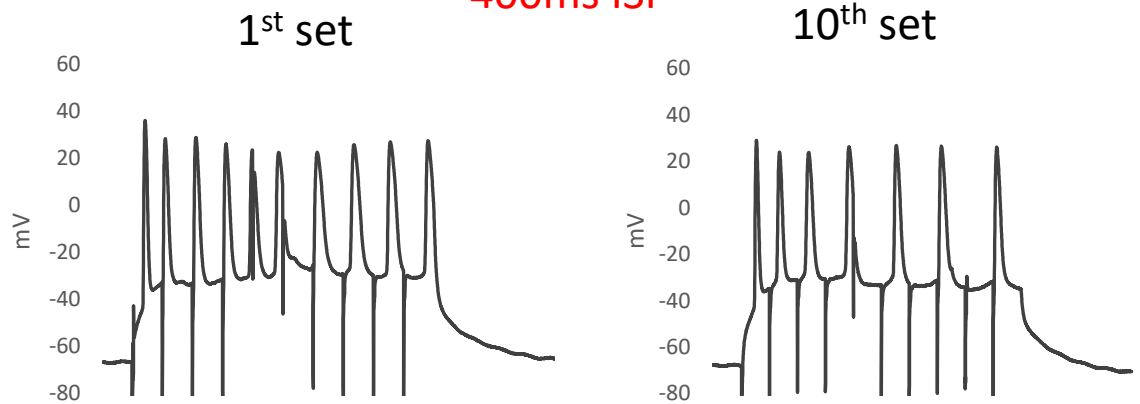
200ms ISI, postsynaptic injection only (380pA)



200ms ISI

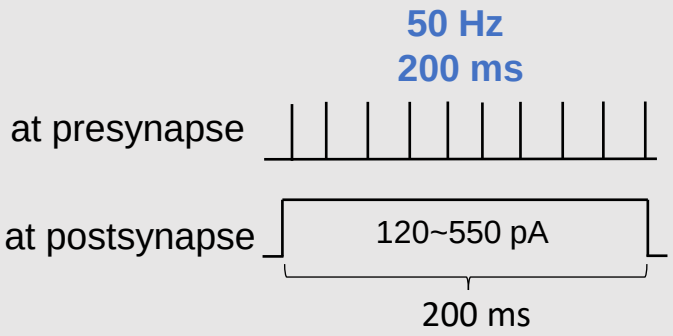


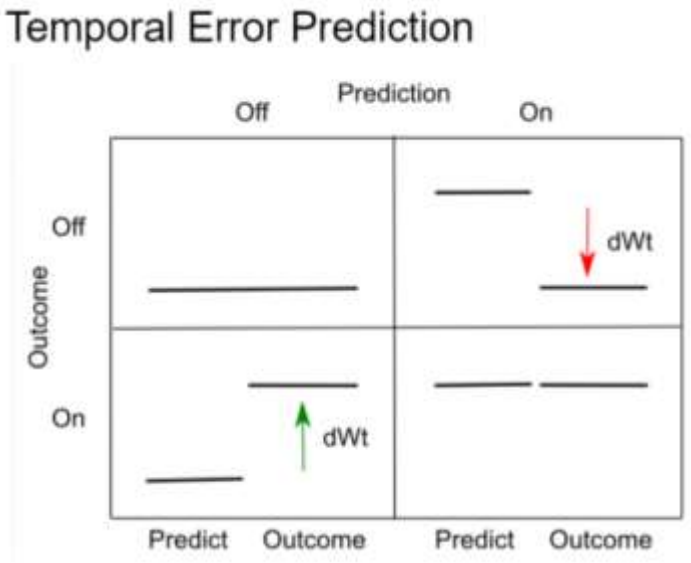
400ms ISI



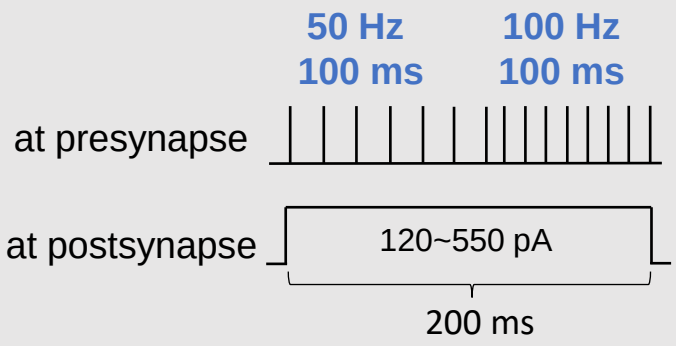
Experiment protocols

Flat
50/50 Hz

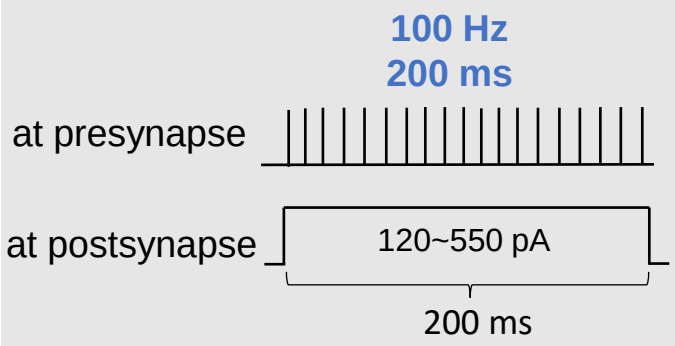




Increase
50/100 Hz

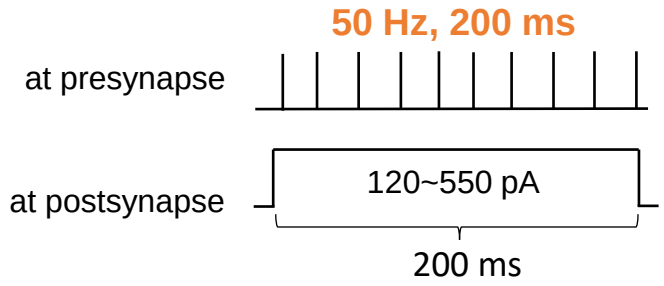


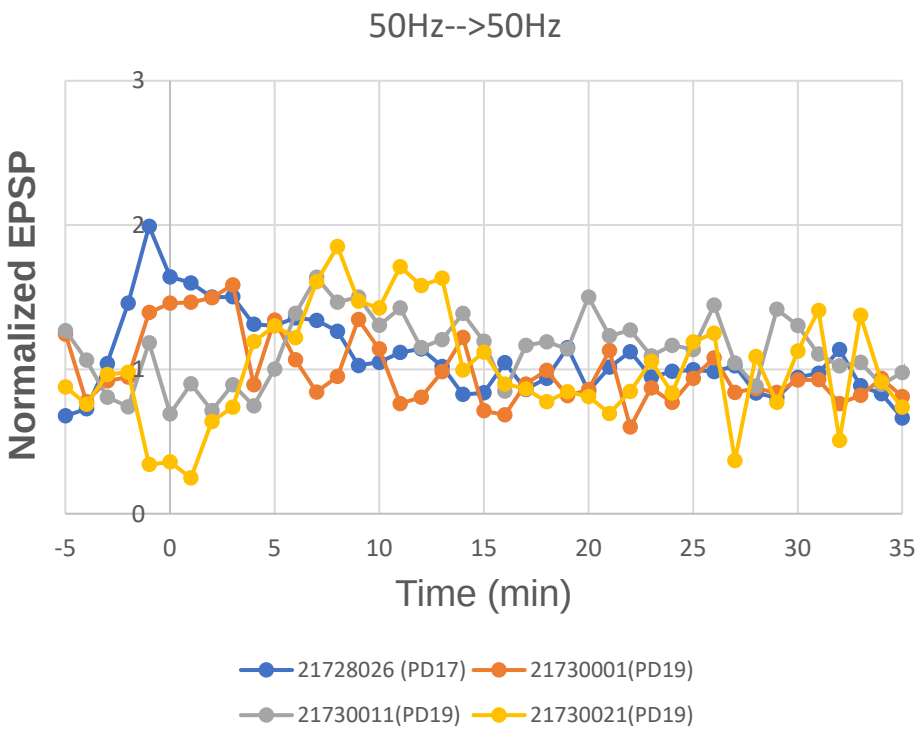
Flat
100/100 Hz

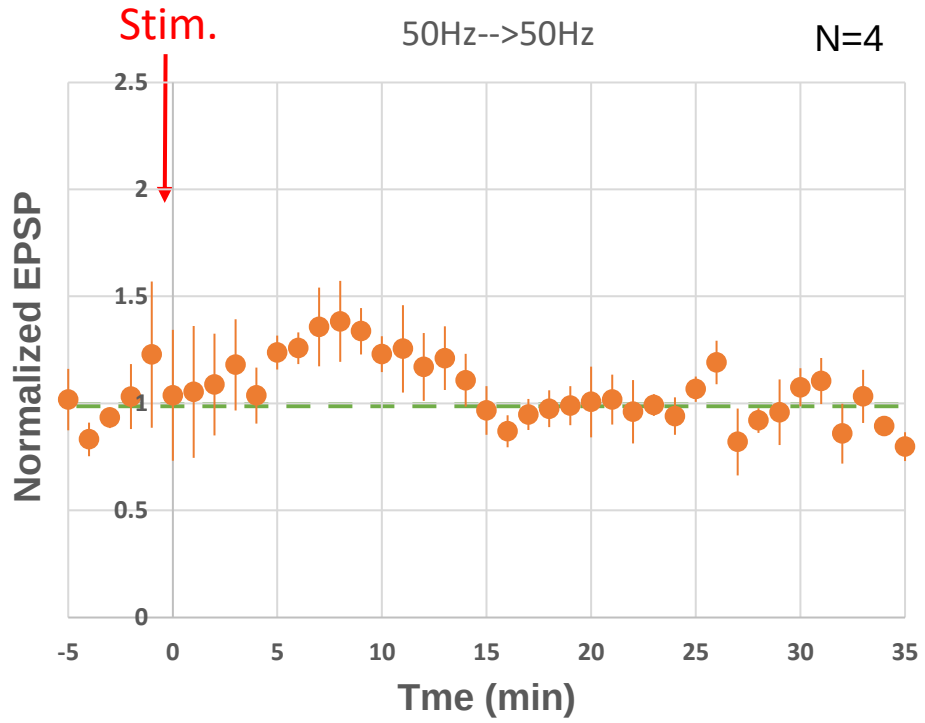


Results

Flat
50/50 Hz
400ms ISI

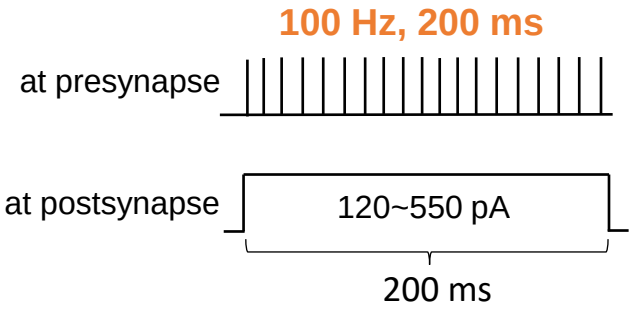


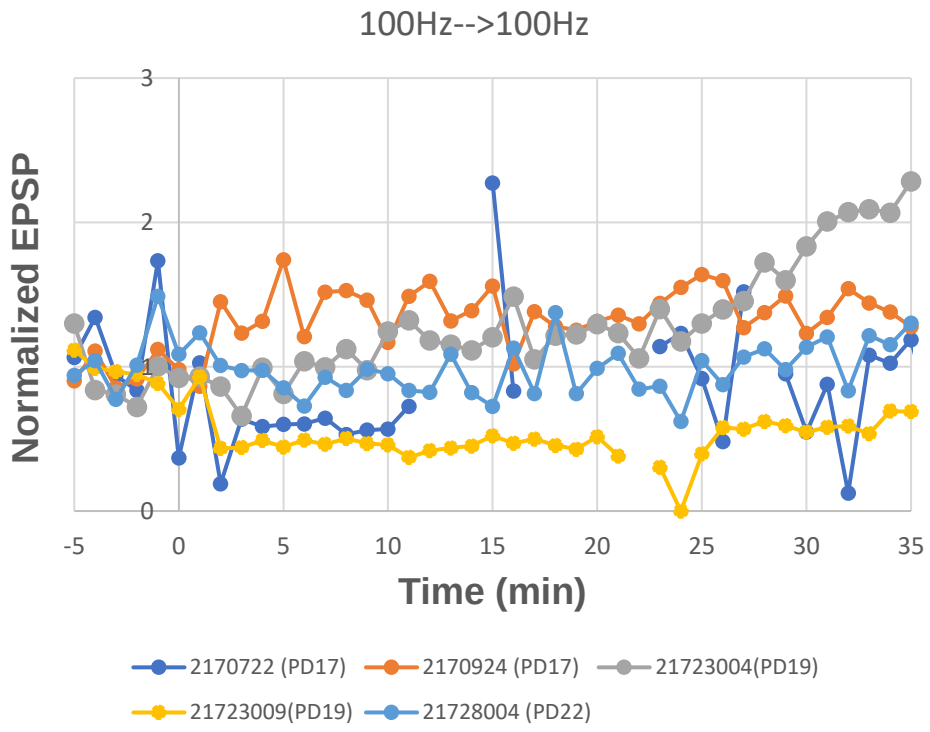


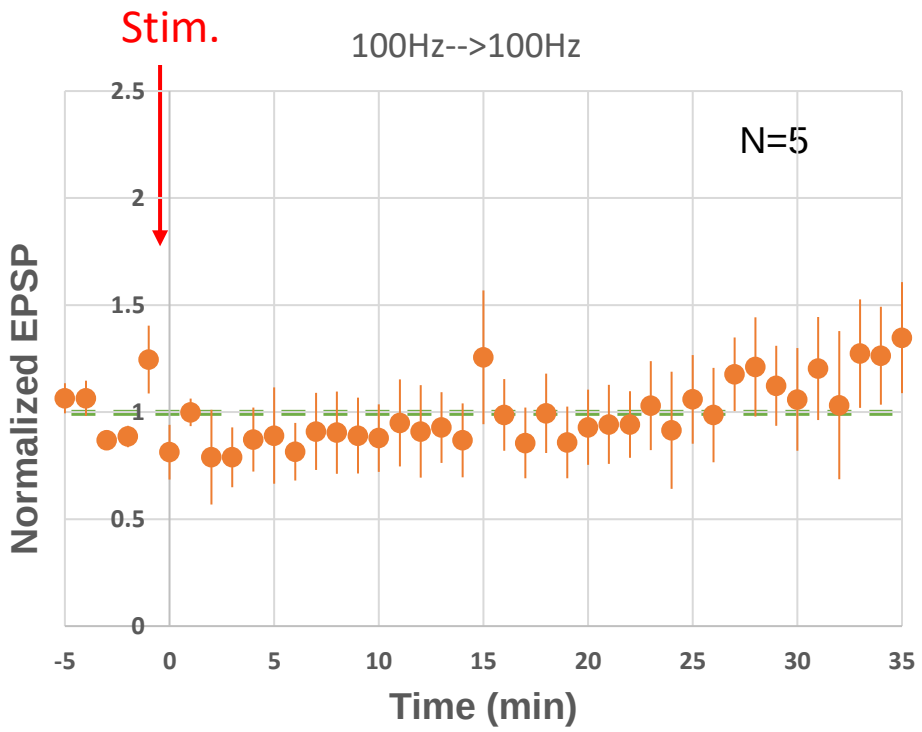


Results

Flat
100/100 Hz
400ms ISI

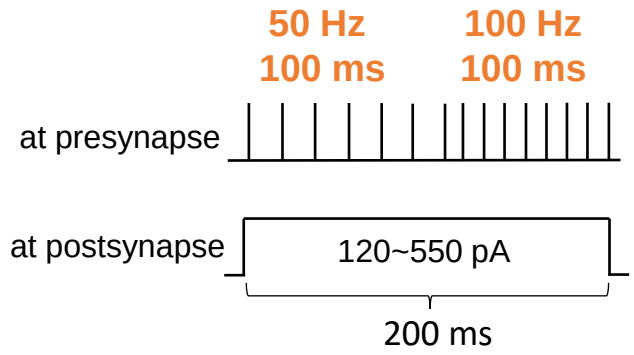


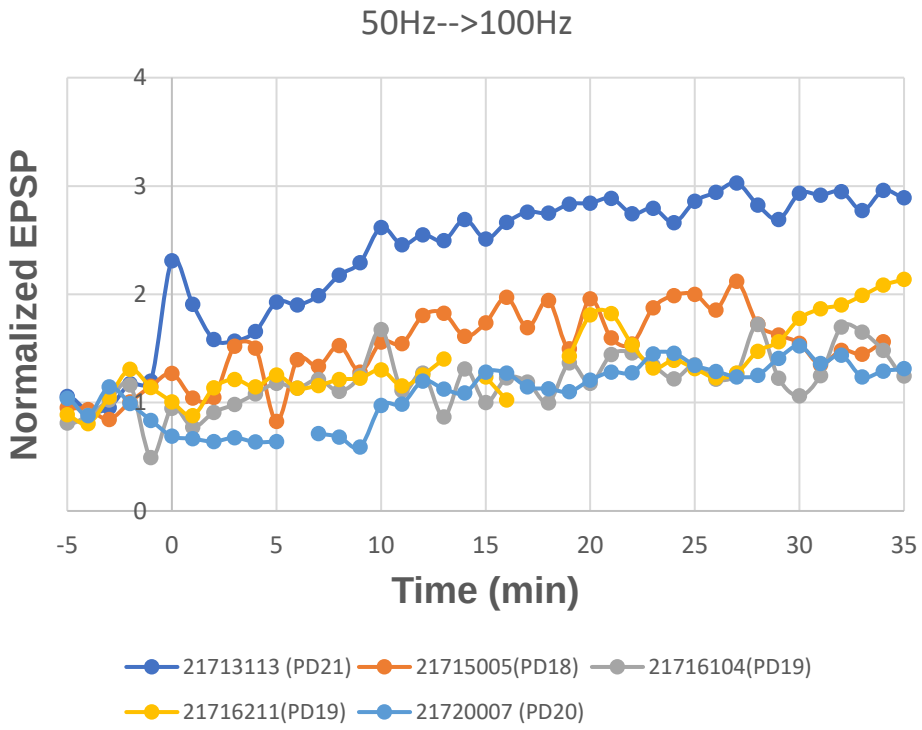


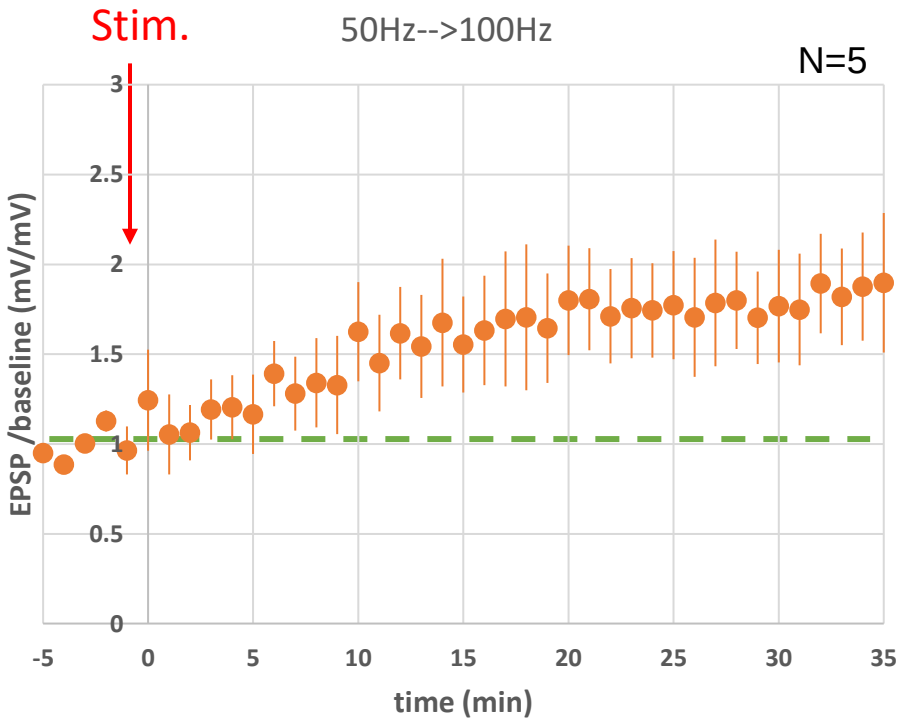


Results

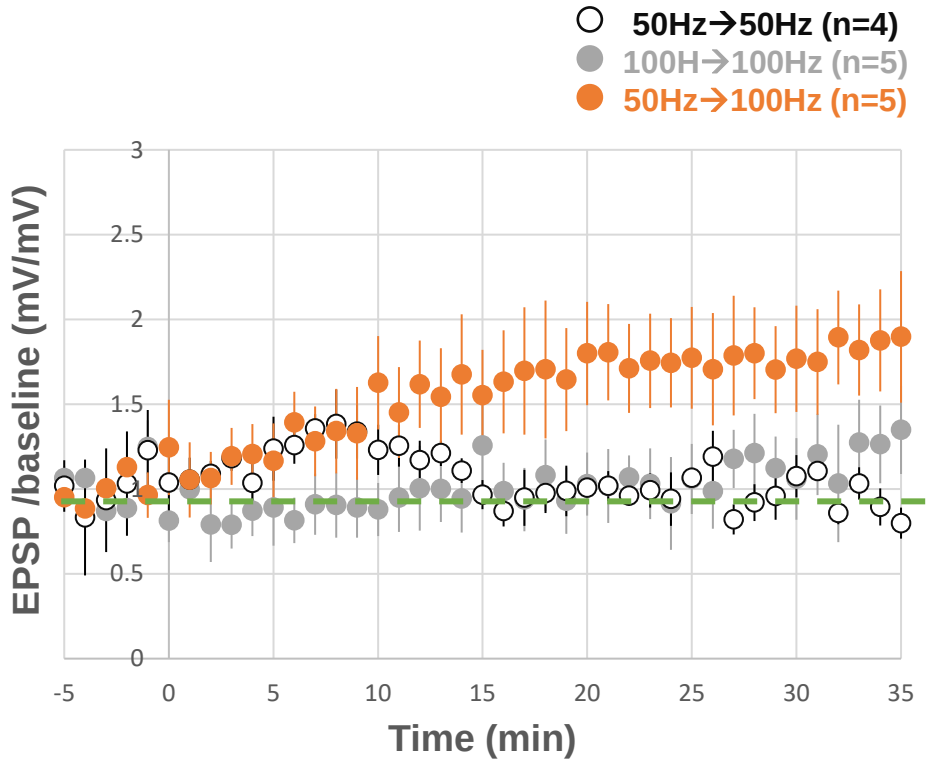
Increase 50/100 Hz
400ms ISI

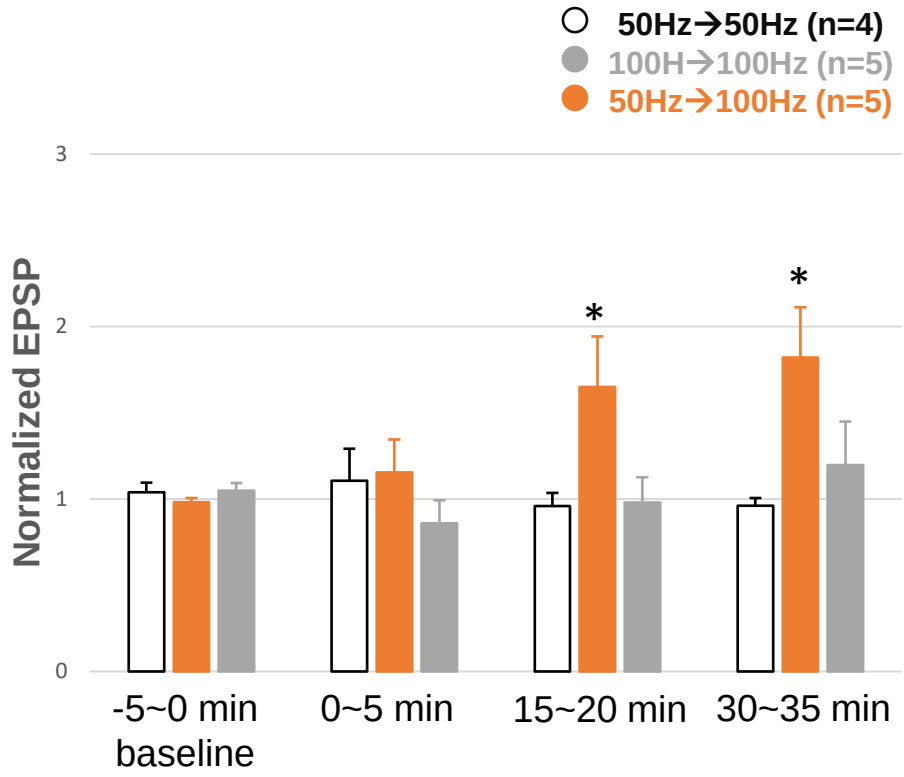






Summary





- Increase (50Hz→100Hz) stimulus induced LTP.
- Flat (50Hz→ 50Hz) didn't change synaptic strength.
- Flat (100Hz →100Hz) didn't change synaptic strength.

Future plans

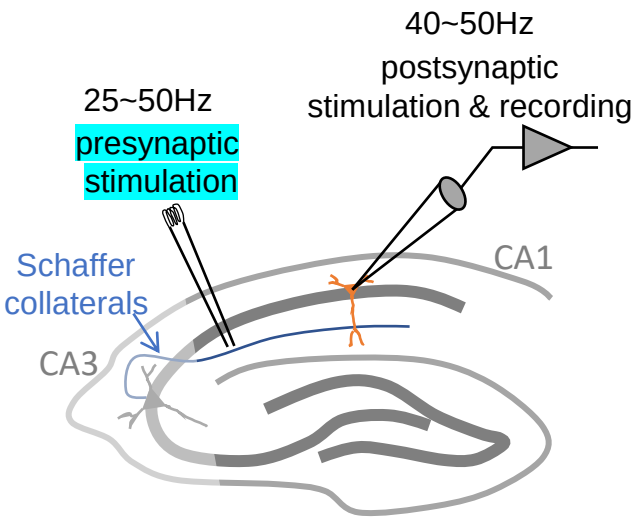
How can I increase the yield of the experiment?

- 1-1.5 cell / day
- Cell health is the critical to the success of the experiment
- 2~3 hr after acute brain slice preparation, cells are not sufficiently healthy to long time recording.

I’m going to…

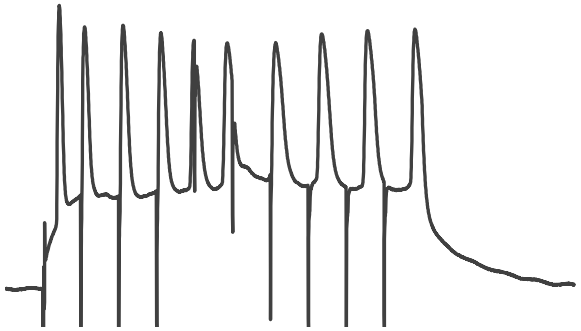
1. Test using mice from different vivariums (Cole B, MedNeuro, Sound booth in MedNeuro).
2. Test different slice cutting solutions.
3. Test different slice recovery solutions and recovery time.

Future plans



acute hippocampal slice

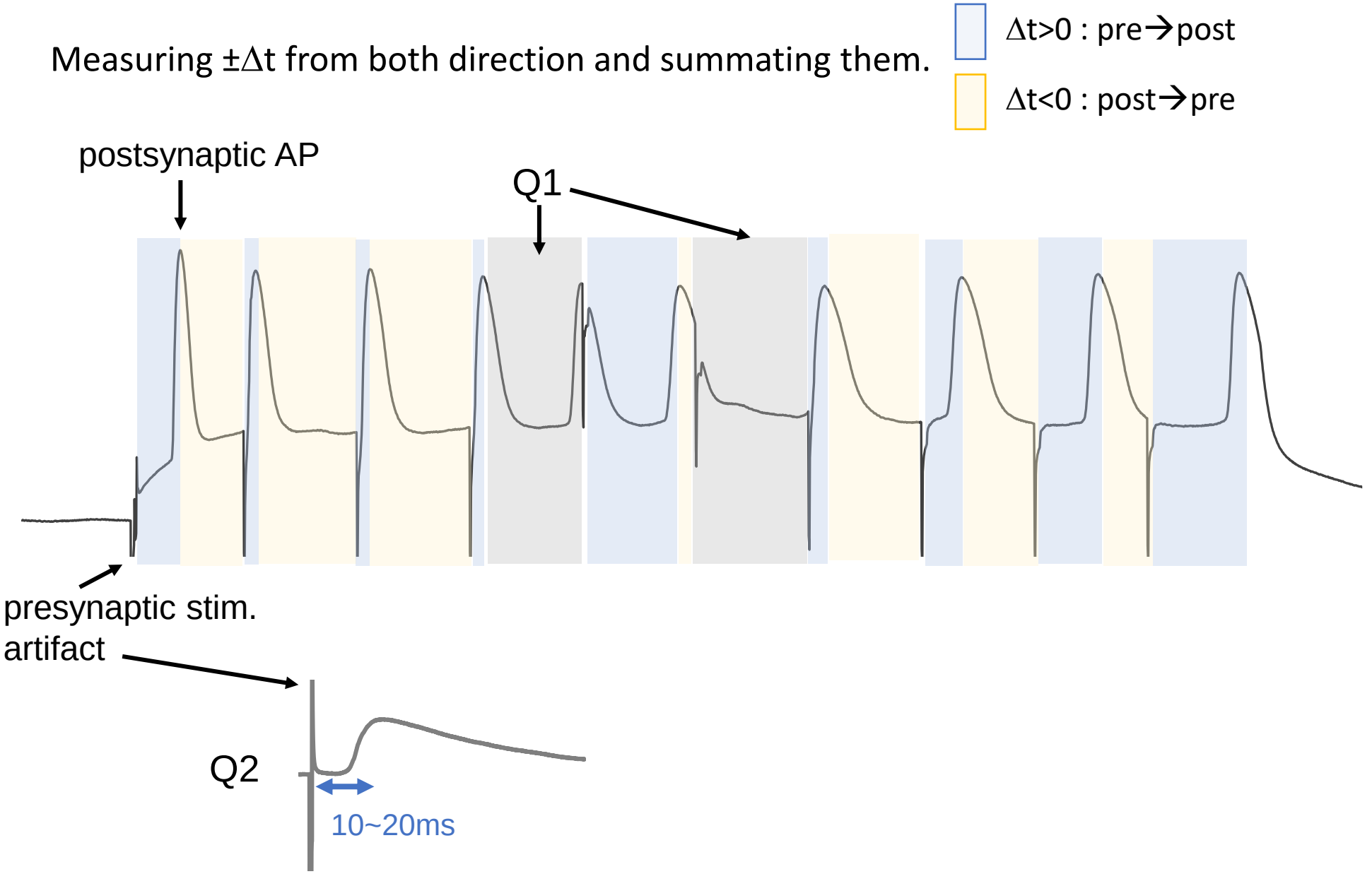
1. Get more data with 50Hz/50Hz (2-3 cells), 50Hz/100Hz (1-2 cells), and 100Hz/100Hz (1-2 cells).
2. Test On-then-Off (100Hz→50Hz) stimulation and get data with it (6-7 cells).
3. Test same stimulus paradigm with lower presynaptic frequency range (25~50Hz ?).



4. Analyze Δt between presynaptic stimulation and postsynaptic action potential.

How is Δt measured?

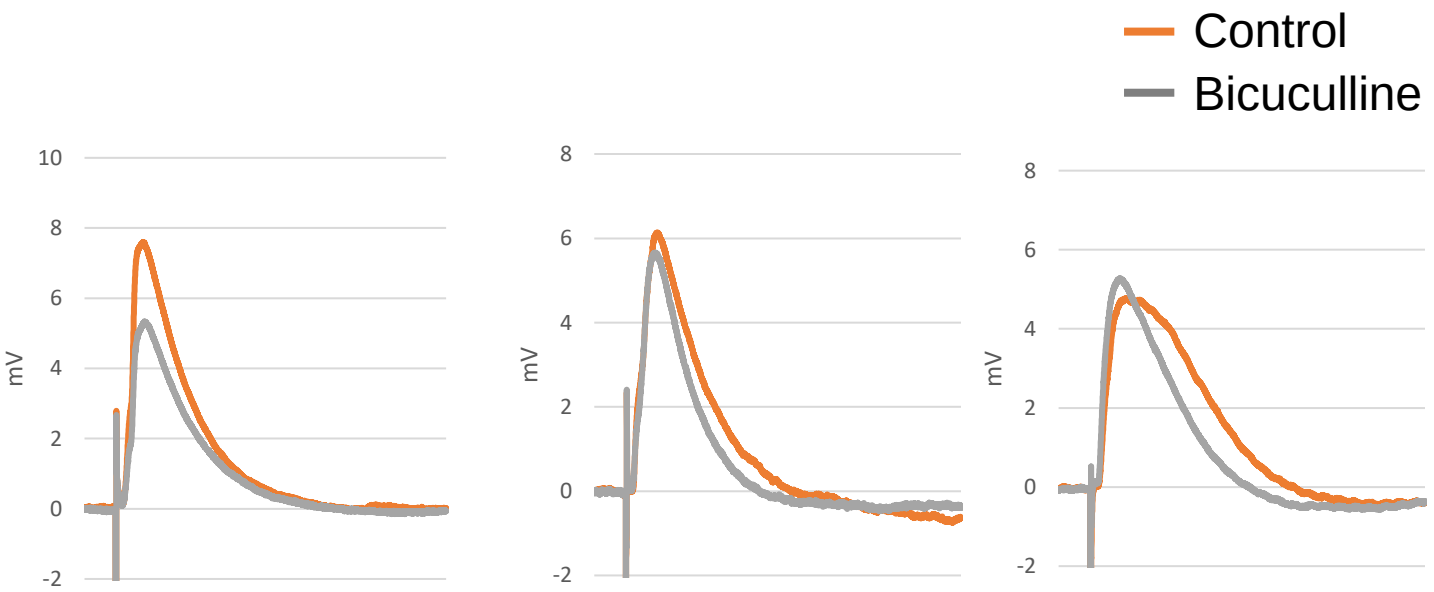
Measuring ±Δt from both direction and summating them.



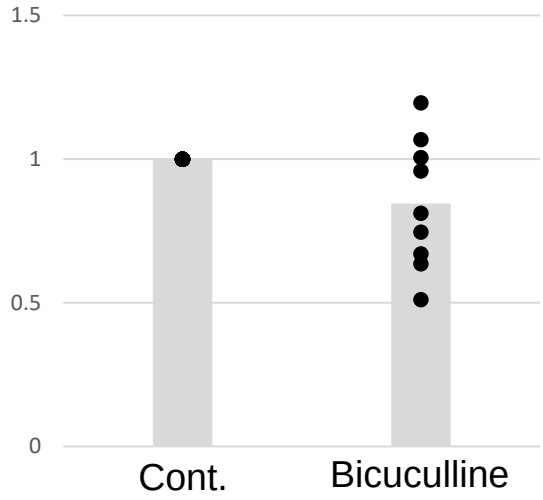
Test GABAergic synaptic activity in EPSPs

- 10 μM Bicuculline added end of the experiment (50Hz→100Hz, 400ms).
- Orange traces are recorded before applying bicuculline.
- Gray traces are recorded 5-10 min after bicuculline application.

Bicuculline: $GABA_A$ antagonist



n=9



Decreased > 2mV : 3 cells/13 cells
No changes < ±2mV: 8 cells/13 cells
Increased > 2mV : 2 cells/13 cells