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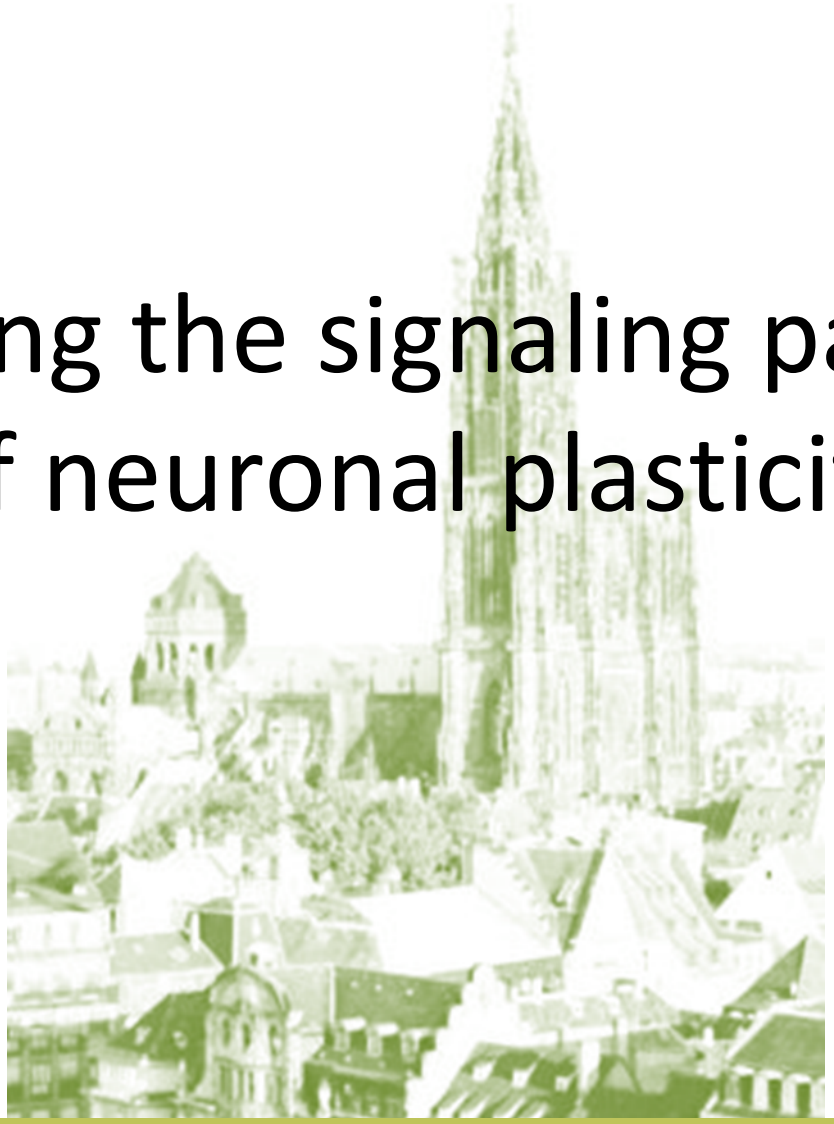
Technologies pour la santé

Modelling the signaling pathways of neuronal plasticity



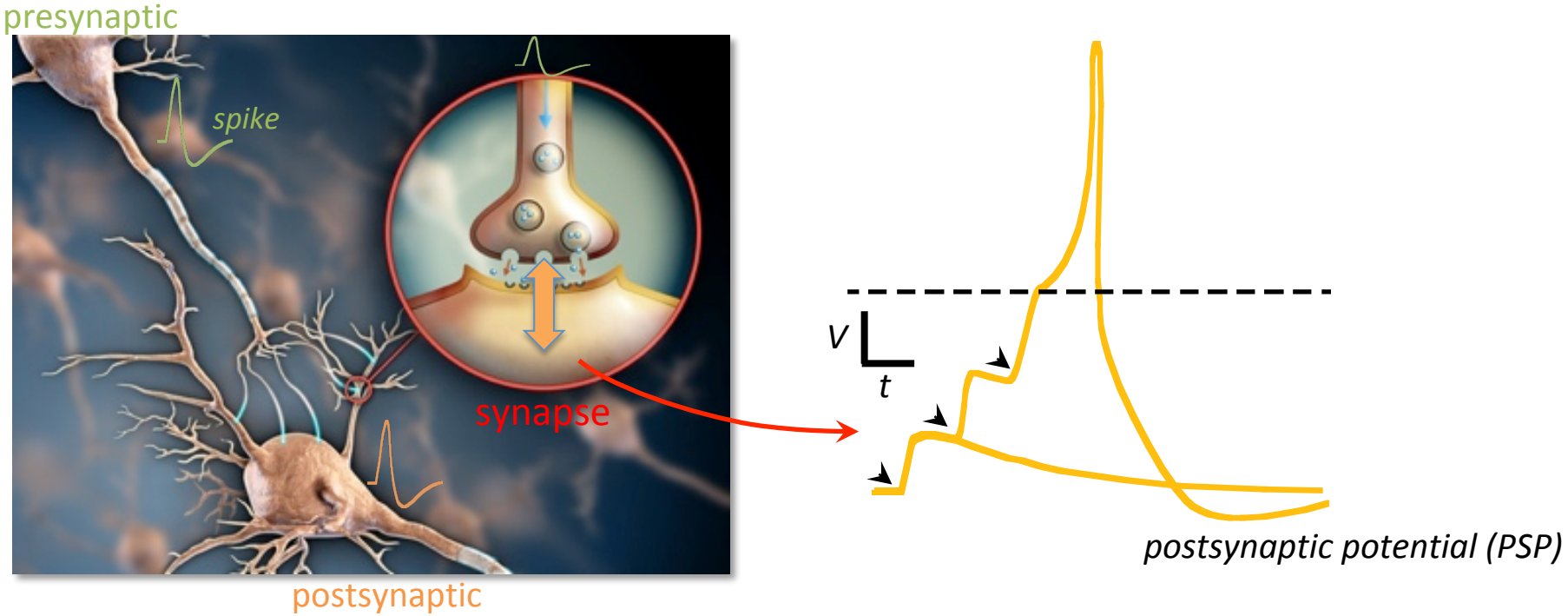
Hugues Berry
Inria, Lyon

www.inrialpes.fr/Berry

Laurent Venance
CIRB, Paris

www.college-de-france.fr/site/en-cirb/venance.htm

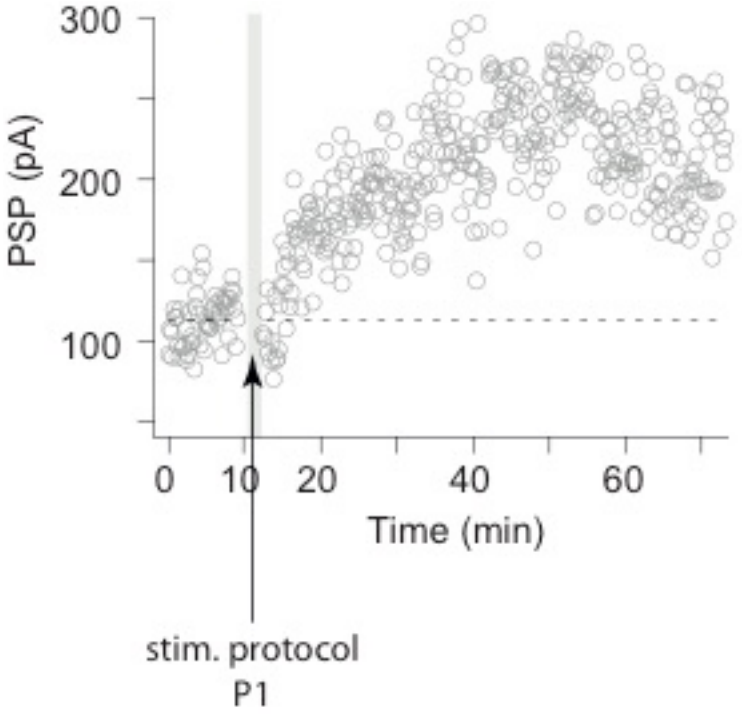
A primer on synaptic transmission



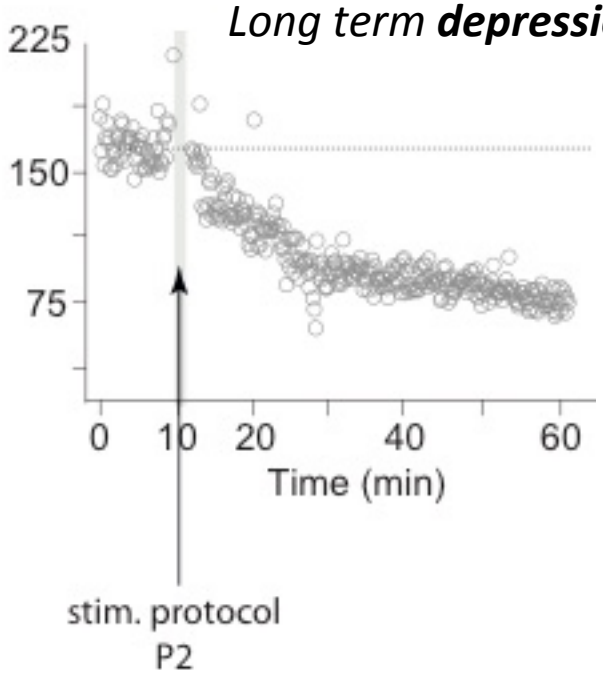
- The amplitude of each PSP is a measure of the influence of presyn. ⟶ postsyn.
- It is called the *synaptic weight*

Synaptic plasticity = changes of synaptic weight by neuronal activity

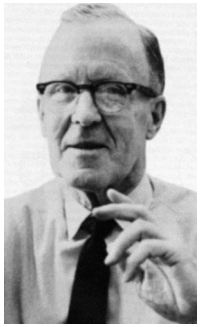
*Long term **potentiation***



*Long term **depression***

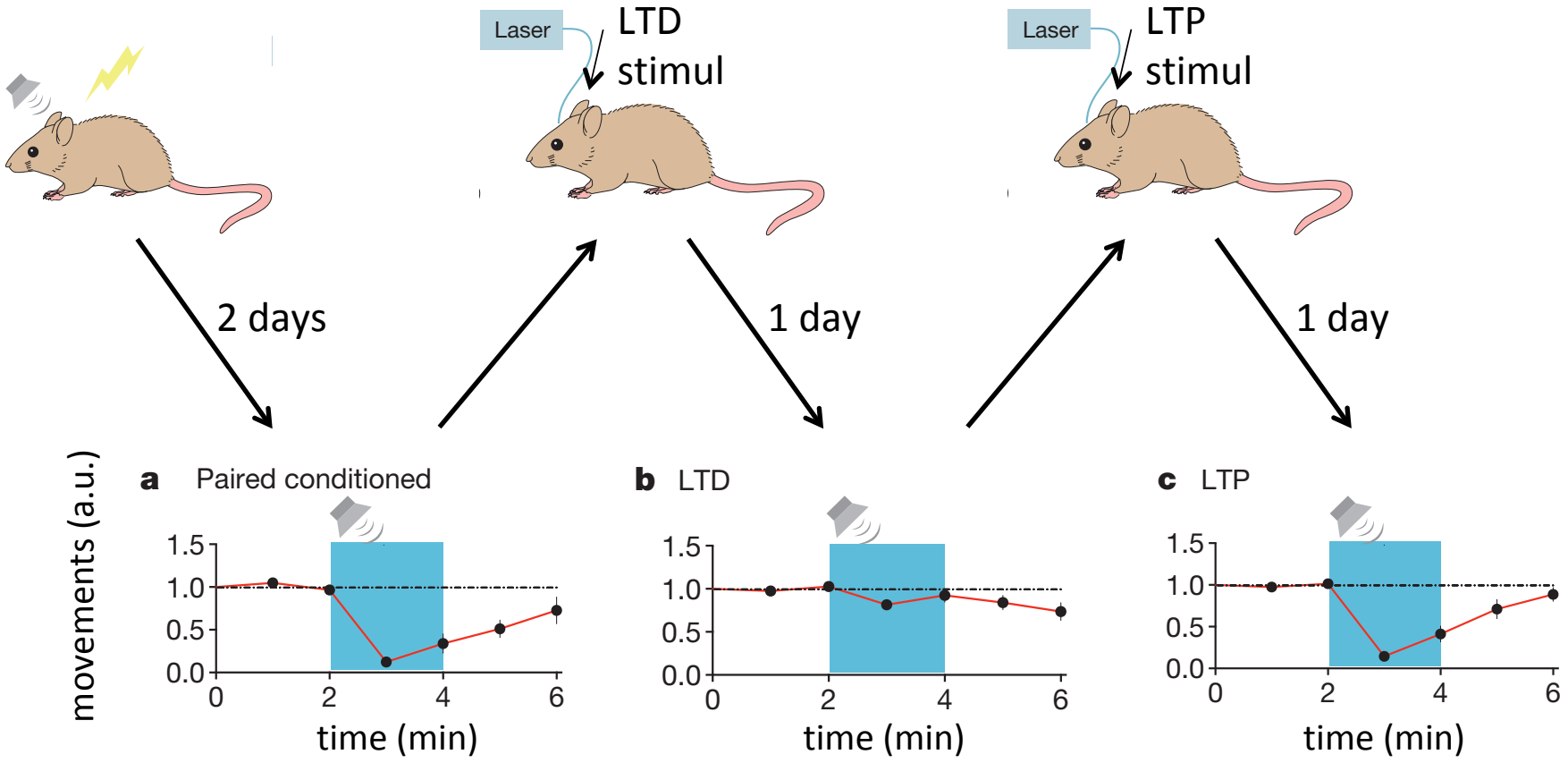


D.O. Hebb, 1949



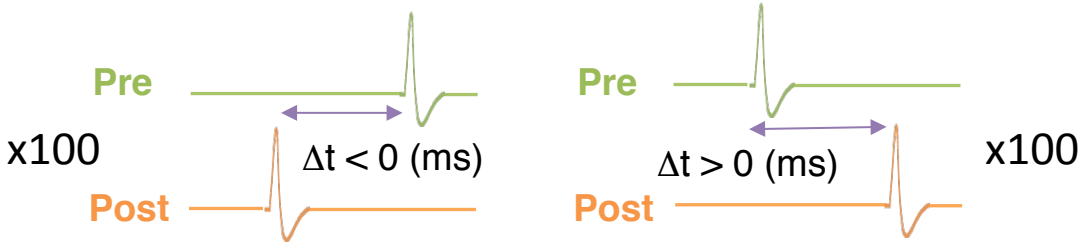
Weight changes maintained = memory

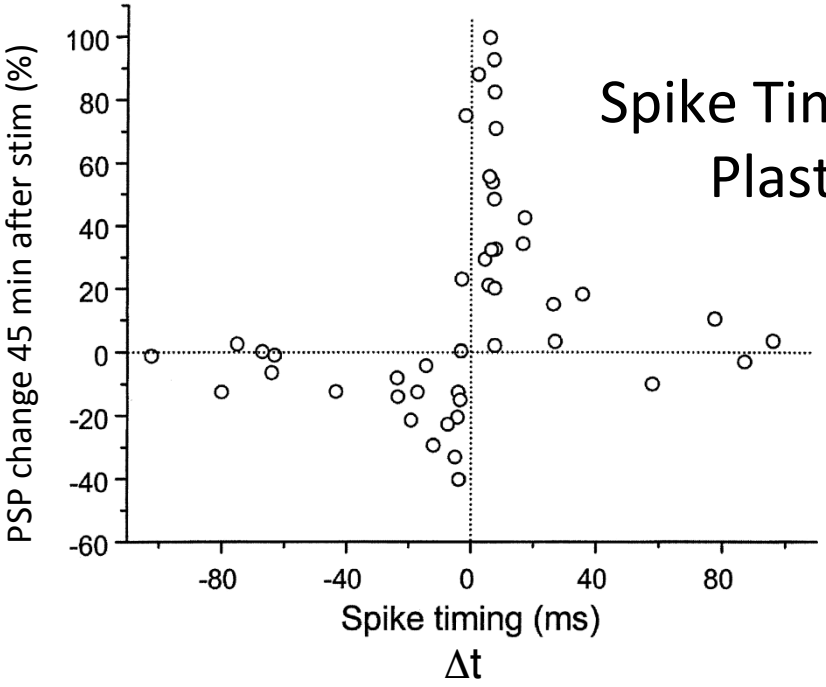
Long term plasticity is one substrate of learning & memory



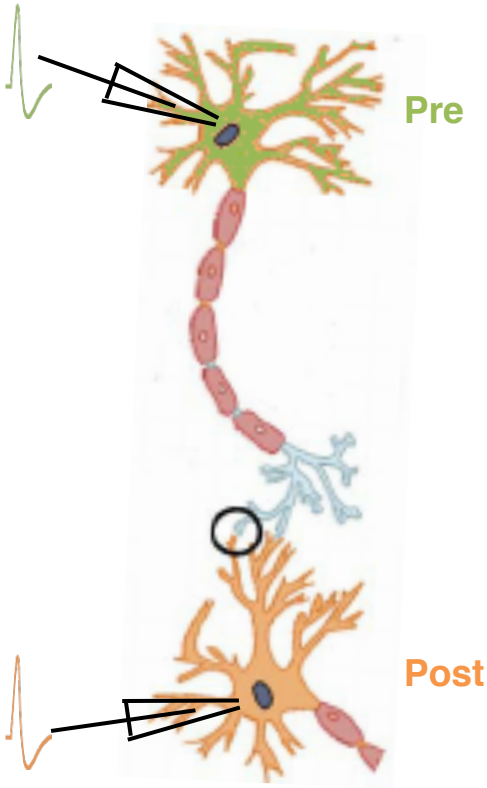
Nabavi et al., *Nature* 2014

Spike-timing controls plasticity





Spike Timing Dependent Plasticity (STDP)

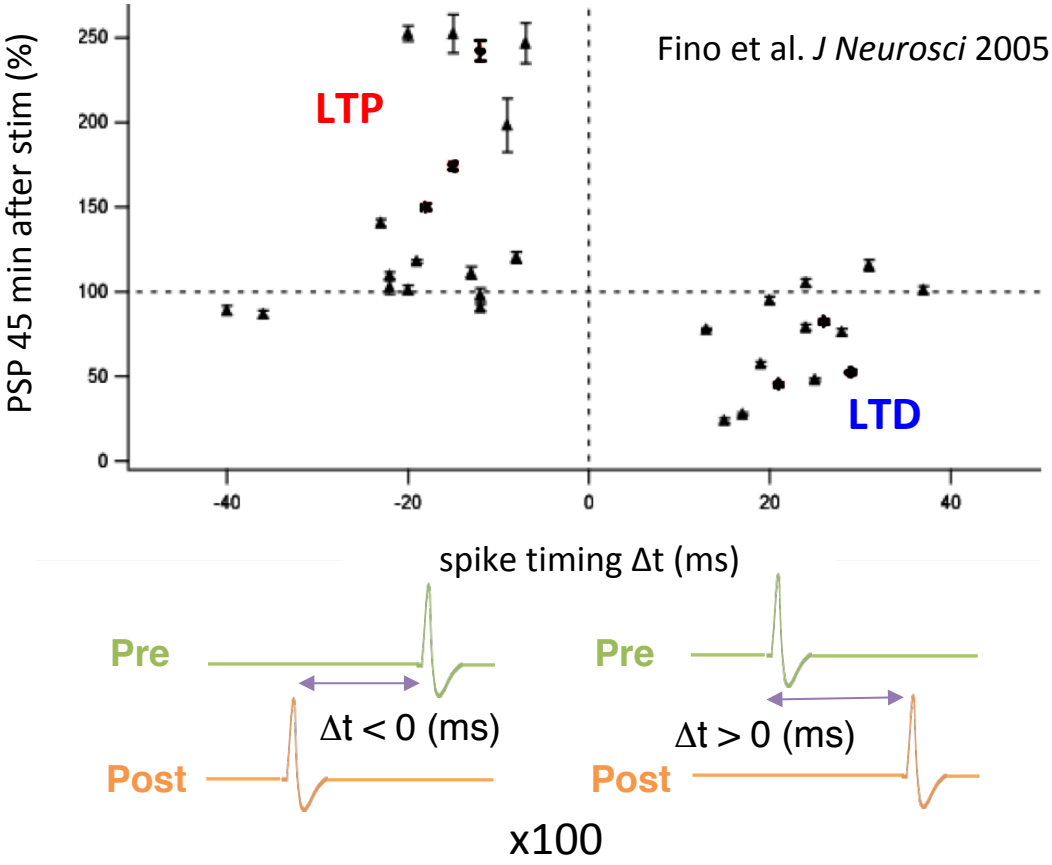


Markram et al., 1997 *Science*
Bi and Poo 1998 *J Neurosci*

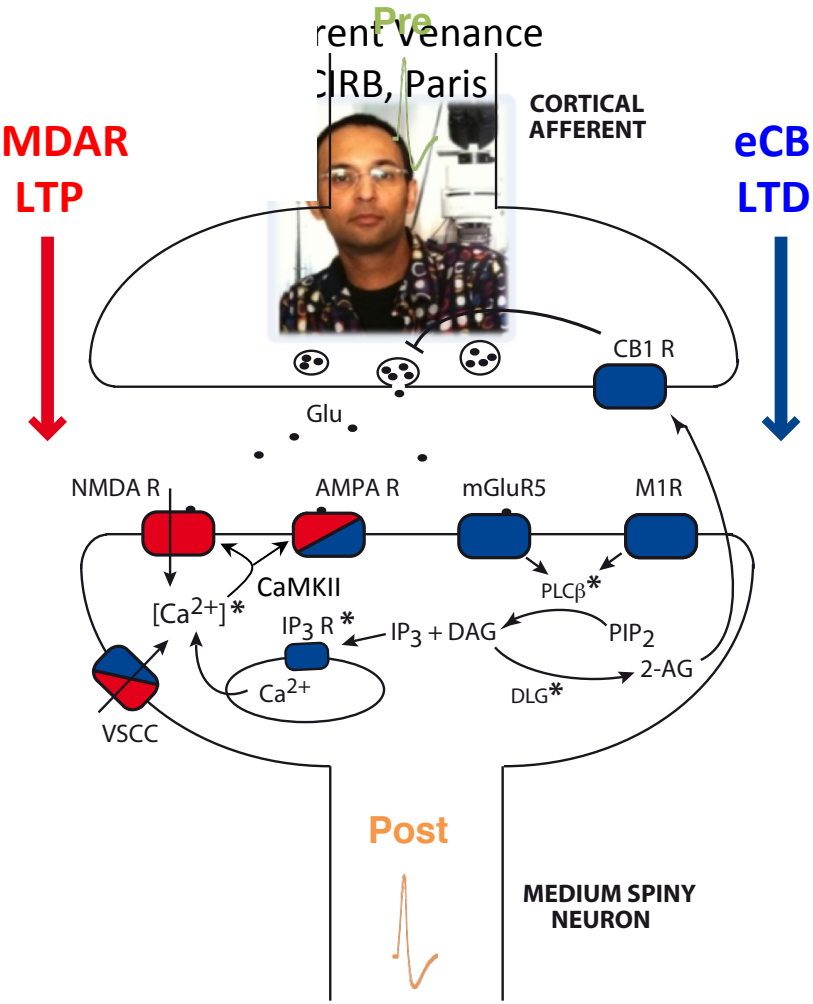
Open questions in STDP

- *in vivo* expression
- causal role in learning and memory
- variable depending on brain areas, external modulation (dopamine, serotonine)
- how Is it implemented by signaling networks
- implication in pathologies

STDP in the striatum

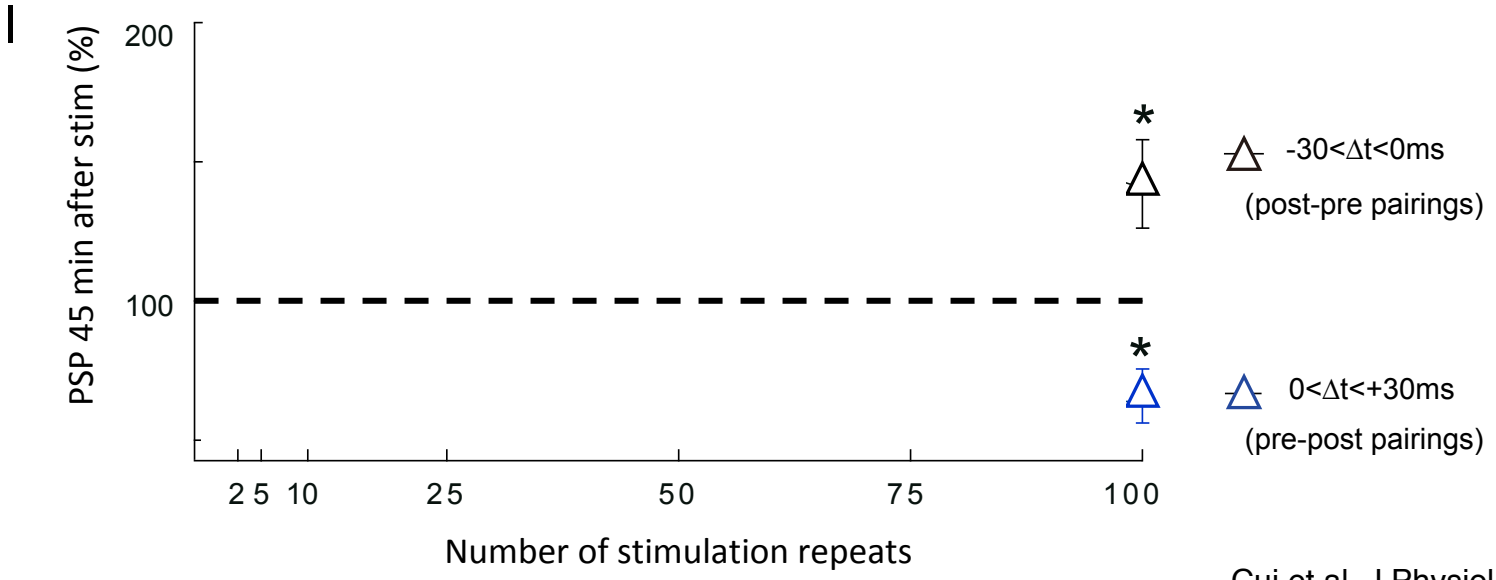


Fino et al. *J Neurosci* 2005



Fino et al. J Physiol. 2010

What happens with less stimulation?

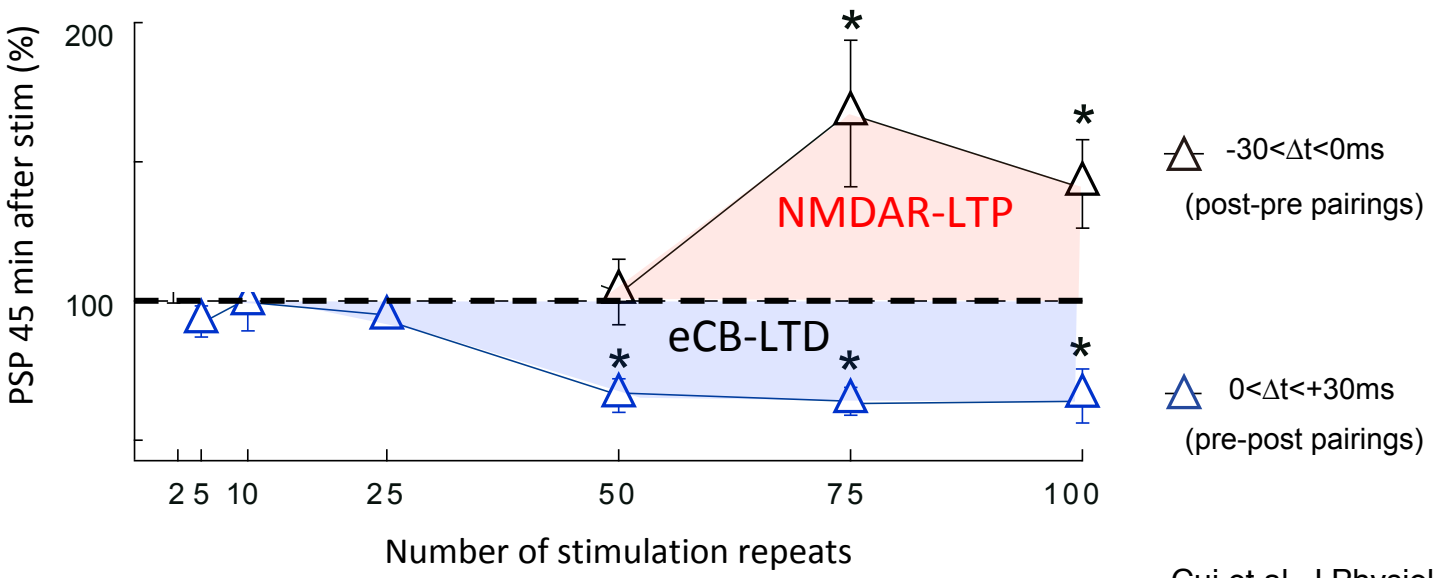


Cui et al. J Physiol 2015

What happens with less stimulation?

LTP and LTD both progressively disappear

I

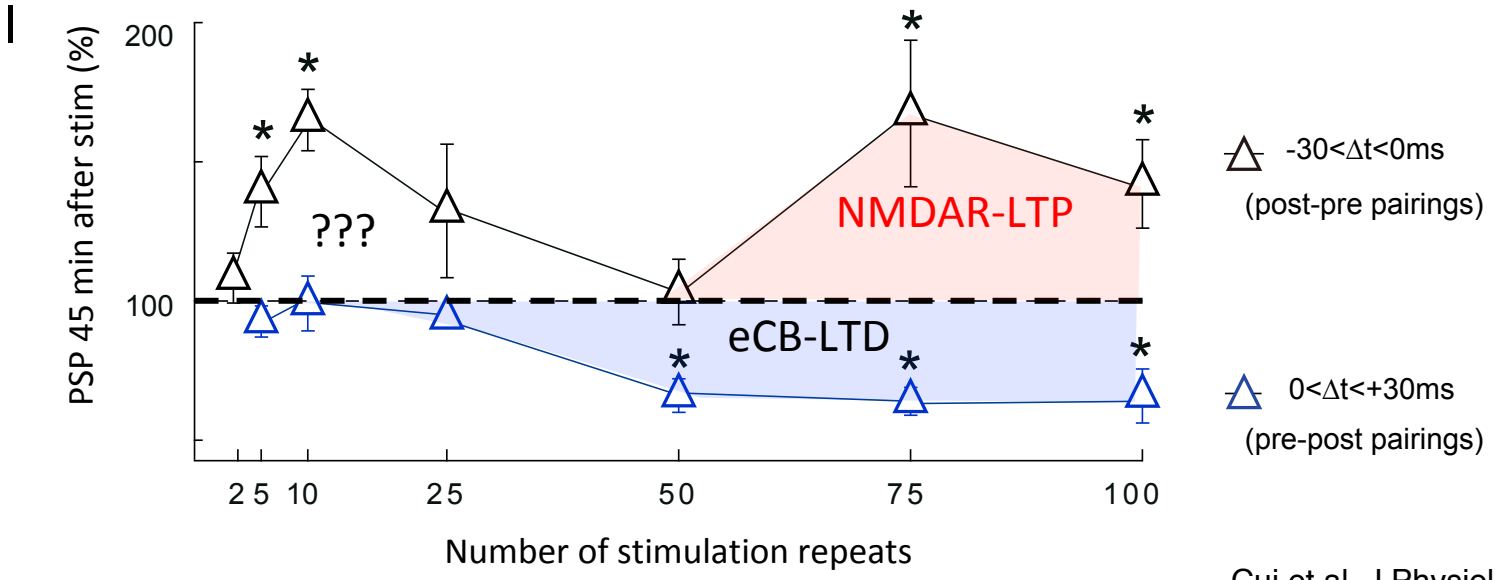


Cui et al. J Physiol 2015

What happens with less stimulation?

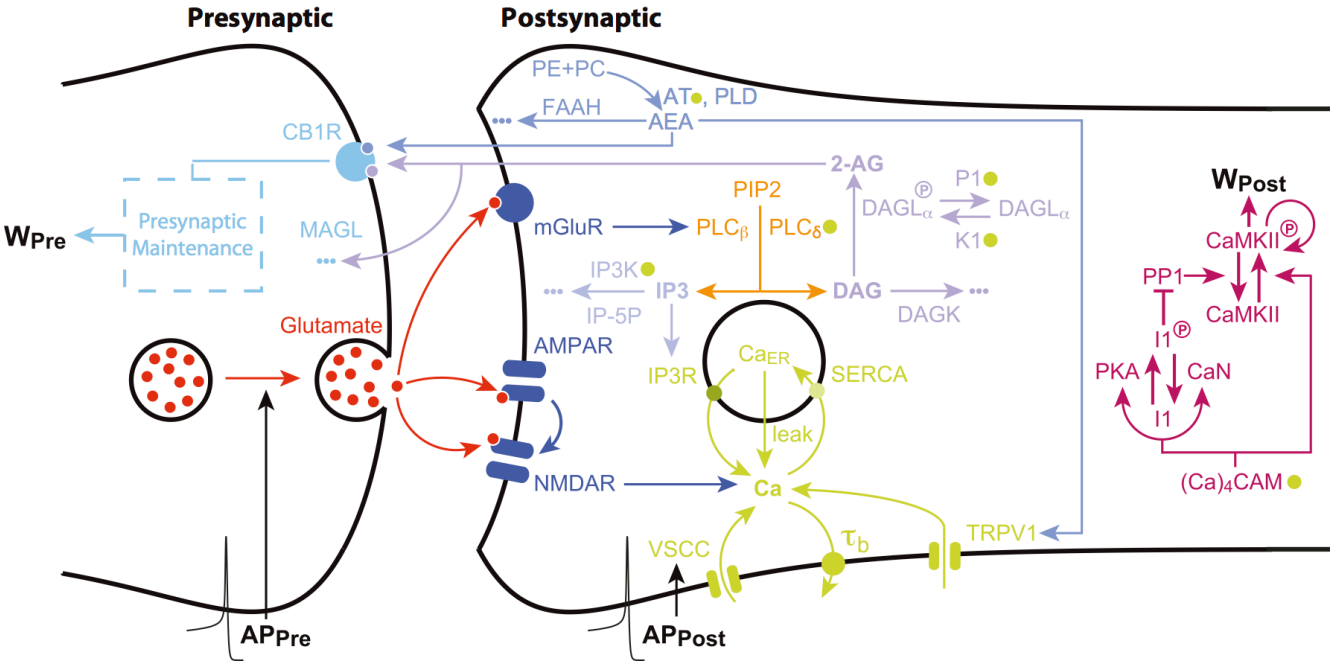
A new LTP appears low stimulation counts (5-25)

- *molecular mechanism*? Not NMDAR, eCB=LTD
- *disappear* ?



Cui et al. J Physiol 2015

A mathematical model of the signaling Lego

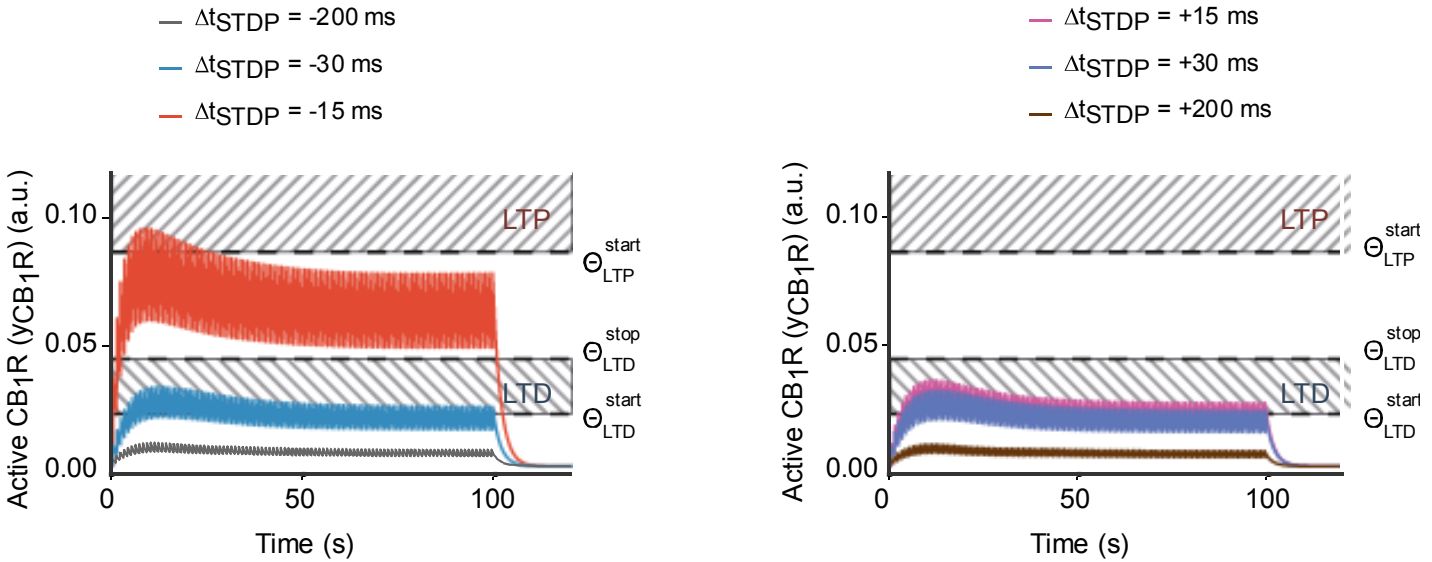


ex.:

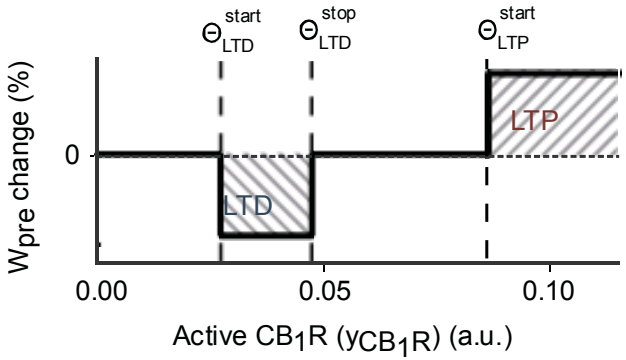
$$\frac{dDAG}{dt} = P_{PLC\delta}(Ca) + P_{PLC\beta}(Glu) - r_{DAGL} DAGL^* \frac{DAG}{K_{DAGL} + DAG} - r_{DAGK} DAG$$

$$\frac{d2AG}{dt} = r_{DAGL} DAGL^* \frac{DAG}{K_{DAGL} + DAG} - r_{MAGL} 2AG$$

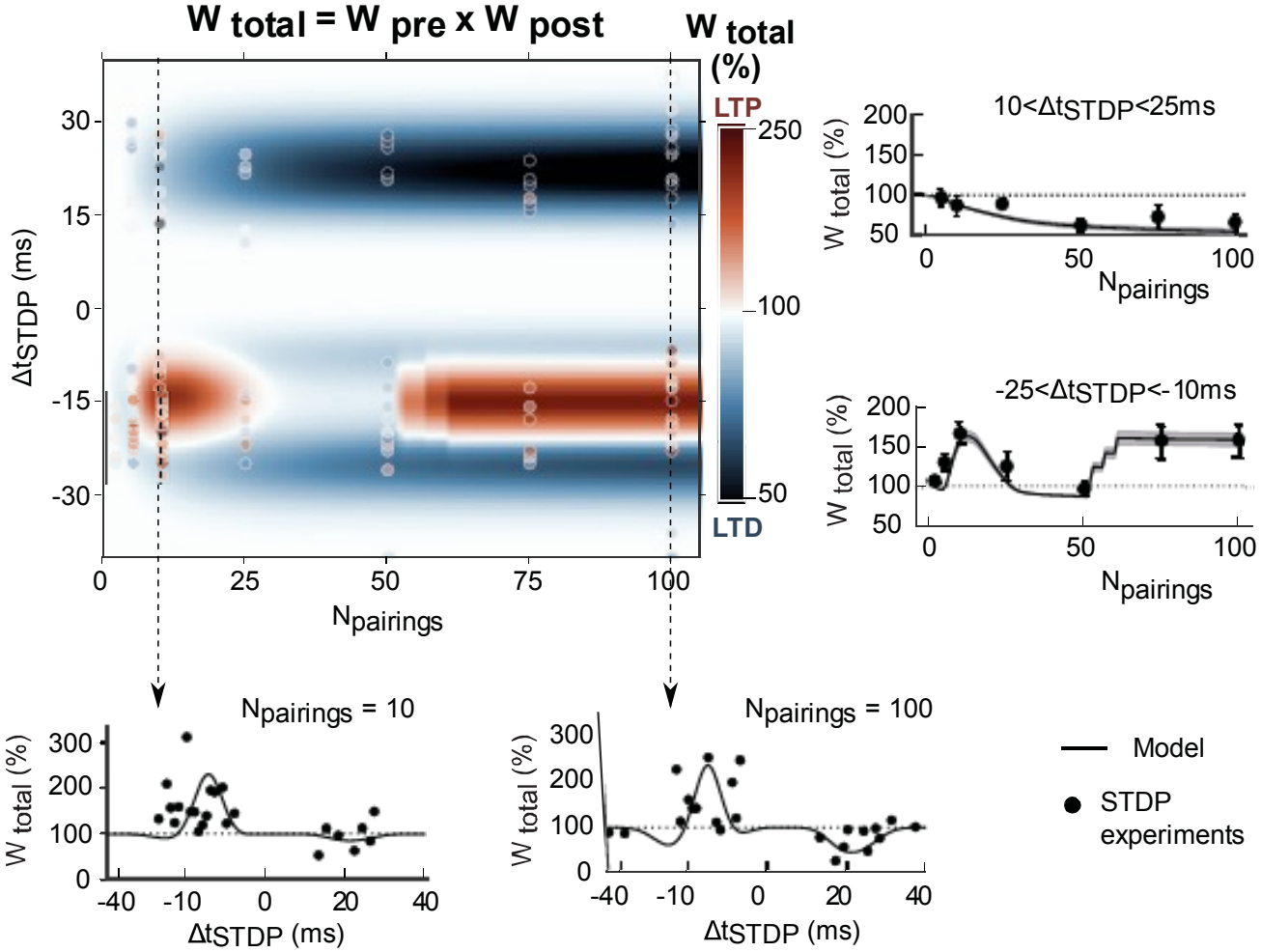
Model suggestion for activated CB1R dynamics



➔suggests a control of Wpre by which very large CB1R activation leads to eCB-LTP



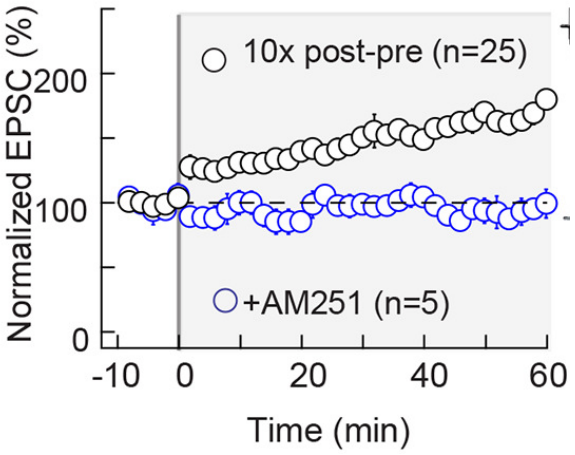
This prediction emulated experimental data

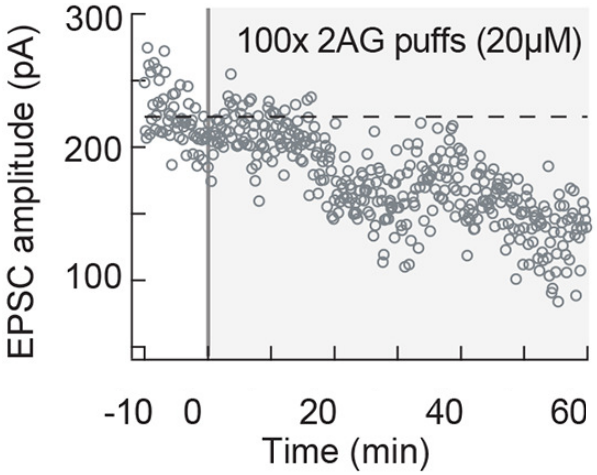


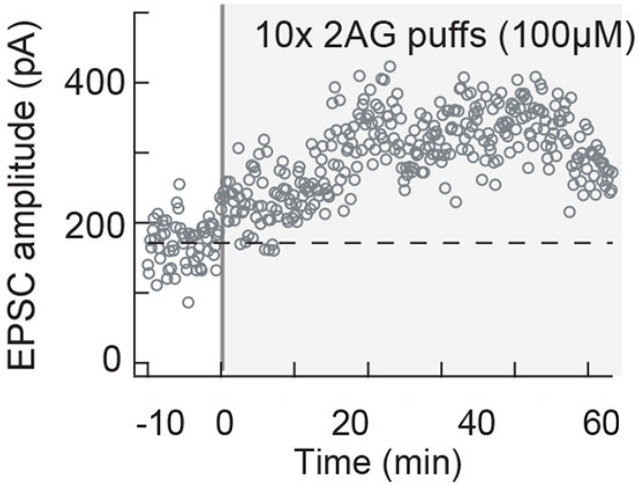
Cui et al. eLife 2016

And turned out to be true...

Cui et al. eLife 2016
Cui et al, Sci Rep 2018



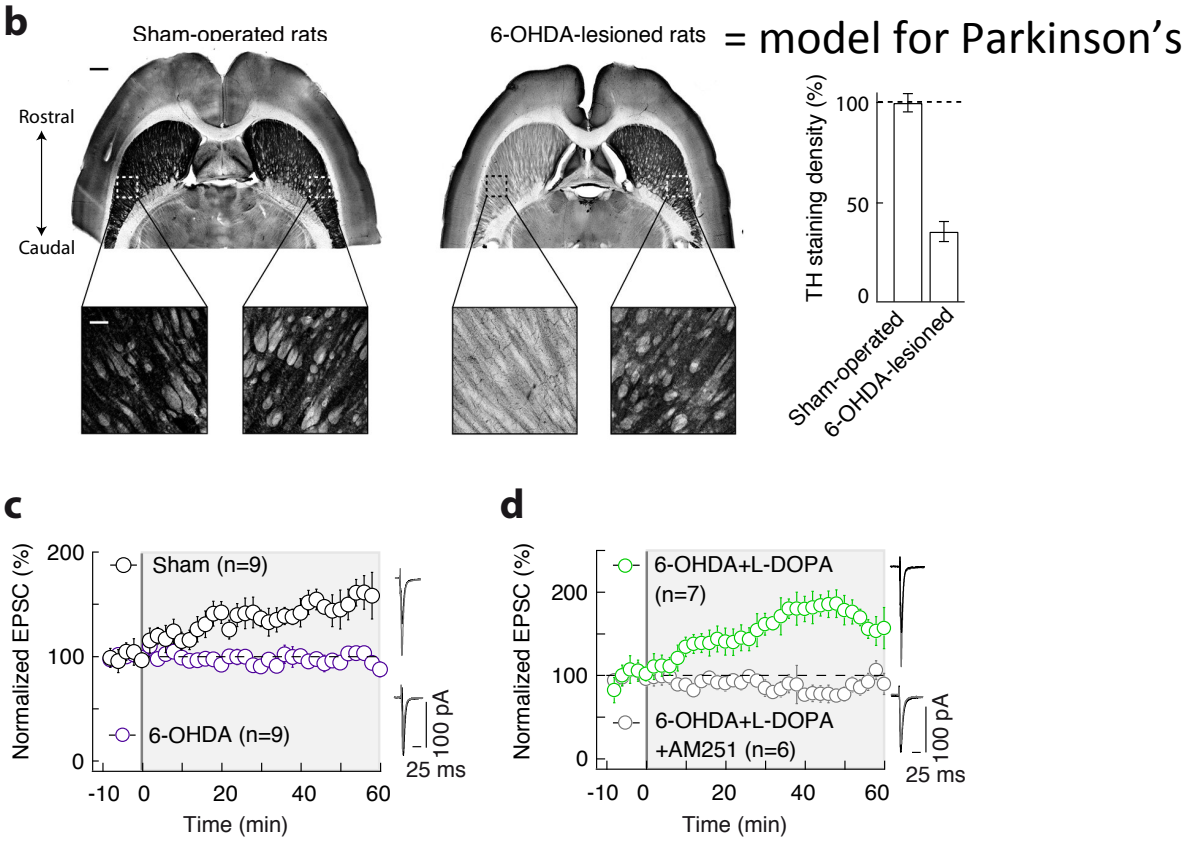




... the LTP with 10 stimulations is eCB-dependent

How can CB1R implement both LTP and LTD?

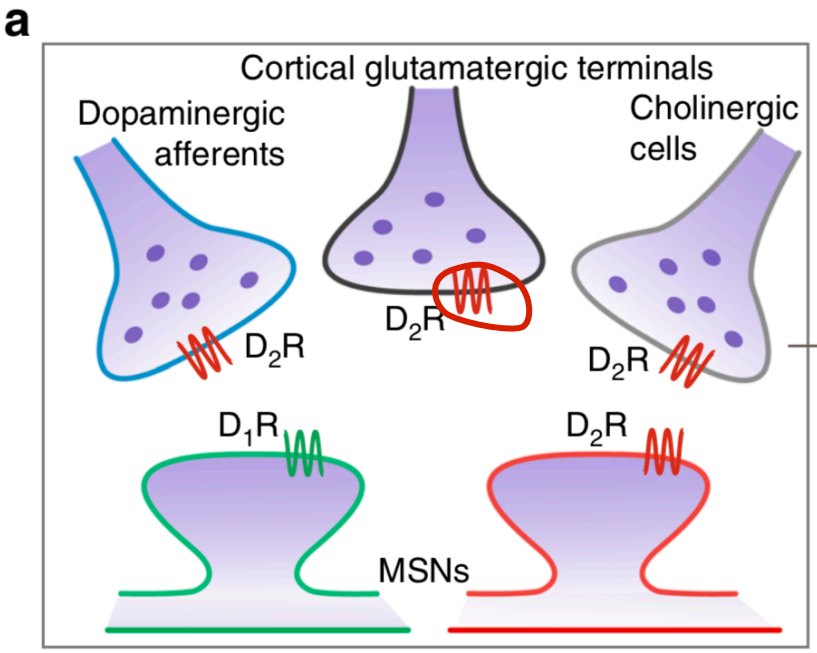
Ask Dopamine!

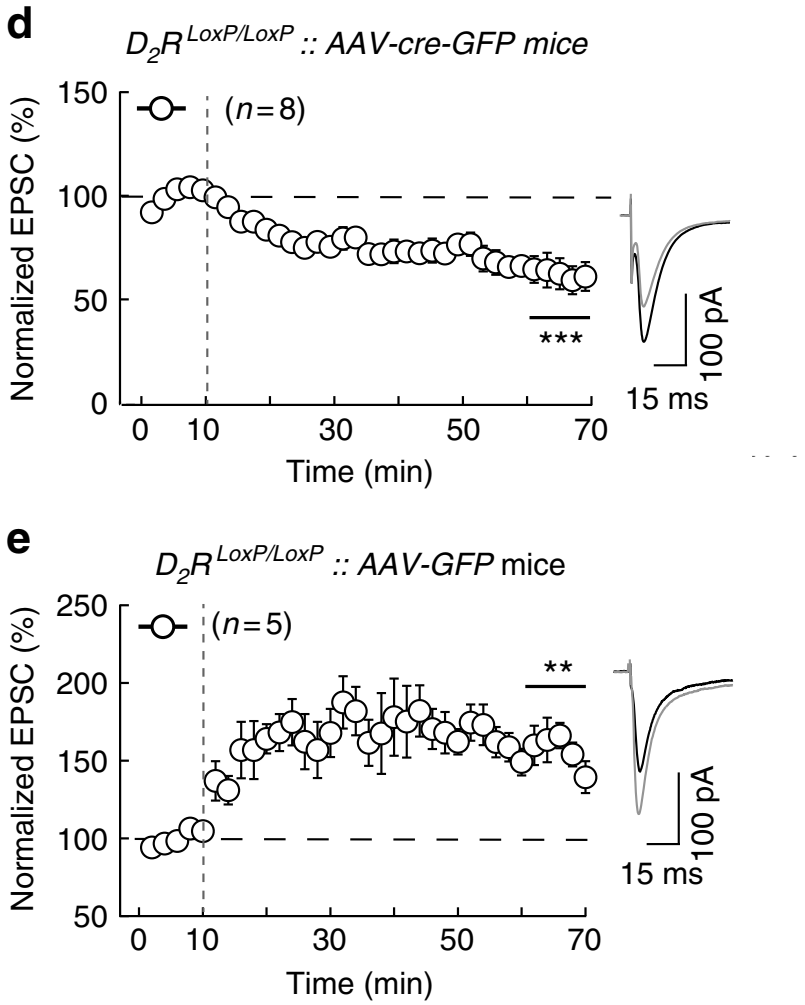


= model for Parkinson's

Hao et al, Nature Comm 2018

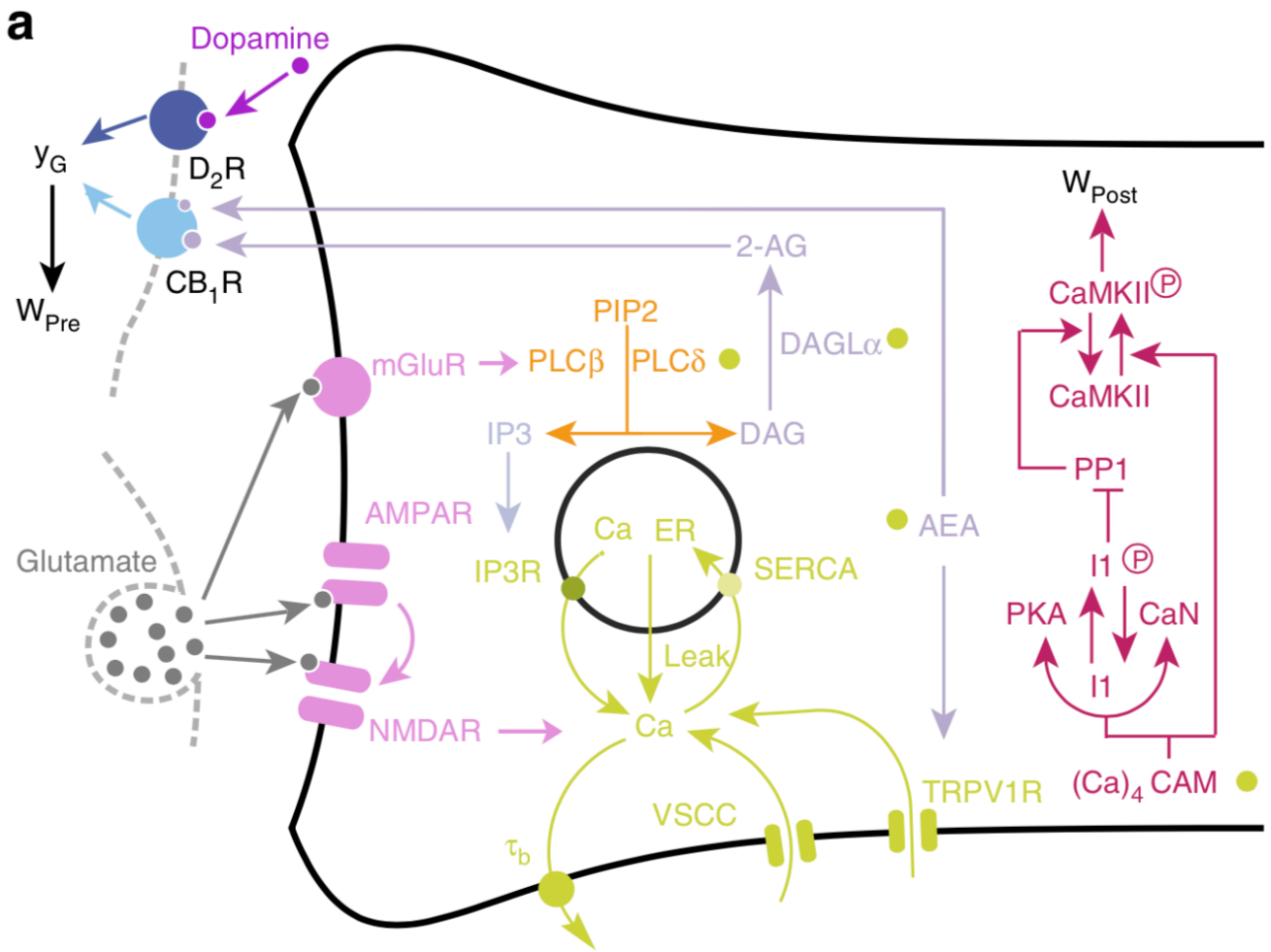
eCB-LTP is controlled by presynaptic D2R



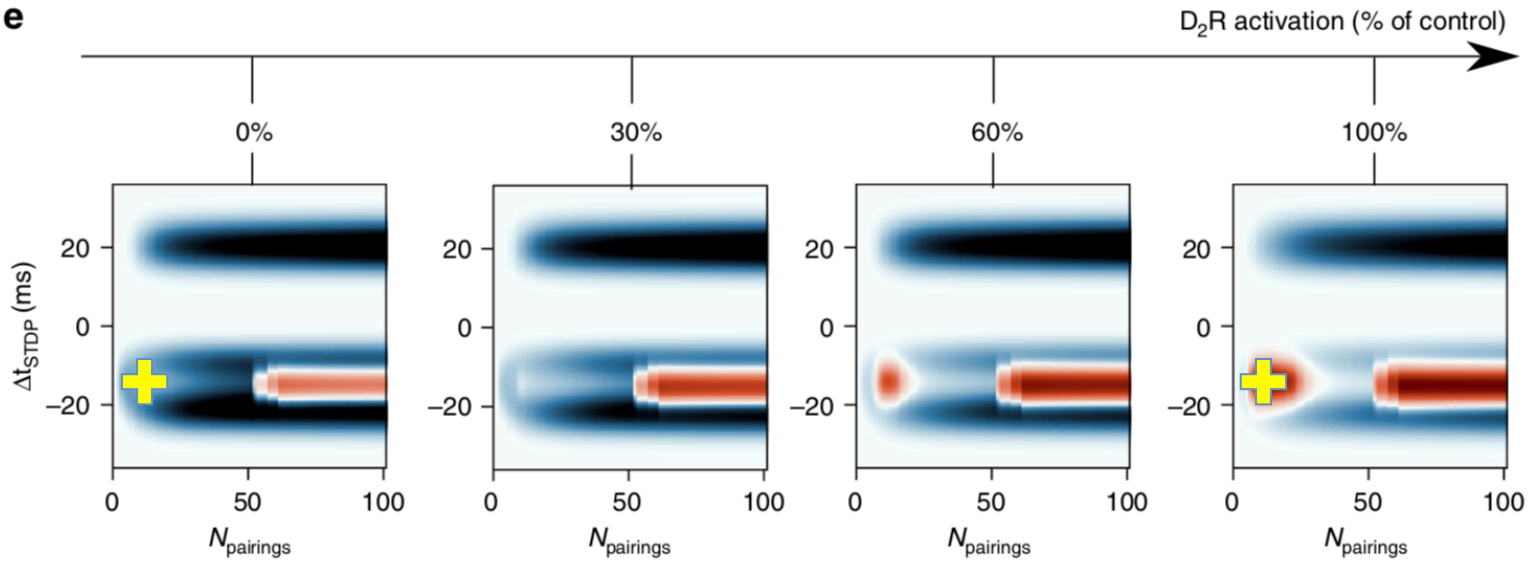


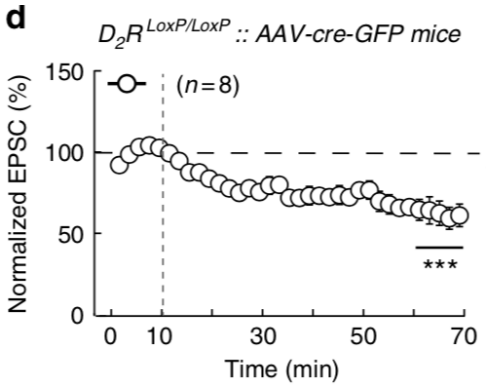
Hao et al, Nature Comm 2018

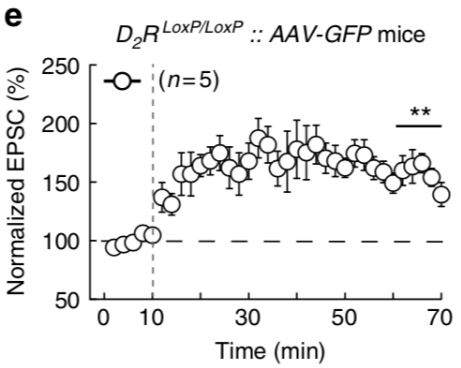
A simple hypothesis: CB1R & D2R are additive



Simple but enough to reproduce the data



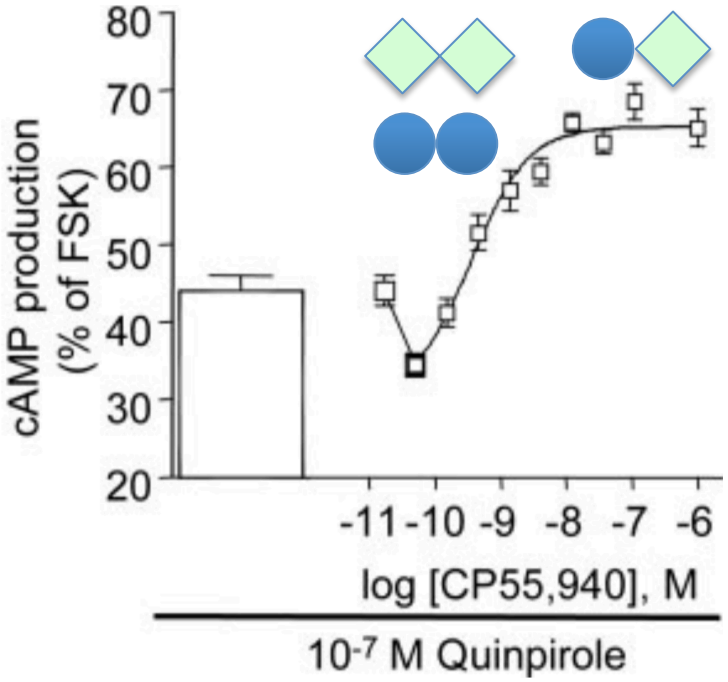




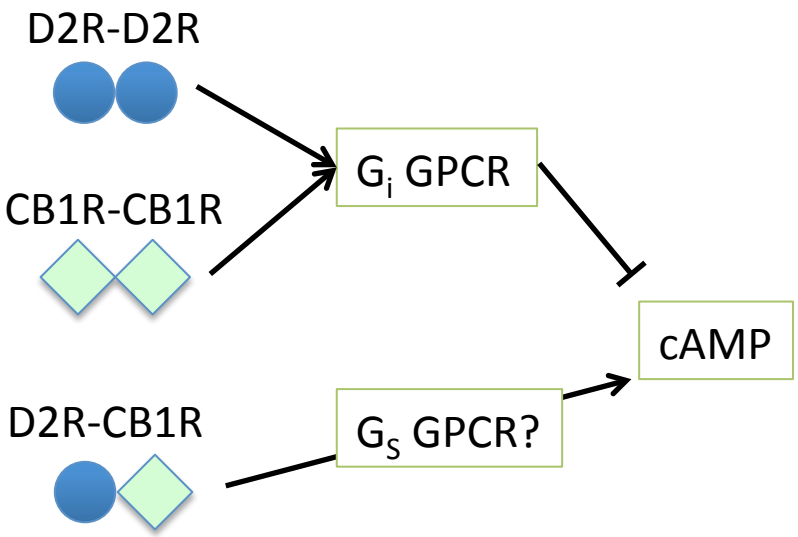
Hao et al, Nature Comm 2018

Additive effects suggest co-localization of CB1R & D2R

hetero-dimers CB1R-D2R may exist and be gated by the ligand but only observed in expression systems or cell culture



Kearn et al, Mol Pharmacol 2005



Conclusion and perspectives

- a new form of LTP, eCB-LTP, expressed at low stimulation

- this eCB-LTP is :
  - modulated by Dopamine through presynaptic D2R
  - suppressed in animal models of Parkinson's and restored by L-DOPA treatment

- ongoing works:
  - check ligand-controlled hetero-dimerization and reversal of cAMP production in slices (w/ biosensors)
  - causality of eCB-LTP in rat models of Parkinson's (w/ behavior)

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Thanks

MARIE CURIE ACTIONS

SEVENTH FRAMEWORK PROGRAMME

PROJET FINANCÉ PAR L'ANR - PROJECT FUNDED BY THE ANR

Inserm

École des Neurosciences Paris Île-de-France

informatics mathematics

Inria Lyon

H. Berry
I. Prokin
A. Foncelle
M. De Pittà

CIRB Collège de France Paris

L. Venance
Y. Cui
H. Xu
E. Fino

The whole story

- Cui *et al.* (2015) *J Physiol* 593:2833
- Cui *et al.* (2016) *eLife* 5:e13185
- Cui *et al.* (2018) *Sci Rep* 8:81!9
- Xu *et al.* (2018) *Nature Comm* 9:4118