Inhibitory Gating in the Dentate Gyrus

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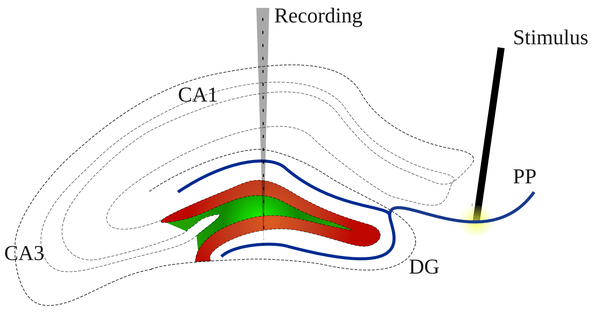
Abstract

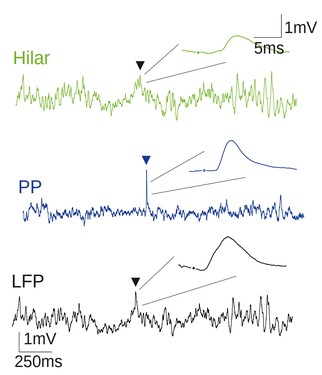
- Electrophysiological recordings have demonstrated the existence of a tight inhibitory control of hilar interneurons over Dentate Gyrus granule cells (DGgc).
- Our experiments show that LTP induced in the perforant pathway (PP) potentiates glutamatergic synapses and reduces feed-foward inhibition in the DG.
- To investigate this phenomenon we implemented a model that includes entorhinal cortex (EC) neurons, DGgc, mossy cells, basket cells and Hil cells.
- Our results show that the increase of the glutamatergic inputs results in a net inhibition of the basket cell population.
- Results of the model are supported by experiments *in vitro* where the LTP has been performed *in vivo*, obtaining this effect in the slice without antagonist GABAa.
- Our findings suggest that LTP applied at the EC outputs modifies the excitation/inhibition balance in the Dentate Gyrus facilitating communication with CA3

Changes of excitation/inhibition balance induced by LTP

Independent Component Analysis (ICA) of the LFP in the Dentate Gyrus discriminates different generators of the LFP. In this particular structure, there are two contributions: an excitatory generator (from the Perforant Pathway) and an inhibitory generator (from the Hilar region).

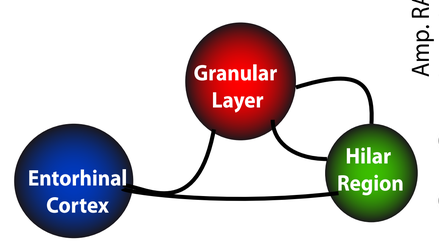


Scheme of the experiment. The Hilar region is indicated by the green color and the Granular Layer by the red one. The Perforant Pathway is indicated with blue line.

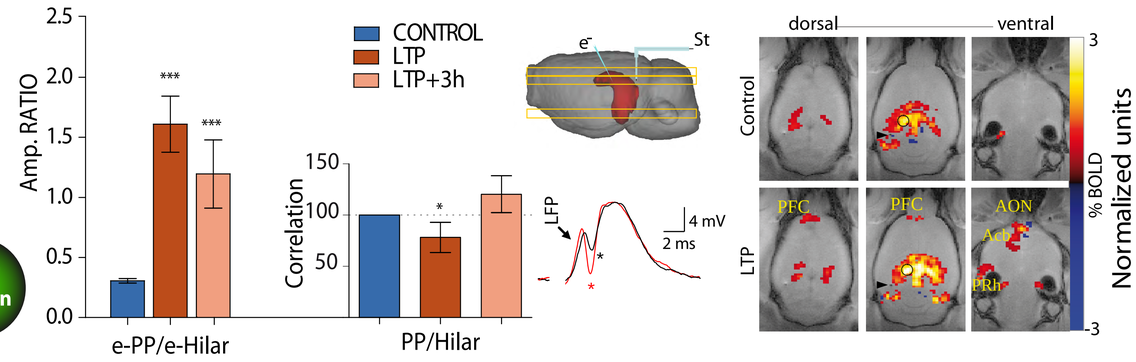


LTP reduces the inhibition over Granular cells

How is the neuronal circuit reorganized?



LTP in the Perforant Pathway (PP) reduces the feed-foward inhibition over DGgc and changes the functional circuit improving the spread of the signal to external structures of the Hippocampus.[1]



Modelling of the Dentate Gyrus

The proposed circuit is composed by 5 neuronal populations. Neurons are described by the Izhikevich model and connected via chemical synapses that include AMPA, NMDA and GABA receptors.

Each neuron receives an external noisy current with Poisson distribution.

Izhikevich model

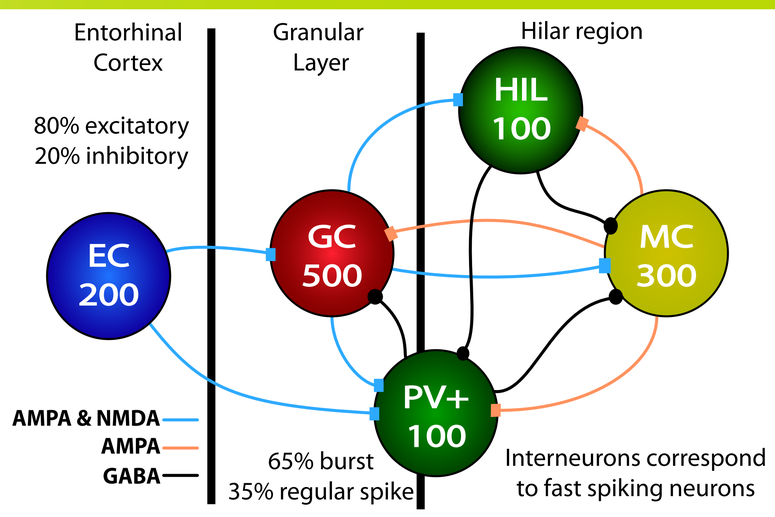
$$\dot{v}_i = 0.04v_i^2 + 5v_i + 140 + I_{Poisson} + I_{isyn} - u_i$$
$$\dot{u}_i = a_i(b_i v_i - u_i)$$

reset condition: $v_i \geq 30\ mV \quad v_i = c_i \quad u_i = u_i + d_i$

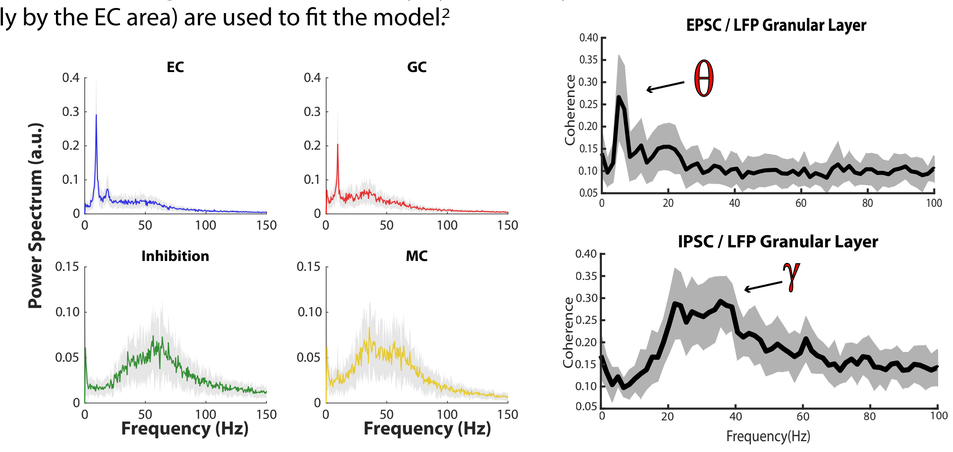
Synaptic current

$$I_{isyn} = -g_k \sum_{j\epsilon\varepsilon} r_{ji}(v_i - E_{rk}))$$
$$\tau_k \dot{r}_{ji} = -r_{ji} + \alpha_{ji}\delta(t - t_j)$$

i: post synaptic neuron
j: pre synaptic neuron
k: kind of synapse

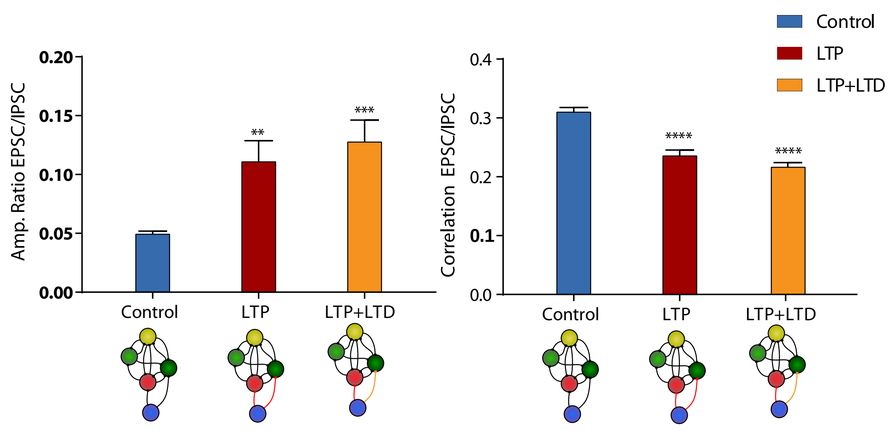


Connectivities and weights of the synaptic currents were fitted to reproduce previously published results.Coherence in gamma (induced mainly by the activity of Hilar neurons) and theta (induced mainly by the EC area) are used to fit the model.[2]



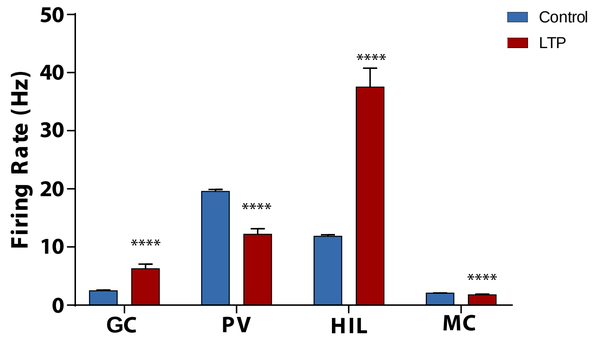
Model predictions in the presence of LTP

LTP was simulated by permanently changing the synaptic weights in the PP pathway. The ratio and the maximum value of the correlation between the Inhibitory Post Synaptic Currents (IPSC) and Excitatory Post Synaptic Currents (EPSC) in the granular layer were computed to compare with the experimental findings.



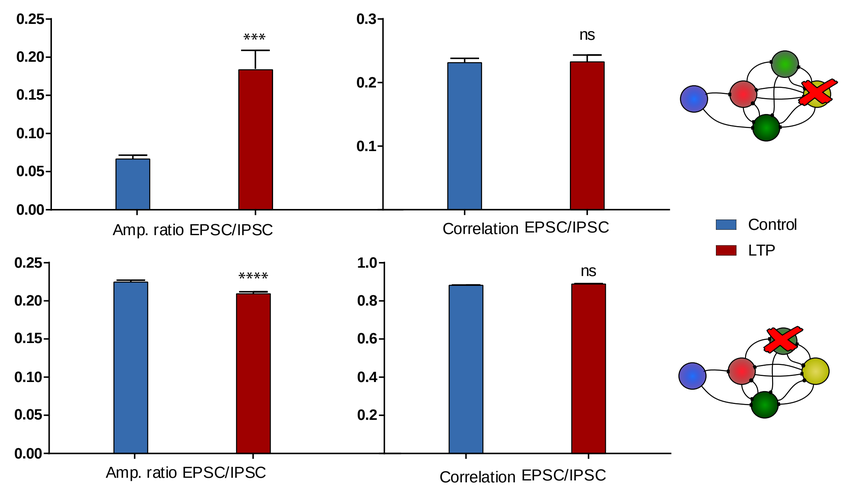
Activation of the inhibitory circuit by LTP

Our model predicts that after LTP, granular cells are more active due to a decrease of the IPSCs. The sequence occurs as follow: a larger activity in granular cells produces more activity in Mossy, Hil and PV+ cells. The extra activity in Hils cells inhibits more PV+ cells and consequently the IPSC in GCs reduces. Our results predict that during the LTP there is a temporal window where inhibition is reduced.



Minimal neural cirtcuit

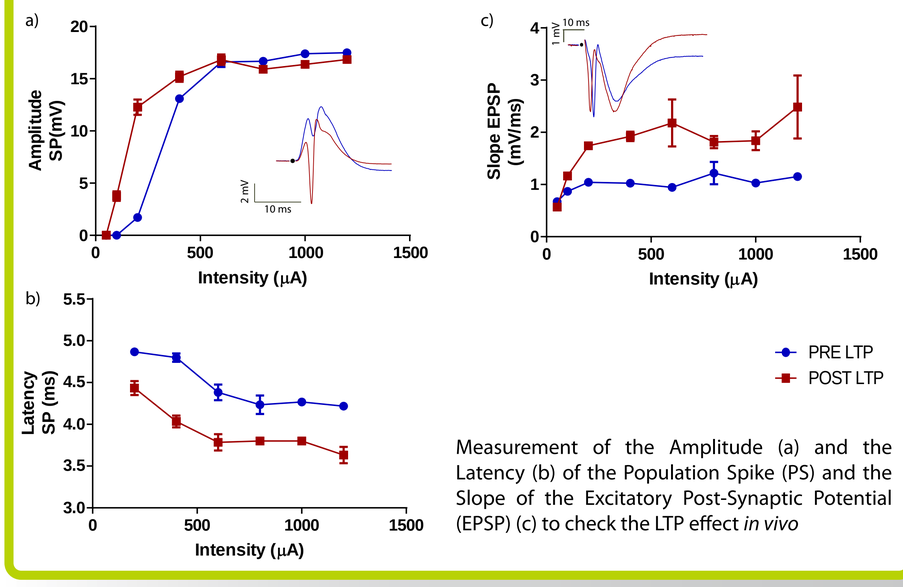
The proposed circuit is the minimal neural circuit that allows us reproducing the experimental findings induced by the potentation of PP.



Checking the model with *In vitro* Experiment

Induction of LTP *In Vivo*

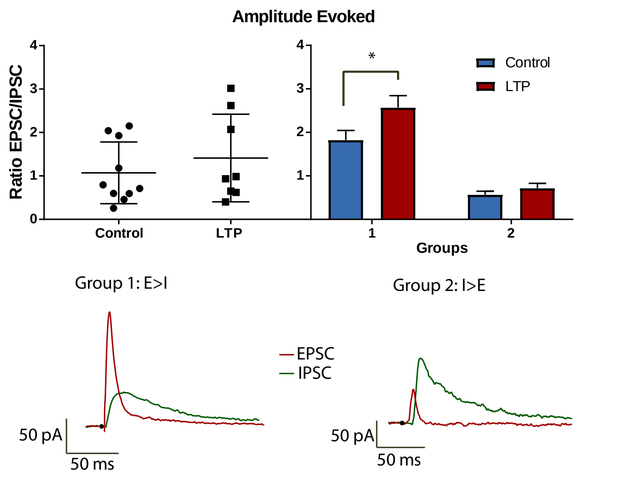
Because of the local inhibition over granule population the induction of LTP in the Dentate Gyrus without antagonist GABAa in the *in vitro* slice is unlikely. The LTP is induced in the total network *in vivo*. Once the effect is induced in the brain, the in vitro experiment is performed in the same mouse.



Measurement of the Amplitude (a) and the Latency (b) of the Population Spike (PS) and the Slope of the Excitatory Post-Synaptic Potential (EPSP) (c) to check the LTP effect *in vivo*

In vitro evoked potentials

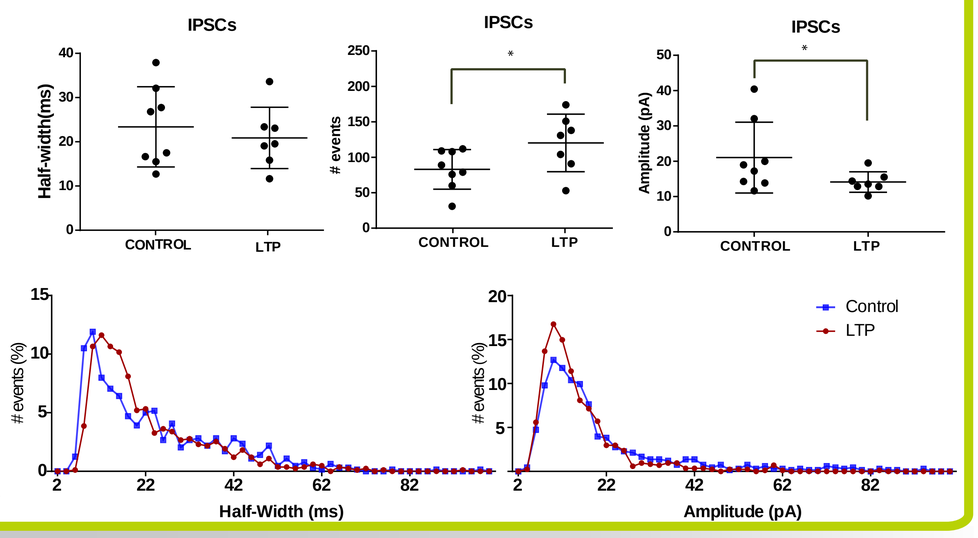
Whole-Cell Patch-Clamp in the DGgc shows an increment of the ratio excitation/inhibition. This result goes in the same direction than the *in vivo* experiment in rats and the model. Moreover, there are two groups of DGgcs. Group 1 has an excitatory post-synaptic current larger than the inhibitory post-synaptic current, whereas Group 2 is the opposite case.



Traces of evoked response due to a stimulation of 50 uA in the middle Molecular Layer

In vitro spontaneous potentials

Recordings of three minuts of spontaneous signal show an increment of inhibitory events. However, events have smaller amplitude and larger half-width. This fact indicates that the perisomatic inhibition (from Basket cells) decreases and dendritic inhibition increases. Then, it supports the idea that the population of Basket cells is silenced by another population of interneurons, that are more activated reflected in an increment in the frequency of dendritic inputs in the DGgc.



Conclusions

Inhibition over Dentate Gyrus is a crucial mechanism in the learning process: experiments show that if a reduction in the inhibition over the Dentate Gyrus occurs, the animal learns faster. To understand how this phenomenon occurs we built a neural population model using Izhikevich equations. Our results predict that the potentiation of glutamatergic synapsis from the EC into GCs increases its activity. As a result, the full circuit dynamics yields more inhibition into PV+ cells resulting in a reduced inhibition over GCs. A combination of in vivo and in vitro experiments have been performed to validate the hypothesis of the computational circuit. The result obtained support the mechanims proposed by model.

References: 1) Álvarez-Salvado E., Pallarés V., Moreno A., Canals S. *Phil. Trans. R. Soc.* **369**. 2014 2) Pernía-Andrade A.J., Jonas P. *Neuron* **81**(1). 2014