Hybrid modeling of personnalized brain stimulation in the kHz range

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Background

● **Neuromodulation** is emerging as an **alternative to drugs**, but the involved mechanisms are still elusive [Heck et al. 2014, Gooneratne et al. 2016].

● **Dosimetry** of the electric field induced in brain tissue is often neglected, despite its recognized importance to understand inter-individual variability in experiments [Laakso et al., 2019].

● **kHz stimulation** is a relatively unexplored frequency range, with encouraging evidence of potential therapeutic use (e.g., spinal cord stimulation for chronic pain).

➔ Our objective was to couple dosimetric assessments with *in vivo* recordings of kHz brain stimulation to assess possible anti-epileptogenic effects.

Materials and Methods: *in silico*

● We solved the **Laplace equation**:

$$\nabla \cdot \mathbf{J}(r, z) = 0$$

that describes the distribution of the electrical potential V, which induces an electric field **E**:

$$\mathbf{E} = -\nabla V \qquad \mathbf{J} = (\sigma + j\omega\varepsilon_0\varepsilon_r)\mathbf{E}$$

We aimed at quantifying the electric field induced by the tip of the **pair of electrodes** placed in brain tissue, modeled by the setup illustrated in Figure 1.

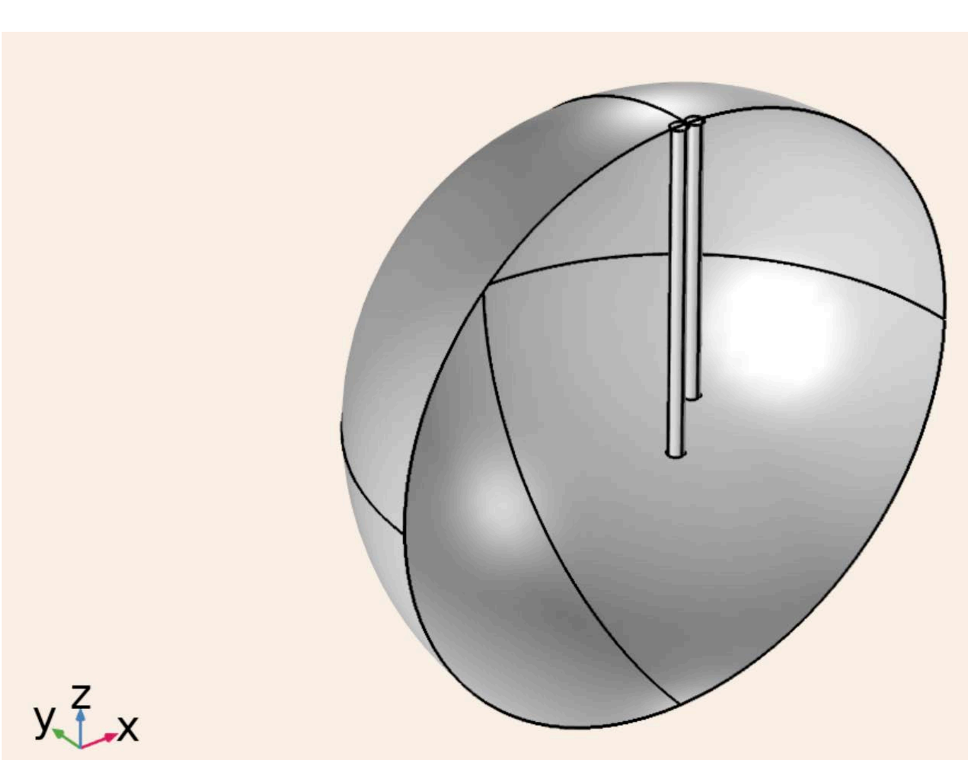

Figure 1. Numerical model of the twisted-pair electrode. The sphere represents brain tissue with dispersive EM properties (only half is depicted).

Materials and Methods: *in vivo* recordings

● **Kainate model** of epilepsy: involves intra-hippocampal injection of kainic acid.

● Excitotoxicity induces functional and anatomical re-organizations in the hippocampus (**epileptogenesis** phase).

● Epileptiform events termed hippocampal paroxysmal discharges become **more frequent** and increase in **duration** throughout epileptogenesis [Riban et al. 2002]

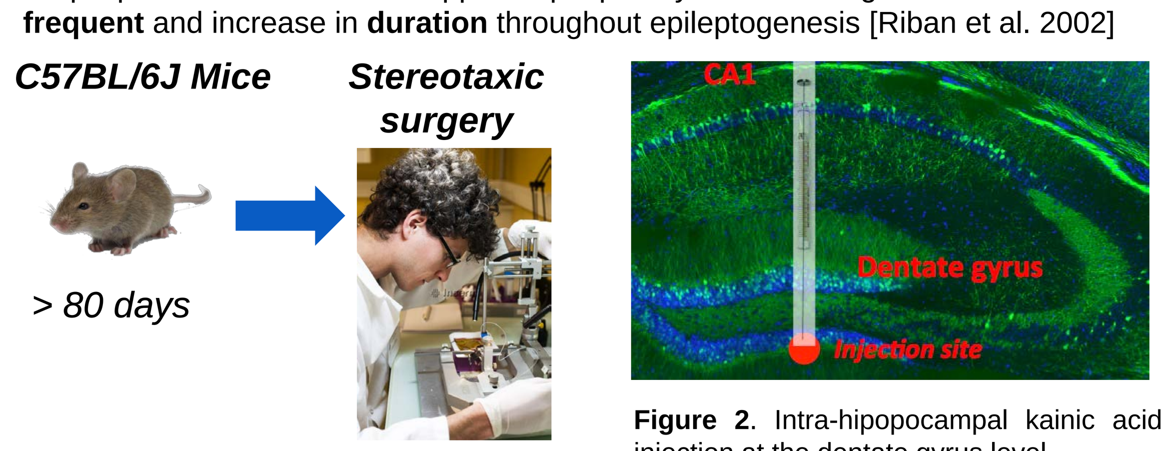

Figure 2. Intra-hippocampal kainic acid injection at the dentate gyrus level.

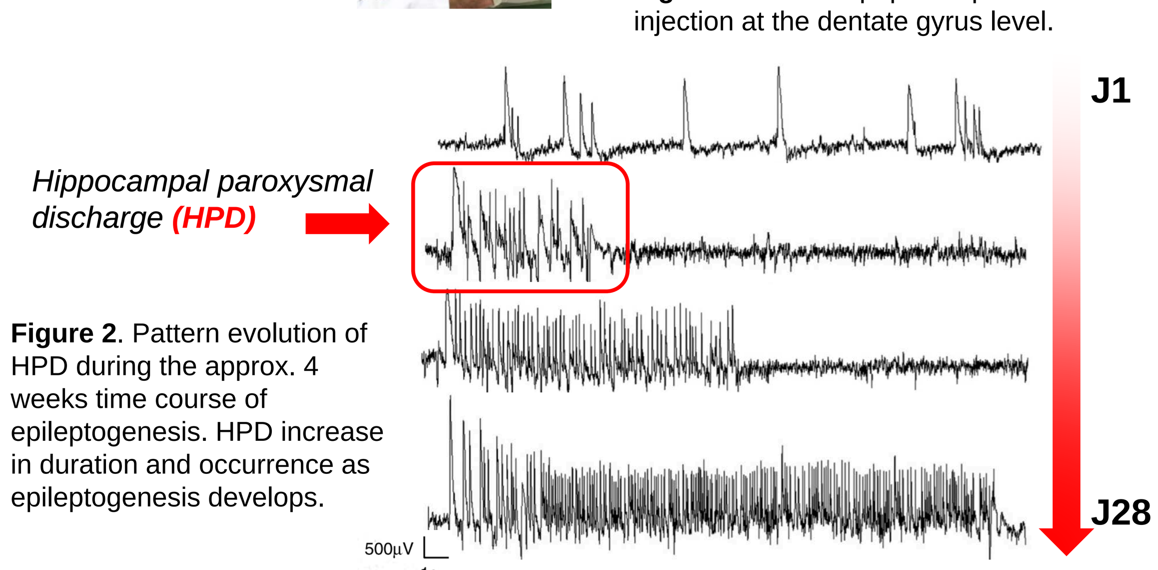

Figure 2. Pattern evolution of HPD during the approx. 4 weeks time course of epileptogenesis. HPD increase in duration and occurrence as epileptogenesis develops.

Materials and Methods: *in vivo* stimulation protocol

● A total of N=6 mice were included in the **experimental protocol** detailed in Figure 3 below.

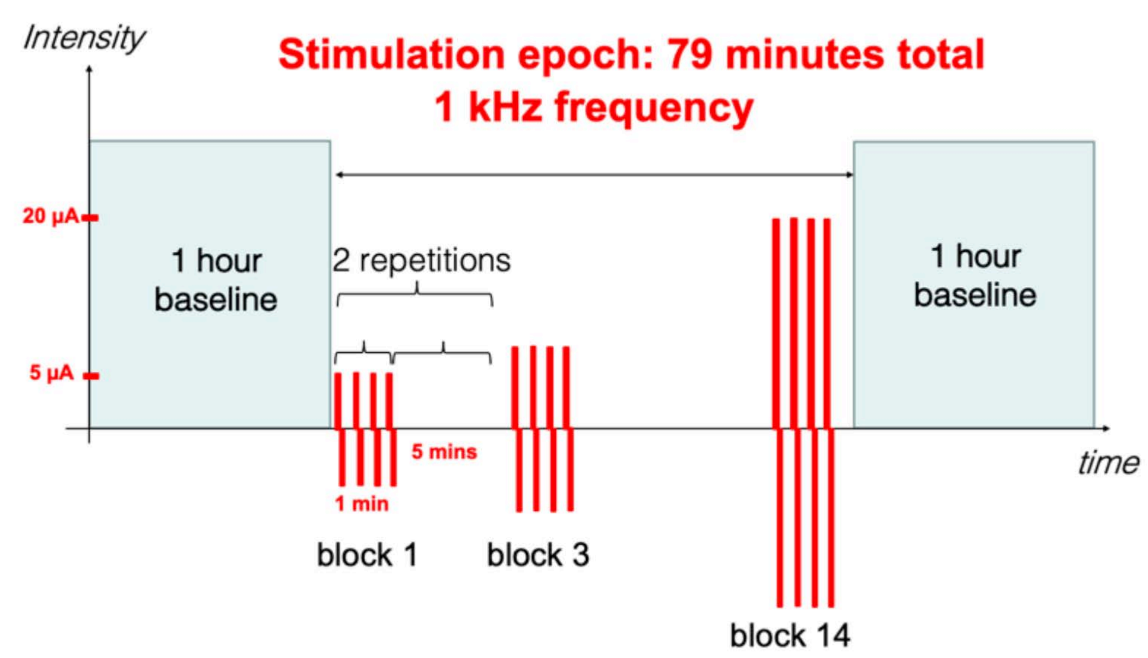

Figure 3. Stimulation protocol used in this pilot study, consisting in gradually increasing the intensity from 5 to 20 µA during stimulation blocks of 1 minute (5 minutes free of stimulation in between).

● **Electrical stimulation** delivered using twisted wires electrodes (400 µm apart).

● **Stimulation intensity** tested (Protocol 2): **5-20 µA** (Grass S88X stimulator) during 1 minute, 14 blocks, cathodal stimulation.

● We computed the **occurrence rate [events/minute]** and **duration [s]** of HPD for each stimulation epoch.

● These two markers are **proportional to the excitability** of brain tissue: more frequent / longer HPD involve a higher excitability state.

Results: *in silico*

● We computed the **electric potential** in brain tissue induced by the biphasic stimulation pulse, as shown in Figure 4.

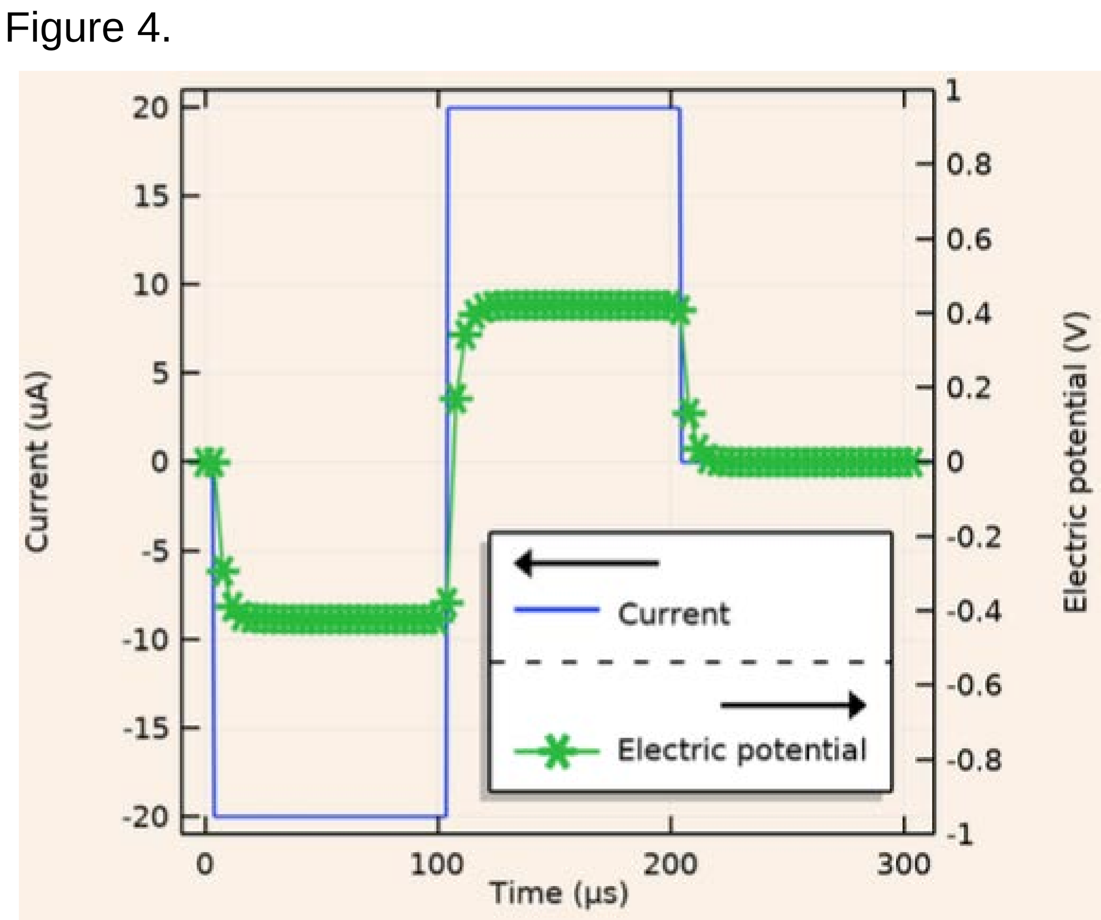

Figure 4. Electric potential induced in brain tissue by the stimulation pulse used experimentally.

● We quantified the **induced electric field** in brain tissue near the electrodes' tip, as illustrated in Figure 5.

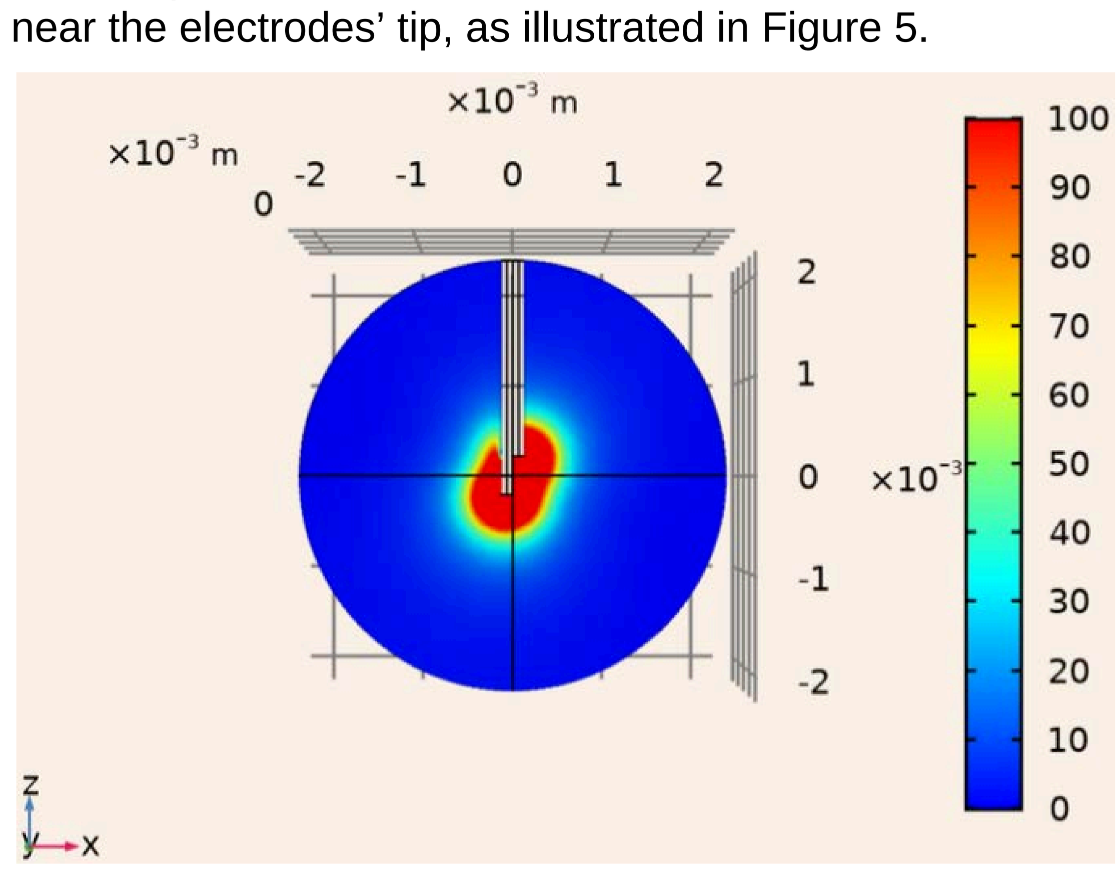

Figure 5. E-field response to a 20 µA, 0.2 ms biphasic pulse (charge-balanced, rectangular).

Results: *in vivo*

● The **average duration** of HPDs was **significantly reduced** during the 5-minute stimulation epoch post-stimulation, with a decrease proportional to the stimulation intensity, as evidenced in Figure 6.

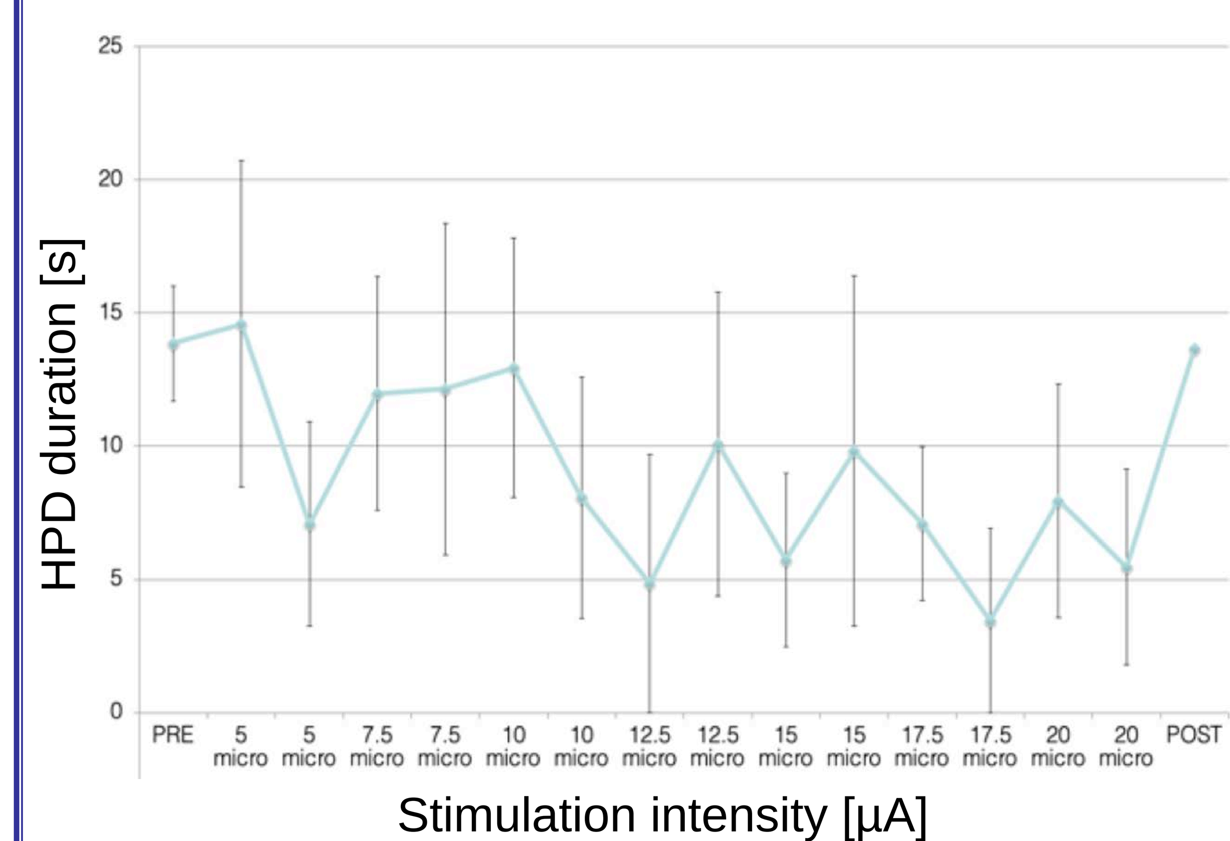

Figure 6. Evolution of the mean HPD duration as a function of current intensity.

● Similarly, the **occurrence rate of HPDs drastically decreased** under kHz stimulation (approx. reduced by a factor 5), as shown below in Figure 7.

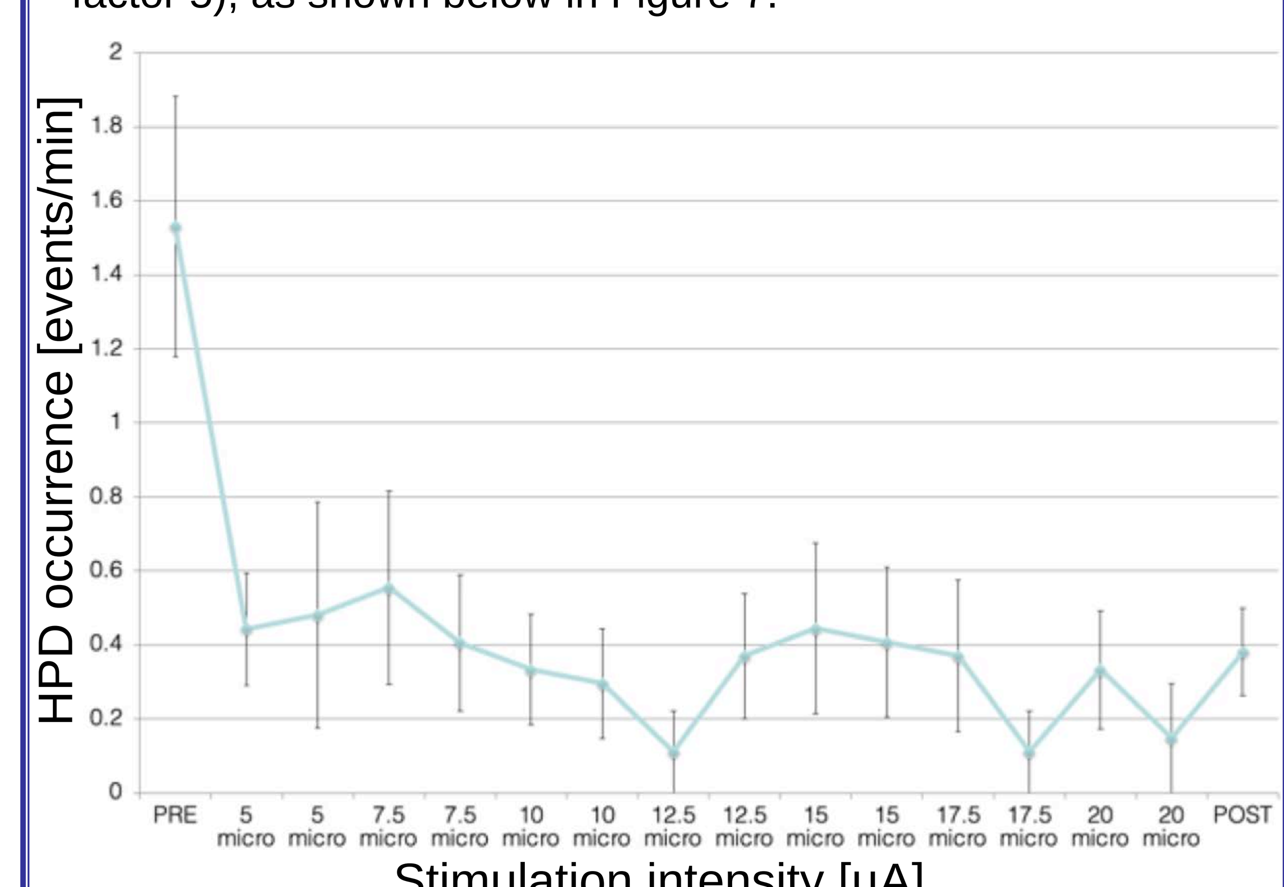

Figure 7. Evolution of the mean HPD occurrence rate as a function of current intensity.

Conclusion

● Electric fields between 1 and 10 V/m at 1 kHz can **drastically reduce epileptiform activity** in epileptic mice.

● Hypothesized **mechanism**: depolarization of GABAergic interneurons.

● Future directions: investigate the validity of the quasi-static approximation, possibility of **using higher frequencies** (possibly as carrier).

References

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Acknowledgments

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