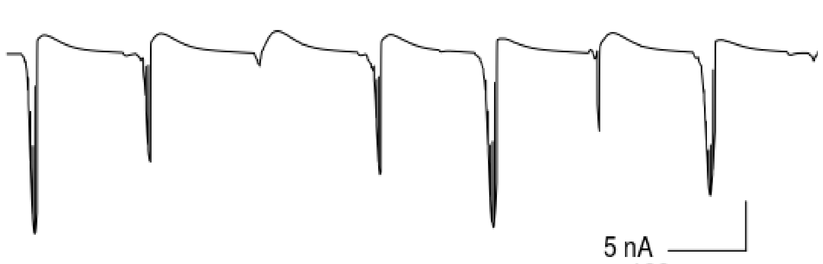
Phase dependence of the termination of absence seizures by cerebellar input to thalamocortical networks

Julia Goncharenko*[1], Lieke Kros[2], Reinoud Maex[1], Neil Davey[1], Christoph Metzner[1,3], Chris de Zeeuw[2], Freek Hoebeek[2], Volker Steuber[1]

1 Biocomputation Research Group, Centre for Computer Science and Informatics Research, University of Hertfordshire, Hatfield, AL10 9AB, UK
2 Department of Neuroscience, Erasmus MC, Wytemaweg 80, 3015 CN, Rotterdam, the Netherlands
3 Neural Information Processing Group, Institute of Software Engineering and Theoretical Computer Science, Technische Universität Berlin, Berlin, Germany

Background and aims

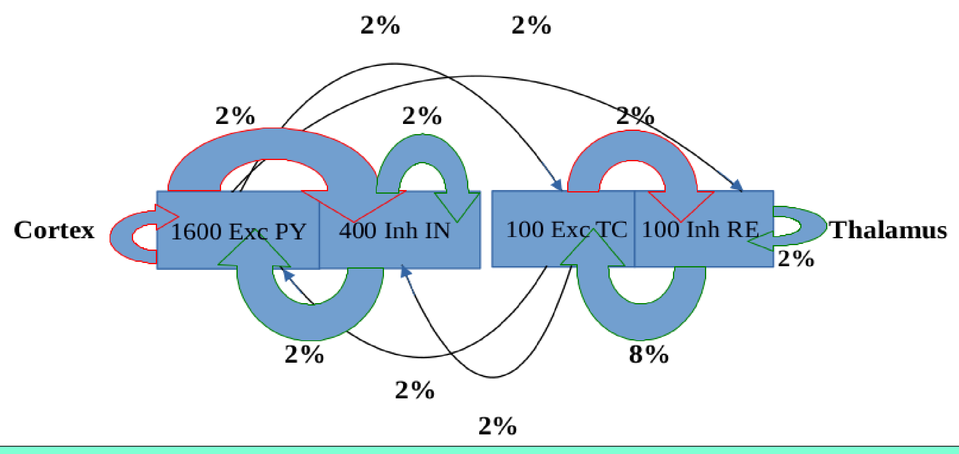


Absence seizures are the most common form of epilepsy in children [1]. They start and finish abruptly, last for 10-20 seconds on average and can be detected by generalised spike-and-wave discharges (GSWDs) in the electroencephalogram [2]. These GSWDs (see Figure on the left) are based on neuronal oscillations in thalamocortical networks, which can be caused by excessive inhibition in the thalamus or excessive cortical activity [2]. Absence seizures can be triggered by switching of the normal asynchronous neuronal activity in thalamocortical networks to synchronised oscillations, and terminated by the reverse process, switching from synchronised oscillations to asynchronous activity [2].

Experimental studies have shown that thalamic stimulation can lead to disruption of oscillatory activity in thalamocortical networks [3]. More recently, it was also found that optogenetic activation of neurons in the cerebellar nuclei (CN) can stop epileptic absence seizures and reset the oscillatory activity, for example in a closed loop system [4]. However, the underlying mechanism of the disruption of thalamocortical oscillations and the termination of absence seizures by CN stimulation is not yet clear.

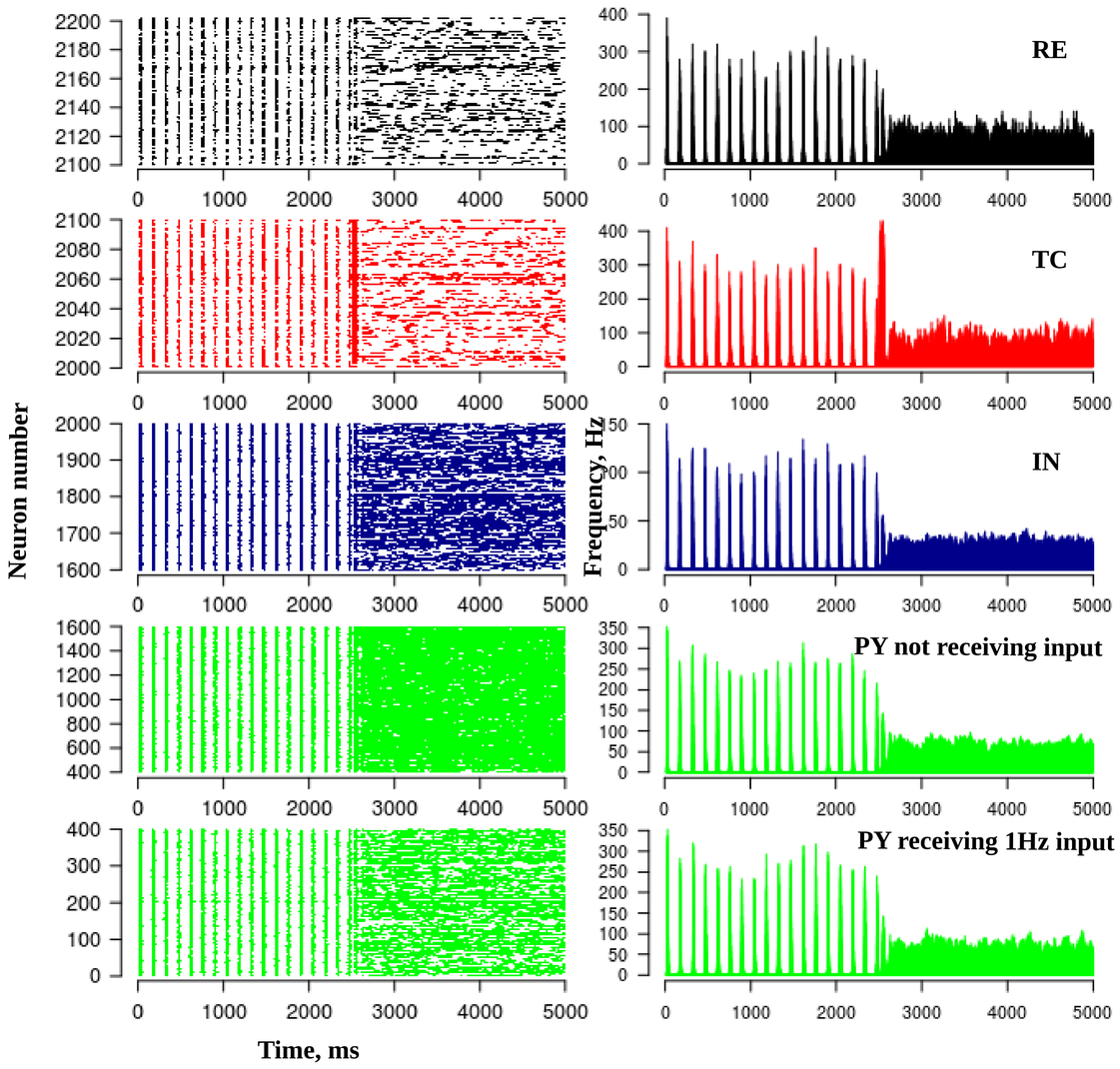
Methods

To investigate the mechanism of the termination of absence seizures by thalamic input from the CN we used computer simulations. We simulate a thalamocortical network model (see Figure on the right) with adaptive exponential integrate-and-fire neurons, displaying complex intrinsic properties such as low-threshold spiking, regular spiking, fast spiking and adaptation [5]. The conductance change in the post-synaptic neurons is modeled by alpha synapses. The network activity can exhibit oscillatory or asynchronous irregular (AI) dynamics, depending on the time constants of the inhibitory synaptic conductance, which are 5 ms (AI) and 15 ms (oscillatory) respectively. An increase in the inhibitory decay time constant reflects a change from $GABA_A$ dominated inhibition to more $GABA_B$, which can result in GSWDs, given that the "wave" components of GSWDs are related to slow $GABA_B$ -mediated K^+ currents [6].

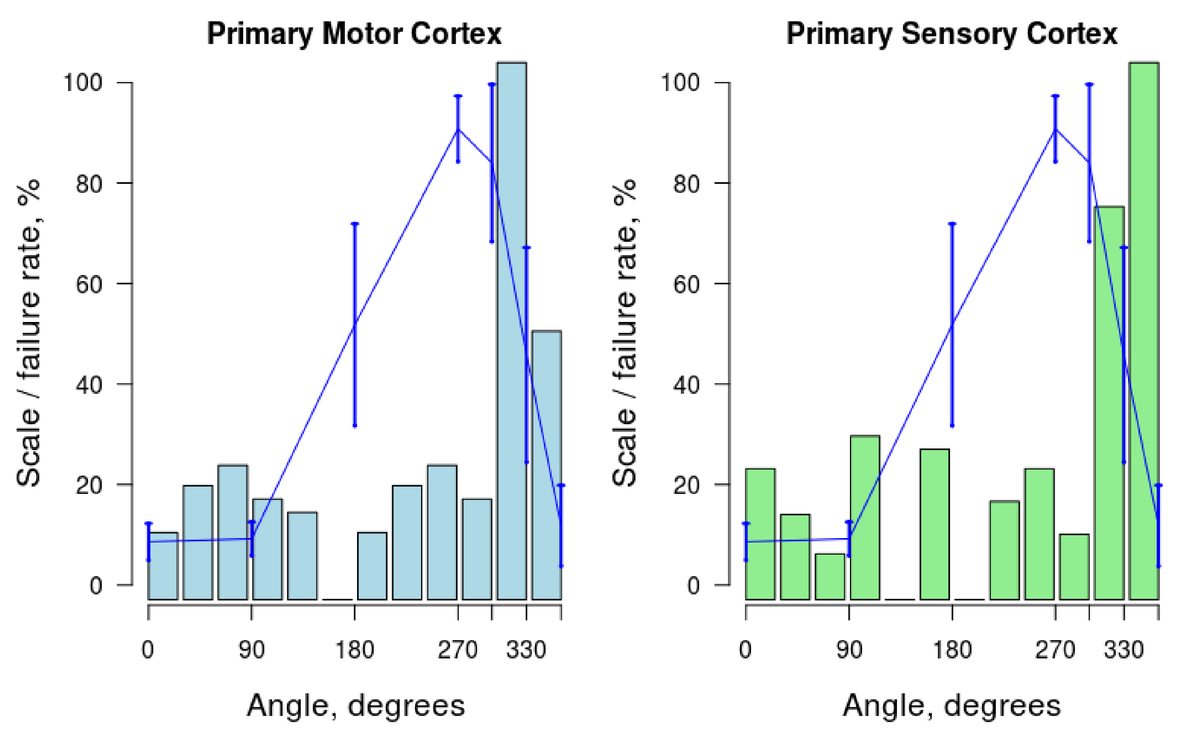


Results

We provide CN input to all thalamocortical neurons to study the mechanism of reverting from abnormal (ictal) oscillatory activity to the normal AI state.



Raster plots (left panel) and PSTHs (right panel) of different neuronal populations in the thalamocortical network model (RE thalamic reticular, TC thalamocortical, IN cortical inhibitory interneurons, PY cortical pyramidal cells). The oscillatory activity during the ictal state is terminated by excitatory AMPA CN input to all TC cells (for 50 ms at 2500 ms), which results in earlier spiking in the TC cells and desynchronisation of the network.



Comparison of the phase angle dependence of seizure termination in experiments ([4], bars) and in our simulations (blue line). Phase angles indicate the time of stimulus application relative to GSWD bursts, where 0 and 360 degrees are stimuli applied at the peak of the burst. The scale indicates the minimum stimulus strength as a factor of synaptic conductance between the CN and thalamocortical neurons that is required to terminate the GSWDs. Simulated CN input was most effective when applied at the peak of the burst, while experimental data indicate similar effectiveness (small failure rates) across a wider range of phase angles.

Conclusion

We found that input from the CN can control oscillatory activity in thalamocortical networks. Furthermore, the effectiveness of this input exhibits phase-dependence. In our simulations, CN input terminates epileptic absence seizures most effectively when it arrives at the peak of GSWDs, while the least efficiency for seizure termination is observed in between the GSWD bursts. This finding is potentially relevant for therapeutic applications of CN stimulation in closed-loop systems to terminate seizures.

References

1. Berg AT, Berkovic SF, Brodie MJ, et al.: Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010, 51:676–685.
2. Snead OC III: Basic mechanisms of generalized absence seizures. Ann Neurol 1995, 37(2):146–157.
3. Paz JT, Davidson TJ, Frechette ES, et al.: Closed-loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. Nat Neurosci 2013, 16:64–70.
4. Kros L, Eelkman Roda OHJ, Spanke JK, et al.: Cerebellar Output Controls Generalised Spike-and-Wave Discharge Occurrence. Ann Neurol 2015, 77(6):1027–1049.
5. Destexhe A: Self-sustained asynchronous irregular states and up-down states in thalamic, cortical and thalamocortical networks of nonlinear integrate-and-fire neurons. J Comput Neurosci 2009, 27:493–506.
6. Destexhe, A: Spike-and-Wave Oscillations Based on the Properties of $GABA_B$ Receptors. Journal of Neurosci 1998, 18(21):9099-9111.

* corresponding author: i.goncharenko@herts.ac.uk