The thalamocortical system – roles in consciousness, sleep and neurological disorders

Physiologically, the thalamocortical (TC) system is a central neural circuit that connects the thalamus to the cerebral cortex and is essential for processing and relaying sensory and motor information. The thalamus acts as a "gateway to the cortex" and thus controls consciousness by filtering and evaluating almost all incoming sensory stimuli (except for the sense of smell). In addition, the thalamus has a fundamental function as a rhythm generator during sleep. Spindle and delta waves are particularly important during deep sleep stages. During periods of alertness, the thalamus generates rapid rhythms (β- and γ-oscillations) as well as tonic activity, the frequency of which depends on the incoming sensory stimulus intensity. Cell type-specific sets of ion channels underly these peculiar activity pattern. Here, two pore domain K^+ (K_{2P}) background channels, hyperpolarization-activated and cyclic nucleotide-gated cation (HCN) channels, T-type Ca^{2+} (Ca_V3) channels, subthreshold-activated delayed rectifier K^+ (K_V7) channels and Ca^{2+}-dependent K^+ (K_{Ca}) channels are of special interest.

Pathophysiologically, thalamocortical dysrhythmia (TCD) describes a disruption in the electrophysiological communication between the thalamus and the cerebral cortex, in which neuronal oscillations become irregular. A characteristic feature is a shift from high frequency activity to slower EEG oscillations (theta and delta band) during wakefulness, indicating problems with the timing of neuronal signals. This dysrhythmia is discussed as a causal mechanism for various neurological and neuropsychiatric disorders, including absence epilepsy, chronic tinnitus, neuropathic pain, Parkinson's disease, and depression. The disrupted interaction results in faulty network loops, which are perceived as "positive symptoms". A number of these pathological conditions are characterized as channelopathies with altered expression and function of ion channels (including HCN and K_V7 channels) and are associated with increased neuronal excitability in the TC system. Here absence epilepsy (AE) and multiple sclerosis (MS) are of special interest. Recently, K_{Ca} channels that play a crucial role in the formation of action potential patterns and the excitability of thalamic and cortical neurons came into focus.

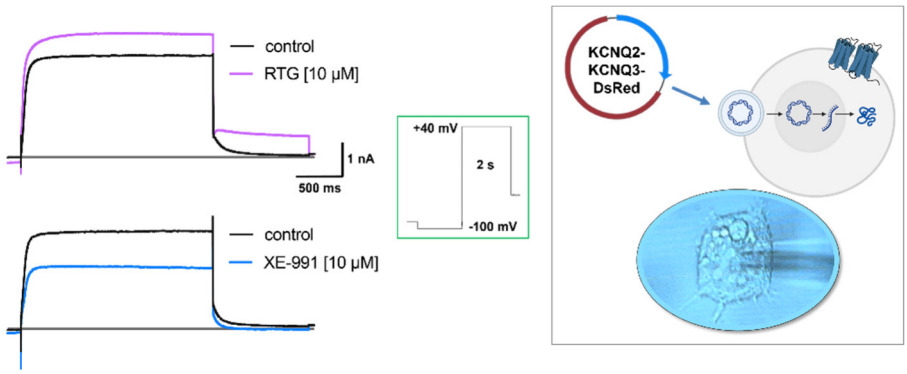


Fig. 1: Whole-cell patch clamp recordings of IM in transfected HEK-293FT cells showing currents elicited by membrane depolarization (the voltage protocol is shown in the green box) to +40 mV (black traces). IM is enhanced by retigabine (RET; purple trace) and inhibited by XE-991 (blue trace). Zero current is shown in gray. The lower panel of the blue box shows a typical transfected cell with the patch pipette approaching from the right side.

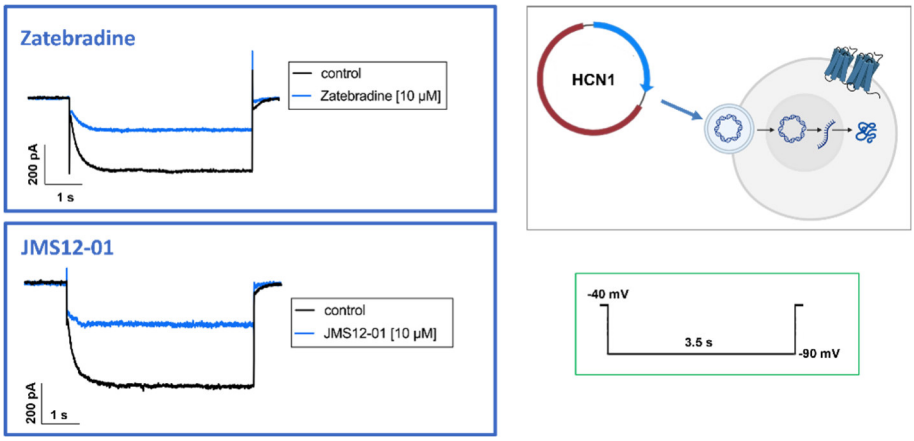


Fig. 2: Whole-cell patch clamp recordings of Ih in transfected HEK-293FT cells showing currents elicited by a voltage step (protocol is shown in the green box) to -90 mV (black traces). Ih is blocked by zatebradine (upper blue box) and the new derivate JMS12-01 (lower blue box).

Based on the central research idea to gain insights into the multiple functions of ion channels and to address their chemical biology, the Research Training Group "Chembion" was established. To this end, chemical methods were used to develop powerful pharmacological tool compounds to investigate the physiology and dysfunction of ion channels. The focus is on the analysis and manipulation of molecular, cellular and integrative (patho)physiological processes through small molecules and probes that are tailored to interact with ion channels in a subtype-specific manner. Two principal investigators of Chembion (Annika Lüttjohann; Thomas Budde) in the institute characterize the function and dysfunction of ion channels in the TC system. On the one hand, K_V7 (Fig. 1) and HCN (Fig. 2) channels in expression systems, the hyperpolarization-activated inward current (I_h) in native neurons (Fig. 3) and the current through KCa3.1 channels in tumor cells (Fig. 4) are analyzed. On the other hand, electrophysiological recordings in the brain (Fig. 5; Fig. 6) and the connectivity of the TC network are analyzed.

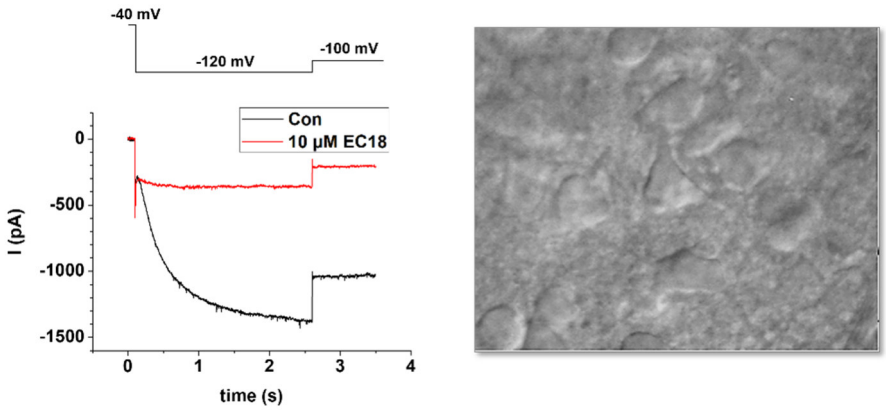
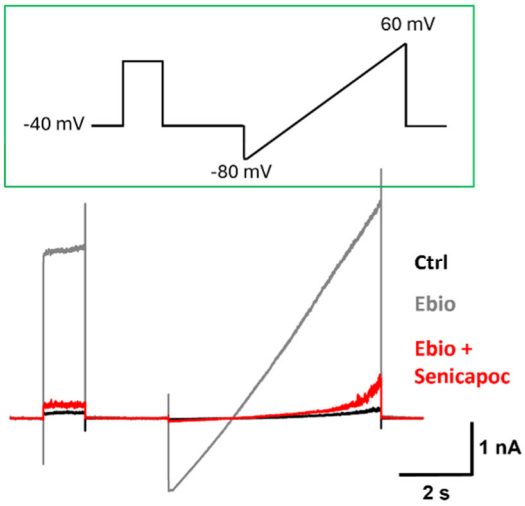


Fig. 3: Whole-cell patch clamp recording showing Ih reduction in a thalamocortical relay neuron in a brain slice by 10 µM of the HCN4-prefering blocker EC18. Ih in the presence (red line) and absence (black line) of the drug was elicited by a hyperpolarizing voltage step to -120 mV (as indicated above the current traces). The right box shows typical multipolar TC neurons using Infrared Differential Interference Contrast (IR-DIC) optics.



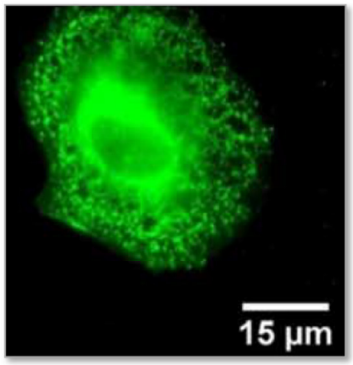


Fig. 4: Senicapoc blocks the current generated by KCa3.1 channels in an A549-3R cell in cell culture (a cell labeled with a fluorescent senicapoc derivate is shown in the right inset): Representative current traces show the outward K+ current under control conditions (black), after pharmacological activation with EBIO (grey) and simultaneous application of EBIO and senicapoc (red). The voltage protocol is shown in the green box.

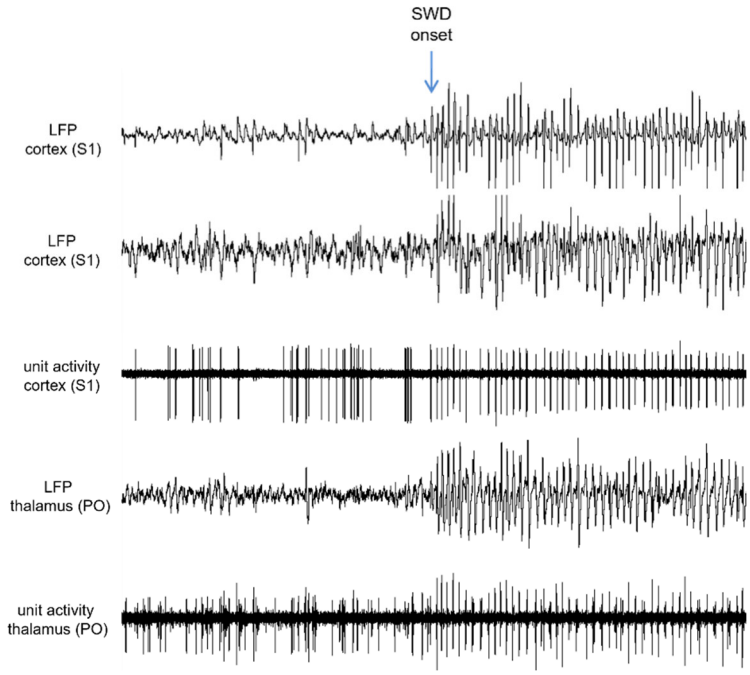


Fig. 5: Unraveling spatio-temporal network dynamics in absence epilepsy. Representative LFP and single unit recording of a state switch from pre-ictal activity into seizure activity (Lüttjohann et al., 2019).

In order to investigate AE, a prototypical TCD which is in the focus of our institute more systemic approaches are used. AE is a neurological disorder, which can be found in young children. Its main diagnostic criterion is the appearance of spontaneous, frequently occurring bilateral generalized spike and wave discharges which can be recorded in the EEG of patients and induce a sudden loss of conscious.

By employing a well validated rat model of AE with a proven high prognostic validity to the human condition, the institute studies these spontaneous phase shifts between physiological and pathophysiological by means of multi-site local field potential as well as ensemble recordings of individual neurons in freely behaving rats (Fig 5). We aim to explore the relevant spatiotemporal dynamics within the thalamocortical system that are needed for the generation and generalization of seizures and aim to identify relevant attractors that are responsible for the sudden switch between physiological and pathophysiological activity. By means of advanced mathematical network analysis we analysis of pre-SWD → SWD transition periods with the aim to identify precursor activity that can help us to predict the generation of an upcoming seizure in real time.

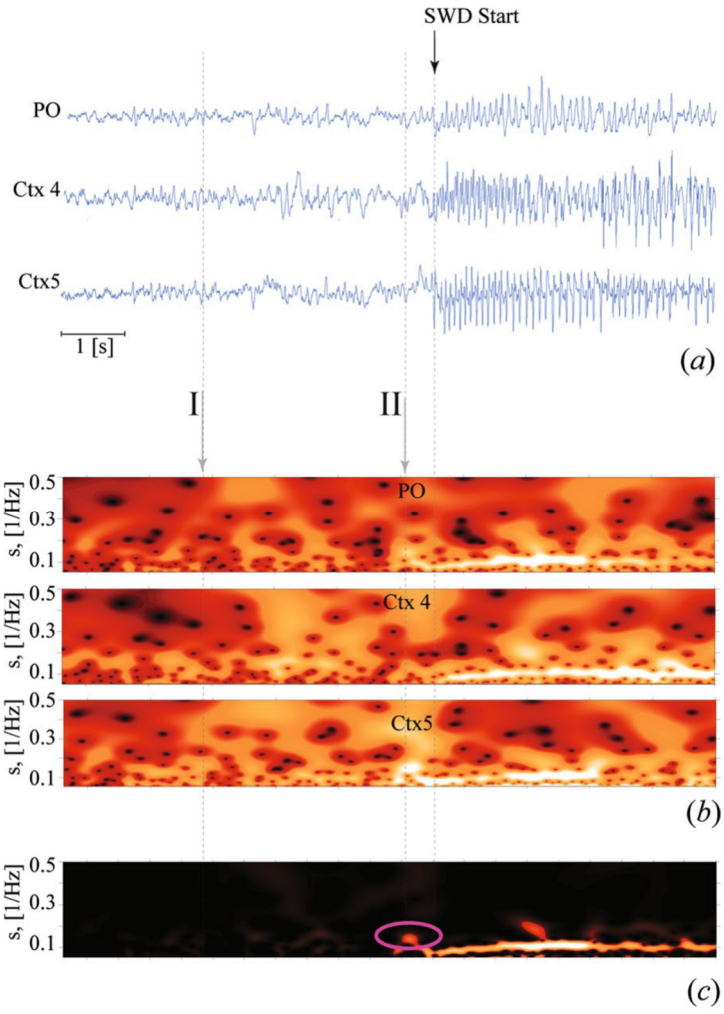


Fig. 6: Precursor activity detected by real-time wavelet analysis in local field potential recordings in cortex and thalamus of absence epileptic rats. Seizure activity was shown to be presictable with a sensitivity of 88% (Maksimenko et al., 2017)

The latter then allows us to establish brain-computer interfaces in which the real time detection of a precursor triggers either an electrical stimulation (deep brain stimulation) or a neuron type-specific optogenetic stimulation that is aimed to rebalance the network and prevent the pathophysiological switch (Fig 6).

Moreover, by comparing developmental trajectories in network coupling of epileptic and non-epileptic animals by means of non-invasive fMRI recordings (Fig 7) we aim to study the process of epileptogenesis (i.e. the more gradual developmental changes that render a brain susceptible to generate seizures later in life) to delineate early critical change points in network states that might predict individual trajectories in patients and might allow the development a preventive patient tailored treatment strategies.

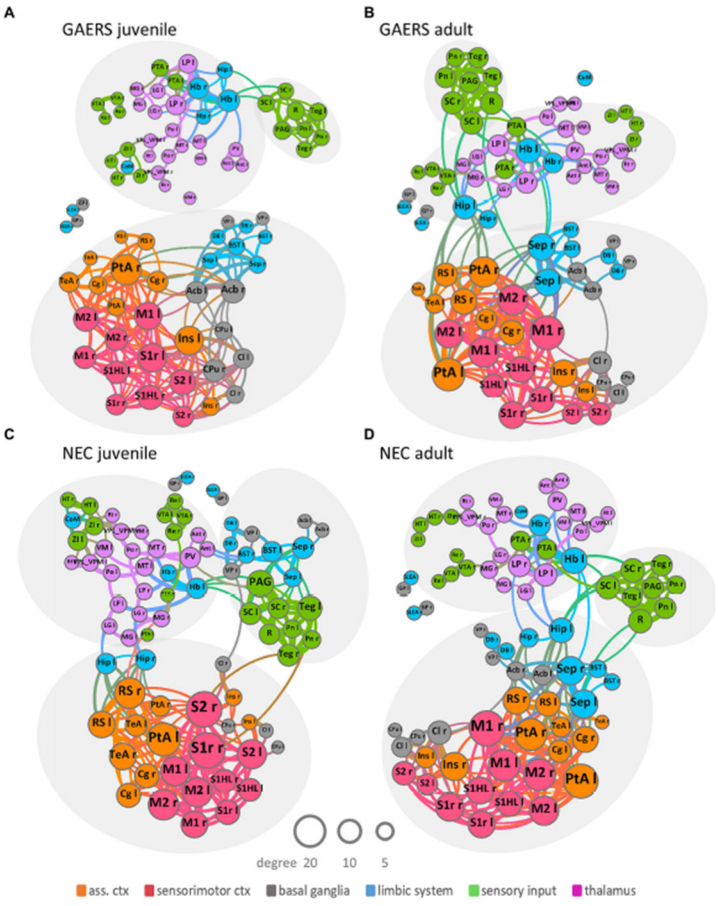


Fig. 7: Differences in brain-wide resting state connectivity between absence epileptic rats (GAERS) and age matched non-epileptic control rats (NEC) as identified in non-invasive fMRI recordings (Wachsmuth et al, 2024).

Last but not least by comparing electrophysiological properties of normal physiological oscillations that are generated within the TC system like sleep spindles of slow cortical oscillations seen during sleep and anesthesia, we aim to establish a network-integrity centered approach to identify and rebalance hyperexcitability.