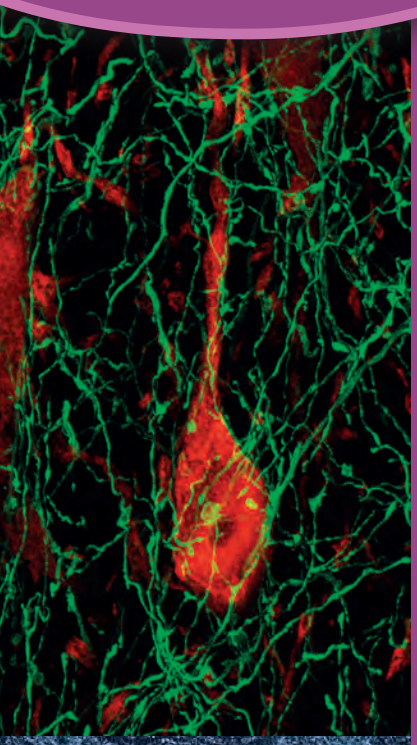
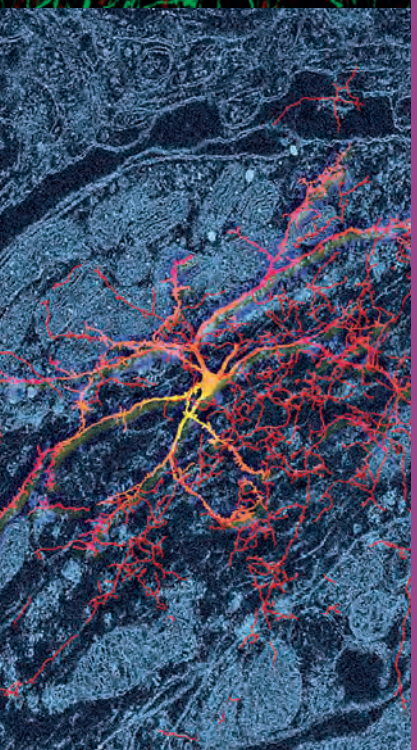
László Acsády

Laboratory of Thalamus Research

Department of Cellular and Network Neurobiology

Head of Laboratory:
László Acsády, PhD





Mission statement

All higher order brain operations require continuous interaction between thalamus and neocortex. Every cortical territory is in reciprocal connection with the thalamus and the lesion of any thalamic nucleus causes symptoms similar to that of the cortical area it is connected to. Thalamus and cortex develop together during the ontogenesis and evolve together during the phylogenesis. Normal communication between thalamus and cortex is disrupted in the major neurological and neuropsychiatric diseases. *These data indicate that thalamus and cortex form one functional unit and one cannot be understood without the other.* Still presently thalamus is mainly studied in isolation, we lack a coherent view on thalamocortical functions. We know especially little about the role of non-sensory thalamus which constitutes the majority of this structure.
Our research shows that the basic synaptic architecture of individual thalamic regions is highly variable. As a consequence the principles of information transfer in the thalamus display region specific features.

Therefore the mission of the Laboratory of Thalamus Research is:

- *to understand the generation and function of nucleus specific thalamocortical signals in normal and diseased states*
- *to understand the nature and significance of the perpetual two-way interaction between thalamus and cortex.*

To this end László Acsády's group utilizes a combined morphological and *in vivo* electrophysiological approach. The technological repertoire consists of light, electron, confocal, and superresolution microscopy, immunocytochemistry, virus mediated gene transfer, transgenic technology, juxta- and intracellular recording and labeling, optogenetics and the use of multishank, multisite silicon probes *in vivo.*

Senior scientists: Péter Barthó, Hajnalka Bokor, Csaba Dávid, Ferenc Mátyás
Postdoctoral fellows: Gergely Komlósi, Nóra Hádinger
Students: Zita Rovó, Viktor Plattner, Lejla Faradzs-Zade, Ákos Babitzky
Technician: Krisztina Faddi

MAJOR RESULTS AND RESEARCH DIRECTIONS

A novel inhibitory system in the thalamus

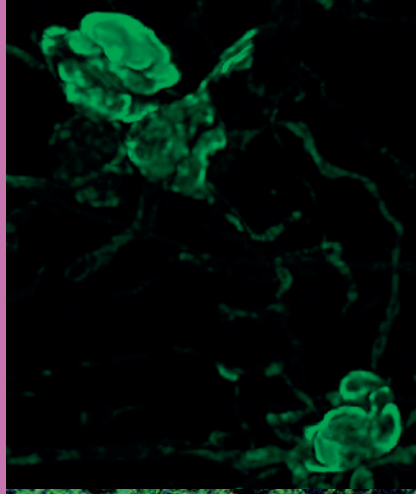
The major inhibitory input of the thalamus arises from the reticular thalamic nucleus, which provides GABAergic afferents to all thalamic nuclei. László Acsády's group revealed another inhibitory system which selectively innervates higher order thalamic relays (Barthó et al., 2002; Bokor *et al.,* 2005). In collaboration with Prof. Anita Lüthi's group (Univ. of Lausanne) they demonstrated that this system (called "extrareticular" or "extrathalamic" inhibition) is different from the reticular inhibition in synaptic organization, postsynaptic targets kinetics, short term plasticity connectivity and firing pattern (Wanaverbecq et *al.*, 2008). The novel system proved to be very powerful. The axons formed large terminals with multiple synapses, which exerted non-depressing inhibitory currents even at high presynaptic firing rates and effectively altered the firing pattern of the target cells. The organization of extrareticular afferents did not depend on the locus of origin (e.g. basal ganglia, or diencephalon,) or the species (rat or monkey) (Bodor *et al.*, 2008). Since its description, the role of extrareticular inhibition has been demonstrated in sensory transmission, central pain and epileptic activity.

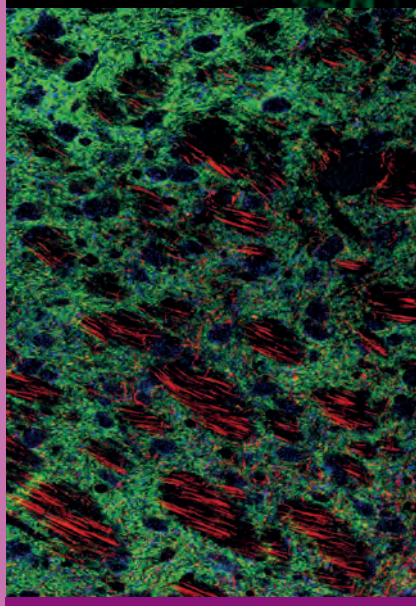
Sensory physiology – the whisker system

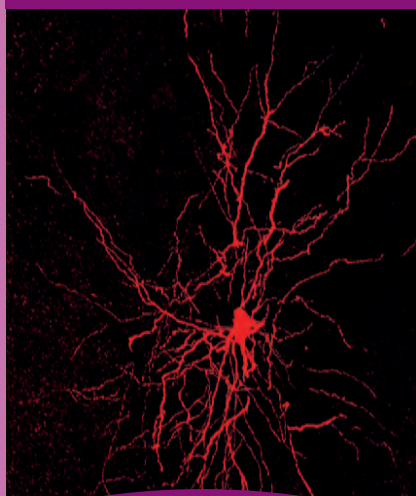
The rat whisker system is one of the best characterized sensory systems. László Acsády's group used the whisker system as a model to test specific predictions emerging from the organization of extrareticular inhibition. Together with Prof. Martin Deschenes's laboratory (Univ. of Lavalle), they demonstrated that extrareticular inhibition is able to block the peripheral sensory transmission in the thalamus via a feed-forward inhibitory mechanism (Lavallee *et al.*, 2005). They also demonstrated a novel principle of thalamic synaptic organization in the somatosensory nucleus of n. posterior (Groh, Bokor et al., 2013, see below). These results clearly show that certain thalamic nuclei are not designed for faithful transmission of sensory information, as earlier suspected, but their activity is regulated in a more complex manner probably using disinhibition and integration of signals of distinct origin.

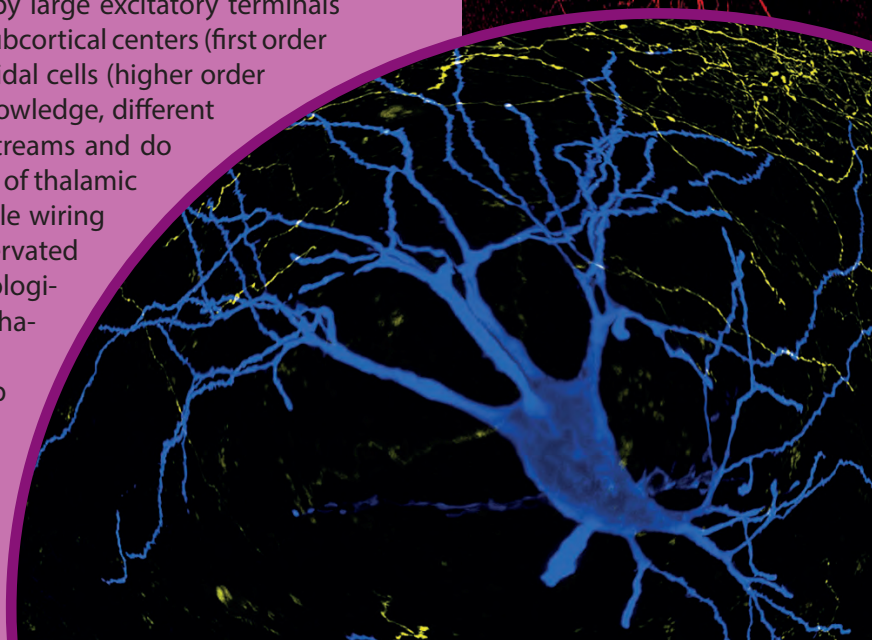
The thalamic computational unit

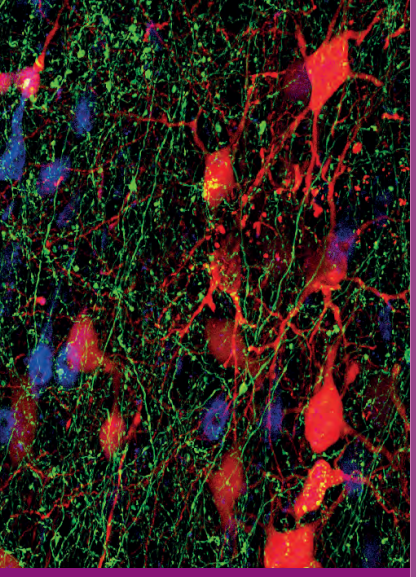
The activity of thalamic neurons is driven by large excitatory terminals (called "drivers"), which originates either in subcortical centers (first order thalamic nuclei) or in cortical layer 5 pyramidal cells (higher order thalamic nuclei). According to text book knowledge, different driver pathways are organized in parallel streams and do not interact at the thalamic level. Separation of thalamic information channels is achieved by a simple wiring principle, a single thalamic relay cell is innervated by a single type of driver input. This morphological unit was thought to underlie the basic thalamic function – the faithful relay.
In contrast to this, a recent study of the group (Groh, Bokor et al., 2013) demonstrated that drivers of different origin (cortex and brainstem) can converge on single thalamic neurons. The two drivers interacted syner-

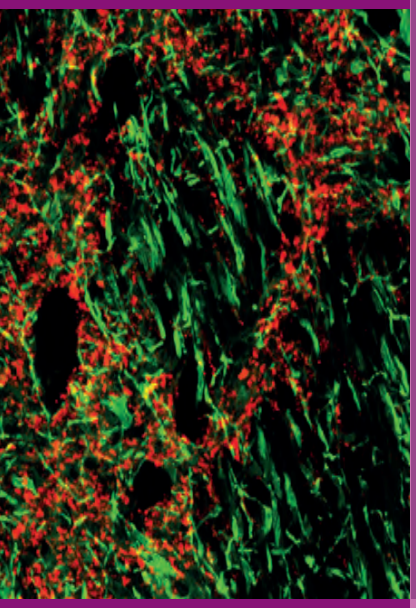


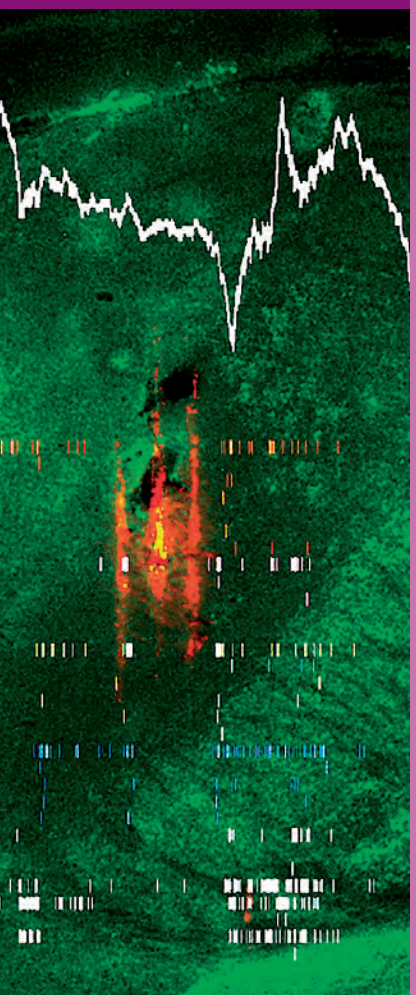












gistically in a time-dependent manner and when co-activated, supralinearly increased the output of thalamus. Convergence of different drivers in single thalamocortical cells was unexpected, demonstrated a novel type of computational unit in the thalamus and questioned the general validity of the relay concept. Together with the data about extrareticular inhibition the results indicated *that integration of different excitatory and inhibitory information channels* rather than simple relay is the main operational principle in several thalamic nuclei. Indeed, analyzing the morphology of drivers in the primate thalamus the group found that classical subcortical drivers are actually present in only 40% of the thalamus (Rovó *et al.*, 2012).

Motor thalamus and basal ganglia

Parkinson's, Huntington's and other major diseases of the basal ganglia cause debilitating syndromes. A recent discovery of the Thalamus Research Group is that the basal ganglia terminals in the motor thalamus, display identical morphological features to the extrareticular terminals described earlier in the sensory thalamus (Bodor *et al.*, 2008). This indicates that basal ganglia terminals are tailored for faithful inhibitory signal transmission even at high presynaptic firing rates, which can explain their effectiveness in controlling thalamocortical activity in normal and pathological states. Interestingly, rodent and primate basal ganglia terminals were identical in the thalamus demonstrating the evolutionary conserved nature of this pathway.

Thalamocortical oscillations

Oscillations in different frequency ranges bind the activity of neuronal populations in time. Using simultaneous thalamic and cortical recordings the Thalamus Research Group demonstrated that thalamic and cortical activity is timed to each other in a cycle-be-cycle manner during slow oscillation and cortical influence on thalamic activity is nucleus specific (Slézia *et al.*, 2011).
More recently, using viral mediated gene transfer and pharmacogenetic approaches they identified the role of extrasynaptic GABA-A receptors in thalamocortical oscillations (Rovó *et al.*, 2014). In another study, by simultaneously recording the somatic activity of excitatory thalamocortical cells together with axonal activity of reciprocally coupled inhibitory reticular thalamic cells they were able to show that during natural sleep a dynamically fluctuating thalamocortical network controls the duration of sleep spindles via the major inhibitory element of the circuits, the nRT (Barthó *et al.*, 2014).

Emerging technologies

The Thalamus Research Group recently implemented and successfully used the following state-of-the art techniques, which are now indispensible to study brain functions.

1) *Recording neuronal ensemble activity in the thalamocortical system* (Barthó et al., 2014).
2) *Control of neuronal activity in a spatially and temporally coordinated manner* (Rovó, Mátyás et al., 2014;, Barthó et al., 2014).
3) *Superresolution microscopy* (Rovó, Mátyás et al., 2014).

FUTURE DIRECTIONS

The Laboratory of Thalamus Research continues to study non-sensory functions of the thalamus by combining morphological and in vivo physiological approaches. In the near future the laboratory aims to include behavioral analysis into its repertoire. Ongoing/planned projects, briefly:

- synaptic organization and function of basal ganglia recipient thalamic nuclei
- the role of intralaminar nuclei in the coordination of large scale electrical activity and behavior
- the role of midline thalamus in arousal, appetitive and aversive behavior

Selected publications from the last 10 years:

- Barthó P., Slézia A., Mátyás F., Faradzs-Zade L., Ulbert I., Harris K. D., & Acsády L. (2014) Ongoing Network State Controls the Length of Sleep Spindles via Inhibitory Activity. *Neuron*, 82, 1367–1379.
- Rovó Z., Mátyás F., Barthó P., Slézia A., Lecci S., Pellegrini C., Astori S., Dávid C., Hangya B., Lüthi A., & Acsády L. (2014) Phasic, Nonsynaptic GABA-A Receptor-Mediated Inhibition Entrains Thalamocortical Oscillations. *J. Neurosci.*, 34, 7137–7147.
- Groh A., Bokor H., Mease R. A., Plattner V. M., Hangya B., Stroh A., Deschenes M., & Acsády L. (2013) Convergence of Cortical and Sensory Driver Inputs on Single Thalamocortical Cells. *Cereb. Cortex.* Epub ahead of print
- Rovó Z., Ulbert I., & Acsády L. (2012) Drivers of the primate thalamus. *J. Neurosci.*, 32, 17894–17908.
- Slézia A., Hangya B., Ulbert I., & Acsády L. (2011) Phase advancement and nucleus-specific timing of thalamocortical activity during slow cortical oscillation. *J. Neurosci.*, 31, 607–617.
- Wanaverbecq N., Bodor A. L., Bokor H., Slézia A., Lüthi A., & Acsády L. (2008) Contrasting the functional properties of GABAergic axon terminals with single and multiple synapses in the thalamus. *J. Neurosci.*, 28, 11848–11861
- Bodor A. L., Giber K., Rovó Z., Ulbert I., & Acsády L. (2008) Structural correlates of efficient GABAergic transmission in the basal ganglia-thalamus pathway. *J. Neurosci.*, 28, 3090–3102.
- Bokor H., Frere S. G., Eyre M. D., Slezia A., Ulbert I., Luthi A., & Acsady L. (2005) Selective GABAergic control of higher-order thalamic relays. *Neuron*, 45, 929–940.
- Lavallee P., Urbain N., Dufresne C., Bokor H., Acsady L., & Deschenes M. (2005) Feedforward inhibitory control of sensory information in higher-order thalamic nuclei. *J. Neurosci*, 25, 7489–7498.

Standing, from left: Krisztina Faddi, Gergely Komlósi, Viktor Plattner, Ákos Babiczky, László Acsády, Ferenc Mátyás, Péter Barthó, Csaba Dávid
Sitting: Nóra Hádinger, Hajnalka Bokor, Lejla Faradzs-Zade