Labortory of Network Neurophysiology

Department of Cellular and Network Neurobiology
Head of Momentum-supported Laboratory:
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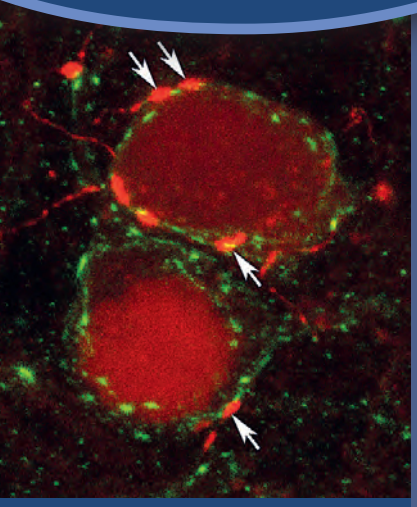
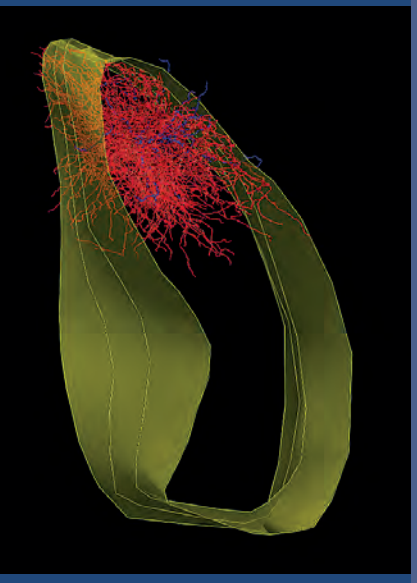
Mission statement

Information flow in neuronal networks composed of different cell types is primarily determined by structural and functional properties of synaptic communication. Thus, on one hand, the actual number and the precise spatial location of synaptic junctions between pre- and post-synaptic neurons influence the efficacy of signal transfer. On the other hand, the probability of transmitter release and the number, types and distribution of transmitter receptors shape the synaptic transmission. On top of this complexity, plasticity of synaptic signaling at short and long time-scales controls the spread of the information within a microcircuit. *The mission of the Lendület Laboratory of Network Neurophysiology is to uncover the principles of information processing in cortical microcircuits at cellular and network levels.* Specifically, the group of Norbert Hájos aims to understand the logic of synaptic connectivity among distinct types of cortical neurons at both structural and functional levels; to uncover the synaptic mechanisms underlying the generation and propagation of synchronous neuronal activities in local cortical networks, and to elucidate the precise mechanisms of how synaptic communication among neurons is controlled under physiological and pathological conditions. In order to reach these goals, light and electron microscopy, electrophysiology, imaging techniques and optogenetic tools are combined.
A new research direction of the group is to elucidate the organization of inhibitory neuronal circuits in the amygdalar nuclei. The amygdala plays a significant role in emotional reactions and memory formation. This brain region is tightly controlled by subcortical afferents (carrying



Boutons of a parvalbumin-expressing basket cell (red) surround the somata of excitatory principal cells (green). Arrows indicate the contact sites.



3D reconstruction of a parvalbumin-expressing fast spiking basket cell in the basolateral amygdala. Dendrites in blue, axons in red, borders of the BLA in yellow.

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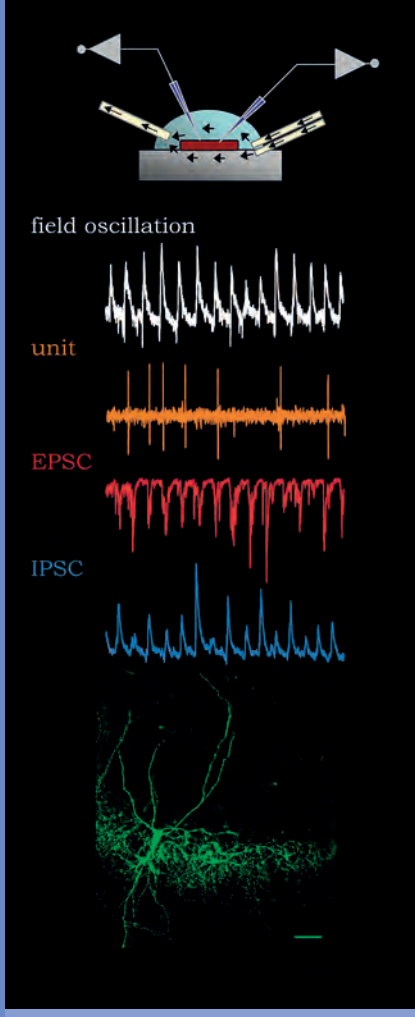
information about emotions, motivation and autonomic states) that likely impact the activity of principal neurons via local inhibitory cells. Uncovering the neuronal operation in amygdalar networks could help in understanding the cellular mechanisms that underlie psychiatric disorders including anxiety, depression or panic attack.

Synaptic mechanisms of hippocampal oscillations

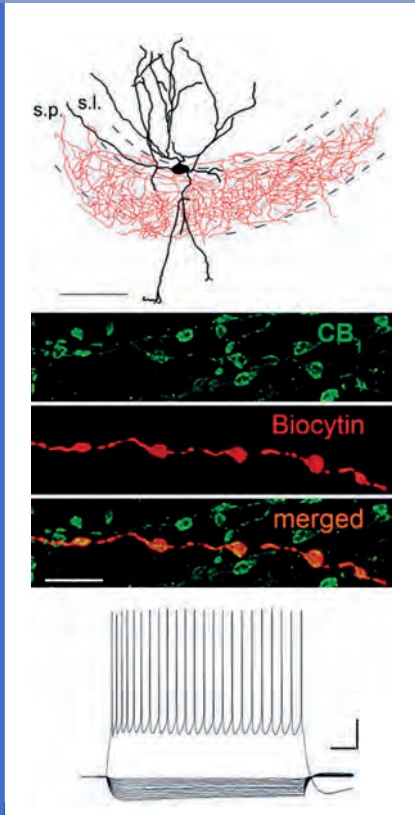
Oscillations in local field potentials are generated by synchronous neuronal activities. Rhythms with characteristic frequency bands and spatial outspread can be recorded during different brain states, suggesting that they emerge from the distinct behaviour-dependent operation of neuronal circuits. In order to reveal the cellular and synaptic mechanisms underlying the generation of distinct types of oscillations, *in vitro* models should be introduced. Norbert Hájos designed a novel type of recording chamber, which allows the maintenance of oscillatory activities in brain slice preparations in combination with high-resolution optical imaging. Using this new design, the group of Norbert Hájos revealed that the oscillations at gamma (30-50 Hz) frequencies emerging intrinsically in the CA3 region of the hippocampus propagate in the neighbouring hippocampal CA1 area by entraining local, inhibitory interneurons within CA1. Thus, in contrast to locally emerging gamma oscillations, where reciprocal recurrent feed-back mechanisms generate these fast network activities, the spread of gamma oscillations into other regions is mediated by rhythmic recruitment of feed-forward inhibition. In addition, Norbert Hájos teamed up with Attila Gulyás, working in the laboratory of Tamás Freund, to clarify the synaptic mechanisms underlying the generation of sharp wave-ripples in the CA3 area, synchronous events that are known to play a role in memory processes. They found that the sharp wave-ripples in CA3 are generated by a microcircuit composed of excitatory pyramidal cells and fast spiking basket cells, similarly to the generation of gamma oscillations. Thus, the same microcircuit is able to generate distinct synchronous network activities within the hippocampus, most likely depending on the different cellular and synaptic parameters.

Control of synaptic communication by endocannabinoids

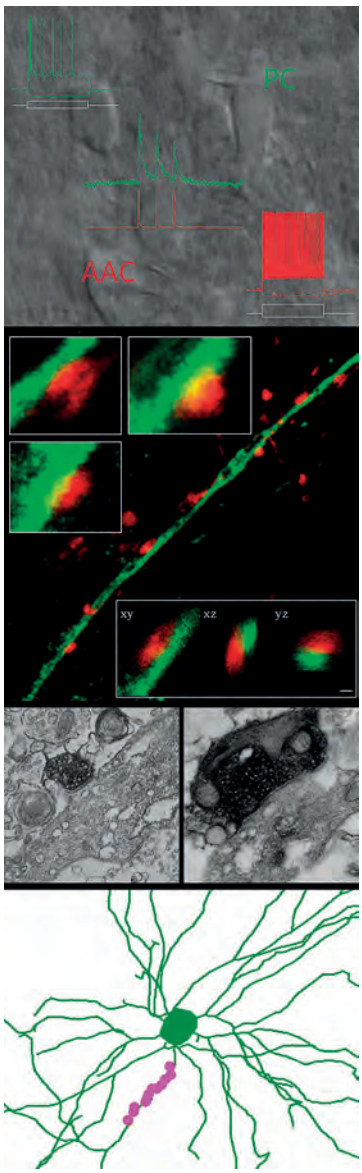
The majority of axon terminals in cortical structures are equipped with CB_1 cannabinoid receptors. Thus, the endogenous ligands of these receptors, the endocannabinoids are in the position to have a widespread impact on the synaptic communication in neuronal networks. The Hájos group revealed that CB_1 activation at excitatory synapses onto fast spiking basket cells by exogenous ligands was responsible for the suppression of network oscillations in the hippocampus. These data have elucidated the synaptic mechanisms of how administration of marihuana can impact the cognitive processes in animals and humans. Furthermore, they discovered together with István Katona's laboratory that, in addition to excitatory pyramidal cells, GABAergic interneurons in the hippocampus could also produce endocannabinoids and these retrograde signalling molecules mediated long-term depression of synaptic communication at excitatory inputs. In addition, teaming up with Zoltán Nusser's group, they clarified



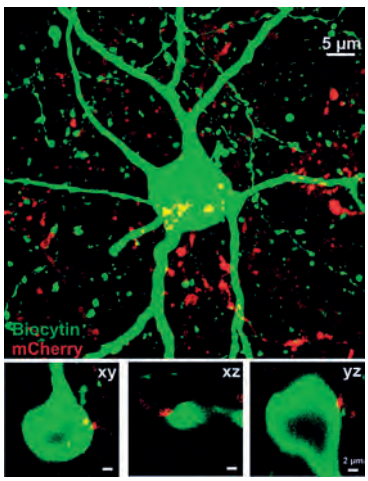
Schematic diagram of the flow in the dual-superfusion slice chamber. Simultaneous measurements of the oscillation and neuronal firing followed by monitoring the synaptic currents recorded in a fast-spiking basket cell in the CA3 region of the hippocampus (in green).



A basket cell in the hippocampus expresses CB_1 cannabinoid receptors on its axon terminals. Dendrites in black, axons in red. Below: voltage responses of the cell upon current injection.



An axo-axonic cell (red) specifically innervates the axon initial segment of a principal cell (green) in the basolateral amygdala.



GABAergic afferents from the basal forebrain (red) contact a GABAergic interneuron in the basolateral amygdala (green).

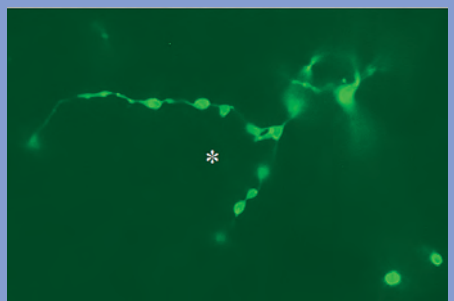
that activation of CB_1 receptors at inhibitory synapses reduced GABA release by suppressing Ca^{2+} entry into presynaptic axon terminals via N-type Ca^{2+} channels. Thus, the control of the intraboutonal Ca^{2+} concentration in GABAergic axon terminals by CB_1 function leads to the effective reduction of synaptic inhibition. These results substantially contribute to our understanding how endocannabinoid-mediated signalling regulates synaptic communication within cortical networks.

Microcircuits in the basolateral amygdala complex

The amygdala is a part of a complex system, the so-called emotional brain. Formed by several nuclei with specific functions this brain region is essential both in memory formation and the execution of relevant behavioural responses upon stress or emotional impact. The Hájos group has begun to define the principles of the synaptic organization within neuronal networks of the basolateral amygdala complex. This cortical structure is composed of excitatory principal cells and GABAergic interneurons, but the connectivity among neurons, which is pivotal to understanding the circuit operation, is unknown. Using light and electron microscopic techniques and *in vitro* electrophysiological recordings they examine the structural and functional properties of the synaptic output of inhibitory neurons innervating the principal neurons in the basolateral amygdala. For instance, the group clarified that a special cortical interneuron type, the axo-axonic cell (AAC) innervating the axon initial segments of principal cells, inhibits or delays the firing of their postsynaptic targets. Importantly, they found that single AACs preferentially innervate the portion of the AIS where action potentials are generated with the highest likelihood, regardless of the number of synapses forming a given connection. These results defined a fine organization of AAC innervation, maximizing their inhibitory efficacy by strategically positioning synapses along the AISs. In the future, the connectivity of other interneuron types will be uncovered in detail to build a functional wiring diagram of the inhibitory networks in the basolateral amygdala.

Subcortical modulation of amygdalar networks

Each cortical structure receives inputs from subcortical areas, which convey information about the external world and the internal state of the organism. The basal forebrain, one of the subcortical regions involved in attention, learning and memory processes, gives rise to both cholinergic and GABAergic innervations to its target cortical areas. The basolateral amygdala is innervated by cholinergic and GABAergic neurons located in a part of the basal forebrain, specifically within the ventral pallidum and substantia innominata. While cholinergic afferents influence both the excitability and the synaptic communication widespread within the basolateral amygdala, the GABAergic components of this subcortical input target preferentially, if not exclusively, local GABAergic interneurons. Using optogenetic tools combined with *in vitro* electrophysiology, the group investigates the cellular and network impact of this subcortical GABAergic input on amygdalar

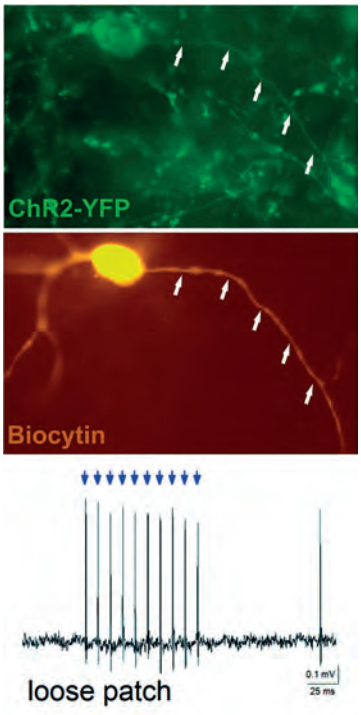


Channelrhodopsin 2-expressing GABAergic boutons from the basal forebrain (green) surround the soma of an interneuron (asterisk) in the basolateral amygdala.

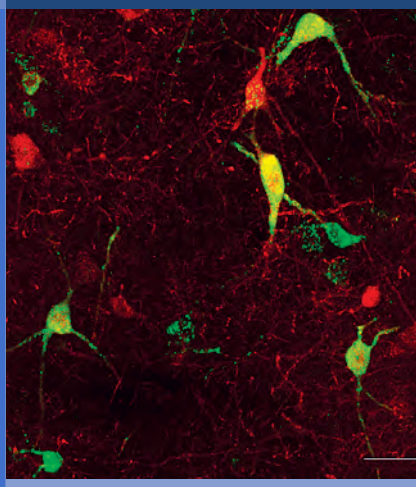
network operation. The overall aim is to clarify how basal forebrain inputs can gate the information processing driven by cortical and thalamic inputs at the amygdalar level.

Selected publications from the last 10 years:

- Szabó GG, Lenkey N, Holderith N, Andrási T, Nusser Z and Hájos N. Presynaptic calcium channel inhibition underlies CB_1 cannabinoid receptor-mediated suppression of GABA release. J Neurosci. 34:7958-63 (2014)
- Zemankovics R, Veres JM, Oren I and Hájos N. Feedforward inhibition underlies the propagation of cholinergically induced gamma oscillations from hippocampal CA3 to CA1. J Neurosci. 33:12337-51. (2013)
- Hájos N, Karlócai MR, Németh B, Ulbert I, Monyer H, Szabó G, Erdélyi F, Freund TF and Gulyás AI. Input-output features of anatomically identified CA3 neurons during hippocampal sharp wave/ripple oscillation in vitro. J Neurosci. 33:11677-91. (2013)
- Papp OI, Karlócai MR, Tóth IE, Freund TF and Hájos N. Different input and output properties characterize parvalbumin-positive basket and axo-axonic cells in the hippocampal CA3 subfield. Hippocampus 23:903-18. (2013)
- Nagy AG, Botond G, Borhegyi Z, Plummer NW, Freund TF and Hájos N. DAG-sensitive and Ca^{2+} permeable TRPC6 channels are expressed in dentate granule cells and interneurons in the hippocampal formation. Hippocampus 23:221-32. (2013)
- Péterfi Z, Urbán GM, Papp OI, Németh B, Monyer H, Szabó G, Erdélyi F, Mackie K, Freund TF, Hájos N, Katona I. Endocannabinoid-mediated long-term depression of afferent excitatory synapses in hippocampal pyramidal cells and GABAergic interneurons. J Neurosci. 32:14448-63 (2012)
- Holderith N, Németh B, Papp OI, Veres JM, Nagy GA, Hájos N. Cannabinoids attenuate hippocampal gamma oscillations by suppressing excitatory synaptic input onto CA3 pyramidal neurons and fast spiking basket cells. J Physiol. 589:4921-34 (2011)
- Hájos N, Ellender TJ, Zemankovics R, Mann EO, Exley R, Cragg SJ, Freund TF, Paulsen O. Maintaining network activity in submerged hippocampal slices: importance of oxygen supply. Eur J Neurosci. 29:319-27. (2009)
- Hájos N, Mody I Establishing a physiological environment for visualized in vitro brain slice recordings by increasing oxygen supply and modifying aCSF content. J Neurosci Meth. 183:107-13. (2009)



Blue light-induced firing in a channelrhodopsin 2 (ChR2)-expressing parvalbumin-containing neuron in the basal forebrain.



Neurons expressing parvalbumin (red) in the basal forebrain project into the basolateral amygdala indicated by the content of a retrograde tracer, Fluogold.

Standing, from left: Richárd Kozma, László Végh, Tibor Andrási, Norbert Hájos, Attila Vikor, Attila Gergő Nagy
Sitting: Erzsébet Gregori, Orsolya Papp, Éva Krizsán, Judit Veres