Laboratory of Cellular Neurophysiology

Department of Cellular and Network Neurobiology

Head of Laboratory: Zoltan Nusser

The most fundamental function of nerve cells is the integration of their synaptic inputs to generate their propagating output signal, the action potential. *The major aims of the laboratory of Dr Nusser are to understand how identified presynaptic nerve cells release neurotransmitters; how the released transmitter molecules activate their postsynaptic receptors; and how the generated postsynaptic potentials are integrated to generate an action potential.* The Laboratory of Cellular Neurophysiology focuses on four major project areas using a variety of molecular, neuroanatomical, *in vitro* electrophysiological and imaging approaches:

1) Investigate the intrinsic electrical and morphological properties of GABAergic interneurons of the main olfactory bulb and their roles in the microcircuit using *in vitro* electrophysiology and cellular neuroanatomy.

2) Identify the roles of defined neuron types in olfaction utilizing a pharmaco-genetic approach.

3) Reveal how the ultrastructure of pre- and postsynaptic specializations influences the functional properties of synapses such as the probability and short-term plasticity of transmitter release and the extent of postsynaptic receptor activation. This is investigated by combining *in vitro* electrophysiology, two-photon imaging, light- and electron microscopy.

4) Create a molecular map of the neuronal surface by determining the location and density of various voltage- and ligand-gated ion channel subunits in defined subcellular compartments of identified nerve cells, using quantitative light- and electron microscopic immunolocalization.

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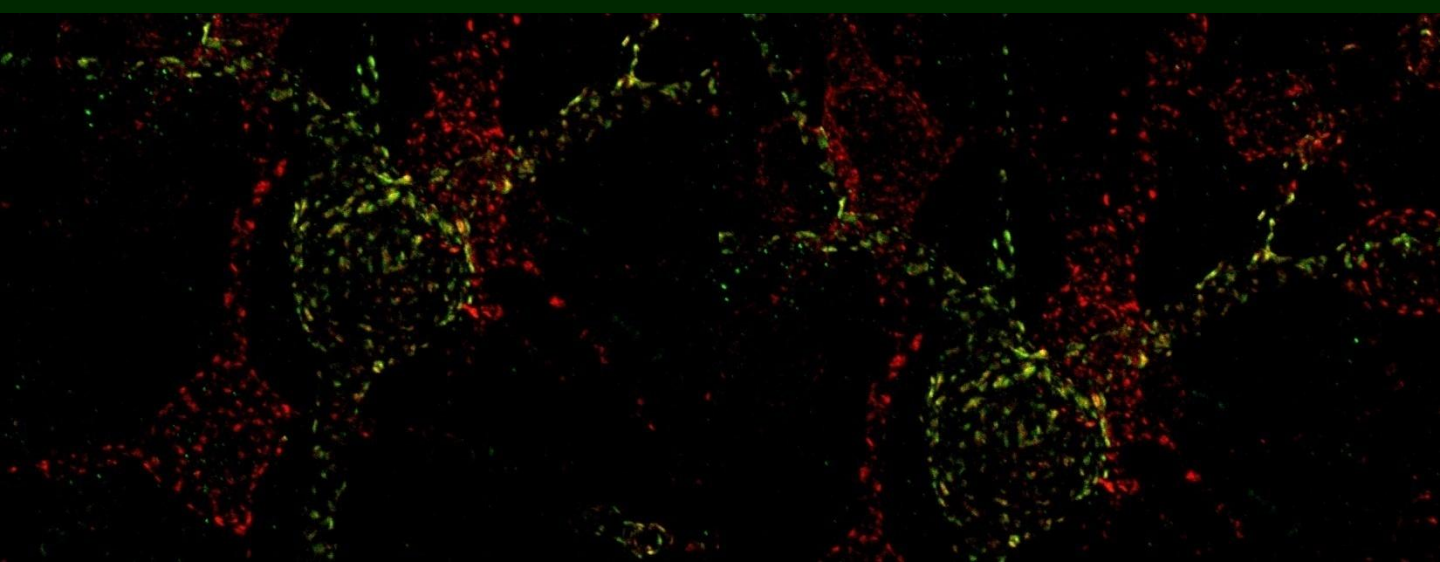


1. Understanding the cellular elements and synaptic connectivity of the olfactory bulb

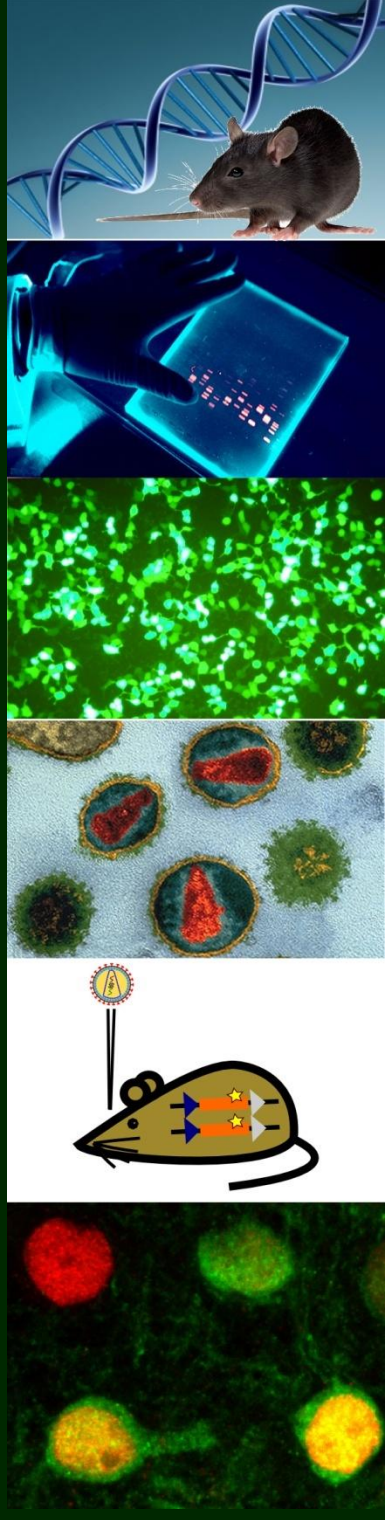
The main olfactory bulb (MOB) is the first relay station of the olfactory pathway where information from the primary sensory neurons is transmitted to the projection neurons, the mitral and tufted cells (M/T). M/T cells in turn send their axons to the primary olfactory cortex where they innervate glutamatergic pyramidal cells. The MOB also contains GABAergic local circuit interneurons (IN); granule cells, periglomerular cells, superficial- and deep-short-axon cells. The classical view regarding the connectivity of INs has been that they mainly innervate M/T cells. Several roles of GABAergic INs have been proposed, including generating oscillations at theta and gamma frequencies or sharpening the response properties of M/T cells through surround inhibition. Recently, the laboratory of Dr Nusser identified several novel IN subtypes, called GL-, EPL-, and GCL-dSACs, which do not innervate M/T cells, but are specialized to control the activity of other GABAergic INs (GABAergic IN-selective INs). They also demonstrated that these dSAC subtypes have distinct places in the circuit, innervate different postsynaptic target cells in a subtype-specific manner, have different firing patterns and express distinct sets of voltage-gated ion channels and neurotransmitter receptors.

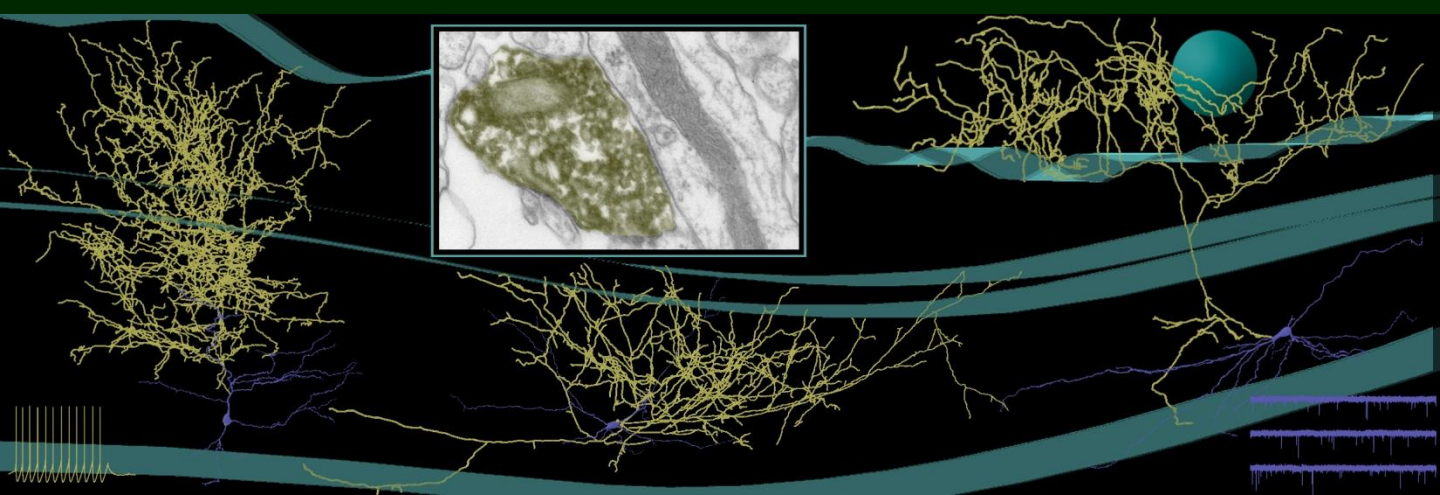
Dr Nusser's laboratory aims to understand the microcircuit of the MOB with special emphasis on GABAergic INs. They apply combined cellular neuroanatomical, immunohistochemical and *in vitro* electrophysiological approaches to investigate the origin and precise operation of input and output synapses of INs.

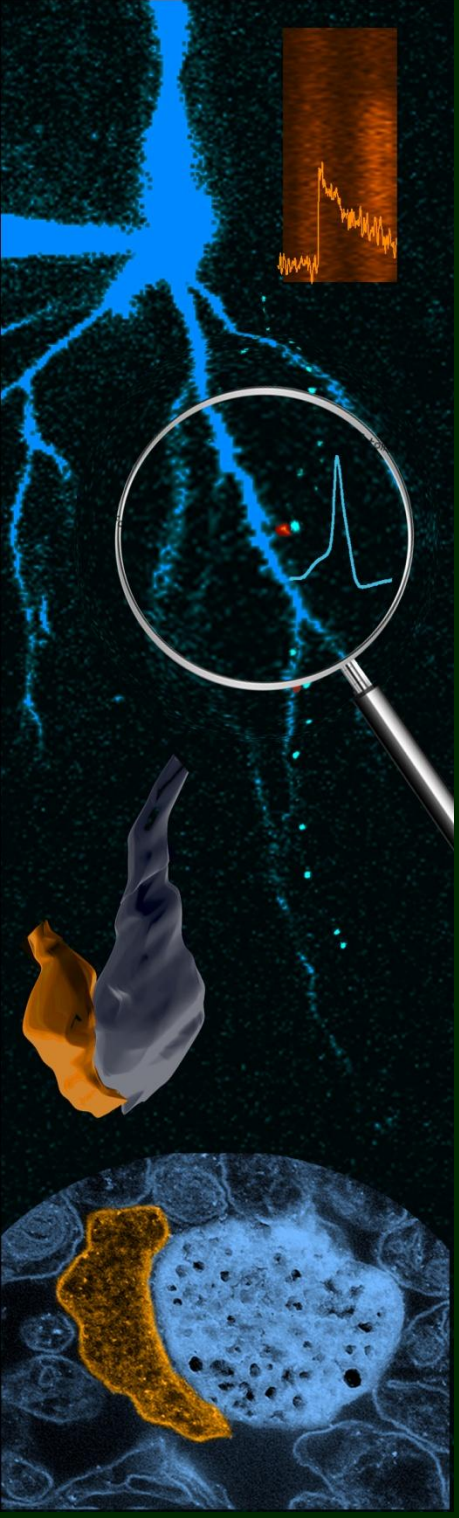
2. Determining the role of identified neurons in olfaction

The extraordinary diversity of nerve cells was already recognized over a century ago. It is now widely accepted that within most brain regions, including the MOB, glutamatergic principal cells are rather homogeneous, whereas GABAergic INs form a diverse cell population. As mentioned above, the laboratory of Dr Nusser has identified novel GABAergic IN subtypes in the MOB, which showed unique connectivity patterns. An interesting issue regarding the diversity of INs is identifying the role individual cell types might play in olfaction.

The laboratory of Dr Nusser embarks on this issue using a pharmaco-genetic approach. Current flowing through γ2 subunit-containing GABAA receptors is sensitive to potentiation by the benzodiazepine site agonist zolpidem. This potentiation can be prevented by a point mutation, resulting in the replacement of the 77th amino acid of the γ2 subunit. Such a point mutation was introduced as a deletable variant of the γ2 subunit and a transgenic mouse line was generated in which all GABAA receptors in the entire brain are zolpidem insensitive. Using virus mediated gene transfer, the laboratory aims to replace the zolpidem insensitive γ2 subunits with wild type, zolpidem-sensitive ones in a brain region and cell type-specific manner. Such a manipulation would allow the selective reduction of the activity of certain cell populations following the systemic administration of zolpidem. The effect of removing certain cell types on olfaction will be tested using a variety of behavioral paradigms.







3. Understanding the functional consequences of ultrastructural diversity of GABAergic and glutamatergic synapses in the brain

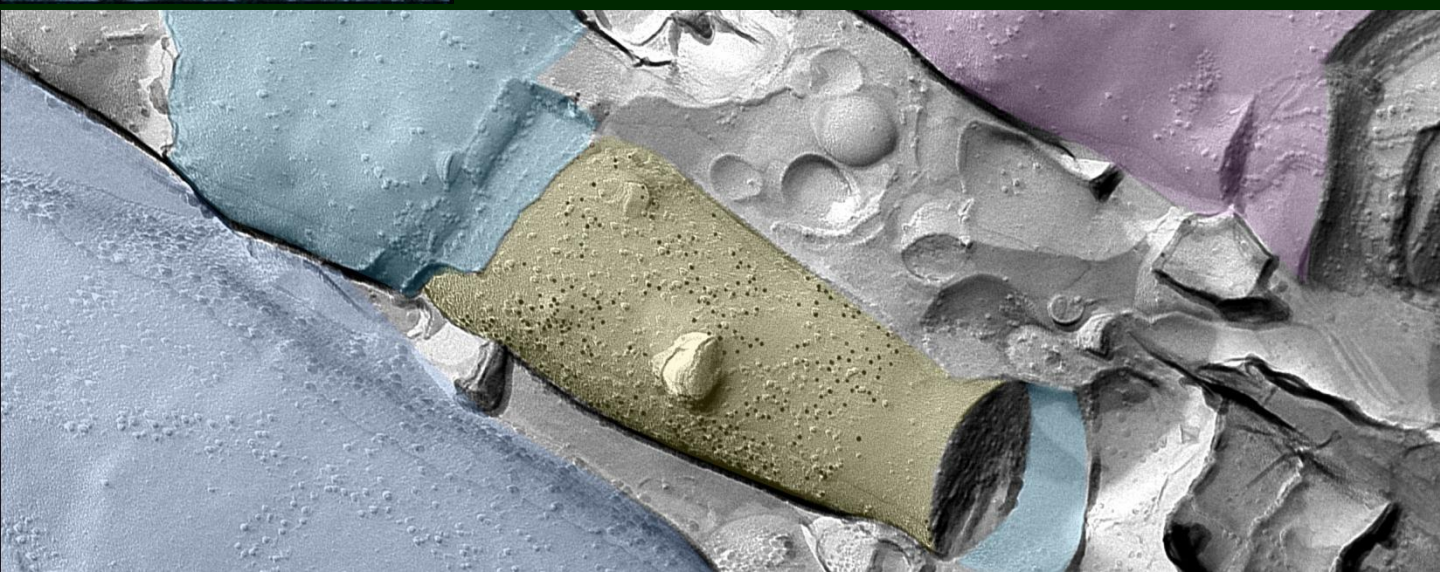
Understanding chemical synaptic neurotransmission in the CNS has been in the spotlight of neuroscience in the past decades. A tremendous amount of information has been gathered regarding the molecular events leading to the release of neurotransmitter from synaptic vesicles, the diffusion of neurotransmitter molecules to their receptors and the activation of these receptors. At the same time ultrastructural analysis of synaptic junctions has revealed enormous diversity in the shape and size of pre- and postsynaptic specializations among central synapses. It is still unknown how differences in the functional properties of synapses are related to their ultrastructure and how alterations in synaptic geometry affect function.

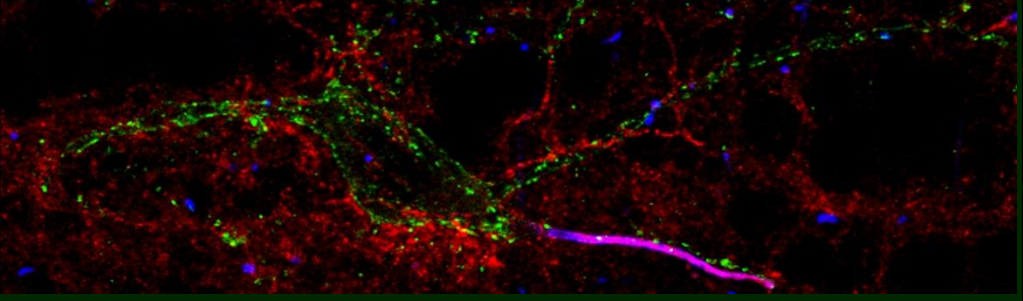
The Laboratory of Cellular Neurophysiology combines *in vitro* electrophysiology and two-photon Ca2+ imaging with electron microscopic analysis of the synapses to address how diversity in the release probability of distinct synapses correlates with the size and shape of the presynaptic active zones. Furthermore, they employ quantitative electron microscopic immunohistochemistry to reveal heterogeneities in the molecular composition of functionally distinct release sites and to determine how the identity, number and density of postsynaptic neurotransmitter receptors affect postsynaptic receptor occupancy and open probability.

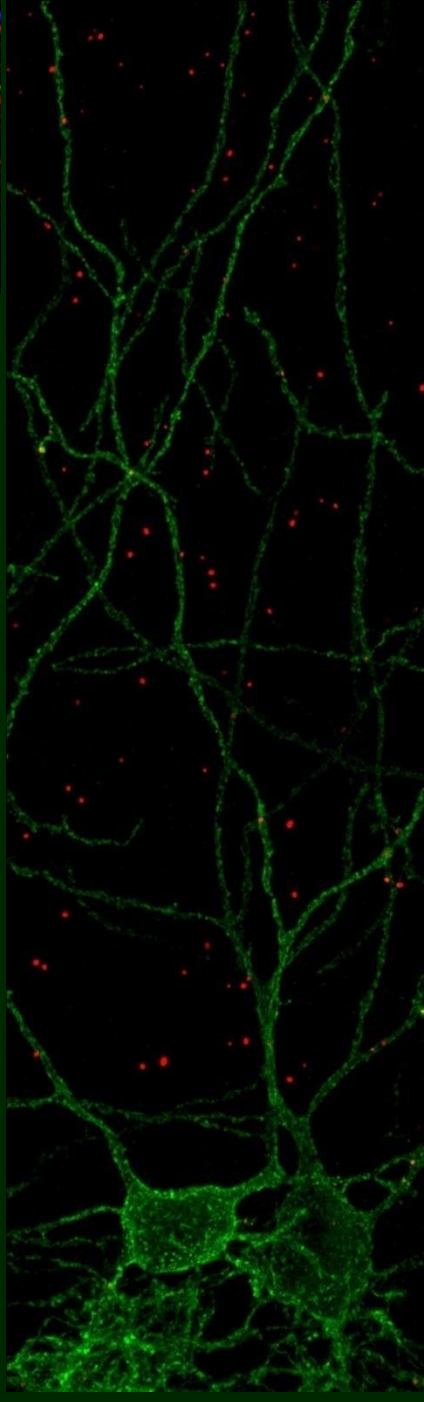
4. Revealing the subcellular distribution of voltage- and ligand-gated ion channels on the surface of identified nerve cells

The most fundamental function of nerve cells is the integration of their synaptic inputs to generate action potentials (APs). It is a generally accepted view that APs are generated in the axon initial segment. However, input synapses are usually distributed over an enormously large dendritic tree. Because of this spatial arrangement, the distance between a synapse and the site of output generation varies to a tremendous extent, resulting in differential filtering of postsynaptic responses by the dendrites. Thus, assuming a passive dendritic tree, the effect of a synapse on the output generation depends on its dendritic location. However, in the past decade, it became apparent that dendrites are not passive, but contain a large number of active, voltage-dependent conductances, which endow dendritic trees with unanticipated computational power. The molecular identity, exact location and density of these ion channels in small subcellular compartments on the axo-somato-dendritic surface determine their roles in dendritic integration.

The laboratory of Dr Nusser has investigated the subcellular distribution of hyperpolarization-activated and cyclic nucleotide gated channels (HCN), A-type and delayed rectifier potassium channels (Kv) and sodium channels (Nav) in distinct types of nerve cell using immunohistochemical approaches. Their results revealed cell type- and subunit-specific distribution patterns. For example, the density of the HCN1 subunit increases along the proximo-distal axis of hippocampal pyramidal cell dendrites, has a rather uniform density in olfactory bulb external tufted cell dendrites, but is restricted to the axons of cortical basket cells. Considering a single cell type, the distribution patterns of distinct voltage-gated ion channels are very different. Namely, the density of HCN1 increases, whereas that of Nav1.6 decreases in hippocampal pyramidal cell apical dendrites as a function of distance from the soma. In future experiments, the laboratory aims to extend their investigations to other voltage-gated ion channels and to test the functional roles of specific distribution patterns.







10 most important publications from the last 10 years:

1. Lőrincz, A. & **Nusser, Z**. Molecular identity of dendritic voltage-gated sodium channels. SCIENCE: 328: 906-909 (2010)
2. Vervaeke, K., Lőrincz, A., Gleeson, P., Farinella, M., **Nusser, Z**. & Silver, R.A (2010) Rapid desynchronization of an electrically coupled interneuron network with sparse excitatory synaptic input. NEURON, *67,* 435-451.
3. Lőrincz, A. & **Nusser, Z**. Cell type-dependent molecular composition of the axon initial segment. J NEUROSCI 28: 14329-14340 (2008)
4. Eyre, M.D., Antal M. & **Nusser, Z**. Distinct deep short-axon cell subtypes of the main olfactory bulb provide novel intrabulbar and extrabulbar GABAergic connections. J NEUROSCI 28: 8217-8229 (2008)
5. Biro, A.A., Holderith, N.B. & **Nusser, Z**. Release probability-dependent scaling of the postsynaptic responses at single hippocampal GABAergic synapses. J NEUROSCI 26: 12487-12496 (2006)
6. Kollo, M., Holderith, N.B. & **Nusser, Z**. Novel subcellular distribution pattern of A-type K+ channels on neuronal surface J NEUROSCI 26: 2684-2691 (2006).
7. Biro, A.A., Holderith, N.B. & **Nusser, Z**. Quantal size is independent of the release probability at hippocampal excitatory synapses. J NEUROSCI 25: 223-232 (2005)
8. Farrant, M., & **Nusser, Z**. Variations on an inhibitory theme: phasic and tonic activation of GABAA receptors. NAT REV NEUROSCI 6: 215-229 (2005)
9. Losonczy, A., Biro, A.A., & **Nusser, Z**. Persistently active cannabinoid receptors mute a sub-population of hippocampal interneurons. PROC NATL ACAD SCI USA 101: 1362-1367 (2004)
10. Lőrincz, A., Notomi, T., Tamás, G., Shigemoto, R. & **Nusser, Z**. Polarized and compartment-dependent distribution of the hyperpolarization-activated channel HCN1 in pyramidal cell dendrites. NATURE NEUROSCI 5: 1185-1193 (2002)