

Session 1: Circuit function and behavior in animal models

chaired by Stéphane Ciochi, Department of Physiology, University of Bern.

Abstract

A fundamental objective in modern neurosciences is to understand the neural mechanisms of learning and memory in both healthy and pathological conditions. Fear and anxiety are well conserved across different animal species, which reflects their evolutionary importance for survival in dangerous environments. Nevertheless, in humans, persistent fear and/or chronic anxiety represent a strong personal and societal burden affecting several million people in Europe[1]. Existing therapies remain unspecific and are not generally effective, because the detailed neurobiological understanding of anxiety disorders is lacking. **To develop better cures, translational strategies relying on animal models are proven indispensable to understand the brain regions, neuronal circuits and mechanisms underlying normal and pathological brain function.**

The hippocampus is a high-order cortical area[2] and core brain network for emotions, mood and cognition[3-5]. The ventral subdivision of the hippocampus (anterior hippocampus in primates) is mostly involved in behaviours such as contextual fear conditioning or anxiety[6-12]. Contextual fear conditioning is an associative learning process leading to the memorisation of life-threatening environments, which is essential for adaptive behaviour in animals. The function of the hippocampus in contextual fear conditioning is further supported by its direct synaptic connections with brain regions also implicated in emotional processing such as the amygdala or the medial prefrontal cortex[13-16]. Within the hippocampus, neuronal populations can be separated into two major classes: excitatory pyramidal cells, which use glutamate as neurotransmitter and establish both local and distant axonal projections, and interneurons, which use GABA (γ -amino butyric acid) as neurotransmitter and control the activity and timing of pyramidal cells mostly by local axons. Pyramidal cells of the CA1 area of the hippocampus represent the main output of the hippocampus. Most CA1 pyramidal cells can discharge as place cells which activity at the population level is thought to enable the formation of context-specific memories[17, 18].

The activity of CA1 pyramidal neurons is controlled by a set of very diverse GABAergic interneuron types that have been characterised in the rodent CA1 hippocampus *in vivo* based on the expression of signalling molecules, synaptic targets and dendritic distribution, and contribution to network oscillations[19-23]. In the hippocampus several forms of network oscillations have been described based on frequency, amplitude and behavioural correlations[24-27]. Theta oscillations (4-12 Hz) represent the "on-line" state of the hippocampus and are observed during spatial navigation or rapid-eye-movement sleep[28]. Sharp wave-associated ripples (120-250 Hz) are observed during consummatory behaviour, behavioural immobility and slow-wave sleep[24, 29]. Ripples reflect a highly synchronous activity of hippocampal neurons and are connected to temporally compressed replay of information and memory

consolidation[30-32]. Different network oscillations might be generated by or in cooperation with GABAergic interneurons and provide a temporal framework for the emergence of large-scale cell assemblies in distributed cortical areas[33-35]. The diversity of hippocampal GABAergic interneurons evolved to serve a division of labour enabling a dynamic redistribution of inhibition over neuronal subcellular domains during network oscillations and behaviour.

The objective of this BENEFRI workshop session is to present neural mechanisms and circuits within the rodent hippocampus underlying learning and memory processes. Speakers will detail state-of-the-art techniques for recording and manipulating neural activity in identified hippocampal circuits using appropriate behavioural tasks and animal models.

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Session 2: **Circuits in sensory perception**

chaired by Shankar Sachidhanandam, Department of Physiology, University of Bern.

Abstract

We use our senses to perceive with the world around us, and based on our perceptions we can then take necessary actions to interact with our environment. In order to identify the cellular and network mechanisms underlying sensory processing, we use the mouse as an experimental animal model. The genetic tractability of the mouse renders it extremely useful to label and study specific groups of genetically distinct neurons, in both anaesthetized and head-fixed awake mice. The mouse whisker system is well characterized and is extensively used as a model system in sensory processing. This session begins by exploring the role of synaptic plasticity in sensory processing, at the single-cell and network level in the mouse somatosensory barrel cortex (S1). It then moves on to characterize the diversity of sensory circuits in the mouse cerebellum. Finally, the session ends with the role of higher order sensory cortices in sensory perception and goal-directed behavior.

Session 5: **Animal model systems for studying neurodegeneration**

chaired by Preeti Yadav, Department of Neurology, University Hospital Bern

Abstract

We will talk about three experimental systems and how they are used to study neurodegenerative mechanisms in amyotrophic lateral sclerosis (ALS: first two presentations) and in Alzheimer's disease (AD: last presentation). The first presentation shows new results from wildtype (wt) mice and two genetically modified mouse lines that are used as models for ALS to do *in vivo* intracellular electrophysiology in spinal cord motor neurons and to compare their excitability and vulnerability.

In the second presentation, we will talk about the development of patient derived inducible pluripotent stem cells as an *in vitro* model system of ALS. The aim is to derive human motor neurons from skin fibroblasts of both familial and sporadic ALS as well as control patients using cellular reprogramming. This undertaking will provide us with a relevant ALS platform to screen a small molecule compound library and identify

molecules that are able to reduce cellular and axonal stress and protect motor neurons from degeneration.

The last presentation will finally deal with the analysis of disrupted information processing in neuronal circuits of APP/PS1 mice, a well characterized model for AD. This analysis is based on two-photon calcium imaging in vivo in wt and in genetically modified AD mice.

Session 6: **Therapies and approaches in disease and regeneration**

chaired by Hans Rudolf Widmer, Department of Neurosurgery, University Hospital Bern

Abstract

This session will address three aspects of the topic from animals to humans.

First, Doctor Basil Grüter and his colleagues will speak about experimental studies on rats and rabbits in the context of finding improved protocols for the treatment of hemorrhagic stroke. He will discuss on a new rabbit model for the study of early brain injury after subarachnoid hemorrhage and the role of microclot formation in this model. Moreover, he will present technical aspects of the rabbit blood-shunt model to study sequelae of acute and late subarachnoid hemorrhage. Furthermore, he and his colleagues have shown that early brain injury linearly correlates with reduction in cerebral perfusion pressure during the hyperacute phase of subarachnoid hemorrhage. Finally, the results of studies investigating the role of wall cellularity in aneurysm healing following coil embolization and the feasibility of bioresorbable stents in rat aneurysm model are presented.

The second speaker Doctor Stefano Di Santo shows ways to reduce and to replace the number of experimental animals by means of a cell free approach. His strategy is based on his longstanding efforts in the field of paracrine factors released by stem and progenitor cells. So he and his colleagues demonstrated previously that intramuscular injection of endothelial progenitor cells-derived conditioned medium (EPC-CM) is as effective as cell transplantation for promoting tissue revascularization and functional recovery. This observation not only laid the basis for reducing number of animals for harvesting donor tissues but importantly also circumvents the need of immunosuppressive drugs for the host animals in transplantation approaches. In the course of his lecture he will also address various aspects of the underlying mechanisms involved in the EPC-CM mediated effects.

The third speaker Doctor Claudio Pollo will give first an overview on neurodegenerative diseases with emphasis on Parkinson's disease. In this context, the potential of deep brain stimulation (DBS) in neurological and psychiatric diseases will be discussed and recent progress in the use of DBS illustrated.