Sensory, motor and decision information in the mouse cortex

Sylvain Crochet

Laboratory of Sensory Processing, Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Switzerland

Even simple sensorimotor transformations require a sequence of processes occurring across highly distributed brain areas. Where and how sensory information is transformed into motor command in an experience-dependent manner remains to be determined and requires recording of neuronal activity from multiple brain regions. We study sensorimotor transformation in head-restrained water-restricted mice trained to lick a water spout for reward in response to a brief single-whisker stimulus. Using multisite local field potential as mice learned the whisker-detection task, we found that learning resulted in a progressive recruitment of the dorsal hippocampus (dCA1) and medial prefrontal cortex (mPFC) - both areas being necessary for the execution of the task. The learning of the task was also correlated to a selective increase in 3-4 Hz activity in the mPFC, and increase in interareal coherence in the same frequency band, pointing to increased cortical functional connectivity. We then performed high-density extracellular recordings during the execution of the whisker-detection task in the whisker primary somatosensory cortex (wS1), tongue-jaw primary motor cortex (tjM1) and mPFC to investigate where sensory, motor and decision information were represented. We found that the nature of the sensory stimulus was best encoded in wS1 and to a lesser extent in mPFC but poorly in tjM1. Movement initiation was broadly distributed across areas, but fine movement kinematics were best encoded in tjM1. Decision was also distributed among the recorded areas, but neurons responding only to the association of the stimulus and motor output (Hit selective) where found more in mPFC. Analysis of single trials from simultaneous recordings also revealed that failure in the sensorimotor transformation could occur at different levels of the processing. Altogether, multisite electrophysiological recordings in task-performing mice begins to unravel key brain regions involved in sensorimotor transformation and flows of information between those areas.

Multi-regional imaging of the neuromodulatory and brain activity

Yaroslav Sych

Institute of Cellular and Integrative Neuroscience, Strasbourg, France

Animal behavior originates from neuronal activity distributed across brain-wide networks. However, techniques available to assess large-scale neural dynamics in behaving animals remain limited. I will present compact, chronically implantable, high-density arrays of optical fibers that enable multi-fiber photometry and optogenetic perturbations across many regions in the mammalian brain. It is possible to do photometric calcium recordings and recordings of neuromodulatory release from networks of 12–48 brain regions, including striatal, thalamic, hippocampal and cortical areas. I demonstrate the versatility of the approach in both head-fixed and freely moving mice engaged in decision-making tasks. Additionally, it is possible to combine such multi-regional recording with optogenetic perturbations of brain activity. In my talk I will present several examples of perturbations and discuss main limitations of the method. Finally, I will demonstrate multi-fiber photometry in freely moving animals, including simultaneous recordings from two mice during social interaction. High-density multi-fiber arrays are versatile tools for the investigation of large-scale brain dynamics during behavior.

Brain pericytes -a century of speculations and controversy

Annika Keller

Department of Neurosurgery, Zürich University Hospital, Zürich University, Switzerland

Pericytes, perivascular cells found along capillaries, are in direct contact and share the vascular basement membrane with the endothelium. The longitudinal pericyte coverage of the central nervous system vasculature reaches 100 %. Pericytes were first described by Eberth in 1871 and as a first function it was suggested that they regulate the blood flow. However, even until now it is not fully understood how pericytes regulate cerebral capillary diameter. I will discuss studies which have demonstrated the role of brain pericytes by using various transgenic mouse models in controlling organ specific characteristics of brain endothelial cells. In addition, I will present our analysis of cell-cell communication pathways between pericytes and endothelium which lead to the identification of pericyte subtypes in mouse brain.

New insights into cerebrospinal fluid circulation and clearance pathways

Steven. T. Proulx

Theodor Kocher Institute, University of Bern, Switzerland

Cerebrospinal fluid (CSF) is produced by choroid plexuses within the ventricles of the brain and circulates throughout the subarachnoid space surrounding the brain and spinal cord. From the subarachnoid space, CSF has long been considered to clear through arachnoid villi directly to venous sinuses within the dura mater meningeal lining of the central nervous system. However, evidence for lymphatic vessels draining at least some component of this fluid has been presented in studies dating back 150 years. The pathways through which the CSF can reach lymphatic vessels are currently an area of great controversy. The bulk of the literature supports pathways through the cribriform plate and along cranial nerves to reach lymphatic vessels outside the skull. However, in the last few years researchers have rediscovered a network of lymphatic vessels in the dura mater and have suggested that this could represent a more direct outflow route for CSF.

We have developed fluorescence imaging methods that can non-invasively assess the dynamics of near-infrared tracer outflow to lymphatic vessels or to the systemic blood circulation after injections into the lateral ventricle or cisterna magna of mice. Surprisingly, we found that tracers were cleared predominantly by lymphatic vessels with no evidence suggesting a direct blood vascular uptake within the ventricles or subarachnoid space. Tracer outflow from the skull was detected at the exits of the cranial nerves, including at the cribriform plate, optic canal and jugular foramina, to drain to deep cervical and mandibular lymph nodes. CSF tracer distribution through two anatomically distinct routes down the spine to reach spinal outflow pathways and the spread of the CSF tracers through paravascular spaces on the brain surface through the intact skull could also visualized in living mice. Confirmation of these CSF pathways was demonstrated with 9.4 T MRI.

Together, these in vivo imaging approaches allow a system-wide assessment of CSF flow pathways and has enabled a new model of CNS fluid flow to be developed. Further studies are needed to test the model in pathological conditions and to confirm these findings in humans.

UNIVERSITÉ DE FRIBOURG
UNIVERSITÄT FREIBURG

BENEFRI
Neuroscience

UNIVERSITÄT BERN

When, where and how do seizures start and stop?

Core concepts

Timothée Proix,

Department of Fundamental Neurosciences, University of Geneva, Switzerland

Illustrative examples from the lab and clinics

Maxime Baud

Center for Experimental Neurology (ZEN) Inselspital, Bern University Hospital, Bern, Switzerland

This session will introduce basic concepts to explain how seizures are generated in the brain. The mere observation that any brain can seize attests to the fact that the basic machinery to produce epileptic seizures is the same that produces perception, movements and thoughts. The clinical phenomenology of seizures and epilepsy will be presented along with scientific explanations. The journey will take you from neurons to convulsions, passing through a few mathematical equations. For each concept the view of an empiricist and that of a theorist will be compared.

There's a time for everything: Tracking the temporal dynamics of memory and decision-making with time-resolved pattern analysis of neural data.

Nicholas Myers

University of Nottingham, United Kingdom

Successful behaviour depends on accurate timing. From a pedestrian deciding when to cross a busy road to a foraging animal knowing when to switch to another patch, timing pervades almost all aspects of cognition. However, neuroimaging studies often ignore the crucial role of time for the sake of simplicity, providing a skewed view of the neural basis of cognition. Here I will present two case studies of how incorporating a temporal dimension can provide new mechanistic insights into reward-based and working-memory-dependent decision-making in temporally variable environments. I will also discuss how methods such as representational similarity analysis can be used to disentangle the overlapping neural patterns related to different aspects of a dynamically evolving decision and arbitrate between different quantitative models of temporally unfolding cognition.

Timing in the auditory predictive brain: electrophysiological correlates and prediction of coma outcome

Athina Tzovara

Institute of Computer Science, University of Bern, Switzerland

When hearing a sound our brains generate automatic responses that manifest across multiple timescales. Neural responses to auditory stimuli can be preserved even when consciousness is lost, for example when someone falls into a coma. In this seminar I will first present our recent studies showing that the integrity of auditory processing in post anoxic coma is predictive of patients' chances to regain consciousness, assessed via measures of neural synchrony, and with deep convolutional neural networks for electroencephalography (EEG). The second part of the talk will focus on investigating the timing of auditory responses in the temporal lobe, measured with intracranial EEG in patients with epilepsy. I will present evidence that intrinsic brain dynamics of the temporal lobe at rest are locally regulated and can explain the timing of neural responses to sounds.

Retinal organoids to model development and disease

Magdalena Renner

Institute of Molecular and Clinical Ophthalmology, Basel, Switzerland

Human organoids are 3D cellular ensembles that are grown in vitro from adult or pluripotent stem cells and reproduce some morphological, functional and transcriptomic features of human organs. Organoids engineered to harbour disease-causing mutations or grown directly from patient cells could provide mechanistic insights into diseases. We performed single cell RNA sequencing of developing retinal organoids and from the periphery, fovea, pigment epithelium and choroid of light-responsive adult human retinas. Cell types in organoids matured in vitro to a stable 'developed' state at a rate similar to human retina development in vivo and the transcriptomes of organoid cell types converged towards the transcriptomes of adult peripheral retinal cell types.

We are currently working on methods to scale up retinal organoid production for screening applications and the development and integration of cell types currently missing in retinal organoids.

Non-visual responses to light in health and disease

Ludovic S. Mure

Department of Ophthalmology, Inselspital, University of Bern, Switzerland

In mammals, changes in the ambient light are detected not only by rods and cones but also by a class of intrinsically photosensitive retinal ganglion cells (ipRGCs) that express the light-sensing protein melanopsin. ipRGCs constitute only ~2% of retinal ganglion cells but they play a critical role in non-visual responses to light such as synchronizing the circadian clock to the day-night cycle and regulating sleep, mood, alertness, and the pupillary light reflex.

While the morphological characterization of ipRGCs in the human retina has advanced in recent years, there is a gap in our understanding of human ipRGC responses. I will describe the human donor retina preparation that we developed to fill this gap and that preserved at least some function of each photoreceptive system (rods, cones, and ipRGCs) for several hours after the death of the donors. This preparation allowed us to record for the first time direct responses from human ipRGCs and to characterize their sensitivity and spectra. Based on these response properties, we distinguished at least 3 functional subtypes that differ regarding their response properties (latency, duration, discharge rate) and their sensitivity to light.

I will also discuss the opportunities that this new donor retina preparation will offer in particular in pathological contexts and illustrate this point with some preliminary data suggesting ipRGCs functional alteration in Alzheimer's disease patients.

How oligodendrocytes influence axonal function and energy metabolism

Aiman Saab

Institute of Pharmacology and Toxicology, University of Zurich, Switzerland

Glial cell support functions appear critical in maintaining long-term neuronal integrity and brain energy metabolism. However, the mechanisms by which neuronal compartments interact with surrounding glial cells, and if/how/when glial cells control neural energy homeostasis, remain poorly understood. The talk will focus on the role of myelinating oligodendrocytes in regulating axonal energy metabolism. We use two-photon microscopy and metabolite sensor imaging in optic nerve preparations to study the mechanisms underlying axon-glial metabolic interactions. Our future goals are to elucidate how dysfunctions in glial metabolic support contribute to axonal damage and the pathogenesis of neurodegenerative diseases.

Studying neuronal repair on a microcircuit level

Anna-Sophia Wahl

Brain Research Institute, University of Zurich, Switzerland
Institute for Stroke and Dementia Research, University of Munich, Germany

The brain exhibits astonishing capacities to deal with even large structural damage on different levels: On the macroscopic level, all kinds of functional map shifts and reorganizations of brain areas are found, both in humans but also animal models e.g. after CNS injury such as stroke. However, how single, surviving neurons behave in response to brain injury and how these neurons interact in networks to rewire and to compensate for the brain damage is not well understood. Here we discuss recent findings in my lab using mice stroke models to understand functional recoding of neurons for the recovery of sensorimotor function or the prevention of cognitive decline. We use a combination of chronic 2photon calcium imaging in active mice with deep learning paradigms to decode neuronal activity in relation to the behavioral phenotype in the healthy condition during learning and after stroke induction. Our goal is to reveal novel targets to enhance neuronal repair and lay a basis for the development of restorative therapies e.g. for stroke patients.