2nd Swiss Early-Career Researchers Symposium

21.2.2020

University of Bern

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Keynote lecture

Involvement of ventral pallidal neurons in reward seeking and punishment avoidance

Dr. Marcus Stephenson-Jones; *Sainsbury Wellcome Centre, London UK*

The ventral pallidum (VP) is critical for invigorating reward seeking and is also involved in punishment avoidance, but how it contributes to such opposing behavioural actions remains unclear. Here we show that GABAergic and glutamatergic VP neurons selectively control behaviour in opposing motivational contexts. In vivo recording combined with optogenetics in mice revealed that these two populations oppositely encode positive and negative motivational value, are differentially modulated by animal's internal state and determine the behavioural response during motivational conflict. Furthermore, GABAergic VP neurons are essential for movements towards reward in a positive motivational context, but suppress movements in an aversive context. In contrast, glutamatergic VP neurons are essential for movements to avoid a threat but suppress movements in an appetitive context. Our results indicate that GABAergic and glutamatergic VP neurons encode the drive for approach and avoidance, respectively, with the balance between their activities determining the type of motivational behaviour.

Special Topic

Journal of Trial and Error – Revising Science in the Making

Max Bautista Perpinyà; *Utrecht University, NL*

What if we rethink what a scientific result actually is? What if we shift our focus from spectacular and groundbreaking discoveries to the day to day reality of trying and erring? The Journal of Trial and Error came as an idea to contribute constructively to the sciences and the humanities. JOTE presents itself as a conversation starter. In this session, we want to provide a historical and philosophical context on publishing 'failed research', and like to discuss with the audience in which way we can improve science. Together.

Oral presentations

Modulating interhemispheric functional connectivity during auditory speech perception

Basil Preisig, *University of Zürich*

Functional connectivity plays a major role for information encoding, transfer, and integration. Duplex perception describes the phenomenon that different auditory cues presented to the left and the right ear (dichotic listening) can become integrated into a unified speech sound. This phenomenon presumably relies on interhemispheric functional connectivity. In a recent study, we found evidence for this hypothesis showing that the modulation of oscillatory synchrony by means of bilateral high-density transcranial alternating current stimulation (TACS) modulates speech cue integration. Here, we aim to establish a direct link between the modulation of oscillatory synchrony, effective connectivity, and speech cue integration applying bilateral TACS during fMRI. We found that the modulation of oscillatory synchrony influences effective connectivity from right and the left auditory cortex in a phase lag specific way: while synchronized TACS (0° phase lag) perturbed effective connectivity, desynchronized TACS (180° phase lag) enhanced effective connectivity. The stronger the perturbation in the synchronized condition, the lower the proportion of integrated speech cues. Our results suggest a functional role of oscillatory synchrony in auditory speech perception. Moreover, they propose bilateral TACS as a valid method to manipulate long-range cortico-cortical oscillatory coupling.

Fear extinction impairments in rats selected for blunted glucocorticoid responsiveness

Silvia Monari, *EPFL*

Humans show inter-individual differences in vulnerability to develop post-traumatic stress disorder (PTSD) following exposure to traumatic events. Although initial observations linked low cortisol levels to PTSD pathophysiology, whether inter-individual differences in glucocorticoid responsiveness are implicated in the development of PTSD is not yet clear. To address this question, our lab has generated lines of Wistar rats selected for their differential habituation of their glucocorticoid responses to repeated stressor exposure at puberty. Strikingly, when compared to animals with 'normative' glucocorticoid responses, rats with blunted corticosterone responses to stress exhibit fear extinction deficits. Importantly, similar to PTSD patients, these rats show smaller hippocampi than controls. Given the role of glucocorticoids in memory consolidation during sleep, sleep/wake cycle was examined. Low responder rats displayed an altered sleep architecture, with shorter bouts of NREM sleep and markedly longer bouts of REM sleep, reminiscent of the excessive REM sleep described in PTSD patients. Post-extinction corticosterone treatment in the low responder rats rescues immediate deficits in extinction memory and prevents fear relapse. Our findings strongly support a causal involvement of blunted glucocorticoid responsiveness in physiological and behavioral traits indicative of higher vulnerability to PTSD, consistent with the evidence linking low cortisol levels to PTSD pathophysiology in humans.

Reward-related functional changes in tuft dendrites of L5 pyramidal neurons in S1 during learning of a tactile discrimination task

Gwendolin Schoenfeld, *University of Zürich*

Neuronal circuit are affected by reward and punishment during learning of reward-based operant conditioning. A previous study (Lacefield et al, 2019) reported increased calcium signals upon reward-delivery in dendritic tufts of L5 pyramidal neurons in mouse barrel cortex. However, how reward- and stimulus-related dendritic signals are established during learning remains elusive. Here, we investigated how reward responses emerge in L5 tufts of S1-to-S2 projecting neurons during learning of a Go/Nogo tactile discrimination task. We measured calcium signals in dendritic tuft branches and respective apical trunks using virally expressed GCaMP6f and monitored the signals longitudinally over the learning process using multi-plane two-photon imaging. We found a subset of dendrites that transiently showed trial-related dendritic responses to reward in the beginning of learning, even before behavioral performance improved. Furthermore, in expert mice, the frequency of localized branch-specific calcium events, which occurred independently of somatic activation, was also increased during reward-delivery. We aim to reveal potential relationships of global and local calcium events with trial-related events (e.g. contextual cues, whisking etc.), the animal´s decision and learning progress.

Dissecting aspects of social interaction encoded by Dopamine neurons within the Ventral Tegmental Area

Clément Prévost-Solié, *University of Geneva*

Dopamine neurons of the Ventral Tegmental Area (VTA DA neurons) play an important role in modulating social interaction and deficits in the mesolimbic system have been previously associated to psychiatric disorders. Using an operant conditioning task for social exploration and recording VTA DA neurons in freely behaving mice, we proved that interaction with a novel conspecific is rewarding and that DA neuron activity guide social reinforcement learning. Remarkably, during free social novelty interaction, phasic activity of VTA DA neurons increases only during reciprocal interaction and habituates during familiarization, strongly suggesting that VTA DA neurons modulate the investigation of a novel conspecific. In conclusion these findings revealed how VTA DA neurons encode specific aspects of social novelty interaction and suggest that VTA DA activity may represents an important learning signal during social behavior.

Modulation of the sense of agency in functional neurological disorders using non-invasive brain stimulation. A multimodal fMRI-TMS study.

Guiseppe Zito, *Hôpital Pitié-Salpêtrière, Paris, FR*

Patients affected by functional neurological disorders (FND) experience neurological symptoms in the absence of lesions of the nervous system. These symptoms have been related to an abnormal sense of agency (SoA), the sense of control over voluntary actions. Interestingly, FND patients also show abnormal activity in the right temporo-parietal junction (rTPJ), a brain area involved in agency processing. In this study we tested whether transcranial magnetic stimulation (TMS) over the rTPJ modulates the SoA in FND patients and healthy controls (HC). First, we engaged 23 FND patients and 19 HC in a task designed to target the SoA during fMRI, and studied the activity of the rTPJ in the two groups. Second, we applied TMS in both groups in a sham-controlled, cross-over trial with excitatory, inhibitory, or sham stimulation. Our results showed that the rTPJ of FND patients was abnormally active, compared to HC. Inhibitory TMS over that area decreases the the SoA in HC, whereas it improved it in FND patients. We found evidence that, by restoring normal cortical activity in the rTPJ of FND patients, we improved the SoA. Our study opens to potential rehabilitation strategies for FND using non-invasive brain stimulation.

Chronotypes in focal epilepsy

Marc Grau Leguia, *University of Bern*

Epilepsy, one of the most common neurological disorders, is characterized by spontaneous, seemingly random seizures. Personalized treatments for seizure prevention may be possible but depend on the ability to anticipate seizure timing. In a recent analysis of 37 patients with epilepsy implanted with a device that provides chronic intracranial EEG recording (cEEG; RNS ® System, NeuroPace, Inc.), we uncovered multidien (multi-day) rhythms of interictal epileptiform activity (IEA) that are biomarkers for seizure risk (Baud et al., 2018). Here, we extend these findings to a larger cohort of RNS® System patients (N=236) who charted their seizures on a daily basis over years (median: 9.5 years). First, we characterized multidien rhythms of IEA in chronic EEG. Using the wavelet transform against surrogate testing, we found a broad distribution of multidien periodicities. Second, we found that the timing of clinical seizures reported by patients depended on multidien IEA phase (phase-locking values: 0.2-–0.8, average=0.33). Finally, we found patient-specific seasonal rhythms. The prevalence of multidien IEA rhythms and seasonal rhythms in this large cohort suggest that seizure risk estimation using these biomarkers may have broad applicability. Our findings underscore the power of chronic recordings of brain activity to reveal patterns that influence seizure timing

Compartment-specific plasticity in the lateral amygdala during fear learning

Simon D'Aquin, *FMI Basel*

During auditory fear conditioning, a tone (conditioned stimulus, CS) is paired with an aversive event such as a mild electrical shock (unconditioned stimulus, US). Mice learn the CS-US association and develop a fear response to the CS, however the mechanisms underlying this association remain elusive. The neuronal inputs conveying the tone and shock information converge onto the lateral amygdala (LA), a region known to play a crucial role in fear memory formation. Here we use in vivo chronic head-fixed two-photon deep brain calcium imaging to record CS and US responses in dendrites and somata of LA principal neurons and to investigate how the CS representation develops during fear conditioning in different cellular compartments. We found that dendrite-specific activity during tones in naive animals is controlled by local somatostatin-expressing interneurons and that fear conditioning induces bidirectional somatic but unidirectional dendritic plasticity. Our results indicate that somatic and dendritic plasticity of CS response during learning are regulated by distinct synaptic and circuit-level mechanisms.

ASD-like behavioral phenotypes in Shank3-/- mice reflect specific deficits to engage to novelty

Sebastian Krüttner, *FMI Basel*

Autism Spectrum disorders (ASD) is a mental condition with a strong genetic component that affects 1% of the population. Despite the identification of a large variety of genes involved, the underlying mechanisms are still poorly understood. Recent studies suggested that the onset and development of deficits can vary even among patients harboring the same genetic defect, suggesting that genetic predisposition alone might not be sufficient to trigger the full extent of ASD symptoms. Thus, we lack knowledge whether the observed behavioral alterations are merely a direct consequence of genetic alterations or display a secondary consequence due to altered perception and learning of the environment. Using Shank3-/- mice, we searched for experience-dependent mechanisms which might acutely control manifestation of ASD symptoms. We show that experience of a novel context induces long-lasting and context-specific sensitization, which accounts for several characteristic ASD phenotypes including repetitive locomotion and failure to engage with novelty. Based on these findings, we identify the prelimbic cortex (PreL) to mediate failures to engage to novelty in Shank3-/- animals. We developed behavioral, pharmacological and pharmacogenetic interventions schemes and show that dopamine-dependent consolidation might serve as a basis to develop rational therapies to prevent and treat core symptoms of ASD.

Antagonistic but coordinated action of direct/indirect pathway medium spiny neurons in learned fear

Michael Kintscher, *EPFL*

Animals need to learn about cues in their environment that are possible predictors of threatening events. In this study we focus on the Astria, the most ventral region of the tail striatum in order to access its impact on cued fear learning. We use in-vivo optogenetics during cued fear conditioning to show that the inhibition of either Drd1-MSNs or Drd2-MSNs during aversive conditioning leads to a reduced discrimination of fear behavior on the following retrieval day. Notably, the inhibition of the indirect pathway leads to an increase of unspecific freezing in between cues, whereas the same manipulation of the direct pathway leads to a reduction of freezing during cues. These effects seem to be antagonistic but act in a temporally coordinated manner to apparently ensure discriminative fear behavior under physiological conditions. In further experiments we use trans-synaptic tracing to show that the main cortical input to the Astria arises from the insular and sensory cortices and proof this connection to be functional in electrophysiology recordings. Together the data give rise to an additional model of threat learning, where defensive behaviors might be regulated by corticostriatal inputs to the basal ganglia in order to ensure adequate discriminative fear responses.

Network dynamics in the Anterior Cingulate Cortex

Mario Acuña, *University of Bern*

Pain serves as a very important survival mechanism. However, due to malfunction of the nervous system, pain can become chronic. The anterior cingulate cortex (ACC) has emerged as a brain region important in processing the emotional aspect of pain. The role of the ACC in the sensory component of pain is however not yet fully understood. Moreover, how the functional organisation of ACC neuronal microcircuits is affected in chronic pain remains unknown. Therefore, we address whether the ACC possesses specialised neurons processing nociceptive and innocuous information and how this putative neuronal circuit dynamics is affected in chronic pain. Using in vivo two-photon calcium imaging we have characterise the dynamism over time of the network encoding for different stimuli in naive animals. Additionally, we have identified an expansion of the network encoding for non-painful stimuli towards painful representations in chronic pain condition. Using machine learning classification methods, we were able to demonstrate that the consequence of this expansion is an increased performance of decoding non-nociceptive inputs as nociceptive. Our results thus suggest that sensory information is codified by the activity of a discrete population of neurons in the ACC and is degraded in chronic pain.

Inferring the subjective value of juvenile zebra finch's own song during motor learning

Hazem Toutounji, *University of Zürich and ETH Zürich*

Juvenile male zebra finches learn to produce songs by imitating the songs of adult male tutors. Songs consist of a stereotyped sequence of syllables with distinct spectral features like pitch. Reinforcement learning (RL) both explains adult pitch-shifting escape behavior when aversive stimuli are presented as reinforcement, and accounts for impaired, non-externally reinforced juvenile learning when dopaminergic projections are ablated. Our previous work has shown that in learning a new target song involving pitch changes, juveniles tend to make the minimal pitch adjustment necessary to match the target repertoire. Here we posit that, in the absence of external reinforcement, an intrinsic reward drives learning through dopaminergic release that is proportional to similarity in pitch between sung and target syllables. We identified the juvenile's intrinsic metric of pitch-similarity evaluation by inferring RL model parameters from one set of pitch data. We found that reward around target pitch for most birds is confined within a small pitch range but changes little for small deviations. This result allowed us to make several predictions that we confirmed both experimentally and through model simulations. Our approach further highlights potential neural mechanisms of juvenile song learning that are empirically testable in future research.

Poster presentations

Risk factors of Addiction: development of a new strategy

Ridouane Achargui; *University of Geneva*

Natural stimulation of the mesolimbic dopamine system reinforces goal-directed behavior. Besides, repetitive activation by chronic drug use or optogenetic dopamine neuron self-stimulation (oDASS) can transform the natural reinforcement into a compulsive reinforcement. When confronted to the possibility of such stimulation, only part of the mice called “perseverant” maintain their behavior in spite of the electric shock while “renouncing” mice give up the stimulation. This compulsive reinforcement, one of the characterizing symptoms of addiction, is in part related to an alteration of the transmission of the Orbitofrontal cortex. However, little is known about the genetic risk factors that could predispose a given mouse to become sensitive or perseverant to major negative consequences in order to maintain its compulsive reinforcement. Here we propose to set up a strategy to identify such risk factors.

Imaging of SNARE-Dependent Spontaneous and Evoked Synaptic Transmission

Raphaela Seeger; *University of Bern*

The communication between neurons is based on the exocytosis of neurotransmitter filled vesicles. The communication between CNS synapses depends on the very low basal vesicle fusion rate and the ability to rapidly upregulate that rate upon stimulation. The SNARE complex connects the synaptic vesicles and the presynaptic cell membrane mediating vesicle fusion. Several proteins that are part of the SNARE complex were identified as keyplayers in several mental diseases, such as SNAP-25 in Attention Deficit Disorder. It was shown that by introducing electrostatically positive charged mutations into SNAP-25 lowered the energy barrier of a fusion event between the two (negatively charged) membranes. However, the effects of such a mutation on the general architecture, specifically on the connectivity of the SNARE complex in general are still uncertain. Cryo-electron tomography (cryo-ET) is being used to study the vesicle exocytosis and the involved filamentous proteins. To analyze the obtained 3D high-resolution data, we are developing a machine-learning framework for image segmentation and statistical analysis in collaboration with the SciITS, Bern.

Cardiac phase modulates endogenous and exogenous ERPs and HEP predicts awareness at the visual threshold

Viviana Leupin; *University of Fribourg*

We can investigate neural correlates of consciousness by measuring the brain response to different perceptual outcomes of the same stimulus (e.g., sensory threshold stimuli perceived in 50% of trials). Differences in perceptual awareness can arise from i) evoked brain responses for different perceptual outcomes and ii) from the pre-stimulus differences in brain activity. Cyclic variations of bodily signals can also influence perceptual awareness: baroreceptor activity during the systolic phase interferes with sensory stimulus processing, and the pre-stimulus response of the brain to the heartbeat (HEP) differs for stimuli subsequently seen or not. We presented subjects with near-threshold stimuli (Gabors overlaid with random-dot-noise) and compared i) the ERPs and ii) the HEP for the same stimuli when consciously seen and not. ERPs for seen and unseen differed as a function of cardiac phase: early sensory potentials (P1) were modulated during systole, while later cognitive potentials (VAN) were modulated during diastole. The HEP amplitude, topographic and source space differences indicated that the default-mode-network is recruited for subsequently unseen stimuli and that the saliency-network is recruited for subsequently seen stimuli. Taken together, we show that the cardiac phase and the brain response to the heartbeat can influence conscious awareness at the visual threshold.

Electrophysiological characterization of retinal bipolar cells in health and disease

Giulia Schilardi; *University of Bern*

Bipolar cells, the first retinal interneurons, are responsible of decoding and fine tuning the signal captured by the photoreceptors. In photoreceptor degenerative diseases, the first cells to be affected are the photoreceptors, leaving a light-insensitive retina. The inner retinal layers, including the bipolar cells, however, remain intact for months to years after photoreceptor death, making them good targets for optogenetic restoration. However, despite remaining functional, degeneration causes changes in protein expression of bipolar cells, which may impact the quality of restoration. By characterizing bipolar cells in healthy and degenerated mouse retinas, determining all their electrophysiological features, we aim at optimizing restorative approaches and improving functional output. I have recorded from different types of bipolar cells that have specific electrophysiological properties and respond differently to the same electrophysiological stimulus showing I / V curves relationships in voltage clamp and current clamp plots consistent and specific for each category. Bipolar cells in degenerated retinas are characteristically depolarized, potentially due to the malfunction of hyperpolarizing channels. One such channel is the BK channel, a high conductance calcium and voltage dependent potassium channels. The voltage and calcium dependence are closely related and are responsible for oscillations of the membrane potential, which may underlie the typical oscillatory activity of the blind, degenerated retina. I was able to specifically activate and block BK channels by using the specific agonist of NS-1619 and the specific blocker paxilline. In combination with analysis of gene regulation we hope to in the future be able to complement bipolar cells in the degenerated retina with proteins that re-establish natural signaling.

Investigating the role of primary cilia during neural circuit formation.

Elkhan Yusifov; *University of Zürich*

Primary cilia are microtubule based cell surface structures that play an important role in vertebrate development by serving as signaling hubs for signals, such as Sonic hedgehog. C5orf42 is the most frequently mutated gene in Joubert syndrome, a ciliopathy subtype. Patients with mutated C5orf42 showed craniofacial abnormalities, polydactyly and intellectual disabilities. C5orf42 is essential in the formation of primary cilia but a link to neural development was not known. Knocking down C5orf42 in an animal model revealed defects in neural circuit formation. As a first step towards a better understanding of ciliary function in neural circuit formation in the PNS, it was necessary to analyze the presence of primary cilia during development. By studying chicken embryos between E3 and E7, we have demonstrated the presence of primary cilia in migrating NCC but also in their derivatives. In addition, primary cilia were present in all Dorsal Root Ganglion (DRG) neurons in vivo, as well as in DRG explants, but not in dissociated neurons. Furthermore, we found primary cilia on Schwann cell precursors and on sympathetic neurons. Future studies will focus on the role of cilia in neural circuit formation, by knocking down candidate genes.

Superior Colliculus to Ventral Tegmental Area pathway controls social orientation

Alessandro Contestabile; *University of Geneva*

Social interactions are highly complex behaviors that ask to adapt constantly to a stimulus. Indeed, interactions among conspecific are highly dynamic, are influenced by internal states and past experiences and are characterized by high-level complexity of communication through multiple sensory modalities. Recent studies have shown that dopamine (DA) neurons of the ventral tegmental area (VTA) play an important role in social behavior but how the VTA DA activity is modulated during interaction is still unclear. Using optogenetic tools and in-vivo and in-vitro recordings, we here investigate how VTA integrates information during social interaction from two different pathways: the Superior Colliculus (SC) and the Anterior Cortex (AC). We report that while both SC and AC send excitatory inputs onto VTA, optogenetic stimulation of their terminals changes social interaction in opposite direction. Stimulation of SC-VTA pathway alters orientation towards conspecific and decreases social interaction while stimulation of AC-VTA pathway promotes interaction without changing orienting behavior. Our data therefore propose that, in the context of unfamiliar conspecific interaction, signals from the SC to the VTA trigger orientation towards salient stimuli to favor interaction while signals from the AC to the VTA promote seeking behavior. Our data not only elucidate the brain circuits underlying conspecific interaction but also help to understand the aberrant neural mechanisms underlying social deficits in psychiatric disorders.

Neural circuits for emotional conflicts and decision making in the ventral CA1 hippocampus

Carlo Cerquetella; *University of Bern*

The hippocampus (HC) is a core brain structure for memory, executive processing, stress, emotion, and affect. Its function in emotions is primarily mediated by the ventral region (vHC) but the involvement of the vHC in arbitrating approach-avoidance emotional conflicts is still unclear. To test whether pyramidal cell assemblies within the ventral CA1 hippocampus (vCA1 HC) represent motivational states during emotional conflicts, we have characterized the spiking activity of vCA1 hippocampal neurons in mice facing emotional conflicts using novel behavioral tasks and single-unit recordings. Moreover, an important target of the vCA1 HC – thought to be crucial for the coordination of decision-making behavior – is the medial prefrontal cortex (mPFC). For this reason, I have used viral tools to identify vCA1 to mPFC projections. Our preliminary results show a modulation of the activity of vCA1 cells that correlates to the anxiogenic level and a remapping of peak activity to the anxiogenic context. Taken together, these results suggest a tuning of the vCA1 HC in representing different anxiogenic situations and pave the way to test the hypothesis that pyramidal cell assemblies within the vCA1 HC represent emotional conflicts.

Dissecting a vestibular circuit controlling motion sickness

Pablo Machuca-Márquez; *EPFL*

Motion sickness (MS) is an autonomic physiological alteration occurring in individuals undergoing passive movement. It is currently believed that MS is encoded in the brain as a "toxic shock", mirroring key aspects of toxic-induced nausea. Consistently, MS is characterized as an unpleasant feeling, accompanied by reduction in spontaneous ambulatory activity, appetite suppression, hypothermia and the establishment of conditioned taste aversion (CTA) –an association between a novel flavor and nausea-related gastrointestinal malaise–. It is widely accepted that MS develops with the occurrence of neural mismatches between the integrated input of motion-related sensory information and correlated past memory. In the brainstem, vestibular nuclei (VN) are classically associated with MS. Provocative motion activates VN neurons, recapitulating MS-related signs. However, the genetic identity of VN neurons mediating MS-related autonomic regulation and aversive learning, and their MS-relevant downstream projections remain largely unknown. Here, we identify that glutamatergic vestibular (Vglut2-VN) neurons are necessary to elicit MS-related autonomic regulation and aversive learning. Moreover, we identify a cholecystokinin-expressing, glutamatergic VN (Cck-VN) subpopulation that projects to the parabrachial nucleus (PBN), dissecting a functionally-relevant circuit selectively controlling MS-related CTA. Together, these findings provide ground-breaking insight in understanding MS neurobiological regulation, unravelling key genetically-defined neural substrates and a vestibulo-parabrachial circuit.

vCA1 Activity Discriminates Contexts Associated with Fear and Safety

Robin Nguyen; *University of Bern*

The ability of an animal to adapt its behavior to changing environments is critical for survival. Previously learned threat associations that become irrelevant in a given environment must be suppressed to effectively engage in motivated behaviours. This process involves extinction— learning a new inhibitory memory through repeated exposure to the conditioned stimulus in the absence of the threat. Context plays an essential role in retrieving appropriate cued associations, and may therefore resolve competition between extinction and fear memories. Notably, neurons in the ventral CA1 region (vCA1) are recruited by environments with emotional value, including fear-associated contexts. However, the neural dynamics of the vCA1 during extinction memory formation and retrieval remain poorly understood. We performed single-unit electrophysiological recordings from the vCA1 as mice underwent discriminative fear conditioning and extinction training, followed by presentations of the conditioned stimulus in the extinction context and the original fear context. We observed vCA1 neurons that discriminated their activity between the extinction and fear contexts. Furthermore, preference for either context emerged following extinction training. These findings suggest the vCA1 associates salient stimuli with contexts to form emotional maps of the environment.

Functional characterization of Opto-mGluR6 optogenetic gene therapy in blind mouse retinas using multi-electrode arrays

Jakub Králik; *University of Bern*

Retinitis pigmentosa (RP) represents a heterogeneous group of genetic disorders responsible for massive photoreceptor degeneration and subsequent gradual loss of vision in patients. Such event also affects inner neural layers resulting in cellular disorganization, aberrant expression of proteins or pathological neuronal activity. Despite these changes, there is still possibility of intervention and restoration of light sensitivity and eventually vision in blind retinas. In this study, we employ the chimeric protein of mammalian origin Opto-mGluR6. With exclusive ON-bipolar cell expression, it combines the light-sensitive domains of melanopsin and intracellular domains of metabotropic glutamate receptor mGluR6, which naturally mediates light responses in these cells. This next-generation optogenetic tool already demonstrated reliable vision restoration at the level of the retina, but also at the cortical and behavioral levels. The aim of this study was to characterize and compare the potencies of the different Opto-mGluR6 variants driving retinal light responses in an otherwise blind retina, with a particular focus on their temporal and kinetic properties. These results will allow us to select the optimal variant/s for a potential future human therapy, but also to elucidate prosthetic signaling mechanisms on the background of degeneration.

Untangling ventral hippocampus dynamics during contextual emotional memory

Joana Mendes Duarte; *University of Bern*

Assessing and acting on memories of rewarding and aversive events is critical for animal survival. Behavioral manipulation studies revealed the ventral hippocampus (vHip) involvement in the encoding and retrieval of contexts associated with positive or negative stimuli. However, little is known about the neurophysiological substrates in the vHip that underlie emotional memory spaces. Here, we designed a two-stage behavioral protocol that allowed for the assessment of contextual fear and reward learning, and simultaneous monitoring of single-unit electrophysiological vHip activity. The behavioral protocol starts with the social place preference (SPP) task, where mice were trained to associate one of the two distinctive compartments with a social reward odor. At the second part, the animals were subjected to a contextual fear conditioning (CFC) task that was performed in two different novel contexts, in which one will be associated with an aversive stimulus. We identified putative vHip interneurons and pyramidal cells based on their spike waveform features and autocorrelogram. These representations can be divided in two groups: Learning cells that showed an increased firing rate after learning; Context-specific cells that were spatially tuned at the emotional context after learning. These results suggest that emotional memories are accompanied by context-specific activity in the vHip.

Circuit and synaptic mechanisms of approach and avoidance social interaction

Pedro Espinosa; *University of Geneva*

Social behavior is defined as any modality of communication and interaction between two or more conspecifics. At the very basis of this social behavior, an individual need to decide whether to approach (positive valence/appetitive) or avoid (negative valence/aversive) a conspecific. Among the brain regions that codify for social behavior, the Nucleus Accumbens (NAc) is a key element of the mesocorticolimbic circuits for evaluating appetitive and aversive information. Recent studies revealed the importance of NAc in social behavior, but how the valence is codified at synaptic level is still an open question. The NAc is composed in a ~95% by medium spiny neurons (MSNs) that express the dopamine receptor 1 or 2 (MSN-D1 and MSN-D2). Classically, D1-MSN have been related to rewarding and motivational aspects of behavior, meanwhile D2-MSN exhibit aversive properties i.e. social avoidance. Despite this dichotomy, still remains elusive how the MSNs in the NAc are involved in the conspecific interaction. Here, using a free social interaction paradigm with a positive (juvenile conspecific) or negative (CD1) valence, we examine the response of D1 and D2-MSNs using fiber photometry. While, D2 neurons were activated by negative (aggression) interaction, we found D1-MSN where active either during positive (nose-nose contact) and negative (aggression) interaction. Interestingly, D1-MSN revealed valence-dependent form of synaptic plasticity . Studying the circuits mechanisms controlling socially appetitive and aversive stimuli, we will pave the path for a causal understanding of the processes underlying disruption of complex social behaviors in psychiatric disorders.

Plasticity mechanisms in layer 5 pyramidal neurons of the anterior cingulate cortex

Liselot Spierenburg; *University of Bern*

The anterior cingulate cortex (ACC) is a brain region involved in higher cognitive function, like error detection and pain processing. Synaptic plasticity is instrumental for cortical processing. Spike-timing-dependent plasticity (STDP) is a cellular mechanism for learning and memory formation. STDP rules can be influenced by neuromodulatory inputs, such as dopamine. The ACC is highly regulated by neuromodulatory inputs. However, spike-timing-dependent mechanisms, and the role neuromodulation plays in this type of plasticity in the ACC, are still elusive. Our results show that when electrically stimulated at proximal or distal dendritic sites, synapses onto layer 5 (L5) ACC pyramidal neurons do not appear to be plastic. However, neuromodulation by dopamine facilitated STDP at both proximal and distal synapses. Specifically, in presence of dopamine pre-post pairing at proximal synapses led to LTP, while this same pairing protocol induced LTD at distal synapses. Furthermore, input specific pairing of contralateral-ACC inputs onto ACC L5 neurons showed LTD at distal, but not proximal synapses. In the presence of dopamine no such plasticity occurred at distal synapses while at proximal synapses it led to LTD. These results indicate that dopaminergic neuromodulation can selectively differentiate specific inputs at different synaptic sites, potentially acting as a plasticity switch mechanism.

Variability in the Transition from Adolescence to Adulthood: a behavioral and neuroimaging study of maturation in word production

Tanja Atanasova; *University of Geneva*

To date, the transition period from childhood to adulthood received only little attention in comparison to language development in children and childhood or to changes related to ageing, even though it is well-known that adolescence reflects a key period in cognitive, social and cortical maturation. Here I aim to shed light on behavioral and neurodevelopmental maturation in word production. In particular, I will try to pinpoint the factors underlying the variability in maturation in adolescents; our preliminary results on electrophysiological changes in a word production task show a remarkable variability of brain activation in adolescence, which was neither explained by age nor by performance in other cognitive tasks and was observed in a specific time-window, likely associated with visual and lexical-semantic processes in picture naming tasks. My goal here is to improve the understanding of the inter-individual variability. To this purpose, I will verify and refine our preliminary results of different EEG/ERP brain activation patterns identified among adolescents and to relate them to behavioral and biological (puberty scale) predictors.

A circuit model of limbic seizures

Kristina Slabeva; *University of Bern*

A circuit model of limbic seizures Authors: Kristina Slabeva, Antoine Adamantidis, Maxime Baud Purpose The hippocampus is part of the Papez 33erform and forms recurrent connections with the entorhinal cortex (Ent). In our model of limbic seizures we show that optogenetic stimulation of either Ent or CA1 subfield elicits seizures in freely moving, non-epileptic animals. Methods We expressed channelrhodopsin specifically in glutamatergic cells of the 33erformant pathway in adult mice (C57/Bl6) and implanted them with electrodes in different nodes of the Papaez circuit, as well as optic fibers in the Ent and CA1. We measured delays of peaks in LFP upon single- pulse optogenetic stimulation and used 20Hz stimulations in Ent and CA1 to induce seizures. Results We tracked single evoked potentials originating in the Ent respectively CA1 across different nodes of the Papez circuit, bidirectionally. By stimulating either in the Ent or in the CA1, we were able to induce seizures with similar electrographic features, duration (Ent: mean=28.2s ±6.6, CA1: mean=26.7 ±9.8) and similar required stimulation time (Ent: mean=7.7 ±3.8s ,CA1: mean=6.3s ±1.6s). Conclusion In our model, we show that optogenetic stimulation of either CA1 or Ent pyramidal neurons can elicit seizures. The ability to track single pulses across the circuit makes our model suitable for circuit-based epilepsy studies in non-epileptic mice using optogenetics.

Neural correlates for anxiety and its prediction in the ventral CA1 hippocampus

Konstantinos Koukoutselos; *University of Bern*

Neural correlates for anxiety and its prediction in the ventral CA1 hippocampus Konstantinos Koukoutselos1 and Stéphane Ciocchi1 1Department of Physiology, University of Bern, Switzerland Anxiety is a “future-oriented” emotional state triggered by incidental, potential or anticipated threats. Direct exposure of rodents to an anxiogenic environment is recruiting neuronal cell populations within the ventral CA1 hippocampus (vCA1) that correlate their activity with anxiety behaviors. Despite our knowledge on the implication of the ventral hippocampus in eliciting affective behaviors, the neural representation of anticipated/predicted anxiogenic events compared to their direct experience is still elusive. We hypothesize that distinct cell populations in the vCA1 either reflect the direct anxiogenic experience itself or its anticipation/prediction without directly facing anxiety situations. We developed a novel behavioral task (the forced emotional-shifting task) to investigate the neural activity within the vCA1 both in response to a direct anxiogenic situation (elevation, luminosity, openness) but also its anticipation/prediction. Using single-unit recordings in freely behaving mice, we collected evidence for neural correlates for anxiety in the forced emotional-shifting task and identified selective patterns supporting predictive coding of emotions in the form of a ramping activity. Altogether, our results suggest a distinct neural representation for anxiety (anxiety cells) and its anticipation/prediction (ramp cells) within the vCA1 hippocampus.

Uncovering the Neural Representation of Epistemic Curiosity

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Epistemic curiosity has been identified as a reward in the past decade. We will investigate the neural representation of epistemic curiosity during reward anticipation and consumption stages. Using multivariate pattern analysis and machine classifier techniques, we will compare curiosity-related activations patterns in humans with intrinsic (e.g. olfactory) and extrinsic (e.g. monetary) reward activation patterns.

Cortical excitability as a marker of epileptic seizures susceptibility in the mouse hippocampus

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Background: Epileptic seizures are characterized by a paroxysmal and transitory pathological activity of neurons. They may occur spontaneously in the epileptic brain or be triggered by conditions perturbing neuronal homeostasis even in a healthy brain. The episodic nature of seizures, with normal or subnormal neural activity in between, indicates fluctuation of seizure susceptibility across time. However, the exact nature of this fluctuation, and the methods to measure it, remains to be determined. Aim: Using optogenetic stimulation of pyramidal neurons in the mouse hippocampus, we aim characterizing the correlation between cortical response to short perturbations and seizure likelihood. Methods: We measured the EEG response to a single pulse and paired pulses of light as a biomarker of cortical excitability, and compared its variations with seizure likelihood. We used the duration of optogenetic stimulation needed to elicit a seizure as a measurement of the seizure susceptibility threshold ("time-to seizure"). We explored how these markers varied in the pre- and post-ictal period. We used injection of Diazepam, a GABA-A receptor agonist to artificially vary the seizure threshold. Results: In this preliminary study we found that the cortical response to single optogenetic light pulses greatly diminished after a seizure, correlating with changes in seizure susceptibility. Moreover, we found that time-to-seizure could be used to quantify the seizure threshold, as it increased with pharmacological modulation and during the refractory period present after a seizure. Conclusion: Probing cortical excitability using very short perturbation of ongoing activity may be a good indicator of the current cortical excitability state. Our model of optogenetic "on demand" hippocampal seizures could be useful to investigate the nature and the determinants of seizure susceptibility.

REM sleep stabilizes hypothalamic representation of feeding behavior

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During rapid eye movement (REM) sleep, behavioral unresponsiveness strongly contrasts with intense brain-wide neural network dynamics. Yet, the physiological functions of this cellular activation remain unclear. Using in vivo calcium imaging in freely behaving mice, we found that inhibitory neurons in the lateral hypothalamus (LHvgat) show unique activity patterns during feeding. During REM, but not NREM, sleep these maps are associated with high neuronal activation and REM-sleep specific optogenetic silencing of Lhvgat cells induced a re-organization of these activity patterns during subsequent feeding behaviors accompanied by decreased food intake. Our findings provide evidence of a role for REM sleep in the maintenance of cellular representations of innate behaviors.

Dissecting the role of sensory cues in driving sociability in mice

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Social interaction is a complex and highly conserved behavior that guarantees survival and reproductive success. It requires detection of conspecifics, exploration, motivation, and problem-solving abilities. Although rodents use olfaction to collect information about the environment and to guide appropriate behavior, social stimuli are composed by multisensory cues that provide comprehensive information regarding the social experience. Here, using the three chambers test in mice, we have dissected the contribution of isolated social cues in driving sociability. Our data provide evidences that social odor cues but not reciprocal tactile interaction or social visual cues elicit sociability. Remarkably, mice prefer to explore complex social stimuli compared to the isolated sensory cues suggesting that individual sensory cues in mice only partly contribute to sociability. Current studies in the lab aim at determine whether social olfactory cues and complex social stimuli activate similar brain circuits. By deconstructing social stimuli in their different sensory components, we will gain knowledge on the mechanisms that drive conspecific interaction.

Deciphering the role of parvalbumin interneurons in the ventral CA1 hippocampus during anxiety

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Anxiety is the emotional response elicited upon the perception of potential threats. The ventral hippocampus is a high-order cortical area implicated in emotional behaviours. Neuronal populations of the CA1 region (vCA1 HC) demonstrate enhanced neural activity in the open (anxiogenic) arms of the elevated-plus-maze (EPM) in rodents. However, the mechanisms underlying this selective activation remain unknown. We hypothesise that parvalbumin (PV+) interneurons are involved in the approach-avoidance aspect of anxiety and control the formation of anxiety-related pyramidal cell assemblies through their GABAergic synaptic interactions. Using single-unit recordings and optogenetics in freely-moving mice, we showed that subsets of putative pyramidal cells and interneurons have anxiety-related firing patterns during EPM navigation. Importantly, the majority of optogenetically-identified PV+ interneurons increased their activity at the centre of the EPM, whereas their inhibition resulted in fewer entries in the open arms. These results indicate an involvement of PV+ interneurons during the confrontation to anxiogenic situations and risk assessment. Additional experiments will determine whether the activity of PV+ interneurons is necessary for the emergence of cell assemblies and anxiety 39ehavior.

Computations involved in birdsong template formation

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Songbirds learn to imitate a song from a tutor by memorizing an auditory song template, which is viewed as a trace of the song model's essential auditory features. Currently, little is known about the feature extraction mechanism that guides the developing bird towards faithful imitation. Previous work has shown that when young birds are exposed to a pitch-shifted version (target song) of their learned (source) song, they will tend to drop the source in favor of the target song. Here, we test whether this holds true also when differences between source and target songs are small. In serial tutoring experiments using playback of artificial songs containing source and target syllables separated by only one semitone, we find that birds adopt an intermediate pitch level. However, when the source syllable is replaced by two target syllables one semitone below and above the source, we observe that dropping of the source and acquisition of one target is more likely. We propose that feature extraction is governed by Bayesian inference: when birds infer a common cause of both source and target syllables, they update the source. We plan to embed this model in a reinforcement learning framework of vocabulary learning in songbirds.

Investigations into the role of HCAR1 in the hippocampus circuitry and functions in physiological or pathological condition

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The purpose of this research is to delineate the role of the HCAR1 lactate receptor in the regulation of hippocampal circuits. In the hippocampus, we found that HCAR1 is mainly present in the neurons of the dentate gyrus, especially in mossy cells (MCs), a class of excitatory cells. No expression of the receptor was found on astrocytes. By using electrophysiology, we investigated effects of HCAR1 activation by its agonist, 3Cl-HBA, on cells passive properties, in particular MCs and granules cells (GCs). Our results showed a decrease of the sEPSCs frequency and of the excitability of GCs under activation of HCAR1 in mouse acute slices. The partial loss of MCs is a major hallmark of temporal lobe epilepsy. The ability of HCAR1 to diminish neuronal excitability makes it interesting to study in the context of epilepsy. We prepared acute slices from human patients who underwent surgery of epilepsy and found that application of HCAR1 agonist decreased the frequency of both spontaneous Ca2+ spikes and sEPSCs. Our results demonstrate the consequence of HCA1R activation as a non-metabolic action of lactate on neuronal activity, providing evidence that lactate can act as a gliotransmitter and a neuromodulator.

Sensory perception and mismatch in the posterior parietal cortex

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The posterior parietal cortex (PPC) is a multimodal association area involved in higher cognitive functions such as perceptual decision-making, visual attention, navigation and movement planning . Recently, it has been shown PPC can report mismatches in sensory sequences, such as the omission of an expected stimulus. Using 2-photon calcium imaging coupled with a chronic cranial window in awake head-fixed mice, we show that PPC can report auditory and whisker (tactile) stimuli. Furthermore, PPC can make rapid associations between these stimulus sequences and reliably report mismatches, in the form of stimulus omissions or unexpected stimuli. Our findings reaffirm the role of PPC in generating an internal model of the external world based on incoming sensory information, as proposed within the framework of predictive processing.