Wednesday, June 8, 2022 // 18:20 – 19:00

Johannes Kasper
AK Kell, Cognitive Neuroscience

Confirmation behavior in sensorimotor control

Confirmation bias refers to the tendency to conserve prior beliefs by dismissing incompatible evidence. We investigated whether similar mechanisms are at play during sensorimotor control.
21 professional musicians kept the continuously randomly perturbed pitch of a synthetic sound close to that of a reference sound by compensating the pitch perturbation using a trumpet valve-like button. Every few seconds, fast jump-like pitch perturbations occurred.
6% – 40% (median 13%) of such sudden pitch shifts evoked quick “catching” responses following the direction of the pitch shift rather than compensating it. Such seemingly counter-productive responses cannot be explained by standard motor control models.
The majority of them occurred when participants were in the course of moving the button in the opposite direction of the pitch shift, which would imply a mirrored auditory-motor contingency. This is compatible with a confirmation bias for the directionality of sensorimotor contingencies, where putative evidence for a novel audio-motor mapping is not used to update the learned sensorimotor law when the evidence is strongly incompatible with it. Instead, in such cases, a post-hoc motor response compatible with the observed sensory event under the established law reconfirms and thereby actively stabilizes it. Additionally, the pre-jump quasi-periodic button movements showed a higher inter-trial phase alignment among catching than compensating responses, which suggests a behavior-dependent modulation of the sensitivity to contingency changes.
We developed a computational model of an adaptive controller that can qualitatively account for both response classes while displaying desired characteristics of plasticity leading to implicit anticipation of slow pitch fluctuations.

Micaela Domingues
AG Zipp

Synaptic interleukin-4 receptor signaling modulates neuronal network activity

There is emerging evidence that immune responses not only play a part in the central nervous system (CNS) in disease, but may also be relevant for healthy conditions. We have previously shown neuro-protective and –regenerative effects of interleukin-4 (IL-4) in neuroinflammation and identified a direct neuronal signaling pathway via IRS1-PI3K-PKC, leading to axonal repair (Vogelaar et al., STM, 2018). Based on this signaling pathway, we now hypothesized a homeostatic role in synaptic function. We discovered a major role for the IL-4/IL-4Rα signaling pathway in synaptic processes. IL-4Rα is expressed presynaptically and locally available IL-4 regulates synaptic transmission (Hanuscheck et al, JEM, 2022). IL-4Rα-deficient neurons displayed reduced synaptic vesicle pools, altered postsynaptic currents and a higher excitatory drive in cortical networks. IL-4 treatment of wild type neurons led to increased inhibitory postsynaptic currents, mediated via PKCγ signaling. In fact, deficiency of IL-4Rα resulted in increased network activity in vivo, accompanied by altered exploration and anxiety-related learning behavior. We conclude that neuronal IL-4Rα and its presynaptic prevalence appears relevant for maintaining homeostasis of CNS synaptic function.

Jan Marker
Triesch Lab

Dynamics close to criticality support long synaptic lifetimes in cortical circuits

The connectome of the brain is highly dynamic, exhibiting high turnover of synaptic connections even under basal conditions. Nevertheless, our brains are able to maintain life-long memories. How are such memories formed and safeguarded in such a dynamic environment? We hypothesize that plastic recurrent neural networks can generate self-sustaining connectivity patterns if they operate in the reverberating regime close to criticality. To test this hypothesis, we simulate spiking neural networks with spike timing-dependent, homeostatic, and structural plasticity. Structural plasticity creates new excitatory-to-excitatory (EE) synapses and randomly prunes those below a certain threshold. We find that the reverberating regime promotes long survival times of EE synapses, while the sub-critical regime shows more pruning/creation events and a lack of very long synaptic life times. Furthermore, we find that random Kesten processes, a popular model of synaptic fluctuations, reproduce the short survival times of the sub-critical regime but fail to account for the long synaptic life times of the reverberating regime. Together, these findings indicate that long synaptic and memory life times may be explained by self-sustaining synaptic weight patterns shaping network activity so as to reinforce their own existence.

Yong Wang
Neuroprotection group

Early microglia/macrophage depletion leads to long-term sex-dependent effects on inflammation and neuronal maintenance after traumatic brain injury in mice.

There is a need for early therapeutic interventions after traumatic brain injury (TBI) to prevent long-term neurodegeneration. Microglia/macrophage depletion and repopulation by intermittent treatment with CSF1R inhibitors reduces neurodegeneration. The present study investigates the long-term consequences after CSF1R inhibition during the early phase after TBI.
Methods
Sex-matched mice were subjected to TBI and CSF1R inhibition by PLX3397 for 5 days and sacrificed 30 days post injury. Brain tissues were examined for histo- and molecular pathological markers.
Results
Following PLX3397 discontinuation and forced microglia/macrophage turnover, brain tissue loss was attenuated regardless of sex, as well as hippocampal atrophy, thalamic neuronal loss and microglia/macrophage infiltration in males. Selected gene markers of brain inflammation and apoptosis were reduced in males but increased in females as compared to corresponding TBI vehicle groups. RNAseq and gene set enrichment analysis (GSEA) of injured brains revealed more genes associated with dendritic spines and synapse function after early CSF1R inhibition as compared to vehicle, suggesting improved neuronal maintenance and recovery. In TBI vehicle mice, GSEA showed high oxidative phosphorylation, oxidoreductase activity and ribosomal biogenesis suggesting oxidative stress and increased abundance of metabolically highly active microglia/macrophage. More genes associated with immune processes and phagocytosis in PLX3397 treated females vs. males, suggesting sex-specific differences in response to intermittent CSF1R inhibition after TBI.
Conclusions
Microglia/macrophage depletion during the early phase of TBI attenuates long-term brain tissue loss, improves neuronal maintenance and recovery. Overall effects were not sex-specific but there is evidence that male mice benefit more than female mice.

Marlon Wendelmuth
AG Schweiger

Inhibition of blood coagulation improves mental resilience

Anhedonia, or diminished interest or pleasure in rewarding activities, characterizes depression and reflects deficits in brain reward circuitries. An animal model for studying depression is the chronic social defeat stress (CSDS) model. In this model, mice are subjected to CSDS induced by CD-1 aggressor mice. Exposure to CSDS causes long-lasting impairments in social interaction and hedonic behavior in most tested animals. Different studies in the recent years suggested that chronic social stress reduces blood-brain barrier (BBB) integrity thereby promoting depression-like behaviors in C57BL/6J mice and linking neurovascular health and stress susceptibility. Here we examined the influence of CSD on mouse models with increased barrier permeability. EPCR (endothelial protein c receptor) was shown to play a critical role in mediating activated protein c (APC)-induced cytoprotective signaling via PAR1. In contrast to EPCR-dependent PAR1 signaling, thrombin cleavage of PAR1 leads to barrier disruption. We have analyzed behavioral outcome in mice with full KO of EPCR in endothelial and hematopoetic cells as well as in mice with mislocated EPCR. In addition we investigated the influence of thrombin inhibitor NAPc2 treatment on the phenotype. The results showed that mice with depletion or mislocation of EPCR were all susceptible. No resilient behavior was observed in this group. Treatment with NAPc2 improved social interaction of stressed animals with EPCR deficiency. Our data support previous findings associating increased blood-brain barrier permeability with susceptibility. Furthermore, we could link stress susceptibility with blood coagulation pathway and could demonstrate that inhibition of the coagulation cascade substantially improves mental resilience.

Verena Engelhardt
AG Schweiger

Epigenetic modulation during early development in a mouse model of tuberous sclerosis.

Tuberous sclerosis (TSC) is a developmental disorder and a syndromic form of autism spectrum disorder (ASD) that is caused by mutations in TSC1 or TSC2. Heterozygous mutations in TSC2 lead to hyperactivity of the mechanistic target of rapamycin (mTOR) signaling pathway. In addition to tumors in multiple organs, patients suffer from TSC-associated neuropsychiatric disorders (TAND) such as epilepsy, intellectual disability, and ASD. In a mouse model of tuberous sclerosis carrying a heterozygous mutation in Tsc2, expression analysis showed that Tsc2 levels are reduced during early developmental stages, whereas Tsc2 deficiency (which is causative in the mouse model) was compensated to wild-type level thereafter. Further molecular and behavioral analysis indicated that the clinically relevant disease phenotype develops later and arises independently of the primary defect. Therefore, we hypothesize that there is a window of vulnerability during early brain development when Tsc2 expression is reduced. In in vitro experiments on treated murine primary cortical neurons (mPCNs) from heterozygous Tsc2 animals, we observed significant rescue effects of Tsc2 expression from the intact allele using the histone deacetylase 1 inhibitor tacedinaline (CI994) and the histone methyltransferase inhibitor 3-deazaneplanocin A (DZNep). In the next step, we will attempt to stimulate Tsc2 expression from the intact allele in vivo using these epigenetic modulators during the critical period. We suggest that this could be sufficient to balance the system and ameliorate or even rescue the phenotype. If the strategy is successful in a mouse model of TSC, it could be a promising approach for translation into patients.

Vera Laub
Schulte lab

From neurogenesis to leukemogenesis: Comparing transcriptional activity of PBX1 and TCF3

Neurogenesis begins in early embryonic development and continues lifelong in neurogenic niches of the adult mammalian brain. Two transcription factors (TF) critical for neurogenesis are pre-B-cell leukemia homeobox 1 (PBX1) and bHLH transcription factor 3 (TCF3). Both TFs were first described in t(1;19) acute lymphoblastic leukemia (ALL) in which chromosomal translocation induces an oncogenic TCF3-PBX1 fusion protein. Whether both native TFs co-operate in healthy tissues is presently unknown.

In this study, we addressed the physiological roles of PBX1 and TCF3 by a coordinated program of genome-wide approaches in murine neural stem- and progenitor cells. ChIP-Seq uncovered PBX1 binding to a large number of genomic sites, implicating PBX1 in neurogenic differentiation as well as broader biological functions. MEME-ChIP secondary motif analysis identified TCF3 as putative PBX1-interacting protein. Co-IP of both factors confirmed complex formation. Analyzing ChIP-Seq data retrieved from the public domain showed striking co-localization of TCF3 and transcription machinery components (RNA POLII, MED1) with PBX1 specifically in neurogenic contexts. Subsequent siRNA mediated kd of Pbx1 or Tcf3 followed by RNA-seq revealed commonly regulated target genes. Interestingly, several genes involved in DNA replication were downregulated, while genes implicated in neuronal differentiation were upregulated upon kd of either TF, suggesting a common role in balancing progenitor cell proliferation with differentiation. At present, this hypothesis is transferred back and tested in leukemogenesis. Collectively, our results suggest a previously unrecognized link between PBX1 and TCF3, whereby the leukemogenic fusion hijacks physiological cooperation of both TFs in neurogenesis and adapts it to a pathophysiological context.

Bastian Eppler
Matthias Kaschube

Abrupt transitions of activity patterns in response to gradual changes of network connectivity

Recent experimental studies show substantial ongoing remodeling both on the level of synaptic connections and on the level of neuronal population activity. It is, however, unclear, how changes in neuronal activity can be linked to changes in the underlying synaptic connectivity.
We study a firing rate model to investigate the effect of gradual changes in a network's connectivity on its activity.
Apart from an input dominated uni-stable regime (one response per stimulus independent of the network) and a network dominated uni-stable regime (one response per network independent of stimulus), we also find a multi-stable regime for strong recurrent connectivity and a high ratio of inhibition to excitation. In this regime the model reproduces properties of neural population activity in mouse auditory cortex, including a broad distribution of firing rates and clustering of stimuli into a set of response modes.
Applying gradual drift to the network connectivity we find periods of stable responses, interrupted by abrupt transitions altering the stimulus response mapping. We study the mechanism underlying these transitions by analyzing changes in the fixed points of this network model, employing a method similar to Sussilo and Barak, 2013. We find that such abrupt transitions typically cannot be explained by the mere displacement of existing fixed points, but involve qualitative changes in the fixed point structure in the vicinity of the response trajectory.
We conclude, that gradual synaptic drift can lead to abrupt transitions in stimulus responses and that qualitative changes in the network's fixed point topology underlie such transitions.

Shuailong Li
Department of Anaesthesiology University Medical Center Mainz

Microglia subtypes show substrate-specific phagocytosis preferences and phenotype plasticity

Microglia are phagocytosis competent CNS cells comprising a spectrum of subtypes with beneficial and/or detrimental functions in acute and chronic neurodegenerative disorders. The heterogeneity of microglia suggests differences in phagocytic activity and phenotype plasticity between microglia subtypes.
To study these issues, primary murine glial cultures were cultivated in the presence of serum, different growth factors and cytokines to obtain M0-like, M1-like, and M2-like microglia as confirmed by morphology, M1/M2 gene marker expression, and nitric oxide assays.
Single-cell analysis after 3 hours of phagocytosis of E.coli particles or IgG-opsonized beads showed equal internalization by M0-like microglia, whereas M1-like microglia rather internalized E.coli particles and M2-like microglia rather internalized IgG beads, suggesting subtype-specific preferences for different phagocytosis substrates.
Time-lapse live imaging over 16 hours revealed further differences between microglia subtypes in phagocytosis preference and internalization dynamics. M0- and, more efficiently, M1-like microglia continuously internalized E.coli particles for 16 hours, whereas M2-like microglia discontinued internalization after 8 hours. IgG beads were continuously internalized by M0- and M1-like microglia but strikingly less by M1-like microglia. M2-like microglia initially showed continuous internalization similar to M0-like microglia but again discontinuation of internalization after 8 hours suggesting that the time of substrate exposure differently affect microglia subtypes.
After prolonged exposure to E.coli particles or IgG beads for 5 days all microglia subtypes showed increased internalization of E.coli particles compared to IgG beads, increased nitric oxide release and up-regulation of M1 gene markers, irrespectively of the phagocytosis substrate, suggesting phenotype plasticity towards M1-like phenotypes. In summary, microglia subtypes show substrate- and time-dependent phagocytosis efficiencies. The results further suggest that prolonged phagocytosis substrate exposure enhances M1-like profiles and M2-M1 repolarization of microglia. Similar processes may also take place in conditions of acute and chronic brain insults when microglia encounter different types of phagocytic substrates.

Elena Andres
AG Kalisch

Prediction error related neural representation of extinction learning and consolidation

Extinction learning of fear to a stimulus or situation is driven by the unexpected omission of the feared outcome. This prediction error (PE) based mechanism strongly relies on dopaminergic activity, signaling a better-than-expected outcome and thereby resembling appetitive reward learning. Previous human neuroimaging studies have reported PE-related activity in the ventral striatum over the course of extinction learning, a target region of midbrain dopaminergic neurons. After extinction learning the newly formed extinction memory is consolidated. During consolidation, in the ventromedial prefrontal cortex (vmPFC) a spontaneous reactivation of a neural activation pattern based on PE during extinction has been shown to be predictive for later retrieval of the extinction memory. Combining four datasets (behavior lab (1) and MRI scanner (3), n=173) of a conditioning (day 1) and extinction (day 2) paradigm, we first used a data-driven method for identifying extinction learning trajectories based on skin conductance responses. We found two distinct learning types, a slow and a fast extinguisher group. Second, in the fMRI datasets we observed ventral striatal PE-related activity at the beginning of extinction in the fast extinguisher, and at the end of extinction in the slow extinguisher group, mapping extinction learning trajectories. Lastly, in one fMRI dataset we added extinction memory retrieval test (day 3) and replicated the finding of a vmPFC pattern reactivation during consolidation, where a higher number of reactivations predicted better extinction memory retrieval at test. These results support the crucial role of dopaminergic prediction error activity for extinction learning and memory consolidation.

Ann-Sophie Pabst
AG Schweiger/ Winter/ Linke

BRCA2 haploinsufficiency influences brain development and brain function

Full loss-of-function of BRCA2 is causative for Fanconi's-anemia that is characterized by anemia, microcephaly and neurodevelopmental delay pointing towards a substantial role for BRCA2 in the CNS.
In a cohort of 169 patients with neurodevelopmental delay, we identified heterozygous, protein-truncating mutations of BRCA2 in three patients, presenting with intellectual disability and behavior aberrations. No other causative mutations were found suggesting a disease-causing role for BRCA2-haploinsufficiency. Family histories suggested adverse conditions during pregnancy caused by maternal stress with one presenting with a secured history of alcohol abuse.
Tan et altera had shown (2017) that the BRCA2 protein is sensitive to aldehydes, metabolites of alcohol. We hypothesize that the reduction of BRCA2 protein in brain tissue of BRCA2-haploinsufficient patients has an adverse effect on proliferating NPCs, which increases with alcohol consumption.
In neural precursor cells (NPCs) carrying a BRCA2-heterozygous mutation we found a reduction of BRCA2 protein by 50% compared to controls and a significantly stronger dropping of BRCA2 protein after formaldehyde treatment, suggesting particular vulnerability to aldehyde. Furthermore, preliminary data in neurospheres show a significantly reduced proliferation rate of BRCA2-haploinsufficient cells compared to controls. Analysis of effects of additive aldehyde treatment is ongoing.
Summarizing, we will analyze the effect of BRCA2-haploinsufficiency on brain development and adult stem cells and the interaction of BRCA2 mediated vulnerability and alcohol consumption during pregnancy and in later life. We will use patients with BRCA2 mutations from the FBREK network to verify effects of alcohol consumption in humans.

Thursday, June 8, 2022 // 11:40 – 12:00

Nicholas Hananeia
ICAR 3R

Multi-scale modeling of synaptic plasticity induced by Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a widely used method of non-invasive brain stimulation. However, its cellular mechanisms of action still remain somewhat unknown. Here, we implement a modified version of a validated model of the rat hipppocampal CA1 pyramidal cell in the NeMo-TMS framework and endow it with a voltage-based biophysical model of synaptic plasticity in AMPA/NMDA synapses, and show that this combination of cell and synaptic model is capable of reproducing LTP induction data under conditions both with and without inhibition.

With a plasticity model implemented in NeMo-TMS, we reproduce induction of LTP in the dendrites of the cell (Lenz 2014). This LTP induction is strongly distance dependent, and is concentrated in the proximal synapses of the cell. We predict a noticeable frequency dependence in the LTP amplitude produced in a 10Hz rTMS protocol versus an equivalent length 1Hz and 5Hz protocol.

Finally, we investigate the ability of the model to produce LTP in distal perforant path synapses using a theta-burst stimulation (TBS) protocol. This potentiation is strongly facilitated by the presence of dendritic spikes, and with electrical stimulation only, only occurs absent inhibition. We also implemented a cTBS TMS protocol, which was able to induce distal LTP even when the electrical-only protocol was unable to.

Susanne Stefanie Babl
AG Sigurdsson

Distinct roles of the dorsal and ventral hippocampus in spatial working memory and in signaling spatial information to the medial prefrontal cortex

The cognitive process of spatial working memory (SWM) engages both the medial prefrontal cortex (mPFC) and the hippocampus. The interaction of the dorsal and ventral hippocampus (dHPC, vHPC) with the mPFC can be observed on the level of neuronal firing rates and in local field potentials. But it is not clear in which phases of SWM - encoding, maintenance and retrieval - the two hippocampal poles are involved and which task-relevant information they transmit to the mPFC.
To address these questions, we infused mice with the viral construct AAV5-CamKII-ArchT-GFP in dHPC or vHPC and trained them to perform a delayed non-match-to-sample T-maze task. Pyramidal neurons in either dHPC or vHPC were optogenetically inhibited during the different phases of SWM while simultaneously recording neuronal activity in the mPFC.
Our results indicate a complementary function of the two hippocampal poles. dHPC inhibition during goal encoding and retrieval strongly impaired behavioral performance. The vHPC on the other hand was only critically involved in encoding, but not in maintenance or retrieval. In the mPFC, a subpopulation of neurons was modulated both by dHPC or vHPC inhibition. Goal-selective firing of mPFC neurons was however only disrupted by vHPC inhibition during the encoding phase, and unaffected by dHPC inhibition. In contrast, mPFC neuronal encoding of the distance traveled between start and goal of the maze was modified both by dHPC and vHPC inhibition. These findings indicate distinct roles of the dorsal and ventral hippocampal poles in signaling task-related spatial information to the mPFC.

Anna Leah Zier
Attention and Working Memory

Rapid TMS Localization of Finger Movement in the Brain: A Pilot Study

Transcranial magnetic stimulation (TMS) is able to provoke motor evoked potentials (MEPs) by triggering electrical fields (Efields) in the brain. By utilizing these characteristics, Numssen et al. (2021) proposed a novel approach to localize the precise cortical origin of finger muscles. Their protocol requires to apply 1000 TMS pulses alternating in their position with an interstimulus interval (ISI) of 5 seconds. This pilot study aims to investigate the possibility to determine the same cortical origin for the finger muscles with a shorter ISI. However, shorter ISIs than 5 seconds may alternate the MEPs. Four participants underwent two experiments: one experiment (E1) with 5 seconds and one (E2) with 1 second. Both stimulation rates should reliably predict the corresponding cortical origin of motor functions. For two participants, the cortical origin was indeed predicted very reliable. For the remaining, the results were inconclusive. Generally, E2 demonstrated lower MEP amplitudes. However, as almost identical hotspots could be demonstrated for half of the participants despite the depression effects, it is likely not the reason for the deviation of localization of the other participants. The most probable reason is rather due to the sequence of coil positions which led to a higher correlation in the induced Efields between cortical locations. This is supported by the lower reliability of localization from one finger muscle that was possibly stimulated less due to its distant location compared to the other muscles. Nevertheless, this pilot study has demonstrated the possibility to perform a localization with a shorter stimulation rate.

Jonas Schroer
Luhmann Group

Activity-dependent regulation of cell death in a caspase3 overexpression model

In the mammalian cortex, a substantial number of neurons undergo apoptosis during development to ensure proper structural and functional development. A key player in this process is neuronal activity, with low levels of activity associated with increased cell death and high levels of activity associated with increased neuron survival.
To investigate this pro-survival effect of neuronal activity, we are working with an AAV-based model of activated caspase3 overexpression in primary cortical cultures. In this pro-apoptotic context, neuronal network disinhibition leads to significantly higher survival. To study how disinhibition attenuates cell death in neurons overexpressing aCasp3, we examine network and individual neuron activity using MEA recordings in combination with Ca2+-imaging. We demonstrated that aCasp3-overexpressing cells participate in synchronous network activity.
Important regulators of apoptosis are the pro-apoptotic factor Bax and its counterpart BCL-2. Upon disinhibition of the network, the Bax/BCL-2 ratio shifts toward the pro-survival side. Remarkably, this ratio peaks in mouse cortex at the end of the first postnatal week in vivo, coinciding with the peak of apoptosis and the appearance of high-frequency synchronized activity patterns. Inhibition of the mitochondrial apoptosis pathway results in survival rates similar to those observed in disinhibited cultures.
Interestingly, in our overexpression model, the activity level of caspase3 does not change with increased neuronal activity.
In recent years, caspase3 has been shown to be involved in different neuronal homeostatic processes. Along this line, our data suggest that neurons with high activity have higher tolerance to aCasp3 and are more likely to survive.

Davide Warm
AG Luhmann

Early spontaneous activity predicts survival of developing cortical neurons

Spontaneous activity plays a crucial role in brain development by coordinating the integration of immature neurons into emerging cortical networks. High levels and complex patterns of spontaneous activity are generally associated with low rates of apoptosis in the cortex. However, it remains an open question whether spontaneous activity patterns encode for survival of individual cortical neurons during development. Here, we longitudinally investigated spontaneous activity and apoptosis in developing cortical cultures and assessed how activity features contribute to the survival of individual neurons. By combining extracellular electrophysiology with calcium imaging, we characterized spontaneous firing patterns of cortical neurons at an immature stage, taking into account structural and functional properties of the network. These experiments demonstrated that the early occurrence of calcium transients was strongly linked to neuronal survival. Silent neurons exhibited a higher probability of cell death, whereas high frequency spiking and burst behavior were almost exclusively detected in surviving neurons. In local neuronal clusters, activity of neighboring neurons exerted a pro-survival effect, whereas on the functional level, networks with a high modular topology were associated with lower cell death rates. Using machine learning algorithms, cell fate of individual neurons was predictable through the integration of spontaneous activity features. Our results indicate that high frequency spiking activity constrains apoptosis in single neurons through sustained calcium rises and thereby consolidates networks in which a high modular topology is reached during early development.