



SPP 1665:

Resolving and manipulating neuronal networks in the mammalian brain – from correlative to causal analysis

Newsletter, fifth edition, July 2016

The Priority Program 1665 was recently introduced in a profile report in the journal of Pan European Networks – Science & Technology (edition June 2016):

“Resolving and Manipulating Neuronal Networks” by Ileana Hangan-Opatz

<http://www.paneuropeannetworkspublications.com/ST19/files/assets/basic-html/page-208.html#>

1) Publications

New publications of the troikas:

- a. Krabbe S, Duda J, Schiemann J, Poetschke C, **Schneider G**, Kandel ER, Liss B, ***Roeper J**, *Simpson EH (*Co-Senior Authors) (2015): Increased dopamine D2 receptor activity in the striatum alters the firing pattern of dopamine neurons in the ventral tegmental area. Proc Natl Acad Sci U S A. 112: E1498-1506

<http://www.ncbi.nlm.nih.gov/pubmed/25675529>

Abstract:

There is strong evidence that the core deficits of schizophrenia result from dysfunction of the dopamine (DA) system, but details of this dysfunction remain unclear. We previously reported a model of transgenic mice that selectively and reversibly overexpress DA D2 receptors (D2Rs) in the striatum (D2R-OE mice). D2R-OE mice display deficits in cognition and motivation that are strikingly similar to the deficits in cognition and motivation observed in patients with schizophrenia. Here, we show that in vivo, both the firing rate (tonic activity) and burst firing (phasic activity) of identified midbrain DA neurons are impaired in the ventral tegmental area (VTA), but not in the substantia nigra (SN), of D2R-OE mice. Normalizing striatal D2R activity by switching off the transgene in adulthood recovered the reduction in tonic activity of VTA DA neurons, which is concordant with the rescue in motivation that we previously reported in our model. On the other hand, the reduction in burst activity was not rescued, which may be reflected in the observed persistence of cognitive deficits in D2R-OE mice. We have identified a potential molecular mechanism for the altered activity of DA VTA neurons in D2R-OE mice: a reduction in the expression of distinct NMDA receptor subunits selectively in identified mesolimbic DA VTA, but not nigrostriatal DA SN, neurons. These results suggest that functional deficits relevant for schizophrenia symptoms may involve differential regulation of selective DA pathways.

- b. Stitt I, Galindo-Leon E, Pieper F, Hollensteiner KJ, Engler G, **Engel AK** (2015): Auditory and visual interactions between the superior and inferior colliculi in the ferret. *Eur J Neurosci* 41:1311-1320

<http://www.ncbi.nlm.nih.gov/pubmed/25645363>

Abstract:

The integration of visual and auditory spatial information is important for building an accurate perception of the external world, but the fundamental mechanisms governing such audiovisual interaction have only partially been resolved. The earliest interface between auditory and visual processing pathways is in the midbrain, where the superior (SC) and inferior colliculi (IC) are reciprocally connected in an audiovisual loop. Here, we investigate the mechanisms of audiovisual interaction in the midbrain by recording neural signals from the SC and IC simultaneously in anesthetized ferrets. Visual stimuli reliably produced band-limited phase locking of IC local field potentials (LFPs) in two distinct frequency bands: 6-10 and 15-30 Hz. These visual LFP responses co-localized with robust auditory responses that were characteristic of the IC. Imaginary coherence analysis confirmed that visual responses in the IC were not volume-conducted signals from the neighboring SC. Visual responses in the IC occurred later than retinally driven superficial SC layers and earlier than deep SC layers that receive indirect visual inputs, suggesting that retinal inputs do not drive visually evoked responses in the IC. In addition, SC and IC recording sites with overlapping visual spatial receptive fields displayed stronger functional connectivity than sites with separate receptive fields, indicating that visual spatial maps are aligned across both midbrain structures. Reciprocal coupling between the IC and SC therefore probably serves the dynamic integration of visual and auditory representations of space.

- c. **Sigurdsson T, Duvarci S** (2016): Hippocampal-Prefrontal Interactions in Cognition, Behavior and Psychiatric Disease. *Front Syst Neurosci.* 9:190

<http://www.ncbi.nlm.nih.gov/pubmed/26858612>

Abstract:

The hippocampus and prefrontal cortex (PFC) have long been known to play a central role in various behavioral and cognitive functions. More recently, electrophysiological and functional imaging studies have begun to examine how interactions between the two structures contribute to behavior during various tasks. At the same time, it has become clear that hippocampal-prefrontal interactions are disrupted in psychiatric disease and may contribute to their pathophysiology. These impairments have most frequently been observed in schizophrenia, a disease that has long been associated with hippocampal and prefrontal dysfunction. Studies in animal models of the illness have also begun to relate disruptions in hippocampal-prefrontal interactions to the various risk factors and pathophysiological mechanisms of the illness. The goal of this review is to summarize what is known about the role of hippocampal-prefrontal interactions in normal brain function and compare how these interactions are disrupted in schizophrenia patients and animal models of the disease. Outstanding questions for future research on the role of hippocampal-prefrontal interactions in both healthy brain function and disease states are also discussed.

- d. Helfrich RF, **Herrmann CS, Engel AK, Schneider TR** (2015): Different coupling modes mediate cortical cross-frequency interactions. *Neuroimage pii: S1053-8119(15)01057-5*

<http://www.ncbi.nlm.nih.gov/pubmed/26608244>

Abstract:

Cross-frequency coupling (CFC) has been suggested to constitute a highly flexible mechanism for cortical information gating and processing, giving rise to conscious perception and various higher cognitive functions in humans. In particular, it might provide an elegant tool for information integration across several spatiotemporal scales within nested or coupled neuronal networks.

However, it is currently unknown whether low-frequency (theta/alpha) or high-frequency gamma oscillations orchestrate cross-frequency interactions, raising the question of who is master and who is slave. While correlative evidence suggested that at least two distinct CFC modes exist, namely, phase-amplitude-coupling (PAC) and amplitude-envelope correlations (AEC), it is currently unknown whether they subserve distinct cortical functions. Novel non-invasive brain stimulation tools, such as transcranial alternating current stimulation (tACS), now provide the unique opportunity to selectively entrain the low- or high-frequency component and study subsequent effects on CFC. Here, we demonstrate the differential modulation of CFC during selective entrainment of alpha or gamma oscillations. Our results reveal that entrainment of the low-frequency component increased PAC, where gamma power became preferentially locked to the trough of the alpha oscillation, while gamma-band entrainment enhanced AECs and reduced alpha power. These results provide causal evidence for the functional role of coupled alpha and gamma oscillations for visual processing.

- e. **Wagner S**, Burger M, **Wolters CH** (2015): An optimization approach for well-targeted transcranial direct current stimulation. available as arXiv reprint arXiv:1506.07744<7i>
- f. Santos RM, Laranjinha J, Barbosa RM, **Sirota A** (2015): Simultaneous measurement of cholinergic tone and neuronal network dynamics in vivo in the rat brain using a novel choline oxidase based electrochemical biosensor. Biosens. Bioelectron. 69, 83-94
<http://www.ncbi.nlm.nih.gov/pubmed/25706061>
Abstract:
Acetylcholine (ACh) modulates neuronal network activities implicated in cognition, including theta and gamma oscillations but the mechanisms remain poorly understood. Joint measurements of cholinergic activity and neuronal network dynamics with high spatio-temporal resolution are critical to understand ACh neuromodulation. However, current electrochemical biosensors are not optimized to measure nanomolar cholinergic signals across small regions like hippocampal sub-layers. Here, we report a novel oxidase-based electrochemical biosensor that matches these constraints. The approach is based on measurement of H₂O₂ generated by choline oxidase (ChOx) in the presence of choline (Ch). The microelectrode design consists of a twisted pair of 50µm diameter Pt/Ir wires (sensor and sentinel), which is scalable, provides high spatial resolution and optimizes common mode rejection. Microelectrode coating with ChOx in chitosan cross-linked with benzoquinone is simple, mechanically robust and provides high sensitivity (324±46nAµM⁻¹cm⁻²), a limit of detection of 16nM and a t₅₀ response time of 1.4s. Local field potential (LFP)-related currents dominate high-frequency component of electrochemical recordings in vivo. We significantly improved signal-to-noise-ratio compared to traditional sentinel subtraction by a novel frequency domain common mode rejection procedure that accounts for differential phase and amplitude of LFP-related currents on the two channels. We demonstrate measurements of spontaneous nanomolar Ch fluctuations, on top of which micromolar Ch increases occurred during periods of theta activity in anesthetized rats. Measurements were not affected by physiological O₂ changes, in agreement with the low biosensor K_m for O₂ (2.6µM). Design and performance of the novel biosensor opens the way for multisite recordings of spontaneous cholinergic dynamics in behaving animals.
- g. Wilde C, **Bruder R**, **Binder S**, **Marshall L**, **Schweikard A** (2015): Closed-loop transcranial alternating current stimulation of slow oscillations. Current Directions in Biomedical Engineering, 1:1(85-88)

- h. Marguet SL, Le-Schulte VTQ, Merseburg A, Neu A, Eichler R, Jakovcevski I, Ivanov A, **Hanganu-Opatz IL**, Bernard C, Morellini F, **Isbrandt D** (2015): Treatment during a vulnerable developmental period rescues a genetic epilepsy. Nat Med 21, 1436-1444
<http://www.ncbi.nlm.nih.gov/pubmed/26594844>

Abstract:

The nervous system is vulnerable to perturbations during specific developmental periods. Insults during such susceptible time windows can have long-term consequences, including the development of neurological diseases such as epilepsy. Here we report that a pharmacological intervention timed during a vulnerable neonatal period of cortical development prevents pathology in a genetic epilepsy model. By using mice with dysfunctional Kv7 voltage-gated K(+) channels, which are mutated in human neonatal epilepsy syndromes, we demonstrate the safety and efficacy of the sodium-potassium-chloride cotransporter NKCC1 antagonist bumetanide, which was administered during the first two postnatal weeks. In Kv7 current-deficient mice, which normally display epilepsy, hyperactivity and stereotypies as adults, transient bumetanide treatment normalized neonatal in vivo cortical network and hippocampal neuronal activity, prevented structural damage in the hippocampus and restored wild-type adult behavioral phenotypes. Furthermore, bumetanide treatment did not adversely affect control mice. These results suggest that in individuals with disease susceptibility, timing prophylactically safe interventions to specific windows during development may prevent or arrest disease progression.

- i. Bahr A, Abu-Saleh L, Schroeder D, **Krautschneider WH** (2015): Development of a Neural Recording Mixed Signal Integrated Circuit for Biomedical Signal Acquisition. Biomed Eng Abstr BMT 2015 49. DGBMT Jahrestagung, Lübeck
- j. Bahr A, Abu-Saleh L, Schroeder D, **Krautschneider WH** (2015): 16 Channel Neural Recording Mixed Signal ASIC. CDNLive EMEA 2015 Conference Proceedings
- k. Karalis N, Dejean C, Chaudun F, Khoder S, Rozeske RR, Wurtz H, Bagur S, Benchenane K, **Sirota A**, Courtin J, Herry C (2016): 4-Hz oscillations synchronize prefrontal - amygdala circuits during fear behavior. Nat Neurosci doi:10.1038/nn.4251
<http://www.ncbi.nlm.nih.gov/pubmed/26878674>

Abstract:

Fear expression relies on the coordinated activity of prefrontal and amygdala circuits, yet the mechanisms allowing long-range network synchronization during fear remain unknown. Using a combination of extracellular recordings, pharmacological and optogenetic manipulations, we found that freezing, a behavioral expression of fear, temporally coincided with the development of sustained, internally generated 4-Hz oscillations in prefrontal-amygdala circuits. 4-Hz oscillations predict freezing onset and offset and synchronize prefrontal-amygdala circuits. Optogenetic induction of prefrontal 4-Hz oscillations coordinates prefrontal-amygdala activity and elicits fear behavior. These results unravel a sustained oscillatory mechanism mediating prefrontal-amygdala coupling during fear behavior.

- l. Ciocoveanu R, Bahr A, **Krautschneider WH** (2016): Design of a Rail-to-Rail Folded Cascode Amplifier with Transconductance Feedback Circuit. ICTOpen 2016 Conference Proceedings
- m. Bahr A, Saleh LA, Schroeder D, **Krautschneider WH** (2016): Integrierter Schaltkreis zur Aufnahme von Biosignalen. Proceedings of the Workshop Biosignal Processing

- n. Gutierrez HC, Carus CM, Jegu S, **Ponomarenko A**, Korotkova T, Adamantidis A (2016): Hypothalamic feedforward inhibition of thalamocortical network contr. *Nature Neurosci.* 19(2):290-300
<http://www.ncbi.nlm.nih.gov/pubmed/26691833>
Abstract:
During non-rapid eye movement (NREM) sleep, synchronous synaptic activity in the thalamocortical network generates predominantly low-frequency oscillations (<4 Hz) that are modulated by inhibitory inputs from the thalamic reticular nucleus (TRN). Whether TRN cells integrate sleep-wake signals from subcortical circuits remains unclear. We found that GABA neurons from the lateral hypothalamus (LHGABA) exert a strong inhibitory control over TRN GABA neurons (TRNGABA). We found that optogenetic activation of this circuit recapitulated state-dependent changes of TRN neuron activity in behaving mice and induced rapid arousal during NREM, but not REM, sleep. During deep anesthesia, activation of this circuit induced sustained cortical arousal. In contrast, optogenetic silencing of LHGABA-TRNGABA transmission increased the duration of NREM sleep and amplitude of delta (1-4 Hz) oscillations. Collectively, these results demonstrate that TRN cells integrate subcortical arousal inputs selectively during NREM sleep and may participate in sleep intensity.
- o. **Binder S, Gao X, Bender F, Wiegert S, Bruder R, Ponomarenko A, Marshall L** (2016) Investigations on the function of transcranial oscillatory stimulation. *Acta Physiologica* 216 (Suppl 707):174
- p. Rahmati V, **Kirmse K**, Markovic D, **Holthoff K, Kiebel SJ** (2016): Inferring neuronal dynamics from calcium imaging data using biophysical models and Bayesian inference. *PLoS Comput Biol* 12(2): e1004736
<http://www.ncbi.nlm.nih.gov/pubmed/?term=rahmati+v>
Abstract:
Calcium imaging has been used as a promising technique to monitor the dynamic activity of neuronal populations. However, the calcium trace is temporally smeared which restricts the extraction of quantities of interest such as spike trains of individual neurons. To address this issue, spike reconstruction algorithms have been introduced. One limitation of such reconstructions is that the underlying models are not informed about the biophysics of spike and burst generations. Such existing prior knowledge might be useful for constraining the possible solutions of spikes. Here we describe, in a novel Bayesian approach, how principled knowledge about neuronal dynamics can be employed to infer biophysical variables and parameters from fluorescence traces. By using both synthetic and in vitro recorded fluorescence traces, we demonstrate that the new approach is able to reconstruct different repetitive spiking and/or bursting patterns with accurate single spike resolution. Furthermore, we show that the high inference precision of the new approach is preserved even if the fluorescence trace is rather noisy or if the fluorescence transients show slow rise kinetics lasting several hundred milliseconds, and inhomogeneous rise and decay times. In addition, we discuss the use of the new approach for inferring parameter changes, e.g. due to a pharmacological intervention, as well as for inferring complex characteristics of immature neuronal circuits.
- q. Rekauzke S, Nortmann N, Stadt R, Hock HS, Schöner G, **Jancke D** (2016): Temporal asymmetry in dark-bright processing initiates propagating activity across primary visual cortex. *J Neurosci*, 36: 1902-1913
<http://www.ncbi.nlm.nih.gov/pubmed/26865614>

Abstract:

Differences between visual pathways representing darks and lights have been shown to affect spatial resolution and detection timing. Both psychophysical and physiological studies suggest an underlying retinal origin with amplification in primary visual cortex (V1). Here we show that temporal asymmetries in the processing of darks and lights create motion in terms of propagating activity across V1. Exploiting the high spatiotemporal resolution of voltage-sensitive dye imaging, we captured population responses to abrupt local changes of luminance in cat V1. For stimulation we used two neighboring small squares presented on either bright or dark backgrounds. When a single square changed from dark to bright or vice versa, we found coherent population activity emerging at the respective retinal input locations. However, faster rising and decay times were obtained for the bright to dark than the dark to bright changes. When the two squares changed luminance simultaneously in opposite polarities, we detected a propagating wave front of activity that originated at the cortical location representing the darkened square and rapidly expanded toward the region representing the brightened location. Thus, simultaneous input led to sequential activation across cortical retinotopy. Importantly, this effect was independent of the squares' contrast with the background. We suggest imbalance in dark-bright processing as a driving force in the generation of wave-like activity. Such propagation may convey motion signals and influence perception of shape whenever abrupt shifts in visual objects or gaze cause counterchange of luminance at high-contrast borders.

- r. **Deckert M, Lippert MT, Takagaki K, Brose A, Ohl F, Schmidt B** (2016) Microfabrication and Packaging of 3D-Capable μ ECoG - MEAs. International Conference on Systems in Medicine and Biology, Kharagpur
- s. **Spoida K, Eickelbeck D, Karapinar R, Eckhardt T, Mark MD, Jancke D, Ehinger B, König P, Dalkara D, Herlitze S, Masseck OA** (2016): Melanopsin Variants as Intrinsic Optogenetic On and Off Switches for Transient versus Sustained Activation of G Protein Pathways. Current Biology, (accepted March 1st 2016)
- t. Nüssing A, **Wolters CH**, Brinck H, Engwer C (2016): The Unfitted Discontinuous Galerkin Method for Solving the EEG Forward Problem: A Second Order Study. Proceedings of the Workshop Biosignal Processing 2016, April 7th - 8th Berlin, Germany
- u. Lau S, Güllmar D, Flemming L, Grayden DB, Cook MJ, **Wolters CH**, Haueisen J (2016): Skull Defects in Finite Element Head Models for Source Reconstruction from Magnetoencephalography Signals. Frontiers in Neuroscience, April, Volume 10, Article 141.
- v. **Schander A**, Tessmann T, Stokov S, **Stemmann H, Kreiter AK, Lang W** (2016): In-vitro Evaluation of the Long-term Stability of PEDOT:PSS Coated Microelectrodes for Chronic Recording and Electrical Stimulation of Neurons. Conf Proc IEEE Eng Med Biol Soc 2016 (accepted May 2016)
- w. Fiederer LDJ, Lahr J, Vorwerk J, Lucka F, Aertsen A, **Wolters CH**, Schulze-Bonhagen A, Ball T (2016): Electrical Stimulation of the Human Cerebral Cortex by Extracranial Muscle Activity: Effect Quantification with Intracranial EEG and FEM Simulations. IEEE 2016
- x. **Schander A, Stemmann H**, Tolstosheeva E, Roese R, Biefeld V, Kempen L, **Kreiter AK, Lang W** (2016): Design and fabrication of novel multi-channel floating neural probes for

intracortical chronic recording. *Sensors and Actuators A: Physical* Vol 247:125-135

<http://www.sciencedirect.com/science/article/pii/S0924424716302746>

Abstract:

This paper presents a novel design approach and production process flow for the fabrication of multi-channel silicon probes with highly flexible ribbon cables integrated monolithically on wafer level. The integrated flexible cables are based on the biocompatible polymer polyimide BPDA-PPD. Compared to state-of-the-art silicon probes, this novel design allows a floating chronic implantation of the probes into the cortex with reduced mechanical coupling to the skull. The electrode area is additionally coated with the electrical conductive and biocompatible polymer poly(3,4-ethylenedioxythiophene)polystyrene sulfonate (PEDOT:PSS) to reduce the electrode interface impedance. In-vitro electrical impedance spectroscopy measurements demonstrate the functionality of these novel probes and verify a significant reduction of the electrode impedance using PEDOT:PSS coating. For precise and complete insertion of these neural probes in the cortex an insertion tool was developed, which can be attached to a variety of different electrode drives. Using this tool the silicon probes were successfully implanted into rat motor cortex. Prior to implantation the probes were steam autoclaved at 121 °C, 1 bar for 20.5 min for sterilization. Electrophysiological recordings as well as in-vivo electrical impedance spectroscopy supported the results of the in-vitro functional tests. After an initial increase of electrical impedance in the course of the first week after implantation the average impedance of the electrodes settled for the following weeks. Recordings of single- and multi-unit activity along with the local field potential were successful for more than 7 weeks after implantation and are still continuing. These current results indicate an appropriate chronic use of the presented neural probes.

- y. Hartung H, Brockmann MD, Pöschel B, De Feo V, **Hanganu-Opatz IL** (2016): Thalamic and entorhinal network activity differently modulates the functional development of prefrontal-hippocampal interactions. *J Neurosci*

<http://www.ncbi.nlm.nih.gov/pubmed/27030754>

Abstract

Precise information flow during mnemonic and executive tasks requires the coactivation of adult prefrontal and hippocampal networks in oscillatory rhythms. This interplay emerges early in life, most likely as an anticipatory template of later cognitive performance. At neonatal age, hippocampal theta bursts drive the generation of prefrontal theta-gamma oscillations. In the absence of direct reciprocal interactions, the question arises of which feedback mechanisms control the early entrainment of prefrontal-hippocampal networks. Here, we demonstrate that prefrontal-hippocampal activity couples with discontinuous theta oscillations and neuronal firing in both lateral entorhinal cortex and ventral midline thalamic nuclei of neonatal rats. However, these two brain areas have different contributions to the neonatal long-range communication. The entorhinal cortex mainly modulates the hippocampal activity via direct axonal projections. In contrast, thalamic theta bursts are controlled by the prefrontal cortex via mutual projections and contribute to hippocampal activity. Thus, the neonatal prefrontal cortex modulates the level of hippocampal activation by directed interactions with the ventral midline thalamus. Similar to the adult task-related communication, theta-band activity ensures the feedback control of long-range coupling in the developing brain.

2) Other Contributions

- a. Pan European Networks - Special Report
“Setting the right rhythms” by Ileana Hanganu-Opatz
<http://www.paneuropeannetworks.com/reports/>

3) Gender Equalities

During the three years of the run-time of the Priority Program two female students did take the chance to get a closer look into the insights of some troika works. The feedback of them has been very positive and hopefully other students will follow their example.

We would like to thank Wolfgang Krautschneider for having supported Mariya Kiriya at the Technical University of Hamburg-Harburg and Florian Böhner for his involvement concerning the student Stefanie Scülfort at the Zentralinstitut für Seelische Gesundheit Mannheim.

4) Annual Meeting, February 29th – March 2nd in Frankfurt

The annual meeting aimed to summarize the achievements of the consortium by introducing recently developed tools (e.g. electrodes and microchips for monitoring brain activity in different species, novel opsins for silencing neuronal activity), dissection of neuronal circuits in the adult and developing brain and new analytical approaches and data-constrained models. The PIs presented the results of their intra- and inter-troika collaborative efforts, whereas the coordinator of the Program highlighted the added value of the consortium better understanding of the brain function and for tailored training and promotion of young scientists.

During the two days of the meeting 76 researchers directly involved in the SPP discussed their results and planned the projects for the 2nd funding period that will start in Fall 2016. They received feedback from Michael Hausser (University College London), Ofer Yizhar (Weizmann Institute of Science Israel), Thomas Klausberger (Medical University Vienna), Francesco Battaglia (Donders Institute Nijmegen) and Yiota Poirazi (Institute of Molecular Biology and Biotechnology Heraklion) who gave keynote lectures at the meeting .



5) Upcoming events

| Events 2016 | | | |
|---------------------------------|----------------|---|-----------------------------|
| Date | Place | Event | Organization |
| <i>September 1st</i> | | <i>Start of next funding period</i> | |
| <i>January 26-28, 2016</i> | <i>Hamburg</i> | <i>Kick-off Meeting 2nd funding period</i> | <i>Ileana Hanganu-Opatz</i> |

Next newsletter to be expected in December 2016