SPP 1665:

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

Newsletter, forth edition, December 2015

1) Publications

New publications of the troikas:

a. Wietek J, Beltramo R, Scanziani M, **Hegemann P**, **Oertner TG**, Wiegert JS (2015): An improved chrolide-conducting channelrhodopsin for light-induced inhibition of neuronal activity in vivo. Scientific Reports 5, 14807
http://www.ncbi.nlm.nih.gov/pubmed/26443033

Abstract:
Channelrhodopsins are light-gated cation channels that have been widely used for optogenetic stimulation of electrically excitable cells. Replacement of a glutamic acid in the central gate with a positively charged amino acid residue reverses the ion selectivity and produces chloride-conducting ChRs (ChloCs). Expressed in neurons, published ChloCs produced a strong shunting effect but also a small, yet significant depolarization from the resting potential. Depending on the state of the neuron, the net result of illumination might therefore be inhibitory or excitatory with respect to action potential generation. Here we report two additional amino acid substitutions that significantly shift the reversal potential of improved ChloC (iChloC) to the reversal potential of endogenous GABAA receptors. As a result, light-evoked membrane depolarization was strongly reduced and spike initiation after current injection or synaptic stimulation was reliably inhibited in iChloC-transfected neurons in vitro. In the primary visual cortex of anesthetized mice, activation of iChloC suppressed spiking activity evoked by visual stimulation. Due to its high operational light sensitivity, iChloC makes it possible to inhibit neurons in a large volume of brain tissue from a small, point-like light source.

b. **Stitt I**, Galindo-Leon E, Pieper, F, Engler G, Fiedler E, Stieglitz T, **Engel AK** (2015): Intrinsic coupling modes reveal the funcional architecture of cortico-tectal networks. Sci Adv 2015, e1500229
http://www.ncbi.nlm.nih.gov/pubmed/26601226

Abstract:
In the absence of sensory stimulation or motor output, the brain exhibits complex spatiotemporal patterns of intrinsically generated neural activity. Analysis of ongoing brain dynamics has identified the prevailing modes of cortico-cortical interaction; however, little is known about how such patterns of intrinsically generated activity are correlated between cortical and subcortical brain areas. We investigate the correlation structure of ongoing

cortical and superior colliculus (SC) activity across multiple spatial and temporal scales. Ongoing cortico-tectal interaction was characterized by correlated fluctuations in the amplitude of delta, spindle, low gamma, and high-frequency oscillations (>100 Hz). Of these identified coupling modes, topographical patterns of high-frequency coupling were the most consistent with patterns of anatomical connectivity, reflecting synchronized spiking within cortico-tectal networks. Cortico-tectal coupling at high frequencies was temporally parcellated by the phase of slow cortical oscillations and was strongest for SC-cortex channel pairs that displayed overlapping visual spatial receptive fields. Despite displaying a high degree of spatial specificity, cortico-tectal coupling in lower-frequency bands did not match patterns of cortex-to-SC anatomical connectivity. Collectively, our findings demonstrate that neural activity is spontaneously coupled between cortex and SC, with high- and low-frequency modes of coupling reflecting direct and indirect cortico-tectal interactions, respectively.

c. Bauer M, Pursiainen S, Vorwerk J, Köstler H, **Wolters CH** (2015): Comparison Study for Whitney (Raviart-Thomas) Type Source Models in Finite Element Method Based EEG Forward Modeling. IEEE Trans Biomed Eng. 2015 Nov;62(11):2648-56
http://www.ncbi.nlm.nih.gov/pubmed/26054057

Abstract:
This study concentrates on finite-element-method (FEM)-based electroencephalography (EEG) forward simulation in which the electric potential evoked by neural activity in the brain is to be calculated at the surface of the head. The main advantage of the FEM is that it allows realistic modeling of tissue conductivity inhomogeneity. However, it is not straightforward to apply the classical model of a dipolar source with the FEM, due to its strong singularity and the resulting irregularity. The focus of this study is on comparing different methods to cope with this problem. In particular, we evaluate the accuracy of Whitney (Raviart-Thomas)-type dipole-like source currents compared to two reference dipole modeling methods: the St. Venant and partial integration approach. Common to all these methods is that they enable direct approximation of the potential field utilizing linear basis functions. In the present context, Whitney elements are particularly interesting, as they provide a simple means to model a divergence-conforming primary current vector field satisfying the square integrability condition. Our results show that a Whitney-type source model can provide simulation accuracy comparable to the present reference methods. It can lead to superior accuracy under optimized conditions with respect to both source location and orientation in a tetrahedral mesh. For random source orientations, the St. Venant approach turns out to be the method of choice over the interpolated version of the Whitney model. The overall moderate differences obtained suggest that practical aspects, such as the focality, should be prioritized when choosing a source model.

d. Cho JH, Vorwerk J, **Wolters CH**, Knösche TR (2015): Influence of the head model on EEG and MEG source connectivity analysis. Neuroimage. 2015 Apr 15;110:60-77. doi: 10.1016/j.neuroimage.2015.01.043
http://www.ncbi.nlm.nih.gov/pubmed/25638756

Abstract:

The results of brain connectivity analysis using reconstructed source time courses derived from EEG and MEG data depend on a number of algorithmic choices. While previous studies have investigated the influence of the choice of source estimation method or connectivity measure, the effects of the head modeling errors or simplifications have not been studied sufficiently. In the present simulation study, we investigated the influence of particular properties of the head model on the reconstructed source time courses as well as on source connectivity analysis in EEG and MEG. Therefore, we constructed a realistic head model and applied the finite element method to solve the EEG and MEG forward problems. We considered the distinction between white and gray matter, the distinction between compact and spongy bone, the inclusion of a cerebrospinal fluid (CSF) compartment, and the reduction to a simple 3-layer model comprising only the skin, skull, and brain. Source time courses were reconstructed using a beamforming approach and the source connectivity was estimated by the imaginary coherence (ICoh) and the generalized partial directed coherence (GPDC). Our results show that in both EEG and MEG, neglecting the white and gray matter distinction or the CSF causes considerable errors in reconstructed source time courses and connectivity analysis, while the distinction between spongy and compact bone is just of minor relevance, provided that an adequate skull conductivity value is used. Large inverse and connectivity errors are found in the same regions that show large topography errors in the forward solution. Moreover, we demonstrate that the very conservative ICoh is relatively safe from the crosstalk effects caused by imperfect head models, as opposed to the GPDC.

e. **Schander A**, Tolstosheeva E, Biefeld V, Kempen L, **Stemmann H**, **Kreiter A**, **Lang W** (2015): Design and fabrication of multi-contact flexible silicon probes for intracortical floating implantation. Transducers 2015; Alaska, USA, pp. 1739 - 1742; published in IEEE Xplore **http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=7181281&newsearch=true&queryText=schander%20a**

Abstract:

This paper reports on a novel design and process flow development for the fabrication of multi-contact silicon probes with monolithically integrated highly flexible ribbon cables on wafer level, based on the biocompatible polymer parylene-C. Compared to the state-of-the-art silicon probes, this novel development allows for the first time a floating implantation of these neural probes in the cortex with reduced destructive forces applied to the brain tissue. In-vitro electrical impedance spectroscopy measurements and first in-vivo measurements in the cortex of a rat demonstrate the functionality of these probes.

f. **Kirmse K**, **Kummer M**, Kovalchuk Y, Witte OW, Garaschuk O, **Holthoff K** (2015): GABA depolarizes immature neurons and inhibits network activity in the neonatal neocortex in vivo. Nat Commun 2015 Jul 16;6:7750; published in pubmed http://www.ncbi.nlm.nih.gov/pubmed/26177896

Abstract:

A large body of evidence from in vitro studies suggests that GABA is depolarizing during early postnatal development. However, the mode of GABA action in the intact developing brain is unknown. Here we examine the in vivo effects of GABA in cells of the upper cortical plate using a combination of electrophysiological and Ca(2+)-imaging techniques. We report that at postnatal days (P) 3-4, GABA depolarizes the majority of immature neurons in the occipital cortex of anaesthetized mice. At the same time, GABA does not efficiently activate voltage-

gated Ca(2+) channels and fails to induce action potential firing. Blocking GABA(A) receptors disinhibits spontaneous network activity, whereas allosteric activation of GABA(A) receptors has the opposite effect. In summary, our data provide evidence that in vivo GABA acts as a depolarizing neurotransmitter imposing an inhibitory control on network activity in the neonatal (P3-4) neocortex.

g. Kummer M, **Kirmse K**, Witte OW, Haueisen J, **Holthoff K** (2015): A method to quantify accuracy of position feedback signals of a three-dimensional two -photon laser-scanning microscope. Biomed Opt Express 6 (10):3678-3693 http://www.ncbi.nlm.nih.gov/pubmed/26504620

Abstract:
Two-photon laser-scanning microscopy enables to record neuronal network activity in three-dimensional space while maintaining single-cellular resolution. One of the proposed approaches combines galvanometric x-y scanning with piezo-driven objective movements and employs hardware feedback signals for position monitoring. However, readily applicable methods to quantify the accuracy of those feedback signals are currently lacking. Here we provide techniques based on contact-free laser reflection and laser triangulation for the quantification of positioning accuracy of each spatial axis. We found that the lateral feedback signals are sufficiently accurate (defined as <2.5 µm) for a wide range of scan trajectories and frequencies. We further show that axial positioning accuracy does not only depend on objective acceleration and mass but also its geometry. We conclude that the introduced methods allow a reliable quantification of position feedback signals in a cost-efficient, easy-to-install manner and should be applicable for a wide range of two-photon laser scanning microscopes.

g. Ambrus GG, Pisoni A, Primaßin A, **Turi Z**, **Paulus W**, Antal A (2015): Bi-frontal transcranial alternating current stimulation in the ripple range reduced overnight forgetting. Front Cell Neurosci 2015 Sep 24;9:374
http://www.ncbi.nlm.nih.gov/pubmed/26441544

Abstract:
High frequency oscillations in the hippocampal structures recorded during sleep have been proved to be essential for long-term episodic memory consolidation in both animals and in humans. The aim of this study was to test if transcranial Alternating Current Stimulation (tACS) of the dorsolateral prefrontal cortex (DLPFC) in the hippocampal ripple range, applied bi-frontally during encoding, could modulate declarative memory performance, measured immediately after encoding, and after a night's sleep. An associative word-pair learning test was used. During an evening encoding phase, participants received 1 mA 140 Hz tACS or sham stimulation over both DLPFCs for 10 min while being presented twice with a list of word-pairs. Cued recall performance was investigated 10 min after training and the morning following the training session. Forgetting from evening to morning was observed in the sham condition, but not in the 140 Hz stimulation condition. 140 Hz tACS during encoding may have an effect on the consolidation of declarative material.

h. Augustin M, **Ladenbauer J**, **Obermayer K** (2015): Low-dimensional spike rate dynamics of coupled adaptive model neurons. BMC Neurosci (in press)

i. **Bender F**, **Gorbati M**, Cadavieco MC, Denisova N, **Gao X**, Holman C, Korotkova T, **Ponomarenko A** (2015): Theta oscillations regulate the speed of locomotion via a hippocampus to lateral septum pathway. Nat Commun (2015) 6:8521. doi: 10.1038/ncomms9521.
http://www.ncbi.nlm.nih.gov/pubmed/26455912

Abstract:
Hippocampal theta oscillations support encoding of an animal's position during spatial navigation, yet longstanding questions about their impact on locomotion remain unanswered. Combining optogenetic control of hippocampal theta oscillations with electrophysiological recordings in mice, we show that hippocampal theta oscillations regulate locomotion. In particular, we demonstrate that their regularity underlies more stable and slower running speeds during exploration. More regular theta oscillations are accompanied by more regular theta-rhythmic spiking output of pyramidal cells. Theta oscillations are coordinated between the hippocampus and its main subcortical output, the lateral septum (LS). Chemo- or optogenetic inhibition of this pathway reveals its necessity for the hippocampal regulation of running speed. Moreover, theta-rhythmic stimulation of LS projections to the lateral hypothalamus replicates the reduction of running speed induced by more regular hippocampal theta oscillations. These results suggest that changes in hippocampal theta synchronization are translated into rapid adjustment of running speed via the LS.

j. Sieben K, Bieler M, Röder B, **Hanganu-Opatz IL** (2015): Neonatal Restriction of Tactile Inputs Leads to Long-Lasting Impairments of Cross-Modal Processing. PLoS Biol. 2015 Nov 24;13(11):e1002304. doi: 10.1371.
http://www.ncbi.nlm.nih.gov/pubmed/26600123

Abstract:
Optimal behavior relies on the combination of inputs from multiple senses through complex Interactions within neocortical networks. The ontogeny of this multisensory interplay is still unknown. Here, we identify critical factors that control the development of visual-tactile processing by combining in vivo electrophysiology with anatomical/functional assessment of cortico-cortical communication and behavioral investigation of pigmented rats. We demonstrate that the transient reduction of unimodal (tactile) inputs during a short period of neonatal development prior to the first cross-modal experience affects feed-forward subcortico-cortical interactions by attenuating the cross-modal enhancement of evoked responses in the adult primary somatosensory cortex. Moreover, the neonatal manipulation alters cortico-cortical interactions by decreasing the cross-modal synchrony and directionality in line with the sparsification of direct projections between primary somatosensory and visual cortices. At the behavioral level, these functional and structural deficits resulted in lower cross-modal matching abilities. Thus, neonatal unimodal experience during defined developmental stages is necessary for setting up the neuronal networks of multisensory processing.

2) Poster contributions

a. **Gee CE**, Scheib U, Stehfest K, Fudim R, Koerschen H, **Hegemann P**, **Oertner TG**: The rhodopsin-guanylyl cyclase of the aquatic fungus Blastocladiella emersonii enables fast optical control of cGMP signaling. SFN Meeting Chicago 2015

c. **Gärtner M**, **Duvarci S**, **Roeper J**, **Schneider G**: Joint pausiness in parallel spike trains. CNS 2015 Prague

d. Albert S, Messer M, Rummell B, **Sigurdsson T**, **Schneider G**: Multi-scale detection of rate and variance changes in neuronal spike trains. CNs 2015 Prague

e. Messer M, Albert S, Schiemann J, **Roeper J**, Neininger R, **Schneider G**: A multi scale method for change point detection in point processes. Statistische Woche in Hamburg, September 2015

f. Vorwerk J, Engwer C, Ludewig J, **Wagner S**, **Wolters CH**: A discontinuous Galerkin finite element approach for the EEG forward problem. BACI 2015, International Conference on Basic and Clinical Multimodal Imaging, Utrecht, The Netherlands, Sept. 1-5, 2015.

g. **Wagner S**, **Homölle S**, Burger M, **Wolters CH**: An optimization approach for well-targeted transcranial direct current stimulation, BACI 2015, International Conference on Basic and Clinical Multimodal Imaging, Utrecht, The Netherlands, Sept. 1-5.

h. Nüssing A, **Wolters CH**, Brinck H, Engwer C: The unfitted discontinuous Gerkin method in brain research. BACI 2015, International Conference on Basic and Clinical Multimodal Imaging, Utrecht, The Netherlands, Sept. 1 – 5.

i. **Ehinger BV**: TBA 2015 Blind Spot Bayesian Summerschool, Amsterdam, NL 10- 14-Aug 2015

j. Ossandon J, **Ehinger BV**, **König P**: Predictions of visual content across eye movements and their modulation by inferred information Gordon Research Conference: Eye movements, Boston 26-31-Jul 2015

k. **Ehinger BV**, **König P**, Ossandón J: Prediction of visual content across eye movements and their modulation by inferred information in the blind spot Brain Conference Kopenhagen, 19-24-Apr 2015

l. **Ehinger BV**, **König P**, Ossandón J: Prediction errors are modulated by inferred information from the blind. ECEM 2015, Wien 16-20-Aug 2015

m. **Aspart F**, **Ladenbauer J**, **Obermayer K**: Extending integrate-and fire model neurons to account for the effects of weak electric fields in the presence of dendrites, Poster presentation, CNS 2015, Prague, July 18-23 2015

3) Talks

a. **Ehinger BV**, **König P**, Ossandón J (2015): Prediction errors are modulated by inferred information from the blind. 7th MMN Conference Leipzig

b. Ossandon J, **Ehinger BV**, **König P** (2015): Predictions of visual content across eye movements and their modulation by inferred information. Gordon Research Seminar: Eye movements Boston, 25-26-Jul-2015

4) Successful phd and master thesis

a. *Magna cum laude* **- Sven Wagner** (August 2015): Optimizing tCS and TMS multi-sensor setups using realistic head models. Department of Maths/Computer Science of the University of Münster.

b. **Ümit Aydin** (March 2015): Combined EEG and MEG source analysis of epileptiform activity using calibrated realistic finite element head models. PhD thesis, Fakultät für Informatik und Automatisierung, TU Ilmenau

c. **Britte Agsten** (2015): Comparing the complete and the point electrode model for combining tCS and EEG. Master Thesis in Mathematics, Fachbereich Mathematik und Information of the University of Münster

d. **Sven Homölle** (2015): Comparison of optimization approaches in high-definition transcranial direct current stimulation in the mammalian brain". Master Thesis in Mathematics, Fachbereich Mathematik und Informatik, University of Münster

Congratulations!

5) Analytical Workshop, Hamburg, 23rd – 25th of October 2015

The workshop “Analysis and Modulation of Brain Networks” was organized in cooperation with the SFB936 by Andreas K. Engel, Christoph S. Herrmann, Guido Nolte, Ileana Hanganu-Opatz, Christian Gerloff, and Sina A. Trautmann-Lengsfeld on October 23rd-25th 2015 at the University Medical Center Hamburg-Eppendorf, Germany.

The workshop focused (1) on EEG and MEG data investigated with functional coupling (Pascal Fries, Michael Wibral, Guido Nolte, Arne Ewald), (2) on brain stimulation with tACS in brain networks (Andreas Engel, Christoph Herrmann, Lisa Marshall, Phillip Ruhnau, Tuomas Mutanen) as well as (3) optogenetics in animals (Peter Hegemann, Joachim Ahlbeck).

It encompassed lectures by internationally recognized speakers in the mornings, followed by introductory tutorials and hands-on sessions about cutting edge methods of coherence and cross frequency coupling, tACS artefact correction, and optogenetics on both simulated and real data in the afternoon.

Furthermore, the workshop offered a unique opportunity to exchange expertise between participants and lecturers as well as ample of opportunities for scientific discussions. (Text by S.A. Trautwein-Lengsfeld/ A. Engel)

6) Gender Equality

The SPP 1665 is still taking every opportunity to support young families and to improve the conditions of female researchers as the underrepresented gender. The activities taken by the SPP 1665 this year in these matters have been quite divers:

a. The research group of Ileana Hanganu-Opatz has taken part in the organization of this year's Girls' Day, taken place at the UKE on April 23rd. Six girls and one boy did take the chance to gain an insight look in the work and atmosphere of working in a lab as a researcher or a technical assistant. After having been introduced in the daily routine and the lab processes even a small experiment with active participation has been shown. The day ended with a lively discussion about the motivation of doing research and with the concluding remarks of its importance for society.

b. The official strike of nursery teachers for several weeks this spring/summer have caused quite a lot of organizational and even financial problems for families. The SPP 1665 has volunteered to offer financial support for researchers to absorb some of the inconvenience and to ensure the continuation of work.

c. The SPP 1665 has invented the tool of a short-term course of studies for interested researchers (reserved to the "underrepresented" gender). Until now two young students have benefitted from this opportunity. Mariya Kiriyak from the TUHH (Wolfgang Krautschneider) pioneered in this field and did support the SPPs work over 3 months focusing on the question of "Low power operation at reduced supply voltage". The outcomes of her work are so explicit that they cannot be published in our newsletter, but will be available on the SPP 1665 webpage. Another young female researcher, Stefanie Scülfort just started her studies at the the group of Wolfgang Kelsch and will provide us with her results hopefully in May next year.

7) Miscellaneous

We are very happy to announce the birth of Ilka Diester's first child: Her daughter Mauna Kea was born on November, 17th at 21h40. Congratulations and the best wishes to the new-arrival!

8) Upcoming events

Annual Meeting, Frankfurt, February 29th – March 2nd 2016

On August 31st 2016 the first funding period of the SPP 1665 will come to an end with the second 3-year period starting directly thereafter. The original planning of having a midterm meeting was therefore changed into the organization of a 3 days retreat in Frankfurt with more time for discussions and exchanges. Besides the DFG, there will be 5 internationally established speakers attending the meeting to support the pre-evaluation process with feedback and input (Michael Hausser, University College London; Ofer Yizhar, Weizmann Institute of Science Israel; Thomas Klausberger, Medical University Vienna; Panayiota Poirazi, Institute of Moleculare Biology and Biotechnology Heraklion; Francesco Battaglia, Donders Institute Nijmegen). The preliminary program has already been sent around and will be published on the webpage of the SPP 1665.

Events 2016			
Date	**Place**	**Event**	**Organization**
February 29th – March 2nd	**Frankfurt**	**Annual Meeting**	**Ileana Hanganu-Opatz**
February 1 – March 31		***Call for proposals for next funding period***	
April – June		***Evaluation***	
September 1st		***Start of next funding period***	

Next newsletter:

To be expected for June 2016.

We wish you all a peaceful Christmas time and happy holidays!