SPP 1665:

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

Newsletter, first edition, June 2014

1) Publications

The outcome of collaborative efforts within the troikas of the SPP 1665 has been recently pushed:

Wietek, J., Wiegert, J.S., Adeishvili, N., Schneider, F., Watanabe, H., Tsunoda, S.P., Vogt, A., Elstner**, M., Oertner, T.G., Hegemann, P**. (2014) Conversion of Channelrhodopsin into a light-gated chloride channel. Science 344, 409 – 412.
Science 344, 409 – 412. http://www.sciencemag.org/content/344/6182/409.full.pdf
Comment: Hayashi, S. (2014) Silencing Neurons with Light. Science 369 – 370. http://www.sciencemag.org/content/344/6182/369.full.pdf

Abstract:
The field of optogenetics uses channelrhodopsins (ChRs) for light-induced neuronal activation. However, optimized tools for cellular inhibition at moderate light levels are lacking. We found that replacement of E90 in the central gate of ChR with positively charged residues produces chloride-conducting ChRs (ChloCs) with only negligible cation conductance. Molecular dynamics modeling unveiled that a high-affinity Cl(-)-binding site had been generated near the gate. Stabilizing the open state dramatically increased the operational light sensitivity of expressing cells (slow ChloC). In CA1 pyramidal cells, ChloCs completely inhibited action potentials triggered by depolarizing current injections or synaptic stimulation. Thus, by inverting the charge of the selectivity filter, we have created a class of directly light-gated anion channels that can be used to block neuronal output in a fully reversible fashion

2. Rampersad, S. M., Janssen, A. M., Lucka, F., Aydin, Ü., Lanfer, B., Lew, S., **Wolters, C. H.,** Stegeman, D. F., Oostendorp, T. F. (2014) Simulating Transcranial Direct Current Stimulation With a Detailed Anisotropic Human Head Model. Neural Systems and Rehabilitation Engineering, IEEE Transactions on (Volume: 22 , Issue: 3), 441 – 452.
http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6750748&searchWithin%3DC+H+Wolters%26sortType%3Dasc_p_Sequence%26filter%3DAND%28p_IS_Number%3A6807532%29

Abstract:
Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique able to induce long-lasting changes in cortical excitability that can benefit cognitive functioning and clinical treatment. In order to both better understand the mechanisms behind tDCS and possibly improve the technique, finite element models are used to simulate tDCS of the human brain. With the detailed anisotropic head model presented in this study, we provide accurate predictions of tDCS in the human brain for six of the practically most-used setups in clinical and cognitive research, targeting the primary motor cortex, dorsolateral prefrontal cortex, inferior frontal gyrus, occipital cortex, and cerebellum. We present the resulting electric field strengths in the complete brain and introduce new methods to evaluate the effectivity in the target area specifically, where we have analyzed both the strength and direction of the field. For all cerebral targets studied, the currently accepted configurations produced sub-optimal field strengths. The configuration for cerebellum stimulation produced relatively high field strengths in its target area, but it needs higher input currents than cerebral stimulation does. This study suggests that improvements in the effects of transcranial direct current stimulation are achievable.

3. Cichon, N. B., **Denker, M., Gruen, S., Hanganu-Opatz, I. L.** (2014) Unsupervised classification of neocortical activity patterns in neonatal and pre-juvenile rodents. Front Neural Circuits. 2014 May 27; 8:50
http://www.ncbi.nlm.nih.gov/pubmed/24904296

Abstract:
Flexible communication within the brain, which relies on oscillatory activity, is not confined to adult neuronal networks. Experimental evidence has documented the presence of discontinuous patterns of oscillatory activity already during early development. Their highly variable spatial and time-frequency organization has been related to region specificity. However, it might be equally due to the absence of unitary criteria for classifying the early activity patterns, since they have been mainly characterized by visual inspection. Therefore, robust and unbiased methods for categorizing these discontinuous oscillations are needed for increasingly complex data sets from different labs. Here, we introduce an unsupervised detection and classification algorithm for the discontinuous activity patterns of rodents during early development. For this, firstly time windows with discontinuous oscillations vs. epochs of network "silence" were identified. In a second step, the major features of detected events were identified and processed by principal component analysis for deciding on their contribution to the classification of different oscillatory patterns. Finally, these patterns were categorized using an unsupervised cluster algorithm. The results were validated on manually characterized neonatal spindle bursts (SB), which ubiquitously entrain neocortical areas of rats and mice, and prelimbic nested gamma SB. Moreover, the algorithm led to satisfactory results for oscillatory events that, due to increased similarity of their features, were more difficult to classify, e.g., during the pre-juvenile developmental period. Based on a linear classification, the optimal number of features to consider increased with the difficulty of detection. This algorithm allows the comparison of neonatal and pre-juvenile oscillatory patterns in their spatial and temporal organization. It might represent a first step for the unbiased elucidation of activity patterns during development.

4. Masseck, O.A., Spoida, K., Dalkara, D., Maejima, T., Rubelowski, J.M., Wallhorn, L., Deneris, E.S. and **Herlitze, S.** (2014) Vertebrate cone opsins enable sustained and highly sensitive rapid control of Gi/o signaling in anxiety circuitry. Neuron 19(81): 1263-73.
http://www.ncbi.nlm.nih.gov/pubmed/24656249

Abstract:
G protein-coupled receptors (GPCRs) coupling to Gi/o signaling pathways are involved in the control of important physiological functions, which are difficult to investigate because of the limitation of tools to control the signaling pathway with precise kinetics and specificity. We established two vertebrate cone opsins, short- and long-wavelength opsin, for long-lasting and repetitive activation of Gi/o signaling pathways in vitro and in vivo. We demonstrate for both opsins the repetitive fast, membrane-delimited, ultra light-sensitive, and wavelength-dependent activation of the Gi/o pathway in HEK cells. We also show repetitive control of Gi/o pathway activation in 5-HT1A receptor domains in the dorsal raphe nucleus (DRN) in brain slices and in vivo, which is sufficient to modulate anxiety behavior in mice. Thus, vertebrate cone opsins represent a class of tools for understanding the role of Gi/o-coupled GPCRs in health and disease.

5. Spoida, K., Masseck, O.A., Deneris, E.S. and **Herlitze, S.** (2014). Gq/5-HT2c receptor signals activate a local GABAergic inhibitory feedback circuit to modulate serotonergic firing and anxiety in mice. Proc. Natl. Acad. Sci., USA, 111(17):6479-84.
http://www.ncbi.nlm.nih.gov/pubmed/24733892

Abstract:
Serotonin 2c receptors (5-HT2c-Rs) are drug targets for certain mental disorders, including schizophrenia, depression, and anxiety. 5-HT2c-Rs are expressed throughout the brain, making it difficult to link behavioral changes to circuit specific receptor expression. Various 5-HT-Rs, including 5-HT2c-Rs, are found in the dorsal raphe nucleus (DRN); however, the function of 5-HT2c-Rs and their influence on the serotonergic signals mediating mood disorders remain unclear. To investigate the role of 5-HT2c-Rs in the DRN in mice, we developed a melanopsin-based optogenetic probe for activation of Gq signals in cellular domains, where 5-HT2c-Rs are localized. Our results demonstrate that precise temporal control of Gq signals in 5-HT2c-R domains in GABAergic neurons upstream of 5-HT neurons provides negative feedback regulation of serotonergic firing to modulate anxiety-like behavior in mice.

2) Troika work and co-operations

This Priority Program offers a great opportunity for the participating researchers to benefit from the knowledge not only within the own troika, but also from others. During the kick-off symposium in March all participants had the opportunity to get in contact with each other and initiate such inter-troika collaborations.

As an example, the troika of Andreas Engel, Christoph Herrmann and Carsten Wolters started to collaborate with the troika of Walter Paulus, Nikos Logothetis and Klaus Obermayer. Just 10 days

after the kick-off, Sven Wagner, a PhD student working with Carsten Wolters, participated in a 3 days meeting in Göttingen with Walter Paulus and Christoph Herrmann, where he took advantage of a NWG practical course transcranial magnetic and electrical stimulation (TMS/tDCS/tACS/tRNS). The exchange between the troikas was intensified in April during the workshop on “Nicht-invasive Rekonstruktion neuronaler Netzwerke durch kombinierte EEG/MEG Quellenanalyse und Manipulation der Netzwerke durch sensor-optimierte tACS”("non-invasive reconstruction of neuronal networks through combined EEG/MEG analysis and manipulation of networks through sensor-optimized tACS") that was organized in April 2014 in Berlin by the groups of K. Obermayer and C. Wolters.

3) Lab rotations

First lab rotations have been individually organized by the students of the SPP 1665. Sven Wagner spent 3 days in Göttingen to participate to the NWG practical course. In addition Sebastian Bitzenhofer and Joachim Ahlbeck (Hanganu-Opatz group) have visited the lab of Ilka Diester in Frankfurt and of Michael Denker in Jülich. Within the following lines Sebastian and Joachim give a brief overlook on their experience:

Ilka Diester Lab in Frankfurt, date: 29.01.2014 - 31.01.2014
“Optogenetics provide a powerful tool to causally investigate network function, interaction and development in the intact rodent brain. We are currently establishing the technique of optogenetics in our lab to combine it with electrophysiological recordings. This approach enables to deepen the understanding of the developing prefrontal-hippocampal network.
We visited the lab of Ilka Diester at the Ernst Strüngmann Institute in Frankfurt for a three day period to be introduced to their work with optogenetics in adult rodents. During the lab rotation we got familiar with their optogenetic and electrophysiological setups and trained in troubleshooting many of the issues that commonly arise when setting up and using such a system for the first time. Furthermore, we were introduced to surgical methods such as insertion of the optical fiber needed for delivering the light to the designated brain area.”

Michael Denker in Juelich, date: 02.04.2014
“We visited Michael Denker in Juelich, the “analysts” of our troika. One aim of the “one-day brain storming” was to identify the analytical necessities of the project, the strategies for the development of data transfer and corresponding metadata. Moreover, we set the framework for development of new analytical tools.”

4) Gender Equality

Thanks to the efforts of Wolfgang Krautschneider, a new female student will join the troika Isbrandt, Sirota and Krautschneider. Mariya Kiriyak will support the Krautschneider group at the TU Harburg from June to September. She will focus on the development of electric circuitry and the technique of measurement for the EEG recording at new born mice.

In line with the feedback from the participants from the survey we will organize a workshop on “conflict management”. The workshop will be open for both female and male researchers.

5) Workshops/ upcoming events

As already announced during the kick-off symposium in March, an analytical and an optogenetic workshop will take place in 2014 and 2015. The analytical workshop will be split into two parts. The first workshop will be organized by Sonja Grün and Michael Denker in Jülich in 2014 (see information below). The second one will take place in Hamburg in spring 2015 and will be organized by Andreas Engel (further information on this will follow as soon as possible).

Analytical Workshop (Jülich, 24 – 27, November 2014)

- **Topic:** **"Analysis and Management of Electrophysiological Activity Data"**
- **Organisation:** **Sonja Grün and Michael Denker (Forschungszentrum Jülich)**
- **Date:** **24 -27 November 2014**
- **Place:** **Jülich**
- **Structure:** **Morning: Lecture 2*1.5 hours**
  Afternoon: Exercises 2pm – 6 pm with 3 - 4 tutors per day (incl. wrap-up)
- **Participants:** **20 people max.**
- **Requirements:**
  - **Basic general knowledge about programming (not python specific; loops, variables, functions...)**
  - **Basic knowledge about electrophysiological signals (spikes, LFPs,...)**
  - **Analysis and Management of Electrophysiological Activity Data**

Preliminary Program:

1) NN
Python for analysis of electrophysiological data; Analysis Workflows
2) Prof. Martin Nawrot, FU Berlin
Characterization of single neuron activity
3) Prof. Sonja Grün, Forschungszentrum Juelich
Spike Synchrony: From cross-correlations to higher order analysis methods
4) Dr. Junji Ito, Forschungszentrum Juelich
Characterization of the local field potential and its relation to spiking activity

For registration and additional information on travel arrangements, cost etc. to this workshop, please contact Kathrin Harringa (kathrin.harringa@zmnh.uni-hamburg.de). As we only have free spaces for max. 20 people, we will handle registrations following the "first come - first served" method.

Upcoming events

Events 2014			
Date	**Place**	**Event**	**Organization**
Nov., 24 – 27	**Jülich**	**Analytical Workshop (I)** **"Analysis and Management of Electrophysiological Activity Data"**	**Sonja Grün, Michael Denker**
Events 2015			
Date	**Place**	**Event**	**Organization**
March, 18 - 21	**Göttingen**	**Progress report (during the NWG meeting in Göttingen)**	**Ileana Hanganu-Opatz**
April, 20 – 24	**Bochum**	**Optogenetics Workshop**	**Ilka Diester, Stefan Herlitze**
Mai	**Hamburg**	**Analytical Workshop (II)**	**Andreas Engel**
October, 8 - 10	**Hamburg**	**Annual Meeting**	**Ileana Hanganu-Opatz**

Next newsletter

Scheduled for November/ December 2014.