SPP 1665:

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

Newsletter, sixth edition, July 2017

1) Second funding period

The second funding period of the Priority Program 1665 has started on September 1st 2016, with now 11 projects being funded by the DFG.

The kick-off meeting was held at the Clinical University Hamburg-Eppendorf on January 26 and 27 this year, where the troikas presented themselves and established new collaborations. The meeting highlighted also one novel focus of the Program during the second funding period, the collaboration with recently launched national and international initiatives on similar topics. On the national side, interactions with two newly established Priority Programs, SPP 1926 "Next Generation Optogenetics" (launched in 2016) and SPP 2024 "Computational Connectonics" (launched in 2017) are envisaged. Both Priority Programs were represented by their coordinators, Alexander Gottschalk and Jochen Triesch. Moreover the International Program for the Advancement of Neurotechnology (IPAN), funded by the National Science Foundation (NSF) as well as the FENS KAVLI Network of Excellence have been brought up for international exchanges.

The meeting was furthermore enriched with talks from four renowned speakers from Norway (Menno Witter), England (Kenneth Harris), Spain (Guillermina Lopez-Bendito) and the United States (Wim Vanduffel), referring to research highlights closely related to the Priority Program's subject.

The second funding period's consortium at the kick-off meeting with co-workers and guest speakers.

2) Publications

a. Carus-Cadavieco M, **Gorbati M**, Ye L, **Bender F**, van der Veldt S, Kosse C, Börgers C, Lee SY, Ramakrishnan C, Hu Y, Denisova N, Ramm F, Volitaki E, Burdakov D, Deisseroth K, **Ponomarenko A**, Korotkova T (2017): Gamma oscillations organize top-down signalling to hypothalamus and enable food seeking. Nature 2017 Feb 9;542(7640):232-236. doi: 10.1038/nature21066
https://www.ncbi.nlm.nih.gov/pubmed/28146472

Abstract:
Both humans and animals seek primary rewards in the environment, even when such rewards do not correspond to current physiological needs. An example of this is a dissociation between food-seeking behaviour and metabolic needs, a notoriously difficult-to-treat symptom of eating disorders. Feeding relies on distinct cell groups in the hypothalamus, the activity of which also changes in anticipation of feeding onset. The hypothalamus receives strong descending inputs from the lateral septum, which is connected, in turn, with cortical networks, but cognitive regulation of feeding-related behaviours is not yet understood. Cortical cognitive processing involves gamma oscillations, which support memory, attention, cognitive flexibility and sensory responses. These functions contribute crucially to feeding behaviour by unknown neural mechanisms. Here we show that coordinated gamma (30-90 Hz) oscillations in the lateral hypothalamus and upstream brain regions organize food-seeking behaviour in mice. Gamma-rhythmic input to the lateral hypothalamus from somatostatin-positive lateral septum cells evokes food approach without affecting food intake. Inhibitory inputs from the lateral septum enable separate signalling by lateral hypothalamus neurons according to their feeding-related activity, making them fire at distinct phases of the gamma oscillation. Upstream, medial prefrontal cortical projections provide gamma-rhythmic inputs to the lateral septum; these inputs are causally associated with improved performance in a food-rewarded learning task. Overall, our work identifies a top-down pathway that uses gamma synchronization to guide the activity of subcortical networks and to regulate feeding behaviour by dynamic reorganization of functional cell groups in the hypothalamus.

b. **Bitzenhofer SH**, **Ahlbeck J**, Wolff A, Wiegert JS, **Gee CE**, **Oertner TG**, **Hanganu-Opatz IL** (2017): Layer-specific optogenetic activation of pyramidal neurons causes beta-gamma entrainment of neonatal networks. Nat Commun 2017 Feb 20,8:14563 doi: 10.1038/ncomms14563
https://www.ncbi.nlm.nih.gov/pubmed/28216627

Abstract:
Coordinated activity patterns in the developing brain may contribute to the wiring of neuronal circuits underlying future behavioural requirements. However, causal evidence for this hypothesis has been difficult to obtain owing to the absence of tools for selective manipulation of oscillations during early development. We established a protocol that combines optogenetics with electrophysiological recordings from neonatal mice in vivo to elucidate the substrate of early network oscillations in the prefrontal cortex. We show that light-induced activation of layer II/III pyramidal neurons that are transfected by in utero electroporation with a high-efficiency channelrhodopsin drives frequency-specific spiking and boosts network oscillations within beta-gamma frequency range. By contrast, activation of layer V/VI pyramidal neurons causes nonspecific network activation. Thus, entrainment of neonatal prefrontal networks in fast rhythms relies on the activation of layer II/III pyramidal neurons. This approach used here may be useful for further interrogation of developing circuits, and their behavioural readout.

c. **Gärtner M**, **Duvarci S**, **Roeper J**, **Schneider G** (2017): Detecting joint pausiness in parallel spike trains. Journal of Neuroscience Methods 285: pp. 69-81
https://www.ncbi.nlm.nih.gov/pubmed/28495371

Abstract:
BACKGROUND:
Transient periods with reduced neuronal discharge - called 'pauses' - have recently gained increasing attention. In dopamine neurons, pauses are considered important teaching signals, encoding negative reward prediction errors. Particularly simultaneous pauses are likely to have increased impact on information processing.
COMPARISON WITH EXISTING METHODS:
Available methods for detecting joint pausing analyze temporal overlap of pauses across spike trains. Such techniques are threshold dependent and can fail to identify joint pauses that are easily detectable by eye, particularly in spike trains with different firing rates.
NEW METHOD:
We introduce a new statistic called pausiness that measures the degree of synchronous pausing in spike train pairs and avoids threshold-dependent identification of specific pauses. A new graphic termed the cross-pauseogram compares the joint pausiness of two spike trains with its time shifted analogue, such that a (pausiness) peak indicates joint pausing. When assessing significance of pausiness peaks, we use a stochastic model with synchronous spikes to disentangle joint pausiness arising from synchronous spikes from additional 'joint excess pausiness' (JEP). Parameter estimates are obtained from auto- and cross-correlograms, and statistical significance is assessed by comparison to simulated cross-pauseograms.
RESULTS:
Our new method was applied to dopamine neuron pairs recorded in the ventral tegmental area of awake behaving mice. Significant JEP was detected in about 20% of the pairs.
CONCLUSION:
Given the neurophysiological importance of pauses and the fact that neurons integrate multiple inputs, our findings suggest that the analysis of JEP can reveal interesting aspects in the activity of simultaneously recorded neurons.

d. **Messer M**, Costa KM, **Roeper J**, **Schneider G** (2017): Multi-scale detection of rate changes in spike trains with weak dependencies. Journal of Computational Neuroscience 42:pp 187-201 DOI:10.007/s10827-016-0635-3
https://www.ncbi.nlm.nih.gov/pubmed/28025784

Abstract:
The statistical analysis of neuronal spike trains by models of point processes often relies on the assumption of constant process parameters. However, it is a well-known problem that the parameters of empirical spike trains can be highly variable, such as for example the firing rate. In order to test the null hypothesis of a constant rate and to estimate the change points, a Multiple Filter Test (MFT) and a corresponding algorithm (MFA) have been proposed that can be applied under the assumption of independent inter spike intervals (ISIs). As empirical spike trains often show weak dependencies in the correlation structure of ISIs, we extend the MFT here to point processes associated with short range dependencies. By specifically estimating serial dependencies in the test statistic, we show that the new MFT can be applied to a variety of empirical firing patterns, including positive and negative serial correlations as well as tonic and bursty firing. The new MFT is applied to a data set of empirical spike trains with serial correlations, and simulations show improved performance against methods that assume independence. In case of positive correlations, our new MFT is necessary to reduce the number of false positives, which can be highly enhanced when falsely assuming independence. For the frequent case of negative correlations, the new MFT shows an improved detection probability of change points and thus, also a higher potential of signal extraction from noisy spike trains.

e. Engwer C, Vorwerk J, Ludewig J, **Wolters CH** (2017): A discontinuous galerkin method to solve the EEg forward problem using the subtraction approach. SIAM J Sci Comput 39 No 1: pp B138-B164

Abstract:

In order to perform electroencephalography (EEG) source reconstruction, i.e., to localize the sources underlying a measured EEG, the electric potential distribution at the electrodes generated by a dipolar current source in the brain has to be simulated, which is the so-called EEG forward problem. To solve it accurately, it is necessary to apply numerical methods that are able to take the individual geometry and conductivity distribution of the subject's head into account. In this context, the finite element (FE) method (FEM) has shown high numerical accuracy with the possibility to model complex geometries and conductive features, e.g., white matter conductivity anisotropy. In this article, we introduce and analyze the application of a discontinuous Galerkin (DG) method, an FEM that includes features of the finite volume framework, to the EEG forward problem. The DG-FEM approach fulfills the conservation property of electric charge also in the discrete case, making it attractive for a variety of applications. Furthermore, as we show, this approach can alleviate modeling inaccuracies that might occur in head geometries when using classical FE methods, e.g., so called\skull leakage effects," which may occur in areas where the thickness of the skull is in the range of the mesh resolution. Therefore, we derive a DG formulation of the FEM subtraction approach for the EEG forward problem and present numerical results that highlight the advantageous features and the potential benefits of the proposed approach.

f. Pursiainen S, Lew S, **Wolters CH** (2017): Forward and inverse effects of the complete electrode model in neonatal EEG. J Neurophysiol 117:876-884
https://www.ncbi.nlm.nih.gov/pubmed/27852731

Abstract:

This paper investigates finite element method-based modeling in the context of neonatal electroencephalography (EEG). In particular, the focus lies on electrode boundary conditions. We compare the complete electrode model (CEM) with the point electrode model (PEM), which is the current standard in EEG. In the CEM, the voltage experienced by an electrode is modeled more realistically as the integral average of the potential distribution over its contact surface, whereas the PEM relies on a point value. Consequently, the CEM takes into account the subelectrode shunting currents, which are absent in the PEM. In this study, we aim to find out how the electrode voltage predicted by these two models differ, if standard size electrodes are attached to a head of a neonate. Additionally, we study voltages and voltage variation on electrode surfaces with two source locations: 1) next to the C6 electrode and 2) directly under the Fz electrode and the frontal fontanel. A realistic model of a neonatal head, including a skull with fontanels and sutures, is used. Based on the results, the forward simulation differences between CEM and PEM are in general small, but significant outliers can occur in the vicinity of the electrodes. The CEM can be considered as an integral part of the outer head model. The outcome of this study helps understanding volume conduction of neonatal EEG, since it enlightens the role of advanced skull and electrode modeling in forward and inverse computations.NEW & NOTEWORTHY The effect of the complete electrode model on lectroencephalography forward and inverse computations is explored. A realistic neonatal head model, including a skull structure with fontanels and sutures, is used. The electrode and skull modeling differences are analyzed and compared with each other. The results suggest that the complete electrode model can be considered as an integral part of the outer head model. To achieve optimal source localization results, accurate electrode modeling might be necessary.

g. Vorwerk J, Engwer C, Pursiainen S, **Wolters CH** (2017): A Mixed Finite Element Method to Solve the EEG Forward Problem. IEEE TRANSACTIONS ON MEDICAL IMAGING, Vol 36, No 4, April 2017
https://www.ncbi.nlm.nih.gov/pubmed/27831869
Abstract:
Finite element methods have been shown to achieve high accuracies in numerically solving the EEG forward problem and they enable the realistic modeling of complex geometries and important conductive features such as anisotropic conductivities. To date, most of the presented approaches rely on the same underlying formulation, the continuous Galerkin (CG)-FEM. In this article, a novel approach to solve the EEG forward problem based on a mixed finite element method (Mixed-FEM) is introduced. To obtain the Mixed-FEM formulation, the electric current is introduced as an additional unknown besides the electric potential. As a consequence of this derivation, the Mixed-FEM is, by construction, current preserving, in contrast to the CG-FEM. Consequently, a higher simulation accuracy can be achieved in certain scenarios, e.g., when the diameter of thin insulating structures, such as the skull, is in the range of the mesh resolution. A theoretical derivation of the Mixed-FEM approach for EEG forward simulations is presented, and the algorithms implemented for solving the resulting equation systems are described. Subsequently, first evaluations in both sphere and realistic head models are presented, and the results are compared to previously introduced CG-FEM approaches. Additional visualizations are shown to illustrate the current preserving property of the Mixed-FEM. Based on these results, it is concluded that the newly presented Mixed-FEM can at least complement and in some scenarios even outperform the established CG-FEM approaches, which motivates a further evaluation of the Mixed-FEM for applications in bioelectromagnetism.

h. Kirmse K, Huebner CA, Isbrandt D, Witte OW, Holthoff K (2017): GABAergic Transmission during Brain Development: Multiple Effects at Multiple Stages. Neuroscientist. 2017 Apr 1:1073858417701382. doi: 10.1177/1073858417701382
https://www.ncbi.nlm.nih.gov/pubmed/28378628
Abstract:
In recent years, considerable progress has been achieved in deciphering the cellular and network functions of GABAergic transmission in the intact developing brain. First, in vivo studies in non-mammalian and mammalian species confirmed the long-held assumption that GABA acts as a mainly depolarizing neurotransmitter at early developmental stages. At the same time, GABAergic transmission was shown to spatiotemporally constrain spontaneous cortical activity, whereas firm evidence for GABAergic excitation in vivo is currently missing. Second, there is a growing body of evidence indicating that depolarizing GABA may contribute to the activity-dependent refinement of neural circuits. Third, alterations in GABA actions have been causally linked to developmental brain disorders and identified as potential targets of timed prophylactic interventions. In this article, we review these major recent findings and argue that both depolarizing and inhibitory GABA actions may be crucial for physiological brain maturation.

3) Poster

a. **Gärtner M, Duvarci S, Roeper J, Schneider G**. Detecting joint pausiness in parallel spike trains. CNS 2017 Antwerpen

b. **Gärtner M, Duvarci S, Roeper J, Schneider G**. Joint pausiness in parallel spike trains. 12th Göttingen Meeting of the German Neuroscience Society

4) Workshop

Mini-workshop on Electric Stimulation - From Signal Output to Analyses; June 23, 24 2017 (Friday/Saturday), University of Lübeck

Participating troikas:

• Individualized closed-up transcranial alternating current stimulation - (Till Schneider, Carsten Wolters, Christoph Herrmann)

• Interareal phase coherence as a mechanism for attention-dependent neuronal signal routing: A model-guided causal analysis using new, multi-contact floating silicon probes for intracortical chronic stimulation and recording in primates - (Andreas Kreiter, Walter Lang, Udo Ernst)

• Weak electric current stimulation and optogenetics to investigate sleep-dependent memory consolidation and ensemble reactivation (Lisa Marshall, Achim Schweikard, Alexey Ponomarenko)

• Causative Mechanisms of Mesoscopic Activity Patterns in Auditory Category Discrimination - (Frank Ohl, Bertram Schmidt, Sonja Grün)

Summary:

Four troikas participated in a constructive mini-workshop aimed to interact on experimental setups, protocols and analyses with a focus on electric stimulation procedures, handling stimulation artefacts, and closed-loop stimulation methods in humans and non-human laboratory animals. The first day consisted of 8 scheduled presentations ranging from basic physics related to applied currents to presentations of preliminary data. In depth open discussions arose spontaneously. The basic motto being, to give a short background, give an insight into present research which leads into the questions or message intended for the consortium. After a short summary Saturday morning topics were inter- as well as intra-troika discussions in smaller circles were. It was an opportunity not only to obtain an insight into closely related research with its caveats and solutions, but also to establish new collaborations.

5) Activities

a. **Inter Troika Meeting Herrmann/ Schneider/ Wolters**, 6th – 7th April 2017 in Münster, including the workshop "Theory and praxis for simulation of transcranial electric stimulation (tES) using SimBio with outlook to DUNEuro" on the second day of the meeting.

b. **Common teaching project of the Troika Roeper, Duvarci, Sigurdsson**, Schneider during the SS2017: Punktprozessmodelle in der Neurophysiologie (http://www.math.uni-frankfurt.de/~schneide/StatPrakt17.html)

6) Exchange Fellowship

Sebastian Bitzenhofer from the lab of Ileana Hanganu-Opatz (Hamburg) visited the lab of György Buzsáki (New York University) for two weeks in March 2017 in exchange of the SPP1665 and the IPAN PIRE program. During the stay, he was trained in the application of new optoelectrodes using on-board diodes with waveguides, or micro-LEDs to achieve local control of opsin-expressing neurons in head-fixed awake mice. These techniques will be applied in the context of the current SPP1665 project of the troika to elucidate the cellular mechanisms that underlie coordinated neuronal activity within developing hippocampal-prefrontal networks, and to uncover their importance for the maturation of cognitive abilities.

7) Upcoming events

Events 2017/ 2018			
Date	**Place**	**Event**	**Organization**
June 4th – 6th, 2018	***Mainz***	***Experimental Workshop***	***Albrecht Stroh***
June 7th – 9th, 2018	***Frankfurt***	***Analytical Workshop***	***Gaby Schneider, Torfi Sigurdsson, Jochen Triesch (SPP 2024)***
July 6th, 2018	***Berlin***	***Satellite Symposium***	***Ileana Hanganu-Opatz in cooperation with Jochen Triesch (SPP 2024) and Alexander Gottschalk (SPP 1926)***

Next newsletter to be expected in December 2017