SPP 1665:

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

Newsletter, seventh edition, Dezember 2017

1) Publications

a. Schwalm M, Schmid F, Wachsmuth L, Backhaus H, Kronfeld A, Aedo Jury F, Prouvot PH, Fois C, Albers F, van Alst T, Faber C, **Stroh A** (2017): Cortex-wide BOLD fMRI activity reflects locally-recorded slow oscillation-associated calcium waves. Elife 2017 Sep 15;6.
https://www.ncbi.nlm.nih.gov/pubmed/28914607
Abstract:
Spontaneous slow oscillation-associated slow wave activity represents an internally generated state which is characterized by alternations of network quiescence and stereotypical episodes of neuronal activity - slow wave events. However, it remains unclear which macroscopic signal is related to these active periods of the slow wave rhythm. We used optic fiber-based calcium recordings of local neural populations in cortex and thalamus to detect neurophysiologically defined slow calcium waves in isoflurane anesthetized rats. The individual slow wave events were used for an event-related analysis of simultaneously acquired whole-brain BOLD fMRI. We identified BOLD responses directly related to onsets of slow calcium waves, revealing a cortex-wide BOLD correlate: the entire cortex was engaged in this specific type of slow wave activity. These findings demonstrate a direct relation of defined neurophysiological events to a specific BOLD activity pattern and were confirmed for ongoing slow wave activity by independent component and seed-based analyses.

b. Rahmati V, **Kirmse K**, **Holthoff K**, Schwabe L, **Kiebel SJ** (2017): Developmental Emergence of Sparse Coding: A Dynamic Systems Approach. Sci Rep 7:13015
https://www.ncbi.nlm.nih.gov/pubmed/29026183
Abstract:
During neocortical development, network activity undergoes a dramatic transition from largely synchronized, so-called cluster activity, to a relatively sparse pattern around the time of eye-opening in rodents. Biophysical mechanisms underlying this sparsification phenomenon remain poorly understood. Here, we present a dynamic systems modeling study of a developing neural network that provides the first mechanistic insights into sparsification. We find that the rest state of immature networks is strongly affected by the dynamics of a transient, unstable state hidden in their firing activities, allowing these networks to either be silent or generate large cluster activity. We address how, and which, specific developmental changes in neuronal and synaptic parameters drive sparsification. We also reveal how these changes refine the information processing capabilities of an in vivo developing network, mainly by showing a developmental reduction in the instability of network's firing activity, an effective availability of inhibition-stabilized states, and an emergence of spontaneous attractors and state transition mechanisms. Furthermore, we demonstrate the key role of GABAergic transmission and depressing glutamatergic synapses in governing the spatiotemporal evolution of cluster activity. These results, by providing a strong link between experimental observations and model behavior, suggest how adult sparse coding networks may emerge developmentally.

c. **Bitzenhofer SJ**, **Ahlbeck J**, Wolff A, Wiegert JS, **Gee CE**, **Oertner TG**, **Hanganu-Opatz IL** (2017): Methodological Approach for Optogenetic Manipulation of Neonatal Neuronal Networks. Front Cell Neurosci 2017 Aug 14;11:239
https://www.ncbi.nlm.nih.gov/pubmed/28848399
Abstract:
Coordinated patterns of electrical activity are critical for the functional maturation of neuronal networks, yet their interrogation has proven difficult in the developing brain. Optogenetic manipulations strongly contributed to the mechanistic understanding of network activation in the adult brain, but difficulties to specifically and reliably express opsins at neonatal age hampered similar interrogation of developing circuits. Here, we introduce a protocol that enables to control the activity of specific neuronal populations by light, starting from early postnatal development. We show that brain area-, layer- and cell type-specific expression of opsins by in utero electroporation (IUE), as exemplified for the medial prefrontal cortex (PFC) and hippocampus (HP), permits the manipulation of neuronal activity in vitro and in vivo. Both individual and population responses to different patterns of light stimulation are monitored by extracellular multi-site recordings in the medial PFC of neonatal mice. The expression of opsins via IUE provides a flexible approach to disentangle the cellular mechanism underlying early rhythmic network activity, and to elucidate the role of early neuronal activity for brain maturation, as well as its contribution to neurodevelopmental disorders.

d. Baltus A, **Wagner S**, **Wolters CH**, **Herrmann CS** (2017): Optimized auditory transcranial alternating current stimulation improves individual auditory temporal resolution. Brain Stimulation 2017 Vol 10 Iss 6
http://www.sciencedirect.com/science/article/pii/S1935861X17309415?via%3Dihub
Abstract:
Background
Temporal resolution of cortical, auditory processing mechanisms is suggested to be linked to peak frequency of neuronal gamma oscillations in auditory cortex areas (individual gamma frequency, IGF): Individuals with higher IGF tend to have better temporal resolution.
Hypothesis
Modulating ongoing gamma activity with transcranial alternating current stimulation (tACS) is expected to improve performance in gap detection (GD) tasks (shorter GD thresholds) if the frequency is higher and to decrease GD performance (longer GD thresholds) if the frequency is lower than IGF.
Methods
For 26 healthy participants the IGF and temporal resolution were identified using an auditory steady state response (ASSR) paradigm and a between-channel GD task. Finite element modelling was used to generate an optimized tACS electrode montage (one channel per hemisphere: FC5-TP7/P7 and FC6-TP8/P8). Afterwards, GD thresholds were examined during tACS (tACS frequency group A: above IGF, tACS frequency group B: below IGF). Relative changes of GD thresholds were compared between groups. Additionally, effects of tACS on oscillatory activity were investigated comparing relative changes of ASSR amplitudes before and after stimulation.
Results
Performance of group-A-participants improved significantly during tACS in comparison to performance of group-B-participants. Significant relative changes of ASSR amplitudes were found in both groups.
Conclusion
The possibility to improve gap detection with individualized stimulation protocols for tACS further supports the link between oscillatory activity and temporal resolution, whereby the improvement of temporal resolution is particularly relevant for the clinical aspect of auditory tACS.

e. Pursiainen S, **Agsten B**, **Wagner S**, **Wolters CH** (2017). Advanced boundary electrode modeling for tES and parallel tES/EEG. IEEE Trans Neural Syst Rehabil Eng 2017 Sep28
https://www.ncbi.nlm.nih.gov/pubmed/28961118
Abstract:
This paper explores advanced electrode modeling in the context of separate and parallel transcranial electrical stimulation (tES) and electroencephalography (EEG) measurements.We focus on boundary condition based approaches that do not necessitate adding auxiliary elements, e.g. sponges, to the computational domain. In particular, we investigate the complete electrode model (CEM) which incorporates a detailed description of the skin-electrode interface including its contact surface, impedance and normal current distribution. The CEM can be applied for both tES and EEG electrodes which is advantageous when a parallel system is used. In comparison to the CEM, we test two important reduced approaches: the gap model (GAP) and the point electrode model (PEM). We aim to find out the differences of these approaches for a realistic numerical setting based on the stimulation of the auditory cortex. The results obtained suggest, among other things, that GAP and GAP/PEM are sufficiently accurate for the practical application of tES and parallel tES/EEG, respectively. Differences between CEM and GAP were observed mainly in the skin compartment, where only CEM explains the heating effects characteristic to tES.

f. **Albert S**, **Messer M**, Schiemann J, **Roeper J**, **Schneider G** (2017). Multi-scale detection of variance changes in renewal processes in the presence of rate change points. Journal of Time Series Analysis Nov 2017 Vol 38 Iss 6
http://onlinelibrary.wiley.com/doi/10.1111/jtsa.12254/full
Abstract:
Non-stationarity of the rate or variance of events is a well-known problem in the description and analysis of time series of events, such as neuronal spike trains. A multiple filter test (MFT) for rate homogeneity has been proposed earlier that detects change points on multiple time scales simultaneously. It is based on a filtered derivative approach, and the rejection threshold derives from a Gaussian limit process L which is independent of the point process parameters.
Here, we extend the MFT to variance homogeneity of life times. When the rate is constant, the MFT extends directly to the null hypothesis of constant variance. In the presence of rate change points, we propose to incorporate estimates of these in the test for variance homogeneity, using an adaptation of the test statistic. The resulting limit process shows slight deviations from L that depend on unknown process parameters. However, these deviations are small and do not considerably change the properties of the statistical test. This allows practical application, for example, to neuronal spike trains, which indicates various profiles of rate and variance change points.

g. **Messer M**, **Albert S**, Plomer S, **Schneider G** (2017). MFT: The Multiple Filter Test for Change Point Detection (R package version 1.3).
https://rdrr.io/cran/MFT/

h. Kasten FH, **Herrmann CS** (2017). Transcranial Alternating Current Stimulation (tACS) Enhances Mental Rotation Performance during and after Stimulation. Frontiers in Human Neuroscience 11:2; 2017
https://www.ncbi.nlm.nih.gov/pubmed/28197084

Abstract

Transcranial alternating current stimulation (tACS) has been repeatedly demonstrated to modulate endogenous brain oscillations in a frequency specific manner. Thus, it is a promising tool to uncover causal relationships between brain oscillations and behavior or perception. While tACS has been shown to elicit a physiological aftereffect for up to 70 min, it remains unclear whether the effect can still be elicited if subjects perform a complex task interacting with the stimulated frequency band. In addition, it has not yet been investigated whether the aftereffect is behaviorally relevant. In the current experiment, participants performed a Shepard-like mental rotation task for 80 min. After 10 min of baseline measurement, participants received either 20 min of tACS at their individual alpha frequency (IAF) or sham stimulation (30 s tACS in the beginning of the stimulation period). Afterwards another 50 min of post-stimulation EEG were recorded. Task performance and EEG were acquired during the whole experiment. While there were no effects of tACS on reaction times or event-related-potentials (ERPs), results revealed an increase in mental rotation performance in the stimulation group as compared to sham both during and after stimulation. This was accompanied by increased ongoing alpha power and coherence as well as event-related-desynchronization (ERD) in the alpha band in the stimulation group. The current study demonstrates a behavioral and physiological aftereffect of tACS in parallel. This indicates that it is possible to elicit aftereffects of tACS during tasks interacting with the alpha band. Therefore, the tACS aftereffect is suitable to achieve an experimental manipulation.

i. **Stecher HI**, Pollok TM, Strüber D, Sobotka F, **Herrmann CS** (2017). Ten Minutes of α-tACS and Ambient Illumination Independently Modulate EEG α-Power. Frontiers in Human Neuroscience 11:257, 2017.
   https://www.ncbi.nlm.nih.gov/pubmed/28572761

Abstract

Transcranial alternating current stimulation (tACS) sees increased use in neurosciences as a tool for the exploration of brain oscillations. It has been shown that tACS stimulation in specific frequency bands can result in aftereffects of modulated oscillatory brain activity that persist after the stimulation has ended. The general relationship between persistency of the effect and duration of stimulation is sparsely investigated but previous research has shown that the occurrence of tACS aftereffects depends on the brain state before and during stimulation. Early alpha neurofeedback research suggests that particularly in the alpha band the responsiveness to a manipulation depends on the ambient illumination during measurement. Therefore, in the present study we assessed the brain's susceptibility to tACS at the individual alpha frequency during darkness compared to ambient illumination. We measured alpha power after 10 min of stimulation in 30 participants while they continuously performed a visual vigilance task. Our results show that immediately after stimulation, the alpha power in the illumination condition for both the stimulated and sham group has increased by only about 7%, compared to about 20% in both groups in the 'dark' condition. For the group that did not receive stimulation, the power in darkness remained stable after stimulation, whereas the power in light increased by an additional 10% during the next 30 min. For the group that did receive stimulation, alpha power during these 30 min increased by another 11% in light and 22% in darkness. Since alpha power already increased by about 10% without stimulation, the effect of illumination does not seem to have interacted with the effect of stimulation. Instead, both effects seem to have added up linearly. Although our findings do not show that illumination-induced differences in oscillatory activity influence the susceptibility toward tACS, they stress the importance of controlling for factors like ambient light that might add an independent increase or decrease to the power of brain oscillations during periods, where possible persistent effects of stimulation are explored.

k. Dreyer A, **Herrmann CS**, Rieger JW (2017). Tradeoff between User Experience and BCI Classification Accuracy with Frequency Modulated Steady-State Visual Evoked Potentials. Frontiers in Human Neuroscience 11:391, 2017
https://www.ncbi.nlm.nih.gov/pubmed/28798676
Abstract
Steady-state visual evoked potentials (SSVEPs) have been widely employed for the control of brain-computer interfaces (BCIs) because they are very robust, lead to high performance, and allow for a high number of commands. However, such flickering stimuli often also cause user discomfort and fatigue, especially when several light sources are used simultaneously. Different variations of SSVEP driving signals have been proposed to increase user comfort. Here, we investigate the suitability of frequency modulation of a high frequency carrier for SSVEP-BCIs. We compared BCI performance and user experience between frequency modulated (FM) and traditional sinusoidal (SIN) SSVEPs in an offline classification paradigm with four independently flickering light-emitting diodes which were overtly attended (fixated). While classification performance was slightly reduced with the FM stimuli, the user comfort was significantly increased. Comparing the SSVEPs for covert attention to the stimuli (without fixation) was not possible, as no reliable SSVEPs were evoked. Our results reveal that several, simultaneously flickering, light emitting diodes can be used to generate FM-SSVEPs with different frequencies and the resulting occipital electroencephalography (EEG) signals can be classified with high accuracy. While the performance we report could be further improved with adjusted stimuli and algorithms, we argue that the increased comfort is an important result and suggest the use of FM stimuli for future SSVEP-BCI applications.

l. **Herrmann CS**, Strüber D (2017). What Can Transcranial Alternating Current Stimulation Tell Us About Brain Oscillations? Current Behavioral Neuroscience Reports 4:128-137, 2017
https://link.springer.com/article/10.1007/s40473-017-0114-9
Abstract
Purpose of the Review
Transcranial alternating current stimulation (tACS) allows to interfere with oscillatory brain activity. Here, we provide an overview of novel approaches for removing the tACS artefact to elucidate the mechanisms responsible for on-line tACS effects. Furthermore, we review recent findings on tACS after-effects and clinical applications.
Recent Findings
tACS-induced entrainment of alpha oscillations was demonstrated in on-line electroencephalography (EEG) and magnetoencephalography (MEG) recordings. On-line effects have also been revealed by innovative tACS protocols utilizing amplitude modulation, cross-frequency coupling, non-sinusoidal waveforms, and non-electrical physiological measures. tACS after-effects on alpha power exceeding 1-h duration have been reported, and a behavioral relevance of these physiological changes was shown for the first time.
Summary
Our understanding of tACS on-line effects greatly benefited from new artefact removal approaches. After-effects of varying duration have been consistently reported but the underlying mechanism is still unclear. tACS as a neurotherapeutic is only emerging, but first evidence for successful tACS interventions in neuropsychiatric and neurological disorders is encouraging.

m. Douglass AM, Kucukdereli H, Ponserre M, Markovic M, Gründemann J, Strobel C, Alcala Morales PL, **Conzelmann KK**, Lüthi A, **Klein R** (2017). Central amygdala circuits modulate food consumption through a positive-valence mechanism. Nature neuroscience 2017 Oct; 20(10):1384-1394 https://www.ncbi.nlm.nih.gov/pubmed/28825719

Abstract

The complex behaviors underlying reward seeking and consumption are integral to organism survival. The hypothalamus and mesolimbic dopamine system are key mediators of these behaviors, yet regulation of appetitive and consummatory behaviors outside of these regions is poorly understood. The central nucleus of the amygdala (CeA) has been implicated in feeding and reward, but the neurons and circuit mechanisms that positively regulate these behaviors remain unclear. Here, we defined the neuronal mechanisms by which CeA neurons promote food consumption. Using in vivo activity manipulations and Ca2+ imaging in mice, we found that GABAergic serotonin receptor 2a (Htr2a)-expressing CeA neurons modulate food consumption, promote positive reinforcement and are active in vivo during eating. We demonstrated electrophysiologically, anatomically and behaviorally that intra-CeA and long-range circuit mechanisms underlie these behaviors. Finally, we showed that CeAHtr2a neurons receive inputs from feeding-relevant brain regions. Our results illustrate how defined CeA neural circuits positively regulate food consumption.

n. Wietek J, Rodriguez-Rozada S, Tutas J, Tenedini F, Grimm C, **Oertner TG**, Soba P, **Hegemann P**, Wiegert JS (2017). Anion-conducting channelrhodopsins with tuned spectra and modified kinetics engineered for optogenetic manipulation of behavior. Scientific Reports 2017 Nov 2;7(1):14957 https://www.ncbi.nlm.nih.gov/pubmed/29097684

Abstract

Genetic engineering of natural light-gated ion channels has proven a powerful way to generate optogenetic tools for a wide variety of applications. In recent years, blue-light activated engineered anion-conducting channelrhodopsins (eACRs) have been developed, improved, and were successfully applied in vivo. We asked whether the approaches used to create eACRs can be transferred to other well-characterized cation-conducting channelrhodopsins (CCRs) to obtain eACRs with a broad spectrum of biophysical properties. We generated 22 variants using two conversion strategies applied to 11 CCRs and screened them for membrane expression, photocurrents and anion selectivity. We obtained two novel eACRs, Phobos and Aurora, with blue- and red-shifted action spectra and photocurrents similar to existing eACRs. Furthermore, step-function mutations greatly enhanced the cellular operational light sensitivity due to a slowed-down photocycle. These bi-stable eACRs can be reversibly toggled between open and closed states with brief light pulses of different wavelengths. All new eACRs reliably inhibited action potential firing in pyramidal CA1 neurons. In Drosophila larvae, eACRs conveyed robust and specific light-dependent inhibition of locomotion and nociception.

o. Korotkova T, **Ponomarenko A**, Monaghan CK, Poulter SL, Cacucci F, Wills T, Hasselmo ME, Lever C (2017). Reconciling the different faces of hippocampal theta: the role of theta oscillations in cognitive, emotional and innate behaviors. Neuroscience Biobehavior Revue SO149-7634(17),30084-2. https://www.ncbi.nlm.nih.gov/pubmed/28887226

Abstract

The theta oscillation (5-10Hz) is a prominent behavior-specific brain rhythm. This review summarizes studies showing the multifaceted role of theta rhythm in cognitive functions, including spatial coding, time coding and memory, exploratory locomotion and anxiety-related behaviors. We describe how activity of hippocampal theta rhythm generators - medial septum, nucleus incertus and entorhinal cortex, links theta with specific behaviors. We review evidence for functions of the theta-rhythmic signaling to subcortical targets, including lateral septum. Further, we describe functional associations of theta oscillation properties - phase, frequency and amplitude - with memory, locomotion and anxiety, and outline how manipulations of these features, using optogenetics or pharmacology, affect associative and innate behaviors. We discuss work linking cognition to the slope of the theta frequency to running speed regression, and emotion-sensitivity (anxiolysis) to its y-intercept. Finally, we describe parallel emergence of theta oscillations, theta-mediated neuronal activity and behaviors during development. This review highlights a complex interplay of neuronal circuits and synchronization features, which enables an adaptive regulation of multiple behaviors by theta-rhythmic signaling.

2) Poster

a) Farassat N, Costa KM, **Albert S**, Somayaji M, **Schneider G**, **Roeper J**. Differences in phasic activity in vivo revealed by axonal projection-specific characterization of DA neurons within the medial substantia nigra. SfN 2017

b) **Duvarci S**, Simpson EH, **Schneider G**, Kandel ER, **Roeper J**, **Sigurdsson T**. Impaired task-related firing and long-range 4 Hz synchrony of dopamine neurons underlies working memory deficits in a mouse model of cognitive dysfunction. SfN 2017

3) Awards

a) **Franziska Bender** from Alexander Ponomarenko Group received two travel awards, from FENS and from the FMP-Institute Graduate School to present her supported by the SPP studies at SfN 2017 and at FENS-FRM meeting in Pecs, Hungary

b) **Marta Carus-Cadavieco**, also from the Alexander Ponomarenko Group, received the Junior Brain Price by the Lundbeck Foundation for her SPP supported work

4) Lab rotation

a) From November 6 - 10 2017, **Jan-Ole Radecke**, a member of the workgroup of Till Schneider (Hamburg) visited the workgroup of Carsten Wolters (Münster) to exchange information on methodological aspects of transcranial electrical stimulation (tES).

One focus of the lab visit was the preparation of realistic multicompartment finite-element head models based on the segmentation of individual brain volumes. Realistic head models can be of use in the modeling of current flow through the brain. Another application-related focus of the lab visit was the optimization of electrode positioning for tES. Thereby, a defined functional brain area can be stimulated with an increased precision, in order to facilitate potential effects of tES.

The results of the lab visit are now integrated into the experimental framework of current projects in Hamburg to examine the role of oscillatory brain activity during attention tasks.

5) Upcoming events

Events 2018			
Date	**Place**	**Event**	**Organization**
June 4th – 6th, 2018 ***June 7th – 9th, 2018***	***Mainz*** ***Frankfurt***	***Experimental Workshop*** ***Analytical Workshop***	***Albrecht Stroh*** ***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 July 2018

Seasonal greetings to everyone and

a Happy New Year 2018!

Best wishes

Ileana and Kathrin