UNIVERSITÄT
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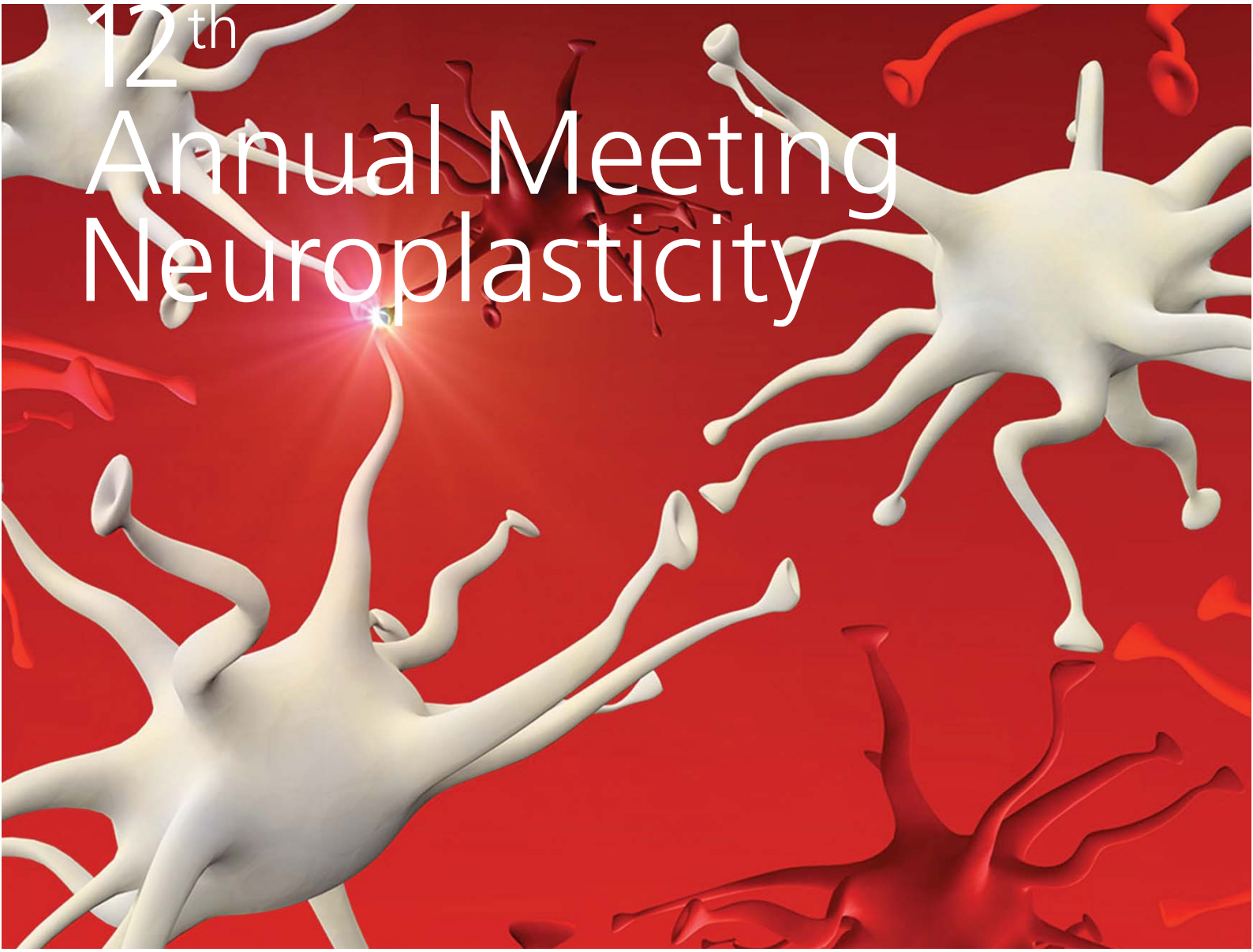
Clinical Neuroscience Bern

Friday, 8th of September 2017, 9.00 – 17.45
Inselspital, Auditorium Ettore Rossi, Kinderklinik
Entrance 31b

12th Annual Meeting Neuroplasticity



Program 12th Annual Meeting
Clinical Neuroscience Bern

«Neuroplasticity»
Friday, 8th of September 2017, 9.00 – 17.45
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08.00 – 09.00	Registration and Poster Setup
09.00 – 09.15	**Welcome addresses** Hans-Uwe Simon, Dean Faculty of Medicine Claudio Bassetti, for the CNB Strategic Board
09.15 – 10.00	**Key-note 1** *The plastic human brain: specialisation of the specialists* Lutz Jäncke, Department of Psychology, University of Zurich Chair: Sebastian Walther
10.00 – 10.30	Coffee break
10.30 – 11.30	**Short talks, 4 selected abstracts à 10 minutes** Chair: Sebastian Walther
11.30 – 12.15	**Key-note 2** *Journey through the development of neuroprosthetic technologies to restore leg motor control after spinal cord injury* Grégoire Courtine, Center for Neuroprosthetics and Brain Mind Institute, EPFL Chair: Tobias Nef
12.15 – 13.45	**Poster Session + Lunch**

13.45 – 14.45	**Parallel symposium I** *Gestural and fine motor deficits across neuropsychiatric disorders* Chair: Stephan Bohlhalter & Sebastian Walther Auditorium Ettore Rossi	**Parallel symposium II** *Regenerative neuroscience* Chair: Volker Enzmann Dermatologie Hörsaal B113
14.45 – 15.15	**Coffee break**	
15.15 – 16.15	**Parallel symposium III** *Promoting neuronal plasticity in neuropsychiatric disorder* Chair: Stefan Klöppel & Christoph Nissen Auditorium Ettore Rossi	**Parallel symposium IV** *Neuroinflammatory diseases* Chair: Anna Oevermann Dermatologie Hörsaal B113
16.30 – 16.45	**Poster awards + closing remarks** – Clinical research – Basic research animal – Basic research human Chair: Sebastian Walther	
16.45 – 17.45	**CNB Group leader's meeting** on special invitation only Chair: Tobias Nef	
17.45	**End of Meeting**	

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Key-Note Lecture 1

The plastic human brain: specialisation of the specialists

Prof. Lutz Jäncke

University Zurich, Department of Neuropsychology, University Research Priority Program "Dynamic of Healthy Aging"

The advent of modern brain imaging methods enabled the study of cortical and subcortical plasticity in healthy human subjects. The availability of this technique has boosted plasticity research in the last 20 years. Thus, the study of cortical plasticity in the human brain is one of the most challenging undertakings of current neuroscience research. In principle, three different approaches to studying plastic processes are possible: (1) the cross-sectional approach in which experts and non-experts are compared with respect to anatomical or functional brain measures. This approach has been widely used and has provided many interesting findings. But the basic caveat with it is that the uncovered differences are simply correlational, thus meriting caution in drawing overly strong causal inferences from the data. (2) Short-term longitudinal studies in which subjects have undergone a specific training intervention. These studies are typically designed according to a pre-post design and the subjects are enrolled in training programs lasting several hours to several months. (3) Long-term longitudinal studies in which subjects have undergone a longer (at least year-long) training. In my presentation, I will summarize the findings of cross-sectional and longitudinal research on cortical plasticity as uncovered in my lab, placing greater emphasis on structural and functional plasticity in one specific expert group, namely musicians. In addition, I will also demonstrate that due to the experience-related influences, the human brain is highly individual even in terms of brain anatomical features.

Key-Note Lecture 2

Neuroprosthetic technologies to restore leg motor control after spinal cord injury

Fabien Wagner

Center for Neuroprosthetics and Brain Mind Institute, School of Life Sciences, Swiss Federal Institute of Technology (EPFL)

Over the past decade, we have developed a multipronged intervention that restored supraspinal control over leg movements in animal models of spinal cord injury. The intervention acts over two time scales. Immediately, electrochemical neuromodulation of spinal circuits enables motor control of the paralyzed legs. In the long term, will-powered training regimens enabled by electrochemical neuromodulation and robotic assistance promote neuroplasticity of residual connections — an extensive rewiring that reestablishes voluntary control of movement. To identify the physiological principles underlying the therapeutic effects of this intervention, we used computational modelling, inactivation techniques and genetic manipulations. We found that our electrochemical neuromodulation therapy enables motor control through the modulation of proprioceptive feedback circuits. This framework steered the design of spatially selective spinal implants that specifically target these circuits to modulate muscle synergies responsible for flexion and extension of the legs. To reproduce the natural activation pattern of these muscle synergies during locomotion, we interfaced the leg motor cortex activity with the electrochemical neuromodulation of the spinal cord. This wireless brain-spine interface instantly restored robust locomotor movements of a paralyzed leg in a non-human primate model of spinal cord injury. Preliminary clinical studies suggest that these concepts and technologies are directly translatable to therapeutic strategies to augment motor recovery after spinal cord injury in humans.

Short talk abstracts

Clinical research

Effects of Parkinson's disease and subsequent dopaminergic therapy on lateralization of the motor network

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Movements are known to recruit primarily contralateral cortical regions, contralateral basal ganglia and ipsilateral cerebellum, leading to highly asymmetric activations as observed through fMRI. An increase in symmetry of motor activation has been reported in healthy aging (Naccarto, 2006; Wu, 2005), following unilateral brain lesions and stroke (Carr, 1993; Guzzetta, 2007; Rehme, 2011a; Shimizu, 2002), and in drug-naïve Parkinson's disease (Wu, 2015). We used fMRI to study motor activations in long-term Parkinson's disease (PD) patients as well as in healthy subjects during unilateral upper and lower limb movements. Ten right-handed, left side symptom-dominant PD patients (5 female) were tested once after their usual dopaminergic medication - 'ON' state - and in a separate session, after withdrawal of medication - 'OFF' state. Eighteen right-handed age-matched healthy controls (HC) were scanned in a single session. We estimated activation laterality in three cortical regions of interest - the primary motor cortex (M1), the supplementary motor area (SMA) and the premotor cortex (PMC), during each of the four movement conditions - right hand, left hand, right foot and left foot movement. Laterality was significantly decreased in PD ON as compared to HC in M1 during left hand and left foot movements, as well as in PD ON and PD OFF as compared to HC in the PMC during left hand movements. We sought to investigate the functional reorganization underlying these lateralization changes by estimating the effective connectivity between ROIs using dynamic causal modelling (DCM). We considered a model space of 12 models divided into two families according to whether movement-associated changes in effective connectivity (DCM.B matrix) were symmetrical or lateralized to the side contralateral to the movement. We used Bayesian model selection to conduct family-level inference on the lateralized versus symmetrical families within each group of subjects. The winning family for both PD OFF and PD ON was the symmetrical model family (PD OFF: exceedance probability of 0.65, PD ON: exceedance probability of 0.853) whereas in HC, the two families were almost tied (exceedance probability of 0.496 vs. 0.504, for lateralized vs. symmetrical families). These results suggest that PD results in increased involvement of structures ipsilateral to movement side, which becomes manifest as decreased activation laterality. In conclusion, our results offer a more complete picture of functional cortical reorganization associated with long-term Parkinson's disease and its interaction with dopaminergic medication.

Keywords: Parkinson's disease, functional magnetic resonance imaging, laterality index, dynamic causal modelling, cortical reorganization

Short talk abstracts

Basic research animal

Potent and selective endocannabinoid reuptake inhibitors (SERIs) to treat neuropsychiatric disorders

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Selective endocannabinoid reuptake inhibitors (SERIs) represent a new class of modulators of the endocannabinoid system (ECS) which are potentially more effective and safer than other cannabinoid drugs. Unlike the covalent inhibitors of endocannabinoid (EC) degrading enzymes (e.g., FAAH, MAGL), SERIs can modulate EC actions in a time- and space-restricted manner, thus potentially avoiding broad effects. Recently, we reported the identification of the first SERI prototype (WOBE437) and its biological and pharmacological characterization in vitro and in vivo (Chicca et al., 2017). WOBE437 inhibited anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) uptake in different cell types with nanomolar potency and high selectivity towards all the other components of the ECS. Using a radiolabeled 14C-WOBE437 analog, we showed that the molecule only marginally penetrates into the cytosol and hits a saturable membrane target. In vivo, WOBE437 behaved as an "indirect CB1-agonist" showing pronounced anti-inflammatory, analgesic and anxiolytic effects in mice lacking the high-dose anxiogenic effects seen with direct agonists of CB1 receptors. WOBE437 underwent a preliminary safety screen against a panel of several CNS-related targets and metabolic stability tests using human and liver microsomes. It showed a potentially good bioavailability and brain penetration upon oral administration in mice. Intriguingly, WOBE437 robustly and specifically modulated EC levels in the brain, primarily increasing 2-AG. Over 7 days of treatment, WOBE437 induced a moderate but significant 1.5 times rise of both AEA and 2-AG compared to vehicle, without triggering a loss of functional CB1 receptors in the brain (desensitization). In pharmacological experiments, the time-dependent distribution of WOBE437 was quantified and correlated to its effects on different metabolites. Using LC-MS/MS and targeted lipidomics, we showed that WOBE437 specifically modulate AEA and 2-AG levels in mice and ex vivo in human whole blood. This effect is in agreement with the potent anti-endotoxemia, anti-inflammatory, analgesic and anxiolytic effects of WOBE437 in mice. Interestingly, EC reuptake inhibitors significantly raise corticosterone levels upon repetitive treatment in mice. In conclusion, WOBE437 and other SERIs may represent a promising and innovative therapeutic strategy to treat neuropsychiatric disorders, in particular characterized by low EC levels and hypocortisolism. Although stress conditions, anxiety related disorders and depression are generally associated with higher cortisol levels, a growing amount of clinical evidence indicate that in certain forms of chronic stress, PTSDs, depression and in the "burnout syndrome", cortisol levels are significantly lower as compared to normal conditions (Yehuda et al., 2011 Lennartsson et al., 2015).

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Keywords: endocannabinoid system; anandamide; 2-arachidonoyl glycerol; endocannabinoid reuptake; inhibitor; anxiety

Absence of the Junctional Adhesion Molecule (JAM)-B Ameliorates Experimental Autoimmune Encephalomyelitis

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In multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE) autoaggressive CD4+ T cells cross the blood-brain barrier (BBB) and cause neuroinflammation. Therapeutic targeting of CD4+ T-cell trafficking into the central nervous system (CNS) using the humanized anti-a4-integrin antibody natalizumab has proven beneficial for the treatment of MS, however comes with the risk of progressive multifocal leukoencephalopathy, probably caused by inhibition of CD8+ T cell entry into the CNS. We have recently shown that CD8+ T cell indeed employ a4b1-integrins to migrate across the BBB. Besides vascular cell adhesion molecule - 1 (VCAM-1) we identified junctional adhesion molecule -B (JAM-B) localized in BBB tight junctions as alternative vascular a4b1-integrin ligand mediating CD8-T cell trafficking across the BBB. Using a novel transgenic mouse model with constitutive lack of JAM-B we here investigated the role of JAM-B in mediating T-cell trafficking into the CNS during EAE. Although JAM-B-/- C57BL/6 mice developed ameliorated EAE when compared to wild-type littermates, we found higher numbers of infiltrating immune cells in the CNS of JAM-B-/- C57BL/6 mice suffering from EAE. The majority of inflammatory cells was trapped behind the BBB in leptomeningeal and perivascular spaces. This suggests that although JAM-B is not required for T-cell diapedesis across the BBB absence of JAM-B limits inflammatory cell entry into the CNS parenchyma. The signalling events downstream of vascular JAM-B leading to amelioration of EAE are presently investigated.

Keywords: experimental autoimmune encephalomyelitis, tight junction, blood brain barrier

Short talk abstracts

Basic research human

Bilateral temporal tDCS enhances sleep-dependent episodic memory consolidation

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Introduction: Human sleep and its role in memory consolidation have been investigated intensively (Born, 2012). It has been found that non-rapid eye movement (NREM) sleep plays a crucial role in hippocampus-dependent declarative memory consolidation (Diekelmann, 2009). In particular, slow waves (SW), which occur mainly during slow wave sleep (SWS), correlate strongly with episodic memory performance (Mander, 2013). While many psychiatric patients suffer from sleep disturbances and memory impairments beside their main symptoms, a possible relation of diminished SWS and memory deterioration has not been sufficiently investigated. In the current proof-of-concept study, we aimed to enhance SW during SWS by inducing weak direct currents with transcranial direct current stimulation (tDCS) to the temporal lobes (including the hippocampi) of healthy participants. Our hypothesis was that increasing the cortical excitability during SWS, sleep-dependent memory consolidation should benefit from tDCS as compared to a placebo condition. **Methods:** A randomized, placebo-controlled double-blind crossover study design was conducted to apply bi-temporal anodal tDCS. DC with 2 mA (current density 0.03 mA/cm2, electrode size 35cm2 each) was delivered during SWS. Before sleep, participants performed an episodic memory task (face-occupation associations). Memory performance was measured by the number of correctly remembered items (hits). To obtain a value for sleep-dependent memory consolidation, the number of hits at delayed retention were subtracted from the number of hits at baseline. This value was taken to calculate the difference between tDCS and placebo which resulted in the tDCS memory effect. To test if the memory performance was related to the amount of stimulated SW, a partial correlation of the tDCS memory effect coefficient and the amount of SWS during stimulation was computed, with fatigue scores and learning duration as control variables. To this end, a 22-channel EEG was recorded for online sleep-staging and to timely engage the stimulation during SWS. EEG data was preprocessed including ICA, re-referencing to average reference, automatic tDCS-artifact detection, and filtering (0.5-2.0 Hz). Moreover, the data was segmented into 10s epochs that corresponded to clean EEG at SWS after the first stimulation. Finally, SW peak-to-peak amplitudes (> 75 µV) were extracted for comparison between tDCS and placebo stimulation. **Results:** Data of 13 participants (mean age 24, 21-32; 7 females, 6 males) was analyzed. The partial correlation between tDCS memory effect and amount of SWS stimulation showed a strong correlation of $r = 0.89$ and $p < 0.01$ ($df = 5$). The same analysis with the amount of SWS placebo stimulation did not reveal any effect ($r = -0.22$, $df = 7$, $p = 0.56$). Focusing on the electrophysiological tDCS effect, there was a moderate increase of SW amplitude in the tDCS compared to the placebo condition (tDCS: $M = 93.8$, $SD = 5.7$; placebo: $M = 90.4$, $SD = 6.9$; $T = 2.2$, $p < 0.05$). **Discussion:** This study indicates that it is possible to improve sleep-dependent memory consolidation by increasing cortical excitability using tDCS during SWS. Namely, the more SW were stimulated in participants, the better their episodic memory performance. This effect was independent from individual fatigue and learning strategies and was not observed in the placebo condition. Moreover, the increased SW amplitudes in the tDCS condition add electrophysiological evidence of the behavioral tDCS-effect which is in line with our expectations. Yet a few limitations have to be considered. The small sample size leads to a low certainty of the statistical effects. A general issue found in studies using tDCS is the low replication rate. Therefore, replication of the current results is needed in another cohort and also with patients before considering clinical application. Last, an fMRI study would reveal if tDCS increases hippocampal activation as targeted.

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Keywords: EEG, Learning, Memory, Sleep, tDCS

Poster abstracts

Clinical research

1.01
Neural Correlates of Semantic Priming in Psychosis

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Psychoses are aetiologically complex disorders that affect about 1 - 2% of the population during their lifetime. Psychotic symptoms are thought to represent disturbances in higher-order brain functions that can be grouped according to their dysfunction in one or more of the following three neural brain circuitries: language, affect, motor function. Dysfunction of the neural language brain circuitry has already been linked to disturbances in expressive speech and formal thought disorders. However, it remains currently unknown if the language brain circuitry is only disturbed in psychosis, or if already individuals at familial or clinical high-risk show some extend of aberrancy. To examine the whole spectrum from health to psychosis, four different subject groups are being examined: healthy controls (HC), first-degree relatives of psychosis patients (REL), a clinical high-risk group (CHR) and psychosis patients (PAT). In total, 120 subjects (30 per group) will complete a lexical priming task during electroencephalography and functional magnetic resonance imaging. On a behavioural level, we expect to find subtle language dysfunction in the REL and CHR group. Furthermore, we hypothesize that aberrant neural activation patterns are present during the language task in PAT, CHR and REL groups in comparison to HC individuals. Finally, we aim to depict that aberrant neural activation in language-related brain areas is most pronounced in the PAT group and to a lesser extend present in the REL group. With this study, we hope to improve diagnostic strategies, treatments and outcome predictions.

Keywords: Psychosis, Language, Semantic Priming, EEG, fMRI

1.02
APOE*E4-related effect on the topological brain network attributes in Mild Cognitive Impairment: A three-year follow-up study

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The apolipoprotein E ε4 allele (APOE*E4) has been consistently associated with a higher risk of developing late-onset Alzheimer's disease (LOAD). Previous studies in Mild Cognitive Impairment (MCI), considered a disease prodromal phase, have reported increased risk of LOAD progression and rapid cognitive decline in APOE*E4 carriers. However, inheriting the allele does not mean that MCI patients will definitely develop Alzheimer's. In the present study, we investigated how APOE*E4 status modulates the topological organization of structural brain networks in MCI depending on their clinical progression. We used graph theory and cortical thickness obtained from 762 T1-weighted structural magnetic images to study brain network properties during a 3-year follow-up period. The sample comprised 64 APOE*E4-positive ('carriers') MCI and 63 APOE*E4-negative ('non-carriers'). The groups were stratified into converters and non-converters. All subjects were selected from the ADNI database. The co-variation patterns among anatomical regions showed the double of differences in MCI carriers converters compared to non-converters. Large co-variations patterns differences between these groups involved structures like inferior parietal cortex and precuneus described previously as a core of regions highly connected. The MCI carrier's converters showed a significant increase in characteristic path length, clustering index, local efficiency, global connectivity and a global efficiency decrease. However all these measures were significant lower compared to carriers non-converters. Others topological properties like target attack and modularity indicated an

aberrant network organization in MCI carrier's converters over time. Our findings suggest that whole-brain topological attributes could improve prediction of LOAD conversion in MCI who are APOE*E4 positive.

Keywords: APOE*E4 allele, MCI, graph analysis, cortical thickness, structural network, brain connectivity

1.03
Spatial Distribution of Perseverations in Neglect Patients Depends on the Integrity of the Right Putamen

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Deficient inhibitory control, leading to perseverative behaviour, is often observed in neglect patients. Previous studies investigating the relationship between response inhibition and visual attention have reported contradictory results: some studies found a linear relationship between neglect severity and perseverative behaviour, whereas others could not replicate this result. The aim of the present study was to shed further light on the interplay between visual attention and response inhibition in neglect, and to investigate the neural underpinnings of this interplay. We administered the Five-Point Test - representing a novel approach in the context of neglect - and hypothesised that it would accurately assess both visual attention as well as perseverative behaviour. We assessed 46 neglect patients with right-hemispheric stroke, and performed voxel-based lesion-symptom mapping (VLSM) to identify neural substrates of perseverative behaviour as well as the spatial distribution of perseverations. Our results showed that the Five-Point Test can reliably measure neglect and perseverative behaviour. We did not find any significant relationship between neglect severity and the frequency of perseverations. However, within the subgroup of neglect patients who displayed perseverative behaviour, the spatial distribution of perseverations significantly depended on the integrity of the right putamen. We discuss the putative role of the putamen as a subcortical hub to modulate the complex integration between visual attention and response inhibition processes.

Keywords: Neglect; Visual Attention; Response Inhibition; Five-Point Test; Lesion mapping; Putamen

1.04
Emotional Dysregulation - Systems Neuroscience of Affect in Psychosis

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Objectives: Psychosis symptoms occur in around 1-2% of the population during their lifetime. Despite identical diagnosis, patients with psychosis show a variety of clinical symptoms. Various psychosis symptoms relate to a disturbed perception, experience, regulation or expression of emotions. Previous research indicates that emotional dysregulation may form a distinct psychosis symptom dimension that is linked to aberrant function and structure of the limbic system and its cortico-basal ganglia and cortico-cortical connections. However, the nature of emotional dysregulation in psychosis has not been studied extensively yet. It can be expected that disturbed affect in psychosis may be best conceptualized as a dimension, that varies with psychosis vulnerability. As such, we hypothesize that symptoms of disturbed emotional processing worsen with increasing psychosis vulnerability and that these are associated with increasingly aberrant neural activation in limbic brain structures. **Methods**: Neural activation patterns are investigated using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) from four different subject groups: patients with psychosis, subjects at clinical

high-risk for psychosis, first-degree relatives of patients with psychosis and healthy controls. During fMRI and EEG examination, a specifically developed face perception task is being used. The presented stimuli are short animations of faces that vary in certain characteristics: gender (male, female), aesthetic (high, low), head movement (up, down) and gaze direction (direct, averted). Subsequently, all face stimuli are rated with regard to gender, dominance, trustworthiness, aggressiveness, health and attractiveness. **Results/Conclusion:** We hypothesize that the four study groups differ in terms of brain activation patterns and event-related potentials in affect-related brain regions. Furthermore, we expect that these differences are being linked to different measures of emotionality and emotional processes as emotion regulation and perception. The expected results will give further insights in the underlying psychopathology of psychosis and might improve future prevention, diagnostic and treatment options.

Keywords: Psychosis, Affect, EEG, MRI, Symptom Dimensions

1.05
Relaxing virtual reality stimulation for intensive care unit patients: Feasibility and proof of concept of a virtual reality setup

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Background: Around 70% of patients in the intensive care unit (ICU) suffer long-term functional deficits and reduction of quality of life after prolonged stay in the ICU. It is assumed that the noisy and stressful ICU environment exposes patients to both stimulus overload and deprivation and puts them at risk of alterations in sensory perception that can result in cognitive dysfunction. **Aim:** The aim of this proof-of-concept study was to measure the effects of audio-visual virtual reality (VR) stimulation on visual exploration behaviour and physiological stress in healthy participants in an ICU setting. **Method:** The VR procedure consisted of a head-mounted display that isolated patients from disturbing environmental audio- and visual input in combination with an eye tracker to measure the level of attention as well as sensors to assess physiological parameters. The VR stimulation featured three immersive nature scenes, each five minutes in length. The setting was tested in 37 healthy subjects. **Results:** Heart rate, blood pressure and respiratory rate significantly decreased during the audio-visual stimulation. However, the decrease in eye movement data over time was very small and not significant. Fixation/saccade ratio was decreased when no visual target was presented, reflecting enhanced visual search and reduced visual processing. **Conclusion:** Overall stimulation had a strong relaxing and calming effect without any adverse effects. Furthermore, during stimulation the visual search activity was reduced when participants attended to a target, compared to the other parts of the video. From these findings we conclude that VR stimulation in ICU settings is feasible and beneficial for critically ill patients.

Keywords: Virtual reality, Audio-visual stimulation, Critical illness, Intensive care unit, Cognition

1.06
Optimizing acquisition and fitting conditions for 1H MRS investigations of global brain pathology

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Introduction: Achieving high quality spectra for quantitative evaluation of metabolite content is a challenge in clinical Magnetic Resonance Spectroscopy (MRS), where a high Signal-to-Noise-Ratio (SNR), but also good resolution is essential. For non-focal disease, the voxel size (VS) can be increased to achieve better SNR and

hence smaller fitting inaccuracies, reflected in Cramer-Rao Lower Bounds (CRLB). However, for very large VS the resolution may suffer due to uncompensatable field inhomogeneity. In addition, outer-volume artifacts may arise due to spurious lipids [1-3]. Hence, it is worthwhile to investigate what VS will optimize the fitting accuracy, i.e. minimize the CRLB as a compromise between increasing SNR and decreasing linewidth under the side-constraint of minimal artifact levels. Furthermore, given modern multichannel receive coils, it is also interesting whether optimized signal combination from different channels [4] is really best in case of large VS - or whether fitting of spectra from individual coil elements with or without incorporation of respective lineshapes may be superior. Here, both aspects were investigated in an exploratory fashion. **Methods:** 3T MR Scanner (Prisma, Siemens) with multi-channel receive head coil, semi-Laser localization sequence [5], 2nd order shimming. Series of spectra (32 acquisitions each) of 8 different VS's (8 to 99 cm^3) in a phantom and in vivo from two human volunteers (supraventricular region). Simulation of limited field homogeneity by intentionally decreasing the shim quality. Data processing by jMRUI[6] - model fitting of interrelated spectra using FiTAID [7,8]. **Results and Discussion:** As expected, SNR and linewidth increase with VS. The standard averaged spectra showed decreasing CRLB with larger VS to an optimum VS of ~80 cm3 for several metabolites. Missetting the shim led to higher CRLB and a less steep decrease of the CRLB with VS. For large VS, exclusion of certain receive channels reduced the artifact level substantially with minor loss in SNR. The unsuppressed water signal may be used for weighting the subspectra and to provide lineshape information for individual coil elements, which featured substantial lineshape differences. Conclusions: Increasing VS up to ~ 80 cm^3 leads to decreasing CRLB. Individual treatment of multi-channel data offers the possibility of incorporating artifact levels and lineshapes from single coil elements as additional optimization criteria on top of SNR for construction of the overall spectrum. Optimal VS and evaluation method will depend on shim performance and voxel location as well as head-shape. Further in-depth investigation is needed before drawing firm conclusions.

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Keywords: Brain, MR spectroscopy; model fitting; Cramer-Rao Lower Bounds; parameter optimization

1.07
The role of the Sense of Agency in Functional Neurological Disorders: an fMRI - TMS Study

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Background: Functional neurological disorders (FNDs), formerly called Hysteria, represent a frequent disorder at the edge between neurology and psychiatry. Functional neurological patients typically present neurological symptoms (e.g. paralysis, tremor, convulsions) for which no organic lesion of the nervous system is found. It has been estimated that up to 18% of the neurological patients with "unexplained" symptoms are currently diagnosed with FND. A common element in FND is a distorted sense of agency, associated with an abnormal activation pattern of the right temporo-parietal junction (TPJ). The sense of agency is a fundamental aspect of human self-consciousness, and allows us to make judgements about whether we did something ourselves or not. **Goal:** This project aims at clarifying the role of the sense of agency in patients suffering from functional neurological disorders, by means of non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS). **Methods:** We plan to recruit 20 patients with FNDs and 20 age- and sex-matched healthy controls to participate in our study. The study is designed as a single blind, within-subject, sham controlled, randomized, cross-over trial where participants will perform a computer-based game targeting the sense of agency, under functional magnetic resonance imaging (fMRI). After the first game phase, participants will undergo 5 min of excitatory TMS (intermittent theta burst stimulation - iTBS) over the right TPJ. Stimulation will be randomly

assigned to real or sham. After the stimulation, they will perform the computer-based game again under fMRI. After at least 1 week from the first session, a second one will take place. The order of the stimulation conditions (real/sham) in the respective sessions will be counterbalanced across participants. In order to test the effects of TMS on the sense of agency, we will compare pre- and post-stimulation performance on the computer-based game, in FND patients and healthy controls. **Relevance of the study:** If the source of the functional neurological symptoms is a distorted sense of agency, real TMS will restore normal activation patterns in the right TPJ and improve symptoms production. This project will therefore develop a proof-of-concept for a possible treatment option of FND, based on non-invasive brain stimulation.

Keywords: Functional neurological disorders, TMS, fMRI

1.08
Evaluating Resective Surgery Targets in Epilepsy Patients: A Comparison of Quantitative EEG Methods

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Quantitative analysis of intracranial EEG is a promising tool to assist clinicians in the planning of resective brain surgery in patients suffering from pharmacoresistant epilepsies. Quantifying the accuracy of such tools, however, is nontrivial as a ground truth to verify predictions about hypothetical resections is missing. As one possibility to address this, we examine in this study the consensus of two methods to evaluate hypotheses about surgery targets, that is, the brain tissue which upon resection is expected to render a patient seizure free. One method uses machine learning techniques to enable the predictive modeling of EEG time series. The other is based on functional network theory and estimates the nonlinear interrelation between EEG channels. Both methods were independently shown to distinguish patients with excellent post-surgical outcome (Engel class I) from those without improvement (Engel class IV) when assessing the electrodes associated with the tissue that was actually resected during brain surgery. Using customized hypotheses tests, we examine the agreement of the methods on a common set of patients. Both methods' assessments correlate strongly positively with the similarity between a hypothetical resection and the corresponding actual resection in class I patients. Moreover, the Spearman rank correlation between the methods' patient rankings is significantly positive. We conclude that although conceptually completely independent, there is a relation between the predictions obtained from both methods. Their broad consensus suggests their application in clinical practice to provide physicians additional information in the process of presurgical evaluation.

Keywords: epilepsy; quantitative EEG; resective surgery; predictive modeling; functional network; method validation

1.09
How puzzled are you? Preliminary results from a casual puzzle game difficulty rating study

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Background: Recent studies suggest preliminary cognitive and emotional benefits of casual puzzle game intervention in older and cognitively impaired adults. For cognitive rehabilitation interventions, progression of difficulty level of training task is important in order to match the patients level of skill and progress with the intervention, as well as for learning and transfer. Casual puzzle games have a unique potential since they are easy to interact with, are enjoyable and allow for generating large sets of training materials. **Objective:** The aim of this planned study is to evaluate the difficulty of large sets of puzzles using two casual puzzle games (Connect-

the-dots puzzle, Flow Free, Big Duck Games LLC and Tile-matching match-three puzzle, Bejeweled, PopCap Games) and using a recently published method that takes parameters of the puzzle game manipulated to increase difficulty (e.g. board size, number of elements etc) and combines them into a difficulty equation (Van Krefeld et al, 2015). The difficulty equation is then trained with difficulty ratings from participants playing a sample of different puzzle levels. In addition, the cognitive processes engaged by the puzzle games will be tested by looking at the relation between the performance on the video games and on standardized neurocognitive tests. **Methods:** Two existing casual puzzle games were developed using the software Unity 3D. Data collected from the puzzle games include time-stamped touch inputs and the current state of the puzzle board allowing the calculation of a wide range of in-game performance metrics (completion status, completion time, number of moves, wrong moves etc.). For the connect-the-dots puzzle, a set of 40 levels were taken from an online repository. Puzzles were sorted by grid size, number of paths, number of turns and average city block distance and 8 levels were randomly picked for each grid size (5x5, 6x6, 7x7, 8x8). For the tile-matching match-three puzzle we created levels by manipulating the puzzle board size (s; height and width) and number of gem types (g). First, puzzle board sizes (s) using all combinations of height and width (sh, sw) = {4, 5, 6, 7, 8} × {4, 5, 6, 7, 8} were created. Second, levels were created by combining the basic 25 puzzle boards with different numbers of gem types. The number of gem types per basic puzzle board was limited from 4 types of gems to the maximal value of either the height or width (e.g. 4 × 5 puzzle board: 4 and 5 gem types). A recursive code was written to generate playable levels with 4 moves (i.e. 4 patterns that can be matched) with only 1 match pattern per move to control for number of targets (i.e. match patterns). In the study, participants first completed a battery of standardized neurocognitive tests that include cognitive game components (visual search/attention, processing speed, working memory and spatial reasoning) proposed to be engaged by casual video games (Baniqued et al, 2013). Secondly, in the playtest part, participants will play a random subset of both puzzle games, providing a difficulty rating after each puzzle level. **Discussion:** With this study we intend to automatically estimate the difficulty of large sets of puzzles for casual game training. Furthermore, this study allows to examine whether manipulating particular game parameters can successfully increase game difficulty while the neurocognitive tests will allow us to examine the cognitive processes engaged by the two puzzle games. For a later planned training study we will then be able to develop an algorithm for dynamic difficulty adjustment that will allow us to train participants optimally through difficulty scaling.

Keywords: casual puzzle games, cognitive intervention, difficulty adjustment

1.10
Long-term observational study monitoring mobility, behavior and other health related parameters using multimodal sensors

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Background: In our aging society, prolonged independent living is a question of individual preference in addition to an economic one. A study from OBSAN [Weavre, 2008] showed, that increasing home care in comparison to institutionalisation, may have a significant effect in lowering healthcare cost projections. Additionally, it is obvious that most seniors want to age in their well-known environment for as long as possible. Often assessing the actual health-state - be it mental or physical - is based on self-reporting, [Rosenman, 2011] which may be highly subjective and thus result in a response bias. New sensor technology could provide an objective alternative to ordinary evaluations forms - such as questionnaires. In this study, we want to investigate whether the sensor technology could not only increase safety through the automatic detection of serious events, like falls, but also enable a better tailored care by providing objective health-status information. **Methods:** Forty-six participants (> 70 years, living alone) have been recruited and will be measured throughout a year, using a set of wearable and ambient sensors. Wearable sensors include a mobile ECG (Preventice Health-Guardian) and a Fitness Watch (FitBit) for 50% of the participants, while the other 50% of participants will be provided with an armband (Biovotion Everion) and an accelerometer (Axivity AC3). Ambient sensors include motion and door sensors (Domo-Safety System) as well as a bed sensor. Simultaneously, questionnaires and muscle strength measures will be recorded, while local caregivers will visit the participants twice a week to get information about lifestyle changes, accidents and other unforeseeable events. **Outlook:** We aim to combine different algorithms such as activities of daily living

detection (ADL), stress- recognition or anomaly detection towards building models that can effectively evaluate the current health state and ideally give some predictive information about future states.

Keywords: Sensors, Ambient, Wearable, Monitoring, Activities of Daily Living, Physiological data, Big Data

1.11
Tele-rehabilitation as an add-on to Face-to-face Speech and Language Therapy in Post-stroke Aphasia

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Background: Aphasia is the loss or impairment of language functions that occurs following brain damage. This communication disorder affects different combinations of language modalities (i.e. understanding, speaking, reading, and writing) and differs in levels of severity. Stroke affects about 15,000 patients per year in Switzerland, 30% of which develop aphasia. A recent Cochrane intervention review revealed evidence for the effectiveness of using speech and language therapy (SLT) for people with aphasia following stroke in terms of functional communication, receptive and expressive language. Findings particularly highlight positive effects of higher training frequency on functional outcome. One possible approach to increase training frequency and duration is to complement face-to-face SLT with home-based tele-rehabilitation SLT. To this end, an aphasia tele-rehabilitation application (Bern Aphasia App) was developed within a multidisciplinary team of speech and language therapists, neurologists, psychologists and computer engineers. With this application patients can train independently and the therapists still have access to the patients' performance and can select exercise types and adjust the difficulty level. **Aim:** The aim of this project is to investigate the effects of high-frequency short duration tablet-based SLT in chronic stroke outpatients in a clinical trial. **Methods:** In this study aphasia outpatients will be recruited and randomly assigned to two different treatment arms. Both groups will perform a 4-week intensive tele-rehabilitation SLT (2 hours a day) in addition to weekly face-to-face therapy session (45 minutes). In the experimental group 80% of the training time will be devoted to tele-rehabilitation SLT and 20% to tablet-based cognitive training and vice versa in the control group. At three time-points (pre-, post-test and 8-week follow-up) the patients' language skills are measured. **Outlook:** With tablet-based applications both patients and therapists can benefit from an intuitive, touch-based reliable product which fits well with the current trend of moving health treatment from hospital to home. In Switzerland aphasia outpatients get less therapy than guidelines would recommend, hence positive results in the clinical trial would have a great socioeconomic impact.

Keywords: Aphasia, Language disorder, tele-rehabilitation, patient-interface, stroke

1.12
White matter correlates of impaired gesture performance and recognition in schizophrenia

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Previous studies have shown that schizophrenia patients are significantly impaired in gesture performance and recognition. However, white matter correlates of gesture performance are unknown. Therefore, we investigated the relationship between white matter abnormalities and impaired gesture performance and recognition in schizophrenia using TBSS and fiber tractography. We hypothesized that gesture deficits are related to reduced fractional anisotropy (FA) of the superior longitudinal fascicle, uncinate fascicle and the corpus callosum, which

connect key regions of the praxis network. In 43 patients with schizophrenia, gesture performance was assessed by the Test of Upper Limb Apraxia (TULIA) and gesture recognition by the Postural Knowledge Task (PKT). Performance was video recorded and blindly rated. Structural brain imaging was measured using a 3-T MR Scanner. Whole brain white matter analysis was conducted using TBSS and FA of specific tracts was measured using fiber tractography. FA values were correlated with TULIA and PKT including age and chlorpromazine equivalents as covariates. The TULIA score correlated with white matter microstructure at $p < 0.05$ (corrected) in clusters of the corpus callosum and the left and right anterior corona radiate. The PKT score was associated with white matter at $p < 0.05$ (corrected) in the same fibers and additionally in the superior corona radiate. In both tests, superior performance was associated with increased FA. The results of the fiber tractography will be finished by September 2017. Aberrant white matter of the corpus callosum and the anterior and superior corona radiate are associated with poor gesture performance and recognition in schizophrenia. In addition, we expect correlations of gesture performance with the superior longitudinal fascicle and uncinate fascicle. Conclusions for the pathogenesis of nonverbal communication can be drawn from these results, as they argue for a contribution of specific brain structural alterations for gesture deficits.

Keywords: Gesture, schizophrenia, white matter

1.13
Integrating linguistic measures in aphasia tele-rehabilitation

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Background: Aphasia is the loss or impairment of language functions that occurs due to brain damage. It affects the four linguistic modalities (speaking, understanding, writing and reading) in different combinations and levels of severity. As standard, affected patients are provided face-to-face speech and language therapy (SLT). A key factor for a successful SLT is dose frequency. Tablet-based aphasia tele-rehabilitation increases access to high frequency SLT while reducing cost. To this end, an aphasia tele-rehabilitation application called Bern Aphasia App was developed within a multidisciplinary team of speech and language therapists, neurologists, psychologists and computer engineers. The application consists of different exercise types and many of which using a multiple-choice format. To generate multiple-choice questions, the quality and selection of distractors (incorrect answers) is crucial. The difficulty of multiple-choice questions is influenced by different factors which can be expressed using linguistic measures (e.g. word frequencies, syllable length, semantic or phonematic relatedness between words). **Aim:** The aim of this project is to incorporate linguistic measures into our aphasia tele-rehabilitation. The first focus lies on semantic relatedness. In a first step, different measurers for the semantic relatedness between words will be evaluated in healthy participants. In a second step, we will use these measures for the semantic relatedness together with other linguistic quantifications to predict the task difficulty in aphasia patients. **Methods:** In this project, healthy participants assess semantic relatedness between words using questionnaires and response times in multiple-choice tasks to evaluate the existing quantifications of semantic relatedness from data bases. To predict the difficulty level of exercises for aphasia patients, we will use data from an ongoing clinical trial, where our research group wants to investigate the effects of high frequency tele-rehabilitation SLT (one-hour training per day for 4 weeks). To quantify the semantic relatedness, we will use measures from the lexical data base GermaNet and a machine learning algorithm word2vec. We trained word2vec using the whole German Wikipedia and German medias. **Outlook:** We expect a considerable socio-economic impact of offering aphasia patients high frequency training programs using tele-rehabilitation SLT. The generation of exercises for rehabilitation is time-consuming and matching the exercise difficulty to the patients is influenced by various factors. Based on this we will develop a method with which we can predict the difficulty level of an exercise for a specific patient and implement an algorithm that can be used to generate new exercises. This will allow therapists to create exercises that dynamically match the patients level of skill as they progress.

Keywords: Aphasia, tele-rehabilitation, semantic relatedness, GermaNet, word2vec, exercise generating algorithm

1.14
The effect of past and present chronic stress on neuroplasticity

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Brain-derived neurotrophic factor (BDNF) is a brain-wide distributed protein with functions in neuronal development and survival. Because of its role in adult neurogenesis, BDNF is regarded as a key regulator and a marker of synaptic plasticity. BDNF serum level is decreased by chronic stress. Especially stress occurring during childhood may have relevant impact, as BDNF is involved in developmental processes of the central nervous system. The aim of the present investigation was to find out if BDNF serum levels differ between chronic stress patients with and without a history of childhood stress. In a specialized unit for stress-related disorders, 71 in-patients suffering from the burnout syndrome were included. At admittance (pre) and discharge (post) serum BDNF as well as symptoms of burnout and depression were quantified. For analysis, two groups were formed according to the categorization on the childhood trauma questionnaire (CTQ) (no/low vs. moderate/severe traumatization). Patients with a history of childhood stress had lower BDNF serum levels at admittance as well as at discharge. However, there was a significant increase in BDNF from pre to post in both groups, indicating beneficial therapy effects irrespective of traumatization. Regarding the severity of burnout and depression symptoms, no difference was found between groups neither at admittance nor at discharge. BDNF level reduction in response to chronic stress seems to be potentiated in patients with a history of childhood stress, which might entail reduced neuronal plasticity. Interestingly, this putative deficit is not manifested on the level of symptoms of depression and burnout.

Keywords: brain-derived neurotrophic factor (BDNF), chronic stress, burnout

1.15
Formal thought disorder in schizophrenia and white matter abnormalities

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The current study examined the hypothesis that a fronto-temporal disconnection in the language network underpins formal thought disorder (FTD) in schizophrenia. 49 patients with a schizophrenia spectrum disorder (27 with mild FTD, 22 with severe FTD) and 26 healthy controls (HC) from two diffusion tensor imaging studies were included. Overall psychopathology and FTD were assessed by the Positive and Negative Syndrome Scale and the Thought, Language, and Communication scale, respectively. White matter (WM) microstructure was analysed using Tract-Based Spatial Statistics. Fractional anisotropy (FA) was investigated in language-related WM tracts including the arcuate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus. Compared with HC, the total patient group showed lower FA in all the investigated language-related WM tracts as well as across the whole WM skeleton. However, patients with severe and patients with mild FTD did not differ in FA. Although FA in language-related tracts did not significantly correlate with severity of FTD, FA extracted from the genu/body of the corpus callosum correlated inversely with

negative FTD. These results are compatible with earlier studies reporting impairments in widely spread WM tracts, including those related to the language network, and indicate that WM deficits in the corpus callosum may contribute to negative FTD in schizophrenia.

Keywords: diffusion tensor imaging (DTI); fractional anisotropy (FA); thought disorder (FTD); psychosis; arcuate fasciculus (AF); inferior fronto-occipital fasciculus (IFOF); inferior longitudinal fasciculus (ILF); superior longitudinal fasciculus (SLF); uncinate fasciculus (UF).

1.16
Vitamin D supplementation differentially affects seasonal multiple sclerosis disease activity

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Background and objectives: Low ultraviolet-B (UVB) radiation causes hypovitaminosis D, which is a known risk factor for multiple sclerosis (MS) and associated with MS disease activity. Our objective is to test whether vitamin D supplementation is most effective in lowering disease activity during the period of the year with low UVB radiation and consequently low serum 25-hydroxyvitamin D_3 ($25(OH)D_3$) concentration. **Subjects and Methods:** Retrospective analysis of medical records from our outpatient department identified 40 MS patients with available data of at least 6 months before and during oral vitamin D supplementation. Serum $25(OH)D_3$ concentration was analyzed using immunoassay. UVB radiation data was provided by the local government. Annualized and quarterly relapse rates before and during vitamin D supplementation served as outcome parameters. **Results:** During vitamin D supplementation (18,950 international units/week (mean, SD 3,397)), serum $25(OH)D_3$ concentration increased by 51 nmol/L and the UVB related seasonal variability of $25(OH)D_3$ levels ceased (rho = -0.13, $p > 0.05$). Furthermore, the annualized relapse rate decreased by approximately 50%. This decrease remained significant after adjusting for immunotherapies, vitamin D supplementation, MS Phenotype, sex, age and disease duration (regression coefficient for vitamin D supplementation, -0.24; 95% confidence interval, -0.61 to -0.02; $p = 0.04$). Notably, the reduction in relapse rates was almost solely driven by the prominent reduction of the quarterly relapse rate in late winter/early spring, when $25(OH)D_3$ levels of non-supplemented patients were the lowest. **Conclusions:** Our study demonstrated the modulation of seasonal MS disease activity through vitamin D supplementation. Given the prominent reduction of the quarterly relapse rate in late winter/early spring, our data indicate a beneficial effect of supplementing MS patients with vitamin D, especially during this period of the year.

Keywords: Vitamin D, Multiple Sclerosis, Seasonality, Autoimmunity

1.17
Local signal complexity and dynamic functional connectivity associated with Alzheimer's severity

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Introduction: Alzheimer's disease (AD) has been characterized as a disconnection-syndrome (Villain, 2010). Depending on the disease severity, atrophy in grey matter and disruptions in white matter (WM) are observed. These structural changes are accompanied by functional decline on a symptomatic level, and in intrinsic

functional connectivity (FC) of brain networks. In AD, FC alterations are found in several resting-state networks (RSN) such as default mode network (DMN), salience network (SAL) or executive control networks (ECNs). These RSNs can be characterized by their properties of region to region static FC across the duration of an MRI BOLD scan, the variability of the dynamic modulations of this FC (dynFC). In addition to the relation between signal fluctuations between brain areas, the regularity/complexity of BOLD signal fluctuations can be assessed by means of multi-scale entropy (MSE; Smith, 2014) and has been shown to be related to cognitive function in elderly controls (Yang, 2013). Hence, we investigated alterations of dynFC between and MSE of signals within brain regions of these RSNs in early AD patients as compared to elderly controls (EC). Furthermore, we were interested in the relationship of these network characteristics and the MMSE score. **Methods:** Data from 14 EC (age=67.9, SD=3.7; MMSE=28.6, SD=0.8) and 16 patients with AD (age=67.3, SD=9.7; MMSE=25.2, SD=3.6; Mann-Whitney UEC-AD=19.5, $p<0.001$) were analyzed. BOLD fMRI acquisition was done on a Siemens 3T scanner (400 volumes, 26 slices, 3x3x4mm, TR/TE 1600ms/35ms). Preprocessing included motion realignment, regression of 12 motion parameters and WM and CSF signal fluctuations, normalization to MNI space and smoothing (8mm FWHM Gaussian kernel). DMN, ECNs and SAL nodes were defined from template-RSNs (Shirer, 2012). Using a sliding window approach (length 20TRs), the dynamic changes in interregional FC was computed. MSE was calculated with the average sample-entropy across 30 coarse-sampled temporal scales (pattern length m=2, matching threshold r=0.3). We first tested for differences in MSE and dynFC between networks and groups using ANOVA. Second, a potential global association between network connectivity and network complexity was investigated with a correlation of overall dynFC and overall MSE. Finally, we correlated dynFC with MMSE scores to identify aberrant connections related to AD severity. **Results:** The ANOVA for MSE yielded a group effect, but no network effect ($F(network)=0.38$ p=n.s. $F(group)=4.00$ $p<0.05$). The DMN showed a reduced MSE in AD compared to EC ($t=2.23$, $p<0.05$). No differences in dynFC were found on the network level. For the combined groups a correlation between MSE and dynFC was observed for SAL and both ECNs ($rLECN=-0.58$ $p<0.001$, $rRECN=-0.42$ $p<0.05$, $rSAL=-0.46$ $p=0.01$). In other words, the more variable the connections, the less predictable the network. The correlation between MMSE and MSE/dynFC was negative in the DMN and SAL between MMSE and global dynFC ($rDMN=-0.40$ $p<0.05$, $rSAL=-0.46$ $p<0.05$). No correlation was found for the ECNs and MMSE. A detailed region-to-region analysis revealed that the dynFC specifically in LECN was positively correlated with MMSE in EC whereas in AD this was lacking. In contrast, the AD group showed overall negative relations between MMSE and dynFC within the other networks (except LECN). **Discussion:** We did not find any dynFC differences between the groups in any RSN. This unexpected outcome might be explained by the mild AD severity and small sample size; however, future studies need to investigate this speculation. Nevertheless, there is a negative relation between the signal complexity within network nodes and variability in connectivity, which indicates a reduced potential to establish stable connections with remote areas. This is in line with the finding that in AD most networks displayed an inverse relation between MMSE and dynFC suggesting that communication between network nodes is impaired.

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Keywords: Alzheimer's disease, fMRI, dynamic functional connectivity

1.18
Resting-state connectivity and executive functions after pediatric arterial ischemic stroke

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Background: The aim of this study was to compare the relationship between core executive functions and frontoparietal network connections at rest between children after arterial ischemic stroke and typically developing controls. **Methods:** Children diagnosed with arterial ischemic stroke more than two years before recruitment and typically developing controls were included. Executive function measures comprised inhibition, fluency, processing speed, divided attention, working memory and conceptual reasoning tasks. High-resolution T1-weighted magnetic resonance (MR) structural images and resting-state functional MR imaging were acquired. Independent component analysis was used to identify the frontoparietal network. Functional connections were obtained through correlation matrices; associations between cognitive measures and functional connections through Pearson's correlations. **Results:** Twenty participants after stroke (7 females; mean age 16.0 years) and 22 controls (13 females; mean age 14.8 years) were examined. Patients and controls performed within the normal range in all executive tasks. Children after stroke performed significantly worse in tests of fluency, processing speed and conceptual reasoning than controls. Resting-state functional connectivity between the left and right inferior parietal lobe was significantly reduced in children after stroke. Fluency, processing speed and perceptual reasoning correlated positively with the interhemispheric inferior parietal lobe connection in patients and controls. **Conclusion:** Decreased interhemispheric connections after stroke in childhood may point towards a disruption of typical interhemispheric interactions necessary for higher level cognition. The present results emphasize the tight relationship between functional organization of the brain at rest and cognitive processes.

Keywords: resting-state fMRI, pediatric arterial ischemic stroke, frontoparietal network, executive functions

1.19
Brain signals to optimise directional DBS programming in Parkinson's disease

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Recently introduced directional deep brain stimulation leads represent an advance in DBS technology. The potential to steer stimulation current in multiple directions through segmented contacts increases programming flexibility and allows for a more individual adaptation of the stimulation field. However, programming directional leads is much more time consuming and exhausting for the patient compared to conventional leads with cylindrical contacts. Hence supportive tools are strongly needed to optimally benefit from the advance provided by the directional leads. Here we validate local field potentials recorded from the subthalamic nucleus as a predictor for the most efficient contacts for stimulation in patients with Parkinson's disease. Local field potentials from the subthalamic nucleus were recorded in 12 patients with Parkinson's disease from all directional contacts during DBS surgery. The individual and normalized beta peak amplitude (range: 13-35Hz) was calculated for each directional contact and compared with the results of the blinded clinical contact review (gold standard) performed after 4-6 months. Subthalamic nucleus beta activity recorded from the directional contacts is spatially differently distributed and was positively correlated with the contact's clinical efficacy (rigidity improvement/stimulation current). The two contacts with the highest beta activity included the most efficient stimulation contact in up to 92 % of cases and that with the widest therapeutic window in 74% of cases. Directional local field potentials are predictive for the most efficient stimulation contacts and may provide a useful tool for an optimal and fast programming of directional/multi contact DBS leads.

Keywords: Deep brain stimulation; Parkinson's disease; Basal ganglia electrophysiology

1.20
Metabolite diffusion measured by MR spectroscopy without water suppression yields an improved reproducibility

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Introduction: Diffusion weighted spectroscopy (DWS) is limited by low SNR especially for high b-values. Hence, averaging over a multitude of measurements is inevitable, which prolongs the measurement time and, thus, leads to a high susceptibly for motion artifacts. The use of a non-water-suppressed sequence could alleviate some of the problems allowing the use of the water signal as an inherent reference not only for optimal frequency, eddy current, and phase correction as in previous applications, but also for compensation of a motion related signal drop. This work aims to demonstrate that the measurement of diffusion coefficients (ADC) of brain metabolites substantially profits from using water as internal reference for signal correction in MRS with metabolite cycling MC) instead of water presaturation. **Methods:** The new DWS sequence uses the water signal as reference allowing for compensation of motion-related signal distortions in post-processing. The data were analyzed by a newly implemented simultaneous 2D fitting approach in the fitting tool FiTAID to determine the ADCs. Before in vivo applications the motion-compensation algorithms were tested in vitro for two different types of motion: a rotating and a linearly moving phantom. Finally, the effect of motion-compensation was investigated on in vivo data of 13 healthy volunteers estimating ADC's of 17 brain metabolites. **Results:** As expected signal loss due to motion is strongest in the rotating phantom. By selecting non-distorted signals as reference, a post processing correction of motion induced ADC overestimation is achieved. In case of linear motion, signal rephrasing already yields ADC's close to ground truth. However, even for these little distorted signals an improved ADC estimation is found with the motion-compensation scheme. Spectral analysis shows that motion-compensation facilitates correction of motion induced signal drop especially at high b-values. The estimated metabolite ADC's in the human cohort are reduced for all metabolites after application of the motion-compensation scheme. Furthermore, SNR improved with correction leading to more reliable fits and decreased variance of ADC's. **Conclusion:** MC MRS combined with 2D modeling allows for optimized determination of metabolite diffusion information. This yields improved inter- and intra-subject reproducibility.

Keywords: diffusion, mr spectroscopy, cellular microstructure, brain

1.21
Cross-modal processing affects attentional asymmetries in right-hemispheric patients with neglect

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In cross-modal search, spatial congruency between auditory cues and visual targets is known to improve healthy participants' search performance. However, whether such multisensory processing might affect the spatial deployment of attention in neurological patients with attentional disorders, particularly in patients with left-sided neglect, is poorly understood. The aim of this study thus consisted in investigating the effects of cross-modal processing on the performance in a visual search task in patients with a right-hemispheric lesion and left-sided neglect. Two groups of patients with right-hemispheric lesions (i.e., patients with and without left-sided neglect) and a group of age-matched healthy controls completed a visual search task with spatially congruent, incongruent, non-informative, and without auditory cues. Moreover, to assess participants' accuracy in localizing the auditory cues, a unimodal sound localization control task was also administered. As expected, preliminary results revealed that neglect patients showed a worse performance for left- than right-sided visual targets in the absence of auditory cues. Additional auditory cues affected search performance exclusively in the left hemifield: spatial congruency improved search performance, and incongruence deteriorated it. Crucially, these effects were

modulated by the sound localization accuracy, as measured by the control task. In healthy participants and in right-hemispheric patients without neglect, auditory cues affected visual search performance both in the left and the right hemifield. Whereas healthy controls showed no left/right asymmetries in their search performance, such asymmetries only emerged with the additional presentation of a congruent auditory cue in right-hemispheric patients without neglect. Overall, the present findings demonstrate that multisensory processing differentially modulates asymmetries in spatial attentional deployment in patients with right-hemispheric lesions, with and without neglect, thereby further clarifying the interactions between spatial attentional deployment and cross-modal processing.

Keywords: Hemispatial neglect, multisensory attention, spatial attention

1.22
Automatic detection of microsleep episodes

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Objectives: Microsleep episodes are short sleep fragments occurring in patients suffering from excessive daytime sleepiness as well as in healthy individuals. The maintenance of wakefulness test (MWT) is often used to assess fitness to drive in patients suffering from excessive daytime sleepiness. **Methods:** Thirteen patients were recorded during a MWT and in the driving simulator with electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), electrocardiography (ECG), respiration sensors, and face videography. Microsleep episodes in the EEG were visually identified and marked by experienced scorers. Spectrograms were calculated from an occipital derivation using an autoregressive model of order 16. Spectra were determined on 1-s moving windows. To classify sleep fragments, several features were derived from the spectrogram and EOG: power in delta, theta, alpha and beta bands normalized to baseline, ratio theta/(alpha+beta) activity, median frequency, and eye movements. Two classification algorithms were trained with these features: support vector machine (SVM; linear kernel) and random forest (RF, 100 trees). The classifiers were trained on 12 patients, and validated on 1 patient. **Results:** Sleep fragments were successfully identified with a specificity of 0.74 for SVM and 0.72 for RF, and a sensitivity of 0.99 for both classifiers. Similar performance was observed with both SVM and RF algorithms. **Conclusions:** Our preliminary analysis provides a proof of concept that automatic detection of microsleep episodes is feasible. For practical applications, the classifiers have to be trained on larger number of individuals to obtain a generalized classifier. Furthermore, inclusion of additional features may be beneficial.

Keywords: EEG, microsleep, machine learning, MWT

1.23
Effects of Parkinson's disease and subsequent dopaminergic therapy on lateralization of the motor network

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Movements are known to recruit primarily contralateral cortical regions, contralateral basal ganglia and ipsilateral cerebellum, leading to highly asymmetric activations as observed through fMRI. An increase in symmetry of motor activation has been reported in healthy aging (Naccarto, 2006; Wu, 2005), following unilateral brain lesions and stroke (Carr, 1993; Guzzetta, 2007; Rehme, 2011a; Shimizu, 2002), and in drug-naïve Parkinson's disease (Wu, 2015). We used fMRI to study motor activations in long-term Parkinson's disease (PD) patients as well as in

healthy subjects during unilateral upper and lower limb movements. Ten right-handed, left side symptom-dominant PD patients (5 female) were tested once after their usual dopaminergic medication - 'ON' state - and in a separate session, after withdrawal of medication - 'OFF' state. Eighteen right-handed age-matched healthy controls (HC) were scanned in a single session. We estimated activation laterality in three cortical regions of interest - the primary motor cortex (M1), the supplementary motor area (SMA) and the premotor cortex (PMC), during each of the four movement conditions - right hand, left hand, right foot and left foot movement. Laterality was significantly decreased in PD ON as compared to HC in M1 during left hand and left foot movements, as well as in PD ON and PD OFF as compared to HC in the PMC during left hand movements. We sought to investigate the functional reorganization underlying these lateralization changes by estimating the effective connectivity between ROIs using dynamic causal modelling (DCM). We considered a model space of 12 models divided into two families according to whether movement-associated changes in effective connectivity (DCM.B matrix) were symmetrical or lateralized to the side contralateral to the movement. We used Bayesian model selection to conduct family-level inference on the lateralized versus symmetrical families within each group of subjects. The winning family for both PD OFF and PD ON was the symmetrical model family (PD OFF: exceedance probability of 0.65, PD ON: exceedance probability of 0.853) whereas in HC, the two families were almost tied (exceedance probability of 0.496 vs. 0.504, for lateralized vs. symmetrical families). These results suggest that PD results in increased involvement of structures ipsilateral to movement side, which becomes manifest as decreased activation laterality. In conclusion, our results offer a more complete picture of functional cortical reorganization associated with long-term Parkinson's disease and its interaction with dopaminergic medication.

Keywords: Parkinson's disease, functional magnetic resonance imaging, laterality index, dynamic causal modelling, cortical reorganization

1.24
A brain-penetrant 5-HT7 receptor agonist alleviates chronic pain behavior

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Neuropathic pain is a debilitating pathological condition. Irreversible peripheral and centralsensitization is responsible for the establishment and maintenance of the painful condition. The Anterior Cingulate Cortex (ACC) is considered to play a central role in the processing of the emotional aspects of chronic pain. Changes in the neuronal activity in this brain area are causally linked to the development of neuropathic pain. We tested the influence of a new serotonin receptor (5-HT 7 R) agonist (LP-211) that crosses the blood-brain barrier on neuropathic pain. With electrophysiological and behavioral tests we quantified the modulatory effect of LP-211 in the ACC. We found that LP-211 recovered the resonance properties of layer 5 pyramidal neurons that were impaired in the neuropathic pain state. Acute i.p. injection of LP-211 had an antihyperalgesic effect, increasing the mechanical threshold in neuropathic pain animals that was partially explained by an action on the ACC. Finally, the acute treatment with LP-211 blocked the switch in the Place Escape/Avoidance Preference test in the animals affected by neuropathic pain. We conclude that a direct modulation of the ACC through the activation of 5-HT 7 receptors dampens the emotional aspects of pain. Nevertheless, the systemic effect of LP-211 involves also other parts of the nociceptive system resulting in a substantial alleviation of the painful condition.

Keywords: Chronic Pain, Serotonin, ACC

1.25
Systems Neuroscience of Motor Function on the Continuum from Health to Psychosis

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Psychotic disorders are highly complex with regard to their symptomatic characteristics and aetiology. About 1-2% of the population are affected by psychosis during their lifetime. Impairments in motor function that occur in psychosis have been associated with aberrant neural activity and structure. It is still unclear whether differences in motor ability in healthy individuals are similarly related to distinct brain activation patterns in motor-related brain areas, suggesting that impairments in psychosis patients are extreme values on a trait continuum. In the present study, we examine the neural underpinnings of motor function on the spectrum from health to psychosis. We investigate the neural correlates by conducting electroencephalography (EEG) as well as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) in 120 subjects from four different groups: psychosis patients, subjects with a clinical high-risk for psychosis, first-degree relatives of psychosis patients and healthy controls. During MRI and EEG measurement, subjects perform an ankle movement task as well as a biological motion recognition task, using the point light walker paradigm. In addition, physiological markers such as heart rate variability and force variability are recorded. We hypothesize functional and structural neural abnormalities in the motor areas in relation to the strength of the behavioural disturbances. Our results will provide new insights into the neural basis, as well as the aetiology of motor function in psychosis.

Keywords: Psychosis, fMRI, EEG

Poster abstracts

Basic research animal

2.01
Lipid components contribute to the angiogenic and cytoprotective effects of EPC-derived conditioned medium.

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Evidence accumulated over the past years that stem / progenitor cells support tissue regeneration mainly by paracrine factors. So, it has been reported that endothelial progenitor cells (EPC) play an important role in revascularization and regeneration of numerous tissues. In the present work, we investigated the cytoprotective properties of secreted factors from EPC (EPC-CM) in an in vitro model of ischemia. In addition, we attempted to characterize the type of factors involved in the EPC-CM mediated functions. For that purpose, rat brain-derived endothelial cells (rBCEC4 cell line) were exposed to EPC-CM pretreated with proteolytic digestion, heat inactivation and lipid extraction. Moreover, the involvement of VEGF and IL-8, as canonical angiogenic factors, was investigated by means of neutralizing antibodies. We could demonstrate that EPC-CM significantly protected the rBCEC4 cells against an ischemic insult mimicked by induced by oxygen-glucose deprivation followed by reoxygenation. The cytoprotective effect was displayed by higher viable cell numbers and reduced caspase 3/7 activity. Heat inactivation, proteolytic digestion and lipid extraction resulted in a significantly reduced EPC-CM dependent increase of rBCEC4 viability, tube formation and survival following the ischemic insult. Importantly to note, we observed that VEGF and IL-8 neutralization did not affect the actions. In sum, our findings show that paracrine factors released by EPC activated a cytoprotective response on brain microvascular cells which relied on the concerted action of lipids and proteinaceous factors.

Keywords: paracrine factors, endothelial progenitor cells, oxygen-glucose deprivation, VEGF

2.02
Network dynamics of nociceptive and aversive processing in the anterior cingulate cortex

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The Anterior Cingulate Cortex (ACC) plays a central role in the evaluation of the affective and emotional aspects of pain. Accumulating evidence indicates that abnormal neuronal plasticity and a resulting hyperactivity of the ACC is the cause for the manifestation of the emotional distress that characterizes chronic pain conditions. However, little is known on how the functional organization of ACC microcircuits is affected in chronic pain. Apart from its involvement in pain perception, the ACC is engaged in a variety of other cognitive and emotional processes such as working memory, inhibitory control, conflict monitoring, fear, attention, salience and reward expectancy. How neuronal populations in the ACC can be involved in such a diversity of functions is a matter of debate. One intriguing hypothesis would be that the ACC is composed of multiple sub-circuits mediating separate aspects of behavior. Here we addressed whether the ACC possesses specialized neurons that process nociceptive information and how this putative microcircuit organization is affected in chronic neuropathic pain. Using in vivo recording of spiking activity in the mouse ACC, we have identified a subpopulation of neurons that are activated in response to nociceptive stimulation. Interestingly, this “nociceptive neurons” showed a preferential increase in spontaneous activity during chronic pain, suggesting that ACC hyperactivity might be restricted to a sub-network of pain-related cells. In order to gain insight into the organization and plasticity of the ACC, we are using in vivo two-photon calcium imaging to monitor the activity of the same network of neurons with single cell resolution on subsequent days during the transition to chronic pain. Our preliminary results show that nociceptive inputs are codified by the activity of a discrete and partially stable assembly of ACC neurons. This fine-tuned

representation is degraded after peripheral nerve injury resulting in a wide-spread neuronal representation of noxious events.

Keywords: Anterior Cingulate Cortex, Chronic pain, Aversion, Calcium imaging, neuronal microcircuits

2.03
Involvement of Müller glia cells in retinal degeneration/regeneration in zebrafish and mouse

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The aim of the project is to identify and compare the role of Müller glia cells (MCs) during retinal degeneration/regeneration in two different animal models: one with high regeneration capacity (zebrafish) and the other with low regeneration capacity (mouse). Even if it might be difficult to compare MC role between species as mouse and fish inhabit different environment, understanding the mechanisms by which zebrafish can regenerate a damaged retina may suggest strategies for stimulating retinal regeneration in mammals and, in particular, in humans. Furthermore, modulation of endogenous repair mechanism will minimize adverse effects including rejection or tumor formation seen after transplantation of retinal or stem cells. Therefore, activation, proliferation and differentiation of MCs and the pathways involved in these processes will be investigated.

Keywords: Cellular biology, zebrafish, laser treatment, retina, degeneration, regeneration, Müller cells, optical coherence tomography

2.04
Central nervous system neurodegeneration: The mechanism of ionic zinc neurotoxicity

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The inability of central nervous system (CNS) pathways to regenerate after injury can lead to lifelong, devastating functional losses. Although research over the past years has identified several strategies to enhance neurons intrinsic growth state, the extent of recovery is still limited. Data on the role of zinc in the healthy nervous system or its role in brain injury is scarce. It is known, however, that zinc is essential for many cell functions. In many neurons, zinc is packaged in the synapses in tiny vesicles, together with the neurotransmitters that these cells use to communicate with other cells. Zinc release is normally tightly controlled, because high levels are toxic to cells. Recently, we were able to get retinal ganglion cells, the projection neurons of the eye, to survive and regenerate their axons following an injury of the optic nerve, by simply chelating ionic zinc that is released as a result of the injury itself (Li Y, Andereggen L, et al., Proc Natl Acad Sci U S A. 2017 Jan 10). Here, we explore the mechanisms of ionic zinc neurotoxicity, and elucidate its involvement in the nigrostriatal system, providing novel insights into mechanisms of CNS neurodegeneration.

Keywords: Zinc, cell survival, axon regeneration, Parkinson's disease

2.05
Dynamical modulation of theta-gamma coupling during REM sleep

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Theta phase modulates gamma amplitude during spatial navigation and rapid eye movement sleep (REMs). Although the REMs theta rhythm has been linked to spatial memory consolidation, the underlying mechanism remains unclear. We investigate dynamics of theta-gamma interactions across multiple frequency and temporal scales in simultaneous recordings from hippocampal CA3, CA1, subiculum, and cortical EEG. We show that theta phase significantly modulates three distinct gamma bands during REMs, dynamically. Interestingly, we further show that theta-gamma coupling swings between different hippocampal and cortical sites during REMs and tends to increase over a single REMs episode. Comparing to active wake, theta-gamma coupling during REMs is significantly increased for subicular and cortical, but not for CA3 and CA1, recordings. Finally, we show that optogenetic silencing of septohippocampal GABAergic projections significantly impedes both theta-gamma coupling and theta coherence, two neural mechanisms of working and long-term memory. We hypothesize that theta-gamma coupling provides a predominant mechanism for information processing within each brain region, while the switching of coupling activity between regions establishes a specific phase-space coding of information during memory processes and sleep.

Keywords: Rapid eye movement sleep; theta rhythm; phase-amplitude coupling; contextual memory; optogenetics; GABAergic neurons.

2.06
Potential beneficial effect of CNS autoimmunity on experimental stroke

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Background: Experimental data indicate similar molecular mechanisms in cerebral hypoxia and autoimmune neuroinflammation. Consequently, potential effects of immunomodulatory MS therapeutics on secondary stroke-associated inflammatory damage were investigated in clinical trials. Mutual interactions of autoimmune, antigen-specific inflammatory reactions and cerebral ischemia have not been extensively investigated thus far. **Objective:** To investigate the effects of autoimmune antigen-specific CNS inflammation on cerebral ischemia. **Methods:** Active MOG_{35-55} experimental autoimmune encephalomyelitis (EAE) vs. sham control (CFA-immunized animals) was induced in male C57Bl/6 mice. Transient middle cerebral artery occlusion (tMCAO, 60 minutes) was performed in the acute phase of EAE or in sham-immunized mice. Brain tissue was collected after 24h. Infarct and edema size and immune cell infiltration were analyzed histopathologically. **Results:** Actively immunized mice showed gradually smaller infarct sizes inversely correlating with EAE score ($p<0.005$, $\tau b=-0.38$, $n=43$). This held similarly true for edema size ($p=0.006$, $\tau b=-0.32$) and combined damaged tissue (infarct+edema size; $p<0.001$, $\tau b=-0.408$). Group comparisons of severely diseased mice (score 5-7, $n=6$) versus both non-diseased immunized ($n=21$) and control mice ($n=34$) demonstrated significantly smaller infarct sizes ($p=0.003$ and 0.005) and smaller areas of combined tissue damage ($p=0.004$ and 0.008). In addition, we detected a shift in immune cell infiltration in favor of both diffuse and partially rim-like configuration of CD45+ cells 24h after tMCAO in the ipsilateral hemisphere. **Conclusions:** Our data indicate a positive influence of antigen-specific CNS autoimmunity on both infarct size as primary tissue damage and edema as an early consequence of the ischemic insult. This hints at a very early involvement of immune mechanisms in this experimental model of stroke. As this is not detected in both control (CFA) and MOG-immunized mice which did not develop clinical signs, this effect appears to be linked to active CNS involvement of an antigen-specific inflammatory reaction. This ongoing work will contribute to a better understanding of interactions between CNS autoimmunity and cerebral ischemia.

Keywords: Multiple Sclerosis, stroke, neuroinflammation, cerebral ischemia, autoimmunity

2.07
Functional regulation of abcg2 by apolipoprotein E in context of immunotherapies for multiple sclerosis

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Background: The multi-drug resistance transporter ABCG2, a member of the ATP-binding cassette (ABC) family, mediates the efflux of different immunotherapeutics, e.g. teriflunomide (teri) and mitoxantrone (MX), across cell membranes and organelles. Functional relevance of ABCG2 on MX-treatment was demonstrated in MS and its animal model, experimental autoimmune encephalomyelitis (EAE), but data are lacking for teri. Apolipoprotein E (apoE) is known to have modulatory effects on ABC-transporter activity as demonstrated in experimental stroke. We therefore hypothesize that *apoE* affects teri-efficacy via *abcg2*-modulation. **Objective:** To investigate effects of *apoE*-deficiency on *abcg2*-transporter expression and its functional impact on teri-induced cellular effects *in vitro*. **Methods:** *abcg2*-mRNA expression (spleen/splenic T cells and B cells) from wildtype (wt) and *apoE*$^{-/-}$-mice were analyzed by qRT-PCR. Stimulated T cells from wt, *apoE*$^{-/-}$ and *abcg2*$^{-/-}$-mice (anti-CD3, 10µg/ml + anti-CD28, 10ng/ml; 48h) were treated with teri (12.5-100µM). T cell apoptosis (annexinV/PI) and proliferation (CSFE) were analyzed by flow cytometry. **Results:** We observed a 1.8-fold (p=0.003) higher *abcg2*-mRNA expression in splenic T cells from *apoE*$^{-/-}$-mice compared to wt, which was not present in B cells (p=ns). Consistently, inhibition of T cell proliferation was 1.2-1.6-fold lower in *apoE*$^{-/-}$-mice than in wt (p<0.05, 50-100µM teri, 48h). In line with the hypothesized effect of abcg2 on teri-efficacy, T cells from *abcg2*$^{-/-}$-mice revealed increased inhibitory effects of teri (1.3-1.9-fold increase compared to wt, p<0.05, 12.5-100µM teri, 48h). Teri-induced T cell apoptosis as independent functional readout demonstrated analogous results (*apoE*$^{-/-}$: 1.2-fold decrease, p<0.01, 50µM teri and *abcg2*$^{-/-}$: 1.2-fold increase, p<0.05, 12.5µM teri; each compared to wt). **Conclusions:** Our data indicates that regulation of *abcg2*-expression by *apoE* has functional effects on cellular effects of teri. This ongoing work aims at contributing to an understanding of inter-individual differences in efficacy and adverse events of prominent ABCG2-transporter substrates such as teri.

2.08
REM sleep reactivation of lateral hypothalamus neurons associated with goal-oriented behaviors conditions food intake during wakefulness.

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In mammals, the sleep-wake cycle and feeding are conserved behaviors engaging a broad range of brain regions. The hypothalamus is a key hub for the integration and regulation of these two behaviors as it receives information from central and peripheral origins and modulates brain activity through widespread projections. Here, we investigate how single GABAergic and glutamatergic cells in the lateral hypothalamus (LH^{vgat}, LH^{vglut2}, respectively) modulate food intake, sleep and arousal. We first measure the neuronal activity of LH^{vgat} or LH^{vglut2} neurons during sleep and food intake paradigms by targeting the expression of the calcium sensor GCaMP6s to the LH of vgat-IRES-Cre or BAC-vglut2::Cre mice, respectively, and subsequently imaging Ca^{2+} transients from single neurons with a miniaturized fluorescence microscope in freely-behaving mice. We found that a large proportion of LH^{vgat} and LH^{vglut2} neurons show maximal activity during REM sleep, while other subsets of cells were active during wakefulness. When the animals were subjected to a free-access feeding paradigm we found that most LH^{vgat} neurons showed maximal activity during food approach or -intake, whereas LH^{vglut2} neurons were predominantly active in behaviors unrelated to feeding. When comparing the functional identity of the neurons for sleep and feeding, we found that LH^{vgat} cells associated with food approach or food intake identity were

significantly more likely to be active during REM, but not NREM, sleep episodes. No such specialization was observed for LH^{vglut2} neurons. Interestingly, food-approach and food-intake LH^{vgat} neurons showed a sequential activation profile according to the animal behavior, however, they were reactivated during REM sleep in a random fashion, independently of their functional identities. These findings indicate that LH^{vgat} neurons are multi-functional encoding aspects of both, sleep- and metabolic function. Furthermore they propose that LH^{vgat} neuron activation in REM sleep may modulate circuits for homeostatic integration via non-experience dependent mechanisms.

Keywords: hypothalamus, GABA, glutamate, wakefulness, REM sleep, goal-oriented behavior, metabolism, calcium imaging

2.09

The role of endothelial antigen-presentation in the migration of CD8+ T cells across the blood-brain barrier in neuroinflammation

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Multiple sclerosis (MS) is the most common inflammatory disease of the central nervous system (CNS) with unknown etiology to this date. Accumulating evidence points to a critical role of CD8+ T cells in MS pathogenesis. Immune cell recruitment into the CNS is controlled by the blood-brain barrier (BBB). The molecular mechanisms mediating the multi-step migration of CD8+ T cells across the BBB are incompletely understood. It has been suggested that endothelial antigen (Ag)-presentation contributes to CD8+ T-cell entry into the CNS. This prompted us to study if BBB endothelium can present Ag and if this process may contribute to CD8+ T-cell trafficking across the BBB. Using primary mouse brain microvascular endothelial cells (pMBMECs) as in vitro model for the BBB we found up-regulation of MHC-class I expression but also of the co-inhibitory molecule PD-L1 after 24 hours of stimulation with TNF-a/IFN by immunofluorescence (IF) staining. To investigate whether stimulated pMBMECs can induce Ag-dependent T-cell proliferation, we co-cultured CSFE-labeled T-cell receptor transgenic OT-I CD8+ T-cells recognizing the ovalbumin peptide SIINFEKL in the context of H2Kb, with Ag-pulsed stimulated pMBMECs. Irrespective of the presence or absence of SIINFEKL, pMBMECs induced the proliferation of the naïve OT-I T cells as visualized by CFSE-dilution employing flow cytometry. Also, β2-microglobulin deficient (β2M -/-) pMBMECs induced OT-I cell proliferation suggesting that pMBMECs can induce proliferation of naïve OT-I cells in an antigen and MHC class I independent fashion. At the same time we observed that OT-I cells killed WT but not β2M-/-pMBMECs in the presence of the SIINFEKL peptide, suggesting that full activation of OT-I effector functions needs engagement of OT-I cells with endothelial MHC class I presenting their cognate antigen. By employing in vitro live cell imaging, we finally asked if endothelial Ag-presentation contributes to the multi-step extravasation of activated OT-I cells across the BBB under physiological flow. Presence or absence of SIINFEKL peptide on MHC-class I expressing pMBMECs did not affect OT-I cell arrest on pMBMECs under physiological flow. However, in presence of SIINFEKLOT-I cell crawling was significantly reduced. This was accompanied by rapid OT-I cell mediated killing of pMBMECs under flow. Thus brain endothelial Ag-presentation triggers rapid CD8+ T-cell mediated killing of BBB endothelial cells under physiological flow in vitro. Taken together out data suggest that Ag-presentation by brain endothelial cells may lead to CD8+ T-cell mediated focal BBB breakdown, which is recognized as a major hallmark of MS pathogenesis.

Keywords: Multiple Sclerosis; Blood-Brain Barrier; T Cells; Immune Cell Trafficking

2.10
Centromedial thalamus (CMT) control of cortical state during sleep

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Mammalian midline thalamus consists of five nuclei of ambiguous function whose integrity is obligatory for maintenance of consciousness, cognition and sleep. Each of these functions relies on a tightly regulated UP-DOWN-states of thalamo-cortical networks. Here, we investigated the role of the midline thalamus on control of local and global cortical states during sleep. We found that CMT spiking activity is modulated across sleep states. CMT local field potentials show a phase-advancement over other midline-thalamic nuclei and cingulate cortex during the UP state of spontaneous NREM slow waves, which is consistent with a CMT-Cingulate monosynaptic pathway. We further found that optogenetic activation of CMT entrains cortical spiking activity in cingulate, parietal and occipital cortex and was accompanied by wakefulness. Interestingly, parietal and occipital entrainment occurred simultaneously, lagging behind responses observed in the cingulate. Using dual activation-silencing stimuli, we showed that spike and LFP transfer to parietal an occipital cortex, as well as wakefulness, is dependent on the dorsal thalamus. In contrast, stimulation of VB did not result in wakefulness. Collectively these results implicate the CMT as the main driver of local cortical UP-states via monosynaptic input to the cingulate. However, changes in global cortical state and wakefulness, are dependent on a functional relay located in the dorsal thalamus. These results support both a correlative and causal role of midline and dorsal thalamus in control of frontal and global cortical states during sleep and propose a novel target for deep brain stimulation for disorders of consciousness.

Keywords: Sleep, Thalamus, Optogenetics

2.11
Two-photon imaging of T-cell interactions with the cervical spinal cord microvasculature during EAE

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T-cell migration across the blood-brain barrier (BBB) is a crucial step in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS). Two-photon intravital microscopy (2P-IVM) has been established as a powerful tool to study cell-cell interactions in inflammatory EAE lesions in living animals. In EAE, central nervous system (CNS) inflammation is strongly pronounced in the spinal cord, an organ in which 2P-IVM imaging is technically very challenging and has been limited to the lumbar spinal cord. In addition cervical spinal cord lesions are seen in MS. We have therefore established a novel spinal cord window preparation allowing to use 2P-IVM to image immune cell interactions with the cervical spinal cord microvascular endothelium during EAE over extended time. We observed differences in the angioarchitecture of the cervical spinal cord versus the lumbar spinal cord, which will entail different hemodynamic parameters in these different vascular beds and thus may influence T-cell trafficking to different parts of the spinal cord. We presently employ this novel window preparation to directly compare the multi-step extravasation of encephalitogenic Th1 versus Th17 across cervical spinal cord microvessels in vivo. This analysis includes investigation of the cellular pathway of T-cell diapedesis across the BBB by visualization of endothelial junctions in this vascular bed.

Keywords: Cervical spinal cord window, Two-photon intravital microscopy, experimental autoimmune encephalomyelitis, blood-brain barrier, T-cell migration

2.12
Effects of Intracerebral Hemorrhage on the Extrapyramidal System and Endogenous Neurogenesis

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Intracerebral hemorrhage (ICH) constitutes one of the most devastating forms of cerebrovascular disease. Dysfunction of the nigrostriatal dopaminergic system might be involved in neurological deficits seen after striatal ICH. Stimulation of endogenous neural stem cell proliferation might be involved in structural brain plasticity after ICH. In the present study, we investigated the effects of deep basal ganglia hemorrhage on the dopaminergic projection system and on endogenous neurogenesis in a rat model of ICH. ICH was induced in rats by combining a striatal microtrauma with slow infusion of 30 ul autologous blood. Amphetamine-induced rotational behavior was assessed after 7, 20 and 30 days, and the numbers of tyrosine hydroxylase (TH) expressing dopaminergic neurons and total neuronal cells in the SN were analyzed at days 2 and 30 post ICH. Effects on endogenous stem cell proliferation in the subventricular zone (SVZ) and hippocampus were assessed using the 5-bromo-2-deoxyuridine (BrdU) incorporation method. Rats suffering ICH showed an increase in ipsiversive rotational behavior at day 7 post ICH, followed by a partial recovery at days 20 and 30 ($p < 0.05$). ICH resulted in a decrease of 45% and 15% in the number of TH-immunoreactive cells in the ipsilateral SN at day 2 and 30, respectively ($p < 0.05$). In contrast, the loss of total neuronal cells was less pronounced with a decrease of only 25% at day 2 ($p < 0.05$) and no significant difference at day 30. Rats with ICH also exhibited significantly higher numbers of BrdU-positive cells in the ipsilateral SVZ ($p < 0.05$) and hippocampus ($p < 0.05$). These observations indicate that ICH induces a transient downregulation of TH expression in a subpopulation of SN neurons and promotes endogenous stem cell proliferation. Our results provide evidence that the ipsilateral nigrostriatal dopaminergic system is significantly affected by striatal ICH. Stimulation of neurogenesis at remote sites influences cerebral plasticity and might constitute a rudimentary endogenous repair mechanism after the insult. Neuroprotective strategies for dopaminergic neurons and/or dopamine substitution, as well as modulation of adult neural stem cell proliferation, might therefore be effective for improving the functional outcome after striatal ICH.

Keywords: brain, intracerebral hemorrhage, dopamine, neurogenesis, plasticity

2.13
Potent and selective endocannabinoid reuptake inhibitors (SERIs) to treat neuropsychiatric disorders

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Selective endocannabinoid reuptake inhibitors (SERIs) represent a new class of modulators of the endocannabinoid system (ECS) which are potentially more effective and safer than other cannabinoid drugs. Unlike the covalent inhibitors of endocannabinoid (EC) degrading enzymes (e.g., FAAH, MAGL), SERIs can modulate EC actions in a time- and space-restricted manner, thus potentially avoiding broad effects. Recently, we reported the identification of the first SERI prototype (WOBE437) and its biological and pharmacological characterization in vitro and in vivo (Chicca et al., 2017). WOBE437 inhibited anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) uptake in different cell types with nanomolar potency and high selectivity towards all the other components of the ECS. Using a radiolabeled 14C-WOBE437 analog, we showed that the molecule only marginally penetrates into the cytosol and hits a saturable membrane target. In vivo, WOBE437 behaved as an "indirect CB1-agonist" showing pronounced anti-inflammatory, analgesic and anxiolytic effects in mice lacking the high-dose anxiogenic effects seen with direct agonists of CB1 receptors. WOBE437 underwent a preliminary safety screen against a panel of several CNS-related targets and metabolic stability tests using human and liver

microsomes. It showed a potentially good bioavailability and brain penetration upon oral administration in mice. Intriguingly, WOBE437 robustly and specifically modulated EC levels in the brain, primarily increasing 2-AG. Over 7 days of treatment, WOBE437 induced a moderate but significant 1.5 times rise of both AEA and 2-AG compared to vehicle, without triggering a loss of functional CB1 receptors in the brain (desensitization). In pharmacological experiments, the time-dependent distribution of WOBE437 was quantified and correlated to its effects on different metabolites. Using LC-MS/MS and targeted lipidomics, we showed that WOBE437 specifically modulate AEA and 2-AG levels in mice and ex vivo in human whole blood. This effect is in agreement with the potent anti-endotoxemia, anti-inflammatory, analgesic and anxiolytic effects of WOBE437 in mice. Interestingly, EC reuptake inhibitors significantly raise corticosterone levels upon repetitive treatment in mice. In conclusion, WOBE437 and other SERIs may represent a promising and innovative therapeutic strategy to treat neuropsychiatric disorders, in particular characterized by low EC levels and hypocortisolism. Although stress conditions, anxiety related disorders and depression are generally associated with higher cortisol levels, a growing amount of clinical evidence indicate that in certain forms of chronic stress, PTSDs, depression and in the "burnout syndrome", cortisol levels are significantly lower as compared to normal conditions (Yehuda et al., 2011 Lennartsson et al., 2015).

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Keywords: endocannabinoid system; anandamide; 2-arachidonoyl glycerol; endocannabinoid reuptake; inhibitor; anxiety

2.14
Absence of the Junctional Adhesion Molecule (JAM)-B Ameliorates Experimental Autoimmune Encephalomyelitis

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In multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE) autoaggressive CD4+ T cells cross the blood-brain barrier (BBB) and cause neuroinflammation. Therapeutic targeting of CD4+ T-cell trafficking into the central nervous system (CNS) using the humanized anti-a4-integrin antibody natalizumab has proven beneficial for the treatment of MS, however comes with the risk of progressive multifocal leukoencephalopathy, probably caused by inhibition of CD8+ T cell entry into the CNS. We have recently shown that CD8+ T cell indeed employ a4b1-integrins to migrate across the BBB. Besides vascular cell adhesion molecule - 1 (VCAM-1) we identified junctional adhesion molecule -B (JAM-B) localized in BBB tight junctions as alternative vascular a4b1-integrin ligand mediating CD8-T cell trafficking across the BBB. Using a novel transgenic mouse model with constitutive lack of JAM-B we here investigated the role of JAM-B in mediating T-cell trafficking into the CNS during EAE. Although JAM-B-/- C57BL/6 mice developed ameliorated EAE when compared to wild-type littermates, we found higher numbers of infiltrating immune cells in the CNS of JAM-B-/- C57BL/6 mice suffering from EAE. The majority of inflammatory cells was trapped behind the BBB in leptomeningeal and perivascular spaces. This suggests that although JAM-B is not required for T-cell diapedesis across the BBB absence of JAM-B limits inflammatory cell entry into the CNS parenchyma. The signalling events downstream of vascular JAM-B leading to amelioration of EAE are presently investigated.

Keywords: experimental autoimmune encephalomyelitis, tight junction, blood brain barrier

2.15
Cellular and molecular mechanisms directing the pathway of Th1 versus Th17 T-cell diapedesis across the blood-brain barrier

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The endothelial blood-brain barrier (BBB) maintains central nervous system (CNS) homeostasis and strictly controls T-cell trafficking into the CNS. During multiple sclerosis (MS) or its animal model, experimental autoimmune encephalomyelitis (EAE), autoaggressive γ-interferon-producing CD4+ Th1 or IL-17-producing CD4+ Th17 enter the CNS causing neuroinflammation. The molecular mechanisms mediating Th1 cells migration across the BBB are quite well studied, and we could previously show that endothelial cell surface levels of ICAM-1 direct CD4+ T cell to paracellular or transcellular sites for diapedesis. It has been suggested that Th17 cells may use different mechanisms from Th1 cells to extravasate. This prompted us to directly compare the cellular and molecular mechanisms used by those two CD4+ T-cells subsets to cross the BBB. Using primary mouse brain microvascular endothelial cells (pMBMECs) as an in vitro BBB model, we compared the multi-step extravasation of in vitro polarized myelin oligodendrocyte (MOG) transgenic T-cell receptor Th1 and Th17 cells by live cell imaging under physiological flow. Our preliminary observations show that higher numbers of Th1 than Th17 cells arrested on pMBMECs under noninflammatory and inflammatory conditions, whereas Th17 cells have higher tendency to detach. After subsequent polarization, Th1 cells crawled with higher speed over the pMBMECs compared to Th17 cells. Similar numbers of diapedesis events were observed for both subsets. It remains to be shown if Th1 and Th17 cells cross the BBB preferentially via the paracellular or transcellular route. Thus, we have demonstrated that the dynamic interaction of Th1 cells with the BBB is distinguishable from that of Th17 cells. To analyse their potential molecular mechanism, we are currently comparing the trafficking molecule signature of both T-cell subsets by multi-parameter flow cytometry. To identify genes involved in regulating the cellular pathway of T-cell diapedesis across the BBB, we have performed RNAseq analysis from pMBMECs expressing high or low levels of endothelial ICAM-1 and thus favouring trans- versus paracellular T-cell diapedesis, respectively. After sequential selections, we have identified a set of candidate genes for biological validation. Identification of distinct molecular mechanisms mediating Th1 and Th17 cells' migration across the BBB will allow to accurately foresee CNS-specific adverse effects of the increasing numbers of therapies in many chronic inflammatory diseases targeting T-cell trafficking or even depleting peripheral T cells. Furthermore, our approach will allow to identify novel therapeutic targets within the successful framework of therapeutic targeting of immune cell trafficking to the CNS for the MS treatment.

Keywords: Blood Brain Barrier, T-cell trafficking, T-cell diapedesis route, T-cells subsets in Multiple Sclerosis

2.16
Claudin-3 deficient C57BL/6 mice display intact brain barriers

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The blood-brain barrier (BBB), composed by highly specialized microvascular endothelial cells, and the blood-cerebrospinal fluid barrier (BCSFB), formed by the choroid plexus epithelial cells, are the principle barrier sites between the blood and the brain. During neurological disorders, such as multiple sclerosis or its animal model experimental autoimmune encephalomyelitis (EAE), focal loss of brain barriers' integrity is observed. Claudin-3 is localized at the tight junctions (TJs) of the BBB and the BCSFB and a specific contribution in BBB integrity has been suggested by its selective loss in microvessels surrounded by inflammatory infiltrates in EAE. This prompted us to study the role of claudin-3 in barrier integrity in the homogenous genetic background of C57BL/6 mice. To this end, we have generated claudin-3-/- mice and studied the development of EAE in these mice and their wild-type littermates. To our surprise, we did not observe any significant difference in disease development in claudin-3-/- mice when compared to the WT. This in vivo study was accompanied by in vitro investigations on the barrier properties of our BBB and BCSFB cellular models. Immunofluorescent stainings and measurement of

transelectrical resistance and permeability of different molecular tracers across our models revealed no differences in barrier properties of WT or claudin-3-/- mice. Furthermore, we decided to investigate if there would be a compensatory mechanism of other TJs proteins in the absence of claudin-3 that would explain the normal functionality of the brain barriers in the absence of this important TJ molecule. To do so, we performed RNA seq with our BBB in vitro model and we noticed that there is no claudin-3 expression. Absence of claudin-3 in the BBB was also observed in vivo, through qPCR and Western blot analysis of freshly isolated brain capillaries from WT and claudin-3-/- mice. Additionally, we also concluded that claudin-5 and occludin levels were not altered in the absence of claudin-3 when compared to the WT. On the other hand, we observed that we have an up-regulation of claudin-1 and claudin-2 protein levels in the BCSFB, in vitro and in vivo, in the absence of claudin-3. In conclusion, we report the surprising finding that claudin-3 is not being expressed in the brain capillaries, which explains the negative results we had with our in vivo and in vitro experiments. However, claudin-3 is present in the BCSFB and its absence leads to an upregulation of other TJs proteins of the BCSFB, namely claudin-1 and claudin-2, contributing to a normal barrier functionality.

Keywords: claudin-3, blood-brain barrier, blood-cerebrospinal-fluid barrier, experimental autoimmune encephalomyelitis

Poster abstracts

Basic research human

3.01
Who is cooperative and why: Baseline activation in brain areas involved in perspective-taking and self-control explains individual differences in cooperative behavior

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A key feature of human societies is their members' willingness to cooperate, yet not all people are equally cooperative. Human cooperative behavior is characterized by substantial individual differences. Attempts to investigate the factors behind this heterogeneity have so far mainly relied on subjective measures with little predictive power. Here, we used resting electroencephalography to measure objective and stable individual differences in neural baseline activation in combination with an ecologically valid cooperation task that allowed us to classify people into different behavioral types using a model-free clustering approach. The behavioral results showed three distinct types of cooperators: strong cooperators (cooperation level clearly above average), conditional cooperators (demonstrating an intermediate cooperation level that is adjusted to the expected cooperative behaviour shown by other people) and non-cooperators (cooperation level clearly below average). The brain results revealed that strong cooperators and conditional cooperators had higher baseline activation in the right temporo-parietal junction (rTPJ) than non-cooperators, and that conditional cooperators had higher baseline activation in the left lateral prefrontal cortex (lLPFC) than strong cooperators and non-cooperators. These brain regions play key roles in perspective-taking (rTPJ) and self-control (lLPFC). Due to the fact that higher baseline activation is associated with improved functioning, we speculate that increased capacity to engage in perspective-taking increases the propensity to cooperate, while increased self-control capacity allows for the adjustment of this cooperative propensity, thereby enabling individuals to minimize the potential risk of being exploited by others. Overall, these findings suggest that distinctive cognitive processes may underlie the heterogeneous cooperative behaviors observed in humans.

Keywords: cooperation, individual differences, conditional cooperation, resting EEG, neural trait, temporo-parietal junction, lateral prefrontal cortex, perspective-taking, self-control

3.02
Resting EEG activity in TPJ/pSTS explains individual differences in the feeling of being looked at

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Direct eye gaze is a powerful stimulus in social interactions, yet people vary considerably in the range of gaze lines that they accept as being direct (cone of direct gaze, CoDG). Here, we searched for a possible neural trait marker of these individual differences. We measured the width of the CoDG in 137 healthy participants and related their individual CoDG to their neural baseline activation as measured with resting electroencephalogram (EEG). Using a source-localization technique, we found that resting theta EEG activity in the left temporo-parietal junction (TPJ) and adjacent posterior superior temporal sulcus (pSTS) was negatively correlated with the width of CoDG. Higher levels of resting theta EEG activity have been shown to be an inverse indicator of cortical activation, so the higher the baseline activation in left TPJ/pSTS, the wider the CoDG and thus the more liberal the individuals' judgments were in deciding whether a looker stimulus was making eye contact or not. These findings are the first demonstration of the neural signatures underlying individual differences in the feeling of being looked at.

Keywords: resting EEG, neural trait marker, eye gaze, cone of direct gaze, mentalizing network

3.03
Bilateral temporal tDCS enhances sleep-dependent episodic memory consolidation

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Introduction: Human sleep and its role in memory consolidation have been investigated intensively (Born, 2012). It has been found that non-rapid eye movement (NREM) sleep plays a crucial role in hippocampus-dependent declarative memory consolidation (Diekelmann, 2009). In particular, slow waves (SW), which occur mainly during slow wave sleep (SWS), correlate strongly with episodic memory performance (Mander, 2013). While many psychiatric patients suffer from sleep disturbances and memory impairments beside their main symptoms, a possible relation of diminished SWS and memory deterioration has not been sufficiently investigated. In the current proof-of-concept study, we aimed to enhance SW during SWS by inducing weak direct currents with transcranial direct current stimulation (tDCS) to the temporal lobes (including the hippocampi) of healthy participants. Our hypothesis was that increasing the cortical excitability during SWS, sleep-dependent memory consolidation should benefit from tDCS as compared to a placebo condition. **Methods:** A randomized, placebo-controlled double-blind crossover study design was conducted to apply bi-temporal anodal tDCS. DC with 2 mA (current density 0.03 mA/cm2, electrode size 35cm2 each) was delivered during SWS. Before sleep, participants performed an episodic memory task (face-occupation associations). Memory performance was measured by the number of correctly remembered items (hits). To obtain a value for sleep-dependent memory consolidation, the number of hits at delayed retention were subtracted from the number of hits at baseline. This value was taken to calculate the difference between tDCS and placebo which resulted in the tDCS memory effect. To test if the memory performance was related to the amount of stimulated SW, a partial correlation of the tDCS memory effect coefficient and the amount of SWS during stimulation was computed, with fatigue scores and learning duration as control variables. To this end, a 22-channel EEG was recorded for online sleep-staging and to timely engage the stimulation during SWS. EEG data was preprocessed including ICA, re-referencing to average reference, automatic tDCS-artifact detection, and filtering (0.5-2.0 Hz). Moreover, the data was segmented into 10s epochs that corresponded to clean EEG at SWS after the first stimulation. Finally, SW peak-to-peak amplitudes (> 75 µV) were extracted for comparison between tDCS and placebo stimulation. **Results:** Data of 13 participants (mean age 24, 21-32; 7 females, 6 males) was analyzed. The partial correlation between tDCS memory effect and amount of SWS stimulation showed a strong correlation of $r = 0.89$ and $p < 0.01$ ($df = 5$). The same analysis with the amount of SWS placebo stimulation did not reveal any effect ($r = -0.22$, $df = 7$, $p = 0.56$). Focusing on the electrophysiological tDCS effect, there was a moderate increase of SW amplitude in the tDCS compared to the placebo condition (tDCS: $M = 93.8$, $SD = 5.7$; placebo: $M = 90.4$, $SD = 6.9$; $T = 2.2$, $p < 0.05$). **Discussion:** This study indicates that it is possible to improve sleep-dependent memory consolidation by increasing cortical excitability using tDCS during SWS. Namely, the more SW were stimulated in participants, the better their episodic memory performance. This effect was independent from individual fatigue and learning strategies and was not observed in the placebo condition. Moreover, the increased SW amplitudes in the tDCS condition add electrophysiological evidence of the behavioral tDCS-effect which is in line with our expectations. Yet a few limitations have to be considered. The small sample size leads to a low certainty of the statistical effects. A general issue found in studies using tDCS is the low replication rate. Therefore, replication of the current results is needed in another cohort and also with patients before considering clinical application. Last, an fMRI study would reveal if tDCS increases hippocampal activation as targeted.

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Keywords: EEG, Learning, Memory, Sleep, tDCS

3.04
Modelling the multi-step migration of human T cells across the human blood-brain barrier under physiological flow in vitro: Introduction of a novel nanomembrane based flow chamber system

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The endothelial blood-brain barrier (BBB) in central nervous system (CNS) microvessels establishes an important interface between the immune system and the CNS. In multiple sclerosis (MS) BBB properties change and promote the migration of pathogenic T cells into the CNS. To this end molecular mechanisms mediating T-cell entry into the CNS has largely been studied in animal models, but translation of these findings in human models is still lacking. Recently a new human BBB model has been established by coculturing endothelial cells differentiated from human CD34+ cord blood cells with bovine pericytes. This model exhibits strong BBB characteristics like a low permeability and the expression of tight junction molecules like ZO-1 and claudin-5. Here we introduce successful adaptation of this in vitro BBB model to a flow chamber allowing for live cell imaging of T-cell migration across the BBB under physiological flow. This included adaptation of culture conditions for endothelial cell growth and BBB differentiation on nanoporous nitride membranes with high optical characteristics, as well as the replacement of the pericyte co-culture. To enable investigation of the interaction of small numbers of patient derived T cells with the BBB the flow chamber design was adapted accordingly. Using this novel in vitro model of the human BBB we started to study the multi-step extravasation of human T cells across the human BBB under flow in vitro. We introduce our novel BBB model as a powerful tool to investigate extravasation of rare patient derived T cells across the BBB under physiological flow.

Keywords: blood-brain barrier ; human ; in vitro model ; flow condition

3.05
Defining the cellular and molecular mechanisms mediating the migration of human CD4+ effector T-cell subsets across the human BBB in vitro: the role of PECAM-1 and CD99

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The blood-brain barrier (BBB) maintains central nervous system (CNS) homeostasis and strictly controls lymphocyte entry into the CNS. Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the CNS that causes pathological changes in the white and grey matter of the brain and spinal cord, and results in clinical disability. BBB breakdown, with a subsequent intrusion of inflammatory cells and soluble mediators into the CNS, is an early key step in the pathogenesis of MS. Natalizumab is a humanized monoclonal antibody that selectively targets the α4-subunit of the integrin VLA-4 and inhibits VLA-4 mediated interaction of autoagressive T cells with endothelial VCAM-1 on the BBB. This drug showed remarkable efficacy in preventing clinical and radiological relapse of MS patients and suggested that the BBB is the useful target for treatment of MS. Unfortunately, the use of this drug is associated with the development of progressive multifocal leukoencephalopathy (PML), which may be due to natalizumab mediated inhibition of CNS immunosurveillance. So, ultimate demand is to identify disease relevant pathogenic T-cell subsets and to investigate the differences in the molecular mechanisms used by each T-cell subset for crossing the BBB. To this end molecular mechanisms mediating T-cell entry into the CNS have largely been studied in animal models (experimental autoimmune encephalomyelitis: EAE), but EAE did not expect the occurrence of PML. Moreover, it is not possible to identify T-cell subsets relevant for immunosurveillance of the human CNS in animal models. Therefore studies with human cells are mandatory. We have recently established a novel in vitro model for the human by co-culturing brain like

endothelial cells (BLECs) differentiated from human CD34+ cord blood cells on a 0.4μm pore filter in two-chamber setup with bovine pericytes. Here we have adapted this model such that BLECs are grown to confluency on 3μm pore filters allowing for the subsequent study of T-cell migration across the BBB in vitro. To study if human CD4+ effector T cells cross the BBB through the endothelial junction (paracellular) or through a pore in the endothelial cells (transcellular) we have started to investigate the role of the junctional molecules PECAM-1 and CD99 in this process. PECAM-1 and CD99 have been shown mediate paracellular diapedesis of neutrophils across peripheral vascular beds. Their role in mediating the migration of human CD4+ effector T cell subsets across the human BBB remains to be explored.

Keywords: blood-brain barrier, multiple sclerosis, PECAM-1, CD99, T-cell

3.06
Cognitive Conflicts Impair Subsequent Free Recall Performance

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Encountering a cognitive conflict impairs immediate task performance, expressed as slowing and/or lower accuracy. However the consequences of encountering a conflict on subsequent memory are not clear. The current study was designed to investigate the impact of two types of cognitive conflict, task switching (vs. task repetition) and stimulus incongruency (vs. congruency), on subsequent free recall performance. In a study phase, participants had to switch between two semantic classification tasks with two simultaneously presented words. In Experiment 1, the stimuli were presented auditorily, in Experiment 2, they were presented visually. The experimental trials consisted either of two identical words (rendering them congruent) or two different words (rendering them incongruent). Following this study phase, participants completed a surprise free recall test. The results showed lower recall performance for switch compared to repetition stimuli. Moreover, congruent stimuli were better remembered than incongruent stimuli. Our results indicate that cognitive conflicts hurt subsequent memory performance.

Keywords: Task Switching, Stimulus incongruency, Free Recall, cognitive Conflict

3.07
Re-fixations in visual exploration for neglect patients and healthy controls

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Background: Visual attention and response inhibition are functionally linked together and are essential for successful control of eye movements. In patients with visual neglect deficits in response inhibition, resulting in perseverative behavior, are often observed. Empirically, visual perseverations can be operationalized using re-fixations. Previous studies using visual search tasks provide evidence that neglect patients show a tendency to re-fixate items in the right visual space. However, this has not yet been studied using free visual exploration tasks. Although a recent study using free visual exploration tasks could show that neglect patients fixate image regions of higher saliency on the left side of the visual space, findings on whether this is also true for re-fixations are lacking. **Objective:** In this study, we compared for both the left and right side of the visual space (1) the likelihood of re-fixating a previously fixated location and (2) the influence of saliency on the likelihood of a re-fixation between neglect patients and healthy controls. **Methods:** In this study, patients who suffered from visual neglect after a right-hemispheric stroke and healthy subjects participated. Participants performed a free visual exploration task (48 images from natural scenes or urban public places) presented on a monitor while their eye movements were recorded. For all the images in the free visual exploration task saliency maps were calculated using the computational model of Itty et al. 1998. As primary outcome, we considered the re-fixation rate, i.e. the number of re-fixations divided by the number of fixations. **Results:** There was a significant interaction between the subject

group (neglect patients or healthy controls) and the horizontal position (left or right visual space). For neglect patients, the re-fixation rate was significantly higher in the right than in the left visual space, while for healthy participants there was no significant difference in the re-fixation rates between the right and left visual space. Moreover, neglect patients had a significantly higher re-fixation rate than healthy participants in the right visual space, whereas there was no significant difference between the two groups in the left visual space. In a next step, we included saliency as variable in the models and tested for the interaction between subject groups, horizontal position and saliency. The effect of saliency on the re-fixation rate for neglect patients in the left visual space was significantly higher than in the right visual field, whereas in healthy subjects there was no significant difference in the effect of saliency between the left and right visual space. **Discussion:** This study showed that the previous findings on the re-fixations in neglect patients in visual search tasks also applies to free visual exploration tasks. For neglect patients, the likelihood that a fixation falls on a previously fixated region is higher in the right than in the left visual space. Moreover, our results show in accordance with previous results that the saliency is more pronounced in the left than in the right side for neglect patients. We found that besides the tendency to fixate more salient regions in the left visual space, saliency plays an even more important role for re-fixations. The present results indicate deficit in inhibitory control in neglect patients, since neglect patients re-fixate more in the right visual space and tend to re-fixate regions in left visual space more often with increasing saliency.

Keywords: Neglect, visual attention, response inhibition, perseverative behavior, refixation, saliency model

3.08
Ghostbusters for MRS: Automatic Detection of Ghosting Artifacts using Deep Learning

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Introduction: One of the major problems in clinical magnetic resonance spectroscopy (MRS), which has hindered its widespread use, is the need for local human expertise for quality assessment, given that artefacts are often not eye-catching for the inexperienced eye. There has been recent progress for automated quality filtering based on machine learning techniques, but their general use is by far not established and thus automatic detection of specific artifacts in spectra - and even more so the restoration of the affected spectra - would be extremely valuable to enhance the routine use of clinical MRS. One particular type of artifact that is targeted in this work is the so-called ghost or spurious echo. In spectroscopy, spurious echoes result from insufficient spoiling gradient power. Ghosting artifacts are problematic because they superimpose with metabolite peaks at varying frequencies and may thus preclude reliable area estimation. Ghost artifact detection by human experts is possible but takes time, is subjective and obviously relies on local expertise. So, automatic ghost detection and removal using machine learning could be a useful alternative method. **Methods:** Sixty-thousand brain metabolite spectra with and without ghosting artifacts were simulated such that they best mimic in-vivo spectra. Scripts were written in Python using the Keras library on top of the Theano backend to build the Deep Learning (DL) models. Simulated spectra were used for training DL models then used for predicting previously unused simulated and in-vivo spectra. Ghost detection: For the identification of ghosting artifacts, we defined deep learning models using Fully Connected Neural Networks (FCNNs) and Deep Convolutional Neural Networks (D-CNN). Approximately two-thirds of the spectra were used as input for training and then tested on one-third of the simulated data and 65 in-vivo spectra (32% with ghosting artifacts). Classification accuracy was evaluated based on the predicted and the true class labels. Ghost removal: Stacked What-Where Auto Encoders (SWWAE) built on residual blocks were used for removing the ghosting artifacts from spectra. Spectra with ghosting artifacts (25k) were used as input and corresponding spectra without artifacts (25k) were given as ground truth images. The trained SWWAE was tested on 5k independent spectra with ghosting artifacts to predict the artifact free spectrum. **Results and Discussion:** In this study, we show that it is possible to use deep learning to detect and remove ghosting artifacts. The initial results are extremely promising, reaching almost 100% accuracy in detecting ghosting artifacts on simulated and in-vivo spectra. Ghost removal using DL model also looks good on simulated spectra. This initial trial can be extended to larger testing sets of in vivo spectra with other acquisition parameters, pathology and or including other artifacts. Further extension of the methodology should address the detection and restoration of other artifacts.

Keywords: Deep learning, MR spectroscopy, Artifacts

3.09
Evidence for a synaesthesia specific advantage in episodic memory

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Synaesthesia is a phenomenon in which a certain perceived inducer, for instance a letter, elicits a secondary experience - the concurrent - for instance a colour. Several case and group studies have shown a memory advantage that could result from this synaesthetic experience. The goal of the present study was it to test for a general or a synaesthesia specific memory advantage. We tested four different types of synaesthetic participants: 29 grapheme-colour, 22 sound-colour-, 27 grapheme-colour-and-sound-colour- and 24 sequence-space synaesthetes compared to their matched controls. A recognition task for three different types of stimuli that were either inducer-related, concurrent-related or neither (word-, music- and colour-stimuli) was conducted. Results showed a general benefit for synaesthetes overall. Further, grapheme-colour-and-sound-colour synaesthetes showed an inducer specific advantage for music. A concurrent specific benefit for colour stimuli resulted for grapheme-colour- and sound-colour synaesthetes. These results indicate that if a memory advantage occurs, it is either related to inducer or concurrent and not both at the same time.

Keywords: synaesthesia, episodic memory, inducer, concurrent

3.10
Neural mechanisms mediating the effect of social cognition on control-averse behavior

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When others try to control our decisions, many of us will feel the urge to counteract and thereby reestablish our valued freedom of choice. This can lead to control-averse behavior with far-reaching consequences, such as breaking the law or noncompliance to medical treatments. The neural mechanisms underlying control-averse behavior, however, remain poorly understood. To close this gap we combined a social decision making task with functional magnetic resonance imaging in a sample of 51 healthy adults. While being scanned subjects allocated money to themselves and varying, anonymous interaction partners. Critically, their interaction partners either let them choose freely (Free condition) or requested a minimum amount to be returned, thereby controlling the subjects' choice options (Controlled condition). After each decision, subjects rated their feeling of being controlled and negative affects on pictorial assessment scales. The amount to which subjects returned less in the Controlled than in the Free condition measured individual control-averse behavior. After scanning, subjects indicated how strongly a list of social cognitions, such as perceived distrust, had influenced their decisions. The results show that in the Controlled compared with the Free condition, subjects report feeling more controlled and return smaller amounts. Their individual control-averse behavior also correlates positively with social cognitions. A whole-brain analysis reveals that control over the subjects' choice by the interaction partner is signaled in the temporoparietal junction (TPJ), a brain area that contributes to decision making when a social (or nonsocial) context is relevant for current behavior. Moreover, we find that individual control-averse behavior is associated with specific changes of neural connectivity between the right TPJ and an area in the dorsolateral prefrontal cortex (dlPFC) that has been associated with context-dependent value-based decisions. Critically, this TPJ-dlPFC connectivity mediates the effect of social cognition on control-averse behavior. Our results suggest that control aversion is associated with the integration of relevant social cognition into context-dependent decision making. The results show that in the Controlled compared with the Free condition, subjects report feeling more controlled and return smaller amounts. Their individual control-averse behavior also correlates positively with social cognitions. A whole-brain analysis reveals that control over the subjects' choice by the interaction partner is signaled in the temporoparietal junction (TPJ), a brain area that contributes to decision making when a social (or nonsocial) context is relevant for current behavior. Moreover, we find that individual control-averse behavior is associated with specific changes of neural connectivity between the right TPJ and an area in the dorsolateral prefrontal cortex (dlPFC) that has been

associated with context-dependent value-based decisions. Critically, this TPJ-dlPFC connectivity mediates the effect of social cognition on control-averse behavior. Our results suggest that control aversion is associated with the integration of relevant social cognition into context-dependent decision making.

3.11
Memory Consequences of Proactive and Reactive Cognitive Control

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Recent research on the influences of selective attention demands in cognitive conflict situations on remembering showed inconsistent memory consequences of cognitive control. The aim of the present study was to find an explanation for the conflicting results by disentangling proactive from reactive control mode. To this end a study by Richter and Yeung (2012) was extended to include the two conditions in a between subjects design. During the study phase participants were asked to perform two alternating decision tasks: An object and a word classification task. The proactive control group had predictable task switches, whereas the tasks alternated in random order for the reactive control group. The study phase was immediately followed by a surprise recognition memory test, where participants rated the stimuli as old versus new. Results of the study phase showed that the typically observed switch costs emerged in both conditions, which implies a higher need for cognitive control in switch trials. However, distinct patterns of results for the both groups were found by comparing the recognition performance. The memory consequences of reactive control strategies confirmed the outcomes of the study by Richter and Yeung: Memory for attended items was worse on switch trials than on repeat trials, this pattern was reversed for unattended items. Critically, the results of the proactive control group showed the opposite pattern. Collectively, our findings implicate differing influences of proactive and reactive control on selective attention, which in turn promotes encoding.

Keywords: Proactive and reactive cognitive control, memory, attention, task switching

3.12
No effects of transcranial DLPFC stimulation on implicit task sequence learning and consolidation

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Neurostimulation of the dorsolateral prefrontal cortex (DLPFC) can modulate performance in cognitive tasks. In a recent study, however, transcranial direct current stimulation (tDCS) of the DLPFC did not affect implicit task sequence learning and consolidation in a paradigm that involved bimanual responses. Because bimanual performance increases the coupling between homologous cortical areas of the hemispheres and left and right DLPFC were stimulated separately the null findings may have been due to the bimanual setup. The aim of the present study was to test the effect of neuro-stimulation on sequence learning in a uni-manual setup. For this purpose two experiments were conducted. In Experiment 1, the DLPFC was stimulated with tDCS. In Experiment 2 the DLPFC was stimulated with transcranial magnetic stimulation (TMS). In both experiments, consolidation was measured 24 hours later. The results showed that sequence learning was present in all conditions and sessions, but it was not influenced by stimulation. Likewise, consolidation of sequence learning was robust across sessions, but it was not influenced by stimulation. These results replicate and extend previous findings. They indicate that established tDCS and TMS protocols on the DLPFC do not influence implicit task sequence learning and consolidation.

Keywords: implicit task sequence learning, memory consolidation, transcranial stimulation, dorso-lateral prefrontal cortex (DLPFC)

3.13
Anti-Inflammatory Effects of Extracellular Vesicles Derived from Wharton's Jelly Mesenchymal Stem/Stromal Cells on Microglia

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Microglia cells are the resident immune cells of the central nervous system and are the main mediators of neuroinflammation leading to neurodegenerative disorders. Wharton's jelly mesenchymal stem/stromal cells (WJ-MSC) derived from umbilical cords have the capacity to reduce neuroinflammation and induce tissue regeneration in animal models of perinatal brain damage despite of their low long-term survival in host tissue. The therapeutic function of WJ-MSC is mainly ascribed to their complex paracrine machinery involving the release of cell-derived extracellular vesicles (EV). The aim of this study is to evaluate the anti-inflammatory potential of WJ-MSC-derived EV on microglia cells in vitro. The microglia cell line BV-2 was activated by 6 h and 24 h of lipopolysaccharide (LPS) stimulation and used as an in vitro model for infection-associated perinatal brain damage. WJ-MSC-derived EV were isolated from cell culture supernatants using a protocol consisting of several steps of successive high-speed and ultracentrifugations. WJ-MSC-derived EV pre-stained with the fluorescent cell tracker dye CM-DiI were co-cultured with microglia cells before visualization with immunocytochemistry (ICC). Microglia cells with or without co-culture with WJ-MSC-derived EV were evaluated for their production of pro-inflammatory cytokines in response to LPS stimulation by real-time PCR and enzyme-linked immunosorbent assay (ELISA). The effects of WJ-MSC-derived EV on LPS-induced activation of signaling pathways downstream of the toll like receptor 4 (TLR-4) were evaluated by Western Blotting. In co-culturing experiments, WJ-MSC-derived EV co-localize with microglia cells and suppress their activation-induced morphological changes in response to 6 h LPS stimulation. Furthermore, WJ-MSC-derived EV dampened the upregulation of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 and suppressed the production of inducible nitric oxide synthase (iNOS) in response to 6 h LPS stimulation. WJ-MSC-derived EV also suppressed the increase in TNF-α-secretion in response to 24 h LPS stimulation. Furthermore, WJ-MSC-derived EV also prevented LPS-induced activation of TLR-4 signaling pathways such as the suppression of the NF-κB inhibitor alpha (IκBα) and the phosphorylation of extracellular signal-regulated kinases (ERK) 1/2. In conclusion, we demonstrate that WJ-MSC-derived EV are potent modulators of microglia activation. Hence not only WJ-MSC, but also WJ-MSC-derived EV are able to support tissue regeneration by reducing neuroinflammation. As a result, WJ-MSC-derived EV represent a potential cell-free approach to treat perinatal brain damage.

Financial support by Gottfried and Julia Bangerter-Rhyner Foundation.

Keywords: Microglia Mesenchymal Stem/Stromal Cell Neuroinflammation Extracellular Vesicles

3.14
The effect of a single dose of escitalopram on sensorimotor networks

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The present study was intended to establish the effect of a single dose of escitalopram on motor task performance in humans. Ten healthy volunteers including five females and of median age 63 years performed a tactile manipulation task in two fMRI sessions using a double-blind cross-over design. The sessions began approximately three hours after ingestion of 20 mg escitalopram or of placebo presented in pseudorandom order. Each session consisted of two acquisitions each consisting of 24 presentations of 6 s duration with intervals

between object presentations varying pseudorandomly between 8 and 12 s. Principal component analysis of pre-processed fMRI time-series provided the basis for comparison of the two conditions. Correlation of the principal component (PC) time courses with the hemodynamic response function served to identify PCs related to the task. The corresponding PC image volumes could be classified by computing volume correlation coefficients with two mean component images obtained in a previous study using the same activation task and methods. Each condition yielded two mean components. Whereas the dominant component, representing a neuronal network for directed motor control, presented almost identical image volumes in both conditions, their expression in terms of temporal expression coefficients was significantly greater in the verum group. Dynamic causal modelling confirmed enhanced motor output as a result of a significantly increased connectivity between primary motor cortex and dorsal premotor cortex. The second component, representing a neuronal network associated with less motor control, was more often and more strongly expressed in the placebo condition.

Keywords: sensorimotor networks, escitalopram, fMRI, principal component analysis, dynamic causal modeling

3.15
Spatial asymmetries in free visual exploration and line bisection tasks - relationship and time-course

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When freely exploring pictures of natural scenes, neurologically intact individuals show a leftward bias in the direction of their first eye movement. This so called pseudoneglect, which is marked by an attentional bias towards the left side of the space, has been reported in both line bisection as well as in free visual exploration tasks. Whereas performance in line bisection tasks has been shown to be modulated by age, gender, and handedness; the free visual exploration pattern can be modulated by tonic alertness. To this end, the present study investigated whether the free visual exploration pattern can be predicted by the performance in a line bisection task, and whether additional factors such as age, gender, handedness, chronotype-derived alertness and tonic alertness can modulate the performance in these visuo-spatial tasks. Moreover, the time-course of spatial asymmetries in the free visual exploration task was investigated. Here we report data of 47 neurologically healthy adults (age range 22-86) who were instructed to freely explore a set of 120 photographs of natural and urban landscapes while their gaze was recorded by means of a contact-free eye-tracking system. A line bisection task was administered, and information concerning handedness, chronotype-derived alertness, and tonic alertness was obtained. To detect asymmetries in visual exploration, we analyzed the spatial location and the cumulative duration of participant's fixations as well as the direction of their saccades. Gaze data were regressed with the performance in the line bisection task and the effects of age, gender, handedness, chronotype-derived alertness and tonic alertness were analyzed. The results showed that the free visual exploration pattern was associated with the performance on the line bisection task (R2=.179, p=.003). Specifically, participants who showed a leftward (or rightward) deviation in the line bisection task had, on average, more fixations in the left (or right) side of the images, respectively. Notably, only chronotype-derived alertness contributed to the explained variance in the performance on the line bisection task (R2=.084, p=.045), with lower level of alertness being associated with a rightward bias in bisecting the lines. Moreover, none of the five factors contributed to the visual asymmetries in the free visual exploration task (R2=.075, p=.062). The analysis of the direction of the first saccade indicated that 62% of first saccades moved leftward. Most importantly, the detailed analysis of the time-course of free visual exploration pattern revealed that this leftward bias in image exploration is not restricted to the first eye movement, but that it lasted for approximately 1.7 seconds. A further second-by-second analysis showed that the average horizontal gaze position at second one (r=.334, p=.022) as well as second five (r=.290, p=.022) were positively correlated with the deviation in the line bisection task, thus extending our previous results and highlighting the importance of temporal dynamics when investigating attentional phenomena. Our study concurs with previous research providing evidence that the free visual exploration of natural scenes starts with the left side of the image, but it extends it in two important ways. Firstly, by directly comparing the outcome of two attentional tasks of visuo-spatial nature in a sample of neurologically healthy adults ranging from young adults to elderly

individuals; secondly, by providing a systematic and detailed time-course investigation of spatial asymmetries during scene perception.

Keywords: Visuo-spatial attention, Pseudoneglect, Free Visual Exploration, Line Bisection

3.16
In vivo characterization of the downfield part of 1H MR spectra of human brain at 9.4T: Magnetization exchange with water and relation to conventionally determined metabolite content

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Introduction: In the human brain, magnetic resonance spectroscopy is able to measure various metabolites of interest, visualized as peaks along a spectrum, which can be related to metabolism and functional processes. It is also able to measure chemical exchange at equilibrium, without disrupting the system. Typical clinical studies focus on the upfield (0 - 4.7 ppm) region of the spectrum; however, the downfield part at 5 - 10 ppm is much less well characterized, and could provide new information for clinical work and other exchange-based contrast methods. In this study, the downfield spectrum and corresponding proton exchange between water and urea have been measured for the first time in human brain in vivo, at 9.4 tesla, the highest magnetic field strength human scanner available worldwide. The use of ultra-high field strengths allows for increased separation between the peaks and also leads to an improved signal to noise ratio. **Materials and Methods:** Magnetic resonance spectroscopy data were acquired on a 9.4 T magnet in a white matter region of the brain in eleven healthy volunteers (two data sets were later removed due to artifacts) and in the occipital lobe of the brain (with a higher grey matter component) in a further eleven volunteers. Exchange with water was measured using an inversion transfer experiment, which involves specifically perturbing (inverting) the water proton magnetization, and waiting for certain delay times before data acquisition in order to measure varying amounts of exchange between the water protons and the other metabolites such as urea. The data were averaged and a model was developed to fit the fourteen visible peaks in the averaged spectra, including urea, at the various delay times. **Results and discussion:** The inversion transfer average series demonstrated peaks that were strongly modulated in intensity by exchanging magnetization with the inverted water signal. In particular, the fast-exchanging peaks included urea at 5.8 ppm and amide protons (related to proteins) in the 8.2-8.5 ppm range. The preliminary fitting model captured most of the peaks very well, and the improved peak separation at ultra-high field has allowed for more peaks to be included in the model compared to the ones used at lower magnetic field strengths such as 3 T (clinical strength). Exchange rates and T1 relaxation values for the exchanging peaks were obtained by Bloch McConnell simulations, and values were an agreement between the two brain locations. Correlations comparing metabolite concentrations upfield and peak areas downfield indicated that there was no significant contribution of upfield metabolites or macromolecules in the downfield peaks.

Keywords: proton MR spectroscopy; 9.4T; human brain; metabolites; ultra-high field

3.17

Inter-hemispheric balance and the impact of attentional load on visuospatial attentional deployment: a tDCS study

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Attention is crucial in everyday activities. The deployment of visual attention in space can also be affected by non-spatial attentional aspects, such as attentional load. In fact, in dual tasks, which require the concurrent execution of a non-spatial and a spatial attentional task, healthy participants show a rightward bias in visuospatial attentional deployment with increasing demands of the concurrent non-spatial task (i.e., with increasing attentional load). However, to date, the neural substrates of this attentional shift under high attentional load are poorly understood. The aim of the present study was to investigate the neural mechanisms subtending the impact of attentional load on the spatial deployment of attention by applying biparietal transcranial direct current stimulation (tDCS). Participants completed a dual task paradigm in which attentional load was manipulated by means of a non-spatial working memory task, and visuospatial attention was assessed by means of a detection task with lateralized targets. During completion of the dual task, tDCS was applied over the posterior parietal cortices (PPCs) of both hemispheres, in order to modulate the inter-hemispheric balance of excitability between these two homologous areas. Overall, participants completed a total of 3 sessions with the following tDCS protocols: sham stimulation, anode over left/cathode over right PPC (i.e., excitatory stimulation over left/inhibitory over right PPC), cathode over left/anode over right PPC (i.e., inhibitory stimulation over left/excitatory over right PPC). Preliminary results revealed no left/right asymmetries when reacting to lateralized targets of the spatial attentional task during low attentional load. However, a left/right asymmetry (i.e., increased reaction times for left- compared to right-sided targets) emerged under high attentional load in the sham condition. This asymmetry was exacerbated during biparietal anodal left/cathodal right tDCS, and disappeared with the reversed polarity (i.e., cathodal left/anodal right). Overall, the present findings demonstrate polarity specific effects of biparietal tDCS on visuospatial attentional deployment under high attentional load. They thus suggest that the impact of attentional load on the spatial deployment of attention is mediated by the PPCs and, in particular, by the inter-hemispheric balance of excitability between these two areas. Results are discussed within the framework of current attentional theories.

Keywords: Attentional load, visuospatial attention, non-spatial attention, transcranial direct current stimulation (tDCS)

Parallel symposium I

Gestural and fine motor deficits across neuropsychiatric disorders (Chair: S. Bohlhalter, S. Walther)

Assessment and treatment of fine motor deficits in Parkinson's disease

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Patients with Parkinson's disease (PD) often suffer from dexterous deficits, affecting different activities of daily living (ADL), such as dressing, tying shoe laces, using computer key-boards. These impairments add to the burden of PD, and therefore are expected to reduce quality of life (QoL). Standardized assessments, including Nine Hole Peg test and coin rotation test, provide a quick, reliable and valid impression about dexterous function. Besides that, patient recorded outcome measures, such as the DextQ-24, provide insight into difficulties with respect to dexterity related ADL. Based on a profound assessment, targeted rehabilitation interventions can be planned. These can be done on a one to one basis, supervised by a trained specialist, but can also be home based, being unsupervised. Newer technologies, including virtual reality Kinect based tools and app tablet based exercises may further support home based training.

Keywords: Dexterity, assessment, treatment, Parkinson's disease

Imaging of dexterity deficits in Parkinson's disease

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Parkinson's disease (PD) patients frequently suffer from dexterous deficits leading to impaired activities of daily living. Clinical studies suggest that dexterous deficits are associated with limb kinetic apraxia (LKA) rather than bradykinesia. Furthermore, it is suggested that LKA and ideo-motor apraxia (IMA) can occur concurrently and ultimately leading to poor outcome and impaired quality of life. In PD neuroimaging findings of LKA and IMA are sparse. In fact, only one group has investigated functional correlates of LKA (as well as IMA) in PD. However, there was some methodological criticism leaving the need for robust imaging data on LKA in PD. Therefore, we designed two studies using different neuroimaging approaches to examine neural correlates of LKA in PD in depth. Our first study examined neural correlates and functional connectivity during a LKA task compared to a bradykinesia test. We revealed an association of LKA with increased fMRI activation of the left praxis network in PD. In fact, this mirrors a neural correlate for the behavioral dissociation of LKA and bradykinesia. In addition, patients showed an increased functional connectivity of the left inferior parietal lobe (IPL) with the bilateral hippocampus and a decreased functional connectivity with the DLPFC. Therefore, PD may require more effort for executive control as an attempt to compensate for impaired motor skills. However, whether this altered connectivity is the cause or the consequence of altered IPL function in PD needs to be further evaluated. Our second study examined resting state cerebral blood flow (rCBF) changes measured with arterial spin labeling associated with LKA and IMA in PD and controls. We revealed that in controls increased left IPL perfusion is associated with better LKA and IMA performance. In addition, greater SMA perfusion is associated with better LKA performance in controls. However, patients seem to have lost this association.

Imaging of hand gesture impairments in schizophrenia

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Background: Schizophrenia is characterized by social interaction deficits. In particular, hand gesture use is impaired contributing to poor functional outcome. The neural correlates of impaired performance of gestures are currently unclear. Methods and results: In a in a set of interlocking and constitutive studies we investigated structural and functional neural correlates of impaired gesturing in schizophrenia. For the first time, we demonstrated that defective hand gesture use is linked to frontal lobe dysfunction and frontal grey matter deficits. Moreover patients with deficits in gesture production show cortical thinning in 12 key regions of a fronto-parieto-temporal network relevant for gesture performance. Using an event-related paradigm assessing brain activation during gesture planning and execution we demonstrate less prefrontal, but more IPL and limbic activity during gesturing in schizophrenia patients. In detail, we demonstrate less prefrontal, but more inferior parietal lobe (IPL) and limbic activity during gesturing in schizophrenia. IPL activity was associated with performance accuracy, whereas limbic activity was linked to delusion severity. Conclusion: These findings have implications for the understanding of the nature of gesture deficits in schizophrenia as they provide new insights into the neural underpinnings. Altered neural may reflect impaired social action planning and a limbic interference with gestures in schizophrenia contributing to poor gesture performance and consequently poor social functioning in schizophrenia.

Keywords: schizophrenia, gesture, social interaction, nonverbal communication, limbic system

Effects of Transcranial Magnetic Stimulation on motor symptoms of patients with psychiatric disorders

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Background: Repetitive Transcranial Magnet Stimulation (rTMS) has the potential to alter brain states underlying psychiatric symptoms. However, little is known about its effect on motor retardation, which is commonly found in schizophrenia and affective disorders. **Methods:** The study design is a single site four arm randomized, double-blind, sham-controlled trial to unravel the pathophysiology of psychomotor retardation. Patients with either schizophrenia or major depression, as well as reduced psychomotor performance are assigned to one of four groups, receiving sessions of rTMS of different stimulation parameters (inhibitory over DLPFC, inhibitory over SMA, facilitatory over SMA, and sham). Regardless of the type and the frequency of TMS, the stimulation protocol consists of 15 daily sessions during a 3 week period. Outcome is evaluated as improvement in gross motor behaviour (actigraphy, Salpetriere Retardation Rating Scale (SRRS)), fine motor function (finger tapping, coin rotation test), and hand gesture performance (TULIA). Intention to treat analysis with last-observation carried forward method was applied. **Results:** After inclusion of 18 patients (approximately 20% of intended) the first results demonstrate a significant change of motor retardation (SRRS) over time, with a time x group interaction. Other parameters still lack significant effects over time due to limited statistical power. **Conclusion:** Preliminary results show a positive effect of rTMS on motor retardation.

Parallel symposium II

Regenerative neuroscience (Chair: V. Enzmann)

Culture of Lgr5-positive cells from the early postnatal murine retina.

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Recently it has been shown that the retina harbors a cell population which expresses the Leucine-rich repeat containing G-protein receptor 5 (Lgr5). This marker was identified as an adult stem cells marker in the intestine and was found to be expressed in several other adult SC populations of epithelial tissues. In the retina Lgr5 is expressed in glycinergic amacrine interneurons. Even though Lgr5-postive amacrine cells demonstrate properties of differentiated interneurons they also contribute to the generation of new retinal cells in adult animals. Therefore, we would like to investigate if Lgr5-postive cells can be cultured and expanded in vitro and whether they can differentiate into different retinal cell types. For the experiments Lgr5EGFP-Ires-CreERT2 knock-in mice were used. In a first step whole retinae from P1 and P5 animals were cultured as spheres in low adherence culture plates. In the neonatal mouse retina Lgr5 can be detected from P4. In accordance with this finding no GFP-positive cells were initially found in P1 cultures. Yet after 8 days in culture GFP expression could be detected. Immunohistochemistry performed on 3rd generation spheres showed that not all Lgr5-positive cells expressed Syntaxin, a marker of mature amacrine cells. Furthermore, Lgr5-positive cells from P5 retinae were sorted by FACS and cultured as spheres. However, the cells did not proliferate under the chosen culture conditions. These preliminary results demonstrate that Lgr5-positive cells can be cultured in vitro, albeit no proliferation was seen. Therefore, in a next step different culture conditions will be assessed. Furthermore, Syntaxin-negative Lgr5-cells will be further investigated to analyze whether these cells correspond to a progenitor-like cell type.

Keywords: Retina Regeneration

Beneficial effect of ProteinY* on hearing loss during experimental pneumococcal meningitis

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Over 5% of the world's population suffer from hearing loss. Sensorineural hearing loss is also the most common long-term deficit after pneumococcal meningitis, occurring in up to 30% of surviving patients. Treatment options for inner ear pathologies are currently limited and novel pharmaceutical treatments are highly needed. Here, we tested the putative otoprotective properties of the recombinant ProteinY* with previously reported anti-inflammatory, anti-apoptotic and neuronal protective functions, in an experimental model of pneumococcal meningitis. Pneumococcal meningitis was induced in infant rats (n=28). Animals were randomized for treatment of systemically applied ProteinY (3x 50 µg) (n=13) or vehicle (n=15). Hearing thresholds were assessed by measuring auditory brain stem responses (ABR) 1 and 3 weeks after infection and spiral ganglion neuron and hair cell density were determined by histological analyses 3 weeks after infection. We observed lower ABR thresholds in animals receiving the compound versus untreated animals, reaching significant levels 1 week post infection for clicks and pure tones at 4 kHz and 16 kHz and 3 weeks post infection at frequencies of 8 kHz and 32 kHz. Moreover, we observed a reduced percentage of animals presenting high hearing thresholds (80-100dB) in the compound treated cohort. Spiral ganglion neuron density did not differ significantly when comparing infected untreated versus ProteinY-treated animals. The same holds true for numbers of inner and outer hair cells.

Nevertheless, when animals were stratified according to the severity of hearing loss, we observed statistically significant higher numbers of remaining inner and outer hair cells in the ProteinY-treated group compared to the untreated group in animals with severe hearing loss (threshold above 80 dB). In conclusion, ProteinY appears to be a promising therapeutic option with the potential to improve hearing thresholds as well as to protect hair cells in case of severe bacterial meningitis. *ProteinY (Patent currently being filed).

Keywords: bacterial meningitis, sensorineural hearing loss, hair cells, spiral ganglion neurons, streptococcus pneumonia

An ex vivo model for ischemic brain injury induced by cardiac arrest

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Introduction: Sudden cardiac arrest (CA) is the most important cause of global brain ischemia. Due to a lack of effective therapies to treat the subsequent brain damage, most patients are left with incomplete neurological recovery. Several brain regions, including the hippocampus, are particularly affected by a transient hypoxic-ischemic insult. This selective vulnerability" is observed in rodent models as well as in humans. **Objectives:** To develop an ex vivo surrogate for the in vivo rat model of cardiac arrest/resuscitation, using organotypic hippocampal cultures (OHCs) for the evaluation of regenerative therapeutic approaches using grafting of neuronal stem and progenitor cells (NPCs). **Methods:** Hippocampi from rats pups were cut into slices, cultivated for one week, and then subjected to oxygen-glucose deprivation (OGD) to reproduce in vitro the hypoxic-ischemic injury observed after CA. Duration of OGD was optimized to reproduce the extent and pattern of damage observed in vivo. Neuronal damage was quantified by Fluoro-Jade B (FJ) staining, specific for degenerating neurons. For grafting experiments, NPCs were isolated from hippocampi of newborn rats, expanded as neurospheres and grafted into injured cultures. Immunohistochemistry was used to characterize the cellular composition of neurospheres. **Results:** OHCs submitted to 33 minutes of OGD developed hippocampal damage to a similar extent as observed in the in vivo model. A significantly higher amount of FJ-positive cells was found after OGD in the hippocampal CA1 segment compared to the normoxic control. The cellular composition of the neurospheres, showed the presence of numerous nestin-, doublecortin- and Ki67-positive cells, confirming the presence of NPCs. Differentiation of these cells towards neurons for one week yielded a significant proportion of βIII-tubulin-positive cells. After NPCs transplantations into OGD-injured OHCs, viable cells were found at different time points after grafting, confirming the overall feasibility of the procedure. **Conclusions:** We successfully reproduced damage to CA1 neurons of the hippocampus ex vivo after OGD, as observed in vivo after CA. Neurospheres contained proliferating neuronal progenitors with the potential to differentiate into mature neurons. The survival, migration and differentiation of grafted cells are currently assessed using NPCs isolated from Green Fluorescent Protein transgenic rats, therefore facilitating the identification of the grafted cells. This project represents a first step towards a cell-based regenerative therapy for ischemic brain damaged consecutive to CA.

Keywords: Ischemic brain damage, regenerative therapy, neuronal stem cells

Anti-Inflammatory Effects of Extracellular Vesicles Derived from Wharton's Jelly Mesenchymal Stem/Stromal Cells on Microglia

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Microglia cells are the resident immune cells of the central nervous system and are the main mediators of neuroinflammation leading to neurodegenerative disorders. Wharton's jelly mesenchymal stem/stromal cells (WJ-MSC) derived from umbilical cords have the capacity to reduce neuroinflammation and induce tissue regeneration in animal models of perinatal brain damage despite of their low long-term survival in host tissue. The therapeutic function of WJ-MSC is mainly ascribed to their complex paracrine machinery involving the release of cell-derived

extracellular vesicles (EV). The aim of this study is to evaluate the anti-inflammatory potential of WJ-MSC-derived EV on microglia cells in vitro. The microglia cell line BV-2 was activated by 6 h and 24 h of lipopolysaccharide (LPS) stimulation and used as an in vitro model for infection-associated perinatal brain damage. WJ-MSC-derived EV were isolated from cell culture supernatants using a protocol consisting of several steps of successive high-speed and ultracentrifugations. WJ-MSC-derived EV pre-stained with the fluorescent cell tracker dye CM-DiI were co-cultured with microglia cells before visualization with immunocytochemistry (ICC). Microglia cells with or without co-culture with WJ-MSC-derived EV were evaluated for their production of pro-inflammatory cytokines in response to LPS stimulation by real-time PCR and enzyme-linked immunosorbent assay (ELISA). The effects of WJ-MSC-derived EV on LPS-induced activation of signaling pathways downstream of the toll like receptor 4 (TLR-4) were evaluated by Western Blotting. In co-culturing experiments, WJ-MSC-derived EV co-localize with microglia cells and suppress their activation-induced morphological changes in response to 6 h LPS stimulation. Furthermore, WJ-MSC-derived EV dampened the upregulation of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 and suppressed the production of inducible nitric oxide synthase (iNOS) in response to 6 h LPS stimulation. WJ-MSC-derived EV also suppressed the increase in TNF-α-secretion in response to 24 h LPS stimulation. Furthermore, WJ-MSC-derived EV also prevented LPS-induced activation of TLR-4 signaling pathways such as the suppression of the NF-κB inhibitor alpha (IκBα) and the phosphorylation of extracellular signal-regulated kinases (ERK) 1/2. In conclusion, we demonstrate that WJ-MSC-derived EV are potent modulators of microglia activation. Hence not only WJ-MSC, but also WJ-MSC-derived EV are able to support tissue regeneration by reducing neuroinflammation. As a result, WJ-MSC-derived EV represent a potential cell-free approach to treat perinatal brain damage.

Financial support by Gottfried and Julia Bangerter-Rhyner Foundation.

Keywords: Microglia Mesenchymal Stem/Stromal Cell Neuroinflammation Extracellular Vesicles

Parallel symposium III

Promoting neuronal plasticity in neuropsychiatric disorders (Chair: S. Klöppel, C. Nissen)

The role of sleep in recovery following ischemic stroke

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Despite advancements in understanding the pathophysiology of stroke and the state of the art in acute management of afflicted patients as well as in subsequent neurorehabilitation training, stroke remains the most common neurological cause of long-term disability in adulthood. To enhance stroke patients' independence and well-being it is necessary, therefore, to consider and develop new therapeutic strategies and approaches. We postulate that sleep might play a pivotal role in neurorehabilitation following stroke. Over the last two decades compelling evidence for a major function of sleep in neuroplasticity and neural network reorganization underlying learning and memory has evolved. Training and learning of new motor skills and knowledge can modulate the characteristics of subsequent sleep, which additionally can improve memory performance. While healthy sleep appears to support neuroplasticity resulting in improved learning and memory, disturbed sleep following stroke in animals and humans can impair stroke outcome. In addition, sleep disorders such as sleep disordered breathing, insomnia, and restless legs syndrome are frequent in stroke patients and associated with worse recovery outcomes. Studies investigating the evolution of post-stroke sleep changes suggest that these changes might also reflect neural network reorganization underlying functional recovery. Experimental and clinical studies provide evidence that pharmacological sleep promotion in rodents and treatment of sleep disorders in humans improves functional outcome following stroke. Taken together, there is accumulating evidence that sleep represents a "plasticity state" in the process of recovery following ischemic stroke. However, to test the key role of sleep and sleep disorders for stroke recovery and to better understand the underlying molecular mechanisms, experimental research and large-scale prospective studies in humans are necessary. The effects of hospital conditions, such as adjusting light conditions according to the patients' sleep-wake rhythms, or sleep promoting drugs and non-invasive brain stimulation to promote neuronal plasticity and recovery following stroke requires further investigation.

Keywords: Ischemic stroke, Sleep disorders, Recovery, Neurorehabilitation, Neuroplasticity, Sleep architecture, EEG

Optogenetic Modulation Of Sleep Slow Wave After Focal Ischemic Stroke

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Objectives: Disturbances of sleep-wake cycle and brain state oscillations are frequent after stroke and are associated to sub-optimal rehabilitation and negative long-term behavioural outcomes. Experimental studies demonstrated that sleep supports the reorganization of neuronal connections and neuroplasticity during stroke recovery. In this study, we investigate the role of sleep oscillations on brain plasticity following stroke using optogenetic techniques combined to in vivo electrophysiology in mice. **Methods:** We expressed ChR2 (activation), ArchT (inhibition) or mCherry (control) in inhibitory (VGAT) or excitatory (CamKII) deep layer cortical cells of the peri-infarct area to render them light sensitive. These were delivered using adeno-associated viruses (AAV2DIO-EF1-ChR2-EYFP, AAV2DIO-EF1-ArchT-EYFP, AAV2DIO-EF1-EYFP, CamkII-ChR2-EYFP, CamkII-ArchT-EYFP,

CamkII-ArchT and CamkII-mCherry) and were injected into layer V of forelimb somatosensory cortex of Tg(VGAT)-IRES::Cre and wild type mice, respectively. Animals were chronically implanted with optical fibers and multiple tetrodes in ipsi-and contra-lateral cortical layer V. Experimental stroke was induced by Middle Cerebral Artery Occlusion (MCAO). Tetrodes recording and optical stimulation were conducted 24h before and after the stroke. **Results:** 24h after stroke down state rate was reduced during slow-wave-sleep in the peri-infarct area, while rapid-eye-movement sleep duration decreased as well as cross frequency coupling between theta and gamma oscillations. To optogenetically investigate the contribution of excitatory versus inhibitory cortical neurons to altered sleep oscillations we firstly confirmed the presence of transfected cells within the layer V, forelimb somatosensory cortex through immunohistochemistry. Amongst all the stimulation protocols tested, we found that optical silencing of pyramidal cells in layer V of the cortex robustly induced both LFP and single unit spike activity similar to a down-state of the neuronal network that correlates with a quiescent period of the recorded unit activity. **Conclusion:** We successfully targeted the layer V neuronal cells of the somatosensory cortex in both transgenic and wild type mice and showed that optogenetical induction of down state is possible and represents the first step in the modulation of sleep-like oscillation.

Keywords: Sleep Slow Waves, stroke recovery, sleep, optogenetic modulation of cortical network

The synaptic plasticity model of therapeutic sleep deprivation in major depression

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Therapeutic sleep deprivation (SD) is a rapid acting treatment for major depressive disorder (MDD). The current presentation integrates to two major hypotheses of MDD and sleep, the synaptic plasticity hypothesis of MDD and the synaptic homeostasis hypothesis of sleep-wake regulation, into a novel synaptic plasticity model of therapeutic SD in MDD. The model puts the idea forward that sleep/wake-dependent shifts in synaptic plasticity, i.e., the neural basis of adaptive network function and behavior, represent a critical mechanism of therapeutic SD in MDD. Particularly, it proposes that therapeutic SD, by homeostatically enhancing cortical synaptic strength, shifts the initially deficient inducibility of associative synaptic long-term potentiation (LTP) in patients with MDD in a more favorable window of associative plasticity. Further determining the mechanisms of action of SD is expected to contribute to the development of novel fast acting treatments for MDD, one of the major health problems worldwide.

Effects of transcranial direct current stimulation on synaptic plasticity

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While transcranial direct current stimulation (tDCS) is widely tested as a new tool for neuromodulation, be it as a neuroenhancer used by healthy young individuals or in a clinically relevant context for the treatment of cognitively impaired patients, its mechanism of action remains largely unknown. So far, it is assumed that the excitability of neurons in the brain area beneath the anode increases whereas cathodal stimulation leads to a decrease in neuronal excitability in the targeted region. Furthermore, animal studies have shown that tDCS can amplify synaptic plasticity exhibiting characteristics that are evocative of long-term potentiation, the process underlying learning and memory. Despite these insights, large response heterogeneities, observed both within and across subjects, still hamper the reliability of tDCS as a therapeutic agent. With regards to behaviour, a lower baseline performance seems to be the prerequisite for tDCS-induced benefits. Additionally, links between neurotransmitter levels, γ-Aminobutyric acid and glutamatergic metabolites in particular, and behavioural tDCS gains have been uncovered. Ultimately, understanding the workings of tDCS on a biological level and consequentially construing biological markers for its beneficial application are crucial steps in the optimization of the technique especially concerning an individualized treatment.

Keywords: transcranial direct current stimulation, synaptic plasticity, long-term potentiation, neurotransmitters

Parallel symposium IV

Neuroinflammatory diseases (Chair: A. Oevermann)

Combining adjuvant daptomycin with doxycycline reduces neuroinflammation and neurofunctional sequela in in experimental pneumococcal meningitis

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Background: Bacterial meningitis is associated with high mortality and morbidity rates. An overshooting inflammatory reaction resulting from immune activation by bacterial components drives the pathophysiology leading to brain damage. Neurofunctional deficiencies resulting from brain damage and hearing loss after meningitis are particularly detrimental during the period of learning and behavioural development in children. We aim to improve the outcome of pneumococcal meningitis by synergistically targeting different pathophysiological mechanisms responsible for brain damage in bacterial meningitis by combining adjunctive therapies previously shown to be neuroprotective when used as monotherapies. **Methods:** Eleven day old Wistar rats were infected intracisternally with 7.1 ± 3.5 x 105 cfu/ml S.pneumoniae and randomized for treatment with a combination adjuvant therapy (n=78) consisting of daptomycin (10mg/kg, s.c., single application) plus ceftriaxone (100mg/kg, i.p. every 12 hours) plus doxycycline (30mg/kg, i.p, once daily combined with ceftriaxone), or a monotherapy (n=78) with ceftriaxone (100mg, i.p., every 12 hours) plus saline (s.c., single application) in control animals. Cortical damage and hippocampal apoptosis were assessed histomorphometrically 42 hours after infection. Cytokine expression levels were analysed using a magnetic multiplexing system. Three weeks after infection, evoked auditory potentials (ABR) were used to assess the hearing thresholds of the rats. Cochlear histology was performed to quantify cochlear fibrosis and damage to the spiral ganglion neurons. **Results:** At 42 hours after infection, combined adjuvant therapy with daptomycin plus doxycycline increased the survival rate from 64.1% in controls to 85.8% (log-rank p=0.007) and alleviated weight loss compared controls (+1.0% weight gain with combination therapy vs 2.8% weight loss in monotherapy, p=0.002). The cortex of infected rats showed significantly less damage in the animals with the combined treatment regimen (1.2% vs 5.0% damage of total cortex volume, p=0.03). In addition, expression of the inflammatory cytokines IL-1β, IL-6 and IL-10 were significantly ($p<0.05$) reduced in the combined treatment group. Animals treated with combined adjunctive therapy showed a strong trend towards better hearing capacity three weeks after the infection (median hearing threshold of 65dB vs 80dB in controls, p=0.077). Mildly infected animals were protected from meningitis-induced hearing loss (median hearing threshold of 40dB vs 80dB in controls, p=0.048) and showed a significant reduction of cochlear fibrosis (from 10.2% in controls to 1.2%, p=0.008). **Conclusion:** The combination therapy with the non-lytic antibiotic daptomycin and doxycycline with its inhibitory effect on microglia and matrix-metalloprotease (MMP) showed to be neuroprotective and otoprotective. These findings, together with the lower mortality identify the combination of adjuvant daptomycin with doxycycline as a promising therapeutic option to improve the outcome of pneumococcal meningitis.

Keywords: pneumococcal meningitis, neuroinflammation, infant rat model

Prevention of canine distemper virus-mediated neurological disorders

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Despite the availability of efficient vaccines, measles virus (MeV) and canine distemper virus (CDV) still induce important economical and health impairments. Both viruses initially target immune cells for viral amplification, which in turn results in viremia and further dissemination to other tissues (including the brain). Although antivirals may synergize with vaccination campaigns, lack of molecular understanding of both viruses' mode of action precludes the rationale design of potent inhibitors. Latest data suggest that brain invasion relies on the presence of an unknown "brain receptor" as well as a functional viral entry complex. The latter machinery consists of two

interacting surface glycoproteins (termed H and F), which act in concert to fuse the viral envelope with the host cell plasma membrane. In more details, upon receptor engagement, the tetrameric H-protein undergoes sequential conformational changes that trigger F-structural refolding for membrane fusion. The H-ectodomain contains a membrane-proximal tetrameric stalk region that interacts with two membrane-distal dimeric head units via four putative flexible connectors. While H-heads bind to cognate receptors and H-stalk triggers F, the precise role of the H-connectors in the cell entry process remains to be elucidated. Here, structure-guided mutagenesis of the H-connectors coupled with functional, biochemical and virological analyses strongly suggested that structural plasticity within the H-connectors is strictly required to productively promote F-activation. In summary, our data provided evidence that antivirals targeting and stabilizing the H-connectors may translate into beneficial clinical interventions, including prevention of virus-mediated neurological diseases.

Keywords: Canine distemper virus, brain invasion, cell entry machinery, H protein-microdomain, antivirals

Vitamin D increases glucocorticosteroid efficacy in Multiple Sclerosis

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Background: Glucocorticosteroid (GC)-resistance in acute relapse therapy increases disability in MS. GC-resistance is associated with reduced GC-receptor (GCR) expression. **Objective:** We investigated the potential of vitamin D (VD) to modulate GC-efficacy. **Methods:** GC-induced apoptosis in human/murine T cells was analyzed by FACS (annexinV/PI). GCR-expression was quantified by ELISA. Functional relevance was investigated in vitro and in vivo (MOG35-55 EAE) using GCR- (BalbC GRdim$^{-/-}$; C57BL/6-LckCre/GCR$^{fl/fl}$) deficient. 25(OH)D_3 levels from MS patients with stable disease (n=56), steroid-resistant relapse (n=30) and steroid-responsive relapse (n=24) were analyzed by immunoassay. **Results:** In human T cells 1,25(OH)$_2D_3$ (10nM) upregulated GCR (1.4-fold; $p<0.05$) leading to a 60%-increase of GC-induced apoptosis. This functional VD-GC synergism was absent in T cells with GCR-impairment (GRdim$^{-/-}$ mice). In line, VD-GC combination therapy ameliorated EAE, but only in animals with functional GCR in T cells. 25(OH)D_3 levels in steroid-resistant MS patients (median, IQR: 21.9, 21.3 nmol/l) were lower compared to stable (48.8, 36.9 nmol/l) and steroid-sensitive patients (33.5, 53.6 nmol/l, each $p<0.05$). In contrast to GC-responsive patients, steroid-resistant MS patients showed an increase of MPS-induced T cell apoptosis when co-incubated with VD in vitro ($p<0.05$). **Conclusions:** Our data demonstrates that VD modulates GCR-dependent GC-signaling. Our findings will assist to identify mechanisms to overcome steroid resistance during MS relapse therapy.

The role of endothelial antigen-presentation in the migration of CD8+ T cells across the blood-brain barrier in neuroinflammation

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Multiple sclerosis (MS) is the most common inflammatory disease of the central nervous system (CNS) with unknown etiology to this date. Accumulating evidence points to a critical role of CD8+ T cells in MS pathogenesis. Immune cell recruitment into the CNS is controlled by the blood-brain barrier (BBB). The molecular mechanisms mediating the multi-step migration of CD8+ T cells across the BBB are incompletely understood. It has been suggested that endothelial antigen (Ag)-presentation contributes to CD8+ T-cell entry into the CNS. This prompted us to study if BBB endothelium can present Ag and if this process may contribute to CD8+ T-cell trafficking across the BBB. Using primary mouse brain microvascular endothelial cells (pMBMECs) as in vitro model for the BBB we found up-regulation of MHC-class I expression but also of the co-inhibitory molecule PD-L1 after 24 hours of stimulation with TNF-a/IFN by immunofluorescence (IF) staining. To investigate whether stimulated pMBMECs can induce Ag-dependent T-cell proliferation, we co-cultured CSFE-labeled T-cell receptor

transgenic OT-I CD8+ T-cells recognizing the ovalbumin peptide SIINFEKL in the context of H2Kb, with Ag-pulsed stimulated pMBMECs. Irrespective of the presence or absence of SIINFEKL, pMBMECs induced the proliferation of the naïve OT-I T cells as visualized by CFSE-dilution employing flow cytometry. Also, β2-microglobulin deficient (β2M -/-) pMBMECs induced OT-I cell proliferation suggesting that pMBMECs can induce proliferation of naïve OT-I cells in an antigen and MHC class I independent fashion. At the same time we observed that OT-I cells killed WT but not β2M-/-pMBMECs in the presence of the SIINFEKL peptide, suggesting that full activation of OT-I effector functions needs engagement of OT-I cells with endothelial MHC class I presenting their cognate antigen. By employing in vitro live cell imaging, we finally asked if endothelial Ag-presentation contributes to the multi-step extravasation of activated OT-I cells across the BBB under physiological flow. Presence or absence of SIINFEKL peptide on MHC-class I expressing pMBMECs did not affect OT-I cell arrest on pMBMECs under physiological flow. However, in presence of SIINFEKLOT-I cell crawling was significantly reduced. This was accompanied by rapid OT-I cell mediated killing of pMBMECs under flow. Thus brain endothelial Ag-presentation triggers rapid CD8+ T-cell mediated killing of BBB endothelial cells under physiological flow in vitro. Taken together out data suggest that Ag-presentation by brain endothelial cells may lead to CD8+ T-cell mediated focal BBB breakdown, which is recognized as a major hallmark of MS pathogenesis.

Keywords: Multiple Sclerosis; Blood-Brain Barrier; T Cells; Immune Cell Trafficking