UNIVERSITÄT BERN

Clinical Neuroscience Bern

Thursday, 31st March 2016, 9.00 – 17.30
University of Bern, vonRoll, Hörraumgebäude,
Fabrikstrasse 6, Bern

11th Annual Meeting
Brain Connectivity

Program and abstracts

Welcome

Dear Participants

It is my pleasure to welcoming you to the 11th annual meeting of Clinical Neuroscience Bern, an inter-faculty research focus of the University of Bern. It will take place in the vonRoll area of Bern on March 31st, 2016 and is focused on brain connectivity.

Established by the faculties of medicine and human science in 2004, Clinical Neuroscience Bern will further pursue its aim to promote knowledge, communication and collaboration between related fields of neuroscience. At present, it includes more than 150 researchers involved in clinical and translational neuroscience in a variety of disciplines such as neurology, psychiatry, psychology, neurosurgery, neuroradiology, neurophysiology, neurobiology and neurogenetics. Interested scientists from other faculties are also welcomed. We cordially invite members and non-members to attend our annual meeting and to submit research abstracts. It is an opportunity to present results and future projects to colleagues and scientists in related fields of research.

The board of Clinical Neuroscience Bern continues to develop the network and also decides on structural reorganisation. This year's annual meeting therefore has a special focus on informing members about the new structure, especially the new strategic board of CNB and the election of the new executive committee.

We are also very pleased and honored that our event will start with an opening address given by Christian Leumann, vice-rector for research of the University of Bern and elected rector of the University of Bern from Summer 2016. The program will include two key-lectures on Network Asymmetry and Human Cognition (Marco Catani, London) and on Cellular Resolution Connectomics (Moritz Helmstaedter, Frankfurt am Main). There will be six short presentations selected from the submitted abstracts followed by a poster session. In the afternoon, we would like to introduce you to the new structure by presenting a part of the work of some research groups.

I hope that the program piques your interest.

Claudio L. Bassetti
on behalf of the board of Clinical Neuroscience Bern CNB

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«Brain connectivity»
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08.00 – 09.00	Registration and Poster Setup	Foyer
09.00 – 09.15	**Welcome addresses** Christian Leumann, Vice-Rector for Research University of Bern and elected Rector of the University of Bern from summer 2016 Claudio Bassetti, Speaker Clinical Neuroscience Bern (CNB)	Hall 001
09.15 – 10.00	**Key-note 1** **Network Asymmetry and Human Cognition** Marco Catani, Natbrainlab, King's College London (UK) Chair: René Müri, Department of Neurology, Inselspital, Bern	
10.00 – 10.30	Coffee break	Foyer
10.30 – 11.30	**Short presentations, 6 selected abstracts à 10 minutes** Chairs: Thomas Dierks, University Hospital of Psychiatry, Bern Walter Senn, Department of Physiology, University of Bern	Hall 001
11.30 – 14.00	Lunch	Foyer
11.30 – 12.30	**CNB group leader's meeting** on special invitation, for CNB group leaders only	Hall 004
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14.00 – 14.45	**Key-note 2** **Cellular resolution connectomics** Moritz Helmstaedter, Max-Planck-Institut für Hirnforschung, Frankfurt am Main (D) Chair: Thomas Nevian, Department of Physiology, Bern	Hall 001
14.45 – 15.00	Coffee break	Foyer
15.00 – 15.05	**New CNB structure: Clusters and Networks** Claudio Bassetti, Speaker CNB, Bern	
15.05 – 15.20	**Cluster I: Center for Cognition, Learning and Memory CCLM** Katharina Henke, Institute of Psychology, Bern	
15.20 – 15.35	**Cluster II: Bern Network for Epilepsy,** **Sleep and Consciousness BENESCO** Claudio Bassetti, Department of Neurology, Inselspital, Bern	
16.00 – 16.15	**Cluster III: Regenerative Neuroscience** Daniel Surbek, Department of Obstetrics and Gynecology, Inselspital, Bern and Volker Enzmann, Department of Ophthalmology, Inselspital, Bern	Hall 001
16.15 – 16.30	**Cluster IV: Basic Neuroscience** Thomas Nevian, Department of Physiology, University of Bern	
16.30 – 16.45	**Cluster V: Neuroimaging** Roland Wiest, University Institute for Diagnostic and Interventional Neuroradiology, Inselspital Bern	
16.45 – 17.00	**Cluster VI: Translational Psychiatry** Werner Strik, University Hospital of Psychiatry, Bern	
17.00 – 17.30	**Poster Awards** – Clinical research – Basic research animal – Basic research human Chair: Werner Strik, Speaker CNB, Bern	

Key Note Lecture 1

Network Asymmetry and Human Cognition

Prof. Marco Catani
Natbrainlab, King's College London (UK)

Chair: René Müri, Department of Neurology, Inselspital Bern

Key Note Lecture 2

Cellular resolution connectomics

Prof. Moritz Helmstaedter,
Max-Planck-Institut für Hirnforschung, Frankfurt am Main (D)

Chair: Thomas Nevian, Department of Physiology, Bern

Brains are highly interconnected networks of millions to billions of neurons. For a century, we have not been able to map these connectivity networks. Only recently, using novel electron microscopy techniques and machine-learning based data analysis, the mapping of neuronal networks has become possible at a larger scale. This new field of connectomics is still limited by technology and requires next-generation human-machine interaction for data analysis, but it is already starting to provide exciting insights into how neuronal circuits operate in the brain. Our goal is to make connectomics a high-throughput screening technique for neuroscience, to use connectomes for discovering brain-implemented algorithms, which may inspire novel machine learning, to map the imprints of sensory experience onto neuronal networks in the brain, and to investigate connectome alterations in models of psychiatric disease.

Poster abstracts by discipline
1. Clinical research

1.01 Scanning surveillance of neuroinfectious viruses in cattle livestock

Truchet Laura, Vetsuisse Faculty Bern, University of Bern, NeuroCenter, Division of Neurological Sciences, Bern
Walland, Julia, NeuroCenter, Division of Neurological Sciences, Vetsuisse Faculty Bern, University of Bern, Bern
Boujon, Céline, NeuroCenter, Division of Neurological Sciences, Vetsuisse Faculty Bern, University of Bern, Bern
Selimovic-Hamza, Senija, NeuroCenter, Division of Neurological Sciences, Vetsuisse Faculty Bern, University of Bern, Bern
Posthaus, Horst, Department of Infectious Diseases and Pathobiology, Vetsuisse Faculty Bern, University of Bern
Schüpbach, Gertraud, Veterinary Public Health Institute, Vetsuisse Faculty Bern, University of Bern, Bern
Oevermann, Anna, NeuroCenter, Division of Neurological Sciences, Vetsuisse Faculty Bern, University of Bern, Bern
Seuberlich, Torsten, NeuroCenter, Division of Neurological Sciences, Vetsuisse Faculty Bern, University of Bern, Bern

Neuroinfectious viral diseases in cattle are mostly neglected, although representing a severe problem to animal health as well as a potential consumer issue. The cause of these diseases often remains unidentified, due to unspecific symptoms, lack of cow-side diagnostic tests and infrequent follow-up investigations. Scanning surveillance, namely in the framework of pathological investigations, assists (i) in the prevalence estimation of endemic diseases, (ii) in the identification of new or re-emerging pathogens and (iii) in early warning systems for disease outbreaks. The aim of this study is to generate baseline data on the prevalence of neuroinfectious viruses in cattle., A histopathological survey was performed using a representative number of brainstem samples (n=1816) of adult Swiss cattle that died on farm. Samples were classified according to the lesions and inflammatory pattern shown in H&E staining. We focused on the samples presenting non-suppurative inflammation and therefore indicating a viral etiology. Virus identification was conducted by family-wide pan-PCR protocols and subsequently Sanger sequencing. , Inflammatory lesions were found in 9,5% of the animals 2,3% were of a non-suppurative pattern. Our preliminary results confirmed the presence of bovine astrovirus CH13, ovine herpesvirus 2, bovine herpesvirus 6, and other herpesviridae that still need to be classified., These results provide important data on the prevalence and nature of neuroinfectious diseases in the Swiss cattle population. Pathology-based scanning surveillance may therefore be a valuable component of early-warning strategies.

Keywords: ---

1.02 Episodic memory network in very preterm-born children

Everts Regula, Childrens University Hospital, Inselspital, Neuropaediatrics, Development and Rehabilitation, Bern
Mürner-Lavanchy, Ines, Neuropaediatrics, Development and Rehabilitation, Childrens University Hospital, Inselspital Bern
Lüchinger, Bettina, Neuropaediatrics, Development and Rehabilitation, Childrens University Hospital, Inselspital Bern
Weisstanner, Christian, Institute of Diagnostic and Interventional Neuroradiology, University Hospital, Inselspital Bern
Steinlin, Maja, Neuropaediatrics, Development and Rehabilitation, Childrens University Hospital, Inselspital Bern

Very preterm-born children are at risk for lower levels of cognitive performance including reduced memory capacity. Given the centrality of episodic memory for learning and school achievement and given its susceptibility for impairment, it is critical to understand how episodic memory is represented in the childs brain. The aim of this study was to examine the episodic memory network during encoding and recognition and to determine the effect of age and memory performance on the episodic memory network in very preterm-born and full-term children. Brain activation during fMRI was examined using a block-designed verbal episodic memory task in 40 very preterm-born and 34 full-term children aged 7 to 12 years. Children had to memorise and later recognize visually presented word pairs in the scanner and performed a verbal memory task outside the scanner. In very preterm-born children, the encoding and recognition network was more widespread than in full-term children but the intensity of brain activation did no differ significantly between groups. In both groups, brain activation during encoding was more widespread than during recognition. During encoding and recognition there was an overlap of activation in left frontal brain regions. Age and episodic memory performance was not conclusively associated with the episodic memory network, neither in preterm-born nor in full-term children. The results of this study revealed that preterm-born children recruit a more widespread activation network during episodic memory performance than full-term children. This might reflect different pathways of processing episodic memory information, with compensatory processes likely occurring in preterm-born children.

Keywords: episodic memory, fMRI, encoding, recognition, very preterm-born children

1.03 Gesture Production in Aphasic Patients

Eggenberger Noëmi, Inselspital Bern, Departments of Neurology and Clinical Research, Bern
Preisig, Basil, Departments of Neurology and Clinical Research, Inselspital, University Hospital Bern, Switzerland
Schumacher, Rahel, Departments of Neurology and Clinical Research, Inselspital, University Hospital Bern, Switzerland
Meichtry, Jurka R., Departments of Neurology and Clinical Research, Inselspital, University Hospital Bern, Switzerland
Müri, René M., Departments of Neurology and Clinical Research, Inselspital, University Hospital Bern, Switzerland

Aphasia is a common consequence of left hemispheric brain damage. The influence of aphasia on gesturing as means of nonverbal communication remains rather unclear. Some aphasic patients use hand gestures as a compensation for impaired verbal capacities, however, in others, the gestural outputs seems to parallel the language disorder, leading to impaired gesturing. In the present study, we tested spontaneous gesture production in aphasic patients. 25 aphasic patients and 25 healthy controls were presented with video excerpts in two conditions: either action-loaded (e.g. a cartoon sequence with characters chasing each other and running around) or language-loaded (e.g. an excerpt from a talk show, where several interlocutors were visible in a static scene, engaging in a discussion on an abstract topic such as composing pop songs). After watching each sequence, participants were asked to retell the sequence to the experimenter while being videotaped. All gestures produced by the participants were recorded, sampled and coded. All participants produced more gestures in the action-loaded condition. Furthermore, all participants produced mostly semantic gestures. Interestingly, aphasic patients production of semantically meaningful gestures was highly correlated with their verbal impairments: the more severe aphasic patients were, the more semantic gestures they produced. This finding was pronounced for the verbally more demanding language-loaded condition. In general, gesturing in aphasic patients did not differ compared to healthy controls, but patients produced more gestures in relation to their language impairments. The more severely impaired patients were in terms of verbal capabilities, the more they produced semantically meaningful gestures, in particular with higher verbal task demands. We interpret these preliminary results in terms of compensational mechanisms for impaired verbal capacities in aphasic patients.

Keywords: Aphasia, gesture production

1.04 Development of a Novel Motion Encoding Scheme for Magnetic Resonance Elastography and the Data Processing Pipeline

Gilani Irtiza, University Hospital Bern (Inselspital), Support Center for Advanced Neuroimaging (SCAN), Department of Neuroradiology, Bern
PD Dr. El-Koussy, Marwan, Support Center for Advanced Neuroimaging (SCAN), Department of Neuroradiology, University Hospital Bern (Inselspital), Bern, Switzerland.
Dr. Kiefer, Claus, Support Center for Advanced Neuroimaging (SCAN), Department of Neuroradiology, University Hospital Bern (Inselspital), Bern, Switzerland.

Purpose/Introduction: We investigated the shear modulus variation in a magnetic resonance elastography (MRE) phantom using a new implemented MRE sequence without need for an external vibrator just using the (physiological) pulsation of a flexible balloon. These developments can aid in analyzing the mechanical properties of the soft tissue of the human brain by just using its physiological pulsation. Methods: Thereafter, the acquired data is processed by using an in-house developed MATLAB package. The data processing pipeline consists of initial processing of the phase images, low-pass filtering, displacement maps calculation, selection of the appropriate spatial frequency components, band-pass filtering and the spatial derivate computation for calculating the shear modulus of the imaged sample. Results: For both abovementioned samples, the resulting shear modulus/stiffness maps are compared. The ROIs in the corresponding maps are selected based on the main direction of the propagating wave, which can be observed in the displacement maps. The shear modulus/stiffness ratio of the modes of the ROIs of both samples is approximately equal to the ratio of the viscosity values of the compared samples. Discussion/Conclusion: We present a proof-of-concept of a new motion-encoding scheme for MRE and develop an efficient data processing pipeline for processing the acquired data and computing the mechanical properties such as shear modulus. The developed methods can be applied to the human brain data in order to study the mechanical properties of soft tissue of the human brain. Acknowledgements: We gratefully acknowledge the support of the ARTORG team, Dr. Nicola Gerber and Benjamin Schmid, for the phantom development.

Keywords: Magnetic Resonance Elastography (MRE). Mechanical Properties of Tissue/Stiffness.

1.05 White matter correlates of the DSM-5 schizophrenia symptom dimensions

Viher Petra, University Hospital of Psychiatry and Psychotherapy, Translational Research Center, Bern
Stegmayer Katharina, University of Bern, University Hospital of Psychiatry and Psychotherapy / Translational Research Center, Bern
Giezendanner Stéphanie, University of Bern, University Hospital of Psychiatry and Psychotherapy / Translational Research Center, Bern
Federspiel Andrea, University of Bern, University Hospital of Psychiatry and Psychotherapy / Translational Research Center, Bern
Bohlhalter Stephan, Department of Clinical Research, Inselspital, Bern / Neurology and Neurorehabilitation Center, Luzerner Kantonsspital, Luzern
Vanbellingen Tim, Department of Clinical Research, Inselspital, Bern / Neurology and Neurorehabilitation Center, Luzerner Kantonsspital, Luzern
Wiest Roland, University of Bern, Support Center of Advanced Neuroimaging (SCAN), University Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern
Strik Werner, University of Bern, University Hospital of Psychiatry and Psychotherapy / Translational Research Center, Bern
Walther Sebastian, University of Bern, University Hospital of Psychiatry and Psychotherapy / Translational Research Center, Bern

Diffusion tensor imaging (DTI) studies have provided evidence of widespread white matter (WM) abnormalities in schizophrenia. Although these abnormalities appear clinically significant, the relationship to specific clinical symptoms is limited and heterogeneous. This study examined the association between WM microstructure and the severity of the five main DSM-5 schizophrenia symptom dimensions. DTI was measured in forty patients with schizophrenia spectrum disorders. Using Tract-Based Spatial Statistics controlling for age and antipsychotic dosage, our analysis revealed significant negative relationships between WM microstructure and two DSM-5 symptom dimensions: Whereas abnormal psychomotor behavior was particularly related to aberrant WM of motor tracts, negative symptoms were associated with WM abnormalities of the prefrontal lobe. However, we found no associations between WM alterations and delusions, hallucinations or disorganized speech. These data highlight the relevance of characteristic WM disconnectivity patterns as markers for negative symptoms and abnormal psychomotor behavior in schizophrenia providing evidence for relevant associations between brain structure and aberrant behavior.

Keywords: Diffusion tensor imaging, Tract-Based Spatial Statistics, neurobiological correlates, negative syndrome, motor abnormalities

1.06 Tablet-based rehabilitation of speech and language for Brain-Injured Patients with Aphasia

Januth Silvan, University of Bern, Gerontechnology and Rehabilitation Group, Bern
Urwyler, Prabitha, University of Bern, Gerontechnology and Rehabilitation Group, Bern
Perny, Sandra, University Hospital Inselspital, Department of Neurology, Division of Cognitive and Restorative Neurology, Bern
Wyss, Corina, University Hospital Inselspital, Department of Neurology, Division of Cognitive and Restorative Neurology, Bern
Renggli, Julia, University Hospital Inselspital, Department of Neurology, Division of Cognitive and Restorative Neurology, Bern
Mitache, Andrei, University of Bern, Gerontechnology and Rehabilitation Group, Bern
Müri, René, University Hospital Inselspital, Department of Neurology, Division of Cognitive and Restorative Neurology, Bern
Nef, Tobias, University of Bern, ARTORG Center for Biomedical Engineering Research, Bern

Language is the most important means of communication and plays a central role in our everyday life. Aphasia is the loss or impairment of language functions that occurs following brain damage due to stroke, trauma, tumors or infection. This disorder hinders the ability to understand and be understood and can be affected in different combinations and levels of severity. Every year, more than 5000 people are affected by aphasia in Switzerland. Affected patients undergo intensive face-to-face speech and language therapy aiming to improve their communication and language skills. Since aphasia is highly individual, the level of difficulty and the content of tasks have to be adapted continuously by the speech therapists. Computer-based assignments allow patients to train independently at home and thus increasing the frequency of therapy., The aim of this project was to develop a tablet application that enables patients to train language related tasks autonomously and, on the other hand, allows speech therapists to assign exercises to the patients and to track their results online. A dedicated interface for the creation of novel exercises was implemented and 520 exercises were developed together with speech therapists. A user management system separates the application into two parts (patient interface, therapist interface). Usability and acceptance was tested in 15 healthy participants, 5 aphasia patients, and 5 speech therapists. System Usability Scale (SUS) was used as main outcome measure. SUS scores for the patient interface are 98/100 for patients, 92.7/100 for healthy, and 68/100 for the therapist interface. The novel therapy application was very well accepted by patients and therapists. Usability of the therapist interface is currently under improvement. 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.

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

1.07 Going with the Flow: A planned study on Automated Puzzle Difficulty Evaluation.

Chesham Alvin, University of Bern, ARTORG Center, Gerontechnology & Rehabilitation, Bern
Mitache Andrei, Gerontechnology & Rehabilitation Group, University of Bern
Mosimann Urs Peter, Privatklinik Wyss, Münchenbuchsee
Müri Rene Martin, Division of Cognitive and Restorative Neurology, Department of Neurology, Inselspital, University of Bern
Nef Tobias, ARTORG Center for Biomedical Engineering Research, University of Bern

Background In recent studies, casual video games have emerged as a promising tool to improve cognitive abilities of older adults. From survey and playtest studies it is known that older adults have a strong preference for casual puzzle games (i.e. slower-paced games with an intellectual challenge). More recent studies have shown promising results using casual puzzle games as training tools for both improving cognition and mood. To optimally use casual puzzle games for training purposes, however, it is quintessential that the difficulty levels of the puzzle game match the players level of skill (difficulty scaling) so that players will enjoy playing games that are neither too hard/frustrating nor too easy/boring. The fact that difficulty slopes games are closely related to the players enjoyment and motivation has important implications for maintaining adherence to potential casual game interventions. Traditionally, difficulty levels of larger sets of puzzles have been determined by game designers or via user rating approaches that suffer from being subjective and heavily time-consuming. Objective The aim of this planned study is to evaluate the difficulty of large sets of puzzles using two existing commercial casual puzzle games (Flow Free, Big Duck Games LLC and Bejeweled, PopCap Games). A user study will be conducted to rate difficulty using a subset of the puzzles that will later be used to train a recently published automated difficulty equation. The difficulty function can then be used to estimate the difficulty of all puzzles in the set. Methods Two existing casual puzzle games will be cloned using the software Unity 3D. A large dataset of puzzles (up to 20k) will be created from online sources and/or using puzzle generation algorithms. First, features of the puzzle games determining difficulty will be selected and sorted along those variables. Secondly, a user study with difficulty ratings for a selection of the puzzles will be conducted to determine the

Keywords: Casual Games, Healthy Older Adults, Video Game Training, Difficulty

1.08 Longitudinal changes in cortical thickness and in executive function after treatment of high-grade carotid artery stenosis.

Burren Yuliya, Inselspital & University Hospital of Psychiatry and Psychotherapy University of Bern, Neuroradiology & Clinical Psychological Service, SCAN, Bern
Christian Rummel, Institute of Diagnostic and Interventional Neuroradiology Inselspital Bern
Pietro Ballinari, Institute of Diagnostic and Interventional Neuroradiology Inselspital Bern
Marwan El-Koussy, Institute of Diagnostic and Interventional Neuroradiology Inselspital Bern
Roland Wiest, Institute of Diagnostic and Interventional Neuroradiology Inselspital Bern
Beat Meier, Department of Psychology University of Bern

Introduction: Chronic reduction of the regional blood flow leads to cerebral cortical thinning without evidence of gross tissue loss at the same time as potentially negatively impacting on cognitive performance. 1. Several studies have found the degree of carotid artery stenosis (CAS) to be significantly related to cognitive impairment, especially in the executive function 2, 3. In particular, our longitudinal study examines whether revascularization treatment improves cortical thickness and, as a result, cognitive function in patients with high-grade CAS one year after revascularization. Because cognitive function is related to cortical thickness 1, it can be hypothesized that the cerebral cortical thinning can reverse after revascularization. Methods: Longitudinal anatomical data were acquired in 24 patients with high-grade (NASCET 70%) before and after treatment. All the patients were screened for cognitive deficits by standardized tests. Cortical thickness was estimated from the structural MR images using FreeSurfer software. Region-of-interest analyses were used in the anterior cingulate cortex. Results: Behavioral results: One-sided Wilcoxon signed-rank test showed significant improvement after one year for stroop inference control (p=0.027), verbal fluency (p=0.034), word production (p=0.042) and short term memory (p=0.000). Verbal memory,

processing speed and verbal memory did not improve after treatment. Imaging data results: only the left side showed a reduction in cortical thickness in anterior cingulate cortex. Conclusion: This is the first study to examine longitudinal treatment effects of changes in cortical thickness one year after treatment in patients with high-grade CAS. This study is supported by the SNF Grant - SPUM 33CM30-124114, References: Jorn Fierstra, MSc et al. Stroke. 201142:1631-1637, Xue-Li Chang et al. Neuroscience and Biobehavioral Reviews.201337:14931499, Everts Regula et al. Swiss Med Wkly. 2015145:w14226

Keywords: high-grade carotid artery stenosis, executive function, cortical thickness, longitudinal study.

1.09 Inefficient preparatory fMRI-BOLD network activations predict working memory dysfunctions in patients with schizophrenia

Bänninger Anja, University Hospital of Psychiatry and Psychotherapy, Translational Research Center, Bern
Laura Diaz Hernandez, Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern
Kathryn Heri, Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern
Judith M. Ford, Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA
Mara Kottlow, Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern
Thomas Koenig, Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern

Working memory (WM) deficits are known as core feature in schizophrenia. These deficits are highly treatment resistant and are indirectly related to poor functional outcome. Patients with schizophrenia show abnormal dynamics and structure of temporally coherent networks (TCNs) assessed using fMRI, which undergo adaptive shifts in preparation for a cognitively demanding task. During WM tasks, patients with schizophrenia show persistent deficits in TCNs as well as EEG indices of WM. Studying their temporal relationship during WM tasks might provide novel insights into WM performance deficits seen in schizophrenia. In this study, we used simultaneous EEG-fMRI during the performance of a verbal Sternberg WM task with two load levels (load 2 & load 5) in 17 patients with schizophrenia and 17 matched healthy controls. Using covariance mapping, we investigated the relationship of the activity in the TCNs before the memoranda were encoded and EEG spectral power during the retention interval. We assessed four TCNs default mode network (DMN), dorsal attention network (dAN), left and right working memory networks (WMNs) and three EEG bands theta, alpha, and beta. In healthy controls, there was a load dependent inverse relation between DMN and frontal-midline theta power and an anti-correlation between DMN and dAN. Both effects were not significantly detectable in patients. In addition, healthy controls showed a left-lateralized load-dependent recruitment of the WMNs. Activation of the WMNs was bilateral in patients, suggesting more resources were recruited for successful performance on the WM task. Our findings support the notion of schizophrenia patients showing deviations in their neurophysiological responses before the retention of relevant information in a verbal WM task. Thus, treatment strategies as neurofeedback targeting pre-states could be beneficial as task performance relies on the preparatory state of the brain.

Keywords: Schizophrenia, working memory (WM), temporally coherent networks (TCN), state dependent information processing, simultaneous EEG-fMRI, covariance mapping

1.10 The influence of young age at diagnosis for cognitive performance in brain tumor patients before treatment

Eggenberger Noëmi, Inselspital Bern, Department of Pediatric Neurology, Development and Rehabilitation, Bern
Zimmermann, Kathrin, Department of Pediatric Neurology, Development and Rehabilitation, University Childrens Hospital, Inselspital, Bern, Switzerland
Leibundgut, Kurt, Department of Pediatric Hematology and Oncology, University Childrens Hospital, Inselspital, Bern, Switzerland
Steinlin, Maja, Department of Pediatric Neurology, Development and Rehabilitation, University Childrens Hospital, Inselspital, Bern, Switzerland
Heinks, Theda, Department of Pediatric Neurology, Development and Rehabilitation, University Childrens Hospital, Inselspital, Bern, Switzerland

Pediatric cancer survivors have a high risk for a wide range of cognitive difficulties. Such dysfunctions can be caused by the lesion itself and /or its surgical removal, as well as subsequent treatments (chemo- or radiation therapy). In a recent study, we found that survivors of brain tumors performed significantly worse in tests of working memory, verbal memory and attention compared to children with cancer

without central nervous system (CNS) involvement even before the start of medical treatment (Margelisch et al., 2015). Within our ongoing project, we now further aim to investigate the influence of age at diagnosis on neuropsychological functions in these patient samples. So far, 47 children (20 younger children 7-12 years and 27 older children 13-17 years) were included and evaluated with an extensive neuropsychological battery. A two-way MANOVA revealed that younger children performed significantly worse (all ps .05) in measures of working memory, verbal episodic memory and attention when the CNS was affected by cancer, whereas no such differences could be found in the group of older children. According to previous findings, we could show that CNS involvement affects cognitive performance, particularly in measures of memory and executive functions. Furthermore, and extending previous reports, we preliminarily conclude that CNS involvement modulates neuropsychological performance in younger patients already at diagnosis. Thus, younger children with brain tumors are at particular risk for cognitive difficulties and this patient group might benefit thoroughly from close monitoring and early onset of cognitive intervention and remediation programs as early as possible.

Keywords: pediatric cancer, brain tumor, central nervous system, neuropsychological performance

1.11 Investigating machine learning approaches for quality control of clinical magnetic resonance spectra of brain tumors

Kyathanahally Sreenath P, University of Bern, Depts. Radiology and Clinical Research, Bern
Mocioiu, Victor, Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Universitat Autònoma de Barcelona, Barcelona, Spain
Pedrosa de Barros,Nuno Miguel, DRNN, Institute of Diagnostic and Interventional Neuroradiology/SCAN, University Hospital Bern, Bern, Switzerland
Slotboom, Johannes, DRNN, Institute of Diagnostic and Interventional Neuroradiology/SCAN, University Hospital Bern, Bern, Switzerland
Wright, Alan J, CRUK Cambridge Institute, University of Cambridge, Cambridge, United Kingdom
Julià-Sapé,Margarida, Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Universitat Autònoma de Barcelona, Barcelona, Spain
Arús,Carles, Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Universitat Autònoma de Barcelona, Barcelona, Spain
Kreis,Roland, Depts. Radiology and Clinical Research, University of Bern, Bern, Switzerland

Introduction , A major hurdle for successful application and robust use of Magnetic Resonance Spectroscopy (MRS) in the clinic is the need for local technical expertise to prevent inappropriate interpretation of bad MR spectra. A previous study1 suggested an automatic procedure based on support-vector-machine classification to rate MRS tumor data as good or bad to eliminate the need for the human specialist and associated subjectivity. We tried to verify its performance on a much larger database and upon finding poor performance, we aimed to pinpoint the reasons for this and developed a more robust tool. Methods and Results: Wrights method1 performed well when applied to a small class - balanced dataset (144 spectra) but when applied to the large dataset (1916 spectra), the highest specificity (i.e. the proportion of bad spectra that are correctly identified) was ~45%.To test whether the huge imbalance of classes (13% bad) and simplistic independent components were the reasons for the bad performance, we used the random undersampling & boosting (RUSBoost) classifier, which handles imbalance, along with 24 highly ranked features. With these features and classifier, the specificity improved to 83%. Extending this, we moved to a 3 class grading instead of just good or bad (poor if one of three spectroscopists accepted the spectrum). The specificity increased substantially to 92%. Conclusions: Classification tends to be easier when the classes are nearly balanced. Here, since we have a skewed data base, we trained the RUSBoost classifier. It gave an improved specificity with an independent test-set of data when compared to previously published methods. In addition, our results suggest that multiclass labels (3 classes) may be beneficial for improved classification performance. The final classifiers had a comparable performance to the panel of human expert spectroscopists in rejecting spectra. 1. Wright et al. Magn Reson Med 2008 59(6):1274-1281

Keywords: MR spectroscopy, Quality assessment, Brain tumor

1.12 Cortical morphometry and cognition in very preterm- and term-born children

Mürner-Lavanchy Ines, Childrens University Hospital Bern, Neuropediatrics, Development and Rehabilitation, Bern
Steinlin Maja, Childrens University Hospital, Division of Neuropediatrics, Development and Rehabilitation, Inselspital, Bern
Rummel Christian, Support Center for Advanced Neuroimaging (SCAN), University Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern
Everts Regula, Childrens University Hospital, Division of Neuropediatrics, Development and Rehabilitation, Inselspital, Bern

Premature birth may have serious consequences on brain development. Alterations in cortical thickness (CTh) and cortical surface area (CSA) have been detected in very preterm children. These alterations have been suggested to parallel cognitive functioning, which is often at risk in those children. There is a lack of studies on the relationship between CTh, CSA and cognitive functioning in very preterm and term born children. Forty very preterm children (32 weeks gestational age and/or 1500 gram birth weight) and 30 term-born controls were included in the study. The automated surface reconstruction software FreeSurfer was applied to obtain CTh and CSA measures. Comprehensive neuropsychological testing was administered prior to MRI examination. In preterms, right-hemispheric CTh correlated positively with working memory, visuomotor skills, verbal learning and shifting performance. Left-hemispheric CTh correlated positively with working memory and verbal learning performance. Right- and left-hemispheric CSA correlated positively with inhibition, visuomotor skills and shifting performance in preterms. In controls, no significant structure-function relationships were found. To sum up, better cognitive performance was associated with higher CTh and larger CSA in preterms but not in term born controls. As our earlier publications suggest, preterms might show a slight developmental delay. It is possible that cognitive functions in preterms do not yet rely on highly specialized neurons so that thicker cortex and larger cortical surface area is needed to fulfill requested cognitive operations.

Keywords: preterm birth, cognition, cortical thickness, cortical surface area, structure-function relationship, cortical morphology

1.13 Predictive modeling of post-surgical outcome in epilepsy treatment

Müller Michael, Inselspital, Bern University Hospital, University of Bern, Department of Neurology, Bern
Steimer Andreas, Inselspital, Bern University Hospital, University of Bern, Department of Neurology
Schindler Kaspar, Inselspital, Bern University Hospital, University of Bern, Department of Neurology

Resective surgery of the epileptogenic zone is one of the last resorts for epilepsy patients who cannot be treated successfully by pharmacological means. Since in many cases this zone cannot be extracted by visual inspection of the raw intracranial EEG data, one may alternatively construct a statistical model of the EEG spatio-temporal dynamics. These models can then be used to predict the evolution of such dynamics under different, simulated brain resection paradigms (that is, simulated manipulations of signals from one or more EEG channels). For several patients with different surgical outcomes (Engel classes I and IV), we generated spatio-temporal predictive models (Bayesian networks mixed by a Hidden Markov Model) and analyzed their predictions on seizure evolution. We simulated the resection of those EEG channels that were truly resected during the surgery and compared the results to the simulated resection of random sets of channels. In six of the seven class I patients, we could confirm the clinical significance of the truly resected channels, by observing a significantly and massively reduced probability of entering the seizure state. In the remaining case, reduction was insignificant. On the other hand, for two of the three class IV patients reduction was neither massive nor significant, where as in the remaining case reduction was unintentionally massive and significant. In summary, for eight out of ten cases, our model confirmed the (ir)relevance of the truly resected channels for clinical outcome. Hence, our results pave the way for the development of objective analysis tools in future epilepsy research.

Keywords: epilepsy, periictal intracranial EEG, statistical modeling, bayesian inference, prediction of EEG spatio-temporal dynamics, prediction of surgical outcome

1.14 Control the Voices in Your Head! , A Neurofeedback-Training to Treat Auditory Verbal Hallucinations

Heri, Kathryn, University Hospital of Psychiatry Bern, Translational Research Center, Psychiatric Electrophysiology Unit, Bern
Rarra, Marie-Hélène, University Hospital of Psychiatry Bern, Translational Research Center, Psychiatric Electrophysiology Unit, Bern
Moor, Nicolas, University Hospital of Psychiatry Bern, Translational Research Center, Psychiatric Electrophysiology Unit, Bern
Hubl, Daniela, University Hospital of Psychiatry Bern, Translational Research Center, Psychiatric Electrophysiology Unit, Bern
Dierks, Thomas, University Hospital of Psychiatry Bern, Translational Research Center, Psychiatric Electrophysiology Unit, Bern
Koenig, Thomas, University Hospital of Psychiatry Bern, Translational Research Center, Psychiatric Electrophysiology Unit, Bern

Background: Previous studies showed a global reduction of the event-related potential component (ERP) N100 in schizophrenia patients, which is even more pronounced during the event of auditory verbal hallucinations (AVH). This assumingly results from a dysfunctional activation of the primary auditory cortex by inner speech, which reduces its responsiveness to external stimuli. Aim: The idea of this study is to enhance the responsiveness of the primary auditory cortex to external stimuli with an upregulation of the event-related potential component N100 through neurofeedback. Our main interest stands on the behavioral level, specifically in the change of the subjective intensity of AVHs., Methods: Therefore, 15 healthy control subjects and 9 with chronic schizophrenia or schizoaffective disorder diagnosed patients underwent a neurofeedback training. Patients with the age range between 18 - 65 years have been randomly assigned to the treatment or the placebo group. Our design was scheduled with 16 training sessions starting and ending with a collection of questionnaires., Results: In healthy controls, we found an unspecific habituation effect that lowered the N100 amplitude over the session. The used linear mixed effect model showed also a significant learning effect within session across subjects tied to the neurofeedback training. In patients, a similar picture has been seen in the preliminary data. The results of 4 patients of the treatment group showed a tendency for within session learning as well. On the behavioral level, one of the patients in the training group reported that the negative impact of the voices decreased even further two weeks after the training., Conclusion: The training results of the healthy controls points at an important role of habituation in neurofeedback training on sensory ERP components. The patient data suggests that the chosen intervention may interact with AVH, but larger case numbers are necessary to draw well justified conclusions.
Keywords: Neurofeedback, Event-Related Potentials, N100, Schizophrenia, Learning

1.15 High resolution magic angle spinning 1H NMR spectroscopy of listeria brainstem encephalitis in small ruminants: preliminary results

Precht Christina, University of Bern, Vetsuisse-Faculty, Department of Clinical Veterinary Medicine, Clinical Radiology, Bern
Gaëlle Diserens, Depts. Radiology and Clinical Research, University of Bern, Switzerland
Martina Vermathen, Dept. of Chemistry & Biochemistry, University of Bern, Switzerland
Anna Oevermann, Dept. of Clinical Research and Veterinary Public Health, University of Bern, Switzerland
Torsten Seuberlich, Dept. of Clinical Research and Veterinary Public Health, University of Bern, Switzerland
Josiane Lauper, Dept. of Clinical Veterinary Medicine, University of Bern, Bern, Switzerland
Daniela Gorgas, Dept. of Clinical Veterinary Medicine, University of Bern, Bern, Switzerland
Chris Boesch, Depts. Radiology and Clinical Research, University of Bern, Switzerland
Peter Vermathen, Depts. Radiology and Clinical Research, University of Bern, Switzerland

Neurolisteriosis is associated with a high mortality rate in humans and ruminants. The purpose of our study was to investigate metabolic changes associated with listeria brainstem encephalitis in small ruminants as a model for an inflammatory CNS disease., Bilateral brainstem and thalamus biopsies were obtained from 7 healthy control animals (6 sheep, 1 goat) and 8 diseased animals (4 sheep, 4 goats) diagnosed by histopathological examination. 1H HR-MAS NMR (1D Carr-Purcell-Meiboom-Gill (CPMG) sequence) were performed on a Bruker Avance II spectrometer (500.13 MHz). Principal Component Analysis (PCA) and Partial Least Squares Regression (PLS) were used to determine differences between groups in Matlab., Histopathologically, all animals of the diseased group showed moderate to severe inflammatory changes in the brainstem. In contrast, in the thalamus of the majority of diseased animals no or only mild inflammatory infiltrates were observed. Chemometric analysis of the brainstem biopsies achieved near complete separation of the diseased and control group in unsupervised PCA, and a complete separation in PLS. Important discriminators were N-acetylaspartate, choline, phosphocholine, glycerophosphocholine and lactate. In contrast, for the thalamus biopsies no separation between the control and diseased group could be achieved by PCA. However, taking the grade of histopathological changes into account, a trend towards a clustering could be observed in PLS., Differences in the metabolic profile in the primarily affected location,

the brainstem, could be identified by NMR spectroscopy, and will be used to build a model to be tested on a second data set. Not surprisingly, in the commonly un- or mildly affected thalamus no separation could be achieved by unsupervised PCA. However, the trend towards a clustering with the use of prior knowledge by PLS may indicate the high sensitivity of NMR spectroscopy to detect metabolic changes, even before inflammatory infiltrates occur.

Keywords: Listeriosis, brainstem encephalitis, HR-MAS NMR spectroscopy

1.16 Simultaneous Echo Refocusing (SER) Reconstruction Filters

Achenbach Sven, University Hospital Bern, Inselspital, Institute of Diagnostic and Interventional Neuroradiology, Bern
Wiest Roland, Kiefer Claus

A challenging aim in neuroscience Magnet Resonance Imaging (MRI) techniques is to reduce the acquisition time without decreasing the image quality and changing essential parameter values. For this purpose, research focuses on the development of new MRI scanning and data filtering techniques. The MRI scanning technique Simultaneous Echo Refocusing (SER) 1 allows to decrease the scanning time by generating a series of Radio Frequency (RF) pulses and suitable gradient pulses before the Repetition Time (TE) is reached. However, those SER acquired images have to be adequately post processed. The aim of this project is to optimize the quality of SER acquired images 1 by applying an appropriate filter technique before image reconstruction. , Five different filters (Hamming, Hanning, Gaussian, Zero Padding and Wavelets) were applied before image reconstruction to SER acquired MRI data. The quality of the filtered images was evaluated visually and by calculating the Root Mean Square Error (RMSE) as well as the Cross-Correlation (CC) between filtered images and reference images. The reference images were previously acquired with Single Spin Echo (SSE) MRI scanning technique. A minimal search optimization algorithm with fixed intervals and two different cost functions (Joint Histogram, Summation Error) was used to define the filter orders and standard deviations. Furthermore, the difference between one and twelve channels MRI acquired data was analyzed by calculating the RMSE and CC. We could successfully reconstruct images with a low RMSE without using the SIEMENS MRI software by parsing the raw data from an acquisition data file (generated by the MRI scanner). The CC results of the filtered images have not shown significant differences compared to the reconstruction. The RMSE of the wavelet filtered images was the lowest compared to the other filters and have reconstructed a suitable images quality. Furthermore, MRI data acquired with twelve channels decreases the RMSE

Keywords: Simultaneous Echo Refocusing, Wavelet Filter

1.17 A patient with optic ataxia and visual hemiagnosia new insights in the hierarchical organization of visual streams

Meichtry Jurka, University of Berne, Neurology, Berne
Gutbrod Klemens, Department of Neurology
Chaves Silvia, Department of Neurology
Müri René M., Department of Neurology

Introduction: The concept of two hierarchically organized pathways in the primate visual system, the ventral (what) and dorsal (where) stream, is an influential model. Lesions of these streams produce in humans distinct syndromes. It is generally accepted that a lesion of the ventral stream produces visual agnosia (VA) and a lesion of the dorsal stream produces optic ataxia (OA). Both syndromes are rare, and most of our knowledge in humans is based on small case series of patients with large cerebral lesions. Case report, We present a 59-year-old, left-handed female suffered from an intracerebral haemorrhage in the left posterior parietal cortex (PPC) and the underlying white matter. In the course of three months, an isolated VA and OA to the right hemifield remained. Optic ataxia has been assessed as suggested by Borchers and coworkers, 2013. The patient displayed highly significant deficits for right-sided stimuli, more pronounced with the right compared to the left hand. A comprehensive series of tachistoscopic experiments, with lateralized stimulus presentation revealed visual hemiagnosia for visual in the contralesional hemifield. The overlap analysis of the MRI revealed that both the left SLF II and of the left ILF of the patient are damaged., Discussion, This exceptional case with a circumscribed lesion in the PPC affecting the SLF II and the ILF allowed us to investigate the hierarchical organization of ventral and dorsal visual streams. Based on our results and the literature, we propose an extension of the dual visual system model,

which postulates two parallel and hierarchical visual processing streams. In addition, 1) there might be a constant update of object information between both streams before converging in the human prefrontal cortex and 2) in case of damage of one stream a remainder functioning is preserved via anatomical inter-stream connections information transfer.

Keywords: visual system, optic ataxia, visual hemiagnosia, brain lesion

1.18 ASSIP - Attempted Suicide Short Intervention Program. A Novel Brief Therapy for Patients with a history of attempted suicide.

Gysin-Maillart Anja, University Hospital of Psychiatry, University of Bern, Switzerland, Outpatient Department, Berne
Schwab Simon, Translational Research Center, University Hospital of Psychiatry, University of Bern, Switzerland
Soravia Leila, Translational Research Center, University Hospital of Psychiatry, University of Bern, Switzerland
Megert Millie, Psychiatric Department, General Hospital, Thun, Switzerland
Michel Konrad, Outpatient Department, University Hospital of Psychiatry, University of Bern, Switzerland

Background: Attempted Suicide is the main risk factor for further suicidal behavior. Only limited evidence is given for effective treatment to reduce this risk. The Attempted Suicide Short Intervention Program (ASSIP) is based on the understanding of suicide in the context of a patient-oriented model of suicidal behavior and the concept of the suicidal mode as an extraordinary state of mind which can be triggered in moments of high mental pain. The goal of ASSIP is to help patients develop and implement new strategies to stop the activation of the suicidal mode. A major objective of the study was to evaluate the efficacy of this novel brief therapy. Methods: In the 24-months follow-up randomized controlled study 120 patients who attempted suicide were randomly allocated to treatment as usual and ASSIP (n=60) or treatment as usual plus structured interview (n=60). ASSIP was offered in addition to the treatment as usual and did not replace a long-term treatment. The three to four session therapy was followed by personalized letters and was conducted in a real world clinical setting at the University Hospital of Psychiatry in Berne. Results: In a 24 months follow-up period, five participants were reattempting suicide (8.3%) in the ASSIP group in contrast to 16 (26.7%) in the control group. Of these, five repeat suicide attempts were found in the intervention group and 41 reattempts in the control group. ASSIP was associated with an approximately 80% reduced risk of participants making at least one repeat suicide attempt. Moreover ASSIP participant spent 72% fewer days in the hospital during the 2 year follow-up period. Conclusions: The Brief Therapy ASSIP, which is administrated in addition to the treatment as usual setting, is highly effective in reducing the suicidal risk over a 24 months period. Furthermore, this manual-based treatment could reduce the long-term health care costs. PLoS Medicine 13(9):e1001968. doi:10.1371/journal.pmed.1001968.

Keywords: Suicide Prevention, Brief Therapy, Treatment, Clinical Research

1.19 ApoE 4-related effects on the brain cortical thickness co-variation patterns in Mild Cognitive Impairment converters to Alzheimers Disease

Sanabria-Diaz Gretel, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Laboratoire de recherche en neuroimagerie (LREN), Lausanne
Sanabria-Diaz, Gretel, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Laboratoire de recherche en neuroimagerie (LREN), Lausanne
Kherif, Ferath, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Laboratoire de recherche en neuroimagerie (LREN), Lausanne
Melie-Garcia, Lester, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Laboratoire de recherche en neuroimagerie (LREN), Lausanne

The apolipoprotein E 4 allele (ApoE 4) is a strong genetic risk factor for developing Alzheimers disease (AD). The evidences support the existence of aberrant brain connectivity in large-scale networks in AD and Mild Cognitive Impairment (MCI) however, how these changes are related to this genetic risk remains unknown. In the present work we characterized the impact of ApoE 4 on the cortical thickness covariance networks (CTNC) in MCI. To carry out our study we used 200 MCI structural Magnetic Resonance Images (sMRI) coming from ADNI database. The MCI subjects were subdivided in 100 converters (C) to AD and 100 non-converters (NC) (50 carriers (one ApoE 4 allele), 50 non-carriers (without ApoE 4). The mean cortical thickness in a set of 148 structures was obtained using FreeSurfer software. The CTNC difference between carriers and non-carriers was studied using the graph theory framework. The statistical similarity

between two regions was measured by computing the Pearson correlation across subjects. We used the Z statistic to compare the transformed z values in order to define the group differences. Our results revealed a different cortical thickness co-variations pattern between carrier and non-carrier in MCI C and NC. The insular, parietal and frontal regions in NC are involved in a considerable number of differences between carrier and non-carrier compared to C where were localized in frontal, temporal and parietal regions. In MCI C the twice of co-variation differences were found between the two evaluations compared to MCI NC. It is important to remark on the differences observed between MCI C carrier and non-carrier in structures belonging to the Default Mode Network. In the present study we have shown that APOE 4 allele modulates the topological organization of the cortical thickness networks in MCI converting to AD. This work sheds light on the necessity of exploring genetic factors underlying the brain network organization in AD and MCI.

Keywords: Apolipoprotein E, Alzheimers Disease, Mild Cognitive Impairment, brain network, cortical thickness, connectivity, graph theory.

1.20 Inflammatory markers in pediatric stroke: An attempt to better understanding the pathophysiology

Steinlin Maja, University Childrens Hospital, Inselspital, Berne, Switzerland, Neuropaediatrics, Development and Rehabilitation, Bern
Buerki, Sarah E, Division of Neurology, Department of Pediatrics, Childrens Hospital and University of British Columbia, Canada
Grandgirard, Denis, Institute for Infectious Diseases, University of Bern, Neuroinfectiology Laboratory, Institute for Infectious Diseases, Postfach 8571, CH-3001 Bern, Switzerland
Datta, Alexandre N., University Childrens Hospital Basel, Spitalstrasse 33, CH-4056 Basel, Switzerland
Hackenberg, Annette, University Childrens Hospital Zu¨ rich, Kinderspital Zu¨ rich, University Childrens Hospital Zuerich, Steinwiesstrasse 75, CH-8032 Zuerich, Switzerland
Martin, Florence, Childrens Hospital Winterthur, Kantonsspital Winterthur, Brauerstrasse 15, Postfach 834, CH-8401 Winterthur, Switzerland
Schmitt-Mechelke, Thomas, Childrens Hospital Lucerne, Luzerner Kantonsspital, Kinderspital Luzern, CH-6000 Luzern 16, Switzerland
Leib, Stephen L., Biology Division, Spiez Laboratory, Swiss Federal Office for Civil Protection, Spiez, Switzerland
Steinlin, Maja, Department of Neuropediatrics, Development and Rehabilitation, University Childrens Hospital, Inselspital, Berne, Switzerland

Background: The mechanisms of childhood and perinatal arterial ischemic stroke (AIS) are poorly understood. Multiple risk factors include cerebral arteriopathy, congenital cardiac disease, infection, sickle cell disease, and maternalefetal conditions in neonates. For infections and parainfectious conditions being the most important a possible inflammatory pathophysiology has long been suspected. This pilot study aims to detect, whether there are any abnormalities of inflammatory markers associated with childhood and neonatal stroke. Methods: The concentration of 23 different metalloproteinases (MMPs), tissue inhibitors of MMPs (TIMPs), endothelial factors, vascular cell adhesion proteins, and cytokines in, plasma were measured in 12 children with AIS, 7 healthy age matched controls and 6 full term neonates with perinatal AIS., Results: At the time of the acute event children with AIS had significantly elevated levels of MMP-9, TIMP4, IL-6, IL-8 and CRP compared to controls (p 0.05). Except for lower IL-6 and CRP levels the pattern of children with a history of varizella-zoster virus (VZV) and other viral infections did not differ to the non-infectious group. Median levels of MMP-1, MMP-2, TIMP-1, TIMP-2, sE-selectin, sICAM-1, sVCAM-1, IL-8, IL-10, TNF-alpha, VEGF, Fetuin A were found to be higher in the neonatal group when compared with older children., Conclusion: This pilot study supports the assumption of an inflammatory process and up-regulation of metalloproteinases and their inhibitors, and altered pattern of circulating pro-inflammatory cytokines, CRP and vWF levels in pediatric and neonatal AIS. It highlights the feasibility but also difficulties for similar larger future studies that should aim to clarify childhood stroke etiopathogenesis and consecutive further therapeutic options.

Keywords: Pediatric arterial ischemic stroke, Inflammation, Biomarker, Metalloproteinases

1.21 Development and Evaluation of a new computer based Saccadic Training for Brain-Injured Patients with Hemianopia

Schweizer Nadia, University of Bern, Gerontechnology and Rehabilitation Group, Bern
Mitache Andrei, University of Bern, Gerontechnology and Rehabilitation Group, Bern
Urwyler Prabitha, University of Bern, Gerontechnology and Rehabilitation Group, Bern

Mosimann Urs Peter, Private Hospital Wyss, Münchenbuchsee, Switzerland
Gutbrod Klemens, University Hospital Inselspital, Departments of Neurology and Clinical Research, Perception and Eye Movement Laboratory, Bern
Müri René, University Hospital Inselspital, Departments of Neurology and Clinical Research, Perception and Eye Movement Laboratory, Bern
Nef Tobias, University of Bern, ARTORG Center for Biomedical Engineering Research, Bern

Visual field deficits, for example hemianopia, are common functional impairments after acquired brain injury. Though early recovery is expected in around half of cases within the first 3 months after injury, patients with hemianopia are often disabled in several activities of daily living as reading, walking or driving. This occurs, together with the visual field loss, because of the uncontrolled and small saccadic eye movements. Rehabilitative approaches generally target eye movement training which are needed to build upon compensatory strategies to improve explorative saccades. Our aim is to develop a computer based training tool for patients with homonymous hemianopia based on a visual search paradigm that is portable, inexpensive, and easy to deploy. We hypothesize that the training will improve the efficiency of eye movements and enable patients to realize controlled eye movements. The training will consist of a visual search (saccadic) task which is based on a compensation strategy. These tasks will comprise of randomly positioned target and distractor element on different backgrounds. A number of static images will be evaluated using saliency maps to select the backgrounds for the tasks. Patient response are via key inputs (left key target, right key distractor).The patient has to detect a specific target and differentiate it from a distractor using the assigned keys. Performance will be assessed by examining response time, error rates in visual search task. An advantage of the new training program is the automatic adjustment of the difficulty level in par with the performance and individual capacity of the patient, which will insure patient motivation and participation. Pre-studies in healthy people will be used to evaluate the difficulty rating of the different parameters. The new training program will insure patient compliance and improve quality of life of patients suffering from visual field deficits.

Keywords: hemianopia, saccadic training, visual exploration, rehabilitation

1.22 Automatic Quality Filtering of MR Spectroscopy Data: A Common Trap

Kreis Roland, University Bern, Radiology and Clinical Research, Bern
Kyathanahally, Sreenath Pruthviraj, University Bern, Depts Clinical Research & Radiology, Bern

PURPOSE: To evaluate the effect of automatic quality filtering of MR spectroscopy (MRS) data based on relative Cramér Rao error bounds., INTRODUCTION: Cramér Rao estimation of the lower bounds of fitting errors has become the standard way of estimating the minimum error associated with a MRS measurement. It reflects the maximum trust that can be associated with a peak area (and thus concentration) estimated in model fitting. Cramér Rao lower bounds (CRLB) include limitations due to the specific fitting model and are proportional to the noise in the spectrum. CRLB are also very popular as a means for unsupervised quality filtering. In particular, relative CRLB, expressed as percentage (CRLB%) of estimated metabolite content, are often used for this purpose. The notion is that if a measured value has a high relative uncertainty, its reliability and thus usability must be low, and that one should better eliminate the associated data to improve the accuracy of cohort averages. Unfortunately, this is a wrong concept, given that the CRLB do not depend on the size of the estimated area parameter itself, but that CRLB% obviously inversely scale with the size of the estimated parameter. This contribution demonstrates this ill-suitability of CRLB% for quality filtering1. METHODS : To illustrate this misconception, artificially constructed sets of data and a simulated spectrum were set up. RESULTS and DISCUSSION: In example studies, it is demonstrated that CRLB% filtering easily leads to wrong conclusions A) either to believe in metabolic alterations where there are none, or B) to miss significant alterations when they exist. In addition, rejection of data with high CRLB% prevents the clinical use of MRS to diagnose any disease leading to low metabolite levels. , CRLB are a valuable to judge the maximum trust one can have in a MRS-based measurement, but it has to be judged either as an absolute value or relative to normal metabolite levels. 1. Kreis. Magn Reson Med 201675:15

Keywords: Magnetic Resonance, brain, quality assessment, error estimation

1.23 Searching for meaning in meaningless gestures - aberrant limbic interference and reduced DLPFC activity hampers correct gesturing in schizophrenia

Stegmayer Katharina, University Hospital of Psychiatrie, Bern, Translational Research Center, Bern
Bohlhalter, Stephan, Neurology and Neurorehabilitation Center, Kantonsspital Luzern, Switzerland Department of Clinical Research, University Hospital, Inselspital, Bern, Switzerland
Vanbellingen, Tim, Neurology and Neurorehabilitation Center, Kantonsspital Luzern, Switzerland Department of Clinical Research, University Hospital, Inselspital, Bern, Switzerland
Federspiel, Andreas, University Hospital of Psychiatry, Bern, Switzerland
Wiest, Roland, Institute of Neuroradiology, Inselspital, Bern, Switzerland
Müri, Rene M., Department of Neurology, University Hospital, Inselspital, Bern, Switzerland
Strik, Werner, University Hospital of Psychiatry, Bern, Switzerland
Walther, Sebastian, University Hospital of Psychiatry, Bern, Switzerland

Background: Schizophrenia is characterized by poor social interaction contributing to poor functional outcome. Particularly nonverbal communication is disturbed. Neural correlates of impaired gesture performance are currently unclear. We thus tested functional correlates of gesturing in schizophrenia patients and healthy controls. , Methods: In total, 22 patients and 25 controls matched for age, gender and education level participated. We used an event-related (instructed delay) paradigm to dissociate brain activation during planning and execution of familiar (e.g. use scissors) and novel (e.g. spread little finger outwards) gestures. Performance was assessed by video monitoring and analyzed by raters blinded for diagnosis and clinical status., Results: During planning and execution of gestures both groups activated brain areas of the praxis network. However, patients had reduced dorsolateral prefrontal cortex (DLPFC) activity and increased inferior parietal lobe (IPL) activity. Performance accuracy was associated with IPL activity in patients. Furthermore, during gesture planning additional activity in temporal poles, amygdala and hippocampus was associated with delusion severity. Finally, patients demonstrated increased dorsomedial prefrontal cortex activity during planning of novel gestures. , Conclusions: We demonstrated less prefrontal, but more inferior parietal and limbic activity during gesturing in schizophrenia. IPL activity was associated with performance accuracy, whereas limbic activity was linked to delusion severity. These findings may reflect impaired action planning and a limbic interference with gestures in schizophrenia. Together these alterations may contribute to poor gesture performance in schizophrenia.

Keywords: Nonverbal communication gesture performance action planning delusions fMRI

1.24 Longitudinal resting-state changes following sub-acute arterial ischemic stroke in a seven-year-old boy

Kornfeld Salome, Inselspital, Bern, Division of Neuropaediatrics, Development and Rehabilitation, Bern
Juan Antonio Delgado Rodríguez, Inselspital, Bern, Division of Neuropaediatrics, Development and Rehabilitation
Sebastian Grunt, Inselspital, Bern, Division of Neuropaediatrics, Development and Rehabilitation
Regula Everts, Inselspital, Bern, Division of Neuropaediatrics, Development and Rehabilitation
Roland Wiest, Inselspital, Bern, Institute of Diagnostic and Interventional Neuroradiology
Christian Weisstanner, Inselspital, Bern, Institute of Diagnostic and Interventional Neuroradiology
Claus Kiefer, Inselspital, Bern, Institute of Diagnostic and Interventional Neuroradiology
Maja Steinlin, Inselspital, Bern, Division of Neuropaediatrics, Development and Rehabilitation

Background/aim: Data on reorganizational patterns in resting-state brain networks of children after an arterial ischemic (AIS) stroke is rare when compared to adults. We therefore examined changes in resting-state activity of a seven-year-old boy with a small right-sided, periventricular lesion one, four and seven months post-stroke and related them to neuropsychological and neurological performance. Methods/design: Because of acute hemiparetic and speech symptoms, resting-state activity of the ipsilesional precentral gyrus (rPCG) and pars triangularis (rPT) were investigated. MR images were acquired using a 3T scanner. High-resolution T1-weighted MR structural images and functional imaging were performed. Conn toolbox 15 was used to descriptively compare resting-state-activity. One and seven months post-stroke, a neurological and a neuropsychological examination were performed. Results: One month post-stroke, activation is bilateral in the rPCG and unilateral in the rPT. Four months post-stroke, right-sided pronounced activation occurs in the rPCG, the rPT is bilaterally activated. Seven months post-stroke, the activation becomes more widespread. The rPCG reveals a pronounced right-sided and the rPT a bilateral activation. Clinically, the boy showed normal neuropsychological and neurological performance at one and seven months post-stroke. Conclusions: The results suggest that in the childs brain, dynamic reorganiza-

tion processes in resting-state-activity occur, supporting clinical recovering before resting-state connectivity returns to normal. Resting-state activity becomes more widespread over time. The childs brain might use contralateral support during reorganization in order to improve clinical function on the lesion side. The present results are based on one single case only, but may serve as an important indicator for function-preserving changes in the pediatric brain connectivity after stroke.

Keywords: Pediatric arterial ischemic stroke, resting-state fMRI, longitudinal reorganization, neuropsychological performance, neurological performance

1.25 Clinical evaluation of a fully automatic segmentation method , for longitudinal brain tumor volumetry

Knecht, Urspeter, University Hospital, Inselspital Bern, Department of Neuroradiology
Meier, Raphael, University of Bern, Institute of Surgical Technolgy and Biomechanics (ISTB), Bern
Wiest, Roland, University Hospital, Inselspital Bern, Department of Neuroradiology
Reyes Mauricio, University of Bern, Institute of Surgical Technolgy and Biomechanics (ISTB), Bern

The accurate reproducible measurement of tumor extent and the change of the tumor volume over time is of crucial importance for diagnosis, treatment planning and therapeutic monitoring for brain tumors. A comparison between a fully automatic segmentation method (BraTumIA) and manual segmentation showed an inter-rater disagreement comparable to human raters. The results suggest the use of BraTumIA as a surrogate tool for time-consuming manual tumor volumetry.

Keywords: Brain Neoplasms Glioblastoma Glioma High Grade Glioma Brain Tumor Volumetry Tumor Volume Brain Tumor Segmentation Magnetic Resonance Imaging BraTumIA Therapy Response

1.26 Challenge of the audioverbal self-monitoring system by delayed auditory feedback in patients with and without auditory verbal hallucinations First results of a behavioural analysis

Moor, Nicolas, University Hospital of Psychiatry and Psychotherapy, University of Bern, Centre for translational Psychiatry, Bern
Kindler, Jochen, University Hospital of Child and youth Psychiatry and Psychotherapy, University of Bern, Centre for translational Psychiatry, Bern
Mara Kottlow, University Hospital of Psychiatry and Psychotherapy, University of Bern, Centre for translational Psychiatry, Bern
Thomas Dierks, University Hospital of Psychiatry and Psychotherapy, University of Bern, Centre for translational Psychiatry, Bern
Thomas König, University Hospital of Psychiatry and Psychotherapy, University of Bern, Centre for translational Psychiatry, Bern
Daniela Hubl, University Hospital of Psychiatry and Psychotherapy, University of Bern, Centre for translational Psychiatry, Bern

Introduction: Audioverbal hallucinations (AH) are thought to be generated by misattribution of inner speech to an external source caused by deficient audioverbal self-monitoring. This system was challenged in schizophrenia patients with AH, without AH (NH) and controls (C). We expected greatest disturbances in AH. Method: 120 words were visually presented to the subjects (11AH, 9NH, 31C), spoken into a microphone and presented via headphones. In the No Delay (ND) condition words were presented directly, in the Delay (D) condition, the words were delayed randomly between 60 and 220ms. Reaction time (RT) and correctness were assessed. We compared log-transformed RT between groups for ND and D using ANOVA and post-hoc t-tests. Results: RT in AH was for the ND=3.00±0.10 and for the D=3.03±0.15, in NH: ND=2.90±0.10 and D=2.97±0.13, in C: ND=2.81±0.16 and D=2.78±0.22. In the ANOVA, significant effects were found in ND and D (p0.01). Post-hoc analysis showed for the D condition that C were significantly faster than AH and NH (p0.01) without differences between patients groups. In the ND condition we found that C were faster than patients (AH: p0.01, NH: p=0.07). Between patients, NH were faster in ND than AH (p=0.05)., Correctness in AH was for ND=0.94±0.10 and D=0.62±0.22, in NH: ND=0.87±0.16 and D=0.56±0.19, in C: ND=0.96±0.05 and D=0.86±0.19. The ANOVA indicated significant effects for ND (p=0.03) and D (p0.01). Post-hoc, C were significantly better in the D condition than patients (vs AH p=0.05 vs NH p0.01) without differences between the patients groups. In the ND condition, no diffe-

rences were found post-hoc. Within each group, correctness was higher in the ND than in the D condition (p0.01). Discussion: C answered faster and more correct than both patients groups independent of the condition. AH answered slower but more correct than NH, reaching significance for reaction time in the ND condition, being in line with our hypotheses.

Keywords: audioverbal self-monitoring system, delayed auditory feedback, schizophrenia, audioverbal hallucinations

1.27 ERP Microstates of Alcohol Cue Processing

Rohde, Kristina B., Translational Research Center, Division of Clinical Research, Addiction Research Group, University of Bern, Bern, Switzerland
Fey, Werner, Translational Research Center, Division of Clinical Research, Addiction Research Group, University of Bern, Bern, Switzerland
Moggi, Franz, Translational Research Center, Division of Clinical Research, Addiction Research Group, University of Bern, Bern, Switzerland
Koenig, Thomas, Translational Research Center, Division of Clinical Research, Psychiatric Electrophysiology Unit, University of Bern, Bern, Switzerland
Stein, Maria, Translational Research Center, Division of Clinical Research, Addiction Research Group, University of Bern, Bern, Switzerland

Patients with alcohol use disorders (AUD) show altered brain reactions to alcohol cues as compared to healthy controls. Event-related potential (ERP) studies mostly focus on relatively late components such as the P3, which is usually diminished in AUD. Little is known about earlier ERP components in reaction to alcohol cues. The present studys aim was to comprehensively examine the spatio-temporal brain dynamics in reaction to alcohol cues along the information processing stream. To this end, alcohol-related and neutral pictures were presented to 15 inpatients with AUD and 15 healthy controls while multichannel-EEG was recorded from 70 scalp electrodes. To explore the effects of the psychological context on alcohol cue processing, an imagination procedure was introduced before the cue reactivity task. ERP microstate analyses discovered transient changes in the ongoing electrical brain activity that could be linked to functionally discrete stages of neural processing. Several of these processing steps were altered in patients with AUD as compared to controls. Patients displayed deficits in initial perceptual processing. Whereas for controls the discrimination between alcohol and neutral cues took already place at an early perceptual level, for patients, this discrimination occurred only at a later processing stage at the intersection between perceptual and top-down processing. At higher-order processing stages (P3), patients showed again blunted electrophysiological responses. Interestingly, individual subjective craving was correlated with initial perceptual processing. This pattern of results suggests that deficient perceptual processing in AUD patients might be pivotal to understand cue reactivity processes in the brain and in the subjective experience of craving.

Keywords: Alcohol Use Disorders, Addiction, Cue Reactivity, ERP, Microstates

2.01 Inhibition of Hippocampal Regeneration by Adjuvant Dexamethasone in Experimental Infant Rat Pneumococcal Meningitis

Grandgirard Denis, University of Bern, Institute for Infectious Diseases, Neuroinfection Laboratory, Bern
Bally, Lia, Insel University Hospital Bern, Department of Endocrinology, Diabetes and Clinical Nutrition, Bern
Leib, Stephen, University of Bern, Institute for Infectious Diseases, Bern

Pneumococcal meningitis (PM) causes neurological sequelae in up to half of the surviving patients. Neuronal damage associated with poor outcome is largely mediated by the inflammatory host response. Dexamethasone (DXM) is used as an adjuvant therapy in adult PM, but its efficacy in the treatment of pneumococcal meningitis in children is controversially discussed. While DXM has previously shown to enhance hippocampal apoptosis in experimental PM, its impact on hippocampal cell proliferation is not known. This study investigated the impact of DXM on hippocampal proliferation in infant rat PM. Eleven days old nursing Wistar rats (n=90) were intracisternally infected with Streptococcus pneumoniae to induce experimental meningitis. Treatment with DXM or vehicle was started 18h after infection, concomitant with antibiotics (ceftriaxone 100 mg/kg ip, bid). Clinical parameters were monitored and the amount of cells with proliferating activity was assessed using in vivo incorporation of bromodeoxyuridine (BrdU) and an in vitro neurosphere culture system at 3d and 4 d post-infection. DXM significantly worsened weight loss and survival. Density of BrdU-positive cells, as an index of cell with proliferating activity was significantly lower in DXM-treated animals compared to vehicle controls (p0.0001). In parallel, DXM reduced neurosphere formation as an index for stem/progenitor cell density compared to vehicle treatment (p=0.01). Our findings provide clear evidence that DXM exerts an anti-proliferative effect on the hippocampus in infant rat PM. We conclude that an impairment of regenerative hippocampal capacity should be taken into account when considering adjuvant DXM in the therapeutic regimen for PM in children.

Keywords: pneumococcal meningitis dexamethasone hippocampus regeneration, stem cells

2.02 Repeated Intranasal Delivery of Umbilical Cord-derived Mesenchymal Stem Cells Is Neuroprotective in a Model of Preterm White Matter Injury in Rats

Oppliger Byron, University of Bern, Department of Obstetrics and Gynecology and Department of Clinical Research, Bern
Joerger-Messerli, Marianne, Department of Obstetrics and Gynecology and Department of Clinical Research
Müller, Martin, Department of Obstetrics and Gynecology and Department of Clinical Research
Reinhart, Ursula, Department of Obstetrics and Gynecology and Department of Clinical Research
Schneider, Philipp, Department of Obstetrics and Gynecology and Department of Clinical Research
Surbek, Daniel V., Department of Obstetrics and Gynecology and Department of Clinical Research
Schoeberlein, Andreina, Department of Obstetrics and Gynecology and Department of Clinical Research

The majority of the infants born preterm with brain injuries develop non-csystic, diffuse white matter injury (WMI), characterized by an overall hypomyelination of the brain. Preterm brain injury is an important cause for long-term disability. To date, no cure has been found to treat such lesions. Intranasal delivery of Whartons jelly mesenchymal stem cells (WJ-MSC) derived from umbilical cords might be the ideal therapeutic approach to restore the damaged brain. Therefore, our goal is to find an ideal treatment regimen of intranasal delivered WJ-MSC to achieve a maximum recovery after brain injury. A total of 12 l containing WJ-MSC (84000 cells/l) were delivered intranasally to Wistar rat pups that were previously brain-damaged. Rat pups received either one, two or three treatments, at two days intervals. Animals were sacrificed 7 days after the application of the cells. After fixation of the brains, several immunohistochemical analyses followed. Additionally, RNA was extracted to perform real-time PCR analysis. Treatment with WJ-MSC increased myelination and decreased astro- and microgliosis. Repeated intranasal delivery seemed not to be more effective than single treatment as assessed by immunohistochemistry. However, multiple administrations increased the expression of brain-derived neurotrophic factor (Bdnf) compared to single administration. In conclusion, intranasal delivery of WJ-MSC to the newborn brain after preterm brain damage has a neuroregenerative potential probably mediated by a decreased astro and microgliosis and an increased expression of important neurotrophic factors like Bdnf. Further studies should include behavioral experiments to see how functional outcome might be improved by treatment with WJ-MSC. If the positive effect might be confirmed, intranasal delivery of stem cells to the brain may be the preferred method for stem cell treatment of perinatal brain damage. Financial support by Cryosave Switzerland and The Eagle Foundation.

Keywords: Mesenchymal Stem Cells, Preterm Brain Injury, Neuroprotection

2.03 The Severity of Infection Determines the Localization of Damage and Extent of Sensorineural Hearing Loss in Experimental Pneumococcal Meningitis

Perny Michael, University of Bern, Institute for Infectious Diseases, Neuroinfection Laboratory, Bern
Roccio, Marta, University of Bern, Inner Ear Research Laboratory, Department of Clinical Research, Bern
Grandgirard, Denis, University of Bern, Neuroinfection Laboratory, Institute for Infectious Diseases, Bern
Solyga, Magdalena, University of Bern, Inner Ear Research Laboratory, Department of Clinical Research, Bern
Senn, Pascal, Dept. of Otorhinolaryngology, Head & Neck Surgery, Hôpitaux Universitaires de Genève
Leib Stephen L., University of Bern, Neuroinfection Laboratory, Institute for Infectious Diseases, Bern

Hearing loss is an important sequela of pneumococcal meningitis (PM), occurring in up to 30 % of survivors of the infection. The role of the severity of infection on hearing function and pathomorphological consequences in the cochlea secondary to PM have not been investigated to date. Therefore, we systematically investigated functional hearing outcome and the long-term fate of neurosensory cells in the cochlea, i.e. hair cells and SGNs, with a particular focus on the pathomorphological localization of the damage, in a well-established animal model of PM. Intracisternal infection of infant rats with increasing inocula of Streptococcus pneumonia resulted in dose-dependent increase in levels of Interleukin(IL)-1, IL-6, Tumor necrosis factor (TNF-), IL-10 and Interferon- (IFN-) in the cerebrospinal fluid during the acute phase of the disease at 18 hours after infection. Severity of long-term hearing loss at 3 weeks after infection, measured by auditory brainstem response recordings, correlated to the bacterial dose used for infection and to the levels of TNF- during the acute phase. Quantitative histomorphology of the cochlea revealed a significant loss of SGNs and outer hair cells that strongly correlated to the level of bacterial infection with the most severe damage occurring in the basal part of the cochlea, while Inner hair cells (IHCs) were not significantly affected throughout the entire cochlea. However, surviving IHCs lost synaptic connectivity to remaining SGNs in all cochlear regions, which was dependent on disease severity. These findings provide evidence that the inoculum concentration, i.e. severity of disease, is the major determinant of long-term morphological cell pathologies in the cochlea and functional hearing loss underlining the importance of the prompt institution of antibiotic therapy in patients suffering from PM.

Keywords: Pneumococcal meningitis, Streptococcus pneumonia, Sensorineural hearing loss, Cochlea, Organ of corti, Hair cells, Spiral ganglion neurons, Ribbon synapse, Cerebrospinal fluid, Animal model

2.04 Synaptic vesicle exocytosis visualized by cryo-fluorescence and cryo-electron microscopy in millisecond resolution

Radecke, Julika, University Bern, Institute of Anatomy, Bern
Goldie, Kenneth, University Basel, Biozentrum, Basel
McMahon, Harvey T, Medical Research Council, Laboratory of Molecular Biology, Cambridge
Kudryashev, Misha, University of Frankfurt, MPI of Biophysics and BMLS, Frankfurt
Stahlberg, Henning, University Basel, Biozentrum, Basel
Zuber, Benoît, University Bern, Institute of Anatomy, Bern

Exocytosis at the chemical synapse is orchestrated by a pool of vesicles tethered to the active zone plasma membrane by the SNARE fusion machinery. Upon depolarization the SNARE complex is remodeled and a hypothesized curvature of both the active zone plasma membrane and the synaptic vesicle is induced. This curvature would destabilize the two opposing membranes and overcome the energy barrier for membrane fusion. However, to date the molecular mechanism remains elusive due to the fact that it is a process that can be as fast as 0.2 ms. To visualize exocytosis we use isolated functional synapses (synaptosomes) rapidly frozen milliseconds after depolarization. This method allows a close-to-native state preservation of the sample and analysis of exocytosis events captured as fast as 1 ms to achieve both high temporal and structural resolution at the same time. The analysis is done by cryo-correlative fluorescence and electron microscopy followed by 3D reconstruction of the obtained data. Our data show membrane curvature events prior to fusion of the vesicle, full-collapse fusion events as well as signs of kiss-and-run events. This could not be found in control synaptosomes. Based on our ex vivo observations we are able to show curvature events previously hypothesized to exist based on biochemical data and models. And we might be able to contribute some new findings on a debate that is ongoing for over 60 years now of whether fusion occurs via full collapse fusion or kiss-and-run or if it is actually both states as shown here.

Keywords: Synaptosomes, Cryo-correlative fluorescence and electron microscopy, Synaptic vesicle exocytosis, Full collapse fusion, Kiss-and-run

2.05 Novel compounds with anesthetic activity.

Maldifassi Maria Constanza, University of Bern, Institute for Biochemistry and Molecular Medicine, Laboratory Dr. Erwin Sigel, Bern
Maldifassi, Maria Constanza, University of Bern, Institute for Biochemistry and Molecular Medicine, Bern
Baur, Roland, University of Bern, Institute for Biochemistry and Molecular Medicine, Bern
Forman, Stuart A., Massachusetts General Hospital, Dept. of Anesthesia Critical Care & Pain Medicine, Boston, USA
Sigel, Erwin, University of Bern, Institute for Biochemistry and Molecular Medicine, Bern

A key site of action of numerous clinically important drugs for example benzodiazepines, anxiolytics and anesthetics such as propofol and etomidate is the major inhibitory receptor in the mammalian central nervous system, the -aminobutyric acid type A (GABAA) receptor. These receptors are composed of five homologous subunits organized around a central Cl- selective channel. The most abundant GABAA receptor in the brain comprises 1, 2 and 2 subunits, with a subunit arrangement of. The site of action of diverse anesthetics has been located to subunit interfaces in the intramembrane region of the receptor. Recently, our group described experiment-guided virtual screening (EGVS), a method that was used to identify new ligands of the classical benzodiazepine-binding pocket located at the (Middendorp et al., ACS Chem. Biol., 2014). This screen also identified novel ligands for intramembrane low affinity diazepam site(s). First we determined the concentration response curves for the new compounds in 122 GABAA receptors expressed in Xenopus oocytes using electrophysiological techniques. Novel compounds were compared with propofol and etomidate. The new compounds acted mainly through the two +/ subunit transmembrane interfaces of GABAA receptors. We then used concatenated receptors to demonstrate that individual +/ interfaces contribute to the action for all compounds studied to a different degree. Additionally the novel compounds were tested in vivo for their anesthetic activity. LORR (loss of righting reflex) was determined in Xenopus tadpoles. These compounds had anesthetic potencies similar to propofol. Thus the newly identified compounds may serve as scaffolds for the development of novel anesthetics.

Keywords: Electrophysiology GABAA receptors Xenopus oocyte New anesthetics

2.06 Functional improvement in rat model of Parkinsons disease after neutralization of Nogo-A

Seiler Stefanie, Universtiy of Bern / Inselspital, Department of Neurosurgery, , Bern
Di Santo, Stefano, Department of Neurosurgery, Neurocenter and Regenerative Neuroscience Cluster, University Hospital Bern, Switzerland University of Bern, Inselspital, CH-3010 Bern, Switzerland
Widmer, Hans Rudolf, Department of Neurosurgery, Neurocenter and Regenerative Neuroscience Cluster, University Hospital Bern, Switzerland University of Bern, Inselspital, CH-3010 Bern, Switzerland

Transplantation of fetal human ventral mesencephalic dopaminergic neurons into the striatum is a promising strategy to compensate for the dopamine deficit observed in Parkinsons disease. This therapeutic approach, however, is currently limited by the high number of fetuses needed for transplantation and the poor survival and functional integration of grafted dopaminergic neurons into the host brain. Accumulating evidence indicates that contrasting inhibitory signals endowed in the CNS might support neuronal regeneration. Hence, in the present study we aimed at improving survival and integration of grafted cells by neutralizing Nogo-A, a potent neurite growth inhibitors in the CNS. Therefore, ventral mesencephalic tissue cultures were transplanted into rats with a 6-OHDA lesion and concomitantly treated for two weeks with intra-ventricular infusion of neutralizing anti-Nogo-A antibodies. Motor behavior using the cylinder test was assessed prior to and after transplantation as functional outcome. At the end of the experimental period the number of dopaminergic fibers growing into the host brain, the number of surviving dopaminergic neurons in the grafts as well as graft size was examined. We found that anti-Nogo-A antibody infusion significantly improved the asymmetrical forelimb use observed after lesions. Importantly, a significantly three-fold higher dopaminergic fiber outgrowth from the transplants was detected in the Nogo-A antibody treated group as compared to controls. Furthermore, Nogo-A neutralization showed a tendency for increased survival of dopaminergic neurons in the grafts. No significant differences were observed for graft volume and the number of dopaminergic neurons co-expressing GIRK2 between groups. In sum, our findings support the view that neutralization of Nogo-A in the host brain may offer a novel and therapeutically meaningful intervention for cell transplantation approaches in Parkinsons disease.

Keywords: Parkinsons disease, Nogo-A, cell transplantation, dopaminergic neurons, behavior, rat

2.07 Linking the Pathogen to the Disease: Frequency of Astrovirus Infection in Cattle with Non-Suppurative Encephalitis

Selimovic-Hamza, Senija, University of Bern / Vetsuisse Faculty, DCR-VPH, Bern
Bouzalas, Ilias, University of Bern / Vetsuisse Faculty, DCR-VPH, Bern
Oevermann, Anna, University of Bern / Vetsuisse Faculty, DCR-VPH, Bern
Truchet, Laura, University of Bern / Vetsuisse Faculty, DCR-VPH, Bern
Boujon, Céline, University of Bern / Vetsuisse Faculty, DCR-VPH, Bern
Seuberlich, Torsten, University of Bern / Vetsuisse Faculty, DCR-VPH, Bern

Since the 1960s our neuropathological diagnostic services have recorded non-suppurative sporadic encephalitis in 15% of neurologically diseased bovines. Neuropathologically the disease is characterized by the presence of perivascular cuffs, gliosis and neuronal loss, affecting regions of the central nervous system to a different extent. The inflammatory pattern suggests a viral etiology, but in most cases the pathogen remains unknown. Using next-generation-sequencing and bioinformatics we recently identified two novel bovine astroviruses (BoAstV-CH13, BoAstV-CH15) in brains of cattle with non-suppurative encephalitis of previously unknown etiology. The aim of the present study was to assess the frequency of BoAstV-CH13 infection in cattle and to gain insights into a possible causal relationship with the disease. Formalin-fixed and paraffin-embedded tissues of caudal brainstem, cerebellum, cerebrum and hippocampus of a total of 99 cases of histologically confirmed non-suppurative encephalitis and 59 negative controls were selected. By in-situ hybridization using two distinct digoxygenin-labelled RNA probes the presence of BoAstV-CH13 RNA was evaluated. Furthermore, sections were submitted to hematoxylin-eosin staining to compare the anatomical distribution of lesions with that of the viral RNA. 39 animals with encephalitis (39.4%) showed a clear neuronal labelling in at least one brain region. Labelling was absent in tissues of negative controls. Interestingly, the comparison of neuroanatomical localizations of lesions to the presence of BoAstV-CH13 showed a spatial correlation only in half of all BoAstV-CH13 positive cases. The study provides evidence of a clear association between BoAstV-CH13 infection and non-suppurative encephalitis. Considering the still unresolved cases of non-suppurative encephalitis and the correlation of viral presence to the lesions this study also points out a possibility of involvement of other factors in disease pathogenesis.

Keywords: encephalitis, non-suppurative, astrovirus, bovine, BoAstV-CH13

2.08 mESC-derived neurons grown on multi-electrode arrays as a new in-vitro bioassay for the detection of Clostridium botulinum neurotoxins

Jenkinson Stephen Philip, University of Bern, Institute for Infectious Diseases, Bern
Grandgirard, Denis, University of Bern, Institute for Infectious Diseases, Bern
Heidemann, Martina, University of Bern, Department of Physiology, Bern
Tscherter, Anne, University of Bern, Department of Physiology, Bern
Avondet, Marc-André, Biology Division, The Spiez Laboratory, Swiss Federal Office for Civil Protection, Spiez
Leib, Stephen L., University of Bern, Institute for Infectious Diseases, Bern

Clostridium botulinum neurotoxins (BoNTs) are the most poisonous naturally occurring protein toxins known to mankind, the toxicity range in humans starting as low as 0.3 ng/kg when administered intravenously. All BoNT serotypes consist of two subunits, a 100-kDa heavy chain (HC) and a 50-kDa light chain (LC). Upon binding to specific membrane receptors on the neurolemma of neurons, the HC translocates the LC over the membrane where it exerts its cleaving activity against SNARE proteins, thus inhibiting neurotransmitter release. Currently, the potency of biologically active BoNT is monitored using the murine LD50-assay. By using differentiated neurons from mouse embryonic stem cells (mESC), we have developed an in-vitro assay capable of detecting BoNT activity using electrophysiological recording techniques., mESC are differentiated towards neurons and the cells are cultured for 3 weeks on multi-electrode arrays (MEAs) allowing the extracellular recording of spontaneous neuronal activity. The cultures are then treated with different concentrations of BoNT serotype A (BoNT/A) and spontaneous network bursts, evoked through synaptic transmission, as well as total network activity are recorded 6 hours after exposure to the toxin., Exposure to BoNT/A for 6 hours resulted in a significant decrease of the burst rate for toxin concentrations of 25ng/ml (49.5 ± 27.2 p0.0005 n=7) and 2.5ng/ml (66.7 ± 42.5 p0.005 n=16) compared to untreated cultures (100 ± 20.3 n=25). A significant decrease in the total network activity was observed for toxin concentrations of 25ng/ml (45.5 ± 48.0 p0.005 n=7) and 2.5ng/ml (78.0 ± 70.9 p0.05 n=16) compared to untreated cultures (100 ± 31.9 n=25) , The present assay detects toxin activity of BoNT/A. Thus proof of principle has been achieved. Given sufficient robustness and a further increase in sensitivity to detect

BoNT/A, this assay may replace the murine LD50-assay in e.g. the batch control of pharmaceutical products.

Keywords: murine embryonic stem cells, neurotoxins, BoNT, multi-electrode arrays, in-vitro bioassay

2.09 MitoQ restores mitochondrial impairments and ameliorates pathology in spinocerebellar ataxia type 1 (SCA1)

Stucki David Manuel, University of Bern, Institute of Cell Biology, Saxena group, Bern
Prof. Dr. Saxena, Smita Stucki, David Manuel, University of Bern, Institute of Cell Biology, Bern
Ruegsegger, Céline, University of Bern, Institute of Cell Biology, Bern
Steiner, Silvio, University of Bern, Institute of Cell Biology, Bern
Radecke, Julika, University of Bern, Institute of Anatomy, Bern
Odriozola, Adolfo, University of Bern, Institute of Anatomy, Bern
Prof. Dr. Benoît Zuber, University of Bern, Institute of Anatomy, Bern
Prof. Dr. Michael P. Murphy, Mitochondrial Biology Unit, University of Cambridge, Cambridge

SCA1 is a fatal neurodegenerative disorder that is characterized by the progressive atrophy of the cerebellum, causing motor symptoms like ataxia and dysphagia. The etiology is due to an elongated polyglutamine tract in the ataxin-1 protein resulting in a toxic gain of function. Despite the mutant protein being ubiquitously expressed, the neuropathology is primarily restricted to cerebellar purkinje cells (PCs). The mechanisms leading to selective PC vulnerability in SCA1 remains unelucidated. Here, we focused on identifying cellular changes that specifically appear during symptomatic phase of the SCA1 disease. To this end, we performed mass spectrometry analysis at postnatal day 100 and compared the proteome of the vulnerable PCs and disease resistant granular cells in wild type and Sca1154Q/2Q mice. The results indicated mitochondrial impairments in PCs, but not in granule cells. Indeed, electron microscopy and Immunohistochemistry studies revealed that mitochondria in PCs of Sca1154Q/2Q mice were shorter in length and vesicular (spherical) shaped. A colorimetric assay further highlighted functional impairments in the electron transport chain (ETC) complexes I,II,IV and V, whose activity was significantly reduced in mutant PCs. Moreover, PCs consistently exhibited higher levels of oxidative stress marker 80HDG at symptomatic stage but not at earlier, hinting towards the involvement of oxidative stress in the progressive development of mitochondrial dysfunction. Therefore, we performed a proof of concept experiment by treating Sca1154Q/2Q mice with the mitochondria-targeted antioxidant MitoQ. Indeed, mitochondrial morphology was significantly improved and the functioning of ETC complexes was restored. In addition, the treated Sca1154Q/2Q mice exhibited improved motor coordination and reduced neuropathology. This work demonstrates that mitochondrial impairments are linked to the observed SCA1 symptoms and unravels MitoQ treatment as promising therapeutic approach.

Keywords: ---

2.10 An improved simple rat model for global cerebral ischaemia by induced cardiac arrest

Frick Tamara, University Hospital Bern - Inselspital, Department of Intensive Care Medicine, Bern
Haenggi, Matthias, University Hospital Bern - Inselspital, Department of Intensive Care Medicine, Bern
Springe, Dirk, University Hospital Bern - Inselspital, Department of Intensive Care Medicine, Bern
Grandgirard, Denis, Neuroinfection Laboratory, Institute for Infectious Diseases, University of Bern
Leib, Stephen, Neuroinfection Laboratory, Institute for Infectious Diseases, University of Bern
Jakob, Stephan, University Hospital Bern - Inselspital, Department of Intensive Care Medicine, Bern
Takala, Jukka, University Hospital Bern - Inselspital, Department of Intensive Care Medicine, Bern

Objectives: Cerebral hypoxic-ischaemic injury following cardiac arrest is a devastating disease affecting thousands of patients each year. There is a complex interaction between post-resuscitation injury after whole-body ischaemia-reperfusion and cerebral damage which cannot be explored in in vitro systems only there is a need for animal models. In this study, we describe and evaluate the feasibility and efficiency of our simple rodent cardiac arrest model. Methods: Ten wistar rats were subjected to 9 and 10 minutes of cardiac arrest. Cardiac arrest was introduced with a mixture of the short-acting beta-blocking drug esmolol and potassium chloride. Results: All animals could be resuscitated within 1 minute, and survived until day 5.General health score and neurobehavioural testing indicated substantial impairment after cardiac arrest, without differences between, groups. Histological examination of the hippocampus CA1 segment, the most vulnerable segment of the cerebrum, demonstrated extensive damage in the cresyl violet staining, as well

as in the Fluoro-Jade B, staining and in the Iba-1 staining, indicating recruitment of microglia after the hypoxic-ischaemic event. Again, there were no differences between the 9- and 10-minute cardiac arrest groups. Discussion: We were able to establish a simple and reproducible 9- and 10-minute rodent cardiac arrestmodels with awell-defined no-flow-time. Extensive damage can be found in the hippocampusCA1 segment. The lack of difference between 9- and 10-minute cardiac arrest time in the neuropsychological, the open field test and the histological evaluations is mainly due to the small sample size.

Keywords: Cardiac arrest, Resuscitation, Esmolol, Rat model

2.11 Spinal cord injury in the petri dish: transplantation of neuron-restricted precursors promotes functional regeneration

Tscherter Anne, Universität Bern, Institut für Physiologie, Bern
Heidemann, Martina, Universität Bern, Institut für Physiologie
Kleinlogel, Sonja, Universität Bern, Institut für Physiologie
Streit, Jürg, Universität Bern, Institut für Physiologie

Transplantation of neuronal stem cells or precursors after spinal cord injury has been shown to improve recovery in some animal models. These beneficial effects may be related to the generation of neuronal relay circuits or of a more permissive environment for the regeneration of the host tissue. To distinguish between these possibilities we compared the effects of different grafts on functional regeneration in a previously developed culture model. This model consists of two adjacent organotypic spinal cord slices of embryonic rat cultured on multi electrode arrays (MEA). We have previously shown that the spontaneous electrical activity in these cultures propagates from one slice to the other due to the formation of synaptic connections. After a complete mechanical separation of the slices at 21 days in vitro (DIV) the activity propagation between the slices does not re-establish showing that the ability for functional regeneration is lost. We found that the transplantation of dissociated cell suspensions from E14 rat spinal cord or forebrain displayed an impressive improvement of functional regeneration from less than 10% to more than 80 % of activity propagation. However, when the same cell populations were kept as neurospheres for two weeks prior to grafting, they lost their ability to promote functional recovery. Using patch clamp we found that functional graft neurons were incorporated into the host circuits for the dissociated cell but not for the neurosphere grafts. To find out whether the graft neurons carried the propagation of activity between the slices we used an optogenetic approach. We found that silencing the graft neurons through halorhodopsin illumination interrupted the propagation of activity between the slices. We conclude from these findings that the differentiation of transplanted lineage restricted precursors into mature neurons is required to improve functional recovery.

Keywords: Transplantation, spinal cord injury, regeneration, multi electrode arrays, neuronal precursors

2.12 Synaptic zinc dyshomeostasis regulates axon regeneration in the central nervous system

Andereggen Lukas, University of Bern and Harvard Medical School, Department of Neurosurgery and F.M. Kirby Neurobiology Center, Inselspital Bern and Boston Childrens Hospital, Switzerland and USA, Research Unit, Pavillon 47, Bern
Li Yiqing, Department of Neurosurgery and F.M. Kirby Neurobiology Center, Boston Childrens Hospital and Harvard Medical School, Boston MA 02115, USA
Yuki Kenya, Department of Neurosurgery and F.M. Kirby Neurobiology Center, Boston Childrens Hospital and Harvard Medical School, Boston MA 02115, USA
Hershfinkel Michal, Department of Physiology and Cell Biology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel
Lippard Stephen, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.
Rosenberg Paul, Department of Neurology and F.M. Kirby Neurobiology Center, Boston Childrens Hospital and Harvard Medical School, Boston MA 02115, USA
Benowitz Larry, Department of Neurosurgery and F.M. Kirby Neurobiology Center, Boston Childrens Hospital and Harvard Medical School, Boston MA 02115, USA

Under normal conditions, neurons in the adult central nervous system (CNS) cannot regenerate damaged axons, placing severe limitations on the amount of recovery that can occur after spinal cord injury, stroke, traumatic brain injury, and neurodegenerative diseases. Although research over the past years has identified several strategies to enhance neurons intrinsic growth state, provide trophic factors, or stem cells, the

extent of recovery is still limited, suggesting that other important suppressors of structural plasticity remain to be identified. Because ionic zinc (Zn2+) has been implicated as a critical mediator of neuronal injury, we investigated its possible role in central nerve regeneration. , We discovered that shortly after injury to the optic nerve, a widely studied example of a CNS pathway that does not regenerate, levels of Zn2+ increase markedly in the synapses between GABAergic interneurons and retinal ganglion cells (RGCs), the projection neurons of the eye. Presynaptic Zn2+ accumulation precedes any other changes that have been reported in this system so far and requires nitric oxide production via NOS1and slc30a3, the gene encoding the vesicular Zn2+ transporter ZnT-3. This rapid increase is followed by a slow buildup of Zn2+ within RGCs themselves. Selective chelation of Zn2+ or deleting slc30a3 promotes extensive axon regeneration. In addition, removing Zn2+ leads to enduring survival of RGCs for months after the optic nerve has been injured. Thus, synaptic Zn2+ dyshomeostatis represents a previously unrecognized, negative regulator of axon regeneration in the CNS. , Chelation of Zn2+ might become a new way to enhance recovery in patients with CNS damage.

Keywords: Axon regeneration, cell survival, central nervous system, zinc

2.13 Primary postnatal bovine dorsal root ganglion (DRG) neurons culture from slaughtered calves

Fadda Angela, Vetsuisse Faculty, University of Bern, Division of neurological sciences, Bern

Neurological disorders in ruminants have an important impact on veterinary health but very few host-specific in vitro models have been established to study diseases affecting the nervous system. Here we describe a primary neuronal DRG dorsal root ganglia (DRG) culture derived from calves regularly slaughtered for food consumption. The study focuses on the in vitro characterization of the bovine DRG cellular populations by immunofluorescence analysis. Moreover the effects of various growth factors (GF) on neurite outgrowth and arborisation have been evaluated by morphological analysis. Bovine DRG neurons are able to survive for more than 4 weeks in culture. GF supplementation is not required for neuronal survival but promotes neurite outgrowth and branching. Bovine DRG culture represents a new host specific model for the investigation of neurological diseases in bovines, particularly for infectious diseases sustained by pathogens suspected to travel to the CNS via peripheral nerves.

Keywords: dorsal root Ganglion, sensory Neurons, bovine , neurobiology

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

Bisco Alberto, University of Bern, Department of Physiology, Bern

Neuropathic pain is a debilitating pathological condition. Irreversible peripheral and central sensitization 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-HT7R) 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-HT7 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 neuropathic pain, Serotonin 5HT7 receptors, Place Escape/Avoidance Preference test, LP-211, Anterior Cingulate Cortex

Poster abstracts by discipline
3. Basic research human

3.01 Natural Gradient for Spiking Neurons

Kreutzer Elena, University of Bern, Departement of Physiology, Bern
Senn, Walter

Optimal synaptic plasticity rules are typically described as gradient rules. In reinforcement learning, optimal plasticity follows the reward gradient, in supervised learning, it follows the negative error gradient. , Various parameters can be adapted within a synapse such as the amplitude of the postsynaptic potential at the sub-synaptic site, the postsynaptic receptor density, or e.g. the number of presynaptic release sites. While changing these parameters in the direction of their local gradient, the synaptic contribution to the somatic potential also changes. These somatic potential contributions eventually determine the firing behavior, and one may directly derive the gradient rule for these postsynaptic potentials (PSP) produced by the individual synapses., For the theory to be consistent, it should not matter whether the optimal PSP changes originate in an optimal change of the number of presynaptic release sites, the postsynaptic receptor densities, or the local potential amplitudes. Yet, the local gradients induce different PSP changes, and hence the theory lacks consistency. To resolve the issue, the standard Euclidean gradient calculations need to be replaced by the natural gradient (Amari, Neural Comput., 1998)., We derive the natural gradient learning rule for spiking neurons. Instead of the Euclidean metric, this rule calculates the gradient with respect to a local metric on the synaptic weight space that is given intrinsically by the neurons input-output distribution. As compared to the Euclidean gradient, the natural gradient shows a scaling by the total synaptic strength on the dendritic tree, and an additional hetero-synaptic term that favors a bimodal weight distribution within a single tree. In addition, it is coordinate invariant and hence independent of which specific synaptic parameters are adapted during plasticity.

Keywords: Supervised learning, Natural Gradient, Synaptic Plasticity

3.02 Evidence for a perception memory continuum: an EEG study in a healthy population

Ovalle Fresa Rebecca, University of Berne, Institute of Psychology, Bern
Rothen, Nicolas, University of Bern, Institute of Psychology, Bern

In line with current memory theories of a perception-memory continuum along the ventral visual pathway, there is evidence that the specific profile of enhanced memory in special populations (e.g. synaesthesia) is based on increased perceptual sensitivity. The main goal of this study was to test in a more general population, if increased perceptual sensitivity is indeed associated with enhanced memory performance. We measured ERPs in response to simple perceptual stimuli biasing either the ventral or the dorsal route and established if perceptual sensitivity in response to ventrally (but not dorsally) processed stimuli is associated with visual short term memory performance in a change detection task. Preliminary results confirm the hypothesis and strengthen the assumption of a perceptual-memory-continuum.

Keywords: ---

3.03 Optimizing Diffusion weighted MR Spectroscopy of the Brain: Simultaneous modeling and correction for motion-related signal distortions.

Adalid Víctor, University Bern, Departments of Clinical Research and Radiology, Bern
Döring, André, Departments of Clinical Research and Radiology
Brandejsky, Vaclav, Departments of Clinical Research and Radiology
Kreis, Roland, Departments of Clinical Research and Radiology

Synopsis: Diffusion-Weighted MR Spectroscopy (DW-MRS) can provide information on metabolite diffusion and tissue microstructure based on the fact that metabolitesunlike waterprobe intracellular space only. This information relies crucially on a correct estimation of apparent diffusion coefficients (ADCs). Small head motion is responsible for spurious signal attenuation at high diffusion weighting, which can easily be misinterpreted for faster diffusion. The combination of simultaneously-modeled ADC fitting with water-reference signal correction promises an improved ADC estimation. Methods: 1. DW-MRS with simultaneous acquisition of a water reference was implemented at 3T. 11 subjects were examined to test the scheme in vivo for human gray matter. 2. Our 2D fitting toolbox was modified to allow simultaneous ADC and spectral fitting. Simulated DW-MRS data was created and fitted for validation. Results: 1. Scaling of metabolite signals based on the water reference before frequency alignment and averaging corrected largely for motion

induced signal drops. With correction, ADC values were lowered for all subjects and metabolites. Furthermore, a better resolution for multiplet-pattern metabolites (mI, Glu) was achieved. 2. Simultaneous fitting reduced bias and improved accuracy of ADC estimation. Discussion: The water reference correction leads to increased signal intensity at high b-values, improves spectral quality and lineshape and also reduces ghosting artifacts. Hence, a more accurate and stable fit, closer to the true ADC valuesbetter suited for physiological interpretationis achieved., In addition, simultaneous fitting of spectra and metabolite ADCs has been shown to improve accuracy and precision of estimated ADC values for simulated data and preliminary in vivo applications., Overall, improved estimation of cell-type specific molecular diffusion properties seems feasible with the proposed methods.

Keywords: Diffusion, Magnetic Resonance Spectroscopy , Fitting, Motion Correction, Brain

3.04 Thirst dependent activity of the insular cortex reflects its emotion related subdivision: a cerebral blood flow study

Meier Lea, University of Bern, University Hospital of Psychiatry, Translational Research Center, Division of Systems Neuroscience of Psychopathology, Bern
Meier, Lea, Division of Systems Neuroscience of Psychopathology, Translational Research Center, University Hospital of Psychiatry, University of Bern, Bern
Federspiel, Andrea, Psychiatric Neuroimaging Unit, Translational Research Center, University Hospital of Psychiatry, University of Bern, Bern
Jann, Kay, Ahmanson-Lovelace Brain Mapping Center, Department of Neurology, University of California Los Angeles, California
Wiest, Roland, Institute of Diagnostic and Interventional Neuroradiology, Inselspital, University of Bern, Bern
Strik, Werner, Division of Systems Neuroscience of Psychopathology, Translational Research Center, University Hospital of Psychiatry, University of Bern, Bern
Dierks, Thomas, Division of Systems Neuroscience of Psychopathology, Translational Research Center, University Hospital of Psychiatry, University of Bern, Bern

Recent studies investigating neural correlates of human thirst have identified various subcortical and telencephalic brain areas. The experience of thirst represents a homeostatic emotion and a state that slowly evolves over time. Therefore, the present study aims at systematically examining the neural network reflecting the parametric progression of thirst. We measured subjective thirst ratings, serum parameters and cerebral blood flow in 20 healthy subjects across four different thirst stages: intense thirst, moderate thirst, subjective satiation and physiological satiation. Imaging data revealed thirst related perfusion differences in previously identified brain areas, such as the anterior cingulate cortex, the middle temporal gyrus and the insular cortex. However, significant differences across all four thirst stages (including the moderate thirst level), were exclusively found in the posterior insular cortex. In a previous study, we could show that disgust, a sensory-evoked emotion, activates the anterior insula, and that the interaction between thirst and disgust, when both are perceived simultaneously, occurs in the middle insula. These findings add to our understanding of the insular cortex as a key player in human emotional processing, since it comprises both specific representations of homeostatic and sensory-evoked emotions and it represents the site of cortical interaction between the two levels of emotions.

Keywords: Dehydration, Emotion, Insula, Cerebral blood flow (CBF), Arterial spin labelling (ASL)

3.05 Prefrontal cortex transcranial direct current stimulation (tDCS) does not modulate implicit task sequence learning and consolidation

Branislav Savic, University of Bern, Center for Cognition, Learning, and Memory, Institute of Psychology, Bern
Müri René, Bern University Hospital Inselspital, and Center for Cognition, Learning, and Memory
Meier Beat, Institute of Psychology, University of Bern and Center for Cognition, Learning, and Memory

With the task sequence learning paradigm (TSL), implicit sequence learning can be measured without the involvement of a motor sequence. Moreover, by repeating the TSL in two sessions consolidation can be measured. The aim of this study was to disentangle the role of the dorso-lateral prefrontal cortex (DLPFC) for implicit sequence learning and consolidation. In the first of two experiments, participants received transcranial direct current stimulation (tDCS) above the DLPFC and fifteen minutes later they started the TSL. After 24 hours, participants re-performed the TSL but without tDCS. The second experiment was identical to the first one except that tDCS started with the start of the TSL. The results showed that impli-

cit sequence-specific learning was present in both sessions. Additionally, the performance in the sequenced blocks improved from session one to session two. Critically, in both experiments tDCS did not influence participants performance. In conclusion, the two tDCS protocols do not modulate implicit task sequence learning and consolidation.
Keywords: task sequence learning (TSL), implicit sequence learning, consolidation, dorso-lateral prefrontal cortex (DLPFC), transcranial direct current stimulation (tDCS)

3.06 The Role of White Matter Connectivity in Cortical Maturation

Maeder Cecilia, CHUV-UNIL, Department of Radiology, Lausanne
Griffa, Alessandra, CHUV-UNIL, Department of Radiology, Lausanne and Signal Processing Laboratory (LTSS), EPFL, Lausanne,
Schneider, Juliane, CHUV-UNIL, Clinic of Neonatology and Follow-up, Department of Pediatrics, Lausanne and The Hospital for Sick Children, University of Toronto, Division of Neurology, Toronto
Hüppi, Petra, HUG-UNIGE, Division of Development and Growth, Department of Pediatrics, Geneva
Truttmann, Anita, CHUV-UNIL, Clinic of Neonatology and Follow-up, Department of Pediatrics, Lausanne
Hagmann, Patric, CHUV-UNIL, Department of Radiology, Lausanne

Introduction: Distinct sequential maturation patterns are described for gray and white matter (GM,WM). However, neither the driving mechanisms, nor the relationship between maturation of these structures are well understood. Maturation processes such as myelination, dendritic arborization and synaptic plasticity depend on neural activity and animal studies provide evidence that part of this activity is related to sensory experience and is relayed hierarchically from primary to higher order processing areas. Here, we aim to investigate the role of brain connectivity architecture in these maturation processes., Methods: 1) We use the Apparent Diffusion Coefficient (ADC) to measure brain maturation in 9 cerebral low-risk prematurely born neonates examined at term equivalent age. Each subject is imaged with MP2RAGE enabling GM/WM segmentation, and DTI enabling ADC mapping in 90 GM regions of interest (ROIs), tractography with mean ADC calculation along WM tracts and connectome mapping. 2) We use a computational random walk model to simulate the evolution of brain tissue maturation. We hypothesize that maturation particles seeded in primary sensory areas and traveling along WM connections would reproduce experimental maturation patterns., Results: 1) ADCs in GM ROIs and incident WM tracts strongly correlate (r=0.67, p.01) and increase significantly (p.01) across 4 function-related groups (subcortical/primary/secondary/tertiary processing areas). 2) The number of particle transits at a given simulation time point is interpreted as a maturation score for GM ROIs and WM tracts, which reproduce experimental patterns of GM (r=0.75, p.01) and WM (r=0.68, p.01) maturation. Conclusion: We report similar hierarchical maturation patterns for GM and incident WM tracts, and propose a random walk model for investigating GM/WM network maturation interplays. This suggests a strong interdependence between development of GM structures and the underlying WM connectivity network.

Keywords: human brain development Diffusion MRI ADC connectome gray matter white matter random walk maturation

3.07 A functional model of early LTP

Leimer Pascal, University of Bern, Department of Physiology, Bern
Senn, Walter, University of Bern, Department of Physiology, Bern

For some synaptic plasticity protocols the induced change in the synaptic strength decays partially back with a time constant of minutes before it reaches the long-term value. This early phase of long-term plasticity can be observed both for long-term potentiation (LTP) and for long-term depression (LTD)., We hypothesize that the synaptic weight overshoot of early LTP is advantageous for learning in an environment where one context follows another. In different contexts, similar sensory stimuli may require different responses. Consolidating all synaptic weight changes in one context may therefore cause learning interferences in a next context and lead to the forgetting of previously learned stimulus-response associations. , Early LTP and its consolidation process is one of natures choice to deal with the plasticity-stability dilemma. To keep the benefit of strong synaptic plasticity while avoiding context interferences, the network should only consolidate a minimum number of synapses, but still be able to change enough synapses if required by novel learning. We show in the framework of reinforcement learning that fast synaptic plasticity which only decays to zero when the postsynaptic neuron is not active, solves this conflict. The activity of the postsynaptic neuron sets a tag that protects synapses from forgetting. The plasticity rule is derived from gradi-

ent descent procedure of a cost function which is composed of the expected reward and a penalty term that punishes strong synaptic weights and large voltage deflections. The rule gives a functional explanation for the biological phenomena of early/late LTP and synaptic tagging.

Keywords: ---

3.08 Downfield MR Spectroscopy at Ultrahigh Magnetic Fields

Fichtner Nicole, University of Bern, Radiology and Clinical Research, Bern
Henning, Anke, Max Planck Institute for Biological Cybernetics, Tuebingen
Giapitzakis, Ioannis, Max Planck Institute for Biological Cybernetics, Tuebingen
Zoelch, Niklaus, Institute for Biomedical Engineering, UZH and ETH Zurich, Zurich
Avdievich, Nikolai, Max Planck Institute for Biological Cybernetics, Tuebingen
Boesch, Chris, Radiology and Clinical Research, University Bern, Bern
Kreis, Roland, Radiology and Clinical Research, University Bern, Bern

Introduction: Magnetic resonance spectroscopy benefits from using ultrahigh field scanners, as both the signal to noise ratio (SNR) and the separation of peaks improve. Inclusion of the downfield part of the spectrum (left of water peak) in addition to the generally used upfield part of the 1H MR spectrum is expected to allow for better monitoring of pathologies and metabolism in humans. The downfield part at 5-10ppm is less well characterized than the upfield spectrum, although some data is available for animal brain at high fields, as well as human brain at 3T. Experiments have been performed to elucidate the downfield spectrum in human brain and to quantify metabolite relaxation times T1 and T2 in grey matter at 7T using series of spectra with variable inversion recovery (IR) and echo time (TE) delays. Initial downfield experiments have also been performed in humans at 9.4T. Materials and Methods: Acquisition methods at 7T used a Philips 7T whole body scanner (UZH/ETH Zürich), with a voxel of interest placed in the visual cortex. A series of TEs and IRs was acquired in a total of 22 healthy volunteers. At 9.4T, spectra were acquired in three healthy volunteers on a Siemens whole-body MRI scanner (MPI Tuebingen). Results and Discussion: The spectra acquired at 7T and 9.4T demonstrate significant improvements in SNR and peak separation compared to those at lower field strengths. The averaged data sets from the 7T series were combined to develop a spectral model of partially overlapping signals this heuristic model describes the experimental data well and the results for many of the peaks are very consistent across subjects. T1 values found at 7T are mostly higher than those found at 3T, in particular for the NAA peak. Several peaks show a particularly short T1 in comparison to the others, indicating that they predominantly originate from macromolecules. The T2 values are in general much shorter than those found for upfield peaks.

Keywords: magnetic resonance spectroscopy ultra-high field grey matter human downfield

3.09 Spatial attentional asymmetries in a cross-modal visual search task

Diana Lorenzo, University of Bern, Gerontechnology and Rehabilitation Group, Bern, Switzerland
Paladini, Rebecca E., University of Bern, Gerontechnology and Rehabilitation Group, Bern, Switzerland
Zito, Giuseppe A., University of Bern, Gerontechnology and Rehabilitation Group, Bern, Switzerland
Mitache, Andrei V., University of Bern, Gerontechnology and Rehabilitation Group, Bern, Switzerland
Nyffeler, Thomas, Luzerner Kantonsspital, Center of Neurology and Neurorehabilitation, Lucerne, Switzerland
Mosimann, Urs P., University of Bern, University Hospital of Old Age Psychiatry, Bern, Switzerland
Müri, René M., University Hospital Inselspital, Perception and Eye Movement Laboratory of the Departments of Neurology and Clinical Research, Bern, Switzerland
Nef, Tobias, University of Bern, ARTORG Center for Biomedical Engineering Research, Bern, Switzerland
Cazzoli, Dario, University of Bern, ARTORG Center for Biomedical Engineering Research, Bern, Switzerland

The integration of stimuli of different sensory nature (e.g., visual and auditory) is a crucial process when we explore the surrounding space. Yet, relatively little research has been devoted to the study of cross-modal effects in paradigms assessing the spatial deployment of visual attention, such as visual search tasks. In the present study, we investigated how the search of a visual target would be affected by the presentation of an auditory stimulus in different conditions of spatial congruency. After the presentation of a tone, participants were asked to find a target among a set of distractors. 4 conditions were tested: the tone could come from the same location as the target (congruent condition) from a different location (incongruent condition) the tone had no spatial properties (mono sound condition) or, no sound was

presented (no sound condition). Furthermore, in a separate control task, participants were asked to localize, on a blank screen, the origin of a tone coming from different locations. The control task showed that, on the horizontal axis, participants were more accurate in localizing peripheral sounds than central ones. On the main experiment, the spatial congruency between tone and target was associated with the fastest reaction times, whereas spatial incongruency with the slowest reaction times. No significant difference was present between the mono sound and the no sound conditions. Interestingly, in the incongruent condition, a significant spatial asymmetry emerged between left peripheral targets and right peripheral ones, with the latter being found more quickly. This result shows that asymmetrical mechanisms may underlie reorienting to visual targets when attention is previously engaged elsewhere by a stimulus of auditory nature. By exploring cross-modal interactions in a visual search task, our study highlights novel congruency-related spatial asymmetries.

Keywords: Visuospatial attention, multisensory integration, visual search

3.10 Effect of enactment on immediate and delayed memory performance

Pacozzi Luca, University of Bern, Department of Psychology, , Bern
Prof. Dr. Beat Meier, University of Bern, Department of Psychology, Division of Experimental Psychology and Neuropsychology
Prof. Dr. Klemens Gutbrod, Inselspital Bern, Universitätsklinik für Neurologie, Abteilung für kognitive und restorative Neurologie

The enactment effect refers to the superior memory performance for phrases which have been encoded using pantomimes compared to those that have been simply read (e.g. close the blinds). In several studies, this effect has been demonstrated to be fairly robust across different age groups but in these studies the interval between encoding and test was typically short, (i.e. a few minutes only). In the present study we investigated the enactment effect across an interval of seven days. In addition, we assessed confidence ratings using the remember/know paradigm to test the contribution of recollection and familiarity. We present first results from a sample of older adults (65-95 years) and discuss clinical applications. Specifically, the method may be relevant for clinical purposes. Accelerated long-term forgetting (ALF) is a phenomenon often observed in patients with epilepsy. These patients usually show no deficits in traditional neuropsychological memory tests (30 minutes after encoding), but significant problems in everyday life for remembering materials over longer retention intervals.

Keywords: enactment, recognition, remember/know, epilepsy, ALF, familiarity, recollection

3.11 Entrained oscillatory activity modulates long-range neuronal transmission efficacy

Fehér Kristoffer, University Hospital of Psychiatry, University of Bern, Translational Research Center, Bern
Morishima, Yosuke, University Hospital of Psychiatry, University of Bern, Translational Research Center, Bern

Brain oscillations are considered as a fundamental mechanism of signal transmission in neural networks, pivotal for flexibly adjusting communication among brain areas to meet the environmental demand at hand. However experimental evidence for the causal role of oscillatory activity in modulating signaling-efficacy is missing. We addressed the causal relationship through the simultaneous use of transcranial alternating current stimulation (tACS), transcranial magnetic stimulation (TMS) and EEG. Through tACS we entrained oscillatory activity in two regions of the frontoparietal network the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC). We applied 6 Hz tACS to the DLPFC, or to the DLPFC and PPC simultaneously in an in-phase or antiphase manner. For assessing resultant changes in transmission in the network, we simultaneously applied weak single-pulse TMS over the DLPFC at four different phases of tACS (0, 90, 180, and 270 degree phases) and measured the spread of TMS-evoked EEG potentials (TEPs). The amount of current spread is modulated by the functional status of the neural network, and therefore provides a measure of changes in signaling efficacy. We found that the amplitude of TEPs depended on the phase of the entrained 6 Hz activity. In the antiphase condition, the phase-dependency of TEPs disappeared in the occipital area, suggesting that the tACS-induced de-synchronization of the frontoparietal network limited the communication of the network. We also found that accumulation of applied tACS current over 23 milliseconds before TMS better explains the resultant TEPs than a linear relationship to the amplitude of the current at the moment of TMS. Our results demonstrate the causal role of brain oscillations in modulating neuronal communication, and provide a novel neurophysiological mechanism of tACS: tACS-induced modulation of cortical excitability would be explained by accumulation of applied current in neuronal cells.

Keywords: Electroencephalography (EEG), Transcranial Magnetic Stimulation (TMS), Transcranial Alternating Current Stimulation (tACS), Neural oscillations, Oscillatory entrainment

3.12 Networks of the Brain Tissue Properties Covariance in normal aging

Melie-Garcia Lester, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Laboratoire de recherche en neuroimagerie (LREN), Lausanne
Melie-Garcia, Lester, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Lausanne
Ruef, Anne, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Lausanne
Lutti, Antoine, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Lausanne
Kherif, Ferath, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Lausanne
Draganski, Bogdan, Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Lausanne

The networks of anatomical covariance have been widely used for studying the connectivity patterns in both normal and pathological brains. This type of networks is based on the concurrent changes of quantitative morphometric measures (expressing shape: cortical thickness, gray matter volume) between cortical structures across subjects (Evans 2013). Here we extended the concept by using quantitative measures of the brain tissues composition as a physiological measure. We aimed at studying how tissue properties inferred from MRI techniques like myelination, iron content covariate between different brain regions. We denominated these networks Anatomical Networks of the brain tissue properties covariance (Tiss-Net). We employed the brain regional tissue properties in 114 structures based on Neuromorphics Atlas and graph theory approach to characterize the topological attributes of the Tiss-Nets. For each structure the mean effective transverse relaxation rate (R2*) for iron content, magnetization transfer saturation (MT) for myelin content, longitudinal relaxation rate (R1) were calculated using the established VBQ approach (Draganski et al., 2011) using MRI measurements. Here is studied for the first time the co-variation patterns of some brain tissue properties like myelination. The origin of these covariance patterns may arise from genetic influences on normal development and aging, or from experience-related plasticity or by shared vulnerability processes as is though for morphological networks. Our research sheds light on the organizational principles of the brain tissues composition by exploring synchronous changes of the tissue composition across the brain in particular those like myelination and iron content that are essential in normal brain functioning and the cause of some neurodegenerative diseases.

Keywords: brain connectivity, graph theory, aging, multiparametric mapping, myelination

3.13 Task switching hurts memory encoding

Friedli Michèle, University of Bern, Switzerland, Insitute of Psychology and Center for Cognition, Learning, and Memory. Bern
Michèle Friedli, Insitute of Psychology and Center for Cognition, Learning, and Memory, University of Bern, Switzerland
Prof. Beat Meier, Insitute of Psychology and Center for Cognition, Learning, and Memory, University of Bern, Switzerland

Goal-directed behavior in a changing environment requires a balance between stability and flexibility. In the present study, we investigated the impact of these cognitive control demands on subsequent memory performance. A task switching paradigm was used in which participants had to carry out two binary classification tasks in a predictable AABB order. In experiment 1, they classified animals (bird vs. mammal) and objects (kitchen utensils vs. musical instruments), thus the stimuli were specific for each task (i.e., univalent). In experiment 2, they classified pictures according to size (bigger or smaller than a soccer ball) and an animacy task (natural vs. fabricated) and thus, the stimuli were bivalent. In both experiments, recognition memory for switch and repetition stimuli was tested subsequently. During encoding, task switching resulted in slower reaction times and lower accuracy (switch costs) in both experiments. Critically, subsequent memory was consistently lower for switch compared to repetition stimuli. Thus, flexibility during task switching seemed to hurt the encoding of stimulus-specific information. Consequently, the enhanced demands of task switching are associated with an increased encoding time but lower subsequent memory performance.

Keywords: cognitive control, recognition memory, task switching

3.14 Validation of a new questionnaire for a domain-specific assessment of creativity

Lunke Katrin, University of Bern, Psychology, Bern

Meier, Beat, University of Bern, Department of Psychology, Bern

The goal of the present study was to take a new look at the relationship between creativity and cognitive functioning. We tested more than 300 healthy volunteers with standard tests of divergent and convergent thinking and with a new questionnaire - the Artistic Creativity Domains Compendium (ACDC) - that was developed to assess interest, ability and performance in different domains of artistic creativity. We present fine-grained analyses on the internal and external validity of the questionnaire and on the relationship between creativity, working memory, attention, and intelligence. Our results indicate domain-specific associations between creativity and attention as well as working memory. We conclude that the ACDC is a valid instrument to assess artistic creativity and that a fine-grained analysis reveals distinct patterns of relationships between separate domains of creativity and cognition.
Keywords: artistic creativity, Artistic Creativity Domains Compendium (ACDC), divergent, convergent, intelligence, attention, working memory

3.15 Unconscious Memory Formation

Schneider Else, University of Bern, Psychology, Bern
Henke, Katharina, University of Bern

Episodic memory allows for remembering what happened when and where. Like other higher-order mental capabilities, episodic memory is widely believed to depend on conscious perception and conscious mentation. But there is growing evidence against this conscious-centred view. Findings suggest that humans can learn and retrieve new associations rapidly even if the information is presented subliminally, i.e. invisible to the conscious mind. In this project, we investigated whether humans were able to unconsciously encode and further to retrieve complex associations as episodes in time and space. Therefore, we presented 36 distinct film clips subliminally to 48 participants. These film clips showed cartoons about five animals entering and respectively leaving a shelter. Importantly, several animals could linger in the shelter at the same time. After every third film clip, participants underwent a forced-choice memory task, targeting temporal and spatial aspects of the three preceding clips. Participants were presented with two out of the five animals in each trial and had to decide whether these two animals had met inside the shelter or not. Although the accuracy in this test was at chance level, participants exhibited a behavioural effect in the reaction latency of their choice: They gave correct choices significantly faster than incorrect choices. Participants viewing behaviour also evidenced unconscious encoding of the film clips. In the forced choice memory task participants eyes rested differently long on the right-hand animal whether it did meet versus did not meet the left-hand animal inside the shelter. We interpret these effects as suggestive of an unconscious encoding and retrieval of the complex storylines and thus suggestive of an unconscious form of episodic memory.

Keywords: episodic memory, consciousness

3.16 Chronotypical variations in alertness influence spatial attentional aspects: behavioural and physiological correlates

Paladini Rebecca E., University of Bern, Gerontechnology and Rehabilitation Group, Bern
Müri, René M., University Hospital Inselspital, Perception and Eye Movement Laboratory of the Departments of Neurology and Clinical Research, Bern
Nef, Tobias, University of Bern, ARTORG Center for Biomedical Engineering Research, Bern
Mast, Fred W., University of Bern, Department of Psychology, Bern
Mosimann, Urs P., University of Bern, University Hospital of Old Age Psychiatry, Bern
Cazzoli, Dario, University of Bern, ARTORG Center for Biomedical Engineering Research, Bern

Attention is a complex cognitive function that is crucial in everyday life. According to an influential model, non-spatial (e.g., alertness) and spatial aspects of visual attention are controlled by two distinct, yet interacting, cortical networks in the human brain. The aim of the present study consisted in further elucidating these interactions, by assessing the impact of an alertness manipulation on spatial attentional aspects in healthy participants, both on a behavioural and on a physiological level., For this purpose, participants alertness level was manipulated through the (a)synchronicity between their chronotype and the time of the day. On a behavioural level, the spatial allocation of visual attention was assessed by means of free visual exploration with eye-tracking. On a physiological level, the cortical excitability of the left and the

right posterior parietal cortices (PPCs) critical nodes of the spatial attentional network was directly assessed by means of a transcranial magnetic stimulation (TMS) twin-coil approach., The results of the behavioural assessment showed that participants fixation distribution was significantly modulated by their alertness level. A significant rightward shift in the central part of the visual exploration field, and a bilateral narrowing in the periphery of the latter, were observed during low alertness. On a physiological level, the patterns of cortical excitability of the left and the right PPCs significantly differed during low and high alertness, and there were significant correlations between behavioural and physiological measures., Our findings support the idea that non-spatial attentional aspects, such as alertness, can have a substantial influence on the spatial allocation of visual attention, and these effects are measurable both on a behavioural and on a physiological level. Possible implications for healthy individuals and for patients with attentional disorders, such as hemispatial neglect, are discussed.
Keywords: spatial attention, non-spatial attention, alertness, transcranial magnetic stimulation (TMS), eye movements

3.17 The asymmetrical influence of increasing time-on-task on attentional disengagement

Paladini Rebecca E., University of Bern, Gerontechnology and Rehabilitation Group, Bern
Diana, Lorenzo, University of Bern, Gerontechnology and Rehabilitation Group, Bern
Nyffeler, Thomas, Luzerner Kantonsspital, Center of Neurology and Neurorehabilitation, Lucerne
Mosimann, Urs P., University of Bern, University Hospital of Old Age Psychiatry, Bern
Nef, Tobias, University of Bern, ARTORG Center for Biomedical Engineering Research, Bern
Müri, René M., University Hospital Inselspital, Perception and Eye Movement Laboratory of the Departments of Neurology and Clinical Research, Bern
Cazzoli, Dario, University of Bern, ARTORG Center for Biomedical Engineering Research, Bern

As shown by previous research, fatigue resulting from increasing time-on-task differentially affects the allocation of visual attention to the left and the right hemifield. In healthy participants, increasing time-on-task commonly leads to a growing rightward bias. However, to date, it is unknown whether specific mechanisms involved in the spatial allocation of visual attention are differentially affected by prolonged time-on-task. With the present study, we aimed to investigate whether a specific mechanism involved in the allocation of visuospatial attention, namely attentional disengagement, would be affected in an asymmetrical fashion by increasing time-on-task. For this purpose, healthy participants completed a prolonged gap/overlap saccadic paradigm, with left- and right-sided target stimuli. This oculomotor paradigm allowed us to quantify disengagement costs according to the direction of the subsequent attentional shifts, and to evaluate the temporal development of disengagement costs with increasing time-on-task., Our results demonstrate that, with increasing time-on-task, disengagement costs became significantly lower for rightward compared to leftward saccades. These effects were specific, since concurring lateralized differences in saccadic latencies were found only for overlap trials (requiring attentional disengagement), but not for gap trials (requiring no or less attentional disengagement). Furthermore, the results showed a non-lateralised decrease in saccadic peak velocity with increasing time-on-task, a common finding indicating an increasing level of fatigue. These findings show that a manipulation of non-spatial attentional aspects, such as fatigue due to increasing time-on-task, can substantially affect the spatial allocation of visual attention, more specifically its disengagement, depending on the direction of the subsequent attentional shifts.

Keywords: spatial attention, non-spatial attention, fatigue, eye movements

3.18 Behavioral differences in the upper and lower visual hemifields for perception of shape and motion

Zito Giuseppe Angelo, University of Bern, ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation, Bern
Cazzoli, Dario, University of Bern / Gerontechnology and Rehabilitation, ARTORG Center for Biomedical Engineering Research, Bern
Müri, René M., University Hospital Inselspital / Division of Cognitive and Restorative Neurology, Department of Neurology, Bern
Mosimann, Urs P., University of Bern / University Hospital of Old Age Psychiatry and Psychotherapy, Bern - Privatklinik Wyss /

Münchenbuchsee
Nef, Tobias, University of Bern / Gerontechnology and Rehabilitation, ARTORG Center for Biomedical Engineering Research, Bern

Background: Visual performance is known to be influenced by stimuli location. Visual accuracy seems to be enhanced in the lower visual hemifield for motion and space detection, and in the upper visual hemifield for object and face processing. The origins of such asymmetries were found in attentional biases across the visual field, and in the structural account of the visual cortex., Objective: In this study we tested content-dependent visual asymmetries in different regions of the visual field., Methods: 25 healthy volunteers participated in this study. They performed three visual tests involving perception of shapes, orientation and motion, in the four quadrants of the visual field., Results: The results of the visual tests showed that visual performance was better in the lower than in the upper visual field for motion perception, better in the upper than in the lower visual field for shape perception. Orientation perception did not show any vertical bias. No difference was found when comparing right and left visual hemifields., Conclusions: The neuro-anatomical structure of the visual cortex seems to indicate that the dorsal and the ventral visual streams, responsible for motion and shape perception, respectively, show a certain degree of segregation.

Keywords: Visual perception, Upper and lower visual field, shape perception, motion perception

3.19 High-Precision All-Optical Method for Cell-Based Drug Screening on Voltage-Gated Ion Channels

Streit Jonas, University of Bern, Department of Physiology, Bern
Sonja Kleinlogel, University of Bern, Department of Physiology, Bern

Voltage-gated ion channels regulate many vital functions such as neuronal communication, heartbeat and muscle contraction and are therefore central targets for pharmaceutical intervention. Furthermore, drug compounds under development must undergo cardiac safety screening on vital voltage gated ion channels such as the cardiac hERG channel. However, current high-throughput drug screening methods such as automated patch-clamp or dye-based ion-flux assays are both costly and throughput-limited or use non-physiological mechanisms for channel activation. We introduce a novel, entirely optical drug screening technique for fast voltage-gated ion channels, which combines optogenetic channel activation with an optical voltage readout. Optogenetics is based on the heterologous expression of light-activated microbial rhodopsins. These are ion channels and ion pumps capable of de- and hyperpolarizing the membrane potential of a target cell under physiological conditions. For optical readout we simultaneously image channel activity with the far-red voltage-sensitive dye Di-4-ANBDQPQ or the genetically encoded voltage sensor QuasAr1. We demonstrate proof-of-principle by all-optical assessment of dose-response drug inhibition of the human voltage-gated sodium channel hNav1.5 in undifferentiated neuroblastoma cells expressing an optogenetic pull-push and QuasAr1. Furthermore, we show an easy and reliable all-optical assay for compound safety screening on the cardiac hERG channel in human embryonic kidney cells stably expressing the ChR2 mutant CatCh and stained with Di-4-ANBDQPQ. Taken together, we show for the first time how a fully optical screening assay for voltage-gated ion channel under physiological conditions can be implemented using cutting-edge optogenetic tools.

Keywords: Optogenetics Voltage-gated ion channels Drug screening

3.20 Subliminal encoding and flexible retrieval of objects in scenes

Wüthrich, Sergej, University of Bern, Center for Cognition, Learning and Memory, Bern, Switzerland
Hannula, Deborah E., University of Wisconsin-Milwaukee, Department of Psychology, Milwaukee, USA
Mast, Fred W., University of Bern, Center for Cognition, Learning and Memory, Bern, Switzerland
Henke, Katharina, University of Bern, Center for Cognition, Learning and Memory, Bern, Switzerland

Our episodic memory stores what happened when and where in life. Episodic memory requires the rapid formation and flexible retrieval of where things are located in space. Consciousness of the encoding scene is considered crucial for episodic memory formation. Here, we question the necessity of consciousness and hypothesize that humans can form unconscious episodic memories. Participants were presented with subliminal scenes, i.e., scenes invisible to the conscious mind. The scenes displayed objects at certain locations for participants to form unconscious object-in-space memories. Later, the same scenes were presented supraliminally, i.e., visibly, for retrieval testing. Scenes were presented absent the objects and rotated by 90°-270° in perspective to assess the representational flexibility of unconsciously formed memories. During

the test phase, participants performed a forced-choice task that required them to place an object in one of two highlighted scene locations and their eye movements were recorded. Evaluation of the eye tracking data revealed evidence for unconscious memory of object locations early after target onset, irrespective of changes in viewing perspective. This effect of gaze was related to correct placements of objects in scenes, and an intuitive decision style was necessary for unconscious memories to influence intentional behavior to a significant degree. We conclude that conscious perception is not mandatory for spatial episodic memory formation.

Keywords: Episodic memory, objects in space, subliminal, long-term retention, consciousness, allocentric

3.21 Implicit probabilistic sequence learning within a single session:, Correlated streams and sequence length matter

Walter Stefan, University of Bern, Experimental Psychology and Neuropsychology, Bern
Meier, Beat, University of Bern / Experimental Psychology and Neuropsychology, Bern

We investigated whether a pure perceptual stream is sufficient for probabilistic sequence learning to occur within a single session or whether correlated streams are necessary, whether learning is affected by the transition probability between sequence elements, and how the sequence length influences learning. In each of three experiments, we used six horizontally arranged stimulus displays which consisted of randomly ordered bigrams xo and ox. The probability of the next possible target location out of two was either .50/.50 or .75/.25 and was marked by an underline. In Experiment 1, a left vs. right key response was required for the x of a marked bigram in the pure perceptual learning condition and a response key press corresponding to the marked bigram location (out of 6) was required in the correlated streams condition (i.e., the ring, middle, or index finger of the left and right hand, respectively). The same probabilistic 3-element sequence was used in both conditions. Learning occurred only in the correlated streams condition. In Experiment 2, we investigated whether sequence length affected learning correlated sequences by contrasting the 3-elements sequence with a 6-elements sequence. Significant sequence learning occurred in all conditions. In Experiment 3, we removed a potential confound, that is, the sequence of hand changes. Under these conditions, learning occurred for the 3-element sequence only and transition probability did not affect the amount of learning. Together, these results indicate that correlated streams are necessary for probabilistic sequence learning within a single session and that sequence length can reduce the chances for learning to occur.

Keywords: ---

3.22 In vitro differentiation of adult human bone marrow-derived stem cells towards RPE-like cells by co-culture with human retinal epithelial cells

Trepp Carolyn, Inselspital Bern, University Bern, Department of Ophthalmology, Bern
Mathivanan Isai, Insespital, Department of Haematology, Bern
Brunold Claudio, Insespital, Department of Haematology, Bern
Baerlocher Gabriela, Insespital, Department of Haematology, Bern
Enzmann Volker, Inselspital, Department of Ophthalmology, Bern

The goal of this study was to assess the in vitro differentiation capacity of human bone marrow-derived stem cells (hBMSCs) along retinal lineages. Mononuclear cells (MNC) were isolated from human bone marrow (BM) and mobilized peripheral blood (mPB) using Ficoll-Paque density gradient centrifugation, and were sorted by magnetic activated cell sorting (MACS) for specific hematopoietic cell subsets (CD34+CD38+/CD34+CD38-). These cells were then co-cultured on human retinal pigment epithelium cells (hRPE) for 7 days. The expression of stem cell, neural and retinal specific markers was examined by immunostaining and the gene expression profiles were assessed after FACS separation of the co-cultured cells by quantitative reverse transcription polymerase chain reaction (qRT-PCR). Furthermore, in vitro functionality of the differentiated cells was analyzed using phagocytosis of CY5-labeled rod outer segments (ROS). After 7 days of co-culture, hBMSCs adopted an elongated epithelial-like morphology and expressed RPE specific markers such as RPE65 and bestrophin. In addition, these differentiated cells were able to phagocytose ROS, one of the main characteristic of native RPE cells. Our data demonstrated that human CD34+CD38- BMSC may differentiate towards an RPE-like cell type in vitro and could become a new type of donor cells for regenerative therapy in retinal degenerative diseases.

Keywords: ---

3.23 Influence of stable and changeable aspects of face perception on peri-encoding predictors of memory formation

Padovani Tullia, University of Bern, Neuropsychology, Bern
Marinescu Diana, Institute of Psychology, University of Bern, Switzerland
Bombari Dario, Department of Organizational Behavior University of Lausanne, Switzerland
Martarelli Corinna, Institute of Psychology, University of Bern, Switzerland
Koenig Thomas, University Hospital of Psychiatry, University of Bern, Switzerland
Mast Fred, Institute of Psychology, University of Bern, Switzerland
Perrig Walter J., Institute of Psychology, University of Bern, Switzerland

Effective encoding relies on the neural activity before and after the presentation of a stimulus (Padovani et al. 2011, 2013). In the present experiment we investigate how identity and emotional aspects of face processing modulate peri-encoding neural activity. A set of unfamiliar faces were presented to 27 participants. Immediately before, two types of cues indicated either to perform an age judgment or an emotional judgment on the upcoming faces. The results suggest that the neural activity preceding and following face presentation is modulated by the nature of the task to be performed and can predict whether the face will be later recognized., Before stimulus presentation, the brain activity during the age and emotional tasks differed in topography from -1300/ -700ms, suggesting the recruitment of different generators in the two conditions, according to the model of Haxby et al. (2000). In the same time interval, the brain activity for recognition performance showed different amounts of activation between subsequently remembered and forgotten faces. After stimulus presentation, the N170 component involved in face perception differed in amplitude in both conditions and between subsequently remembered and forgotten faces. Additionally, encoding activity related to recognition performance differed in topography in a time window from 500-750ms and from 1000-1500ms between the two conditions. Our data provide evidence that focusing on stable or changeable aspects of face processing such as age-identity or emotional expressions, differentially modulate processes that enable successful encoding of unfamiliar faces. The predictions of the Haxby et al. model were confirmed even during task preparation. In the prestimulus period, the interplay between encoding and face perception was assessed. In conclusion, these results show that human preparedness to learn depends also from task-specific preparatory processes, which also influence our perception.

Keywords: neural predictors of memory encoding, EEG, face processing, emotions

3.24 Random Sampling with Interspike-Intervals of the, Exponential Integrate and Fire Neuron:, A Computational Interpretation of UP-States

Steimer Andreas, Inselspital Bern / Bern University Hospital / University of Bern, Department of Neurology, Bern
Schindler, Kaspar, Inselspital Bern / Bern University Hospital / University of Bern, Department of Neurology

Oscillations between high and low values of the membrane potential (UP and DOWN states respectively) are an ubiquitous feature of cortical neurons during slow wave sleep and anesthesia. Nevertheless, a surprisingly small number of quantitative studies have been conducted only that deal with this phenomenons implications for computation and cognition. Here we present a novel theory that explains on a detailed mathematical level the computational benefits of UP states. As a neural correlate of psychophysical studies that have shown random sampling to be a promising computational candidate for explaining basic aspects of human perception and inference, our theory is grounded on basic electrophysiological properties of neurons for the biological implementation of random sampling. Random sampling is proposed to work by means of interspike intervals (ISIs) of the exponential integrate and fire (EIF) model neuron. As we show, the EIFs exponential sodium current, that kicks in when balancing a noisy membrane potential around values close to the firing threshold, leads to a particularly simple, approximative relationship between the neurons ISI distribution and input current. Approximation quality depends on the frequency spectrum of the current and is improved upon increasing the voltage baseline towards threshold.

Keywords: UP states, slow wave sleep, neural computation, Bayesian inference, random sampling, interspike interval distribution

3.25 Wrist Resistance Robot: a new method for characterization of wrist rigidity

Urwyler Prabitha, University of Bern, Gerontechnology and Rehabilitation Group, Bern
Feuerstein, Flurin, Univeristy of Bern, Gerontechnology and Rehabilitation Group, Bern
Caranzano, Leonardo, Centre Hospitalier Universitaire Vaudois, Department of Clinical Neurosciences, Lausanne

Shamsollahi, Mohammad Javad, Univeristy of Bern, Gerontechnology and Rehabilitation Group, Bern
Pal, Natassja, Centre Hospitalier Universitaire Vaudois, Department of Clinical Neurosciences, Lausanne
Benninger, David, Centre Hospitalier Universitaire Vaudois, Department of Clinical Neurosciences, Lausanne
Nef, Tobias, University of Bern, ARTORG Center for Biomedical Engineering Research

Central nervous system disorders such as Parkinsons disease (PD) and stroke lead to diminished motor control such as spasticity, rigidity, hyperreflexia and clonus. Rigidity can be defined as a constant and increased resistance to a passive movement. Assessment of wrist muscle tone, including resistance to movement belongs to the standard clinical examination for PD patients. For the assessment of therapeutic progress, accurate, quantitative and sensitive outcome measures are needed. This study presents a novel electromechanical device, the Wrist Resistance Robot, used to quantify healthy and pathological muscle tone of the wrist joint i.e. resistance of the wrist joint. The Wrist Resistance Robot is equipped with an electrical motor to move the wrist joint over its full range of motion with different velocity profiles. The feasibility of the measurement procedure was tested in 12 healthy volunteers and in 4 PD patients. Each participant completed the procedure using three velocity profiles, tested in a randomized order, of 10°/s, 50°/s, and 100°/s. Unpaired t-test for unequal variance was used for statistical comparison of values. The outcome of the quantitative resistance of the wrist joint evaluation was consistent across groups. The comparison of the mean values between the groups (CI = 95%) showed a significant total difference for the right hand extension ($p = 0.045$) and flexion respectively ($p = 0.005$). More specifically, the 10°/s velocity showed good significant difference between the groups for both extension ($p = 0.007$) and flexion ($p = 0.020$), while the 50°/s and 100°/s velocity profiles showed the greatest significant difference for both extension (50°/s: $p = 0.0004$, 100°/s: $p = 0.0003$) and flexion (50°/s: $p = 0.005$, 100°/s: $p = 0.002$) respectively., The Wrist Resistance Robot is able to provide useful information on wrist joint movement due to the fact that it differentiates quantitative resistance of the right hand extension from flexion.

Keywords: Wrist muscle tone, Quantitative assessment, Parkinsons disease, Electro-mechanical wrist resistance measurement

3.26 Evaluation of a novel Serious Game assessment tool for patients with Alzheimers disease: preliminary results

Vallejo Vanessa, ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation, Bern
Mitache, Andrei V., ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation, Bern
Tarnanas, Ioannis, ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation, Bern
Müri, René M., Division of Cognitive and Restorative Neurology, Department of Neurology, Inselspital, Bern
Mosimann, Urs P., Private Hospital Wyss, Münchenbuchsee
Nef, Tobias, ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation, Bern

Background: Alzheimers disease (AD) is the most common form of dementia and requires early diagnosis in order to ensure better therapy outcomes. Laboratory tests are common methods in order to evaluate the cognitive abilities. However these tests do not indicate the functioning in daily living. To investigate the performance in instrumental activities of daily living (IADL), questionnaires are used. These questionnaires have the disadvantage of being subjective and being under the influence of patients anosognosia. Thus, Serious Games offer the possibility to recreate a virtual environment with daily living activities and cognitive evaluation. , Objective: The idea of the present study is to develop and evaluate a new Serious Game based Assessment tool for patients with Alzheimers disease. , Method: 9 patients (2 Male, Age M = 75 MoCA M = 19.8) and 18 healthy controls (12 Male, Age M= 74.5 MoCA M = 28.77) were recruited to participate in this study. A virtual scenario consisting of 4 daily living tasks was created: a navigation task, a shopping task, a cooking task and a table preparation task. The goal of the game was to accomplish these 4 daily living activities following a story line. , Results: Preliminary results indicate a significant difference for the task duration ($Ws = 78$, $z = -3.16$, $p = .002$) and inactivity time ($Ws = 78$, $z = -3.16$, $p = .002$) in shopping, going back home ($Ws = 89$, $z = -2.03$, $p = .045$ $Ws = 84$, $z = -2.53$, $p = .011$) and for inactivity time in cooking ($Ws = 87$, $z = -2.21$, $p = .027$). Furthermore, only patients pressed instructions button, forgot ingredients during the shopping task and needed more actions with less precision to achieve tasks. Conclusion: The new Serious Game based Assessment tool is an ecological way to evaluate cognitive abilities and it allows to distinguish Alzheimers patients performance from healthy controls.

Keywords: Alzheimers disease, Serious Game, virtual reality, assessment tool, activities of daily living, cognition

Light in Sight: Optogenetic gene therapy to recover vision

Kleinlogel Sonja, University of Bern, Institute of Physiology, Optogenetics group, Bern
Michiel van Wyk, Institute of Physiology
Anand David, Institute of Physiology
Elmar Hulliger, Institute of Physiology

Photoreceptor degeneration is one of the most prevalent causes of blindness and there are currently no treatments for patients with late-stage disease in which photoreceptors have been lost. Despite photoreceptor loss, the inner retina and central visual pathways remain intact over an extended time period, which has led to creative optogenetic approaches to restore light sensitivity in the surviving inner retina. The major drawbacks of all optogenetic tools recently developed and tested in mouse models are their low light sensitivity and lack of physiological compatibility. To overcome these limitations, we designed a next-generation optogenetic tool tailored for the retinal ON-bipolar cells, Opto-mGluR6. Opto-mGluR6 is a chimeric protein consisting of the intracellular domains of the ON-bipolar cellspecific metabotropic glutamate receptor mGluR6 and the light-sensing domains of melanopsin. As mGluR6 is a G-protein-coupled receptor that activates endogenous Gi/o signaling, Opto-mGluR6 profits from an increased light-sensitivity due to endogenous signal amplification. The retinal photopigment melanopsin is structurally similar to mGluR6 and presents a superior light antenna compared to rhodopsin and cone opsin due to its bistability (not bleachable). We showed that Opto-mGluR6 reliably recovers vision in a gene therapeutically blind Retinitis pigmentosa mouse model at the retinal, cortical, and behavioral levels under moderate daylight illumination. Currently we are adapting the molecular tools (viruses and promoters) for human use and investigate what visual performance an optogenetic therapy is able to recover.

Keywords: Retina, vision recovery, gene therapy, optogenetics, mouse, human donor tissue, adeno-associated virus, molecular engineering, Retinitis pigmentosa

Chronic pain blocks the induction of NO-dependent LTD in mouse ACC

Krebs Norbert, University of Bern, Department of Physiology, Bern
Prof Nevian, Thomas, University of Bern, Department of Physiology

Synaptic plasticity has been implicated both in learning and memory and in many pathological conditions including chronic pain. Chronic pain is a health problem with high prevalence. The perception and evaluation of pain involves several brain regions comprising the pain matrix. The Anterior Cingulate Cortex (ACC) is an essential part of the pain matrix and it is especially important for the emotional aspects of pain., We studied spike-timing dependent plasticity (tLTD) at synapses onto layer 5 pyramidal neurons in the ACC in adult mouse using whole cell patch clamp recordings in a slice preparation. Pairing of post- and presynaptic activity (t = -25 ms) resulted in LTD depending on postsynaptic calcium-influx through NMDARs triggering the synthesis of nitric oxid (NO). Bath application of a NO donor induced LTD of synaptic transmission. Strikingly, if mice were subjected to chronic constriction injury (CCI) of the sciatic nerve tLTD induction was occluded. Wash in of the NO donor, however, led to depression both in control and in CCI animals suggesting that neuropathic pain affects the synthesis of NO but not the subsequent downstream signalling pathway. To identify which cellular mechanism within the tLTD induction cascade is impaired in neuropathic pain we analysed the role of NMDARs and revealed an increase in NMDAR:AMPAR ratio in the CCI condition. Since NMDARs are essential for tLTD induction, we suggest that an altered NMDAR channel function might be the reason for the occlusion of tLTD in the neuropathic pain condition.

Keywords: chronic pain, LTD, NMDAR, NO

Implicit memory for the content but not the speaker of sleep-played messages

Ruch Simon Dr., University of Bern, Department of Psychology and Center for Cognition, Learning and Memory, Bern
Romi Zäske, Friedrich-Schiller-University of Jena, Institute of Psychology - Department for General Psychology and Cognitive Neuroscience, Jena (Germany)
Marc Alain Züst, Department of Psychology and Center for Cognition, Learning and Memory
Stefan Robert Schweinberger, Friedrich-Schiller-University of Jena, Institute of Psychology - Department for General Psychology and Cognitive Neuroscience, Jena (Germany)
Katharina Henke, Department of Psychology and Center for Cognition, Learning and Memory

We presented 28 sentences uttered by 28 unfamiliar speakers to sleeping participants to investigate whether humans can encode new verbal messages, learn voices of unfamiliar speakers, and form associations between speakers and messages during EEG-defined deep sleep. After waking, participants performed three tests which assessed the unconscious recognition of sleep-played speakers, messages, and speaker-message associations. Recognition performance in all tests was at chance level. However, response latencies revealed implicit memory for sleep-played messages but neither for speakers nor for speaker-message combinations. Only participants with excellent implicit memory for sleep-played messages also displayed implicit memory for speakers but not speaker-message associations. Hence, deep sleep allows for the semantic encoding of novel verbal messages.

Keywords: sleep learning consciousness implicit memory EEG

Vocabulary acquisition during sleep

Züst Marc MSc, University of Bern, Departement of Psychology, Bern
Ruch, Simon, University of Bern, Department of Psychology & Center for Cognition, Learning and Memory (CCLM), Bern
Wiest, Roland, University Hospital of Bern, Support Center for Advanced Neuroimaging (SCAN) and Institute of Diagnostic and Interventional Neuroradiology, Bern
Henke, Katharina, University of Bern, Department of Psychology & Center for Cognition, Learning and Memory (CCLM), Bern

Can we learn while asleep? To investigate this ancient dream of mankind, we presented pairs of German words and fictitious translations for vocabulary acquisition during deep sleep. After waking, participants performed two implicit memory tests: 1) a cued-recall test and 2) a (re)learning test. For (re)learning, participants committed sleep-played translations and novel translations to memory during four learning runs. Functional MRI was performed during the cued-recall test. Behavioral data in both implicit tests evidenced unconscious relational word encoding during sleep. Hippocampus supported unconscious retrieval performance: the larger the hippocampal signal during retrieval, the better relational retrieval performance and the larger word pair-evoked EEG activity during sleep. We conclude that paired-associative memory encoding during deep sleep is feasible and supported by hippocampus.

Keywords: slow-wave sleep, long-term memory, associative learning, implicit retrieval, EEG, fMRI.

Talk abstracts
Clinical research

Does automated morphometric screening support MRI diagnostics in temporal lobe epilepsy patients?

Rummel Christian PhD, University Hospital Bern, University Institute for Diagnostic and Interventional Neuroradiology, Support Center for Advanced Neuroimaging (SCAN), Bern
Nedelina Slavova, University Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern
Andrea Seiler, Department of Neurology, Inselspital, Bern
Eugenio Abela, University Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern
Martinus Hauf, Epilepsy Clinic, Tschugg
Yulia Burren, Department of Psychiatry, Bern
Christian Weisstanner, University Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern
Kaspar Schindler, Department of Neurology, Inselspital, Bern
Roland Wiest, University Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern

Introduction: Volumetric and morphometric group analyses of T1-weighted MRIs have provided in-depth insight about structural alterations in the epileptic brain. To render these observations useful for clinical practice the question arises to which extent morphometric abnormalities may be inferred in individual patients and if they may contribute to syndrome classification and individual diagnostics.

Methods: We developed a fully automatic analysis pipeline based on the free software packages FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and FreeSurfer (https://surfer.nmr.mgh.harvard.edu) to evaluate nine morphometric parameters regionally. Individual patient MRIs were compared to a data base of 322 healthy controls. The framework was evaluated on 47 MRIs of 37 electro-clinically confirmed temporal lobe epilepsy (TLE) patients by two experienced raters specialized on imaging of epilepsy.

Results: The agreement of automatically detected abnormality patterns with the human raters and with syndromal templates both showed characteristics of typical screening tests (large negative predictive values and small to moderate positive predictive values). Morphometric analysis in individual patients and statistical comparison to large control data sets does not outperform expert assessment in general. However, there is a considerable subset of inconclusive cases where complementary diagnostic information is provided. Additional findings encompass morphometric abnormalities of the folded cortical band (especially surface areas and curvatures, which can hardly be assessed by visual interpretation of cross-sectional images).

Discussion: As the automated morphometric analysis does not allocate human time and resources and can help to exclude unsuspicious brain regions, this tool should be used to support the neuroradiologist in the identification of structural abnormalities associated with epileptic lesions.

Keywords: structural MRI, temporal lobe epilepsy, surface based morphometry, voxel based morphometry, personalized medicine

Hyperactive premotor cortex drives behavioural inhibition: resting state perfusion of the Supplementary Motor Area and Catatonia syndrome in schizophrenia

Walther Sebastian PD Dr. med., University of Bern, University Hospital of Psychiatry, Translational Research Center, Bern
Schäppi, Lea, University Hospital of Psychiatry, Bern
Federspiel, Andrea, University Hospital of Psychiatry, Bern
Wiest, Roland, Institute of Neuroradiology, Bern
Strik, Werner, University Hospital of Psychiatry, Bern
Stegmayer, Katharina, University Hospital of Psychiatry, Bern

Background: Catatonia is a psychomotor syndrome that frequently occurs in the context of schizophrenia. The neural correlates of catatonia remain unclear, due to small sized studies. We therefore compared resting state cerebral blood flow (rCBF) between schizophrenia patients with current catatonia, without catatonia and healthy controls.

Methods: We included 44 schizophrenia patients and 41 controls. Catatonia was currently present in 15 patients (scoring two items on the Bush Francis Catatonia Rating Scale screening). Patients did not differ in antipsychotic medication or positive symptoms. We acquired whole brain rCBF using arterial spin labeling (ASL) on a 3T MRI scanner. Preprocessing included co-registration, normalization, realignment, re-slicing and spatial smoothing. We compared whole brain perfusion over all, and between the groups using a one-way ANOVA (F-test and T-tests). A uniform threshold of p 0.001, minimum voxel size 100 was applied. Results: We found a group effect (F-test) within bilateral supplementary motor area (SMA), anterior cingulate cortex, dorsolateral prefrontal cortex, left interior parietal lobe and cerebellum. T-tests indicated specificity of one cluster (SMA) in catatonia. Significant hyperperfusion in the SMA was detected in catatonia compared to patients without catatonia. Moreover, retarded catatonia with maximum behavioural inhibition had higher SMA perfusion than any other group (excited catatonia, non-catatonia patients and healthy controls).

Conclusions: SMA resting state hyperperfusion is a marker of current catatonia in schizophrenia. This is highly compatible with a dysregulated motor system in catatonia, particularly affecting premotor areas. Further studies need to clarify whether the findings also hold true for catatonia of different origin.

Keywords: movement disorder schizophrenia ASL

Cluster I: Center for Cognition, Learning and Memory CCLM

Prof. Katharina Henke, Institute of Psychology, Bern

CCLM is one of seven strategic research centers of the University of Bern. All of these research centers were launched by the university leadership on the foundation of outstanding work of various scientists. By promoting innovative and qualitatively outstanding research on cognition, learning and memory, the University of Bern seeks to strengthen this research focus and Bern as a research location. The main objective of CCLM is to investigate basic processes of cognition, learning and memory from a psychological and neuroscientific perspective. Research results are applied in a practical context and conveyed to educational settings. CCLM can be divided into three parts: Basic research, education and knowledge transfer, and application. CCLM currently consists of 14 interdisciplinary research groups embracing the fields of psychology, psychiatry, neurology, neuropediatrics, biology, and physiology. All group leaders are professors with an international profile. Their PhD students, postdocs and scientific and technical personnel are also part of CCLM. The 14 research groups are led by:

1. Antoine Adamantidis & Claudio Bassetti
2. Thomas Dierks & Thomas König & Werner Strik
3. Daria Knoch
4. Regula Everts & Maja Steinlin
5. Katharina Henke
6. Janek Lobmaier & Fred Mast
7. Beat Meier
8. Tobias Nef
9. René Müri
10. Thomas Nevian
11. Walter Perrig
12. Thomas Rammsayer
13. Claudia Roebers
14. Walter Senn

www.cclm.unibe.ch

Cluster II: Bern Network for Epilepsy, Sleep and Consciousness BENESCO

Prof. Claudio Bassetti, Department of Neurology, Inselspital Bern

The Bern Network for Epilepsy, Sleep and Consciousness (BENESCO) embraces scientists and clinicians of the University of Bern, the Neurocenter of Southern Switzerland in Lugano and collaborating groups at the University of Fribourg and at the clinic Barmelweid (Aargau) specialized in sleep medicine and psychosomatic disorders.

The aim of the Network is to promote multi-disciplinary and translational knowledge, exchange of expertise and collaborations among researchers and clinicians in the domain of epilepsy, sleep and disorders of consciousness.

The three core pillars are:
- Basic translational research from animal to human on epilepsy, sleep and disorders of consciousness.
- Exchange of expertise and education of young researchers within the BENESCO Seminar.
- Transfer of knowledge into the clinical routine to improve diagnosis and treatment of patients with sleep disorders, epilepsy and disorders of consciousness.

The BENESCO consists of 21 interdisciplinary research groups from the fields of Neurology, Pneumology, Psychiatry, Psychology and Sports Science specialized in sleep medicine, epilepsy and research on altered states of consciousness. All group leaders are researchers and/or clinicians with an international profile.

www.benesco.ch

Cluster III: Regenerative Neuroscience

Prof. Daniel Surbek, Department of Obstetrics and Gynecology, Inselspital Bern
Prof. Volker Enzmann, Department of Ophthalmology, Inselspital Bern

The interdisciplinary collaboration between five research groups of the Inselspital and the University of Bern was inspired by the emerging field of stem cell research, which offers interesting new therapeutic options for a variety of disorders of the brain and the sensory organs of the head. These approaches include cell-free treatments, delivery of stem cell-derived progenitors, pre-differentiated neuronal or sensory cells to the damaged site as well as the promotion of local cellular repair using endogenous stem cell mechanisms. Hence, our research efforts aim to promote common stem cell-related projects. Thereby, emphasis will be given to multidisciplinary approaches focused on injury and its regeneration in the central nervous system. An important aspect of the cluster consists in the opportunity to offer teaching and continuous education to young researchers.

In the course of already existing scientific interactions, we realized that our research projects would substantially benefit from more intense collaboration. In 2009 the foundation for the cluster was laid during staffing the newly built research building in Murtenstrasse 50. A common lab space for the cluster members was thereby discussed. Finally, the Cluster of Regenerative Neuroscience was established by the research groups from the University Departments and Clinics of Infectiology; Neurosurgery; Obstetrics & Gynecology; Ophthalmology and Otorhinolaryngology, Head & Neck Surgery. In 2011 a common stem cell research laboratory in the mentioned building was set up by the cluster members. Recently, it moved into Murtenstrasse 40. Since the beginning scientific and administrative issues are shared and discussed at regular monthly meetings. All this led to several common research projects and proposals. Furthermore, social interactions between the lab members have been also flourishing in several come together meetings.

Cluster IV: Basic Neuroscience

Prof. Thomas Nevian, Department of Physiology, University of Bern

The "basic neuroscience cluster" is now in the process of being established. It comprises scientists performing preclinical and fundamental neuroscience research on the cellular and circuit level. Topics cover a broad spectrum from theoretical neuroscience, the biophysics of ion channels, chemical signaling to neuronal and network function in health and disease. The aim of the cluster is to share techniques and to establish collaborations and exchange of knowledge and ideas. In the future the visibility of the basic neurosciences in Bern will be promoted by joint seminars and symposia.

Cluster V: Neuroimaging

Prof. Roland Wiest, University Institute for Diagnostic and Interventional Neuroradiology, Inselspital Bern

Cluster VI: Translational Psychiatry

Prof. Werner Strik, University Hospital of Psychiatry, Bern

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List of participants in alphabetical order

Achenbach Sven	University Hospital Bern, Inselspital Institute of Diagnostic and Interventional Neuroradiology Bern
Adalid Víctor	University Bern, Departments of Clinical Research and Radiology, Bern
Adamantidis Antoine, Prof. Dr.	University of Bern / Inselspital, Department of Neurology, Bern
Affentranger Thomas, Dr. phil.	IV-Stelle Kanton Bern, Regionaler Ärztlicher Dienst BE-FR-SO, Bern
Altorfer Andreas, PD Dr. phil.	University Hospital of Psychiatry, Translational Research Center Music and Emotion, Bern
Andereggen Lukas, MD	University of Bern and Harvard Medical School, Department of Neurosurgery and F.M. Kirby Neurobiology Center, Inselspital Bern and Boston Childrens Hospital, Switzerland and USA Research Unit, Pavillon 47, Bern
Arnold Marcel, Prof. MD	Inselspital, Department of Neurology, Bern
Bänninger Anja	University Hospital of Psychiatry and Psychotherapy, Translational Research Center, Bern
Bassetti Claudio	Prof. Dr. med., Universität Bern / Inselspital, Universitätsklinik für Neurologie, Bern
Bisco Alberto	University of Bern, Department of Physiology, Bern
Branislav Savic	University of Bern, Center for Cognition, Learning, and Memory, Institute of Psychology, Bern
Brügger Karin	Spital STS AG, Psychiatrische Dienste Thun, Thun
Burgunder Jean-Marc, Prof. Dr. med.	Neurology Neurozentrum Siloah, Gümligen
Burren Yuliya, Psychologist FSP	Inselspital & University Hospital of Psychiatry and Psychotherapy University of Bern, Neuroradiology & Clinical Psychological Service SCAN, Bern
Capper-Loup Christine, PhD	European Huntingtons disease network, Siloah Foundation Neurology, Gümligen
Catani Marco, Prof.	King's College, Natbrainlab, London
Cazzoli Dario, Dr. phil.	University of Bern, ARTORG Center, Gerontechnology and Rehabilitation Group, Bern
Chesham Alvin, M.Sc.	University of Bern, ARTORG Center, Gerontechnology & Rehabilitation, Bern
Diana Lorenzo, M.Sc.	University of Bern, Gerontechnology and Rehabilitation Group, Bern
Diaz Hernandez Laura	University of Bern, Translational Research Center, Bern
Dierks Thomas, Prof. Dr. med.	Universitäre Psychiatrische Dienste Bern, Universitätsklinik für Psychiatrie und Psychotherapie Bern
Eggenberger Noëmi	Inselspital Bern, Department of Pediatric Neurology, Development and Rehabilitation, Bern Inselspital Bern, Departments of Neurology and Clinical Research, Bern
Enzmann Volker, Prof.	University of Bern, Ophthalmology, Experimental Ophthalmology, Bern
Everts Regula, PD Dr. phil.	Childrens University Hospital, Inselspital, Neuropaediatrics, Development and Rehabilitation Bern
Fadda Angela	Vetsuisse Faculty, University of Bern, Division of neurological sciences, Bern
Federspiel Andrea, Prof	University Hospital of Psychiatry and Psychotherapy, Translational Research Center, Psychiatric Neuroimaging Unit, Bern
Fehér Kristoffer	University Hospital of Psychiatry, University of Bern, Translational Research Center, Bern
Fichtner Nicole	University of Bern, Radiology and Clinical Research, Bern
Fischer Urs, Prof. Dr. med.	University of Bern / Inselspital, Department of Neurology, Bern
Frick Tamara	University Hospital Bern - Inselspital, Department of Intensive Care Medicine, Bern
Friedli Michèle, MSc	University of Bern, Switzerland Insitute of Psychology and Center for Cognition, Learning, and Memory, Bern
Furger Stephan	University Hospital of Psychiatry Bern, Translational Research Center, Division of Systems Neuroscience of Psychopathology, Bern
Gaviria Julian	University of Geneva Neuroscience, Neurology and Imaging of cognition lab (Labnic), Geneva
Gilani Irtiza, Dr.	University Hospital Bern (Inselspital), Support Center for Advanced Neuroimaging (SCAN), Department of Neuroradiology, Bern
Grandgirard Denis, Dr	University of Bern, Institute for Infectious Diseases, Neuroinfection Laboratory, Bern
Gutbrod Barbara	Universitätsklinik für Neurologie, Abteilung für Kognitive und Restorative Neurologie, Bern
Gutbrod Klemens, Prof. Dr.	Bern, Neurology, Bern

Gysin-Maillart Anja, Ph.D.	University Hospital of Psychiatry, University of Bern, Outpatient Department, Bern
Hathaway Lucy, Dr	University of Bern, Institute for Infectious Diseases, Bern
Helmstaedter Moritz, Prof.	Max-Planck-Institut für Hirnforschung, Frankfurt am Main
Henke Katharina, Prof. Dr.	Universität Bern, Institut für Psychologie, Division of Experimental Psychology and Neuropsychology, Bern
Heri Kathryn	University Hospital of Psychiatry, Bern, Translational Research Center, Bern
Herschkowitz Elinore	
Herschkowitz Norbert, Prof. Dr. med.	
Hubl Daniela, Prof.	University of Bern, University Hospital of Psychiatry and psychotherapy, Bern
Jäggi Marietta	Luzerner Psychiatrie, Memory Clinic, Sursee
Januth Silvan	University of Bern, Gerontechnology and Rehabilitation Group, Bern
Jenkinson Stephen Philip	University of Bern, Institute for Infectious Diseases, Bern
Kanzler Susanne	Universität Bern, APN/SPSN, Bern
Kasanetz Fernando	University of Bern, Physiology, Nevian Group, Bern
Käser Ursula	Inselspital, Department of Neurology, Bern (coordinator CNB)
Kleinlogel Sonja	University of Bern, Institute of Physiology Optogenetics group, Bern
Knecht Urspeter, MD	University Hospital, Inselspital Bern, Department of Neuroradiology, Bern
Köhli Jessica	Klinische Psychologe NeuroZentrum Siloah, Psychologie, Gümligen
Kornfeld Salome	Inselspital, Bern, Division of Neuropaediatrics, Development and Rehabilitation, Bern
Krebs Norbert	University of Bern, Department of Physiology, Bern
Kreis Roland, Prof. Dr.	University Bern, Radiology and Clinical Research, Bern
Kreutzer Elena	University of Bern, Departement of Physiology, Bern
Kunzelmann Katharina, Dipl.-Psych.	University Hospital of Psychiatry, Translational Research Center Division of Systems Neuroscience of Psychopathology, Bern
Kyathanahally Sreenath, P	University of Bern, Depts. Radiology and Clinical Research, Bern
Leib Stephen, Prof. Dr. med.	University of Bern, Institute for Infectious Diseases, Bern
Leimer Pascal	University of Bern, Department of Physiology, Bern
Leitao Joana	Universite de Genve Department of Neurosciences, Geneve
Leumann Christian, Prof. Dr.	Universität Bern, Research, Bern
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Lopes Sabrina	Universität Bern, Klinische Psychologie und Neurowissenschaften, Bern
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Mayr Patrizia	University of Bern, Abteilung für Allgemeine Psychologie und Neuropsychologie, Bern
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Meier Beat, Prof. Dr.	Bern, Psychology, Bern
Meier Lea, PhD	University of Bern, University Hospital of Psychiatry, Translational Research Center, Division of Systems Neuroscience of Psychopathology, Bern
Meier Raphael	University of Bern, Institute for Surgical Technology & Biomechanics, Bern
Melie-Garcia Lester, PhD	Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques, Laboratoire de recherche en neuroimagerie (LREN), Lausanne
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Moor Nicolas	University Hospital for Psychiatry and Psychotherapy, University of Bern, Centre for translational Psychiatry, Bern

Morishima Yosuke	University Hospital of Psychiatry, University of Bern, Translational Research Center, Bern
Möseneder Laura, M Sc	Universität Bern, Clinical Psychology and Psychotherapy, Bern
Moser Tony	Bern, Psychologie, Aarau
Müller Michael	Inselspital, Bern University Hospital, University of Bern, Department of Neurology, Bern
Müller Stefanie, Dipl.-Psych.	University of Bern, University Hospital of Psychiatry, Translational Reseach Center, Division of Molecular Psychiatry, Bern
Muri Lukas, MSc	Uni Bern, IFIK, Leib, Bern
Muri Raphaela	Universität Bern, APN/KPP, Bern
Müri René, Prof	University of Bern, Department of Neurology, Perception and Eye Movement Laboratory, Bern
Mürner-Lavanchy Ines	Childrens University Hospital Bern, Neuropediatrics, Development and Rehabilitation, Bern
Nevian Thomas, Prof. Dr.	Universität Bern, Institut für Physiologie, Bern
Oppliger Byron	University of Bern, Department of Obstetrics and Gynecology and Department of Clinical Research, Bern
Ovalle Fresa Rebecca	University of Berne, Institute of Psychology, Bern
Pacozzi Luca	University of Bern, Department of Psychology, Bern
Padovani Tullia, PhD	University of Bern, Neuropsychology, Bern
Paladini Rebecca E.	University of Bern, Gerontechnology and Rehabilitation Group, Bern
Papmeyer Martina, Dr.	University Hospital of Psychiatry Bern, University of Bern, Translational Research Center, Bern
Peitsch Camille	UniBern, Institut für Anatomie, ExMo, Bern
Perny Michael, MSc	University of Bern, Institute for Infectious Diseases, Neuroinfection Laboratory, Bern
Pfeiffer Christian, Dr.	Centre Hospitalier Universitaire Vaudois, Clinical Neuroscience, Laboratoire de Recherche en Neuroimagerie, Lausanne
Pollo Claudio, Prof. Dr. med.	Universität Bern / Inselspital, Universitätsklinik für Neurochirurgie, Bern
Precht Christina, Dr. med. vet.	University of Bern, Vetsuisse-Faculty, Department of Clinical Veterinary Medicine, Clinical Radiology, Bern
Preisig Basil	University of Bern, Departments of Neurology and Clinical Research, Perception and Eye Movement Laboratory, Bern
Radecke Julika	University Bern, Institute of Anatomy, Bern
Reyes Mauricio, Prof. Dr.	University of Bern, Institute for Surgical Technology and Biomechanics, Medical Image Analysis, Bern
Richardson Peter	University of Bern, Institute of infections diseases, Bern
Roccio Marta, PhD	University of Bern, Department of Clinical Research, University of Bern and Otorhinolaryngology, Head & Neck Surgery, Inselspital, Inner Ear Research Lab, Bern
Rohde Kristina B., Dr. phil.	University of Bern, Translational Research Center, Division of Clinical Research, Addiction Research Group, Bern
Ruch Simon, Dr.	University of Bern, Department of Psychology and Center for Cognition, Learning and Memory, Bern
Rüegsegger Daniela	University Berne, Student in Psychology, Bern
Rummel Christian, PhD	University Hospital Bern, University Institute for Diagnostic and Interventional Neuroradiology Support Center for Advanced Neuroimaging (SCAN), Bern
Sanabria-Diaz Gretel, MSc	Centre Hospitalier Universitaire Vaudois (CHUV), Département des neurosciences cliniques Laboratoire de recherche en neuroimagerie (LREN), Lausanne
Saulin Anne	University of Bern, Social Neuroscience, Bern
Schindler Kaspar, Prof.	University Department of Neurology, Neurology, Bern
Schneider Else	University of Bern, Psychology, Bern
Schoeberlein Andreina, PD Dr. sc. nat.	University of Bern, Department of Clinical Research, Laboratory for Prenatal Medicine, Bern
Schumacher Rahel	Inselspital, Bern University Hospital, Department of Neurology, Division of Cognitive and Restorative Neurology, Bern

Schweizer Nadia	University of Bern, Gerontechnology and Rehabilitation Group, Bern
Seiler Stefanie	Universtiy of Bern / Inselspital, Department of Neurosurgery, Bern
Selimovic-Hamza Senija, MSc BSc	University of Bern, Vetsuisse Faculty, DCR-VPH, Bern
Senn Walter, Prof. Dr.phil.nat.	Universität Bern, Institut für Physiologie, Bern
Soravia Leila Maria, Dr. phil.	University Hospital of Psychiatry, Division of Systems Neuroscience of Psychopathology, Translational Research Center, Bern
Spicher Dominik	University of Bern, Physiology, Bern
Stalder Franziska, Dr. phil.	Universität Bern, Dienstleistungszentrum CCLM, Bern
Stefano Di Santo, PhD	Bern University Hospital, Department of Neurosurgery, Research Laboratory and Regenerative Neuroscience ClusterBern
Stegmayer Katharina, M.D.	University Hospital of Psychiatrie, Bern, Translational Research Center, Bern
Steimer Andreas, Dr.sc.	Inselspital Bern, University Hospital / University of Bern, Department of Neurology, Bern
Steinlin Maja, Prof. Dr. med.	University Childrens Hospital, Inselspital, Bern, Neuropaediatrics, Development and Rehabilitation, Bern
Streit Jonas	University of Bern, Department of Physiology, Bern
Streit Jürg, Prof. Dr. med.	Universität Bern, Institut für Physiologie, Bern
Strik Werner, Prof. Dr. med.	Universitäre Psychiatrische Dienste Bern, Universitätsklinik für Psychiatrie und Psychotherapie, Bern
Stucki David Manuel, Msc	University of Bern, Institute of Cell Biology, Saxena group, Bern
Studer Barbara, Dr.	University of Bern, CCLM, Bern
Surbek Daniel, Prof. Dr. med.	Universität Bern / Inselspital, Departement Klinische Forschung (DKF), Dept of Obstetrics and Gynecology, Bern
Theiler Romina	Universität Bern, Universitätsklinik für Neurologie, Bern (coordinator CNB)
Toepel Ulrike, Dr.	CHUV & UNIL, Radiology Department, Lausanne
Trepp Carolyn	Inselspital Bern, University Bern Department of Ophthalmology, Bern
Truchet Laura	Vetsuisse Faculty Bern, University of Bern, NeuroCenter, Division of Neurological Sciences, Bern
Tscherter Anne, Dr.	Universität Bern, Institut für Physiologie, Bern
Urwyler Prabitha, Dr.	University of Bern, Gerontechnology and Rehabilitation Group, Bern
Vallejo Vanessa	ARTORG Center for Biomedical Engineering Research, Gerontechnology & Rehabilitation, Bern
Viher Petra	University Hospital of Psychiatry and Psychotherapy, Translational Research Center, Bern
Wagner Markus, Dr. d. Chiropraktik	Schweizerische Chiropraktorengesellschaft, Ausbildung, Bern
Walter Stefan	University of Bern, Experimental Psychology and Neuropsychology, Bern
Walther Sebastian, PD Dr. med.	University of Bern, University Hospital of Psychiatry, Translational Research Center, Bern
Weber Nico, pract med	University Bern, Translational Research Center, Psychiatric Neuroimaging Unit, Bern
Widmer Hans Rudolf, Prof. Dr.	University of Bern, Neurosurgery, Bern
Widmer Sara, M.Sc.	Memory Clinic Sursee, Luzerner Psychiatrie, Sursee
Wiest Roland, Prof. Dr. med.	Universität Bern / Inselspital, Universitätsinstitut für Diagnostische und Interventionelle Neuroradiologie, Bern
Winkelbeiner Stephanie, M.Sc.	University of Bern, Division of Systems Neuroscience of Psychiatry, Bern
Witmer Joelle, M Sc	University of Bern, Psychology, Bern
Wüthrich Sergej	University of Bern, Institute of Psychology, Bern
Zengaffinen Francilia Sabrina	University Hospital of Psychiatry (UPD), Division of Systems Neuroscience of Psychopathology Translational Research Center, Bern
Zito Giuseppe Angelo, PhD	University of Bern, ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation, Bern
Zuber Benoît, Prof.	University of Bern, Institute of Anatomy, Bern
Züst Marc, MSc	University of Bern, Departement of Psychology, Bern

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University of Bern
Clinical Neuroscience Bern
inter-faculty focus
c/o INSELSPITAL, University Hospital
Department of Neurology
CH-3010 Bern
Phone: +41 (0)31 632 25 38
E-mail: ursula.kaeser@insel.ch
www.neuroscience.unibe.ch