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Program and Abstracts for the
Third Meeting of the

Clinical Neuroscience Bern

28th November 2007

University Hospital
of Psychiatry
Bern

Program

08:00 – 09:00	Poster attaching
09:00 – 09:05	Opening Adress W.K. Strik, University Hospital of Psychiatry, Bern
09:05 – 09:45	Main Lecture: ”TMS in clinical neuroscience – new approaches” R. Müri, Department of Neurology, Inselspital, Bern
09:45 – 10:15	Coffee Break
10:15 – 12:15	Short presentations Chair: C.W. Hess, Department of Neurology, Inselspital Bern
12:30 – 14:30	Postersession and Lunch
14:30 – 16:15	Workshops
16:15	Poster Award / End of the meeting

Abstracts by Discipline

Short Presentations

Posters

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Short Presentations: Selected abstracts

Chair: Christian W. Hess

SPP-1

Signal processing in small dendrites of neocortical pyramidal neurons

Thomas Nevian[1]

[1]*Department of Physiology, University of Bern, 3010 Bern, Switzerland*

Basal dendrites receive the majority of synapses that contact neocortical pyramidal neurons, yet our knowledge of synaptic processing in these dendrites has been hampered by their inaccessibility for electrical recordings. A new approach to patch-clamp recordings enabled us to characterize the integrative properties of these cells. Despite the short physical length of rat basal dendrites, synaptic inputs were electrotonically remote from the soma (>30-fold excitatory postsynaptic potential (EPSP) attenuation) and back-propagating action potentials were significantly attenuated. Unitary EPSPs were location dependent, reaching large amplitudes distally (>8 mV), yet their somatic contribution was relatively location independent. Basal dendrites support sodium and NMDA spikes, but not calcium spikes, for 75% of their length. This suggests that basal dendrites, despite their proximity to the site of action potential initiation, do not form a single basal-somatic region but rather should be considered as a separate integrative compartment favoring two integration modes: subthreshold, location-independent summation versus local amplification of incoming spatiotemporally clustered information.

Neurobiology (PSB), Neurology (PSN)

SPP-2

Integration of bottom-up and top-down inputs at the cellular level

Matthew Larkum[1]

[1]*Department of Physiology, University of Bern, 3010 Bern, Switzerland*

Bottom-up and top-down cortical pathways tend to target different layers. This means that neurons of the cortex, articularly pyramidal neurons which have dendrites spanning several cortical layers, receive inputs which are segregated into specific regions of their dendritic trees. Combined with complex intracellular signaling mechanisms involving local dendritic spikes. This provides a rich substrate for complex intracellular interactions. I propose here a theory for the integration of bottom-up and top-down inputs which serves as an organizing principle for cortex explaining the morphology and properties of pyramidal neurons as well as the laminar structure of the cortex itself.

Neurobiology (PSB), Neurology (PSN)

SPP-3

Evidence for grey matter increase due to second language learning

Maria Stein[1]

[1]*University Hospital of Psychiatry, Department of Psychiatric Neurophysiology Bern*

Research on bilingualism has repeatedly demonstrated that the human ability to learn a second language is linked to functional changes in neuronal networks subserving language processing. Contrary to that, evidence for structural changes related to second language learning is still sparse.
We examined 12 native English-speaking exchange students learning German in Switzerland at two points in time: before and after a 5 months period of increased second language learning. On both examination days, the subjects participated in a German language tests and in MRI measurements. Using the method of voxel based morphometry, we assessed the increase of cortical grey matter density (GMD) from first to second measurement. In a region in the left inferior frontal gyrus, the increase in GMD correlated significantly with the increase in second language proficiency, as assessed by the language test.
These findings can be interpreted as a direct sign of plasticity originated by the sustained training of a second language leading to an increased proficiency. The present study demonstrates for the first time in a longitudinal design structural changes related to second language learning.

Neurobiology (PSB), Neuropsychology/ Psychiatry (PSP)
bilingualism, neuronal plasticity

SPP-4

Glucocorticoids reduce phobic fear in humans

Leila Maria Soravia[1]

[1]*Department of Psychiatric Neurophysiology, University Hospital of Psychiatry Bern, 3000 Bern 60, Switzerland,*

Background: Phobias are characterized by excessive fear, cued by the presence or anticipation of a fearful situation. Whereas it is well established that glucocorticoids are released in fearful situations, it is not known whether these hormones, in turn, modulate perceived fear. Previous studies indicate that elevated glucocorticoid levels impair the retrieval of emotionally arousing information. We therefore hypothesize that glucocorticoids might also inhibit retrieval of fear memory associated with phobia and, thereby, reduce phobic fear. Method: We investigated whether acutely administrated glucocorticoids reduce phobic fear in two double-blind, placebo-controlled studies in 40 subjects with social phobia and 20 subjects with spider phobia. Social phobic patients received 25 mg of cortisone orally 1 h before a socio-evaluative stressor, whereas spider phobics received 5 times 10 mg of cortisone 1 h before exposure to a spider photograph. Results: Cortisone treatment significantly reduced self-reported fear during the anticipation, exposure and recovery phase of the stressor in social phobics, whereas repeated oral administration of cortisol induced a progressive reduction of stimulus-induced fear in spider phobic patients. Conclusion: The present findings in two distinct types of phobias indicate that glucocorticoid administration reduce phobic fear.

Neuropsychology/ Psychiatry (PSP)
Glucocorticoids, Phobia, Cortisol

SPP-5

An Analysis of the Processes Contributing to Deficient Risky Decision-making in Patients with Ventromedial Prefrontal Damage

Céline Eggen[1]

[1]*Department of Psychology, University of Berne, 3010 Berne, Switzerland*

Damage to the ventromedial prefrontal cortex is often associated with a defect in real-life risky decision-making; however, most other cognitive functions remain unimpaired. So far, most experimental results in the neuropsychological decision-making research have been obtained with the Iowa Gambling Task. The conclusions drawn from this task have been challenged in recent years though. Therefore, a different approach has been used in this study, assessing decision-making by means of more everyday-life like decision tasks. To explore possible processes contributing to deficient risky decision-making in patients with ventromedial prefrontal damage, 25 subjects (13 brain-damaged patients, 12 healthy controls) were tested. The performance of the two groups was comparable. This result suggests that patients with ventromedial prefrontal damage might have trouble in implementing ideas into actions.

Neurology (PSN), Neuropsychology/ Psychiatry (PSP)
Ventromedial Prefrontal Cortex, decision-making, implementation

SPP-6

Sleepiness is not always perceived prior to falling asleep in healthy sleep deprived subjects. A confirmatory follow-up study.

Uli S. Herrmann[1]

[1]*Centre of Sleep Disorders, University Hospital Inselspital, 3010 Berne, Switzerland*

Introduction: Most experts assume, that nobody can fall asleep without prior awareness of sleepiness. However, others found only a moderate ability to subjectively judge alertness, particularly in tasks without any feed back information. We prospectively evaluated the awareness of subjective sleepiness (SS) prior to sleep onset during the maintenance of wakefulness test (MWT), the most commonly used method to assess alertness in a clinical environment.

Methods: Twenty-eight young healthy students (mean age 22.4 years; 13 females) underwent 4 MWTs after a night of total sleep deprivation. The subjects were instructed to press an event button to signal sleepiness and were given the following written and oral directive: "Indicate your earliest symptoms of sleepiness and try to stay awake as long as possible". Overt sleep (OS) was scored according to Rechtschaffen and Kales, and microsleeps (MS), defined as sleep-EEG of 3 seconds' duration or more, was scored separately. In a first series with 12 subjects (6 females) no reward was given. In a second series with 16 subjects (7 females) a financial reward was offered for both optimal recognition of SS and as well as longer sleep latency.

Results: Overall 17 of 28 subjects (60.7%) presented either a MS- or an OS fragment before indicating SS at least in one of four trials. This pattern was observed in 45.8% of all 48 MWT-trials without reward and in 31.2% of all 64 MWT-trials with reward (difference n.s.). Trials with this pattern showed on average a shorter sleep latency than trials where SS was properly indicated before sleep onset ($p < 0.001$). Without reward, female subjects more reliably recognized SS than male subjects ($p<.02$) who increased their performance ($p<.014$) to the same level as females after having been offered a reward.

Conclusion: Our unexpected finding that 17 of 28 young sleep deprived healthy subjects did not recognize their SS before onset of microsleep or overt sleep in at least one of four MWT-trials, and that this happened in 30-40% of all trials, is in sharp contrast to the general assumption, that nobody can fall asleep without prior awareness of sleepiness. If this findings is confirmed in larger series and also in patients, the simply advice to sleepy patients not to drive when feeling sleepy would no longer be sufficient. Motor vehicle crashes due to microsleeps could no longer be indiscriminately interpreted as being the result of negligently ignoring symptoms of sleepiness and hence be judged as due to "reckless driving". Prevention strategies against sleepiness induced motor vehicle crashes would have to include efforts to improve recognition of SS, also comprising the potential use of in-build alarming devices in cars and lorries. We recommend to assess SS recognition in the standard MWT, although its value in the judgement of fitness to drive has still to be defined.

Neurology (PSN), Neurophysiology (NP)
Maintenance of wakefulness test; sleepiness; subjective sleepiness; microsleep; motor vehicle crash

Neurophysiology

NP-1

Interhemispheric control of attention – the effect of theta burst stimulation over the left and right posterior parietal cortex

Thomas Nyffeler[1], Dario Cazzoli[1], Pascal Wurtz[1], Roman von Wartburg[1], Mathias Lüthi[1], Silvia [1], Tobias Pflugshaupt[1], Anouk Déruaz[1], Christian W. Hess[1], René M. Müri[1]

[1]*Perception and Eye Movement Laboratory*

The ability to detect left-sided stimuli during a visual extinction paradigm was studied in healthy subjects after one train of theta burst stimulation (TBS) over the right posterior parietal cortex (PPC). Stimuli were either uni- or bilaterally presented arrow heads. As for the latter, different horizontal and vertical distances were applied. After TBS, subjects showed left visual extinction over a period of thirty minutes, i.e. they omitted the contralateral stimulus in bilateral trials. However, this left visual extinction could be neutralized when a second train of TBS was applied over the left PPC. Our results suggest that visual extinction is due to an interhemispheric imbalance of PPC function. Furthermore, they suggest a possible therapeutical approach for patients with visual extinction.

Neurophysiology (NP)
Theta burst stimulation, attention, posterior parietal cortex, visual extinction

NP-2

Fiberoptic imaging of dendritic calcium activity in layer 5 neocortical pyramidal cells in freely behaving animals

Masanori Murayama[1], Enrique Pérez-Garci[1], Hans-Rudolf Lüscher[1], Matthew E. Larkum[1]

[1]*Dept. of Physiology, University of Berne, 3012 Berne, Switzerland*

Due to methodological limitations, our knowledge about dendritic activity stems mostly from in vitro experiments. However, it has been speculated that regenerative Ca^{2+} events in the distal dendrites of layer 5 (L5) neocortical pyramidal neurons correlate with distinct behavioral states. Therefore, it will be crucial to record Ca2+ activity in the freely-moving, behaving animal. Here, we present a novel approach for recording Ca^{2+} signals in the dendrites of populations of L5 pyramidal neurons in freely moving rats which ensures that all recorded fluorescence changes are due to intracellular Ca^{2+} changes in the apical dendrites. The method has two main features: 1) bolus loading of L5 with a membrane permeant Ca^{2+} dye resulting in specific loading of pyramidal cell dendrites in the upper layers and 2) a fiberoptic cable attached to a gradient index lens and a prism reflecting light horizontally at 90° to the angle of the apical dendrites. We demonstrate that the in vivo signal-to-noise ratio recorded with this relatively inexpensive and easy-to-implement fiberoptic-based device is comparable to conventional camera-based imaging systems used in vitro. In addition, the device is flexible and light-weight and could easily be adapted for recording Ca^{2+} signals in other species such as mice, cats and monkeys. Controls in vitro showed that Ca^{2+} spikes in the dendrites produce a far larger signal than synaptic input or backpropagating APs. Under urethane or isoflurane anesthesia, spontaneous fluctuations of Ca^{2+} signals were much smaller than in the behaving state, suggesting that dendritic Ca^{2+} activity is more pronounced in the awake state.

Neurophysiology (NP)
Calcium Imaging, Freely Moving Rat, Dendtite

NP-3

Serotonin and muscarine increase the number of intrinsically spiking cells in spinal cord cultures

Czarnecki Antonny[1], Magloire Vincent[1], Streit Jürg[1]

[1]*Dept. of Physiology, University of Berne, 3012 Berne, Switzerland*

The vertebrate spinal cord is equipped with a number of neuronal networks, the central pattern generators (CPGs) that underlie repetitive patterns of behavior. Activity in such networks is mediated or influenced by intrinsic cellular properties as well as by the synaptic coupling through neurotransmitters and neuromodulators. Indeed, serotonin (5-HT) stabilizes fictive locomotion induced by NMDA, and acetylcholine (Ach) induces rhythmic activity in the neonatal rat spinal cord. The current challenge is to understand the mechanisms underlying rhythm generation in more detail.
In this study, we focused on the modulation of the intrinsic activity by 5-HT and by muscarine (Ach- R agonist) in spinal cord cultures from E14 rats. We used cultures form organotypic slices and dissociated cells that form unstructured networks in vitro. We investigated these cultures on the network level using extracellular recording by multielectrode arrays (MEAs) and on the cellular level using whole cell patch clamp. All cultures showed bursting network activity, which is based on repetitive activation of the network by intrinsically spiking cells through recurrent excitation. Intrinsically firing neurons discharge spontaneously after inhibition of the major synaptic inputs with bicuculline (20µM), strychnine (1 µM), CNQX (10 µM) and APV (50 µM) and form a burst generator localized mainly in the ventral part of the slices.
MEA recordings on slices in the absence of fast synaptic transmission show that 5-HT (20 µM) and Muscarine (20 µM) lead to a several fold increase of the intrinsic activity due to an increase in the event rate at some electrodes and to a greater number of active electrodes.
We then tested the effects of both neurotransmitters on intrinsic and non-intrinsic spiking cells with patch clamp experiments in the current clamp mode on dissociated cells. Surprisingly, when we studied the intrinsic properties of neurons in absence of synaptic transmission, neither 5-HT nor muscarine had an effect on the activity of intrinsically spiking cells. However, a percentage of the cells that were not intrinsically spiking under these conditions were transformed into intrinsically spiking cells by 5-HT (34% of the cells) and muscarine (31% of the cells).
We conclude from these findings that serotoninergic and cholinergic modulation can turn silent into spontaneously spiking neurons. This neuromodulation may thus activate new sources for rhythm generation in spinal networks.

Neurophysiology (NP)
Spinal networks, Rhythmic activity, serotonin, muscarine

NP-4

Probing the Blood / Brain Barrier in Neonates: 1H-MR Spectroscopy Shows Low Protection against High Phenylalanine

Roland Kreis[1], Karin Zwygart[1], Chris Boesch[1], Jean-Marc Nuoffer[2]

[1]Dept. Clinical Research, University Bern, [2]Metabolic Unit, University Children's Hospital Bern

Introduction
Phenylketonuria (PKU) is the most frequent inborn disorder of amino acid metabolism, caused by a deficiency of phenylalanine (Phe) hydroxylase. This leads to accumulation of Phe in plasma and brain. Clinical features of PKU include severe impairment of brain development in untreated infants, but also acute reversible neurotoxic effects on brain function. The pathophysiology of both clinical manifestations is still unclear. 1H-MRS has been used to determine the blood/brain ratio for Phe and the kinetics of Phe influx into the brain in adult subjects (1-4). While the exact value for the blood/brain ratio is still disputed, there is consensus that the Phe concentration is considerably (2-4 times) lower in brain than blood for adult patients. The most crucial time in determining intellectual outcome is early childhood where the brain is particularly sensitive to toxins. Hence, dietary treatment is aimed at achieving very low blood Phe values in childhood. However, very little is known about the age-dependence of the blood brain barrier protection against high Phe values (5). We report on 1H-MRS studies to determine the blood/brain ratio for Phe in 2 neonates with PKU.
Methods and Subjects
All spectra were recorded on a clinical 1.5T MR scanner. Data acquisition and processing was reported earlier (3). Neonates: Two PKU patients, investigated soon after diagnosis and before dietary treatment (Pt A, 43 weeks gestational age [GA], 9 days after birth, Pt B. 36 weeks GA, 9 days after birth). Pt. B was rescanned under treatment 5 days later. Two healthy neonates served as controls (43 and 44 weeks GA). All examinations performed during postprandial sleep without sedation. Adults: 5 PKU patients (23±6 years old), 6 healthy subjects (23±3 years old). Blood Phe values were determined on an automatic amino-acid analyzer.
Results
The neonatal spectra were of excellent quality allowing quantitative evaluations for Phe, in spite of the smaller ROI size. The main features in the downfield region of neonates compared to spectra from adults are the smaller contribution from the amide proton of NAA (N-acetylaspartate, a putative neuronal marker) at 7.8 ppm and of the peak at 7.0 ppm. The background signals for Phe at 7.3 ppm do not show much age-dependence. The spectral contribution of Phe at 7.3 ppm is particularly striking for Patient A with a fairly high blood Phe content. The brain/blood ratio for Phe is strikingly higher for neonates than for adults. After treatment, brain Phe values drop to normal levels in parallel with blood levels in patient B.
Discussion
The present study shows that the human blood/brain barrier does not provide the same protection against high blood Phe values for the newborn as for the adult. At identical blood Phe levels, the newborn PKU patients brain is exposed to much higher Phe levels. This underlines the importance of strictest dietary control for infants with PKU.
References
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MR-Methodology (PSM), Neurophysiology (NP)
MR spectroscopy, PKU, blood-brain-barrier, brain development

NP-5

The physiological basis of psychogenic blindness

Andrea Federspiel[1], Thomas J. Müller[1], Roland Wiest[2], Wilhelm Felder[3]

[1]Dept. of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Bern, [2]Neuroradiology and Neurology, Inselspital Bern, University of Bern, Bern, [3]Child and youth Psychiatry, University of Bern, Bern

Purpose: To investigate into the psychophysiology basis of psychogenic blindness.

Methods: One 25 old women suffering from psychogenic blindness was examined two times: the first time in March 2006 (scan 1) and the second time during September 2007 (scan 2). During both sessions we recorded structural magnetic resonance images (MRI) and diffusion tensor images (DTI) as well as functional data during a (fMRI) experiment. All images were acquired on the 3T Siemens scanner (Siemens Vision, Erlangen, Germany). The fMRI experiment consisted in the visual presentation of i) full field checkerboard stimulation at 8Hz, ii) apparent motion stimulus at alternating frequency of 8Hz, and iii) visual presentation of black & white images of faces. The fMRI recordings was performed with multi-slice single-shot T2*-weighted echo planar imaging sequence, with 33 interleaved axial oblique slices. 192 dynamic scans were collected in each subject (TR = 2000 ms, TE = 30 ms). The analysis of the fMRI data was performed using BrainVoyager QX 1.9.9 and the analysis of the DTI data was performed using the PASTA tool of Joens et al. 1. Activation effects for the visual cortex, the extrastriate cortex and the right fusiform face area (FFA) were identified using Student t-test between time series and boxcar model function (threshold: $p < 0.01$). Additional, the resting cerebral blood perfusion (CBF) was assessed using the noninvasive arterial spin labeling (ASL) method 2,3.

Result: Scan1: Resting CBF was reduced on the right occipital/temporal lobe as compared to frontal regions. We observed reduced area in early visual areas (V1) activated by checkerboard stimulus, reduced area on the left MT/V5 region and no activation of the right FFA. Scan 2: Resting CBF showed normal values in all brain regions. We observed increased area in early visual areas (V1) activated by checkerboard stimulus, increased area on the left MT/V5 region and activation of the right FFA due to images of faces. Tractography within the occipital lobe revealed an intact structure of fiber bundles connecting the early visual area (V1) and thalamic nuclei.

Conclusion: Using a multimodal approach we were able to demonstrate an impaired activation pattern evoked by visual stimuli. By means of cognitive therapy the activation pattern in the primary- and higher order visual areas showed normal spatial extent and temporal properties. Structural properties revealed an intact network subserving the processing of visual information. These findings suggest that the structural and functional properties of the visual system of psychogenic blindness can be impaired. However, during an extensive and guided therapeutic approach, these originally impaired areas can be reactivated in its functions leading to a total recover of the lost visual abilities.

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MR-Methodology (PSM), Neurophysiology (NP), Neuropsychology/ Psychiatry (PSP)
Psychogenic Blindness; MRI; DTI; CBF

NP-6

Sleepiness is not always perceived prior to falling asleep in healthy sleep deprived subjects. A confirmatory follow-up study.

Uli S. Herrmann[1], Christian W. Hess[1], Adrian Guggisberg[1], Corinne Roth[1], Matthias Gugger[1], Johannes Mathis[1]

[1]*Centre of Sleep Disorders, University Hospital Inselspital, 3010 Berne, Switzerland*

Introduction: Most experts assume, that nobody can fall asleep without prior awareness of sleepiness. However, others found only a moderate ability to subjectively judge alertness, particularly in tasks without any feed back information. We prospectively evaluated the awareness of subjective sleepiness (SS) prior to sleep onset during the maintenance of wakefulness test (MWT), the most commonly used method to assess alertness in a clinical environment.

Methods: Twenty-eight young healthy students (mean age 22.4 years; 13 females) underwent 4 MWTs after a night of total sleep deprivation. The subjects were instructed to press an event button to signal sleepiness and were given the following written and oral directive: "Indicate your earliest symptoms of sleepiness and try to stay awake as long as possible". Overt sleep (OS) was scored according to Rechtschaffen and Kales, and microsleeps (MS), defined as sleep-EEG of 3 seconds' duration or more, was scored separately. In a first series with 12 subjects (6 females) no reward was given. In a second series with 16 subjects (7 females) a financial reward was offered for both optimal recognition of SS and as well as longer sleep latency.

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Conclusion: Our unexpected finding that 17 of 28 young sleep deprived healthy subjects did not recognize their SS before onset of microsleep or overt sleep in at least one of four MWT-trials, and that this happened in 30-40% of all trials, is in sharp contrast to the general assumption, that nobody can fall asleep without prior awareness of sleepiness. If this findings is confirmed in larger series and also in patients, the simply advice to sleepy patients not to drive when feeling sleepy would no longer be sufficient. Motor vehicle crashes due to microsleeps could no longer be indiscriminately interpreted as being the result of negligently ignoring symptoms of sleepiness and hence be judged as due to "reckless driving". Prevention strategies against sleepiness induced motor vehicle crashes would have to include efforts to improve recognition of SS, also comprising the potential use of in-build alarming devices in cars and lorries. We recommend to assess SS recognition in the standard MWT, although its value in the judgement of fitness to drive has still to be defined.

Neurology (PSN), Neurophysiology (NP)
Maintenance of wakefulness test; sleepiness; subjective sleepiness; microsleep; motor vehicle crash

NP-7

Multimodal imaging – complementary information?

Kay Jann[1], Chris Boesch[2], Werner Strik[1], Thomas Dierks[1], Thomas Koenig[1]

[1]Dept. of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, 3000 Bern 60, Switzerland, [2]Dept. of Clinical Research, Magnetic Resonance Spectroscopy and Methodology, University and Inselspital Bern, 3010 Bern, Switzerland

Combining the information of different imaging modalities such as EEG and fMRI during cognitive processes may be more informative than the sum of information procedure by all methods used alone. In pilot recordings, we measured 3 women performing a classical Go-NoGo task during simultaneous EEG/fMRI acquisition (92 scalp electrodes, 2 EOG, 2 ECG / TR 3100ms, TE 30ms, 35 slices, 220 volumes).
EEG preprocessing included scanner induced artifact removal and bandpass filtering (1-30Hz). fMRI preprocessing included slice-scan time correction, linear trend removal and motion correction. Based on these datasets we performed four different kinds of analysis:
i) Classical ERP analysis and calculation of their topographic maps for NoGo vs Go condition showed the well known No-Go anteriorization of the P300.
ii) Classical fMRI analysis using the stimulation-protocol contrasting NoGo versus Go condition identified an activation pattern including primary and pre- motorcortex, putamen, thalamus and deactivations in posterior cingulum, middle temporal gyrus and parahippocampal gyrus.
iii) Spatial Independent component analysis (ICA) on the fMRI BOLD signal targeting at the identification of synchronously oscillating networks revealed several functionally meaningful networks.
iv) Temporal ICA on the EEG data separating it into factors coding for different features (eg. eyeblinks, alpha-wave and specifically factors such temporally associated with the task). In each subject we found an ICA-factor showing significant correlation with the task-condition (t-test Go vs NoGo) in the P300 latency and moreover with a topography similar to the P300-map of the classical ERP analysis. These factors were transformed to predict the BOLD signal and voxelwise correlations were calculated. The resulting correlation pattern includes anterior and posterior cingulum, DLPFC, caudate head and parahippocampal gyrus.

Conclusion:
The different approaches seem to produce complementary results indicating that different imaging modalities and investigation of the unimodal as well as the conjoint data improves comprehension of the ongoing cognitive processes.

With the support of the Swiss National Foundation (Grant no. 320000-108321/1)

MR-Methodology (PSM), Neurophysiology (NP)
multimodal imaging, EEG/fMRI, CPT

NP-8

Sensitivity of Dendritic Calcium Spike Firing to Extracellular Ionic Changes in Layer 5 Neocortical Pyramidal Neurons

Sarah Potez[1], Matthew E. Larkum[1]

[1]*Dept. of Physiology, University of Berne, 3012 Berne, Switzerland*

The *in vitro* slice preparation has been a vital tool for understanding the integrative properties of dendrites. It remains the only system in which multiple dendritic sites can be probed simultaneously. However, the ion composition of the extracellular solution chosen does not usually correspond exactly to the estimated interstitial fluid composition of the brain particularly with respect to calcium concentration which is usually much higher in common slice perfusate. Furthermore, *in vivo* some electrolytes concentrations can fluctuate greatly in an activity-dependent manner. Since we were interested in the properties of dendritic calcium spikes, the influence of Ca^{2+} ion concentration is central. In this study, we investigated the effects of lower extracellular calcium concentration and of interstitial *in vivo*-like condition on primary somato-sensory cortex by perfusing acute brain slices with different external solutions. We investigated the generation of dendritic calcium spikes and the somatic firing properties in L5 pyramidal neurons using somatic whole-cell recordings. Decreases in extracellular calcium concentration reduced the size of dendritic calcium spikes, but facilitated their initiation. Interstitial *in vivo*-like conditions produced similar effects in enhancing dendritic excitability, exacerbating the facilitation to generate calcium spikes. Lower calcium and *in vivo*-like solutions enhanced somatic excitability through different actions and increased burst-firing. Thus, minor electrolytes changes in the interstitial environment compatible with *in vivo* situations generated strong modulations in somatic and dendritic excitability which may have major repercussions at the network level.

Neurophysiology (NP)
Dendrite, Calcium Spikes, Ion, Cortex, Rat

NP-9

Amplitude asymmetry of the occipital EEG Alpha background is determined by structural features (brain torque), not by hemispheric dominance

Aekaterini Galimanis[1], Christoph Ozdoba[2], Johannes Mathis[1], Arto C. Nirkko[1]

[1]Neurology, University of Bern, [2]Neuroradiology, University of Bern

In routine EEG, a moderate asymmetry of the normal occipital alpha background activity is often seen, usually with higher amplitudes on the right side. It is commonly assumed that the greater amplitudes are found on the non-dominant hemisphere, usually the right one in right handers, although there is no convincing explanation for this. In most subjects, a structural hemispheric asymmetry, which is termed „brain torque“ and mainly affects the occipital lobe, can be found on neuroimaging. This asymmetry means that the occipital end of the interhemispheric fissure points to the right side. The occipital alpha activity is blocked by visual input and is generated by the primary visual cortex. This calcarine area is not located at the surface of the convexity but mesially, adjacent to the interhemispheric fissure. Our hypothesis was that the asymmetry of the interhemispheric fissure could explain the amplitude asymmetry of alpha background activity.

In 20 subjects with the normal asymmetry and 20 subjects with a reversed EEG asymmetry (alpha amplitude predominance on the left side), we found a correlation, with the reversed EEG asymmetry assiciated with a reversed structural asymmetry (interhemispheric fissure pointing to the left side). No correlation was found with handedness.

We conclude that the amplitude asymmetry of the occipital EEG alpha background is determined by structural features (brain torque), not by hemispheric dominance. The potential relevance includes adaptation of source reconstruction methods such as low resolution EEG tomography (LORETA) to individual brain asymmetries and the clinical interpretation of amplitude differences during hemifield stimulation in visually evoked potentials (VEP).

Neurobiology (PSB), Neurology (PSN), Neurophysiology (NP)
EEG, MRI, asymmetry, brain torque.

Neurobiology

PSB-1

GDNF pre-treatment of ventral mesencephalic neurons was not effective for graft survival and function in the 6-OHDA rat model of Parkinson's disease.

Lukas Andereggen[1], Angélique Ducray[1], Morten Meyer[2], Hans Rudolf Widmer[1]

[1]Department of Neurosurgery, University of Bern, Inselspital, Bern, [2]Dept. Anatomy & Neurobiology, Institute of Medical Biology, Univ. of Southern Denmark, DK-5000 Odense C, Denmark.

Parkinson's disease (PD) is a neurodegenerative disorder mainly characterized by a progressive loss of dopaminergic (DA) neurons in the substantia nigra. The transplantation of fetal dopaminergic neurons offers an experimental therapy for this at present incurable disease. The poor survival of transplanted dopaminergic neurons and the limited availability of fetal donor tissue are major obstacles for a successful application of this approach in PD. We have previously shown that glial cell line-derived neurotrophic factor (GDNF) is a potent neurotrophic factor with growth- and survival-promoting capabilities for developing dopaminergic neurons. Hence, in the present study we examined whether pretreatment of ventral mesencephalon free-floating roller tube (FFRT) cultures with GDNF would improve graft survival and function. Cultures were prepared from solid pieces of embryonic (E14) rat ventral mesencephalon and maintained 2 or 4 days in vitro with or without the presence of GDNF [10 ng/ml] and grafted into the striatum of 6-hydroxydopamine-lesioned rats. D-amphetamine-induced rotation was monitored 3 and 6 weeks post transplantation and number and fiber growth of surviving tyrosine hydroxylase-immunoreactive (TH-ir) neurons was assessed in the grafted brain at 9 weeks post transplantation.
We observed that all groups of rats showed a reduction in D-amphetamine-induced rotations at 6 weeks post transplantation. Notably rats transplanted with GDNF pretreated tissue cultured for four days demonstrated a faster recovery and displayed a significantly larger graft volume as compared to corresponding controls. No significant differences, however, were observed in number of TH-ir neurons per grafts in both the 2 and 4 days groups for GDNF-pretreated and control rats. While there was a tendency for higher TH-ir fiber outgrowth from the transplants in the GDNF pretreated groups as compared to corresponding controls a significant difference between control and GDNF pretreatment was only detected in rats transplanted with tissue cultured for four days.
Taken together, our findings demonstrate that a storage period of 2 and 4 days is well suited to maintain embryonic rat ventral mesencephalon with the free-floating roller tube culture technique prior to transplantation. However, pretreatment with GDNF as a new strategy to improve graft survival and function was not effective. We hence propose that neurotrophic factors should be applied also after transplantation.

Neurobiology (PSB)
Parkinson disease, GDNF, ventral mesencephalon, Transplantation

PSB-2

Angiotensinergic Neurons in Sympathetic Coeliac Ganglia Innervating Rat and Human Mesenteric Resistance Blood Vessels

Jaspal Patil[1], Eva Heiniger[1], Thomas Schaffner[2], Oliver Mühlemann[1], Hans Imboden[1]

[1]Institute for Cell Biology, University of Bern, 3012 Bern, Switzerland, [2]Institute for Pathology, University of Bern, 3010 Bern, Switzerland

In contrast to the current believe that angiotensin II (Ang II) interacts with the sympathetic nervous system only as a circulating hormone, we document here the existence of endogenous Ang II in the neurons of rat and human sympathetic coeliac ganglia and their angiotensinergic innervation with rat and human mesenteric resistance blood vessels. Angiotensinogen - and angiotensin converting enzyme-mRNA was detected by using quantitative real time polymerase chain reaction in total RNA extracts of rat coeliac ganglia, while renin mRNA was untraceable. Cathepsin D, a protease responsible for cleavage beneath
other substrates also angiotensinogen to angiotensin I, was successfully detected in rat coeliac ganglia indicating the possibility of existence of alternative pathways. Angiotensinogen mRNA was also detected by in situ hybridization in the cytoplasm of neurons of rat coeliac ganglia. Immunoreactivity for Ang II was demonstrated in rat and human coeliac ganglia as well as with mesenteric resistance blood vessels. By using confocal laser scanning microscopy we were able to demonstrate the presence of angiotensinergic synapses en passant along side of vascular smooth muscle cells. Our findings indicate that Ang II is
synthesized inside the neurons of sympathetic coeliac ganglia and may act as an endogenous neurotransmitter locally with the mesenteric resistance blood vessels.

Neurobiology (PSB)
RAS; Angiotensin II; SNS; Synapses en passant.

PSB-3

Immature dopaminergic neurons co-express the enzyme TH and 5-HT in rat midbrain cultures.

Angélique Ducray[1], Hans Rudolf Widmer[1]

[1]*Department of Neurosurgery, Inselspital*

Detailed knowledge about the development of neuronal subpopulations in the ventral mesencephalon (VM) is essential for the therapeutic use of cell transplantation approach for Parkinson's disease. It has been reported that some neurons in the VM of adult rats co-express the neurotransmitters dopamine and GABA. Moreover, in cultured neuroblasts co-localization of the dopaminergic marker tyrosine hydroxylase (TH) with GABA and ChAT has been described. The present study investigated by means of co-localization analyses for the possible expression of GABA or serotonin (5-hydroxytryptamine, 5-HT) in TH-immunoreactive (-ir) neurons. For that purpose E14 and E18 fetal rat VM were cultured for up to seven days in vitro (DIV). We first detected that 6%, 30% and 3.5% of total neuronal number in our cultures at DIV5 were immunoreactive for TH, GABA and 5-HT, respectively. Interestingly, we did not observe that any of the TH-ir neurons co-localized with GABA. In contrast, we found that 35% of TH-ir neurons also expressed 5-HT. In order to further substantiate this observation, co-localizations were performed using the specific markers for dopaminergic and serotonergic neurons, Nurr1 and SERT, respectively. In agreement to the outcome seen for TH and 5-HT, we could demonstrate co-expression of Nurr1 and SERT in VM neurons. Interestingly, TH and 5-HT co-expression was not observed in vivo in the ventral mesencephalon or other brain areas at E14, E18 days and also at postnatal day 2. We found that in E14 VM cultures the number of TH-ir neurons also expressing 5-HT first increased between DIV2 and DIV5 (from 9% to 34%, respectively) and then decreased between DIV5 and DIV7 (to 18%). Treatment with brain derived neurotrophic factor (BDNF) resulted in an increase of TH-ir neurons also expressing 5-HT at DIV2 (9% vs 14%), no significant difference at DIV5, and a decrease at DIV7 (18% vs 7.5%) for control and BDNF-treated cultures, respectively. In E18 VM cultures an ongoing decrease was observed with time in culture (i.e. from 10% at DIV2 to 3.5% at DIV5 and 0% at DIV7). In conclusion, our findings illustrate that a subpopulation of dopaminergic neurons do also contain serotonin in cultured rat VM. Moreover, we demonstrated that environmental factors like growth factors provide signals, which have an effect on emerging neuronal phenotypes in the developing midbrain.

Neurobiology (PSB)
culture, dopaminergic neurons, serotonergic neurons, BDNF

PSB-4

Evidence for grey matter increase due to second language learning

Maria Stein[1], Andrea Federspiel[1], Thomas Koenig[1], Miranka Wirth[1], Roland Wiest[2], Werner Strik[1], Daniel Brandeis[3], Thomas Dierks[1]

[1]University Hospital of Psychiatry, Department of Psychiatric Neurophysiology Bern, [2]Institute of Diagnostic and Interventional Neuroradiology, Inselspital, University of Bern, Switzerland, [3]Brain Mapping Research, Department of Child and Adolescent Psychiatry, University of Zürich, Switzerland

Research on bilingualism has repeatedly demonstrated that the human ability to learn a second language is linked to functional changes in neuronal networks subserving language processing. Contrary to that, evidence for structural changes related to second language learning is still sparse.
We examined 12 native English-speaking exchange students learning German in Switzerland at two points in time: before and after a 5 months period of increased second language learning. On both examination days, the subjects participated in a German language tests and in MRI measurements. Using the method of voxel based morphometry, we assessed the increase of cortical grey matter density (GMD) from first to second measurement. In a region in the left inferior frontal gyrus, the increase in GMD correlated significantly with the increase in second language proficiency, as assessed by the language test.
These findings can be interpreted as a direct sign of plasticity originated by the sustained training of a second language leading to an increased proficiency. The present study demonstrates for the first time in a longitudinal design structural changes related to second language learning.

Neurobiology (PSB), Neuropsychology/ Psychiatry (PSP)
bilingualism, neuronal plasticity

PSB-5

The Blood-brain barrier in acute brain injury

Ruth Lyck[1], Oliver Steiner[1], Urban Deutsch[1], Axinia Doering[1], Caroline Coisne[1], Britta Engelhardt[1]

[1]*1Theodor-Kocher Institute, Unversity of Berne, 3012 Berne, Switzerland*

Recruitment of cells of the innate and adaptive immune system into the central nervous system contributes to acute brain injury pathogenesis. In order to gain access to the neuronal tissue the immune cells have to overcome the blood-brain barrier (BBB) formed by highly specialized endothelial cells. The sequence of molecular steps involved in the recruitment of different leukocyte subpopulations across the BBB is not completely understood. Using in vitro and in vivo experiments we investigate the traffic signals involved in lymphocyte extravasation from the blood into the CNS. We and others have shown that alpha4-integrins play a predominant role in T lymphocyte recruitment across the BBB, whereas the precise contribution of LFA-1 and its endothelial ligands ICAM-1 and ICAM-2 remains to be investigated. Detailed knowledge about the molecular and cellular pathways of leukocyte migration across the BBB is mandatory to specifically prevent the migration of pathogenic leukocytes into the CNS, while at the same time maintaining the recruitment of potential repair cells.

Neurobiology (PSB)
Blood brain barrier, leukocyte extravasation, acute brain injury, inflammation

PSB-6

Development of an improved *in vitro* model of cerebral hypoxic preconditioning

Sebastian von Arx[1], Donna M. Ferriero[2], Stephan Christen[1]

[1]Institute of Infectious Diseases, University of Bern, [2]Departments of Neurology and Pediatrics, University of California San Francisco

At least in animal models, cerebral ischemic injury is significantly reduced when the brain has experienced a non-lethal stress, such as a short episode of hypoxia, before the insult ("preconditioning"). This phenomenon has attracted considerable interest because the understanding of this endogenous neuroprotective state may lead to new therapies for ischemic brain diseases. However, the molecular mechanisms involved in preconditioning are not completely understood. To study the mechanisms of preconditioning, several *in vitro* systems have been established. They are either based on isolated primary brain cells, which maintain many of their *in vivo* properties, but are difficult to handle (e.g., poor transformability, only small quantities of material for analysis) and rarely represent a completely homogenous cell population, or on undifferentiated neuronal cell lines, which are easy to manipulate and provide enough and homogenous material for subsequent analysis, but do not possess the properties of mature, post-mitotic neurons. To combine the advantages and avoid the disadvantages of these two approaches, we established a model of hypoxic preconditioning in rat pheochromocytoma PC12 cells differentiated with nerve growth factor (NGF). PC12 cells were differentiated on laminin-coated dishes in a defined serum-free medium used for culturing primary neurons (Neurobasal + B27) and adopted a neuronal phenotype upon exposure to NGF for 5 days. Using these cells, we found that 5 hours of hypoxia 24 hours prior to oxygen-glucose deprivation, an in vitro equivalent of ischemia, reduced cell death by ~50% ($P<0.05$). Thus, our system based on differentiated PC12 cells may serve as a useful model to study the mechanisms involved in the induction of cerebral ischemic tolerance. Preliminary results show that several signaling pathways implicated in preconditioning protection (e.g., HIF-1, ERK) are induced in this model.

Neurobiology (PSB)

PSB-7

Upregulation of platelet-activating factor receptor in brain microvascular endothelial cells by hydrogen peroxide

Elke Reiter[1], David Raemy[1], Stephan Christen[1]

[1]*Institute of Infectious Diseases, University of Berne, Friedbühlstrasse 51, 3010 Berne, Switzerland*

Phosphocholine residues in the cell wall of *Streptococcus pneumoniae*, a meningitis-causing pathogen, have been shown to interact with the platelet-activating factor receptor (PAFR) on brain microvascular endothelial cells (BMEC). This interaction is thought to initiate and promote the translocation of the pathogen across the blood-brain barrier (BBB), by mediating endocytotic uptake. The pro-inflammatory cytokine TNF-a has been shown to enhance pneumococcal invasion of BMEC. The TNF-a-mediated enhanced invasion is blocked by PAFR antagonists, suggesting that TNF-a may upregulate BMEC PAFR and thus promote the translocation of S. pneumoniae across the BBB. However, neither stimulation of rat or human BMEC with TNF-a resulted in enhanced expression of PAFR mRNA or protein, while it caused activation of the NF-kB pathway and increased the expression of ICAM-1 on the cell surface. In contrast, hydrogen peroxide (H2O2), a metabolic by-product of *S. pneumoniae*, dose-dependently caused increased expression of PAFR mRNA in BMEC, which was dependent on de novo transcription. H2O2-mediated upregulation of PAFR mRNA was inhibited by the p38MAPK inhibitor SB203580 and the JNK inhibitor SP600125, suggesting that it is AP-1-mediated. H2O2-mediated PAFR mRNA upregulation appears to be associated with enhanced expression of PAFR on the cell surface. We are currently investigating whether H2O2-mediated PAFR upregulation promotes increased uptake of S. pneumoniae by BMEC.

Neurobiology (PSB)

MR-Methodology

PSM-1

The Use of Order Statistics Filtering in MRS for the Elimination of Patient-Motion Related Artifacts

Johannes Slotboom[1], Dirk van Ormondt[2], Bernadette Bachofen[3], Werner ZGraggen[3], Arto Nirkko[3]

[1]Neuroradiology, Inselspital, Univeristy of Berne, Bern, Switzerland, [2]Applied Physics, TU Delft, The Netherlands, [3]Neurology, Inselspital, Univeristy of Berne, Bern, Switzerland

Introduction and Purpose - In order to obtain a clinically acceptable signal-to-noise ratio (SNR), in vivo Magnetic Resonance Spectroscopy (MRS) entails addition of M consecutive identical measurements ('signal-averaging'). We define one measurement as the sum signal of one complete EXORCYCLE. In practice, M equals e.g. 20, in theory yielding an SNR improvement by a factor of sqrt(20). Typically, the total measurement time is about four minutes. During this time slot, a patient may well move, causing strong perturbation of several of the 20 consecutive measurements.
The signal-average is affected by this phenomenon. The present work introduces an alternative to signal-averaging that is virtually insensitive to patient-motion.

Materials and Methods - Our strategy is to replace signal-averaging by so-called median-filtering [1].
A median-filter orders a series of M samples according to size. Its output is the resulting middle value, the median. Hence, instead of averaging a series of M samples, we take its median value. In absence of patient motion, median-filtering yields almost the same result as signal-averaging, albeit that the SNR is reduced by a factor of maximally sqrt(2/pi). Patient-motion strongly perturbs a number of samples. A median-filter 'pushes' these samples to the upper and lower ends of the re-ordered series. The median (middle) value remains virtually 'untouched' by patient-motion.

Results - A median filter was implemented in an locally developed application for prior knowledge based MR-spectrum quantitation. The performance of the filter is demonstrated on an in-vivo spectrum recorded of the tibialis anterior which is perturbed by patient movement. The difference between classical signal averaging and median filtering will be shown.

New Work - We are the first to apply median-filtering to in vivo MRS signals.

Conclusion - In the presence of patient-motion, median filtering supersedes averaging.

Reference
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MR-Methodology (PSM)
Magnetic Resonance Spectroscopy, non linear filtering, artifacts, quantitation

PSM-2

Optimized plaque imaging on a 3Tesla MR- scanner

Claus Kiefer[1], Luca Remonda[1], Marwan El-Koussy[1], Gerhard Schroth[1], Krassen Nedeltchev[2]

[1]Institute for Diagnostic and Interventional Neuroradiology, University Hospital Bern, Switzerland, [2]Dept. of Neurology, University Hospital Bern, Switzerland

Objective
Carotid atherosclerosis is a major cause of stroke. Traditionally, the degree of stenosis has been used to assess the risk of thromboembolism originating from an atherosclerotic plaque. Recent data suggest that the total volume and the histological composition of the plaque might also be related to plaque vulnerability. The essential technical optimizations for successful plaque imaging on a 3T MR-scanner are demonstrated.

Methods
Optimal signal-to-noise for plaque imaging was achieved by performing the imaging on a 3.0Tesla TIM-Trio scanner and using a special carotids surface coil (Machnet).
In order to avoid signal contributions and artifacts from the flowing blood, a pulse triggered turbo spin echo sequence with a blood-nulling preparation part is used. The sequence parameters, especially the echo time, were optimized with respect to the contrast of the plaque components.

Results
The best results were achieved by the Machnet 4-channel surface coil. The 8-channel coil unfortunately was impractical in handling and positioning and surprisingly provided the worse signal-to-noise compared to the 4-channel coil on identical sequence parameters. The iPAT-options are therefore not available which causes a longer measurement time of about 17min for N=4 averages.

Conclusion
The presented technical optimizations are essential for the non-invasive detection of vulnerable carotid atherosclerotic plaques. In the course of the study the in vivo findings of high-field (3 Tesla) MRI of the carotid bifurcation in patients scheduled for carotid endarterectomy (CEA) will be compared to those of matched histologic sections from the endarterectomy specimen. 2) To evaluate the relationship between morphologic features of plaque vulnerability (large volume, presence of a large lipid core, intraplaque hemorrhage or unstable fibrous cap) and the total amount of MR-lesions within the territory of the internal carotid artery (ICA).

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MR-Methodology (PSM)
Carotid Atherosclerosis Plaque MRI

PSM-3

The Q-Ball approach and its clinical impact on deep brain stimulation

Claus Kiefer[1], Christoph Ozdoba[1], Alain Kaelin-Lang[2], Alexander Stibal[3], Gerhard Schroth[1], Tarja Lönnfors-Weitzel[1]

[1]Institute for Diagnostic and Interventional Neuroradiology, University Hospital Berne, Switzerland, [2]Dept. of Neurology, University Hospital Berne, Switzerland, [3]Dept.of Neurosurgeon, University Hospital Berne, Switzerland

Objective
DBS (Deep Bain Stimulation) has become one of the standard methods for IP-Parkinson disease treatment in the most modern neurological centers. Tremor, Rigor or other syndromes caused from Parkinson disease can be treated by stimulation of the deep brain with electrical current. The positioning of the electrodes within the brain using the standard approaches of currently available navigation software is very critical because it does not consider individual variability or disease related atrophy. The proposed techniques for non-invasive localization are based on T2 and diffusion MR modalities.

Methods
Q-Ball imaging [1] was performed on a 3.0T Trio-TIM whole body scanner using a modified N=42 directional twice-refocused EPI sequence. Connectivity studies based on the Q-Ball algorithm according to [2] and information from co-registered 3D-T2-data were used to localize (sub-)thalamic nuclei and loops and to control the successful positioning of electrode implants. The coordinates of the pixels along the path between selected nuclei are marked on the co-registered T2 and will be used to show the neurosurgeon the way to insert the electrode.

Results
Visualisation of thalamic nuclei, mainly Nucleus ventro intermedius (VIM), hypothalamic nuclei and the differentiation of Gpi from Globus pallidus externus (Gpe) is considerably higher on T2w images at 3 Tesla compared with routine MRI at 1,5 Tesla. QBI confirmed the target typical connections. The DBS electrode was by now several times implanted by this method. Neurophysiology and complete disappearance of the symptoms have confirmed the correct position of the electrodes.

Conclusion
The Q-Ball approach represents an innovative and important concept for the successful pre- and post-clinical treatment of deep brain stimulation.

References
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MR-Methodology (PSM)
Q-Ball diffusion MRI DBS

PSM-4

Direct Neuroradiological identification and characterization of different targets for Deep Brain Stimulation (DBS) at 3 Tesla

Tarja Lönnfors-Weitzel[1], Christoph Ozdoba[1], Alain Kaelin-Lang[2], Alexander Stibal[3], Claus Kiefer[1]

[1]Institute for Diagnostic and Interventional Neuroradiology, University Hospital Berne, Switzerland, [2]Dept. of Neurology, University Hospital Berne, Switzerland, [3]Dept.of Neurosurgeon, University Hospital Berne, Switzerland

Objective:
Deep brain stimulation is an established treatment for severe tremor in Parkinson's disease and in an increasing frequency, for other movement disorders, mood disorders and for intractable pain. Each indication has a different or several possible targets, with slightly different success-rates. Until recently targets were aimed at according to arithmetical stereotactic coordinates, which do not allow for individual variability or disease related atrophy. Therefore methods for direct identification of different thalamic, hypothalamic, subthalamic targets and of Globus pallidus internus (Gpi) and their integration within the functional loops are needed before DBS.

Methods:
Preoperative imaging was performed at 3 Tesla TIM-Trio (Siemens Medical Solutions, Erlangen, Germany) to visualise the necessary target. A high resolution 0,57 mm3 3D–T2-TSE sequence with a matrix 448x448 with variable flip angels was acquired. In addition a modified QBI (q-ball imaging) sequence (42 directions , 15 min acquisition time, 2.2mm iso-voxel) was performed to confirm the connections of the chosen target.

Results:
Visualisation of thalamic nuclei, mainly Nucleus ventro intermedius (VIM), hypothalamic nuclei and the differentiation of Gpi from Globus pallidus externus (Gpe) is considerably higher on T2w images at 3 Tesla compared with routine MRI at 1,5 Tesla. QBI confirmed the target typical connections. The DBS electrode was by now several times implanted by this method. Neurophysiology and complete disappearance of the symptoms have confirmed the correct position of the electrodes.

Conclusion:
Direct neuroradiological identification of different targets in DBS is feasible by using 3 Tesla MRI with highly selective sequences. The T2 and the q-ball based GFA and connectivity parameter provide the essential complementary information for the unambiguous identification of the targets within their functional loops.

MR-Methodology (PSM), Neurology (PSN), Neurosurgery (PSS)
DBS Q-Ball T2 MRI

Neurology

PSN-1

Loss of vertical saccades after unilateral frontal eye field damage

Tobias Pflugshaupt[1], Thomas Nyffeler[1], Roman von Wartburg[1], Christian W. Hess[1], René M. Müri[1]

[1]*Perception & Eye Movement Laboratory, Depts. of Neurology & Clinical Research, University Hospital, 3010 Bern, Switzerland*

Despite their relevance for locomotion and social interaction in everyday situations, little is known about the cortical control of vertical saccades in humans. Results from microstimulation studies indicate that both frontal eye fields (FEF) contribute to these eye movements. Here we present a patient with a damaged right FEF, who hardly made vertical saccades during visual exploration. This finding suggests that for the cortical control of exploratory vertical saccades, integrity of both FEF is indeed important.

Neurology (PSN)
vertical saccades

PSN-2

Visual exploration of natural scenes in patients with macular degeneration

Anouk Déruaz[1], Tobias Pflugshaupt[1], Roman von Wartburg[1], Pascal Wurtz[1], Silvia Chaves[1], Mathias Lüthi[1], Dario Cazzoli[1], Thomas Nyffeler[1], René Müri[1]

[1]*Perception and Eye Movement Laboratory, dpts of Clinical Research and of Neurology, Inselspital, Bern Switzerland*

Age-related macular degeneration is characterised by the development of a central macular scotoma. Adaptation to such a scotoma requires a reorganisation of oculomotor strategies in order to direct fixation onto a peripheral area of the retina. Obstruction of the visual field by the scotoma, as well as the development of new reference coordinates for the oculomotor system are likely to affect visual exploration. However, visual exploration and its systematic optimisation as potential rehabilitation procedures has never been considered in such patients. Twelve patients were presented with natural scenes and instructed to freely explore the images and to report the apparition of specific stimuli. Patients' data were compare to that of controls who performed the same task under two different conditions: with focused and with blurred images. The number of hits, number of fixation, fixation duration, sum of fixation, amplitude of saccades, length and amplitude of the scanpath were assessed and finally an exploration factor was computed. We compared patients data with both control conditions to assess the effect of the reduction of visual acuity and the effect of the eccentric fixation. We performed a "scotoma versus no scotoma" analysis based on the perimetry results to measure the impact on eye movements and performances of the presence of the lesion on a particular part of the visual space. Patients' eye movements characteristics were closer to those of the control groups in the focused image condition than those of the control group in the blurred images condition. The "scotoma vs no scotoma" analysis revealed showed an effect on the number of hits and the exploration factor only. The exploration factor and the number of hits were highly correlated. Patients eye movements characteristics can be explained by the adaptation to the perception and exploration of blurred images but also by their instability of the fixation. We found a very high correlation showing that the position of the scotoma relative to the fixation point during the binocular octopus exam indicates the direction in which patients will have problems to perform efficient scanning saccades.

Neurology (PSN), Rehabilitation (PSR)
visual field, central macular scotoma, eye movements

PSN-3

Visual Vector Inversion in the Posterior Parietal Cortex

Matthias Hartmann[1], Thomas Nyffeler[1], Pascal Wurtz[1], Roman von Wartburg[1], Tobias Pflugshaupt[1], Sylvia Chaves[1], Anouk Déruaz[1], Christian W Hess[1], Réné Müri[1]

[1]*Perception and Eye Movement Laboratory, Inselspital Bern*

In the antisaccade task, participants have to perform a saccade towards the mirror location of a lateral target. Thus, spatial accuracy of the antisaccade is achieved if the visual vector derived from stimulus location is correctly inverted from one visual hemifield to the other. The posterior parietal cortex (PPC) has recently been shown to be implied in this visual vector inversion. However, the exact timing of this parietal control over the inversion is not known. In the present study, transcranial magnetic stimulation was applied over the right PPC during an antisaccade task to examine this issue. Preliminary results show that an early stimulation (100 ms after target onset) induces a marked hypometria of ipsilateral antisaccades, whereas a later stimulation (333ms and 450 ms after target onset) provokes a hypoemtria of contralateral antisaccades. This double dissociation suggests that the human PPC a) is implied in inversion of the visual vector 100 ms after target appearance, and b) has received and stored the inverted vector signal, transferred from the contralateral PPC, at 333ms and 450ms.

Neurology (PSN), Neuropsychology/ Psychiatry (PSP)
Visual vector inversion, posterior parietal cortex, TMS, antisaccade

PSN-4

Implicit sequence learning in patients with Parkinson's disease

Marianne Anke Stephan[1], Sabine Weber Zaugg[1], Alain Kaelin-Lang[1]

[1]*Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Switzerland*

Several evidences suggest that secondary long-term neuronal changes occur in Parkinson's disease (PD) in addition to the primary neurodegenerative processes. These changes may lead, among other functional disorders, to Levodopa induced dyskinesia (LID). Studies in humans and animals have in particular revealed disturbed synaptic plasticity in individuals with LID that could not be normalized by the application of dopamine.
Our hypothesis is that an abnormal plasticity in PD patients with LID leads to impairments in the concurrent learning of two similar motor sequences.
Fifteen PD patients (6 dyskinetic and 9 non-dyskinetic) under dopaminergic therapy and 15 age-matched healthy subjects performed an implicit motor sequence learning task on a special "response box" provided with 4 response keys and 4 lamps. Subjects had to press as fast as possible the corresponding key in response to the turning-on of the lamps. Unbeknownst to the subjects, the lamps turned on in 2 different specific sequences. Each sequence was repeated 10 times in succession before (1st repetition period) and 10 times after a short resting period (2nd repetition period).
We found a significant general learning effect from the 1st to the 2nd repetition period ($p<0.05$) in healthy subjects as well as in PD patients without LID. In contrast, PD patients with LID did not show this learning effect. Additionally, a specific interference parameter, measuring the interaction between the two sequences, was significantly greater in PD patients with LID than in healthy controls ($p<0.05$).
We thus conclude that the concurrent learning of similar motor tasks is impaired in patients with LID whereas patients without LID perform very similar to healthy subjects. We suggest that these results are due to secondary plastic changes in PD patients with LID which are not compensated by the application of Levodopa.

Neurology (PSN), Neuropsychology/ Psychiatry (PSP)
parkinson's disease, levodopa-induced dyskinesias, implicit sequence learning

PSN-5

Intra-arterial Thrombolysis of Acute Iatrogenic Intracranial Arterial Occlusion due to Neuroendovascular Procedures or Coronary Angiography

Marcel Anca[1], Urs Fischer[1], Gerhard Schroth[2], Krassen Nedeltchev[1], Jörg Isenegger[3], Luca Remonda[2], Stephan Windecker[4], Caspar Brekenfeld[2], Heinrich P Mattle[1]

[1]Dept. of Neurology, University of Berne, 3010 Berne, Switzerland, [2]Institute of Diagnostic and Interventional Neuroradiology, University of Berne, 3010 Berne, Switzerland, [3]Dept. of Internal Medicine, University of Berne, 3010 Berne, Switzerland, [4]Dept. of Cardiology, University of Berne, 3010 Berne, Switzerland

Background: For selected stroke patients intra-arterial thrombolysis (IAT) has been shown to be an effective treatment option. However knowledge of safety and efficacy of IAT in patients with acute stroke as a complication of arterial catheter interventions is limited.
Methods: We analysed clinical, radiological findings, and functional outcomes in consecutive patients, 3 months after treatment with IAT for periprocedural strokes occurring during neuroendovascular or cardiac catheter interventions. To measure outcome, the modified Rankin Scale score (mRS) was used.
Results: Of a total of 432 patients treated with IAT, 12 (4 women and 8 men; mean age, 60 years) were treated because of an ischemic stroke following a neuro-endovascular procedure (n=6) or coronary angiography (n=6). The median baseline National Institutes of Health Stroke Scale score was15. Recanalization was complete (thrombolysis in myocardial infarction [TIMI] grade 3) in 6, partial (TIMI 2) in 5, and minimal (TIMI 1) in one. Nine patients (75%) had a favorable outcome (mRS 0-2), and 3 a poor outcome (mRS 3 or 4). All patients with complete recanalization had a favorable outcome, whereas only 3 of 6 patients with partial or minimal recanalization (p=0.18) had a favorable outcome. Follow-up brain imaging was normal in 2 and showed new ischemic lesions in 10 patients. Two patients (17%) suffered a symptomatic intracerebral hemorrhage.
Conclusion: In acute stroke due to arterial catheter interventions IAT is feasible and has the potential to improve outcome in these patients. A high recanalization rate could be achieved.

Neurology (PSN)
stroke acute, thrombolysis coronary angiography

PSN-6

Assessment of Tryptophan Metabolism and Cytokine Profile in Cerebrospinal Fluid Samples from Patients with Bacterial Meningitis

Leonam Gomes Coutinho[1], Caroline L Bellac[2], Denis Grandgirard[2], Matthias Wittwer[2], Roney S Coimbra[1], Stephan Christen[2], Luiz Alberto Marinho[1], Stephen L Leib[2], Lucymara F Agnez-Lima[1]

[1]Dept. Cell Biology and Genetics, Universidade Federal do Rio Grande do Norte, Natal, Brazil, [2]Institute for Infectious Diseases, University of Bern, 3010 Bern, Switzerland

OBJECTIVES: Activation of the kynurenine (KYN) pathway (KP) has been observed in experimental bacterial meningitis (BM). Here we assessed the association of chemo-/cytokine levels with the concentration of KP metabolites in CSF and plasma samples from patients with BM.
METHODS: CSF samples were collected from 22 hospitalized patients. Nine patients were diagnosed with bacterial meningitis, 6 patients with viral meningitis and 7 patients with non-infectious neurological disorders. Microsphere-based multiplex assays (Lincoplex®, Linco Research Inc., St Charles, MA, USA) was used to assess the concentrations of 14 chemo-/cytokines separately in CSF and serum. The CSF and serum concentration of metabolites from the kynurenine pathway was assessed by high pressure liquid chromatography.
RESULTS: The concentration of TNF-alpha, IL-6, IL-1beta, INF-gamma, IL-10, IL-1 receptor antagonist, MIP-1alpha, MIP-1beta, MCP-1 and G-CSF were 100-fold higher in CSF from patients with BM compared to the two other groups. In all CSF samples the concentration of IL-2, IL-12(p70), IL-4 and GM-CSF was below the detection limit.
In plasma samples the concentrations of IL-6, IL-10, IL-1 receptor antagonist, MCP-1 and G-CSF were significantly increased in patients with BM. The concentrations of the KP metabolites kynurenine, anthranilic acid and kynurenic acid were 10-fold higher in CSF of patients with BM compared to the other two groups. In contrast to what was found in CSF, the concentrations of KP metabolites in the plasma were not significantly different between the three groups. Tryptophan levels in plasma samples were higher than in CSF samples and were significantly decreased in patients with BM.
CONCLUSION : BM is associated with increased levels of pro-inflammatory cytokines and KP metabolites. This increase in KP metabolites is most likely due to activation of KP by INF-gamma and TNF-alpha. Based on the comparison of tryptophan and KP metabolite concentrations between plasma and CSF samples we conclude that the activation of the tryptophan pathway upon BM occurs within the brain.

Neurology (PSN)
Bacterial Meningitis, Kynurenine, Cytokines

Neuropsychology / Psychiatry

PSP-1

An Analysis of the Processes Contributing to Deficient Risky Decision-making in Patients with Ventromedial Prefrontal Damage

Céline Eggen[1], Klemens Gutbrod[2], Walter Perrig[1], Oswald Huber[3], Arlette Bär[3], Odilo W. Huber[3], René Müri[2]

[1]Department of Psychology, University of Berne, 3010 Berne, Switzerland, [2]Department of Neurology, University Hospital of Berne, Switzerland, [3]Department of Psychology, University of Fribourg, Switzerland

Damage to the ventromedial prefrontal cortex is often associated with a defect in real-life risky decision-making; however, most other cognitive functions remain unimpaired. So far, most experimental results in the neuropsychological decision-making research have been obtained with the Iowa Gambling Task. The conclusions drawn from this task have been challenged in recent years though. Therefore, a different approach has been used in this study, assessing decision-making by means of more everyday-life like decision tasks. To explore possible processes contributing to deficient risky decision-making in patients with ventromedial prefrontal damage, 25 subjects (13 brain-damaged patients, 12 healthy controls) were tested. The performance of the two groups was comparable. This result suggests that patients with ventromedial prefrontal damage might have trouble in implementing ideas into actions.

Neurology (PSN), Neuropsychology/ Psychiatry (PSP)
Ventromedial Prefrontal Cortex, decision-making, implementation

PSP-2

Glucocorticoids reduce phobic fear in humans

Leila Maria Soravia[1], Markus Heinrichs[2], Dominique J.-F. de Quervain[3]

[1]Department of Psychiatric Neurophysiology, University Hospital of Psychiatry Bern, 3000 Bern 60, Switzerland, [2]Department of Clinical Psychology and Psychobiology, University of Zurich, Switzerland, [3]Division of Psychiatry Research, University of Zurich, Switzerland

Background: Phobias are characterized by excessive fear, cued by the presence or anticipation of a fearful situation. Whereas it is well established that glucocorticoids are released in fearful situations, it is not known whether these hormones, in turn, modulate perceived fear. Previous studies indicate that elevated glucocorticoid levels impair the retrieval of emotionally arousing information. We therefore hypothesize that glucocorticoids might also inhibit retrieval of fear memory associated with phobia and, thereby, reduce phobic fear. Method: We investigated whether acutely administrated glucocorticoids reduce phobic fear in two double-blind, placebo-controlled studies in 40 subjects with social phobia and 20 subjects with spider phobia. Social phobic patients received 25 mg of cortisone orally 1 h before a socio-evaluative stressor, whereas spider phobics received 5 times 10 mg of cortisone 1 h before exposure to a spider photograph. Results: Cortisone treatment significantly reduced self-reported fear during the anticipation, exposure and recovery phase of the stressor in social phobics, whereas repeated oral administration of cortisol induced a progressive reduction of stimulus-induced fear in spider phobic patients. Conclusion: The present findings in two distinct types of phobias indicate that glucocorticoid administration reduce phobic fear.

Neuropsychology/ Psychiatry (PSP)
Glucocorticoids, Phobia, Cortisol

PSP-3

Selective Response Selection Impairment After Theta Burst rTMS Over the Right Dorsolateral Prefrontal Cortex: An Eye Movement Study

Mathias Lüthi[1], Roman von Wartburg[1], Pascal Wurtz[1], Katharina Henke[1], Thomas Nyffeler[1], René Müri[1], Christian Hess[1]

[1]*Dept. of Clinical Research, University of Berne, 3010 Berne, Switzerland*

This study was aimed at investigating the effects of theta burst repetitive transcranial magnetic stimulation (rTMS) over the right dorsolateral prefrontal cortex (rDLPFC) on planning functions. 18 neurologically healthy subjects completed a computerised trail making test (TMT). Task difficulty was manipulated in two ways, corresponding to an increase in set-shifting demands and secondly, to an increase in response selection demands. Subjects were instructed to click on either ascending numbers (TMT-A) or numbers and letters (TMT-B) as fast as possible while eye movements and mouse clicks were recorded. Second, displays featured either no distractors, distractors dissimilar to targets, or distractors similar targets. Anticipatory eye movements on subsequent stimuli were considered as evidence for planning, e.g. fixations on target number 4 before a click on target number 3 was made. After rTMS, a significant decrease in planning was observed, which was in turn associated with task solving time, a measure of overall task performance. Further analysis revealed that compromised planning after rTMS could be attributed to a deficit in response selection, but not a set-shifting impairment. The effects thus shed light on the role of the rDLPFC in planning functions necessary to solve complex tasks such as the TMT.

Neuropsychology/ Psychiatry (PSP)
rTMS, Planning, Dorsolateral Prefrontal Cortex, eye movements

PSP-4

Structural Basis of Auditory Verbal Hallucinations

Daniela Hubl[1], Vérène Chauvin[2], Markus Zeller[2], Andrea Federspiel[2], Chris Boesch[3], Werner Strik[1], Thomas Dierks[2], Thomas Koenig[2]

[1]University Hospital of Psychiatry, Bern, Switzerland , [2]Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, Bern, Switzerland , [3]Department of Magnetic Resonance Spectroscopy and Methodology, Department of Clinical Research, University of Bern, Switzerland

Background The auditory and language cortices are essentially involved in the functional anatomy of auditory verbal hallucinations (AVH), including primary auditory cortex. But, structural findings of the primary auditory region are rare and unequivocal. Therefore, in the present study we further analysed a data set with demonstrated white matter microstructural differences between two groups of patients, classified according to their history on AVH, in respect of macroscopy, i.e. volume, laterality and cortical folding of the primary auditory regions.
Methods A clinically carefully selected sample of 13 patients with a history of AVH, 11 patients without lifetime AVH and 13 controls, all right handed, were recruited. High-resolution T1-weighted 3-D anatomical MR scans were obtained. Heschl's gyrus (HG) as marker for the primary auditory cortex and the planum temporale were gained by manual segmentation. Gyral pattern, absolute and relative measures and asymmetries were analysed.
Results Right HG was tendentially more often duplicated than left HG in the hallucinating patients. Concerning asymmetry, in patients the normal left-greater-than-right laterality of HG and the PT was attenuated, without difference between the groups. There were no statistical group effects for any volume measure. But, in the hallucinating group, right HG white matter was significant bigger than the left sided; this not the case in any other group.
Conclusions Volumetric studies on the temporal lobe in hallucinations are unequivocal, maybe due to only very small if at all differences in macrostructural markers. In a sample with demonstrated microstructural changes we did not find differences between the groups with only suggested evidence for white matter plasticity associated with hallucinations.

Neuropsychology/ Psychiatry (PSP)
hallucinations, schizophrenia, volumetry

PSP-5

Having a look at the Brentano Illusion: An eye movement study

Pascal Wurtz[1], Matthias Grieder[1], Tobias Pflugshaupt[1], Roman von Wartburg[1], Thomas Nyffeler[1], Anouk Déruaz[1], Silvia Chaves[1], Matthias Lüthi[1], Christian W. Hess[1], René Müri[1]

[1]*Perception and Eye Movement Laboratory, Depts. of Clinical Research and Neurology, Inselspital*

In the Brentano version of the Müller-Lyer (ML) Illusion, one half of the line looks longer than the other. Recently, it has been shown that different versions of the ML-Illusion do not only affect manual bisection performance, but also eye movements. Patients suffering from visuo-spatial neglect after brain injuries show systematic spatial asymmetries in eye movements as well as in bisection of simple lines.
The present study was aimed at investigating illusion effects in neglect patients by comparing the relationship between eye movements and manual bisection performance in different versions of the Brentano Illusion. Results suggest that illusion effects in both oculomotor and manual behaviour are modulated (e.g. left-right asymmetries, position effects) by hemispatial neglect.

Neuropsychology/ Psychiatry (PSP), Rehabilitation (PSR)
hemispatial neglect, length illuson, eye movements

PSP-6

Subliminal semantic associative memory can alter behaviour

Dominik Moser[1], Gianina Toller[1], Katharina Henke[1]

[1] *Institute of psychology, university of berne.*

This experiment tested wheter the human brain is capable of recording and associating information of abstract and nonperceptual nature without awarness. Subjects were pimed subliminally with faces and profession words. Thereafter they were shown the faces and asked wheter these people were rather academics or artists. If the priming had an effect, people needed to make an sublimnal association between the word and the face. This was indeed the case, as answering patterns differed significantly from those in a control condition.
It is hard to fathom a area in the brain other than the hippocampus, being responsible for such a feat. If this was actually true, this would render the standard model of long term memory (Squire & Knowlton 1995) false

Neuropsychology/ Psychiatry (PSP)
subliminal semantic memory hippocampus

PSP-7

Behavioral Elements during Face Processing: Eye and Head Movement Activity and their Connection to Physiological Arousal

Andreas Altorfer[1], Marie-Louise Kaesermann[1], Ulrich Raub[1], Othmar Wuermle[1]

[1]*Department of Psychiatric Neurophysiology, University of Bern, Bolligenstrasse 111, CH-3000 Bern 60, Switzerland*

Emotion recognition, validation, and appraisal are tasks of everyday life that are crucial for social interaction. As a prerequisite for emotion processing – as a sender or a receiver - one has to use a perceptual apparatus that includes eyes and head (eye-movements, gaze shifts). For sending and hiding emotional cues to the environment one has to direct the face to other persons in a way that they can recognize the facial activity. This is done usually by turning the head and if required by changing the body position. For receiving stimuli out of the environment a distinct orienting is needed if the oculomotor range of about +/- 55° is exceeded. Additionally, for this analysis three-dimensional head movements are involved. However, the subtle coupling between eye and head movements is still debated. The oculocentric view suggested by Bizzi is reexamined in favoring a gaze feedback hypothesis which proposes that eye and head positions are monitored by corollary processes calculating an internal representation of the required gaze position. Based on the lack of knowledge concerning these perceptual interrelations, several experiments are done to investigate eye-head coordination especially in emotion recognition. Additionally data are reported that point to the relevance of head movement as purposeful behavioral expression. In this respect the behavioral analysis is expanded by using psychophysiological indices to validate the emotional as well as the communicative device of head movement patterns.

Neuropsychology/ Psychiatry (PSP)
Eye-Head coordination, psychomotor activity

PSP-8

Sustained Attentional Performance in Healthy First-Degree Relatives of Schizophrenia Patients

Caroline Hilti[2,3], Leonie M Hilti[1,3], Erich Seifritz[2], Katja Cattapan-Ludewig[2]

[1]Institute of Psychology, University of Bern, [2]University Hospital of Psychiatry, University of Bern, [3]The authors contributed equally to this study

Sustained attention is discussed as a core deficit in schizophrenia and as a candidate endophenotype. Various neuropsychological tasks are thought to measure sustained attention, such as the Rapid Visual Information Processing Task (RVIP), which resembles the Continuous Performance Task (CPT). Previous studies have shown that chronic schizophrenia patients as well as first-episode schizophrenia patients have severe problems in performing the RVIP task. Here, we investigated whether healthy first-degree relatives of schizophrenia patients show reduced sustained attentional performance (i.e. a reduced sensitivity index A') as measured by the RVIP, respectively whether RVIP performance could be a possible endophenotype.

Twenty-three healthy first-degree relatives of schizophrenia patients and 88 healthy controls without schizophrenic relatives participated in this study. They all performed a demanding version of the RVIP which lasted 9 min. Numbers between 0 and 9 appeared pseudo-randomly on the computer screen and the participant had to respond as soon as he/she saw the last number of three target sequences (2-4-6, 3-5-7 and 4-6-8). Hits, false alarms and reaction time were recorded during RVIP performance for each subject. The sensitivity index A' (is a measure which includes both the probability of hits and the probability of false alarms) was derived from this data.

The ANCOVA controlling for the confound variables age and education revealed that the relatives were significantly less sensitive (A') in detecting target sequences than the controls, $p < .004$.

The result supports the assumption that sustained attention, as measured with a difficult RVIP version, could be a possible endophenotype in schizophrenia. However it is assumed that this result could also be influenced by the working memory amount of this RVIP version. Future studies therefore need to evaluate the contribution of WM in RVIP performance.

Neuropsychology/ Psychiatry (PSP)
Schizophrenia, attention

PSP-9

The Association between Target and Action Affects Prospective Memory Performance Differently Across the Lifespan

Sibylle Matter[1], Beat Meier[2]

[1]Dept. of Psychology, University of Bern, 3000 Bern 9, Switzerland, [2]Dept. of Psychology, University of Bern, 3000 Bern 9, Switzerland

Prospective memory is the ability to make plans, retain and execute them on an appropriate occasion in the future. A prospective memory test consists always of a prospective and a retrospective component. The prospective component refers to the self-initiated remembering that something has to be done and is defined as recognizing a prospective memory target. The retrospective component refers to remembering what has to be done and is defined as remembering the intended action. In the present study we varied the retrospective component by associating the to-be-performed action with the target event in on condition, but not in the other. We investigated whether the association between prospective memory target and action influences prospective memory performance differently across the lifespan.
Toward this goal we tested a total of 120 participants of 3 age groups, 40 children (M =11 years, SD=0.48), 40 young adults (M = 24; SD = 4.9) and 40 older adults (M=69 years, SD=4.9). The participants were asked to perform a prospective memory test which was embedded in a picture comparison task. In the picture comparison task two pictures of the same object were presented on a computer screen. Participants had to decide whether two objects were identical. To keep the task running participants had to permanently press the shift-key with their left index finger. The prospective memory task was to lift the index finger and press a specific key on the computer keyboard whenever a picture of one of the 4 categories clothes, furniture, plants or animal appeared on the screen. Thereby the retrospective component was manipulated by introducing an association between target and action in one condition. In the association condition participants had to press the key which corresponds to the first letter of the target category. In the non-association condition participants were told to press a specific number key for each category.
The results showed a significant main effect of the association between target and action on the retrospective component. In all age groups the performances were better in the association condition compared to the condition without association. Independent of age, it is obviously easier to remember the first letter of four categories than four specific numbers. Further we investigated whether the association between target and action also influenced performances on the prospective component in the three age groups. The results showed that only young adults performed better in the association condition than in the non association condition. The children performed equally in both conditions and the old adults even tended to perform better in the non-association condition.
The association between target and action improved performance on the retrospective component across the lifespan. Concerning the prospective component only young adults benefited from the association between target and action. The results suggest that the target-action association effect on the remembering, that something has to be done, depends on the availability of processing recourses.

Neuropsychology/ Psychiatry (PSP)
prospective memory, lifespan, prospective component, retrospective component

PSP-10

Theta Burst TMS in a visual exploration task: a gender study

Silvia Chaves[1], Pascal Wurtz[1], Roman von Wartburg[1], Tobias Pflugshaupt[1], Anouk Déruaz[1], Mathias Lüthi[1], Dario Cazzoli[1], Thomas Nyffeler[1], Christian W. Hess[1], René Müri[1]

[1]*Perception and Eye Movement Laboratory, Department of Neurology, Inselspital, 3010 Berne, Switzerland*

Repetitive transcranial magnetic stimulation (rTMS) provides the possibility to transiently interfere with brain activity and lead to a modified human behaviour in cognitive tasks. The aim of this study is to investigate the influence of rTMS on visual exploration during an angle discrimination task. We applied rTMS to the superior parietal lobe as this region is known to play a crucial role in performing visuospatial tasks. The stimuli were designed in order either to facilitate (with cues) or to make more difficult (without cues) subjects' use of a visual exploration strategy. Preliminary results suggest that rTMS only affects the cued condition in which the development of a strategy is feasible. This effect was only found for women.

Neuropsychology/ Psychiatry (PSP)

PSP-11

Working memory training in 9-11 year old children: Influence on reading and episodic memory

Sandra V. Loosli[1], Martin Buschkuehl[1,2], Walter J. Perrig[1], Susanne M. Jaeggi[1,2]

[1]Division of Experimental Psychology and Neuropsychology, University of Bern, Switzerland, [2]Department of Psychology, University of Michigan, USA

Up to the present, few studies with the aim of improving working memory (WM) in children without developmental disorders have been conducted. Studies concerning WM-trainings mostly involved children with WM-deficits. In healthy children, transfer effects on other cognitive functions could only rarely be obtained.
In the current study, 24 healthy children between 9 and 11 years old undertook an adaptive, computerized WM-training for two weeks. The training duration was 12 minutes per day and it was conducted in two groups of 12 children each. Its influence on attention, memory, fluid intelligence and reading was examined and compared to a matched, non-trained control group.
A specific training effect was observed, that is, the children who undertook the training showed a significant performance increase in the trained WM-task. No improvements were noticed in other WM-tasks. However, compared to the control group, they enhanced their performance in several reading tasks and in an episodic memory task. Trends appeared in an attention task and in additional memory and reading tasks. Furthermore, effects of gender and strategy use were observed in the average performance on the training task, i.e., girls trained on average on a higher level than boys and children with strategy use were on a higher level than children without strategy use.
These findings show for the first time that a WM-training can affect reading and episodic memory in children. Additionally, an interview revealed that the children enjoyed the training and that therefore, it can be recommended to other children as well.

Neuropsychology/ Psychiatry (PSP)
Working Memory, Training

PSP-12

Thought abstraction in patients at clinical risk for psychosis

Andor E. Simon[1], Katja Cattapan-Ludewig[2], Angelika Berger[3], Kerstin Gruber[1], Daniel Umbricht[4]

[1]Psychiatric Outpatient Services Bruderholz, Switzerland, [2]Universitäre Psychiatrische Dienste Bern (UPD) , University of Bern, Switzerland;, [3]Child and Youth Psychiatric Department, Department of Psychiatry, 4101 Bruderholz, Switzerland, [4]Translational Medicine Neuroscience, Exploratory Development, Novartis Pharma AG, 4056 Basel, Switzerland

Background: Disorders of thought and language are considered a core symptom of schizophrenia. For many decades now, researchers and clinicians have regarded proverb interpretation as a potential tool assisting in the diagnosis of disordered thinking in patients suffering from schizophrenia (Finckh 1906, Vigotsky 1934, Gorham 1956, Chapman 1960, de Bonis et al. 1997). Compared to normal individuals, schizophrenia patients tend to interpret proverbs less accurately (Brune & Bodenstein 2005), more idiosyncratically (Harrow et al. 1972; Sponheim et al. 2003), and tend to stick to the literal meaning of the expressions, a clinical phenomenon which since Bleuler (1911) has been known as 'concretism'.
Traditionally, the problems of schizophrenia patients with proverb interpretation as an example of figurative language processing deficit has been linked to the inability of abstract thinking (Benjamin 1994, Goldstein 1959). Current explanations of impaired thought abstraction in patients with schizophrenia include a reduction of working memory (WM) capacities (Spitzer et al. 1994, Titone et al. 2002).
Methods:
Proverb interpretation ability was compared between 42 first episode (FE) patients, 64 patients meeting ultra high-risk criteria (UHR) for psychosis, 25 patients meeting basic symptom at-risk criteria (BS) for psychosis, and 42 patient controls (Pco). Associations with 3 WM tasks (letter number span, LNS; 2-back, 2-b, backward digit span, bDS) were investigated. Further, we examined the influence of age, education and IQ.
Results:
Progression of symptom severity was paralleled by increasing proverb interpretation difficulties. LNS in UHR and FE groups were significantly more impaired than in Pco and BS groups, while 2-b and bDS showed no between-group differences. LNS and 2-b were highly correlated with proverb interpretation in all groups, except LNS in the FE group. Digit span backwards WM task was not correlated with proverb interpretation in any of the study groups. IQ influenced thought abstraction, however, age and education did not.
Conclusions:
Our results support the WM deficit model of impaired thought abstraction. In higher demand WM tasks (e.g. LNS), no influence of WM on proverb interpretation ability seems to be present any longer in patients after transition to a first psychotic episode. Against the background of well-known WM deficits in patients with established schizophrenia (Lee & Park 2005) and in first episode patients (Simon et al. 2007), this seems to suggest that the contribution of WM to proverb interpretation may be weakened by transition to psychosis. This results in a loss of correlation between higher demand WM tasks and proverb interpretation, while lower demand WM tasks are not influenced by this process.
Future research into this field may need to consider the various dimensions of thought abstraction (concrete, literal, idiosyncratic-bizarre, abstract).

Neuropsychology/ Psychiatry (PSP)
Thought abstraction, proverb interpretation, psychosis

PSP-13

The early context effect reflects activity in the temporo-prefrontal semantic system – evidence from electrical neuroimaging of abstract and concrete word reading

Miranka Wirth[1], Helge Horn[1], Thomas Koenig[1], Maria Stein[1], Andrea Federspiel[1], Thomas Dierks[1], Beat Meier[2], Werner Strik[1]

[1]University Hospital of Psychiatry, Bern, Switzerland, [2]University of Bern, Institute of Psychology, Bern, Switzerland

Spatial and temporal characteristics of lexico-semantic retrieval are frequently examined with semantic context (i.e. priming) paradigms. These paradigms measure context (i.e. priming) effects in word processing evoked by semantically related context. Besides the well-known attention-dependent N400 context effect (> 250ms), recent studies demonstrate early automatic context effects in the P1-N1 time period (< 200ms). However, in visual words the semantic origin of the early effects remains debated. This study assesses spatio-temporal activation dynamics of the early context effect as well as the sensitivity of the effect to differences in verbal semantic structure present in abstract and concrete words. The visually-displayed words were preceded by semantically related and unrelated single word context. Spatial and temporal aspects of the early context effect were analyzed by applying electrical neuroimaging methods on the word-triggered Event Related Potentials. In abstract words the early context effect was enhanced compared to concrete words as indicated by a topographic dissimilarity in the P1-N1 transition period (116 – 140ms). This concreteness-dependent modulation indicates the sensitivity of the early context effect to differences in structure and accessibility of verbal semantics. Furthermore, the early context effect in abstract words was explained by enhanced activation in the left (inferior)prefrontal cortex for related compared to unrelated words in addition to temporo-parietal generators recruited in both conditions. The result suggests an automatic feed-forward of context-related information in the temporo-prefrontal system critical to semantic retrieval. Taken together the findings show that the early context effect reflects activation processes in verbal semantic memory.

Neuropsychology/ Psychiatry (PSP)
semantic memory, language, priming, inferior frontal gyrus, temporal cortex, concreteness, N400

PSP-14

Neurophysiological correlates of inner speech in hallucinating and non-hallucinating schizophrenic patients and healthy controls

Claudia van Swam[1], Daniela Hubl[1], Thomas Koenig[1], Werner Strik[1], Thomas Dierks[1]

[1]*Dept. of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern*

Regarding the genesis of auditory verbal hallucinations still the hypothesis is being discussed, that auditory verbal hallucinations derive from a deficit in self-monitoring resulting in confusion between self generated and alien speech. Indeed earlier studies have shown abnormal structural and functional connectivity between primary auditory cortex, and Broca's and Wernicke's area in hallucinating schizophrenic patients.

The aim of this study is to investigate the brain electrical activity of the primary auditory cortex and the main language areas during an intermittent silent verbal fluency (VF) task (inner speech) in hallucinating and non-hallucinating chronic schizophrenic patients as well as in healthy controls using 76-channel EEG.

22 chronic schizophrenic patients (AH), with persistent AVH lasting for at least 4 years, 17 non-hallucinating chronic schizophrenic patients (NH), and 12 healthy controls (C) have been investigated so far. The EEG was frequency transformed and sLORETA current densities were computed for frequency bands.

Preliminary results demonstrated that the healthy controls show activation of the motor speech area; the patients with AVH had significantly activated Wernicke's area in the non speech dominant hemisphere. Furthermore an activation of the primary auditory cortex in the speech dominant hemisphere was observed. The non-hallucinating patients showed a significant deactivation in the Wernicke's area of the non speech dominant hemisphere.
This suggests that the generally existing inhibition of the auditory system during inner speech is missing in hallucinating patients, leading to activation in this system. This activation may 'label' self generated speech as coming from outside, and give it an alien character, a sensation which is then termed hallucination.

Neuropsychology/ Psychiatry (PSP)
Schizophrenia, Hallucinations, EEG

PSP-15

"Is prospective memory spared in amnesic patients?"

Severin Fanger[1], Klemens Gutbrod[2], Sibylle Matter[1], Beat Meier[1], René Müri[2]

[1]Dep. of Experimental Psychology and Neuropsychology, University of Berne, Switzerland, [2]Dep. of Neurology, Division of Neuropsychological Rehabilitation, University Hospital of Berne, Switzerland

Prospective memory is the ability to form an intention and retrieve it later as planned. A prospective memory task comprises two components: the prospective component (recognizing the target event; remember that something must be done) that presumably depends mainly on executive functions and the retrospective component (remembering what to do) that is similar to retrospective episodic memory. Amnesic patients are known to have a profound deficit in episodic memory. Therefore they should be able to detect the prospective target events, but probably they fail to remember what they have to do. There is a lack of empirical evidence about prospective memory performance in patients with dense amnesia. In order to test whether noticing prospective target events is spared in amnesic patients, we measured performance in fifteen densely amnesic and fifteen matched control subjects. They were tested with an episodic (Experiment 1) and a habitual (Experiment 2) prospective memory task. In both tasks the prospective and retrospective components were assessed separately. In Experiment 1 half of the prospective memory targets were preceded by associated primes and in addition, half of the prospective targets were presented as specific cues during the planning phase (thereby creating a sequential processing overlap). We expected that associated primes and sequential processing overlap would enhance performance in the prospective memory task. The results confirmed our expectations, but only in the control group. The amnesic patients showed a substantial performance deficit, however, performance was not at floor, indicating some preserved prospective memory capacity. Experiment 2 contained frequent and repeated prospective memory targets and with feedback after each failure of prospective memory target recognition. The interval between prospective memory targets was also manipulated (i.e., short vs. long). We expected better performance after short delays. The results showed that overall performance of amnesics was below that of healthy controls. There was no difference between the two interval conditions, but there was a significant improvement in the second half of the task for both groups. These results indicate that despite their strong retrospective memory deficit, amnesic patients are able to carry out prospective memory tasks, but at a lower level than healthy controls.

Neuropsychology/ Psychiatry (PSP)
prospective memory and amnesia

PSP-16

Impaired incidental sequence learning in patients with ventromedial prefrontal lesions

Laura Jundt[1], Beat Meier[1], Klemens Gutbrod[2], René Müri[2]

[1]Institute of Psychology, University of Bern, [2]Department of Neurology, University of Bern

Recent studies have shown the important role of the ventromedial prefrontal cortex in decision making, personality and social behaviour. The objective of this study was to investigate the role of the ventromedial prefrontal cortex in incidental sequence learning.
Although several prefronto-striatal pathways have been implicated in incidental sequence learning, there is a lack of studies examining patients with prefrontal lesions and particular with lesions in the ventromedial prefrontal cortex. We investigated 13 patients with ventromedial prefrontal lesions and 13 controls, matched for age, sex and education level, with a new task sequence learning paradigm. Participants were required to classify words into different categories. For animals they had to decide whether it was a mammal or a bird, for objects they had to decide whether it is a kitchen utensil or a musical instrument, and for plants they had to decide whether it is a flower or a tree. Participants were required to press a different response key with their left or right index finger for each of the three decision tasks. The order of tasks was sequenced. The to-be-pressed order of responses was also sequenced and correlated with the task sequence. After six sequenced blocks, a different sequence of tasks and responses was introduced as a “distractor” block and in the last block the original sequence was presented again. The control group, but not the patients, showed an increase in reaction times in the distractor block indicating the acquisition of specific sequence knowledge. This result indicates that patients with ventromedial prefrontal lesions have a deficit in their ability to acquire sequence knowledge incidentally and it implicates that the ventromedial prefrontal cortex is an essential part of the neuronal circuit that mediates this type of learning.

Neuropsychology/ Psychiatry (PSP)

PSP-17

"Episodic" recognition memory can be boosted with semantic memory in a Patient with Developmental Amnesia

Patrizio Colella[1], Klemens Gutbrod[2], Beat Meier[1]

[1]Department of Experimental Psychology and Neuropsychology, University of Bern, 3000 Bern 9, Switzerland,
[2]Department of Neurology, Division of Neuropsychological Rehabilitation, University Hospital of Bern, 3010 Bern, Switzerland

Episodic memory refers to the conscious recollection of specific previous events including temporal and spatial information about the episode. Semantic memory refers to knowledge about the world without specific memory of the circumstances under which it was acquired. A current controversy concerns the question whether information is encoded serially in semantic memory before being enriched with episodic details. This model predicts that episodic memory is not necessary for the acquisition of new knowledge. Evidence supporting this model comes from a condition called developmental amnesia, in which bilateral hippocampal pathology acquired early in childhood leads to strong and persistent amnesia. In the present study we report the case of a patient who fits the criteria of developmental amnesia and we compared his episodic memory performance with nine control subjects, matched for IQ, age and gender. We conducted two experiments to separate episodic recollection processes from familiarity processes. The latter are assumed to rely on semantic rather than episodic memory. In Experiment 1, the patient showed a deficit in both item recognition and associative recognition and a floor effect in cued recall. In Experiment 2, the patient showed an intact mirror effect in a word frequency recognition task, indicating a higher hit rate and a lower false alarm rate for low compared to high frequency words. While recognition performance as indicated by the difference between hits and false alarms of high frequency words was close to chance and well below the control group, performance on low frequency words was high and did not differ from performance of the control group. The latter result is surprising at the first glance because performance of low frequency word recognition is thought to indicate episodic recollection. However, our results may indicate that the patient can use (semantic) familiarity information to boost his episodic recognition. Such a strategy could explain how patients with developmental amnesia can acquire "episodic" knowledge.

Neuropsychology/ Psychiatry (PSP)
Developmental Amnesia; Episodic Memory; Recollection; Familiarity; Hippocampus

PSP-18

Impaired incidental sequence learning in Patients with Parkinson's disease

Brigitte Weiermann[1], **Beat Meier[1]**, Marianne-Anke Stephan[2], Alain Kälin-Lang[2]

[1]Institute of Psychology, University of Bern, , [2]Department of Neurology, Inselspital, Bern University Hospital, and University of Bern

People can profit from responding to a sequence of stimuli even when they are not aware of the presence of the sequence. This ability has been investigated with the classical serial reaction time (SRT)-task, in which a sequence of stimulus locations is presented on a computer screen. Subjects must respond to the location with a corresponding keypress. After repeated presentation of the sequence the reaction times decrease, but when the ordered sequence of stimuli is switched to a different (or a random) sequence, there is a sudden increase in reaction times. The latter is taken as evidence for sequence learning. As this type of learning is of a motor (i.e., a response sequence) and a visuo-motor type (i.e., a location sequence) it is assumed that the basal ganglia are involved. To test this assumption many studies have investigated incidental learning in patients with Parkinson's disease (PD). Although the findings are somewhat inconsistent, overall they indicate that Parkinson patients' incidental sequence learning performance is reduced. In order to test whether this deficit affects not only perceptuo-motor learning, but also conceptuo-motor learning a new task sequence learning paradigm was used. A total of 14 non-demented PD patients and a healthy control group, matched in age, gender, education and handedness was tested. Participants were required to classify words into different categories. For animals they had to decide whether it was a mammal or a bird, for objects they had to decide whether it is a kitchen utensil or a musical instrument, and for plants they had to decide whether it is a flower or a tree. Participants were required to press a different response key with their left or right index finger for each of the three decision tasks. The order of tasks was sequenced. The to-be-pressed order of responses was also sequenced and correlated with the task sequence. After six sequenced blocks, a different sequence of tasks and responses was introduced as a "distractor" block and in the last block the original sequence was presented again. The control group, but not the patients, showed an increase in reaction times in the distractor block indicating the acquisition of specific sequence knowledge. This result indicates that Parkinson patients sequence learning deficit is not restricted to perceptuo-motor sequences, but extends to conceptuo-motor sequences. It implicates that the basalganglia are at the core of the neuronal circuit recruited for this type of learning.

Neuropsychology/ Psychiatry (PSP)

PSP-19

Deficits in information processing in patients with Parkinson's disease

Ariane Orosz[1,2], Marianne Stephan[3], Alain Kaelin-Lang[3], Joram Feldon[1], Katja Cattapan-Ludewig[2]

[1]Laboratory of Behavioral Biology, ETH Zürich, Switzerland , [2]University Hospital of Psychiatry, Bern, Switzerland , [3]Department of Neurology, Laboratory of Neuromorphology, University of Bern, Switzerland

Latent inhibition (LI) is thought to be a measure of information processing, especially of the ability to filter out irrelevant stimuli. It refers to the reduction of associative learning (learning that one stimulus predicts another stimulus) that normally occurs if the subject is familiar with one of the to-be-associated-stimuli. LI is thought to be modulated by dopamine, because amphetamine (dopamine agonist) causes LI deficits, while antipsychotic drugs (dopamine receptor blockers) enhance LI. Furthermore, LI has been consistently reported to be deficient in acute schizophrenia, which is associated with high dopamine levels in the mesocorticolimbic dopamine system. In order to find out more about the dopaminergic modulation of LI, we measured LI in patients with Parkinson's disease. With regard to dopamine levels, Parkinson's disease is virtually complementary to schizophrenia. Therefore, we hypothesized enhanced LI in patients with Parkinson's disease. We tested 16 patients with Parkinson's disease (4 unmedicated, 12 medicated with L-Dopa or dopamine agonists) and 16 age- and gender-matched control subjects with a computerized within-subject, target-recognition LI paradigm which involves a reaction time task. Subjects were instructed to respond to the target which appeared either after novel ("relevant") or after familiar ("irrelevant") stimuli. Control subjects showed normal LI in terms of significantly lower reaction times to targets presented after novel stimuli than to targets presented after familiar stimuli. Parkinson patients exhibited LI deficits, deriving from equally high reaction times after the novel and the familiar stimuli. These results indicate that patients with Parkinson's disease were impaired in learning about the novel stimuli. However, this was not the same kind of LI deficits found in acute schizophrenia. While the latter show LI deficits due to better learning about familiar stimuli, patients with Parkinson's disease do not show LI because of impaired learning about the novel stimuli. In line with our results, studies investigating cognitive performance in patients with Parkinson's disease reported that they seem to have a general impairment of responding to novel stimuli. Based on previous experience with the same test paradigm and alternative statistical analysis, the present findings cannot be explained by differences in medication among the patients.

Neurobiology (PSB), Neurology (PSN), Neuropsychology/ Psychiatry (PSP)
latent inhibition, schizophrenia, Parkinson's disease, dopamine, information processing

PSP-20

Psychophysiological signature of prospective memory and emotional reactions

Nicolas Rothen[1], Beat Meier[1]

[1]*Dept. of Psychology, University of Berne, 3012 Berne, Switzerland*

Prospective memory is required to perform an intended action at the appropriate occasion. The specific occasion (i.e., the prospective memory cue) can be more or less specific and due to the necessity for self-initiated retrieval the occurrence of the situation may be accompanied by an emotional response (e.g. surprise). It is well known that emotional reactions influence psychophysiological measures such as electrodermal activity. In this study we assessed the physiological signature of encountering a prospective memory target. In addition, we tested whether inducing an emotional state by presenting a surprising picture immediately before the prospective memory target would affect prospective memory performance and the resulting electrodermal signature. A total of 120 university students were engaged in a picture comparison task with an embedded prospective memory task. For the prospective memory task participants had to press a specific key whenever a particular picture appeared. Depending on the experimental condition, the particular picture was defined as a picture of an animal, a picture of a bird, or a picture of an eagle. We investigated whether the signature of different specificity levels of prospective memory targets – a variable well known to affect prospective memory performance – would also influence the electrodermal response. The results showed that detecting prospective memory targets increases electrodermal activity and this increase was somewhat higher when the prospective target was not preceded by a different surprising event.

Neurophysiology (NP), Neuropsychology/ Psychiatry (PSP)
Psychophysiology; Prospective Memory, Emotion

PSP-21

Effects of Theta Burst rTMS on length perception: An eye movement study

Matthias Grieder[1], Pascal Wurtz[1], Tobias Pflugshaupt[1], Roman von Wartburg[1], Thomas Nyffeler[1], Matthias Lüthi[1], Silvia Chaves[1], Anouk Déruaz[1], Dario Cazzoli[1], René Müri[1]

[1]*Perception and Eye Movement Laboratory, Depts. of Clinical Research and Neurology, Inselspital*

Certain alignments of arrows terminating and bisecting horizontal lines distort the perceived line length which leads to an illusion of length. As preliminary studies have revealed, neglect patients show the prevalent rightward bias while bisecting the so-called Brentano illusion, but with different magnitudes depending on illusion direction and spatial positioning of the figure. In this eye movement experiment, Theta Burst repetitive transcranial magnet stimulation (rTMS) was applied over the right temporo-parietal cortex of healthy subjects to further investigate the contribution of this area in visuo-spatial tasks including illusions of length. Results show first that rTMS is capable of inducing temporary 'virtual lesions' and second that it elicits eye movment patterns similar to those in neglect patients.

Neuropsychology/ Psychiatry (PSP)
rTMS, length illuson, eye movements

Rehabilitation

PSR-1

Evaluation of Bone Anchored Hearing Aid (BAHA) Transducers

Flurin Pfiffner[1], Christof Stieger[1], Andreas Arnold[1], Claudia Candreia[1], Martin Kompis[1], Rudolf Häusler[1]

[1]*Department of ENT, Head and Neck Surgery, Inselspital, University of Berne*

Background

Many patients with a substantial conductive or mixed (sensorineural and conductive) hearing loss benefit from specialized, so called bone anchored hearing aids (BAHA). These aids consist of a titanium screw, which is usually implanted behind the ear and a special bone conduction BAHA transducer, which can be attached by means of a snap coupling to the screw. The BAHA transducer applies mechanical vibrations directly to the skull and propagates the amplified sound via bone conduction directly to the inner ear.

Objectives

Bone conduction from the BAHA titanium screw to the inner ear is a complex process and poorly understood. This research aims at providing a better understanding of induced wave propagation (bone conduction) from the BAHA transducer to the inner ear and built a basis to optimize future BAHA's. As a prerequisite cadaver heads with the so called Thiel fixation have to be evaluated.

Materials and Methods

BAHA titanium screws were implanted on Thiel fixated cadaver heads. Access to the round window (mastoidectomy) conserving middle ear structures was realized. Five BAHA transducers were directly electrically stimulated in the audible frequency range (amplitude and frequency dependant signals). The induced vibrations at the round window were measured using laser Doppler Vibrometry. The vibration amplitude at the round window at a constant stimulation level of 31mV is tested for all tested transducers.

Results & Conclusion

Preliminary results show that the Thiel fixated cadaver heads are an appropriate model for these BAHA measurements. The amplitude of the vibrations at the round window is clearly distinguishable from the noise level for frequency between 400Hz and 5kHz. Different resonance frequencies are observed (850Hz, 2,4kHz and 3,4kHz). Output may be improved by more than 20dB Amplitude by using the optimal transducer.

Rehabilitation (PSR)
Hearing loss, Hearing aid, Bone conduction, BAHA

PSR-2

Using strengths of character in new ways increases life satisfaction: A random-assignment, placebo-controlled study

Bernhard Sollberger[1]

[1]*Department of General Psychology and Neuropsychology, University of Berne, 3000 Berne 9, Switzerland*

Only recently, Peterson and Seligman (2004) have described and classified 24 strengths of character (e.g., curiosity, persistence, gratitude, hope) that enable human thriving. Strengths are regarded as individual differences that exist in degrees, so that each person possesses his/her own strengths profile. In a random-assignment, placebo-controlled study, Seligman et al. (2005) have shown that using the personal five highest ("signature") strengths in a new and different way increases happiness. I investigated whether using strengths on positions 6 to 10 of the strengths profile in new ways also has a positive effect on well-being measures. To this aim, participants were randomly assigned to an experimental condition (n = 24) or to a validated placebo control condition (n = 28) used by Seligman et al. (2005). Participants in the experimental condition first identified their strengths profile and then used one of the strengths on positions 6 to 10 in a new way every day for one week, whereas participants in the control condition wrote about early childhood memories every evening for one week. Life satisfaction was measured just before, and one week and one month after the end of the intervention. Results revealed that the change scores in life satisfaction from the pre-test to both post-tests were significantly more positive in the experimental condition than in the control condition. I conclude that just as well as the five highest strengths, strengths on positions 6 to 10 of the strengths profile can be used in new ways to increase well-being, enlarging the spectrum of possibilities to implement strengths-based happiness interventions.

Rehabilitation (PSR)

Workshop 1: Acute brain injury: From mechanisms to therapy

Chairs: Stephan Christen & Stephen Leib

WS-1-1

Clinical Aspects of acute brain injury in bacterial meningitis

Johann Sellner[1]

[1]*Department of Neurology, Inselspital, University of Bern, 3010 Bern, Switzerland*

Until the introduction of antibiotics including sulfonamides and penicillins in the 1930s and 1940s, acute bacterial and in particular pneumococcal meningitis was fatal in most cases. Since then it has become a potentially curable disease but mortality and morbidity from the disease remain unacceptably high. Apart from epidemics, at least 1·2 million cases of bacterial meningitis are estimated to occur each year, rating this disease among the top-ten infectious cause of death worldwide. Moreover, neurological and neuropsychological sequelae are reported to affect up to half of survivors.
Clinical studies have shown that a fatal outcome of the disease is often due to central nervous system (CNS) complications including cerebrovascular involvement, brain edema formation, and hydrocephalus resulting in increased intracranial pressure and seizure activity. Focal cerebral abnormalities are commonly caused by stroke, seizures, or a combination of these two. Cerebral infarction and cytotoxic edema care caused by vasculitis and thromboembolic events.
The brain structure responsible for learning and memory function is the hippocampus. This structure is specifically targeted by brain injury in bacterial meningitis . In the hippocampal dentate gyrus neuronal apoptosis has been observed in humans dying from bacterial meningitis. Apoptosis almost exclusively affected the subgranular zone of the dentate gyrus, a brain region which continues to produce new neurons throughout life.
Sensorineural hearing loss (SNHL) is the most common sequel of bacterial meningitis and is observed in up to 30% of survivors when the disease is caused by Streptococcus pneumoniae. SNHL results from involvement of the inner ear due to inflammation due to cerebrospinal fluid (CSF) containing pneumococci and leukocytes extending from the subarachnoid space via the cochlear aqueduct to the perilymph.

Neurobiology (PSB), Neurology (PSN)

WS-1-2

Bacterial meningitis: experimental approaches

Stephen L. Leib[1], Matthias Wittwer[1], Denis Grandgirard[1]

[1]*Institute for Infectious Diseases, University of Bern, 3010 Bern, Switzerland*

For a better understanding of the mechanisms leading to brain jury, and for the development of novel therapeutic strategies, relevant disease models are prerequisite. Bacterial meningitis is a devastating infectious disease leading to neurological sequelae in up to 50% of the survivors, as a consequence of brain damage. Cortical ischemic necrosis and hippocampal apoptosis, two distinct forms of acute brain injury have been identified as histomorphologic correlates of neurological sequelae. In bacterial meningitis, the host's reaction to the infecting bacterial pathogen triggers an inflammatory reaction that contributes to cortical ischemic injury and damage of the inner ear. In the hippocampus, neurons undergo apoptotic cell death, which is associated with the learning and memory deficits frequently observed in affected patients. Being a multifactorial disease that is modulated by the interaction of the microbial pathogens with the hosts immune defense, bacterial meningitis is a prime target for multidisciplinary efforts combining disease models with analytic molecular methods. Some of the pathophysiologic processes in experimental bacterial meningitis have been identified, providing insights into the molecular basis of brain injury and potential targets for therapy. This has led to the evaluation of new therapeutic modalities, such as attenuation of the pathogen derived triggers of inflammation by the use of non-bacterioloytic antibiotics, and the modulation of the hosts immune response e.g. by inhibition of matrix metalloproteinases. Interventions that protect the brain from acute damage or support regeneration are further evaluated for their potential to preserve neurointegrative functions.

Neurobiology (PSB), Neurology (PSN)
acute brain injury, infectious diseases, bacterial meningitis, disease model, pathophysiology, therapy

WS-1-3

The Blood-brain barrier in acute brain injury

Ruth Lyck[1], Oliver Steiner[1], Urban Deutsch[1], Axinia Doering[1], Caroline Coisne[1], Britta Engelhardt[1]

[1]*1Theodor-Kocher Institute, University of Berne, 3012 Berne, Switzerland*

Recruitment of cells of the innate and adaptive immune system into the central nervous system contributes to acute brain injury pathogenesis. In order to gain access to the neuronal tissue the immune cells have to overcome the blood-brain barrier (BBB) formed by highly specialized endothelial cells. The sequence of molecular steps involved in the recruitment of different leukocyte subpopulations across the BBB is not completely understood. Using in vitro and in vivo experiments we investigate the traffic signals involved in lymphocyte extravasation from the blood into the CNS. We and others have shown that alpha4-integrins play a predominant role in T lymphocyte recruitment across the BBB, whereas the precise contribution of LFA-1 and its endothelial ligands ICAM-1 and ICAM-2 remains to be investigated. Detailed knowledge about the molecular and cellular pathways of leukocyte migration across the BBB is mandatory to specifically prevent the migration of pathogenic leukocytes into the CNS, while at the same time maintaining the recruitment of potential repair cells.

Neurobiology (PSB)
Blood brain barrier, leukocyte extravasation, acute brain injury, inflammation

WS-1-4

Transcriptomics of Pneumococcal Meningitis

Matthias Wittwer[1], Denis Grandgirard[1], Stephen Leib[1]

[1]*Institute for Infectious Diseases, University of Berne, 3010 Berne, Switzerland*

BACKGROUND: Bacterial meningitis causes brain injury, characterized by neuronal apoptosis in the hippocampal dentate gyrus and ischemic necrosis in the cortex. The aim of our study was to define the cellular processes underlying brain injury in the cortex and hippocampus during the acute and late phase of the disease.

METHODS: An infant rat model of experimental pneumococcal meningitis was used. Cortex and the hippocampus were dissected form animals in acute and late disease i.e. at 24 and 72h after infection. Gene expression profiles were assessed using Affymetrix GeneChip® Rat 230 2.0 arrays. Cell proliferation in the dentate gyrus was investigated using BrdU incorporation for 3 consecutive days after infection and in uninfected controls.

RESULTS: In cortex and hippocampus during the acute diseases phase genes found to be significantly regulated predominantly fell in the category of the host immune response and inflammation followed by cellular turnover processes, and apoptosis. In contrast, during the late phase of the disease the general categories of transcriptomic changes diverge between the 2 brain regions. The predominant process in the cortex were those associated with immune response, while in the hippocampus genes related to tissue remodelling, neuronal neogenesis and axonal guidance processes were predominantly regulated. BrdU incorporation revealed a significant increase in proliferation in the neurogenic dentate gyrus region of the hippocampus.

CONCLUSION: We found that in the hippocampal dentate gyrus tissue regeneration is initiated as early as 72h after infection as we found a pronounced increase of genes involved in neuronal proliferation and axonal guidance. These observations were confirmed by in vivo analysis, demonstrating an increase in BrdU cell incorporation in the subgranular zone of the dentate after the infection. The data indicate that treatment strategies that support tissue regeneration e.g. by trophic factors, may be beneficial as early as 3 days after infection while antiproliferative therapies e.g. steroids may be detrimental.

Neurology (PSN)
Infectious Disease, Bacterial Meningitis, Transcriptomics

WS-1-5

Role of pro-apoptotic and pro-survival signaling pathways in meningitis-induced neuronal apoptosis

Matthias D. Sury[1], Claudia Agarinis[1], Hans-Rudolf Widmer[2], Stephen L. Leib[1], Stephan Christen[1]

[1]Institute for Infectious Diseases, University of Berne, Berne, Switzerland, [2]Department of Neurosurgery, University of Berne, Berne, Switzerland

Brain damage in bacterial meningitis is characterized by apoptosis of immature post-mitotic neurons in the dentate gyrus of the hippocampus. The death of these cells is thought to be responsible for the learning and memory deficits presented by patients surviving the disease. Studies in models of acute brain injury such as caused by cerebral ischemia have implicated activation of c-Jun NH_2-terminal kinase (JNK) to be responsible for hippocampal neuronal apoptosis. Here we show in a well-established infant rat model of pneumococcal meningitis that neuron-specific JNK3 is activated in the hippocampus and accompanied by increased phosphorylation of its major down-stream target c-Jun in immature postmitotic neurons in the dentate gyrus. Intracerebroventricular administration of the specific JNK inhibitors D-JNKI-1 or AS601245 inhibited the infection–associated increase in c-Jun phosphorylation but had no effect on hippocampal neuronal apoptosis. Immature developing neurons undergo apoptosis, unless they receive extrinsic growth factor signals, which activate survival pathways such as the phosphatidylinositol-3-OH kinase (PI3K) – protein kinase B (PKB/Akt) pathway. Preliminary results show an infection-associated decrease in Akt phosphorylation coinciding with apoptosis. Inhibition of PI3K exacerbates meningitis-induced Akt de-phosphorylation and apoptosis, while inhibition of the Akt upstream phosphatase PTEN restores Akt phosphorylation and almost completely prevents apoptosis. These results strongly suggest that perturbation of the Akt survival pathway is responsible for hippocampal apoptosis in pneumococcal meningitis.

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Neurobiology (PSB)

WS-1-6

Neurogenesis in brain injury and repair after meningitis

Denis Grandgirard[1], Stephen Leib[1]

[1]*Institute for Infectious Diseases, University of Bern, Switzerland*

Introduction: Patients who survived bacterial meningitis often suffer from permanent neurological sequelae. In particular, children who had suffered from bacterial meningitis during their first year of life showed a 10-fold increase in the risk of severe or moderate disabilities like learning difficulties, neuromotor disabilities, seizure disorders, hearing problems, and behavioural problems, when compared to a control group. In experimental pneumococcal meningitis, learning deficit assessed by water maze test three weeks after injury is associated with apoptotic neuronal injury in the hippocampal dentate gyrus. This brain region continuously produces new neurons and would therefore be particularly suited to effectively repair injury.
Aim: We investigated whether injury to the hippocampal dentate gyrus in pneumococcal meningitis was compensated by an increase in neurogenesis as an effective repair mechanism.
Methods: The rate of cell proliferation in the hippocampal dentate gyrus was assessed in animals after pneumoccocal meningitis and in uninfected control littermates. Animals were pulsed with the thymidine analogue BrdU at several times after meningitis (3 days, 3 weeks and 6 weeks later) and the density of BrdU-positive cells in the dentate gyrus determined by immunofluorescence analysis. The time between BrdU pulse and measurement of density was varied (24 hours and 3 weeks after last pulse) to determine the survival rate of the newly produced cells.
Results: Cell proliferation was significantly increase at 3 days and 3 weeks after meningitis. In contrast, no increase was detected at 6 weeks after infection. The increase in cell proliferation observed 3 days after infection was not reflected by an increase in BrdU positive cells 3 weeks after labelling, suggesting that the majority of the newly generated cells were short-lived and were eventually eliminated.
Conclusion: These results suggest that the compensatory increase in cell proliferation initiated shortly after pneumococcal meninigitis is not effective at replacing cell loss observed during the acute phase of the disease. The ineffective repair may contribute to the persistent deficits in learning performance observed in survivors of the disease.

Neurobiology (PSB), Neurology (PSN)
bacterial meningitis, neurogenesis, hippocampus

WS-1-7

Cell replacement Therapy

Hans Rudolf Widmer[1]

[1]*Department of Neurosurgery, University of Bern, Inselspital, Bern*

There is increasing interest in the search of therapeutic options for diseases and injuries of the central nervous system, for which currently no effective treatment strategies are available. The concept of neural transplantation has evolved as an instrument for replacing the neurons lost in degenerative processes, trauma, and vascular lesions, as well as for replacing glial cells in the context of demyelinating lesions. Major advances in basic research have enabled first clinical trials, which have proved that this approach is feasible. Some promising results particularly in neurodegenerative disorders, like Parkinson's and Huntington's disease are reported. Most of our knowledge on cell replacement therapy hence comes from clinical trials for Parkinson's and Huntington's disease. Recent studies, however, have also highlighted the great potential of cell transplantation therapy for stroke. Nevertheless, using cell replacement approaches for stroke, it remains at present unclear if the transplanted neurons themselves promote functional recovery or if the transplants modulate the response of the brain to ischemic neurogenesis, synaptogenesis, angiogenesis and inflammation. In this line, it is tempting to speculate that transplanted cells influence endogenous stem cell proliferation. From the Parkinson's disease trials we learned that a number of major limitations need to be overcome, such as, suboptimal survival and functional integration of transplanted cells. Indeed, specific neuronal growth factors have been reported to improve graft properties. Furthermore, human fetal tissue from abortion does not offer a sufficient source for grafting a large number of patients. Moreover, it represents a not well-characterized donor tissue asking for alternatives. Replacement of damaged cells and restoration of function can be accomplished by transplantation of cells derived from different sources, such as genetically modified cell lines, embryonic or somatic stem cells. It is important that we know more on issues such as the presence of potential side effects, on factors influencing migration, growth and differentiation of transplanted stem and progenitor cells. In addition, a number of ethical issues need to be addressed. In sum, a collaborative effort between neuroscientists, neurosurgeons, and neurologists is essential to translate cell transplantation therapy successfully into the clinic in a timely but safe and effective way.

Neurosurgery (PSS)
Neural transplantation, neurotrophic factors, stem cells, regenerative medicine

WS-1-8

Stem cell therapy for the neuroregeneration in perinatal brain injury

Andreina Schoeberlein[1], Pierre Rollini[1], Daniel V. Surbek[1]

[1]*Laboratory of Prenatal Medicine, Department of Clinical Research, University of Bern and University Women's Hospital, Inselspital, Bern University Hos*

Preterm delivery is a major cause of neonatal morbidity and mortality. Approximately one percent of all newborns are affected by neurological injuries leading to significant learning disabilities, cerebral palsy or mental retardation later in life. The prevention or treatment of brain inury in the premature infant is one of the highest research priorities in medicine. Brain lesions observed in preterm newborns later developing cerebral palsy mainly consist of periventricular white matter injury, which is characterized by the loss of oligodendrocyte progenitors, and is caused by two main factors: ischemia due to maturation-dependent reduced cerebral blood flow and maternal/fetal infection and inflammation which are usually present in early preterm delivery. While several potential neuroprotective measures have so far shown little success in vivo, studies in animal models of neurodegenerative disorders have suggested that transplantation of stem cells could lead to the regeneration of injured neural tissue in the fetus and newborn. Embryonic stem cells (ESC) derived from the inner cell mass of preimplantation blastocysts possess long-term self-renewal potential, and can be differentiated into cell types from all embryonal germ layers, including neural progenitors and differentiated neural cells. These ESC-derived neural cells have already shown promising results in various animal transplantation models of neurodegenerative dysfunctions, including stroke, Parkinson's disease, spinal cord injury, multiple sclerosis and metabolic storage disorders. Human ESC may represent a promising cell source for the development of stem cell therapies to prevent and/or to treat degenerative disorders of the central nervous system. The aim of the project is to test whether transplantation of oligodendrocyte progenitors derived from human ESC could lead to functional neuroregeneration in a well described rat model of perinatal brain injury. In this model, intracervical administration of the bacterial toxin lipopolysaccharide to pregnant dams causes an intrauterine inflammation, resulting in white matter damage in newborns associated with measurable developmental sensory-motor sequelae in the neonatal period. Human ESC will be differentiated into neural and further into oligodendrocyte progenitors, which will be transplanted intraventricularly either in utero at embryonic day 15.5 or into neonatal pups. The engraftment, migration and differentiation of donor cells in the injured compared to normal brains will be evaluated. Donor-derived cells will be identified, characterized and quantified. Finally, functional improvement will be assessed by established neurobehavioral tests of the sensory-motor and learning ability of transplanted versus non-transplanted rats. The project addresses the therapeutic potential of ESC-derived oligodendrocyte progenitor transplantation for neuroregeneration following perinatal brain damage. Confirmation of engraftment and in vivo differentiation together with sensory-motor improvement after transplantation will serve as proof of principle and should pave the way for the development of stem cell therapies in affected newborns.

Neurobiology (PSB), Rehabilitation (PSR)
stem cell therapy

Workshop 2: Applications in Eye Movement Research

Chair: René Müri

WS-2-1

The analysis of reading strategies as a tool for understanding and training eye movements in patients with central field loss

Anouk Déruaz[1]

[1]*Perception and Eye Movement Laboratory, Inselspital, 3010 Bern, Switzerland*

Basal dendrites receive the majority of synapses that contact neocortical pyramidal neurons, yet our knowledge of synaptic processing in these dendrites has been hampered by their inaccessibility for electrical recordings. A new approach to patch-clamp recordings enabled us to characterize the integrative properties of these cells. Despite the short physical length of rat basal dendrites, synaptic inputs were electrotonically remote from the soma (>30-fold excitatory postsynaptic potential (EPSP) attenuation) and back-propagating action potentials were significantly attenuated. Unitary EPSPs were location dependent, reaching large amplitudes distally (>8 mV), yet their somatic contribution was relatively location independent. Basal dendrites support sodium and NMDA spikes, but not calcium spikes, for 75% of their length. This suggests that basal dendrites, despite their proximity to the site of action potential initiation, do not form a single basal-somatic region but rather should be considered as a separate integrative compartment favoring two integration modes: subthreshold, location-independent summation versus local amplification of incoming spatiotemporally clustered information.

Neurobiology (PSB), Neurology (PSN)

WS-2-2

Investigating spatial attention by means of a visual illusion

Pascal Wurtz[1]

[1]*Perception and Eye Movement Laboratory, Inselspital, 3010 Bern, Switzerland*

In the Brentano version of the Müller-Lyer (ML) Illusion, one half of the line looks longer than the other. Recently, it has been shown that different versions of the ML-Illusion do not only affect manual bisection performance, but also eye movements. Patients suffering from visuo-spatial neglect after brain injuries show systematic spatial asymmetries in eye movements as well as in bisection of simple lines.
The present study was aimed at investigating illusion effects in neglect patients by comparing the relationship between eye movements and manual bisection performance in different versions of the Brentano Illusion. Results suggest that illusion effects in both oculomotor and manual behaviour are modulated (e.g. left-right asymmetries, position effects) by hemispatial neglect.

Neuropsychology/ Psychiatry (PSP), Rehabilitation (PSR)
hemispatial neglect, length illuson, eye movements

WS-2-3

Angle discrimination: an eye movement study

Silvia Chaves[1]

[1]*Perception and Eye Movement Laboratory, Inselspital, 3010 Bern, Switzerland*

In this study we investigated the characteristics of visual exploration strategies in a visuospatial task. For this purpose we used an angle discrimination task using clock-like stimuli. Subjects had to decided whether a given angle matched 60° or not and to press the corresponding button. Subjects' performances were measured once without and once with TMS stimulation on the parietal cortex. The visuospatial properties of the clock-like stimuli were manipulated in three ways: angle disparity, length of clockhands and presence of cues. Using this visuospatial approach we could demonstrate that task demand had an influence on the visual exploration and to show that magnitude effects such as the size congruity effect could explain differences in visual exploration. We additionally could show that the eye movements' pattern during was modified after TMS stimulation.

Neuropsychology/ Psychiatry (PSP)
Angle discrimination, eye movements

WS-2-4

Oculomotor findings in a patient with simultanganosia

Thomas Nyffeler[1]

[1]*Perception and Eye Movement Laboratory, Inselspital, 3010 Bern, Switzerland*

Oculomotor recovery in a patient with simultanagnosia due to biparietal lesions is described. Visual exploration as well as basic oculomotor tasks were applied in three consecutive test sessions – i.e. 8 weeks, 14 weeks, and 37weeks after brain damage had occurred. The results show that an impaired disengagement of attention persisted while visual exploration remarkably improved. This improvement is interpreted within an oculomotor network theory and implications for a deficit-specific recovery from simultanagnosia are discussed.

Neuropsychology/ Psychiatry (PSP), Rehabilitation (PSR)
simultanagnosia, eye movements

WS-2-5

A case study about mirrored vision

Tobias Pflugshaupt[1]

[1]*Perception and Eye Movement Laboratory, Inselspital, 3010 Bern, Switzerland*

The combination of acquired mirror writing and reading is an extremely rare neurological disorder. It is encountered when brain damaged patients prefer horizontally mirrored over normal script in writing and reading. Previous theories have related this pathology to a disinhibition of mirrored engrams in the non-dominant hemisphere, possibly accompanied by a reversal of the preferred scanning direction. Here we report the experimental investigation of PR, a patient who developed pronounced mirror writing and reading following septic shock that caused hypoxic brain damage. A series of five oculomotor experiments revealed that the patient's preferred scanning direction was indeed reversed. However, PR showed striking scanpath abnormalities and mirror reversals that cannot be explained by previous theories. Considered together with mirror phenomena she displayed in neuropsychological tasks and everyday activities, our findings suggest a horizontal reversal of visual information on a perceptual level. In addition, a systematic manipulation of visual variables within two further experiments had dramatic effects on her mirror phenomena. When confronted with moving, flickering, or briefly presented stimuli, PR showed hardly any left-right reversals. Not only do these findings underline the perceptual nature of her disorder, but also allow interpretation of the pathology in terms of a dissociation between visual subsystems. We speculate that early visual cortices are crucially involved in this dissociation.

Neuropsychology/ Psychiatry (PSP), Rehabilitation (PSR)
Human, brain damage, mirrored writing, mirror reading, eye movements

Workshop 3: In search of meaning in unconscious priming and implicit learning

Chair: Walter Perrig

WS-3-1

Emotion effects in unconscious priming

Walter Perrig[1]

[1]*Department of Psychology, University of Berne, 3010 Berne, Switzerland*

Mood-congruency effects in explicit memory are well documented in the literature, although the nature of these effects is not yet clear. In this contribution an experiments is presented in which the influence of mood induction on unconscious mood-congruency priming is investigated. To our knowledge there is no other such study in the literature so far.
The results show that the induction of positive mood had an effect on mood-congruent priming. The effect of the invisible positive prime seems to be strengthened, while the effect of the invisible negative prime seems to be inhibited. Induction of negative mood however had no effect at all on unconscious priming. In relation with mood-congruency effects in explicit memory this mood asymmetry in unconscious priming is explained by the mood-dependent mode of information processing.

Neuropsychology/ Psychiatry (PSP)

WS-3-2

Brain states before stimulus encoding predicts success of stimulus retrieval

Tullia Padovani[1], Thomas Koenig[2], Walter Perrig[1]

[1]Department of Psychology, University of Berne, 3010 Berne, Switzerland, [2]Dept. of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, 3000 Bern 60, Switzerland

Memory formation is thought to mainly rely on brain activity following an event.
In the present experiment we challenge this assumption by analyzing the electrical activity elicited by a cue presented before a target word in two different conditions: the first in which the cue induced an emotional-semantic judgment on the following target and the second in which the cue induced a pure semantic judgment.
By using the subsequent memory paradigm, our preliminary results suggest that the neural activity preceding the word presentation predicts whether the word will later be recollected. Moreover, we have found significant differences between the two conditions both in the frequency and time domain, respectively in the memory related Theta frequency band and in the ERPs before the stimulus onset. These potentials differences indicate that in the emotional condition it is possible to predict earlier if the items will be remembered or forgotten.
These effects may reflect preparatory processes important for efficient encoding into episodic memory and the anticipation in the affective condition could be explained with the notion that emotional stimuli have a privileged access to processing resources, hence also to memory formation.

Neuropsychology/ Psychiatry (PSP)

WS-3-3

Unconscious episodic learning

Katharina Henke[1]

[1]*Department of Psychology, University of Berne, 3010 Berne, Switzerland*

The hippocampus is crucial for conscious, explicit memory but it is uncertain whether it is also involved in nonconscious, implicit memory. We investigated with functional magnetic resonance imaging whether implicit learning engages the hippocampus and interacts with subsequent explicit learning. The presentation of subliminal face – written profession pairs for implicit learning was followed by the explicit learning of supraliminal pairs composed of the same faces combined with written professions conceptually incongruous to those presented subliminally (experiment 1), conceptually congruous professions (experiment 2) or identical professions (experiment 3). We found that implicit face-profession learning interacted with explicit face-profession learning in all experiments impairing the explicit retrieval of the associations. Hippocampal activity increased during the subliminal presentation of face-profession pairs versus face-nonword pairs and correlated with the later impairment of explicit retrieval. These findings suggest that implicit conceptual associative learning engages the hippocampus and influences explicit memory.

Neuropsychology/ Psychiatry (PSP)

WS-3-4

Perceptual and conceptual components in incidental sequence learning

Beat Meier[1] & Josephine Cock[1]

[1] *Institute of Psychology, University of Berne, 3010 Berne, Switzerland*

Many of the tasks performed in everyday life are organized in sequences. Often people do not necessarily need to be aware of these sequential regularities to profit from them. In order to investigate the processes underlying this kind of incidental learning we developed a new paradigm that allowed the separate assessment of motor, perceptual and conceptual components. Tasks and/or to-be-pressed responses were presented in a randomised or sequenced order. In Experiment 1 we used a sequence of tasks that required a perceptual decision (i.e., color-, size- and shape-tasks) and we independently manipulated whether the order of tasks and whether the to-be-pressed order of responses was sequenced. In Experiment 2 we used a sequence of conceptual tasks which involved category decisions about words (i.e., object-, animal-, and plant-tasks) and again, we independently manipulated whether the order of tasks and whether the to-be-pressed order of responses was sequenced. The results showed consistent learning effects, but only in the conditions where both, tasks and to-be-pressed responses were conjointly sequenced. The size of the effect was comparable for perceptual and conceptual tasks indicating that learning is based on conceptuo-motor rather than perceptuo-motor processes.

Neuropsychology/ Psychiatry (PSP)

List of authors

Hartmann	Matthias	PSN-3
Häusler	Rudolf	PSR-1
Heiniger	Eva	PSB-2
Heinrichs	Markus	PSP-2
Henke	Katharina	PSP-3, PSP-6, WS-3-3
Herrmann	Uli S.	NP-6
Hess	Christian W.	PSN-1, PSN-3, NP-1, PSP-3, PSP-10, PSP-5, NP-6
Hilti	Caroline	PSP-8
Hilti	Leonie M	PSP-8
Horn	Helge	PSP-13
Huber	Odilo W.	PSP-1
Huber	Oswald	PSP-1
Hubl	Daniela	PSP-14, PSP-4
Imboden	Hans	PSB-2
Isenegger	Jörg	PSN-5
Jaeggi	Susanne M.	PSP-11
Jann	Kay	NP-7
Jundt	Laura	PSP-16
Jürg	Streit	NP-3
Kaelin-Lang	Alain	PSP-19, PSM-3, PSM-4, PSN-4
Kaersermann	Marie-Louise	PSP-7
Kälin-Lang	Alain	PSP-18
Kiefer	Claus	PSM-2, PSM-3, PSM-4
Koenig	Thomas	PSP-13, PSP-14, PSP-4, NP-7, PSB-4, WS-3-2
Kompis	Martin	PSR-1
Kreis	Roland	NP-4
Larkum	Matthew E.	NP-2, NP-8
Leib	Stephen L.	PSN-6, WS-1-2, WS-1-4, WS-1-5, WS-1-6
Lönnfors-Weitzel	Tarja	PSM-3, PSM-4
Loosli	Sandra V.	PSP-11
Lüscher	Hans-Rudolf	NP-2
Lüthi	Mathias	NP-1, PSP-10, PSN-2, PSP-3, PSP-5, PSP-21
Lyck	Ruth	PSB-5, WS-1-3
Marinho	Luiz Alberto	PSN-6
Mathis	Johannes	NP-6, NP-9
Matter	Sibylle	PSP-15, PSP-9
Mattle	Heinrich P	PSN-5
Meier	Beat	PSP-13, PSP-15, PSP-16, PSP-17, PSP-18, PSP-20, PSP-9, WS-3-4
Meyer	Morten	PSB-1
Moser	Dominik	PSP-6
Mühlemann	Oliver	PSB-2
Müller	Thomas J.	NP-5
Murayama	Masanori	NP-2
Müri	René M.	PSP-1, PSP-10, PSP-15, PSP-16, PSN-2, PSP-3, PSP-5, PSP-21, NP-1, PSN-1, PSN-3
Nedeltchev	Krassen	PSM-2, PSN-5
Nirkko	Arto	PSM-1, NP-9
Nuoffer	Jean-Marc	NP-4
Nyffeler	Thomas	PSN-1, NP-1, PSP-10, PSN-2, PSP-3, PSN-3, PSP-5, PSP-21, WS-2-4
Orosz	Ariane	PSP-19
Ozdoba	Christoph	PSM-3, PSM-4, NP-9

Padovani	Tullia	WS-3-2
Patil	Jaspal	PSB-2
Pérez-Garci	Enrique	NP-2
Perrig	Walter	PSP-1, PSP-11, WS-3-1, WS-3-2
Pfiffner	Flurin	PSR-1
Pflugshaupt	Tobias	PSN-1, NP-1, PSP-10, PSN-2, PSN-3, PSP-5, PSP-21, WS-2-5
Potez	Sarah	NP-8
Raemy	David	PSB-7
Raub	Ulrich	PSP-7
Reiter	Elke	PSB-7
Remonda	Luca	PSM-2, PSN-5
Rollini	Pierre	WS-1-8
Roth	Corinne	NP-6
Rothen	Nicolas	PSP-20
Schaffner	Thomas	PSB-2
Schoeberlein	Andreina	WS-1-8
Schroth	Gerhard	PSM-2, PSM-3, PSN-5
Seifritz	Erich	PSP-8
Sellner	Johann	WS-1-1
Simon	Andor E.	PSP-12
Slotboom	Johannes	PSM-1
Sollberger	Bernhard	PSR-2
Soravia	Leila Maria	PSP-2
Stein	Maria	PSP-13, PSB-4
Steiner	Oliver	PSB-5, WS-1-3
Stephan	Marianne A.	PSN-4, PSP-18, PSP-19
Stibal	Alexander	PSM-3, PSM-4
Stieger	Christof	PSR-1
Strik	Werner	PSP-13, PSP-14, PSP-4, NP-7, PSB-4
Surbek	Daniel V.	WS-1-8
Sury	Matthias D.	WS-1-5
Toller	Gianina	PSP-6
Umbricht	Daniel	PSP-12
van Ormondt	Dirk	PSM-1
van Swam	Claudia	PSP-14
Vincent	Magloire	NP-3
von Arx	Sebastian	PSB-6
von Wartburg	Roman	PSN-1, NP-1, PSP-10, PSN-2, PSP-3, PSN-3, PSP-5, PSP-21
Weber Zaugg	Sabine	PSN-4
Weiermann	Brigitte	PSP-18
Widmer	Hans Rudolf	PSB-1, PSB-3, WS-1-5, WS-1-7
Wiest	Roland	NP-5, PSB-4
Windecker	Stephan	PSN-5
Wirth	Miranka	PSP-13, PSB-4
Wittwer	Matthias	WS-1-2, WS-1-4, PSN-6
Wuermle	Othmar	PSP-7
Wurtz	Pascal	NP-1, PSN-2, PSN-3, PSP-3, PSP-5, PSP-10, PSP-21, WS-2-2
Zeller	Markus	PSP-4
ZGraggen	Werner	PSM-1
Zwygart	Karin	NP-4

List of participants

Dr.	Alfieri	Alex	Neurochirurgie	Inselspital	SWITZERLAND
Dr.	Altorfer	Andreas	Psychiatric Neurophysiology	University Hospital of Psychiatry	SWITZERLAND
Dr.	Arnold	Marcel	Neurology	Bern	SWITZERLAND
Dr.	Arsiero	Maura	Dep. of Physiology	Univ. of Bern	SWITZERLAND
Dr.	Baas	Ulrike	Abteilung für Neuropsychologische Rehabilitation	Inselspital	SWITZERLAND
Dr.	Baciu	Dan	Psychiatry	University Bern	SWITZERLAND
Mrs.	Baumann	Brigitta	Allgemeine Psychologie und Neuropsychologie/ Entwicklungspsychologie	Universität Bern	SWITZERLAND
Mrs.	Bergomi	Claudia	Abteilung für Psychotherapie	UPD	SWITZERLAND
Mrs.	Bivetti	Anna Tina	Abteilung für Neuropsychologische Rehabilitation	Inselspital	SWITZERLAND
Mrs.	Blaser	Cornelia	Institute of Infectious Diseases	University of Bern	SWITZERLAND
Mrs.	Blaser	Daniela	Abteilung für Allgemeine Psychologie und Neuropsychologie	Universität Bern	SWITZERLAND
Mrs.	Bodmer	Linda	Psychology	Universität Bern	SWITZERLAND
Mrs.	Broicher	Sarah Dinah	Neuropsychology	University of Bern	SWITZERLAND
Dr.	Cattapan-Ludewig	Katja	University Hospital of Psychiatry	University of Bern	SWITZERLAND
Mr.	Cazzoli	Dario	Perception and Eye Movement Laboratory - Dpts. of Neurology and Clinical Research - Inselspital Bern	University of Bern	SWITZERLAND
Mrs.	Chaves	Silvia	Department of neurology and clinical research	University of Bern	SWITZERLAND
Dr.	Christen	Stephan	Institute for Infectious Diseases	University of Berne	SWITZERLAND
Dr.	Claussen	Thomas	Psychiatry	Bern	SWITZERLAND
Mr.	Colella	Patrizio	Experimental Psychology and Neuropsychology	University of Bern	SWITZERLAND
Mr.	Coutinho	Leonam	Cell Biology and Genetics	Universidada Federal Do Rio Grande Do Norte	BRAZIL
Dr.	Czarnecki	Antonny	Physiology	Bern	SWITZERLAND
Dr.	Déruaz	Anouk	Perception and Eye Movement laboratory, Dpts Neurology and Clinical research	Inselspital	SWITZERLAND
Prof.	Dierks	Thomas	Universtity Hospital of Psychiatry, Bern	University of Bern	SWITZERLAND
Dr.	Ducray	Angélique	Neurosurgery	Bern/ Inselspital	SWITZERLAND
Mrs.	Eggen	Céline	Psychology	University of Bern	SWITZERLAND
Mr.	Fanger	Severin	Neuropsychology	Bern	SWITZERLAND
Mrs.	Fankhauser	Sonja	Psychology APN	Bern	SWITZERLAND
Dr.	Federspiel	Andrea	Psychiatric Neurophysiology	Univeristy Hospital of Psychiatry	SWITZERLAND
Mrs.	Feuz	Stefanie	Department of Psychotherapy	University Hospital of Psychiatry	SWITZERLAND
Mrs.	Fisler	Melanie		University Berne	SWITZERLAND
Mrs.	Frischknecht	Eveline	Abteilung für klinische Psychologie und Psychotherapie	Universität Bern	SWITZERLAND
Mrs.	Giezendanner	Stéphanie	Neuropsychologie	Universität Bern	SWITZERLAND
Dr.	Grandgirard	Denis	Institute for Infectious Diseases	University of Bern	SWITZERLAND
Mr.	Grieder	Matthias	Depts of Clinical Research and Neurology	Inselspital	SWITZERLAND
Dr.	Gutbrod	Klemens	Neurology	Bern	SWITZERLAND

Mr.	Hartmann	Matthias		University of Bern	SWITZERLAND
Dr.	Heinks-Maldonado	Theda	Neuropsychology Hospital Insel in Bern	UCSF	SWITZERLAND
Prof.	Henke	Katharina	Dept. of Psychology	University of Bern	SWITZERLAND
Mr.	Herrmann	Uli Simon	Sleep Labaratory, Dpt. Neurology, Inselspital University Hospital Bern	University of Bern	SWITZERLAND
Prof.	Herschkowitz	Norbert	-	Bern	SWITZERLAND
Prof.	Hess	Christian W.	Neurology	University Hospital Berne	SWITZERLAND
Mrs.	Hilti	Caroline	Psychiatric Neuorphysiology	Universität Bern	SWITZERLAND
Mrs.	Hofer	Sandra	Institut für Infektionskrankheiten	Universität Bern	SWITZERLAND
Dr.	Hofer	Helene	Abteilung für Neuropsychologische Rehabilitation	Inselspital Bern	SWITZERLAND
Dr.	Horn	Helge	Universtity Hospital of Psychiatry, Bern	University of Bern	SWITZERLAND
Mrs.	Howald	Sandra	Institute of Psychology	University of Bern	SWITZERLAND
Dr.	Hubl	Daniela		University Hospital of Psychiatry	SWITZERLAND
Mrs.	Ihle	Sabine	Neuropsychologie	Uni Bern	SWITZERLAND
Prof.	Imboden	Hans	Institute of Cell Biology	University of Bern	SWITZERLAND
Mr.	Jann	Kay	Department of Psychiatric Neurophysiology	University of Bern / University Hospital of Psychiatry	SWITZERLAND
Mrs.	Jundt	Laura	-	University of Bern	SWITZERLAND
Dr.	Katharina	Eitel	Psychiatrische Poliklinik, UPD	Bern	SWITZERLAND
Mr.	Kiefer	Claus	Neuroradiology	University Hospital Berne	SWITZERLAND
Dr.	Kleinlogel	Horst	Department of Psychiatric Neurophysiology	University Hospital of Psychiatry, University of Bern	SWITZERLAND
Prof.	Kreis	Roland	Dept. of Clinical Research	University Bern	SWITZERLAND
Prof.	Larkum	Matthew	Physiology	University of Bern	SWITZERLAND
Prof.	Leib	Stephen	Institute for Infectious Diseases	University of Bern	SWITZERLAND
Mrs.	Loosli	Sandra	Division of Experimental Psychology and Neuropsychology	University of Bern	SWITZERLAND
Prof.	Lüscher	Hans	Physiology	University of Bern	SWITZERLAND
Mr.	Lüthi	Mathias	Dept. of Clinical Research and Neurology	University of Berne	SWITZERLAND
Dr.	Lyck	Ruth	Theodor Kocher Institut	Universität Bern	SWITZERLAND
Dr.	Markopoulos	Foivos	Institute of Anatomy	University of Bern	SWITZERLAND
Mrs.	Matter	Sibylle	Allgemeine Psychologie und Neuropsychologie	Universität Bern	SWITZERLAND
Dr.	Meier	Beat	Psychology	Bern	SWITZERLAND
Mrs.	Meier	Nadja	Psychology	University of Berne	SWITZERLAND
Mr.	Moser	Dominik	Psychology	Bern	SWITZERLAND
Dr.	Murayama	Masanori	Department of Physiology	University of Bern	SWITZERLAND
Dr.	Müller	Thomas	Universtity Hospital of Psychiatry, Bern	University of Bern	SWITZERLAND
Prof.	Müri	René M	Depts. of Clinical Research and Neurology	Inselspital	SWITZERLAND
Dr.	Neubauer	Florian	Institut für Physiologie	University of Bern	SWITZERLAND
Dr.	Nirkko	Arto C.	Neurology	University of Bern	SWITZERLAND
Dr.	Nyffeler	Thomas	Neurology	Perception and Eye Movement Laboratory, Bern	SWITZERLAND
Mr.	Oelhafen	Stephan	Institut für Psychologie	Bern	SWITZERLAND
Mrs.	Oggier	Sereina	psychology	Bern	SWITZERLAND
Mrs.	Orosz	Ariane	APN	Universtity Hospital of Psychiatry, Bern	SWITZERLAND
Mrs.	Padovani	Tullia	Neuropsycology	University of Bern	SWITZERLAND
Mr.	Patil	Jaspal	Insitute For Cell Biology	University of Bern	SWITZERLAND
Prof.	Perrigh	Walter	Experimental Psychology and Neuropsychology	University of Bern	SWITZERLAND
Mr.	Pfiffner	Flurin	Department of ENT, Head and Neck Surgery	Inselspital, University of Berne	SWITZERLAND
Dr.	Pflugshaupt	Tobias	Neurology & Clinical Research	Perception & Eye Movement Laboratory	SWITZERLAND
Mrs.	Potez	Sarah	Institut für Physiologie	Universität Bern	SWITZERLAND

Mrs.	Razavi	Nadja	Departement of Psychiatric Neurophysiology	University Hospital of Psychiatry	SWITZERLAND
Dr.	Reinert	Michael	Neurosurgery	Inselspital Bern	SWITZERLAND
Mrs.	Reiter	Elke	Institute of Infectious Diseases	Universitiy of Berne	SWITZERLAND
Mr.	Rothen	Nicolas	Institut für Psychologie	Bern	SWITZERLAND
Mrs.	Schindler	Brigitte	Experimental Psychology and Neuropsychology	University of Berne	SWITZERLAND
Dr.	Schoeberlein	Andreina	Departement für Klinische Forschung	Universität Bern	SWITZERLAND
Dr.	Sellner	Johann	Neurology	Inselspital Bern	SWITZERLAND
Prof.	Senn	Walter	Department of Physiology	University of Bern	SWITZERLAND
Dr.	Simon	Andor	Early Psychosis Outpatient Service	Department of Psychiatry, Bruderholz	SWITZERLAND
Dr.	Slotboom	Johannes	DRNN-DIN		SWITZERLAND
Mr.	Sollberger	Bernhard	General Psychology and Neuropsychology	University of Bern	SWITZERLAND
Dr.	Soravia	Leila Maria	Department of Psychiatric Neurophysiology	University Hospital of Psychiatry Bern	SWITZERLAND
Dr.	Stein	Maria	Department of Psychiatric Neurophysiology	University Hospital of Psychiatry	SWITZERLAND
Mrs.	Stephan	Marianne	Neurology	Inselspital Bern	SWITZERLAND
Dr.	Stieger	Christof	ENT Head and Neck Surgery	University of Berne	SWITZERLAND
Prof.	Streit	Juerg	Department of Physiology	University of Bern	SWITZERLAND
Prof.	Strik	Werner	Universtity Hospital of Psychiatry, Bern	University of Bern	SWITZERLAND
Mr.	Sury	Matthias	Institute for Infectious Diseases	University of Bern	SWITZERLAND
Mrs.	Thomke	Christa	Abteilung für Psychiatrische Neurophysiologie	Universitäre Psychiatrische Dienste, Bern	SWITZERLAND
Mr.	Thüring	Martin	Physiologisches Institut Bern	Bern	SWITZERLAND
Mr.	Thurley	Kay	Department of Physiology	University of Bern	SWITZERLAND
Mrs.	van Swam	Claudia	Psychiatric Neurophysiology	University Hospital of Psychiatry	SWITZERLAND
Mr.	Vincent	Magloire	Physiology	Bern	SWITZERLAND
Dr.	Vladimirskiy	Boris	Physiology	University of Bern	SWITZERLAND
Mr.	von Arx	Sebastian	Institute of Infectious Diseases	University of Bern	SWITZERLAND
Dr.	von Wartburg	Roman	DKF / Uni Psychologie	Universität Bern	SWITZERLAND
Dr.	Walther	Sebastian	University Hospital of Psychiatry	University of Bern	SWITZERLAND
Mrs.	Wang	Ying	Department of Physiology	University of Bern	SWITZERLAND
Mr.	Wassmer	Claudio	WTWG	University of Bern	SWITZERLAND
Mrs.	Weber	Anna	Psychology	University of Bern	SWITZERLAND
Dr.	Widmer	Hans Rodolf	Neurosurgery	Bern/ Inselspital	SWITZERLAND
Mr.	Wingeier	Kevin Samuel	Neuropsychology Hospital Insel in Bern	University of Bern	SWITZERLAND
Dr.	Wirth	Miranka	Department Psychiatric Neurophysiology	University Hospital of Psychiatry	SWITZERLAND
Mrs.	Witschi	Rahel	Neuropsychology Hospital Insel in Bern	University of Bern	SWITZERLAND
Dr.	Wittwer	Matthias	Institut für Infektionskrankheiten	Universität Bern	SWITZERLAND
Mr.	Wurtz	Pascal	Depts of Clinical Research and Neurology	Inselspital	SWITZERLAND
Mrs.	Zingg	Christina	Psychology	Private Hospital Meiringen	SWITZERLAND