Program and Abstracts for the
Second Meeting of

Clinical Neuroscience Bern

6th December 2006
14.00 – 17.30

University Hospital
of Psychiatry
Bern

Dear participants

We are glad to welcome you to the 2nd Meeting of the Clinical Neuroscience Network in Bern. More than 80 scientific presentations have been registered and about 120 researchers from all different neuroscience-related disciplines will attend the meeting. Due to this large attendance and limited time, only a selected few oral presentations are possible. We hope that the postersessions will demonstrate the large spectrum of research of clinical neuroscience within the network and provide the opportunity for a fruitful discussion, to make new contacts and to intensify joint research. We wish to further establish this tradition on this second meeting and we are convinced that we will experience a lively exchange of experience and knowledge, which will further strengthen the inter-faculty Clinical Neuroscience Network within the University of Bern.

Prof. Dr. C.W. Hess
Speaker
Clinical Neuroscience Bern

Organization:

L. Badertscher (University Hospital of Psychiatry Bern)
T. Dierks (University Hospital of Psychiatry Bern)
P. Wurtz (Neurology, University Hospital Bern)

Program

13:30 -14:00 Poster attaching
14:00 -14:15 Introduction: Main lecture hall, UPD Waldau, Bern
     Prof. Dr. W. Strik
     Director, University Hospital of Psychiatry, Bern
     Prof. Dr. C.W. Hess
     Speaker, Clinical Neuroscience Bern
     P. Wurtz
     Web-Coordinator, Clinical Neuroscience Bern
14:15 -15:00 Short oral presentations
15:00 -15:30 Coffee Break
15:30 -17:30 Guided Postersessions
17:30 -18:30 Apéro

14:15-15:00 Oral Session:
Location: Main lecture hall, UPD Waldau, Bern
Chair: H-P Lüscher

PSB-12 (p. 11)
Dopamine differentially affects the input-output relationship of layer 5 pyramidal neurons in the prefrontal cortex
Kay Thurley[1], Walter Senn[1], Hans-Rudolf Lüscher[1]

PSNP-18 (p. 29)
Formation of cortical object representation via Hebbian and homeostatic plasticity
Yihwa Kim1, Boris Vladimirski1, Stefano Fusi2, Walter Senn1

PSP-9 (p. 39)
Better Memory and Neural Efficiency in Young Apolipoprotein E ε4 Carriers
Christian R.A. Mondadori[1], Dominique J.-F. de Quervain[1], Andreas Buchmann[1], Henrietta Mustovic[1], M. Axel Wollmer[1], Conny F. Schmidt[3], Peter Boesiger[3], Christoph Hock[1], Roger M. Nitsch[1], Andreas Papassotiropoulos[1], **Katharina Henke[2]**

PSNP-23 (p. 32)
Functional brain connectivity in combined EEG and fMRI
Thomas Koenig[2], Kay Jann[2], Chris Boesch[1], Werner Strik[2]

PSNP-10 (p. 25)
Correlated streams of information are necessary for incidental learning: Evidence from task sequence learning
Beat Meier[1], Josephine Cock[1]

PSNP-8 (p. 23)
Neglect-like exploration behaviour after theta burst TMS
Dario Cazzoli[1], Thomas Nyffeler[1], Tobias Pflugshaupt[1], Pascal Wurtz[1], Roman von Wartburg[1], Silvia Chaves[1], Mathias Lüthi[1], Christian W. Hess[1], René Müri[1]

PSP-6 (p. 36)
Activation in Heschl gyrus during inner speech in schizophrenia – an ongoing EEG study
Claudia Ehrlich[1], Daniela Hubl[1], Thomas Koenig[1], Werner Strik[1], Thomas Dierks[1]

PSP-2 (p. 34)
To look or not to look at threat? Scanpath differences within a group of spider phobics
Tobias Pflugshaupt[1], Urs P. Mosimann[1], Wolfgang Schmitt[2], Roman von Wartburg[1], Pascal Wurtz[1], Mathias Lüthi[1], Thomas Nyffeler[1], Christian W. Hess[1], René Müri[1]

Posters by discipline

Postersession 1
Location: Alte Klinik: Alter Hörsaal
Chair: R. Wiest

Postersession 2
Location: Aufnahmeklinik, Turnhalle
Chair: W. Perrig

Postersession 3
Location: Aufnahmeklinik, Turnhalle
Chair: T. Dierks

Postersession 4
Location: Aufnahmeklinik, Stockwerk J, Konferenzraum
Chair: R. Müri

Postersession 1
Location: Alte Klinik, Alter Hörsaal
Chair: R. Wiest

Neurobiology (PSB)

PSB-1

Angiotensinergic innervation of blood vessels: a new concept for the sympathetic nervous system

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

[1]*Dept.of Biology, Institute of Cell Biology, University of Bern, 3012 Bern, Switzerland*

The control of the blood pressure is regulated through two important contributors – the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS). The RAS plays an important role e.g. in controlling cardiovascular functions and maintenance of body fluid homeostasis. Also numerous studies demonstrated that the circulating octapeptide angiotensin II (Ang II) itself interacts with the SNS at different sites and can directly stimulate the sympathetic activity. It can act in the brain to increase sympathetic outflow, directly on the sympathetic ganglia or to the adrenal gland medulla to increase catecholamine release. It is very important that circulating Ang II can directly influence at synaptic nerve endings, e.g. with blood vessels, facilitate sympathetic neurotransmission through an enhanced norepinephrine release.

The aim of the present study is to show that Ang II interacts not only as a hormone with the SNS, but in addition, it is synthesized inside the SNS and is acting as an endogenous neurotransmitter locally with distinct blood vessels.

Over the last twenty years we have studied different transmitter systems, especially the RAS and related systems in human-, rat- and mouse central nervous system (CNS) and in peripheral organs in normal, healthy specimens. Our studies of the fundamental background and using tools such as cDNA's and self generated monoclonal antibodies to components of the RAS have enabled us to examine normal and pathological tissues. The analysis started with homogenates of interested tissues by RT-PCR and SDS/Western, and then followed by a combination of in situ hybridization and immunocytochemistry both at cellular resolution.
These investigations, combining the four different methods, within the same tissue and at a single cell resolution, help to localize accurate components of the RAS in the SNS.

To show the innervation of the SNS with blood vessels, a monoclonal antibody to Dopamine-ß-Hydroxylase (indirectly for norepinephrine) was used. As expected, a very intense innervation for the SNS was found, but furthermore, a particularly strong angiotensinergic innervation could also be detected in the same blood vessel. In longitudinal sections with rat blood vessels, a very strong and clear angiotensinergic, segmental innervation over the blood vessel with a distance of about 15 to 20 µm can be established. By using confocal LSM we were able to show discrete Ang II-staining in fibres and moreover, fibres building "synapse en passant" with these blood vessels.
We still have to investigate, whether in these blood vessels the adrenergic and angiotensinergic systems are co-localized or not and also if the segmental distance of the innervation corresponds to the size of the vascular smooth vessel cells. Additionally we have to study the existence of different components of the RAS with blood vessels and within the corresponding sympathetic ganglia.
Further studies will be done with different tissues from rats and humans (normotensive and hypertensive specimens).

The intense angiotensinergic innervation of distinct blood vessels confirms that the RAS plays a very important system e.g. in regulating blood circulation directly with blood vessels. The expected value of the new elaborated results will possibly help to understand in more detail the involvement of components of the RAS and interacting systems in normal and pathological physiology.

PSB-2

Measuring neuronal activity on the network level *in vitro*

Florian Neubauer[1], Thomas Berger[1]

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The significance of monitoring neuronal and glial activity on a large scale *in vivo* (EEG, fMRI) is often limited due to lack of information about the exact location and extent of underlying electrical processes at the level of networks. *In vivo* there are several limitations for additional simultaneous measurements which could fill this gap.

We show that fundamental properties of electrical activity on the network level can be studied in an *in vitro* preparation. Acute thalamo-cortical mouse brain slices provide good accessibility to all cortical layers and subcortical structures and can be subjected to specific electrical or pharmacological stimulation. Maintained in a potassium-rich solution (4.5 mM K+, 0.5 mM Mg++, 1.5 mM Ca++), the slices are capable of exhibiting much more distributed and stable activity – named "upstate" – than previously thought. To detect upstate activity we use large-area (4x4 mm) calcium-sensitive dye epifluorescence imaging in combination with whole-cell patch clamp recordings.

Upstates in cortical columns arise spontaneously at 0.1 to 0.3 Hz per 1.5 square millimeters with a duration of 0.5 to 3 seconds per event and propagate up to several millimeters. In addition, upstates can be evoked electrically in the thalamus. With pharmacological tools we identify synaptic and intrinsic conductances related to the rise and decay of upstates. 100 μM barium amplifies sub- and suprathreshold network activity by blocking GIRK and CIRC potassium channels whereas 20 μM baclofen silences the cortex via activation of upstream GABA-B receptors. 10 μM cyclothiazide as an enhancer of AMPA receptor-mediated depolarization increases activity whereas CNQX plus AP5 (10μM/50 μM), antagonists of glutamatergic transmission, abolish all activity.

Our results improve understanding of activity patterns at the network level and thereby the link between single-cell properties and cognitive function.

PSB-3

Displaced clusters of PSANCAM neurons in the olfactory cortex of Reeler and ApoEr2 / VLDLr double mutant mice

Alessandra L Scotti[1], Hans H Bock[2], Gudrun Herrmann[1]

[1]*Institute of Anatomy, University of Bern,* [2]*Medizinische Klinik II Zentrum für Neurowissenschaften Albertstrasse 23, D79104 Freiburg*

In the piriform cortex numerous PSANCAM-immunoreactive (-IR) interneurons are present within layer II. Their density is higher in the posterior piriform cortex as compared to the anterior region and seems to proportionally decrease with age. They appear morphologically heterogenous but are all non- GABAergic. They all do not express reelin while a subset is coexpressing the reelin receptor APOEr2 but not the VLDL receptor. PSANCAM-IR neurons with two radially oriented processes are regularly scattered between the external capsula and piriform cortex layer II. One and two weeks after ip BrdU administration few clusters of BrdU, NeuN and NCAM labeled cells were found scattered through layer II suggesting that these interneuron population is renewed/implemented during postnatal life. Thus these cells resemble those PSANCAM neurons shown to migrate from the subventricular zone to the temporal lobe in the primate and the rabbit. In the Reeler mouse layer II cells are displaced into the deep zone of the piriform cortex. Randomly oriented and loosely distributed PSANCAM-IR cells were located below the putative layer II of the Reeler piriform cortex. In addition strong PSANCAM-IR, densely packed cell clusters accumulated at the border to the external capsula. These cell clusters could also be detected at the very same location by antibodies recognizing, doublecortin and NCAM. Cells in the clusters were APOEr2r-IR but did not contain the VLDL receptor. Colocalization with GFAP was absent although GFAP positive structures appeared to ensheath the PSANCAM-IR cell clusters. Such dense clusters could not be detected along the capsula externa of control mice.
In VLDLr-/- ApoEr2 -/+ mutants the distribution of PSANCAM-IR interneurons was similar to the one of control mice, while VLDLr-/- ApoEr2 -/- double mutants showed the same accumulation of deeply located PSANCAM cells as Reeler mice. Thus Reelin signalling may influence not only the differentiation of this neuron population during embryonal development and its final position but also their periodic postnatal renewal.

PSB-4

Reelin and its APOEr2 receptor in the olfactory bulb of macrosmatic and microsmatic mammals

Gudrun Herrmann[1], Alessandra L Scotti[1]

[1]*Institute of Anatomy, University of Bern*

We compared the distribution of reelin and its APOEr2 receptor in the main olfactory bulb (OB) of mice, rat and macaque monkey. Mitral cells, OB the principal neurons, contain reelin and its receptor APOEr2 in rodents and primates. Neurons coexpressing reelin and APOEr2 receptor and resembling putative Blane cells were scattered at low density through the granular layer (grl) of all species studied. Mitral cells and putative Blanes interneurons of the grl may synthesize and release reelin and respond to it in an autocrine fashion since they are also displaying APOEr2 as a reelin receptor. The glomerular layer (gL) of rodents and macaque monkey contains a subpopulation of reelin positive periglomerular cells (PGc). They may be excitatory glomerular interneurons in all species studied. In fact the reelin labelling did not colocalize with markers of GABAergic neurons like glutamic acid decarboxylase and tyrosin hydroxylase, known to be coexpressed in a large subset of PGc. In rodents reelin containing cells represent a subpopulation of calbindin containing PGc. APOEr2 expressing PGc are also non GABAergic and their large majority appeared to colocalize with calbindin. However APOEr2 and reelin colocalization in PGc was poor suggesting the presence of two subgroups of calbindin expressing cells: one releasing reelin and the other receiving it. In contrast to rodents and according to the literature calbindin positive PGc are absent in the macaque monkey. Reelin positive and APOEr2 containing cells were thus calbindin negative nor they belonged to the subpopulation of calretinin expressing PGc. As observed in rodents, however, there was little overlap between the reelin synthetizing PGc and those fitted with the reelin receptor APOEr2 in the macaque. Thus reelin mediated extrasynaptic communication in OB seem conserved across microsmatic and macrosmatic mammals despite relevant differences in the outfit of OB neurons with neurotransmitters and Ca2+ binding proteins.

PSB-5

The Effect of Anesthetics on Dendritic Calcium Spike Firing in Layer 5 Pyramidal Neurons.

Sarah POTEZ[1], Matthew E. LARKUM[1]

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Dendritic calcium (Ca^{2+}) spikes are able to control the integrative process and the output of layer 5 (L5) pyramidal neurons. Understanding when they occur in the intact brain has so far been investigated using anesthetized animals. It is therefore important to determine the effect of the anesthetics themselves on the regenerative properties of the dendrites.

We addressed this issue by performing whole-cell patch clamp recordings both *in vitro* and *in vivo* in the somatosensory cortex of rats (P28-70). The effect of 3 common anesthetics (urethane, pentobarbital and ketamine/xylazine) on dendritic Ca^{2+} spikes was examined. Dendritic Ca^{2+} spikes were evoked by 3-4 somatic action potentials (APs) above the critical frequency (CF). The presence of the dendritic regenerative response was detected by the after-depolarizing potential (ADP) following the last AP at the soma. Using dual dendritic and somatic patch recordings *in vitro* we also measured the fidelity of back-propagating APs along the dendrite and the size of Ca^{2+} spikes in the dendritic initiation zone.

In vitro, we could reliably find the CF in nearly all cells. Both Urethane (20mM) and pentobarbital (200μM) shifted the CF to higher values, reduced the dendritic Ca^{2+} spike amplitude and the somatic ADP. On the other hand, ketamine/xylazine (400μM/50μM) reduced the CF, strongly increased the dendritic Ca^{2+} spike and the somatic ADP amplitude. Thus, urethane and pentobarbital had a generally inhibitory effect on the generation of dendritic Ca^{2+} spikes whereas ketamine/xylazine enhanced Ca^{2+} spike regenerativity. None of the anesthetics modified the propagation of APs along the dendrite.

In vivo the incidence of CFs was reduced. We found an indication of the CF in 43% of cells anesthetized with urethane, 38% with pentobarbital and 56% with ketamine/xylazine. We conclude that the generation of Ca^{2+} spikes is partially suppressed in the anesthetized preparation. Urethane and pentobarbital are likely to suppress them further whereas ketamine/xylazine anesthesia counteracts this effect and is therefore a more appropriate anesthetic to use when studying Ca^{2+} spikes *in vivo*.

PSB-6

In Experimental Pneumococcal Meningitis Vitamin B6 Attenuates Cellular Energy Depletion and Neuronal Apoptosis in the Hippocampal Dentate Gyrus

Matthias Wittwer[1], Caroline L. Bellac[1], Roney S. Coimbra[1], **Stephen Leib[1]**

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Objectives: In pneumococcal meningitis (PM) the cellular energy status may contribute to neuronal apoptosis in the hippocampal dentate gyrus. In experimental PM we evaluated the effect of Vitamin (Vit) B6 on i) cellular energy status in the hippocampus by assessment of NAD+ levels and ii) on apoptosis in the hippocampal dentate gyrus.
Methods: Eleven day old Wistar rats (n=39) were infected intracisternally with 10 microL of saline containing 1.00E+06 cfu/ml Streptococcus pneumoniae (SP; serogroup 3). Animals were randomized for treatment with Vit. B6 (600mg/kg s.c. 0 and 18 h after infection, n=20) or an equal volume (360 microL) of saline (n=17). Brains were analyzed for the extent of hippocampal apoptosis by histomorphometry at 36 h after infection. For assessment of cellular energy status NAD+ levels were measured at 0, 12, 18, 24 and 36 hours after infection in hippocampal tissue from animals with PM treated with Vit. B6 or with saline and in uninfected age matched littermates (n=3 for each experimental group and time).
Results: In experimental PM, Vit. B6 prevented the decrease of NAD+ in the hippocampus and significantly (p < 0.03) reduced hippocampal apoptosis from 0.44 (0 - 1.67) [median score (range)] in saline treated controls to 0.12 (0 - 0.79).
Conclusion: In experimental PM Vit. B6 prevents the decrease in cellular energy stores in the hippocampus during the acute disease phase of PM when hippocampal apoptosis develops. This improved energy status is associated with a significant attenuation of neuronal apoptosis in the hippocampal dentate gyrus at 36 h after infection. Thus, Vit.B6, a well tolerated and relatively cheap compound may represent a suitable candidate for adjunctive therapy of PM.

PSB-7

Fetal antigen-1/delta-like protein in the ventral mesencephalon: expression pattern during development and after a 6-OHDA lesion in the adult rat brain.

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Fetal antigen 1/delta-like (FA1) protein is a member of the epidermal growth factor superfamily. FA1 is of particular interest in relation to Parkinson's disease as it is found in the adult rat ventral mesencephalon (VM), and has been postulated as a potential alternative marker protein for immature dopaminergic neurons. Moreover, FA1 has been proposed to be a growth and/or differentiation factor expressed in immature cells during development. The present study investigated the expression pattern of FA1-immunoreactive (-ir) cells in the VM during postnatal (P) development (at P0, P7, P14 and P21) and in the adult brain.
We detected FA1-ir cells predominantly distributed in the substantia nigra pars compacta (SN) and the ventral tegmental area. Phenotypical characterization of FA1-ir cells in the VM showed that a great number also expressed tyrosine hydroxylase (TH). Analyses in the SN revealed a significant increase in the number of FA1-ir cells during development (P0 to P21), whereas the number of TH-ir cells did not change. In unilateral 6-hydroxydopamine lesioned animals the loss of TH-ir neurons in the SN along with the disappearance of striatal TH immunoreactivity correlated with the disappearance of FA1-ir cells in the SN and the loss of FA1-ir fibers in the striatum. Preliminary data showed higher numbers of FA1-ir cells in the denervated striatum as compared to the unlesioned side.
In sum, FA1 expression is developmentally regulated in the rat VM, which suggests a potential role during cell differentiation. In addition, FA1 expression was demonstrated to be a competent supplementary marker for dopaminergic neurons in adult SN.

PSB-8

Hippocampal apoptosis in pneumococcal meningitis: Contribution of decreased cellular NAD+ levels?

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Objectives: Apoptosis in the hippocampus (HC) is a characteristic feature of neuronal damage in pneumococcal meningitis (PM) and represents the histomorphological correlate for learning and memory deficits as a sequel of PM. Depletion of intracellular NAD+ and the resulting decrease in ATP is known to trigger cell death. Whether decreased NAD+ levels contribute to apoptosis in PM has not been demonstrated. NAD+ is either recycled from nicotinic acid or nicotinamide or is synthesized de novo through the kynurenine (KYN) pathway, which we have previously shown to be induced in PM. Here we measured NAD+ levels in the HC during acute PM and modulated the biosynthetic pathways of NAD+ to assess the role of NAD+ in the pathogenesis of hippocampal apoptosis in PM.
Methods: An established infant rat model of PM was used to determine hippocampal NAD+ levels at defined time points of acute PM. NAD+ was measured by fluorescence assay. Pharmacologic interventions were done with specific inhibitors of the KYN pathway (Ro-61-8048 for inhibition of kynurenine 3-hydroxylase, and oMBA for kynureninase) and nicotinamide. Apoptotic damage in the HC was evaluated by histomorphometry at 36 h after infection.
Results: Compared to uninfected littermates, PM led to a significant reduction in NAD+ levels at 24h after infection (100% in mock-infected controls (n = 6) vs 45 ± 18 % in infected animals (n = 10); p< 0.01). Simultaneous inhibition of the two major enzymes of the KYN pathway resulted in increased apoptotic damage in the HC of infected animals (apoptotic score of 1.5 ± 0.6 in infected double inhibited animals (n = 8) vs. score 0.5 ± 0.6 in infected vehicle treated animals (n = 31), p< 0.01). Inhibition of the KYN pathway had no effect on NAD+ levels in infected animals. Treatment with nicotinamide increased apoptotic damage, despite high NAD+ levels at 36h p.i. (195 ± 29% in infected treated animals (n = 6) vs. 100% in mock-infected controls (n =7), p < 0.01).
Conclusion: While pneumococcal meningitis causes a significant depletion in hippocampal NAD+, the exact consequence of this decrease is presently not clear. Pharmacologic inhibition of de novo synthesis of NAD+ increased hippocampal apoptosis without affecting NAD+ levels compared to untreated infected animals at 24h and 36h after infection. We conclude that the activation of the KYN pathway is insufficient to restore cellular NAD+ in the hippocampus during acute PM.

PSB-9

The olfactory system in vitro: a culture model to study synaptic degeneration, regeneration and plasticity

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The mammalian olfactory system constitutes a widely used model to study synaptic plasticity, neuronal proliferation and migration. We have recently developed an in vitro model to investigate phenomena of synaptic degeneration, regeneration and plasticity in the olfactory system, using slice cultures which preserve the olfactory bulb and the olfactory cortex connected to each other. The large preservation of the lateral olfactory tract projection was verified by fluorescent DiI tracing in living cultures where mitral cell axons could be anterogradely traced into the molecular layer of the piriform cortex. Since morphogenesis of the olfactory bulb is prolonged into postnatal life, a spectrum of different early postnatal ages (P1-P10) in mice was examined. One-week-old pups yielded a better preservation of the olfactory bulb organotypicity. Immunocytochemistry for marker proteins of olfactory bulb periglomerular neurons and granule cells revealed a better preservation of the olfactory bulb glomerular and granular layers during in vitro culturing of brains dissected at this age. Immunohistochemical labeling for markers of piriform cortex principal neurons, such as reelin and calbindin and of interneuron populations, such as calretinin, GAD and PSA-NCAM, evidenced that the neurochemical characteristics of the olfactory cortex were also preserved in our culture system. Preliminary experiments aiming to further develop this model of the central olfactory pathways to a co-culture system with olfactory epithelium explants have been conducted.

PSB-10

Induction of heme oxygenase-1 causes cortical non-heme iron increase in experimental pneumococcal meningitis: evidence that concomitant ferritin upregulation prevents iron-induced oxidative damage

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Desferrioxamine inhibits cortical necrosis in neonatal rats with experimental pneumococcal meningitis, suggesting that iron-induced oxidative damage might be responsible for neuronal damage. We therefore examined the spatial and temporal profile of changes in cortical iron and iron homeostatic proteins during pneumococcal meningitis. Infection was associated with a steady and global increase of non-heme iron in the cortex, particularly in neuronal cell bodies of layer II and V, and in capillary endothelial cells. The non-heme iron increase was associated with induction of heme oxygenase-1 (HO-1) in neurons, microglia and capillary endothelial cells, while HO-2 levels remained unchanged, suggesting that the non-heme iron increase might be the result of HO-1-mediated heme degradation. Indeed, treatment with the heme oxygenase inhibitor tin protoporphyrin (which completely blocked the accumulation of bilirubin detected in HO-1 positive cells) completely prevented the infection-associated non-heme iron increase. The same cells also exhibited a marked increase of ferritin, which occurred independently of heme oxygenase activity. At the same time, no increase in DNA/RNA oxidation was observed in infected animals (as assessed by in situ detection of 8-hydroxy[deoxy]guanosine), strongly suggesting that ferritin upregulation protected the brain from iron-induced oxidative damage. Thus, while pneumococcal meningitis leads to an increase in cortical non-hem iron, protective mechanisms upregulated in parallel prevent iron-induced oxidative damage. Cortical damage does therefore not appear to be a direct consequence of increased iron.

PSB-11

The Impact of Input Fluctuations on the Frequency-Current Relationships of Layer 5 Pyramidal Neurons in the Rat Medial Prefrontal Cortex

Maura Arsiero[1], Hans-Rudolf Lüscher[1], Brian N. Lundstrom[2], Michele Giugliano[1,3]

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In this study we demonstrate that layer 5 (L5) pyramidal (PY) neurons of the rat medial prefrontal cortex (mPFC) compute in a very different way compared to many other neurons present in other areas of the cortex.

Current vs. firing-rate (f-I) relationship is a classic approach at classifying neocortical neurons, as it quantifies the transformation of a DC input into an output spike train. Here, we consider its extension to the study of the neuronal response to fluctuating current stimuli. In fact, inputs that a cortical cell receives in vivo are more likely to be continuously fluctuating over short time scales.
Previous reports in the somatosensory cortex (SSC), showed that neurons progressively become insensitive to input fluctuations, for larger values of the input mean. This results in converging f-I curves obtained for different fluctuation amplitudes.
Similarly, simple biophysical models, e.g. Connor-Stevens, Traub-Miles, Hodgkin-Huxley (HH), show insensitivity to input fluctuations at high DC levels, suggesting that this is indeed a typical behavior of many cells.
In this work, we examined f-I curves of L5 PY neurons in slices of the rat mPFC. In contrast to the results in SSC, we found that these neurons compute in a fundamentally different way. Specifically, mPFC PY neurons retain an increased sensitivity to the variance of the input and loose their sensitivity to the mean, resulting in diverging f-I curves. Our work is complemented by a mathematical and computational investigation. We show that incorporating a slow inactivation component of Na+ conductance into single-compartment HH-like models causes f-I curves to become divergent as seen in the experiments.
Our data suggest that neurons from associative areas might be particularly well-suited to encode and propagate information specifically conveyed by the input fluctuations rather than by input mean. This might be reflected in single-neuron discharge properties, differentially modulated between sensory and associative areas, as found experimentally.
Finally, by the computational models we predict that the features of mPFC L5 PY neurons greatly enhance the stability of persistent discharge states, which are typically observed in vivo in associative areas only and thought to underlie working-memory tasks.

Dopamine differentially affects the input-output relationship of layer 5 pyramidal neurons in the prefrontal cortex

Kay Thurley[1], Walter Senn[1], Hans-Rudolf Lüscher[1]

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Prefrontal cortical activity plays a primary role in working memory; the mental ability to transiently store and manipulate information to guide forthcoming actions. Stored information can, for example, be the representation of a sensory stimulus or a memory item retrieved from long-term memory, or maybe a combination of both. Working memory is supposed to be represented by persistent neural activity in the prefrontal cortex (PFC), which outlasts the stimulus and enables a delayed response [Goldman-Rakic (1995) *Neuron* **14**]. Such persistent activity is hypothesized to be sustained by synaptic reverberation in an excitatory recurrent neural circuit [Wang (2001) *TINS* **24**], as it is composed of the pyramidal neurons in the PFC. In addition, in vivo animal experiments revealed that dopamine (DA) input to the PFC is critical for the regulation of working memory properties [see e.g. Seamans & Yang (2004) *Progress in Neurobiology* **74**].

To understand the actions of DA in the PFC at cellular level, we studied the influence of DA onto the activity of single layer 5 pyramidal neurons in the PFC in vitro. Using gaussian input currents to emulate realistic in vivo-like input, we determined the input-output response function (f-I curve) of the pyramidal neurons in absence and presence of DA. The approach revealed excitability increase as well as decrease by DA depending on the amount of input current: The response and gain of the cell increased for small input currents after DA application; for large input, however, the response frequency decreased.

Inspired by our experimental results, we performed computer simulations in order to understand how the effect of DA onto single neuron activity translates into the behavior of the recurrent network of PFC pyramidal neurons. The experimentally determined f-I curves were fitted with an integrate-and fire neuron model, which then was used to simulate a network of recurrently connected neurons. The simulations predict that under DA the emergence of persistent activity in the network is facilitated and becomes stabilized against distracting inputs compared to the DA free state.

Investigations of the Blood-Brain-Barrier in Phenylketonuria by 1H-MR Spectroscopy

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[1]*Dept. of Clinical Research, University of Berne, Switzerland,* [2]*Childrens Clinic, University Hospital Berne, Switzerland,* [3]*Dept. of Neuropediatrics, University Of Heidelberg, Germany*

Phenylketonuria (PKU) is an inherited disorder of phenylalanine (Phe) metabolism, where a deficiency in Phe hydroxylase leads to elevated blood Phe levels. Untreated PKU leads to severely disturbed brain development, which can be prevented by early institution of a Phe-restricted diet. The PKU diet is burdensome and includes daily amino acid supplementations. The recommendations for blood Phe level control are age-dependent and recommended blood Phe levels vary from one country to the next.

It has been shown that elevated Phe levels impair brain function also acutely in early-treated patients. Despite tremendous progress in the understanding of the molecular basis of PKU, the causes of brain damage in untreated patients as well as the mechanisms of impaired brain function with acutely elevated Phe levels are still unclear. Direct effects of Phe as well as imbalances of the large neutral amino acids (LNAA) in brain tissue are thought to be the major causes. Other contributing factors include impaired brain energy supply. As the Phe-restricted diet is not always rigorously adhered to and is often relaxed after adolescence, alternative treatment regimens have been tried. To over-come suspected cerebral dopamine and serotonin depletion, it was tried to treat PKU patients with the precursors tyrosine or tryptophan. To reduce Phe influx into brain, branched-chain amino acids have been supplemented. Both approaches did not gain acceptance. Our work [1] confirming an acutely blocked influx of Phe into brain upon supplementation with the whole set of the other LNAA has sparked interest anew.

1H-MR spectroscopy, a quantitative method to determine metabolite concentrations in humans, is the ideal versatile and non-invasive tool to study cerebral levels and dynamics of Phe in patients with PKU [1-7].

We illustrate, how 1H-MRS is and has been used in PKU to answer the following questions:

1. What are the brain Phe concentrations at different blood Phe levels.

2. Are the blood / brain concentration ratios for Phe similar in all PKU patients, or are they individually different such that 1H-MRS measurements of cerebral Phe are needed for individual dietary adjustment?

3. Can one measure Phe influx dynamics at the blood / brain barrier in PKU patients and healthy controls?

4. If so, can one confirm blockage of Phe influx by overload of the common amino acid carrier by oral LNAA load?

5. Is there a brain energy dysbalance in PKU patients?

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Nigrostriatal dopaminergic neurodegeneration after intracerebral hemorrhage

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Intracerebral hemorrhage (ICH) in the basal ganglia constitutes one of the most severe forms of cerebrovascular disease, with the majority of the survivors suffering from disabilitating neurological sequelae. Currently available therapy is mainly supportive, consisting in maintenance of homeostasis and treatment of brain edema. No direct treatment of the brain damage caused by ICH is currently available.

We have previously developed a model of basal ganglia hemorrhage in the rat which mimics the clinical situation in the human by combining a striatal microtrauma with slow infusion of 30 ml autologous blood. Due to the standardized reproduction of deep striatal ICH and preservation of the perihematomal area, this model is particularly well adapted to study restorative strategies after the insult and to investigate the effects on other brain regions. Rats with ICH exhibit transient spontaneous rotational asymmetry with a tendency to turn ipsilateral to the lesion side. Hence, in the present study, we investigated the effects of the deep basal ganglia hemorrhage on the number of tyrosine hydroxylase (TH) expressing dopaminergic neurons and on the number of total neuronal cells in the substantia nigra.

Immunohistochemical analyses revealed that striatal ICH resulted in a significant decrease of 45% and 15% in the number of TH-immunoreactive cells in the substantia nigra ipsilateral to the lesion at day 2 and 30 post ICH, respectively. In contrast, loss in total number of neuronal cells was observed to be less pronounced with a decrease of only 25% at day 2 post ICH. 30 days after the ICH no significant differences were observed between TH-immunoreactive and total number of neuronal cells. This observation hints to the notion that the ICH induced a transient downregulation of TH expression in a subpopulation of substantia nigra neurons.

In conclusion, our results provide evidence that the dopaminergic nigrostriatal projection system is significantly affected by ICH in the striatum. Therefore we speculate that neuroprotective strategies for dopaminergic neurons and/or dopamine substitution might be an effective means to increase the functional outcome after striatal ICH.

MR-Methodology (PSM)

PSM-1

Time series analysis of fMRI data using vector autoregression (VAR)

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Owing to recent technological advances with high-Tesla MRI scanners, functional imaging of neural tissues with high resolution of the temporal as well as spatial domains comes within reach. Thus, an increasing demand for tools that allow the modeling and evaluation of temporal data, i.e. data that carry sequential information, will likely result. Time series models based on such data can be computed to study the dynamical connectivity of brain structures. We focused on the method of vector autoregression (VAR) by which the strength of sequential interactions among multiple variables can be assessed. Such variables may be the blood oxygenation levels of different regions in the brain acquired by fMRI. The method of time series analysis was applied in data sets from 20 subjects listening to auditory stimuli. These stimuli were of an emotional nature (a person sobbing; a person laughing) and control stimuli (backward-sobbing, backward-laughter, silence). Each data set consisted of 207 consecutive MR scans. Models composed of 6 variables (i.e., the following regions of interest: Amygdala left/right; Insula left/right; Auditory cortex left/right) were computed. VAR of these variables resulted in a statistically significant model of the sequential interactions among these variables in the sample. It was found that the auditory cortex was directly influenced by the independent variables (the auditory stimuli). Several further interactions were observed, prominently among these an inhibiting effect of the auditory cortex on the amygdalae. In addition to these functional results, the methodological merits and limits of the proposed method are discussed. It is concluded that it is both a feasible and appropriate method to study and test hypotheses about brain functioning on the basis of fMRI data.

PSM-2

Improvement of Fetal Cerebral MRI using Navigator Echo Imaging

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Purpose:
To evaluate the quality of navigator-echo triggered vs. untriggered intrauterine imaging techniques.
Methods:
20 women were examined during their 24-30 weeks of their pregnancy with fetal MRI. Pathological ultrasound findings, performed in all cases in advance, lead to MR indication. All patients received conventional T1 and T2 weighted spin echo and gradient echo sequences with and without navigator echoes. The quality of the images was rated with a visual rating scale from 1 (imaging quality: not diagnostic) to 5 (excellent quality), concerning the germinal matrix, grey and white matter, CSF, brain stem and cerebellum and a quantitative measure of the signal intensities.
Results:
All except two patients showed clear benefit from the navigator echo technique. In two patients, who were examined during early pregnancy (week 24), imaging quality was severly harbored by motion artifacts and CSF pulsations, both in conventional SE and navigator echo imaging. In two patients with malformations of cortical development, correct diagnosis was solely feasible by navigator echo imaging.
Conclusion:
Application of navigator echo imaging to fetal MRI is a safe and reliable technique, which helps to overcome the well known limitations of fetal MRI, i.e. CSF pulsation and motion artifacts.

PSM-3

Event related fMRI of primary- and higher cognitive cerebral function using Pulsed Arterial Spin Labeling Perfusion

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In the field of functional neuroimaging the use of blood oxygen level-dependent (BOLD) fMRI has been extremely successful. There is evidence of a coupling between neuronal activation, metabolism, and blood flow. However, the degree and the mechanism of coupling remain largely not understood. This could pose a limitation for the application of BOLD fMRI especially in the clinical field where factors influencing the coupling may be altered. Furthermore, the spatial functional resolution of BOLD fMRI might be limited, because vessels responsible for the increase of blood flow and blood volume feed or drain somewhat large territories. One possible way to overcome this shortcoming is the use of event-related cerebral blood flow (CBF) Perfusion fMRI experiments. Several studies demonstrated the feasibility of event-related Perfusion fMRI experiments using Arterial Spin Labeling (ASL). In these studies one single trial type was used in separate runs to reconstruct the hemodynamic response function (HRF). In the present pilot study we investigated four different trial types within the same run. The following hypothesis was formulated: i) it is possible to localize the activation evoked by each trial separately; ii) it is possible to reconstruct the HRF of all trial types within the same run. If these hypotheses holds, then event related CBF fMRI offers several advantages as compared to block design experiments; i.e. intermix of trials of different types and the option to categorise each trial type to the behaviour of the subjects. The later is of importance when comparing controls with patients group.

PSM-4

Normative data and diagnostic potential of muscle functional magnetic resonance spectroscopy (fMRS) during imposed exercise

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Objectives: Muscle metabolites are of special interest in the clinical diagnostics of muscle and nerve diseases. Functional magnetic resonance spectroscopy (fMRS) allows for a well-standardized, non-invasive monitoring of the energy turnover before, during and after electrically imposed muscle activity. The aim of this study was to derive normal values for the extent and kinetics of metabolite depletion and recovery, and to estimate their diagnostic clinical potential.

<u>Methods</u>:
28 healthy volunteers and 2 patients (myopathy and neuropathy) were assessed. The peroneal nerve was stimulated with a supramaximal (30-60 mA) electrical pulse train of 20 Hz during 2 min to achieve an isometric maximal tetanic muscle contraction. Proton (1H) magnetic resonance spectra (MRS) of the anterior tibial muscle were repetitively acquired with a 12 s temporal resolution before, during and after stimulation. Subject dyscomfort was assessed on a pain rating scale from 0 to 10. Serum creatin kinase (CK) and myoglobin levels were measured before stimulation and 1 hour after.
Results: All measurements were technically successful and yielded a robust pattern of a decrease of the phosphocreatine (CrP) associated peaks (Cr2 immediate, Cr3 with a small delay) during, and an incomplete recovery in the first minutes after stimulation, together with a decrease in acetyl carnitine (AcCt) during, and an increase with overshoot after the stimulation. The results from the patients deviated from the healthy volunteers. The electric stimulation was tolerated by all subjects, with an average pain rating of 5.6. There was a weak correlation between pain and stimulus current (r=0.4). A clinically irrelevant increase of serum myoglobin by 4.9 µg/l, starting from a baseline of 30 µg/l (normal upper limit < 110), was statistically significant (p < 0.002). Serum CK did not change.
Discussion: In healthy volunteers, the decrease and recovery of the CrP associated peaks correlate with the phosphorylation state of creatine. The small delay of the Cr3 response might be due to an intracellular compartment shift as one reason for the change in 1H MRS visibility. The AcCt response indicates an early involvement of fatty acid oxydation at these conditions of maximal workload, the overshoot probably being related to paying back the oxygen deficit. Differing results from patients indicate a clinical potential.
Conclusion: The application of the method is straightforward, allows for assessment of muscle metabolites during electrically imposed maximal exercise in a clinical setting, and reliable normal values as well as promising results on patients were obtained.

PSM-5

A modified Q-Ball algorithm with high reproducibilty and fast convergence

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Purpose
Q-Ball imaging was performed on a 3.0T Trio-TIM whole body scanner using a modified N=42 directional twice-refocused EPI sequence. The Q-Ball algorithm [1] was optimized with respect to performance and robustness to fiber crossings using very fast re-annealing [2] and a concept of variation of virtual fibers according to a filtered beta probability density function.

Subjects and Methods
The beta probability density function for a given value x and given pair of parameters a and b is $y = f(x¦a,b) = x^{a-1}(1-x)^{b-1}I_{(0,1)}(x) / B(a,b)$, where B(·) is the Beta function. The result, y, is the probability that a single observation from a beta distribution with parameters a and b will have value x. The indicator function I(0,1)(x) ensures that only values of x in the range (0 1) have nonzero probability. The uniform distribution on (0 1) is a degenerate case of the beta pdf where a = 1 and b = 1. R = betarnd(A,B,m,n) generates an m-by-n matrix containing random numbers from the beta distribution with parameters A and B. Each new path during the simulated annealing process is weigthed by a low-pass filtered disturbance $d = f(x¦4,4)*(0.5 - betarnd(4,4,N,1))$

Results
The connectivity for an VMI-STN fiber is determined using the modified q-ball algorithm (Vapnik stiffness parameters e = 0.01, k = 0.1). The anatomical fiber crossings (arrow) are very well reproduced. The calculation time for one fiber varies between 1-3min dependent on the length of the path. All experiments were performed on a Siemens 3.0T Trio-TIM whole body scanner. The parameters of the modified twice-refocused EPI sequence were as follows: N=42 directions, b=1300s/mm2, 55 slices (gap=0), NEX=2, TR=7600ms, TE=95ms, 12-Channel coil, 2.2mm-iso-voxel, Grappa (iPAT=2, Ref.lines=24, Auto(Triple) mode), BW=1346 Hz/Px, Pulse-Triggered (delay 200ms).

Conclusion
Including the concepts of "Very fast simulated re-annealing" and anatomically adapted fiber variation to the Q-Ball algorithm allows for a higher performance and reproducibility of connectivity and thus presents a further step towards clinical practicability.

PSM-6

T2*-mapping depending on different states of blood-pressure

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Purpose
The concept of blood-pressure dependent T2*-mapping is introduced to examine its usefulness for tumor classification and stroke related penumbra-core-differentiation.

Results
dT2*-Maps for an Astrocytoma WHO grade II reveal tumor-related signal abnormalities, which have a different extent from the changes seen on the T2-weighted images. The neoplasm is hypointense on T1-weighted images and reveals no significant post-contrast enhancement.

Subjects and Methods
A pulse triggered single-shot multi-echo EPI sequence [1] was performed on a 1.5T clinical scanner for two different trigger delays dt = 0,300ms after R-peak. The two fitted T2*-maps representing the different physiological states were subtracted afterwards (dT2*-Maps). The sequence parameters were as follows: 1.sequence: M=64, 12 slices, TR =1780ms, Acquisition window 2080ms, pulse trigger delay 300ms, delay in TR 0ms, TE = 15,46,77,108 ms, BW=1735 Hz/Px, N=9 averages. 2.sequence: M=64, 12 slices, TR =2080ms, Acquisition window 2080ms, pulse trigger delay 0, delay in TR 300ms, TE = 15,46,77,108 ms, BW=1735 Hz/Px, N=9 averages - total measurement time 46sec. In this way the effective TR in both sequences is the same, so there are no saturation or T2 effects to be expected in the difference maps, except liquor pulsation effects.

Conclusion
Blood-pressure dependent T2*-Mapping (dT2*) accentuates the subtle changes of intra-lesional blood oxygenation state in pathological brain regions whereas undesirable T2- and field inhomogeneity effects are eliminated. The dT2*-maps of healthy volunteers did not show any significant regional differences. This method thus gives insight into further functional aspects of the underlying pathophysiology. The short measurement time makes this modality also suitable for acute stroke.

PSM-7

The relevance of motion selective sequences and spatial ICA for the differentiation of vascular territories

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Purpose
The concept of spatial independent component analysis (sICA) in the context of flow weighted experiments is introduced. For this purpose a modified stimulated echo sequence [1] was performed at different mixing times TM = 10,..,100ms at 1.5T.

Subjects and Methods
The stimulated echo sequence [1] has been extended by two inherently refocused gradient shapes (fig. 1), modulated by a function $g(t) = cos(wmt)t2(1-n2p/wm)2$. The frequencies wm are determined by the reciprocal correlation times of spin motion components wm=1/tc, with tc ranging from 101 ms to 102 ms (perfusion, flow). Placed between the first and the second excitation rf-pulse and the third rf-pulse and the ADC, they act as a sort of bandpass filter. The integrated effect q(t) of g(t), the accumulated phase (1 Hz modulated pulsation) and their Fourier transforms are shown in figure 1. At short mixing times TM = 10,..,100 ms the stimulated echo signal is strongly weighted by relaxation effects according to $S \sim sin(a)sin(b)(sin(g)/2)exp(-2t1/T2)exp(-TM/T1)$. To compensate for these effects, the relaxation times have to be quantified which entails additional measurement time. As an alternative the relevant signal contributions also can be determined via spatial ICA. Considering flow, relaxation and static J-coupling effects to depend on statistically independent physical causes - the contribution to each coherence pathway can be written as a product of related factors - the spatial ICA is able to assign the related information to different channels. A fast ICA routine was applied to a matrix S(m,k)/S0 containing the q-space (m modulation frequencies wm) data for k voxel and a TM=50ms. S0 represents a measurement with g(t)=0.

Results
The ICA maps were sorted according to their kurtosis.

Conclusion
The sICA tends to be able to separate the vascular territories, if the „bandpass" gradient shapes are modulated in a suitable way as shown in the method part.

PSM-8

A new sequence analyzer

Claus Kiefer[1], Gerhard Schroth[1]

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Purpose
A new sequence analysis tool (Matlab) is presented that uses the sequence information (*.sqi) from the IDEA sequence simulator. The program enables an automatic determination of all magnetization pathways, the echo times, signal amplitude weighting and phase factors, including arbitrary gradient and rf pulse shapes, off-resonance effects, diffusion and flow effects.

Subjects and Methods
The generalized k-space concept [1] expresses the Fourier coefficients of the magnetization according to a suitable basis. As a completion to [1] the echo times are derived in a more consistent and automated way. The command tool is based on a data structure that contains the entire information on the signal amplitude and phase factors, the magnetization pathway - described by the indices of the basis (1,2,3), on which the echo occurs, and the echo times in milliseconds for every magnetization state m_i along all paths and knots k_i.

Results
A stimulated echo sequence with three rf-pulses (90°) and rf center times: t_0= 0.11, 47.09, 149.75ms was analysed. The theoretically determined echo times are in exact agreement with the echo times derived from the sequence tool (t_1 = 46.98ms, t_2=102.66ms): 1) $te = t_0 + 2t_1 = 94.07$ ms, 2) $te = t_0 + 2t_1 + t_2 = 196.73$ ms, 3) $te = t_0 + 2t_2 = 205.43$ ms, 4) $te = t_0 + t_1 + 2t_2 = 252.41$ ms, 5) $te = t_0 + 2t_1 + 2t_2 = 299.39$ ms (t_1: time interval between pulse 1 and 2, t_2: time interval between pulse 2 and 3).

Conclusion
The new Matlab software package is an outstanding extension to the IDEA sequence simulator. It provides all necessary information on the magnetization behavior with respect to the simulated sequence parameters.

Postersession 2
Location: Aufnahmegebäude, Turnhalle
Chair: W. Perrig

Neurophysiology / Neuropsychology (PSNP)

PSNP-1

Having a look at the Brentano Illusion: An Eye-movement study

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

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In the Brentano version of the Müller-Lyer Illusion one half of the line looks longer than the other. A prominent explanation of this phenomenon is related to the concept of "size constancy" in perception. This view however, has increasingly been challenged by efferent theories explaining such an illusion by the observers readiness to interact with environmental events (e.g scanning the environment with eye movements). Recently several studies have shown that different versions of the Müller-Lyer Illusion do affect Eye-Movements.
Patients suffering from visuo-spatial neglect following brain injuries show systematic spatial asymmetries in eye-movements as well as in bisection of simple lines. Surprisingly neglect patients are, as healthy controls, misled by the Müller-Lyer illusion. The aim of the present study is to clarify the discrepancy between line bisection and illusion effects in neglect patients. We approach this issue by investigating the relationship between eye movements and the Brentano version of the Müller-Lyer Illusion.

PSNP-2

Visual exploration strategies in angle discrimination

Silvia Chaves[1], Pascal Wurtz[1], Roman von Wartburg[1], Tobias Pflugshaupt[1], Daniela Hubl[2], Thomas Dierks[2], Thomas Nyffeler[1], Mathias Lüthi[1], René Müri[1]

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Many everyday activities such as driving, playing football or clock reading require the ability to distinguish between different angles. The aim of this study was to investigate the influence of task demand on visual exploration in an angle discrimination task. To this end, a presentation of different angles on clock-like displays was applied. The instruction was to decide for each stimulus whether or not the angle matched 60°. Task demand was varied by the use of five different angles, three different lengths of clock hands, and the presence or absence of 5-minutes-segmentation lines. Reaction time and decision accuracy from a group of healthy participants was used to determine task difficulty. In addition, eye movement parameters such as the duration and number of fixations were used to identify visual exploration strategies and their relation to task demand.

PSNP-3

The functional relationship between yawning and vigilance: an electrophysiological study

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BACKGROUND: Although yawning is a ubiquitous and phylogenetically old phenomenon, its purpose remains unclear. The study aimed at testing two widely held hypotheses suggesting that yawning communicates drowsiness (communication hypothesis) and reverts or delays the process of falling asleep (arousal hypothesis).
METHODS: Subjects complaining of excessive sleepiness were spontaneously yawning while trying to stay awake in a quiet and darkened room. Changes in their electroencephalogram (EEG) and heart rate variability (HRV) associated with yawning were compared to changes associated with isolated voluntary body movements. Special care was taken to remove eye blink- and movement-artefacts from the recorded signals.
RESULTS: Yawns were preceded and followed by a significantly greater delta-activity in EEG than movements (p£0.008). Alpha-rhythms were attenuated, decelerated, and shifted towards central brain regions after yawning (p£0.01), whereas they were attenuated and accelerated by movements (p<0.02). A significant transient increase of HRV occurred at the onset of yawning and movements, which was followed by a significant slow decrease peaking 17 s after onset (p<0.0001). No difference in HRV changes was found between yawns and movements.
CONCLUSIONS: Yawning occurred during periods with increased drowsiness and sleep pressure, but was not followed by a measurable increase of the arousal level of the brain. It was neither triggered nor followed by a specific autonomic activation. Our results therefore support the communication hypothesis of yawning, but do not provide evidence for the arousal hypothesis.

PSNP-4

The rise and decline of prospective memory performance across the lifespan

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In the present study, the trajectory of prospective memory across the lifespan was investigated in a total of 200 participants from five age groups (4- to 6-year-old children, 13- to 14-year-old adolescents, 19- to 26-year-old adults, 55- to 65-year-old adults and 65- to 75-year-old adults). In an event-based prospective memory task the prospective and the retrospective components were assessed separately. For the prospective component, the results showed better performance for adolescents and young adults than for children and 65- to 75-year-old adults. In addition, participants belonging to the latter group were more likely to forget the retrospective component after having noticed the prospective memory targets. Overall, these results indicate that across the lifespan prospective memory performance follows a similar inverted u-shape function as is well known for retrospective episodic memory.

PSNP-5

Show me the way! Examination of visual spatial memory

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Contrasting the large number of examination methods for the neuropsychological examination of verbal memory functions, there are only few „nonverbal" examination methods. Previous studies that investigated visual-spatial mnestic performances point out that visual spatial memory is built up in different ways, depending on the task design. Therefore, two long-term memory tasks, presented on the very same visual spatial quasi-naturalistic template, were developed. As such, these tasks hardly allow patients to solve them through verbalisation. The two long-term memory versions were studied: a) a task during which patients had to learn spatial locations and b) another task that required patients to learn a route. It is a fact that patients with spatial neglect typically show difficulties in mental representation. Therefore, common visual spatial diagnostics and learning, recall and recognition performances of healthy subjects and patients with spatial neglect were studied. Preliminary results show that 1) the formation of spatial representations depends strongly on the task design in both groups and 2) neglect patients show particular difficulties in route learning. Moreover, visual spatial working memory was studied by using the very same visual spatial template and stimuli: a) spatial locations and b) part of a route. The working memory performances of healthy subjects and patients with frontal or parietal lesions clearly point out that the working memory requirements differ between the maintaining of spatial locations and the maintaining of an integrated spatial representation.

PSNP-6

Impaired Cognitive Control After Theta Burst rTMS Over the Right Dorsolateral Prefrontal Cortex: An Eye Movement Study

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Cognitive control is defined as the ability to guide thought and action in accord with internal intentions. In experimental tasks, this often requires selective attention to a relevant stimulus in order to minimise interference effects produced by an irrelevant stimulus. Depending on task demands, more or less attentional resources are necessary to keep response conflict low. Hence, the allocation of cognitive control reflects the ability to strategically adjust performance by adopting an adequate problem solving strategy to account for task demands. This study is aimed at exploring the effects of theta burst repetitive transcranial magnetic stimulation (rTMS) over the right dorsolateral prefrontal cortex (rDLPFC) on cognitive control. Subjects completed a computerised trail making task. They were instructed to click on target stimuli in an ascending order while eye movements and more voluntary mouse clicks were recorded. Task demands were manipulated using different types of target stimuli and distractors. Also, subjects were instructed to either complete the task as fast as possible, or to favour accuracy over speed. Preliminary within – subjects comparisons suggest an impaired monitoring due to rTMS over the rDLPFC compared to the control condition without rTMS. After stimulation, subjects showed shorter fixation time on the stimuli, but longer fixation time on task irrelevant areas of the display with increasing task difficulty. In contrast, the opposite pattern was observed in the control condition, reflecting a more adequate problem solving strategy. Also, there was an interaction between rTMS and instruction for some measures of visual exploration. This could suggest that in the control condition, performance was in accordance with the instruction to a greater degree compared to the rTMS condition. Additional evidence of decreased cognitive control after rTMS over the rDLPFC could come from an analysis of post-error behaviour.

PSNP-7

Analysing visual exploration in patients with central macular scotomas

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

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Age-related macular degeneration is characterised by the development of a central macular scotoma. Adaptation to this central scotoma requires a reorganisation of the oculomotor strategies in order to centralise 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 in such patients and its systematic optimisation as potential rehabilitation procedures has never been considered. The presented method aims at testing the ability of affected patients to perform visual exploration, characterising eye movements and studying scanpaths obtained in order to eventually determine major factor underlying adaptation to central retinal disorders.

PSNP-8

Neglect-like exploration behaviour after theta burst TMS

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Patients suffering from parieto-temporal lesions of the right hemisphere often show unilateral neglect symptomatology, which is characterised by a rightward shift of attention during visual exploration. This pathology heavily affects everyday activities and can have lasting effects on therapy outcome. In our experiment, we tried to induce neglect-like symptoms in healthy participants for a limited period of time by means of theta burst repetitive Transcranial Magnetic Stimulation (rTMS) over the right parieto-temporal cortex. The participants were asked to visually explore pictures of real-life scenes while their eye movements were recorded. Several oculomotor variables were evaluated, including spatial distribution and duration of fixations on different Regions Of Interest (ROI). Our results suggest that neglect-like symptoms are inducible with the applied theta burst protocol, provoking a general rightward shift of visual attention. Moreover, our effects seem to depend on the gender of the participants. These findings are discussed within the framework of current hypotheses about pathological mechanisms in unilateral neglect and gender-specific representation of cognitive functions in the brain. Implications and perspectives for a clinical application of rTMS are also mentioned.

Cue-content overlap affects prospective memory performance

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Prospective memory is the ability we use to formulate intentions, to make plans, and promises, and to retain and execute them at the appropriate place or time. A prospective memory test always consists of a prospective and retrospective component. The prospective component involves remembering that something has to be done (i.e., recognizing a target cue); the retrospective component refers to remembering what has to be done (i.e., remembering the content of an intention). The prospective component is a distinguishing feature between a prospective and a retrospective memory test, and so far most research has focused on this component. To do so, the retrospective component is kept constant and as simple as possible. It is not clear, whether the prospective component and the retrospective component are independent or whether features of the retrospective component may influence prospective memory performance. In this study we address this question in two experiments.

The prospective memory task was embedded in a picture comparison task, in which two pictures of the same object were presented on a computer screen. Half of these object pairs were edited such that the objects differed in a small detail and the participants had to decide whether the two objects were identical or not. To keep this task running participants had to permanently press a key with their left index finger. The prospective memory task was to lift the index finger and to press one of four keys when a picture of a certain target category (i.e., clothing, furniture, plant, and animal) appeared on the screen. With this procedure the prospective component (lift the finger) and the retrospective component (press a specific key) were assessed separately. In one condition, participants were instructed to press the key that corresponded to the first letter of the target category (e.g., "c" for clothing), in the other condition participants were instructed to press a specific number key (1, 2, 3, and 4) for each target category (e.g., "1" for clothing). Thereby, the retrospective component of the former condition corresponded to the prospective component of the prospective memory task (i.e., the overlap condition), while in the latter condition no such correspondence existed (i.e. the non-overlap condition). If both components are independent, prospective memory performance should be identical. However, if the nature of the retrospective component influences prospective memory performance a benefit would be expected for the overlap condition.

Consistent with the latter hypothesis, in Experiment 1 performance was higher in the overlap condition than in the non-overlap condition. Separate analyses of the prospective component (i.e., lifting the finger) and the retrospective component (pressing the correct key) revealed that the result is not due to simply forgetting the retrospective component. In Experiment 2 ongoing task load was manipulated. The results replicated the cue-content overlap effect, but only in the low load condition. The results showed that the cue-content overlap effect requires processing resources.

The results indicate dependence between the prospective and retrospective component of a prospective memory test. They also suggest that even with exactly identical prospective memory target events their recognition depends on the content of the intention.

PSNP-10

Correlated streams of information are necessary for incidental learning: Evidence from task sequence learning

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What is the basis for incidental sequence learning? With the standard sequence learning paradigm, the serial reaction time task (Nissen & Bullemer, 1987), correlation of the stimulus location sequence and the motor-spatial response sequence is an intrinsic part of the design. Therefore, the existence of correlated streams of information may be a necessary pre-condition if learning is to be found. To investigate this hypothesis we used a task sequence paradigm. In order to avoid the necessity of providing (a correlated sequence of) instructional cues to indicate which task to perform, we used univalent stimuli. Tasks were presented in sequenced or randomized order. Additionally, in Experiment 1, the sequence of required left or right-hand responses followed either a repeated or random order. In Experiment 2 the stimulus position on the screen was also manipulated such that it followed either a sequenced or randomized order. We hypothesized that only conditions containing correlated sequences would produce learning effect. Our results were consistent with this expectation. Therefore the existence of correlated streams of sequenced information rather than the mere existence of a single sequence of events may be responsible for incidental sequence learning.

PSNP-11

Body neglect: a disorder of body representation?

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The aim of the present study is to examine whether neglect of the left body is due to a disturbance of body representation (c.f. Mesulam, 1985).
In a study of Coslett (1998), three patients with left-sided neglect had to evaluate whether central presented single hands – presented as palm or back of the hand – were a left or a right hand. He showed that these patients had particular difficulties with the evaluation of left hands. Coslett (1998) argued that hemispatial neglect could be associated with a disorder of body representation. However, his patients were only tested for visual and not for body neglect. Thus, it is unclear whether these difficulties in the so-called "body-schema" are specifically linked with left-sided body neglect or hemispatial neglect in general. Therefore, we study patients with or without personal and/or extrapersonal neglect using a similar design as Coslett (1998). Additionally, reaction times are measured.
Preliminary results from 35 right brain-damaged patients with right-hemisphere lesions suggest that neither personal nor extrapersonal neglect seems to be a sufficient condition for problems with left sided body representation and that only severe personal and extrapersonal neglect is associated with difficulties in representing the left half of the body, perhaps due to extended lesion size.
From these results, the conclusion can be drawn that body neglect does not seem to be due to problems with representation of the left body half (Mesulam, 1985), but is rather caused by an attentional disorder for incoming somatosensoric stimuli (Semenza, 1991)

PSNP-12

THE IMPORTANCE OF BEHAVIOURAL MEASURES IN INTERPRETING FUNCTIONAL DATA: EVIDENCE FROM A WORKING MEMORY STUDY

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PURPOSE

Cognitive decline with advancing age is reflected in age-related neuronal changes in the brain as observed on structural but also on functional level. However, the significance of those changes along with behavioural changes is not well understood. While poorer performance in older adults is sometimes correlated with reduction in activity in some brain areas compared to young adults, there are other findings where the elderly express higher activities in some task-related areas. These higher activations have been interpreted in functional compensation processes in order to fulfil the required task demands.

APPROACH/METHODS

Since the larger part of such studies is conducted with older adults, we performed a study with middle-aged, i.e. 50-60 year-old adults. We investigated load-dependent processing in young and middle-aged adults by using a parametric working memory task, i.e. the n-back task. The task was used as dual task as we wanted to reach and exceed capacity limits in each participant. To assess the correlating neural activity, we used whole brain and high resolution fMRI with a blood oxygenation level dependent (BOLD) echo-planar imaging (EPI) sequence (matrix 128 x 128 x 48 slices x 108 measurements, resulting in 1.5 x 1.5 x 3 mm x TR 7500 ms; TE 60 ms) on a 1.5-T whole-body MRI scanner (Magnetom Vision, Siemens Medical Systems, Erlangen, Germany).

FINDINGS

Preliminary results with 7 middle-aged participants suggest that the above-mentioned compensation view holds true: Compared to a young healthy sample (reported in detail in Jaeggi et al., in press.), the middle-aged sample showed lower accuracy and a higher BOLD-response, thus, reflecting developmental changes. Interestingly, taking performance groups into account, behavioural and fMRI data in the middle-aged sample were comparable to those of low-performing young participants.

CONCLUSION

It can be suggested that the higher activity pattern reflects compensatory processes on neuronal level. However, these activation patterns are not easily explained as a function of age-related processes, since the behaviour of the middle-aged sample did not differ from the young low-performing group. Therefore, the fMRI-data are rather interpreted in terms of an unspecific attentional and effort-related recruitment of resources, which seems either not relevant or even detrimental to performance; independent of age, but dependent on performance. In sum, this study underlines the importance of behavioural measures in interpreting functional data.

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Synaesthesia creates opportunities for emotional learning

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In synaesthesia the sensory input of one modality activates brain areas which are normally not involved in processing the input of that modality. In grapheme-colour synaesthesia for example, a number or letter elicits a photism, that is, a visual experience of a specific colour. However, recent research has shown that an externally presented inducing stimulus is not even necessary to trigger a photism and that simply activating the concept of a grapheme is sufficient (Dixon et al., 2000). In this study we investigated the consequences of synaesthesia for basic associative learning. Specifically, we were interested to see whether conditioning a startle response to a specific colour would be sufficient to produce a generalized startle response for graphemes that were associated with that particular colour for individual synaesthetes: Is it possible in synaesthesia to learn an association between a grapheme and an emotional response for graphemes that have never been physically associated?
We tested a group of 13 grapheme-color synaesthetes and a matched control group with a conditioning procedure introduced by Bechara et al. (1995). Across three phases (habituation, conditioning, and extinction) participants were presented with colored squares. In the conditioning phase one specific color (i.e., red or blue), the conditioned stimulus (CS), was followed immediately by a loud startling sound, which served as unconditioned stimulus (US). For each individual synaesthete and his matched control person, the CS-color was selected such that it matched the synaesthete's specific concurrent color experience (i.e., red or blue) corresponding to an individual grapheme. We expected that all participants would show a startle reaction for the CS as indicated by an increase in skin conductance response (SCR). In addition, if it is possible to learn an association between a grapheme and an emotional response for graphemes that have never been physically associated in synaesthesia, we expected that synaesthetes, but not controls would show a generalized startle reaction for graphemes eliciting a concurrent color that matched the CS. The results confirmed these expectations. Our results indicate that learning environments offer synaesthetes a variety of opportunities for associative emotional learning that are not present for non-synaesthetes.

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PSNP-14

Cognitive Transfer Effects After Working Memory Capacity Training: Improved Free Recall and Fluid Intelligence

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There is a whole line of knowledge about the benefit of strategic memory training. Less is known about basic and attention-related capacity training, and even less is known whether such training transfers to other cognitive domains. We used an adaptive and demanding working memory task to train healthy young adults. We show that there is a specific performance increase in the trained task, but moreover, we found reliable transfer effects in a wide variety of cognitive tasks, extending to explicit memory and fluid intelligence, providing evidence for cognitive transfer not shown to that extent before.

Unsupervised Perceptual Learning Through Top-Down Suppression of Intrinsic V1 Circuitry

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The primary visual cortex (V1) is known to extract basic geometric features such as position and orientation of edges (bars). Collinear edge detectors in V1 mutually enhance their activity in a nonlinear way, thereby allowing to highlight lines [1]. However, this basic wiring may be disadvantageous when subjects need to judge whether a segment within a line is brighter than a reference bar which is not part of the line, as required in the classical brightness discrimination task [2,3]. Global attention, suggested to enhance the neuronal gain in V1 [4], would additionally favor collinear edge detectors if it were unspecifically increasing the gain of the intrinsic V1 circuitries. On the other hand, task-specific attention and perceptual learning in brightness discrimination seem to undo the deteriorating effect of the collinear edge enhancement, without affecting the intrinsic wiring in V1. How is it possible that perceptual learning, typically ascribed to synaptic modifications in sensory areas, can improve the discrimination capability without touching the synaptic organization within V1 [2,3]?

We suggest a model of top-down interactions in V1 according to which attention selectively increases the gain of pyramidal neurons while simultaneously driving inhibitory populations in V1. The task-specific gain increase enhances the stimulus sensitivity of V1 pyramidal neurons, and the activation of inhibitory neurons suppresses the intrinsic V1 circuitry favoring collinear edges. Our model quantitatively reproduces the performance increase in humans and monkeys during ongoing brightness discrimination training [2]. It simultaneously reproduces the response modulations of V1 neurons by collinear line segments with and without focal attention [3].

Perceptual learning in our model is explained by a Hebbian strengthening of top-down projections to V1 which both enhance the gain and suppresse intrinsic interactions in V1. In this interpretation, perceptual learning appears to be mediated by top-down rather than feed-forward synaptic modifications as commonly assumed. Learning through top-down modulation has the advantage of leaving the intrinsic V1 circuitry intact for the basic operations attributed to V1.

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Rising sound intensity as an intrinsic warning cue

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Human subjects overestimate rising sound intensity compared to falling sound intensity. Rising sound intensity has therefore been proposed to be an intrinsic warning cue, signalling potential danger. In order to test this hypothesis, here we presented rising, falling and constant intensity sounds to healthy humans and gathered psychophysiological and behavioral responses. Brain activity was measured by event-related functional magnetic resonance imaging (fMRI). We found that rising compared to falling sound intensity facilitates autonomic orienting reflex and acoustic cue detection. Rising intensity sounds produced neural activity in the amygdala, which was accompanied by activity in intra-parietal sulcus, superior temporal sulcus and temporal plane. Our results indicate that rising sound intensity is an elementary cue signalling danger, recruiting attentional and physiological resources, and activating the brain's fear system.

PSNP-17

Bottom-up vs. top-down control of eye movements during scene perception

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Three groups of healthy subjects (n = 54) viewed 48 natural scene images under different task conditions, i.e. free viewing, preparation for a recognition task, and a detail memory task. During viewing, the eye movements of the participants were recorded. Irrespective of the task, we found a consistent pattern of various eye movement measures in the temporal domain. First, fixation durations continually increased over time. Second, saccade amplitudes initially increased and slowly decreased afterwards. Third, the between-subject similarity of the spatial distribution of fixations is highest during the first one or two seconds. An additional analysis shows that the visual saliency of targets fixated during the early viewing time was higher. These results suggest that during the first one or two seconds, fixation locations (and thus visual attention) are predominantly controlled by bottom-up mechanisms, which are less idiosyncratic and thus lead to the observed higher between-subject similarity of fixated locations. Top-down mechanisms, which are thought to differ more between subjects, start to exert their influence only later during viewing.

PSNP-18

Formation of cortical object representation via Hebbian and homeostatic plasticity

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The primate inferotemporal cortex (IT) lies in the final stage of the visual ventral pathway and is involved in object recognition. Neurons in IT selectively respond to complex objects via the distributed activation of patches of neurons ([1]). This selectivity is shaped by unsupervised learning and experience ([2]), and reflects the structure of the environment. However, many salient features such as the inputs, organization, and response structure of neural networks in IT remain unclear.

LTP and LTD are commonly accepted as a biological mechanism underlying the learning of input-output correlations, and the Hebbian plasticity paradigm is often used in this context ([3]). This paradigm, however, suffers from synaptic weight saturation, i.e.,
the synapses of neurons with high levels of synaptic input in the beginning will have their synaptic weights reach their maximum strength, whereas the synapses of neurons with low levels of synaptic input will reach their minimum strength. Homeostatic plasticity has been proposed to eliminate this problem ([4], [5]), allowing the brain to make more optimal use of its resources in allocating different neurons for different input patterns (symmetry breaking). However, the previous studies have not treated important quantitative issues, such as the time constants of Hebbian and homeostatic plasticity or the actual projection distance of IT neurons.

We introduce a minimal, biologically-based model which explains the development of selectivity in the form of distributed patches. The key feature of this development is the competition among the active patches through global inhibition, which also leads to patch size being independent of the feedforward input strength. Due to the global inhibition, the representation in IT may be non-additive, adding a feature in the stimulus may reduce the number of activated patches. This non-additive representation is qualitatively different from the situation in lower visual areas where an object is represented merely as a sum of its individual features. Finally, we show that the fraction of active neurons depends on the slope and threshold of the transfer function of the inhibitory neurons. The modulation of the inhibitory transfer function could therefore be a possible mechanism for changing object representation specificity.

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PSNP-19

Extending lifetime of plastic changes in the human brain

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The ability of the brain to adjust to changing environments and to recover from damage rests on its remarkable capacity to adapt through plastic changes of underlying neural networks. We show here with an eye movement paradigm that lifetime of plastic changes can be extended to several hours by repeated applications of theta burst transcranial magnetic stimulation (TMS) to the frontal eye field (FEF) of the human cortex. The results suggest that repeated application of the same stimulation protocol consolidates short-lived plasticity into long lasting changes.

PSNP-20

Semantic sentence processing and second language proficiency: a longitudinal ERP study.

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The N400 has been investigated in a number of cross-sectional studies on second language processing. In our longitudinal study we investigate ERP changes accompanying increasing language proficiency in second language learners at an earlier and later stage of second language acquisition.

74-channel ERPs to German sentences with congruent or incongruent endings were recorded from 16 English speaking exchange students learning German in Switzerland at the beginning of their stay (day1) and after 5 months (day2). Signal strength, computed as global field power (GFP), as well as topography of ERP difference maps (incongruent minus congruent) were compared between days.

The N400 effect, consisting of the well-known widespread centro-parietal negativity, was more pronounced on day 2 as shown by GFP-differences in the time window 416-456 ms. TANOVAs revealed topographical differences between day 1 and 2 in the time window 576-636 ms which were due to an altered processing of the correct sentences showing a lower GFP and an altered topography on day 2 as compared to day 1.

Our study shows that quantitative (different levels of engagement of neuronal structures) as well as qualitative changes (involvement of partially different neuronal structures) in semantic processing accompany an increase in second language proficiency.

PSNP-21

Differential aspects of neural efficiency related to visuospatial processing

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The question, whether differences in task performance between subjects are associated with less or greater individual brain activity is still a matter of debate. Using a visuospatial task, we here investigated how between subjects variability in neural efficiency and its effect on reaction time (RT) can be explained by two subject specific parameters modelling the blood oxygenation level dependent (BOLD) signal time course in left and right superior parietal lobe (SPL). In a first step, for each subject and each hemisphere a task demand independent (state activity) and a task demand dependent BOLD predictor has been computed for left and right SPL. In a second level analysis, these two predictors could be shown to explain 62% (based on left SPL activity) and 84% (based on right SPL activity) of the variance of mean RT across subjects. Interestingly variability in task performance is differentially associated with task demand independent and task demand dependent activity: Whereas increased performance is related with decreased task-independent (i.e. state) activation, it is associated with stronger intraindividual increase in activation due to increased task demand. This study sheds some new light on the link between neural efficiency and interindividual differences in visuospatial performance.

PSNP-22

Increasing second language proficiency reduces activation differences between first and second language

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Differences in representation and processing of a bilingual's first (L1) and second (L2) language have been investigated in a number of studies. One of the potential factors influencing the degree of separation and overlap between L1 and L2 is second language proficiency. In the present longitudinal event-related functional magnetic resonance imaging (fMRI) study, we addressed the question whether activation differences between single word processing in L1 and L2 are minimized with increasing second language proficiency. Native English speaking exchange students learning German in Switzerland were examined once at the beginning of their stay and a second time about 5 month later, when their second language skills had significantly increased. With low second language proficiency, we found higher activation for L2 in a distinct cortical network located in bilateral inferior frontal gyri, left middle frontal gyrus, inferior parietal lobule, SMA and cingulated gyrus. When second language proficiency was higher, the activation of L2 was significantly reduced as compared to day1 in most of these regions. Our results demonstrate plasticity in the adult language system and support the view that second language proficiency influences the degree of separation and overlap of single word processing in different languages.

PSNP-23

Functional brain connectivity in combined EEG and fMRI

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Brain information processing is assumed to require transient binding of extended neural patches, forming shortlasting neurocognitive networks. It has been proposed that this binding is achieved by neural oscillations that are synchronous over all regions involved in a processing step. Once that processing step terminates, the network disconnects and the following processing step is initiated, forming another transient network of synchronously oscillating brain regions.

We propose that there are two types of connectivity that need to be considered separately: The first type is the transient binding of neural patches, the second type the preferential sequence of processing steps. The first, 'binding' type of connectivity can only yield EEG patterns that are characterized by a single time-course with a stable spatial configuration. Across electrodes, no shift in time or phase can occur. The existence of such transient, spatially stable EEG oscillations has been shown repeatedly, and the predominant configurations appear consistently across subjects. By correlating the number or intensity of these oscillations with the fMRI BOLD signal acquired during simultaneous EEG fMRI recordings, we can identify the location of the neural patches that formed or coordinated these transient networks.

We will present data of an initial study in awake, resting subjects where simultaneous EEG and fMRI has been gathered. It becomes apparent that the global amount of binding and synchronization of cortical oscillations is controlled by subcortical and namely thalamic structures. The global amount of activity is associated with cortical regions.

PSNP-24

Theta burst transcranial magnetic stimulation (TMS) of the frontal eye field (FEF) – a combined 3 Tesla fMRI study.

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In a previous study, we found that theta burst TMS of the FEF has an inhibitory effect on saccade triggering on the behavioural level for 30 minutes. The aim of the current study was to examine the changes and temporal evolution in the cortical oculomotor network (FEF, parietal eye fields/PEF) after theta burst TMS of the right FEF.

Eight healthy subjects were tested (mean age: 31.3 years). Activation evoked by saccadic eye movements were measured in five BOLD sensitive fMRI scanning sessions (one pre-TMS-examination and four post-TMS-examinations [5, 20, 35, and 60 min after stimulation of the right FEF]) in each subject. The fMRI design followed a classical block design (Bandettini): Each trail consisted of 16 blocks; 8 stimulation blocks were alternated with 8 resting blocks that served as baseline. Furthermore, high-resolution 3-D anatomy was measured for co-registration. A 3-T whole-body MRI system (Trio, Siemens Medical Systems, Erlangen, Germany) was used for the investigation. For data analysis, registration, and visualization, the fMRI software package BrainVoyagerQX® (BrainInnovation, Maastricht, Netherlands) was used.

Results are shown in Figure 1: The difference of the BOLD signal between pre-TMS and post-TMS activation is shown for the different time intervals. Theta burst TMS of the right FEF (R_FEF) decreased the BOLD signal of all oculomotor regions within 5 to 20 minutes after stimulation. The maximum decrease of the BOLD signal was found for the right FEF at 35 minutes after stimulation. Interestingly, at this time, the inhibition of saccade triggering starts to disappear on the behavioural level. This may be due to compensatory mechanisms eventual the contralateral left FEF, in which the BOLD increased already at this time point.

PSNP-25

Awareness of Sleepiness prior to falling asleep

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Background: Sleepiness induced motor vehicle crashes are one of the most important cause of severe accidents and death in industrialized countries. Excessive daytime sleepiness (EDS) is most often due to insufficient sleep or due to a sleep disorder. Prevention of such accidents is urgent and deserves a better understanding of the process how and why sleepy people continue to drive a motor vehicle.
In order to evaluate prospectively the awareness of sleepiness prior to sleep onset we have investigated the subjective reporting of sleepiness during maintenance of wakefulness test (MWT) in healthy subjects after total sleep restriction.

Methods: 12 healthy students (mean age 24.1, SD 1.7; 6 women) underwent 4 MWT trials (= 48 trials) during the day after a night with total sleep restriction. At the beginning of the MWT they received a written task as follows without further explanations: "Your task is to indicate your sleepiness at the first appearance of sleepiness symptoms and to stay awake". Sleep was scored according to Rechtschaffen and Kales (R&K) (>15 sec stage = I). In addition microsleeps (MS) of at least 3 seconds duration were scored. From the simultaneous video zoomed on the face, slow eye lid movements, head nodding and eye lid dropping were scored.

Results: Any duration of sleep (> 3s) occurred in all 48 MWT trials overall and in 44 trials full blown sleep according to R&K (>15sec) was scored indicating a severe sleepiness in all subjects after 24 hours of wakefulness. In 22 trials MS or sleep appeared before the subject indicated subjective sleepiness (45,8%). Only 4 subjects (3 females) did indicate their subjective sleepiness before sleep onset in all 4 trials. Females were more often aware of their sleepiness before MS occurred (17 of 24 MWT trials; 70,8%) as compared to male subjects (9 of 24 trials; 37,5%) ($p < 0.02$).

Conclusion:
Our unexpected finding, that only 4 of 12 young healthy people did always recognize subjectively their sleepiness prior to the appearance of microsleep or full blown sleep and that sleep onset was missed almost in 50% of all trials, might have major impact on prevention strategies of sleepiness induced motor vehicle crashes. Until now it was assumed that sleepiness is almost always perceived by the sleepy subjects prior to falling asleep and therefore the focus for prevention was put on the adequate behaviour after the realization of sleepiness.
If our finding will be confirmed in a larger group of subjects, prevention does have to focus also on the reason why some persons do not report their sleepiness. In this respect the gender difference found in our subjects will be an important issue.

Postersession 3
Location: Aufnahmegebäude, Turnhalle
Chair: T. Dierks

Psychiatry (PSP)

PSP-1

Encoding deficit during early stage face processing in Schizophrenia

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Background: Face processing is crucial for social interaction, but impaired in schizophrenia. One important functional region for early stages of human face processing is the right fusiform face area. Thus, this very region might also be affected by functional alterations in schizophrenia.
Methods: In a rapid event-related fMRI design encoding of new faces as well as the recognition of newly learned, famous, and unknown faces was investigated in 13 schizophrenics and 21 healthy controls. Region of interest analysis was applied to each individual`s right fusiform face area.
Results: Controls displayed more BOLD activation during the memorization of faces that were later successfully recognized. In schizophrenics this effect was not present. During the recognition task schizophrenics had lower BOLD responses as well as longer reaction times to famous and unknown faces.
Conclusion: Our results support the hypothesis that impaired face processing in schizophrenia is related to early stage deficits during encoding and immediate recognition of faces.

PSP-2

To look or not to look at threat? Scanpath differences within a group of spider phobics

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Predicting the behavior of phobic patients in a confrontational situation is challenging. While avoidance as a major clinical component of phobias suggests that patients orient away from threat, findings based on cognitive paradigms indicate an attentional bias towards threat. Here we present eye movement data from 21 spider phobics and 21 control subjects, based on 3 basic oculomotor tasks and a visual exploration task that included close-up views of spiders. Relative to the control group, patients showed accelerated reflexive saccades in one of the basic oculomotor tasks, while the fear-relevant exploration task evoked a general slowing in their scanning behavior and pronounced oculomotor avoidance. However, this avoidance strongly varied within the patient group and was not associated with the scores from spider avoidance sensitive questionnaire scales. We suggest that variation of oculomotor avoidance between phobics reflects different strategies of how they cope with threat in confrontational situations.

PSP-3

Longitudinal Assessment of Neurocognition Can Reveal Acute and Persisting Factors in Depression

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Background and aims. To clarify the relationships between neurocognition, psychopathology and social functioning in depressive disorders using a longitudinal research design. Methods. 38 outpatients with depressive disorders where tested at intake and at discharge from a community based day treatment program (ATK, UPD Bern). Neurocognition was assessed with a comprehensive battery of neuropsychological tests. Symptoms and social functioning were examined at both time points. Change scores and residual change scores were calculated and relationships between neurocognition and clinical improvement were analysed. Results. The overall degree of neurognitive impairment was moderate. Although symptoms improved markedly over the course of treatment, there were only minor improvements in neurocognition. Neurocognition at discharge was most strongly related to other variables, including persisting symptoms and residual change of social functioning. A strong relationships between verbal memory (California Verbal Learning Test) at discharge and the degree of remission from depression was found in symptom measures, subjective measures and measures of global functioning. Conclusions. Impairments of verbal memory assessed in stabilised depressive states seem to reflect persisting factors of depression that have a strong impact on the symptom course. A longitudinal assessment of neurocognition, psychopathology and social functioning can reveal transient as well as persisting factors of depressive disorders. Hypothetically, these transient and persisting factors may be related to specific neurobiological processes and pathways involved in depressive disorders.

PSP-4

Cognitive functioning in the schizophrenia prodrome

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In the last decade, there has been an increasing interest in cognitive alterations during the early course of schizophrenia. From a clinical perspective, a better understanding of cognitive functioning in putative at-risk states for schizophrenia is essential for developing optimal early intervention models. Two approaches have more recently been combined to assess the entire course of the initial schizophrenia prodrome: The predictive 'basic symptoms' as described by Klosterkötter et al. (2001) and the ultra high-risk (UHR) criteria (Yung et al., 1996; McGlashan et al., 2001). Basic symptoms are considered to be present during the entire disease progression, including the initial prodrome, while the onset of symptoms captured by the UHR criteria expresses further disease progression towards frank psychosis. The present study investigated the cognitive functioning in 93 subjects who met either basic symptom or UHR criteria and thus were assumed to be at different points on the putative trajectory to psychosis. We compared them to 43 patients with a first episode of psychosis and to 49 helpseeking patient controls. All groups performed significantly below normative values. Both at-risk groups performed at intermediate levels between the first episode group and normative values. The UHR group demonstrated intermediate performance between the first episode and basic symptom at-risk groups. Overall, cognitive functions requiring frontal lobe integrity were impaired the most, with strongest impairments found on an auditory working memory task, reaching -1.5 standard deviations in the UHR group.
Our results suggest that cognitive impairments may still be modest in the early stages of the initial schizophrenia prodrome and thus support current efforts to intervene in the early course of impending schizophrenia, as early intervention may prevent or delay the onset of frank psychosis and thus prevent further cognitive damage.

PSP-5

Increase of P300-NoGo-anteriorisation in first-episode schizophrenia patients during Continuous Performance Test

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Objectives: It was found that in chronic schizophrenia patients the NoGo anteriorisation (NGA) in a cued Continuous Performance Test (CPT) was markedly reduced [1]. Our study was performed to reproduce this result in first-episode schizophrenic patients by microstate (MS) analysis [2].

Methods: 18 schizophrenic patients and 18 healthy subjects matched for gender and age were investigated with a cued CPT. Event-related potentials (ERP) were recorded with 21 EEG-channels. Go trials must be answered by pressing a button. In each subject the resulting 150 instantaneous topographical maps of the analyzed 600ms-interval of the Go- and NoGo-average ERP were clustered into 5 topographical classes. MS were defined as continuous time periods belonging to the same class. During the P300 the maximal amplitude and the respective latency within the corresponding MS as well as its start, end and duration were determined. At MS-maximum the positive centroids of the Go- and NoGo-maps and their distance, the NGA, were determined

Results: In schizophrenia patients the following significant effects were found: Increase of NGA, reaction time and NoGo-latency as well as decrease of Go- and NoGo-amplitudes and NoGo-MS-duration. Beginning of NoGo-MS was retarded.

Conclusions: The result of [1] was not reproduced. Whereas most of the P300-parameters reflecting attention are typically decreased already in first-episode schizophrenia patients, frontal function represented by the increase of NGA seems to be intact in first-episode but decreases during chronification of schizophrenia. It is a matter of discussion, whether in the initial phase of schizophrenia prevention of psychotic episodes could decrease cognitive impairment.

References
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PSP-6

Activation in Heschl gyrus during inner speech in schizophrenia – an ongoing EEG study

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Auditory verbal hallucinations (AVH) may result from deficits in auditory self monitoring during inner speech, resulting in confusion between self generated and alien speech. In hallucinating schizophrenic patients, abnormal structural and functional connectivity between primary auditory cortex, and Broca's and Wernicke's area were found indeed. Using 76-channel EEG, this study investigates the (co-) activation of primary auditory cortex and the main language areas during an intermittent silent verbal fluency (VF) task (inner speech).

11 chronic schizophrenic patients (AH) with persistent AVH lasting for at least 4 years and 11 healthy controls (C) were investigated so far. The EEG was frequency transformed and sLORETA current densities were computed for frequency bands. The (preliminary) statistical analysis compared group wise current densities during task execution and baseline using voxel-wise t-tests.

In the beta band, we found that patients showed an increased activity in the left Heschl's gyrus during task execution . No such increase was observed in the controls.

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.

PSP-7

Neuropsychological Evidence For Prefrontal Dysfunction In First-Episode Schizophrenia

Caroline Hilti[1,2,4], Tarik Delko[2], Ariane Orosz[1,2,5], Kathrin Thomann[2], Stefan Ludewig[2], Marc Geyer[3], Franz Vollenweider[4], Joram Feldon[5], Katja Cattapan-Ludewig[1,2]

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The nature of specific deficits in tests of sustained attention, planning and set-shifting and their underlying neurobiological basis has not been fully investigated in drug-naïve first-episode (FE) schizophrenia patients yet. Moreover, it is not clear whether patients' cognitive performances are stable or if they fluctuate in response to medication. We predicted that drug-naïve patients performed worse than controls and that their performance was improved following medication.

FE patients and healthy controls performed three computerized tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) measuring sustained attention (RVIP), planning abilities (SOC) and set-shifting abilities (IDED). The same patients and controls were tested at baseline (38 patients, 34 controls), after one month (24 patients, 32 controls) and two months (9 patients; 16 controls). All three tests were administered at baseline and after two months; additionally, the RVIP was also administered after one month. The patients were drug-naïve at baseline and then received antipsychotic medication for one and two months. Most of the patients were on atypical antipsychotic medication for one month (17 atypical / 1 typical / 6 combination) and two months (8 atypical / 1 typical). The patients' psychopathology was assessed using the PANSS.

Drug-naïve FE patients were significantly impaired on the RVIP and SOC. Set-shifting abilities, however, seemed to be relatively intact. An effect of short-time medication on the RVIP and SOC did not become evident two months after the start of medication. Moreover, the performance on the IDED worsened significantly in between these two months. Cognitive deficits in attentional (RVIP) and planning tasks (SOC) already appear to be present at early stages of the development of schizophrenia and might point to dysfunctional neural circuits including the prefrontal lobes. These findings accord with the neurodevelopmental model of schizophrenia. Unlike the RVIP and SOC, the IDED seems to be less effective in differentiating controls' and drug-naïve FE patients' performance. A positive effect of a two-month antipsychotic treatment did not become evident in the present schizophrenic group. The presence of significant deterioration in set-shifting on the IDED after two months, however, will need to be investigated in further studies with larger patient groups and longer treatment periods. A difference between type of medication could not be observed.

PSP-8

Facets of sleepiness in patients with (hypersomnolent) depression in comparison to narcoleptic and obstructive sleep apnoea patients

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Background: Excessive day time sleepiness (EDS) is the major subjective complaint of patients with various sleep disorders including narcolepsy and idiopathic hypersomnia. Conversely patients with major depression typically report on daytime fatigue or lack of energy. However, a subgroup of patients with depression (hypersomnolent depression) may present without insomnia but with EDS. This group is particularly difficult to differentiate from monosymptomatic narcolepsy or idiopathic hypersomnia on a pure clinical basis.

We have tested whether subjective and objective vigilance tests could help in the differential diagnosis of ambiguous cases with EDS.

Method: We have prospectively performed actigraphy, polysomnography, the Epworth score, multiple sleep latency test (MSLT), steer clear test, pupillography (PUI) in patients referred to the centre of sleep disorders with a complaint of EDS. When no obvious cause of EDS could be diagnosed based on clinical and paraclinical findings, a psychiatric assessment was done in order to diagnose (hypersomnolent) depression.

In the recruitment period between 3/01 and 11/05 19 patients with (hypersomnolent) depression were diagnosed who fulfilled all the above exclusion criteria. As control group we analysed data of the first 23 patients with narcolepsy and the first 46 patients with OSAS (apnoea-hypopnoea index above 10/hours).

Results: The female rate was 63% in the depression group, 47% in the narcoleptics but only 9% in the OSAS group. This sex difference was not statistically different in depression and narcolepsy. The great predominance of male subjects in OSAS is well established in the literature. This OSAS group also showed a significant higher age ($p < .001$) which was used as a covariate in the statistical analysis of the variables. As expected by the selection criteria of EDS, the Epworth score confirmed a moderate to severe subjective EDS in all patient groups and no group differences. The mean latency of the MSLT was significantly shorter in the narcoleptic group compared to both other groups underlying the much greater sleep propensity in narcolepsy. There was no difference for sleep latency between OSAS and depression. The borderline mean sleep latency of 8 minutes in the group with depression (normal > 10 minutes) indicates a mild objective EDS in these patients. In the steer clear reaction time test narcoleptics made more errors than OSAS patients (7.9 vs. 5.9%; p 0.03) but rather unexpectedly depressed patients showed an even greater error rate (10.4%) which was statistically not different to the result of the narcoleptics. A similar trend was found for the PUI which was greatest in narcoleptics (11.5) but in depression (9.2) as high as in OSAS (7.4) (n.s.).

Discussion: The main finding was an unexpected high error rate in the steer clear reaction time test in (hypersomnolent) depression, statistically not different to the result in narcolepsy. This finding is astonishing in the view of a rather mild sleepiness in our depression group as assessed by the MSLT. Our interpretation of a relatively bad result in depressed patient in an active reaction time test is based on neuropsychological factors unrelated to EDS such as motivation and attention in this group. We conclude that a high error rate in the steer clear reaction time test in subjectively sleepy (Epworth) but objectively (MSLT) not or only borderline sleepy patients is suggestive for (hypersomnolent) depression.

Better Memory and Neural Efficiency in Young Apolipoprotein E ε4 Carriers

Christian R.A. Mondadori[1], Dominique J.-F. de Quervain[1], Andreas Buchmann[1], Henrietta Mustovic[1], M. Axel Wollmer[1], Conny F. Schmidt[3], Peter Boesiger[3], Christoph Hock[1], Roger M. Nitsch[1], Andreas Papassotiropoulos[1], **Katharina Henke[2]**

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The apolipoprotein E (APOE) e4 allele is the major genetic risk factor for Alzheimer's disease (AD), but an APOE effect on memory performance and memory-related neurophysiology in young, healthy subjects is unknown. We found an association of APOE e4 with better episodic memory compared to APOE e2 and e3 in 340 young, healthy persons. Neuroimaging was performed in a subset of 34 memory-matched individuals to study genetic effects on memory-related brain activity independently of differential performance. ?4 carriers decreased brain activity over three learning runs, while e2 and e3 carriers increased activity. This smaller neural investment of e4 carriers into learning reappeared during retrieval: e4 carriers exhibited reduced retrieval-related activity with equal retrieval performance. APOE isoforms had no differential effects on cognitive measures other than memory, brain volumes, and brain activity related to working memory. We suggest that APOE e4 is associated with good episodic memory and an economic use of memory-related neural resources in young, healthy humans.

Neurosurgery (PSS)

PSS-1

Role of Pure Collagen in the Laser Tissue Irradiation

Alex Alfieri[1], Angelique Ducray[1], Hans Rudolf Widmer[1], Katharina Jetzer[1], Robert Andres[1], Pasquale Mordasini[1], Mihai Costantinescu[2], Martin Frenz[3], Serge Bogni[3], **Michael Reinert**[1]

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BACKGROUND - Laser tissue welding and soldering is based on thermal tissue alteration, why the quality of tissue fusion depends on the breadth of the thermal injury. Optimal tissue soldering with laser would allow a sufficient surgical tensile strength with only minimal immediate and long-term tissue denaturalization. Today knowledge about the nature of the bonding is still unsatisfactorily.The main hypothesis of the laser-inducted tensile strengths is the conformational alteration of collagen in the laser irradiated tissues. Previous studies analyzing the covalent forces after laser irradiation with collagen-rich substrates containing more or less cellular component have reported results so far controversial most likely due to the simultaneous use of protein solder and complex multi-cellular tissues.

OBJECTIVE - Aim of the present study is to analyze the impact of laser irradiation on 100% pure cell-free collagen molecules, using ICG for light absorption without albumin solder.

MATERIALS AND METHODS – Pure rabbit and equine type I collagen were subjected to laser irradiation. In the first part of the study rabbit and equine collagen were compared using identical laser and irradiation settings. In the second part of the study equine collagen was irradiated at increasing laser powers. Changes in covalent bonding were studied indirectly using the SDS-PAGE technique. Tensile strengths of soldered membranes were measured with a calibrated tensile force gauge.

RESULTS - No changes were observed in the distribution of the bands when comparing the non-irradiated with the laser irradiated pure rabbit type I and pure equine type I collagen. Two most pronounced bands were observed between 100 and 150 kDa as compared to the standard in all studied samples. No new bands appeared following laser irradiation. Virtually no adherence of the pure collagen layers was observed following laser irradiation. The tensile strength of the laser welded pure equine collagen membranes was practically inexistent irrespective of the applied laser powers and irradiation duration. Adding albumin had no effect on tensile strength.

CONCLUSIONS - The results of this study elucidate that laser irradiation of pure collagen, at irradiation parameters used for laser tissue welding and soldering, does not have any relevance in the covalent bonding of the irradiated collagen molecules. Pure collagen can neither generate alone, nor in combination with albumin solder the tensile strength observed in combined cell-rich tissues upon welding or soldering. While the collagen matrix may have a scaffolding role for the actual binding forces, a cellular component appears to be indispensable for successful laser tissue soldering.

PSS-2

Sutureless End-To-Side Arterial Non Occlusive Vessels Anastomosis with Platinum Ring and Omnex

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Introduction:Vascular anastomoses by microsurgical suturing is a time-consuming procedure determining mortality and morbidity. Anastomosis techniques devoid of any microsuture are being studied.
Methods: End-to-side anastomosis using rabbit aorta and sealant polymerization for sutureless vascular anastomosis with 2-octyl cyanoacrylate and butyl lactoyl cyanoacrylate (Omnex, Ethicon J&J, Switzerland) was analyzed in vitro. Eight rabbit aortas were used as recipient arteries, and eight rabbit aortas were prepared with at the end an 8.0-sutured small platinum ring (2.6 mm, ELANA BV, Netherlands). Non occlusive anastomosis were performed by narrowing the two arteries followed by the uniform distribution of Omnex around the contact surface. The perforation of the vessel was obtained using an excimer laser (Spectranetics BV, Amsterdam, Netherlands) and the ELANA laser catheter for vascular perforation (ELANA, BV, Netherlands). The vessels graft was tested by pressure burst gauging tests and the tensile strength was measured with a force gauge BFG50 (Mecmesin Ltd., West Sussex, UK) and a moving table.
Results: A strong vascular anastomosis was induced in each fusion experiment with the best value of 2310 mN and the mean value of 1524.44 mN plus minus 591 mN (SD). The integrity of the anastomosis and the leakage test with water filled was proved in 0.87. The excimer laser perforation was successful in seven cases.
Conclusions:The described microanastomosis technique was successful repeated in all experiments. The results of this sutureless adhesive technique and potential pitfalls with use Omnex in association with excimer laser perforation are analysed.

PSS-3

Tight Contact Technique Improves Tensile Strength in Side-to-Side Laser Tissue Soldering of Rabbit Aortas

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BACKGROUND – The laser tissue welding using the thermal effect has demonstrated an improvement by the addition of a biological solder such as the protein albumin and is referred to as laser tissue soldering. Several reports using laser tissue soldering for blood vessels have reported on a successful short term in vivo end to end anastomosis technique with the aid of an intravascular balloon technique.
OBJECTIVE - Aim of the present study is to lead reproducible and stronger tensile strength by a tight contact of vessels during laser tissue soldering, and compare the results with the loose soldering technique.
MATERIALS AND METHODS –A total of 24 rabbit aortas were studied. The loose soldering of vessels consisted in overlaying the vessel using no compression with the custom designed device to approximate the tissue. For the tight contact soldering the vessels where additionally embedded between two glasses and inserted into the device under a constant pressure. As laser source a GaAlAs (gallium aluminum arsenide) diode laser system DL50 (FISBA Optic, St. Gallen) emitting near infrared radiation at 808 nm and for temperature registration an infrared camera Radiance HS (Raytheon, Waltham, MA, USA) was used.
RESULTS - The overall tensile strength in the tight (1093.3mN ± 160.7) versus loose (235.7mN ± 39.7) contact soldering procedure were significantly higher (p<0.0005) using the 30-second continuous irradiation. In the pulsed irradiation series the overall tensile strength values for the tight (638.3mN ± 65.1) versus loose (198.3mN ± 38.6) contact soldering procedure were significantly higher (p<0.0005), however the absolute values were lower. The overall tensile strength in the continuous irradiation mode were higher, however in a non-significantly trend. The histological analysis of the samples with the tight contact sandwich technique has shown no apparent difference compared to loose technique using a 30 second irradiation mode.
CONCLUSIONS - Tight contact laser tissue soldering of abdominal aorta of the rabbit has shown to produce significantly higher tensile strength, while histological post-laser soldering appearance is unchanged.

PSS-4

Optimizing the benefit of bone anchored hearing aids for hard of hearing people

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Many patients with a substantial conductive or mixed hearing loss benefit from specialized, so called bone anchored hearing aids (BAHA). These aids consist of titanium screw, which is usually implanted behind the ear and a special bone conduction hearing aid, which can be attached by means of a snap coupling to the screw.

Despite its unquestionable benefit in terms of increased speech recognition, the need for a screw penetrating the skin limits the use and cosmetic acceptability of the device. In this research, we investigate methods to improve bone anchored hearing aids by optimizing the place and direction of stimulation. Screws on cadaver heads are implanted at different sites and the effect of the acoustic stimulation is measured using laser Doppler vibrometry. First results show a non-negligible influence of the place of implantation.

PSS-5

Multimodal Imaging at 3 Tesla MRI for optimized Patient Selection before Deep Brain Stimulation (DBS)

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

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Objective: DBS is an expanding sector of functional neurosurgery. The current methods do not always enable a unequivocal identification of particular targets. Individual variations and disease associated degeneration complicate target definition. Our aim is to improve neuroimaging methods for individual targeting based on morphological MRI combined with tractography (DWI) and functional MRI.

Methods: 20 volunteers were examined at 3 Tesla Trio (Siemens Medical Solutions, Erlangen, Germany) with high-resolution T2-3D MRI for morphological imaging. The fMRI was performed with a self-initiated complex motor task of the hand in a block-paradigm. DWI sequences were performed using different parameter settings. Anisotropy values were calculated with seeds in the thalamic nuclei, globus pallidus and nucleus subthalamicus. Tractography from the seeds was performed according to the Parker algorithm as a part of a house intern algorithm.

Results: The 3 Tesla MR imaging allowed a reliable identification of the nucleus subthalamicus, the globus pallidus internus and the main thalamic targets in all subjects. Fibres tracking confirmed several assumed anatomical connections of the targets. Finally, fMRI visualised functional activation of particular targets.

Conclusions: The multimodal approach with 3Tesla MRI enables an exact targeting by direct visualization of the individual morphology including an estimation of functional activation. This multimodal approach could improve the patient selection process and the postoperative outcome.

PSS-6

Detailed image analysis improves preoperative grading of esthesioneuroblastoma: A suggested new classification based on imaging findings

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Purpose:
To improve current classification schemes of esthesioneuroblastoma by detailed analysis of imaging findings and to correlate tumor extent with recurrence and survival rates.

Material/Methods
Over a period of fifteen years (1989-2004), 15 patients (nine men, six women, 16-77 yrs, mean age 52.4 yrs) were operated for esthesioneuroblastoma. 12 patients had pre-operative MR imaging, in three cases, CT was performed. All imaging studies were retrospectively evaluated for exact delineation of tumor boundaries and assessment of structures infiltrated by the tumor. A grading scheme was developed that rated infiltration from one point (e.g., nasal cavity) to five points (e.g., dural infiltration) for 23 anatomic structures. A total of 76 points was possible.

Results:
The mean tumor infiltration rating was 45.5 points. Although all tumors were classified as Grade 4 in conventional classification schemes, our grading system provided a finer differentiation; the range was 25 to 68 points.
Tumor recurrence was markedly earlier in cases with > 50 points.

Conclusion:
Current grading schemes for esthesioneuroblastoma are not sufficiently detailed. Infiltration of surrounding structures alone does not necessarily mean that a tumor is inoperable; only a large degree of infiltration into surrounding structures does markedly reduce the recurrence-free interval.

Postersession 4
Location: Aufnahmegebäude, Stockwerk J, Konferenzraum
Chair: R. Müri

Neurology (PSN)

PSN-1

Fosphenytoin as a Neuroprotectant in High-Risk Thoracic Aortic Surgery: a Randomized, Placebo-Controlled Clinical Trial

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Background:
Neurological complications are still a major problem in thoracic aortic surgery: the incidence of stroke is 21% in patients older than 60 years [1]; the incidence of temporary neurological dysfunction is 15 – 19%, and the incidence of permanent neurological dysfunction 9% [2,3]. Furthermore, postoperative cognitive dysfunction after cardiac surgery occur in 75 % up to 90 % [4]. Fosphenytoin (a prodrug of phenytoin) acts as a selective neural sodium-channel blocker thereby attenuating the influx of Na+ into the cell during the excitotoxic cascade [5]. The neuroprotective potential of fosphenytoin and phenytoin has been shown in different studies in vitro and in vivo [6-8].

Trial objectives:
To examine the efficacy and safety of a prophylactic single iv dose of fosphenytoin to reduce the postoperative incidence of the following adverse cerebral outcomes in patients undergoing high-risk thoracic aortic surgery: 1) individual postoperative neurocognitive deterioration; 2) new postoperative focal deficits including stupor and coma.

Patients and Methods:
Single-centre, double-blinded, randomized, placebo-controlled trial in a cohort of 40 patients undergoing thoracic aortic surgery in deep hypothermia with or without deep hypothermic circulatory arrest (DHCA) at high risk of perioperative neurological deterioration. Prophylaxis consists of intravenous infusion of a single bolus of 20 mg PE/kg fosphenytoin (Cerebyx®); plazebo is NaCl 0,9%. The patients will undergo neuropsychological and neurological testing 1 week before, 1 week after and 6 month after operation.

Assessments
Primary outcome: Neuropsychological functions will be assessed by a recently well-validated neuropsychological test battery of the Swiss Association of Neuropsychology [9]. In pre- and postoperative testing alternative forms will be used to avoid practice effects. All raw scores will be transformed into age- and education-scaled standard T-scores (M = 50; SD = 10) [10]. Tests were selected to measure all main aspects of neuropsychological functions.
Secondary outcomes: 1) Incidence of stroke, hypoxic encephalopathy, coma, and seizure. 2) Correlation between intraoperative parameters of cerebral tissue oxygenation (NIRO200, Hamamatsu, Germany) and postoperative neurological outcome. 3) S100b (there is a strong correlation between 24-h S-100b level and cerebral injury) [10].

Statistics
After the intended number of 40 patients has been studied, a power analysis will show the final number of patients to detect a significant perioperative deterioration of neuropsychological parameters (power 0.8, alpha 0.05).

Agenda
Patient recruitment 2006-2007, last follow up in June 2008.

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PSN-2

Non-bacteriolytic daptomycin for the treatment of pneumococcal meningitis: beneficial effects over current bacteriolytic ceftiaxone therapy.

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Background: Bacteriolytic antibiotics cause the release of bacterial components that augment the host inflammatory response, therefore contributing to the pathophysiology of brain injury in bacterial meningitis. In the present study in experimental pneumococcal meningitis, antibiotic therapy with non-bacteriolytic daptomycin vs. bacteriolytic ceftriaxone was evaluated for an effect on inflammation and brain injury.
Methods: Eleven day old rats were injected intracisternally with $1.3 \pm 0.5 \times 10^4$ colony forming units (cfu) of *Streptococcus pneumoniae* serotype 3 and randomized for therapy with ceftriaxone (100 mg/kg s.c., n=55) or daptomycin (50 mg/kg s.c., n=56) starting at 18 h after infection. Cerebrospinal fluid was assessed for bacterial count, matrix metalloprotease-9 and TNF-a at 18, 20, 24 and 40 h after infection. Cortical brain damage was evaluated at 40 h after infection.
Results: Daptomycin vs. ceftriaxone cleared bacteria more efficiently from the CSF within two hours after initiation of therapy ($\log_{10} 3.6\pm1.0$ vs. $\log_{10} 6.3\pm1.4$ cfu/ml, P<0.02), reduced the inflammatory host reaction assessed by concentration of matrix metalloprotease-9 in CSF at 40 hours after infection (P<0.005), and prevented the development of cortical injury (cortical injury present in 0/30 vs. 7/30 animals, P<0.001).
Conclusion: By clearing bacteria more rapidly from the CSF and by causing less inflammation, daptomycin prevented the development of cortical brain injury in experimental pneumococcal meningitis. Non-bacteriolytic antibiotic therapy with daptomycin may therefore represent an advantageous alternative over current bacteriolytic antibiotics for the therapy of pneumococcal meningitis.

PSN-3

Evidence for a sympathetic origin of idiopathic periodic leg movements in sleep

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BACKGROUND: Idiopathic periodic leg movements in sleep (i-PLMS) are frequently accompanied by EEG- signs of arousal or sleep instability and increasing heart rate, but the significance of these changes for the pathophysiology of i-PLMS is not well understood. In particular, it is not clear whether i-PLMS are the cause or the consequence of these autonomic and EEG arousals. Periodic leg movements in sleep apnea syndrome are a part of the arousal terminating respiratory events.
METHODS: Whole-night polysomnographies (PSG) of 24 subjects fulfilling the criteria of either periodic leg movements disorder (N=8, PLMD), obstructive sleep apnea syndrome (N=7, SAS), or normal PSG (N=9) were selected. Spectral EEG- and heart rate-changes were analyzed by calculating the event related synchronization/desynchronization and the heart rate variability (HRV), respectively. Changes associated with i-PLMS were compared to changes associated with non-periodic (Non-PLMS) and respiratory related leg movements (RRLMS). Furthermore, the influence of sleep stage and movement pattern (amplitude, duration, interval) on spectral EEG and heart rate changes was assessed.
RESULTS: All types of leg movements were preceded and associated with largely the same temporal sequence beginning with an increased HRV up to 8 seconds before movement onset followed by an increased Delta-activity, then showing an increased Theta-, Alpha-, Beta- and Gamma-activity, and ending with a decreased spindle-activity after movement onset. These changes occurred symmetrically over both hemispheres, and were sleep stage dependent. Low frequency HRV oscillations, but not the EEG changes were correlated with PLMS amplitude and index. Delta-synchronization and heart rate variability had greater peaks for i-PLMS and RRLMS than for Non-PLMS, whereas Gamma-synchronization began 1-2 seconds earlier for Non-PLMS and RRLMS than for idiopathic PLMS.
CONCLUSION: All types of leg movements in sleep were clearly preceded by autonomic changes occurring before EEG arousals favoring an origin on brainstem level. This activation progressively ascended to the cortex, as indicated by Delta-bursts and increased high-frequency EEG-oscillations. EEG signs of cortical arousal clearly preceded muscle activity in Non-PLMS and RRLMS, but began only shortly before or at the same time as i-PLMS. Also, the markers for autonomic activation peaked more for i-PLMS than for the other movement types, and were correlated with PLMS magnitude. Therefore, i-PLMS are more likely to be triggered directly by autonomic processes than by a cortical arousal.

PSN-4

Interventional stroke treatment: Evaluation of two mechanical revascularization techniques in an animal model

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Background: Mechanical thrombectomy is a promising new modality of interventional stroke treatment. The various devices are available so far. Systematic in-vivo evaluation of such devices concerning efficacy and complication rate are missing so far. The present study assesses two different mechanical approaches in an animal model that has been established at the Univeristy of Bern.
Methods: Angiography and embolisation with a radioopaque whole blood thrombus was performed in 10 swine. Mechanical thrombectomy was performed in 20 cranial vessels using a proximal aspiration device (Vasco 35 catheter) and a distal basket-like device (Catch device) with and without proximal balloon occlusion. 56 retrieval attempts were made. Success rate, thrombus-device interaction, time needed for revascularization and complications were evaluated.
Results: The proximal device allowed fast repeated application with a low risk of thromboembolic events (3%) and vasospasm, but it had a significantly lower success rate (39.4%) in retrieving thrombotic material than the distal device (82.6%; odds ratio 7.3; 95% CI 2.0 to 26.4). The compaction of the thrombus during retrieval with distal devices increased the risk of vessel wall irritation significantly ($P<0.01$) and complicated retrieval into the guiding catheter. The number of embolic events was significantly higher with distal devices (26%; odds ratio 11.3; 95% CI 1.35 to 101.6) unless proximal balloon occlusion was used.
Conclusions: The proximal and the distal approaches to mechanical thrombectomy proved to be effective at achieving recanalization of cranial vessels. The PD is faster in application and allowed repeated attempts with a low complication rate. The DD is more successful at removing thrombotic material, but its method of application and attendant thrombus compaction increases the risk of thromboembolic events and vasospasms.

PSN-5

Visuomotor learning in patients with Parkinson's disease

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Several studies indicate that procedural sequence learning is impaired in patients with Parkinson's disease (PD), probably due to dopamine deficiency. However it is unclear to what extend procedural learning is influenced by the two processes that are intrinsically tied to sequence learning: visuomotor learning and motor fatigue.
The aim of the present study was to investigate the learning of motor responses to visual stimuli in patients with PD. Eight subjects with PD had to press as fast as possible 1 of 4 keys in response to visual stimuli appearing in random order on a computer screen. They performed 7 blocks of 100 trials, which were separated by 1 min resting periods. We measured the 'reaction time', i.e. the time delay between stimulus presentation and key press and the 'accuracy', i.e. whether the response was correct or not. We divided for analysis each block in 10 cycles of 10 trials each and calculated the median of each cycle. Analysis was performed for the mean of all cycles of each block and for the first and last cycle of each block.
Results showed a significant decrease of reaction time from the first to the second training block. We found no significant change of accuracy throughout the entire session. More detailed analysis within each block revealed that the reaction time of the first cycle of each block decreased in the course of the experiment, corresponding to visuomotor learning. In contrast, the reaction time of the last cycle increased in the course of the experiment. This finding, which we interpreted as within-block fatigue, correlated significantly with a decrease in reaction time across the resting periods. In other words, the more fatigue within a block developed, the greater was the recovery during the subsequent resting period.
Our data demonstrate that fatigue and rest significantly influence reaction times in patients with PD. These findings extend basic knowledge about visuomotor learning in PD and must be taken into account in the interpretation of procedural sequence learning tasks.

PSN-6

Frequency limits for repetitive nerve stimulation in clinical diagnostics

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Objectives:
High frequency nerve stimulation can be used to test for presynaptic dysfunction of the motor endplate and for metabolic muscle disease (McArdle). Frequencies up to 50 Hz are used for this purpose, but a drop in compound muscle action potential (CMAP) can be observed already in healthy subjects. The goal of this study was to derive normal values for 20 and 50 Hz nerve stimulation of the peroneal nerve and to determine the reason for the normal decrease of CMAP.
Methods:
The peroneal nerve was stimulated supramaximally at the capitulum fibulae. Surface recordings were obtained from the tibialis anterior muscle. Repetitive nerve stimulation was performed with a pulse rate of 20 and 50 Hz and a pulse train duration of 2 minutes. In addition, direct distal stimulation of the anterior tibial muscle with single supramaximal stimuli was performed during repetitive nerve stimulation to test for changes in muscle exitability.
Results:
20 Hz stimulation of the peroneal nerve resulted in an initial small increase of the CMAP followed by an only slight decrease in amplitude over a time period of 2 minutes. In contrast, 50 Hz nerve stimulation resulted in a drop of CMAP amplitude by more than 60% of the initial amplitude. Additional single supramaximal direct (post-synaptic) muscle stimuli during 50 Hz peroneal nerve stimulation resulted in only slightly reduced CMAP amplitudes which exceeded the remaining response amplitudes from the concurrently applied nerve stimulation.
Conclusion:
High frequency nerve stimulation of 50 Hz results in a large drop of CMAP amplitude over time which appears mostly to be due to changes in synaptic transmission efficiency at the neuromuscular endplate. Stimulation at 20 Hz may be more adequate for clinical purposes.

PSN-7

Long-term Effect of Intra-arterial Thrombolysis in Stroke

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Background: Thrombolysis has been shown to improve the 3-months outcome of patients with ischemic stroke, but knowledge of the long-term effect of thrombolysis is limited.
Patients and Methods: The present study compares the long-term outcome of stroke patients who were treated with intra-arterial thrombolysis (IAT) using urokinase with the outcome of patients treated with aspirin. The modified Rankin scale (mRS) was used to assess the outcome. 173 patients treated with IAT and 261 patients treated with aspirin from the Bernese Stroke Data Bank were eligible for the study. A matching algorithm taking into account patients' age and stroke severity on admission (as measured by the National Institute of Health Stroke Scale, NIHSS) was used to assemble an IAT and an aspirin group.
Results: 144 patients treated with IAT and 147 patients treated with aspirin could be matched and included in the comparative analysis. The median NIHSS score was 14 in each group. At 2 years, 56% of the patients treated with IAT and 42% of the patients treated with aspirin achieved functional independence (mRS 0 to 2; P = 0.037). Clinical outcome was excellent (mRS 0 to 1) in 40% of the IAT and in 24% of the aspirin patients (P = 0.008). Mortality was 23% and 24%, respectively.
Conclusion: The present study provides evidence for a sustained effect of IAT when assessed 2 years after the stroke.

PSN-8

Detection of regional blood perfusion changes in epileptic seizures with dynamic brain perfusion CT

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Background and Purpose:
Perfusion CT (P-CT) is used for acute stroke management, not, however, for evaluating epilepsy. To test the hypothesis that P-CT may identify patients with increased regional cerebral blood flow during subtle status epilepticus (SSE), we compared P-CT in SSE to different postictal conditions.

Methods:
Fifteen patients (mean age 47 years, range 21-74) underwent P-CT immediately after evaluation in our emergency room. Asymmetry indices between affected and unaffected hemispheres were calculated for regional cerebral blood volume (rCBV), regional cerebral blood flow (rCBF), and mean transit time (MTT). Regional perfusion changes were compared to EEG findings.

Results:
Three patients in subtle status epilepticus (group 1) had increased regional perfusion with electro-clinical correlate. Six patients showed postictal slowing on EEG corresponding to an area of regional hypoperfusion (group 2). CT and EEG were normal in six patients with a first epileptic seizure (group 3). Cluster analysis of asymmetry indices separated SSE from the other two groups in all three parameters, while rCBF helped to distinguish between chronic focal epilepsies and single events.

Conclusion:
Preliminary results indicate that P-CT may help to identify patients with SSE during emergency workup. This technique provides important information to neurologists or emergency physicians in the difficult clinical differential diagnosis of altered mental status due to subtle status epilepticus.

PSN-9

Better Outcome in Patients with Acute Stroke and Hyperdense Middle Cerebral Artery Sign After Treatment With Intraarterial Compared to Intravenous Thrombolysis

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Background: Several studies indicate that recanalization of middle cerebral artery (MCA) occlusion independently predicts a favourable outcome and is better achieved with intra-arterial (IAT) than intravenous (IVT) thrombolysis. The aim of this study was to compare in consecutive patients with first MCA territory stroke and suspicion of MCA occlusion at cranial CT the clinical outcome after treatment with IAT and IVT.
Methods: Retrospective analysis of prospective data collected in two stroke centers, which have a similar stroke unit management with the exception that patients with symptomatic MCA occlusion and a hyperdense middle cerebral artery (HDMCA) at CT scan underwent IAT in the 6 hours (h) window in one centre, and IVT in the 0-3 h window in the other centre. The frequency of a favourable outcome defined by a modified Rankin Scale (mRS) score of 0-2 and mortality were compared between patients treated with IAT and IVT.
Results: We included 55 patients treated with IAT and 57 with IVT. A favourable clinical outcome was more frequent in patients treated with IAT (n=29, 52.7%) than IVT (n=13, 22.8%; p=0.001). Mortality was higher in the IVT group (IAT, n=4, 7.3%; IVT, n=13, 22.8%; p=0.022). Baseline variables did not differ between both groups except for a shorter mean time interval from symptom to treatment onset in the IVT group (156 ± 21 versus 244 ± 63 minutes; p=0.0001). On multiple regression analysis IAT remained independently associated with a favourable outcome (p=0.003) and tended to be associated with a lower mortality (p=0.192)
Conclusion: As compared to stroke patients with HDMCA treated with IVT, those treated with IAT were more likely to have a favourable clinical outcome despite a longer time to treatment.

PSN-10

Gender Differences in Spontaneous Cervical Artery Dissection

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Background: Spontaneous cervical artery dissection (sCAD) is a frequent cause of ischemic stroke in both sexes, manly affecting young and middle-aged subjects. Gender differences have not been systematically analyzed yet.
Methods: Demographic data, risk factors and clinical presentation of consecutive sCAD patients from 3 academic centers were recorded. Clinical outcome of ischemic stroke patients (n=408) was analyzed at 3 months using the modified Rankin scale (mRS). Data were compared between the two sexes.
Results: We included 696 patients, 399 (57%) men and 297 (43%) women (p<0.0001). Women were younger than men (42.5 ± 9.9 years versus 47.5 ± 9.3 years; p<0.0001). Men showed a higher frequency of hypertension (31% versus 15%; p<0.0001), and migraine was more frequent in women (47% versus 20%; p<0.0001). Presenting symptoms and signs were similar in both sexes except for a higher frequency of pulsatile tinnitus in women (16% versus 8%; p=0.001). Multiple dissections occurred more often in women (18% versus 10%; p=0.001). The percentage of stroke patients with a favorable outcome at 3 months (mRS 0 or 1) did not differ between women (58%) and men (55%; p=0.57).
Conclusions: Women with sCAD are younger than men and have more often multiple dissections. The usual female preponderance of migraine and a male preponderance of hypertension were observed. Presenting clinical signs and clinical outcome did not differ between both sexes.

PSN-11

Desynchronization of motor neuron discharges after transcranial magnetic stimulation: A quantitative analysis

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Background: Motor evoked potentials (MEPs) after transcranial magnetic brain stimulation (TMS) are smaller than responses after peripheral nerve stimulation, because TMS induced motor neuron (MN) discharges are not synchronized, inducing phase cancellation. Previously we described a triple stimulation technique (TST, Magistris et al., Brain 1998), eliminating the effects of MN desynchronization after TMS. TST responses are therefore larger than MEPs.
Objective: To characterize mechanisms causing desynchronization of MN discharges.
Methods: TST and MEP responses were obtained using identical stimulation parameters, and the amplitude ratio of TST/MEP was calculated to quantify desynchronization. Two target mus-cles (abductor digiti minimi, ADM; abductor hallucis, AH) were compared in 11 healthy subjects and 68 patients with multiple sclerosis (MS).
Results: The TST/MEP ratio was greater in AH vs. ADM (healthy AH: 2.98 (SD 1.35); healthy ADM: 1.68 (0.78); p < 0.001). In MS, the TST/MEP ratio was increased in patients with pro-longed central motor conduction time (CMCT; AH: 3.84 (1.88); ADM: 2.52 (1.58); p < 0.0001), but not in patients with normal CMCT. There was a linear correlation between TST/MEP ratio and CMCT, which was identical for patients and healthy subjects and both muscles.
Discussion: MN discharge desynchronization is proportional to the CMCT, suggesting that it is caused by dispersion of conduction velocities within the corticospinal tract. It increases "along the way"; resulting in greater desynchronization at growing distance (i.e., AH vs. ADM), or after prolonged conduction in MS. The latter indicates homogeneous involvement of all corticospinal fibre contingents in MS.

PSN-12

Effect of ischemia on muscle metabolites assessed with functional magnetic resonance spectroscopy (fMRS) during electrically imposed exercise

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Objectives:
Functional magnetic resonance spectroscopy (fMRS) allows for a well-standardized, non-invasive, continuous monitoring of metabolites involved in energy turnover before, during and after muscle activity imposed by repetitive electrical nerve stimulation. The aim of this study was to assess the effects of ischemia on metabolite depletion and recovery during imposed exercise.

Methods:
6 healthy volunteers were assessed with single voxel (20x20x40 mm) fMRS (TR 1500 ms, TE 270 ms, 8 averages, repeated with a temporal resolution 12 sec) of the anterior tibial muscle during isometric contraction imposed by peroneal nerve stimulation at 20 Hz during 2 minutes. Three separate experiments with A) stimulation without ischemia, B) stimulation starting after 2 min during a 5 min period of ischemia, and C) ischemia without stimulation, were performed on each subject. At least an additional 2 min baseline before, and 5 min recovery after (without stimulation or ischemia), was always measured.

Results:
The depletion of the phosphocreatine (CrP) associated peaks (Cr2 and Cr3) and of the acetyl carnitine (AcCt) peak during imposed exercise was more complete during ischemia. Furthermore, as long as the ischemia was maintained, these changes persisted even after the stimulaton stopped. Only after release of the ischemia, the CrP peaks recovered and the AcCt peak overshot above baseline, whereas without ischemia, this happened immediately after the contraction stopped.

Conclusion:
Anaerobic pathways are exhausted after short but intense muscle exercise: metabolite recovery is dependent on blood supply, probably especially oxygen supply. Regarding clinical diagnostics of muscle diseases, ischemic muscle due to peripheral arteriopathy must also be expected to yield pathological fMRS responses.

PSN-13

**"iMed", a new database for
monitoring patients with multiple sclerosis**

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Background:
Multiple sclerosis (MS) is a chronic, immune-mediated CNS disorder. Course and symptoms of MS are highly variable. Therefore, careful documentation of disease characteristics in a large cohort of patients is essential to identify diagnostic and prognostic factors that can be used for therapeutic decisions in an individual patient.

Methods:
"iMed" is a database for monitoring of patients with multiple sclerosis. All disease characteristics including clinical history, physical examination, neuroradiological, laboratory, electrophysiological findings, treatment and disease course can be visualized both for each individual patient and selected groups of patients.

Results:
Actually 585 patients are registered in our database. Our preliminary data demonstrate, that first MS lesions are evenly distributed throughout the central nervous system. Most frequent course of the chronic CNS-disorder is the relapsing-remitting form affecting mostly young women. Further, a late disease onset is rather associated with a chronic-progressive course. Approximately half of our patient group is treated with immunomodulatory drugs while Mitoxantrone (Immunosuppressive therapy) is used for patients with a high relapse rate.

Conclusion:
Our results are comparable with prior studies (Confavreux et al. 2000; TintorÉ et al. 2005) and represent a basis for further, prospective studies, for example the identification of prognostic factors of the chronic CNS-disorder.

PSN-14

Case Report: Reversible Posterior Leukoencephalopathy Syndrome in a Patient with Hypoplastic Middle Cerebral Artery – Investigation of Brain Perfusion with continuous Arterial Spin Labeling (CASL)

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We report the unusual case of a 28 yrs. old woman presenting with atypical Reversible Posterior Leukocencephalopathy Syndrome (RPLS) due to a hypoplastic middle cerebral artery. Besides well established morphologic Magnetic Resonance Imaging, we have applied Arterial Spin Labelling, an upcoming MR technique allowing a quantified measure of arterial perfusion.The clinical course and imaging findings are discussed with regard to different imaging techniques and their implications on the pathophysiology of RPLS.

PSN-15

Imaging of innervaton patterns with muscle BOLD fMRI

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Objectives:
We applied functional magnetic resonance imaging (fMRI) using blood oxygenation level dependent (BOLD) endogenous contrast to assess the response of human skeletal muscle to exercise, and it's innervation pattern. Methods:Supramaximal repetitive electrical stimulation of the peroneal or ulnar nerve was applied to impose a maximal isometric contraction during 2 minutes. Series of BOLD echo planar images (EPI) of the corresponding muscles were acquired before, during and after stimulation.

Results:
A selective $T2^*$ lengthening was observed in the contracting muscles. After cessation of stimulation, the BOLD signal further increased up to 80% above baseline. Non-contracting control muscles showed no signal changes. Partial (sub-maximal) nerve stimulation resulted in a somatotopically reduced responding muscle area, not in a submaximal response in the whole innervation region. In structurally still normal anterior tibial muscles of patients with neuropathy and myopathy, no fuctional response was obtained. Innervation anomalies (median-ulnar forearm anastomosis) could be demonstrated through visualization of the response pattern, as verified by electrophysiology.

Conclusion:
The vascular response of skeletal muscle is strictly confined to the exercised areas. The signal change is much larger than with brain fMRI. This is explained by the low resting metabolism and its large increase during excercise, as compared with the continuous high metabolic demands of the brain. A diseased muscle can yield an abnormal response, and innervation anomalies can be visualized.

PSN-16

Localization of the irritative zone in epilepsy using simultaneous EEG/fMRI and ICA

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Purpose
Combining fMRI with EEG is a promising addition to the current battery in the workup of epilepsy patients for resective surgery. Areas of fMRI activation related to interictal EEG spikes are likely to represent the irritative zone, which is itself a reflection of the epileptogenic zone. This information may guide depth electrode and grid placement as well as tailoring resections. The present project aims to develop a feasible path to overcome the deficiencies of EEG and fMRI in spatial and temporal resolution, and to provide information about brain regions involved into the generation of epileptic seizures and their network.

Methods
Eleven patients, 5 females and 6 males, age 44.4 ± 15.2 years with focal and generalized epilepsies (six with frontal lobe epilepsy, FLE; four with temporal lobe epilepsy; TLE) and one with juvenile myloclonus epilepsy, who displayed interictal spikes or slowing on EEG, were examined with simultaneous EEG-fMRI recordings (3Tesla Siemens Magnetom Trio).
We assumed that epileptic activity occurs independently from normal physiological brain activity. Therefore we applied an Independent Component Analysis (ICA) to the EEG data, identifying factors representing epileptiform activity. Such factors were convolved with a hemodynamic response function (HRF) to match the much slower time-scale of the fMRI BOLD signal. Voxelwise correlations between the ICA-predictors and the BOLD signal were computed. Regions with significant correlations were interpreted as having been active during the time course of the interictal discharges.

Results
In 10 patients, our method detected the irritative zone, as displayed by the interictal spike activity. In four patients, we found a decreased BOLD signal in the irritative zone, indicating an increased metabolic demand or neuronal inhibition. Six patients had an increased BOLD signal, indicating neuronal activity. The interictal focus localization was in accordance with previously and simultaneously recorded EEG sources and fitted the clinical semiology and imaging findings.

Conclusions
Our preliminary data suggest that simultaneous EEG/fMRI recordings are a safe, noninvasive and promising technique which provides hypothesis independent information about the irritative zone in partial epilepsies. However, developing a tool for clinical use would require EEG/fMRI recordings to be at least equal to intracranial EEG, ictal SPECT and interictal PET in determining which tissue can be removed in surgery without detrimental effect on the patient. Thus, the next step would be the validation of our method in terms of surgery outcomes.

PSN-17

Imaging inherited leukodystrophy – new data from a family with orthochromatic leukodystrophy

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Background and Purpose:
Leukodystrophies are inherited white matter diseases due to abnormalities occurring in myelin synthesis and/or maintenance. Magnetic resonance (MR) imaging has become the primary imaging modality in patients with leukodystrophy and plays an important role in the identification, localisation, and characterization of underlying white matter abnormalities in affected patients. Although the classical MR imaging features of leukodystrophy are often nonspecific, new MR techniques as Diffusion Tensor Imaging (DTI) and MR-Spectroscopy (MRS) may permit a narrower differential diagnosis. This is the first report of DTI and MRS images in a family with a pigmentary form of orthochromatic leukodystrophy.

Methods:
Two patients of a kindred with a history of 4 affected subjects underwent structural MR, DTI and MRS at a Siemens Sonata 1.5 T whole body scanner. The MR protocol included a T1-MPRAGE-Sequence (TR=2000ms, TE=3.93 ms, matrix 256x256, FA 15°), a spin echo EPI-sequence for DTI acquisition (TR=3700 ms, TE=87 ms, matrix 96x128 in 6 diffusion encoding gradient directions) and a MR-Spectroscopy (single voxel PRESS, TE=135ms and 30 ms and a 2-D CSI-Sequence).

Results:
Clinically subjects present with epileptic seizures, frontal disinhibition behavior and diffuse cognitive decline starting at the age of 40, fatal within 3 years in one case. Structural MRI revealed symmetric bifrontal subcortical T1w hypo/ T2w hyperintensities with relative sparing of the U-fibers. Rupture of the blood/brain-barrier was not a feature. Quantitative and voxel-based DTI showed a markedly reduced anisotropy in the frontal lobes as the hallmark of focalised subcortical fiber degeneration. Neuronal degeneration was confirmed by frontal NAA reduction in MRS.

Conclusion:
For the first time this series characterises white matter alterations by DTI and MR-Spectroscopy in a familial, pigmentary form of orthochromatic leukodystrophy. The pattern of decreased anisotrophy restricted to the frontal lobes with relative sparing of the U-fibers has not yet been reported in other forms of leukodystrophies.

Rehabilitation (PSR)

PSR-1

Coping with Brain Injury: First Results of the Bernese-Psychotherapy-Study

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Brain damage is the most common cause of handicap which is acquired during adulthood. Reintegration into society and the return to normal daily routine in life is an enormous challenge. Apart from the emotional pressure of handling the impairment, it is always a question of learning to live with the handicap. The patient will be faced with psychological problems such as, Adjustment Disorders, i.e. complicated grief and depressive symptoms. These represent an important and frequently limiting factor for rehabilitation and are a considerable heavy burden for the family to cope with (Schütte, 2002). In the present study, the coping process and the effectiveness of psychotherapy in the management of grief after a brain injury will be investigated. An objective is to outline the central aspects of the therapeutic process and to find out conditions under which psychotherapy after brain injury is helpful. Ten (10) patients were recruited for this study. The therapy usually took 20 - 25 sessions during a period of 12 - 18 months. In accordance with preliminary data, a significant change can be noted in the area of "Rumination", "Search for Social Integration" and "Cognitive Processing Style". From the results, the conclusion can be drawn that psychotherapy can help these patients to improve self-awareness and hence to realistically evaluate their deficits and their residual capacity to re-establish more satisfactory interpersonal relationships.

PSR-2

Neuropsychological rehabilitation of children and young adults after paediatric ALL, brain tumor and Non-Hodkin-Lymphoma

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Purpose: Long-term survivors of pediatric cancer often show cognitive sequelae (i.e. attention deficits, reduced memory functions, non-verbal learning disability) which may influence the quality of life by failure at school, problems in professional training or social and emotional problems. Cognitive deficits, their pathogenesis, and illness- / treatment-related risk factors have been extensively studied. However, little is known about effective cognitive rehabilitation therapy. The aim of this study was to collect data about the benefit of individually tailored neuropsychological interventions on cognitive outcome and quality of life measurements for survivors of paediatric cancer.
Methods: Clinical phase III study with survivors of paediatric cancer, treated at the university hospital in Berne fulfilling the following criteria: diagnosis maximally 11 years ago, medical treatment finished, at least 6 years old at study entry. After a comprehensive neuropsychological assessment patients with neuropsychological deficits were randomly assigned to a treatment group (6 month of individually tailored neuropsychological rehabilitation measure) or the control group (no treatment / standard treatment). After 6 and 12 month the progresses were evaluated.
Results: The number of study participants was smaller than expected: 45 of 103 persons (aged 6 to 26, 21 males) attended the first examination. 8 showed no neuropsychological deficits, 10 neuropsychological therapies could be performed, 10 persons attended standard therapies, 16 participants got no therapeutic intervention. A first analysis of the neuropsychological data at study entry showed, that the group as a whole scored within the normal range, but significant more individual participants than expected scored below average in the following domains: working speed, memory and flexibility. More heavily affected thereby were the participants who fall ill at a younger age and/or underwent radiation. Statistic evaluation of group differences in cognitive functioning and quality of life as a function of type of intervention is in progress. First data analysis showed significant gains in Performance-IQ in the neuropsychological treatment group compared with the standard treatment group.
Conclusion: Participants profit from individually tailored neuropsychological therapy. Therapies cause individual cognitive improvements (attention, memory, visual perception) still detectable 6 months after the end of therapy. These improvements lead to better school performance which in turn effects well-being and self-confidence. Neuropsychological assessment and neuropsychological therapy should begin shortly after medical treatment is completed.

PSR-3

Reactivation of latent bilateral cognitive networks after stroke in childhood

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Rationale: The infant brain disposes a remarkable flexibility to recover from adverse events such as stroke. Cognitive sequelae are scarce; especially language functions are known to recover well, while visuo-spatial skills are more affected from brain damage, independent on the hemispheric side of lesion. The present study intends to collect data about the mechanisms of reorganisation of cognitive functions after stroke in childhood and aims to search for variables influencing cognitive outcome.

Methods: 11 children after unilateral stroke (10-19 years, 6 left hemispheric lesion, 5 right hemispheric lesion) and 20 healthy controls (8-20 years) were examined with fMRI and neuropsychological tests (Verbal-IQ WISC-III, Copy and Recall of Rey-Figure). fMRI paradigms intended to activate predominantly unilateral networks of the right hemisphere (visual search tasks) and left hemisphere (language tasks) respectively.

Results: Controls data showed that laterality of language and visual search increased significantly throughout childhood and adolescence in left frontal ($r=.391$, $p=.049$) and central areas ($r=.510$, $p=.018$) for language functions and in right parietal ($r=-.608$, $p=.004$), central ($r=-.503$, $p=.024$), and frontal ($r=-598$, $p=.004$) areas for visual search functions. There was a positive correlation between the strength of laterality and Verbal-IQ ($r=.551$, $p=.027$). Patients showed a dislocation of cognitive functions independent of the localisation of the lesion or the age at stroke. Following a left hemispheric lesion, language reorganized likelier within the damaged hemisphere while visual search functions dislocated trans-hemispherically, coinciding with a decrease of visuo-spatial functioning. Bilateral activation in the contralateral hemisphere of patients after stroke occurred in the same brain areas that were active in the youngest of the healthy controls, but not active in older children.

Conclusion: The increase in laterality of cognitive functions throughout development in healthy controls possibly occurs due to cognitive specialisation and hence strengthening of cognitive networks. This increase in laterality might result from a selective elimination of synapses from functional components that become redundant in the process of cognitive specialisation. The correlation between functional and behavioural data indicates a relation between laterality of a function and its performance level. Consequently, after paediatric stroke performance level is better in case of reorganisation within the damaged hemisphere, coinciding with stronger laterality. After stroke, activation foci occur in homotopic areas of the contralateral hemisphere – the same areas which are involved in cognitive processing in younger children, but regress during development. For this reason, a reactivation of latent bilateral cognitive networks is thought to be responsible for the remarkably good recovery of cognitive functions after brain lesion in childhood.

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