NeuroNRW

NeuroVisionen 7

ABSTRAKTBAND

Nachwuchstagung

NeuroVisionen 7

07. Oktober 2011

Veranstaltungsort:

Hörsaal, OPZ II

Universitätsklinikum Essen

Universitätsklinikum Essen

Grußwort

Liebe Nachwuchswissenschaftlerinnen und liebe Nachwuchswissenschaftler,
liebe Kolleginnen und Kollegen,

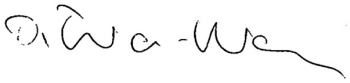
im Namen des Kompetenznetzwerks Neurowissenschaften des Landes Nordrhein-Westfalen (NeuroNRW) möchten wir Sie zur 7. NeuroVisionen Nachwuchstagung herzlich willkommen heißen. Wir freuen uns sehr, die Tagung dieses Jahr am Universitätsklinikum Essen auszurichten. Die Nachwuchstagung soll talentierte Nachwuchswissenschaftler/innen aus allen neurowissenschaftlichen Standorten NRWs zusammen bringen, um wissenschaftliche Arbeiten vorzustellen und zu diskutieren. Die Veranstaltung besteht aus einer Postersitzung sowie einer vielfältigen und wissenschaftlich interessanten Vortragsreihe von Nachwuchswissenschaftler/innen aus NRW.

Nordrhein-Westfalen weist in der dichtesten Hochschullandschaft Europas eine ausgewiesene Expertise in den Neurowissenschaften auf. Die Forschungsaktivitäten reichen von zellulären Grundlagen der Neurophysiologie bis zur Erforschung des Gehirns und seiner Erkrankungen.
Im Sommer 2002 wurde das Kompetenznetzwerk Neurowissenschaften des Landes Nordrhein-Westfalen (NeuroNRW) durch das Wissenschaftsministerium des Landes gegründet, um ein Forum für Neurowissenschaftler aus ganz NRW zu schaffen, gemeinsam den Forschungsstandort Nordrhein-Westfalen zu stärken, und eine Kommunikationsbasis für interdisziplinäre Forschungskooperationen unter Neurowissenschaftlern aufzubauen.
Ziele sind die Förderung interdisziplinärer und anwendungsorientierter Forschungsprojekte, die Nachwuchsförderung und die Darstellung des Netzwerkes und damit der Kompetenz auf dem Gebiet der Neurowissenschaften aus Nordrhein-Westfalen. Die Kontakte der Neurowissenschaftler/innen untereinander sollen gestärkt werden und Synergieeffekte zum Tragen kommen.

Die Hauptstandorte der Neurowissenschaften sind Aachen (RWTH Aachen), Bielefeld (Universität Bielefeld), Bochum (Ruhr-Universität Bochum), Bonn (Rheinische Friedrich-Wilhelms-Universität Bonn), Düsseldorf (Heinrich-Heine-Universität Düsseldorf), Duisburg-Essen (Universität Duisburg-Essen), Jülich (Forschungszentrum Jülich), Köln (Universität zu Köln, Max Planck Institut für Neurologische Forschung und die Deutsche Sporthochschule) und Münster (Westfälische Wilhelms-Universität), und werden durch Standortvertreter/innen repräsentiert. Diese Standortvertreter bilden gemeinsam ein Gremium, welches unterstützende und interaktionsbildende Maßnahmen durchführt, um die Kommunikation innerhalb der Forschergruppen der neurowissenschaftlichen Standorte sowie die Sichtbarkeit der Neurowissenschaften in NRW zu erhöhen. Ein Hauptaugenmerk der Arbeit von NeuroNRW besteht in der Förderung und der Stärkung des neurowissenschaftlichen Nachwuchses.
Das Netzwerk hat bereits eine Reihe erfolgreicher Netzwerktagungen, Publikumsveranstaltungen sowie Poster- und Publikationswettbewerben veranstaltet.

Wir freuen uns, in diesem Jahr auf dem Gelände des Universitätsklinikums Essen die 7. NeuroVisionen Nachwuchstagung veranstalten zu können. Wir wünschen Ihnen eine informative und spannende Veranstaltung, viele neue Ideen sowie Anreize für Ihre eigene Forschung und vor allem einen anregenden Tag des Austausches, der hoffentlich auch Impulse zur Vertiefung und Erweiterung laufender Forschungsprojekte geben wird. Die Tagung wird mit der freundlichen Unterstützung der Forschungskommission und der neurowissenschaftlich arbeitenden Kliniken und Institute des Essener Universitätsklinikums sowie des Research Department of Neuroscience der Ruhr-Universität Bochum ermöglicht .

Mit herzlichen Grüßen,
Ihre



Prof. Dr. Dagmar Timmann-Braun

Standortsprecherin Duisburg-Essen
Neurologische Klinik

Prof. Dr. Sigrid Elsenbruch

Inst. f. Med. Psychologie &
Verhaltensimmunbiologie

Programm

8:30 Uhr	**Einführung und Begrüßung** **Prof. Dr. Dagmar Timmann** *(Standortsprecherin Uni Duisburg-Essen)* **Prof. Dr. Joachim Weis** *(Sprecher des Kompetenznetzwerkes-NeuroNRW)*
8:40 Uhr	**Grußwort NN** *(Ministerium für Innovation, Wissenschaft und Forschung des Landes NRW*
8:50 Uhr	**Grußwort Prof. Dr. Jan Buer** *(Prodekan für Forschung & wissenschaftlichen Nachwuchs, Universitätsklinikum Essen)*
9:00-9:45 Uhr	**Keynote lecture** **Prof. Dr. Manfred Schedlowski** *(Institut für Medizinische Psychologie und Verhaltensimmunbiologie, Universitätsklinikum Essen)* **„Expectations and associations that heal: Placebo/nocebo effects and their neurobiology"**
9:45 Uhr	**Vorträge von Nachwuchswissenschaftlern/innen**
9:45-10:00 Uhr	Standort **Duisburg Essen** **Dr. Philipp Dammann** *(Klinik für Neurochirurgie, Universitätsklinikum Essen)* **„Cerebrovascular disease in the ultra-highfield MRI"**
10:05-10:20 Uhr	Standort **Aachen** **Prof. Dr. Florian Zepf** *(Klinik für Psychiatrie, Psychosomatik und Psychotherapie des Kindes- und Jugendalters; Universitätsklinikum Aachen)* **„Neural correlates of processing emotional stimuli in children and adolescents with ADHD - An fMRI study on serotonergic modulation"**
10:25-10:40 Uhr	Standort **Münster** **PD Dr. Dr. Udo Dannlowski** *(Klinik für Psychiatrie und Psychotherapie, Universitätsklinikum Münster)* **„Neurogenetics of emotion processing"**
10:45 Uhr	**Kaffeepause (Vorbesprechung der Jury)**
11:15-14:00 Uhr	**Posterausstellung NeuroVisionen 7 und Posterbegutachtung**

14:00 Uhr	**Vorträge von Nachwuchswissenschaftlern/innen**
14:00-14:15 Uhr	Standort **Bochum** **Dr. Christian Bellebaum** *(Institut für Kognitive Neurowissenschaft, Ruhr-Universität Bochum)* **„Neural mechanisms of behavioural adaptation in humans“**
14:20-14:35 Uhr	Standort **Jülich** **Dr. Ralph Weidner** *(Institut für Neurowissenschaften und Medizin, Forschungszentrum Jülich)* **„Just an illusion? Size perception in the human brain“**
14:40-14:55 Uhr	Standort **Bonn** **Dr. Stefan Remy** *(Klinik für Epileptologie, Universitätsklinikum Bonn)* **„Synaptic signal computation on neuronal dendrites“**
15:00-15:15 Uhr	Standort **Köln** **Dr. Maria Adele Rüger** *(Klinik und Poliklinik für Neurologie, Universitätsklinikum Köln)* „Imaging endogenous neural stem cells in vivo using Positron Emission Tomography“
15:20-15:35 Uhr	Standort **Düsseldorf** **Dr. David Kremer** *(Neurologische Klinik, Heinrich-Heine-Universität Düsseldorf)* **„Identification of novel targets relevant for remyelination in multiple sclerosis“**
15:40 Uhr	**Kaffeepause**
16:00-16:30 Uhr	**Bekanntgabe der Gewinner/innen des Poster-Wettbewerbs und anschließende Preisverleihung; Schlusswort**
16:30-17:30 Uhr	Treffen der Standortvertreter/innen

Abstrakts

Structural and functional imaging in the mouse brain: Multimodal imaging of murine neural progenitor cells

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Introduction: In order to restore brain function after stroke, implantation of stem cells has been under investigation. To better understand the role of stem cells in promoting recovery, the location and function of grafted cells must be monitored *in vivo* using noninvasive imaging. Here we describe a novel combination of two noninvasive modalities for imaging neural progenitor cells, namely ^{19}F Magnetic resonance imaging (MRI) and Bioluminescence imaging (BLI). ^{19}F MRI presents the advantage of a high spatial resolution and a lack of background signal, permitting the unambiguous localization and quantification of cells in the host organ. In combination with a ^{1}H MRI scan, detected cells can be placed within their anatomical context. BLI, on the other hand, can provide insight into the functional status and viability of cells.

Methods: A neural progenitor cell line transfected to stably express the membrane-bound form of the Gaussia luciferase was incubated with a perfluoropolyether (PFPE) emulsion. *In vitro* ^{19}F MR spectroscopy of fixed, labeled cells was carried out at 11.7T (Bruker BioSpec, Ettlingen, Germany) using a single pulse sequence. Quantification of cellular uptake was carried out by comparing the areas under the peaks of a KF standard and of the PFPE to determine the number of ^{19}F spins per cell in the sample. The optimum concentration of PFPE to maximize the ^{19}F MR signal was determined and employed for all subsequent experiments. The effects of labeling on cell vitality, proliferation, migration, and differentiation were assessed, using the Trypan blue exclusion assay, a Neubauer chamber, a scratch assay and immunocytochemical stainings. Labeled cells were implanted into the striatum of mice. 48 h later, *in vivo* ^{19}F MRI and ^{1}H MRI scans were conducted at 11.7 T using turbo spin echo sequences (total acquisition time = 1.5 h). For BLI experiments, different amounts of transfected and wild-type cells were seeded, the substrate coelenterazine was added, and samples were placed into an optical imaging system (Biospace, Paris, France). Scanned cells were harvested, fixed, and seeded in two different quantities and ^{19}F MRI was conducted for multimodal detection.

Results: *In vitro* ^{19}F MR scans proved consistent, high cellular uptake of PFPE. Labeling did not affect cell vitality, migration and differentiation. However, it transiently slowed cell proliferation. Using *in vivo* ^{19}F MRI, labeled cells could easily be detected and localized. Cells could also be detected *in vitro* using BLI and a linear correlation of the BLI signal and the cell number was found. The multimodal detectability of the cells was proven through the subsequent ^{19}F MRI.

Conclusions: For the first time, ^{19}F MRI and BLI were combined to image neural progenitor cells. Multimodal imaging of implanted cells provides a combination of structural and functional information, which will permit to further optimize preclinical protocols for stem cell-mediated functional recovery in acute and neurodegenerative disorders of the brain.

Acknowledgements: This work was financially supported by grants from the Volkswagen Foundation (I/83 443) and the ENCITE EU-FP7 (HEALTH-F5-2008-201842) program.

Increased intrinsic network connectivity in grapheme-colour synaesthesia

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Introduction: Although to date the underlying neural mechanisms of synaesthesia remain elusive, it has often been hypothesized that the concomitant synaesthetic perception of a sensation not inherent to the stimulus is caused by an increased connectivity between the relevant brain regions. That is, in the case of grapheme-colour synaesthesia, occipital and temporal brain regions involved in grapheme and colour processing, but also parietal and frontal areas involved in binding processes. Support for increased *structural* connectivity in grapheme-colour synaesthetes is provided by diffusion tensor imaging studies. However, an investigation (with functional magnetic resonance imaging, fMRI) of coherent neuronal activity, i.e. *functional* connectivity in synaesthesia, is lacking to date.

Methods: Twelve grapheme-colour synaesthetes and twelve control subjects (matched for gender, age, IQ, and handedness) were scanned with fMRI during a resting-state period of 10 minutes. Intrinsic connectivity networks (ICNs) were extracted from the resting-state fMRI (rs-fMRI) data by applying independent component analysis. A multiple spatial regression analysis revealed seven synaesthesia-relevant ICNs: medial and lateral visual network, auditory network, left and right fronto-parietal network, and medial and lateral parietal network. For each subject, the functional network connectivity (FNC) was characterized by calculating pairwise zero-lag time course correlations between these seven ICNs using the FNC toolbox.

Results: The FNC analysis of the seven synaesthesia relevant ICNs revealed five significant connections for the control group (as indexed by significant correlations between the time courses of the seven ICNs). In stark contrast, 15 significant connections between the seven ICNs were present in the synaesthetes. Furthermore, the direct group comparison revealed that two specific network connections were significantly stronger in the synaesthetes: the connections between the medial and lateral visual networks and the right fronto-parietal network. The connection between the lateral visual and auditory networks showed a trend towards significance. Moreover, increased intrinsic network connectivity correlated significantly with the consistency of synaesthetic experiences.

Discussion: Supporting neurobiological models of synaesthesia which hypothesize increased connectivity in synaesthesia, the current rs-fMRI study reveals, for the first time, increased global and specific (intrinsic) *functional* network connectivity in grapheme-colour synaesthetes, complementing earlier findings of increased

structural connectivity. Our data are consistent with prior data suggesting that differences in intrinsic network connectivity are directly related to the phenomenology of human experiences: persons with additional experiences (either extraordinary, as in the case of synaesthesia, or pathologically, as in schizophrenia) exhibit increased functional network connectivity, while persons with neurological or psychiatric deficits resulting in limited experiences (e.g., as in dementia) exhibit reduced functional connectivity.

PDE4-Inhibition Facilitates Hippocampal Synaptic Plasticity and Rescues MK801-induced Long-term Impairment in LTP and Object Recognition Memory in Freely Moving Rats

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Inhibition of phosphodiesterase type 4 (PDE4) by Rolipram (4-(3-(Cyclopentyloxy)-4-methoxyphenyl)-pyrrolidin-2-one) has been the focus of many behavioral and molecular studies in the recent years. Rolipram exhibits a memory-enhancing effect in rodents. *In-vitro* studies have shown that long-term potentiation (LTP), which is believed to comprise a cellular substrate for learning, is also enhanced by Rolipram. However, effects have not been assessed *in-vivo*. Rolipram has antipsychotic properties. Psychosis affects cognition, and in animal models of psychosis LTP is impaired. In this study, we investigated if PDE4-inhibition improves LTP in healthy animals *in-vivo*. Furthermore, we explored if PDE4-inhibition rescues impaired LTP and prevents object recognition memory deficits in an animal model of psychosis.

Male Wistar rats (7 – 8 weeks old) were implanted chronically with a bipolar stimulation electrode in the medial perforant pathway and a monopolar recording electrode in the dentate gyrus granule cell layer, as well as with a cannula in the ipsilateral cerebral ventrical to enable drug application. In vivo electrophysiological experiments were conducted ca. 10 d after surgery. Short-term potentiation (STP) or LTP were elicited by using high frequency tetanisation (three bursts of 15 pulses at 200 Hz and 10 sec interburst interval or ten bursts of 15 pulses at 200 Hz and 10 sec interburst interval, respectively) in freely moving rats. Rats were injected systemically with either MK801 or saline. 1 week later LTP or object recognition was assessed. Rolipram was applied either intracerebrally or subcutaneously.

In healthy animals, both intracerebral and subcutaneous treatment with Rolipram, facilitated short-term potentiation (STP) into LTP, suggesting that PDE4 inhibition may play a permissive role in plasticity mechanisms that are relevant for learning and memory. One week after a single systemic treatment with the irreversible N-methyl-D-aspartate antagonist, MK801, LTP and object recognition memory were significantly impaired, but were rescued by PDE4 inhibition.

These data suggest that the relief of cognitive disturbances in psychosis models by Rolipram, may be mediated in part by a rescue of hippocampal LTP and that PDE4-inhibition could be given consideration as a therapeutic strategy in the treatment of psychosis-related diseases.

Attentional Modulation by tDCS in stroke

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Background: Attentional deficits are a common consequence after stroke, particularly in the early phase. Yet, especially a functioning attentional system is essential for all cognitive and visuospatial processes and thereby an important precondition for rehabilitative interventions during stroke recovery. Being the most basic intensity aspect of attention, alertness is considered to be a prerequisite for more complex attention processes. Transcranial direct current stimulation (tDCS) has proven to be a helpful device in the treatment of motor and spatial deficits after stroke; hence it might also be a promising option in attentional recovery. **Objective:** Enhancement of right hemispheric (RH) stroke patients' alertness levels by stimulating their right and left dorsolateral prefrontal cortex. Examining the feasibility of this sort of tDCS study with stroke patients.

Methods: So far two subacute RH stroke patients from a university hospital and one RH stroke patient from the chronic phase were included. Anodal (excitatory) real tDCS (2mA for 20 min) and sham stimulation (2mA for 1 min) was applied. Post stimulation effects and pre stimulation baseline attentional function were assessed by three subtests that constitute the minimal set of the computerized Tests for Attentional Performance (TAP) battery: the alertness, divided attention and the Go/NoGo (selective attention) subtests.

Results: In the chronic patient, alertness performance increased significantly after left sided tDCS. A significant increase in alertness performance after tDCS in the subacute patients could not be shown with the sample size of two. In order to measure tDCS related attention improvement, the alertness task is a feasible means of examining alertness, whereas the divided attention task seems to be too difficult. Feasibility of the Go/NoGo task remains to be further investigated.

Conclusion: Preliminary results of 3 patients indicate feasibility of the study protocol with minor adjustments in order to investigate improvement effects of tDCS on alertness performance: The TAP divided attention task will be excluded; self-report questionnaires to control for motivation-, practice and fatigue effects will be added.

Social Cognition during Experimental Human Endotoxemia: an fMRI Study

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Background: Acute inflammation with corresponding increases in peripheral cytokines is discussed to affect neuropsychological functions. The aim of this functional magnetic resonance imaging (fMRI) study was to investigate the effects of experimentally induced acute inflammation on social cognition performance and neural response in healthy subjects.

Methods: In a double-blind, randomized crossover study, 18 healthy, right-handed male volunteers received an injection of lipopolysaccharide (LPS; 0.4ng/kg E.coli) or saline. Plasma levels of pro- and anti-inflammatory cytokines and cortisol as well as mood ratings were analyzed together with brain activation during a social cognition task (Reading the Mind in the Eyes Test).

Results: LPS administration induced pronounced transient increases in pro- (IL-6, TNF-α) and anti-inflammatory (IL-10, IL-1ra) cytokines as well as cortisol plasma concentrations. Further, positive mood was decreased and state anxiety elevated. However, social cognition performance was not affected by acute inflammation. In contrast, the LPS condition showed increased responses in the fusiform gyrus, middle temporal gyrus, temporo-parietal junction, superior temporal gyrus and precuneus during the social cognition task.

Discussion: The increased task-related responses in the LPS condition may reflect a compensatory strategy of the brain to maintain normal task performance and ensure social support from others during physical weakness.

Funding: German Research Foundation (Sche 341/14-1)

Exercise during pregnancy mitigates Alzheimer-like pathology in mice offspring

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Introduction: Physical activity protects brain function in healthy individuals and those with Alzheimer's disease (AD). Evidence for beneficial effects of parental exercise on the health status of their progeny is sparse and limited to non-diseased individuals. Here, we questioned whether maternal running interferes with offspring's AD-like pathology and sought to decipher the possible underlying mechanisms in the transgenic (TG) CRND8 mouse model for AD.

Methods: Maternal stimulation was provided by voluntary wheel running compared to standard housing during pregnancy. TG and wild type (WT) offspring were housed in standard cages immediately after birth for five months. After monitoring the cognitive performance, the brains of these mice were examined for AD-related pathology and/or plasticity changes.

Results: Running during pregnancy resulted in improved memory performance in healthy and diseased offspring. This effect was accompanied by reduced beta-amyloid (Aβ) plaque burden, mediated by decreased amyloidogenic processing of the amyloid precursor protein, diminished inflammation as indicated by reduced microgliosis and down-regulation of other pro-inflammatory mediators, mitigated oxidative stress as nitro-tyrosine level declined, and improved neurovascular function by orchestrating different Aβ transporters and increasing angiogenesis in TG offspring. Furthermore, plasticity changes were found not only in TG but also in WT progeny.

Conclusion: These results suggest that exercise during pregnancy provides long-lasting protection from neurodegeneration and improves cognitive performance and brain plasticity in the otherwise unstimulated progeny.

Positive and negative monetary feedback learning in alcohol dependent patients

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Introduction: Chronic and excessive consumption of alcohol leads to structural, physiological and functional changes in multiple regions of the human brain – including the prefrontal cortex, the medial temporal lobe and the structures of the reward system – and influences cognitive, emotional and behavioral capacities. As recent investigations revealed alcohol-associated changes in the processing of reward stimuli, the present study intended to examine the ability of alcohol dependent patients to learn probabilistic stimulus-reward contingencies and to transfer the acquired knowledge to new contexts. During transfer, the potential bias to learn from positive or negative feedback (monetary reward and non-reward, respectively) was also assessed.

Methods: Twenty-four recently detoxified alcohol dependent patients and 20 healthy control subjects performed a feedback learning task with monetary rewards. Acquisition of stimulus-response-outcome contingencies, transfer performance and the tendency to learn from positive or negative feedback were assessed. The relationship between different learning parameters and clinical variables related to drinking behavior as well as personality traits such as harm avoidance, impulsivity and reaction inhibition were also examined.

Results: Alcohol dependent patients did not show a general learning deficit in the acquisition phase. In the transfer phase, which was reached by 13 alcohol dependent patients and 15 healthy control subjects, the patients showed generally lower performance compared to controls. There was no between-group difference with regard to better learning from positive or negative feedback. The only near-significant (negative) correlation emerged for harm avoidance and positive learning in healthy controls.

Conclusions: Our findings propose that feedback learning in alcohol dependent patients is altered compared to learning in healthy control subjects. But patients do not show deficits in learning stimulus-outcome associations. Rather they are impaired in the transfer of the learned associations to new contexts. This possibly reflects impaired declarative learning. Hence, we discuss possible dysfunctions in medial temporal lobe and/or prefrontal brain structures.

Funding: Ministerium für Innovation, Wissenschaft und Forschung des Landes Nordrhein-Westfalen; MIWF – grant number 334-4

The impact of tDCS current strength on visual attention

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Objectives: Transcranial direct current stimulation (tDCS) is a painless and non-invasive stimulation technique with polarity-specific effects on cortical excitability. In the present study we used cathodal tDCS to investigate the impact of different current strengths on visuo-spatial attention networks. Stimulating the right intraparietal sulcus (rIPS), as a critical node of the dorsal fronto-parietal attention network, was expected to alter behavioural visual attention parameters as a function of stimulation strength.

Methods: 20 healthy, right-handed subjects (mean age 25.86 years, 10 males) were investigated in a within-subject design tDCS study, including four different sessions of stimulation (cathodal 1mA, 285.7A/m^2, 20min and sham, cathodal 2mA, 571.4A/m^2, 20min and sham). Correct electrode placement over the rIPS and the contralateral orbita was assured using stereotactical neuronavigation. Subjects performed a partial report task and were asked to name target letters defined by a relevant colour. A target was presented either on its own or simultaneously with a second item, which could be either another target or a distractor, in the same or opposite hemifield.

Results: In sham conditions, detection performance was highest for target alone conditions, while the presence of a second item (target or distractor) impaired performance. For displays comprising two items, performance was poorer when the second item was a target and when both stimuli were presented within the same hemifield. The effect of tDCS versus sham stimulation on behavioural performance was tested with separate ANOVAs for the 1mA and 2mA conditions. For the two-item conditions, cathodal tDCS differentially modulated performance in conditions with distractor stimuli. While this effect was restricted to distractors presented in the same hemifield in the 1mA condition (stimulation[cathodal/sham] x display[same/other hemifield] x relevancy[target/distractor] interaction effect, ($F(1,19)=6.785$; $p<0.02$)), the 2mA tDCS effect was independent of the display configuration (stimulation[cathodal/sham] x relevancy[target/distractor] interaction effect, ($F(1,19)=4.505$; $p<0.05$)).

Conclusions: tDCS over rIPS modulates performance in the partial report paradigm, with qualitatively different effects depending upon current strength. The data suggest a specific impact of cathodal tDCS on different cortical attention networks and contribute to a further understanding of the neurobiological effects of cathodal tDCS on cognitive processes.

Repair of Visual System Lesions by Neural Stem Cell Populations

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Introduction: Regeneration of the central nervous system (CNS) after lesion is severely limited in mammals. One strategy to improve function in the diseased CNS is the implantation of neural stem/progenitor cells. The visual cortex represents an appropriate model system for regeneration and plasticity studies due to its convenient accessibility and the extensive knowledge about synaptic plasticity and reorganisation in this region. A particular emphasis will be given to extracellular matrix (ECM) molecules which are known modulators of cell division, migration, differentiation and integration. Before transplantation, an understanding of the ECM composition and of the involved glial cell types in the lesioned brain is essential. Here, we present the findings we made so far in the mouse visual cortex.

Methods: In a first step we established laser lesions of a defined size in the murine visual cortex. Laser lesions in rat visual cortex are well described, while the mouse system offers the advantage of manifold available knock out strains. The ECM as well as the cells appearing in the penumbra are analyzed employing immunohistochemistry and *in situ* hybridization. Later, integration of transplanted neural stem/progenitor cells, labeled with the green fluorescent protein (GFP), and their effect on regeneration will be analyzed *in vivo* and *in vitro*.

Results: The lesion site was characterized with regard to the different glial subtypes involved in reactive gliosis and to the ECM composition three days after lesion. Glial subtypes expressing the markers nestin, glial fibrillary acidic protein (GFAP), vimentin or S100β were not distributed equally, they rather showed typical distributions. Three days after lesion, nestin was found near the lesion, GFAP showed a widespread up-regulation, while vimentin was found in an intermediate pattern. Subpopulations of cells expressed either one of the markers alone or coexpressed different markers. An altered ECM composition was observed: The stem cell-related DSD-1-epitope was expressed on the surface of astroglia-like shaped cells near the lesion core. Tenascin-C, a glycoprotein expressed in the CNS during development and after injury, was found up-regulated in the lesioned cortex in GFAP-positive astroglia.

Conclusions: Reactive gliosis was observed as expected after lesion. The spatial distribution of different glial subtypes was examined, showing a specific expression pattern of the markers nestin, GFAP, vimentin and S100β. The characterization of the extracellular matrix composition showed the expression of the DSD-1-epitope and tenascin-C in the penumbra. GFAP and vimentin expression is typical of reactive astrocytes, while nestin and the DSD-1-epitope

are also characteristic of radial glia and progenitor cells. Therefore these cells are candidates for neurosphere-forming progenitors observed postlesionally in the rat (Sirko *et al*., 2009). In the light of a neurogenic potential described for cells in the penumbra, this suggests a model where some astroglial cells, probably expressing the stem cell-related DSD-1-epitope, provide a potential intrinsic source of newborn neurons. Transplantation of neural stem/progenitor cells into the lesioned tissue will allow us to study their migration, differentiation and integration as well as their effect on regeneration. Also here, the study will focus on effects mediated by extracellular matrix molecules.

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Screening for anorexia nervosa via measurement of serum leptin levels

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Introduction: Due to their sub-normally low fat mass, leptin levels in patients with acute anorexia nervosa (AN) are well below reference levels for age and sex matched controls. This hypoleptinemia entails endocrinological and behavioural characteristics observed in AN patients during starvation.

Methods: We aimed to study appropriateness of hypoleptinemia as a diagnostic marker for AN by assessing sensitivity, specificity and likelihood-ratios for different referral serum leptin levels for predicting anorexia nervosa and healthy leanness. For prediction we additionally generated a score based on a multivariate logistic model including body mass index (BMI; kg/m²) and leptin level. For this purpose we measured leptin levels in 74 female patients with acute AN upon admission for inpatient or outpatient treatment. Adolescent and adult patients were recruited according to DSM-IV criteria from two multi-center studies. Additionally, leptin levels were measured in 65 female healthy underweight students.

Results: Mean serum leptin level was significantly decreased in patients with AN compared to underweight controls (0.87 ± 0.90µg/L vs. 6.43 ± 3.55µg/L, $p<0.001$). Leptin predicted AN independently of BMI; we confirmed a cut-off value in the range of 2µg/L as having both high specificity and sensitivity.

Conclusions: Hypoleptinemia represents a state marker of acute AN and is useful for a laboratory-based diagnostic screening.

Metabolic profiling in patients with anorexia nervosa: Comparison of metabolic profiles of acutely ill and weight recovered patients with anorexia nervosa reveals alterations of 29 out of 163 metabolites

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Introduction: Metabolomics serves as a powerful tool to identify biochemical pathways affected by diseases and as a link between genotype and phenotype. Starvation represents an extreme state of an organism and entails numerous endocrinological and metabolic adaptations. The large-scale application of metabolomics to patients with acute anorexia nervosa (AN) could lead to the identification of both state markers characteristic of the starvation associated with this mental disorder and trait markers which are specific for anorexia nervosa itself. Whereas previous studies have revealed alterations of single amino acids and fatty-acids of patients with AN in comparison to healthy controls, novel metabolomics technology has not yet been applied to this eating disorder.

Methods: We studied 163 metabolites in 29 patients with AN in the acute stage of starvation (T0) and after weight gain (T1). Metabolite concentrations that differed significantly between the acute and weight recovered states were then compared to concentrations obtained in 25 age and gender matched controls; we hypothesized that concentrations are similar in weight recovered patients and controls.

Results: Twenty nine of the metabolite serum levels were significantly different between the acute stage (T0) and after weight gain (T1). Interestingly, for most of these metabolites concentrations of controls differed more strongly from those of AN patients after weight gain than at the acute stage of starvation.

Conclusion: We conclude that AN entails profound and long lasting alterations of a number of serum metabolites; further studies are warranted to distinguish between state and trait related alterations and to establish diagnostic sensitivity and specificity of the thus altered metabolome.

Activation of the dentate nucleus in a verb generation task: A 7T MRI study.

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Background: There is increasing evidence of a topographic organization within the human cerebellar cortex for motor and non-motor functions. Likewise, a subdivision of the dentate nucleus in a more dorsal and rostral motor domain and a more ventral and caudal non-motor domain has been proposed by Dum and Strick (2003) based on anatomical studies in monkey. In humans, however, very little is known about topographic organization within the dentate nucleus.

Methods: Activation of the dentate nucleus in a verb generation task was examined in young and healthy subjects using ultra-highfield 7T functional magnetic resonance imaging (fMRI) with its increase in signal-to-noise ratio. Data of 17 subjects were included in statistical analysis. Subjects were asked to (i) read words (nouns) aloud presented on a screen, (ii) silently read the same nouns, (iii) silently generate the appropriate verbs to the same nouns and (iv) to silently repeat the names of the months. A block design was used. For image processing, a recently developed region of interest (ROI) driven normalization method of the dentate nuclei was applied.

Results: Activation related to motor speech (contrast aloud reading minus silent reading) was strongest in the rostral parts of the dentate nucleus. Dorsorostral activations were present bilaterally. Activation related to verb generation (contrast verb generation minus silent reading) was found in the ventrocaudal parts of the dentate nucleus on the right.

Discussion: The present findings are in good accordance with the anatomical data in monkeys and suggest that the human dentate nucleus can be subdivided into a rostral and more dorsal motor domain and a ventrocaudal non-motor domain.

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Crossmodal working memory performance in professional musicians and non-musicians

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Introduction: An influential model on working memory suggests that visual input is automatically transferred into its phonological code to support rehearsal. This transformation process has been investigated in a former study, where we investigated crossmodal processing (visual and auditory) in working memory. We could demonstrate that the matching of visual and auditory stimuli activated the primary auditory suggesting a recoding of visual stimuli when being compared with their auditory probe. To further study crossmodal processing in both directions (auditory - visual, visual - auditory) professional musicians reflect a perfect population because they are trained in reading musical notes and transcribing auditory music into its written form.

Methods: 15 professional musicians and 15 non-musicians performed a new designed 2-back task with changing and non-changing modalities namely visual and auditory rhythm pattern. Inverse efficiency scores served as a measure of behavioral performance. Brain activations were assessed using event-related functional magnetic resonance imaging (fMRI).

Results: The professional musicians did not differ significantly in the uni- and crossmodal trials of the 2-back task on the behavioral level. The non-musicians' performance was significantly lower in unimodal auditory and crossmodal auditory-visual conditions. Imaging data revealed in accordance with recent studies the activation of the primary auditory cortex during matching of visual and auditory stimuli in both groups. In contrast, when matching of auditory and visual stimuli was required, both groups activated extrastriate visual areas along the ventral stream, namely the lateral occipital complex and the fusiform gyrus extended into the cerebellum, but only the professional musicians additionally activated the right dorsolateral prefrontal cortex (DLPFC).

Conclusions: Our findings support and strengthen the consideration of an active recoding rather than rehearsal process of crossmodal material in general. Further, common and shared neural networks of crossmodal processing in the two populations were identified: Both groups showed a transformation of visual input into auditory information in the primary auditory cortex (which might be a basic skill) and activations in the ventral stream during transformation of its counter piece. But only professional musicians were able to use top-down control to solve the latter task as reflected by activation of right DLPFC (this process of transcription has to be intensely trained during musical education). This finding

yields empirical evidence that expertise in musicians may lead to far transfer in working memory domain and to the use of more efficient neuronal networks due to intense and extensive training from early childhood. Hence, professional musicians provide an ideal model for brain plasticity.

The Amphibian Olfactome

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Background: The sense of smell helps animal species to evade predators, localize prey and recognize viable mates. Odors are a rich source of information, and are perceived by sophisticated olfactory systems, that have evolved over time. In humans, memoirs, thoughts, emotions, and associations are more readily reached through the sense of smell than through any other channel, suggesting that olfactory processing may differ considerably from processing in other sensory modalities. The molecular age in olfaction initiated in 1991 with the discovery of a large multigene family of olfactory receptors in rat by Linda Buck and Richard Axel (Buck and Axel, 1991).

Methods: Our study focuses on Western clawed frog (*Xenopus tropicalis*), a diploid organism that can be considered an evolutionary bridge between aquatic and terrestrial life. Several distinct differences between teleost and tetrapods olfactory receptor repertories have been reported, and a stringent analysis of the olfactory system of early and partially still aquatic tetrapods such as *Xenopus* should throw light on the evolutionary events leading to this transitions. Two olfactory receptors vomeronasal type1 and vomeronasal type 2 (V1R,V2R) receptor families of *Xenopus tropicalis* were retrieved, using homology data mining on publically available genomic databases for the vomeronasal type 1 (V1Rs) and vomeronasal type 2 (V2Rs) receptors families followed by Phylogenetic analysis. We have also begun to analyze the expression of olfactory receptors by *in situ* hybridization of tadpole olfactory epithelium.

Results: We identified 23 vomeronasal type 1 (V1Rs) and more than 500 vomeronasal type 2 (V2Rs) olfactory receptors, considerably more than previously published (Saraiva and Korsching, 2007; Ji et al, 2009) and for V2Rs the largest repertoire of any species analyzed so far.

Discussion: Working with *Xenopus tropicalis* as a model organism can help us to understand the evolutionary history of the olfactory system in vertebrates. Our analysis shows:

- *X. tropicalis* has undergone massive expansion in the V2R gene family, presumably to accommodate between water to air odor detection.
- *X. tropicalis* V1R represent the transition between the teleost and tetrapods V1R repertoire, as they underwent moderate species specific expansion.
- In comparison to fish, Xenopus have formed an additional olfactory organ called vomeronasal organ (VNO), which however houses only one of the receptor family out of two known to be expressed in mammalian VNO.

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Nutzen einer automatisierten MRT-Bedienungssoftware für Kopfuntersuchungen

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Fragestellung: Der Arbeitsaufwand für MTRAs von neuroradiologischen Untersuchungen zweier 1,5 T MRT Geräte mit bzw. ohne automatisierte Bedienungssoftware “day optimizing throughput (dot) engine” werden intraindividuell verglichen.

Methode: 34 prospektiv eingeschlossene Patienten wurden gemäß ihrer Erkrankung mit vier standardisierten Protokollen jeweils in zwei 1.5 T MRT Scannern mit „dot engine“ (Siemens MAGNETOM Aera, VD 11D) bzw. mit konventioneller Bedienungssoftware (Siemens MAGNETOM Avanto, VB 17) untersucht. Der Arbeitsaufwand der MTRAs pro Sequenz und pro Untersuchung wurde gemessen und die Bedienungsfreundlichkeit beider MRT-Geräte durch die MTRAs anhand eines Fragebogens analysiert. Statistisch wurden die Daten mittels T-Test ausgewertet.

Ergebnisse: Das MRT-Gerät mit „dot engine“ reduzierte die durchschnittliche Untersuchungszeit von 25:07 auf 20:02 Minuten und die erforderliche MRTA-Aktivität auf 62 %. Laut der MTRA-Fragebögen war die Bedienungsfreundlichkeit dem älteren Gerät überlegen.

Schlussfolgerung: Die neue „Dot workflow engine“ ist eine zeitsparende Software-Applikation, die den Arbeitsaufwand von MTRAs signifikant vermindern und durch partielle Automatisierung der Arbeitsabläufe einen schnelleren Arbeitsfluss im Vergleich zu herkömmlichen Anwendungen ermöglichen kann.

Inflammation und Kognition: Zur Assoziation von hochsensitivem C-reaktivem Protein und Mild Cognitive Impairment in der Heinz Nixdorf Recall Studien Kohorte

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Fragestellung: Es gibt Hinweise auf eine Assoziation zwischen erhöhten Inflammationsparametern und der Abnahme kognitiver Leistung. Diese Fall-Kontroll Studie untersucht deshalb den Zusammenhang von hochsensitivem C-reaktiven Protein (hsCRP) und leichten kognitiven Einschränkungen (mild cognitive impairment, MCI) in einer großen, prospektiven, populationsbasierten Studie.

Methode: Probanden wurden im Rahmen der populationsbasierten Heinz Nixdorf Recall Kohortenstudie rekrutiert. Für diese Analyse sind Fälle und Kontrollen aus einem Stamm von 4359 Probanden (Alter 50-80) ausgewählt worden. HsCRP Werte wurden an 2 Zeitpunkten gemessen: 5 Jahre vor (Ersterhebung) und zum Zeitpunkt der neuropsychologischen Untersuchung (Zweiterhebung). Bei 148 Probanden wurde die Diagnose MCI (106 amnestic MCI (aMCI), 42 non-amnestic MCI (naMCI)) gestellt. Zusätzlich wurden 148 alters-, geschlechts- und bildungsgematchte Probanden ohne kognitive Einschränkungen als Kontrollen rekrutiert. Die Assoziation zwischen hsCRP und MCI (MCI allgemein/aMCI/naMCI) wurde mit Hilfe von binär- und multinomial logistischen Modellen (Odds Ratio (OR); 95% Konfidenzintervall (CI)) bestimmt und für potentielle Einflussfaktoren (koronare Herzerkrankungen, Schlaganfall, ApoE4, nichtsteroidale Antirheumatika, Alkoholkonsum, BMI und Hypertonus) adjustiert.

Ergebnisse: Bezogen auf die Ersterhebung zeigt sich (immer im Vergleich zum niedrigsten Quartil und für das volladjustierte Modell), dass hsCRP Level im dritten und vierten Quartil die Wahrscheinlichkeit einer MCI Diagnose mehr als verdoppeln (OR=2.28, 95%CI, 1.02-5.08, viertes Quartil). Bezogen auf die MCI Subtypen zeigen sich ähnliche Ergebnisse für aMCI (OR=2.62, 95%CI, 1.09-6.35, viertes Quartil), jedoch nicht für naMCI (OR=1.61, 95%CI, 0.47-5.49, viertes Quartil). Betrachtet man die hsCRP Werte zur Zweiterhebung, so zeigt sich für das vierte Quartil eine signifikante Assoziation mit der Diagnose MCI (OR=3.57, 95%CI, 1.57-8.13). Dies ließ sich ebenfalls für aMCI (OR=3.44, 95%CI, 1.43-8.26) und naMCI (OR=4.28, 95%CI, 1.16-15.72) nachweisen.

Schlussfolgerung: Hohe hsCRP Werte sind mit einer erhöhten Wahrscheinlichkeit für die Entwicklung von MCI in den folgenden fünf Jahren assoziiert. Diese Ergebnisse legen die Beteiligung von Inflammationsprozessen bei der Entwicklung und dem Vorliegen kognitiven Störungen nahe.

Examination of the mechanisms underlying the effects of environmental enrichment on hippocampal synaptic plasticity

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Introduction: Epiphenomena such as behavioural state, behavioural experience and environmental enrichment (EE) have a strong influence on the nature and persistency of synaptic plasticity. All of these factors promote neural activation, signalling and metaplasticity, which in turn modify the persistency, quality and form of the memory engram. EE comprises an experimental model of the effects of an optimised social, sensory and motoric environment on the brain. EE causes profound changes in neuronal signalling and levels of excitation and plasticity throughout the entire central nervous system. Little is known, however, about the cellular basis of EE and, in particular, which intracellular cascades are altered due to EE. Given its participation ina key intracellular cascades leading to activation of the cAMP response element binding protein (CREB), we investigated whether brain-derived neurotrophic factor (BDNF) contributes to the enhancement of synaptic plasticity elicited by EE.

Methods: In order to study whether BDNF-Trk signalling is modified following EE in the hippocampal CA1 region, mice that had a modified expression of BDNF ($BDNF^{+/-}$ -transgenic mice) were used. Immediately after weaning, male littermates were housed in EE together. After three weeks of exposure to EE, the mice's short-term and long-term non-spatial memory was tested by an object recognition test. Long-term potentiation (LTP) was assessed in the hippocampus using hippocampal slices. Field excitatory postsynaptc potentials (fEPSPs) were evoked in the CA1 Stratum radiatum by stimulation of the Schaffer collaterals.

Results: Application of HFS at 100 Hz (1 train of 100 pulses at 100 Hz) resulted in LTP. LTP of enriched mice showed higher magnitudes in comparison to non-enriched mice. $BDNF^{+/-}$ mice showed decreased LTP in comparison to control mice, whereas LTP in enriched $BDNF^{+/-}$ mice was not different from controls. Twenty four hours after first exposure to the objects, mice of all groups were able to recognize the object. However, $BDNF^{+/-}$ non-enriched mice, in contrast to all other groups, could not remember the object after one week of first exposure to the object.

Conclusion: These data indicate that EE has an enhancing LTP and facilitates long-term memory in transgenic $BDNF^{+/-}$ mice. On the other hand, our data suggest BDNF contributes to synaptic modifications that contribute to synaptic facilitation in EE.

Increasing or impairing - which influence has stress on memories of the stressful situation?

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Background: The fact that learning and memory performance is modulated by stress and thereof resulting hormonal changes is well documented. Depending on the timing of the stressor in relation to encoding, consolidation and retrieval, stress can either have enhancing or impairing effects on learning and memory. Most experimental studies establishing and supporting these findings have tested memory performance under stress for previously learned material, often unrelated to the stressor. Only few studies investigated the influence of stress on the memory of the stressful episode itself. However, this seems to be highly relevant considering patients suffering from long lasting and strong memories of stressful and traumatic events.
Thus, we aimed to investigate in an experimental study which aspects of a stressful episode are remembered. We expected participants exposed to a psychosocial stressor remembering central details of the stressor better than participants who were not stressed.

Methods: Sixty-three participants took part in the study. Half of them were exposed to a laboratory psychosocial stressor (modified version of the Trier Social Stress Test, TSST), the other half was exposed to a newly developed, non-stressful control condition (friendly-TSST). During both conditions, participants were exposed to stimuli of different modalities. These included an ambient odor, visual stimuli in the form of office objects and a word list. Hormonal and affective changes due to the stressor were assessed before and after the manipulation. The next day, participants engaged in several unexpected recall and recognition tasks.

Results: As expected, stressed participants showed higher negative and lower positive affect as well as higher salivary cortisol levels after the TSST compared to not stressed participants. Stressed participants recognized objects central to the stressful situation better than not stressed participants. The ambient odor was recognized better by stressed participants as well. In contrast, the word list was rememered better by participants from the control group.

Conclusion: Visual items central to the situation are remembered better when the situation is stressful than when it is not. Odors seem to play a special role for stressful memory processes possibly reflecting the fact that olfactory information reaches the amygdala without thalamic gating. The word list, which was presented at the end of the stress or control situation apparently was not

perceived as central to the situation by stressed participants and was thus remembered poorer by them. In sum, what we remember from a stressful episode appears to be determined by the sensory modality of the stimuli as well as by the strength of the association between the stressor and the to be remembered material.

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Perceived treatment group affects behavioral and neural responses to visceral pain in a deceptive placebo study

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Background: Pain is a highly subjective experience that is sensitive to many different types of modulation, including expectations and learning processes. Placebo analgesia (PA) is an elegant and well-established model to study the complex mechanisms mediating pain with obvious clinical implications. Although placebo treatment is part of any placebo-controlled study and is often used in clinical practice, it remains unclear if and to what extent subjectively perceived treatment is associated with responses to placebo treatment. Therefore, we analyzed data from an experimental placebo analgesia pain paradigm using visceral pain stimuli to test the hypothesis that perceived treatment (i.e., drug vs. placebo) affects behavioural and neural responses to placebo.

Methods: In this fMRI study, N = 36 healthy subjects received painful rectal distensions. To model the situation in a typical placebo-controlled trial, subjects were instructed that the probability of receiving a potent analgesic drug was 50 %. In reality, all subjects received saline. Following repeated distensions in the scanner, subjects completed visual analogue scales (VAS) assessing perceived pain, discomfort, and urge to defecate. In addition, participants indicated subjectively perceived treatment, i.e., *"potent analgesic"; "saline solution / placebo"* or *"I do not know"*. All analyses compared the perceived drug treatment group and the perceived placebo treatment group. To detect signal differences in blood oxygenation level dependent (BOLD) responses during pain anticipation and pain, a two sample t contrast was used in a region-of-interest (ROI) analysis.

Results: Of the total N = 36 subjects, N = 20 (55.6 %) believed that they had received a placebo, N = 13 (36.1 %) felt that they had received a potent analgesic drug, and N = 3 (8.3 %; excluded from analyses) were unsure. In the perceived drug treatment group, rectal pain-induced discomfort ratings were significant lower when compared to the perceived placebo treatment group ($p < 0.05$). Further, the perceived drug treatment group revealed significant lower activation in the insula ($t = 4.99$, $p_{FWE} < 0.05$), the posterior cingulate cortex ($t = 4.63$, $p_{FWE} < 0.05$), and the anterior cingulate cortex ($t = 4.15$, $p_{FWE} < 0.05$) when compared to the perceived placebo treatment group during cued pain anticipation. During pain, BOLD-signal of the anterior cingulate cortex was significant lower in the perceived drug treatment group ($t = 4.41$, $p_{FWE} < 0.05$).

Discussion: In this placebo analgesia paradigm, retrospectively assessed treatment perceptions were associated with reduced pain-induced discomfort and reduced neural activation in subjects who believed that they had received a potent painkiller. These findings may reflect a reduction in pain amplification by emotions of fear and anxiety in placebo responders. A more refined understanding of the role of individual treatment expectations has multiple implications for our understanding of placebo responses and the design of clinical trials involving placebos.

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Retrieval of high-level and low-level chunks in hierarchically structured stimulus sequences

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Background: The fundamental cognitive process of *chunking* enhances memory capacity and reduces cognitive load by the integration of bits into bigger units, so-called chunks. When two or more low-level chunks (chunks of bits) are put together, high-level chunks evolve (chunks of chunks). By this integration, which can be repeated on further levels, hierarchical structures with increasing chunking levels develop. The main goal of the present fMRI study was to investigate, which neural correlates subserve the retrieval of increasing chunking levels.

Methods: Eighteen healthy volunteers participated in the study. They were required to learn by trial and error and to retrieve 16-digit stimulus sequences with three chunking levels in a two-choice paradigm. Behavioral as well as functional data were analyzed time-locked to chunk-boundaries, i.e. first elements of chunks. The neural responses entered a parametric statistical analysis.

Results: Behavioral analysis revealed that selection times increased with increasing chunking levels. Neural responses time-locked to chunk boundaries of each level revealed the frontopolar cortex (Brodmann Area (BA) 10) to be preferentially activated in the retrieval of high-level chunks while frontolateral areas along the left inferior frontal sulcus (IFS) were mainly activated in the retrieval of low-level chunks.

Discussion: Findings corroborate the notion of a functional posterior-to-anterior gradation of the prefrontal cortex. In particular, activation of the IFS indicate that the retrieval of low-level chunks points to item by item selection among maintained information and to the prediction of object sequences, whereas activation of BA 10 indicates that the retrieval of high-level chunks is related to planning of complex future events and to cognitive branching.

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Common and distinct mechanisms for mental rotation of external objects, body parts and complex scenes?

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Background: The existence of distinct mechanisms for different mental-rotation tasks seems to be supported by neuroimaging studies which found that object, hand and whole-body rotation activates different brain areas. However, the activation pattern differed not only between stimulus categories, but also between author groups using the same category, and results and conclusions were inconsistent. Therefore, the present study introduces a fresh approach to compare mental rotation with three different stimuli: letters, body parts and complex scenes. We administer all three categories of mental-rotation stimuli to the *same* subjects using the *same* experimental procedure, and analyze not only across-subject means but also individual differences: if those subjects who performed well with one stimulus category also excel with another category, this would argue against completely distinct mechanisms. To our knowledge, this is the first study which compares all three stimulus categories.

Methods: 24 subjects saw letters judging whether they were mirror-reversed or not (task LETTER), saw pictures of a hand indicating whether it was a right or a left one (task HAND), and saw drawings of a person at a table on which a weapon and a rose laid and deciding whether the weapon was right or left (task SCENE). Material could be in canonical orientation or rotated by up to 180°. Our analyses focused on intra-subject correlations between reaction times of the different tasks.

Results: We found reaction times for stimuli in canonical orientation co-varied in HAND and LETTER, the increase of reaction times with increasing object rotation co-varied in HAND and SCENE, and reaction times for 180° rotations co-varied between all tasks.

Discussion: We suggest that basic processes like visual perception and decision-making are distinct for scenes versus letters and body parts, that the mechanism for mental rotation of letters is distinct from that for mental self- and body part rotation, and suggest an extra mechanism for 180° rotations, shared among all tasks; this mechanism could exploit the geometrical equivalence between a 180° rotation and double axis inversion.

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Evaluation of the role of CEACAM1 in the developing neonatal rat brain

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Introduction: Encephalopathy of prematurity subsumes the two main neuropathological disorders of preterm white matter injury and neuronal/axonal disease. Factors such as hypoxia–ischemia, drug exposure, hyperoxia and maternal/neonatal inflammation are causal. Particularly with regards to infection/inflammation a significant role of CEACAM1 in different diseases has been proposed. CEACAM1, the founder molecule of the family of carcinoembryonic antigen-related cell adhesion molecules, is a glycoprotein which is existent in different isoforms influencing distinct signaling cascades. It contributes i.e. to morphogenesis of new blood vessels, cell proliferation, apoptosis, insulin metabolism, infection and inflammation. An expression of CEACAM1 was also found in endothelial cells of developing rat brain but its role in neuronal and glial cells is not yet investigated.
The aim of the current study is to evaluate the physiological regulation of CEACAM1 expression in the developing brain in newborn rats. In a second step we plan to evaluate the role of CEACAM1 in a rat model of encephalopathy of prematurity caused by hyperoxia and inflammation.

Methods: Brains of Wistar rats were analyzed from day 1 to 15. CEACAM1 protein expression was detected in serial brain sections by immunohistochemistry. Additionally, double labeling of CEACAM1 and brain cell subpopulation markers such as myelin basic protein (MPB), glial fibrillary acidic protein (GFAP), neurofilament and nestin was performed. Furthermore, RNA from brain hemispheres was isolated to detect the different isoforms of rat CEACAM1. Immunocytochemistry for CEACAM1 was performed on cultured mixed glia cells, pre-oligodendrocytes and mature oligodendrocytes with and without stimulation by CEACAM1 ligands.

Results: CEACAM1 expression was detected in broad areas of the brain beginning on day 5 in brain stem and afterwards in the forebrain. CEACAM1 is expressed on oligodendrocytes, a finding that was confirmed on cultivated primary brain cells. CEACAM1 expression showed a close spatiotemporary connection to myelination. On RNA level, expression of the CEACAM1-4L and -S splice variants as well as the soluble CEACAM1-4C2 splice variant were detected.

Conclusion: Our results show for the first time an expression of CEACAM1 in oligodendrocytes in the developing brain. This is of special interest as one major component of encephalopathy of prematurity is a myelination disorder. Thus, precise definition of the role of CEACAM1 in myelination is content of our current investigations.

Impact of neonatal Propofol anaesthesia on long-term neurodevelopmental outcome

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Background: Perinatal brain damage is a leading cause of disability and even death in preterm born infants, which comprise of 5-11% of all live births. Clinical studies have shown, that these children are at higher risk to suffer from cognitive impairments, ranging from cerebral palsy to deficits such as attention deficit and hyperactivity disorder (ADHD). At the exception of inflammation and hypoxia-ischaemia, major factors in the aetiology of perinatal brain injury, preterms are additionally challenged by their unphysiologic environment and iatrogenous interventions. In order to minimise pain and discomfort, these interventions often include the use of anaesthetic agents, such as Propofol. Recent reports, hovever, raised concern about the safety of these drugs. Animals studies indicated that an administration of Propofol during the period of synaptogenesis, induces neural apoptotic cell death by a, so far, poorly understood mechanism. Especially the resulting long-term effect on neurodevelopment and cognitive function is uncertain. **Aim:** In this study we investigated the neurodevelopmental outcome of Propofol sedation in adolescent and adult aged animals to supplement our ongoing investigations assessing the neurodegenerative properties of this drug.

Methods: Six day old Wistar rats (P6) were randomly assigned to receive either three i.p. injections of 30 mg/kg Propofol or 0.9% NaCl solution every 90 min. In order to assess activity (locomotion, travel distance, and speed) and anxiety related behaviour as well as the nature and rate of habituation, an open field test (OFT) was performed on four consecutive days at two time points (P30, P120). Memory function was assessed by the novel object recognition test which subsequently followed the OFT both time points using an inter-trial interval of 6 and 12 hrs.

Results: We were able to observe increased levels of activity (locomotion and travel distance) in Propofol treated animals on the first day of the open field test (P30). This increase however was only transient, as both parameters dropped to levels observed in control animals on the second day and were found to be similar on the following days, which was persistent up to P124. We therefore hypothesise that the hyperactive response of Propofol treated animals was triggered by the novel environment on the first day of observation. There was no significant difference in the average velocity of the animals movements indicating that the increased travel distance was mainly influenced by the increased time in motion. In contrast to a previous report, we observed no impairment in the animals ability to habituate to the testing procedure. The assessment of memory function revealed that, at 30 days of age, both groups were able to remember a previously presented object after 6 hrs but failed to do so after 24 hrs. At the age of 120 days both groups failed to clearly distinguish between the old and the new object after both intervals.

Conclusion: We observed a change in the activity of adolescent animals at the age of 30 days as expressed by a transient increase in locomotion and travel distance on the very first day of observation. These changes may be a hint that the use of Propofol during the neonatal period increases the risk to suffer from ADHD in adolescence. We therefore suggest that the long-term behavioural development following neonatal sedation with Propofol should be scrutinised in clinical trials.

Sphingosin-receptor modulation in hyperoxia-mediated perinatal brain damage

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Background and aims:
Substantial neurologic morbidity occurs in survivors of premature birth. Experimental studies revealed that oxygen, which is widely used in neonatal medicine for resuscitation and treatment of pulmonary hypertension, triggers widespread neural apoptosis leading to gray and white matter damage. Within the last years it became evident that modulation of the sphingosine-1-phosphate (S1P)-receptor system, by the S1P analogue FTY720, not only affects immune responses but also shows neuroprotective capacities. Since we recently demonstrated a detrimental role of elevated oxygen-concentrations (80 %, hyperoxia) to the developing white matter in vitro and in vivo, we were now interested whether FTY720 might protect developing oligodendrocytes against hyperoxia-mediated cell death and how S1P-receptors are regulated in this experimental setup.

Methods:
Primary oligodendrocyte precursor (pOLN) cells were purified from mixed glia cultures, obtained from two-day old Wistar rat brains, by using the shake-off method. Purified cells were cultured 5-7 days under non-differentiating conditions. Hyperoxia-mediated modulations of S1P-receptors were determined by real time PCR (RT-PCR). To investigate the effect of FTY720 cells were treated with different concentrations of FTY720 (10, 100, 1000 nM or vehicle). Cell death was investigated by biochemical methods, immunocytochemistry and flowcytometry.

Results:
We observed a marked induction of S1P-receptor mRNA-expression after 24 h hyperoxia that is to some extend counterregulated by the S1P analogue FTY720. Moreover, we observed a partial inhibition of hyperoxia-mediated apoptosis by FTY720. As such, LDH release was reduced in FTY-treated cells as compared to control cells. Flowcytometry analysis further revealed that the number of pro-apoptotic cells is reduced in the presence of this substance.

Conclusion: Our data imply that the modulation of the S1P receptor system might be highly relevant for hyperoxia induced white matter damage in the neonatal brain and therefore might present a potential therapeutic target. The next step will be to test our hypothesis in the *in vivo* model of hyperoxia.

Evaluation eines Modells zur transkraniellen Gleichstromstimulation in der Ratte

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Einleitung: Die transkranielle Gleichstromstimulation (tDCS) wird im Rahmen von Studien beim Menschen eingesetzt, um unter anderem funktionelle Defizite nach einem Schlaganfall zu behandeln. Dabei ist die genaue Wirkungsweise der Therapie bislang nur unzureichend bekannt, unter anderem erscheint eine Beeinflussung neuroinflammatorischer Prozesse möglich. Die aktuelle Studie hatte das Ziel, die Wirkungsweise der tDCS auf zelluläre inflammatorische Prozesse in der Ratte zu evaluieren. Es sollte eine Stromstärke gefunden und ein Zeitraum bestimmt werden, bei der es zu einer inflammatorischen Reaktion des stimulierten Gewebes, nicht jedoch zu einer strukturellen Läsion des Gehirns kommt.

Methode: Insgesamt sieben Ratten wurden mittels tDCS kathodal stimuliert, davon zwei Tiere einmalig mit 1mA über 30 min, und fünf Tiere täglich (repetitiv) mit je 500µA für 15 min über einen Zeitraum von fünf Tagen. Sieben Tage nach der ersten tDCS wurden die Tiere unter tiefer Narkose dekapitiert und die Gehirne histologisch weiter aufbereitet. Die Hirnschnitte wurden zur Beurteilung der Morphologie mit Hämatoxylin/Eosin (HE) gefärbt. Zur Beurteilung der Mikrogliaaktivierung wurde deren Oberflächenantigen CD11b immunhistochemisch angefärbt. Die Expressionsstärke von CD11b wurde auf der Basis einer Bildausschnitts-Analyse als Surrogatparameter für das Ausmaß der Mikrogliaaktivierung quantifiziert und mit der kontralateralen Hemisphäre verglichen.

Ergebnisse: Die einmalig mit starker Stromstärke (1mA) stimulierten Ratten zeigten klare strukturelle Läsionen unterschiedlicher Größe, eines der Tiere wies zusätzlich eine rechtsseitige Hemiparese auf. Die Ratten der niedriger dosierten (500µA), dafür über fünf Tage repetitiven tDCS, wiesen dagegen keine strukturellen Gewebsschädigungen auf. Mit Hilfe der quantitativen Bildanalyse konnte dennoch eine signifikante Aktivierung von Mikroglia in der stimulierten Hemisphäre nachgewiesen werden. Mit diesen Untersuchungen konnten wir somit erstmalig zeigen, dass tDCS inflammatorische Reaktionen im Gehirn hervorrufen kann.

Schlussfolgerung: Die Etablierung eines nicht-läsionellen Modells zur transkraniellen Gleichstromstimulation in der Ratte war erfolgreich, auch repetitive Stimulationen konnten bei entsprechend gewählter Stromstärke vorgenommen werden, ohne strukturelle Läsionen zu verursachen. Darüber hinaus konnten wir erstmals eine durch tDCS ausgelöste neuro-inflammatorische Reaktion im Gehirn nachweisen. Diese Methode wird in zukünftigen Studien helfen, die genauen Wirkmechanismen der bereits in klinischen Studien angewandten tDCS zu entschlüsseln.

Kognitive Funktionsstörungen bei chronischer Niereninsuffizienz

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Einleitung: Weltweit leiden mehr als 500 Mio. Menschen an chronischer Niereninsuffizienz (CKD), im Zuge der „alternden Gesellschaft" wird die Prävalenz von CKD weiter ansteigen. Zahlreiche Studien konnten bereits kognitive Funktionsstörungen bei CKD-Patienten aufzeigen. Es bestehen erste Hinweise auf eine Verbindung zwischen komorbiden kardiovaskulären Risikofaktoren und kognitiven Einschränkungen bei CKD-Patienten - die genaue Natur der Verbindung zwischen Niereninsuffizienz und kognitiven Funktionen bleibt jedoch bislang unklar, da selten betrachtet wurde, inwieweit CKD per se mit kognitiven Defiziten einhergeht.

Methoden: In der vorliegenden Studie wird diese Fragestellung näher untersucht, indem Patienten mit CKD Stadium 3-4 (CKD 3-4) im Rahmen einer prospektiven Untersuchung mit Patienten mit CKD im Endstadium unter Dialyse (CKD 5) und einer Kontrollgruppe (KG) mit kardiovaskulären Risikofaktoren, aber ohne CKD in Bezug auf ihre Leistung in verschiedenen neuropsychologischen Tests sowie klinischen und Labordaten verglichen werden. Außerdem wird regressionsanalytisch betrachtet, wie kardiovaskuläre Risikofaktoren die kognitive Leistung beeinflussen und ob hierbei Unterschiede zwischen den Gruppen bestehen.

Ergebnisse: CKD-Patienten zeigten in fast allen neuropsychologischen Tests eine signifikant schlechtere Leistung im Vergleich zur KG. Patienten mit CKD 5 wiesen zudem eine signifikant schlechtere Leistung im visuokonstruktiven Vermögen sowie einen niedrigeren Wert der globalen Kognition (Anzahl unterdurchschnittlicher Testleistungen) auf verglichen mit CKD 3-4 und der KG. Bedeutsame Prädiktoren für die kognitive Leistung bei CKD 3-4 waren Fibrinogen, Parathormon und Intima-Media-Dicke der Arteria carotis communis. Bei Patienten mit CKD 5 hingegen wurde die kognitive Leistung vor allem durch HbA1c und BMI vorhergesagt.

Schlussfolgerung: CKD ist mit spezifischen kognitiven Defiziten verbunden, wobei eine stärkere Einschränkung der Nierenfunktion mit einer stärkeren Beeinträchtigung kognitiver Funktionen verbunden ist. Unterschiede bestehen auch bei der Vorhersage der kognitiven Leistung, was auf verschiedene Ätiologien kognitiver Defizite hinweist.

The role of intima-media thickness of the common carotid artery in addition to clinical risk factors in stroke prediction

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Introduction: Predictive scores like the Framingham Risk Score are useful for evaluating a patient's risk of future (cerebro)vascular events. However, results of recent studies suggested that additional assessment of subclinical atherosclerotic markers might improve risk prediction and help to optimize prevention strategies. The present study investigates the predictive value of the common carotid artery intima-media thickness (CIMT) as a non-invasively accessible marker of atherosclerosis for stroke risk in addition to variables included in the Framingham risk score (FRS).

Methods: In 3669 initially stroke-free subjects from the population-based Heinz Nixdorf Recall Study (60 ± 8 years, 51% male) various cardiovascular risk factors were measured and stroke events were registered during a mean time interval of 85.32 months (SD=17.36). Baseline characteristics were calculated for both genders for subjects subsequently developing or not developing strokes, for three age cohorts (45-54 years, 55-64 years, ≥65 years) and three CIMT terciles. Cox proportional hazards regressions were used to evaluate determinants of stroke risk including Framingham risk variables [sex, age, low-density lipoprotein (LDL), high-density lipoprotein (HDL), systolic blood pressure (SBP), diabetes mellitus and smoking] plus CIMT and in a next step compound risk groups made up from FRS and CIMT terciles.

Results: In a multivariate Cox regression analysis, CIMT was an independent stroke predictor (hazard ratio 1.201, confidence interval 1.004-1.438; $p<0.05$) in addition to age (1.458, 1.212-1.753; $p<0.001$), systolic blood pressure (1.161, 1.040-1.296; $p<0.01$) and smoking (1.957, 1.142-3.351; $p<0.05$). Separate analysis of this significant risk factors in men and women revealed that whereas only age (HR 1.453, CI 1.149-1.837; $p< 0.01$) and CIMT (1.313, 1.073-1.607; $p<0.01$) predicted stroke events in men, stroke risk was associated with age (1.526, 1.139-2.045; $p<0.01$), systolic blood pressure (1.245, 1.058-1.464; $p<0.01$) and smoking (2.732, 1.152-6.452; $p< 0.05$), but not CIMT (0.940, 0.667-1.325; n.s.) for women. In subjects belonging to the highest FRS (>13%) and CIMT (>0.715 mm) terciles stroke risk was particularly elevated; in the first and second FRS tercile group, increases in CIMT did not indicate a significant increase in stroke risk ($p=0.80$ and $p=0.62$ for trend, respectively).

Conclusions: CIMT is an independent stroke predictor in addition to age, systolic blood pressure and smoking. Its predictive value is gender-specific as only for men high CIMT values are associated with an increased stroke risk/incidence. Further, CIMT predicts stroke risk particularly in subjects with a Framingham risk score above 13%, implying that conventional risk factors potentiate the CIMT-related stroke risk.

Intracerebroventricularly delivered VEGF promotes contralesional corticorubral plasticity after focal cerebral ischemia via mechanisms involving anti-inflammatory actions

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Background: Vascular endothelial growth factor (VEGF) has potent angiogenic and neuroprotective effects in the ischemic brain. Its effect on axonal plasticity and neurological recovery in the post-acute stroke phase was unknown.

Methods: Using a behavioural test battery that we combined with anterograde tract tracing studies as well as with immunohistochemical and molecular biological analysis, we herein examined effects of a delayed i.c.v. delivery of recombinant human $VEGF_{165}$, starting 3 days after stroke, on functional neurological recovery, corticorubral plasticity and inflammatory brain responses in mice submitted to 30 min middle cerebral artery occlusion.

Results: Slowly progressive improvements of motor grip strength and coordination were noted in VEGF-treated ischemic mice from 14 to 42 days post-ischemia (dpi) that were accompanied by enhanced sprouting of contralesional corticorubral fibres which branched off the pyramidal tract in order to cross the midline and innervate the ipsilesional parcocellular red nucleus. Infiltrates of CD45+ leukocytes were noticed in the ischemic striatum of vehicle-treated mice that closely corresponded to areas exhibiting Iba-1+ activated microglia. VEGF attenuated the CD45+ leukocyte infiltrates at 14 but not 30 dpi and diminished the Iba-1+ immunoreactivity. The VEGF-induced anti-inflammatory effect was associated with the downregulation of a broad set of inflammatory cytokines and chemokines in both brain hemispheres.

Conclusion: Our data suggest a link between VEGF's immunosuppressive and plasticity-promoting actions that may be important for successful brain remodeling. Accordingly, growth factors with anti-inflammatory action may be promising therapeutic options in the post-acute stroke phase.

A novel mouse model with a null mutation in Ccdc66 (coiled-coil domain containing 66) exhibits retinal degeneration and dysfunction

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Background: Retinitis pigmentosa (RP) is a group of human retinal disorders, with more than 100 genes involved in retinal degeneration. Canine and murine models are useful for investigating human RP based on known, naturally occurring mutations. In Schapendoes dogs, for example, a mutation in the CCDC66 gene has been shown to cause autosomal recessively inherited, generalised progressive retinal atrophy (gPRA), the canine counterpart to RP in man (Dekomien et al., Neurogenetics. 2010, 11:163-74).

Methods: A novel mouse model with a disrupted Ccdc66 gene was investigated in order to reveal the function of protein CCDC66 and the pathogenesis of this form of gPRA with molecular biological methods on the DNA, RNA and protein levels; immuno- and electron microscopy as well as physiological assessment of retinal function by electroretinography (ERG).

Results: Homozygous Ccdc66 mutant mice with a gene trap 5' to Ccdc66 exon 4 lack retinal Ccdc66 RNA and protein expression. Light and electron microscopy reveal an initial degeneration of photoreceptors already at 13 days of age, followed by slow, progressive retinal degeneration over months. Retinal dysfunction causes reduced scotopic a-wave amplitudes, declining from 1 to 7 months of age as well as an early reduction of the photopic b-wave at 1 month, improving slightly at 7 months, as evidenced by electroretinography. In the retina of the wildtype (WT) mouse, protein CCDC66 is present at highest levels after birth, followed by a decline until adulthood, suggesting a crucial role in early development. Protein CCDC66 is expressed predominantly in the developing rod outer segments as confirmed by subcellular analyses.

Conclusion: These findings illustrate that the lack of protein CCDC66 causes early, slow progressive rod-cone dysplasia in the novel Ccdc66 mutant mouse model, thus providing a sound foundation for investigating the role of Ccdc66 in retinal function and the development of therapeutic strategies.

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Chronic Cluster Headache shows no association with REM-Sleep

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Introduction: Custer Headache [CH] is a rare primary headache disorder. Some authors reported association of nightly headache attacks and different sleep stages, particularly with regards to rapid eye movement [REM] sleep in patients with episodic CH. Nevertheless sequential polysomnography [PSG] has not been performed in patients diagnosed with chronic CH to investigate typical attacks arising from sleep and the relation to particular sleep stages.

Methods: To specify which sleep stages are associated with nightly headache attacks, we performed PSG in five patients diagnosed with chronic CH during four consecutive nights. Chronic CH was diagnosed according to the diagnostic criteria of the international headache society (ICHD-II).
An independent specialist in sleep medicine, blinded to the diagnosis, evaluated a total of 20 nights and staged sleep stages according to the criteria of Rechtschffen and Kales. Participants were instructed to document each headache in terms of time of onset, pain intensity, and autonomic symptoms. Furthermore they reported each nightly headache attack to the sleep technicians.

Results: Eighteen typical CH attacks were reported by the study participants. Thirteen of these attacks arose from sleep. The beginning of headache attacks were distributed statistically threw out the different non-REM sleep stages. Three attacks began from sleep stage I, nine were reported after awakening from sleep stage II, and one attack occurred from sleep stage III. Another 5 CH attacks were reported after rise in the morning or before going asleep.

Discussion: Appearance of nightly CH attacks is not associated with a particular sleep stage. Particularly there was no association with REM sleep. Underlying pathophysiology remains unclear.
We fund a rise in heart rate without another reason (e.g. desaturation or arousal). Thus this acceleration of heart rate might indicate the beginning of headache during sleep. If this is the case we found a correlation of the beginning of headache and transitions from one non-REM sleep stage to another might be possible. Further research seems to be worthwhile.

Dynamic causal modeling of the network underlying the Müller-Lyer illusion

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The Müller-Lyer illusion is an optical illusion that alters the perceived length of a line via arrows attached to its end. Recent imaging studies revealed that ventral and dorsal stream areas contribute to the processing of the Müller-Lyer illusion (Weidner et al., 2010; Weidner & Fink, 2007).
Here we investigated [using dynamic causal modeling (DCM; Friston, Harrison, & Penny, 2003)] the effects of this illusion on the effective connectivity of the brain areas involved in coding illusion strength. Strength of the Müller-Lyer illusion was parametrically modulated while participants performed either a landmark task or a non-spatial control task.
Relative to the control task, the landmark task increased neural activity in lateral occipital cortex and right superior parietal cortex dependent upon illusion strength. Based on these findings DCM was used to investigate the possible interactions between ventral and dorsal visual stream. Bayesian model selection (Stephan et al., 2009) indicated that a model involving bi-directional connections between dorsal and ventral stream areas most accurately accounted for the underlying network dynamics. In this model, illusion strength enhanced bi-directional couplings of bilateral lateral occipital cortex and the right superior parietal cortex.
The data suggest that the Müller-Lyer illusion arises due to recurrent processing between dorsal and ventral stream areas. Additionally, connectivity was selectively modulated by top-down control, implying that the processes generating the Müller-Lyer illusion are, at least in part, under endogenous control.

Structural and behavioural differences between high and low trait-anxious individuals

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Background: Learning, conditioning and a genetic predisposition influence the processing of negative emotional stimuli and present the basis for the development of anxiety disorders. This study focuses on the learning-process, memory-consolidation and the associated neural fibre-connections in subjects with low and elevated trait-anxiety. Latter individuals are particularly prone to develop anxiety-disorders and differ from people with reduced or average trait-anxiety with regard to the processing, evaluation and memory of threat-related stimulus-material (McCabe, 1999; Russo et al., 2006; Mitte, 2008; Waldhauser et al., 2011). To date, studies on memory-biases in subclinical anxiety patients do not add up to a consistent picture. While some authors strongly support the existence of a memory bias, others blame findings on unpropitious experimental designs (Dowens & Calvo, 2003) or insufficient criterions (Russo et al 2009). It is the intent of this study to clarify if and how subclinical high and low trait anxious individuals differ from each other.

Methods: The State Trait Anxiety Inventory (Spielberger et al., 1983) was used to form two groups: one high and one low in trait-anxiety (each n=27). An associative word-learning training was implemented to investigate the development of a bias for negatively arousing stimuli. Thereby, 60 neutral word stimuli (e.g. foha) were linked with negative arousing colour pictures (e.g. an attacking shark). To check for memory-biases, we implicitly and explicitly tested the learned word-material. These tests were carried out directly after training and two weeks later. The latter served to investigate the impact of consolidation. A subgroup of n=34 female subjects were additionally scanned via Diffusion Tensor Imaging (DTI). Tract-based spatial statistics from FSL-toolbox were applied to investigate differences regarding white matter integrity between groups via calculation of fractional anisotropy (FA).

Results: Results of the recall test show significant group-differences, indicating an explicit memory-bias. Higher recall-rates were exclusively found in high anxiety individuals; thus, replicating the previously found (but highly debated) interaction effect between factors anxiety and arousal-type. Results of the valence-rating show a main effect for factor group. However, responses during the training display increasing learning curves for all subjects but do not indicate differences between groups. Thus, no evidence for the development of a bias during the acquisition of the new word-material was found. Analysis of the DTI-data revealed significant differences in dorsolateral Prefrontal Cortex (dlPFC) regions with the low-anxiety group exhibiting higher FA-Values, hence stronger integrity of white matter.

Conclusions: Overall, the results clearly emphasize neuroanatomical and behavioural differences between subclinical high and low trait-anxious individuals. Behavioural differences regarding learning are stronger for explicit than implicit memory. The absence of group-differences during the training suggests that development of the memory-bias takes place at later learning-stages such as consolidation or retrieval. Consolidated implicit responses of the high anxiety group indicate a generalization-bias, which might be due to different consolidation-mechanisms and which is associated with lower white matter integrity in right-hemispheric dlPFC regions. This interpretation is discussed in relation to current theories on anxiety disorders and major depression.

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Funktionelle Magnetresonanztomographie des Cerebellums bei der Prismenadaptation

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Hintergrund: An der Prismenadaptation als Beispiel einer visuomotorischen Adaptation ist das Kleinhirn beteiligt. Welche Regionen im Kleinhirn-Kortex für diese Adaptation wesentlich sind, konnte in tier- und humanexperimentellen Studien noch nicht abschließend geklärt werden. Eine funktionelle Einbindung der Kleinhirn-Kerne in die Prismenadaptation wurde bislang nicht untersucht. Besonders interessant ist die Darstellung des Aktvierungsmusters des Nucleus dentatus, da Hinweise auf eine funktionelle Aufteilung in eine dorso-rostrale motorische und ventro-caudale nicht-motorische Domäne vorliegen. Arbeitshypothese ist, dass die nicht-motorische Domäne im Besonderen während des Adaptationsvorgangs aktiviert ist, nicht aber während einer motorischen Kontrollbedingung.

Methode: Gesunde, rechtshändige Probanden (20 Probanden, 14 männlich, 6 weiblich, Durchschnittsalter 26,65 Jahre (21-33)) wurden in die Studie eingeschlossen. In einem Blockdesign erfolgte zuerst eine motorische Kontrollaufgabe bestehend aus Zeigebewegungen der rechten Hand auf ein visuelles Ziel. Nachfolgend erfolgte die Adaptation der Zeigebewegungen an ein optisches Prisma mit 20° Lateralverschiebung nach rechts. Während der Bewegungsausführung wurden fMRT Aufnamen des Kleinhirns im Ultrahochfeld (Magnetom 7T, Siemens Healthcare) gemacht. Die statistische Analyse der fMRT Daten erfolgte mit Hilfe der Software Statistical Parametric Mapping (SPM8). Zur exakten anatomischen Zuordnung aktivierter Kleinhirnareale wurden probabilistische Atlanten des Kleinhirnkortex und der Kleinhirnkerne herangezogen.

Ergebnisse: Bei den bisher ausgewerteten Probanden zeigen sich im Kleinhirn-Kortex während der Zeigebewegungen Aktivierungen vermal und rechts paravermal im oberen (Lobulus V, VI) und unteren (Lobulus VIII) Handareal. Während der Adaptation lassen sich keine signifikanten Unterschiede der Aktivierung im Vergleich zur Kontrollbedingung mittels Subtraktionsanalyse feststellen. Im Nucleus dentatus zeigte sich eine Aktivierung im motorischen Anteil beidseits während der Zeigebewegungen. Zusätzlich lassen sich während der Adaptation Aktivierungen im nicht-motorischen Anteil des ipsilateralen Nucleus dentatus zeigen.

Diskussion: Für den Kleinhirnkortex konnten keine Unterschiede im Aktivierungsmuster zwischen Prismenadaptation und motorischer Kontrollbedingung beobachtet werden. Mit unseren Untersuchungen konnten wir eine adaptations-spezifische Aktivierung im nicht-motorischen Anteil des

Nucleus dentatus nachweisen. Dieses fMRT-Ergebnis ist gut vereinbar mit tierexperimentell beschriebenen Verbindungen zwischen dem ventro-kaudalen Anteil des Nucleus dentatus und dem posterioren parietalen Kortex, der eine zentrale Rolle bei der visuo-motorischen Adaptation einnimmt.

Förderung: Deutsche-Heredo-Ataxie Gesellschaft e.V. (DHAG), IFORES Stipendium der Medizinischen Fakultät

Isolierte zerebrale Suszeptibilitätsartefakte bei Patienten mit malignem Melanom: Metastase oder nicht?

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Einleitung: Beim zerebralen Staging von Patienten mit malignem Melanom finden sich häufig isolierte Suszeptibilitätsartefakte in T2*/SWI gewichteten Sequenzen ohne Korrelat in der kontrastgestützten T1 Gewichtung. Differenzialdiagnostisch kommen Kavernome, Mikrohämorrhagien aber auch melaninhaltige Früh-Metastasen ohne Kontrastmittelanreicherung in Frage. Wir untersuchten retrospektiv den Verlauf solcher Signalauslöschungen in unserem Patientenkollektiv, um klären zu können, wie häufig sie Metastasen entsprachen.

Methoden: Es wurden MRT Untersuchungen (1,5T) von 20 Patienten (6 Männer, 14 Frauen) mit malignem Melanom aus den Jahren 2006 bis 2009 ohne MR tomographisch gesicherte zerebrale Metastasierung im Initialstaging, aber mit Signalauslöschungen in der T2*/SWI Sequenz, retrospektiv im Verlauf ausgewertet. Der durchschnittliche Beobachtungszeitraum lag bei 19,6 Monaten (6- 46 Monate).

Ergebnisse: Die Patienten zeigten zwischen einer und fünf hypointenser Läsionen in der T2*/SWI Sequenz. Es entwickelte sich bei keinem Patienten eine Metastase aus einer dieser Läsionen.

Schlussfolgerung: Bei isolierten Suszeptibilitätsartefakten in T2*/SWI gewichteten Sequenzen ohne Korrelat in der kontrastgestützten T1 Gewichtung scheint die Differentialdiagnose einer zerebralen Metastasierung bei Melanompatienten nachrangig zu sein.

Functional connectivity reveals the mid-cingulate cortex as center axis of intentional motor control

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Background: We recently showed that the anterior mid-cingulate cortex (aMCC) plays a crucial role in the intentional initiation of movements. In particular, the aMCC featured not only increased activity for internal movement selection but even higher levels of activation when the timing of movement execution was free, i.e., not cued. It has furthermore been suggested that multiple prefrontal, parietal, and premotor areas interact with the aMCC in context of self-initiated movements of various types. The aMCC may thus represent an interface between cognitive and motor networks. Here we tested this assumption comparing functional connectivity patterns of the MCC at "rest", i.e., during the absence of an external task, and in the context of explicit task conditions.

Methods: Functional connectivity of the aMCC was assessed by means of two complementary approaches. Using the BrainMap database we first identified all databased experiments that featured activation in the aMCC. We then performed an ALE meta-analysis over these experiments in order to reveal significant co-activation patterns by meta-analytic connectivity modeling (MACM). Furthermore, we conducted a seed-based connectivity analysis on "resting-state" fMRI obtained from 79 healthy subjects. Following spatial preprocessing, removing the effects of potential confounds and band-pass filtering, each voxels time-course was correlated with the time course of the aMCC seed. A group analysis was then performed by means of a one-sample t-test on the Fisher's Z transformed individual correlation-coefficients. All results were (cluster-level) corrected for multiple comparisons ($p < 0.05$) and compared by a conjunction analysis over task-related (i.e. MACM) and task-free (i.e. resting state) connectivity patterns. Finally, a conjunction analysis was performed over the resulting functional connectivity map and our former fMRI study comparing free timed action selection with reactive movements in 35 healthy subjects.

Results: MACM and resting-state analysis yielded virtually identical connectivity maps, indicating a consistent functional connectivity of the aMCC during explicit (externally driven) tasks and a task-free state. Moreover, the subsequent connectivity network also overlapped considerably with the contrast "internally vs. externally driven movements" in the fMRI study. The conjunction over all three analyses (co-activation, resting-state correlation and activation by internally driven movements) indicated consistent functional connectivity of the aMCC with both sensorimotor and "cognitive" brain regions. Bilateral activity in sensorimotor-related regions was found in the dorsal and medial premotor cortices, the putamen, cerebellum, and thalamus. "Cognitive" regions interacting with the aMCC were dorso-lateral prefrontal cortex, Ares 44/45, anterior insula and rostral inferior parietal cortex.

Discussion: We assessed the functional connectivity of the aMCC by independently analyzing the dynamics of the "resting" and the active brain. That is, a specific co-activation pattern of the aMCC was equally present in states where subjects had to engage in structured, externally purported tasks as well as in a task-free "resting" state. Our results demonstrated a close correspondence between both states, which points to a rather fundamental underlying feature of the aMCC relating to functional connectivity. The MCC is associated with complex cognitive functions like reward guided action selection or anticipated response conflict and error likelihood. We here provide evidence for a more fundamental functional role of the MCC for initiating and implementing intentional motor control by connecting higher order and motor systems in the brain.

A high-resolution 7T protocol for clinical depiction of brain vasculature

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Introduction: High-quality pre-operative / pre-interventional images are essential for the treatment of intra-cerebral vascular pathologies. Digital subtraction angiography (DSA) is still the gold standard, but with new ultra-high field MRI scanners, MR angiography (MRA) has the opportunity to become even more competitive. Especially the visibility of the vasculature in time-of-flight (TOF) MRA highly profits from increased field strengths [1]. The goal of this study was to set up a 7T whole-brain vasculature examination protocol within a clinically acceptable overall acquisition time. Main optimization targets were high-resolution TOF MRA and susceptibility-weighted imaging (SWI) for the evaluation of the arterial and venous systems, respectively. For the TOF, the variable rate selective excitation (VERSE) algorithm [2-4] and modified venous saturation pulses were used to ameliorate SAR restrictions.

Material and Methods: A 7T whole-body system (Magnetom 7T, Siemens) equipped with a 32-channel Rx/Tx head coil (Nova Medical) was used. The following modifications in sequence source code were implemented: GRAPPA acceleration factors up to R=8 in phase-encoding direction (2D) and doubling of the number of acquirable slices. The VERSE algorithm was applied to the excitation / saturation pulses of the TOF sequence [2, 3]. The saturation pulses were optimized in duration and flip angle to minimize TR. In the MP-RAGE the adiabatic inversion recovery (IR) RF pulse was replaced by an adiabatic Wideband Uniform Rate Smooth Truncation (WURST) [5] pulse with higher bandwidth and less sensitivity to 7T-intrinsic B_1 inhomogeneities. The protocol was optimized in 5 healthy volunteers and performed in 20 patients with cerebral aneurysm, arteriovenous malformation (AVM), or Moyamoya syndrome (N=11/6/3). The overall quality of all sequences was rated by visual assessment by an experienced neuroradiologist on a three-point scale: 1=poor/non-diagnostic, 2=acceptable/diagnostic, 3=excellent quality.

Results: MP-RAGE: TA=4min 58s, GRAPPA R=2, 0.7x0.7x0.7mm³. 3D FLASH TOF: TA=6min 40s per slab, GRAPPA R=4, 0.22x0.22x0.41mm³, VERSE cut-off threshold 50% / 20% for excitation/saturation (2,5ms, α_{SAT}=35°, every TR) pulse. 3 slabs to cover the entire brain were merged via weighted overlapping into a 3D dataset. 3D SWI: TA=14min 34s, GRAPPA R=4, 0.5x0.5x0.5mm³. 2D TSE: TA=4min 24s, GRAPPA R=2, 0.5x0.5x3.0mm³.All volunteers and patients tolerated the examination well and could be successfully examined within 1 hour. All images were rated acceptable to excellent. The MP-RAGE provided clinical T1 contrast in ultra-high isotropic resolution and is additionally perfect as a localizer for all other sequences due to bright vessel depiction [1]. The WURST IR pulse afforded uniform inversion

without visible contrast changes e.g. in the cerebellum. The TOF sequence enabled MIP images of the complete vascular tree with a voxel volume of smaller than 0.02 mm³. The VERSE algorithm enabled the application of optimized saturation pulses within a TR of 20ms; no venous overlay was visible. The SWI provided excellent T2* contrast, which is valuable for the delineation between arteries and veins. Finally, the double-contrast turbo spin echo completed the clinical 7T protocol with PD/T2 contrast: 43 slices permit (nearly) whole-brain coverage with adequate resolution for clinical diagnosis.

Discussion: This study shows a complete clinical 7T brain protocol. Especially the high-resolution TOF MRA seems to provide excellent results for depicting the cerebral arterial structures. The complete arterial vasculature of the brain is visible in a single 3D dataset. In the future, (dynamic) contrast-enhanced scans (with high temporal resolution) or arterial spin labeling may add additional information regarding blood flow, especially interesting when depicting cerebral AVMs.

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Der Einfluss akuter Schlaganfall induzierter Basalganglienläsionen auf belohnungsabhängiges Lernen

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Einleitung: Die Basalganglien (BG) spielen eine entscheidende Rolle beim Lernen durch Feedback. Man geht davon aus, dass insbesondere Fehler in der Belohnungserwartung eine zentrale Rolle bei dem Prozess durch Verstärker zu lernen spielen. Die Beteiligung spezifischer Regionen der BG wird bisher widersprüchlich diskutiert. Eine vorangegangene Studie von Bellebaum et al. (2008) konnte bereits Defizite in der Fähigkeit des Umlernens bei Personen mit einem chronischen BG-Infarkt zeigen, insbesondere das dorsale Striatum scheint hierbei eine entscheidende Rolle zu spielen. Interessanterweise weisen Patienten mit Schlaganfällen in den BG eine schlechtere motorische Funktionserholung auf als Patienten mit kortikalen Läsionen.

Methode: Fünf Patienten mit akuten linkshemisphärischen ischämischen Insulten im dorsalen Striatum, sowie neun neurologisch gesunde Probanden mit vergleichbaren kardio-vaskulären Risikofaktoren vervollständigten bisher eine probabilistische Lernaufgabe. Untersucht wurden dabei wichtige Komponenten des belohnungsabhängigen Lernens, wie Akquisition, Umkehrung des Gelernten, Einfluss der Belohnungsstärke und kognitiver Transfer von erworbenen Zusammenhängen, sowie weitere Aspekte der aktuellen kognitiven Leistungsfähigkeit.

Vorläufige Ergebnisse: Patienten wiesen keine Defizite im Paradigma zum belohnungsabhängigen Lernen auf. Darüber hinaus konnte kein Einfluss der Belohnungsstärke (hoch vs. niedrig) gezeigt werden. Konsistent mit der Annahme, dass der Test Zahlenspanne (WMS-R) insbesondere die Effizienz der Aufmerksamkeit erhebt, eine Funktion, welche insbesondere mit der linken Hemisphäre assoziiert ist, wiesen die Patienten Defizite der verbalen Merkfähigkeit und des verbalen Arbeitsgedächtnisses auf. Diese Defizite korrelierten jedoch nicht mit der Leistung im computerbasierten Paradigma zum belohnungsbasierten Lernen.

Schlussfolgerung: Patienten mit Läsionen im dorsalen Striatum, einem Areal, welches insbesondere mit der Unterscheidung von positivem und negativem Feedback in Verbindung gebracht, wird wiesen keine Defizite im Lernen durch Feedback auf. Daher scheint es plausibler, dass die vorgefundenen Defizite im verbalen Arbeitsgedächtnis und der verbalen Merkfähigkeit einen entscheidenden Einfluss auf die motorische Funktionserholung ausüben.

Fingerprints of neural activity after peripheral immune challenge in freely moving rats

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Background: Immune-to-brain communication has repeatedly been documented. However, the specificity by which the central nervous system (CNS) detects or "senses" peripheral immune changes are still poorly understood. The amygdala (Am) and the insular cortex (IC) are important brain regions for the acquisition of peripheral immune borne signals. In order to analyze how peripheral immune responses differently affect brain activity, we recorded neural activity in these specific brain regions of adult male rats during a stereotypic immune response.

Methods: In a between subjects design, animals were challenged with the potent T cell dependent superantigen staphylococcal enterotoxin B (SEB). After a single (naïve) as well as after repeated (desensitization) antigen administrations, the neural activity of the same individuals was analyzed via stereotactically implanted deep brain monopolar electrodes and a telemetry recording system. Body temperature and cytokine concentration measurements were performed to confirm the biological activity of the antigens and the success of the immune-desensitization protocol.

Results: Already within the first 200 min after antigen inoculation, the dynamics and magnitude of the electrical activity recorded from the IC and Am were different depending on the antigen administration protocol: single (naïve) versus repeated (desensitization) SEB treatment. Moreover, in the same individuals, we documented that the immune history significantly affects the neural response to the same antigen challenge; i.e. after desensitization both antigens induced a different neural response, indicating a different perception of the same antigenic challenge.

Discussion: The results indicate that neural activity of the Am and IC is not only specific for the type of immune challenge (Saline vs. SEB) but also sensitive to the different immune state (SEB naïve vs. SEB desensitization). These findings indicate that the brain is able to express specific electrical activity patterns related to the modality of a peripheral immune activation, as well as to the intensity of the stimulation, supporting the conceptualization of the immune system as a "sensory organ".

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The influence of a confrontation with alcohol related cues on the inhibitory control in alcohol dependent patients

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Introduction: Studies investigating social and alcohol-dependent drinkers show impaired performances in tasks requiring inhibitory control if participants are confronted with alcohol-related cues (Muraven et al., 2006; Gauggel et al., 2010). The study at hand investigates the influence of a cue exposure on the inhibitory control in alcohol-dependent patients and the associated neuronal correlates. It is assumed that a cue exposure has a negative impact on the performance in a task requiring inhibitory control and that the corresponding neuronal correlates of the relevant conditions are associated with motivational control of behaviour.

Methods: In this study 11 alcohol-dependent male patients (age *M*=44; *SD*=11) performed a task requiring the ability to inhibit certain responses (Stop-Signal-Task, Logan, 1994) while lying in a Magnet Resonance Tomograph. The task was executed either after exposure to the smell of the patients` most favourite alcohol (A) or after smelling an orange flavour. Before and after cue exposure the urge to drink was assessed with a questionnaire (Alcohol-Craving-Questionnaire, Singleton et al., 1995).

Results: The patients report a significantly stronger urge for alcohol after the application of A compared to after smelling the orange flavour. However, this was not reflected in reaction time differences in the task. When comparing the neuronal correlates of the alcohol cue exposure with the confrontation with the orange smell, differential activation became evident in the hippocampus and the amygdala. During the inhibition task both conditions showed typical activation intermingled in inhibitory processes (i.e., inferior frontal gyrus).

Discussion: The confrontation with alcohol related cues triggered a stronger urge for the substance compared to the control condition. The urge for alcohol lasted over the whole experiment and seems to be associated with differential activation of the amygdala and hippocampus. In agreement with the behavioural data neuronal activation was found expectedly in regions relevant for the performance of the Stop-Signal-Task. However, these results cannot support the view that induced alcohol craving necessarily leads to poorer inhibitory control.

Visualization of macroscopic cerebral vessel anatomy – a new and reliable technique in mice

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Introduction: The visualization of the cerebral vasculature in the rodent brain has become an important tool in experimental stroke research and related cerebrovascular studies. In this context, transcardial or intraarterial perfusion with colored latex has been the method of choice until recently. However, this technique still has some technical limitations compromising the reproducibility of vessel staining. Thus, we describe a simple and reproducible method for permanent visualization of macroscopic cerebral vessels in mice.

Methods: A mixture of two commercially available carbon black inks with different viscosities was injected into the thoracic aorta in mice.

Results: The method yielded efficient filling of cerebral vessels with dye, providing a high contrast visualization of vessel architecture. The feasibility of this technique has been validated by identifying the anastomotic points between the anterior and the middle cerebral arterial territories after focal cerebral ischemia. We also investigated the relationship of the distribution of these vascular zones with the infarction volume for different ischemic durations at various reperfusion time points.

Conclusion: This new vessel staining technique will open up further opportunities in a variety of cerebrovascular research applications.

New function of synapses: Synaptic innervation of interneuron precursors directs their migration

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Background: Interneurons typically originate from neuroepithelia far from their final positions and thus have to migrate extensively before they may be synaptically integrated to form a functional adult network. The mechanisms directing interneuronal migration are only poorly understood. Here we addressed the question how migration and eventual synaptic innervation might relate. At which time during their development get interneuron precursors innervated? As a model, we studied electrophysiological characteristics and migratory behaviour of early postnatal precursors of inhibitory cerebellar basket/stellate neurons. They migrate from the ventricular epithelium through the white matter into the cerebellar cortex.

Methods: We used 200 - 300 µm thick acute sagittal slices from the cerebellar vermis of 7 - 9 day old transgenic Pax2-GFP mice, in which basket/stellate cells and their precursors (collectively referred to as "Pax2-cells" below) may be identified due to expression of green fluorescent protein. We recorded currents mediated by AMPA- and $GABA_A$-receptor agonists and looked for spontaneously occurring post-synaptic currents in Pax2-cells. In some cases, electrophysiological data were measured after verifying that the cells actively migrate by monitoring the translocation of the cells eventually patched.Further, we employed two-photon time-lapse recordings (xyzt) to define the migratory behaviour of Pax2-cells. For all Pax2-cells, we calculated isosurfaces, centres of mass and corresponding quantitative parameters of cell migration using Imaris software (Bitplane, Zürich, Switzerland). To assess the effect of synaptic innervation, we compared migration parameters before ("control") and after blocking release of presynaptic vesicles with 100 µg/ml tetanus toxin.

Results: All Pax2-cells, irrespective of their position in the cerebellar anlage (and hence developmental stage), expressed AMPA- and $GABA_A$-receptors, two subtypes of ionotropic transmitter receptors. Unexpectedly, once they entered the cerebellar cortex, but long before finally settling, most Pax2-cells received synaptic input, both glutamatergic and GABAergic. Block of presynaptic transmitter release altered the speed of migrating Pax2-cells only moderately. However, in contrast to the control situation, following presynaptic blockade most cells lost directionality and remained very close to their initial position. This indicates that not the speed but the straightness of migration is significantly impaired after disruption of synaptic innervation.

Discussion: It is generally assumed that migrating neuronal precursors first settle down at their final destination before they synaptically integrate. Indeed, synaptic integration is often considered the hallmark of terminal neuronal differentiation. In contrast, we find that cerebellar inhibitory interneuronal precursors receive synaptic input while still migrating. This constitutes a hitherto unknown mode of cellular interaction in the CNS. Our data strongly suggest that these developmental synaptic contacts are critical to direct the migration and proper positioning of immature cerebellar interneurons.

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Time to make a change: Relation between reversal learning performance and feedback-related negativity

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Introduction: A core part of the reinforcement learning (RL) theory of the feedback-related negativity (FRN), an event-related potentials component reflecting activity of the anterior cingulate cortex (ACC), suggests that in RL tasks, less expected negative feedback leads to an increase of ACC activity and thus larger FRN amplitude. While this prediction could be confirmed in previous studies, another prediction of the RL-FRN theory – linking the FRN to subsequent behavioural optimisation – has not been supported by empirical evidence to date. This study aimed to elucidate whether the FRN immediately *following contingency reversals* is linked to adaptation of behaviour.

Methods: 15 subjects completed a feedback-based reversal learning task in which they had to choose one of two symbols presented on a computer screen on each of 750 trials. Following their choice, positive ("correct", + 10 points) or negative ("incorrect", - 10 points) feedback was displayed. Unknown to the subjects, the probabilities of positive feedback for the symbols, 80 % and 20 % respectively, were reversed whenever performance accuracy reached a level of 70 % correct responses. The feedback allowed behavioural adjustment in order to optimise performance. Throughout the task, electroencephalography was recorded. Based on performance, subjects were assigned to the groups of slow and fast reversal learners respectively.

Results: Both overall and when considering only unexpected negative feedback directly after reversals, the FRN was more pronounced in fast compared to slow reversal learners. This effect was not related to between-group differences in feedback frequency. For both groups, the FRN was larger for more unexpected negative feedback.

Conclusion: Increased FRN amplitude in fast reversal learners supports the view that higher ACC activity leads to faster behavioural adaptation. This assumption is in line with the recent finding of larger FRN amplitudes following negative feedback which precedes altered choice behaviour in a gambling task. In rule-based reversal learning tasks, however, early detection of reversals is most important for optimised behavioural adaptation. Therefore, immediately *following reversals*, higher ACC activity as reflected in a larger FRN facilitates adequate change of choice behaviour and – in consequence – higher performance.

KCNQ channels in the thalamus: role of a neuronal brake in sensory perception

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Background: KCNQ channels are low-threshold potassium channels which are known to be composed of subunits of the Kv7 K^+ channel family (Kv7.1-Kv7.5). Four of these (Kv7.2-Kv7.5) are expressed in the nervous system, and Kv7.2 and Kv7.3 are the principal molecular components of the slow voltage-gated M-channels. Since they do not inactivate, they generate a steady voltage-dependent outward current called the M-current. It stabilizes the membrane potential in the presence of depolarizing inputs and may have a key role in regulating the excitability of various central and peripheral neurons. The present study aims at elucidating the role of M-channels in thalamocortical signalling, in the regulation of the sleep/wake cycle, and in absence seizures in the thalamic ventrobasal nuclei. In addition, those nuclei are also involved in a variety of physiological functions, such as sensory discrimination or transmission and modulation of pain signals. Moreover, it will be investigated whether they are capable of modulating signals along the pain pathway.

Methods: M-channels are closed by receptors coupled to Gq, such as M1 and M3 muscarinic receptors, and several endogenous and exogenous compounds can modulate their gating properties. Here, a modulation of these channels is obtained pharmacologically by using the M-channel blocker XE991 which decreases M-current amplitude, and the enhancer Retigabine, a broad-spectrum anticonvulsant and an effective analgesic, which increases this current. Moreover, in order to understand the role of thalamic M-channels in pain sensation, the Hot plate test has been performed after Retigabine intrathalamic injection in freely behaving animals.

Results: *In vitro* Retigabine application, as expected, induces an increase in M-current amplitude and, interestingly, this effect seems to be age-dependent, with the current amplitude reaching its peak at P20. Also muscarinic receptor agonists and antagonists effectively modulate these channels in the thalamus. Additionally, *in vivo* Retigabine administration seems to be able to increase latency in hot plate test.

Discussion: M-channels in thalamus seem to modulate the cell excitability by regulating spike frequency adaptation. Since M-channels have been found to play an important role in modulating animal response to thermic pain stimuli, it is reasonable to think that they could play a role in discriminating other kinds of pain input in thalamic ventrobasal nuclei.

Genetic risk factors associated with increased body mass index in a genome-wide association study for childhood attention-deficit/hyperactivity disorder

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Objective: Children with attention-deficit/hyperactivity disorder (ADHD) have a higher rate of obesity than children without ADHD. Hence, gene variants predisposing to obesity might be relevant for ADHD. We examined whether known risk alleles for an increased body mass index (BMI) are associated with ADHD. 32 risk alleles of single nucleotide polymorphisms (SNP) were screened in a GWAS sample of patients with ADHD and controls.

Methods: A genome wide association study (GWAS) was performed in 495 children with ADHD (Illumina; HumanHap550v3 BeadArrays) and 1,300 population based controls (Illumina; Human660W-Quadv1 BeadArrays).

Results: We detected significant association of the C-allele at SNP rs3798560 ($p=0.000278$, corrected for 32 SNP: 0.0089; OR 1.376) with childhood ADHD. SNP rs3798560 is located within the intronic region of *nudix (nucleoside diphosphate linked moiety X-type motif 3 gene;* NUDT3). Additionally, SNP alleles near the genes for mitogen-activated protein kinase kinase 5 (MAP2K5), melanocortin 4 receptor (MC4R), mitochondrial carrier 2 (MTCH2) and solute carrier family 39 (zinc transporter) member 8 (SLC39A8) were nominally associated with ADHD at a trend level ($p < 0.1$). Risk alleles for BMI and ADHD were directionally consistent

in 18 of 32 loci.

Conclusions: We identified association of an obesity risk allele to ADHD. Thus, we describe a chromosomal region that harbors a candidate gene that is potentially relevant for both ADHD and obesity.

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Involvement of the human medial temporal lobe in a visual discrimination task

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Introduction: The structures of the medial temporal lobe (MTL) are traditionally believed to be specialized for declarative and relational learning and memory and hence are labeled the "medial temporal lobe memory system". However, recent imaging and lesion studies suggest that the human MTL, including the hippocampus and the parahippocampal gyrus, could be involved in processing and discrimination of complex visual stimuli. Patient studies show a possible double dissociation of the putative perceptive functions: While patients with selective hippocampal damage are impaired in the visual discrimination of morphed scenes but not morphed faces, patients with selective MTL damage show the opposite pattern. Another functional difference has been shown for recognition memory: While the hippocampus seems to be strongly linked to recollection memory, the perirhinal cortex might be involved in the processing of familiarity memory. The aim of this study is to further elucidate the contributions of different MTL structures to perceptual and mnemonic processing using functional magnetic resonance imaging (fMRI).

Methods: 20 healthy right-handed subjects participated in the fMRI study, each attending two experimental sessions in a 3T magnetic resonance scanner. In the first task (T1), participants had to discriminate visual stimuli (faces and scenes) in an oddball task. Three trial unique stimuli were presented simultaneously to minimize memory demands. In the second task, participants had to memorize a set of unfamiliar faces and scenes. One week later (T2) these stimuli were presented together with distractors and additional stimuli from the oddball task. Subjects had to indicate whether they recognized the presented pictures and how sure they were about this judgement.

Results: Imaging data reveals strong bilateral activity in primary visual areas extending through the ventral stream to the parahippocampal gyrus for the visual discrimination task (without explicit memory demands). Behavioural data also shows that only a small fraction of the stimuli from this task was encoded incidentally, as opposed to the stimuli that had to be memorized explicitly in the second task.

Conclusions: By minimizing the memory demand and controlling for incidental encoding we could show a significant activation of MTL structures for a visual discrimination task, which points to an involvement beyond memory processing. Therefore, these results show further support for a perceptual-mnemonic theory of the MTL.

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Modulation of TASK channels in the rat thalamocortical relay neurons

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Background: The thalamocortical relay (TC) neuron can operate with two different firing modes according to the arousal state of the brain. The relay mode under the condition of vigilance, during which the thalamus relays afferent sensory information to the cortex and the burst mode, which is associated with rhythmic bursts of high frequency action potentials during sleep, drowsiness and epileptic seizures. The switch between these activity modes is mediated by neurons of the ascending brainstem system including brainstem cholinergic neurons that release acetylcholine (ACh). These neurotransmitters act by depolarizing the membrane potential of TC neurons, leading to cessation of rhythmic bursts and occurrence of tonic activity. One crucial step of membrane depolarization is the decrease in a leak K^+ conductance, which is mainly carried by members of the two pore domain K^+ (K_{2P}) channels, namely TASK-1 and TASK-3 (TASK-TWIK related acid sensitive potassium channel) . Therefore the aim of the present work was to analyze the role of TASK-1 and TASK-3 channels in controlling the activity modes of the thalamocortical neuron.

Methods: In the present study we combined electrophysiology with immunohistochemistry in brain slices. Long Evans rats, postnatal age of 13-25 days, were taken as the experimental animals and were handled as approved by the local authorities. 250µM thick coronal thalamic slices were prepared on a vibratome. Whole cell voltage clamp and current clamp recordings were performed on visually identified TC neurons in the dorsal lateral geniculate nucleus (dLGN) of the rat thalamus at room temperature. TC neurons were held at a potential of -28mV and standing outward current (Iso) amplitude was analyzed.

Results: Muscarinic signaling to TASK channels in TC neurons depends on muscarinic acetylcholine receptors 1 and 3, M1AChR and M3AChR. Inhibition of G-protein signaling results in strong reduction of the muscarinic effect on Iso. This effect is comparable to the reduction of muscarinic signaling by inhibiting TASK channels directly (low pH, THA). ATP depletion results in a current run down and a reduced muscarinic effect on Iso. Muscarinic signaling mediated through G-alpha coupled phospholipase- PIP_2 pathway can change the functional activity of the TC neuron by changing the state of TASK channel functioning.

Discussion: TASK channels are the leak potassium channels which contributes to the resting membrane potential in many neurons. The modulation of these channels helps in determining the functional activity modes of the TC neurons which is crucial to understand the mechanism of sleep wake cycle, alertness and epileptic seizures.

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Does the proteoglycan NG2 influence neuron-NG2 cell synaptic signaling?

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Introduction: Glial cells expressing the proteoglycan NG2 are widely distributed throughout the developing and adult gray and white matter of the CNS. Several properties distinguish them from astrocytes, mature oligodendrocytes and microglia. NG2 cells express different types of voltage-gated K^+, Na^+, and Ca^{2+}-channels. They also express a variety of ligand-gated receptors including group I metabotropic glutamate receptors and ionotropic AMPA- and $GABA_A$-receptors. Furthermore, NG2 cells are the only non-neuronal cells in the CNS that form synapses with neurons. In this respect, it is interesting that the NG2 protein (i) binds to the postsynaptic Glutamate Receptor Interaction Protein (GRIP) and (ii) contains two Laminin G/Neurexin/Sex Hormone Binding Globulin (LNS) domains in the extracellular region. GRIP is considered important for clustering of the GluR2 subunit of AMPA receptors. LNS domains are characteristic for postsynaptic neurexins that, by binding to presynaptic neuroligins, are important for synapse formation in neurons.
In this study we asked whether the NG2 protein is crucial for the formation of functional NG2 cell synapses, by influencing clustering of postsynaptic receptors.

Methods: We investigated synaptic transmission between glutamatergic neurons and NG2 cells in NG2-EYFP-knockin (+/- and -/-) and wildtype littermate mice (p8-14). Whole-cell membrane currents from hippocampal NG2 cells were recorded during electrical stimulation of Schaffer collaterals in presence of the $GABA_A$-receptor blocker picrotoxin and the kinetics of the evoked excitatory postsynaptic currents (eEPSCs) were analyzed subsequently. By applying paired-pulse protocols and determining the paired-pulse ratio we also investigated short-time synaptic plasticity at neuron-NG2 cell synapses of the different genotypes.

Results: NG2 cells from mice of the different genotypes exhibited time-correlated eEPSCs upon Schaffer Collateral stimulation. Comparison of the rise- and decay time of these eEPSCs revealed no significant differences among the tested genotypes. Furthermore NG2 cells possess a strong paired-pulse facilitation which is not influenced by a loss of the NG2 proteoglycan.

Discussion: We conclude that the NG2 proteoglycan is not necessary for general synapse formation between glutamatergic neurons and NG2 cells in the hippocampus. As no significant differences were detectable regarding the kinetics of eEPSCs, it is unlikely that subunit composition and AMPA-receptor clustering are influenced in NG2-knockout animals. Furthermore, our results suggest that presynaptic features are also not affected by a loss of the NG2 protein, since short-term synaptic plasticity is indistinguishable among the tested genotypes. It remains to be tested whether miniature EPSCs, which are not synchronized by presynaptic action potentials, are influenced in NG2-deficient mice.

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How psychosocial stress affects executive functions as measured by the modified version of the Wisconsin Card Sorting Test.

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Background: The involvement of the prefrontal cortex (PFC) in emotion processing and executive functioning is commonly accepted. Studies have shown that executive functions can be impaired by stress due to interference in frontal lobe structures. To follow up on these results, we investigated if stress would impair executive functions such as set shifting and concept formation as measured by the modified version of the Wisconsin Card Sorting Test (MCST).

Methods: 180 (88 female) young and healthy subjects were recruited. Half was assigned to a stress group and half to a control group. To induce stress participants of the stress group underwent the Trier Social Stress Test (TSST) while subjects in the control group underwent the placebo-TSST. As a marker of the activation of the hypothalamic-pituitary-adrenal axis salivary cortisol was measured before and after the TSST or placebo-TSST, respectively. The MCST was conducted 35 minutes after the TSST.

Results: Participants from the stress group showed a strong cortisol increase in response to the stressor, while cortisol concentrations declined in controls. Results of the MCST showed a tendency towards improvement within the stress group, performing better concerning non-perseverative errors than the control group ($p = .115$). No difference between the groups could be found for categories finished and perseverative errors.

Discussion: Results of this large sample suggests that 35 minutes after exposure to an acute stressor, executive functions are enhanced rather than impaired. An explanation could be the inverted-u-shape relationship between the level of stress and performance. It should also be considered that the stress effect 35 minutes after the stressor may not be as strong as right after stress occurred.

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THE ENDOGENOUS ROLE OF FGF-2 IN THE NIGROSTRIATAL SYSTEM AND TRANSPLANTATION OF FGF-TRANSFECTED DOPAMINERGIC STEM CELLS IN AN ANIMAL MODEL OF PARKINSON´S DISEASE

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INTRODUCTION: Basic fibroblast growth factor (FGF-2) is involved in the development and maintenance of the nervous system. Exogenous administration of FGF-2 increased dopaminergic (DA) cell survival *in vitro* and improved functional impact of grafted embryonic DA cells. However, cell survival and functional recovery after transplantation are still limited and the identification of grafted cells *in situ* remains difficult.

METHODS: In this set of studies, we analyzed (i) the physiological function of the endogenous FGF-2 system within the nigrostriatal system, (ii) the influence of Schwann cells (SC) overexpressing 18 kDa and 21/23 kDa FGF-2 co-transplanted with DA micrografts into the caudate-putamen unit of unilaterally 6-hydroxydopamine-lesioned "parkinsonian" rats and (iii) the transfection of mesencephalic neural progenitor cells with both, a neurotrophic factor (FGF-2 isoforms) and reporter genes (eGFP, dsRed) using different techniques.

RESULTS: In the first study, we examined the number of DA neurons by stereology in FGF-2 mutant mice after development and after 6-hydroxydopamine lesion. Our results show that FGF-2ko-/- mice reveal more DA neurons within the SNpc than FGF-2ko wildtype. Moreover, we found an increased volume of the SNpc in both, FGF-2ko and transgenic FGF-2 mice. Interestingly, the results are vice versa after 6-OHDA lesion. In the second study, we engineered Schwann cells to overexpress FGF-2. They promoted DA-graft-induced restoration, whether co-transplanted at the same site or grafted at a second more distant site within the CPu. In addition, the 21/23 kDa FGF-2 isoforms resulted in a significantly better reinnervation and survival of dopaminergic micrografts when compared to the 18-kDa FGF-2 isoform. Based on these studies, we expanded and differentiated ventral mesencephalic precursors towards DA neurons *in vitro* and subsequently transplanted these cells into 6-OHDA lesioned rats. We then transfected the stem cells in order to provide them with their own trophic factor. Different techniques for transfection were compared, and the highest transfection rate of up to 47% was achieved by nucleofection. Within the group of transfected cells, many progenitors and several neurons were found. To provide the progenitor cells with a neurotrophic factor, different isoforms of fibroblast growth factor-2 were introduced. To follow the behavior of the transfected cells in vitro, functional tests such as the cell viability assay (water-soluble tetrazolium salt assay [WST-1]) and the cell proliferation assay (5-bromo-2'-deoxyuridine-enzyme-linked immunosorbent assay) were performed. In addition, these transfected cells were viable after transplantation, expressed tyrosine hydroxylase *in vivo*, and could

easily be detected within the host striatum because of their eGFP expression. Our results suggest that they survive microtransplantation and integrate within the striatum both, shown by both, patch clamp recording and behavioural recovery.

CONCLUSION: Taken together, these results suggest, that FGF-2 plays an important physiological role within the nigrostriatal system and is a potent growth factor in stem cell transplantation. This study also indicates, that neural progenitors provide attractive perspectives in neurodegenerative diseases and could be even more promising when transfected with their own neurotrophic factor(s).

Increased blood-brain barrier permeability and brain edema after focal cerebral ischemia induced by hyperlipidemia: Role of lipid peroxidation and calpain-1/2, matrix metalloproteinase-2/9 and RhoA overactivation

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Background: Hyperlipidemia is a highly prevalent risk factor of ischemic stroke. Its impact on brain injury and blood-brain barrier permeability has so far not been assessed in animal models of ischemic stroke.

Methods: Wildtype and ApoE$^{-/-}$ mice, fed with normal or cholesterol-rich high-fat food, were subjected to 30 min middle cerebral artery occlusion. Ischemic injury, brain edema, IgG extravasation, lipid peroxidation, calpain-1/2, matrix metalloproteinase (MMP)-2/9 and RhoA activation, and occludin expression were evaluated 24 hours after reperfusion.

Results: Cholesterol-rich food, but not ApoE deficiency increased IgG extravasation and brain edema, without influencing infarct area and the density of DNA fragmented cells. Increased lipid peroxidation and low density lipoprotein oxidation were noticed in the brain of hyperlipidemic mice that were associated with increased activation of calpain-1/2 and MMP-2/9, overactivation of RhoA and its guanine exchange factor LARG, and downregulation of the tight junction protein occludin in cerebral microvessels.

Conclusions: That post-ischemic blood-brain barrier permeability and brain edema are increased during hyperlipidemia points towards the importance of the recognition and adequate treatment of this highly prevalent risk factor. Translational studies should more adequately mimic risk factors prevalent in human stroke.

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VEGF-induced angiogenesis is followed by improvements of cerebral blood flow, energy metabolism and histological injury in subsequent ischemic stroke

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Background: VEGF induces cerebral angiogenesis and improves brain injury after focal cerebral ischemia. It was so far unknown if induced angiogenesis improves cerebral blood flow during subsequent ischemic episodes.

Methods: Wildtype and ApoE$^{-/-}$ mice, fed on normal or cholesterol-rich Western diet were i.c.v. treated with VEGF (0.02 µg/day) or saline for 3 weeks and subsequently submitted to 90 minutes middle cerebral artery occlusion. After reperfusion, changes in cerebral blood flow, protein synthesis, ATP depletion and tissue pH were evaluated using regional autoradiography, bioluminescence and fluorescence techniques. Angiogenesis, ischemic injury, brain edema, blood-brain barrier integrity and matrix metalloproteinase activity were assessed by histochemistry and zymography.

Results: VEGF improved cerebral blood flow in ischemic tissue and decreased the acidic shift in wildtype animals on normal diet but not in ApoE$^{-/-}$ on Western diet. Consistent with this, the metabolic penumbra was increased in wildtype animals on normal diet, while this effect was less pronounced in ApoE$^{-/-}$ mice on Western diet. VEGF reduced infarct size in wildtype animals on normal diet, but not in ApoE$^{-/-}$ mice on Western diet. VEGF did not influence brain swelling but decreased serum IgG extravasation and MMP-9 activation in wildtype, but not in ApoE$^{-/-}$ mice.

Conclusions: VEGF-induced angiogenesis enhances cerebral blood flow during subsequent ischemic episodes, thus reducing brain injury. Effects of therapeutic angiogenesis are compromised during hypercholesterolemia, which questions the concept of therapeutic angiogenesis under conditions of severe atherosclerosis, where hypercholesterolemia is highly prevalent.

Increased neuronal activation of Ras modulates the adverse phenotype in a mouse model of Rett syndrome

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Background: Mutations in the X-linked gene for Methyl CpG binding protein 2 (MeCP2) cause a neurodevelopmental disorder known as Rett Syndrome (RTT), which mostly affects females. Patients show an apparently normal perinatal development within 6-18 months of age. This is followed by a period of regression, with progressive loss of motor capabilities, language and cognitive functions. MeCP2-Knockout mouse models mimic key clinical features of RTT, including developmental regression leading to motor impairment, irregular breathing, and early mortality. Expression of MeCP2 increases during postnatal development with neuronal maturation, and this correlates with the onset of RTT symptoms. Within this study we were interested in the influence of enhanced neuronal Ras activity on the RTT phenotype.

Methods: In order to investigate the effects of elevated neuronal Ras activity in RTT, we crossbred MeCP2-KO mice and transgenic mice expressing activated human Val12 Ha-Ras under the direction of the synapsin I promoter, selectively in neurons (Heumann et al. 2000). The phenotype of double transgenic animals was investigated in several models of animal behaviour. Besides animal behaviour, the effect of MeCP2-KO on the Ras signalling cascade was investigated by a Ras pulldown assay.

Results: The crossbreeding of heterozygous MeCP2$^{+/-}$-females with transgenic synRas-males lead to a dramatically increased lethality. Furthermore, other than heterozygous MeCP$^{-/y}$-males double transgenic synRas/MeCP$^{-/y}$-males did not survive beyond postnatal day 28. However, double transgenic female mice developed an altered anxiety-like behaviour in the elevated plus maze comparable to that of symptomatic MeCP2$^{-/y}$-males.
MeCP2-KO animals did not show any alterations in the activity of Ras or downstream effector proteins compared to wildtype littermates.

Discussion: We conclude that enhanced neuronal Ras activity aggravates the RTT phenotype in an animal model of RTT, although a MeCP2-KO is not able to induce changes of the Ras/MAPK signalling cascade. The results are discussed in the context of the otherwise protective function of neuronal Ras activation found previously in chemical and mechanical lesion models of the nervous system (Heumann et al. 2000).

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The role of primary cilia in the development of dopaminergic neurons in the murine ventral midbrain

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Introduction: Midbrain dopaminergic (DA) neurons of the substantia nigra and the ventral tegmental area play critical roles in the control of voluntary movement and reward behavior, respectively. DA neurons develop from the floor plate of the ventral midbrain. Sonic Hedgehog (Shh) signaling is essential for the induction of DA progenitors. Shh downstream signaling is mediated by the Gli zinc finger transcription factors Gli2 and Gli3. Studies in spinal cord and forebrain have shown that Shh signaling occurs in primary cilia and that Gli2 and Gli3 are not functional in absence of primary cilia. It was shown that primary cilia have a special kind of transport system, which depends on intraflagellar transport proteins (IFTs). IFTs are not only required for ciliary transport, but also for ciliogenesis. To investigate whether primary cilia are important for Shh signaling in ventral midbrain development, transgenic mice were analyzed, in which IFT88 protein was either severely reduced (*cobblestone* mutation) or completely absent (conditional inactivation of *Ift88*). The phenotypes were then compared with the phenotypes of mice, in which *Gli2* and *Gli3* were inactivated.

Methods: Ventral midbrain development was analyzed using immunohistochemistry and RNA in situ hybridization in the following mutants: a) *Cobblestone (cbs)* mutants, which have reduced levels of IFT88 protein, b) conditional knock-out mice, in which the *Ift88* allele (*Ift88* cko) was inactivated in the midbrain after E8.5 (about a day after the onset of Shh signaling), and c) mutants with a conditional deletion of *Gli2* and *Gli3* (*Gli2/3* cko). The morphology of primary cilia in the *Ift88* mutants was investigated with scanning electron microscopy.

Results: *Cbs* mutants do not develop beyond embryonic day (E) 12.5. Analysis of E10.5-12.5 ventral midbrain showed that the number of DA neurons and their progenitors was severely reduced and disorganized. Previous studies have shown that DA progenitors are not induced in *Shh* null mutants, suggesting that residual Shh signaling might occur in *Cbs* mutants. In the midbrain of *Ift88* cko mutants, in which is *Ift88* is fully inactivated, primary cilia were reduced in number and deformed. In addition, Shh signaling appeared to be abolished. *Ift88* cko mice developed to term, allowing the analysis of DA neuron development up to E18.5. The E18.5 midbrain of *Ift88* cko mice had a smaller DA progenitor domain and the number of DA neurons was reduced. DA neurons and progenitors were also reduced in *Gli2/3*cko embryos. Interestingly, the reduction of DA neurons in *Gli2/3* cko embryos was more severe than in *Ift88* cko mutants.

Conclusion: The data obtained from this study show that *Ift88* plays an important

role in the induction of ventral midbrain DA neurons, likely by maintaining functional primary cilia and consequently normal levels of Shh signaling. Interestingly, the phenotypes observed upon loss of IFT88 protein and primary cilia are milder than in mutants with inactivated Shh signaling. This suggests that low levels of Shh signaling might persist in absence of IFT88 protein.

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Pattern Classification on fMRI-data: A diagnostic approach on psychiatric disorders

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Introduction: Pattern classification techniques have become of growing interest in fMRI research. While early approaches mainly concentrated on within-subjects-classification, recent works also address the diagnostics of psychiatric disorders, like the prediction of depressive patients and controls. This work addresses for the first time the challenge to discriminate fMRI data between unipolar and bipolar depressive patients by using support vector machines.

Methods: A 3T-Scanner was used to collect fMRI data from 10 patients with unipolar disorder and 10 patients with bipolar disorder, both groups currently in an actual depressive state. In a passive viewing task emotional faces were presented during the measurement. After standard pre-processing contrast images were generated (negative > neutral; happy > neutral). The contrast images were masked by the most important structures associated with emotion processing (PFC, ACC, amygdala, ventral striatum). These extracted patterns were entered as input for a support vector machine. Cross validation was performed to calculate the accuracy and statistical significance was determined by permutation tests. Afterwards, discriminative maps were extracted from chosen classifiers to identify regions of the trained patterns, which were mainly responsible for a successful classification.

Results: The contrast “happy faces vs. neutral faces” achieved an accuracy of 90% (p=0.003), while the classifier trained with “negative faces vs. neutral faces” was able to identify 75% correctly (p=0.04). Finally, a classifier trained with both contrast images as one input pattern has an accuracy of 80%. Extracted discriminative maps reveal contrary activations in the amygdala, i.e. unipolar depressive patients react stronger on negative faces, while bipolar depressive patients show higher activity in the amygdala during the presentation of positive faces.

Discussion: The findings of discriminative maps support common theories, where the neurobiological causes of these psychiatric disorders are supposed to differ. For instance it can be assumed, that bipolar disorders lead to an enhanced dysfunctional identification of emotional stimuli, while unipolar disorder tend to amygdala activities which are more restricted but enhanced to negative stimuli. Although the sample size is – especially in regard to pattern classification – very small, this proof of concept shows a possible future application in psychiatric diagnostics.

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7 Tesla Ultrahochfeldbildgebung des intrakraniellen arteriellen Gefäßsystems: native versus kontrastmittelgestützte MPRAGE

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Ziel: Die 7 Tesla Ultrahochfeldbildgebung des Neurokraniums mit Hilfe einer nativen MPRAGE Sequenz zeichnet sich bekanntermaßen durch eine homogen hyperintense Signalintensität der intrakraniellen arteriellen Gefäßstrombahn aus. Ziel dieser Studie war ein intraindividueller Vergleich der diagnostischen Wertigkeit einer nativen versus einer kontrastmittelgestützten MPRAGE-Sequenz hinsichtlich ihrer diagnostischen Wertigkeit zur Beurteilung des intrakraniellen arteriellen Gefäßsystems.

Material & Methoden: Zwölf Probanden wurden mit einer 32-Kanal-Kopfspule (Siemens) an einem 7 Tesla Ganzkörpertomographen untersucht (Magnetom 7T, Siemens Healthcare, Erlangen, DE). Es wurde eine isotrope MPRAGE Sequenz nativ und nach der Applikation von 0,1mmol /kg Gadobutrol (Gadovist®, Bayer Schering Pharma) akquiriert. Folgende Arterien und Gefäßsegmente wurden hinsichtlich Ihrer Abgrenzbarkeit qualitativ (5=sehr gute Bildqualität bis 1= schlechte Qualität) durch zwei Radiologen im Konsensus analysiert: 1) Arteria cerebri anterior, 2) Arteria pericallosa, 3) Arteria carotis interna, 4) Arteria cerebri media (Segmente M 1-3), 5) Arteria communicans posterior, 6) Arteria cerebri posterior und 7) Arteria basilaris.

Ergebnisse: Die visuelle Bildanalyse zeigte eine hochwertige diagnostische Aussagekraft der nativen MPRAGE (Gesamtdurchschnittswert 3,85) für die gesamt intrakranielle arterielle Gefäßstrombahn. Diese, für eine native Gefäßdarstellung sehr hohe diagnostische Wertigkeit, konnte durch die Applikation von Kontrastmittel auf einen exzellenten Durchschnittswert von 4,7 (von maximal zu vergebenden 5 Punkten) gesteigert werden. Insbesondere die Abgrenzbarkeit der A. communicans anterior und der proximalen A. basilaris konnte stark gesteigert werden (3,33 auf 4,50 bzw. 2,67 auf 4,83).

Schlussfolgerung: Die Ergebnisse dieser Pilotstudie konnten die hochwertige diagnostische Wertigkeit der nativen MPRAGE darlegen, die durch die Applikation von Kontrastmtittel deutlich gesteigert werden konnte.

Glatiramer acetate ameliorates the course of disease in the R6/2 transgenic mouse model of Huntington´s disease

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Background*:* Glatiramer acetate (GA) is a random polymer consisting of four basic amino acids mimicking myelin basic protein. It acts as modulator of antigen presenting cells and thus is a FDA approved drug for the treatment of relapsing remitting multiple sclerosis. Recent studies imply that GA may also exert neuroprotective effects via an increased BDNF expression in immune cells (Linker et al., 2010).

Methods: 3-4 week old female R6/2 mice were immunized subcutaneously with 0.25 mg GA in complete Freund´s adjuvant (CFA) or with 0.2 mg of ovalbumin or 0.05 mg myelin oligodendrocyte glycoprotein peptide 35-55 (MOG) in CFA as controls. Mice were weighed and clinically monitored to obtain survival curves. Motor impairment was evaluated by accelerating rotarod and by assessing the clasping score. Histological analyses included immunohistochemistry for ubiquitin, BDNF, the neuronal marker NeuN and microglial activation markers. Quantitative real time PCR was performed to investigate BDNF expression.

Results: In R6/2 mice, treatment with GA prevents weight loss over time. Moreover, immunization with GA or MOG leads to a prolonged survival (median survival in the GA treated group 102 days or 99 days in MOG immunized mice vs. 92.5 days in the control group, $p = 0.02$ by log rank test) and to an attenuated motor impairment as measured by the clasping score or in a rotarod analysis. GA treated R6/2 mice display a twofold higher BDNF expression in the brain as compared to controls. Blinded quantification of neuronal densities in the motor cortex and the basal ganglia, as well as immunohistochemistry for ubiquitin, reveal lower numbers of degenerating neurons after GA treatment, while numbers of huntingtin aggregates were not altered.

Conclusion: Treatment with GA ameliorates the disease course in a model of HD. Further studies with this well-tolerated compound are warranted to investigate its efficacy in HD.

Establishment of a slice culture model for excitotoxicity.

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Introduction: We are interested establishing the technique of using organotypic slice culture as a model of experimental neurodegeneration to mimic some of the events associated with traumatic spinal cord injury or with amyotrophic lateral sclerosis. This approach would facilitate studies of pathophysiological mechanisms in complex tissues while minimising the number of animals required for such studies and reducing the associated costs. Others have established similar organotypic models using hippocampal slice cultures (Roehl et al. 2010) or more recently using spinal cord slice preparations (Guzman-Lenis et al. 2009). The present experiments have been conducted to demonstrate the effects of glutamate induced motoneuronal death in such slice preparations in serum-free medium as well as the neuroprotective effects of serum-containing medium.

Methods: Lumbar organotypic slices (350µm thick) obtained from 7-9 day old Sprague-Dawley rats were grown in either Neurobasal A medium supplemented with B27 or in Eagle's Modified Esential Medium supplemented with Hank's Balanced Salt Solution (25%) and horse serum (25%). Cultures were maintained *in vitro* for up to 14 days, after which they were incubated in different concentrations of glutamate (50µM-2mM) for 30 minutes and thereafter allowed to recover for an additional 48 hours. The ensuing neurodegeneration was assessed by quantifying of the uptake of propidium iodide (PI, 1µg/ml for 30 min) into the nuclei of damaged cells before and after the glutamate insult. Furthermore, astrocytic and motoneuronal responses were determined quantitatively following double immunofluorescence for Glial fibrillary acidic protein (GFAP) and non-phosphorylated 200kDa neurofilament (SMI 32). Stained samples were visualised using either routine epifluorescnece microscopy or 2 photon confocal microscopy.

Results: Organotypic spinal cord slices maintained for 14 days in either serum-free or serum containing medium demonstrated little or no spontaneous uptake of PI, indicating the generally healthy state of the preparations maintained under either condition. Short term exposure of slices to increasing concentrations glutamate (50µM, 100µM or 500µM), caused widespread and extensive uptake of PI in preparations maintained in serum free conditions. Quantification of SMI32 immunofluorescence demonstrated that such elevated PI signals were associated with a clear reduction of neurofilament containing motoneurons in the ventral horn. Exposure of spinal cord slices to elevated glutamate levels (up to 2mM) in serum-containing medium had no such effect. PI uptake in such samples was negligible and the numbers of SMI32-positive motoneurons was indistinguishable from control samples.

Conclusions: We believe that the establishment of this technique and a better understanding of the cell-cell interactions that it supports will allow the development of future investigations into drug- and cell-mediated neuroprotective effects.

Establishment of an *in vitro* system for the evaluation of axon growth promoting properties of 3D bioengineered scaffolds

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Introduction: An *in vitro* model capable of studying the axon growth promoting properties of 3D biomaterials will be useful in the development of scaffolds for the repair of traumatically injured peripheral nervous system (PNS) tissues. The well preserved cytoarchitectural organization of spinal cord organotypic slice cultures (SCOSC) as well as hemisected dorsal root ganglia (DRG) are being used to determine the orientated motor- and sensory axon growth promoting properties of a 3D collagen scaffold.

Methods: Cervical organotypic slices (350µm thick) and hemisected DRG, obtained from 7-9 day old Sprague-Dawley rats were combined with collagen matrices containing orientated microchannels (Matricel GmbH, up to 5mm long). Cultures were maintained for up to 21 days, after which they were fixed by immersion in 4% PFA (1 hour), permeabilized with 95% acetic alcolohol and processed for immunhistochemistry using antibodies against the 200kDa non-phosphorylated neurofilament epitope (NF200, antibody SMI32), α3-Tubulin (TUBB3), low affinity nerve growth factor receptor (NGFr/p75), intracellular calcium binding protein (S100), glial fibrillary acidic protein (GFAP), the ionized calcium binding adaptor molecule 1 (IBA1), and ED1. Samples were then observed using 2-photon scanning confocal microscopy (Olympus) to evaluate the extent and orientation of axonal growth, as well as cell-axon interactions taking place between migrating cells and regenerating axons within the scaffold.

Results: Sensory neurons from hemisected DRGs extended long and highly orientated SMI32-positive axons along the Matricel collagen microchannels. Axons that reached the dorsal horn of the SCOSC crossed the scaffold-SCOSC interface and matrix crossing it and exploring the target tissue of the DH of the SCOSC. Similarly, ventral horn motor neuron axons (also SMI-32 positive) from the slice cultures extend along the scaffold. In both cases, a close interaction between regenerating axonal profiles and NGFr/p75-postive Schwann cells could be seen. Cell migration into the collagen scaffold was strong in both experimental set-ups and included migration by cells that were immunoreactive for NGFr/p75, S100, IBA1 and ED1. A more limited degree of GFAP-positive astrocyte migration was observed close to the SCOSC-scaffold interface

Conclusions: Earlier *in vitro* investigations have focused largely on cell-substrate interactions using cell suspensions and 2D biomaterials. As the field of biomaterial research advances in the development of 3D scaffolds, the utilization of *in vitro* models capable of analyzing the tissue-scaffold interactions may generate much useful information. In particular, it is hoped that such approaches will eventually reduce the number of *in vivo* experiments required in the development of bioengineering strategies intended for PNS repair.

Modality-dependent Experience Modulates Event-related Potentials in Response to Novel Tools

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Introduction: The organization of semantic knowledge in the brain is a central issue of current neuropsychological research. Domain-specific theories argue that evolutionary pressures resulted in a categorical organization. In contrast, the "sensory-functional theory" suggests a modality-specific organization of conceptual knowledge. The latter account predicts that the dominant modality of experience with objects determines their neural representation. In fact, it has been shown that the training to use novel manipulable objects leads to a neural representation in fronto-parietal brain regions and that properties that are differentially weighted for the distinctiveness of category-membership influence the formation of conceptual knowledge. The present study aimed to directly investigate the influence of different types of experience on new neural object representations.

Methods: Participants completed a visual match-mismatch task with pictures of novel manipulable objects before and after they received modality-specific trainings with the objects: In three training sessions participants visually explored one set of objects (visually trained objects - VTO) and manipulated another set of objects (manipulation trained objects - MTO). A third set was not part of the training and served as a control condition (no training objects - NTO). During the match-mismatch task, brain activity was recorded by means of electroencephalography.

Results: Overall, event-related potentials (ERPs) in response to pictures of novel tools were comparable between object sets. After training, the N400, an ERP component related to semantic processing, was significantly reduced for VTO, but not MTO and NTO at electrode site F3 over the left frontal cortex. In addition, there was evidence of N400 enhancement over right frontal sites for MTO relative to the other object sets.

Conclusion: The results suggest that experience within different modalities with novel manipulable objects leads to differential weighting of those modalities in conceptual representations, dependent on the dominant modality during conceptual knowledge acquisition.

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Neuronal Correlates of Performance-Related Feedback in Young and Elderly People

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Introduction

Performance-related feedback can act as an extrinsic reward and hence influence behaviour. Several studies show an association between neural activity in specific brain regions (e.g., anterior cingulate cortex) and the valence of a feedback (Nieuwenhuis, 2005; Van Veen, 2004). It remains to be elucidated, if such differential activation is age dependent or not. Hence, the present study investigates how performance-related feedback is neuronally processed in young and elderly people. Moreover, we aim at investigating whether positive and negative feedback show age-related differential neuronal effects.

Methods

In this study 16 young men (M= 25.2 ± 5.0 years of age) and 16 seniors (M= 69.4 ± 3.8 years of age) participated. Using functional Magnetic Resonance Imaging the volunteers were investigated while performing a modified Flanker-task in the scanner environment. As a function of their individual performance participants received a positive, negative or neutral feedback after each trial of the task.

Results

Behavioural data reveal a significant influence of feedback on subsequent trials. On the neuronal level significant main effects of feedback and age could be found. However, the interaction did not reach significance. In comparison to negative feedback, positive feedback was associated with stronger activation of putmanen, gyrus frontalis and anterior cingulate cortex. Older participants showed stronger activation of middle and inferior gyrus frontalis compared to younger subjects.

Discussion

The reward system was similarly activated in younger and older participants, which implies that feedback can serve as reward both in young and elderly people.

Human mirror neuron system and emotions in Parkinson Disease

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Background: Besides the classical triad of motor symptoms, Parkinson Disease (PD) is characterized by cognitive and affective impairments. For example, a facial emotion recognition deficit has often been reported. Up to now, neural mechanisms underlying this affective impairment are not well understood. Current neuroimaging studies suggest that perception and execution of motor acts (i.e. emotional facial expressions) are closely linked by a special class of visuomotor neurons (mirror neurons) in the ventrolateral premotor cortex (pars opercularis) and that the activation of these neurons during perception triggers intention understanding. The goal of our study was to examine the neural correlates of emotion processing in PD with a specific focus on the probable human mirror neuron system.

Methods: Nine patients with PD and nine matched controls underwent functional magnetic resonance imaging (fMRI). The fMRI experiment was implemented as a two-by-three factorial design with the factors task (observation of facial gestures, expression of facial gestures) and type of facial gesture (happy: smile, non-emotional: lip protrusion, neutral: relaxed expression without movement). Short video clips depicting actors expressing different facial gestures and scrambled video clips were used as stimulus material. Participants were instructed to observe whenever they saw the actors and to execute whenever they saw the scrambled videos. After scanning, participants were asked to complete a short neuropsychological test battery and a facial emotion recognition task. In addition, they had to rate how much happiness they experienced during each condition.

Results: In our preliminary data analysis we found conjoint activation for observation and expression of the emotional facial gesture in visual and frontal areas, in the right inferior frontal gyrus (pars opercularis), the left amygdala, and the right superior parietal lobule, when data were pooled across all participants. In the group comparison, region of interest analysis revealed weaker activation of the right pars opercularis during observation of the emotional facial gesture in patients with PD.

Discussion: The results of our study provide evidence for altered neural processing of emotional facial expressions in patients with PD. It is possible that decreased activation of pars opercularis during observation of emotional facial gestures impedes facial emotion recognition that is impaired in patients with PD. Further analyses are needed to relate the altered neural processing to the performance in the emotion recognition task.

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Synaptic plasticity in the lateral Amygdala in GAD65-deficient mice

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Background: GABAergic mechanisms are crucial for aversive signal processing in the amygdala. Availability of GABA as a transmitter is determined by the rate-limiting enzyme glutamic acid decarboxylase (GAD), which exists in two isoforms GAD67 and GAD65. GAD67 is responsible for metabolic GABA synthesis, whereas GAD65 seems to be the more synaptic activity-dependent isoform. In fact, genetically determined deficiency of GAD65 results in increased anxiety, generalization of conditioned fear and impairment of fear extinction (Bergado-Acosta et al., 2008; Sangha et al., 2009). Therefore the present study was undertaken to characterize the functional role of GAD65 in synaptic transmission and plasticity in the lateral amygdala (LA).

Methods: Whole-cell patch-clamp recordings were performed in acute brain slices containing the LA of GAD65 deficient mice ($GAD65^{-/-}$) and age-matched wild-type littermates ($GAD65^{+/+}$) prepared *in vitro*, and after Pavlovian fear conditioning *ex vivo*.

Results: Obtained results indicate that GAD65 deficiency is associated with (*i*) a significant decrease in efficacy of evoked $GABA_A$ receptor-mediated synaptic responses, whereas glutamatergic responses were unaffected, (*ii*) an impairment of long term plasticity at monosynaptic GABAergic inputs, and (*iii*) a shift from a heterosynaptic associative form of long-term potentiation (LTP) at cortico-thalamic inputs to non-associative forms, which could be mimicked in $GAD65^{+/+}$ by application of CGP55845 blocking presynaptic $GABA_B$ receptors. Importantly, generalized fear obtained upon over-training in $GAD65^{+/+}$ resulted in a shift from associative to non-associative forms of LTP similar to that observed in $GAD65^{-/-}$.

Discussion: These data support the notion that GAD65 is a critical element for providing sufficient amounts of GABA during periods of increased demands such as high synaptic activity. Since lowered GAD plasma activity and polymorphisms in the GAD2 gene-region have been associated with risk factors for anxiety disorders (Unschuld et al., 2009), these findings raise the possibility that GAD65 enzyme dysfunction could be a pathogenic factor in panic disorder.

Pluripotent stem cell-derived neural stem cells as stable source of human oligodendrocytes

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Background: The damage and loss of oligodendrocytes, the myelin-forming cells of the central nervous system, are symptomatic for demyelinating pathologies including multiple sclerosis, leucodystrophies, stroke and spinal cord injury. Thus, efficient generation of human oligodendrocytes (OL) *in vitro* can provide interesting prospects for basic research, screening applications for OL-specific compounds and eventually the development of stem cell-based therapies for diseases requiring OL replacement. In recent years, embryonic stem cells (hESC) have emerged as particularly versatile and unlimited source of neural donor cells. In addition, reprogramming of somatic cells into induced pluripotent stem cells (iPSC) provides fascinating prospects to generate patient-specific PSC. However, while the generation of neural precursors and differentiated neurons from human PSC is well established, efficient differentiation into oligodendrocyte precursor cells (OPC) and modeling of myelin disorders still poses a significant challenge.

Methods: For neural induction hESC and hiPSC were cultured as floating aggregates and differentiated in a three-step protocol in medium with decreasing concentrations of retinoic acid. After 28 days the aggregates were plated on Matrigel-coated tissue culture dishes and cells with stem cell properties were isolated on the basis of the expression of the neural stem cell (NSC) marker CD133 by FACSorting. The NSC fate and regional identity of the isolated cells were characterized at the transcript and protein level. Defined *in vitro* differentiation conditions, in particular for efficient OL differentiation, were used to assess the tripotential differentiation capacity into neurons, astrocytes and OL. Transplantation studies into neonatal shi/shi rag2$^{-/-}$ mice were performed to examine the functional properties of OL *in vivo*.

Results: We were able to establish an adherent and clonogenic population of gliogenic NSC from hESC and hiPSC. These glioNSC express markers characteristic of neural stem/radial glial cells. They exhibit prominent expression of region-specific transcription factors typically found in the posterior hindbrain and anterior spinal cord. Expression patterns of transcription factors specific for dorsal, intermediate and ventral progenitors suggest that glioNSC are not restricted to a dorsal or ventral fate. Upon growth factor withdrawal glioNSC exhibit tripotential differentiation into neurons, astrocytes and OL. Notably, using defined differentiation conditions that induce strong expression of the OL-specific transcription factors OLIG1/2, NKX6.2 and SOX10, glioNSC can be converted into cultures highly enriched in NG2-positive OPC, which further differentiate into O4+, GalC+ und MBP+ OL. Furthermore, upon transplantation into neonatal shi/shi x rag2$^{-/-}$ mice glioNSC-derived OL undergo full maturation and ensheath host axons.

Discussion: The generation of glioNSC provides for the first time a direct and stable source of human OL. Translation of our differentiation paradigm to iPSC from patients suffering from myelin disorders will offer interesting prospects for studying cell-autonomous pathomechanisms directly in human OL.

Effects of inflammatory cytokines and minocycline on cultured neural stem cells

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Introduction: Manipulating endogenous neural stem cells (NSCs) in the adult brain has emerged as an experimental concept, aimed at enhancing the brain's regenerative capacity after insults such as stroke. Neuroinflammatory processes occuring after stroke are mediated by pro-inflammatory cytokines such as TNF-alpha, interleukin-1ß (IL-1ß) and IL-6; however, their effects on NSCs are unknown to date. The tetracycline minocycline has neuroprotective effects in stroke, but – likewise – its effects on NSCs are unclear to date.

Method: NSCs were dissected from fetal rat cortex (E13.5) and grown as monolayer cultures in an undifferentiated state in the presence of fibroblast growth factor 2 (FGF2). To study the effects of various pharmacological agents on NSCs, cultures were treated with various concentrations or combinations of TNF-alpha, IL-1ß, IL-6, and minocycline, and NSC numbers were assessed over time using a photometric assay (MTT). To assess the effects of drugs on NSC proliferation, treated cells were exposed to bromodeoxyuridine (BrdU) for 6hrs, and then stained for BrdU incorporation. The differentiation potential of NSCs was assessed by withdrawing FGF2 for 10 days, followed by immunocytochemical stainings for the three potential fates of NSCs (neurons, astrocytes, and oligodendrocytes).

Results: 10µM and 50µM of minocycline significantly increased NSC numbers over 48 hours compared to control conditions. This effect could not be attributed to an increase in NSC proliferation as assessed by the BrdU-assay, thus indicating a positive effect of minocycline on the survival of NSCs. Minocycline did not affect the differentiation potential of NSCs, as all three cell fates were generated in the same distribution observed in control cells. A cocktail of the pro-inflammatory cytokines TNF-alpha, IL-1ß and IL-6 did neither affect NSC numbers nor their proliferative activity. However, pro-inflammatory cytokines did accelerate the differentiation of NSCs, and promoted a glial fate.

Conclusion: Our data suggest that certain concentrations of the neuroprotective drug minocycline positively affect NSC survival while keeping cells in the tri-potential, undifferentiated state. On the other hand, the pro-inflammatory cytokines TNF-alpha, IL-1ß, and IL-6 accelerated NSC differentiation toward a glial fate. These results should help to establish novel (combinatory) treatments targeting the endogenous NSC niche in stroke.

Beeinflussung der zentralen Schmerzverarbeitung durch Nikotin und Koffein

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Hintergrund: Die Wirkungen von Nikotin und Koffein auf das schmerzverarbeitende System werden in der Literatur kontrovers diskutiert, wobei sowohl analgetische als algetische Effekte beschrieben sind. So werden z.B. koffeinhaltige Mischanalgetika zur Schmerztherapie insbesondere von Kopfschmerzerkrankungen eingesetzt.
Ziel dieser Studie ist, den Einfluss von Nikotin und Coffein auf die trigeminale Schmerzverarbeitung an gesunden Probanden mittels trigeminaler schmerzevozierter Potentiale (PREP) sowie des nozizeptiven Blinkreflexes (nBR) zu untersuchen.

Methodik: Die Schmerzstimulation erfolgt mittels einer planaren Kupfer-Platin-Elektrode, die eine spezifische Stimulation der Aα-Fasern des nozizeptiven Systems erlaubt. Die Applikation des Schmerzreizes erfolgt im Bereich der Stirn (V1) beidseits. PREP und nBR können simulatan abgeleitet werden, so dass gleichzeitig eine Untersuchung des trigeminalen Schmerzsystems auf Hirnstammebene (nBR) aber auch supraspinal (PREP) erfolgen kann. Diese Untersuchung wird sowohl vor als auch nach der Einnahme von 0,4mg Koffein oder dem Rauchen einer Zigarette durchgeführt, so dass die interindividuellen aber auch die intraindividuellen Nikotin- und Koffeinabhängigen Unterschiede bestimmt werden können.

Ergebnisse: Bislang wurden 10 gesunde Probanden untersucht. Es zeigten sich weder im intraindividuellen noch im interindividuellen Vergleich der Latenzen und Amplituden nach Nikotin- oder Koffeineinnahme signifikante Unterschiede. Nach Auswertung der bisher erhobenen Daten besteht bei gesunden Probanden weder eine Fazilitierung noch eine Augmentation der trigeminalen Schmerzverarbeitung durch die zugeführten Substanzen.

Diskussion: Nach Auswertung der bisherigen Daten konnte kein Einfluss von Koffein oder Nikotin auf die trigeminale Schmerzverarbeitung gezeigt werden. Für die Zukunft wird es interessant zu untersuchen, ob sich diese Ergebnisse in einem größeren Probandenkollektiv bestätigen lassen und ob diese nur für gesunde Probanden zutreffen und z.B. Kopfschmerzpatienten ein abweichendes Verhalten zeigen.

Voxel based morphometry showing acute alteration in a visual paradigm.

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Introduction: Previous studies used voxel based morphometry (VBM) for imaging long term alteration within the gray matter of the brain. Increased and decreased densities were reported after special tasks or conditions such as learning to juggle or pain application and were interpreted as signs of cerebral neuroplasticity over time. Acute changes of cerebral activation have been only studied by functional imaging such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). We aimed to investigate whether VBM can also detect acute changes induced by a simple checkerboard paradigm.

Methods: Twenty healthy subjects were investigated using VBM. Three MRIs were applied to each single subject: one before looking at a flickering checkerboard, one right after looking at the checkerboard, and one 1 hour later. For each subject a map of grey matter volumetric differences between the scans of different time points was calculated. After within processing all scans of one time point were aligned together and normalized (Dartel algorithm of SPM 8, Matlab 7). As control experiment we performed regular fMRI with checkerboard stimulation in all participants.

Results: Changes within the primary visual cortex (Brodmann area 17; MNI: x= -6, y=-93, z=-3; p_{FWE}=0.043; T=5.08) were detected after application of the checkerboard paradigm and diminished within one hour. A near-by region showed activation in a regular fMRI block design using a checkerboard design. Additionally gray matter changes were observed in the secondary visual cortex (Brodmann area V5/MT; MNI: x= 59, y=-63, z=7; p_{FWE}=0.035; T=5.19) one hour after application of the checkerboard design.

Conclusion: The observed changes appear to be generated by looking at the checkerboard as they occur in the visual cortex which is known to be activated in visual paradigms of multitudinous previous fMRI and PET studies. Up to now, VBM changes were interpreted as either neuronal growing/degeneration, or dendrite spine and synapse turnover, or changes of the extracellular space/ microvascular volume. In contrast to long term VBM alterations, acute VBM changes rather seem to reflect actions that must occur much faster than the hithero suggested, for instance water displacement. Further studies are needed to illuminate the physiological background of this observation. This phenomenon might explain the wide diversity of results by different VBM studies not controlling for acute changes or using cross sectional design.

Contiguous gene deletions on chromosome 7 including two factors of the Sonic Hedgehog signalling pathway, SHH and GLI3, cause clinical corresponding and overlapping phenotypes

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Introduction: Chromosomal disturbances are the most frequent cause of complex genetic diseases including mental retardation, (cranio)facial dysmorphisms and congenital malformations like neurological anomalies. The microarray analysis is a high resolution technique which allows the identification of small imbalances. Therefore, this technique becomes a commonly used diagnostic tool in the investigation of patients with complex (neurological) phenotypes.

Methods and Results: With the help of microarray technology, we investigated two patients with complex phenotype compatible with disturbances in the *Sonic Hedgehog* signalling pathway. We were able to identify two different contiguous gene deletions on chromosome 7 including *SHH* (7q36.2-q36.3; approximately 4.2 Mb) and *GLI3* (7p14.1-p13; approximately 3 Mb), two factors of the *Sonic Hedgehog* signalling pathway.

Conclusions: A number of severe (neurological) diseases in mammalians are caused by disturbances within the *Sonic Hedgehog* signalling pathway. Although in both of the presented cases divers genes were affected by the heterozygous deletion, the phenotype generally fits with the haploinsuffiency of *SHH* and *GLI3*, respectively. With regard to the fact that SHH and GLI3 belong to the same signalling pathway, the clinical presentation of these patients affirms this on one hand due to clinical overlapping hallmarks including brain and cranium malformations as well as a short stature. On the other hand, the patients presented with "individual" clinical symptoms like muscular hypotonia, heart disturbances, single maxillary incisor, and cleft palate (7q36.2-q36.3 deletion including the *SHH* gene) or syndactyly and delayed dentition (7p14.1-p13 deletion including the *GLI3* gene) or even contrary dysmorphisms like hypotelorism and hypertelorism. Furhtermore, the patient carrying the 7q36.2-q36.3 deletion shows the more severe phenotype, also with regard to the brain malformations. The varying clinical findings as well as the difference in the severity of the phenotype could be the result of the other genes affected by the two deletions on one hand. But on the other hand, they also could be the clinical outcome of the SHH-dependent function of GLI3: while a disturbed SHH-signalling leads to a gene repressor function of GLI3, disturbances in the quantity of GLI3 more affect its gene activator function.

Extended *SIL1* mutation analysis in Marinesco-Sjögren syndrome increases the detection of pathogeneic alterations and the frequency of diagnosed cases

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Introduction: Marinesco-Sjögren syndrome (MSS) is a rare progressive multisystem disorder with autosomal recessive inheritance. The phenotype is characterized by cerebellar ataxia, congenital or infantile cataracts, progressive vacuolar myopathy, mental retardation, and short stature. Mutations in the *SIL1* gene, which encodes an endoplasmic reticulum (ER) resident co-chaperone, were identified as a major cause of MSS. Up to now, 52 cases with proven *SIL1* mutations are published and the primary pathology has remained unknown in apparently non-*SIL1*-related MSS cases.

Methods and Results: We assume that in a part of MSS patients, genetic alterations within the *SIL1* gene, not detectable with Sanger sequencing, are responsible for the MSS pathology. In order to proof this assumption, we carried out an extended *SIL1* mutation analysis. With the help of array-CGH and junction fragment analysis, were able to identify two different large deletions within the *SIL1* gene in two patients presenting a classical MSS phenotype. One patient presented before with a single heterozygous *SIL1* mutation while the other one showed no *SIL1* mutations detectable by Sanger sequencing.

Conclusion: Our data extend the mutational spectrum associated with the *SIL1* gene and highlight the need of extended *SIL1* mutation analysis in MSS diagnostics on one hand in MSS cases heterozygous for one *SIL1* mutation, and, on the other hand in classical MSS cases without *SIL1* mutations detectable by Sanger sequencing. Furthermore, our results indicate that *SIL1*-related MSS is potentially under-diagnosed due to the limitation of screening procedures customarily used in MSS diagnostics.

Neural underpinnings of psychopathy in youth with early onset conduct disorder

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Background: Early onset conduct disorder (CD) is known to have a poor prognosis and a high rate of conversion into antisocial personality disorder. In particular psychopathic or callous-unemotional traits are associated with increased violent behaviour and state a risk factor for ongoing antisocial behaviour. Neuroanatomical findings point towards altered volumes of structures of the limbic system, such as the hippocampus. In this structural MRI-study, we investigated hippocampal volumes and hippocampal subfields of youth with early onset conduct disorder and psychopathic traits compared to age matched healthy controls.

Methods: All subjects underwent 3T-MRI scanning. Hippocampal volumes were assessed by means of automated segmentation with FreeSurfer, Version 5.1, using Bayesian interference models. This method further provides volumes of hippocampal subfields. Psychopathic traits were assessed by means of the Antisocial Process Screening Device (APSD). Age-corrected group comparisons for hippocampal volumes and partial correlations between callous-unemotional traits and hippocampal subfields were calculated.

Results: Total hippocampal volume and left hippocampus volume were smaller in youth with CD and psychopathic traits compared to healthy controls. Right hippocampal volume was by trend smaller in youth with CD and psychopathic traits. Psychopathic traits were associated with smaller volumes of the subiculum and the tail of the hippocampus bilateral.

Discussion: The findings point towards smaller hippocampal volumes in youth with early onset CD and psychopathic traits. Smaller hippocampal volumes as part of the limbic system and are associated with deficits in affect and motivation. Moreover, these data are in accordance with findings of experimental studies proposing that lesions of the dorsal hippocampus impair acquisition of conditioned fear. Following theories on psychopathology of psychopathic traits, deficits in emotion processing such as acquisition of fear are central features in the development of psychopathy.

Habituationsverhalten bei Patienten mit Phobischem Schwankschwindel (PSS)

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Hintergrund: Bei Habituation handelt es sich um eine unbewusste Form des Lernens, bei der wiederholende Reizapplikationen (z.B. leichte Schmerzen) im Rahmen einer Reizgewöhnung zu einer verminderten Reizreaktion und –wahrnehmung im Verlauf führen. Diese Gewöhnung verhindert eine Reizüberflutung durch unbedeutende Reize und hilft die Konzentration des Organismus auf neue möglicherweise wichtigere Stimulationseinflüsse zu wenden. Verschiedene chronische Erkrankungen wie zum Beispiel die Migräne zeichnen sich durch ein sogenanntes Habituationsdefizit aus, bei dem eine solche Reizgewöhnung nicht oder nur unzureichend stattfindet. Der phobische Schwankschwindel (PSS) ist die zweithäufigste diagnostizierte Schwindelursache. Patienten mit PSS leiden unter einem dauerhaft oder episodisch auftretenden Schwankschwindel begleitet von subjektiver Stand- und Gangunsicherheit. Die zugrunde liegenden pathophysiologischen Mechanismen dieser Erkrankung sind bisher weitgehend unbekannt. Das Vorliegen eines Habituationsdefizits bei PSS wurde in der Vergangenheit postuliert, aber noch nicht durch Studien belegt. Ziel dieser Studie ist es zu untersuchen, inwieweit ein Habituationsdefizit bei der Entstehung bzw. Unterhaltung des PSS eine Rolle spielt.

Methode: Das Habituationsverhalten wurde mittels des nozizeptiven Blinkreflexes (nBR) untersucht. Die R2-Antwort des nBR wurde nach schmerzspezifischer Stimulation der Aα-Fasern im Bereich beider Seiten der Stirn (V1) analysiert. Zur Untersuchung der Habituation wurde ein Blockdesign gewählt (10 Blöcke je 6 Schmerzstimulationen; Blockabstand jeweils 2 Minuten), wobei die R2-Antwort jeweils in Abhängigkeit vom ersten Block untersucht wurde und die Habituation als Abnahme der R2-Antwort der Folgeblöcke im Vergleich zu Block 1 definiert wurde. Die Reizstimulation erfolgte mit einer Stimulationsintensität, die 2x die individuelle Schmerzschwelle betrug, wobei die Schmerzstimulationen > 2mA ausgeschlossen wurde, um eine Aα-Faser-Koaktivierung zu verhindern.

Ergebnisse: Bisher wurden von 60 Messungen 16 Patienten mit PSS sowie 16 Alters- und Geschlechts-gematchte gesunde Probanden untersucht. Die bisherigen Auswertungen zeigen einen Trend zu einem Habituationsdefizit in der Patientengruppe im Vergleich zur gesunden Vergleichsgruppe. Eine eindeutige Aussage kann jedoch erst nach Erhöhung der Fallzahl (geplant 30 PSS und 30 gesunde Kontrollen) gemacht werden.

Diskussion: Unsere vorläufige Auswertung detet einen Trend zu einem Habituationsdefizit bei Patienten mit PSS an, der ein Bestandteil der pathophysiologischen Grundlagen dieser Erkrankung darstellen könnte. Zum Beleg dieser Hypothese ist allerdings noch eine Erhöhung der aktuellen Fallzahl notwendig.

Strukturelle Veränderungen bei Patienten mit Phobischem Schwankschwindel - eine Voxel basierte Morphometrie-Studie

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Einleitung: Der phobische Schwankschwindel (phobic postural vertigo, PPV) ist ein sekundär somatoformer Schwindel mit einer bislang weitgehend ungeklärten Pathophysiologie. Der PPV ist in der Altersgruppe der 20- bis 50-Jährigen die häufigste Schwindelform, die Geschlechtsverteilung ist ausgeglichen (m:w 1:1,04). Klinisch ist der PPV charakterisiert durch konfluierenden Schwankschwindel mit subjektiver Stand- und Gangunsicherheit, attackenartiger Fallangst zumeist ohne Stürze und einer Verstärkung der Symptome in typischen auslösenden Situationen (große Menschenmengen, Supermärkte, enge Räume), was häufig zu Vermeidungsverhalten führt. Der PPV folgt häufig einer organischen Schwindelerkrankung. Ziel dieser Studie ist es herauszufinden, ob es hirnstrukturelle Veränderungen bei Patienten mit PPV gibt und ob diese im Zusammenhang mit der Schwere der klinischen Symptome oder der vorausgegangenen Schwindelerkrankung stehen.

Methode: Von jeweils zwanzig Patienten mit PPV und gesunden Kontrollprobanden (KP) ohne Vorerkrankungen (je elf Männer und neun Frauen) wurden in einem 1,5-Tesla Magnetresonanztomographen dreidimensionale T1-gewichtete MPRAGEs (magnetization prepared rapid acquisition gradient echo) erstellt. Diese wurden mittels Voxel basierte Morphometrie (VBM) ausgewertet. Für die Vorverarbeitung und die statistischen Analysen wurde SPM8 (statistical parametric mapping, FIL, UCL, London, UK) genutzt.

Ergebnisse: Sowohl in der Patienten- als auch in der Kontrollgruppe lag das Durchschnittsalter bei 36 Jahren (Spanne zwischen 24. bis 48. Lebensjahr). Bei 65 % der Patienten ließ sich keine vorangegangene Schwindelerkrankung mit organischer Ursache finden, 20 % der Patienten litten zuvor an einer vestibulären Migräne. Ein Drittel der Patienten beklagten täglichen Schwindel, die restlichen zwei Drittel beklagten mehrfach in der Woche respektive im Monat Schwindel. In der PPV Gruppe zeigte sich im Vergleich zu den KPs einer Abnahme der grauen Substanz im posterioren anterioren cingulären Cortex (pACC) sowie im dorsolateralem präfrontalen Cortex (DLPC). Eine Zunahme an grauer Substanz konnte nicht beobachtet werden.

Schlussfolgerung: Patienten mit PPV zeigen im Vergleich zu Normalprobanden eine Reduktion der grauen Substanz im pACC und im DLPC. In zahlreichen vorangegangenen Studien mit Patienten mit chronischen Schmerzen konnte eine Abnahme der grauen Substanz in diesen Arealen beschrieben werden. Wahrscheinlich ist dies Ausdruck einer geteilten Pathophysiologie, da auch beim PPV eine Veränderung der allgemein-sensorischen Verarbeitung denkbar ist. Zudem ist der cinguläre Cortex Teil des limbischen Systems und somit Teil der

emotionalen Bewertung. Die enge Verknüpfung mit dem ebenfalls veränderten Präfrontalkortex könnte den Link zwischen dem Schwindel des PPV und dem typischerweise damit einhergehenden Vermeidungsverhalten darstellen.

Imaging Pain in ultra-high-field. A 7T fMRI study.

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Background: Pain and Headache disorders like Tension-Type-Headache, Migraine are high frequent and partly very disabling conditions. Thereby they are causing serious individual and socioeconomic burden. Up to now various functional and structural imaging studies gave major input to the understanding of pain especially in regard to general central processing, limbic involvement and chronification. But still a significant amount of the pathophysiology of pain is poorly understood. On the other hand ultra high filed MRI and its high signal noise ratio (SNR) is a powerful tool to perform functional magnetic resonance imaging (fMRI) and thereby study the human brain in a functional manner. The aim of our study was to establish a protocol to analyse human pain processing across the whole brain in ultra-high-field fMRI.

Methods: We therefore investigated pain processing in 6 healthy subjects (right handed, Age 24-36Y) using a block design based on a multi-echo echo planar imaging sequence (TE1(ms): 10, TE2 (ms): 23.33, TE3 (ms): 36.66, TE4(ms): 49.99; TR(ms): 3000; Flip angle: 76) in a 7T Siemens MRI test unit based at Erwin L. Hahn Institute for Magnetic Resonance Imaging in Essen. After various security tests and simulations pain was elicited to subject's right hand and foot (pseudo-randomized) by a concentric platinum-copper electrode without significant ferromagnetic properties. The pain specificity of this electrode was demonstrated in multiple previous electrophysiological trials. As control condition we used a checkerboard (CB) with frequent black-white swapping for visual stimulation. fMRI Analysis was done using SPM8 and Matlab 7.6.0 (R2008a).

Results: In the control condition (visual stimulation by CB) we found massive activation of the primary and secondary visual cortex even after correction for multiple comparisons and highering the standard threshold to pFWE<0,005 in all subjects. In painful stimulation all subjects showed activations in major parts of the pain/attention network. In most patients these activations were consistently in primary and secondary somatosensory cortex as well as in the insular cortex, the anterior cingulated cortex and the thalamus. Some of the patients showed additional brainstem-activation. All activations described were robust and survived correction for multiple comparisons (pFWE<0,05). In comparison to 1,5T piloting studies the activations seen in 7T-fMRI appeared to have a higher significance.

Discussion: In this pilot study we were able to establish a protocol to study pain processing in ultra-high-field fMRI. In this protocol pain specificity was guaranteed by the use of a validated pain electing electrode. Activations in pain and in visual stimulation were consistent with neuroanatomical knowledge and previous

structural and functional imaging studies. In total the activations observed in 7T appeared be of a higher significance compared to those seen in lower field strength fMRI using a comparable protocol. Ultra high field pain related fMRI might be able to hunt up smaller activations than standard high-field fMRI and thereby give important input to the deciphering of the complex human pain processing.

Lack of association of a fatty acit amide hydrolase *(FAAH)* gene variant to weight loss in a one-year intervention for obese children and adolescents (Obeldicks)

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Introduction: Recently, it was shown that obese carriers of the A allele of SNP rs324420 in *FAAH* lost more weight and improved associated phenotypes better than non-carriers during an intervention. We tried to replicate this finding in obese children and adolescents undergoing a one year lifestyle intervention (Obeldicks program).

Subjects and methods: 453 overweight and obese children and adolescents (10.8 ± 2.6 years, BMI-SDS 2.4 ± 0.5; 55% girls) were genotyped for rs324420 (C/A) by restriction fragment length polymorphism (RFLP) analysis. Participants received a balanced diet, containing 55 En% carbohydrates, 30 En% fat and 15 En% proteins. Moreover, they took part in an exercise therapy once a week. Blood was taken at baseline and after one year of intervention. Anthropometric (height, weight, BMI and BMI-SDS) and plasma parameters (total cholesterol, LDL-cholesterol, HDL-cholesterol, triacylglycerides, glucose, insulin and HOMA) as well as blood pressure were measured.

Results: Both BMI and BMI-SDS improved significantly among all subjects. The mean systolic blood pressure was also lowered and concentrations of HDL-cholesterol increased significantly. However, none of the measured parameters were associated with *FAAH* rs324420 genotypes.

Conclusion: We did not detect association of *FAAH* genotypes with weight reduction in overweight and obese children and adolescents. Hence, the previous finding in adults could not be confirmed. As the length (1 year vs. 3 months) and the set up (hypo caloric diet in adults versus physical activity plus balanced meals) of the interventions differed, these parameters might have influenced the different results.

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Gene-correction in induced pluripotent stem cell derived neural stem cells using AAV-mediated targeting

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Background: Induced pluripotent stem cells provide a fascinating tool to study disease-associated changes directly in the cell type affected in vivo. In such studies, iPS cells derived from healthy donors are typically used as reference point. However, considering the genetic variability between human individuals, an ideal control for studying monogenic diseases would be gene-corrected iPS cells from the same patient. So far, classic methods of targeted genetic modification have proven inefficient in human pluripotent stem cells. Here we present the efficient gene correction of an expanded polyglutamin-containing allele in human neural stem cells (lt-NES cells; Koch et al., PNAS 106(9):3225-30, 2009) generated from iPSC derived from a patient with Machado Joseph Disease (MJD). In MJD, the monoallelic expansion of a polyglutamin-encoding CAG motif in exon 10 is causative for the formation of ATXN3-containing aggregates and neurodegeneration.

Methods: To exchange the mutation-containing exon we took advantage of the ability of recombinant adeno-associated viral vectors to efficiently target homologous chromosomal loci and introduce defined sequences with high fidelity. Using exon-flanking homology arms the expanded exon was exchanged by the non-expanded exon amplified from the healthy allele from the same patient.

Results: From a single viral transduction of 750.000 cells, an average of 220±40 clonal neural stem cell lines could be generated. Out of 60 clones analyzed by PCR and 22 clones analyzed by Western Blotting, all showed reversion to a non-expanded CAG-containing allele.

Discussion: Our data suggest that AAV-mediated gene correction could represent a fast and efficient approach to generate isogenic controls in iPSC-based disease modeling.

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Genotype-phenotype correlation in caveolinopathy: Pathogenicity of the sequence variant G55S

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Caveolins are structural and functional proteins located in flask-shaped plasma membrane invaginations called caveolae. They have been involved in the signalling and trafficking of growth factor receptors / receptor tyrosine kinases like EGFR. Mutations in Caveolin-3, which is mainly expressed in muscle cells, cause autosomal dominant myopathies of different severity ranging from asymptomatic hyperCKemia to lethal LGMD-1C and cardiomyopathy. In this study, we examined muscle biopsies from two index patients of two unrelated families with hereditary myopathy harbouring the G55S caveolin-3 amino acid change. This sequence variant has been described previously to be either asymptomatic or to cause mild myopathy. In the present families, this sequence variant segregated with moderate to severe myopathy. Histology revealed moderate chronic myopathic changes and reduced sarcolemmal Caveolin-3 immunoreactivity in both cases examined. Caveolin-3 levels were also reduced in immunoblots. Electron microscopy revealed moderately enlarged caveolae in one case. Interestingly, in the other case, a vacuolar myopathy with prominent myonuclear degeneration was found. In RCMH cells transfected with G55S caveolin-3, pathological Caveolin-3 deposits were found to be associated with the Golgi apparatus, but considerable Caveolin-3 levels were still present at the sarcolemma. Phosphoblotting demonstrated that G55S affects the signalling of EGFR. Interestingly, besides the amino acid change the index patients as well as their family members present different SNPs in the *caveolin-3* gene. Our results indicate that the sequence variant G55S is pathogenic and alters the signalling of EGFR. On a more general note, these results further elucidate the pathomechanisms of caveolinopathies. Finally, they illustrate the value of muscle biopsy analysis for the diagnosis of hereditary myopathies in cases of ambiguous molecular genetic data.

Discriminating bodily expressions of emotions: an fMRI study

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Background: The communication of emotional states is fundamental for social life. Whenever spoken language is not sufficient, people engage in bodily actions including facial expressions or gestures to convey information about their emotional state to others. The addressee has to evaluate the intention of the addresser and to categorize the emotional face expressions and gestures as positive or friendly versus negative or aversive in order to react appropriately. In this functional magnetic resonance imaging (fMRI) study we wished to explore the brain areas underlying the discrimination of bodily expressions of emotions.

Methods: Sixteen non-alexithymic healthy subjects (22+/-2ys) were presented with video-clips that showed the evolution of emotional face expressions or emblematic gestures evolving from a neutral starting point to their full meaningful expressions. The subjects were instructed to discriminate in a forced-alternative choice paradigm an angry facial expression from other emotional face expressions and a negative from a positive gesture, respectively, and to convey their decisions by a button press. FMRI scanning was performed on a 3 T Siemens MRI with 44 transversal slices oriented parallel to the bi-commissural plane. Image data were analyzed using a random effects analysis followed by a region of interest analysis of the brain activation beta-indices.

Results: There was a main effect related to the perception of face expressions and gestures in the right inferior temporal gyrus. The inferior temporal gyrus was also active at the time point of discrimination. The right inferior frontal gyrus was active during the perception of the face expressions but became more active at the time point when the subjects made the discrimination. The dorsal medial frontal cortex was activated in relation to perception of the emotional face expressions but was deactivated at the time point of discrimination. The dorsal medial frontal cortex and the right inferior frontal gyrus correlated with the subjective valence of the emblematic gestures during perception. There was an activation of the right dorsolateral prefrontal cortex which occurred only in relation to the discrimination and correlated with the inferior temporal, inferior frontal and dorsal medial frontal activations.

Discussion: The activation of the inferior temporal gyrus is likely to reflect the formal visual analysis of the emotional face expressions and emblematic gestures. Discrimination involved frontal brain areas related valuating of emotions. We suggest that the brain structures identified here for appraisal and discrimination of affective body expressions are key structures mediating social interactions.

Sind Menschen in der Lage, die Emotion Angst mithilfe chemosensorisch wirksamer Signale zu kommunizieren?

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EINLEITUNG: Aus dem Tierreich ist bekannt, dass im Angstzustand geruchsaktive Substanzen mit dem Schweiß abgegeben werden, welche als spezifische Signale innerhalb einer Spezies wirken. Auch Menschen können emotionale Botschaften kommunizieren, ohne dass visuelle und auditorische Sinnessysteme benutzt werden. Spezielle chemosensorisch wirksame Substanzen im menschlichen Schweiß sind für diese Kommunikation verantwortlich.

METHODE: Um die Effekte von chemosensorischen Angstsignalen eines Menschen auf einen anderen Menschen zu untersuchen, haben wir ein neues Modell zur Angstinduktion mit simultaner Schweißgewinnung entwickelt. Hierzu trugen gesunde Probanden Zellstoffpads unter den Achseln, womit sie Übungen in einem Hochseilgarten durchführten. Um die Wirkung der chemosensorischen Angstsignale bewerten zu können, wurde zusätzlich ein neutraler Kontrollreiz gewonnen, während die Probanden auf einem Fahrradergometer trainierten. Die Wirkung der chemosensorischen Angstreizen im Vergleich zu den neutralen Reizen wurde mittels behavioraler, elektrophysiologischer und bildgebender Methoden an einem weiteren Probandenkollektiv untersucht.

ERGEBNISSE: Unsere Ergebnisse zeigen, dass Probanden unter dem Einfluss von chemosensorischen Angstsignalen im Vergleich zu neutralen Kontrollreizen eine höhere Zustandsangst aufweisen. Außerdem wurden zweideutige emotionale Gesichtsausdrücke von den Probanden unter Angsteinfluß als weniger freundlich beurteilt. Während eines Computerspieles reagierten die Probanden mit erhöhter Risikobereitschaft.

SCHLUSSFOLGERUNG: Zusammenfassend stellen wir fest, dass die Ergebnisse dieser Studien Einblicke in die Mechanismen der zwischenmenschlichen Kommunikation der Emotion Angst mithilfe chemosensorischer Substanzen liefern. Erklärungsansätze für dieses modifizierte Verhalten auf Basis der elektrophysiologischen und neuronalen Korrelate der chemosensorischen Angstsignale werden diskutiert.

The role of mTOR-signaling in neuroprotection and axon regeneration in the mature CNS after inflammatory stimulation

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Introduction: Mature retinal ganglion cells (RGCs) do not normally regenerate injured axons, but degenerate after axotomy. However, inflammatory stimulation (IS) enables RGCs to survive axotomy and regenerate axons in the injured optic nerve. Similar effects are achieved by the genetic deletion of phosphatase and tensin homolog (PTEN) and subsequent mammalian target of rapamycin (mTOR) activation.

Methods: We used the optic nerve crush model to functional assess the role of mTOR in axon regeneration as well as Western-blot analysis and immunohistochemical methods.

Results: Here, we report that IS prevents the axotomy-induced decrease of mTOR activity in RGCs in a CNTF/LIF-dependent manner. Inactivation of mTOR significantly reduced the number of long axons regenerating in the optic nerve, but surprisingly, did not affected the initial switch of RGCs into the regenerative state, or the neuroprotective effects associated with IS. In vitro, inhibition of mTOR activity reduced regeneration on myelin or chondroitin sulfate proteoglycans (CSPGs), but not on a growth-permissive substrate.

Conclusion: Thus, mTOR activity is not generally required for neuroprotection or switching mature neurons into an active regenerative state, but it is important for the maintenance of the axonal growth state and overcoming of inhibitory effects caused by myelin and CSPGs.

ERYTHROPOIETIN AMELIORATES EXPERIMENTAL AUTOIMMUNE NEURITIS

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Background: Guillain-Barré syndrome (GBS) is a disabling autoimmune disorder of the peripheral nervous system associated with relevant morbidity and mortality; thus, novel treatment options are warranted. Erythropoietin (EPO) is a pleiotropic cytokine originally identified for its role in erythropoiesis. However, in various preclinical models EPO exhibited protective activity against tissue injury.

Methods: To test the therapeutic potential in experimental autoimmune neuritis (EAN) - an animal model of human GBS - EPO was tested in a prevention and a treatment paradigm.
EAN was induced in female Lewis rats by immunization with bovine peripheral myelin. Animals were treated with EPO prior to or with onset of first clinical signs of disease activity. Assessment included clinical scoring, the degree of inflammation within the peripheral nerve as monitored by immunohistochemistry and the status of myelination in semi-thin sections.

Results: While the treatment in the prevention paradigm ameliorated clinical disease activity during all phases of the disease, the therapeutic administration of EPO improved clinical remission. Immunohistochemistry of sciatic nerves revealed no significant alteration of T cell numbers under treatment. Surprisingly, the number of macrophages was significantly increased in the two treatment groups at peak of disease and also during the recovery phase. The massive number of macrophages seen within the peripheral nerve correlated with the staining for TGF-beta. Significantly more TGF-beta positive cells were detectable in the two treated groups at the peak of the disease and - to a lesser extend - also during the remission phase. Epon sections at day 29 post immunization revealed more demyelination without remyelination and axonal degeneration in the control nerves compared to nerves of animals treated with EPO. *In vitro* EPO reduced antigen-dependent proliferation of T cells in a dose dependent manner and also significantly reduced allogenic T cell activation. Cultivation of peritoneal macrophages or T cells in the presence of EPO had no impact on the secretion of the proinflammatory cytokine IFN-gamma, but increased the amount of anti-inflammatory TGF-beta, as investigated by ELISA.

Discussion: Our data suggest that EPO ameliorates immune-mediated damage to peripheral nerve by the induction of beneficial macrophages within the peripheral nerve. Further studies are warranted to elaborate the clinical usefulness of EPO for treating immune-mediated neuropathies in affected patients.

Quinpramine – a potential new immunosuppressive compound – ameliorates rat experimental autoimmune neuritis and redistributes MHC class II molecules.

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Introduction: Acridine-iminodibenzyl chimeric compounds are a novel class of cholesterol-redistributing substances with antiprion and possibly also anti-inflammatory effects. In previous studies the lead compound quinpramine effectively suppressed manifestation of symptoms in an animal model of human multiple sclerosis. Guillain-Barré syndrome (GBS) is a disabling autoimmune disorder of the peripheral nervous system associated with relevant morbidity and mortality and experimental autoimmune neuritis (EAN) serves as its animal model. **Aim:** To test the therapeutic potential and mechanism of action of quinpramine in EAN.

Methods: EAN was induced in female Lewis rats by immunization with bovine peripheral myelin. Animals were treated with quinpramine prior to or with onset of first clinical signs of disease activity. Assessment included clinical scoring, the degree of inflammation as monitored by immunohistochemistry, and the status of myelination in semi-thin sections. Immune activation was determined by antigen-specific T cell proliferation and by FACS analysis of MHC class II expression *ex vivo* und *in vitro*. To determine the target cell of quinpramine, antigen presenting cells (APCs) and T cells were both pretreated *in vitro* and antigen-specific T cell proliferation was measured.

Results: Quinpramine reduced the clinical and histological severity of EAN. Both, preventive and treatment regimens significantly improved the clinical score, although disease prevention exerted a more pronounced clinical effect. In line with the ameliorated disease severity in treated animals myelin was well maintained and less immune cell infiltration was detectable. Splenocytes from quinpramine treated animals displayed significantly reduced antigen specific proliferation. Again, the effect was more prominent in animals treated preventively. Pretreatment of APCs significantly decreased T cell proliferation, while T cell preincubation with quinpramine did not alter the proliferating capacity. Previous studies had shown the redistribution of cholesterol into intracellular compartments. We therefore also analyzed MHC class II distribution and showed a reduction in MHC class II surface expression on quinpramine treated cells.

Conclusion: Quinpramine reduces clinically and histologically the severity of EAN. MHC class II expression and antigen-specific T cell proliferation were reduced both *in vitro* and *in vivo,* based on an effect on APCs rather than on T cells. Thus, we hypothesize that by redistributing cholesterol rich membrane domains to intracellular compartments quinpramine reduces cell surface availability of MHC class II and therefore inhibits autoimmune (re-) activation. The anti-inflammatory compound quinpramine may constitute a novel therapeutic option in human GBS.

Taxol facilitates axon regeneration in the mature CNS

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Introduction: Mature retinal ganglion cells (RGCs) cannot normally regenerate axons into the injured optic nerve, but can do so after lens injury. However, the outcome of this regeneration is still limited by inhibitors associated with the CNS myelin and the glial scar.

Methods: We used the optic nerve crush model to functional assess the effects of locally applied Taxol on promoting axon regeneration as well as Western-blot analysis and immunohistochemical methods.

Results: The current study demonstrates that Taxol markedly enhanced neurite extension of mature RGCs and PC12 cells by stabilization of microtubules and desensitized axons towards myelin and chondroitin sulfate proteoglycan *(*CSPG) inhibition *in vitro* without reducing RhoA activation. *In vivo* the local application of Taxol at the injury site of the optic nerve of rats enabled axons to regenerate beyond the lesion site, but did not affect the intrinsic regenerative state of RGCs. Furthermore, Taxol treatment markedly increased lens injury mediated axon regeneration *in vivo*, delayed glial scar formation, suppressed CSPG expression, and transiently reduced the infiltration of macrophages at the injury site.

Conclusion: Thus, microtubules stabilizing compounds such as Taxol might be promising candidates as adjuvant drugs in the treatment of CNS injuries particularly when combined with interventions stimulating the intrinsic regenerative state of neurons.

Zebrafish crypt neurons express a single V1R-like olfactory receptor gene

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Introduction: Crypt neurons constitute the third type of olfactory sensory neurons. Unlike the extensively studied ciliated and microvillous neurons, very little is known about them, not even the olfactory receptor family they express. We recently identified a novel olfactory receptor family of six highly conserved G protein-coupled receptors, the *v1r*-like *ora* genes.

Results: We report here that a single member of this family, *ora4*, is expressed in nearly all crypt neurons, defined by S100 immunoreactivity, in zebrafish. None of the other five ora genes are found in this neuronal population. Accordingly, no co-expression of *ora4* with any of the remaining five *ora* genes was observed with double *in situ* hybridization, consistent with the monogenic pattern of expression characteristic of olfactory receptor genes. Furthermore, several lines of evidence suggest the absence of any other olfactory receptors such as ORs, TAARs and the V2R-like OlfCs in crypt neurons.

Discussion: These results suggest that the entire crypt neuron population selects one and the same olfactory receptor gene for expression. This coding strategy is radically different from the expression of large olfactory receptor gene families in both ciliated and microvillous neuron populations. Thus, we have identified a more restricted mode of expression than the well-known 'one neuron – one receptor' rule. This 'one cell type – one receptor' mode is familiar in the visual system, with rhodopsin as the sole light receptor of rod photoreceptor cells, but up to now not suspected to occur in the olfactory system. Identification of the receptor expressed provides the molecular starting-point necessary to unravel crypt neuron signaling and function.

Fingolimod impedes Schwann cell mediated myelination

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Introduction: Fingolimod (FTY720), a sphingosin-1-phosphate (S1P) receptor agonist, is a recently approved drug for treating multiple sclerosis. Experimental evidence suggests that FTY720 not only exhibits anti-inflammatory properties but also promotes myelination in the central nervous system by direct interaction with oligodendrocytes. Aim of this study was to assess the effects of FTY720 on Schwann cells (SCs) and peripheral nerve myelination.

Methods: Receptor expression studies and myelination were investigated in primary rat SCs and rat neuronal/SC co-cultures. Cells were treated with physiologically relevant concentrations of the active phosphorylated form of FTY720 (FTY720P). In addition, S1P receptor expression was corroborated in human and rat peripheral nerve tissue sections.

Results: SCs express all known S1P receptors *in vitro* and *in vivo*. FTY720P did not impede receptor expression levels. In the myelination model treatment with FTY720P resulted in a significant reduction of quantitative myelin formation. FTY720P induced reactive oxygen species (ROS) in SCs leading to apoptosis of these cells, as demonstrated by the detection of caspse-3 and -7, as well as TUNEL labeling. This effect was dependent of S1PR signaling, since blocking of S1PRs ameliorated ROS production and SC apoptosis.

Conclusion: FTY720P induces ROS mediated apoptosis in SCs and may interfere with peripheral nerve myelination.

SCHWANN CELL MIGRATION IN INFLAMMATORY MILIEUS

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Background: While polyneuropathies (PNP) are known as common causes of disability, the underlying molecular mechanisms of degrading and remodelling peripheral myelin are not completely clear. Schwann cells (SCs) as glial cells of the peripheral nervous system (PNS) play a main role in myelin restructuring, a process requiring the ability of SCs to migrate, in damaged peripheral nerves, e.g., in the context of immune-mediated damage to the PNS.

Methods: The present study was designed to identify cytokines secreted by inflammatory cells as mediators of SC locomotion. The correlation between activity of matrix metalloproteinases (MMP), relevant endopeptidases for cell migration, and SCmobility were studied. Furthermore, serum from rats induced with experimental autoimmune neuritis (EAN) at different stages of the disease, interleukin 4 (IL-4) and interferon gamma (IFN-γ) as key cytokines of an inflammatory TH1/TH2 response, as well as toll-like receptor 4 ligand lipopolysaccharides (LPS), were analysed as attractants and modulators of migration. To address these subjects, we purified SCs from sciatic nerves of neonatal rats in order to record SC migration, using systems for directed as well as for undirected migration. We applied transwells and chemotaxismigration-slides to analyse directed horizontal and vertical migration, and stamp plates as well as scratch assays in order to record undirected migration. Long-term imaging was performed in a conditioned microscope chamber up to three days.

Results: We observed an increase of undirected SC mobility after treatment with LPS, and after inhibition of MMP with an nonspecific MMP inhibitor this elevation was diminished. Stimulation with EAN serum had a distinct influence on directed migration, and the pure stimulation with IL-4 and IFN-γ confirmed these findings.

Discussion: We conclude that an unspecific inflammatory stimulus increases the unspecific movement of SCs, to some extent caused via MMP secretion. In respect to chemotaxis, a specific pattern of cytokines during inflammation and regeneration is crucial to conduct and regulate SC locomotion. This study provides new insights into restorative mechanisms of the PNS which may be useful in the development of target therapies.

Alphabetisches Verzeichnis der Poster

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