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Abdulazim, A. - Pannexin 1 : A long hidden co-player in learning and memory [G11]

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**Background:** Pannexin 1 (Panx1) constitute a family of integral membrane proteins which form high conductance (550pS) membrane channels and are permeable to large molecules of up to 1 kDa, like ATP. Previous studies have revealed a contribution of Panx1 channels in pathophysiological processes like inflammation or ischemia. However, the localization of Panx1 channels on postsynaptic hippocampal sites and its NMDA receptor associated activation leads to the assumption of a physiological role of Panx1 in synaptic transmission and plasticity.

**Methods:** In this study we used a transgenic Panx1 knock out mouse model for *in vitro* field excitatory postsynaptic potential (fEPSP) in hippocampal CA 1 neurons of acutely dissected 350 µM hippocampal slices. Under different electrophysiological and pharmacological conditions Panx1 channel properties were characterized. Further learning and memory performances of Panx1 +/+ and Panx1 −/− mice were analyzed.

**Results:** Panx1 −/− derived hippocampal slices showed fEPSP responses significantly shifted towards increased excitability in input-output (IO) relation recordings. High frequency stimulation demonstrated a potently enhanced LTP response in Panx1 −/− slices. The application of either adenosine (3µM) or D-AP5 (50µM) normalized this physiological phenotype. Mefloquine (MEQ) (50nM) a specific Panx1 channel antagonist partly emulated the Panx1 −/− LTP response after addition to Panx1 +/+ derived slices.

Behavioural experiments demonstrated enhanced anxiety and impaired spatial learning and memory of Panx1 −/− mice.

**Conclusion:** Our data indicate for the first time a decisive role of Panx1 channels in the initiation and maintenance of hippocampal neuroplasticity. Thus, a modulatory contribution of Panx1 in learning processes and memory formation seems probable.
Acoustic coordinated reset (CR) neuromodulation causes a significant reduction of tinnitus severity that is paralleled by a reversal of pathological oscillatory activity and is often accompanied with a significant tinnitus pitch change. Here we study if the changes of tinnitus pitch change correlate with changes of tinnitus severity as assessed using visual analog scale (VAS). We also study whether the changes of the pattern of brain synchrony in tinnitus patients, induced by 12 weeks of CR therapy, depend on the amount of tinnitus pitch change. Clinical data and spontaneous EEG from 59 tinnitus patients were analyzed. Changes of VAS scores significantly correlated with the modulus, i.e. the absolute value, of the tinnitus pitch change. Moreover, a significantly stronger decrease in gamma power was found in patients with pronounced tinnitus pitch change in the right parietal cortex (Brodmann area, BA 40), right frontal cortex (BA 9, 46), left temporal cortex (BA 22, 42), and left frontal cortex (BA 4, 6), combined with a significantly stronger increase of alpha (10–12 Hz) activity in the right and left anterior cingulate cortex (ACC; BA 32, 24). In patients with pronounced pitch change a significantly lower functional connectivity in the gamma band between the right dorsolateral prefrontal cortex (BA 46) and the right ACC (BA 32) was found after 12 weeks of CR therapy. Our results indicate a substantial reduction of tinnitus-related auditory binding in a pitch processing network.
Ahuja, G.- Deorphanizing crypt neurons, the third type of olfactory receptor neurons [F02]

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The sense of smell (olfactory sense) plays a vital role in many essential behaviors such as prey detection, predator evasion and reproduction. The small teleost Danio rerio (zebrafish) has been established as model system to study vertebrate olfaction. In the olfactory epithelium of Danio rerio, there are three types of olfactory sensory neurons present: ciliated, microvillous and crypt neurons. Olfactory receptors present on ciliated and microvillous neurons have been studied extensively, but little is known about the receptors, transducing G-protein and further information processing in crypt neurons. Recent work from the lab showed Ora4 receptor to be exclusively expressed in crypt neurons by in situ hybridisation (Ora4). In order to analyze the subcellular localization of Ora4, we have generated and characterized a specific antibody against Ora4 olfactory receptor. The Western blot analysis with anti-ORA4 on protein extracts from olfactory epithelium revealed a unique band of expected molecular weight, which is exclusively present in the affinity purified lot, but absent in the pre-immune serum from the same animal. We find that this antibody co-localizes nearly completely with anti-S100 (a known marker for crypt neurons, although it is selective for crypt neurons only in fresh-frozen tissue sections). In contrast, anti-Ora4 solely labels the crypt neurons under all tested fixative conditions. This makes this antibody a more robust marker for the crypt cells. We report here that anti-Ora4 labeling is heavily concentrated in a spherical apical dot, which corresponds to the position of the crypt and enclosed cilia of the crypt neurons. In fact, this apical dot co-localizes exactly with anti-acetylated tubulin, a ciliary marker. A weak cytoplasmic staining with anti-Ora4 may represent immature receptor molecules en route to the plasma membrane. This subcellular localization supports Ora4 to be a functional olfactory receptor for crypt neurons. Gi1b has been suggested as potential signal-transducing G protein in crypt neurons. We show here, using different anti Gi antibodies that Gi1b exclusively co-labels with crypt neurons. We show the Gi1b promoter to drive specific reporter gene expression in transient transfection experiments, and are currently establishing a transgenic zebrafish line using a pGi1b-Venus construct. We are investigating a potential ligand for this receptor and the other downstream targets to unravel the neuronal circuit associated with crypt neurons.
Alawi, E. M. - fMRI-based social neurofeedback of the ACC specifically modulates cognitive interference processing [B02]

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Introduction: Neurofeedback based on rt-fMRI trains subjects to regulate localized brain activity (Weiskopf et al.,2007). Typically subjects see a visual display that indicates the level of activity in a selected brain region (e.g. Sitaram et al., 2007). We (2010) developed a new paradigm, in which social feedback is used to train participants. A computer generated face (avatar) provides positive social feedback (smiles) when the activity in the region of interest (ROI) increases and it gradually becomes neutral when the activity decreases. Although social learning is essential for adaptive behavior in humans (Adolphs, 2010), it was not used in neurofeedback studies so far. We studied the effectiveness of this feedback on ACC activity and tested the psychological effects on cognitive interference processing in a Simon task.
Objective: Intrauterine infection and inflammation are major reasons for preterm birth. The switch from placenta-mediated to lung-mediated oxygen supply during birth is associated with a sudden rise of tissue oxygen tension that in preterm infants amounts to relative hyperoxia. Both, infection/inflammation as well as hyperoxia have been shown to be involved in brain injury of preterm infants. Since it is unclear how the combination of these two insults might contribute to tissue injury, we investigated the influence of a systemic lipopolysaccharide (LPS) application on hyperoxia-induced white matter damage (WMD) in newborn rats.

Methods: Three-day-old Wistar rat pups received 0.25 mg/kg LPS i.p. and were subjected to 80% oxygen on P6 for 24 hours. The extent of WMD was assessed by immunohistochemistry and western blot analysis. In addition, the effects of LPS and hyperoxia were studied in an in vitro co-culture system of primary rat oligodendrocytes and microglia cells.

Results: Both noxious stimuli, hyperoxia and LPS, induced a significant increase in apoptotic cell death as revealed by elevated cleaved caspase-3 levels and TUNEL-positive cells. Furthermore, both hyperoxia and LPS caused hypomyelination as revealed by western blot and immunohistochemistry. However, single hit and two hit treated pups evoked the same degree of hypomyelination in vivo. Interestingly, LPS pre-incubation reduced premyelinating-oligodendrocyte susceptibility towards hyperoxia in vitro which also involved a modulation of the inflammatory response regarding cytokine expression.

Conclusions: In summary, our data suggest that inflammation as well as hyperoxia strongly attenuate oligodendrocyte cellular dynamics involving apoptotic pathways. Besides, our in vitro data indicate that neuroinflammatory mechanisms contribute to vulnerability of immature oligodendrocytes.
Bertling, F. - Tumor necrosis factor-inducible gene 6 protein: A novel neuroprotective factor against inflammatory developmental brain injury [B05]

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Background: An important factor of developmental brain injury is inflammation. It has been shown that tumor necrosis factor-inducible gene 6 protein (TSG-6) has anti-inflammatory effects in several inflammatory conditions. Nothing is known so far about the role of TSG-6 in the developing brain, its impact on inflammation and its therapeutic potential.

Methods: PCR and Western Blotting was performed according to standard protocols. Brain hemispheres of untreated Wistar rats (p1-p15) were evaluated under developmental aspects of TSG-6. LPS-treated rats (0,25mg/kg LPS i.p. on p3) were evaluated under pathological aspects of TSG-6. To evaluate whether exogenous rhTSG-6 reduces inflammatory-induced brain injury, newborn Wistar rats, exposed to LPS at p3, were treated with rhTSG-6 i.p. (four repetitive doses of 2,25mg/kg every 12h, first dose three hours before LPS-injection).

Results: Investigations of TSG-6’s developmental brain expression showed a linear increase from p1 to p15 on gene level. Additionally, different expression at p6 was detected in Hemispheres, Cortex, Thalamus and Striatum on gene level and Thalamus to other regions on protein level. Expression of TSG-6 after LPS treatment (0-24h) was significantly increased on gene level and tendentiously on protein level. cCaspase-3, a marker of apoptosis, showed a significant down-regulation of ~30% under additional TSG-6 treatment versus sole LPS exposure (n=12-15, p=0,037).

Conclusions: TSG-6 expression is developmentally regulated and increased after LPS exposure. The reduction of activated Caspase-3 demonstrates the neuroprotective potential of exogenous TSG-6 administration in inflammatory-induced developmental brain injury.
Bista, P. - Phosphatidylinositol 4, 5-bisphosphate (PIP$_2$) dependent modulation of thalamic membrane currents and its activity [A12]

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**Introduction:** Recent evidence indicates that a number of ion channels, including certain K$_{2P}$, Ca$^{2+}$ and pacemaker channels are modulated by phosphatidylinositol- 4, 5-bisphosphate (PIP$_2$) a minority phospholipid of the inner leaflet of the plasma membrane. Here we investigated the PIP$_2$-dependency of three membrane currents known to have important roles in the generation of thalamic activity modes, namely the standing outward current (I$_{SO}$), the high voltage-activated Ca$^{2+}$ current (I$_{HVA}$), and the hyperpolarization-activated inward current (I$_{h}$). TASK and TREK channels and L-type Ca$^{2+}$ channels represent major constituents (~35%) of I$_{SO}$ and I$_{HVA}$ of thalamocortical relay (TC) neurons, respectively. Furthermore, HCN2 and HCN4 are the predominant molecular substrate (together ~90%) of I$_{h}$ in these cells.

**Methods:** In the present study we performed electrophysiological recordings in coronal thalamic brain slices (250µM) of Long Evans rats (postnatal age of 12-23 days). Whole cell voltage and current clamp recordings were performed on TC neurons in the dorsal lateral geniculate nucleus (dLGN). Intracellular PIP$_2$ levels were manipulated by direct inclusion to the pipette solution, transferring it from the extracellular to the intracellular compartment by using a PIP$_2$ carrier, scavenging of PIP$_2$ by neomycin (Neo), activation of phospholipase C via the muscarinic ACh receptor agonist oxotremorine (OxoM), and blockade of phosphatidylinositol- 4-kinase (PI-4K) by worthmannin.

**Results:** I$_{SO}$: A dose-dependent decrease in the OxoM-sensitive component was observed with increasing PIP$_2$ concentrations added to the pipette solution. Inclusion of Neo to the pipette solution augmented OxoM-sensitive currents. I$_{h}$: Worthmannin and Neo (dose-dependent effect) induced a decrease in current availability by shifting the activation curve to more hyperpolarized potentials, while intracellular application of PIP$_2$ had no effect. I$_{HVA}$: In comparison to control conditions, Neo (dose-dependent effect) and PIP$_2$ reduced and increased current amplitudes, respectively. Furthermore, application of PIP$_2$ carrier induced an about 5 mV hyperpolarization of the membrane potential under current clamp conditions, thereby mediating a shift from tonic firing to burst firing.

**Conclusion:** All I$_{SO}$, I$_{h}$, and I$_{HVA}$ currents are modulated by PIP$_2$. However the sensitivity of these currents towards this phospholipid seems to be different.

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Bodatsch, M. - Stage related pattern of Mismatch Negativity (MMN) deficits in schizophrenia [F03]

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Background: Auditory MMN is an event-related potential in response to, e.g., tones deviating from standard in either duration (dMMN) or frequency (fMMN). Previous findings suggest that schizophrenia patients may display dMMN deficits already in the prodrome, whereas fMMN might be reduced in later stages only.

Objective: To further investigate a stage related pattern of MMN deficits, we analyzed the MMN in prodromal, first episode, and chronic schizophrenia subjects.

Methods: The study was approved by the local ethics committee. The sample comprised prodromal subjects (N=26, time to conversion: 7.75±8.93 months), first episode schizophrenia patients (N=22, duration of illness: 0.57±0.37 years), and persons suffering from chronic schizophrenia (N=25, duration of illness: 5.81±6.55 years). Healthy subjects (N=31) served as controls. The MMN was obtained in an auditory odd-ball paradigm comprising standard (1000 Hz, 80 msec, 80%), frequency deviant (1200 Hz, 10 %), and duration deviant (40 msec, 10%) tones. Amplitudes at fronto-central electrodes were analyzed.

Results: All patients displayed significantly smaller dMMN in the fronto-central electrodes. Only chronic schizophrenia subjects exhibited significant fMMN deficits compared to healthy controls. fMMN in chronic schizophrenia was significantly smaller compared to both, first episode and prodromal subjects.

Conclusions: Our findings indicate that the duration MMN deviates from healthy controls in all stages of illness, i.e. prodrome, early and late course of schizophrenia. Deficits of the frequency MMN, however, seem to occur only in the later course of illness. Thus, our findings support the hypothesis of a stage related pattern of MMN deficits in schizophrenia.
Bradler, S.H. - Receptorarchitectonic mapping of four new areas in the inferior frontal sulcus of the human brain [E05]

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Functional imaging studies frequently reported activations in the inferior frontal sulcus (ifs), e.g., in sentence comprehension and verbal working memory [1], which cannot be attributed to a Brodmann area [2]. Furthermore, we recently found, that Broca's region and its surrounding is more complex than previously thought [3]. The aim of this study was to analyze the segregation of the ifs using quantitative receptor autoradiography [4].

Seven hemispheres were cut coronally into 20µm thick slices. Alternating sections were labeled with tritiated ligands for receptor binding sites [4]. Seventeen receptor types of different transmitter systems were analyzed. Autoradiographs were digitized, and the gray value information was converted into absolute binding sites densities (fmol/mg protein).

The results proved a receptorarchitectonical differentiation of the ifs from dorsally and ventrally adjacent areas (BA46/9 and 45/44). Four new areas were identified: ifs1-4. They differed in mainly with respect to AMPA, GABA_A, M_1, α_1, and 5-HT_1A receptors. The hierarchical cluster analysis showed that ifs1 and 2 were more similar to each other than both areas to ifs3/4. Furthermore, ifs1-4 were arranged in a rostro-caudal order along the ifs.

In our study four new areas, ifs1-4, were mapped in the human inferior frontal sulcus. Areas ifs1-4 differed in their receptorarchitecture regarding mean binding site densities and laminar distribution patterns. Furthermore ifs1/2 (and ifs3/4) were more similar to each other than to neighboring areas 46, 9 and 45p, indicating a functional distinction of the ifs-areas from neighboring prefrontal areas.
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. The molecular pathogenesis of caveolin-3-related muscular disorders is still largely unknown. Previously, we have shown that patients with R26Q and G55S caveolin-3 mutations develop perinuclear vacuoles which are signs of autophagy and endoplasmic reticulum (ER) stress response. Here we correlate our muscle biopsy findings to the P104L mutant caveolin-3 transgenic mouse model for LGMD-1C. WB assays for the mouse model had already suggested a potential effect of the mutation on the ER stress response (Kuga et al., Hum Mol Genet 2011). In our electron microscopy studies we found peculiar alterations of the nuclear envelope with invaginations reminiscent of myonuclear degeneration in Marinesco-Sjögren syndrome (MSS), a neuromuscular disorder due to mutations in the ER protein Sil1. In association with the degenerated nuclei we found vacuolar structures that often contained membranous structures, indicating autophagy. Ongoing functional studies are focussed on the interaction of mutated Caveolin-3 with further proteins involved in the ER stress response, and more specifically, Sil1 function.
Brünner, Y. - Olfactory performance of patients suffering from autism spectrum disorders (ASD) [102]

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Autism spectrum disorders (ASD) are clinically characterized by a triad of symptom clusters, namely challenges in social interaction and communication as well as repetitive behaviors. Furthermore, ASD represents an innate and neurodevelopmental psychiatric disorder with dysfunctional sensory perception and neural processing. Changes in chemosensory function have been identified in several neurodegenerative or psychiatric disorders, like Parkinson’s and Alzheimer’s disease or depression. Knowledge about chemosensory function in adult ASD patients is sparse due to a small number of patients included in studies and a limited number of different olfactory subtests that have been carried out. Taken together, it is difficult to draw comprehensive conclusions from the existing studies. Therefore, our aim was to compare olfactory performance of 40 adult ASD patients with 40 age- and gendermatched healthy control subjects. Two independent clinicians performed diagnosis of ASD. Furthermore, patients underwent a concise battery of psychological tests including the Autism Diagnostic Observation Schedule (ADOS). We obtained olfactory performance scores by using the Sniffin’ Sticks threshold test (n-butanol), odor discrimination test, and identification test (MONEX-40) as well as pleasantness and intensity ratings. Data was analyzed using means of factor analysis as well as analysis of covariance (ANCOVA). Our results suggest that olfactory performance scores as well as perceptual ratings are diminished in patients suffering from ASD compared to healthy control subjects. Even after correction for confounding parameters (smoking, taking medication, suffering from comorbidities) those results were stable. It is suggested that the decline in olfactory performance as well as perceptual ratings are distinguishing characteristics of ASD patients in comparison to healthy controls. The potential of using olfactory measures as future biomarkers will be discussed.
Marinesco-Sjögren syndrome is a rare autosomal recessive inherited disorder which mainly affects the brain, skeletal muscle as well as lens crystalline. The patients presented with cerebellar ataxia, mental impairment, marked myopathy and cataracts. In 2005, mutations in the SIL1 gene were identified as one pathogenetic factor for MSS. With exception of few missense mutations, nearly all pathogenic sequence alterations lead to a total loss of the corresponding protein which acts as a nucleotide exchange factor for the major ER-resident chaperon BiP. However, there are different in vitro studies focussing on depletion as well as over-expression of the SIL1 protein in different cell systems. Results of the latter ones thereby surprisingly suggest a possible negative effect of SIL1 over-expression on cellular homeostasis. Hence, a significant role of SIL1 expression levels in terms of depletion and up-regulation in health and disease can be assumed. In our study, we focus on the endogenous expression levels of SIL1 in different human tissues and take a closer look on the effect of over-expression in different in vitro systems in order to investigate an assumed pathogenic effect of increased SIL1 levels.
Burciu, R.G. - Brain changes associated with postural training in patients with cerebellar degeneration: a voxel-based morphometry study [D11]

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Recent research indicates that physiotherapy can improve motor performance of patients with cerebellar degeneration. Given the known contributions of the cerebellum to motor learning, it remains unclear whether such changes in performance are mediated by the cerebellum or by cerebral brain areas involved in motor control and learning. The current study addressed this question by assessing the increase in gray matter volume due to sensorimotor training in cerebellar patients using voxel-based morphometry. Nineteen patients with pure cerebellar degeneration and matched healthy controls were trained for two weeks on a balance task. Postural and clinical assessments along with structural magnetic resonance imaging were performed pre- and post-training. The main findings were: First, training enhanced balance performance in cerebellar patients. Second, in comparison to controls patients revealed more post-training gray matter volume increase in neocortical areas (i.e., dorsal premotor cortex, frontal and temporal association areas). Third, increase in gray matter volume within the cerebellum following training was more pronounced in controls than in patients. However, in patients cerebellar gray matter changes were observed in Crus I and II. We conclude that sensorimotor training of patients with cerebellar neurodegeneration induces gray matter changes primarily within non-affected neocortical regions of the cerebello-cortical loop. However, residual function of the cerebellum is still exploited suggesting processes of plasticity in the remaining healthy tissue and/or recovery of degeneration.
Cichy, A. - Electrophysiological characterization of proton detection in the mouse vomeronasal organ [J07]

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The mouse vomeronasal organ (VNO) plays a key role in pheromone-detection and recognition of other social signals. However, the underlying mechanisms of signal detection in the VNO remain largely unknown.

Here, we describe activation of vomeronasal sensory neurons by extracellular protons. To investigate the mechanisms involved, we performed whole-cell patch-clamp recordings from visually identified sensory neurons in acute tissue slices of the mouse VNO. We show that acidic solutions of different pH values elicit robust action potential firing in current-clamp recordings. The same stimuli dose-dependently induce inward currents in voltage-clamp measurements. The ionic characterization of the underlying conductance and the pharmacological profile of the acid-induced responses indicate a possible involvement of different proton-sensitive ion channels and receptors.

On-going biochemical and molecular investigations as well as electrophysiological measurements will provide insight into the functional role of proton-detection in the vomeronasal organ of mice.
Schizophrenia is characterized by psychotic symptoms but also by marked deficits in executive and psychomotor functions. We used a manual stimulus-response compatibility task to investigate the neuronal correlates of disturbed stimulus-response integration in schizophrenic patients. Eighteen patients with schizophrenia and eighteen matched healthy control subjects responded to briefly presented lateralized stimuli with a button press of either the ipsilateral (congruent condition) or contralateral (incongruent condition) hand.

Incongruent vs. congruent responses revealed common activation across groups in a parietal-premotor-prefrontal circuitry. For the main-effect across all conditions, patients revealed significantly lower activation of the right DLPFC and increased activation in a left hemispheric network including parietal and premotor areas and the SMA. When testing for condition specific group differences, patients showed significant increased activation in the former reported left hemispheric network during incongruent responding. However, these activations were even more pronounced than those found for condition unspecific effects and accompanied by additional activation in parietal and premotor regions in the right hemisphere. The present study shows that hypoactivity in the right DLPFC in schizophrenic patients is accompanied by hyperactivity in regions associated with task execution. This hyperactivity is present during task execution but is even more pronounced during incongruent responding. Impaired top-down control due to a dysfunctional DLPFC might thus be partly compensated by an up-regulation of task-relevant regions in schizophrenic patients.
Mechanistic explanations of auditory-verbal hallucinations (AVH) include misattribution of inner speech and imbalance between bottom-up and top-down factors in auditory perception potentially due to dysconnectivity.

We compared functional resting-state connectivity in 49 psychotic patients with frequent AVH and 49 matched controls. The analysis was seeded from the left middle temporal gyrus (MTG), thalamus, angular gyrus (AG) and inferior frontal gyrus (IFG) as these regions are implicated in extracting meaning from impoverished speech-like sounds.

Decreased connectivity was observed between the left MTG and its right homotope, between the left AG and the surrounding inferior parietal cortex (IPC) and the left inferior temporal gyrus, as well as between the left IFG and left IPC, and dorsolateral and ventrolateral prefrontal cortex (DLPFC/VLPFC). Increased connectivity was observed between the left IFG and the supplementary motor area (SMA) and the left insula and between the left thalamus and the left fusiform gyrus/hippocampus.

The predisposition to experience AVH might result from decoupling between the speech production system (IFG, insula and SMA) and the self-monitoring system (DLPFC, VLPFC, IPC) leading to misattribution of inner speech. Furthermore, decreased connectivity between nodes involved in speech processing (AG, MTG) and other regions implicated in auditory processing might reflect aberrant top-down influences in AVH.
Physiological aging was associated with a deficit in emotion recognition ability (Orbelo et al., 2005, Ruffman et al., 2008). Neuroimaging studies have showed that decoding of emotional prosody cues is linked to a frontotemporal network involving superior temporal gyrus and inferior frontal gyrus (Frühholz et al., 2012). However, little is know about the relationship between affective prosodic processing and age-related change in the functional brain. To this end, the present study aims to investigate the aging brain during automatically processing of affective prosody stimuli. Therefore, the aging brain was examined during the presentation of auditory prosodic oddball stimuli (novels) among repeated non-emotional stimuli (standards). Fifty-five healthy volunteers with an age-range between 18 and 75 years old were included in the current study. The results showed that automatical processing of changes in affective prosody involves bilateral superior temporal lobes. Furthermore, these brain areas were found to be influenced by the normal aging, i.e., advancing age is associated with reduced temporal lobe response. Together, these findings suggest the involvement of temporal lobe in detection of emotion in language and that its functioning is affected by normal aging.

References:


In primary motor (MI) and premotor (PM) cortex, the local field potential (LFP) exhibits beta oscillations (15–30Hz) during an instructed delay [1]. These oscillations display wave-like propagation across the cortical surface [2]. Extending previous results [3], we ask how this spatio-temporal organization relates to task-related spike-spike synchronization [4].

Two monkeys were trained to press a switch with one hand, and then to grasp and pull (with high or low force) an object using either a Side Grip or a Precision Grip. To allow the monkey to prepare the movement, the grip type was revealed at the beginning of an instructed delay before the GO signal. LFP and single unit activity was recorded simultaneously from a 96 electrode array implanted at the MI/PMd border.

We analyze oscillatory activity in the beta band with respect to grip type and cortical position. Next, we quantify the spatial inhomogeneity of LFP propagation by its direction and speed in a time-resolved manner. In parallel, we compute significant, precise spike coincidences [4] as a function of temporal, spatial, and directional parameters. The likelihood of synchronized spiking is behaviorally modulated in time and space, and decreases with distance between neurons. Finally, we compare the spatial arrangement of spike synchrony and synchrony expressed by LFP oscillations.


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Intrinsically disordered proteins (IDPs) are involved in a wide variety of human diseases. Ligands binding to IDPs could counteract them by interfering with IDPs' function and/or fibril formation. Unfortunately, rational ligand design has been hampered by the lack of structural information. Here we present a combined NMR/molecular dynamics protocol that provides quantitative information on ligand poses to IDPs. The approach is applied on dopamine in complex with the naturally unfolded protein human α-synuclein (AS), for which NMR structural data are available. Dopamine is known to bind to the C-term and inhibits its fibril formation. Our MD simulation shows that the presence of DOP, mainly bound to 125YEMPS129 and with a minor extent to NAC region, causes conformational rearrangements of distal residues mainly located at the N-term, consistently with 2D 1H-15N SOFAST-HMQC NMR spectral data measured here.

The method developed allows to explain the 2D-NMR spectra as the superposition of two causes: direct contacts with the ligand and conformational rearrangements of the protein residues. Both contribute to experimental NMR signals, but in some protein regions one of these has a predominant effect.

The proposed protocol is very general and it could be used to investigate the pose of novel molecules binding to any IDP.
Dreier, A. - Novel mechanism for Cetuximab resistance through Eme-1 mediated DNA repair [F11]

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Overexpression of the epidermal growth factor receptor (EGFR) is observed in a large number of neoplasms. One frequently applied therapy for EGFR-expressing tumors is the monoclonal antibody Cetuximab/Erbitux (ImClone, Merck). Cetuximab is thought to inhibit EGFR-controlled tumor cell proliferation and survival. Most commonly this antibody is combined with DNA-damaging radio- and/or chemotherapy. However, the application of cetuximab alone or in combination still fails in a high percentage of the treated patients.

In the present study we describe a novel mechanism for cetuximab resistance occurring in both tumor cell lines and in primary human glioma cell cultures. The monoclonal antibody cetuximab inhibited the Erk1/2- and Akt-pathways in tumor cells; but it also prevented the degradation of Eme 1, a heterodimeric nuclease involved in DNA repair. Subsequently the non-degraded protein Eme1 led to increased DNA repair which we could demonstrate via comet assays and BrdU assays. Therefore additional treatment of the tumor cells with DNA-damaging agents (UVC light; γ- Radiation) did not lead to cell death but in contrast it showed a significant better cell survival.

Our in vitro investigations with different tumor cell lines and primary human glioma cell cultures demonstrate that the cancer therapeutic cetuximab not only failed to have the desired effect but it additionally prevented the effectiveness of standard radiotherapy.
The role of serotonin (5-HT) in cognition, especially in response inhibition is not fully understood yet. We aimed to investigate whether response inhibition and response re-engagement are modulated after treatment with escitalopram, a selective serotonin reuptake inhibitor and whether we are able to find different neural correlates after a 5-HT modulation. Therefore, 13 healthy male participants were tested in a placebo-controlled double blind cross-over study after an acute intake of 10 mg escitalopram or placebo. Response inhibition and re-engagement were assessed during fMRI at the time of expected plasma peak escitalopram concentration with the Stop-Change paradigm, which provides a measure for behavioural inhibition and subsequent behavioural adjustment. Behavioural results did not reveal significant main or interaction effects. Preliminary results of imaging data reveal stronger activations in right frontal and parietal areas during response inhibition after the participants’ intake of 10 mg escitalopram as compared to placebo. The right inferior frontal gyrus which is part of the cortical network of response inhibition was more activated during treatment with escitalopram. Thus, results show changes on neuronal level after treatment with escitalopram as compared to placebo but no effect of escitalopram in the behavioural data which might be due to the minimal dose of 10 mg only.
Ehling, P. - Shiga toxin 2 toxicity on thalamic neurons mediates CNS pathophysiology in EHEC-HUS patients [H04]

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Shiga toxin–producing Escherichia coli (STEC) infection causes neurological disorders in addition to bloody diarrhea and hemolytic uremic syndrome (HUS). Approximately 30% of patients with HUS suffer from central nervous system (CNS) complications. Shiga toxin (Stx) is thought to play a main role in STEC infectious disease, with Stx2 more commonly associated with severe symptoms. The outbreak of hemolytic uremic syndrome (HUS) and diarrhea caused by Shiga toxin-producing Escherichia coli O104:H4 in Germany during May to July 2011 involved severe and characteristic neurologic manifestations. We report on 7 adult female patients with uniform neurologic symptoms including bilateral thalamic lesions and encephalopathic changes indicative of a predominant involvement of the thalamus. In experimental studies we revealed the presence of the Stx receptor globotriaosylceramide (Gb3), which induced neuronal depolarization and glial/neuronal calcium activity, associated with apoptosis. The present findings suggest that a direct cytotoxic effect of Stx2 on neurons and astrocytes in the thalamus contributes to the pathophysiology of neuronal complications in HUS patients. Neuronal cytotoxicity was dose-dependent, brain-region specific, and most likely mediated by the Stx2 receptor globotriaosylceramide (Gb3), which is predominantly expressed in thalamic regions of female rats, bridging the laboratory findings to the clinical observations.
Ferger, R. - Adaptation in the auditory midbrain of the barn owl induced by double stimulation [B03]


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Neurons in the external nucleus of the inferior colliculus (ICX) of the barn owl are arranged in a map of auditory space. Each neuron responds to a broad frequency range and represents information about the interaural time difference (ITD) and the interaural level difference (ILD) of a stimulus. The typical response behavior is phasic-tonic. In other words, these neurons exhibit spike-frequency adaptation. Similar to this effect are the neurons’ responses to two subsequently presented stimuli: Neurons will respond with a higher rate to the first stimulus (called masker) than to the second one (called probe). This effect is known as response adaptation.

In this study we investigate with extra cellular recordings how the inter-stimulus-interval between masker and probe (ISI) and the stimulus-level of the probe relative to that of the masker (2nd level) influences response adaptation. The ISI needed to obtain equal response rates to marker and probe, and the increase in level of the probe needed to obtain the same response rate as to the masker are determined. All stimuli consist of broadband noise. We compare our results to those from narrowband neurons.
Diagnoses of schizophrenia is still based on psychopathological assessment and lacking of instrumental tests. One of the potential biomarkers which is frequently discussed in the literature is mismatch negativity. Mismatch negativity (MMN) is an auditory event-related potential component elicited by changes in auditory stimulation patterns (e.g. oddball paradigms). Impaired generation of mismatch negativity in schizophrenia has been consistently observed in EEG and MEG-studies. Moreover, a successful application of fMRI in assessment of auditory mismatch-related brain responses has been demonstrated in healthy population and schizophrenia patients. However, impairment of mismatch responses in schizophrenia was demonstrated only on the group but not on the individual level. Continuing previous research, this study intends to investigate whether a real-time fMRI-based assessment of auditory mismatch responses can be used as a feasible clinical test for schizophrenia diagnostics. To achieve this aim, we applied six standard mismatch paradigms in a 3T Siemens MR scanner using EPI sequences. The presented preliminary results are based on the investigation of 24 schizophrenia patients and 24 healthy control subjects. Data analysis included traditional group comparisons as well as single subject data analysis. The single subject data were analysed in offline as well as online mode based on the GLM-approach.

Preliminary results suggest that the “Optimum paradigm” (Näätänen et al. 2004) applied in a block design is suitable to elicit mismatch responses in 100% of the patients and healthy controls. Furthermore, phonetic oddball paradigms seem to be more sensitive than traditional oddball paradigms concerning the detection of the impaired mismatch responses in schizophrenia.
Genç, E. - Interhemispheric connections and surface area of primary visual cortex predict subjective experience of binocular rivalry waves [A09]

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In binocular rivalry, presentation of different images to the separate eyes leads to conscious perception alternating between the two possible interpretations every few seconds. During perceptual transitions, a stimulus emerging into dominance can spread in a wave-like manner within and across the visual field. These traveling waves of rivalry dominance have been successfully related to the cortical magnification properties and functional activity of early visual areas, including the primary visual cortex (V1). Curiously however, these traveling waves undergo a delay when passing from one hemifield to another. Here we used psychophysics, DTI and fMRI to study the individual neural correlates subserving the propagation of traveling waves in the visual cortex.

We measured the wave propagation within the hemifield and the delay in traveling-wave times ($\Delta TWT$) across hemifields in nineteen participants and repeated this test six weeks later to evaluate the reliability of our behavioral measures. DTI and standard fMRI retinotopic mapping scans of the same participants were also acquired. To investigate whether the strength of interhemispheric connections between the left and right visual cortex might account for the delay of traveling waves across hemifields we used diffusion tensor imaging in connection with fiber tractography to identify parts of the corpus callosum connecting functionally defined visual areas V1-V3. In addition, we estimated the surface area of V1-V3 in each participant to relate subjective wave propagation within visual hemifields to area size.

We found large interindividual variability but also excellent test-retest reliability for individual measures of $\Delta TWT$ and intraTWT. We found that individual differences in $\Delta TWT$ was effectively predicted by the diffusion properties of transcallosal fibers that connected left and right V1, but observed no such effect for neighboring transcallosal visual fibers connecting V2 and V3. We also found that individual within hemifield wave propagation was only predicted by the surface area of V1.

Our results demonstrate that the anatomical characteristics of specific transcallosal connections and cortical areas predict the individual propagation of traveling waves, providing further evidence that V1 is an important site for neural processes underlying binocular rivalry.
Gerardo-Nava, J. - Evaluation of axonal growth in 3D bioengineered constructs using spinal cord organotypic slice cultures [B04]

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Analysis of axonal growth and tissue-biomaterial interactions in 2D and 3D in vitro has been limited mainly to the use of sensory neurons from either dissociated or whole dorsal root ganglion explants preparations or short lived cultures of dissociated neurons from different areas of the central nervous system. Here we demonstrate the potential of the slice culture system to assess tissue-biomaterials interactions in vitro by taking advantage of the long term survival of its cellular components, primarily its motor neurons and its cytoarchitectural preservation.

Rat (P7-9) spinal cord slice cultures (350µm) from the lumbar expansion were generated and paired on their ventral side with either nerve roots, collagen sponges with orientated pores (Matricel) or fibrin gel blocks (5mg/ml). Co-cultures were kept for up to 14 days in vitro, fixed and immunostained for neuronal and non-neuronal markers (SMI32, GFAP, s100, Iba1, ED1, P75). Whole mounts and cryosections were imaged using epifluorescence and multi photon microscopes.

Slice-Root reconstructions showed extensive axonal growth from the slice culture throughout and around the root tissue. Matricel sponges and fibrin gels also presented axonal growth mainly on the structures’ outer surface. Axonal growth throughout the orientated pores of Matricel sponges could better be visualized in cryosections, in comparison to Fibrin gels where growth was limited to the outer surface. Biomaterials showed also cellular migration from the slice cultures as identified by nuclear stain and non-neuronal markers.

In vitro reproducibility of axonal growth through known permissive structures such as root tissue in vivo, demonstrates the potential of this model to test bioengineered structures aimed towards nerve regeneration. Matricel and fibrin gel tests using this model suggest physical queues improve the performance of such bioengineered constructs.
Gliem, M. - Secondary intracerebral hemorrhage due to early initiation of oral anticoagulation after ischemic stroke: an experimental study in mice [I03]

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**Background and Purpose:** The uncertain risk of secondary intracerebral hemorrhage (sICH) frequently keeps clinicians from initiating oral anticoagulation (OAC) early after ischemic cardioembolic stroke. Goal of this experimental study was to determine the risk of sICH depending on the timing of OAC initiation relative to stroke onset and to address the role of hematogenous macrophages for repair processes preventing OAC-associated sICH.

**Methods:** C57BL/6 mice were subjected to transient middle cerebral artery occlusion. Subgroups were treated with either the vitamin K antagonist (VKA) phenprocoumon or the direct thrombin inhibitor dabigatran etexilate (DE). Hematogenous macrophages were depleted using intraperitoneal injections of clodronate-filled liposomes.

**Results:** Time to therapeutic OAC was 48 h with VKA and 0.5 h with DE treatment, respectively. In VKA-treated mice, the risk of sICH was high if effective OAC was already present at stroke onset or achieved within 48 hours after ischemia. With more delayed OAC the risk of sICH rapidly decreased. Compared to VKA treatment, effective anticoagulation with DE was associated with a significantly reduced extent of sICH, either if present at stroke onset or if achieved 48 hours later. Partial depletion of macrophages greatly increased the extent of OAC-associated sICH in the subacute stage of 3 – 4 days after ischemia.

**Conclusion:** Our findings suggest that repair mechanisms involving hematogenous macrophages rapidly decrease the risk of OAC-associated sICH in the first days after ischemic stroke. The lower risk of sICH under DE compared to VKA treatment may facilitate early initiation of OAC after cardioembolic stroke.
Göbel, C.H.H. - Enhancing effects of financial and non-financial reward on motor learning [C09]

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Financial rewards are potent modulators of human behaviour including motor learning. However it is not yet known, what effect non-financial reward, if any, has on the motor system. Here, using a rewarded implicit motor learning task, we demonstrate that both financial and non-financial rewards have enhancing effects on motor learning, which last more than 24 hours. Resulting therapeutic implications are discussed.
Goh, J.J. - Detection of object-space novelty in the CA1 of freely behaving mice induces LTD which is dependent on NMDA and mGlu5 receptor activation [B07]

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Background: The hippocampus is thought to play a major role in the formation of spatial memories and a highly controversial role in object recognition.

Objectives: This study sought to clarify the synaptic changes that occur at the electrophysiological and mechanistic levels in response to object recognition in freely behaving mice.

Methods: Each adult mouse was chronically implanted with a recording electrode in the CA1 stratum radiatum and a stimulating electrode in the afferent Schaffer collaterals. Following a recovery period from surgery, behavioral tasks with concurrent electrophysiological recordings were commenced.

Results: Here we showed that object recognition triggers LTD at the CA1 synapses. The synaptic response was isolated to be an effect of object-space novelty rather than object novelty per se. Novelty detection of such nature was further shown to be dependent on the activation of both the NMDA as well as mGlu5 receptors. A consequential relation between behavioral learning of the tasks and the corresponding synaptic changes were further proved through the pharmacological antagonism of the NMDA and mGlu5 receptors.

Conclusion: The data suggests that spatial component occurs in object recognition, whereby changes to any component of the object-space unit constitutes novelty and induces LTD in the CA1. Effects are dependent upon NMDAR and mGlu5 activation, receptors that are known to be essential for both hippocampal plasticity and memory. Moreover, learning-facilitated plasticity is shown here to be a synaptic property exhibited across different species and not only in rats, hence adding concrete evidence for the postulated role of synaptic plasticity as a memory mechanism.
Individuals differ in their sensitivity towards social information. The construct of empathy has been developed to describe individual differences in the ability to register and interpret social cues. The aim of this study was to investigate whether enhanced empathic skills are associated with heightened neural sensitivity to the salience of social cues. Specifically, we tested the hypothesis that highly empathic individuals would show greater activation in reward-related brain areas (e.g., Nucleus Accumbens/NAcc) during processing of social cues that signal potential social reward compared to non-social cues than individuals with poor empathic skills.

Functional magnet resonance imaging was performed in 35 heterosexual men (15 highly empathic: EQ ≤30 and 20 low empathic EQ ≥ 50 (Baron-Cohen et al., 2004)) while they performed a social and monetary incentive delay task (Spreckelmeyer et al. (2009)). In both tasks, potential gain depended on participants’ ability to respond in time upon a cued target symbol. Cues signaled either potential reward or a neutral outcome (control) with video clips serving as feedback stimuli (social gestures: hit = approval, miss= neutral gaze, control = no gaze; money: hit = coins, miss=no coins, control = confetti).

Imaging data were analyzed in SPM8 using a random-effects, event-related general linear model (2 x 2 x 2 full-factorial design with factors GROUP (high vs. low EQ), TASK (social vs. monetary) and REWARD (reward vs. control)).

Reward-related brain areas, including the NAcc, were activated for REWARD and the superior temporal sulcus for TASK (whole brain, p<0.05, FWE). A ROI-analysis of the NAcc revealed significant interactions of GROUP X TASK X REWARD in the right NAcc, reflecting greater sensitivity to cues of social reward in the high EQ group than in the low EQ group.

Despite unaltered sensitivity to cues of non-social (monetary) reward, male participants with high empathic skills showed greater activity of the NAcc in response to social cues than men with low empathic skills. The data provide evidence that self-reported differences in social sensitivity relate to differences in neural processing of social incentives.
Goswami, A. - Altered degradation and impairment of cellular protein quality control induced by ALS-8 disease–associated mutation of VAPB [13]

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Background: Abnormal accumulation of intracellular protein deposits as inclusion bodies are the causative mechanism of most of the age related neurodegenerative diseases including ALS. ALS-8 is a rare hereditary form of motor neuron diseases found in Brazilian families with an autosomal dominant mutation (P56S) in the VAPB gene. Subsequently the same mutation was discovered in a Germany ALS family and in a patient with Japanese ancestry. The German patient harbours a haplotype that is different from the Brazilian families, suggesting that this P56S mutation is independent of the Brazilian founder. Additionally, a recent study shows a new mutation in a British ALS patient leading to similar molecular defects as the P56S alteration. Mutation in VAPB gene (P56S point mutation) translates into heavily misfolded protein which finally forms cytoplasmic inclusion bodies.

Objectives: The main objective of research is to understand how the inclusion bodies or aggregates induce the neuronal toxicity, specially focussing on the protein quality control and the degradation pathways.

Methods: We analyzed autopsy material from ALS patients, ALS patient's fibroblasts, SOD1 transgenic mice, and cell culture model systems over expressing wt and mutant VAPB, using several biochemical, immunohistological and molecular biology techniques.

Results and conclusions: Our findings suggest that mutant VAPB proteins are resistant to proteolysis and make insoluble inclusion bodies. These inclusion bodies or aggregates can induce severe disturbances of the protein quality control system and interfere with the protein degradation machinery. Furthermore aggregates of VAPB aberrantly interact with several other proteins involved in normal cellular homeostasis. Our study describes the possible role of VAPB in mediating the pathogenesis of ALS and related disorder.
In birds, the axons of cochlear ganglion neurons project into two subdivisions of the cochlear nucleus in the auditory brainstem, the nucleus magnocellularis and the nucleus angularis. Nucleus angularis neurons are contacted by bouton-like synapses. In nucleus magnocellularis however, collaterals of the same fibre can form giant axosomatic terminals, the Endbulbs of Held. The molecular basis for the determination of this giant synapse during development is yet to be found. We established a primary culture of cochlear ganglion neurons of the embryonic chicken as a starting point for the design of a co-culture system, consisting of cochlear ganglion and auditory brainstem neurons.

Tissue from the chicken basilar papilla of Hamburger and Hamilton stage 36 was explanted. Serum-free cell culture media were used. Immunocytochemical stainings against neurofilament revealed a distinct bipolar morphology of the neurons, reminiscent of the in vivo situation. The neurons showed a profound axon outgrowth and were viable up to eight days in vitro. Electrophysiological recordings additionally confirmed the identity of the cochlear ganglion neurons. We also could demonstrate the existence of synaptic markers like synaptic-vesicle protein 2 in the axon terminals, showing that these neurons already express and transport the machinery for synapse formation as early as E10.

Preliminary results of the co-culture system show viable brainstem and cochlear ganglion neurons and indicate that in vitro innervation of brainstem neurons by cochlear ganglion neurons is possible, making this co-culture system an excellent tool for further investigation of molecular aspects of Endbulb-formation and developmental control of synaptic terminal size.
A 23-year-old male patient presented with a history of intermittent and aggravated headache and nuchalgia. Anamnesis and first blood tests did not reveal any underlying disease. Cranial computed tomography (CCT) showed an osteolytic process of the skull base with subtle marginal hypersclerosis and Magnetic Resonance Imaging (MRI) presented a contrast-enhanced necrotic mass of the clivus. As osteolytic metastasis in this young patient seemed to be implausible and extended serologic examinations excluded endocrinological causes as well as various infections, including tuberculosis first of all M. Gorham-Stout was assumed. However marginal hypersclerosis cast doubt on that diagnosis. Finally endoscopic transsphenoidal biopsy of the clivus was initiated and revealed a granulomatous infection caused by Aspergillus oryzae. Systemic fungal infection was ruled out because serological examinations for aspergillus antigen were negative. Moreover additional biptic samples could screen out an infection deriving from the paranasal sinuses. Thus finally the absolute rarity of a bone-derived Aspergillus granuloma without serotyping in an immuno-competent patient was diagnosed and oral antifungal therapy with voriconazol was started. This case illustrates the importance of a precise description and analysis of MR findings in osteolysis, because the subtle marginal hypersclerosis was the initial key to diagnosis and therapy.
Gramsch, C. - Diagnostic value of a 3D Fluid Attenuated Inversion Recovery Sequence in Multiple Sclerosis [A08]

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Purpose: The use of dual-echo sequences has markedly improved the ability of MR imaging to detect cortical and infratentorial MS lesions. The purpose of this study was to find out whether lesion detection could be even more enhanced by use of 3D FLAIR sequences.

Methods and Materials: MR images (1.5 T and 3 T) of 30 patients (19♀, 11♂) with established MS or after first clinical event who received MRI standard protocol and an additional 1mm isotropic 3D FLAIR sequence were reviewed retrospectively. Whole-brain lesion load and number of lesions in juxtacortical and infratentorial localizations in a dual-echo sequence (slice thickness, sth 6 mm) were assessed and compared with identifiable numbers in the 3D FLAIR sequence. Additionally midsagittal slices of the conventional T2-weighted (sth 2 mm) and 3D FLAIR sequence were analyzed in regard to visibility of lesions located in the corpus callosum.

Results: Number of juxtacortical lesions visible in the 3D FLAIR sequence was significant higher than the number of visible ones in the dual-echo sequence. Concerning lesion-detection in infratentorial localizations 3D FLAIR sequence showed marginal benefit. Number of lesions in corpus callosum in midsagittal 3D FLAIR sequence was significant higher than the number of lesions detectable in conventional T2-weighted sequences.

Conclusion: 3D FLAIR sequences can improve detection of brain lesions in patients with MS and are even more sensitive in detecting lesions in juxtacortical localizations than current dual-echo sequences.
Gröne, M. Real-time fMRI neurofeedback of the ACC at 3 and 7 T and its effect on emotion perception in words [E07]

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Recent advances in the development of real-time functional magnetic resonance imaging (rt-fMRI) have made it possible to acquire and process data fast enough to give subjects online-feedback about their current brain activity in a well-defined brain-region of interest. The level of activation in the selected region can be visualized through a moving bar that rises and falls according to the BOLD-response making it possible to learn to control brain-activity with high specificity, i.e. for localized neurofeedback.

One of the established areas to target is the anterior cingulate cortex (ACC), as a central hub to different neural networks subserving attention and motivation regulation, error detection, working memory, concentration and reward-based learning.

In this study we want to investigate the effect of regulation of neural activity in the anterior cingulate cortex (ACC) by neurofeedback on the emotion perception of prosodic pseudowords. We hypothesize that ACC function can modulate the emotional perception of voices and thus potentially of hallucinations as well.

Fifteen healthy subjects were trained to regulate the ACC’s hemodynamic response with contingent rt-fMRI neurofeedback during a two hours training session.

Alternating with the neurofeedback sessions of eight minutes each, we presented pseudowords whose prosody encoded 6 emotions. The words were rated according to their emotional valence and arousal. Throughout the neurofeedback training session the different emotion qualities have been accurately identified and categorized. Significant self-regulation of ACC activity was achieved at 3 T and in 8 individuals at 7 T. However, only for the perception of sadness a linear trend over time emerged and emotion perception did not correlate with the control signal.

Neurofeedback of the ACC is a stable paradigm at 3 and 7 T, but a direct association with emotional perception of voices could not be established in the investigated paradigm. Psychological mechanisms and effects of fMRI-based neurofeedback should be further investigated.
Gronewold, J. - Ankle brachial index is a strong predictor of stroke events in the general population [A10]

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Introduction: Predictors of cerebrovascular events gain importance in secondary stroke prevention. Herein, we investigate the value of the ankle brachial index (ABI), a non-invasive marker of atherosclerosis, as stroke predictor in addition to established risk factors that are part of the Framingham Risk Score (FRS).

Methods: 4299 subjects from the population-based Heinz-Nixdorf-Recall Study (45–74 years; 47.3% men) without previous stroke, coronary heart disease and myocardial infarction, which received detailed baseline assessments, were followed up for ischemic and hemorrhagic stroke events over 7.9±1.7 years. Cox regressions were used to evaluate FRS variables [sex, age, smoking, diabetes, LDL, HDL, systolic blood pressure] and ABI as stroke predictors.

Results: A total of 69 strokes (61 ischemic, 8 hemorrhagic) occurred during the observation period. Patients suffering stroke had significantly lower ABI values at baseline (1.02 vs. 1.13, p<0.001). In multivariable regressions, ABI was a strong independent stroke predictor (hazard ratio=0.76 per 0.1, confidence interval=0.67-0.87; p<0.001) in addition to age (1.49 per 5 years, 1.23-1.79; p<0.001) and systolic blood pressure (1.34 per 10 mmHg, 1.22-1.48; p=0.001). ABI similarly predicted strokes in men and women and in subjects above and below 65 years. In subjects belonging to the highest FRS (>13%) and lowest ABI (≤1.08) tercile stroke risk was particularly elevated. In the latter, low ABI values significantly increased stroke risk (p for trend=0.009).

Conclusion: ABI is a strong independent stroke predictor in addition to age and blood pressure, particularly in subjects with vascular risk profile, where ABI identifies subjects at high stroke risk.
Oxytocin (OXT) is generally thought to improve social cognition, but the empirical support for this view is surprisingly inconsistent. This might be explained by an, so far, unknown modulating factor. First studies suggested that the personality of the subjects could have a significant influence on the effect of OXT. The aim of this study was to investigate the influence of OXT on the neural processing of social feedback in social anxious and not anxious woman, hence social anxiety seems to be an aspect of personality of high relevance for processing social situation.

Twelve social anxious (Liebowitz Social Anxiety Scale, LSAS: score > 55) and 26 healthy female controls participated in a double-blind placebo-controlled functional magnetic resonance imaging (fMRI) study. Subjects got intranasally either 26 IU OXT or a placebo before entering the scanner. During fMRI scanning subjects did a reaction time task in which cues announced either social feedback (pictures of facial expressions) of different intensity or a neutral non social feedback (Social Incentive Delay Task, SID, Spreckelmeyer, 2009).

For behavioral matters no effect of the group or the treatment could be observed. However, the analysis of the brain imaging data exposed a significant OXT effect just in the group of the social anxious subjects. These subjects showed significant less activation of the amygdala during placebo condition in contrast to the control subjects. Due to enhanced amygdala activation in terms of the social anxious women this effect disappears in the OXT condition. Moreover, this interaction could also be shown for the self reported level of arousal of the subjects; just in the placebo condition the social anxious subjects did report significant higher levels of arousal in contrast to the control subjects. Thus OXT seems to have a particular effect in individuals, who have troubles in dealing with social situation.

References:
Grüter, T. - Structural alterations in MK 801 treated rats: new insights into the genesis of schizophrenia [H08]

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Introduction: Schizophrenia is a still poorly understood disease. To date, neither the genesis nor the molecular mechanisms have been elucidated.

Methods: We used the NMDA receptor antagonist, MK801, to simulate a state equivalent to first episode psychosis. We then determined immunohistochemical alterations in GABA, NMDA, dopamine (DA) and metabotropic glutamate (mGlu) receptors in the hippocampus and prefrontal cortex (PFC).

Results: We found an increase of GABA(A) receptor expression and in addition, a downregulation in both mGlu1 and the GluN2B subunit of the NMDA receptor one week after the emulation of the first episode, in both the PFC and hippocampus. GABA(B) receptors were upregulated in the hippocampus. GluN1, GluN2A, mGlu2/3, mGlu5 and DA receptors were unaffected. Four weeks after treatment, GABA(B) and D1 expression was significantly increased in both PFC and hippocampus, GABA(A) was decreased in the PFC and GluN2B was increased in the hippocampus.

Conclusion: The initial changes in GABA(A), GABA(B), GluN2B and mGlu1 expression seen in this study are likely to reflect changes in neuronal networks and communication that occur following the emulated first episode of schizophrenia. Weeks later, chronic changes are quite distinct from this initial profile and include an increase in GABA(B) and D1 expression that might mediate decreased hippocampal and prefrontal activity. GluN2B expression also increases chronically, and as this receptor acts permissively for hippocampal long-term depression (LTD), this might explain why long-term potentiation (LTP) is impaired in MK801-treated rats. These effects could contribute to the cognitive deficits and that have been reported in both this animal model and the human condition.
The coordination of the movement of single and multiple limbs is essential for the generation of locomotion. Movement around single joints and the resulting stepping patterns are usually generated by the activity of antagonistic muscle pairs. In the stick insect, the three major muscle pairs of a leg are the protractor-retractor, the levator-depressor and the flexor-extensor. The protractor-retractor moves the coxa and thereby the leg forward and backward, the levator-depressor moves the femur up and down and the flexor-extensor flexes or extends the tibia around the femur-tibia joint. The underlying neuronal mechanisms for a forward stepping middle leg have been intensively studied in experimental and theoretical studies. However, details about neuronal and mechanical mechanisms driving a single stepping leg in situations other than forward walking remain largely unknown. Here, we present a neuro-mechanical model of the coupled three joint control system of the stick insects middle leg that is able to produce forwards, backwards or sidewards walking. Switching between these three different behaviors is achieved by minimal changes to the central control to the neuro-mechanical model. We hypothesize a neuronal control mechanism that could underlie this behavior in the real animal.
The neural control of forward walking in insects is well studied. However, the mechanisms underlying the flexibility of motor programs between the segmental neural networks that control the individual legs during behaviors such as curved or backward walking remains largely unknown (Büschges & Gruhn, 2008).

We first investigated how middle leg muscle activity of tethered, intact animals, walking freely on a slippery surface changes during optomotor induced curved walking (Gruhn et al., 2009a). No marked changes in cycle period, duty cycle distribution, or the average stepping frequency occurred with a change in function of the leg as outside (oL) or inside legs (iL). Muscle activity and timing in all muscles was virtually the same between the two behaviors except for a small increase in flexor activity and the occasional reversal of phasing in protractor and retractor activity during inside steps. We then studied the influence of descending signals from rostral segments, including front legs, on mesothoracic coxal MN activity in the otherwise deafferented mesothoracic ganglion. During optomotor-induced turning with the front legs (N=17), the mesothoracic protractor and retractor neurons on the inside showed alternating activity, while they often generated tonic activity with rarely occurring alternation on the outside. Results of split bath experiments using the muscarinic agonist pilocarpine (N=5) and unilateral lesion of the connective anterior to the mesothoracic ganglion (N=5) support the notion of a task-dependent descending influence on mesothoracic motor activity for oL and iL walking activity. Our results indicate that turning kinematics of single legs are under individual segmental control and that descending signals from the brain not only affect sensorimotor processing (Hellekes et al., 2012) but also central premotor networks in a hemi-segment-specific fashion to generate flexible locomotor behavior. Supported by DFG grant Bu857.
Halfter, H. - Altered dynamics in the circadian oscillation of clock genes in dermal fibroblasts of patients suffering from idiopathic hypersomnia [J03]

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Objectives: Numerous physiological aspects underlie a 24hour circadian clock mechanism driven by circadian clock genes (CCG). Peripheral tissues such as dermal fibroblasts harbour the same circadian clock mechanism. It is cell-autonomous in isolated primary cell-culture. CCG in fibroblasts display the intraindividual length of circadian rhythm and the dynamics in transcriptional regulation. In order to correlate modifications of circadian gene regulation with the pathophysiology of sleep disorders, our study aims to investigate the dynamic of CCG in fibroblasts of idiopathic hypersomiacs (IH) in comparison to healthy controls (HC).

Methods: The IH were recruited from the department of sleep medicine and screened by polysomnography. They were tested for Multiple Sleep Latency. Pre-existing illnesses such as Restless Legs Syndrome or Obstructive Sleep Apnoe Syndrome were excluded. Dermal fibroblasts were obtained via punch biopsy. The transcriptional expression of circadian clock genes was investigated by RT-PCR analysis. Total RNA of the confluent fibroblasts was isolated over 72h at 14 different time points. Quantitative RT-PCR confirms periodical oscillation of expression of the core CCG Bmal, Per1/2 and Cry1/2 and allows a direct comparison of the dynamics in gene expression between IH and HC.

Results: The amplitude of the periodically expressed CCG Bmal,Cry1/2, and Per1 is significantly dampened by averagely 54% in dermal fibroblasts of IH compared to HC, leading to a diminished dynamic in circadian gene expression in IH.

Conclusion: The study proves an altered dynamic in oscillation of CCG suggesting a genetic impact on the pathophysiology which could explain some features of this idiopathic sleep disorder syndrome.
Background: Pannexin 1 (Panx1) constitute a family of integral membrane proteins which form high conductance (550pS) membrane channels and are permeable to large molecules of up to 1 kDa, like ATP. Previously fEPSP and LTP recordings have indicated a putative role of Panx 1 in the initiation and maintenance of hippocampal plasticity. This study aimed to elucidate the contribution of Panx 1 channels to membrane currents and potentials on a single cell level.

Methods: In this study we used a transgenic Panx1 knock out mouse model for in vitro blind whole cell patch clamp recordings in hippocampal CA 1 neurons of acutely dissected 350 µM hippocampal slices. IV-curves were recorded in the voltage clamp mode, excitatory and inhibitory postsynaptic potentials were recorded in the current clamp mode.

Results: In Panx1 −/− derived hippocampal slices MEQ sensitive membrane currents at hypopolarizing potentials after depolarizing ramp preconditioning were evident indicating Panx1 channel activity. These currents were not detectable in Panx1 +/− derived slices. Single cell recordings in the current clamp mode showed a significant decrease of EPSP and IPSP amplitudes in Panx1 −/− slices. Accordingly MEQ lead to a decrease of EPSP and IPSP amplitudes in Panx 1 +/− tissue. Similarly, suramin, an unselective purine receptor antagonist, evoked a decrease in EPSP and IPSP.

Conclusion: Our data demonstrate a significant impact of Panx 1 channels on membrane currents and potentials in hippocampal CA1 neurons, thus being essential for the integrity of the hippocampal neuronal network.
Hargus, G. - Stem cell-derived oligodendrocytes to study oligodendroglial cell maturation in vitro [J11]

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Over the past few years, a new technology has been developed to derive pluripotent stem cells from somatic cells by exogenous expression of pluripotency-associated reprogramming factors. These induced pluripotent stem cells can be applied to analyze developmental processes and the biology of specialized cell types in vitro. Here, we demonstrate that induced pluripotent stem cells can be differentiated into neuronal and oligodendroglial cells in vitro. We applied induced pluripotent stem cell-derived oligodendrocytes to cerebellar slice cultures and observed surviving and myelinating oligodendrocytes. Such culture systems can be used to study mechanisms of myelination and pathways important for oligodendrocytic maturation in more detail. By deriving induced pluripotent stem cells from patients with white matter diseases, such an approach could also provide an invaluable opportunity to study disease pathogenesis in an in vitro-culture system on human oligodendrocytes at risk, which is often difficult to accomplish in patients due to the unavailability of appropriate tissue.
According to the amyloid cascade hypothesis, beta amyloid (Aβ) peptides play a central role in Alzheimer’s disease pathogenesis. Therefore, inhibition of BACE1 (beta site APP cleaving enzyme) is one potential therapeutic approach. By membrane anchoring of a transition state BACE1 inhibitor in a tripartite structure (Braxmeier et al., International Patent WO2005/097198; Rajendran et al., Science 2008, 320, 520-523), the inhibitor’s potency increased strongly. Here we present data from a structure activity relation study in a SH-SY5Y cell culture model to elucidate the effect of membrane anchor and spacer module on the potency of tripartite structures. Furthermore we show that different literature-known BACE1 inhibitors can be optimised by incorporation into tripartite structures. As read out, Aβ secretion into the cell culture medium is monitored by electrochemiluminescence assays, as well as one and two-dimensional electrophoresis to analyse Aβ patterns secreted by cells overexpressing either wild type or Swedish mutant amyloid precursor protein.
Heller, J. - Therapy of functional voice disorder assisted by mirror neuron activation: a combined treatment and fMRI study [C01]

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Everyone has already experienced transient disturbance of the own voice as for instance hoarseness or loss of voice. People with functional voice disorders suffer from these problems regularly. Attending to physiological or disordered voice could influence voice performance corresponding to the heard phonation. Mirror neurons are discussed as a reason for that. This study aimed at the effects of using mirror neuron activation within conventional voice therapy. For this reason ten people with functional voice disorder received conventional voice therapy from a speech and language therapist twice a week. Four patients were assigned with regular homework, whereas six patients had to listen to audio tapes of good voice performance twice a day instead. Phoniatric effects were assessed according to the recommendations of the European Laryngological Society by a logopedic diagnosis of the voice including voice field measure and a stroboscopic investigation of the larynx. To control for mirror neuron activation five patients were measured by functional magnetic resonance imaging (fMRI) in a pre-post-treatment design. Whereas the two “regular therapy” patients utilized the linguistic attentional network particularly in the pre-treatment fMRI scanning session, the three “mirror neuron therapy” patients showed enhanced post-treatment activations, reflecting increased attention to the auditory presented texts supported by the special therapy. Moreover, the effect of voice therapy per se was revealed by significantly improved phoniatric results along the timeline in both groups. This study will contribute to a better understanding of functional voice disorders and point to a therapeutic improvement by extension to mirror neuron activation.
The research on stimulus awareness and its relation to fear related processing is a basic approach to understanding emotional processing since it addresses the role of primary perceptual processes involved in the acquisition and elicitation of emotional reactions, including anxiety and panic. The relationship between the visibility of a stimulus and the processing of its fear related information has been addressed in many experiments and remains vague to this day. In the classical paradigm, responses to fear related and neutral stimuli (e.g., faces) are compared. To assess whether stimulus awareness or conscious access to its fear relevant features is necessary for differential processing, the stimuli are often masked by a second stimulus presented shortly afterwards that completely overlaps the first (pattern masking). The function of visibility of the target stimulus in these paradigms increases monotonically with increasing stimulus onset asynchrony (SOA) between the target and the mask. At short SOAs, stimuli are assumed to be invisible to the subject and differences between neutral and fear related stimuli are analyzed. Caveats are warranted, as partial awareness can never be excluded when complex stimuli are used. Partial awareness refers to the perceptual phenomenon of stimulus information being available on some but not all representational levels, leaving the subject unable to report the stimulus yet being influenced by its low level features (Kouider, S., & Dupoux, E. (2004). Partial awareness creates the “illusion” of subliminal semantic priming. Psychological Science: A Journal of the American Psychological Society / APS, 15(2), 75-81). Furthermore, this simple dissociation between visibility and fear related response yields no theoretically justified evidence of differential processing of fear related stimuli in the absence of stimulus awareness (Schmidt, T., & Vorberg, D. (2006). Criteria for unconscious cognition: three types of dissociation. Perception & psychophysics, 68(3), 489-504). In our study, we took a correlational approach, using metacontrast masking to manipulate stimulus visibility in consecutive steps (by increasing the SOA between target and mask). In contrast to pattern masking, the function of visibility in metacontrast masking is U-shaped with high visibility at low SOAs, a decline in visibility with increasing SOA to a minimum at around 50ms, followed by a gradual increase in visibility at longer SOAs of 100ms and longer. The target stimuli are usually simple gratings or discs that are followed by equally simple, non-overlapping annuli. We take advantage of the unique temporal course of the first part (“descending branch”) of the masking function up to its minimum as it allows for a double dissociation between stimulus visibility and the time of uninterfered target processing of the target stimulus: Visibility decreases while the time of uninterfered target processing increases with increasing SOA. To answer the question whether fear related processing differences are correlated to stimulus visibility or not, one of two physically identical target gratings was paired with an aversive startle burst in a trace conditioning protocol. We compared the differences in the visual evoked potentials of conditioned and neutral stimuli at three SOAs on the descending branch of the masking function. As this setup allows the comparison of EEG responses to two physically identical stimuli, differences in visual evoked potentials are necessary due to the conditioning procedure and reflect differential processing of fear related stimuli. We find that, while detectability and discriminability of the target stimuli decrease with increasing SOA as expected, the differences in the visual evoked potentials increases with increasing SOA. This double dissociation between stimulus visibility and fear related processing differences is the soundest possible evidence for the hypothesis that fear conditioning is not depending on stimulus awareness. From a theoretical perspective, metacontrast masking is assumed to be caused by feed-forward signals of the mask interfering with recurrent activity of the target. We observe increasing differences in visual evoked potentials to conditioned stimuli at longer SOAs while conscious discriminability and detectability decrease. We assume affective processing to be strongly reliant on feed-forward information. The longer the feed-forward signal of the target is available without interfering feed-forward signals of the mask, the stronger averersely conditioned and neutral stimuli diverge.
Hodde, D. - Directional growth of Schwann cells within nanofibre-containing fibrin hydrogels [C04]

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The current “gold standard” treatment for the repair of large gaps of lesioned peripheral nerve is the autologous nerve graft, but this approach has significant limitations. Therefore, alternative strategies to replace, or at least supplement the autograft are being sought. Among the wide range of materials and designs currently being developed, simple hollow tubes are the only conduits that have received FDA and CE approval for clinical use. The lack of any guidance structures within the lumen of the conduits is widely believed to be responsible for their limited effectiveness: only supporting repair over relatively small distances (2-3cm).

The goal of the present investigation is to determine the influence of 3D arrays of orientated nanofibres on Schwann cells. Using the electrospinning technique, 2D arrays of highly aligned polycaprolactone nanofibres have been collected, stacked onto each other and embedded into fibrin hydrogels. Ongoing in vitro investigations, focussing on Schwann cell growth in 3D fibrin hydrogels have demonstrated the adoption of surprisingly complex morphologies that were remarkably different to those observed in routine 2D cultures. Incorporation of orientated nanofibres into the matrix resulted in the adhesion of Schwann cells to the nanofibres and the extension of simple processes, the trajectory of which closely followed that of the nanofibres. The strong tendency for Schwann cells to identify and follow nano-topographical cues embedded within a 3D hydrogel environment provides a means of controlling cell growth and orientation. The incorporation of such orientated nanofibre-hydrogel combinations into the lumen of hollow nerve guides may prove to be a useful strategy for improving their effectiveness in the repair of large, trauma-induced gaps of the PNS.
Healthy aging is accompanied by a decrease of motor performance, potentially caused by age-related structural loss in particular in the prefrontal cortex and the basal ganglia (BG) [1]. Age related changes in functional connectivity (FC) of the medial prefrontal (anterior midcingulate cortex; aMCC) and BG were delineated using seed based resting-state analysis (n=238, mean age 43.8 ± 16.4). Activity fluctuations of the seed regions were correlated with the rest of the brain. Group main-effects and correlation with age were assessed. The analysis revealed a consistent bilateral FC network comprising bilateral prefrontal and premotor cortices as well as anterior insula, area 44, BG, thalamus and cerebellum. Age-dependent decline of the aMCC’s FC was found for the cingulate cortex, left lateral prefrontal cortex and anterior insula. BG showed decrease in FC only for dorsal striatum, basal forebrain and thalamus. The examination demonstrated a general connectivity decline with age. The aMCC showed age-related FC decrease with cortical areas involved in higher order cognitive processing [2]. FC within the BG decreases with age, which resonates with previous observations of structural atrophy in these regions in healthy aging and may provide a substrate for deterioration of motor control [3].

When we observe sequences of actions, we spontaneously expect them to be unified by an overarching goal. This tendency has been observed even when actions are in fact unrelated. When it is difficult to find an overarching goal, e.g. when actions are performed in an unusual context or when a person performs sequences of unrelated actions, activation in the left inferior frontal gyrus (IFG) is increased. This area is suggested to be involved in semantic retrieval and selection; its increase during sequences of unrelated actions could reflect the search for potential goals that reconcile the observed inconsistency in a plausible way.

In order to test this assumption, we manipulated transition probabilities (TP) in everyday action sequences. Pairs of actions connected by a low TP should make it more difficult to find a higher goal that connects them. This should be reflected in increased IFG activation. High TP could in turn yield activity increase in areas that have been associated to coherence, e.g. the medial BA 9.

Subjects watched video clips of single acts. To assess the TP between two consecutively presented actions, subjects rated in a post-fMRI session how often these two actions are performed one after another in everyday life. The individual rating data was subsequently used as parameter in the analysis of fMRI data. The parametric analysis yielded activity in right IFG for low TP and precuneus and right lateral BA 9 for high TP.

In accordance to the hypothesis, findings indicated IFG to reflect the search for an overarching goal in action sequences. In contrast, actions with high TP activated the precuneus. The latter might reflect a facilitation to retrieve internally generated episodic memories that fit to the obviously associated actions.
Heterotrimeric G-proteins play an important role in cellular signal transduction and their alpha subunits were known to consist of four major classes, Gi, Gq, Gs and G12. In 2009 we discovered a fifth class, Gv, which is phylogenetically as old as the other four classes and encoded by 1–2 gnав genes per species. Gv is conserved across the animal kingdom including vertebrates, arthropods, mollusks, and annelids, but has been lost in many lineages such as nematodes, fruit fly, jawless fish, and tetrapods, concordant with a birth-and-death mode of evolution. All Gv proteins contain the expected motifs of GTP-binding proteins and in particular trimeric G proteins. The genomic structure of vertebrate gnав genes is well conserved and different from those of the other 4 classes. We have begun to characterize the expression patterns of Gv in larval zebrafish, a model vertebrate, to obtain first insights into possible functions of Gv. Among other sites, the inner ear was found to be a prominent site of expression. Several approaches have been used to investigate the function of Gv in the inner ear in vitro and in vivo. The expression was characterized at the cellular level. Our present data suggest that Gv is selectively expressed in hair cells, consistent with a possible role of Gv in mechanotransduction. To test this possibility we are currently developing a behavioral assay for acoustic responses and generating a TALEN-mediated knockout of the Gv gene in zebrafish.
Ongoing neuroinflammation contributes to the pathogenesis of neurodegenerative diseases such as Alzheimer’s. In acute stroke, neuroinflammation with microglia activation (MA) is a key event, but only few reports describe its termination in chronic stages. Here, we investigated (i) persisting neuroinflammatory and neurodegeneration in a rat model of embolic stroke, and (ii) whether these processes can be visualized in vivo by multimodal imaging using Magnetic Resonance Imaging (MRI) and Positron-Emission-Tomography (PET).

In 6 Wistar rats, permanent middle cerebral artery occlusion (MCAo) was induced and infarcts were verified by T2-weighted MRI after 7 days. Multimodal imaging 7 months after ischemia comprised (i) T2-weighted MRI, (ii) T2*-weighted MRI to detect iron deposition, [11C]PK11195-PET to visualize activated microglia, and (iii) dynamic [18F]FDG-PET to assess local cerebral perfusion and glucose metabolism. Imaging was verified using histology and immunohistochemistry.

Neuroimaging and histological investigations did not reveal ongoing neuroinflammation at the lesion site itself after 7 months. However, remote from primarily infarcted areas, a marked hypointensity could be detected in the thalamus using T2*-weighted MRI. In the corresponding area, [11C]PK11195-PET detected persisting microglia activation. Immunohistochemistry confirmed activated microglia with signs of extensive phagocytosis and iron deposition around plaques-like amyloid deposition. Neuronal staining (NeuN) revealed pronounced neuronal loss as surrogate for neurodegeneration of these thalamic areas.

Our data suggest that insufficient phagocytosis of debris, and the extracellular deposition of amyloid material might trigger persisting microglia activation. Therapeutic approaches aimed at terminating MA may be beneficial both in chronic post-stroke conditions as well as in neurodegenerative disorders such as Alzheimer’s disease. Furthermore, [11C]PK11195-PET as well as T2*-weighted MRI allow for the in vivo imaging of thalamic neuroinflammation and neurodegeneration after stroke and can therefore be used to evaluate therapeutic approaches in future studies.
The hippocampal CA1 and CA3 areas have been the focus of memory research extensively. Various studies provide evidence for the idea that the hippocampus serves as an ‘online’ memory system, in which information is retained during temporary delay periods. It has been proposed that persistent neural firing may support short-term retention of memory by intrinsic properties of neuron and/or recurrent synaptic connections. However, which mechanism supports persistent firing in CA3 pyramidal neurons is poorly understood. This study focuses persistent firing activity of hippocampal CA3 pyramidal neurons in rat hippocampal slice preparation using whole-cell patch clamp recording. Our results indicate that CA3 pyramidal neurons are capable of exhibiting persistent firing under cholinergic stimulation (10 microM carbachol). In addition, the persistent firing activity is observed in the presence of glutamatergic and GABAergic ionotropic synaptic blockers. To our knowledge, this study is the first to report persistent firing in the CA3 area as an intrinsic mechanism. We conclude that intrinsic persistent firing could be a mechanism that underlies short term memory retention in the hippocampus.
Jockwitz, C. - 1000BRAINS: Assessing normal ageing of the human brain in a population-based German cohort [C07]


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In a society with a growing number of elderly diseases affecting the central nervous system, e.g. neurodegenerative or vascular diseases, occur more frequently. Considerable research effort has been undertaken to evaluate potential causes and risk factors for these diseases. But little is known about the ‘normal’ process of brain ageing. 1000BRAINS aims at studying the variability of structural and functional changes of the brain in normal ageing with regard to genetic, socioeconomic, and psychosocial risk factors.

1000BRAINS is an ongoing research effort based on the Heinz Nixdorf Recall Study, a prospective population-based cohort study. Subjects of the 10-year follow-up, aged 55-85 years, participate in 1000BRAINS, undergoing extensive neuroimaging, neuropsychological and motor testing, questionnaires, and laboratory and genetic analyses. Brain imaging includes structural, functional, and resting-state scans with a main focus on connectivity-related measures.

Research projects based on the first 150-200 subjects revealed: (i) genetic factors which influence cortical thickness in a genome-wide search; (ii) age-related changes in functional brain networks related to action observation, execution, and imagination; (iii) age-related changes of resting-state functional connectivity in the network for volitional motor behaviour and between largely separated networks for motor and cognitive control.

1000BRAINS allows assessing variability of brain structure and function related to ageing in the general population. This provides a thorough neuroscientific basis for understanding alterations in the diseased brain, at the cut-off between normal variability, disturbed functioning, and manifest disease.
Jüttten, K. - Age-related changes in brain networks involved in action observation, execution, and imagination [G03]

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The mirror neuron system and its potential human homologue have been extensively studied due to their assumed importance for action understanding and motor performance. The related brain networks in humans are well characterized based on numerous functional imaging studies. Ageing affects the function of the motor system in general. It could thus be assumed that the mirror neuron system is also affected by ageing processes which so far is largely unknown. The present study assessed agerelated changes in the recruitment of brain regions during observation, execution, and imagination of an action.

69 subjects of 1000BRAINS, a neuroscientific research effort based on the population-based Heinz Nixdorf Recall Study, underwent functional magnetic resonance imaging (fMRI). They were required to either tap their index finger at a pace at which they could simultaneously imagine the movement (EXE), to watch a video of their own index finger tapping (OBS) or to imagine themselves tapping their index finger (IMA).

Subjects showed no age-related changes in their tapping performance. Age-related increases of the BOLD response were found in intraparietal and ventrolateral prefrontal cortex (OBS), primary and secondary somatosensory and motor cortex (EXE), and caudal area 44 (IMA+EXE). Age-related decreases of the BOLD response were found in extrastriate ventral visual cortex and anterior middle temporal gyrus (IMA).

Increases in BOLD response at constant performance might hint at a compensatory mechanism to maintain performance at older age by additional recruitment of brain areas, here indicating at a higher need for sensorimotor integration. Such a phenomenon has been observed repeatedly and is still widely discussed.
Junger, J. - Neural correlates of male and female voice perception and differences between men and women [G06]

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Human speech is one of the most important sounds in our environment and plays a key role in social interaction (Fitch, 2000). On a neural basis there is first evidence for different activations in fronto-temporo-parietal regions in response to male and female voices. However, whether there is a difference between men and women while perceiving male and female voices is insufficiently resolved (Lattner et al., 2005; Sokhi et al., 2005).

Therefore, the aim of the present study was to examine the behavioral and neural correlates of gender-related voice perception.

The experiment was conducted on a 3T-MRI scanner. In advance, 10 men and 10 women were recorded while reading 6 neutral words (nouns). Each original voice was modified in 2, 4 and 6 semitone steps in the direction to the other gender. In the main fMRI study, 39 healthy controls (20 male/19 female) were asked to indicate the gender of each speaker of the 240 voice stimuli. Accordingly, the task consisted of 8 conditions in a 2 x 4 design with the factors voice (male/female) and morphing (0st/original voice, 2st, 4st, 6st).

Data analysis revealed a) better performance in the identification of opposite-sex stimuli in both sexes, b) increased responses to gender ambiguous voices in the mid cingulate cortex and bilateral inferior frontal gyri, c) stronger activation in men in a widespread prefronto-temporal neural network, especially in response to original female voices, and d) to pitch-shifted male and female voices.

Our results indicate an opposite-sex effect in voice perception on a behavioral and neuronal level. Thus, we suggest that this result reflects higher sensitivity probably due to the evolutionary relevance of voice perception in mate selection.

References:
Justen, C. - Self or other? An EEG/ sLORETA study on the neural correlates of agent judgement based on auditory information [C06]

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Introduction: Agent judgements based on unimodal auditory stimuli have not been well studied. A meta-analysis of several neuroimaging studies by Legrand and Ruby (2009) has identified lateral and medial brain regions in the right hemisphere (e-network). It is argued that the e-network can be seen as the neural correlate of agent judgement based on multimodal stimuli processing. The main goal of the present EEG study was to localize the neural correlates subserving unimodal auditory agent judgement.

Methods: 14 subjects heard prior recorded long jumping sounds (50% own sounds and 50% other sounds). Sounds (duration: 4 s) contained running up, jumping, flying and landing phase. The dependent variable was the accuracy of given responses. EEG was measured using an EEG-cap with 64 electrodes. After pre-processing, EEG data was further analyzed with the sLORETA (standardized low resolution brain electromagnetic tomography) software package in the alpha-band.

Results: Behavioral data analysis shows that subjects identified more self and other long jumping sounds correctly than could be expected by chance. For the processing of self-produced sounds, the sLORETA analysis shows high activations in right temporoparietal junction (rTPJ) and right medial prefrontal cortex (rMPFC), whereas the processing of other-generated sounds shows deactivations in the aforementioned brain regions.

Discussion: Results of the present study are consistent with findings of previous studies investigating multimodal agent judgements. The high activations in brain regions of the e-network seems to have a functional relevance. To test this hypothesis, the aforementioned results will be validated in a subsequent study by applying inhibitory rTMS over rTPJ.
Background: Motor imagery (MI) is a well established method to investigate brain activation of walking tasks in a neuroimaging environment. In the last decades several studies featured the age related deterioration of MI. It remains unclear whether the decreased imagery ability among older adults depends on the spatial constraints and motor complexity of the tasks.

Methods: MI of 21 older (70.3 ±4.7 yrs) and 19 younger adults (24.9 ±3.2 yrs) was estimated by using the mental chronometry paradigm. To simulate an everyday life context, a supermarket was constructed within the laboratory. Participants completed three tasks with different spatial and motor complexity: (i) walking straight, (ii), walking with change of direction, and (iii) walking with change of direction while retrieving products. Task durations were measured initially in the imagined and afterwards in the executed condition. Imagery ability was further measured by using the Controllability of Motor Imagery test.

Results: The results show that MI performance is slightly deteriorated in older adults. This was especially true for motor tasks with high spatial and motor affordances (age x task: F (2, 76) = 3.13; p < .05; η² = .08). Results further revealed a higher intervariability in the old group. MI decline in the supermarket scenario was paralleled by poorer scores in the Controllability of Motor Imagery test. Unexpectedly, results of both tests show no correlation.

Conclusions: Our findings suggest that MI decline in older adults shows individual differences depending on the used methods, setting and task complexity. The interaction effect of age x task should be considered when using MI in a neuroimaging environment and interpreting data of cortical activation in older adults.
Objective: To investigate the involvement of the epidermal small sensory fibers in the neurodegenerative process in amyotrophic lateral sclerosis (ALS).

Methods: In the present study, skin biopsies of 28 patients with ALS were obtained at an average of 34 months after disease onset by history. Protein gene product 9.5 (PGP9.5) immunohistochemistry findings were compared to 17 age-matched controls. The primary endpoint of the study was to evaluate the decrease in the density of small intraepidermal nerve fibers and to compare the prevalence of small-fiber neuropathy in patients with ALS and in controls.

Results: We found a significant reduction in epidermal nerve fiber density in the distal calf of patients with ALS (4.8 +/- 3.7 fibers/mm vs. 12.2 +/- 4.6 in age-matched controls, $p < 0.0001$). The extent of fiber loss was age-dependent. Also, the number of subjects with small-fiber neuropathy was significantly higher in the ALS group than in the controls (79% vs. 12%). Correspondingly, mild sensory symptoms including diffuse dysesthesias, paresthesias, and hypesthesia were found in 7 patients. In 17 biopsies of patients with ALS, but only in 2 controls, we saw larger (1.5 µm in diameter) focal swellings of epidermal axons resembling spheroids, suggesting trafficking defects.

Conclusions: These results indicate that small, distal epidermal nerve fibers are involved in this disease, supporting the concept of distal axonopathy in ALS.
Kattor, J. - Fear conditioning in an abdominal pain model: Neural circuits mediating associative learning and extinction processes in healthy subjects [C11]

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Background & Aims: Fear conditioning models have been shown relevant to elucidate the pathophysiology of anxiety, but disturbed associative learning may also play a role in chronic pain syndromes which often overlap with anxiety disorders. Little is known about associative learning in chronic abdominal pain, and thus far, no fear conditioning studies have employed aversive visceral stimuli from the lower gastrointestinal tract. Therefore, we implemented a fear conditioning paradigm in which the conditioned response to rectal pain stimuli was analyzed with event-related fMRI in healthy subjects during associative learning, extinction and reinstatement.

Methods: During acquisition, visual stimuli were systematically paired with painful rectal distensions as unconditioned stimuli (US), while different visual stimuli were presented without US (differential conditioning). During extinction, all visual stimuli were presented without US. During reinstatement, a single, unpaired US was presented. Conditioned anticipatory neural activation in regions of interest (conditioned stimuli: CS⁺ >/=< CS⁻) were assessed along with contingency and valence ratings after each phase.

Results: Significant contingency awareness and valence changes were found following acquisition. While the CS⁺ became aversive, the CS⁻ turned into a pleasant stimulus. This was paralleled by anticipatory activation in core areas of the central fear network, including the anterior cingulate cortex and the cerebellum (early acquisition) and the amygdala (late acquisition). After extinction, contingency and aversiveness ratings returned to baseline. At the neural level, extinction involved activation of the dorsolateral prefrontal cortex in the opposite contrast (CS⁺ < CS⁻). During reinstatement, a tendency for parahippocampal activation was observed, suggesting possible reactivation of the memory trace.

Conclusions: Fear conditioning with rectal pain stimuli is feasible, involves core areas of the central fear network, and may contribute to the understanding of aversive visceral learning and memory processes relevant to the pathophysiology of chronic abdominal pain.
Kellermann, T.S. - Relationship between patterns of connectivity in a network related to emotional appraisal and regulation and “dysthymic personality traits” [105]

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We recently identified a network where affective processing is susceptible to cognitive modulation comprising bilateral amygdala (AMY), medial orbito-frontal cortex (mOFC), SGC, precuneus (PCu) and the nucleus accumbens (NAcc). In particular, the SGC showed significant resting-state connectivity with all of these regions, indicating that it may represent a central node in this network. It may hence be assumed that dysregulation of the connectivity within the delineated network may contribute to pathophysiology of mood disorders, e.g. dysthymia. We here sought to determine whether resting-state connectivity within this network is related to a (subclinical) dysthymic phenotype as reflected by personality traits (FPI: Freiburger Personality Inventory) and the Beck Depression Inventory (BDI), as we tested for significant correlations between connectivity patterns and personality traits.

In our sample, scores of the FPI-items somatic distress, aggressiveness, openness and strain correlated positively with the BDI (indicating higher expression of these traits being related to dysthymic phenotypes).

Most intriguing was the observation that several dysthymic character traits were associated with a specific pattern of connectivity between the SGC, PCu, NAcc, mOFC and AMY, which included both up- and down-regulated connection strengths. This does not only indicate that traits such as dysthymia may result from altered balances of inter-regional couplings. Rather, it also demonstrates that even within a healthy sample, sub-clinical varieties of "pathological" phenotypes may be related to neurobiological substrates, which may in turn provide vulnerability for mood disorders.
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Background: Working Memory (WM) is the foundation of many substantial cognitive skills like attention, perception or executive functions. Many tasks had been conducted to measure WM across the life span and especially on the decrease in old age. However, WM performance in everyday life and its progress through aging is still unclear.

Methods: WM of 23 older (70.28 ±4.65 years) and 20 younger adults (24.89 ±3.16 years) was estimated by using 4 established WM tasks, which differed in task difficulty and memory domain (verbal vs. visual-spatial). To simulate an everyday life context, a small supermarket was constructed within the laboratory. In this, participants completed to 2 memory tasks. They had to memorize a list of 12 products, seen for 30 s on a screen, (i) in the same order like the supermarket or (ii) in random order. Afterwards participants had to collect as many of the products as possible.

Results: The results show that WM performance is slightly deteriorated in older adults. This was especially true for the supermarket task, where younger adults did benefit by the common environment but older adults did not. Further a factor analysis showed that the 4 WM laboratory tasks measure different memory processes then the everyday life task.

Conclusions: Our findings suggest that WM decline in older adults is especially pronounced in everyday life tasks. Following these findings we recommend an everyday life approach to measure WM besides the established laboratory approaches.
Kettler, L. - A double-stimulus paradigm for investigating adaptation in the barn owl (Tyto alba): a behavioral approach [I01]

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During hunting barn owls attend to sounds as for example rustling generated by prey. The birds typically do not attack upon hearing the first sound, but wait for a second sound. This situation was mimicked with a double-stimulus paradigm. It was tested behaviorally whether and how a first or reference sound influenced the head turning of the birds towards a second sound or probe. The delay between reference and probe was varied between 100 ms and 3200 ms. Additionally, the owls were stimulated with single stimuli also referred to as probe-only condition. Preliminary data collected with three adult barn owls indicate a reduction in the number of behavioral reactions compared with a situation where only the probe was presented. Furthermore, head turning latencies were increased in double-stimulus condition. This indicated response adaptation. Latencies returned to the level of the probe-only condition if the reference-probe delay was increased. The time constant of recovery from adaptation coarsely matched time constants that were determined in electrophysiological experiments. Thus, a first stimulus rather lowers than facilitates the response to a second stimulus under the conditions examined.
Klasen, M. - Quetiapine modulates functional connectivity in brain aggression networks [F09]

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Abstract

Aggressive behavior is associated with dysfunctions in an affective regulation network encompassing amygdala and prefrontal areas such as orbitofrontal (OFC), anterior cingulate (ACC), and dorsolateral prefrontal cortex (DLPFC). Specifically, prefrontal regions have been postulated to control amygdala activity by inhibitory projections, and this process may be disrupted in aggressive individuals. The atypical antipsychotic quetiapine successfully attenuates aggressive behavior in various disorders; the underlying neural processes, however, are unknown. A strengthened functional coupling in the prefrontal-amygldala system may account for these anti-aggressive effects. An inhibition of this network has been reported for virtual aggression in violent video games as well. However, there have been so far no in-vivo observations of pharmacological influences on corticolimbic projections during human aggressive behavior. In a double-blind, placebo-controlled study, quetiapine and placebo were administered for three successive days prior to an fMRI experiment. In this experiment, functional brain connectivity was assessed during simulated aggressive behavior in a violent video game and an aggression-free control task in a non-violent modification. Quetiapine significantly reduced game-induced aggressive affect; furthermore, the drug increased the functional connectivity of ACC and DLPFC with the amygdala specifically during virtual aggression, whereas OFC-amygdala coupling was selectively attenuated. These effects were observed neither for placebo nor for the non-violent control. These results demonstrate for the first time a pharmacological modification of aggression-related human brain networks in a naturalistic setting. The observed modulation of prefrontal-amygldala networks appears to control aggressive behavior and provides a neurobiological model for the anti-aggressive effects of quetiapine.
Klein, A. - Medullary lateral line units of the common rudd, Scardinius erythrophthalmus, are sensitive to Kármán vortex streets [10]

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Fish can sense weak water motions with their lateral line. Fish use lateral line information to detect predators and prey, for schooling, collision avoidance and energy efficient locomotion inside unsteady flow. If exposed to flow a submerged cylinder sheds vortices in a wide range of Reynold numbers. These vortices form a Kármán vortex street. Fish use Kármán vortex streets to reduce locomotory costs. Navigating in hydrodynamic perturbations – like in Kármán vortex streets - is complex and information about the hydrodynamic flow field should be advantageous. Peak spike frequencies but not spike rates of primary lateral line afferents coincide with the vortex shedding frequency. Up to now it was not known whether and how vortex street information is processed in higher brain areas. Therefore rudd were exposed to various types of Kármán vortex streets. The activity of medullary lateral line units was recorded. Activity of medullary units correlated with unsteady flow signatures in terms of spike pattern, spike rate or both. In contrast to the noisy spiking activity of peripheral lateral line units some medullary units showed a sharp representation of vortex street cycles. Particle image velocimetry revealed that the flow field close to the fish highly correlated with the activity of medullary units. In sum medullary lateral line units are involved in the processing of vortex street information.
Klein, S. - Cis-4-[18F]fluoro-d-proline detects secondary thalamic and hippocampal degeneration induced by rat glioma [H10]

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Introduction: In a previous study we demonstrated that cis-4-[18F]fluoro-d-proline (d-cis-[18F]FPro) is a sensitive PET tracer to detect secondary degeneration of thalamic nuclei after cortical infarction [1]. In the present study we explored the intracerebral distribution of d-cis-[18F]FPro uptake in a rat glioma model.

Methods: F98 gliomas were implanted into different brain areas (striatum, motor-, somatosensory-, visual cortex or hippocampus) of 10 rats. After 7 to 14 days cerebral d-cis-[18F]FPro and [6-3H]-thymidine (3H-thymidine) uptake was evaluated by ex vivo dual tracer autoradiography, histological and immunological stainings.

Results: Large tumors were present in all animals which exhibited strong 3H-thymidine accumulation but no d-cis-[18F]FPro uptake. Prominent d-cis-[18F]FPro uptake, however, was noted distant to the tumors in brain areas that showed no structural changes in the histological stainings and no 3H-thymidine uptake. 7/10 animals exhibited d-cis-[18F]FPro uptake in ipsilateral thalamic nuclei according to the thalamocortical projections of cortical areas involved by the tumors. A remarkable finding was ipsilateral d-cis-[18F]FPro uptake in the left hippocampus induced by hippocampal tumor implantation. d-cis-[18F]FPro uptake was accompanied by microglial activation.

Conclusions: The results of this study suggest that brain tumors induce secondary neuronal reactions in remote brain areas which may reflect the initial stage of neurodegeneration and that d-cis-[18F]FPro could be used to detect such effects in humans by PET.

References:
Kobza, S. - Active and Observational Learning from Positive and Negative Feedback is Dissociated in Parkinsonism [12]

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Feedback to both actively performed and observed behaviour allows adaptation of future actions. Positive feedback leads to increased activity of dopamine neurons in the substantia nigra, whereas dopamine neuron activity is decreased following negative feedback. Dopamine level reduction in unmedicated Parkinson’s Disease (PD) patients has been shown to lead to enhanced learning from negative feedback. Recent findings suggest that the striatum plays a less prominent role in observational as compared to active learning. Although behavioural evidence from brain damaged patients is of high importance, it is still missing. In the present study, it was hypothesized that unmedicated PD patients would show a negative learning bias only in active but not in observational learning. In a between-group design, 19 PD patients and 40 healthy controls engaged in either an active or an observational probabilistic feedback-learning task. Transfer phases aimed to assess the bias to learn better from positive or negative feedback. As expected, actively learning patients showed a negative learning bias, whereas controls learned better from positive feedback. In contrast, no difference between patients and controls emerged for observational learning, with both groups showing better learning from positive feedback. These findings add to neural models of reinforcement-learning by suggesting that dopamine-modulated input to the striatum plays a minor role in observational learning from feedback.
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Little is known about gender differences in the neural correlates of stress reaction. Initial results indicate differentiated neural stress networks in women and men [2]. In general, men show enhanced physiological stress reactions whereas women report enhanced subjective reactions [1].

The current study's aim is to characterize the effect of gender on stress reaction at the subjective, physiological and neural levels.

Healthy women and men conducted the „Montreal Imaging Stress Test“ (MIST) [3]; an adaptive design in which inter-individually comparable cognitive demands are employed in a psychosocial stress situation. The neural BOLD-activity, psychophysiological data (cortisol, electrodermal activity), and subjective stress reports were collected.

The preliminary data analysis points to differentiated subjective and physiological stress reactions in women and men, thereby supporting previous findings. Gender differences are also observable on the neural level: while women tend to recruit emotion processing areas, men rely on activation of regulatory areas. These results suggest differentiated neural stress reactions between women and men. On a clinical perspective, data on gender specific, psychosocial stress reactions are essential for understanding stress related psychiatric disorders such as schizophrenia.

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Kossack, H. - Empathic processing of subliminal emotional face expressions: A behavioural and fMRI study [F12]

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In social interactions, facial expressions are mostly expressed in a clear and expressive manner, but some are only visible for a fraction of a second. Being perceived under the threshold of subjective awareness, these very short emotional face expressions might act as affective primes and influence our judgements and behaviour. The aim of the current study was to examine the effect of these subliminal face expressions on judgements of neutral faces and to analyse the brain activation patterns associated with their processing. We hypothesized that according to consciously accessible (supraliminal) face expressions, subliminal expressions trigger empathy. In a combined behavioral and fMRI study healthy right handers were confronted with happy, angry and sad face expressions presented above (400ms) or below (40ms) the level of subjective awareness. Masking with neutral expressions prevented subliminal faces to become aware. In the behavioral study, a forced choice task combined with no prime control conditions was used to reveal the influence of the subliminal expressions. The event-related fMRI study compared the brain areas related to supra- and subliminal face expressions. Our data show that judgements of neutral faces were influenced by the preceding subliminal face expressions. Moreover, supraliminal and subliminal face expressions shared a broad network of brain regions involving the occipito-temporal, anterior cingulate and prefrontal cortex. Importantly, we provide evidence for lower- and higher-level empathic processing in relation to subliminal emotional content. This emphasizes the important role of subtle emotional stimuli in social situations.
Background and Purpose: Previous studies have described a correlation between variants of the circle of Willis and pathological findings such as cerebrovascular diseases. Moreover, anatomic variations of the anterior cerebral artery (ACA) seem to correspond to the prevalence of aneurysms in anterior communicating artery (ACoA). The aim of this study is to assess the prevalence of aneurysms in patients with anatomical/morphological variations of the circle of Willis.

Methods: We retrospectively analyzed 223 patients who underwent cerebral angiography between January 2002 and December 2010 and had cerebral aneurysm of the ACoA. Diagnostic imaging was reviewed and statistically evaluated to detect circle of Willis anomalies, aneurysm size, and rupture. Two hundred and four patients with unrelated diagnosis served as control group.

Results: Variations of the A1 segment were significantly more frequent in the aneurysm group than in the control group. The mean aneurysm size in patients with grades I and III hypoplasia or aplasia was 6.58 mm whereas that in patients with grade II hypoplasia was 7.76 mm. In addition, aneurysms were significantly more often detected via the contralateral internal carotid artery (ICA) than via the ipsilateral or both ACI.

Conclusions: It can be assumed that variations in the A1 segment of the ACAs are correlated with a higher prevalence of ACoA aneurysms than in patients with a symmetric circle of Willis.
Objective: To assess olfactory functioning in patients with Tourette Syndrome (TS)

Background: Olfactory deficits can be found in several movement disorders, like Parkinson-Syndrome, cerebellar diseases or Chorea Huntington. In the pathophysiology of TS the cortico-striato-thalamo-cortical circuit plays a salient role. The structural pathologies include the basal ganglia, the thalamus and the amygdala which contribute as secondary or tertiary olfactory rely points to the sense of smell. At present it is unclear if olfactory deficits can also be found in TS.

Methods: We have assessed 25 patients with TS and age, education as well as sex-matched control subjects. The Sniffin Sticks were applied to assess different olfactory functions (odor threshold, odor discrimination and odor identification). Blockage and other pathology of the nose that may impair sniffing were ruled out by rhinoscopy.

Results: TS patients had significantly lower scores than controls with the odor discrimination and odor identification task (12.0 +/- 2.1 vs. 13.3 +/- 1.7 and 12.4 +/- 1.9 vs. 13.9 +/- 1.5 respectively) while there was no difference between the two groups with the odor threshold task.

Conclusions: Olfactory deficits can also be found in TS. However, olfactory deficits were subclinical as none of the patient reported on an impairment of the sense of smell.
Kuchenbuch, A. - Effects of musical training and standard probabilities on encoding of complex tone patterns [H11]

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The human auditory cortex automatically encodes acoustical input from the environment and differentiates regular sound patterns from noise in order to identify possibly important, irregular events. The Mismatch negativity (MMN) response is a marker for the detection of sounds that are unexpected based on the encoded regularities. It has been shown to be elicited by violations of simple acoustical features but also by violations of more complex regularities like tone patterns. By means of magnetoencephalography (MEG) we investigated the responsiveness of MMNm in a noisy environment by varying the standard probability (70%, 50% and 35%) of a pattern oddball paradigm. In addition we studied the effects of long term music training in the encoding of the patterns by comparing the responses of non-musicians and musicians. A MMNm could still be observed in the noisy condition (35% standards) in response to violations of the predominant tone pattern for both groups. The amplitude of MMNm of the right hemisphere was influenced by the standard probability, and this result was mediated by musical expertise. The results indicate a reduced but still present pattern violation detection processing within a noisy environment and while the left hemisphere is more stable, the standard probability has a stronger impact on the auditory processing of the right hemisphere. Furthermore, non-musicians benefit more from a good signal to noise ratio while musicians auditory processing is dominated by their trained left hemisphere.
Kühn, A.B. - Memory traces after breaches of expectancy: destabilized or adapted prediction [D04]

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The study aimed to investigate the neural correlates of destabilization and adaptation of serial prediction by functional magnetic resonance imaging (fMRI). A former study observed the frontomedian cortex to be activated if a sequence could be predicted well, whereas activation of the same cortical area was reduced / delayed when prediction was destabilized by a preceding omission of subsequences (breach of expectancy). If this reduction / delay of frontomedian activity might be a neural signature of destabilization and of adaptation as well or if other more parietal or temporal areas might reflect adaptation of prediction should be investigated with a somewhat changed design that included repeated and single omissions.

Before the fMRI session subjects (n = 21) were required to learn a sequence of 24 digits. During the fMRI session the sequence was repeatedly presented digit by digit. Unexpectedly digits were omitted without a temporal gap and subjects had to indicate omissions by key presses. Half of all omissions were repeated (double omissions) and half were not (single omissions).

In comparison to omissions sequential elements without preceding omissions (non-destabilized events) activated the frontomedian cortex as in the former study (effect of serial prediction). After double and single omissions the frontomedian activation was delayed compared to non-destabilized events - a signature of destabilization. Further, destabilized events after double omissions compared to that after single omissions revealed an activation increase in temporal areas. The later was interpreted as a cortical signature of adaption. Hence, the study revealed separated cortical areas for destabilization and adaptation of prediction.
Künzel, T. - PSD-95 expression and the development of auditory giant synapses [J01]

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In the cochlear nucleus, auditory nerve axons form giant terminals on a subset of neurons. It is yet unknown how the specific increase in terminal size is regulated. The "postsynaptic-density protein of 95kD" (PSD-95) is a central organizer of the postsynapse, involved in adjusting synaptic strength and size and implicated in the development of the presynapse via interaction with neuroligins/neurexins. We hypothesized that PSD-95 expression should be present in the cochlear nucleus and its dynamics should temporally match the increase in synaptic terminal size.

We test this with fluorescent immunolabeling of PSD-95 and presynaptic proteins in embryonic chicken brain sections, supported by anterograde tracing of the auditory nerve. Staining was visualized with a laser-scanning microscope and analyzed with custom software. We found that PSD-95 was expressed at synaptic sites in the embryonic chicken cochlear nucleus. An increase in the area of PSD-95 signals was evident before and at the time of maximal increase of presynaptic signal area. This was seen in neurons that receive giant terminals, but not in other neuron types. Anterograde tracing corroborated that dynamics of synaptic immunosignals correlate with structural changes of synaptic terminals.

The results support the idea that PSD-95 is involved in regulation of giant synaptic development. The chicken system will allow functional studies of this protein and its binding partners in the future.
Leinwather, S., Nasserani, N. - Pannexin 1 function under pro-inflammatory conditions in neuroblastoma 2a cells [D07]

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Background: Pannexin 1 (Px1) is an integral membrane protein with high conductance properties (550pS) and permeability to large molecules of up to 1 kDa, like ATP. Since contribution of Panx1 to the cellular inflammasome has been described, the putative roles of the protein in immuneregulation on cells of the central nervous system gain in increasing importance. In neuroblastoma 2a (N2a) cells, the endogenously expressed Toll Like Receptor 4 (TLR4) can be utilized as a physiologic interaction partner to investigate putative interactions with Px1 under inflammatory conditions.

Methods: Transient transfection of N2a cells with EYFP linked mouse Px1 DNA vectors and corresponding EYFP vector only transfection was used to investigate membrane current generation under pro-inflammatory stimulation with Lipopolysaccharide (LPS). Whole cell patch clamp recordings were performed in the presence of TLR4 antibody blockade and/or under selective Px1 inhibition. Panx1 mediated ATP release was analysed by ELISA. TLR4 expression was monitored by Western Blot.

Results: Whereas LPS incubation induced moderate changes in Panx1 transfected N2a cells, significant increases in membrane currents were elicited in Panx1 deficient cells. Similar increases in current responses and subsequent effects on current repolarisation were observed under Panx1-, TLR4-, or joint inhibition. Results were underlined on the levels of ATP release and regulation of TLR4 in dependence of Px1 presence.

Conclusion: Our results demonstrate that the presence of both, TLR4 action and Px1 channel activity, is a prerequisite for moderate transmembrane current patterns under pro-inflammatory conditions in neuron like cells under pro-inflammatory conditions.
Lodder-Gadaczek, J. - Analysis of the NAAG metabolism [G05]

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N-acetylaspartylglutamate (NAAG) is an abundant neuropeptide in the mammalian brain, present in micromolar to millimolar concentrations. The NAAG metabolism is not completely clarified. NAA synthase (Nat8l) catalyzes the N-acetylation of aspartate, forming N-acetylaspartate (NAA). NAAG is synthesized in specific neurons by a synthetase catalyzing a condensation of NAA and glutamate. NAAG is released from nerve terminals via synaptic vesicles. The uptake into synaptic vesicles occurs by an unknown transporter. NAAG is then degraded extracellularly by glutamate carboxypeptidase II (GCP-II), liberating NAA and glutamate.

We identified the NAAG synthetase-I (NAAGS-I) and the NAAG synthetase-II (NAAGS-II). Besides NAAGS-II’s production of NAAG we demonstrated the synthesis of an tripeptide N-acetylaspartylglutamylglutamate (NAAG2).

Patients with Salla disease caused by a mutation in the SLC17A5 gene, have an abnormal biochemical concentration of NAAG in the cerebrospinal fluid. The SLC17A5 gene encodes for sialin, the lysosomal transporter of N-acetylneuraminic acid (sialic acid). Because it was shown that the sialic acid transporter can also transport glutamate and aspartate and because of the different level of NAAG in Salla disease, we addressed the question whether SLC17A5 is the above mentioned transporter responsible for transport of NAAG into synaptic vesicles. Taken together our results suggest that SLC17A5 is the supposed transporter for neuronal vesicular uptake of NAAG.
Lucka, F. - Hierarchical Fully-Bayesian Inference for EEG/MEG Combination using Realistic FE Head Models [J10]

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Abstract: Measuring the induced electromagnetic fields at the head surface to estimate the underlying, activity-related ion currents in the brain is a challenging, severely ill-posed inverse problem. Especially the recovery of brain networks involving deep-lying sources by means of EEG/MEG recordings is still a challenging task for any inverse method. Recently, hierarchical Bayesian modeling (HBM) emerged as a unifying framework for current density reconstruction (CDR) approaches comprising most established methods as well as offering promising new methods. Our work examines the performance of fully-Bayesian inference methods for HBM for source configurations consisting of few, focal sources when used with realistic, high resolution Finite Element (FE) head models. In addition, using EEG and MEG alone is compared to a combined data analysis. The main foci of interest are the right depth localization, a well known systematic error of many CDR methods, and the separation of single sources in multiple-source scenarios. Both aspects are very important in clinical applications, e.g., in presurgical epilepsy diagnosis as well as in the analysis of evoked potential and fields, e.g., for auditory or somatosensory stimuli. Our results show that HBM provides a promising and convenient framework for these tasks. In particular, it is able to improve upon established CDR methods like minimum norm estimation (MNE) or sLORETA in many aspects. For challenging multiple-source scenarios where the established methods show crucial errors, promising results are attained.
Ludwig, A. - Cytoarchitecture and mapping of the dorsal striatum of the human brain [I11]

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The dorsal striatum, composed by the putamen and the caudate nucleus, is involved in psychomotor behavior and decision making, through the integration of sensory, motor, cognitive and emotional information. Brockhaus [1] suggested a detailed structural segregation of the dorsal striatum into different components. This segregation, however, is not reflected in the current neuroimaging literature although it can be expected that these components are functionally relevant. In addition, there is currently no data available describing the localization of these components in 3D and their inter-subject variability. We examined therefore serial histological sections of ten adult post-human brains, which were stained for cell bodies. Twelve striatal components, five for the caudate nucleus, four for the putamen, and three for the caudoventral striatum were mapped based on differences in the density of the neurons. The ventral striatum with the fundus differed from the dorsal part mainly by a higher density of neurons. The cytoarchitectonic analysis revealed a highly complex architecture and multiple components of the human dorsal striatum. The borders of these components were traced in images of histological sections using in-house software, spatially normalized to the MNI reference space, and 3D-probabilistic maps were generated [2]. Striatal components do not follow macroscopic landmarks and are not visible in routine MR images. Thus, our 3D-probabilistic maps provide a new and promising tool to localize data from in vivo MR imaging of the healthy and pathologically altered brain.

Lysyansky, B. - Optimal stimulation parameters for desynchronizing Coordinated Reset stimulation [H05]

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This computational study is dedicated to the optimal parameter choice for coordinated reset (CR) stimulation, a stimulation technique developed to effectively counteract pathological synchronization in neuronal populations. The results are presented for two different models of neuronal networks consisting of phase oscillators and FitzHugh-Nagumo spiking neurons. We present a detailed analysis of the parameter space and reveal the optimal values of the stimulation strength as well as the stimulation timing of the intermittent ON-OFF CR stimulation. The optimal CR parameters imply the best desynchronizing effect of the stimulation with a minimal amount of the stimulation current.

We have also found the optimal number of stimulation sites for the most effective control of the undesirable neuronal synchronization. The parameter optimization has been performed with respect to the maximal admissible stimulation-free interval in the ON-OFF protocol, the optimal stimulation strength providing the best desynchronizing effect, and the extent of desynchronization induced by CR stimulation. We have shown that the most preferable number of the stimulation sites depends on the properties of the neuronal tissue, namely, on the spatial decay rate of the administered stimulation current.

Our findings may contribute to a clinically realistic parameter calibration of the CR stimulation protocol for an effective suppression of pathological neuronal synchronization, which is characteristic for several neurological disorders, e.g., Parkinson's disease and tinnitus.
May, S.E. - Lowered frequency and altered stimulus-induced modulation of S1 alpha activity in hepatic encephalopathy [E02]

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Hepatic encephalopathy (HE), a neuropsychiatric complication of liver cirrhosis, is associated with a slowing of oscillatory activity in the motor and visual system (Kahlbrock et al., 2012; Timmermann et al., 2008). Here, we examined somatosensory alpha activity and its modulation by somatosensory stimulation in HE.

21 patients with liver cirrhosis and 7 healthy controls received electrical stimulation of the right median nerve while brain activity was recorded using magnetoencephalography. A clinical and neuropsychometric assessment was performed. In addition, the critical flicker frequency (CFF) was measured, a reliable indicator of HE severity (Kircheis et al., 2002). Using a virtual sensor analysis, source waveforms in the primary somatosensory cortex (S1) contralateral to stimulation were individually reconstructed and (time) frequency analyses performed.

Median nerve stimuli evoked a suppression and later rebound of S1 alpha activity. This rebound significantly differed between patients with manifest HE and healthy controls. Increasing HE severity as quantified by the CFF was associated with a slowing of the S1 alpha peak frequency and a delayed alpha rebound.

The present results extend previous findings of slowed oscillatory activity in HE to the somatosensory system. Furthermore, our data indicate an altered response of S1 to simple somatosensory stimuli. The delayed alpha rebound might represent an impaired capability to return to the default state of activation.
Meessen, J. - Cardiac Awareness and Metacognition [C08]

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**Background:** Performance on tasks depending on metacognitive ability has been studied for different domains, especially concerning memory functioning. Yet little is known about intraindividual relations between metacognitive and somatic awareness despite evidence that both might entail positive psychological implications. This study investigates how awareness for memory performance relates to cardiac awareness.

**Objective:** We hypothesize a comprehensive ability of accurately perceiving internal processes, independent of the respective domain. Consequently, we expect a positive association between accurate perception of internal somatic and cognitive processes.

**Method:** To test the mentioned hypothesis, healthy subjects are investigated, using two well-established paradigms. Concerning the perception of somatic processes, we chose the accurate perception of one's cardiac activity, defined as cardiac awareness and measured by the “Heartbeat Perception Task”. Cognitive processes are represented by the metacognitive awareness of one's memory performance, measured by a “Judgment of Learning” paradigm. Bivariate correlation analyses are conducted.

**Results & Conclusions:** Pilot data will be presented and discussed. In case of findings that corroborate the presumption of a comprehensive ability of accurate perception of internal processes, this would have distinct implications of the conceptualization of metacognition in general and could direct future research initiatives.
Introduction: Visual attention towards information in the environment is controlled by a complex neural system involving prefrontal areas like the dorsolateral prefrontal cortex. The resulting bottom-up / top-down interplay is reflected by a subject’s gaze behavior (GB). Schizophrenia patients (SZ) show a deviant GB during presentation of faces, the most important source of social information. We therefore investigate how GB is associated with social functioning.

Methods: N=28 SZ (mean ± SD, 29.6±7.3yrs, 32% female) and n=28 healthy controls (HC, 30.9±8.5yrs, 32% female) were included. Stimuli consisted of 12 pictures of social interactions presented in a free viewing condition. Scan path data were collected with an SMI iViewX™ Hi-Speed 500 Hz eye tracking system.

Results: Scan path length (SPL) of SZ was significantly shorter (p<.05). In faces, SZ showed a significant lower dwell time (p<.01) and glances count (GC, p<.001) than HC. Less GCs were markedly associated with worse SF (r=.52, p<.001) and worse RF (r=.51, p<.001). LogReg (predictors: SPL, GC) yielded a classification accuracy of 82.1%.

Conclusions: GB of SZ differed markedly from HC regarding time of information perception and cognitively guided information gathering. The latter explained 25% variance of SF and RF. Furthermore, GB enabled very good group discrimination. Considering spontaneous GB may improve treatment of social cognition and skills.
A major well known effect of thyroid hormone (T3) is the regulation of energy consumption, usually attributed to the regulation of Na+/K+-ATPase (NKA) (O. Sharabani et al., 2002). The general activity of NKA would lead hyperpolarization of the neuronal cell membrane, and decreasing the cellular excitability. But the hyperthyroid condition leads to the opposite effect, an increase in neuronal excitability. On the other hand, hypothryoidism shows an irreversible mental retardation during brain development, this is also called cretinism. Several reports claimed that thyroid hormone up regulates NKA during postnatal brain development. This upregulation is governed by voltage activated sodium currents in rat muscle (Harrison & Clausen, 1998). We plan to study whether the upregulation of NKA is a direct effect or an indirect effect, which could be caused by T3 dependent Na+influx of neuronal cell. Our laboratory results from 3[H] labelled Ouabain binding suggest that the expression of NKA α2 & α3 subunits in the membrane which closely parallels the regulation of Na+ current density by T3 treatment. This experiment explained a correlation between Na+ current regulation and the regulation of the Na+/K+-ATPase by thyroid hormone. And western blotting results shows increased expression of NKA α2 subunits in neuron glia mixed culture (1:10) under T3 treatment with insignificant changes of other NKA subunits (α1, α3, β1 & β2). Future experiments are planned under various culture conditions to dissect the factors leading to the differential regulation of the expression of the different subunits and also to check the expression pattern of NKA subunits by blocking Na+ channel.
Mönninghoff, C. - Fall-Kontroll-Studie zur hirnvolumetrischen Differenzierung verschiedener MCI-Subtypen mittels 1,5 T MRT [C03]

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Zielsetzung: Leichte kognitive Einschränkungen (Mild Cognitive Impairment, MCI) gehen mit einer Hirnvolumenminderung und einem erhöhten Demenzrisiko einher. Ziel dieser Fall-Kontroll-Studie ist die Volumetrie von Hirnregionen im 1,5 T MRT, die als Surrogatparameter für die Identifikation von MCI-Subtypen dienen können.

Material und Methodik: Im Rahmen der prospektiven, populationsbasierten Heinz Nixdorf Recall Studie wurden 115 Probanden mit MCI (85 amnestic MCI (aMCI)/30 non-amnestic MCI (naMCI)) und 120 alters-, bildungs- und geschlechtsgematchte Kontrollprobanden magnetresonanztomographisch untersucht. Isotrope T1 und T2 gewichtete 1,5T MRT Sequenzen wurden akquiriert und verschiedene Hirnregionen mittels einer automatisierten Untersucher-unabhängigen Methode zur MRT-Analyse volumetriert. Diese beruht auf Algorithmen von SPM5, eigens erstellten Masken sowie einem probabilistischen Hirnatlas. Die Daten wurden für das individuelle intrakranielle Volumen korrigiert und die Gruppen mithilfe von ANOVAs verglichen.

Ergebnisse: Im Gruppenvergleich zeigten aMCI Probanden ein signifikant niedrigeres Volumen von Hippocampus und Amygdala (Gesamtvolumen aMCI: 9,67±1.05 ml Standardabweichung (SD); naMCI: 10,47±0,96 ml SD; Kontrollprobanden: 10.25±0.83 ml SD; p< 0.001) sowie der grauen Substanz von Frontallappen (p = 0,019), Temporallappen (p = 0,016) und Insula (p = 0,007). Interessanterweise unterschieden sich die naMCI Probanden hinsichtlich dieser Hirnregionen nicht signifikant von den Kontrollprobanden.

Schlußfolgerungen: Da aMCI-Probanden eine höhere Konversion zur Alzheimer-Erkrankung aufweisen als die naMCI-Gruppe kann die Volumenminderung von Hippocampus und Amygdala sowie der frontotemporalen grauen Substanz eine frühzeitige Diagnose untermauern.
Localization of neural activity is a major target in neuroscientific research. Especially, the search for sources with neural activity during cognitive processing (e.g., auditory processing) with a high temporal resolution in the millisecond range is the ultimate goal. The high time resolution of the EEG is perfectly suited for millisecond-precise analysis of ongoing neural processes. Since auditory processing is disturbed in several diseases (e.g., schizophrenia), the goal is to understand in which way these distortions are present and at which time they occur. The main focus is to adequately compute the location and the amplitude of the sources. Source analysis algorithms developed so far suffer from inaccuracy of these variables which are due to the low signal to noise ratio regarding single sources. We developed an advanced mathematical algorithm to reliably compute amplitude and location of sources from the auditory stream during the presence of other disturbing processes.
Müller, V.I. - Crossmodal interactions in audiovisual emotion processing [B06]

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Emotion in daily life is often expressed in a multimodal fashion. Although there exists a wide range of literature concerning the areas which are active during emotion processing, little is known about the neural interactions underlying bottom-up and top-down processes in crossmodal integration. In a previous study, assessing the neural correlates of audio-visual integration, we found that activity in the left amygdala is significantly attenuated when a neutral stimulus is paired with an emotional one compared to conditions with emotional stimuli in both channels. Here we used DCM to investigate the underlying networks of this effect. All 48 models included bilateral fusiform (FFG) and superior temporal gyrus (STG), bilateral posterior superior temporal sulcus (pSTS) and left amygdala and assumed FFG and STG projecting into ipsilateral pSTS. The models differed in a) the pre- and absence of interhemispheric connections between FFG, STG and pSTS b) the region projecting into the left amygdala and c) modulation of the effective connectivity towards the left amygdala. Our results provide evidence in favor of a model family, differing only in the interhemispheric connections. All winning models shared a connection between bilateral FFG into the left amygdala and a modulatory influence of bilateral pSTS on these connections. Moreover a lateralization of the right FFA by stronger face-driven input in this region could be found, whereas such lateralization was not present for sound-driven input into the STG. In summary, our data provides further evidence for a rightward lateralization of the FFG for face stimuli and in particular for a key role of the pSTS in the integration and gating of audio-visual emotional information.


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Autologous nerve transplantation is still regarded as the clinical gold standard in reconstructive plastic surgery to bridge overcritical nerve gaps. As ANT is associated with morbidity at the donor site and the source of autologous material is limited, the development of bioartificial alternatives is crucial. We here present a summary of our pre-clinical research on "NeuroMaix" a two component collagen-based nerve guide to support directed axonal growth after nerve injury. Cytocompatibility of NeuroMaix was evaluated by human Schwann cell seeding followed by electronmicroscopy and two-photon scanning laser microscopy. Additionally, NeuroMaix was compared to ANT and the commercially available collagen nerve tube NeuraGen® (Integra LifeSciences) in the rat Sciatic Nerve Injury Model. Functional regeneration was analyzed by measuring toe spreading and electrophysiological examinations. Structural regeneration was evaluated by histology, morphometry, and retrograde tracing. Biocompatibility of NeuroMaix was evident since HSC migrated into the micropores and adopted spindle shaped morphology with long processes typical for healthy, differentiated Schwann cells. Histology after 12 weeks demonstrated that NeuroMaix supported directed axonal growth without obvious neuroma formation or foreign body reaction. Regenerated and myelinated axons were organized in mini-fascicles and able to regenerate across the 20 mm nerve defect.

Summarizing, the present data demonstrated cytocompatibility of NeuroMaix and the in vivo evidence that directed axonal regeneration is supported. As such, first in human application is suggested.

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Paraskevopoulos, E. - Audio-visual integration of abstract congruency rules is induced by musical expertise: an MEG study [H03]

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Perception of everyday life events relies mostly on multisensory integration. Hence, studying the neural correlates of the integration of multiple senses constitutes an important tool in understanding perception within an ecologically valid framework. The present study used magnetoencephalography to identify the neural correlates of an audio-visual incongruency response, which is not generated due to incongruency of the unisensory physical characteristics of the stimulation, but from the violation of an abstract congruency rule. The chosen rule was comparable to musical reading: “the higher the pitch of the tone – the higher the position of the circle”. In parallel, plasticity effects due to long-term musical training on this response where investigated by means of comparing musicians to non-musicians. The applied paradigm was based on an appropriate modification of the multi-featured oddball paradigm incorporating, within one run, deviants based on a multisensory audio-visual incongruent condition and two unisensory mismatch conditions: an auditory and a visual one. Results indicated the presence of an audio-visual incongruency response, generated mainly in frontal regions, an auditory MMN and a visual mismatch response. Moreover, results revealed that long-term musical training generates plastic changes in frontal, temporal and occipital areas that affect this multi-sensory incongruency response as well as the uni-sensory auditory and visual mismatch responses.
Pavlidou, A. - Anodal stimulation of premotor cortex facilitates the recognition of different forms of movements [E01]

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Recently, premotor cortex (PMC) key role in the processing of human biological motion (BM) has been extended to include the processing of BM of different species, as well as, its involvement in higher form processes such as differentiating between correct and incorrect BM. Here, we were interested in whether transcranial direct current stimulation (tDCS) of PMC influences the visual perception of point light displays (PLD) movements differing in their form and degree of plausibility. Real and sham tDCS over left PMC was administered to 10 subjects while performing a PLD recognition task. Performance (Reaction times (RT) and accuracy) was measured before, during, immediately after, and 30 minutes post tDCS stimulation. Subjects performed 2 experiments. In Experiment 1, five subjects were asked to distinguish between human, bird, and random movements. Human PLD was recognized the fastest, across all testing sessions. Anodal tDCS facilitated the RT for bird and random PLD, whilst cathodal tDCS had a negative effect in subject’s ability to accurately recognize a human PLD. In Experiment 2, five subjects were asked to distinguish between 3 variations of movement; a biomechanically natural, unnatural and random movement. Anodal tDCS led to a significant increase in false reports of unnatural movements as natural. These results extend previous reports on the role of PMC in movement recognition, in particular human BM, and for experiment 1 imply that anodal tDCS over PMC aids in the visual percept of the global form of the PLD. In contrast for experiment 2, anodal tDCS over PMC severely affects the discrimination of the local details of the PLD, increasing subjects’ tendency to report biomechanically unnatural movements as natural.
Philipp, K. - Association of cognitive abnormalities in HIV infection and pattern of neurodegeneration in MRI and CSF [H09]

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Despite the advances in the medical treatment with highly active antiretroviral therapy (HAART), a rising number of HIV infected patients experience cognitive impairment. In order to find reliable biomarkers for the development of HIV-associated neurocognitive disorders (HAND), in this study 94 HIV positive patients with various degrees of infection (82 men and 12 women, mean age 45 +/- 10 years, 8 +/- 7 years since seroconversion, CD4+ count 422 +/- 352 per µl blood, 31,280 +/- 91,602 viral copies per ml blood, mainly CDC stage C3, 68% of the patients received HAART) were examined for peculiarities in magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) and neuropsychological assessment. MRI alterations included global white matter changes, atrophy, degree of periventricular white matter abnormalities, and severity of basal ganglia changes. In cerebrospinal fluid markers indicating neurodegeneration (total-tau, phosphor-tau and beta-amyloid) where measured. Specific MRI abnormalities like global white matter changes and global atrophy were found to be related to cognitive decline, which also has a strong correlation with levels of total tau in CSF but not to phospho-tau or beta-amyloid. This marker protein might be a new useful tool to differentiate HIV associated disturbances from other forms of dementia like Alzheimer’s disease. In regards to the increasing age of the HIV positive population, this distinction will gain importance.
Pishva,E. - Epigenetic mechanisms in gene-environment interactions in psychiatry: Effect of genetic variation in the epigenetic machinery on emotional reactivity in adult life [E06]


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Recent human and animal studies suggest that epigenetic mechanisms mediate the influence of adverse environmental conditions on the development of psychiatric disorders. Polymorphisms in the epigenetic machinery genes might therefore play a crucial role in vulnerability to psychological phenotypes. To evaluate this hypothesis, we conducted a systematic gene-environment interaction study to investigate whether polymorphisms in 30 SNPs over 4 DNA methylation relevant genes (DNMT1, DNMT3A, DNMT3B, and MTHFR) moderate the effect of childhood trauma (CT) on mood and on the emotional response to stressful and rewarding stimuli (i.e stress sensitivity and reward experience). Momentary events and emotional states in daily life were determined with experience sampling methodologies. Regression analyses were used to examine possible interactive effects between SNPs and childhood trauma on positive affect, negative affect, stress sensitivity and reward experience. A two-stage association analysis was employed. First, main effects and interactions were tested in 113 healthy individuals. In the second stage, significant associations (at p<0.05) were replicated in a sample of 380 female twins from a general population. In addition, significant effects in both the original and replication sample were tested in several clinical samples of patients with psychotic disorder (n=108), siblings of patients with psychotic disorder (n=96), and patients with residual symptoms of depression (n=125).

Regression analyses revealed that the associations between CT and stress sensitivity and reward experience are significantly different in healthy individuals with a certain genotype of the DNMT1 and DNMT3a genes but the effects were not consistently significant over the replication and other study groups.

Keywords: Epigenetics, Emotional reactivity, Childhood trauma.
A deficit in empathy has been repeatedly described in individuals with conduct disorder (CD), in particular in subjects with psychopathic traits. Here, we aimed to investigate the neural mechanisms of empathy in CD, and to explore associations with psychopathic traits. Using functional magnetic resonance imaging, 17 boys with CD, and a control group comparable for age (n=18 typically developing boys) were investigated during an empathy task. Emotional faces were presented and participants were either asked to infer the emotional state from the face (other-task) or to judge their own emotional response to the face (self-task). In both groups, the medial frontal gyrus was activated during the other-task as were parahippocampal regions. In the self-task fusiform gyrus activation emerged on both groups. Preliminary findings point towards decreased activation of the hippocampus and parahippocampal networks in the CD-group. This is the first study to specifically investigate neural correlates of empathy in youth with conduct disorder. Previous research on neural correlates of psychopathic traits indicates decreased hippocampal volumes. The findings are discussed in the framework of current findings on empathy and conduct disorder.
Prasath, J - Uptake of O-(2-[18F]fluoroethyl)-L-tyrosine in reactive astrocytosis in the vicinity of untreated and irradiated cerebral gliomas [C05]

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Background and purpose: PET using O-(2-[18F]fluoroethyl)-L-tyrosine (FET) allows improved imaging of tumor extent of cerebral gliomas and is under clinical evaluation for radiotherapy planning. This study explores possible FET uptake in the area of reactive gliosis in the vicinity of untreated and irradiated rat gliomas which may distort the proper definition of the target volume.

Methods: F98-glioma cells were implanted into the caudate nucleus of 33 Fisher CDF rats. Sixteen animals remained untreated and in 17 animals the tumor was irradiated by Gamma Knife 6 – 8 days after implantation (2/ 50 Gy, 3/75 Gy, 6/100 Gy, 6/150 Gy). After 13 – 15 d of tumor growth the animals were sacrificed following injection of FET. Brains were removed, cut in coronal sections and autoradiograms of FET distribution were produced and compared with histology (toluidine blue) and reactive astrogliosis (GFAP staining). FET uptake in the tumors and in areas of reactive astrocytosis was evaluated by lesion to brain ratios (L/B).

Results: All F98-gliomas showed increased FET-uptake in congruency with histological tumor extent. L/B was similar in irradiated and native tumors (3.9 ± 0.8 vs. 4.0 ± 1.3). FET-uptake in the area of reactive astrogliosis in the surroundings of the tumors was significantly lower than in the tumor (L/B: 1.5 ± 0.4 versus 3.9 ± 1.1). In 2/8 animals irradiated with 150 Gy, however, prominent FET uptake was noted in astrogliosis.

Conclusions: Reactive astrogliosis in the vicinity of gliomas generally leads to only a slight FET-enrichment that appears not to affect the correct definition of tumor extent for treatment planning.

Keywords: Cerebral glioma; astrogliosis, O-(2-[18F]fluoroethyl)-L-tyrosine; autoradiography

References:
Prinz, S. - The effect of parental income, personality factors and field of study on risk aversion in a lottery game [J09]

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In Economics and Politics it is generally assumed that individual financial decision making is a cognitive process based upon rational expectations on the corresponding gains, losses, and risks. In economic reality, however, we see that the process is more complex: individual differences in risk aversion or risk seeking behavioural traits may have great impact on individual financial decisions. Personality traits as well as environmental factors such as monetary socialization or the awareness of alternative decision options might cause extraordinary risk-loving or safety-related behaviour. In order to test these individual and environmental factors on financial decision making we conducted the well established lottery paradigm by Holt and Laury (2002). On ten different levels subjects must choose between a riskier lottery with a higher possible payoff and a less risky lottery with a lower payoff. In the ten steps the probabilities of gaining and the possible payoffs change. The point at which a subject switches to the riskier lottery with the higher payoff marks the individual risk aversion.

Whereas there was no significant effect of personality traits, we found lower risk aversion in individuals with higher parental income. Students of economics had lower risk aversion values than students studying to become a teacher. We concluded that, obviously, socialisation has a more pronounced effect on financial decision making than personality traits.
Prokopiak M - Mice deficient for the clock protein BMAL1 show impaired adult neurogenesis [F05]

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Disturbances of the circadian system lead to disintegration of daily body rhythms, reduced life span, cognitive impairment and presenile senescence. A molecular clockwork controls rhythmic cellular processes and is composed of transcriptional regulators such as PER1-2, CRY1-2, CLOCK and BMAL1. BMAL1-deficient mice show altered ROS homeostasis impaired glutamate signal transduction as well as various signs of premature aging and cognitive deficits. However, so far little is known about the reasons for cognitive dysfunctions in BMAL1-deficient mice. As adult neurogenesis is implicated in cognitive function, we analyzed the effect of BMAL1-deficiency on neuronal stem cell proliferation and differentiation in the adult hippocampal subgranular layer. Bromodesoxyuridine (BrdU) was applied intraperitoneally to wild-type and BMAL1-/- mice. BrdU as well as neuronal (doublecortin, neuronal nuclei, NeuroD) and glial (glial fibrillary acidic protein) marker were analyzed in the subgranular layer of the dentate gyrus by immunohistochemistry. We found significantly fewer BrdU- and doublecortin-labelled cells in BMAL1-/- mice as compared to wild-type. This suggests impaired proliferation and differentiation of neuronal stem cells. Moreover, RT-Profiling array of Bmal1+/+ and Bmal1-/- hippocampal tissue showed differential expression of genes involved in cell proliferation and differentiation. Our data suggest an important role of BMAL1 in the regulation of gene expression in neural stem cells.
Pütz, V. - The effects of maternal separation on social pain processing in children in care – an fMRI study [E13]

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Introduction: Early separation (ES) experiences can disrupt the child’s attachment process and interfere with the psychosocial development of an infant. The current study therefore aims to investigate the neural mechanisms by which attachment to and early separation from the primary caregiver influences structural and functional brain development in children. Specifically, early separation experiences are hypothesized to render these children more susceptible to social exclusion and rejection, as reflected in differential activation of, and functional connectivity within the social-pain network including fronto-limbic structures.

Methods: 26 children that grew up with their biological parents (mean age 10.51 ± 1.7; mean IQ= 104.96 ± 9.5) and 25 children with an early parental separation experience (ES) (mean age 10.6 ± 1.7; mean IQ= 101.87 ± 10.6; mean age of separation= 1.3 years ± 1.08) underwent a social-exclusion paradigm (Virtual ball tossing game ‘CyberBall’, Williams, Cheung, & Choi, 2000) in a 3T-MRI scanner to investigate the neural correlates of social exclusion.

Conclusion: We observed robust differences in neural activation in response to social exclusion between the two groups. In line with previous research, the typical “pain matrix” consisting of the d/vACC, left and right insulae and rmPFC was active in control children. Interestingly, activation in the dACC, which has been implicated in signalling situations that require cognitive control was diminished in the ES group, which might suggest an abnormal pain response and reduced affective control when facing ostracism. Moreover, psychophysiological interaction analysis (PPI) revealed stronger connectivity between dACC and dlPFC during exclusion in controls as compared to ES children. ES children on the other hand displayed greater connectivity with ‘downstream’ regions such as VTA and thalamus. These results suggest abnormal social brain functioning in children with an early parental separation experience that could be mediated by impaired PFC-regulation, confirming our hypothesis that early separation has a long-lasting effect on children’s brain activation in socially relevant situations.
Quesada, A.A. - Hyperresponse to acute stress and poorer memory in former preterm children [D10]

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**Background:** Preterm birth is marked by stressful environment in intra- as well as extrauterine life. This environment can affect hormonal and physiological systems and lead to long-term negative outcomes. Despite it, little is known how early-life stress affects preterms later on in childhood. The goals of the current study were threefold: (1) comparing cortisol profile, including cortisol awakening response (CAR), between preterm and full-term children; (2) assessing their memory, behavior and emotion; (3) evaluating if preterms are more responsive to an acute stressor.

**Methods:** Basal cortisol and alpha-amylase (sAA) profiles, including CAR of thirty preterm children were evaluated. Salivary samples were measured in two consecutive days at four time points: awakening, 30 min post-awakening, 1600h and 2100h. Further, we assess memory functions by using the Wide Range Assessment of Memory and Learning and screen behavior/emotion by using Strengths and Difficulties Questionnaire. The results of preterms were compared to an age- and sex-matched control group (n = 31). One week after, the participants were exposed to Trier Social Stress Test for Children (TSST-C).

**Results:** Preterm children had higher cortisol concentrations at awakening, a flattened CAR and an exaggerated response to TSST-C compared to their full-term peers. Preterm children also showed more emotional problems and poorer memory.

**Conclusions:** Our findings illustrate the long-lasting effects of preterm birth on the HPA axis, internalizing behavior and memory. The findings are in line with the idea that early-life stress alters the set-point of the HPA axis thereby creating a more vulnerable phenotype.

**Keywords:** preterm birth, cortisol, CAR, alpha-amylase, memory, behavior, childhood.
Research on nicotine addiction indicates greater ventral striatal activity in smokers compared to non-smokers in response to smoking-associated cues but blunted reactivity to non-drug rewards (David et al., Biol Psychiatry 2005; Martin-Soelch et al., Eur J Neurosci 2003). Furthermore, the only available PET study on dopamine synthesis capacity in nicotine-dependent subjects demonstrated a substantial increase in [$^{18}$F]FDOPA uptake in the striatum in smokers compared to non-smokers (Salokangas et al., Am J Psychiatry 2000). It is completely unexplored, however, whether reward processing and dopamine metabolism change after smoking cessation.

Forty smokers and 35 non-smokers performed two paradigms on a 1.5 T MR scanner investigating reward anticipation and cue reactivity. Secondly, a subsample of 30 smokers and 15 nonsmoking subjects underwent a [$^{18}$F]FDOPA PET scan. All smokers took part in a smoking cessation course. Those smokers who succeeded in staying abstinent for at least three months underwent a second fMRI (N=16) and a second [$^{18}$F]FDOPA PET (N=13) scan.

Preliminary analyses revealed a weaker BOLD activity of the Nucleus Accumbens of smokers during the anticipation of non-smoking rewards in comparison to non-smokers. However, in response to smoking-associated pictures stronger neural responses were found in the caudate nucleus. For both paradigms no effect of smoking cessation could be detected. Preliminary analysis of the baseline PET data revealed a significant decrease in K values in the nucleus accumbens in smokers compared to non-smokers at baseline. K values were also reduced in the caudate nucleus as a whole. Analysis of the follow-up PET data is currently being performed. Together with the fMRI data, it will allow for a definite conclusion, whether the dysfunction of the reward system in nicotine-dependent smokers is long-lasting and persistent in nature.
Reckfort, J. - 3D Polarized Light Imaging – A new technique to visualize fiber pathways in the brain [E10]

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Anatomical connections of mammalian brains are typically studied with MR-based diffusion weighted imaging, tract tracing, myelin staining, or dissection techniques. However, most of these approaches suffer severe restrictions to visualize short and long distance fibers at high resolution for an entire brain.

To overcome some of these limitations, we have introduced 3D polarized light imaging (3D-PLI), a novel optical approach to map fiber pathways including fiber bundles and single nerve fibers in postmortem brains with microscopic resolution.

3D-PLI utilizes an optical property of the myelin sheath surrounding most nerve fibers, known as birefringence. It is caused by the regular arrangement of lipids and proteins in the myelin. Birefringence results in a distinct optical anisotropy, reflecting the spatial fiber architecture and orientation of nerve fibers.

Birefringence can be quantified by passing linearly polarized light through brain tissue what causes measurable local changes in the polarization state of the light. These changes serve as a direct measure of the 3D spatial orientation of the myelinated axons, which can be described by the in-plane angle (\(\phi\)) and the out-of-section angle (\(\alpha\)).

Each histological section can be characterized by a 3D vector field, visualized as a fiber orientation map (FOM). FOMs indicate the prevailing fiber orientation in each voxel. The size of a voxel or the sampling resolution, is hereby defined by the pixel size of the image and the section thickness.

The poster will show the developed measurement setup and the basic procedures used to extract fiber orientations in brain sections by means of polarized light. Fiber orientation maps for different species will demonstrate the great potential of 3D-PLI.
Röhr, D. - Reduced vitamin C uptake causes hypomyelination and sensorimotor impairments by collagen deficiencies in SVCT2+/---mice [D05]

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Vitamin C is essential for in vitro myelination of neurons by its influence on extracellular matrix (ECM) components like collagens. We investigated the role of the sodium-dependent vitamin C transporter 2 (SVCT2) for vitamin C uptake into the peripheral nervous system, since little was known about the effects of vitamin C on the peripheral nervous system in vivo.

In a heterozygous SVCT2-knockout mouse-model the amount of vitamin C, the myelination of axons and the quantity of specific collagens in the ECM in peripheral nerves was determined. The nerve conduction velocity and sensorimotor performance were analysed in functional tests, while all results were compared to those of wild-type-mice.

Real-time PCR, western-blot analyses and IHC were used to elucidate the expression of collagens and SVCT2, which were distinctly reduced in SVCT2+/---mice. Hydroxy-proline assays showed that the ECM defects were caused by transcriptional, not posttranslational effects. The myelination of axons by Schwann cells was investigated by light- and electronmicroscopy, whereby a hypomyelination with increased G-ratios was observed in peripheral nerves of SVCT2+/---mice. Functional tests like rotarod, gait analyses and hot-plate tests showed sensorimotor impairments in SVCT2+/---mice.

In conclusion this study showed that Vitamin C is essential for normal peripheral nerve myelination in vivo by induction of extracellular matrix protein expression and deposition.
Roos, A. - “Woozy” mice are a broad phenocopy of human Marinesco-Sjögren syndrome: an electron microscopic and biochemical longitudinal study [D08]

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Mutations in the human SIL1 gene and disruption of the murine Sil1 gene, both encoding the endoplasmic reticulum (ER) resident co-chaperone Sil1, were identified as a major cause of MSS and of the “woozy”-mouse phenotype, respectively. Marinesco-Sjögren syndrome (MSS) is a rare progressive multisystem disorder with autosomal recessive inheritance. The human phenotype is characterized by cerebellar ataxia, congenital or infantile cataracts, progressive vacuolar myopathy with peculiar myonuclear alterations, mental retardation, and short stature. However, in “woozy” mice, solely the cerebellar atrophy (due to a loss of Purkinje cells and resulting in ataxia) has been described so far. In both phenotypes, loss of Sil1 results in the buildup of misfolded proteins in the endoplasmic reticulum of the affected tissues, which induces a protective reaction known as the unfolded protein response (UPR).

In a longitudinal study, we investigated the vastus muscles of 16-, 26-, and 84-weeks old “woozy”-animals and of healthy wild-type littermates using electron microscopy and biochemical methods. We found marked myopathy in the mouse model, similar to the peculiar myopathic changes in human muscle and including the MSS-specific alterations of the sarcoplasmic reticulum. In the mouse model we were able to study the age-dependent manifestation of the myopathic alterations. On the biochemical level, we found a induction of the UPR in the vastus muscles of Sil-1-deficient mice. Moreover, we generated two SIL1-deficient mammalian cell lines, which serve as MSS cell culture models. In these cell lines, both electron microscopic and biochemical studies revealed changes similar to the alterations detected in the muscles of MSS patients and “woozy”mice.

Here in, we report for the first time a distinct skeletal muscle phenotype in the MSS animal model “woozy”. The muscle changes are age-dependent and are morphologically and biochemically similar to the human MSS phenotype. Our findings link MSS myopathy to disturbances in the homeostasis of the sarcoplasmic reticulum, resulting in the activation of the UPR. The “woozy”-mouse model therefore is a broad phenocopy of MSS. Our mammalian cell lines showing similar alterations confirm our results and provide a suitable in vitro model for the preclinical testing of therapeutica strategies.
N.Rosjat - Dysfunction of the thalamo-cortical loop in schizophrenia: EEG data and mathematical model [H07]

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Preceding experimental results suggest that disturbances of auditory information processing within the thalamo-cortical loop are a core issue relating schizophrenia. Wide differences between schizophrenia patients and healthy controls were found in phase-locking of cortex EEG. We derive a phenomenologically mathematical model based on coupled phase oscillators with continuous distributed frequencies to describe the neural activity of thalamo-cortical loop. At the investigation of our model we use Ott-Antonsen theory and Pikovsky-Rosenblum reduction methods. The results derived from our mathematical model coincide with the experimental data obtained by EEG measurements.
Rüßler, A. - Directed placement of insect neurons in microfluidic devices [J04]

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The investigation of neuronal networks in vitro provides insight into principles of their development, structure and function such as neurite outgrowth, synaptogenesis and plasticity. A more detailed understanding of neuronal networks necessitates the analyses of the activity of individual neurons in low-density networks as well as their synaptic connections. Multielectrode arrays (MEAs) offer the ability to investigate non-invasively network activity over an extended time period. However, the major difficulties are, first, a directed positioning of the neurons and, second, the adherence of neurons on electrode surfaces.

A new approach to overcome the problem of positioning, which usually is a random or manually-guided mechanical process, is use of closed-channel microfluidic devices. Using current flows, neurons can be trapped in defined positions, i.e. certain electrodes on a MEA. Our approach of combining microfluidics and insect cell culture as biological test system is aimed at solving the challenge of positioning of neurons.

One major problem in investigating network activity with MEAs is the weak electrical coupling between cells and electrodes. Using embedding techniques and microscopic analysis we investigate whether there are extracellular or glial sheaths surrounding neurons in cell culture which might interfere with their adherence on electrode surfaces.

In the long run the investigations will result in a microsystem consisting of a microfluidic trapping device and a MEA to establish and analyse small neuronal networks usable for basic research or as screening tool.
Declarative and non-declarative learning strategies can be applied in probabilistic classification learning tasks. Regarding the neural correlates of these strategies, earlier investigations have concentrated on the classification process itself. We investigated differences between declarative and non-declarative learners in the processing of feedback for classification performance. While participants engaged in a modified version of the Weather Prediction Task, event-related potentials (ERPs) were recorded. ERP analysis focused on two ERP components linked to the processing of performance feedback in probabilistic learning tasks, the feedback-related negativity (FRN) and the P300. While FRN amplitude was not influenced by learning strategy, P300 was more pronounced in declarative learners, predominantly at frontal electrodes. Furthermore, P300 topography differed between declarative and non-declarative learners: feedback valence was coded at frontal, but not parietal electrodes in declarative learners. These group differences were also found after declarative learners had changed to a non-declarative strategy. The results suggest different neural mechanisms of feedback processing in declarative and non-declarative learning. Prefrontally mediated processes seem to play a central role in declarative feedback processing.

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Rüther, N.N. - Representations of objects induced by observed manipulation are represented in frontal brain regions [F13]

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Object categorization requires automatic access to semantic concepts. However, the organization of concepts in the brain is still a matter of debate. Modality-specific theories propose the involvement of a large cortical network storing conceptual information depending on object-related experience during concept acquisition. For example, the mere sight of tools would elicit activation of a fronto-parietal network probably reflecting access of action-knowledge, caused by the involvement of these brain regions during tool manipulation. We investigated if access to object representations induced by observation of manipulation of previously unfamiliar tools leads to activation of a fronto-parietal brain network. Thirty-six novel, manipulable objects serving different functions were created and assigned to three different sets. To induce object representations, participants observed object manipulation of one set (OTO). Another set was visually explored by the participants (VTO) whereas a third set served as an untrained control set (NTO). Brain activity was assessed pre- and post-training by means of functional magnetic resonance imaging during completion of a matching task. Training-related changes for OTO were found in frontal regions BA 44, commonly active during sight of tools and BA 45, associated with action observation. VTO activated posterior cingulate cortex that is commonly activated in visual object recognition tasks. In summary, observation of tool-manipulation without active object-related experience leads to representations in frontal brain regions commonly associated with action observation.
Safina, D. - First evidence for low density lipoprotein receptor-related protein 1 (LRP1) function in neural stem precursor cells (NSPCs) [F08]

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LRP1 was originally described as an endocytic receptor, but novel studies revealed that it participates in signaling events, cell survival and migration in various organs including the CNS. However, The role of LRP1 in the developing CNS is still unclear, because the LRP1 gene knock-out is lethal in mice. Our recent investigations revealed that LRP1 is expressed in neural stem/progenitor cells (NSPCs), particularly in the cortical plate and ventricular zone, suggesting that LRP1 could have a regulatory function in the developing CNS.

The aim of the current work was to investigate the basic properties of LRP1 knock-out NSPCs created by means of Cre-loxp mediated recombination. The elimination of LRP1 in vitro was induced by the addition of cell permeable Cre-recombinase to NSPCs derived from embryonic brain of LRP1flox/flox mice. The functional status of LRP1-deficient cells was subsequently studied using proliferation, migration and differentiation assays.

LRP1 knock-out cells maintained as neurospheres, retained the ability to migrate and differentiate. Interestingly, LRP1 knock-out NSPCs generated 3-times less OPCs in comparison to LRP1wt/wt cells. This suggests that LRP1 is involved in the control of the oligodendroglial lineage.
Sakreida, K. - The impact of dorsolateral prefrontal cortex in the control of heart rate variability investigated by transcranial magnetic stimulation [E09]

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The central autonomic network serves as an integral component of an internal regulation system through which the brain controls visceromotor, neuroendocrine, pain, and behavioral responses essential for survival. It includes several predominantly subcortical brain structures, but also medial prefrontal and insular cortex. There is also direct and indirect evidence on the impact of the dorsolateral prefrontal cortex (DLPFC) in central autonomic functions as it integrates sensorimotor input information and anticipations, and thus, regulates behavioural outcome. Moreover, behavioural inhibition is suggested to be a core function of DLPFC. The aim of this study is to provide evidence on effects in heart rate variability by manipulating the cortical excitability of the DLPFC. For that reason neuro-navigated repetitive low frequency transcranial magnetic stimulation will be applied over left and right DLPFC as well as left and right primary motor cortex as control areas. Electrocardiogram will be recorded before, during, and after stimulation. On the poster we will present very first pilot data. Certainly, this study will contribute to a better understanding of autonomic functions and the relationship to the frontal cortex.
The transcription factor AP-2β (TFAP2β) has been shown to impact clinical and neuropsychological properties. Apparently, it regulates the transcription of genes that code for molecules which are part of the catecholaminergic transmission system. This investigation focuses on possible effects of the TFAP2β intron-2 polymorphism on cognitive performance parameters.

This hypothesis-driven investigation examined the effects and interactions of the TFAP2β intron-2 polymorphism, the Val158Met catechol-O-methyltransferase (COMT) polymorphism, and the VNTR-polymorphism of monoamine oxidase A (MAOA) on cognitive performance parameters within a group of 200 healthy women (age: mean, 23.93; SD, 3.33).

The AP-2β polymorphism significantly influenced cognitive performance (in particular, the TMT-B), whereas the MAOA and COMT polymorphisms did not. However, there was an interaction effect of the AP-2β×MAOA×COMT genotypes on the decision bias of the dsCPT. Only the Val158Met COMT polymorphism showed an influence on personality questionnaires (Openness and self-transcendence; NEO-FFI, TCI).

The TFAP2β intron-2 polymorphism had more influence on cognition than the MAOA and COMT polymorphisms did. Possibly, the AP-2β genotype might influence cognition through pathways other than those that regulate MAOA and COMT transcription. Interactions of TFAP2β, COMT, and MAOA polymorphisms suggest higher leverage effects of TFAP2β in subjects with high dopamine availability.
Schelenz, P - Serotonin effects on supramodal emotion integration: a combined fMRI-EEG study [J02]

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Congruency of facial expressions and emotional prosody facilitate integration and recognition of audiovisual social impressions. Posterior cingulate cortex and amygdala were suggested as central hubs for the multisensory integration of emotions information. Serotonin (5-HT) is involved in neural systems underlyng the recognition of emotional faces and other emotion processes.

fMRI and EEG were acquired simultaneously during an recognition task from emotional prosody or facial expression as well as congruent and incongruent combination of them. The influence of 5-HT on the integration of the audiovisual signals was investigated in a double-blind, placebo-controlled, cross-over design with three conditions: 1. increase of post-synaptic 5-HT with the selective serotonin reuptake inhibitor (SSRI) escitalopram; 2. reduction of pre-synaptic 5-HT with acute tryptophan depletion (ATD); and a 3. placebo control.

Analysis with respect to modality and congruency confirmed previous findings and established the experimental design as robust. EEG revealed a late positivity reflecting the cognitive integration during congruent stimulation. Differential pharmacological effects will be analysed after unblinding when the study is completed.

We suggest pharmaco-fMRI-EEG as method to disentangle the role of neural transmitters in specific neural networks.
Schönfeld, F. - Sensory Integration of Place and Head-Direction Cells in a Virtual Environment [H06]

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While navigating novel environments, the rodent hippocampus quickly establishes distinct firing patterns linked to a spatial representation of the animal's immediate surroundings. The responsible cells for doing so are known as place cells, grid cells, and head direction cells; their signaling behavior has been examined in great detail under various conditions over the last years. Our project aims at presenting and verifying a theoretical model which is able to extract similar signals from artificially produced realistic visual input. More specifically, we employ the theoretical slowness principle to extract slowly changing signals from complex, high dimensional input generated by our software. The respectively used algorithm is known as Slow Feature Analysis (SFA), and when employed in a multi-layered hierarchical network structure has already been shown to be able to extract signals from realistic input that approximate the firing behavior of place, grid, and head direction cells without any predefined disposition to navigation.

The current phase of the project is the theoretical half of a joint venture with a neurophysiology laboratory where a virtual environment setup is being used to mirror our simulation experiments with real animals. This enables us to directly compare the results of our simulations with the recordings of cells of live animals traversing the very same environments used in our network hierarchy. Furthermore, by employing virtual reality techniques, we have a unusually high degree of control over the visual input given to the rodent during the experiments. We plan to use this to manipulate the animal's experience in unique ways we can replicate in our computer simulations in order to verify predictions arising from our work with the mathematical theory behind Slow Feature Analysis. In its current iteration our software framework allows us to easily set up a large variety of different virtual environments, as well as offering a concise set of parameters to define the behavior of a virtual rodent navigating in the chosen environment. Based only on the visual data generated by such an experiment, a hierarchical SFA network is able to extract a distinct and rotation invariant place code and/or a translation invariant set of directional signals with clear preferred firing directions.
Individuals with autism spectrum disorder (ASD) often fail to attach context to their memories and are specifically impaired in processing social aspects of contextual information. We investigated the modulatory influence of social vs. non-social context on neural mechanisms during encoding in ASD. Using event-related fMRI, 13 boys with ASD and 13 typically developing boys comparable for age and IQ were investigated during encoding of neutral objects presented either with a social (faces) or a non-social (houses) context. A subsequent memory task was then applied to identify brain activation patterns associated with successful encoding of recollected versus non-recollected objects. On the behavioural level, no significant between-group differences emerged. However, ASD subjects (compared to controls) showed reduced neural activation in the bilateral inferior frontal gyrus, bilateral middle frontal gyrus and right inferior parietal lobule during encoding of subsequently recollected objects presented with a face. Neural activation in the right inferior frontal gyrus was positively correlated with memory performance in controls, but negatively in ASD individuals. During encoding of subsequently non-recollected objects presented in the non-social context, ASD subjects showed increased activation in the dorsal MPFC.

Our findings suggest that in ASD subjects, fronto-parietal brain regions subserving memory formation and the association of contextual information are activated atypically when a social context is presented at encoding. Increased activation in the dorsal MPFC in ASD individuals might reflect supervisory cognitive processes related to the suppression of a distracting non-social context.
Background: Cognitive impairments are frequent findings in chronic kidney disease (CKD). The factors contributing to neuropsychological deficits were largely unknown. It has been hypothesized that vascular risk factors contribute to the manifestation of cognitive deficits.

Methods: In a prospective study of 119 subjects with CKD stages 3-5 (61.5±15.7 years; 63% men) and 54 control subjects with the same age and very similar vascular risk profile, we evaluated links of risk factors and markers of inflammation and atherosclerosis with neuropsychological deficits using tests for memory (digit and block span), information processing speed (trail-making test-A), executive flexibility and interference (trail-making test-B, Stroop), language (lexical and semantical word fluency) and visuo-constructive function (Rey-Osterrieth complex figure), in addition to depression and anxiety (hospital anxiety and depression scale).

Results: Arterial hypertension (94.9%), dyslipidemia (79.8%) and diabetes (38.5%) were highly prevalent in CKD patients. Mean eGFR was 28.2±17.6 ml/min/1.73m², compared with 70.9±9.6 ml/min/1.73m² in controls. 30.3% of CKD subjects revealed cognitive impairments, exhibiting a performance more than one standard deviation below control subjects. Linear regressions (backward method) showed that the factors age ($\beta=-0.54; p<0.001$), HbA1c ($\beta=-0.21; p=0.006$) and fibrinogen ($\beta=-0.16; p=0.038$) were predictors of cognitive performance.

Conclusions: The predictive value of HbA1c and fibrinogen points towards a role of diabetes and inflammation in the development of cognitive deficits in CKD.
Sirin, S - High resolution MRI in the assessment of tumor extension in children with retinoblastoma [F01]


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Background: The aim of this retrospective study (02/2007-05/2012) was to assess the ability of high resolution MRI (HR-MRI) in the evaluation of tumor extension in 170 children with retinoblastoma.

Methods: HR-MRI (voxel size < 0.5x0.5x2 mm) was performed on 1.5T scanners using a head coil and one (118 patients/121 enucleated eyes) or two (52 patients/55 enucleated eyes) orbit surface coils. A standardized examination protocol was applied, with adjusted parameters/sequences over time. Image analysis was performed by two neuroradiologists in consensus blinded to histopathology, statistical analysis by cross-classified tables. Histology served as gold standard.

Results: HR-MRI and histopathological analysis were available in all patients (176 enucleated eyes, mean age 20.0 months, 73 girls, 97 boys). 145 of the 160 eyes with histopathologically proven exclusively intraocular disease were correctly identified by MRI (6 false positive, sensitivity 0.91, specificity 0.63). By improved sequences, new MR scanners and the use of two additional orbit coils, the identification of patients with exclusively intraocular disease increased (49/51, 1 false positive, sensitivity 0.96, specificity 0.75).

Conclusion: High resolution MRI, especially using two orbit surface coils, adapted sequences and newer MR scanner, is a promising tool in the assessment of tumor extension in children with retinoblastoma and should be used for staging.
Sirin, S. - Evaluation of 100 brain examinations using a 3 Tesla MR-compatible incubator - safety, handling and image quality [F04]

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Background: Brain imaging in infants is important. Aim of this retrospective study: to review safety, handling and image quality of MR brain imaging using a new 3 Tesla MR-compatible incubator.

Methods: 100 brain examinations (84 infants, mean gestational age (GA) 32.2±4.7 weeks, mean postmenstrual age (PMA) at imaging 40.6±3.4 weeks) were performed using a 3 Tesla MR-compatible incubator with compatible head coil (02/2011-05/2012). 17 examinations (13 infants, mean GA 35.1±5.4 weeks, mean PMA at imaging 47.8±7.4 weeks) using a standard head coil served as a control. Image analysis was performed by a pediatric radiologist and a neuroradiologist in consensus, statistical analysis using Mann-Whitney U-test.

Results: All but two patients with known apnea were transferred to the MR unit and scanned without problems. Handling was easier and faster with the use of the incubator, need of a repetitive sedation (43.0% vs. 86.7%) and relevant motion artifacts (5.9% vs. 10.8%) were reduced by half. In the absence of motion artifacts, image quality (4.8±0.4 vs. 4.3±0.8, p=0.047) and spatial resolution (4.7±0.4 vs. 4.2±0.6, p=0.011) of T2-weighted images were scored significantly higher in patients imaged with the incubator, SNR increased significantly (171.6±54.5 vs. 80.5±19.8, p<0.001).

Conclusions: Infants can benefit from the use of a 3 Tesla MR-compatible incubator because of its safety, its easier and faster handling and its possibility to obtain high quality MR images even in unstable patients.
Stefanescu, M.R. - A 7T fMRI study of cerebellar activation in sequential finger movement tasks [J05]

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Finger movements are accompanied by activation of specific parts of the superior [lobules (L.) V and VI] and inferior (L. VIII) cerebellum. Within the dentate nucleus, finger movements lead to activations primarily of its dorsorostral part. We were interested in whether or not sequencing demands of the movements are related to the degree of cerebellar and dentate nuclei activation. Nineteen right-handed, healthy participants (mean age 26 years, range 22-33; 10 males) performed three tapping tasks. Tasks involved repetitive tapping of the same sequence ("predictive"), tapping of a random sequence ("non-predictive") and tapping with one finger at a time ("single finger"). Each condition involved the same number of tapping movements of fingers II-V. Scanning was performed using ultra-high-field 7T functional magnetic resonance imaging (fMRI) and analysis with SPM8. Activation was significantly increased in the cerebellar cortex (L. IV/V, VI; but not VIII) ipsilaterally in the non-predictive condition compared to the predictive and the single finger condition. There was no significant difference between the single and predictive condition. Likewise, activation of the dorsorostral dentate was increased in the non-predictive compared to the other conditions. Because finger movements were predictable in the easy sequence and control tasks but not the random sequence condition, increased cerebellar activation in the latter likely reflects increasing motor planning demands of the task.

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Steinberg, F. - Influence of age, cognition and dual-tasking on grasping performance in different behavioural contexts [108]

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It has been documented before that grasping movements in everyday life differ in various aspects from those studied in typical laboratory settings. This context-dependence can’t be traced back to a single underlying cause, since factor analyses yielded multiple orthogonal factors. Here we present three experiments, designed to find out whether context-dependence is modulated by individual personality traits, is modified in old age, and is affected by dual tasking. Subjects performed one and the same grasping movement once in a laboratory context (L: externally triggered and purposeless) and once embedded in an everyday-like context (E: volitional and purposive). We registered a wide range of kinematic, force and gaze parameters, and analysed their means and coefficients of variation. In the first experiment, subjects additionally completed a personality questionnaire, in the second, older people were compared with younger ones, and in the third, a concurrent memory task was administered. We confirmed in all three experiments that L and E differ in a wide range of parameters. In the first experiment, significant correlations were observed between the magnitude of context-dependence and that of a personality trait representing impulsivity versus self-control. The second experiment showed that E was more affected by old age than L, and the third that it was more affected by dual-task interference than L. We conclude that higher mental functions – including those affected by old age – influence grasping in an everyday-like context more than in a laboratory context. A practical implication is that laboratory-based studies may underestimate grasping deficits in older people’s everyday activities.
Stemmler, T. - Is the pupil light reflex transient or sustained encoded? [I09]

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In humans, non-human primates and birds (as the barn owl for an example) a brief flash of light results in a brisk pupilloconstriction in the eyes. Under sustained light condition an additional sustained pupilloconstriction will be obtained. However it is still unclear, if the visual information is integrated over time or is passed directly to the pretectal area. We investigated this via temporal segregation of visual stimuli on a fast CRT Screen (200 Hz). Participants viewed simultaneously two brisk stimuli (natural scenes, one containing an animal), which can either be presented in one frame (5 ms) or evenly distributed on a pixel by pixel bases on up to 3 frames (15 ms). Overall photopic emission of the screen was constant. Participants were instructed to pay attention to the stimuli and had to detect if an animal was present and answer with a saccade towards the animal or had to move a joystick to the corresponding position. Pupil diameter and position were tracked with a video based eye tracker. Preliminary findings will be presented.
Strasser, K. - Hyperoxia changes the balance of the thioredoxin/peroxiredoxin system in the neonatal rat brain [A11]


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Background / Aim: As demonstrated previously, oxygen contributes to the pathogenesis of neonatal brain damage and leading to neurocognitive impairment of prematurely born infants in later life. Reactive oxygen species (ROS) and intrinsic antioxidant defense systems play an important role in both physiological cell signaling processes and many pathological conditions, including neurodegenerative disorders and oxygen-toxicity. Beside the glutathione-system several other redox-modulating proteins are known to be involved in redox-homeostases. The aim of this study was to evaluate potential alterations within the thioredoxin/peroxiredoxin system after exposures to nonphysiologic high oxygen levels in the developing rat brain.

Methods: Six-days old Wistar rats were exposed to 80% oxygen for 6, 12, 24 or 48 hours and littermates kept in room air served as controls (n=6-8). Brains (excluding cerebellum) were evaluated after perfusion with PBS and dissection of both hemispheres for RNA and protein analyses.

Results: We demonstrate that elevated oxygen concentrations change the balance of the ROS-dependent thioredoxin/peroxiredoxin system. Oxygen-toxicity significantly induced upregulation of peroxiredoxins in infant rat brain. In parallel, hyperoxia reduced the level of DJ-1, a hydroperoxide-responsive protein.

Discussion: These findings are highly relevant from a clinical aspect because oxygen administration to neonates is often inevitable, and we recommend that every effort should be made in neonatal medicine to limit exposure of these young patients to high oxygen concentrations. These results may also contribute to receive optimal therapeutical approaches to ameliorate oxygen toxicity.
Syed, A.S. - The Amphibian Olfactome [D01]

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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 repertoires 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 type 1 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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Tan, S.K.H. - The effects of high frequency stimulation of the subthalamic nucleus on mood: a role for the lateral habenula? [C02]

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Objective: High frequency stimulation (HFS) of the subthalamic nucleus (STN) improves motor disability in Parkinson’s disease. A number of patients develop post-operative behavioural complications, including depression. Our previous studies suggested a serotonin (5-HT) dependent mechanism. We hypothesize the lateral habenula (LH) to be an important structure in STN HFS induced 5-HT dependent behavioural side effects. In this study we investigated the role of the LH in STN HFS induced changes in mood.

Method: Naïve male Sprague-Dawley rats (n=40) were implanted with bilateral STN stimulation electrodes (STN HFS or sham HFS) and treated with bilateral LH injections (quinolinic acid lesions or vehicle injections). The rats were divided in the following groups: 1) Sham HFS + LH vehicle injected controls (n=10); 2) STN HFS + LH vehicle injections (n=10); 3) Sham HFS + LH quinolinic acid lesions (n=10) and 4) STN HFS + LH quinolinic acid lesions (n=10). Stimulation was performed with clinical relevant parameters (130Hz, 60μs, 100μA). Sham HFS animals received STN electrode implantations but were not stimulated. Motor, anxiety and mood related behaviour was assessed.
Theysohn, N. - Sex differences in aversive visceral learning: Enhanced reactivation of classically conditioned fear memories in healthy women [B12]

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Background: Sex differences in associative learning and memory processes have not been studied in the context of visceral pain. In a fear conditioning model with rectal pain as unconditioned stimuli, we assessed sex differences in the behavioral and neural processes mediating aversive visceral learning, extinction and reinstatement.

Methods: In volunteers (N = 15 males, 15 females), visual conditioned stimuli (CS+) were paired with painful rectal distensions as unconditioned stimuli (US), while different visual stimuli (CS-) were presented without US. During extinction, all CSs were presented without US, whereas during reinstatement, a single, unpaired US was presented. Males and females were compared with respect to conditioned anticipatory neural activation (CS+ > CS-) along with perceived CS-US contingency and CS unpleasantness.

Results: Pain ratings and distension-induced neural activity were comparable. No sex differences were observed in perceived CS-US contingency, CS+ valence ratings or cortisol. However, in the late acquisition phase, presentation of the CS+ led to significantly greater anticipatory activation of the Insula in women. During extinction, women showed reduced anticipatory activation of the PCC compared to males. During reinstatement, the CS+ led to significantly greater activation of the Hippocampus, Thalamus and Cerebellum in women.

Conclusions: This is the first study to support sex differences in processes of aversive visceral learning and memory. The enhanced neural responses in key brain areas for memory suggest reactivation of a fear memory trace in women. This could play a role in the female preponderance of chronic abdominal pain syndromes.
Theories of lateralized cognitive functions in the human brain propose (for right-handers) a dominance of the left hemisphere for motor control and language, and a dominance of the right hemisphere for attention. Accordingly, neglect is more frequently observed after right-hemispheric stroke, while apraxia and aphasia are a common sequela of left-hemispheric stroke. However, there are also – often neglected - clinical reports of attentional deficits after left hemisphere stroke. To elucidate the neural basis of such atypically lateralized attentional deficits, we here assessed - for the first time - the relationship of inattention and apraxia in chronic left-hemisphere stroke using behavioural and lesion analyses.

Attention and apraxic deficits were each characterized by five neuropsychological tests. Voxel-based lesion-symptom mapping (VLSM) was performed on the basis of clinical imaging.

Apraxic deficits were observed in 46.5% of the patients with chronic left-hemisphere stroke (n= 71). The prevalence of inattention (lateralized and non-lateralized inattention combined) was 18.3%. Interestingly, the severity of attentional and apraxic deficits did not correlate.

Apraxic imitation and object use deficits were significantly associated with left parietal and temporal lesions, respectively. The severity of attentional deficits was related to lesions in vicinity of the left intraparietal sulcus (IPS). Attentional deficits after chronic left-hemisphere stroke are hence more prevalent as commonly assumed, dissociate from apraxic deficits, and are associated with lesions of the left posterior parietal cortex. These findings challenge theories of strictly lateralized attentional functions in the human brain.
Volckmar, A. L. - A novel rare non-synonymous, non-conservative mutation in the SH2B1 gene exclusively detected in overweight or obese individuals [H01]


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The SH2B1 gene (Src-homology 2B adaptor protein 1 gene) is a solid candidate gene for obesity. Large scale GWAS studies depicted markers in near the gene; animal models suggest a potential relevance for human body weight regulation.

We performed a mutation screen (dHPLC) in the SH2B1 coding sequence in 95 extremely obese children and adolescents. Detected variants were genotyped in independent childhood and adult study groups (up to 11,406 obese or overweight individuals and 4,568 controls). Functional implications on leptin mediated STAT3 signaling of the detected variants were analyzed in vitro.

We identified two new rare mutations and five known SNPs (rs147094247, rs7498665, rs60604881, rs62037368 and rs62037369) in SH2B1. Mutation g.9483C/T leads to a non-synonymous, non-conservative exchange in the beta (βThr656Ile) and gamma (γPro674Ser) splice variants of SH2B1. It was additionally detected in two of 11,206 (extremely) obese or overweight individuals, but not in 4,506 population-based normal-weight or lean controls. The non-coding mutation g.10182C/A at the 3' end of SH2B1 was only detected in obese individuals, functional implications are unlikely. For the non-synonymous SNP rs7498665 (Thr484Ala) we observed nominal association of the G risk allele in 705 obesity trios (nominal p= 0.009, OR=1.23) and in 359 cases compared to 429 controls (nominal p=0.042, OR=1.23). The obesity risk-alleles at Thr484Ala and βThr656Ile/γPro674Ser had no effect on STAT3 mediated leptin receptor signaling in splice variants β and γ.

The rare coding mutation βThr656Ile/γPro674Ser in SH2B1 was exclusively detected in overweight or obese individuals. Functional analyzes did not reveal impairments in leptin signaling for the mutated SH2B1.
Vorwerk, J. - Validation and Application of Realistic Head Modelling to MEG [A06]

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While realistic head modelling is nowadays frequently applied in EEG source analysis, it is only rarely used in the evaluation of MEG measurements. One reason is the lower dependency of MEG signals on the volume conductor geometry. A simultaneous evaluation of EEG and MEG is highly desirable for an accurate source reconstruction when considering the complementary strengths of these two modalities, e.g., their sensitivity to different source orientations. When aiming at a symmetric data fusion of EEG and MEG recordings, it is necessary to simulate the magnetic field of neural sources as exact as possible. Thus, the influence of the head geometry on the magnetic field evoked by the volume currents, the so-called secondary magnetic field, should be taken into account by using realistic head models. This demands the application of numerical approaches.

Therefore, we investigated the accuracy of different finite element (FE) approaches to the forward problem of MEG and the influence of realistic head modelling. Accuracy investigations were carried out in different scenarios. First, we investigated the accuracy of the numerical solutions in sphere models using an artificial sensor configuration. Subsequently, we extended our study to realistic head models, investigating the influence of a detailed simulation of secondary magnetic fields in realistic scenarios. Using an analytical solution as reference, we show that all tested FE approaches achieve a high accuracy in sphere models for both realistic and artificial sensor configurations. Furthermore, our results indicate that realistic head modelling has a non-negligible contribution for realistic sensor configurations, especially when aiming at a symmetric data fusion of EEG and MEG.
Wachsmuth, L. - Bimodal Detection of neuronal activity with BOLD-fMRI and optical Ca2+-recordings [E04]

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Background: BOLD fMRI is a widely used method for noninvasive detection of brain activity. Neuronal activity leads indirectly to a local increase in blood flow, blood oxygenation and blood volume. The process of neurovascular coupling is still not fully understood since it is both, temporally and spatially complex.

Objective: Combine optical Ca2+ recordings with BOLD fMRI to allow for simultaneous assessment of local neural activity on a sub-millisecond temporal scale and indirect assessment of global brain activity.

Method: We established a custom-built bimodal setup by combining Ca2+ recordings and fMRI on a 9.4 T small animal scanner.

Results: Ca2+ recordings are not perturbed by the magnetic field. We were able to correlate spatio-temporally precisely short-latency neuronal with the long-latency BOLD response in rats upon electric forepaw stimulation. In our Ca2+ recordings, we found fast-adapting short latency neuronal responses, not depending on the total duration of the stimulation train, in sharp contrast to the prolonged BOLD response, indicating that non-adapting subthreshold synaptic potentials represent the predominant contribution to the BOLD response. Furthermore, we identified a subsequent secondary neuronal population response, related to brain state changes, not being reflected in BOLD contrast.

Conclusion: Ca2+-fMRI allows for the causal determination of the impact of defined neuronal- and non-neuronal cell populations to local and global brain activity.
Wagner, S. - Investigation of tDCS/tACS volume conduction effects in a highly realistic head model [G10]

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Transcranial direct and alternating current stimulation (tDCS/tACS) are non-invasive and inexpensive brain stimulation techniques. Despite of the recent progress, the knowledge about the underlying mechanisms behind tDCS is still limited. In order to gain deep insight in the sophisticated interplay of stimulation, volume conduction and resulting cortical current density distribution, we follow an step-by-step approach. We start with a homogenized isotropic three compartment (skin, skull, brain) head model, where results are still rather obvious. In each consecutive step, we then extent our head model by one additional effect, which is either a tissue layer or an anisotropic instead of a homogenized isotropic compartment. For each additional effect, the resulting changes in the current density distribution are deeply investigated. Our most realistic volume conductor contains six compartments and brain anisotropy.

Major findings of our study include (1) channeling effects of the skin, the skull spongiosa and the CSF compartments; (2) current vectors in lower-conducting regions tend to be oriented towards the closest higher conducting region; (3) anisotropic white matter conductivity causes current flow in directions more parallel to the white matter fiber tracts; (4) highest cortical current magnitudes are not only found close to the stimulation sides; (5) the median brain current density decreases with increasing distance to the electrodes.

We will show that an accurate modeling of the volume conduction effects using highly-realistic multi-compartment anisotropic head models is important for the understanding of tDCS and the guidance of its application in experiments.

Literature
Wolf, D. - Pharmacological imaging of the serotonergic system during violent video game playing - a single subject study [C12]

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Aggressive behavior occurs in various psychological disorders and constitutes a major social problem. Pathological aggression is associated with a dysfunctional neuronal circuit including prefrontal cortex (PFC) regions and amygdala [1]. Current research suggests that neural correlates of violent behavior manifest in dysregulated amygdala activity due to dysfunctional top-down control exerted by PFC regions which may be mediated by serotonin (5-HT) signaling [2]. We wanted to investigate the feasibility of a virtual reality model to study 5-HT modulation on the aggression network in the human. Functional magnetic resonance imaging (fMRI) assessed responses of the PFC-ACC-amygdala network to virtual violence in a double-blind, placebo controlled, repeated measures design with three conditions: 1. increase of presynaptic 5-HT with a selective serotonin reuptake inhibitor (escitalopram; Cipralex®); 2. reduction of 5-HT with tryptophan depletion; and 3. placebo control.

Violence specific deactivation of prefrontal regions and amygdala as well as enhanced connectivity between these areas corroborated previous studies. Both SSRI and tryptophan depletion led to a stronger violence-related deactivation of dorsal ACC. Moreover, functional and directed connectivity to the amygdala was increased in orbitofrontal and ventromedial PFC but no behavioral changes emerged.

The presented design, model and data analysis is conceivably well suited to investigate serotonergic modulation of the aggression network during virtual violence. The design can be employed to study drug effects on neural regulation even before the presence of behavioral effects.

References
Allgemeine Informationen

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