BASIC RESEARCH ANIMAL

ID: 102
Free contribution (poster and short talk)
Topics: Basic Research Animal

Rho-kinase Involvement in Ocular Fibrosis

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Background: Ocular fibrosis, such as subretinal fibrosis in age-related macular degeneration (AMD), fibrovascular membranes in diabetic retinopathy (DR), proliferative vitreoretinopathy (PVR) and epiretinal membranes (ERM) are limiting the long-term visual prognosis of affected patients. To date, limited successful treatment for ocular scarring exists. We aim to investigate the impact of anti-fibrotic compounds on ocular fibrosis. Therefore, we first established a time-dependent animal model of subretinal fibrosis and investigated the effect of rho-kinase (ROCK) isoform-specific inhibitors on ocular fibrosis. We obtained surgically excised human PVR and epiretinal membranes (ERM). Various groups have shown that the rho-associated coiled-coil–containing protein kinase (ROCK) pathway is involved in PVR pathogenesis; however, the presence of rho-kinase in human PVR membranes has not yet been demonstrated.
Methods: We conducted two research projects to test our hypothesis.
P1. To induce CNV-related fibrosis, we used a 532-nm laser inserted in a slit-lamp delivery system. After the development of fibrosis on day 35, C57BL/6 mice were treated intraperitoneally every day with fasudil or belosumodil for two weeks. We performed optical coherence tomography (OCT), autofluorescence and fluorescence angiography every week after laser injury (d7,14,21,28,35,42,49, n=6 mice per timepoint) to document fibrotic changes over time. In addition, we screened choroidal flat mounts and eye sections for CNV and fibrosis.
P2. Membranes were obtained during vitreoretinal surgery from 6 patients' eyes with proliferative vitreoretinopathy (PVR) and 12 eyes with epiretinal membranes (ERM). Immunohistochemistry staining for hematoxylin and eosin, collagen 1, alpha-smooth muscle actin (a-SMA) and rho-kinase isoforms (ROCK1 and ROCK2) were performed. Additionally, RT-PCR was conducted to determine ROCK isoform gene expression levels.
Results: From day 21 to day 49 after laser injury of mice eyes the CNV and leakage decreased and the subretinal fibrosis increased in OCT and fluorescence angiography. The expression of collagen 1 in lesions of choroidal flat mounts increased, whereas isolectin B decreased. After treatment, the volume of fibrosis decreased, and both ROCK inhibitors substantially reduced subretinal fibrosis in vivo. In addition, both ROCK isoforms were detected in PVR and ERM membranes. Conclusion: The current results indicate that rho-kinase might play a role in ocular fibrosis.

ID: 103
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: anterior cingulate cortex, aversive learning, dopamine, long term potentiation

Aversion learning mediated by dopaminergic neurotransmission in the anterior cingulate cortex

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Synaptic plasticity is instrumental for cognitive functions. Moreover, cortical plasticity rules can be influenced by neuromodulatory inputs. The anterior cingulate cortex (ACC) is a brain region involved in error detection, pain processing and aversive learning. The ACC is highly regulated by dopaminergic inputs, mainly from the ventral tegmental area (VTA). However, the relationship between synaptic plasticity and the role of dopamine (DA) in the ACC in the context of aversive learning has not yet been characterized.

We found that chemogenetic inhibition of ACC neuronal activity suppressed aversive learning. Likewise, silencing ACC inputs from the VTA impaired aversive learning. Moreover, at a cellular level, our results demonstrate that at L5 pyramidal neurons in the ACC, DA facilitates plasticity at electrically-evoked proximal, but not distal, synapses in an NMDAR-mediated, dopamine-1-receptor dependent manner. These results suggest that DA contributes to strengthen synaptic connections of ACC L5 pyramidal neurons, a mechanism that in vivo is partly mediated by VTA inputs underlying aversive learning.

ID: 104
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: Chronic pain, nociception, sensory processing, cingulate cortex, mice.

Principles of Nociception in the Anterior Cingulate Cortex

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The perception of pain is a multidimensional sensory and emotional/affective experience arising from distributed brain activity. However, the involved brain regions are not specific for pain. Thus, how the cortex distinguishes nociception from other aversive and salient sensory stimuli remains elusive. Additionally, the resulting consequences of chronic neuropathic pain on sensory processing have not been characterized. Using *in vivo* multi- and single-photon calcium imaging with cellular resolution in mice, we elucidated the principles of nociceptive and sensory coding in the anterior cingulate cortex (ACC), a region essential for pain processing. We found that population activity, not single cell responses, allowed discriminating nociceptive stimuli and associated behavioral responses, ruling out the existence of nociception-specific neurons. Additionally, single-cell stimulus selectivity was highly dynamic over time, but stimulus representation at the population level remained stable. Peripheral nerve injury-induced chronic neuropathic pain led to dysfunctional decoding of sensory events by exacerbation of saliency-detection and impairment of pattern separation and stimulus classification, which were restored by analgesic treatment. These findings provide a novel interpretation for altered cortical sensory processing in chronic neuropathic pain and shed light onto the effects of systemic analgesic treatment in the cortex

ID: 106
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: autoimmune neuroinflammation, multiple sclerosis, angiopoietin-2, immune cell recruitment

Role of the angiogenic factor Angiopoietin-2 in monocyte-derived macrophage recruitment into the healthy and inflamed central nervous system

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In multiple sclerosis (MS) infiltrating monocyte-derived macrophages are the predominant inflammatory cells within central nervous system (CNS) lesions and significantly contribute to disease severity and outcome. Studies in MS patients and its animal model experimental autoimmune encephalomyelitis (EAE) have shown elevated levels of the endothelial angiogenic factor angiopoietin-2 (Ang-2) in the blood and CNS while antibody mediated blocking of Ang-2 was shown to ameliorate EAE. The present study therefore aims to specifically decipher the role of endothelial Ang-2 in monocyte-derived macrophage migration across the blood-brain-barrier (BBB) into the CNS in neuroinflammation. To this end we have established a transgenic mouse model with endothelial cell-specific and inducible overexpression of human Ang-2 crossed into the *CX3CR1*$^{+/GFP}$*/CCR2*$^{+/RFP}$ myeloid cell reporter mouse. This allows us to distinguish the role of endothelial overexpressed Ang-2 on GFP+ CNS-resident myeloid cells versus CNS infiltrating RFP+ monocyte-derived macrophages during steady state and EAE. We observed that endothelial overexpression of Ang-2 increased the number of CCR2+ macrophages but also of CD3+ T lymphocytes in the brain of male but not of female mice at steady state. Immunofluorescence analysis of CNS cryosections revealed that those immune cell infiltrates were however confined to the laminin+ leptomeningeal compartment while the CNS parenchyma was devoid of CCR2+ macrophages and CD3+ T cells. Studying EAE development with endothelial Ang-2 overexpression led to the surprising observation that male but not female transgenic mice presented with an ameliorated disease course. Our present data therefore suggests sex-specific effects of endothelial Ang-2 in neuroinflammation potentially mediated by differential regulation of myeloid cell recruitment to the CNS.

ID: 107
Free contribution (poster and short talk)
Topics: Basic Research Animal

Intracellular activity of cortical pyramidal neurons across the wake-sleep cycle

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Sleep is a rapid reversible behavioural state and an essential biological need for higher vertebrates. Amassing experimental evidence implicate sleep-wake promoting and oscillatory networks in the control of sleep-wake states and ultimately sleep-dependent functions, including synaptic plasticity and memory refinement. Yet, the precise synaptic and subcellular mechanisms occurring during sleep, in particular rapid-eye movement sleep (REMS), remains unclear. Here, we recorded cortical neurons across the wake-sleep cycle using in vivo whole-cell patch-clamp recordings in head-fixed and naturally sleeping mice. We found that the intracellular activity of L2/3 pyramidal neurons from prefrontal (PFC) and retrosplenial (RSP) cortices remarkably differed between wakefulness, REMS and non-REMS (NREMS), likely resulting from alterations in intrinsic excitability, synaptic activities and local excitation/inhibition balance. Indeed, the membrane potential (Vm) recorded during NREMS showed a biphasic slow oscillation (~2 Hz) between DOWN (~ -65 mV) and UP (~ 45 mV) states and was similar between PFC and RSP. On the other hand, the recorded Vm during REMS was remarkably different between cortical regions, with PFC being defined by a fast and low amplitude fluctuation and RSP by a long-lasting somatic depolarization. Collectively, our results are consistent with previous studies and suggest that the excitability of cortical neurons during NREMS and REMS at either postsynaptic and somatic level might provide a mechanism for sleep-dependent synaptic plasticity essential to the optimization of behaviour.

ID: 109
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: anxiety, fear, ventral hippocampus, interneurons

Functional dissociation of ventral hippocampal inhibitory circuits during anxiety and fear behaviors

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The ability to predict potentially harmful environments and escape from dangerous circumstances is vital for wildlife. Mounting evidence suggests that while the dorsal subdivision of the hippocampus is associated with spatial and episodic memory formation, the ventral hippocampus is mostly involved in emotional behaviors. However, the neural circuits and mechanisms within the ventral hippocampus underlying innate or learned emotional behaviors are poorly understood. In the present work, we investigated whether anxiety and conditioned fear are represented by distinct ventral CA1 (vCA1) neural circuits. By utilizing cell-type-specific expression of calcium indicator GCaMPs and in vivo calcium imaging in freely behaving mice via miniature fluorescence microscope, we monitored the neuronal activity of vCA1 pyramidal cells and three sub-classes of GABAergic interneurons (PV+, VIP+, and Sst+) during innate anxiety and conditioned fear behaviors. Our data indicated that vCA1 pyramidal cells and interneurons have distinct activity patterns during anxiety and fear behaviors. Different subpopulations of vCA1 pyramidal cells showed preferential responses to either anxiogenic experiences or fear-conditioned cues. The majority of PV+ interneurons were recruited during anxiety behavior but barely during a cued fear test. By contrast, about half of VIP+ interneurons were involved in conditioned fear learning but not in anxiety behaviors, while Sst+ interneurons displayed inhibition during fear learning, suggesting that an inhibitory microcircuit may gate pyramidal cell activity during fear conditioning. Altogether, our data suggested a division of labor among various vCA1 GABAergic interneurons during different forms of emotional behaviors.

ID: 113
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: chronic pain, depression, anxiety, environmental enrichment

: Impact of long-term and short-term exposure of environmental enrichment on pain-related depression in adolescent mice

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Chronic pain significantly impacts well-being of more than 30% of the world's population. Its comorbidities, such as depression, anxiety, cognitive impairments or sleep disturbances may intensify and exacerbate the overall experience of pain, which consists of physiological as well as psychological aspects. Pharmacological treatments are often effective in reversing these changes, yet carry the risk of side-effects and addiction. Moreover, prescription drugs may be costly, therefore inaccessible to number of individuals. This project aims to characterize the impact of environmental manipulation on animal model of chronic pain, and evaluate if this can prevent the development of anxiodepressive symptoms. In a pilot study, we confirmed the presence of depressive-like behaviors in adult mice after Spared Nerve Injury (SNI) causing long-lasting pain in one hind paw. Subsequently, we randomly assigned 64 mice at 21 days of age into one of eight experimental groups, following two different protocols. Each protocol is applied to four groups: SNI (pain) + standard housing, SNI + enriched environment, sham (control) + standard housing, and sham + enriched environment. Protocols differ in the duration of exposure to enrichment: a) enrichment is interrupted after 6 weeks, simultaneously to conducting SNI/sham surgery; or b) all four groups of animals are housed in the enriched environment until the end of the experiment. Six weeks after surgery, we evaluate mechanical hypersensitivity and depression phenotype, using multiple behavioral tests: von Frey, marble burying, novelty suppressed feeding, splash test, and forced swimming task.

ID: 114
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: intracerebral hemorrhage, stroke, microscopy, cerebrospinal fluid, near-infrared tracer

A Murine Model For Investigating The Circulation And Efflux Of Cerebrospinal Fluid After Intracerebral Hemorrhage

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Objective: Intracerebral hemorrhage (ICH) is responsible for 10% of all observed strokes and is associated with high disability and mortality rates. Most therapeutic approaches lack broad agreement, especially for the reduction of brain edema. Current literature suggests impaired clearance of brain interstitial fluid (ISF) along white matter tracts and perivascular spaces; therefore, we consider diminished ISF clearance as a possible contributing factor to persistent brain edema after ICH. Moreover, because of an increased intracranial pressure, we expect an impaired efflux of cerebrospinal fluid (CSF) along perineural routes of cranial nerves to the cervical lymphatics, which may result in a possible rerouting of CSF down the spine. Our aim is to perform *in vivo* tracer studies of CSF circulation and efflux after intracerebral hemorrhage.

Methods: Experiments are performed in Prox1-EGFP transgenic mice, which allows for visualization of the lymphatic endothelium. ICH is induced by collagenase VII-S injection into the caudoputamen and at several timepoints we assess CSF circulation and efflux using near-infrared (NIR) tracers injected into the cisterna magna. Quantification of tracer distribution is performed by *in vivo* fluorescence microscopy over the thoracic spine, sacrum, the superficial cervical lymph nodes (scLNs) and the saphenous vein. Edema is assessed by wet/dry measurements of the brain tissue.

Results: Our preliminary results suggest a peak of hematoma volume and brain edema one day after ICH and hint at coinciding impairment of CSF flow down the spine. This is followed by increased spinal CSF flow at day three after ICH. Moreover, the data suggests an impaired efflux to the scLNs three days after ICH.

Conclusion: We present a novel approach for studying CSF circulation after ICH using transgenic reporter mice enabling us to visualize *in vivo* NIR tracer circulation in the CNS as well as efflux to the scLNs. Moreover, pilot experiments suggest changes in spinal CSF circulation and efflux of CSF to the scLNs, which may be related to hematoma size and brain edema after ICH.

ID: 115
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: hippocampus, decision-making, emotional conflicts, prefrontal cortex, anxiety

Resolving decision-making during emotional conflicts by ventral hippocampal circuits.

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How the brain computes decisions to support adaptive behaviours under different demands is a long-standing question. Decision-making does not solely rely on cognitive judgements but is likewise influenced by internal states. The ventral hippocampus (vHip) is a higher-order cortical brain region critical for processing emotions such as anxiety. Here, we examined the influence of anxiety levels on decision-making while recording neuronal activity in the vHip and medial prefrontal cortex (mPFC) as mice performed decision-making tasks during emotional conflicts. We observed that the activity of vHip neurons was scaling according to anxiety levels with concomitant remapping of firing fields. This effect was modulated by trajectories with different anxiety levels but was not a mere reflection of novelty. We additionally identified vHip neurons with preferential 'deliberating' and 'anxiety' features as mice made decisions under emotional conflicts. Using selective optogenetic inhibition of vHip terminals in the mPFC, we showed that mice exhibited biased decision-making selectively during trials with higher emotional conflicts. Collectively, these results suggest that vHip circuits targeting mPFC mediate decision-making under emotional conflicts.

ID: 119
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: Pneumococcal meningitis, neuroinflammation, maraviroc

The CCR5 antagonist maraviroc exerts limited neuroprotection without improving neurofunctional outcome in experimental pneumococcal meningitis

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Background

An association between excessive neuroinflammation and brain damage in the cortex and the hippocampus has been extensively documented during pneumococcal meningitis (PM). Maraviroc (MVC) - CCR5 antagonist - was reported to dampen the inflammatory reaction by attenuating activation of brain-resident cells and infiltration of inflammatory cells. This study assesses the anti-inflammatory and neuroprotective effects of MVC in experimental PM.

Materials/methods

In vivo, eleven-day old Wistar rats were infected with *S. pneumoniae* or saline and treated with MVC (100mg/kg) plus ceftriaxone (n=63) or vehicle plus ceftriaxone (n=63) at 18 hours post infection (hpi). Cortical damage and hippocampal apoptosis were evaluated histomorphometrically at 42hpi. Cerebrospinal fluid (CSF) inflammatory cytokines/chemokines and myeloperoxidase (MPO) levels were analyzed at 18, 24 and 42hpi using magnetic multiplexing system and MPO assay. Neurofilament light chain (NfL) was determined using Simoa. For assessing neurofunctional outcomes, animals were treated for two weeks with single daily dose of MVC, followed by learning/memory performance using the Morris water maze test and auditory brainstem response performance to determine PM-induced hearing loss.

Results

In vivo at 42hpi, MVC treatment significantly reduced the number of infected animals exhibiting cortical necrosis ($p<0.0001$) and hippocampal apoptosis ($p=0.0033$) compared to animals receiving vehicle only. In contrast, MVC treatment did not reduce the CSF levels of inflammatory cytokines/chemokines and MPO. Also, NfL levels were not affected by MVC. Further, no significant effects of MVC treatment in infected animals were detected when assessing learning, memory and hearing capacity compared to vehicle treatment.

Conclusions

MVC treatment reduced hippocampal cell apoptosis but did not affect CSF neuroinfammation and neurofunctional outcome after PM. We conclude that MVC treatment only exerted limited effect on the pathophysiology of PM and is, therefore, not sufficiently beneficial in this experimental paradigm of PM.

ID: 125
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: Infant rats; Langat virus; Locomotion; Sleep–wake behavior; Tick-borne encephalitis

Tick-borne encephalitis affects sleep-wake behavior and locomotion in infant rats

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Background/aims: Tick-borne encephalitis (TBE) is a disease affecting the central nervous system. Over the last decade, the incidence of TBE has steadily increased in Europe and Asia despite the availably of effective vaccines. Up to 50% of patients after TBE suffer from post-encephalitic syndrome that may develop into long-lasting morbidity. Altered sleep-wake functions have been reported by patients after TBE. The mechanisms causing these disorders in TBE are largely unknown to date. As a first step toward a better understanding of the pathology of TBEV-inducing sleep dysfunctions, we assessed parameters of sleep structure in an established infant rat model of TBE.

Methods: 13-day old Wistar rats were infected with 1×10^6 FFU Langat virus (LGTV). On day 4, 9, and 21 post infection, Rotarod (balance and motor coordination) and open field tests (general locomotor activity) were performed and brains from representative animals were collected in each subgroup. On day 28 the animals were implanted with a telemetric EEG/EMG system. Sleep recording was continuously performed for 24 consecutive hours starting at day 38 post infection and visually scored for Wake, NREM, and REM in 4 s epochs.

Results: As a novelty of this study, infected animals showed a significant larger percentage of time spend awake during the dark phase and less NREM and REM compared to the control animals ($p < 0.01$ for all comparisons). Furthermore, it was seen, that during the dark phase the wake bout length in infected animals was prolonged ($p = 0.043$) and the fragmentation index decreased ($p = 0.0085$) in comparison to the control animals. LGTV-infected animals additionally showed a reduced rotarod performance ability at day 4 ($p = 0.0011$) and day 9 ($p = 0.0055$) and day 21 ($p = 0.0037$). A lower locomotor activity was also seen at day 4 ($p = 0.0196$) and day 9 ($p = 0.0473$).

Conclusion: Our data show that experimental TBE in infant rats affects sleep-wake behavior, leads to decreased spontaneous locomotor activity, and impaired moto-coordinative function.

ID: 129
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: Optogenetic gene therapy, ion channels, Bipolar cells

Unravelling changes in ON-bipolar cell signalling during retinal degeneration to optimize optogenetic therapies

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The Retina consists of several cell types. Bipolar cells (BPCs) are the retinal interneurons responsible for decoding and fine tuning the light signal captured by the photoreceptors. BPCs can be divided in two main groups, cone BPCs (connected with cone-photoreceptors) and rod BPCs (connected with rod-photoreceptors) (RBCs). RBCs play a key role in retinal degeneration being the rod pathway the first to be affected. In photoreceptor degenerative diseases indeed, death of photoreceptors leaves behind a light-insensitive retina, luckily consisting of still preserved and functional BPCs, that can be used as targets for vision restorative therapies. With the Optogenetic therapy BPCs can be turn in replacement photoreceptors by expressing a light-sensitive protein and basic visual pathway can be restored. However, degeneration causes changes in ion channels expression in BPCs and fosters rewiring of the retinal network, which impact the synthetic vision restoration. Ion channels indeed are responsible of modulating the cell membrane potential that is fundamental for the transmission of electric signals among neurons. We described for the very first time with immunohistochemical, electrophysiological and molecular techniques that: 1) RBCs share one morphological cell type but two different electrophysiological states characterized by specific ion channel dominance; 2) RBCs express BK channels (big conductance potassium channels) on the dendrites, 2) BK channels on RBCs are downregulated in degenerated retina. Before the presented discovery, BK channels were only described in horizontal and amacrine cells. Treatments with BK channel as a target exist due to BK channel's involvement in a variety of diseases characterized by cell hyper excitability. BK channels heterologous expression, together with the optogenetic therapy, could bring back RBCs to the physiological range and consequently improve the synthetic signaling. Together a better understanding of cell's physiology in healthy tissue and in the cellular adaptations of BPCs during retinal degeneration will provide new avenues for future treatment strategies of blindness.

ID: 133
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: Fiber tract identification, Neurosurgery, Mueller polarimetry imaging, Tissue analysis

Robustness of brain white matter fiber tract identification in surgery-like environment using wide-field imaging Mueller polarimetry – an ex vivo study

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Aims

A real-time, non-invasive, dye- and contact-free brain tissue differentiation during tumor neurosurgery is a challenge we address with the wide-field imaging Mueller polarimetry (IMP). In our prior studies, we demonstrated that IMP is capable to detect correctly the in-plane orientation of brain white matter fiber tracts of a flat formalin-fixed thick brain specimen. Here we demonstrate the versatility and robustness of IMP data for the detection of cerebral white matter fiber tracts in adverse conditions similar to those present in neurosurgery, such as uneven surfaces and presence of blood and irrigation fluids.

Methods

We used the non-contact wide-field IMP system operating in a visible wavelength range in reflection configuration for surface imaging in 3 settings using fresh cadaveric calf brain. First, we performed MP images of coronal sections and repeated the images after removing a thin layer of white matter using a cavitron ultrasonic surgical aspirator comparing their respective polarimetric characteristics. Next we mimicked lesion resection by performing 3 cm-deep resection cavities with i) a scalpel and ii) a surgical ultrasonic cavitation device commonly used in neurosurgery in order to compare the corresponding polarimetric maps. Lastly, we performed tests with dilution series of blood spilled on prepared white matter specimen and measured the Mueller matrix images acquired at 550nm and 650nm, processed with Lu-Chipman decomposition algorithm.

Results

The measurements performed with the IMP system maintained their respective sensitivity for uneven surfaces due to ultrasonic aspiration, likewise within resection cavities made with a scalpel and surgical ultrasonic cavitation device. The orientation of the white matter fiber tracts was clearly visualized in the image of the azimuth of the optical axis. At the same time, the presence of blood/saline solution up to a thickness of 2mm did not significantly impact the orientation maps.

Conclusion

Our wide-field IMP system produces robust results on fiber tract visualization under all adverse, neurosurgery-like conditions, rendering it a potential new tool for an intra-operative, real-time, non-invasive identification of brain tumor borders and brain fiber tract orientation.

ID: 140
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: glia limitans, brain barriers, aquaporin-4, imaging, in vivo

In vivo imaging of the glia limitans with a new aquaporin-4-mRuby3 knock-in reporter mouse

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Immune surveillance of the central nervous system (CNS) is maintained by the brain barriers, which establish CNS compartments that differ with respect to their accessibility to immune cells and mediators. One of these barriers is the *glia limitans* formed by astrocyte end-foot processes and the parenchymal basement membrane. The *glia limitans* ensheathes the entire CNS parenchyma towards the surface and the perivascular spaces and provides a barrier to immune cells. Its barrier properties for soluble cerebrospinal fluid-derived molecules are still a matter of debate. Two-photon intravital microscopy (2P-IVM) has advanced our understanding of CNS immune surveillance. Nevertheless, a reporter mouse model allowing for *in vivo* imaging of the *glia limitans* has been lacking.

Therefore, we have established a novel fluorescent reporter mouse model allowing for *in vivo* imaging of the *glia limitans* and its role in CNS immunity. We established a novel aquaporin-4 (AQP4)-mRuby3 C57BL/6 knock-in mouse allowing to visualize the *glia limitans* due to the polarized expression of AQP4-mRuby3 at the astrocyte end-feet. The AQP4-mRuby reporter mice are born at mendelian ratios and have a normal CNS water content. Confocal and 2P-IVM showed correct localization of the AQP4-mRuby3 signal along the surface and perivascular border of the CNS parenchyma. Crossing AQP4-mRuby3 mice with CX3CR1-GFP mice allows to distinguish GFP^+ CNS microglia localized in the CNS parenchyma from GFP^+ border associated macrophages residing in the CSF filled CNS spaces. Imaging the distribution of cisterna magna injected different sized fluorescent tracers and microbeads allowed us to visualize the barrier properties of the *glia limitans.*

Our novel AQP4-mRuby3 reporter mouse is thus suitable for *in vivo* imaging of the barrier properties of the *glia limitans* and will contribute to improve our understanding of the mechanisms maintaining CNS immune privilege.

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Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: Autism spectrum disorder, MET, social dominance, parvalbumin

Mice lacking a novel phosphosite S1014 on the MET receptor tyrosine kinase display ASD-associated behavioral pattern

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Background. Receptor tyrosine kinase MET is an oncogene involved in multiple cellular functions. MET plays its unique role in brain development impacting synapse formation, maturation, and process outgrowth. Functional variants of the MET gene are enriched in patients with autism spectrum disorder (ASD). ASD is a common, highly heritable, neurodevelopmental disorder, characterized by cognitive decline, impaired social communication, and stereotyped behavior. Within a phosphoproteomics study carried out by our group, previously unreported phosphorylation on serine 1016 (mouse S1014) of MET was identified. To study this site, a knock-in mouse model lacking the phosphorylation on S1014 ($MET^{S1014A/S1014A}$) was generated. As the mice showed a stereotypical, circling movement pattern, a plausible sign of autistic behavior, we aimed to study the impact of MET S1014A on the behavior and brain structure of the knock-in mice.

Methods. A behavioral battery (n=12) targeting anxiety and locomotor activity, social domain, repetitive behavior, and cognition was employed. Neuronal density in the brain regions of interest was assessed by Nissl staining (n=4). Immunostaining (n=3) of adult mouse brains targeting parvalbumin (PV) and somatostatin (SOM) proteins was performed. The number of GABAergic inhibitory PV- and SOM-expressing interneurons was quantified.

Results. $MET^{S1014A/S1014A}$ homozygous mice of both sexes demonstrated a significantly higher level of dominance over WT mates. The pattern was particularly strong among mice housed in different cages and paired the first time against each other ($MET^{S1014A/S1014A}$ = 71% vs WT = 29%, $p \leq 0.05$). This finding can be correlated with the reduced anxiety of $MET^{S1014A/S1014A}$ mice described in the “open field” behavioral task and with a higher number of aggressive attacks in the “reciprocal social interaction” task. Additionally, we have detected a significant increase in the number of parvalbumin-expressing interneurons in the striatum ($MET^{S1014A/S1014A}$ = 109.4±31.8 vs WT = 30.2±14.1, $p \leq 0.05$), which is consistent with the data pertaining to known MET knock-out models.

Conclusion. Lack of MET S1014 phosphorylation impacts social behavior and alters the expression of inhibitory PV interneurons. We are currently exploring the underlying molecular mechanisms of these phenomena and the possible disbalance of excitation and inhibition, one of the core mechanisms of ASD development.

ID: 149
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: CSF flow, multiple sclerosis, EAE, immune cell infiltrates, NIR imaging

Aberrant flow of cerebrospinal fluid and its role in the dissemination of meningeal myeloid cell infiltrates during experimental autoimmune encephalomyelitis

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Numerous studies have demonstrated immune cell aggregates in the meninges of multiple sclerosis (MS) patients, as well as in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. We hypothesized that cerebrospinal fluid (CSF) is involved in the formation of meningeal immune cell aggregates during neuroinflammation, such that anatomical structures located downstream of CSF flow pathways are more susceptible to immune cell infiltrates. We infused a mix of near-infrared tracer and ovalbumin-AF647 into the lateral ventricle of CX3CR1-GFP//CCR2-RFP mice, a dual reporter mouse allowing visualization of CNS resident macrophages and blood-derived monocytes during active EAE. Utilizing noninvasive near-infrared imaging (NIR) of the mouse thoracic spine, we recorded CSF dynamic flow down spinal cord for 60 minutes. After NIR imaging, the cranium and spinal column were decalcified for further histological analysis, including immunofluorescence staining and confocal imaging. Our study demonstrates that at all stages, from EAE onset through peak stage to the chronic stage (4-5 weeks post-immunization), CSF flow down the spinal cord was significantly obstructed compared to the healthy control. In parallel to NIR imaging, in decalcified spines of EAE mice at different clinical stages, we observed OVA647 signal in the cervical and thoracic segments of the spine but no further towards the sacrum. In the direction from cervical to sacral spine segments, there was an increasing number of CCR2+ infiltrates in the subarachnoid space and parenchyma. Interestingly, at chronic stage, as CSF flow down the spinal cord started to recover as evidenced by a clear signal at the sacral spinal cord; we also observed significantly increased signal in the saphenous vein, which indicates an enhanced overall CSF turnover during chronic disease compared to healthy controls. In sum, our study has highlighted that significant alterations of the routing and dynamics of CSF flow occur during neuroinflammation which may impact the clinical course of disease.

ID: 151
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: CSF outflow; cribriform plate; arachnoid barrier

Cerebrospinal fluid outflow pathways at the cribriform plate along the olfactory nerves

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Several studies have shown that routes along the olfactory nerves that extend to lymphatic vessels in the nasal submucosa are an important cerebrospinal fluid (CSF) outflow pathway. Previous evidence in our lab showed an accumulation of fluorescent tracers at the cribriform plate, indicating the outflow has also occurred along the olfactory nerves. However, it is still unclear how fluid pathways along the nerves connect to the lymphatic vessels and where the arachnoid barrier is breached. This study aims to define anatomically the connections between the subarachnoid space (SAS) and the lymphatic system.

We made use of Prox1-GFP reporter mice to visualize the lymphatic vessels. To identify the CSF outflow pathways, pegylated (PEG) or unmodified microbeads (2.5 uL of 0.25% v/v in PBS) have been infused intracerebroventricularly in Prox1-GFP mice. At 45 min after the infusion, mice were sacrificed, and a decalcification protocol was used to keep the bone structures of interest intact. Then, 20 um thick slices were obtained at the cryostat, and imaging at the level of the cribriform plate was performed under either a fluorescence stereomicroscope or a confocal microscope. In some samples, we did immunofluorescence staining with an E-cadherin antibody to detect the arachnoid barrier.

As expected, unmodified microbeads remain stuck into the ventricles compared to the pegylated ones. Therefore, they are not ideal for studying the CSF outflow pathways. In the area immediately below the olfactory bulbs, where the olfactory nerves cross the cribriform plate, we observed PEG micro beads around the nerve bundles and into the lymphatic vessels crossing the cribriform plate. In addition, E- Cadherin staining revealed a discontinuous distribution of the arachnoid barrier at the midline under and between the olfactory bulbs.

ID: 155
Free contribution (poster and short talk)
Topics: Basic Research Animal

Sex differences in the efficacy of S1P receptor modulators and S1P receptor expression

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Background – Data on sex differences in Multiple Sclerosis (MS) therapies are sparse despite clinical importance. Sphingosine 1-Phosphate (S1P) Receptor (S1PR) Modulators (S1PRMs) are a class of treatment for MS targeting S1PRs located on lymphocytes surface leading to decreased egress from lymph nodes. With this work, we aim to investigate the sex-specific aspects of S1PRM efficacy.

Methods - To investigate the effect of sex on S1PRM treatment efficacy, we used the MS mouse model myelin oligodendrocyte glycoprotein peptide 35-55 experimental autoimmune encephalomyelitis (MOG_{35-55} EAE). C57BL/6JRj wild-type mice of both sexes were treated for 20 days from immunization with Fingolimod (FTY) dissolved in condensed milk or control orally. Mice were scored daily on a 10-point scale. Spinal cord S1PR1 T cell expression was histologically assessed.

Results – *In vivo*, when stratifying the results by sex, FTY was more effective in male compared to female mice; indeed, no male mice showed any signs of disease when treated with FTY(mean cumulative EAE score: females (n=11) mean: 0.6, 95%-Confidence interval (CI): 0.4-0.9, males (n=5) mean: 0, 95%-CI: 0-0; Mann-Whitney U Test (MWT) p=0.001). Membrane located S1PR1 expression by CNS infiltrating CD3+ T cell was higher in females FTY-treated compared to control-treated mice (FTY group mean: 3.2, 95%-CI: 3.2-3.4, control group mean: 2.9, 95%-CI: 2.8-3.0; MWT p<0.001). This difference was not observed in male mice.

Discussion – Own, unpublished investigations pointed towards age and sex differences in S1PRM treatment efficacy in people with MS, being the rationale for this experiment. Sex may affect the efficacy of FTY treatment in MOG_{35-55} EAE. An exceptional high rate of male mice not sick during treatment has to be considered as a confounder. Reasons for sex differences remain unclear. One plausible mechanism might be the differential expression of S1PR1 with higher receptor expression in female mice. Further investigations will follow during my Ph.D. thesis.

ID: 156
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: Epilepsy, Seizurre, Opotgenetic

GABAergic modulation of cortical excitability and resilience to seizures

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Background:

The limbic circuit is particularly prone to seizures, even in non-epileptic brains. Short stimulation of the entorhinal cortex can evoke self-terminating responses of varying magnitude in the hippocampus. Beyond the circuit's resilience (its capacity to absorb perturbation), more sustained stimulation can result in self-sustained seizures. How the limbic circuit transitions between these regimes is unknown.

Aim: To quantify GABAergic modulation of excitability and resilience in the limbic system in healthy mice.

Methods: We compared states of relatively low and high cortical excitability in freely-moving mice by administering a control vehicle (NaCl) intraperitoneally or low doses of GABAergic agonist (Diazepam (DZ)) or antagonist (Pentylenetetrazol (PTZ) or Picrotoxin (PTX)), respectively. To probe excitability, we stimulated pyramidal cells in the entorhinal cortex, using optogenetics single-pulses and measured evoked responses in the hippocampus. To probe resilience of this circuit, we administered trains of stimulation of increasing duration until a seizure was triggered.

Results:

We found that the magnitude of evoked hippocampal responses was reduced by 29.3% [95%CI, 27.6-31.2] with DZ and increased with PTZ (5.1% [3.0-7.1]) or PTX (9.3% [7.1-11.3]). Additionally, the amount of stimulation needed to induce seizures increased by 78.1% [54.5-113.0] with DZ and decreased by 19.6% [3.0-10.8] and 10.6% [-4.0-18.5] with PTZ or PTX, respectively, corroborating the changes observed in cortical excitability.

Conclusion:

We provide experimental evidence *in vivo* for a direct relevance of using minute perturbations of ongoing activity as markers of cortical excitability and show their correlation with resilience to epileptic seizures.

ID: 157
Free contribution (poster and short talk)
Topics: Basic Research Animal
Keywords: Fatty Acids, Lipofuscin, Mass Spectrometry, Retina, Stargardt Disease

Lipid metabolism in murine Stargardt disease models

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Stargardt disease is the most frequent inherited retinal dystrophy in both children and adults, with reported prevalence of 8-10/100'000. The classical autosomal recessive form of Stargardt disease (STGD1) is caused by homozygous or compound heterozygous pathogenic variants in the ATP-binding cassette (ABC) transporter 4 (*ABCA4*) gene. Impaired retinoid transport in presence of pathogenic *ABCA4* variants leads to accumulation of cytotoxic visual cycle byproducts in outer segments of photoreceptors and in the retinal pigment epithelium.

Autosomal dominant Stargardt disease (STGD3) is caused by heterozygous pathogenic variants in the ubiquitously expressed *ELOVL4* gene encoding the integral membrane fatty acid elongase ELOVL4, which elongates very long chain (VLC) saturated and polyunsaturated fatty acids (PUFAs). Previously, docosahexaenoic acid (DHA) supplementation was shown to delay retinal degeneration and to decrease subretinal bisretinoid accumulation in aging wild-type mice and a STGD3 mouse model (*Elovl4*$^{+/-}$).

We divided 27 animals of three groups (wild-type, STGD1 (*Abca4*$^{-/-}$), and STGD3) in twelve subgroups with control food, food enriched with 5,000 IU vitamin A or 1% DHA, or both. *In vivo* imaging with fluorescence lifetime imaging ophthalmoscopy (FLIO), optical coherence tomography (OCT), and electroretinography (ERG) at 2, 9, and 16 months after feeding was performed. After 18 months, we did histochemical staining and analyzed 28 FAs from 47 single retinas with gas chromatography-coupled mass spectrometry (GC-MS).

DHA supplementation improved photopic and scotopic responses in wild-type mice, but not STGD mouse models, as assessed by ERG. Vitamin A food supplementation lead to decreased photopic and scotopic responses in *Abca4*$^{-/-}$ mice, in line with previous observations and consistent with the increased lipofuscin deposits observed by FLIO. Interestingly, GC-MS showed increased eicosapentaenoic acid (EPA) concentrations in DHA-supplemented *Elovl4*$^{+/-}$ mice. EPA, retro-converted from DHA, may be the preferred substrate for ELOVL4 to generate VLC PUFAs, therefore we will further investigate the effects of EPA supplementation.

ID: 100
Free contribution (poster and short talk)
Topics: Clinical Research

Exploring Functional Paralysis with Advanced Magnetic Resonance Modalities

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In functional neurological disorder (FND), neurological symptoms occur despite intact anatomical pathways. FND pathology is poorly understood with uncertain diagnosis, treatment and prognosis. There are several forms of FND with different types of symptoms. In this study, the focus is on the subtype functional paralysis, where a paralysis is present in certain parts of the limbs.

Recent neuroimaging studies on FND have revealed alterations in several functional networks in patients compared to healthy subjects. For instance, there is evidence of altered activity in the right temporoparietal junction (TPJ), sensorimotor areas, prefrontal cortex and limbic system. Besides the differences in neural correlates of FND, evidence of altered cognitive and affective processes has been shown in patients with FND.

In this study, advanced MR techniques are planned in different modalities to provide a comprehensive understanding of nerve cell metabolism, microstructure and functional connectivity in FND. Since functional paralysis has a similar phenotype of spinal cord injury (SCI), but the underlying causality is different, we will compare the two pathologies, while healthy controls will act as baseline for the comparisons. The overall aim is to identify MR-based markers of FND.

In order to investigate the metabolic profile, magnetic resonance spectroscopy (MRS) will be applied, diffusion tensor imaging (DTI) will be used to investigate diffusion properties in neuronal tissue, and functional magnetic resonance imaging (fMRI) will be performed in the resting and task-related states to analyse functional connectivity. We will focus on inhibitory control, as recent behavioural studies have shown evidence of disturbed inhibition processes in FND. Therefore, we will perform a go/no-go task combined with fMRI to reveal the neural correlates of inhibition processes in FND, as well as standard behavioural parameters such as reaction times and accuracy values.

Data collection is planned to start in September 2022.

ID: 110
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: Instrumented Apartment, Sensors, Motor, and non-motor functions, Activities of daily living

Validation of an Instrumented Apartment To Assess Activities of Daily Living of Patients: The NeuroTec Loft

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Introduction: The performance of activities of daily living at home (e.g., washing hands, cooking, movements during sleep), in detail motor and non-motor functions, are an indicator of the change in health status. The rapid advances in contactless and unobtrusive sensor techniques (e.g., pressure-, radar sensors) offer new possibilities in long-term monitoring at home during day and night and thus foster independent living and finally increasing quality of life. Therefore, the aim of this case study was to develop and validate a multi-sensor system to unobtrusively monitor patients' daily activities in a home like environment.

Method: The developed system consisted of unobtrusive sensors using basic technologies and was installed in an instrumented apartment called NeuroTec Loft at the University Hospital of Bern. To record the activities of daily living, in total, over 200 sensors such as radar sensors, lidar sensors, infrared cameras, pressure sensors, flow meters and video cameras were installed, whereas gold standard medical devices were used as reference systems. The system and thus the assessment of activities of daily living was validated during a stay of a 42-years-old healthy woman.

Results: The system recorded during the stay accurately activities of daily living like preparing dinner by using the microwave oven, tracking the position in different rooms, sleeping, and having coffee as breakfast. The sleep duration was approximately 6,25 hours, whereas the mean heart rate was 63 beats/min, the mean respiration rate was 15 breaths/min and 34 tosses and turns occurred. During the stay, the system had no malfunction and the subject did not report any negative experiences.

Discussion and Conclusion: Overall, the developed multi-sensor system installed in the instrumented apartment allows to bridge the gap between laboratories and patients and older adults' homes. The multi-sensor system advances science in terms of the understanding of human behavior and neurological disorders, to detect diseases at an early stage or indicate a sudden deterioration in health at home. Thus, the instrumented apartment has a great potential to increase quality of life of our aging society and patients.

ID: 112
Free contribution (poster and short talk)
Topics: Clinical Research

Using Sensors to Support Medical Professionals of an Old Age Psychiatry Ward

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Currently, there is a shortage of skilled workers and pressure to reduce costs in the health care system. As the number of psychiatric patients is steadily increasing in the context of increasing life expectancy the shortage of nurses will further increase. However, quality of care is a determinant of patient safety and the effectiveness of medical interventions. Thus, there is a necessity for monitoring systems which support the medical professionals of the ward and reduce their workload and stress. It has been shown that remote monitoring of older people with a multimodal sensor system over longer time periods provides a potential framework to detect health deteriorations. Such systems rely on contactless ambient sensors that collect objective and reproducible data about the patients. This data contains a myriad of information that can be analysed using modern data science and artificial intelligence to extract digital biomarkers, objective clinical measures, that can help to detect slight changes in health status immediately. Currently, we are developing a multimodal sensor system based on upcoming technologies (e.g., radars, LiDARs and pressure sensors) which will be tested and evaluated in a clinical study in the University Psychiatric Clinic Bern.

ID: 116
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: schizophrenia, psychomotor slowing, behavioural data, gait analysis, motor abnormalities

Psychomotor slowing alters gait velocity, cadence, and stride length and indicates negative symptom severity in psychosis

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Background: Schizophrenia is a severe mental disorder, in which around 50% of patients suffer from motor abnormalities such as psychomotor slowing (PS). PS affects fine and gross motor behaviour and adds to the huge burden associated with schizophrenia spectrum disorders. Research has shown that schizophrenia patients exhibit a slowed gait velocity at spontaneous self-selected speed. However, the effect of schizophrenia on other gait parameters (cadence, stride length) or on gait in other walking conditions (maximum speed, head reclination, eyes closed), and especially the effect of PS is unclear. We aimed to disentangle the gait impairments inherent to schizophrenia from the effects of PS using objective means of gait analysis.

Methods: We collected gait data using GAITRite® in 70 schizophrenia patients with PS (Salpêtrière Retardation Rating Scale, SRRS, >15), 22 non-psychomotor slowed schizophrenia patients (SRRS <15), and 42 healthy controls. Trained physicians rated patients on hypokinetic movement abnormalities clinical scales: SRRS (PS), Unified Parkinson Disease Rating Scale (UPDRS, parkinsonism), and Bush-Francis Catatonia Rating Scale (BFCRS, catatonia).

Results: The main ANCOVA demonstrated a significant difference between the three groups for velocity, cadence, and stride length for all walking conditions (all $F>16.18$, all $p<.0001$) with slowed patients presenting a slower velocity, lower cadence, and smaller stride length in all walking conditions compared to healthy controls and the non-slowed having an intermediate performance. In addition, during self-selected and maximum walking speed, lower velocity correlated with severity of PS (self-selected: $r=-.26$, $p=.015$; maximum: $r=-.46$, $p<.0001$) and parkinsonism (self-selected: $r=-.20$, $p=.0056$; maximum: $r=-.51$, $p<.0001$). Stride length showed mostly an association during self-selected speed (all $r>-.26$, all $p<.014$), and cadence during maximum speed (all $r>-.33$, all $p<.0016$).

Conclusion: Here we showed that, although some motor impairment exists in schizophrenia, patients with PS are much more strongly affected. Gait impairment exists in several gait parameters and persists over varied walking conditions in the psychomotor slowed schizophrenia patients, while the non-slowed schizophrenia patients are less affected. Also, across all schizophrenia patients, the severity of objectively assessed gait impairment correlates with expert rated hypokinetic movement disorders; e.g. the slower the gait, the higher the rating of hypokinetic movement disorders.

ID: 117
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: MDD, depression, neuroimaging, psychomotor disturbance, fMRI

Functional connectivity alterations of psychomotor disturbance in major depressive disorder

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Psychomotor disturbance (PmD) is an important symptom complex of major depressive disorder (MDD), affecting up to 70% of patients. It is associated with more severe depression and worse treatment response to medication. Knowledge about its functional neural underpinnings may help understanding the etiology and developing treatments of PmD in MDD.

We selected participants of the Marburg-Münster-Affective-Disorders-Cohort-Study for whom resting-state fMRI, structural images and the Hamilton Depression Rating Scale (HAMD) were available. Patients were categorized as currently depressed or remitted based on a HAMD-sum higher than 8 points, and further separated into slowed, agitated, or no-PmD based on the HAMD-items 8 and 9 (retardation, agitation). We examined functional connectivity between regions-of-interest in the motor network in the brain, comparing healthy controls with the aforementioned patient groups, as well as patient groups with each other. We set thresholds at uncorrected $p<.05$ for connections and FDR-corrected $p<.05$ for cluster-level.

We included 1523 participants, of which 845 were healthy controls, 678 had a diagnosis of MDD (286 currently depressed, 392 remitted). In the currently depressed group, 82 were slowed, 41 agitated, 32 presented agitation and slowing simultaneously, and 131 had no PmD. When compared with controls, patients with MDD diagnosis and currently depressed patients showed higher thalamo-cortical and pallido-cortical, as well as lower cortico-caudate connectivity. Agitated patients additionally showed higher putamino-cortical connectivity, while they had no cortico-cortical or cortico-caudate alterations compared to controls. In an exploratory analysis comparing controls and slowed patients, we observed trend-level higher thalamo-cortical and pallido-cortical connectivity, as well as lower connectivity between bilateral caudates and bilateral superior parietal lobules. However, there were no significant differences in connectivity in the comparison of agitated and not motorically affected patients, as well as no significant differences in any of the comparisons with slowed patients.

We observed evidence for general alterations of functional connectivity in the motor network in MDD, irrespective of PmD. While we found no differences directly comparing patients, differential alterations compared to controls might suggest a lack of compensatory increase of cortico-cortical functional connectivity to cause PmD, while connectivity alterations between subcortical nuclei and cortex might differentiate agitation and retardation.

ID: 121
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: Radar, Gait, Sensors, Unobstrusive Monitoring, Neurodegenerative Diseases

On Doppler Radars to Unobtrusively Assess Gait Parameters in an Instrumented Apartment

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Introduction: In patients suffering from neurodegenerative diseases the changes in gait parameters, representing digital biomarkers, are an indicator of their health status. Therefore, monitoring changes in gait over a prolonged period represents a promising method to trigger patient-specific interventions and thus to maintaining the patient's quality of life, while also fostering independent living. Hence, the aim of this study was to develop an algorithm to extract gait related biomarkers from doppler radar measurements of healthy subjects.

Method: We compared gait parameters and clinical gait tests based on recordings from 60 healthy participants, resulting in 2580 unique walks against two state-of-the-art technologies, a pressure mat (GAITRiTe), and a set of inertial measurement unit sensors (Gait Up).

Results: Preliminary statistical analysis of 21 walks showed that there is a high accuracy (92.72%) with gold standard systems for gait tests (walk time M = 7.27s, SD = 5.81s). Moreover, the developed algorithm can accurately extract gait parameters (e.g., gait speed) and detect different movement activities (e.g., walking and sit-down).

Conclusion: Overall, the preliminary results indicate that doppler radars have the potential to assess gait parameters unobtrusively and accurately on a comparable level of gold standard systems in a home-like environment.

ID: 122
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: MOGAD, SARS-COV-2

Myelin-oligodendrocyte-glycoprotein (MOG) antibody-associated optic neuritis after mild SARS-CoV-2 infection - A case report

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Introduction:

SARS-CoV-2 infection can be associated with neurological manifestations during the acute and post-infectious phase. Case descriptions of patients with neurological autoantibodies such as Myelin Oligodendrocyte Glycoprotein (MOG-) IgG are rare.

Objectives:

To report a case of MOG-IgG-associated disorder (MOGAD) presenting with optic neuritis (ON) after SARS-CoV-2 infection.

Methods:

Case report presenting clinical and paraclinical features (brain and spinal magnetic resonance imaging (MRI), optical coherence tomography (OCT), cerebrospinal fluid (CSF) and laboratory workup, incl. MOG-IgG testing with a cell-based assay).

Results:

A 41-year-old man presented with severe visual loss (0.32 sine correctione, s.c.), relative afferent pupillary defect (RAPD), colour desaturation, and retrobulbar pain exacerbated with eye movements of the right eye (OD). He had tested positive for SARS-CoV-2 and developed mild illness about two weeks before the onset of visual symptoms. Brain MRI revealed longitudinally extended prechiasmatic swelling and gadolinium enhancement of the right optic nerve without other demyelinating lesions in brain and spinal MRI. The first OCT was performed during the acute phase of the disease and showed a generalized swelling of the retinal nerve fibre layer (RNFL) returning to normal thickness values in the follow-up examination after 7 weeks. CSF analysis demonstrated a normal cell count and identical oligoclonal bands in serum and CSF, serologic studies showed no evidence of infectious causes. MOG-IgG titre at initial presentation was 1:160 with gradual increase over two (1:640) and 6 weeks (1:1280). Visual loss resolved already following a five-day intravenous steroid treatment with 1000 mg methylprednisolone per day. Given the parainfectious onset, the favourable response to steroids and for now monophasic disease course, a “watch and wait” strategy was adopted.

Conclusions:

SARS-CoV-2 infection can be associated with demyelinating neurological complications. About ten cases of MOG-IgG-related ON after COVID-19 have been reported and our case sustains this association. Interestingly, this association is not limited to a specific pathogen, since MOG-IgG-associated ON after other viral (Varicella-Zoster virus) and bacterial (Borrelia burgdorferi) infections have been described in recent literature. Molecular mimicry is currently the most postulated mechanism of parainfectious autoimmunity, but further studies are required to confirm this association and to determine the pathophysiology.

ID: 124
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: schizophrenia, negative symptoms, psychomotor slowing, motor abnormalities, psychosis

Negative symptoms in psychosis with psychomotor slowing

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Background: Negative symptoms affect up to 50% of patients with schizophrenia and include the subdomains anhedonia, distress, asociality, avolition, blunted affect and alogia. Another core symptom of schizophrenia are motor abnormalities e.g. psychomotor slowing, which affects up to 50% of schizophrenia patients. Both, psychomotor slowing and negative symptoms, have detrimental effects on patients' lives. However, to date, there are no sufficient treatment options to improve negative symptoms or psychomotor slowing. Thus, we tested Negative Symptom severity between slowed and non-slowed schizophrenia patients and their association with psychomotor slowing.

Methods: We collected data of 75 slowed and 27 non-slowed schizophrenia patients using two expert ratings: (i) Salpêtrière Retardation Rating Scale (SRRS), which combines 15 affective and motor items evaluating psychomotor slowing, and (ii) Brief Negative Symptom Scale (BNSS), assessing negative symptomatology with 13 items. We performed Mann-Whitney-U-Tests comparing BNSS and its subdomains, as well as SRRS and the motor aspect of SRRS (mSRRS), between slowed and non-slowed patients using age and medication as covariates. Finally, Spearman correlations were conducted to explore the associations between BNSS and its subdomains and SRRS/mSRRS.

Results: Slowed patients had higher scores on mSRRS and BNSS than non-slowed patients (all $U \leq 415.5$, all $p\text{-}FDRc = .001$). The subdomains of BNSS asociality, blunted affect and alogia were higher in the slowed than in the non-slowed group (all $U \leq 693.5$, all $p\text{-}FDRc \leq .03$). In slowed patients, all BNSS-subdomains correlated with the total SRRS score (all rho≤.531, all $p\text{-}FDRc \leq .043$) and, except for asociality, with mSRRS (all rho≤.546, all $p\text{-}FDRc \leq .043$). In the non-slowed group only the subdomains anhedonia and avolition were associated with the total SRRS score (all rho≤.671, all $p\text{-}FDRc = .014$) and only blunted affect correlated with mSRRS (rho=.507, all $p\text{-}FDRc = .025$).

Conclusion: Negative symptoms are more pronounced in slowed than in non-slowed schizophrenia patients. Since the subdomain blunted affect is correlating with mSRRS in the slowed as well as in the non-slowed group, it might be a good marker of negative symptomatology as well as motor slowing.

ID: 127
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: CXL, cornea, pulsing, keratoconus

Oxygen kinetics during CXL using symmetrically and asymmetrically pulsed UV-irradiation

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Purpose: To investigate oxygen kinetics during symmetrically pulsed and asymmetrically pulsed crosslinking (p-CXL) with and without supplementary oxygen at different irradiances and corneal depths.

Methods: In de-epithelialized porcine eyes, a fibre-probe was placed in corneal depths of 200 and 300 µm to measure the local oxygen concentration. After riboflavin imbibition, the corneas were irradiated at 9-30 mW/cm^2 for 10 seconds On and 10 seconds Off. All experiments were performed under normoxic (21%) and hyperoxic (>95%) conditions and obtained data were used to identify parameters of a numerical algorithm for oxygen consumption and diffusion. Following the algorithm's development, the suggested asymmetrical pulsing values were experimentally tested. For 9, 18, 30 mW/cm^2 the suggested tested pulsing schemes were 3 seconds On : 9 seconds Off, 2 seconds On : 9 seconds Off and 1 second On : 9 seconds Off, respectively.

Results: The minimum stromal oxygen for p-CXL in normoxic environment was decreasing <1% for all irradiances in 200 and 300 µm. Using optimized p-CXL, the minimum available oxygen increased to 3.8, 1.8 and 2.8 % at 200 µm, for irradiances of 9, 18 and 30 mW/cm^2, respectively, where the periods exhibited an equilibrium state. At 300 µm, 1.1 % of oxygen was available for 30 mW/cm^2. Using a hyperoxic environment, the oxygen concentration was 19.2% using 9 mW/cm^2 in 200 µm, dropping to 17.0% in 300 µm. At 18 mW/cm^2, the concentrations were 3.9% and 1% in 200 and 300 µm, respectively. Using 30 mW/cm^2, all oxygen was depleted below the threshold limit (1% O_2) for both depths. Using optimized pulsing in combination with hyperoxic environment, the oxygen concentration was 42.0% using 9 mW/cm^2 in 200 µm and 43.3% in 300 µm. At 18 mW/cm^2, the concentrations were 24.7% and 16.1% in 200 and 300 µm, respectively. Using 30 mW/cm^2, the minimum oxygen availability was 25.7% and 13.7% in 200 and 300 µm, respectively.

Conclusion: Supplementary oxygen during symmetrical and asymmetrical p-CXL increased the oxygen availability during corneal cross-linking. The pulsed irradiance and the hyperoxic environment potentially increased the efficacy of corneal cross-linking in deeper corneal layers and higher irradiances.

ID: 130
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: psychomotor slowness, schizophrenia, rTMS, cortical excitability

Psychomotor slowing reduction following 3-weeks of inhibitory rTMS over the SMA is associated with an improvement of general excitability of the primary motor cortex.

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Introduction: Psychomotor slowing (PS) affects up to 30 to 50% of patients with schizophrenia. Manifestation of PS include reduced levels of spontaneous motor activity and slowing of gait and fine motor dexterity. PS predicts poor clinical outcomes for the patients. Previous studies show that, PS is linked to connectivity abnormalities, including increased brain connectivity in Supplementary Motor Area (SMA). In the OCOPS study we used Transcranial Magnetic Stimulation (TMS) to evaluate the effect of inhibitory rTMS over the SMA in improving PS in schizophrenia patients.

Methods: From the OCOPS study, we used the data of 19 psychomotor slowed schizophrenia patients (SRRS>15). These patients had two baseline assessments 3-weeks apart followed by 1 daily session over 15 days of inhibitory rTMS over the SMA. We also included data from 42 healthy controls. Cortical excitability was assessed over the primary motor cortex (M1). We recorded the motor evoked potential (MEP) amplitude as a measure of general excitability of M1 and the short-interval intracortical inhibition (SICI) as a measure of cortical inhibition. We compared these two measures between HC and patients, then using the Last Observation Carried Forward method we evaluated the change after rTMS of these two cortical excitability measurements.

Results: Healthy controls presented higher excitability (higher MEP Amplitudes) and stronger cortical inhibition (higher SICI values) than the patients at baseline. During the 3 weeks of waiting we observed no changes in patients neither in SRRS scores, nor on any cortical excitability measure. After rTMS, the patients decreased SRRS (p-value <.0001) and increased MEP amplitude (p-value 0.0114 between Baseline 1 and Post). There was no change in cortical inhibition over time for the slow patients.

Conclusion: PS is associated with poorer clinical outcome and a lower cortical excitability of the motor cortex. After a series of inhibitory rTMS applied over the SMA, slow patients with schizophrenia showed a clinical improvement of PS, measured by the clinical scores (SRRS), associated with an increase of MEP amplitude, though cortical inhibition showed no differenceAn increase in MEP amplitude indicates an improvement of M1 excitability in general, making rTMS a promising therapeutic tool for PS.

ID: 131
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: Functional Neurological Disorders, Persistent Postural-Perceptual Dizziness, Neuropathophysiology, Biomarkers, Neuronal Charateristics

Neuropathophysiological mechanisms in functional neurological disorders (FND): a study on persistent postural-perceptual dizziness (PPPD) - Study Design

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Abstract

Background: Patients with functional neurological disorders (FND) experience neurological symptoms without an underlying organic cause. Several subtypes, such as functional motor disorders, functional cognitive disorders or functional seizures have been delineated. Subtypes can be distinguished, but they share similarities in aetiology and pathophysiology. Recently, a new subtype of FND was added, namely persistent postural-perceptual dizziness (PPPD) which is characterized by alternating symptoms of dizziness, unsteadiness, or non-spinning vertigo. Until now, relatively few is known about the neuropathophysiology of PPPD.

Objective: This study aims to gain further knowledge on PPPD by investigating why patients develop PPPD and how symptoms emerge.

Methods: Twenty patients from each subtype of FND, functional motor disorders, functional cognitive disorders, functional seizures and PPPD, and 20 healthy controls (HC) will participate in study visit 1, which will consist of questionnaires, blood and saliva samples, and structural and functional MRI. The FND patients group will repeat the examination 8 months later at study visit 2.

Planned analysis: To answer why PPPD emerges, clinical data on stressful life events, stress markers and genetic markers will be compared between patients with PPPD, HC and other subtypes of FND. Addressing how symptoms occur, analysis on structural and functional characteristic, such as brain functional connectivity, will be conducted and compared between patients with PPPP, HC and other subtypes of FND.

Relevance: Findings from this study will contribute to a better knowledge of PPPD and therefore, might improve the process of diagnosis and treatment options.

ID: 137
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: neurorehabilitation, stroke, robotics, motor learning, sensorimotor

A Novel Tool for Clinical Neurorehabilitation: Robotic Device for Rehabilitation of Sensorimotor Functions after Stroke

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Stroke is one of the world's most prevalent causes of disabilities. Stroke survivors often suffer from reduced sensorimotor upper-limb functions, resulting in a loss of functional autonomy. To maximize recovery, patients should undergo highly intense and repetitive training. In addition, neuroscience suggests that realistic visual and somatic sensory information should both be considered in rehabilitation training. Robotic devices could potentially provide this kind of training, yet current robot-aided interventions mostly rely on abstract visual feedback, while somatic (tactile and proprioceptive) feedback is underutilized.

To address current limitations in rehabilitation robotics, we have been developing a novel robotic device for upper-limb rehabilitation. We have been employing a clinical-driven design approach in collaboration with the Department of Neurology of the University Hospital Bern. Thereby, we conducted a survey with 33 participants working in neurorehabilitation to assess the requirements, and we have been continuously integrating therapists' feedback into our design. The resulting robotic device allows arm movements in 3D and - due to its unique hand module - a variety of grasping movements. The aforementioned hand module was developed using an optimization approach based on anthropometric databases and offers independent finger (flexion/extension) and thumb (flexion/extension and circumduction) movements. Only the patient's hand is attached during training, which allows for a relatively simple setup compared to other existing devices.

Through fine haptic rendering (physically representing interaction forces with tangible virtual objects), our device can provide important sensory information during training. Patients will perform virtual tasks in specifically developed rehabilitation games that incorporate virtual tangible objects with rich rendered dynamics. In conjunction with the robotic device, these will allow for simultaneous sensory and motor training and improve upper-limb functions which are relevant for activities of daily living, such as reaching and grasping.

As the development of our device prototype is coming to an end, we are currently setting up a usability study with therapists and patients. We hope to not only confirm our design choices but also to collect further feedback to refine the device for future use as a pioneering tool in clinical neurorehabilitation.

ID: 139
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: stroke, neuropsychology, attention, aphasia, auditory

Modality-modulated difficulties in flexible attention allocation after stroke

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Attention, our ability to detect and react to stimuli in the environment, is fundamental for many activities. Attentional impairments are a common consequence of brain lesions but most of the patient-related research on attention focused on patients with right hemisphere lesions and impairments in (visuo)spatial attention allocation. Patients with left hemisphere lesions often have difficulties in language processing – aphasia – and are therefore usually excluded from studies on other cognitive functions. The few studies investigating attentional performance in aphasia often considered only one specific task, stimulus modality, or type of measure and only group-level analyses or data based on experimental tasks were presented.

We aimed at characterizing attentional impairments in this patient group and firstly report analyses on a dataset of patients with chronic post stroke aphasia, including performance on subtests of two standardised attentional test batteries. Patients' performance was compared to normative data, relationships between attention measures and other data were explored with principal component analyses and correlations, and brain-behaviour relationships were assessed with voxel-based correlational methodology. Performance was variable and largely independent of patients' language abilities. Four principal components were underlying patients' attentional performance across tasks, each being associated with distinct neural correlates. Importantly, the highest proportion of impaired performance was noted for complex attention tasks involving auditory stimuli.

The reasons for these potentially modality-specific difficulties are currently not well understood and warrant additional investigations. Therefore, we secondly present preliminary data of an ongoing study including patients with a left- or right-sided stroke. Patients' performance in experimental attentional tasks of varying complexity, each available in an auditory or visual or combined version, was assessed and patterns of performance were analysed. Mirroring our previous findings, patients with left hemisphere lesions performed worse in the auditory conditions. Also, a trend for more pronounced difficulties with the visual modality emerged for patients with right hemisphere lesions.

Taken together, our investigations underscore the importance of assessing this cognitive domain in all stroke patients. The findings are not only helpful to elucidate the brain mechanisms underlying flexible attention allocation, but also pivotal to guide therapeutic interventions on an individual level.

ID: 142
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: psychosis, motor abnormalities, nonverbal communication, functional outcome

Nonverbal social perception mediates psychomotor slowing and functioning in schizophrenia

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Schizophrenia is a severe psychiatric disorder that affects processing speed and movement (psychomotor slowing), as well as, the ability to evaluate others' facial expressions and bodily movements during social interaction (nonverbal social perception). These two core symptoms affect functioning and quality of life in schizophrenia patients. Here, we investigated the impact of psychomotor slowing on poor community functioning in schizophrenia and whether this is mediated by the presence of nonverbal social perception deficits.

We included 58 patients (mean age = 39.9 years; SD = ± 12.0; 50.0% male) and 31 healthy controls (mean age = 41.5 years; SD = ± 11.9; 51.6% male). Psychomotor slowing was assessed with the Salpêtrière Retardation Rating Scale (SRRS), while the nonverbal social perception was tested using the Mini-Profile of Nonverbal Sensitivity (Mini-PONS) task. Functional capacity was evaluated using the University of California San Diego Performance-Based Assessment (UPSA) task, and functional outcome was measured using the Specific Level of Functioning (SLOF) scale. We compared patients and healthy controls in psychomotor slowing and nonverbal social perception, whilst controlling for education. Additionally, we ran two mediation analyses in patients with psychomotor slowing as the initial variable, nonverbal social perception as the mediator variable, functional capacity/outcome as the outcome variable and medication as a covariate. Both mediation analyses were computed using 5000 bootstrapped samples.

Schizophrenia patients had more psychomotor slowing and poorer nonverbal social perception than healthy controls (both $F_{(1, 87)}>8.5$; $p<.01$). In patients, psychomotor slowing predicted poor functional outcome/capacity (both $B<-.3$, $p<.01$). This was true even after controlling for the mediator of nonverbal social perception with $B_{UPSA}=(-.3)*(.8)=-.2$, 95%CI[-.5,-.03] and $B_{SLOF}=(.3)*(.9)=.-3$, 95%CI[.6,-.03]. The effect of the mediator nonverbal social perception accounted for 29% of the total variance on functional capacity ($R^2_{UPSA}=.29$) and 38% of the total variance on functional outcome ($R^2_{SLOF}=.38$).

We demonstrate that psychomotor slowing predicts poor functioning in schizophrenia, as partially mediated by nonverbal social perception. This emphasizes the importance in alleviating both psychomotor slowing and of nonverbal social perception deficits in schizophrenia by means of brain stimulation, cognitive remediation therapy and virtual reality to further improve daily functioning.

ID: 148
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: Carotid free floating thrombus, risk

Natural history of carotid artery free-floating thrombus – a single centre, consecutive cohort analysis

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Introduction

Carotid free-floating thrombus (CFFT) is a rare cause of stroke and is thought to be associated with a high risk of recurrent cerebrovascular ischaemic events. The existing data on the natural history and optimal treatment modalities of CFFT is scanty and no clear recommendations exist.

Objective

A retrospective analysis of a single-centre cohort of consecutive patients diagnosed with CFFT was conducted, investigating the risk for recurrent cerebrovascular ischaemic events.

Methods

We performed a single-centre retrospective analysis including all patients presenting at our tertiary centre between January 2005 and December 2020 with symptoms consistent with ischaemic stroke and/or transient ischaemic attack. Digital subtraction angiography (DSA), computed tomography angiography (CTA) or magnetic resonance angiography (MRA) were used to diagnose CFFT. In all included patients, CFFT was confirmed with a second imaging modality. CFFT was defined on imaging as a defect in contrast filling extending into the carotid lumen. We gathered information on vascular risk factors, diagnosis and follow-up methods, modality of treatment and neurological outcome. A survival analysis was performed, assessing the risk for recurrent cerebrovascular events.

Results

In total, N = 62 patients presenting with symptomatic CFFT were included. Mean age was 68 years, 69% (43/62) of patients were male, 52% (32/62) current or previous smokers, 76% (47/62) suffered from arterial hypertension, 68% (42/62) from dyslipidaemia, and 31% (19/62) from diabetes mellitus. Overall, 71% (44/62) of patients received any kind of intervention (endovascular or surgical carotid thrombo-endartectomy [CEA]) at any time point during follow-up. 16% of patients (10/62) received intervention within 48 hours after diagnosis of CFFT. The survival analysis and Kaplan-Meier model censoring patients at the time of intervention or last follow-up showed that the risk for any recurrent ischaemic stroke was 19.7% within the first 7 days and 27.4% within 3 months after diagnosis. No patients experienced a new ischaemic stroke beyond 11 days after diagnosis of CFTT (n=17).

Conclusions

The risk of recurrent ischaemic events in patients with CFFT is high, especially in the first week after diagnosis. Prospective studies are needed to further investigate the optimal management of these patients.

ID: 150
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: Implicit Association Test, suicidal ideation, suicidal behavior

The Association between implicit Associations and suicidal Ideation/Behavior, pre-liminary results

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Subjects with current Major Depression and suicidal ideation are thought to identify more with ideas related to “death” and “self” than healthy controls. These implicit thought associations can be tested with the implicit association test for suicide (suicide IAT). Whether the associations are features of depression or suicidal ideation remains unknown. The aim of this study is to measure the strength of the associative network between “death” and “self” in three differerent patient samples. We hypothesize that patients with suicide attempt in their life history have significantly stronger implicit associations between "death" and "self" than patients with suicidal ideation but without suicidal behaviour and non-suicidal patients.

This cross-sectional study includes 267 subjects. The sample currently consists of 179 persons. These are divided into three groups: Patients with suicide attempts (n = 57), patients with suicidal thoughts (n = 44) and all other patients (n = 78). The last group contains patients who report neither suicide attempts nor suicidal thoughts, but who are undergoing treatment for a psychiatric illness.

The 3x2 anova revealed neither a significant main effect for the group ($F_{(2, 173)}$ = 1.77, p = .174, two-sided, η^2 = .020) nor a significant main effect for the sequenz ($F_{(1, 173)}$ = 0.71, p = .402, η^2 = .004). A comparison of the D-scores in the IAT between patients with a suicide attempt, patients with suicidal thoughts and non-suicidal patients shows that the patients with a suicide attempt and patients with suicidal thoughts do not have significantly positive D-scores. Moreover, no interaction can be found. ($F_{(2, 173)}$ = 0.27, p = .764, η^2 = .003). The range of D-values illustrates a spread in the non-suicidal group (*Min* = -1.17, *Max* = 0.37), compared to the group with suicidal ideation (*Min* = -0.82, *Max* = 0.90) and the group with suicide attempt (*Min* = -1.03, *Max* = 0.51).

The results show that no group differences are found. The implicit associations do not differ between persons with suicidal thoughts or attempts in the past compared to non-suicidal patients. Further research is needed to refine implicit associations between suicidal and non-suicidal persons.

ID: 152
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: Stroke, Neuroplasticity, Functional Connectivity, tDCS, EEG

tDCS treatment to enhance motor plasticity after stroke: a brain network perspective.

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Patients with mild or moderate motor deficits show high functional connectivity (FC) between motor areas and the rest of the brain in the first weeks after stroke, which is associated with better clinical recovery. In these patients, timely increase of FC may improve motor outcome beyond the proportional rule. We hypothesized that this could be achieved by applying tDCS to the ipsilesional M1 during their regular occupational therapy. To this end, we performed a pilot four-arm parallel study using the following tDCS montages: (1) Conventional Anodal, (2) High-Definition (HD) Anodal, (3) Bi-Hemispherical, and (4) SHAM. This design allowed us to identify the montage with the greatest potential and then compare it to SHAM in a main study that is currently underway.

We recruited 28 patients (24 of whom completed the protocol) with mild and moderate motor deficits within 4 weeks after stroke. Patients received 20 minutes of tDCS six times over a two-week period in conjunction with regular motor training. Pre- and post-treatment assessments included clinical assessments, closed-eye resting high-density EEG, and motor evoked potentials (MEPs). Functional connectivity (FC) of EEG sources was estimated using the absolute imaginary component of coherence. We examined both global and local FC of motor areas.

For clinical outcomes, we observed improved motor function in the Action Research Arm test, but not in our primary outcome, the Fugl-Meyer upper extremity (FMA-UE) assessment in the HD compared to the SHAM group. On a neurophysiological level, the HD montage appears to be the one that most increases cortical excitability in the contralateral hemisphere. The investigation of FC confirmed previous findings that global connectivity in beta band was an early marker of good motor recovery, whereas its late arrival was associated with poorer recovery. Interestingly, a difference was found between groups in local FC change in the theta band, with FC increase positively correlated with change in FMA-UE score. Thus, the connectivity reinforcement between key nodes of the motor network may be a more precise neural target for enhanced recovery. We expect to have deeper insights into this phenomenon once the main study is completed.

ID: 153
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: Intraoperative neurophysiological monitoring, Motor evoked potentials, Brain tumor surgery.

The value of motor evoked potentials in detecting mechanical versus vascular injury during resection of supratentorial mass lesions

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Introduction

During resection of supratentorial mass lesions, motor deficits might be caused by different injury patterns: mechanical (damage of primary motor cortex/corticospinal tract), ischemic (due to coagulation of perforator arteries), or lesion of associative motor areas. Recently, we performed a scoping review to asses motor evoked potentials (MEP) warning criteria. Here we present the data of a subgroup of patients, with focus on the pattern of injury.

Methods

A systematic search of the literature using PubMed, Embase, Scopus, CINAHL and the Cochrane Library was undertaken. Inclusion criteria were electrically elicited MEP with predefined alarm criterion in anesthetized patients undergoing supratentorial brain surgery with quantitative report of motor outcome. For this subgroup analyses we focused on supratentorial parenchymal lesions.

Results

Of the included papers, 54.8% described the intraoperative injury patterns. For permanent motor deficits, 2 groups described exclusive mechanical injury, 6 exclusive vascular and 8 mixed patterns. For transient motor deficits, 3 groups described exclusive mechanical injury, 1 exclusive vascular and 3 mixed patterns. Of 1551 cases, there were 7.8% of permanent deficits (3.2% mechanical, 2.6% vascular, and 1.9% of unclear cause). For mechanical injury 38, 6 and 4 cases had irreversible, reversible and no change of MEP, respectively; whereas for vascular injury the corresponding numbers were 30, 5, and 5. For transient deficits, 27 cases were due to mechanical injury, of which 9 had irreversible, 1 reversible and 17 no change of MEP. For vascular injuries (12 cases) the corresponding numbers were 4, 5 and 3, respectively, with more reversible changes in vascular than mechanical cases (P=0.01-Chi square test).

Conclusion

In the group of patients with transient motor deficits, the subgroup with vascular injury had significantly more reversible MEP changes than the mechanical injury patients. This suggests that an MEP alert may reduce permanent motor deficits caused by ischemia. In the whole group, we observed a slight predominance of mechanical injury. Thus, additional subcortical mapping strategies may improve surgical guidance. Deeper understanding of the mechanisms of injury could help to develop a strategy for a more effective detection of intraoperative lesions, as well as the methodology to avoid permanent deficits.

Top-down and bottom-up interactions at the posterior parietal cortex

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Sensory perception can be represented as the comparison between feedforward bottom-up sensory inputs and feedback top-down expectations of these sensory stimuli. It was recently shown that a subset of posterior parietal cortex (PPC) neurons can report mismatches in audio tactile sensory sequences. We hypothesize that these mismatch neurons report the balance between the bottom-up (sensory input from S1 and A1) and top-down inputs (feedback from premotor M2). To test our hypothesis, we performed simultaneous dual layer two-photon calcium imaging of M2 axons in layer 1 and of layer 2/3 neurons in the PPC. We show that top-down expectancy of the predicted stimuli is reliably reported by M2 axons, while layer 2/3 PPC neurons report auditory and tactile stimuli, as well as mismatches in the sensory sequence. We demonstrate that the PPC can rapidly learn new associations and subsequently report mismatches, while M2 axons update their expectations to the new association. Our results suggest that M2 potentially provides the top-down prediction, which is then compared to the incoming sensory input at PPC. This leads to the subsequent generation of mismatch responses when top-down and bottom up inputs do not match.

ID: 161
Free contribution (poster and short talk)
Topics: Clinical Research
Keywords: Hemifacial spasm, Lateral spread response, Intraoperative neurophysiological monitoring

Modified testing of lateral spread response to guide microvascular decompression for hemifacial spasm

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Introduction

In most patients, hemifacial spasm (HFS) is due to a vascular compression of the facial nerve. The standard for treatment is surgical by microvascular decompression (MVD). Neurophysiological techniques such as lateral spread response (LSR) are used to predict MVD effectiveness. In our institution, we perform a modified selective LSR testing for two branches of the facial nerve (zygomatic = LSRZ and mandibular= LSRM). The aim of the study was to analyze the benefit of the combined LSR testing to predict postoperative short and long-term outcome.

Methods

We included all patients who underwent MVD in our department between 2015 and 2022 and in whom LRS testing was performed. LSRZ and LSRM at the end of the MVD was analyzed. Therefore, three groups of LSR at the end of surgery were build: disappearance, significant reduction, persistence.

Postoperative presence or disappearance of HFS was assessed retrospectively. Statistical analysis was performed calculating sensitivity (Sens), specificity (Spec), positive predictive value (PPV) and negative predictive value (NPV).

Results

Clinical and intraoperative neurophysiological data of 31 patients was analyzed.

In case we categorized the combined LSR (LSRM and LSRZ) into two groups (persistent and complete disappearance/significant reduction) at last follow-up, the data accuracy analysis was: Sens 11%, Spec 100%, PPV 100%, NPV 64%.

If we categorized in the combined LSR in another way into two groups (persistent/significant reduction and complete disappearance), it led to the following: Sens 44%, Spec 71%, PPV 50%, NPV 67%.

Conclusion

In almost all tests, LSR showed high specificity and NPV. Thus, the absence of LSR at the end of the surgery may reassure the surgeon that the patient will not suffer from HFS in the long-term follow-up.

On the contrary, less consistency was found for sensitivity estimates, which were rather low to modest. However, the PPV was ranging from moderate to high indicating that the persistence of LSR at the end of the surgery shows that the patient will still suffer from HFS in the short-term and long-term follow-up.

The modified LSRZ and LSRM testing with accurate placement of stimulation electrodes may further improve surgical guidance during MVD for HFS.

BASIC RESEARCH HUMAN

ID: 101
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: motor sequence learning, electroencephalography, functional connectivity, neural plasticity

Neural mechanisms of motor learning: resting-state network communication vs. local oscillations during training

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Learning new motor skills through practice, also termed motor learning, is central for everyday life. There is abundant evidence that learning is associated with changes in oscillation amplitudes ("event-related power") during training reflecting local activation of motor areas. More recently, another neural mechanism was suggested to influence motor learning: modulation of functional connectivity (FC) that is how much spatially separated brain regions communicate with each other before and during training. The aim of the present study was to disentangle how these mechanisms taken together can predict motor learning. To reach this aim we measured EEG before, during, and after 20 healthy subjects performed a finger-tapping task (FTT). The results showed that global, whole-brain alpha-band FC before and during training of the putamen and medio-temporal lobe (MTL) correlated positively with motor learning. Notably, high learners, i.e., subjects with good learning, showed either high alpha FC before training without local event-related power changes during training or low alpha FC before training with prominent event-related power changes during training. The present results suggest that alpha FC enables efficient neural communication before and during task execution that, in turn, facilitates learning. In contrast, when neural communication is inefficient, as in the case of low alpha FC, event-related power changes take place as a compensation mechanism.

ID: 108
Free contribution (poster and short talk)
Topics: Basic Research Human

Individual differences in intergenerational sustainable behavior are associated with cortical thickness of DMPFC and DLPFC

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There are large individual differences in sustainable behavior, and it is not well understood why some behave sustainably towards future generations while others do not. Moreover, previous research on this topic is rare and has mainly relied on subjective self-report measures.

In this study, we measured cortical thickness as a stable and objective anatomical brain characteristic to explain individual differences in intergenerational sustainable behavior. We combined these neural task-independent data with individuals' behaviors in a behavioral economic paradigm measuring sustainable behavior towards a future generation.

We found that cortical thickness of the left dorsomedial prefrontal cortex (DMPFC), which is associated with perspective-taking abilities, and the left dorsolateral prefrontal cortex (DLPFC), which is associated with self-control capacities, explained individual differences in intergenerational sustainable behavior. Individuals behaving intergenerationally sustainably were marked by greater cortical thickness of the DMPFC and DLPFC compared to individuals behaving intergenerationally unsustainably.

By using a neural trait approach, we were able to differentiate intergenerational sustainable and unsustainable individuals, which in combination with mediation analyses allows us to speculate about the cognitive mechanisms underlying these individual differences.

ID: 111
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: dishonesty, ERP, electrical neuroimaging, microstates, response times

The path of dishonesty: Identification of mental processes with electrical neuroimaging

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Much research finds that lying takes longer than truth-telling. Yet, the source of this response time difference remains elusive. Here we assessed the spatiotemporal evolution of electrical brain activity during honesty and dishonesty in 150 participants using a sophisticated electrical neuroimaging approach – the microstate approach. This uniquely positioned us to identify and contrast the entire chain of mental processes involved during honesty and dishonesty. Specifically, we find that the response time difference is the result of an additional late-occurring mental process, unique to dishonest decisions, interrupting the antecedent mental processing. We suggest that this process inhibits the activation of the truth thus permitting the execution of the lie. These results advance our understanding of dishonesty and clarify existing theories about the role of increased cognitive load. More broadly, we demonstrate the vast potential of our approach to illuminate the temporal organization of mental processes involved in decision making.

Remark from the Author: On the day of the congress, I leave for the United States. Since I still don't know what time I have to be at the airport, I am unsure if I will be able to attend the congress in person. That is why I prefer to decline the possibility of giving an oral presentation as of now.

ID: 120
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: hypnagogia, hypnagogic states, dreams, sleep-paralysis, imagination, extra-sensory perception

Hypnagogic states are quite common: Evidence from a prevalence study with young adults.

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The hypnagogic state refers to the transitional phase between wakefulness and sleep during which vivid experiences occur. There is, however, great ambiguity in the reported prevalences of this phenomenon. In this study, we assessed the prevalence of hypnagogic states and the frequency of experiences in different modalities (visual, auditory, tactile, kinaesthetic, olfactory and gustatory) in three adult samples of a total of 4457 participants. We also asked them to rate their emotional quality, how irritated they felt by their experiences, and how vivid their experiences were. Moreover, we compared hypnagogic states to other states of consciousness, such as dreams, sleep paralysis, imagination, and extra-sensory perception. Hypnagogic states occurred in up to 81.5% of participants and prevalence was comparable across samples. Experiences were most often kinaesthetic (90.3%) and visual (70.9%), and less often auditory (43.1%), tactile (38.3%), and olfactory or gustatory (24.6%). Hypnagogic states were less prevalent than dreams and expressed a different profile of modalities in which they occurred, but were comparable in their emotional quality, the irritation they caused, and their vividness. In conclusion, hypnagogic states are quite common.

ID: 123
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: Adolescence, intraindividual variability of sleep, sleep regularity index, depressiveness

Sleep Regularity in Healthy Adolescents: Associations with Sleep Duration, Sleep Quality and Depressive Symptoms

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Introduction
Current evidence points out the importance of sleep for adolescent physical and mental health. In addition to sleep duration and quality, regularity in the timing of sleep may play an important role. To address this aspect of sleep, the present study investigated daily variability of sleep in adolescents during school days, weekends, and holidays and its association with depressive symptomatology as well as mental health.

Methods

The sample consisted of forty-six adolescents aged 10 to 14 years (mean 12.78 years, SD = 1.07; 23 females). The data presented here were collected as part of a longitudinal study designed to investigate genetic and environmental influences on sleep in adolescents. Through actigraphy, sleep was measured during a 6-month period. Daily variability of sleep was quantified through the sleep regularity index (SRI), and depressive symptomatology was assessed at the end of the 6-months of sleep measurement using the Center for Epidemiological Studies – Depression scale.

Results
Sleep was most regular during school days and less regular during weekends and holidays. More regular sleep on school days was associated with longer total sleep time, shorter sleep onset latency, and higher sleep efficiency. Moreover, higher SRI on school days was associated with fewer depressive symptoms, whereas higher SRI on weekends was associated with less overall psychopathology.

Conclusions
Healthy sleep behaviour is essential for adolescents' physical and mental health. To promote this, adolescents should not only be encouraged to get enough sleep but also to retain regular sleeping patterns, especially during school days. Depressive symptomatology was higher in adolescents that exhibited irregular sleep during the school week.

ID: 126
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: sleep, intervention, dementia, memory, non-invasive, PLAS, SWS, home-use devices, auditory stimulation

The promise of portable remote auditory stimulation tools to boost sleep and prevent cognitive decline

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Dementia is one of the leading causes of mortality globally. Cognitive decline (and, to a lesser extent, normal aging) are associated with sleep fragmentation and loss of slow wave sleep. Evidence suggests a bi-directional causal link between these losses. Phase-locked auditory stimulation (PLAS) has emerged as a promising non-invasive tool to enhance slow-wave sleep, potentially ameliorating cognitive decline. In laboratory settings, PLAS is usually supervised by trained experts. Different algorithms (simple amplitude thresholds, topographic correlation, sine-wave fitting, phase-locked loop, and phase vocoder) are used to precisely target auditory stimulation to a desired phase of the slow wave. While all algorithms work well in younger adults, the altered sleep physiology of older adults and particularly those with neurodegenerative disorders requires a tailored approach that can adapt to older adults' fragmented sleep and reduced amplitudes of slow waves. Moreover, older adults might require a continuous intervention that is not feasible in laboratory settings. Recently, several PLAS-capable portable devices ("Dreem®", "SmartSleep®" and "SleepLoop®") have been developed. We discuss these three devices regarding their potential as tools for science, and as clinical remote-intervention tools to combat cognitive decline. Currently, SleepLoop® shows the most promise for scientific research in older adults due to high transparency and customizability but is not commercially available. Studies evaluating down-stream effects on cognitive abilities, especially in patient populations, are required before a portable PLAS device can be recommended as a clinical preventative remote-intervention tool.

ID: 132
Free contribution (poster and short talk)
Topics: Basic Research Human

Responsiveness to auditory stimulation during slow wave sleep predicts long-lasting increases in memory performance in older adults

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Previous research suggests that phase-locked acoustic stimulation (PLAS) during slow wave sleep (SWS) is able to boost ongoing oscillatory activity and – as a downstream effect – improve sleep-dependent memory consolidation. Due to an assumed bi-directional link between SWS disturbances and memory decline in aging, older adults might profit most from such interventions. Here, 32 healthy older adults (mean age: 68.9) were allocated to an intervention or control group and completed a baseline night with sham (=no) stimulation followed by three consecutive experimental nights with either PLAS (intervention group) or sham stimulation (control group). PLAS induced an entrained slow oscillatory (SO) trough and a peak in all experimental nights compared to sham stimulation. SO power during the stimulation window, spindle power temporally coupled to the entrained SO peak as well as the global number of SO-peak coupled spindles were increased in the experimental nights compared to the baseline night. The Individual magnitude of the increase in the SO and peak-associated spindle band predicted increases in episodic memory performance at post-intervention as well as at a one-week and three-month follow-up. Preliminary evidence suggests that PLAS-induced increases in relative memory performance at the one-week follow up is associated with a beneficial change in plasma amyloid burden. The reported effects are exclusively seen in the intervention but not the control group. In conclusion, we demonstrate for the first time, that PLAS induces long lasting memory benefits in older adults responding well to PLAS, which renders it a promising tool for the treatment of cognitive decline.

ID: 134
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: Hippocampus, Memory, 7T, fMRI, Amnesia

Tracking hippocampal memory traces in healthy humans using 7T fMRI

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Amnesia is conventionally defined as a deficient encoding. However, evidence in rodents suggests that encoding and consolidation of newly formed memories might remain intact in some forms of amnesia resulting in silent memories. A full retrieval is possible if hippocampal engram neurons, i.e., hippocampal neurons that were active during the encoding process, are reactivated artificially by means of optogenetics (Roy et al 2015). Furthermore, evidence in amnesic human patients suggests that memory formation remains possible despite amnesia but the access to these memories becomes unconscious. Therefore, the memories guide the patient's behavior implicitly (Duss et al 2014).

We aimed at simulating amnesia/forgetting in healthy human participants. They learned, consolidated, and retrieved a very large number of person-object combinations. We tracked the fate of the associative memory traces over 2 days using ultra-high field functional magnetic resonance imaging. Functional imaging at higher field strength leads to a better signal-to-noise ratio, which makes it possible to increase the spatial resolution and to scan brain regions with notoriously low signal such as the hippocampus more precisely (Willems, Henke, 2021). Here, we present preliminary data on the fate of the memory representations and their underlying physical memory traces in the hippocampus and across the whole brain.

ID: 135
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: Neurosurgery, Mueller polarimetry imaging, Fiber tract identification

Wide-field imaging polarimetric visualization of healthy brain fiber tracts for tumor delineation during neurosurgery

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Aims

Tumor border identification remains a main challenge in glioma surgery. Difficulties in exact delineation of glioma are the risk factors for both reduced survival rate and neurological deficits. We explore the Mueller Polarimetry Imaging (MPI) for the visualization of fiber tracts of healthy brain by measuring the optical anisotropy and scattering properties of brain tissue. Seeing fiber tracts during brain surgery would enable us to delineate tumors (absence of fiber tracts) and to identify the tracts in sight based on their orientation for safe and complete brain tumor resection.

Methods

We implemented a wide-field MPI system to visualize the white matter fiber tracts using polarimetric maps. The instrument is composed of a white light source, followed by the polarization state generator for polarization modulation of the incident light beam illuminating the sample. Light reflected or backscattered by the sample is collected in the detection arm that includes the polarization state analyzer, followed by the spectral filters and a focusing system to generate the image on the CCD-camera.

Using the MPI system we recorded 16 intensity images for each brain tissue sample. The 4x4 Mueller matrix (MM) images of three thick coronal sections of fresh calf brain, formalin-fixed calf brain, and formalin-fixed human brain were reconstructed from the raw intensity images. The polarimetric maps were obtained by applying Lu-Chipman decomposition algorithm pixel-wise to the experimental MMs.

Results

The acquired in-plane polarimetric images showed that for both formalin-fixed and fresh brain sections, the values of scalar retardance and depolarization in cerebral white matter were higher compared to the corresponding values in gray matter. In addition, it was possible to visualize the orientation of the white matter fiber tracts in sight using the map of the azimuth of the optical axis.

Conclusion

Our results demonstrate that for the three sections of coronal brain tissue, the presence and direction of white matter fiber tracts are clearly detectable using polarimetric maps. The results of our proof-of-concept studies demonstrate the potential of wide-field IMP that offers a fast, reproducible, stain-free, non-invasive method to identify tumor margins indirectly by detecting white matter fiber tracts during neurosurgery.

ID: 136
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: Machine learning, neuroimaging, neurosurgery, white matter tracts

Machine learning for white matter fibre tract visualization in the human brain via Mueller matrix polarimetric data

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Aims
A clear identification of the border between a brain tumor and surrounding healthy tissue during neurosurgery is essential in order to maximize tumor resection while preserving neurological function. However, tumor tissue is often difficult to differentiate from infiltrated brain during surgery. Most existing techniques have drawbacks in terms of cost, measurement time and accuracy. The fibre tracts of healthy brain white matter are composed of densely packed bundles of myelinated axons that form uniaxial linear birefringent medium with the optical axis oriented along the direction of the fibre bundle. Brain tumors, whose cells grow in a largely chaotic way, lack this anisotropy of refractive index. Therefore tumor tissue can be distinguished from of healthy white matter using polarized light.
Methods
A wide-field visible wavelength imaging Mueller polarimetric system was used for the study of formalin-fixed human brain sections measured in reflection geometry. The non-linear decomposition of the Mueller matrices provided the maps of depolarization, scalar retardance and azimuth of the optical axis. We studied the effectiveness of machine learning methods (Deep learning Unet, logistic regression) for distinguishing grey and white matter using polarimetric data.
Results
Manually labelled polarimetric data was used to train a convolutional neural network and a logistic regression model to identify white matter. The Unet achieved a much higher discrimination of white and grey matter (AUC of 0.92) than logistic regression (AUC of 0.81) Within the identified white matter, surface fibre tracts could be visualized and tracked without disturbance from spurious signals in the grey matter.
Conclusion
We expect that Mueller polarimetric imaging modality combined with our ML algorithms for fibre tracking will visualize the directions of fibre tracts in imaging plane during tumor surgery, thus, allowing a neurosurgeon to orient himself, to spare essential fibre tracts and to make surgery more complete and safe.

ID: 138
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: High resolution optical coherence tomography · Spectral domain optical coherence tomography · electron micrographs · photoreceptor cell nuclei

Identification of retinal structures at cellular level by High Resolution Optical Coherence Tomography

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Purpose: The aim of this study was to find out whether improved axial resolution achieved by High Resolution Optical Coherence Tomography (HR-OCT) provides more precise retinal structures at cellular level than current routinely used Spectral Domain Optical Coherence Tomography (SD-OCT) devices.

Methods: Eight healthy volunteers were included in this observational study. Using the SPECTRALIS® High-Res OCT-DMR001 device (Heidelberg Engineering, Heidelberg) macular B-scans where taken and compared to SD-OCT B-scans acquired with a SPECTRALIS® HRA+OCT device (Heidelberg Engineering, Heidelberg). Retinal structures were also compared to hematoxylin-eosin stained sections from a human donor retina.

Results: HR-OCT allowed identification of several retinal structures at cellular level, namely cell nuclei of ganglion cells, displaced amacrine cells, cone photoreceptors and retinal pigment epithelial cells. Rod photoreceptor nuclei were partially detectable. Localization of cell-type specific nuclei were confirmed by histological sections of human donor retina. Additionally, all three plexus of the retinal vasculature could be imaged in high detail. By SD-OCT, the resolution was not sufficient to clearly identify all the above-listed cellular structures.

Conclusion: HR-OCT shows greatly improved visualization of retinal structures to unprecedented cellular details. Given its advanced manufacturing state, HR-OCT has a very high potential to become soon a routine ophthalmologic examination device and may therefore greatly contribute to the assessment of sensitive structural biomarkers in new therapeutic avenues for retinal degeneration.

ID: 141
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: Real-Time Image Processing, Polarimetric Mueller Matrix Imaging, De-noising, Machine-Learning

Towards real-time integration of polarimetric image processing for neurosurgical applications

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Brain tissue characterisation and fibre-tracking can be obtained in vivo by means of Mueller matrix polarimetric imaging. Quantitative physical parameters can be non-invasively determined as to inform local intra-operative guidance and to provide enhanced visual cues in neuro-surgical applications. However, several challenges are currently being tackled to successfully translate Mueller Matrix polarimetric imaging into clinical practice. Among these, the need for a high-performance and nearly real-time image processing framework is paramount, especially in an intra-operative setup. Also, given the sensitivity of Mueller matrix calculation to noise during acquisition, it is common to capture several intensity images for each polarisation state, and to average those measurements before estimation of the Mueller polarimetric parameters. However, large numbers of averages are not compatible with real-time applications in the surgical setting. To overcome these challenges, in this pilot work we first present technical advances aimed to improve the computational performance and scalability of Mueller matrix polarimetric image analysis. In particular, we present a newly developed codebase integrating parallel and multi-processing computing into a python-based library optimised for scalable and stable interfaces including AI and machine-learning designs. The new codebase is demonstrated to reach real-time performance for a localised field of view and is validated against state-of-the-art methods. The codebase is open-source, publicly available and further developments are discussed. Then, building on the codebase, we introduce a novel learning-based denoising design for polarimetric images using denoising diffusion networks (DDNs), to minimise the acquisition time. Here, the goal is to recover accurate, physically consistent and high signal-to-noise ratio (SNR) polarimetric scans from short-time noisy acquisitions. We aim for a novel microstructure-aware denoising strategy in which the inputs are intensity images, with the loss function being determined by the de-noised Mueller matrix and conditioned over the resulting physical parameters consistency. Early results are presented for real polarimetric images from both healthy and pathological brain samples, with varying noise levels and surgical acquisition scenarios. The inferred de-noised images are qualitatively assessed together with the associated polarimetric parameters and quantitatively evaluated against ground-truth data. Computational performance is analysed, and observations are drawn with respect to available state-of-the-art denoising techniques.

ID: 143
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: Three factor model of psychopathology, internalizing problems, externalizing problems, parent-child agreement, sleep quality.

Internalizing problems in early adolescence and their association with reduced sleep quality under consideration of both the parent and child perspective

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Introduction:

Comorbidity of psychiatric conditions in youth is a common phenomenon when using categorial classification systems. Accounting for the high share of co-occurrence, the three-factor model of psychopathology is a dimensional and transdiagnostic approach containing the three higher-order factors internalizing, externalizing, and thought disorders, which can be assessed using parent and child report. Co-occurence predominates in psychiatry, and so do sleep disturbances. However, in dimensional and transdiagnostic conceptualizations, the role of sleep is understudied. Therefore, our goal was to elucidate the relationships between sleep quality and the three-factor model of mental health in adolescence considering both the parent and child perspective.

Methods:

The higher-order factors internalizing problems, externalizing problems, and other problems of the child-behavior checklist (CBCL; parent-report) and its parallel self-report version, the Youth Self Report (YSR; child-report) were used as predictors in a stepwise regression. Moreover, the lower-order syndrome scales of both questionnaires were included to predict subjective sleep quality. The Pittsburg Sleep Quality Index (PSQI) was used to assess sleep quality. The sample investigated consisted of thirty-three adolescents aged 11 to 12 years (mean = 11.73 (± 0.45); 15 girls).

Results:

Both internalizing problems (β = .806, p < .001) and externalizing problems (β = -.512, p = .026) as measured by the CBCL significantly predicted sleep quality (PSQI). Furthermore, the scale withdrawn/depressed, a syndrome scale derived from the YSR (child-report) that was used as a predictor in stepwise regression, significantly predicted PSQI scores (β = .43, p = .014) .

Conclusion:

The association of the CBCL internalizing dimension with diminished sleep quality is consistent with previous results, implying a close link between sleep disturbance and internalizing problems. Moreover, the relationship of withdrawn/depressed symptoms of YSR (also belonging to the internalizing dimension) and diminished sleep quality fits existing evidence as sleep problems are reported by most depressed adolescents. In this study, the relationship between internalizing problems and sleep disturbances is apparent using both parent and child-report, that is, irrespective of the informant. Considering that usually, cross-informant agreement in mental health is modest, this further underlines the salience of this relationship from a categorial and a dimensional standpoint.

ID: 144
Free contribution (poster and short talk)
Topics: Basic Research Human

Motor imagery facilitates spatial memory – Insights from a novel kinesthetic VR-based task

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Spatial memory refers to stored information regarding the location of objects or the self in the three dimensional space and is most frequently studied in the visual domain.
To study the role of vestibular input in spatial memory, we designed a novel, kinesthetic spatial memory task where a target position is encoded and retrieved via active, passive, and imagined head rotations. The passive rotations were performed by a motion platform where participants perceived vestibular input, which enabled them to encode the target position. In the imagination condition the participants were asked to imagine a head rotation onto the target as vividly as possible without executing any head or eye movements. The visual target points were presented using a virtual reality headset. Targets were presented in 14 different positions left and right of the center. 55 participants were tested in this experiment.
We found that the accuracy during retrieval was smaller for the active (median error: 1.83°), than for the passive (median error: 2.34°) rotation condition. The performance in the imagination condition was comparable to active head rotations (median error: 1.87°). A more detailed analysis of the data with respect to the target angles showed that in the active condition all target angles were overestimated. For the passive and imagination condition a more complex relationship between target angle and errors was found. In both conditions, smaller target angles (< 6°) were overestimated, but the large target angles (>= 15°) were underestimated. Interestingly, for the 12° target angle the errors in the passive and imagination condition were smaller than in the active condition.
Our findings suggest, that the availability of only vestibular input is insufficient to reliably encode a head position in 3D space, and that for an optimal encoding vestibular, proprioceptive, and the motor information as available in the active condition are required. The comparable performance in the imagination condition supports the emulation theory of representation, which predicts that motor imagery can produce corollary discharges similar to motor commands while also emulating the sensory consequences of an action (Grush 2004).

ID: 145
Free contribution (poster and short talk)
Topics: Basic Research Human

Effects of concurrent phase-locked tACS-iTBS on neural plasticity in the prefrontal cortex

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Repetitive transcranial magnetic stimulation (rTMS) provides means to alter cortical excitability in an excitatory or inhibitory manner. Theta burst stimulation (TBS) seeks to improve the methodology of rTMS by applying TMS pulses in a way that mimics endogenous theta rhythms, resulting in a much shorter application time compared to standard rTMS protocols. The problem remains that there is high interindividual variability in response to these protocols.

Possible causes of these variabilities could be anatomical variations but also the phase of the ongoing oscillatory activity in which TBS pulses are applied. Previous studies have shown that the extent of the neuronal response to TMS is dependent on this phase: pulses applied at crests elicit greater potentials compared to those applied at throughs. In the case of TBS, pulses are randomly applied and might coincide with throughs of the natural oscillatory activity and thus not able to reach a certain threshold of activation in the cells to induce long-term potentiation (LTP).

Transcranial alternating current stimulation (tACS) can shape the state of cortical excitability in a phase-dependent manner. Applying tACS at theta frequency could be utilized as a sort of priming instrument for TBS. While cortical excitability is increased at crests of the tACS-induced current, applying the TBS triplet pulses at the crests of tACS has the potential to produce larger neuronal responses and thus increase the likelihood of LTP. In our ongoing randomized sham-controlled study, we seek to further increase the cortical excitability of the prefrontal cortex by pairing tACS with a concurrent phase-locked iTBS protocol.

Twenty-six healthy participants will undergo two intermittent TBS (iTBS) sessions, once paired with sham-tACS and once with active tACS in a cross-over design. The effects of the phase-locked concurrent stimulation will be assessed by comparing TMS-induced activity in the EEG before and after the simulation as well as between the two sessions as a measure of cortical excitability. We hypothesize that it will vary significantly between pre- and post-iTBS as well as between sham- and active-tACS sessions.

ID: 147
Free contribution (poster and short talk)
Topics: Basic Research Human
Keywords: Slow wave sleep, auditory stimulation, sleep deprivation, closed-loop stimulation, major depression

Automatized selective slow-wave sleep suppression through auditory closed-loop stimulation

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Introduction:

Recent studies indicate that selective suppression of slow wave sleep (SWS), potentially through modifications of synaptic plasticity, may represent an alternative to therapeutic sleep deprivation in patients with major depression. The purpose of this project was to develop and evaluate a fully automatized selective suppression protocol of SWS based on closed-loop auditory stimulation in a healthy population, which would allow for broader clinical implementation without the need for online supervision.

Methods:

A new automatized SWS suppression approach was developed and evaluated in a healthy, young population (N = 15). Stimulation was applied upon detection of SWS. The SWS detection protocol relied on a topographical template of slow waves. Stimulation consisted of discrete bursts of pink noise with a randomized duration (50-500 ms) and inter-onset interval (1-4 s). A random walk (+-2.5 dB) was superimposed on the linear increase of volume (40-106 dB in 60 s) to add unpredictability in volume.

Results:

The stimulation protocol led to a significant reduction of SWS (-29.6%) and decrease in SWS continuity (-15.0%), with an associated increase in sleep stage N2 (+11.8%), and a decrease in REM sleep (-12.3%) as compared to sham. Slow wave activity during SWS and cumulative slow wave energy at the end of the night were both significantly reduced by about 22% across channels and individuals ($p < 0.05$), without changes in other frequency bands, and with changes specific to SWS.

Conclusions:

We demonstrate that a fully automatized approach can suppress SWS. Future studies are needed to investigate potential functional consequences such as changes to synaptic plasticity and depressive symptomatology in patients with major depressive disorder. Further developments bear the potential for translation to broader and even ambulatory use of automated SWS detection and modulation, and potentially for new treatment developments for major depression.

ID: 154
Free contribution (poster and short talk)
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Targeted metabolomics to assess correlations of signaling lipids and amino acids between human liquor and serum: Pre-analytical challenges for biomarker discovery

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A major challenge for biomarker discovery for central nervous system (CNS) diseases is to understand the association between metabolites in the brain and the periphery. In the context of endocannabinoid system (ECS) drug development, we aim to understand whether signaling lipids and other metabolites correlate between the CNS (cerebrospinal fluid, CSF) and blood (serum). The ECS includes the lipid endocannabinoids 2-arachidonoyl glycerol (2-AG) and anandamide, which are present throughout the CNS but also most peripheral tissues including blood. Lipophilic endocannabinoids might be able to equilibrate from tissues into the circulation via diffusion or transport. Circulating endocannabinoids have been postulated to be potential indirect marker of changes of endocannabinoids in tissues such as the CNS. Several studies reported changes of circulating endocannabinoids in psychiatric disorders. To date, it is unclear whether in humans circulating endocannabinoids reflect the endocannabinoid levels in the brain. To address this, endocannabinoids were quantified with LC-ESI-MS/MS analysis in matched CSF and serum of a human patient cohort (n = 80) in a retrospective study. A low positive correlation of 2-AG could be observed, indicating only a minor association of 2-AG but not anandamide between the CNS and blood. We used targeted metabolomics to associate diverse metabolite classes like amino acids, lipids and glucocorticoids to validate our method.

Further, an impact of pre-analytical processing of blood matrices on endocannabinoid levels was reported. A systematic analysis of different pre-analytical processing protocols for the measurement of endocannabinoids in plasma, serum and total blood cells revealed an impact of coagulation and pro-longed incubation times at room temperature on the endocannabinoid levels. This underlines the importance of the choice of blood matrix and pre-analytical protocol.

Overall, targeted metabolomics is a powerful quantitative method to interrogate associations between central and peripheral metabolites that might serve as biomarkers for certain diseases.

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Abstracts for selected Symposia
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Unravelling changes in ON-bipolar cell signalling during retinal degeneration to optimize optogenetic therapies

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The Retina consists of several cell types. Bipolar cells (BPCs) are the retinal interneurons responsible for decoding and fine tuning the light signal captured by the photoreceptors. BPCs can be divided in two main groups, cone BPCs (connected with cone-photoreceptors) and rod BPCs (connected with rod-photoreceptors) (RBCs). RBCs play a key role in retinal degeneration being the rod pathway the first to be affected. In photoreceptor degenerative diseases indeed, death of photoreceptors leaves behind a light-insensitive retina, luckily consisting of still preserved and functional BPCs, that can be used as targets for vision restorative therapies. With the Optogenetic therapy BPCs can be turn in replacement photoreceptors by expressing a light-sensitive protein and basic visual pathway can be restored. However, degeneration causes changes in ion channels expression in BPCs and fosters rewiring of the retinal network, which impact the synthetic vision restoration. Ion channels indeed are responsible of modulating the cell membrane potential that is fundamental for the transmission of electric signals among neurons. We described for the very first time with immunohistochemical, electrophysiological and molecular techniques that: 1) RBCs share one morphological cell type but two different electrophysiological states characterized by specific ion channel dominance; 2) RBCs express BK channels (big conductance potassium channels) on the dendrites, 2) BK channels on RBCs are downregulated in degenerated retina. Before the presented discovery, BK channels were only described in horizontal and amacrine cells. Treatments with BK channel as a target exist due to BK channel's involvement in a variety of diseases characterized by cell hyper excitability. BK channels heterologous expression, together with the optogenetic therapy, could bring back RBCs to the physiological range and consequently improve the synthetic signaling. Together a better understanding of cell's physiology in healthy tissue and in the cellular adaptations of BPCs during retinal degeneration will provide new avenues for future treatment strategies of blindness.

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Combining somatosensory stimulation and sensory retraining to enhance touch sensibility

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Stroke survivors experience sensory loss, which negatively impacts their independence and life quality. Additionally, sensory loss is associated with a poor neurorehabilitation prognosis. Despite the effects of sensory loss, somatosensory interventions are not the standard of care and receive less attention than motor recovery. One reason for the neglected sensory training in clinics might be that there is still insufficient evidence to drive conclusions on the effectiveness of somatosensory interventions. Somatosensory electrical stimulation (SES) has been found a promising technique to facilitate improvements in motor performance and limb sensation and related brain activity, yet, less is known about the benefits of SES for sensory retraining. Neurophysiological responses to SES during sensory discrimination could help to identify possible benefits of SES for sensory retraining. In this project, we aim to study the effectiveness of SES combined with a sensory discrimination task using a well-controlled virtual environment with robotic haptic rendering to train sensorimotor functions and identify neurophysiological markers that characterize the discrimination of virtual textures during SES.

In a single-session parallel study, we will ask participants to passively explore (with robotic guidance) and discriminate the odd texture among three visually identical textures. The experiment will consist of a familiarization, baseline, intervention, and retention phase. In the familiarization phase, participants will be introduced to the experimental setup and task. During the baseline and retention phase, participants will perform 20 trials of the discrimination task without electrical stimulation. During the intervention phase, participants will perform 60 trials of the discrimination task while we provide SES to their whole hand at the individual sensory intensity (treatment group) or sham stimulation (control group). Moreover, we will record brain activity during the experiment with a 64-channel EEG system. We hypothesize that the treatment group will significantly better discriminate the virtual textures than the control group after the intervention phase and that the effects of SES will be associated with modulated somatosensory brain signals.

This study will provide new insights into the behavioral and neural benefits of somatosensory electrical stimulation for the discrimination of virtual textures and could help to boost sensory retraining in neurorehabilitation.

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Human rapid paired-associative learning, consolidation, and retrieval are supported by hippocampal fast wave ripples

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Episodic memory represents an essential element of human experience, as it allows the integration of experiences into current and future behaviour. For newly encoded episodic information to be available to guide future behaviour, its consolidation is essential. During rest periods following learning, encoded content undergoes replay to strengthen labile memory traces. Specifically, the hippocampus is thought to reinstate neuronal firing patterns to consolidate and thus strengthen the previously encoded memories. Research in rodent models has linked replay to high-frequency oscillations, where hippocampal place cells repeat activity from a previous explorative period during a subsequent rest. In humans, these so-called ripple events have been identified in a variety of cognitive states and seem to be involved in memory processes.
Here, we investigate hippocampal activity recorded during the encoding, consolidation, and retrieval of one-shot episodic memories using intracranial EEG (iEEG) recorded in 8 epilepsy patients. The patients encoded face-written occupation pairs and retrieved the formed semantic face-occupation associations 30 minutes later, following a wake rest period. The results indicate that a single encoding trial is sufficient for the later flexible retrieval of the formed associations and that hippocampal ripples occur during encoding, retrieval, and the wake rest period. We identify ripple events based on relative power changes within the human ripple frequency band (80-120 Hz) and characterise them based on temporal and spectral properties. To investigate their role in episodic memory processes, we relate the ripple count to retrieval performance. We also attempt to identify representations of distinct memory contents based on similarity profiles of ripple activity during consolidation using multivariate pattern analysis. Hippocampal ripple events in humans are reliably detectable during all stages of the episodic memory process and share relevant features with their counterparts in rodents. Their presence during an intermittent wake rest period provides additional evidence for their role in replay and consolidation.