Poster Session – Day 2
Friday, 14th June, 15:30 – 16:45

Group 10: 125 – 137
Thematic Programs: Molecular Mechanisms of Cell Biology & Regeneration of Bones and Joints & Preclinical and Clinical Research for Drug Development & Integrative Structural Biology

(P125) Arginine regulates IL-4 induced Giant Cell Formation

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Multinucleated giant cells (MGCs) are polyploid macrophages that are involved in various chronic inflammatory diseases including tuberculosis, sarcoidosis and schistosomiasis. Besides they are key players in the fibrotic encapsulation of implanted biomaterials, where they are known as foreign body giant cells. Bone resorbing osteoclasts are another type of myeloid derived MGCs. Importantly, a variety of common mediators regulating the process of multinucleation of osteoclasts and IL-4 induced MGCs exist. Previous data indicate that the differentiation of osteoclasts is highly dependent on the availability of certain amino acids including Arginine (Arg). Therefore, we hypothesized that akin to osteoclasts the formation of IL-4 induced MGCs relies on Arg. Indeed, both recombinant Arginase 1 (recArg1) and Arg starvation were able to block *in vitro* MGC generation. Notably, key urea cycle intermediates that fuel into the tricarboxylic acid cycle were able to rescue the detrimental effects of Arg deprivation on MGCs, reversing the metabolic quiescent state of Arg starved cells via restoration of oxidative phosphorylation. Together, these data expand on the types of Arg auxotrophic MGCs, suggesting common themes of Arg utilization for giant cell formation. Importantly, they indicate that Arg depletion via recArg1 might alleviate diseases, where MGCs exert deleterious effects.

(P126) Glucose concentration influences α-tubulin expression in vitro

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(P127) Microbial effector interplay in CRC

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Colorectal Cancer (CRC) is the third most occurring cancer and the fourth most common cause of cancer-related death worldwide. Despite many reports linking the gut microbiome composition to CRC development and therapy response, there is still a lack of mechanistic understanding on how the underlying microbial effectors affect CRC development. Myeloid cells are likely to play a central role in sensing bacterial effectors and modulating the immune composition in tumors. Recent findings by our group show that EGFR expression in tumor-associated myeloid cells (and not tumor cells) promotes CRC. In addition, unpublished data from our laboratory suggest that absence of the EGFR in epithelia increases the concentration of microbiota on the skin while reducing its diversity, thereby promoting inflammation.
We hypothesize that the interaction between microbial effectors and EGFR-expressing intestinal epithelial cells (IECs) and myeloid cells, especially macrophages, impacts inflammatory bowel disease (IBD) and CRC development. To decipher EGFR-dependent effects on microbial signatures and microbial effector interactions in the context of CRC we will perform comparative gut microbiome analyses of mice lacking EGFR in myeloid cells (develop reduced CRC) and wild-type mice utilizing high-throughput 16SrRNA sequencing. Microbes enriched or depleted in an EGFR- dependent manner will be processed to isolate their effector molecules (cell wall fractions including surface polymers or soluble metabolites), which will be subsequently analyzed for their modulator activities on intestinal cells and immune cells. Potent fractions will be analyzed for their modulatory function in vitro, utilizing the purified components. The most potent identified microbial effectors will be tested for their impact on CRC development in genetically engineered CRC mouse models.

(P128) Intra-bladder wall transplantation of bone marrow mesenchymal stem cells improved urinary bladder dysfunction following spinal cordinjury

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(P129) Impact of the lipid metabolism on KP1339 anticancer activity

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(P130) Retinal Neurovascular Coupling in Glaucoma Patients

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Glaucoma is defined by progressive degeneration of retinal ganglion cells (RGCs) resulting in optic nerve head damage and pathognomonic visual field defects. The main risk factor for glaucoma is elevated intraocular pressure (IOP) which is, to date, also the only available therapeutic target. Various approaches to meet the needs of patients who still progress despite adequately lowered IOP are currently under investigation. One of them focuses on the neurovascular unit: As in the brain, retinal blood flow is modulated by neurovascular coupling (NVC). In other words, retinal blood flow increases where light activates neurons to meet the increased metabolic demands. Changes in NVC were shown for several ophthalmologic diseases including glaucoma. In the present study, a total of 96 subjects will be assigned to one of the following groups, depending on the stage and type of glaucoma: primary open angle glaucoma (POAG) with mean deviation (MD) in visual field testing ≤ 10 dB, POAG with MD > 10 dB, normal tension glaucoma (NTG) with MD ≤ 10 dB, NTG with MD > 10 dB. Patients with ocular hypertension, as well as an age- and sex-matched control group will also be included. Flicker induced NVC will be measured using the Dynamic Vessel Analyzer (DVA, Imedos, Germany), a fundus camera-based system quantifying vessel diameter of selected retinal vessels. Also, a custom-built bidirectional fourier-domain optical coherence tomography (FD-OCT) system will be used to assess flicker induced NVC. With this system, it is possible to assess retinal vessel diameters and blood flow velocity simultaneously. The results of this study should help to gain more insight into the pathophysiologic basis of NVC impairment in glaucoma.

(P131) PSORS1C2 is expressed in Hassall´s bodies of the thymus and in terminally differentiated epidermal keratinocytes

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Psoriasis susceptibility 1 candidate 2 (PSORS1C2) encodes a small proline-rich protein of unknown function. Here we determined the expression pattern of PSORS1C2 at the RNA and protein levels in human tissues. RT-PCR showed predominant expression of PSORS1C2 in the skin and weak expression in the thymus. When primary keratinocytes were grown in sub-confluent cultures expression of PSORS1C2 was low, whereas induction of differentiation by post-confluent culture caused upregulation of PSORS1C2. By immunohistochemistry, PSORS1C2 protein was detected in the epidermis and in the thymus. In both tissues, PSORS1C2 was specifically present in cornifying cells of the granular layer and the Hassall´s bodies, respectively. PSORS1C2 is conserved in the mouse and other terrestrial mammals whereas it has been lost in aquatic mammals. The results of this study indicate that the expression of PSORS1C2 is linked to epithelial cell cornification and suggest that the PSORS1C2 protein is a component of the epidermal barrier and might play an important role in topical drug delivery. Based on this study, the PSORS1C2 gene knock down system would be applied to test the structural role of this protein in the differentiated keratinocytes.

(P132) The human ABCG2 Multidrug Resistance Transporter Operates as a Peristaltic Drug Pump Gated by a Hydrophobic Di-Leucine Valve and an Extracellular Lid

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The human ATP-binding cassette half transporter ABCG2 plays critical roles in anticancer resistance, in physiological detoxification, and is implicated in inborn genetic errors such as gout. However, the molecular mechanism of ABCG2-mediated substrate transport remains enigmatic. The atomic structure of ABCG2 predicts a hydrophobic di-leucine motif separating a small upper cavity from a central cavity for intracellular substrate trapping. We show that the architecture of the compact polar roof has a lid-like function, controlling drug release from the upper cavity. Formation of the compact roof, which contains novel residues critical for ABCG2 function, requires the re-entry helix, all putative extracellular loops, as well as stabilization by disulfide bridges and a salt bridge. Remarkably, the di-leucine motif residing below the upper cavity functions as a transporter valve, providing a hydrophobic seal that is crucial for enabling drug extrusion. We propose that substrate translocation from the central to the upper cavities through the di-leucine valve is driven by a squeezing motion, suggesting that ABCG2 operates similar to a peristaltic pump. Our data suggest a new strategy for therapeutic approaches to interfere with ABCG2 function in disease, by targeting the valve or essential residues in the compact extracellular roof.

(P133) Probing the Dynamic Order of Protein Disorder: YAP:TEAD Binding is Facilitated by the Structural Preformation of a Surprisingly Compact State

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Intrinsically Disordered Proteins (IDP) have attracted a lot of attention over the last decade due to both their fascinating structural properties and their involvement in important physiological and pathological processes. The inherent structural flexibility of IDPs, however, requires the application of appropriate experimental methods that can access the distribution of conformational states of disordered proteins. NMR spectroscopy has been developed into a powerful structural biology technique that offers unique opportunities for studying IDPs. In my talk I present our recent findings about the intrinsically disordered TEAD-binding domain of Yes-associated protein (YAP). YAP is a major target and a terminal effector of the Hippo pathway. The Hippo pathway regulates organ size, cell differentiation, and regeneration. The deregulation of the Hippo pathway is associated with cancer development. Therefore, the YAP:TEAD interaction might be a promising therapeutic target for several cancers. For characterization we applied paramagnetic relaxation enhancement, selective labeling with late metabolic precursors, utilization of [up15]N relaxation, and site-directed mutagenesis of key residues for the interaction. Our findings reveal a compact state in YAP that is even more compact than the bound form of YAP. The site-specific [up13]C labeling of sidechain atoms of Phe, Leu, and Met enables us to detect long-range NOEs within this compact state and identify the preformation of a non-canonical secondary structure element in YAP. Furthermore, observed preformed secondary structure elements, which are known to be crucial for the YAP:TEAD interaction, exhibit an interdependence in the locally compact state. In addition, we have shown that the formation of the compact state can be disrupted by mutating crucial residues at the interaction interface. Therefore, they preformation of this state may facilitate the formation of the YAP:TEAD complex.

(P134) Metabolomic profiling and its impact on liver regeneration

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Background & Aims: Postoperative liver dysfunction (LD) still represents a severe complication in patients undergoing liver resection and its incidence is estimated at 10-20%. As postoperative LD commonly develops as a result of delayed liver regeneration, it is most relevant to reach a comprising understanding of this process. Thus, we aimed to investigate the perioperative dynamic of circulating metabolites, as well as differences in the metabolic profile of patients with and without postoperative LD using an unbiased metabolomics approach. Methods Plasma from 95 prospectively included patients was collected preoperatively and on the first and fifth postoperative day (POD5). Per patient and time point 180 metabolites were assessed using the Biocrates p180-kit. Development of LD was prospectively recorded. Results 21 patients (19.95%) suffered from postoperative LD. We observed significant dynamics in the metabolic profile after liver surgery, that tended to normalize upon POD5. Further, we were able to document significant differences of carnosine levels pre- and immediately postoperatively in LD patients versus non-LD patients. Conclusion Within this study we present the first data on the metabolic profile in patients undergoing liver resection and in patients with delayed liver regeneration. While we found a plethora of potential markers for postoperative LD at various time points, we could mainly identify carnosine, a dipeptide based on amino acids, that could adequately differentiate in a preoperative biomarker setting between LD vs non-LD patients.

(P135) Tumor growth rates as independent predictor for therapy response and prognosis of recurrent high grade serous ovarian cancer

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Introduction: The lack of objectifiable predictors for therapy response of patients with high grade serous ovarian cancer (HGSOC) renders estimations of prognosis after chemotherapy for recurrent disease difficult. Therefore, the present study evaluates the prognostic value of a mathematical model (Stein et al 2008) which estimates tumor growth and regression rates based on serial serum CA-125 levels to quantify therapy response and prognosis of patients with recurring HGSOC.
Materials and Methods: The model was validated with data of 141 consecutive patients with advanced HGSOC (stage FIGO IIB-IV) who received primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy at the Comprehensive Cancer Center of the Medical University of Vienna between 2000 and 2013. Correlations between tumor growth and regression rates were assessed by Pearson's correlation coefficient. The impact of tumor growth and regression rates on overall survival was calculated by univariate log rank test and depicted by Kaplan-Meier curves. Multivariate cox regression was used to test influencing factors for statistical independence.
Results: Tumor growth rates ($r= 0.61$; $p<0.001$), but not regression rates ($r= -0.01$, $p<0.91$) correlate with patients' overall survival. In univariate analysis, growth rate constants above the median are associated with a significantly reduced overall survival ($p<0.001$). This result could be confirmed as an independent prognostic factor by multivariate analysis. [$p<0.001$; HR 3.41 (2.16-9.04)]
Conclusions: Tumor growth rate estimates of the model by Stein et al may serve as a promising non-invasive predictor for overall survival in patients with recurrent HGSOC. After clinical validation, the model could provide a non-invasive quantifiable prognostic parameter to assess therapy response and thereby improve treatment decisions and patient counseling.

(P136) Ectopic lymphoid structures in cancer tissues: dissecting complexity and functionality

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Despite accumulated knowledge positioning tumor-infiltrating B cells among powerful contributors to tumor immunity, many questions remain given the complexity of multifarious B-cell subsets and unique ability to assemble into functional ectopic lymphoid structures (ELS). For patients with colorectal cancer metastasis in the liver (CRCLM) our group demonstrated that the presence of CD20+ B cells organized into ELS at the metastatic site is associated with a favorable prognosis. For understanding the assembling mechanisms of ELS and their potential anti-tumor effects, we assessed the cellular composition of ELS established within non-tumorous adjacent colon tissue (NT-tissue), primary colorectal cancer (CRC) and matched CRCLM and compared those structures to germinal centers within secondary lymphoid organ such as tonsil tissue. We developed a computerized microscopy-based algorithm allowing quantitative assessment of various B-cell subsets across large-scale tissue specimens. We stained the tissues for B-cell markers including CD20, AID, IgM, CD27, and CD138. For more detailed characterization we are discriminating the IgM+/CD27+, CD20+/CD27+ memory cells and CD138+/CD27high plasma cells, as well as focusing on CD20/CD3 ratio. Results indicate the tissue type-specific characteristics of lymphoid structures; ELS within NT-tissue and CRC showed similarity in CD20/CD3 ratio, while being different from those detected in CRCLM. The developed algorithm furthermore consolidates the complexity of tumor anatomy and the immune landscape in term of B-cell localization and distribution patterns at primary and metastatic sites.
As outlook, the obtained patient-specific B-cell-attributed immunological imprint, represented by diverse staining-derived data sets, will be aligned with clinicopathological parameters thus aiming to improve patient stratification, get deeper insights into pathobiology of CRC, and propose novel immune checkpoints.

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(P137) 1,25(OH)2D3 Indirectly Effects CD4+ T cell Proliferation and Differentiation via IFN-γ treated hPDLSCs

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Human periodontal ligament stem cells (hPDLSCs), play an important role in periodontal tissue regeneration and homeostasis, partially by affecting the immune and inflammatory responses. Immunomodulatory properties of hPDLSCs are similar to those of other mesenchymal stem cells, which upon priming with pro-inflammatory cytokines like IFN-γ suppress CD4+ T cell proliferation and stimulate regulatory T cell (Tregs) differentiation. 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) directly affects diverse immune cells, like suppressing CD4+ T cell proliferation and triggering Tregs differentiation. However, there are no studies investigating how 1,25(OH)2D3 influences the immunomodulatory effect of hPDLSCs on CD4+ T cell proliferation and Tregs Differentiation. Primary hPDLSCs from 5 individuals were stimulated with 100ng/ml IFN-γ in the absence and presence of 1 and 100nM 1,25(OH)2D3 for 48 hours. Allogenic CD4+ T cells were activated by phytohaemagglutinin and co-cultured with stimulated hPDLSCs for 5 days. T cell proliferation was assessed by CFSE labeling. Tregs differentiation was estimated upon CD4, CD25 and FoxP3 immunostaining, followed by flow cytometry Analysis. In the absence of hPDLSCs, 1,25(OH)2D3 suppressed CD4+ T cell proliferation and triggered Tregs differentiation. Co-culture of IFN-γ treated hPDLSCs with CD4+ T cells resulted in the inhibition of T cell proliferation but had no effect on Tregs differentiation. Surprisingly, under co-culture conditions 1,25(OH)2D3 significantly attenuated the inhibitory effect of IFN-γ stimulated hPDLSCs on CD4+ T cell proliferation and decreased the CD4+ CD25+ FoxP3+ Tregs Population. In summary, 1,25(OH)2D3 exerts different effects on the CD4+ T-cell proliferation and Tregs differentiation depending on the presence of hPDLSCs. The exact role of 1,25(OH)2D3 in the local inflammatory processes during periodontitis and tissue regeneration should be further clarified taking into account interactions between different cell types.

Group 11: 138 – 152

Thematic Programs: Regeneration of Bones and Joints & Cardiovascular and Pulmonary Disease

(P138) Adjunctive antimicrobial measures in surgical peri-implantitis treatment: a systematic review.

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Objectives: The aim of this systematic review was to assess the effect of systemic and local antimicrobial treatments adjunctive to surgical peri-implantitis therapy. The focused question was as follows: Is there a benefit of antimicrobial measures adjunctive to surgical peri-implantitis therapy in terms of clinical and radiographic outcomes?

Methods: A literature search was conducted to identify randomized clinical trials (RCTs) on surgical peri-implantitis treatment with the use of adjunctive antimicrobial measures up to July 2018. RCTs were included (i) that involve surgical peri-implantitis treatment with systemic and/or local antimicrobial therapy; (ii) that provide clinical parameters such as probing pocket depth (PPD), marginal bone level change, and bleeding/suppuration on probing (BoP/SoP); (iii) that have a follow-up of at least 1 year after surgical peri-implantitis treatment; and (iv) that include a minimum of 10 patients.

Results: Out of 540 articles identified, 66 were RCTs. After full-text analysis, 5 RCTs met the inclusion criteria and were chosen for data extraction. Three studies showed that systemic antibiotics might lead to better clinical results based on PPD, BoP, and marginal bone level changes after one year. This beneficial effect, however, is unsustainable based on the 3-year follow up. A total of 3 studies revealed that local chlorhexidine applied intraoperatively failed to support peri-implant bone regeneration based on periodontal as well as radiological parameters.

Conclusions: There is moderate evidence that systemic antimicrobial measures have a transient but beneficial impact on surgical peri-implantitis therapy. There is currently no support for the

use local antimicrobial therapy with chlorhexidine as an adjunctive treatment in this indication. Further studies with more power and longer follow-up periods are needed to gain evidence on the value of antimicrobial measures as an adjunct to surgical peri-implantitis therapy.

(P139) Effect of kaolinite on human periodontal cells and pro-angiogenic marker production in vitro

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(P140) Evaluation of 3D gingival fibroblast toroids as attachment assay for collagen membrane testing

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Guided tissue regeneration involves the attachment of soft tissue to implant biomaterials. For development of biomaterials, in vitro cultures are used, but results often deviate from those in animal testing. 3D cell constructs are more in vivo-like, but have not been evaluated as attachment assays yet. Under the hypothesis that toroidal 3D cell constructs could be used to study attachment behavior of cells, the aim of this study was to evaluate if 3D gingival fibroblast (GF) toroids serve as simple in vitro assay to assess the attachment process of oral fibroblasts onto collagen membranes. 3D ring-like structures (toroids) were produced from human GF using 3D agarose molds. HE-staining was performed on freshly produced GF toroids. GF toroids were seeded onto collagen membranes or plastic surfaces. A resazurin-based toxicity assay was used to test toroid vitality. Light microscopic and fluorescence images were taken to document the attachment process. HE-stainings show normal morphology of cell nuclei in freshly produced GF toroids. GF toroids were metabolically active on collagen membranes and plastic surfaces. On collagen membranes, dilatation of GF toroids could be observed, while on plastic surfaces no changes in the shape of GF toroids were observed. GF toroids show different attachment behavior, depending on the surface material onto which they are seeded. Thus, GF toroids serve as simple assay to study attachment behavior onto biomaterials.

(P141) Milk and dairy products modulate macrophage polarization in vitro

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Objective: Milk holds an anti-inflammatory activity that is particularly relevant to protect infants against necrotizing enterocolitis. Milk might also exert anti-inflammatory effects in adulthood, including the oral cavity where macrophages of the oral mucosal barriers, particular the thin junctional epithelium, are exposed to inflammatory cytokines and saliva. It remains unknown, however, whether milk can modulate the local inflammatory response by affecting the polarization of macrophages.
Material and Methods: To determine whether pasteurized human milk and pasteurized cow milk can provoke macrophage polarization, murine bone marrow macrophages and RAW264.7 cells were exposed to human saliva or the inflammatory cytokines IL1_ and TNF_. Activation of pro-(M1) inflammatory response is indicated by the expression of IL1 and IL8. To determine polarization towards a M2 phenotype, the expression of arginase 1 (ARG1) and chitinase-like 3 (Chil3) was determined by reverse transcriptase PCR and immunoassay. Western blot was done on phosphorylated p38 and JNK.
Results: We show herein that aqueous fractions of human milk and cow milk from different donors and diaries, respectively, significantly decreased the inflammatory response of primary macrophages and RAW264.7 cells when exposed to saliva or IL1 and TNF_. Similar to IL4, human milk and cow milk caused a robust expression of ARG1 and Chil3 in primary macrophages. The polarization of macrophages by pasteurized milk occurred independent of the phosphorylation of p38 and JNK.
Conclusion: These data suggest that pasteurized milk, independent of the origin, can cause the polarization of macrophages from a pro-inflammatory M1 towards a pro-resolving M2 phenotype. Milk might thus have a protective role for the oral cavity by modulation of the macrophage-based innate immune system.

(P142) Effect of vitamin D3 on expression of osteogenesis-related factors by human periodontal ligament stem cells is altered under inflammatory conditions

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Human periodontal ligament stem cells (hPDLSCs) fulfil the minimal criteria of mesenchymal stem cells including differentiation into osteoblasts, chondrocytes and adipocytes. 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$) and 25-hydroxyvitamin D3 (25(OH)D3) have been shown to enhance osteogenic differentiation of hPDLSCs under physiological conditions. Our study aimed to evaluate these effects under inflammatory conditions.

hPDLSCs of six individuals were isolated and stimulated with different concentrations of $1,25(OH)_2D_3$ (0.1-10nM) or 25(OH)D3 (1-100nM) for 48 h. Inflammatory conditions were simulated by addition of either Porphyromonas gingivalis lipopolysaccharide (P.g. LPS) (1µg/ml) or Pam3CSK4 (1µg/ml) in fetal bovine serum free medium. Gene expression levels of osteogenesis-related factors osteocalcin (OC), osteopontin (OPN) and Runt-related transcription factor 2 (RUNX2) were analyzed with RT-qPCR.

Treatment with $1,25(OH)_2D_3$ resulted in a concentration dependent increase of OC and OPN expression in hPDLSCs. In the highest concentration, $1,25(OH)_2D_3$ led to an about 14-fold and 3-fold enhancement of the OC and OPN levels, respectively. In comparison, the presence of Pam3CSK4 decreased the $1,25(OH)_2D_3$-induced OC enhancement to about 7-fold. Same tendency was observed for OPN levels (reduction to ~1,5-fold enhancement), but this effect was statistically not significant. 25(OH)D3 significantly enhanced OC (~7-fold) and OPN (~1,8-fold) expression, which were both significantly decreased by more than 50% in the presence of Pam3CSK4. $1,25(OH)_2D_3$- and 25(OH)D3-triggered OC and OPN gene expression was not affected by addition of P.g. LPS. Further, both vitamin D3 forms had no effect on RUNX2 gene expression.

We observed in our study that inflammatory conditions lead to diminished effects of $1,25(OH)_2D_3$ and 25(OH)D3 on osteogenesis-related factors in hPDLSCs, suggesting a decreased effectiveness of vitamin D3 on local bone metabolism in individuals with inflammatory disease.

(P143) Characterisation of bone and muscle mass development in inbred male mouse strains: a pilot investigation

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Background and aim: Bone and muscle are closely linked to allow tissue function, and according to the mechanostat theory, the muscle-derived forces act as mechanical stimuli that generate strain in the skeleton and drive changes in bone mass and strength. In order to assess potential strain differences in bone and muscle mass development, in this pilot investigation we characterised bone and muscle parameters in male C57BL/6J, DBA/2JRj and C3H/J mice. Methods: Bone microstructure of the femur was assessed by micro-computed tomography and the weight of several muscles (triceps, quadriceps, tibialis anterior, extensor digitorum longus, soleus and gastrocnemius) was measured at the age of 8, 16 and 24 weeks. Results: By 24 weeks, C57BL/6J mice presented with the highest muscle mass at all sites measured. In contrast, C3H/J mice had higher cortical thickness, cortical area and trabecular thickness compared to C57BL/6J and DBA/2JRj mice at all time points. Conclusions: This study shows that these 3 commonly used inbred mouse strains display different bone and muscle phenotypes during growth, with the C3H/J mice displaying the best bone parameters and the C57BL/6J mice presenting with the best muscle parameters. These strain-specific differences should be taken into account in future experimental designs and have potential implications for data interpretation and reproducibility. Acknowledgements: MP is the recipient of a postdoctoral Ernst Mach Fellowship.

(P144) An inducer system of autonomous pellet formation for chondrogenic differentiation

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(P145) Anticoagulation Quality and Frequency of INR Testing in LVAD Patients: A Correlation to Hemocompatibility Related Adverse Events and Outcomes

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Anticoagulation therapy in LVAD patients is essential to reduce hemocompatibility related adverse events (HRAE). Phenprocoumon dose must be adapted/monitored by INR point-of-care-testing (POCT). The study aims to determine if the frequency of INR POCT in LVAD outpatients has an influence on the quality of anticoagulation therapy, HRAE and clinical outcomes.

This retrospective, pseudo-randomized study included n=48 patients who received an LVAD implantation (HMII, HM3 and HVAD) between Jan. 2012 and Oct. 2016. Based on the frequency of weekly INR POCT, we compared a daily (n=36) and a 3x/week (n=12) group, specifically the 1-year anticoagulation quality (% of INR Tests in Range) as well as clinical outcomes, readmissions and HRAE using Kaplan-Meier curves. Readmission profiles and outcomes in three groups, based on the achieved quality of anticoagulation (% of INR Tests in Range) ranging from 0-60% (poor), 60-70% (acceptable), 70-100% (well controlled) were compared.

Daily and 3x/week groups were similar in demographic and pre-operative risk factors, INR target (2.0-3.0, p=0.27) and Aspirin daily doses (p=0.29). Freedom from any HRAE (38.9% vs. 25.0%, p=0.44), any readmission (72.2% vs. 75.0%, p=0.97) and 1-year survival (91.7% vs. 91.7%, p=0.98) were comparable in both groups. The % of INR Tests in Range was significantly higher with the daily self-assessments (73.5% vs. 68.4%, p=0.006). Freedom from any neurological event (91.7% vs. 75.0%, p=0.14) was n.s. higher in the daily POCT group. Well vs. poor controlled INR POCT patients had a significant higher freedom from any neurological event (96.0 vs 69.2%, p=0.024) as well as hemorrhagic strokes (100% vs. 76.9%, p=0.011).

Well controlled anticoagulation of LVAD outpatients results in less neurological events including hemorrhagic stroke. Daily INR POCT and subsequent dose adjustment of vitamin-K antagonists result in a better quality of anticoagulation

(P146) The relation of initial blood gas analysis and ankle-brachial index in emergency department patients with decreased renal function

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Background: Ankle-brachial index (ABI) as a noninvasive test for diagnosis of peripheral artery disease (PAD) is a predictor of future cardiovascular events, and values are suggested to be elevated in chronic kidney injury. However, data on utilization of ABI in an Emergency Department (ED) population are scarce. Methods: From 11/2018 until 03/2019, 140 patients treated at the ED of the Medical University of Vienna were included in an ongoing study screening for subclinical PAD. ABI and pulse-wave velocity (PWV) were obtained additionally to procedures such as blood gas analyses (BGA). The patient subgroup with signs of decreased renal function in initial BGA (creatinine > 1.1 mg/dL) was selected to assess the relation of its parameters with ABI and PWV. Results: Twenty-eight patients (79% male, age 71 ± 13 years, BMI 26 ± 5) were included in this subgroup analysis. Thirteen (46%) had a history of chronic kidney injury, 3 (11%) bared an already-known PAD. Nine (32%) patients showed a pathologic ABI, the median PWV was 14.2 [12.7-16.4] m/sec. Initial BGA showed a creatinine of 1.3 [1.2-1.9] mg/dL and calcium values of 1.4 [1.2-1.9] mmol/L. Serum laboratory results yielded a creatinine of 1.5 [1.2-1.7] mg/dL, a blood urea nitrogen of 29.3 [22.8-37.0] mg/dL and a glomerular filtration rate of 45.3 [32.7-53.8] mL/minute/1.73m2. No correlation between deranged kidney function parameters and ABI or PWV values was observed. A trend towards an indirect correlation between ABI-values and BGA calcium levels was noted (r = -0.3, p = 0.05). Conclusion: In 6 (21%) patients, PAD was newly diagnosed. The relation of kidney function parameters and ABI / PWV measurements must be re-evaluated in a larger collective. Whereas a relation between ABI-values and serum calcium levels is already known, a trend could now also be detected in initial BGA in ED patients. Calcium levels could be added into a combined prediction tool of future cardiovascular events in the main study collective.

(P147) Cardiac pacing and chemotherapy: Pacing threshold reflects cardiotoxic effects and predicts survival: A retrospective trial

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Anticancer therapy includes agents with cardiotoxic side effects. In patients with pacemakers (PM), pacing threshold (PT) reflects conditions of myocardial tissue. The aim of this study was to investigate PT, rates of device and lead replacements and survival in patients undergoing anticancer treatment.In total, 5070 PM patients of the Medical University of Vienna between 2000 and 2015 were included retrospectively. ICD-10 Codes of the category C (malignant neoplasms) and I42 (cardiomyopathy) and mortality data were retrieved. Cancer was diagnosed between first PM implantation and the last documented follow-up of the PM in 321 patients. 4749 non-cancer patients represented the control group. Fist implantation age and rates of dual or single chamber PM was not different. Cardiomyopathy occurred in 16.4% of the cancer patients, and in 12.1% of the non-cancer patients (p=0.03). Device replacement was more likely in patients with cancer (10-year follow-up: 61.1% vs. 36.6%, HR 2.0, 95%CI 1.6-2.5, p<0.001). Lead replacement was increased in cancer-patients (17.6% vs. 5.3%, HR 3.5, 95%CI 1.9-6.5, p<0.001). Ventricular PT showed no difference at the time of PM implantation and increased in the cancer-group by 0.2V (IQR -0.25 - +0.5). There was no change in the non-cancer group (0V IQR 0-0.25, p<0.001). Mean survival was 14.3 years (95%CI 13.5-15.1) in non-cancer-patients and 12.2 years (95%CI 11.1-13.3) in cancer-patients. In a univariate COX regression of the cancer-group, a stronger increase of ventricular PT during the follow-up period was associated with worse 10-years survival (HR 1.4, 95%CI 1.3-1.6, p<0.001). In patients with cancer, PT increases significantly stronger, an increased rate of device and lead-replacement was found, and an increase of the PT was a predictor for worse survival. This might be closely related to the cardiotoxic effects of chemotherapy.

(P148) Sublingual microcirculation in diabetes

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Objective: To study microvascular parameters, ie. glycocalyx dimensions as well as functional and perfused total capillary density in vivo in patients with type 1 and type 2 diabetes mellitus.

Methods: In vivo sublingual sidestream Darkfield videomicroscopy was performed in 36 patients with diabetes mellitus (type 1: n=20, type 2: n=16) and compared to a control group of 36 healthy volunteers.

Results: Patients with HbA1c levels ≥8% had a significantly higher perfused boundary region (signifying the loss of glycocalyx dimensions) compared to patients with HbA1c levels <8%, which was more pronounced in type 1 diabetes (2.08µm [1.95–2.16 µm] vs.1.9µm [1.66-1.94µm], p=0.029).

Capillary density did not differ significantly between patients with diabetes and healthy controls. There was an inverse correlation between total perfused (r=-0.553, p=0.015) capillary density and high density lipoprotein levels in patients with type 1 diabetes. Renal parameters were associated with microvascular perfusion in patients with type 2 diabetes (correlation between eGFR and functional capillary density: r=0. 568, p=0.027/ RBC filling percentage: r=0.657, p=0.008). In addition, the ratio of functional/ total perfused capillary density was associated with CRP levels in type 2 diabetes (r=0.682, p=0.021).

Conclusion: Diabetes is associated with loss of glycocalyx density. This study suggests a multifactorial influence on the microvasculature in diabetic patients.

(P149) EMMPRIN as a potential biomarker for atherosclerotic plaque vulnerability in patients with high-grade carotid stenosis

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(P150) The Correlation Of Coagulation Factor XIII Activity and Anastomotic Leakage In Patients Who Undergo Bowel Resection: A prospective observational study

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Anastomotic leakages (AL) are rare but severe complications of bowel resections. AL occurs in 5% to 10% of bowel resections, its causes are mostly unknown. The authors are testing whether or not there is a correlation between low coagulation factor XIII (CFXIII) activity and AL in a prospective observational study. Preliminary data is to be presented. For the last two years, CFXIII activities of patients who were planned to undergo bowel resection was monitored. CFXIII activity was determined at three stages and is given in per cent: 1) directly before the surgery, 2) on the first or second postoperative day and 3) on the fourth, fifth or sixth postoperative day. After fifteen days patients were divided into two groups: a) a no-leakage-group and b) a leakage-group. To this point 221 patients have been included in the study and analysed. Six had confirmed anastomotic leakages. In the no-leakage-group the medians of CFXIII activities were 125% 1), 92% 2) and 83% 3). Standard deviations were 39.46% 1), 30.49% 2) and 27.35% 3). In the leakage-group the medians of CFXIII activities were 120% 1), 68% 2) and 56% 3). Standard deviations were 45,34% 1), 22,16% 2) and 10,09% 3). Low CFXIII activity could be a contributing factor in AL. The study is to be continued. 400 patients are to be included followed by a comprehensive analysation of other factors such as intraoperative fluid administration.

(P151) Oxygen oscillations as pathomechanism in respiratory failure: Characterization of intercellular communication by miRNA profiling of microvesicles

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Acute respiratory distress syndrome is the most severe form of acute lung failure and is characterized by impaired gas exchange in the lungs due to injury to the cells forming the alveolo-capillary barrier. Treatment includes mechanical ventilation with markedly increased concentrations of inspiratory oxygen. This leads to volu-, baro- and atelectotrauma by mechanical ventilation. Because of cyclic recruitment and derecruitement of atelectatic lung areas oscillations in arterial oxygen content are observed. Our preliminary data from an in vitro study suggests that these oscillating oxygen concentrations are associated with increased endothelial damage. Micro RNAs, originating from these cells, influence gene translation and can be transported via extracellular vesicles to distant cells. The aim of our study is to analyze the micro RNA content of extracellular vesicles of human lung microvascular endothelial cells and their mother cells. We use lung tissue from healthy donor lungs, routinely resected for size adjustement during lung transplantations. Cells are then isolated and purified through either magnetic bead separation or flowcytometry sorting. Cells are then exposed to oscillating oxygen concentrations (0-21%, 0-45%, 0-95%) at 10 cycles per hour or static concentrations (21%, 95%) as control group. Micro RNA levels are then determined using reverse transcriptase and qPCR panels. Examination of extracellular vesicles (size, amount, surface markers) will be done by flowcytometry. Knowledge of micro RNA content might give additional information concerning the pathomechanism of ARDS and could also identify potential targets for future therapeutic intervention. This study is funded by the Fund of the mayor of the city of Vienna, project number 18033.

(P152) Protective effect of Argon against ventilator-induced lung injury: in vivo proof-of-concept study in a mouse ventilator-induced lung injury model

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Group 12: 153 – 163
Thematic Programs: Cardiovascular and Pulmonary Disease & Vascular Biology

(P153) Characterization of left ventricular function, proinflammatory cytokines and NRG-1 in chronic kidney disease model in rat

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The prevalence of chronic renal disease (CKD) is continuously increasing in developed countries and associated with left ventricular hypertrophy (LVH) and diastolic dysfunction (DD). Cardiac microvascular low-grade inflammation and altered expression of endothelium derived Neuregulin-1 (NRG-1) are contributed to left ventricular DD. Therefore, the present study aimed to investigate the effect of CKD on cardiac and kidney levels of NRG-1, as well as cardiac gene expression profile of fibrotic and inflammatory markers. Male Wistar rats were used and randomized into 1) Sham operated and 2) CKD was induced by 5/6 nephrectomy. Nine weeks later serum urea and creatinine levels were measured to verify the development of CKD and transthoracic echocardiography was performed to monitor cardiac morphology and function. Furthermore total RNA was isolated and RT-qPCR was performed to evaluate the expression levels of inflammatory cytokines. In addition, NRG-1 protein levels were measured in both kidney and heart tissue by ELISA. In the 5/6 nephrectomized group, serum urea and creatinine levels were significantly higher ($p<0.05$ vs Sham operated group). There was no difference in LV ejection fraction between the groups, however CKD rats were showed impaired diastolic function (e' was significantly decreased and E/e' was significantly increased; $p<0.05$, respectively). This was accompanied by a significant decrease in NRG-1 protein levels in both cardiac and kidney tissue ($p<0.05$ vs Sham, respectively). Moreover, the expression of TNF-alpha, MMP-9, MCP-1 and TGF-beta mRNA were increased in LV tissue samples in CKD ($p<0.05$ vs Sham, respectively). CKD resulted in left ventricular DD and this was accompanied by the upregulation of pro-inflammatory cytokine expression and decrease in both cardiac and kidney protein expression of NRG-1. Thus, targeting inflammation and NRG-1 represents a novel target for improving the detection, management, and prevention of CKD-induced cardiomyopathy.

(P154) Remote conditioning partially reverses myocardial ischemia and reperfusion induced vascular endothelial dysfunction in aorta

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Myocardial infarction (MI) does not only cause damage to the myocardium, but also remote vasculature often show endothelial dysfunction (ED) and may increase the risk for additional atherothrombotic events. Vascular protective strategies are limited to reverse ED after MI. Remote ischemic perconditioning (RIPerc) is considered as a potential clinical approach to reduce myocardial infarct size and improve endothelial function. Nevertheless, there is a lack of evidence whether RIPerc preserves endothelial function late after MI. Therefore, the aim of this study was to explore the effect of RIPerc on endothelial function studied in the abdominal aorta. Male OFA-1 rats were subjected to 30 min od temporary occlusion of the left anterior descending artery (LAD) followed by 4 weeks of follow-up and separated into three groups: (1) sham operated (Sham, without LAD occlusion; n=6); (2) myocardial ischemic reperfusion (MIR) (n=10) and (3) MIR+RIPerc (n=8) group with three cycles of 5 minutes of I/R on hindlimb performed during myocardial ischemia. Assessment of vascular reactivity in isolated aortic rings was performed by a wire myograph. Accordingly, endothelium dependent relaxations were determined by administration of cumulatively increasing concentrations of Acetylcholine (1nM-10µM) precontracted with Phenylephrine (1nM-10µM). The endothelial-independent relaxation was also tested. Assessment of plasma Malondialdehyde (MDA) levels, as a marker for oxidative stress was performed by HPLC. After 4 weeks follow-up, segments of abdominal aorta from MIR group display endothelium-dependent relaxation in comparison with Sham group ($P<0.05$). In addition, rats with RIPerc showed a preserved endothelial function. The endothelial-independent relaxation was not affected. RIPerc showed a tendecy to preserve endothelial function late after MI without affecting plasma MDA levels. Therefore, RIPerc maybe a novel therapeutic approach in the treatment of ED in patients with MI.

(P155) Progression of cardiac and vascular dysfunction in mouse model of Duchenne Muscular Dystrophy

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Duchenne Muscular Dystrophy (DMD) is an X-linked recessive, progressive muscle wasting disease. Besides skeletal muscle degeneration, an increasingly important source of morbidity and mortality is dilated cardiomyopathy leading to heart failure, arrhythmias and vascular dysfunction. There is substantial evidence that Tenascin C (TN-C) plays role in maladaptive left ventricular remodelling and its serum levels are associated with the severity of left ventricular (LV) dysfunction in patients with ischaemic heart disease and heart failure. In addition, recent studies demonstrate that endothelial dysfunction may contribute to the progression of dilated cardiomyopathy. Aims: Our study was aimed to 1) assess the progression of cardiac and vascular (dys)function in mice (3 and 6 months old) with DMD and 2) explore the role of TN-C, as a potential biomarker for progression of heart failure in DMD. Male mdx and BL/10 mice were used (3 and 6 months old). LV ejection fraction (LVEF) was assessed by echocardiography and hemodynamic function was recorded by an invasive method assessing LV systolic pressure (LVSP) and the rate of LV pressure development (+dP/dt). Vascular reactivity was described by wire myography. RT-qPCR was performed to assess the expression of Tnc mRNA. Plasma levels of TN-C were measured by ELISA. Mice with DMD showed a moderate to severe endothelial dysfunction at age of 3 and 6 months in comparison to Wt littermates ($P<0.05$ and $P<0.001$, respectively). In addition, LV dilatation was observed in DMD mice compared to Wt littermates ($P<0.05$; 6 months old) and plasma levels of TN-C were positively correlating with LV-end systolic ($p<0.01$) and LV-end diastolic ($P<0.01$) diameter. Our study first time demonstrates an early and progressive endothelial dysfunction in mice with DMD. In addition, plasma levels of TN-C increased and correlated with LV dimension. Collectively, our data suggest that targeting early endothelial dysfunction and TN-C upregulation might be a novel therapeutic approach for preserving cardiovascular function in patients with DMD.

(P156) Aspirin for primary prevention of cardiovascular disease – a meta-analysis

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(P157) Assessment of the tissue Renin-Angiotensin-System RAS in a pig model of heart failure

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Background. Plasma renin levles show an excellent correlation with circulating (AngI+AngII) levels in HFrEF patients independent from RAS inhibitor therapy. However, the myocardium and the kidneys are equally capable of synthesizing RAS components resulting in tissue specific angiotensin levels.

Methods. We included 10 pigs into this study, which were randomized to control (n=5) or HF groups (n=5) at 3 months. The animals in the HF-group underwent myocardial infarction (MI) of 90 min via percutaneous balloon occlusion of the left anterior descending coronary artery. At day 3 and at 6 months cardiac MRI (cMRI) was performed. At 6 months plasma samples, left and right ventricular tissues of the myocardium and kidneys were obtained. Plasma renin activity (PRA) was measured. Concentrations of the RAS-fingerprints were investigated.

Results. cMRI confirmed a scar area of 21.5% (IQR 20.2-22.4) of the LV at day 3 and reduced LV EF of 41.8% (IQR 41.3-44.1) at 6 months in the HF-group compared to 53.0% (IQR 51.8-55.0) in the C-group. PRA levels were higher in control compared to HF animals. Kidneys showed a vast amount of angiotensins whereas almost all angiotensin peptides were below the detection limit for LV and RV. There were no differences in tissue angiotensin levels between HF and control animals. Plasma (AngI+AngII) levels were higher for control animals according to higher circulating renin activity [93.0pM (IQR 83.1-178.0) vs 12.9pM (IQR 12.7-19.7), p=0.008]. PRA correlated well with circulating (AngI+AngII) levels [r=0.88, p<0.001] but not with tissue angiotensin levels of the kidneys.

Conclusions. Angiotensin peptide concentrations were minimal in myocardial LV and RV specimens. The kidneys displayed vast amount of angiotensin concentrations with a wide variation. Plasma renin activity, as a surrogate for RAS activation, correlated excellent with circulating angiotensin levels. Tissue angiotensin levels seem to be unrelated to systemic RAS regulation.

(P158) Retinal oxygen saturation is affected in patients with mild cognitive impairment and Alzheimer's disease

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In systemic neurodegenerative diseases such as mild cognitive impairment (MCI) or Alzheimer's disease (AD), structural and functional retinal alterations have been found. The current study was performed to assess oxygen saturation (SO_2) in retinal vessels in patients with either MCI or a mild to moderate degree of dementia due to AD compared to age-matched, healthy control subjects. Inclusion criteria for MCI were normal general cognitive but abnormal memory function and Mini-Mental State Examination (MMSE) score >26, for AD, a diagnosis of probable AD of mild to moderate degree and MMSE 20-26. Oxygen saturation in retinal vessels was measured using a Retinal Vessel Analyzer (Imedos, Jena, Germany). The arteriovenous difference in SO_2 was calculated by subtracting the mean venous SO_2 from the mean arterial SO_2. Retinal nerve fiber layer thickness (RNFLT) was assessed using an optical coherence tomography system (Heidelberg Spectralis OCT, Germany). Forty-one patients and 23 healthy subjects (mean age 72.7[+-]9.2 years vs. 70.0[+-]7.7 years, p=0.23) were included in this study. Oxygen saturation in retinal vessels was not significantly different between patients with MCI or AD and healthy subjects (arteries: 94.4[+-]4.9% vs. 95.6[+-]3.1%, p=0.27, veins: 73.9[+-]7.3% vs. 72.2[+-]5.1%, p=0.32). Conversely, arteriovenous difference in retinal SO_2 was significantly lower in patients with MCI or AD compared to healthy subjects (20.5[+-]5.1% vs. 23.4[+-]3.9%,

p=0.02). RNFLT tended to be lower in patients compared to healthy controls (93.9[+-]13.5 vs. 99.7[+-]9.1µm, p=0.07). The reduction of arteriovenous difference in SO_2 in patients with MCI and AD may reflect changes in retinal oxygen metabolism. These findings are in agreement with previous reports showing changes in retinal oxygen metabolism as well as RNFLT in patients with neurodegenerative disease. Supported by the Austrian Science Fund FWF KLI 529.

(P159) In vitro hypertrophy stimulation in human cardiomyocytes leads to down-regulation of MEF2C and GATA-4: potential role of miRNA-21 and miRNA-29a.

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Introduction: Cardiac hypertrophy is a major problem in clinics due to remodeling of heart tissue, increase of heart muscle size and mass and fibrotic tissue formation that further can lead to heart failure and death. MicroRNAs (miRNA) have shown to play a key role in the molecular regulation of pathological processes. In this study a human cardiomyocyte hypertrophy model using Endothelin-1 (ET-1) or Angiotensin II (AngII) as stimulation agents was established, and new miRNA pathways in cardiac remodeling should be defined.

Methods: Human cardiomyocytes were seeded to 48-plates and stimulated for 6h, 18h and 24h hours with different concentrations of ET-1 and AngII. The expression of MEF2C, GATA-4, miR-21 and miR-29a on the mRNA/miRNA level was examined by qPCR. An ELISA Kit for human proBNP was used to measure the secretion of BNP into the cell culture supernatant.

Results: BNP secretion into the cell culture supernatant showed a dose dependent course with highest expression with 100nM AngII (13,45ng/ml) and 5nM ET-1 (7,45ng/ml) compared to the control (<0,4ng/ml). Gene expression analysis of MEF2c and GATA-4 (myocyte function and development) revealed a down-regulation in all treated samples compared to untreated cells. MiR-21 and miR-29a seem to be differently expressed depending on the stimulation type. miR-21 and miR-29a were down-regulated when stimulated with ET-1. AngII stimulation leads to a controversial miR-21 and miR-29a expression and seems to have an unclear expression pattern depending on treatment dose.

Discussion: The results confirm that hypertrophy was successfully induced in human cardiomyocytes with increased protein expression of BNP and decreased expression of MEF2c and GATA-4 on gene expression level with both simulating agents. The expression of miR-21 and mir29a indicate their potential role in the molecular regulation of pathological processes in cardiac hypertrophy and needs to be further clarified in additional experiments.

(P160) Circular RNA CDR1as detected in porcine heart via qPCR and Sanger sequencing

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Circular RNAs (circRNAs) are a class of non-coding RNAs (ncRNAs) that have attracted recent interest as potential drug targets and novel biomarkers in the cardiovascular field. circRNAs are characterized by a covalently closed loop and lack 5' and 3' ends.

Recent studies have reported an increased expression of the circRNA circCDR1as/ciRS-7 in infarcted murine heart. The pig is an important animal model for translational development in the cardiovascular field, but there is incomplete knowledge of the presence of circCDR1as and other circRNAs in porcine hearts. Therefore, we aimed to identify and characterise porcine circCDR1as and its expression in the myocardium.

Porcine, human and murine genomes were aligned in UCSC genome browser to identify the putative porcine circCDR1as sequence. Divergent primers were designed for amplifying the sequence containing the circCDR1as backsplice junction. PCR products were analysed in agarose gels for purity and molecular weight, followed by Sanger sequencing. We compared the expression of circCDR1as in AMI pigs with non-AMI pigs (control) using qPCR with divergent primers.

Bioinformatic analyses identified a genomic sequence with high homology to human and murine circCDR1as (>75 %), and flanking regions of short interspersed nuclear elements, which are instrumental for generating backsplicing. Our qPCR assay with divergent primers proved the expression of circCDR1as in pig myocardium. Together with sequencing through the backsplicing junction and RNase R digestion, the circular form and the nucleotide sequence was established. Expression of CDR1as increased 11-fold in the infarcted region, but not unaffected heart tissue, compared to non-infarcted controls.

We confirmed the expression of CDR1as in porcine hearts and an increased expression in the infarcted myocardium. Therefore, pigs are suitable models for dissecting CDR1as function and its potential as a biomarker for AMI.

(P161) Surgical models of abdominal aortic aneurysm formation in mice

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Abdominal aortic aneurysms (AAAs) occur in 10% of men over the age of 75 years, are mostly asymptomatic and therefore diagnosed incidentally. AAAs are aortic dilatations due to destruction of the medial layer of the blood vessel and are frequently accompanied by formation of an intraluminal thrombus. As it has been shown previously that neutrophils and neutrophil extracellular traps (NETs) play an important role in the pathogenesis of AAA, we aim to test the therapeutic potential of NET inhibitors on established AAAs in mice. For this purpose, we chose two representative models, the perfusion of porcine pancreatic elastase (PPE) into the infrarenal aorta as well as the systemic treatment with angiotensin-II (Ang-II) through a subcutaneous osmotic pump, leading to suprarenal aneurysm development. While the PPE model relies on acute vessel injury to trigger media destruction and aneurysm formation, the Ang-II model recapitulates risk factors of human disease such as hypertension and hyperlipidemia. In both models, a catheter is implanted into the vena jugularis externa after an aneurysm has been induced, i.e. at established disease (day 7 for the PPE model, day 10 for the Ang-II model) through which daily intravenous injections of various NET inhibitors can be performed. Recently, we have shown that the PPE model induces complications such as partial or complete paraplegia, difficulties which have also been detected in human aortic aneurysm repair and which may be due to prolonged ischemia. Moreover, we have seen that silicone is an incompatible biomaterial with mouse skin, leading to necrosis, requirement for wound revisions and occurrence of secondary wound infections after mouse port implantation. Therefore, we currently focus on the optimization of the surgical procedures and materials used, which will be presented in a comparison of the two mouse models.

(P162) Long term inhibition of Complement C1s in Patients with Cold Agglutinin Disease: Results from a Named Patient Program

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(P163) Pro-inflammatory Macrophage Polarization enhances Neutrophil Extracellular Trap Degradation

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Neutrophil granulocytes are able to extrude their deoxyribonucleic acid in form of so called neutrophil extracellular traps, which were shown to promote thrombus formation and progression by providing a scaffold for platelets and also activating them through their content of associated histones. Macrophages infiltrate thrombi and lead to their reorganization, culminating in the revascularization of thrombotic vessels. Although their ability to degrade fibrin and to promote neovascularization have been studied intensively, it is not known if macrophages degrade neutrophil extracellular traps, which are tangled into the fibrin-network of a thrombus. In this study, we investigated differently polarized macrophages[1] ability to degrade in vitro generated neutrophil extracellular traps as well as the uptake of citrullinated histone H3 (a specific marker for neutrophil extracellular traps) in a co-culture experiment of macrophages with sections of thrombi. Pro-inflammatory polarization of human monocyte-derived macrophages with lipopolysaccharide and interferon-gamma led to significantly increased uptake of citrullinated histone H3 after 6 hours of co-culture. All macrophage subsets were able to degrade neutrophil extracellular traps, but this degradation was accelerated in pro-inflammatory macrophages, leading to significantly enhanced breakdown. Inhibition of phagocytosis by addition of 1µg/ml Cytochalasin D resulted in nearly complete abolishment of the neutrophil extracellular trap degradation in all macrophage subsets. Summarizing, our data show that macrophages are able to degrade neutrophil extracellular traps in vitro and also in thrombi, that this degradation is dependent on phagocytosis and that pro-inflammatory stimulation of macrophages accelerates this breakdown.

Group 13: 164 – 176
Thematic Programs: Vascular Biology & Clinical Neurosciences (CLINS) & Neuroscience

(P164) Molecular glucose steel phenomenon imaged by hybrid PET-MRI: 18F-FDG perfusion-metabolism mismatch 3 days after acute myocardial infarction in a translational pig model of ischemic left ventricular dysfunction

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(P165) Cingulin can protect vascular barrier function

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Allergic diseases and skin cancer are characterized by vascular dysfunction and leak. Inflammatory factors, such as thrombin, histamine, and tumor cell-secreted vascular endothelial growth factor (VEGF) cause an increase in vascular permeability and transendothelial migration of cancer cells. It is now widely recognized, that inflammation and metastasis are not only an active process of the inflammatory- and malignant cell, but also driven by cells in their vicinity. Especially vascularization of the tumor and surrounding tissue is an important factor for tumor progression and metastasis. However, therapies so far mainly target secreted factors that lead to vascular barrier breakdown and little is known about mechanisms that protect barrier function. Endothelial tight junctions (TJ) are responsible for controlling the paracellular pathway. The cytoplasmic adaptor protein cingulin connects these tight junction (TJ) proteins to Rho signaling pathways. Our in vitro data measuring transendothelial-electrical-resistance (TEER) showed that cingulin supports barrier integrity upon thrombin challenge and this is also true in case of histamine- and VEGF-A-induced vascular leak. We also demonstrated that cingulin strengthens junctional barrier function by attenuating myosin light chain 2 (MLC2) phosphorylation and stress fiber formation. In a three dimensional (3D) co-culture model of melanoma and endothelial cells in vitro, cingulin counteracts retraction of adjacent endothelial cells (ECs) and thereby prevents melanoma cell entry into the vasculature. Additionally, our in vivo studies showed that cingulin-deficient mice have a higher permeability of the vasculature. We propose that cingulin plays a crucial role in the regulation of endothelial permeability and contributes cancer cell migration through the endothelium. Our aim is to elucidate the mechanism of how cingulin regulates endothelial barrier function and might serve as a target for possible treatment strategies.

(P166) Cellular Interactions and Molecular Turnover of Thrombospondin-1 Isoforms

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Thrombospondin-1 (TSP-1) is a trimeric 185 kDa glycoprotein secreted by activated platelets and endothelial cells (ECs). It acts in angiogenesis and hemostasis, where it supports platelet adhesion, aggregation and string formation on the endothelium. We have previously observed that the concomitant activation of neutrophils with platelets or ECs results in the release of TSP-1, which is processed by neutrophil proteases (e.g. cathepsin G) to a 160 kDa molecule lacking the N-terminus and exhibits enhanced potency in promoting platelet adhesion on collagen and string formation under flow. The overall aim of this project was to characterize the cellular interactions and molecular turnover of these TSP-1 isoforms (185 kDa, 160 kDa) in order to understand the mechanisms by which proteolytic processing of TSP-1 alters its function. Recombinant TSP-1 proteins with distinct N- and C- terminal tags or fusion with mRuby2 and Clover fluorescent proteins (termed Rover TSP-1) were produced to juxtapose the fate of full-length vs proteolytically processed TSP-1 when incubated with human ECs. Several methods (confocal microscopy, FRET, flow cytometry and analysis of cell extracts) have been compared to deduce the most promising mode of detection. Confocal fluorescence imaging suffered from a high noise-to-signal ratio and FRET analyses were deterred by low efficiency of energy transfer. After optimization, flow cytometric detection of the Clover and mRuby2 signals revealed a time course of full length Rover TSP-1 uptake by ECs over 3 hours, with a rapid fluorescence increase within 60 min. Cathepsin-G processed TSP-1 failed to be internalized which might indicate a prolonged molecule stability and explain the gain in function. However, we are currently addressing detrimental protease effects on ECs, in particular endothelial surface receptors, which may contribute to the results observed.

(P167) Measurement of total retinal blood flow and oxygen extraction in patients with type II diabetes and healthy subjects

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The prevalence of diabetes and diabetes-associated complications such as cardiovascular disease, chronic renal failure, diabetic retinopathy and others are still increasing. These major long-term complications are related to the damage of blood vessels. The possibility of direct visualization of retinal blood vessels increased the interest towards studying the ocular circulation and retinal oxygen metabolism. Using a bi-directional Fourier Domain Doppler Optical Coherence Tomography (FDOCT) total retinal blood flow can be evaluated. In addition a non-invasively fundus camera based system can be used to determine retinal oxygen saturation and out of these values retinal oxygen extraction can be calculated. In a recently published study, reduced retinal oxygen extraction in patients with type I diabetes was found (Fondi et al. 2017). However, to the best of our knowledge no such data is currently available for patients with type II diabetes. The aim of the present study therefore is to determine whether retinal oxygen extraction is reduced in patients with type II diabetes in dependence on clinical severity of the disease. A total of 120 subjects will be included in the proposed project. Patients will be graded according to their clinical severity (no signs of retinopathy, mild diabetic retinopathy or moderate to severe diabetic retinopathy) to differentiate between different stages of diabetic retinopathy and compared to healthy age- and sex- matched control subjects. Our findings will allow us to further assess the role of ocular blood flow and retinal oxygen extraction in patients with type II diabetes.

(P168) Fabrication of a Bio-engineered Pre-Vascularized Islet Organ Generated by Organ Crossover

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Islet transplantation is superior to extrinsic insulin supplementation in severe Type 1 diabetes. However, its efficiency is limited by substantial islet loss post-transplantation due to lack of vascular supply. To overcome these limitations, we bio-fabricated vascularized islet organs (VIOs) *ex vivo*. We utilized perfusion-decellularized rat lung scaffolds as a platform and repopulated them with human endothelial cells (HUVECs) from arterial and venous site (10 million each), followed by delivery of rat pancreatic islets (1500 IEq) and 5 million HUVECs from the airway on the next day. Over seven days of a novel two-phase perfusion culture, islets anatomically and functionally integrated into the surrounding bio-engineered vasculature, generating a functional perfusable endocrine organ. This was confirmed by a significant increase of VIO perfusability (d1: 60.6±7.8% vs. d7: 87.3±3.3%; p=0.0022) and of physiologic insulin release to 16.7 mM glucose exposure (AUC: d1: 109.2±51.8 pg/islet/min vs. d7: 408.2± 89.8 pg/islet/min; p=0.041). When transplanted into diabetic rats, VIOs preserved their morphology and released significantly more insulin upon arterial perfusion compared to intrahepatic transplantation of fresh islets (AUC: VIO 0.216±0.023 mg/ml/60min vs. IHTX 0.155±0.049 mg/ml/60min, p=0.038). This led to a significant reduction in blood glucose over 60 minutes (VIO vs. IHTX; 30 min: 423±23 vs. 495.3±7.4, p=0.006, 45 min: 391±20 vs. 478±5, p=0.002 and 60 min: 359±34 vs. 440±28, p=0.033). In long-term transplants into diabetic mice, subcutaneously implanted VIOs achieved normoglycemia within 25 days in 92.3%, while subcutaneously implanted fresh islets and HUVECs did not reverse hyperglycemia. Notably, 50% of VIOs achieved euglycemia within an average of 2 ± 0.238 days. We conclude that VIOs enable islet engraftment and vascularization prior to transplantation, and thereby help to overcome limited function observed in conventional islet transplantation.

(P169) Effect of ischemic pre-conditioning on expression of cardio- and thrombomiRs in a porcine model of acute myocardial infarction

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(P170) Vascular Morphogenesis in the Context of Inflammation: Self-Organization in a Fibrin-Based 3D Culture System

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Key cellular players of the neovascularization process in an inflammatory setting are immune cells recruited to perivascular niches together with endothelial progenitor cells, where they interact within complex networks with resident endothelial- and stromal cells directly or indirectly through the secretion of paracrine factors. In an attempt to mimic the complexity of an in vivo remodeling process and in order to study vascular morphogenesis in the context of inflammation, we established a 3D fibrin matrix system for the culture of inflamed synovial tissue fragments. To specifically investigate the contribution of perivascular cells to neo-vessel formation, mesenchymal stromal cells MSC) were co-cultured with peripheral blood mononuclear cells PBMC) in the fibrin matrix. Cellular and structural re-arrangement was characterized by confocal laser-scanning microscopy of topographically intact 3D cultures, cytokine levels were evaluated by Bio-Plex assay and ELISA. Neo-vessels originating from both the embedded synovial tissues and from clusters locally formed by emigrated mononuclear cells were closely associated with CD45+ leukocytes and Collagen Col)-IV+ stromal cells. MSC-PBMC co-cultures formed vasculogenic clusters consisting of and surrounded by CD45+ leukocytes and Col-IV+ MSC and matrix structures with emerging cells of endothelial phenotype further developing into complex vascular structures. No vascular structures were observed in control 3D monocultures of PBMC or MSC. Both cultured synovial tissue fragments and MSC-PBMC co-cultures secreted high levels of VEGF, GCSF and IL-6. Cross-talk and cluster formation of MSC with immune cells support neo-vessel growth within the 3D fibrin environment via secretion of pro-angiogenic factors and through self-organization can lead to the emergence of complex vascular structures.

(P171) Lack of tenascin c improves vascular endothelial function and network remodeling of coronary resistance arteries in diabetes

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Background: Tenascin-C (TNC) is a glycoprotein of the extracellular matrix, highly expressed during embryogenesis, tumorigenesis, cardiac and vascular remodeling process. Enhanced expression of TN-C in patients with diabetes was associated with poor clinical prognosis. However, the contribution of TN-C for the development of cardiac and vascular dysfunction in diabetes has not been investigated. Methods: 18-20-weeks-old streptozotocin-induced diabetic AJ and TN-C-KO mice were used. Echocardiography was performed to assess left venticular ejection fraction (LVEF) and vascular reactivity was performed by wire myography. In addition, the whole branching system of the left descendent coronary artery (40 micrometer of diameter) and the coronary network geometry was analyzed. Results: There was no difference in blood glucose levels between the two diabetic groups. However, TN-C-KO diabetic mice showed preserved LV ejection fraction in compared to AJ diabetic mice ($p<0.05$). In diabetic animals, a broken course of larger coronary branches was frequently encountered. TN-C-KO diabetic animals had more rich branching systems in compared to AJ diabetic mice. Aortic segments from AJ diabetic mice displayed impaired endothelium-dependent relaxation ($p<0.05$). This effect was significantly revered in TN-C-KO diabetic mice. Conclusions: Lack of TN-C was associated with a better LV and vascular function in STZ induced diabetic mice. This was associated with richer coronary branching systems of TN-C-KO, suggesting a preserved ventricular tissue perfusion. These results suggest that targeting TN-C is a novel potential therapeutic strategy to protect vascular and cardiac function in diabetes.

(P172) Neuropathology and post-mortem imaging characteristics in autoimmune glial fibrillary acidic protein meningoencephalomyelitis

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Glial fibrillary acidic protein (GFAP) meningoencephalomyelitis is an autoimmune disease of the central nervous system, associated with antibodies against the α-subunit of GFAP. Clinical manifestations include encephalopathy, abnormal movements, seizures and autonomic dysfunction. Brain magnetic resonance imaging (MRI) may show perivascular radial gadolinium enhancement in the white matter. Since GFAP is a cytosolic protein, the pathogenic role of circulating anti-GFAP autoantibodies is unclear. Neuropathological reports of anti-GFAP meningoencephalomyelitis are sparse and type and extent of tissue injury remain to be determined.

We compiled the first report on an autopsy case of anti-GFAP meningoencephalomyelitis and present clinical, neuropathological and imaging characteristics.

A 75-year-old female patient presented with hallucinations, disorientation, rigor of the upper extremities and tetraataxia. MRI displayed bilateral periventricular and hypothalamic hyperintensities and linear gadolinium enhancement in the basal ganglia. Neuroimmunological work-up revealed anti-GFAPα antibodies in the CSF in tissue and cell-based assays. Despite steroid treatment, the patient died from cardio-respiratory failure. Post-mortem 7 Tesla MRI of formalin-fixed brain tissue showed prominent perivascular hyperintensities in the white matter that neuropathologically corresponded to dilated Virchow-Robin-spaces with abundant CD20, CD79a and $CD4^+$ lymphocytic infiltrates. $CD8^+$ T cells were sparse. GFAP immunohistochemistry revealed an extensive subpial band-like gliosis and gemistocytic astrocytes in the deep cortical sulci in topographical association with meningeal inflammation.

Neuropathology supports a prominent role of B cells and $CD4^+$ T cells in the pathogenesis of anti-GFAP meningoencephalomyelitis. Dilated Virchow-Robin spaces and perivascular inflammation are the likely pathological correlates of linear gadolinium enhancement in vivo.

(P173) Global functional connectivity changes induced by standardized associative learning measured with resting-state fMRI

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(P174) The role of auto-antibodies in spinal cord injury-induces maladaptive immune response and autoimmunity

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Background: Up to 7 million patients worldwide live with the debilitating consequences of spinal cord injury (SCI). Poor neurologic and functional recovery may be associated with a maladaptive systemic immune response (MSRI) such as post-traumatic autoimmunity against CNS-neo-antigens or SCI-induced immune deficiency syndrome. Objective: To determine the frequency and clinical relevance of autoantibodies in patients with SCI. Methods: We evaluated IgG antibodies in serum of 73 patients with SCI and isolated vertebral fracture without neurological deficit and 14 healthy individuals. Blood samples were collected 1 week and 10 weeks after the trauma. All samples were screened on an in-house tissue-based assay (TBA) of post-fixed rat spinal cord. The reactivity of antibodies with surface antigens was examined with live neuronal immunofluorescence staining of primary cultures of dorsal root ganglia cells. All samples were analyzed blinded to the clinical diagnoses by two investigators (RH and CS). Results: Among the 73 patients studied with TBA, 14 showed a synaptic staining pattern in the lamina II of the dorsal horn. In 5 of these patients the reactivity was detectable in week 1 and in 9 in week 10 after trauma. The healthy controls were negative. All patients positive in TBA and 43 randomly selected negative patients were subsequently stained on live primary cultures of ganglia cells. 13/14 positives and 1/43 negatives showed a dot-like membrane labeling of ganglion cells. Conclusion: Preliminary findings indicate that a sub-group of SCI patients may develop auto-antibodies against surface antigens of the dorsal horn of the spinal cord.

(P175) Neurite outgrowth inhibitor A is upregulated in white matter lesions of complex cortical malformations

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Purpose: Complex Cortical Malformations (CCMs), as hemimegalencephaly and polymicrogyria, are highly associated with drug resistant epilepsy. The abnormal architecture of both white matter and cortical layering are key factors involved in this process. However, the impact of postnatal brain plasticity in this special setting is still unclear. Therefore we focused on a factor called neurite outgrowth inhibitor A (NogoA), which was shown to be upregulated in brain lesions of epilepsy patients. A characterization of the lesional distribution of NogoA in CCMs could enable a better understanding of the pathobiology and give more insights into potential brain remodeling capacity. Methods: In this study we analyzed epilepsy surgery specimens of CCMs (n=14), and compared them to Mild Malformations of Cortical Development MMCDs (n=6), Focal Cortical Dysplasia IIB FCD IIB (n=22), and Tuberous Sclerosis Complex TSC (n=8) cases. As control group we used normal appearing tissue of autopsy and biopsy cases (n=15). Immunohistochemistry was used to characterize the cellular expression of NogoA. Slides were digitalized and the overall positive immunoreactivity was automatically evaluated with an ImageJ based macro. Results: The results showed a significant increased expression of NogoA in the CCM group compared to controls. Beside CCMs we found also a significant upregulation of NogoA in Focal Cortical Dysplasia IIB lesions. However, other malformations of the cortical development like MMCDs or TSC showed no statistically significant altered expression of NogoA. Conclusion: The presence of NogoA in epileptogenic lesions of CCMs and FCD IIBs could inhibit potential regeneration and may have a negative impact on brain plasticity. Further studies are needed to evaluate if a blockage of NogoA via antibodies would modify lesion architecture and therefore modify seizure susceptibility.

(P176) Neural circuitry underlying learned maternal care behavior in nulliparous mice

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Group 14: 177 – 191
Thematic Program: Neuroscience

(P177) Characterization of novel $GABA_A$ receptor modulators of pyrazoloquinolinone class with low affinity for benzodiazepine binding sites

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Pyrazoloquinolinones (PQs) are a class of $GABA_A$ receptor ligands with very low toxicity and an interesting pharmacological profile, coming from at least three distinct allosteric binding sites on some receptor subtypes. The binding sites of PQs on $GABA_A$ partially overlap with those used by benzodiazepines, such as diazepam. Binding of PQs on these allosteric binding sites can elicit modulatory or functionally silent effects. At benzodiazepine binding sites on extracellular (EC) α+/γ- interfaces, PQs bind with high affinity, while also being able to occupy EC α+/β- interfaces. It was observed in a previous study that introduction of a tert-butyl on R6 position of ring A of PQs abolished the binding affinity for benzodiazepine binding sites for one compound. Ligands with high selectivity for individual α+/β- binding sites and low or close to absent affinity for the benzodiazepine binding sites would be of great interest. In the present study we thus synthesized six PQs with distinct substitutions at the R6 position of ring A to investigate the effect of this position on benzodiazepine site affinity further. We used [^{3}H]-flunitrazepam displacement to test the binding affinity of the ligands to benzodiazepine binding sites. We also tested the modulatory effects of the ligands on $GABA_A$ receptors using two electrode voltage-clamp electrophysiology in *Xenopus* laevis oocytes. Of the six tested ligands, two with hydrophobic residues exhibit low binding affinity to benzodiazepine binding site, which is in line with the previous observations. These two ligands also exhibit strong positive modulation in α1β3 $GABA_A$ receptors, presumably from interaction with the EC α+/β- interfaces. With our results we confirmed that residue at position R6 of ring A in PQs affects binding to benzodiazepine binding sites, while still enabling modulation at the alternative site with useful potency.

(P178) Neuronal circuits of the orbitofrontal cortex for decision confidence

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Decisions are rarely certain; decision makers must constantly modify their actions in response to uncertain evidence in order to survive. Behavioural data from humans, monkeys and rats demonstrate their ability to adjust their actions depending on the degree of uncertainty in decision making, their decision confidence. Rodent data also provide evidence that the orbitofrontal cortex is required for these behavioural adaptations. To investigate the neural substrates of decision confidence, we will isolate functionally unique populations of neurons in the prefrontal cortex microcircuit. I will present the methods and features chosen to separate groups of neurons and observe if they exhibit any functional organisation.

We have two primary approaches for the division of functional subtypes. One approach is to search for anatomically distinct molecular markers. We have sequenced the translating RNA of orbitofrontal cortex populations projecting specifically to the Ventral Striatum, Superior Colliculus and Ventral Tegmental Area. The other approach is to observe the activity of orbitofrontal cortex neurons in freely moving rats performing a confidence reporting task. We have performed juxtacellular recordings and selectively labelled neurons depending on their activity. In combination, these methods search for molecularly, anatomically and functionally distinct populations which can be associated with task correlated activity. These distinct functional groups would provide the first glimpse of an algorithmically defined neocortical microcircuit.

(P179) Molecular characterization of two novel missense mutations in MuSK associated with congenital myasthenic syndrome

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Congenital Myasthenic Syndromes (CMS) are a group of heterogeneous genetic disorders resulting in defects in neurotransmission at the neuromuscular junction (NMJ). They are characterized by varying levels of muscle weakness and can lead to respiratory failure in extreme cases. CMS is caused by mutations in genes encoding proteins involved in the formation of the NMJ. One such protein is the Muscle Specific Kinase (MuSK). The activation of MuSK leads to a signaling cascade that is required for all aspects of NMJ development, such as presynaptic nerve terminal differentiation and clustering of acetylcholine receptors (AChRs) to the postsynaptic membrane. Recently, two novel missense mutations in MuSK have been identified from human CMS patients, namely c.308A > G (p.N103S) and c.1634T > C (p.L545P). However, the effects of these mutations at the molecular level are unknown.

To understand the pathophysiology caused by these mutations, we aim to study MuSK signaling, AChR clustering and NMJ formation in muscle cells that express MuSK N103S and MuSK L545P, respectively. We have generated retroviral constructs carrying the MuSK missense mutations. Subsequently, MuSK knockout muscle cells were used to create two different cell lines that express the MuSK N103S and L545P mutated protein by retroviral transduction. These muscle cell lines will be utilized to investigate important synaptogenesis events such as MuSK expression, activation and downstream signaling including AChR clustering.

The results of this study will shed light on how missense mutations in MuSK impact the synaptogenesis and signaling events at the NMJ. Additionally, it will potentially lead to a better understanding of the underlying genetic etiology of CMS.

(P180) Molecular Neuropathology of HACE1-Deficiency

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HACE1, encoding the HECT Domain and Ankyrin Repeat Containing E3 Ubiquitin Protein Ligase 1, has been of interest to biomedical research groups for its role in cancer, heart function and inflammation. Surprisingly, mutations in HACE1 have recently been shown to cause a rare autosomal recessive neurodevelopmental syndrome called Spastic Paraplegia and Psychomotor Retardation with or without Seizures (SPPRS; OMIM #616756). SPPRS is marked by global delay of developmental milestones, most prominent of which are intellectual disability (ID), hypotonia and ataxia. Magnetic resonance imaging (MRI) findings were variable among patients, but included enlarged ventricles, hypoplastic corpus callosum and atrophy of the cerebrum and brain stem.

Guided by patient clinical descriptions, our group performed detailed phenotypic analyses of Hace1-deficient mice and SPPRS patient fibroblasts and uncovered surprising new roles for HACE1 in both human and mouse brain development. The present study builds on this previous work by working towards and understanding the molecular underpinnings of HACE1-deficiency using cellular models.

(P181) Blood-brain barrier-related proteins in autoimmune encephalitis and demyelinating CNS disorders

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The central nervous system (CNS) is an immune privileged organ separated from the immune system by the blood-brain-barrier (BBB). Glucose-regulated protein 78 (GRP78) is a ubiquitous endoplasmatic reticulum chaperon involved in regulating brain endothelial cells. Recently, anti-GRP78 antibodies were found in neuromyelitis optica spectrum disorder (NMOSD) patients, potentially promoting BBB transit of aquaporin-4 antibodies, contributing to disease development. In mice, administration of anti-GRP78 antibodies from NMOSD patients leads to an increased BBB permeability. However, the role of anti-GRP78 antibodies in other immune-mediated CNS diseases is unclear.

To study BBB-related proteins including GRP78 and their changes during BBB breakdown, we investigated patients with anti-neuronal autoimmune encephalitis, paraneoplastic syndromes, NMOSD, MOG-spectrum disorders, ischemic stroke, and controls. Immunohistochemistry was performed on paraffin-embedded human brain-tissue. In addition, a cell-based assay (CBA) was established to screen for anti-GRP78 antibodies in patients' and control sera using GRP78 transfected HEK293T cells.

Preliminary results suggest differences in endothelial expression patterns of GRP78 in stroke and demyelinating diseases. In the subacute phase of stroke (7-42 days) a widespread upregulation of GRP78 in endothelial cells was found in infarct and peri-infarct areas. In contrast, focal and patchy upregulation was only shown in the periplaque white matter but not in lesions of NMOSD and MOG-spectrum disorders. The CBA resulted in an intracellular protein expression without membrane staining, using a commercial antibody or 20 sera of NMOSD patients.

Varying expression patterns of GRP78 may correlate with pathomechanisms in inflammatory CNS diseases and ischemic stroke. Induction of membrane translocation of GRP78 will be necessary to screen for autoantibodies in selected autoimmune diseases.

(P182) Serine Phosphorylation as a Novel Regulatory Mechanism in Muscle Specific Kinase Signaling

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The muscle specific kinase MuSK is a receptor tyrosine kinase whose activity is essential for the formation of the neuromuscular junction (NMJ), a specialized synapse formed between motor neurons and skeletal muscle fibers. This synapse facilitates the signal transduction from nerves to muscles and thus muscle contraction. In order to allow for proper NMJ formation, the kinase activity of MuSK is strictly regulated. Agrin, secreted by motor neurons, induces dimerization of MuSK via binding to the co-receptor Lrp4. This leads to the autophosphorylation of MuSK and its release from autoinhibition and, ultimately, to NMJ formation. Recently, a novel serine phosphorylation site in position 751 was identified, which is believed to alleviate MuSK autoinhibition.

A crystallography-based structure-function analysis will be performed to determine whether a phosphomimetic S751 mutant favors a conformation of MuSK that could mediate reduced autoinhibition. In addition, we aim to identify which kinase phosphorylates S751. For this, we conducted a kinase profiling assay. Using a radiometric protein kinase assay 245 Ser/Thr kinases were tested for their ability to phosphorylate a peptide containing S751. Interestingly, the highest activity towards the peptide was shown by the beta isoform of the Ca^{2+}/calmodulin-dependent kinase II (CaMKII_) which is known to be localized at the NMJ. Preliminary results have shown that the treatment of myotubes with Staurosporine, a broad spectrum kinase inhibitor, which also inhibits CaMKII, leads to a drastic reduction in the phosphorylation of S751. More specific CaMKII inhibitors will now be applied to avoid affecting other kinases. If CaMKII_ is indeed identified to phosphorylate S751, this would provide a link between MuSK activity and Ca^{2+} concentrations, which have previously been shown to regulate NMJ formation. CaMKII might also be involved in other steps of the as yet only incompletely understood MuSK signaling cascade.

(P183) Pathogenic mechanisms in fulminant Susac's Syndrome

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Susac's Syndrome (SS) is an autoimmune endotheliopathy affecting the precapillary arterioles of the brain, retina and inner ear. The disease cause is still unknown. Case studies provide evidence that antibodies against endothelial cells (AECAs) may play a pathogenic role. On the other hand, SS has been associated with an accumulation and oligoclonal expansion of cytotoxic CD8+ T-cells in the periphery and CNS, where they may cause vascular injury. Our aim was to present a rare entity and evaluate possible underlying pathogenic mechanisms in SS.

We present clinical and imaging characteristics of SS as well as immunological and histopathological features. Laboratory investigations in serum were performed to screen for AECAs.

A 17-year-old girl was referred to hospital presenting with progressive left-sided hemiparesis and acute encephalopathy. MRI showed pathognomonic signs for SS including snowball-lesions in the corpus callosum and punctuate lesions in the internal capsule. Brain biopsy revealed acute ischemic cortical microinfarctions with perivascular lymphocytic inflammation, mainly composed of CD3+ and CD8+ T-cells. Granzyme B expressing cytotoxic CD8+ T-cells were found in microvessels in close proximity to endothelial cells. To investigate, whether the patient may have surface antibodies against endothelial cells, we established a primary culture of rat brain endothelial cells to perform a live immunofluorescence staining of the cell membranes.

Differential diagnostic work-up can be difficult in early stages of SS. Screening for AECAs in patients with SS and other rare neuroimmunological endotheliopathies may provide novel biomarkers and identify underlying pathomechanisms in the disease.

(P184) Anterograde Trafficking of the Creatine Transporter-1

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Apart from mitochondrial and peroxisomal proteins, all eukaryotic membrane proteins are synthesised in the endoplasmic reticulum [ER]. They are delivered to their target membranes via anterograde trafficking in the secretory pathway, which requires sequential budding and fusion of vesicles. Export of proteins from the ER is contingent on their correct folding, which is monitored by ER quality control, and on subsequent recruitment of coat protein complex II [COPII]. The neurotransmitter transporters of the solute carrier-6 [SLC6] family are delivered to the axonal compartment and enriched at the rim of the presynaptic specialization. These SLC6 family members - i.e. the transporters for norepinephrine, dopamine, serotonin, GABA and glycine - interact with either SEC24C or SEC24D. Axonal delivery of SERT and GAT1 is contingent on the recruitment of SEC24C and SEC24D, respectively: point mutations, which disrupted SEC24-binding, allowed for cell surface expression of the mutant transporters. However, these transporters were confined to the somatodendritic territory and this was recapitulated in vivo, in the brain of Drosophila melanogaster. The creatine transporter-1 [CRT1/SLC6A8] also harbours a SEC24-binding motif in its C-terminus. When expressed in rat hippocampal neurons, CRT1 was delivered to the somatodendritic compartment and enriched in the dendritic tree. Accordingly, we posited that CRT1 required a paralogue other than SEC24C or SEC24D. This hypothesis was confirmed by selectively depleting individual SEC24 isoforms using siRNA-mediated knockdown. Taken together, the observations support the concept that sorting decisions in the secretory pathway are already made in the endoplasmic reticulum.

(P185) Cellular diversity in the developing hypothalamus

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The hypothalamus is an evolutionarily ancient part of the brain, it is ventral part of the diencephalon, lying just superior to the anterior pituitary gland. It acts as a master homeostatic regulator to modulate activities that are crucial to life. It is one of the most diverse regions in the brain. The previous study of our laboratory explores hypothalamus by applying single-cell RNA sequencing (scRNA-seq) to adult mice. It showed the highest local molecular diversity of neurons, determining their functions and cell types. Thereby, the aim of this study is revealing the vectors of cellular identities' heterogeneity development in the hypothalamus with scRNA-seq. One way we choose to distinguish this complexity is a transcription convergence model. That may explain the occurrence of intermediate stages in differentiation processes. A feature of hypothalamus development we are considering is a potential of glial line cells for transformation to immature neurons. There is a possible contribution of tanycytes, which are cells representing radial glia, to hypothalamic nuclei. At the same time, the origin of tanycytes is still not clear. We analysed the data we obtained after scRNA-seq hypothalamic cells isolated from mice of several embryonic and early postnatal days to describe the differentiation process using a recently published method called RNA-velocity (based on the analysis of the transcription processes' dynamic). The RNA-velocity approach also admits a fitting gene-relative model. This way we may check how a particular gene related to the transition process. We examine a comprehensive list of related genes. As a conclusion, we integrated the scRNA-seq data from embryonic days 15 and 17, postnatal days 0, 2, 10, 23. We demonstrated the robust process of transformation of radial glia into neurons. Candidates were presented for the transcription factors involved and signalling pathways regulating the interaction.

(P186) Cerebral cortex parcellation based on mRNA expression maps

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Mapping of the human cerebral cortex is an essential part of the neuroimaging field. Established parcellations have been based on cytoarchytecture, e.g. Brodmann areas [1], structural organization, e.g. Desikan-Killiany [2], or functional specialization, e.g. Glasser atlas [3]. Particularly, mapping to the functionally specific regions has become a field of ever-increasing interest. This study is intended to define the areas of the human cerebral cortex by the means of molecular distributions, which form the basis of all brain activity.
In total, 18686 gene expression patterns were interpolated from 3702 original samples taken from the left hemisphere of the Allan Human Brain atlas [4]. mRNA transcriptomes were used as a surrogate for proteomics. A hierarchical representation of the structure of the transcriptomics data set was defined as a result of agglomerative clustering. Ward's method was used as the inter cluster distance measure and the Euclidean norm as the distance metric. Furthermore, the comparison to already existing atlases was calculated using the Dice coefficient, which quantifies the goodness of overlap.
The optimal number of the areas was estimated to 31 for the left hemisphere based on the Bayesian Information Criterion. The clustering solution was compared with the Brodmann areas (19% regions with Dice>0.5), Desikan-Killiany atlas (21% regions with Dice>0.5) and Glasser atlas (30% regions with Dice>0.5). The functional-connectivity-based atlas shows the highest overlap, most likely due to the similarities in the origin of the parcellations.
Presented parcellation of the cerebral cortex is closer to the biology underlying all brain function as it is based on whole transcriptome. In future, it might be used to predict activation and structural patterns associated with psychopharmacological challenges during pharmaco-fMRI.
[1]Brodmann 1909
[2]Desikan et al. 2006
[3]Glasser, M. F., et al. 2016
[4]Gryglewski et al., 2018

(P187) Kv7 channel and inositol phosphate cycle

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Background: *Myo*-inositol, the most abundant stereoisomer of inositol in the human body, is the precursor of phosphoinositides, which are key signaling lipids in cells. In mammalian tissues *myo*-inositol concentrations vary between different organs and tissues and range between 0.1 and 16mM. In the brain *myo*-inositol reaches a level of up to 10mM in cells and in the cerebrospinal fluid a concentration of up 140-400µM. *Myo*-inositol gives rise to the phosphoinositides phosphatidylinositol-4 5-bisphosphatte (PIP2) which is needed by Kv7 channels to open. Kv7 are slow, non-inactivating voltage-gated potassium channels which modulate the excitability of neurons by acting as a "brake" on repetitive action potential firing. Therefore an increased myo-inositol pool would increase the PIP2 concentration in cells which would lead to an increased activation of the Kv7 channel. This increased activation of the Kv7 channel would lead to a decreased excitability in neurons.
Methods: The perforated patch clamp technique with amphotericin B was used to measure excitability in superior cervical ganglia (SCG) neurons. SCG neurons were incubated for 24h with 100µM *myo*-inositol or 400µM *myo*-inositol to increase the *myo*-inositol pool in SCG neurons. Oxotremorine and linopirdine, both Kv7 channel modulators, were used to evoke the maximum action potential firing in SCG neurons due to Kv7 channel closing.
Results: 100µM *myo*-inositol was able to decrease the excitability in SCG neurons, but only 400µM *myo*-inositol was able to significantly decrease excitability in SCG neurons. The membrane potential was not changed by *myo*-inositol incubation.
Conclusion: An increased concentration of *myo*-inositol leads to an increased pool of PIP2 in SCG neurons and therefore modulates the activation of Kv7 channels. An increased activation of Kv7 channels leads to a decreased excitability in SCG neurons and therefore to decreased action potential firing.

(P188) B lineage cells and antibody repertoire in Multiple Sclerosis

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Multiple sclerosis (MS) is a common neurological disease which affects the central nervous system (CNS) and leads to the formation of lesions characterized by inflammation, demyelination and neurodegeneration. So far, treatment strategies modulating the immune system were shown to be highly effective during the relapsing remitting course of the disease but for the progressive stage no treatment currently available seems to be effective. Although it is well established that B lineage cells are found in the MS brain, little is known about these cells. In my PhD-project, I will focus on the following aims for a better understanding of the pathophysiology of B lineage cells in RRMS and PMS: 1) Histological characterisation of B lineage cells in MS brains. 2) Characterisation of the antibody repertoire produced by B lineage cells. 3) Identification of the recognized antigens. Preliminary data show that infiltrating B lineage cells are found in significantly higher numbers during the relapsing/remitting disease course than during the progressive stage. We found mature CD27+ B cells, CD38+ plasmablasts and Ig+ plasma cells in similar frequencies in the relapsing/remitting stages of MS. However, in the progressive disease stages significantly higher numbers of plasmablast were observed. These findings suggest that infiltrating B lineage cells are further differentiated in advanced MS. In a first step towards the identification of the antigens recognized by these B lineage cells, we established protocols for molecular analysis of immunglobulin heavy and light chains of formalin-fixed and paraffin-embedded brains of MS patients. We already identified a single heavy and a single light chain in the brain of a PMS patient, and will now test whether these chains can successfully pair to form a functional antibody, which is a prerequisite for further antigen searches. This work is supported by the Austrian Science Funds (FWF, project I3335-B27).

(P189) Interplay of aminopropyl-benzothiophenes with monoamine transporters

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Aminopropyl-benzofurans (APB) are new psychoactive substances that have been shown to exhibit psychostimulant and MDMA-like properties and have been associated with several deaths since their emergence on the streets. They act as substrates on monoamine transporters, and once taken up cause the reversal of the physiological action of the transporter by releasing the endogenous ligand into the synaptic cleft. Replacement of the oxygen atom in APB compounds with sulfur leads to benzothiophene analogs (APBT) of this class of psychoactive substances. Six APBT isomers which differ in the position of the aminopropyl side chain on the ring structure have been synthesized (2-APBT, 3-APBT, 4-APBT, 5-APBT, 6-APBT and 7-APBT), with the purpose of studying the structure-activity relationship of this class of compounds on monoamine transporters to investigate whether replacement of oxygen with sulfur leads to different properties of the molecules. We assessed the interaction of all six APBT compounds on the human norepinephrine (NET), dopamine (DAT) and serotonin transporter (SERT) by uptake inhibition assays in HEK293 cells stably expressing the transporter of interest. Additionally, we performed radiotracer efflux experiments to identify whether the APBT substances can induce reverse transport. This was corroborated by the Na+/H+ ionophore monensin which is known to enhance efflux. Uptake inhibition assays revealed that all of the APBT compounds interact with the three plasmalemmal transporters with similar potencies, comparable to those of cocaine (with IC50 values ranging from 0.2 to 8 µM), regardless of the position of the aminopropyl side chain. Efflux experiments further elucidated their roles as substrates of plasma membrane monoamine transporters. Our study reports for the first time the pharmacological properties of a new class of sulfur-containing psychoactive substances, aminopropyl-benzothiophenes, which potently interact with all three monoamine transporters.

(P190) Supraspinal neuroinflammation in pain affective disturbances: role of the parabrachial nucleus

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Chronic pain is a major burden that affects up to 30% of the population. Of particular clinical importance are the complex affective comorbidities of pain, such as stress, depression and anxiety. Neuroinflammation, resulting from neuro-immuno-glial interactions, is increasingly recognized not only as a driving force for the sensation of pain, but is also associated with the most prevalent comorbidities of chronic pain. Glial reaction and cytokine induction play key roles in spinal cord. Much less is known regarding the occurrence of neuroinflammation at supraspinal sites in the nociceptive pathway. One of the main relay stations between the spinal cord and higher pain processing regions is the lateral parabrachial area, a brainstem structure known for its role in the emotional processing of noxious stimuli. Neuroinflammation at this level could contribute to the development of maladaptive changes and lead to the worsening of affective disturbances in chronic pain. Here, we investigate if clinically-relevant pain states induce neuroinflammation in the parabrachial nucleus. In male Sprague-Dawley rats, immunohistochemistry methods are used to evaluate the morphological and molecular adaptations of glial-cytokine-neuronal network occurring in parabrachial area following chronic constriction injury of the sciatic nerve, a model for neuropathic pain, or complete Freund adjuvant injection in the hind paw, a model for inflammatory pain. Next, we aim to examine if neuroinflammation can change functional properties of parabrachial neurons and their synaptic connections. By selectively targeting and activating spino-parabrachial synapses using optogenetics, we intend to assess the potential plasticity of the network both in the presence and in the absence of neuroinflammation. Through unravelling neuroimmune mechanisms in the parabrachial nucleus, an area crucial in encoding the aversive nature of pain, we expect to gain a better insight into pain affective disturbances.

(P191) The role of spinal astrocytes in nociception and pain

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Long-term potentiation (LTP) of synaptic strength at spinal C-fibre synapses is a cellular model that may underlie the transition from acute to chronic pain. It was long believed that LTP is an exclusively neuronal mechanism. This view has changed. Glial cells are now recognized as important contributors to LTP and chronic pain. To test whether the selective activation of spinal astrocytes is sufficient to induce pain hypersensitivity in freely moving rats, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) were delivered to the dorsal horn using viral vectors. These receptors are activated via clozapine-N-oxide (CNO). Immunostainings and in vitro calcium imaging were used to assess expression, distribution and functionality of the DREADDs. To assess the paw withdrawal thresholds to mechanical stimulation, we used the von Frey test in freely moving adult rats. To study the effect of the selective astrocyte activation on synaptic strength, we will perform patch clamp recordings in spinal cord slice preparations. Evoked and spontaneous excitatory postsynaptic currents (EPSCs) will be recorded from cells with monosynaptic C-fibre input. We show that the DREADD expression is confined to spinal cord astrocytes. The application of CNO (10 µM) induced a rise in calcium in astrocytes only. On a behavioural level, a single systemic injection of CNO (3 mg·kg-1) induced a reduction in mechanical paw withdrawal thresholds, lasting for at least 5 hours. Our preliminary results suggest a causal role for astrocytes in the induction of pain hypersensitivity. This implies that the activation of astrocytes is sufficient for the induction of pain hypersensitivity. Experiments are currently performed to study the effect of the selective astrocyte activation at spinal C-fibre synapses. Ultimately, we expect a deeper understanding of the cellular and synaptic mechanisms underlying the induction of chronic pain

Group 15: 192 – 204
Thematic Program: Neuroscience

(P192) The parabrachial nucleus: A potential site for opioidergic modulation of pain aversion.

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(P193) Structural correlates of transmitter release, vesicle pools and plasticity at hippocampal mossy fiber synapses

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(P194) Extraocular muscles are target of inflammation in experimental Neuromyelitis Optica

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Neuromyelitis Optica NMO) is an inflammatory disease of the central nervous system &#40,CNS&#41, characterized by the presence of autoantibodies against the water channel Aquaporin-4 AQP4). Recent reports suggest that NMO patients also show extra-CNS muscle-related pathology. On the other hand, Myasthenia Gravis MG) is a neuromuscular disease characterized by autoantibodies against Acetylcholine receptors AChR) located on muscles. Both diseases are rare and interestingly, they have been described by numerous studies to coincide with a much higher probability than expected by chance. Those studies report disease conversion from NMO to MG and vice versa, but the underlying mechanisms are largely unknown. Our preliminary immunohistochemical analyses reveal that extraocular muscles EOM) are much more susceptible than skeletal muscles in the context of experimental NMO ENMO), and show prominent inflammation and EOM tissue destruction. Specifically, Hematoxylin-Eosin staining evidences massive infiltration of granulocytes and eosinophils. Abundant ED1+ macrophages, responsible for tissue damage and antigen presentation, are also shown to invade EOM fibers. Concomitantly, considerable numbers of CD3+ T cells are recruited in the EOM tissue and additional C9neo staining reveals the deposition of membrane attack complexes, which are known to perforate the cellular membranes. In most skeletal muscles however, only the connective tissue compartment contains T cells, macrophages and neutrophils, while the muscle fibers themselves are spared from destruction. Since EOM are also predominantly affected in MG patients, our preliminary data suggest that EOM could play a major role in antigen spreading mechanism from AQP4 to AChR and vice versa, which may further lead to the development of additional autoimmune disease in affected patients.

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(P195) Homeobox protein MOX-2 plays a critical role in nociceptor function

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Homeobox protein MOX-2 (MEOX2) is a transcriptional factor involved in mesoderm patterning and somite differentiation. It plays a role in development of bones and muscles, vasculature and dermatomes. Surprisingly, we have identified dysregulation of MEOX2 in a rare sensory nervous system disorder, Congenital Insensitivity to Pain (CIP). CIP is marked by a complete absence of pain perception due to sensory neuron dysfunction or absence. Previously, we showed MEOX2 abundance to significantly change in fibroblasts of two unrelated patients suffering from PRDM12-associated CIP, compared to fibroblasts of their respective unaffected, sex-matched parents. Based on the important role which MEOX plays in the development of dermatomes and their respective nervous system, we hypothesized that MEOX2 is not only a downstream protein regulated by PRDM12, but that it is also essential for the function of post-mitotic nociceptors, cells specialized for detection of painful stimuli as well. We, therefore, sought out to characterize the function of MEOX2 in vertebrates, by analyzing MEOX2-deficient mice. Here, we report that MEOX2 is expressed in the mouse dorsal root ganglia and spinal cord, and localizes in the nuclei of CGRP-positive sensory neurons, marker for nociceptors. Detailed electrophysiological analysis of cultured nociceptors reviled impaired action potential firing upon depolarization in MEOX2 heterozygotes as compared to controls. Nociceptor firing deficiencies result in impaired behavioral responses. In standard behavioral assays for acute and inflammatory pain, we noted that MEOX2 heterozygotes have impaired responses to noxious heat and intraplantar capsaicin injections. Based on these observations, we conclude that MEOX2 plays a role not only in the developing mesenchyme, but it is also critical in nociception of the developed sensory nervous system and an important downstream mediator of PRDM12 function.

(P196) STAT3 in the serotonergic system and its relevance for psychiatric disorders

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Inflammatory processes have been proposed to play a role in the aetiology of several major mental illnesses, including major depressive disorder [MDD] and schizophrenia [SCZ]. In this context, clinical and preclinical work has consistently highlighted a central role for the cytokine interleukin-6, which exerts its biological effects via the downstream activation of the transcription factor STAT3 [signal transducer and activator of transcription 3]. Due to the importance of the serotonergic system in the regulation of mood and its pivotal implication in the pathophysiology of mental illness, we proposed to investigate the role of STAT3 activity within the serotonergic system of the brain in determining the emergence of a neuropsychiatric phenotype. To this end, a mouse model of serotonergic STAT3 depletion Sert[upCre/+] Stat3[upfl/fl], (STAT3 KO) was developed and, together with littermate control mice, subjected to an extensive characterisation of mood-related behaviours. Neuronal function of the dorsal raphe nucleus [DR], where most serotonergic cell bodies are located, was probed by in vivo electrophysiology and complemented by transcriptomic analysis using RNA-Sequencing. The performance of STAT3 KO mice in specific behavioural paradigms suggests a reduced depression-like phenotype alongside a reduced susceptibility to the development of behaviours relevant to substance abuse disorder, often comorbid with MDD and SCZ in human patients. Consistent with the behavioural phenotype, in vivo electrophysiological recordings of the DR showed a significantly higher firing rate in STAT3 KO than in controls. RNA-Seq revealed differential expression of a number of transcripts previously associated with MDD or SCZ in the DR of STAT3 KO mice. In summary, we identify STAT3 signalling as an important regulatory pathway for the control of neuronal function within the serotonergic system and the manifestation of mood-related behavioural traits in the mouse.

(P197) Firing patterns of GABAergic neurons during gamma oscillations in area CA1 of the mouse hippocampus

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The CA1 area of the hippocampus is a hub of information processing, receiving converging inputs from cortical association areas, upstream hippocampal memory networks (CA3), and subcortical structures. These converging inputs are regulated by electrical oscillatory activities of different frequencies, which are in correlation with the excitability of CA1 pyramidal cells and hence modulate the efficiency of neural communication. The spike-timing of hippocampal principal cells and GABAergic neurons are phase-modulated by theta (5-12 Hz) and ripple (140-200 Hz) oscillations in a cell-type contingent manner. However, the influence of gamma oscillations displaying complex spatiotemporal organization (30-150 Hz) is less well understood. There are three distinct gamma oscillations in the hippocampal CA1 area of mice, with different frequency spectra, phase preference relative to theta oscillation, and distribution along anatomical layers hosting different input pathways, and correspondingly distinct roles in regulating information processing. To investigate the spike timing of various GABAergic neuron types in CA1 referenced to different gamma oscillations, we recorded electrical signals from the hippocampi of awake, head-fixed mice performing unidirectional runs along a linear corridor in a virtual reality environment. We localized slow, mid-frequency and fast gamma oscillations using current source density analysis, and simultaneously recorded the spike timing of multiple CA1 units and identified single CA1 GABAergic neurons using multiple shank silicon probes and extracellular glass microelectrodes, respectively. We will present preliminary data showing that distinct type of interneurons phase lock to different sets of gamma oscillations, and to different phases of the same gamma oscillation. Our data suggest that GABAergic neuron types orchestrate dynamic interactions of CA1 input pathways converging onto the principal cell population.

(P198) Acute intermittent porphyria – pathogenic principles and neurobiological mechanisms

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Background Acute intermittent porphyria AIP) is a rare hereditary metabolic disorder with a dysfunctional heme pathway caused by porphobilinogen-deaminase (PBGD) deficiency. The consequence is an accumulation of the toxic intermediates, aminolevulinic-acid (ALA) and porphobilinogen which are causing peripheral neuropathy, tremor, ataxia and psychiatric manifestations. However the underlying neuropathological mechanisms of neuropsychiatric symptoms are poorly understood. Aims 1.Examine the emotional behavioral phenotype of PBGD-deficient KI) mice. 2. Investigate whether behavioral disturbances in KI mice are associated with disrupted adult hippocampal neurogenesis and altered hippocampal functional activity. 3. Elucidate the signal transduction systems involved in behavioral and neurogenic deficits in KI mice. Methods By using behavioral, immunohistochemical, ex-vivo electrophysiological, biochemical and molecular approaches we investigate the potential behavioral, neurogenic and molecular deficits in the KI mice. Results The genetic mouse model showed an enhanced depression-like-behavior in KI as compared to WT littermates as well as impaired motor-coordination. Adult hippocampal neurogenesis was evaluated where KI mice showed significantly reduced hippocampal progenitor cell proliferation and the differentiation of cells into mature neurons was decreased in KI mice. The radioligand binding assays of Muscimol and Flunitrazepam did not show a difference between KI and WT mice. However in a MRI and RNA sequencing experiment it was shown that myelin is affected in the KI mice. Conclusion this first experimental assessment of the role of emotional disturbances in the pathogenesis of AIP and the molecular approaches may aid in the identification of therapeutically targets for preventive and symptomatic treatment of patients suffering from AIP.

(P199) Heterogeneity of neural crest and Schwann cell precursor populations during development

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Glial cells of the peripheral nervous system are a neural crest-derived population specified during mid-embryogenesis. Peripheral glia can be classified in regard to their location, morphology and function. To date, researchers have greatly unravelled the mechanisms that govern the specification of the peripheral glia lineage while focusing mainly in the part of the lineage that will restrict its fate to myelination. However, even though it is becoming increasingly clear that peripheral glial cells are characterized by a high degree of heterogeneity, there is no clear discrimination in vivo between all the described subtypes and their discrete roles. Additionally, peripheral glia and their precursors are a cellular population with evident multipotency, which is reminiscent of the potential of neural crest cells to give rise to a multitude of cell types.
Here, we assess the heterogeneity of peripheral glial cells on the transcriptional level at different developmental stages and compare this heterogeneous cell type to neural crest cells using next generation deep sequencing, combined with cutting edge bioinformatic methods such as pseudotime ordering and RNA velocity.

(P200) Evaluation of the C9ORF72 Hexanucleotide Repeat Expansion in Austrian Dementia Patients

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The hexanucleotide repeat expansion (RE) in the C9ORF72 gene is the most common mutation in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Healthy people have up to 30 repeats of the nucleotides GGGGCC, while mutation carriers can have thousands. Repeat sizing methods are often only semi-quantitative and it is unknown whether the amount of repeats might influence prevalence or phenotype of different types of dementia.
This study aims to provide further insight into the prevalence and pathology of this genetic variant by the evaluation of the C9ORF72 RE in an Austrian dementia cohort.
DNA was obtained from two dementia biobanks (PRODEM and BIOBANK MUV, n=860). For the detection of the C9ORF72 RE, we performed a three step process: (i) Fragment length analysis to detect changes in the length of the C9ORF72 sequence, (ii) repeat primed PCR to differentiate between healthy homozygous probands and those with pathogenic RE and (iii) Southern blot analysis to assess the length of the RE. The data was analyzed using the Peak Scanner Software v2.0 and was preliminary statistically evaluated with IBM SPSS Statistics 25.
We identified 13 C9ORF72 RE carriers in our cohort. 6 patients are suffering FTD (8.5% of FTD cases), 6 AD (1% of AD cases) and one patient was diagnosed with vascular dementia (VD). 5 FTD patients and 3 AD patients show early age at onset (AAO, <65 years). Southern blotting revealed large expansions over 1000 repeats in 9 patients (5 AD, 4 FTD) and intermediate expansions between 40 and 130 in 4 patients (1 AD, 2 FTD, 1 VD).
Extensive analysis of the influence of large and intermediate C9ORF72 repeat expansions on the phenotype of dementia patients will be performed. Furthermore, it is unclear whether higher repeat units within the normal range are associated with risk for AD or FTD. Therefore, we will also evaluate cases with repeats at the upper limit of the cut off (20-30 repeats).

(P201) Astrocyte diversity in the hypothalamic circuitry

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Displaying a morphological and functional heterogeneity, astrocytes serve as indispensable modulators of brain functioning. However, the grounds of our knowledge concerning astrocyte diversity are still mainly based on their morphology and the use of a few molecular markers. Consequently, the molecular profiles and functional properties of diverse astrocytes in the adult CNS remain largely undefined. Hypothalamus (HY) is one of the environments within which astrocytes may tailor their form and function to match the diverse environmental demands. Therefore, the aim of this study is to inspect the intra-regional astrocytic heterogeneity that may mirror molecular and functional differences amongst distinct hypothalamic nuclei. Following our transcriptome data, showing two possible distinct clusters of astrocytes within the HY, other integrated approaches gave us interesting insights into a possible distinct subpopulation of hypothalamic astrocytes within the arcuate nucleus. This funnel-shaped nucleus represents an aggregation of neurons (secreting NPY/AGRP; POMC/CART) and astrocytes, which help to mediate neuroendocrine and physiological functions. A discrete molecular signature of an astrocytic cluster within the HY shows positivity for latexin- the only endogenous mammalian inhibitor of metallocarboxypeptidases known so far. Besides the identification of a unique labeling pattern, the inspection of possible encapsulations showed latexin-positive astrocytes recruiting POMC neurons. Further inspection of latexin targets and its release mechanisms will help explain possible multifactorial participation of latexin in the neuroendocrine control of metabolism and/or other possible genetic modifications. In sum, this work will set the grounds for the understanding of mechanisms by which astrocytes participate in regional adaptations to the vast spectrum of signals, which is key in the search for adequate treatments of human neurological diseases.

(P202) A three-dimensional in vitro model of the Neuromuscular Junction

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Nerves innervate muscles in vertebrates in a complex process that translates chemical cues into physical activity. This task is accomplished by motor neurons, which are in charge of conducting the information from the brain to the muscle bundles, which are comprised of multiple muscle fibers. The specialized synapse between them is known as the Neuromuscular Junction (NMJ). The impairment of this special structure is related with a wide range of disorders such as congenital myasthenic syndromes, amyotrophic lateral sclerosis or muscular dystrophy. These disorders are life threatening and often lack effective treatments. Therefore, developing in vitro assays that closely recapitulate the physiology of the NMJ is crucial to understand the pathophysiological processes and to develop novel treatment options. The aim of this study is to develop a three-dimensional in vitro model to mimic human NMJs. To achieve this, the system will be composed of a co-culture of skeletal muscle cells, which will be differentiated to form myofibers and iPSC-derived motor neurons. In order to replicate faithfully a human NMJ, skeletal muscle cells from different organisms (human, mouse) will be compared. Motor neurons will be differentiated from iPSCs through the addition of several growth factors once the muscle fiber is formed. In addition, cells will be embedded in a collagen/matrigel matrix to create the ideal 3D environment. Currently, we are in the process of generating a compartmentalized microfluidic chip with three independent but interconnected chambers. Furthermore, we are establishing an efficient protocol for the differentiation of skeletal muscle cells embedded in different hydrogel combinations, and we are investigating the differentiation protocol for iPSCs into motor neurons. We expect that these studies will result in the development of a functional NMJ in vitro model incorporating muscle cells as well as motor neurons.

(P203) Cholesterol in X-linked adrenoleukodystrophy

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X-linked adrenoleukodystrophy (X-ALD) is a progressive neurometabolic disorder caused by ABCD1 mutations, leading to accumulation of very long-chain fatty acids (VLCFAs) in tissues and plasma. X-ALD presents as a spectrum of symptoms with the most severe form, cerebral X-ALD (cALD), characterized by rapid inflammatory demyelination in cerebral white matter, blood–brain barrier disruption and CNS infiltration of macrophages. The exact mechanism leading to cALD remains unknown. The only available option to treat cALD is hematopoietic stem cell replacement, which can halt inflammatory demyelination when performed at an early stage of the clinical course. Several observations emphasize a role of cholesterol in X-ALD: i) electron microscopy revealed intracellular needle-like structures, which are pathognomonic for the lipid burden in X-ALD macrophages, adrenocortical and testicular cells that display high cholesterol turnover; ii) cholesterol-lowering drugs decreased the VLCFA accumulation in primary cultured fibroblasts from X-ALD patients; iii) induction of the functionally redundant ABCD2 gene by sterol depletion significantly reduced the accumulation of VLCFA in X-ALD fibroblasts; iv) in X-ALD mice, plasma cholesterol is elevated and not further increasable by high cholesterol diet; and v)25-hydroxycholesterol and cholesterol 25-hydroxylase are elevated in X-ALD fibroblasts. In the present study, we will characterize potential alterations in cholesterol homeostasis in primary macrophages as well as fibroblasts derived from X-ALD patients or healthy controls by measurement of the cellular content of cholesterol/cholesteryl esters and cholesterol metabolites, as well as the cellular cholesterol efflux capacity, and by evaluation of foam cell formation. The aim is to establish the intracellular consequences of altered cholesterol metabolism in X-ALD, with the goal to increase the knowledge on the interaction of disturbed cholesterol metabolism and inflammation.

(P204) Demyelination and remyelination in X-linked adrenoleukodystrophy (X-ALD)

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X-linked adrenoleukodystrophy (X-ALD) is the most commonly inherited peroxisomal disorder caused by mutations in the ABCD1 gene encoding the peroxisomal ABCD1 transporter. ABCD1 transports the very long chain fatty acids (VLCFAs) from the cytosol into the peroxisomal lumen for degradation and its absence leads to the accumulation of VLCFAs in the tissues and body fluids of X-ALD patients. Approximately 60% of all male X-ALD patients develop the cerebral form of X-ALD (CALD) characterized by the progressive inflammatory demyelination in the brain. For the purposes of our study, we will investigate the process of demyelination as well as tackle the question of remyelination in CALD. To do so, we will perform immunohistochemical analyses on post mortem CALD tissue using markers for oligodendrocytes and myelin sheaths. In order to quantify mature oligodendrocytes as well as evaluate their morphology, we will use tubulin polymerization promoting protein (TPPP/p25) as a marker. Furthermore, we will use myelin protein markers (CNPase, MBP, MOG and MAG) to gain additional information about the status of oligodendrocytes and to look for possible remyelination within the lesions. Finally, we will compare the CALD lesions to multiple sclerosis (MS) lesions exhibiting remyelination in addition to the characteristic inflammatory demyelination. Considering the progressive, demyelinating nature of CALD, we expect to find no evidence for remyelination in these lesions. Our in-depth comparative analysis of CALD and MS lesions will allow us to gain a deeper understanding of the role of oligodendrocytes in the pathobiology of CALD and provide insights into the underlying causes of the lack of remyelination in CALD.

Group 16: 205 - 216
Thematic Programs: Neuroscience & Biomedical Engineering & Medical Informatics, Biostatistics & Complex Systems

(P205) Generation of an in vitro model for Human Specific nAChR Polymorphisms via iPSC Derived Neurons

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Human specific polymorphisms in nicotinic acetylcholine receptor (nAChR) genes have been associated with several disorders including cognitive deficits, epilepsy, language impairment, ASD, ADHD, schizophrenia, hypotonia and eye pathology. The CHRNA7 gene, which encodes for the _7 nAChR subunit, is located on the proximal part of chromosome 15, one of the least stable regions in the genome with frequent microdeletions and duplications. In this unstable region, about 1 Mio years ago, the CHRNA7 gene duplicated partially and fused with the gene FAM7A forming a novel human specific gene called CHRFAM7A. This gene encodes for the dup_7 nAChR subunit, which is slightly truncated at the extreme N-terminus, therefore lacking the agonist binding site, but otherwise shares all structural elements with _7. _7 and dup_7 can co-assemble forming a heteropentameric receptor, however with reduced agonist ligand binding capacities. Since both genes CHRNA7 and CHRFAM7A are both still in unstable gene regions both genes can be duplicated or deleted, resulting in humans with varying copy numbers of either of the two genes. In the current project we want to study the phenotypical effect on neurons, which express constant levels of _7 but increased or reduced levels of dup_. There is a lack of animal models for human specific genes and human neurons as a cell source are even more limited. Therefore, we plan to differentiate human induced pluripotent stem cells (hiPSCs) with different dup_7 expression levels into different neuronal cell types and investigate their functional properties using Fura2-Ca-Imaging and/or Patch-Clamp electrophysiology. First, embryoid bodies (EBs) were obtained from hiPSCs in low attachment plates upon enzymatic treatment. Then, EBs were attached to petri dishes in order to form neural rosettes including neural progenitor cells. Concordantly, terminally differentiated cortical neurons were generated from NPCs.

(P206) In-vitro Measurement of Centering Forces on a Transvalvular Ventricular Assist Device Cannula

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In transvalvular positioned cardiac support devices the cannula-leaflet interaction is of special interest and importance. Valve damage, backflow and thrombus formation might be improved if the cannula is kept in a central position within the valve orifice.

In a pulsatile in-vitro setup, forces acting on transvalvular cannulas were identified and the influence of cannula diameter and transvalvular pressure were investigated.

Radial and tangential forces acting on transvalvular cannulas were measured in a pulsatile setup. Fresh native porcine, bioprosthetic and artificial pericardial tissue valves were mounted in a test rig. The cannula position was deflected from a central position to the wall in 10° rotational step for the whole circular range. Further the cannula diameter (4, 6, 8 mm) and transvalvular pressure (40 - 100 mmHg) were varied.

Centering forces of the aortic cusps in the direction of the coaptation point were identified. At the mid of the leaflets and at the largest deflection the forces were highest (up to 0.8 N). In the commissures lower forces (up to 0.2 N) were measured. In symmetric valves with equal cusp sizes (pericardial tissue valve) the position of the commissures and cusps were clearly pronounced by the force distribution. Natural variations in the valve leaflets affected these distributions but lowest forces were always found in the commissures. A change in cannula diameter had only a minor influence. However rising transvalvular pressure linearly increased the forces, but did not alter the distribution patterns.

Centering forces that act on transvalvular cannulas were identified in an in-vitro setup for several valves and valve types. Lowest centering forces were found in the commissures and highest forces were found directly at the cusps. At low pressures low centering forces and an increased cannula movement can be expected.

(P207) Cardiac respiratory motion detection algorithm development for navigator applications

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Cardiac motion is a major obstacle for cardiovascular magnetic resonance (CMR). This work evaluates an alternative, robust approach for detecting the absolute position of the edges of the heart during the respiratory cycle suitable for real-time applications. Sagittal and coronal images in the cardiac region were acquired from 12 healthy subjects (7 male, 5 female, age: 25±2y, BMI: 23±2kg/m2) in supine position using Magnetom Prisma 3T and 7T scanners (Siemens, Erlangen, Germany). Different MR sequences - gradient echo (GRE) and turbo flash (TFL) - and variation of sequence parameters and slice positions were investigated. Detection was based on signal intensity profiles, related derivatives and a signal threshold for lung tissue. GRE and TFL sequences worked out equally well. ECG triggering, alignment of the heart-liver boarder in phase encoding direction, signal clipping and chest wall removal in post processing were used to increase detection efficiency. In sagittal images cranial of the global maximum of AP signal averages a global minimum in the related derivative and in caudal direction a global maximum represented the heart's edges (HF). Intersection of lung threshold and median signal in HF direction between HF edges corresponded to the posterior edge of the heart. The most suitable sagittal plane was in the apex area. Detection rate for cranial and posterior edge was 98%. The detection rate of the caudal edge was 97% due to low heart-liver contrast. As a next step detection of the lateral edges of the heart is being investigated. In coronal slices a global minimum and maximum of the derivative of HF signal averages represent the lateral edges. Localizing the heart using the algorithm is possible for 3T and 7T datasets. The presented method is a promising step towards the implementation as navigator in CMR. Funded by FWF P 28867-B30

(P208) Small diameter vascular grafts with adjustable mechanical properties

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Aim: The need for surgical revascularization therapies in small diameter applications is constantly increasing. Autologous vessels are gold standard but not always available. Vascular grafts, which are comparable with those, are essential. Electrospinning offers fabrication of fibrous scaffolds imitating the extracellular matrix. During conventional electrospinning fibers are deposited in a chaotic fashion due to various instabilities. Increased control of fiber deposition is essential to manufacture grafts which can mimic the complex layered structure and the biomechanical behavior of the host vessel.
Methods: Polymeric tubular vascular grafts were electrospun from Pellethane® 2363 80A on metal mandrels with a diameter of 2mm. Orientation and fiber alignment was controlled by auxiliary plate-like electrodes using electrodynamic deflection of the electrospinning jet. Prostheses with random, circumferential, longitudinal and 30° fiber direction were fabricated. Grafts were characterized by measuring the wall thickness and gravimetric porosity. Effects of fiber orientation were analyzed in the scanning electron microscope and by measuring the compliance in the physiologic blood pressure range.
Results: The electrospun vascular grafts had a mean wall thickness of 71 ± 6µm. Lowest porosity of 63% was seen in circumferentially electrospun grafts whereas grafts spun with fiber directions in ± 30° showed the highest porosity of 79%. Fiber alignment in the main direction of each selected orientation angle was observed. The prostheses with longitudinal fiber orientation showed a compliance of 18.6 ± 2.8 %/100mmHg, whereas the prostheses with circumferential orientation exhibited the lowest compliance of 7.1 ± 2.6 %/100mmHg.
Conclusion: The developed electrodynamic control method allows to electrospin small diameter vascular prostheses with pre defined fiber orientations.

(P209) Artificial image synthesis and data augmentation for deep learning segmentation in phase contrast images for biomarker discovery in cancer research

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Deep learning (DL) algorithms are achieving or even surpassing human-level performance in tasks like image classification or segmentation. Due to their fast development and exceptional performance, DL algorithms were introduced in various life science domains such as biomedical imaging, bioinformatics or computational biology. However, the outcome of these algorithms on unseen data highly depends on the quality of the training dataset. Thus, there is a need for manual data annotation which is a lengthy and time-consuming process, especially in the field of cell imaging.
We hereby propose a technique to accelerate data annotation by using synthetic phase-contrast images to train deep learning algorithms for cell segmentation.
Uniformity of the statistical data distribution, specific image artefacts modelling or representability were defined, and the method was designed and implemented. The feasibility of the proposed method was demonstrated by training the Mask R-CNN model for instance-aware segmentation using only synthetic images. The evaluation was performed on synthetic and real images as well. The F1 score for real images was 95.68% emphasising the advantage of using synthetic images for the training of DL algorithms.
The segmentation of phase-contrast images enables the subsequent combined analysis of corresponding fluorescent microscopy images on the single cell and sub-cellular level and support biomarker discovery in cancer research.

(P210) Flow field visualization in the assisted isolated heart during mechanical circulatory support

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Intraventricular flow patterns during mechanical circulatory support (MCS) cannot be accessed by clinical imaging and therefore either computational or in-vitro models are used. However, the complex anatomy of the heart cannot be replicated and simulations inherently rely on assumptions and simplifications. In an isolated porcine heart setup the feasibility of flow measurements by Echocardiographic Particle Image Velocimetry (E-PIV) was evaluated. Similar to cardiac transplantation porcine hearts (n=8, animal weight: 80-106 kg) were excised and connected to the isolated heart setup. After resuscitation using blood as perfusate, a rotary blood pump was implanted Microbubbles were injected via the left atrium at different support situations and echocardiographic 3-chamber-view B-mode images were recorded with the highest possible frame rate of up to 141 Hz (Philips iE33, X5 1 xMatrix probe). By iterative PIV algorithms using correlation domain averaging and beam sweep correction, flow fields were evaluated for the different hemodynamic situations. All hearts were successfully resuscitated in the isolated heart setup and different hemodynamic situations were adjusted. In the unsupported heart physiologic flow patterns with a large clockwise vortex structure that warrants washout of the whole cardiac chamber were found. With increasing MCS (2200-2700 rpm) the formation of this flow feature is diminished caused by the additional flow sink at the apex. In full support without aortic valve opening in the left ventricular outflow tract a stagnant structure was identified, that might be connected to thromboembolic events. For the first time, the contribution of the mitral valve apparatus to blood flow patterns especially in the LVOT, which may be linked to energy loss, thrombus formation and valve deterioration during MCS was investigated under realistic conditions.

(P211) Investigation of left ventricular flow fields under LVAD support with synchronized pump speed changes

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Continuous flow left ventricular assist devices (LVAD) are a common treatment method for heart failure patients, however their presence in the ventricle disrupts the natural intraventricular flow behavior. This deviation can introduce blood flow stasis areas, which are associated with a higher risk of thrombotic events. Pump speed modulation has been shown to improve washout inside the left ventricle (LV) and to reduce the amount of blood stasis areas. However, the effects of LVAD speed changes synchronized to specific timepoints within the cardiac cycle are not well documented. The aim of this study is to determine intraventricular flow characteristics with LVAD speed changes initiated at specific points within the cardiac cycle. Particle Image Velocimetry measurements of a transparent dilated LV model with LVAD support were performed in a mock circulatory loop. Two LVAD speed configurations were evaluated: constant speed operation and a simple speed change pattern. The pattern consists of a 200 RPM speed decrease from baseline followed by a speed increase back to baseline after two beats of the cardiac cycle. The experiments were performed with the pump speed changes occurring at several different timepoints within the cardiac cycle. The flow velocity magnitude and kinetic energy densities were used to evaluate these results. Intraventricular flow fields depend highly on the timing of the speed decrease and increase. Decreasing LVAD speed during diastole showed higher kinetic energy values when compared to constant speed and other speed variation timings. This leads to an improvement of washout inside the LV. The LVAD speed increase should occur during systole, to increase the amount of fluid inflow coming from the mitral valve. These findings suggest that the LVAD speed should be varied in specific phases of the cardiac cycle to improve washout in the LV and to minimize the risk of intraventricular thrombosis.

(P212) Extracting and combining concepts of Physiological Control of Left Ventricular Assist devices.

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Left Ventricular Assist Device (LVAD) therapy has become an accepted treatment for end-stage heart-failure. While patient management has improved over the past decades, limitations in caregiver resources necessitate efficient allocation. Decisions on the optimal setting of LVAD support currently occurs in intervals ranging from a few weeks to a few months. However the optimal setting for LVAD support may change multiple times per minute. Thus, automation is the only viable solution to this problem. Physiological control promises to integrate the cardiac assist device into patient physiology even more closely, reacting to varying demands or specifying the load for training of the heart muscle. One important design consideration is the choice of feedback variable. Literature of the past two decades was collected and the presented physiological control concepts were clustered into categories corresponding to functional similarity of feedback variables. It was found that most literature could be summarized into five categories. Control algorithms either used preload, heart rate, ventricular contraction, or afterload as feedback variables or modified the flowrate/headpressure relation. Each of these categories contains information about the cardiac state. While preload variables, most closely resemble the native functioning of the left ventricle, they are inherently difficult to measure without using additional sensors. Chronotropic incompetence might be a limiting factor for heart rate based control. Ventricular functioning might fluctuate over time due to changes in inotropy while afterload is heavily regulated by other autoregulatory mechanisms. The headpressure/flowrate relation suffers from uncertainty regarding the origin of pressure changes. Combining elements of these five categories into one control concept might prove beneficial, as different information could be extracted for the controller, which could then be tuned by the physician.

(P213) Evaluation of motion correction strategies in resting-state functional MRI of the foetal brain

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Fetal fMRI has emerged as a powerful approach for investigating brain development in utero and holds promise for generating developmental disease biomarkers and prenatal diagnosis. However, to date its clinical applications have been limited by unpredictable foetal and maternal motion during image acquisition. Spontaneous fetus movements cause spurious signal fluctuations which can confound different measures of functional connectivity and bias statistical inference about relationships between connectivity and individual differences. As there is no ground truth for the real fMRI data, it is necessary to quantify the quality of data in terms of motion and the success of applying motion correction techniques. Here, we developed data driven quality control benchmarks for systematic evaluation of the efficacy of the existing algorithms for mitigating motion-induced artefacts. Our benchmarks are based on functional connectivity variation and its residual relationship with motion, distance-dependent effects of motion on connectivity, signal intensity changes, and additional degrees of freedom lost in confound regression. Specifically, we compared popular retrospective methods for denoising resting state fMRI data, including regression of the head motion parameters, mean white matter (WM) and cerebrospinal fluid (CSF), anatomical and temporal CompCor, scrubbing, and global signal regression (with and without expansion terms) using fMRI data of 25 foetuses with no detectable developmental abnormalities (mean gestational age: 29.5 week 5.2 days). Results reveal the relative strengths and weaknesses among different denoising methods and underscore the need for greater care in dealing with foetus motion.

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(P214) Effect of atrial inflow conditions on ventricular flow pattern during mechanical circulatory support using particle tracking

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Simulations of the ventricular flow patterns during left ventricular assist device (LVAD) support are mainly performed with perpendicular inflow conditions from the atrium neglecting asymmetries arising due to uneven flow contribution of the pulmonary veins. In this study, the influence of the atrial flow conditions – including rotation and asymmetric flow profiles – on the platelet behavior were investigated via Computational Fluid Dynamics (CFD) simulations.
In a patient-specific LVAD-supported left ventricle (LV) model conditions were applied for three different inflow boundary conditions. First, a simulation was performed with perpendicular velocity to the inflow (LAper, flow rate: 3.5 lit/min), second with an additional rotational component at the inflow (LArot: 35 rpm) and a third simulation was performed with asymmetric inflow conditions (LAasym: 60%/40% left/right flow ratio to replicate physiologic uneven flow distribution of the pulmonary veins). Platelet motion was simulated with a combination of laminar and the Lagrangian methods for 7 s and for quantitative analysis, platelet shear stress histories (SH) and residence times (RT) were calculated over platelet trajectories.
Atrial inflow conditions affect the mean blood velocity magnitude in the apical region of the LV (LAasym: 4.1, LArot: 2.9, LAper: 2.7 cm/s). The cumulative probability that a particle accumulates a higher SH value than 0.6 Pa.s increased under asymmetric inflow conditions (LAasym: 11%, LArot: 5%, LAper: 3%; $p<0.05$); however the cumulative probability that a particle would linger for more than 7s inside the LV increased with perpendicular inflow conditions (LAasym: 13%, LArot: 18%, LAper: 19%; $p<0.05$).
Neglecting the atrial flow conditions could lead to inaccurate simulation of ventricular blood flow. Hence, reliable prediction of platelet behavior traveling through the LV requires the consideration of the atrial inflow conditions.

(P215) Pathway-based drug repositioning for breast cancer molecular subtypes

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Breast cancer is a major public health problem which treatment needs new pharmacological options. In this work, we integrate several tools that exploit disease-specific experimental transcriptomic results in addition to information from biological and pharmacological databases obtaining a contextual prioritization of pathways and drugs in breast cancer subtypes.

Briefly, we obtained two data sets of gene expression experiments (METABRIC and TCGA). Then, the samples were classified in its respective molecular breast cancer subtype according to PAM50 algorithm. After that, we identified the most deregulated pathways in each breast cancer subtype. Each deregulated molecular pathway was associated to its known pharmacological targets according to information from pharmacological databases. Finally, these drug-subtype relations were classified according to information available in both the pharmacological databases as well as information from the gene expression data of the samples themselves.

As a result of this work we obtained an annotated pharmacological database for each breast cancer subtype. As an example of use we show how to query pharmacological targets from this database based on the most deregulated pathways, differential gene expression status, drug type interactions and other characteristics. Finally, we propose a proof of concept of how this methodology could be further extended in a personalized way.

New associations between breast cancer subtypes and pharmacological targets of potential therapeutic utility were proposed. The usefulness of these results should be evaluated in terms of drug repurposing in each breast cancer molecular subtype therapy. In favor of breast cancer patients, this methodology could be further developed to provide personalized treatment schemes. The latter are particularly needed in those breast cancer subtypes with limited therapeutic options or those who have developed resistance to the current pharmacological schemes.

(P216) A Two-Stage U-Net Algorithm for Segmentation of Nuclei in Hematoxylin and Eosin H&E)-Stained Tissues

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Tissue samples extracted from biopsies or surgeries are used for clinical diagnosis and prognosis for millions of patients each year. Decisions of pathologists are mainly based on cell morphology and tissue architecture. In this context, nuclear morphology is one of the central criteria for diagnosis and grading. Consequently, the nucleus is also an important target in image computing. In digital pathology, there is a growing demand for development and optimization of computerized methods related to nuclei detection and segmentation. While many computerized nuclei segmentation methods have been proposed meanwhile, machine learning-based algorithms and in particular deep learning-based models have been shown to deliver better segmentation performance. In this work, we propose a novel approach to segment touching nuclei in Hematoxylin and (EosinH&E)-stained microscopic images using modified U-Net based models in two sequential stages. In the first stage, the algorithm performs semantic segmentation by a classification U-Net which uses the combination of binary cross entropy and dice score as the loss function. In this stage, the nuclei are separated from the background, but touching objects may not be classified correctly. In the second stage, the distance map of each individual nucleus is created using a regression U-Net which exploits mean square error as the loss function. The final instance segmentation masks are then created using a watershed algorithm based on the distance maps which separate the overlapping objects in the images. Evaluated on a publicly available dataset containing challenging images from seven various human organs, the proposed algorithm achieves an average aggregate Jaccard index of 56.87%, outperforming several state-of-the-art algorithms applied on the same dataset.

Group 17: 217 – 229
Thematic Programs: Medical Informatics, Biostatistics & Complex Systems & Medical Physics & Public Health

(P217) Spot detection at the single cell level: a computational approach to analyse I-FISH spots in consecutive sections of heterogeneous neuroblastoma tumors

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(P218) Real-time image-based tracking of B0 shim elements in flexible matrix shim arrays for dynamic B0 shimming of the abdomen

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High-order matrix shimming has proved useful for addressing B0 susceptibility issues in Magnetic Resonance Imaging at high fields (above 3 Tesla) but requires prior knowledge of the shim elements position. For rigid coil formers the shim loops are fixed in space and the field maps can be pre-measured in a phantom. Flexible or movable arrays used in abdominal imaging present a challenge since the element position is patient-specific. Here we introduce a marker system using PDMS, for rapidly detecting the element position prior to or during matrix shimming. Our tests show we can successful determine loop position to accurately generate B0 field maps in good agreement (difference between measurement and simulation < 10%) with experimentally measured maps. Our technique allows detection of the loop position in a flexible AC/DC coil with minimal image post-processing. This will be important for determining the shim basis sets in flexible abdominal coils where the array position varies from patient to patient. A limitation of the approach is that Gibbs ringing can occur if the signal level from the PDMS is too high due to the fact that it is so close to the receive loop.

(P219) Evaluation of 2D and 3D ultrasound calibration methods

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(P220) GATE/Geant4 as a Monte Carlo simulation toolkit for light ion beam dosimetry

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(P221) Variability in NEMA image quality and quality control procedures across PET/MRI imaging sites

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Aim: To assess variability in NEMA image quality (IQ) and local quality control (QC) procedures at European hybrid imaging sites. Further, to provide a set of recommendations for well performance of the PET/MRI systems across centres. Methods: PET/MRI NEMA image quality phantom scans were collected from partner imaging sites involved in the HYBRID consortium (MSCA #764458). Using an on-site NEMA image quality evaluation tool, contrast recovery, background variability (BV) and recovery coefficients (RC) were calculated for each PET/MRI system. Further, the sites involved were surveyed about local frequencies for PET/MRI QC procedures. The survey included 24 standard QC procedures for both the PET and MRI components of the systems. Coefficients of variation (CV) for the IQ measurements and test and testing frequencies for PET/MRI QC procedures are reported. Results: Seven of eight imaging sites provided the NEMA image quality phantom images. CV of contrast recovery for the 10mm, 13mm 17mm, 22mm, 28mm and 37mm spheres were 25[%], 27[%], 14[%], 12[%], 15[%] and 16[%], respectively. CV of BV were 14[%], 18[%], 27[%], 34[%], 39[%] and 48[%], respectively. Most of the RC values for SUV_{mean}, and SUV_{max} fitted within the recovery bandwidth given by the EARL iniative[1]. Moreover, although all sites performed vendor-specific daily QC procedures, significant variations across the centres were observed for other routine QC tests and testing frequencies. Likewise, variations in the daily quality assurance (DQA) procedures implemented by vendors were found. Conclusion: Variability in NEMA IQ results between PET/MRI systems are comparable to those reported previously for PET/CT systems before implementation of harmonisation strategies[2]. Therefore, standardised procedures for PET/MRI are needed. To overcome differences in PET/MRI QC procedures, we provide a consensus recommendation of a minimal set of QC measures for PET/MRI throughout the HYBRID consortium.

(P222) In vitro and in vivo validation of radial fast spin echo based T2 mapping of the liver

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Magnetic resonance is a noninvasive imaging modality that can help in the diagnosis of liver disease. Among other MR parameters, hepatic tissue T2 relaxation times were reported to be affected by many pathological conditions, such as iron overload, fibrosis, steatosis, inflammation. The measurement of T2 values in vivo in human liver is challenging due to the breathing motion in the abdomen. With conventional techniques the measurement takes up to several minutes. Radial fast spin echo (FSE) technique was proposed to overcome this problem. This sequence is sufficiently fast and motion insensitive. Here, we compared a work-in-progress radial FSE T2 mapping with conventional multi-echo spin echo based T2 map on a phantom at 3T system (Siemens Healthineers, Erlagen, Germany). Further-on we tested the efficiency of fat signal suppression on phantoms with variable fat content. Finally, we evaluated T2 values on a heterogeneous group of 21 patients appointed to clinical abdomen examinations via the radial FSE T2 map and spectroscopy-based multi-echo sequence. We found that there is an excellent correlation between radial FSE and the conventional spin echo measured on the phantom in the range of T2s from 260 to 20 ms, but radial FSE overestimates the values with the mean of difference = 40 ms (P = 0.003). Bland-Altman plot shows that the difference is systematic. The application of fat suppression decreased the T2 value in samples with fat fraction over 15%, which demonstrates its efficacy. Comparison of the in vivo acquired hepatic radial FSE T2 map with spectroscopically obtained T2 values showed an overestimation of T2 values by radial FSE based map with the mean of difference = 12 ms (P < 0.0001). To conclude, we could show that radial T2 map works sufficiently well for in vivo liver MRI and that this method can be used to further characterization of diffuse liver diseases within clinically acceptable measurement time.

(P223) Benchmarking a GATE/Geant4 Monte Carlo model to support treatment planning towards MRI guided ion beam therapy

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(P224) Dose reduction in paediatric brain PET imaging: how low can we go?

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Purpose: To evaluate the potential effective dose (ED) reduction by using advanced image reconstruction methods in pediatric imaging with [18F]FDG PET/CT.
Methods and Materials: Data from fifteen pediatric patients with epilepsy were collected. Patients underwent [18F]FDG-PET/CT examination with injected activities of 4.2±1.9 MBq/kg. The patient ED was estimated from the CT and PET acquisitions. The EDCT was defined as the product of the Dose-Length Product (DLP) and CT dose conversion factor (kCT). The DLP was derived from the scan length and CT Dose Index (CTDIvol). The EDPET was calculated as the injected activity and PET dose conversion factor (kPET). The kCT and kPET were obtained from the ICRP-103 publication. The reduced PET injected activity was simulated with reducing the number of counts to 75%, 50%, 35%, 20% and 10% of the total counts. Reconstructions were performed applying OSEM, Maximum-A-Posteriori (MAP) reconstruction with median-root prior (MAP-MRP) and MAP with quadratic prior (MAP-QP). As figure of merit the target-to-background ratio, noise in the uniform region were calculated.
Results: The EDtotal was 5.0±1.3 mSv (EDPET=4.7 mSv, EDCT=0.3 mSv). Relative deviations below 10% were obtained for count reductions down to 50% applying the reconstruction methods OSEM+4mm filter and MAP-MRP. Using 50% of counts ED for PET could be reduced from 4.7 to 2.4 mSv. This results in a reduction of the total ED up to 53%.
Conclusion: A potential reduction of the injected PET activity up to 50% can be achieved without compromising the selected image quality parameters by applying a suitable reconstruction method.

(P225) A new test method to assess the representation of spiculated mass like targets in breast tomosynthesis

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Purpose: In this work we tested different materials to improve dose sensitivity of an existing phantom and possibilities to make the anthropomorphic phantom more realistic. The investigated materials were supposed to be used as 3D printing material for spiculated masses with different numbers of spicules.
Material and Methods: Eight printable materials were exposed together with a PMMA step wedge and material samples with known linear attenuation coefficient to determine PMMA equivalent thickness and linear attenuation coefficient, respectively. The detectability of a 3D printed spiculated mass model embedded into two different printing materials was assessed for Full Field Digital Mammography (FFDM) and Digital Breast Tomosynthesis (DBT). Using the most promising materials (Vero White pure) a spiculated masses featuring 21 and 10 spicules, respectively were printed at five different scales. The number of visible spicules was counted in dependence on different current-time products.
Results and Conclusion: For the materials investigated, Vero White pure has the highest linear attenuation coefficient and was used for the spiculated masses. Dose sensitivity was higher when the objects had 10 spicules instead of 21.

(P226) Fuzzy Radiomics: A novel approach to minimize the effects of target delineation on radiomic models

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Aim: Recently, the characterization of tumours with in-vivo radiomic features from Positron Emission Tomography (PET) imaging has become fashionable. However, the effect of lesion delineation approaches on radiomic values has not yet been fully understood. Our goal was to integrate fuzzy logics in the process of radiomics feature extraction in order to handle uncertainties arising from variations in lesion delineation. Materials and Methods Reconstructed NEMA IQ PET images acquired in 13 PET/CT systems with the same physical phantom were included in our study. The largest sphere 37mm) was delineated with dichotomized fuzzy clustering and gradient maximization approaches to generate 3-dimensional binary volumes-of-interest (VOI) masks. In addition, a fuzzy delineation was executed, which provided a non-binary probability VOI mask for the lesions. Thirteen radiomic features with known minimal multi-centric variations were extracted from the 37mm sphere of the 13 PET acquisitions. This process was repeated over the two binary as well as over the fuzzy VOI masks. The binary VOI masks were used for classic radiomics, while the fuzzy VOI mask was used for modified radiomics calculations, handling non-binary probability membership values. Coefficients of variation (CV) were calculated for each feature and delineation method over the 13 PET acquisitions. Results The average CV of the fuzzy mask with fuzzy radiomics was 21%, while the average CV for the dichotomized fuzzy clustering and gradient maximization approaches built on classic radiomics were 37% and 63%, respectively. Conclusions We demonstrated that performing fuzzy radiomics on a fuzzy probability delineation map approach can minimize variations of radiomic features in a multi-centric environment, thus, pointing towards reproducible quantitative radiomics.

(P227) Functional connectivity of the fetal brain in utero

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During the gestation, the fetal brain undergoes significant changes and the development of corresponding functional brain networks is not yet understood fully. Functional connectivity is a method, which describes the temporal correlation between brain regions, and can help to understand the neural communication and the organization of the fetal brain during the prenatal period. We analyze the evolution of 22 fetal short-range connectivity networks between the 20th and 40th gestational week measured by functional magnetic resonance imaging in utero. The functional connectivity on both brain cortices shows reproducibility development, and the short-range connectivity strengthens with advancing gestational age. The default mode and dorsal attention network showed most short-range connectivity on the left hemisphere, while the frontoparietal, default mode and dorsal attention network showed most short-range connectivity on the right hemisphere. The correlation between the default mode network and the cortex is centered to default mode network and does not change significantly over the gestation.

(P228) mTOR signaling in macrophages contributes to the maintenance of iron homeostasis

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(P229) What happens to bariatric patients who did not attend a structured follow-up program in an outpatient clinic? A questionnaire based study

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While nonadherence to follow-up after bariatric surgery is common, this follow-up visits are necessary for management and treatment of post-operative complications. The aim of this study was to examine if patients who were lost to follow-up, defined as not attending the bariatric outpatient clinic (OC) for their 12 or 18 months appointments, had any other follow-up checkups besides OC.

220 patients underwent sleeve gastrectomy, one anastomoses gastric bypass or Roux-Y gastric bypass for the first time at the General Hospital of Vienna between July 2016 and August 2017. 93 of those did not attend the 12 or 18 months follow-up appointment at OC.

A prospective study was conducted on these 93 patients. They were contacted by telephone and a structured interview regarding follow-up visits at other providers was conducted.

Out of 93 patients, who did not attend their 12 or 18 months follow-up appointment at OC, 68 (73,1 %) responded to the interview questions. The majority indicated regular appointments with/in other institutions (63 (92,8 %)) such as their general practitioner (GP; 29 (42,6 %)). 6 (8,8 %) went to their surgeon (SN), 1 (1,5 %) to an hepatologist and 4 (5,9 %) another outpatient clinic (OOC). Some of the patients choose to attend two or three different providers: 6 (8,8 %) GP and OOC, 11 (16,2 %) GP and SN or diabetologist, 4 (5,9 %) OC and SN, 1 (1,5 %) GP, OOC and SN.

Only 5 (7,4 %) had no kind of post bariatric surgery care. 3 of the 5 patients said that they did not know about any need for a lifelong treatment.

Our study shows that compliance to follow-up 12- and 18-months post-surgery at other providers besides the OC is high. But this study did not ask for quality or content of received care. Hence, almost 70 % of the patients visit their GP future research should focus on the development of standardized methods regarding management and treatment of lifelong aftercare in primary care.

Group 18: 230 – 239
Thematic Program: Public Health

(P230) Multilevel factors associated with repeat adherence to mammography screening in women in Austria

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Austria's decades long, referral-based mammography-screening was replaced with an invitational program in 2015, the Austrian Breast Cancer Early Detection Program. Currently, there is no evidence on the uptake and influencing factors of participation based on representative data.

Cross-sectional survey (n=10 000, women aged 45 to 69 eligible for mammography-screening in 2018) and retrospective analysis of social insurance claims data.

Preliminary analysis shows a response rate of 29.5% (n=2926) in our survey. Women holding an Austrian citizenship are overrepresented (94.8%) as compared to the Austrian general population (89.3%). Further, there are geographical differences in response rates with decreased numbers from Vienna and Tyrol. Overall participation (at least one-time use of mammography) is 78.1%, repeat adherence (according to the recommended two-year interval and age-specific recommendations) is 57.3%.

Preliminary analysis indicates that socio-demographic characteristics, medical data and personal-level information may have effects on mammography-screening adherence.

Following data linkage using social insurance data, hospital claims data and data on the use of prescription drugs, possible influencing factors of single and repeat adherence will be examined using a multivariate regression model.

(P231) Iron metabolism of the human placenta – the key to understand iron transfer from the mother to the fetus

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Iron is an essential element. It is a co-factor in many enzymatic reactions and therefore required for normal cell function. Pregnancy is a time of increased iron demand to supply the growing fetus and to meet the expansion of the maternal erythrocyte mass. Iron deficiency in pregnant women is very common and can have a number of detrimental consequences for the offspring such as growth reduction or neurodevelopmental disorders. During pregnancy, iron is transported from the mother to the fetus across the placenta. Despite its central importance, iron metabolism of the human placenta and its regulation are poorly characterized. However, it is crucial to understand the molecular mechanisms of placental iron transfer.

In humans, the placental barrier consists of the syncytiotrophoplast [STB], the cytotrophoblast [CTB] layer and the fetal endothelial cells [FECs]. One major aim of this study is to determine the transporters involved in the iron uptake into FECs from the placental stroma as well as the release of iron from FECs into the fetal blood. Iron transport will be studied in placental cell lines and primary placental endothelial cells.

The placental iron metabolism will be analysed in relation to the iron status of 60 healthy mother-child-pairs. The combination of basic research with clinical data will be beneficial to better understand how placental iron metabolism affects maternal and neonatal iron status.

(P232) Does the use of T2MR for detection of ESKAPE pathogens in Blood-Stream Infection shorten the time until targeted therapy and influence patients' outcome?

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(P233) The involvement of iron transporters in placental cadmium uptake

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Iron deficiency (ID) is a condition, in which iron bioavailability is insufficient to fulfil physiological demands. Especially pregnant women are at high risk due to elevated iron demands during pregnancy. Iron deficiency causes a number of severe developmental problems in the fetus and newborn child. Furthermore, ID has been associated with a concomitant increase in toxic heavy metals that could aggravate the dire consequences of ID. This is of special interest, since it has been suggested that proteins involved in iron homeostasis participate in uptake of these metals.
The functional role of iron transporters Transferrin Receptor 1 (TFR1), Divalent Metal Transporter (DMT)1, ZRT/IRT like protein (ZIP)8 and Ferroportin 1 (FPN1) in uptake of the heavy metal cadmium was investigated by siRNA-mediated gene knockdown in human trophoblast cell line HTR8/SVneo. Additionally, the influence of iron availability in cell culture media on the uptake of cadmium was assayed in three settings (iron overload, iron depletion, normal iron content). Cellular heavy metal concentrations were analysed via graphite-furnace atomic absorption spectroscopy. One major finding is that DMT1 is crucial for cadmium uptake. Additionally, there was trend for increased cellular cadmium accumulation in iron-depleted cells. Cadmium had no obvious effects on cell proliferation and cell viability, which may be a result of elevated metallothionein levels. This study provides first insights into the complex interplay of placental metal metabolism and emphasizes the importance of proper iron homeostasis.

(P234) Effects of the exposure to mobile phones on heart rate variability in patients with aortic valve replacement

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Introduction: Studies on biological effects of electromagnetic fields (EMF) emitted from mobile phones (MP), particularly on the cardiovascular system have yielded contradictory results. This could be due to differences in the capacity of the cardiovascular system of the individuals investigated to regulate external influences. Therefore, the present study investigated participants who are especially susceptible to cardiac electrical impairment, namely postoperative patients with mechanical aortic valve replacement. Methods: This experimental study was conducted on 40 male participants (17-59 years) who had undergone a mechanical aortic valve replacement. Participants were randomly divided into a control and exposure group. Blood pressure was assessed before and after the exposure period in both groups, and three lead Holter monitors recorded heart rate, QT interval and computed time domain heart rate variability parameters during a 20 min real or sham exposure period and, 10 min before and 10 min after exposure. Results: In the experimental group, mean heart rate significantly decreased during exposure p-value _ 0.05). The mean corrected QT interval was prolonged during MP exposure but this difference did not reach statistical significance. Several heart rate variability parameters increased significantly during exposure p _ 0.05 for SDNN, SDNNI, TRI and RMS-SD in the experimental group. No significant changes in systolic and diastolic blood pressure occurred (p _ 0.05). Conclusion: The study demonstrates that RF exposure from mobile phones may change the balance of the autonomic nervous system through increasing the parasympathetic tone or decreasing the sympathetic tone.

(P235) Hidden suffering Unemployed Voice Concerns about Transmission of Their Health Data to the Job Centre

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Abstract There are only few clinical studies that address the effects of unemployment on somatic health. Only under certain, particularly strict criteria, are unemployed adults to be included in studies as they are subjected to special attention by ethics committees given their status as vulnerable subjects. Our original goal was to obtain data on the risk factor unemployment via a pseudonymized survey and a fitness test (spirometry or ergometry). A problem we faced was that majority of participants were very concerned about answering questions on their state of health. Even with a modified study design, an entirely anonymous survey, the concerns remained. Subsequent expert interviews showed that unemployed people, as patients, even have reservations when talking about their health to their doctors. They fear that the health data stored in the social insurance data set was accessible to the AMS. This behaviour of avoidance could affect the health care of this demographic. Keywords: unemployment, data protection, poverty, ethic, public health, good clinical practice

(P236) Sand fly dispersal in Central Europe: is temperature really critical?

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Sand flies are inconspicuous, hematophagous insects, inhabiting tropical, subtropical, arid as well as temperate regions worldwide. Of approximately 800 species described, 70 species are of medical relevance by transmitting protozoan, bacterial or viral pathogens. Within Europe, sand flies were considered to be endemic only to the Mediterranean regions, until the first findings in Germany in 1999 and 2000. Several recent findings of sand fly species in Austria and bordering countries, including Hungary, Slovenia and Slovakia support the assumption, that the sand fly distribution in Central Europe has not been investigated in sufficient detail yet.
The occurrence of sandflies is known to depend on temperature and humidity, however the role of other important ecological factors has still not been fully elucidated. The aim of this study was to obtain data on the ecology and seasonality of sand fly populations in Austria, which is of crucial importance for the evaluation of new dispersal sites and modalities. A long-term study during the summer months 2018 was conducted to assess sand fly activity and associated ecological factors and to shed light on sand fly ecology in Austria. Four different locations were sampled for four consecutive nights a week over a period of 11 weeks with standardized CDC miniature light traps. Trapped specimens were identified by morphological and molecular analyses. Detailed associations between sand fly activity and associated climatic parameters including temperature, relative humidity, wind speed, precipitation, air pressure and lunar illumination were assessed. All specimens were screened for the presence of Leishmania DNA by PCR. Blood meal analyses of engorged specimens were conducted by MALDI-TOF and PCR with subsequent sequencing.
This study provides the first data on sand fly activity and associated factors in a Central European country and further elucidates environmental requirements of sand flies in temperate regions.

(P237) The kinetics of mercury in the human placenta: Relationship between genotype and phenotype in healthy and diseased placentas

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(P238) A Dynamic Jaw Model with a Finite-Element Temporomandibular Joint

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The human masticatory region is a highly complex biomechanical system of the human body. In the TMJ an articular disc is located between the mandible and the skull. This disc is important for jaw movements as well as absorption and transfer of forces. A connection between temporomandibular disorders (TMD) and increased joint loads has been suggested in previous literature, but in vivo investigations of the joint load are not possible. Hence, biomechanical computer simulation remains an important tool for the investigation of the workings of this complex system.
The model was built using medical imaging data from one symptom-free volunteer. Details on image acquisition and processing have been described in a prior publication. In short, high-resolution MRI scans of both TMJ regions for different mandible positions were used to validate the presented model.
To speed up the simulations we used an elastic foundation contact (EF) approach to model articular cartilage layers. The TMJ discs were segmented from high-resolution MRI scans and were included as FEM models with material parameters taken from literature.
Results for a passive opening simulation show an inter-incisal distance (IID) of 6mm, while an active opening simulation computes an IID of 32mm. Comparison between simulated end positions for opening and protrusion with positions of the TMJ structures from the MRI scans showed good agreement, for the disc as well as for the mandible.
The presented project highlights a novel computational model of the masticatory region. The combination of a muscle-driven rigid body model with a detailed FEM TMJ disc, built from the MRI data of a volunteer, allows the thorough investigation of joint loading during various real-life tasks of the masticatory system. Our accelerated simulation framework will aid in translating high fidelity simulations into the clinic and presents a unique tool for the future investigation of the connection of TMDs and TMJ loading.

(P239) Suicide Risk and Suicide Prevention in Austrian Patients with Chronic Skin Conditions from the Dermatologists´ Point of View

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More than 1,000 Austrian citizens take yearly their own life. One of the suicide risk factors is a chronic illness. The goal of the study was to estimate the rate of suicidal ideations in patients with atopic dermatitis, psoriasis, and acne from dermatologists´ point of view. The link to the online ten-minute questionnaire that was specially developed for this study was emailed to 450 self-employed dermatologists of Austria. 45 doctors have participated. The key result of the study is the low rate of suicide-related behaviors in Austrian dermatological practices. However, the majority of the sample (82%) are aware of the fact that these patients are at higher suicide risk. 60% of the participants also believe, that it rather would not be a problem for them to recognize suicidal ideations in their patients. The most challenging about suicide is for the sample the lack of time and knowledge. The majority of the participants are also interested in cooperation with mental health professionals, implementation of new prevention strategies, and are wishing for more training programs. Statistical data analysis revealed that private specialists are having fewer patients but spending more time with them, compared to the contract physicians. Yet, these differences don't seem to influence the quality of treatment they provide. The quality of treatment was defined as the extent to which doctors tell their patients that additional psychological treatment could be helpful and ask them about their emotional state. The two variables that have an impact on the quality of treatment are female gender and psychological background. The possible explanations for the low rate of suicidal ideations are an advanced Austrian health care system and/or dermatologist´ underestimation of a problem. Implications of the study are to promote the cooperation between dermatologists and mental health professionals and to address the problem of the suicidality from the perspective of the patients.

Group 19: 240 – 252
Thematic Programs: Mental Health and Behavioural Medicine

(P240) Modulation of cortical activity with non-invasive neurostimulation in children and adolescents with autism spectrum disorder – a randomized, double-blind and sham-controlled study

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Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder, characterized by impairments in social interactions and communication as well as restricted, repetitive, and stereotyped patterns of behavior. Patients with ASD have problems to recognize emotions from other peoples' faces. EEG and fMRI studies as well as eye-tracking data reveal a neurophysiological basis of these deficits by linking them to abnormal brain activity. A method able to change aberrant neural activity is transcranial Direct Current Stimulation (tDCS). tDCS has already demonstrated promising results in several neuropsychiatric disorders in adults and children. Accordingly, this study aims to investigate the effects of tDCS on ASD symptoms and their neural correlates in children and adolescents with ASD. Twenty children and adolescents with ASD will be included in this study. The intervention phase comprises ten sessions of active tDCS or sham stimulation within two consecutive weeks. To investigate tDCS-induced effects, psychological, physiological and behavioral data will be collected at pre- and post-measurements. Firstly, psychological ratings will be obtained including self- and parental questionnaires to detect improvements in ASD symptoms. Secondly, physiological measures will be completed involving EEG and fMRI paradigms to investigate changes in resting-state activity as well as in neural responses to emotional and cognitive paradigms. Thirdly, behavioral tests will be performed measuring changes in responses to emotional and social stimuli as well as concurrent gaze behavior via eye-tracking. The results of this study will provide relevant and integrative insights into the neural underpinnings of ASD impairments and their changeability through neurostimulation.

(P241) Autism Spectrum Disorders in Austria – Prevalence, comorbidities & challenges

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(P242) A Preliminary Survey On The Mental Health, Behavioral Problems and The Availability of Caring Adults in Children With A Histroy Of Loss, Violence and Divorce

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Literature on factors in resilience underlines the importance of personal ties as protective factor in the mental health outcomes in children at risk. Still, little is known about the importance of a social resources in grieving children. We run a prospective study on factors in resilience in grieving and traumatized children as outpatients of the low-threshold ambulatory The Buoy (die Boje, www.die-boje.at).Within the first year, N=40 outpatients in need of crisis intervention could be recruited. In the current survey we describe the participants' psychological states and behavioral problems as well as their social resources. The mean T-values of behavioral problems (YSR/11-18R, N=38) and depressive symptoms (DIKJ, N=37) are beyond clinical relevance. Subjects with a history of divorce and violence report being strained by symptoms of anxiety (PHOKI; N=38). Using CBCL/6-18R the legal guardians (N=27) report marginally relevant internalizing and total behavioral problems. Almost all our subjects report at least one available caring adult (97%). The network of attachment figures is mainly comprised by the closer family system, parents are of prime importance and the relationships are described as stable, caring and joyful. The current data indicate few mental health or behavioral problems and the participants report positive personal ties to caring adults. A future attempt will be to monitor the subjects and to compare the mental health outcomes within the groups of different risk factors. Problems in the recruitment could limit the generalizability of our data.

(P243) Anonymous birth: Mental health outcome of adopted children

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For the first time, the current nationwide study assesses adoptive parental reports on mental health in a non-clinical Austrian sample of anonymously born and adopted children between 4 and 15 years.

The current study is ongoing (2018-2019). Thus far, a sample of 48 adoptive parents have reported on their adopted children (4-15 years), they were recruited from 8 child custody services and one private adoption institute. The Child Behavior Checklist (CBCL) for child mental health was used. The CBCL raw scores were transformed into T-scores according to existing German normative data. Independent t-tests were applied.

Preliminary data analyses revealed that 33% of the reported scores lay in the clinically relevant range of the CBCL total score, whereby this prevalence was 29% in the externalizing and 26% in the internalizing subdomain. Furthermore, 20% of these children present signs of aggression and 9% tend to either have dissociative or anxiety behavior pattern problems. However, regarding the CBCL total global mental health ($t(47) = 1.880$; $p = 0.066$) and internalizing behavior score ($t(47) = 1.714$; $p = 0.093$), the mean T-score did not significantly differ from the norm population. For the externalizing behavior subscale, the mean T-score was higher in the observed sample than in the norm population ($t(47) = 2.799$; $p = 0.007$).

These preliminary findings show that anonymously born and adopted children do not significantly differ in their global mental health status from the norm population. These results are similar, besides the externalizing behavior patterns, to those of other types of adopted children studies (Pace, C & Muzi, S, 2017).

(P244) Social Cognitive Impairment in 22q11 Deletion Syndrome Linked to Psychopathology and Social Competence: A Review

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The 22q11 deletion syndrome (DS) is a genetic syndrome that results in highly variable profile of affected individuals of which impairments in social domain and increased psychopathology are the most prominent. Because social cognition has been targeted as one of the risk-factor domains in population with mental disorders, this systematic review will investigate social cognition in individuals with 22q11DS and look for the links across its domains to psychopathology and to social competence/skills/functioning. Furthermore, we will try to explore possible psychotherapeutic targets that could be addressed with mentalization-based treatment (MBT).

Systematic literature review of the studies that include assessments of social cognition, psychopathology and social competence/skills/functioning in individuals with 22q11DS using electronic databases such as PubMed and PsycINFO.

A total of fifteen included studies confirm previously reported deficits in social and psychiatric domains in individuals with 22q11DS. In respect to psychopathology, both aspects of social cognition (perceptual and cognitive) have been primarily related to the diagnosis of schizophrenia/psychosis with distinct focus on positive and negative symptoms. Additionally, behaviors and symptoms associated with autism spectrum disorder (ASD) and the influence of anxiety and other emotional symptoms has also been addressed in the literature. Regarding social functioning, only few studies confirmed associations to the measures of both parts of social cognition. Finally, since mentalizing is found to lay at the core of protective response impacting the neurodevelopmental influence for risk of psychopathology, and given identified complexity behind links to social and psychiatric domains, (age-appropriated) interventions based on MBT are further considered for affected individuals and their parents.

(P245) Personality functioning in At-Risk Mental State and First-Episode Psychosis

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Disturbances in personality functioning and sense of self are considered to constitute core features of patients suffering from psychotic disorders and Ultra-High-Risk for psychosis states, but empirical data is limited. The aim of this ongoing project is to explore personality functioning in individuals at ultra-high risk for psychosis (UHR) and with first-episode psychosis (FEP) integrating a psychodynamic and phenomenological approach.
Individuals fulfilling UHR criteria according to the Comprehensive Assessment of At-Risk Mental State (CAARMS) or the Schizophrenia Proneness Instrument for Adults (SPI-A) and FEP patients with a psychotic disorder pre-existing no longer than five years were included in the study. All participants underwent the Structured Clinical Interview for DSM Disorders (SCID I and II), the Structured Interview for Personality Organization (STIPO) and the Examination of Anomalous Self-Experience (EASE). Data of UHR (n=8), FEP (n=8), borderline personality disorder (BPD) individuals not fulfilling UHR criteria (n=18) and healthy controls (HC, n=15) were compared.
UHR patients showed a significantly lower level of personality organization ($p<.001$), significant deficits in identity integration ($p<.001$) and sense of self ($p\leq.05$), but not a different quality of object relations compared to HC ($p=.18$). UHR individuals had a significantly higher level of personality organization ($p=.022$), a better identity integration ($p=.027$) and a higher quality of object relations ($p=.04$) compared to BPD individuals. There were no differences in these variables between UHR and FEP patients ($p>.05$). Self-disorders (EASE) of UHR patients did not significantly differ from FEP and BPD patients.
These preliminary findings of this small sample suggest that personality organization in UHR individuals lie on a spectrum between healthy and BPD without psychotic symptoms

(P246) Burden of mothers and fathers of children with ADHD

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Attention Deficit Hyperactivity Disorder (ADHD) is a highly prevalent mental disorder in childhood and adolescence. Literature provides an insight into the experiences of parenting a child with ADHD and identifies these parents as a highly vulnerable group. Despite general agreement, that parents of children with ADHD are burdened, studies are missing, which focus on examining the quality and extend of this burden. Therefore, this study aims to measure burden of parents of children with ADHD, which is assumed to be notably increased compared to mothers or fathers of healthy children and to further investigate potential influential factors on burden. This study is designed as a monocentric, cross-sectional study and takes place at the outpatient clinic of the Department of Child and Adolescent Psychiatry at the Medical University of Vienna. It's planned to include 81 study participants, who are parenting a child diagnosed with ADHD according to ICD-10 and is between 5 and 13 years of age. Sociodemographic data and standardized questionnaires assessing the extent of parental burden and stress (Parental Stress Index), individual temperament (TEMPS-M), pediatric ADHD (WURS-K), existing ADHD symptoms (ASRS-V1.1), screening for other psychiatric symptoms (PHQ-D), as well as scale for parental cooperation (Coparenting Relationship Scale) are conducted. Preliminary results indicate an increased extend of stress and burden in mothers of ADHD affected children. Data suggest, that the characteristic of the child is commonly experienced as highly burdensome, whereas parents may vary in their experience of other sources of stress. In conclusion, early findings are in line with the hypothesis of this study pointing out the vulnerability of parents of children with ADHD but also that individual experiences of stress are modulated due to specific intrinsic and extrinsic factors.

(P247) Neurocognition in Depression, Bipolar Disorder and Schizophrenia

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Cognition is essential for self-reliant functioning and quality of life. Psychiatric patients suffer from cognitive impairment as a core feature. The present study assessed whether psychiatric patients with different diagnoses, admitted to a psychiatric department in a defined epidemiological catchment area differ from each other due to their premorbid intelligence and cognitive functioning. Furthermore, the effects of a combination therapy including cognitive remediation were assessed. The screen for cognitive impairment in psychiatry (SCIP, Purdon 2005; German version:Sachs et al.) comprising five subscales (immediate and delayed verbal learning, working memory, verbal fluency, psychomotor speed) was used to detect cognitive dysfunction. Premorbid intelligence was recorded using the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B, Lehrl 1997). Between 2011 and 2017 41 depressed, 31 bipolar and 48 schizophrenic patients (age mean: 36.85 Sd: 12.32, 51 male, 69 female, diagnosed according to the ICD-10 research criteria) underwent the assessment after admission and at discharge from the psychiatric department. Patients received combination treatment with psychotropic drugs and cognitive remediation using COGPACK. The study showed that all patient groups present cognitive impairments over the SCIP domains at admission, while overall premorbid intelligence was estimated as average. Schizophrenic patients showed the highest degree of cognitive dysfunction whereas affective disorders showed an intermediate degree of impairment. At discharge all patient groups showed significantly enhanced global cognition ($p<.001$). Patients with depression performed on a level of healthy subjects, followed by bipolar patients. At discharge, even 15 schizophrenic patients performed on the level of norm population. This is the first study to show cognitive improvement after combination treatment using cognitive remediation in different diagnoses,in non-selected, non-research facility patients.

(P248) Using Technology to manage Self-Harm in Young People: Patients' Expectations for the future Digital Resources

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Self-harm is an important mental health problem that has its peak in adolescence. Lately, we observe an increase in technology-enabled interventions that aim to prevent and treat various mental health problems including self-harm. An important shortcoming of these interventions is that they often do not include the 'voice' of their target group which in turn may lead to lower user engagement with the developed interventions. In this study, we explore patients' expectations for the future interventions. This is an ongoing study and to date we conducted 14 semi-structured interviews with young people aged 12-18 who were in contact with mental health services due to self-harming behaviour. The data was analysed using the thematic analysis approach. Preliminary results show that young people are interested in using technology-enabled tools to manage their self-harming behaviour; however, the current tools often do not meet their needs. Among young people's expectations for the future tools, common patterns included distraction from unpleasant emotions, learning about the alternatives to self-harming behaviour and the possibility of communicating with therapists or other young people. Additional important common aspect was the need for future tools to allow personalization in terms of considering individual differences in triggers for self-harming behaviour and coping strategies. Perceiving intervention as effective was stated as the most important motivation to engage with it. As a practical implication, this study points towards gaps in current digital interventions and stresses the value of taking the perspective of patients into account when designing future interventions in order to increase their relevance for the patients and thereby better respond to their needs.

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(P249) Coparenting intervention for expectant parents effects relationship quality: A pilot study

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(P250) Fostering socio-emotional skills in children with Autism Spectrum Disorder: Results of a multicenter randomized controlled trial with the interactive training app Zirkus Empathico

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Acquiring socio-emotional skills is crucial for social integration and quality of life in children with Autism Spectrum Disorder (ASD), but specialised intervention programs and services for these children are rare. Computer-based trainings are a more time- and cost-effective solution for these lacks of services, besides the technical interest often seen in affected children. The newly developed mobile tablet app Zirkus Empathico (ZE) aims at improving social competences of pre-school and elementary school children with ASD. The training is manualized, tutor-guided and includes modules focusing on I) recognition and verbalization of own emotions, II) recognition of other's emotions from facial expression and III) context, IV) emotional empathy and prosocial behavior and V) generalization into everyday life with an interactive animation facilitating the communication of emotional content. We conducted a randomized, controlled multicenter RCT: ZE group six weeks training (with a minimum of 100 min./week) is compared to an active control group using educational apps not focusing on socio-emotional contents for the same amount of time at three points of assessment baseline, post training, 3 months follow-up in children aged 5-10 with ASD. Primary outcome was emotional and cognitive empathy measured by parent-ratings. Secondary endpoints were autistic behavior and behavioral tests for emotional awareness. The final sample of three study centers consisted of 82 participants. Linear regression models show significant positive effects for primary and secondary outcome variables. Follow-up effects and qualitative data are also presented. Low drop-out rates (T2: 7 %, T3: 13 %) show high acceptance of the training by both tutors and children. Results indicate effectiveness of Zirkus Empathico training for social communication and empathic abilities in parent ratings. We observed a high acceptance of the training app among children and their parents.

(P251) Determinates of social connectedness in early adolescence – systematic literature review

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(P252) Austrian firearm legislation and its effects on suicide and homicide mortality: A natural quasi-experiment amidst the global economic crisis

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