Thieme

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Editors:
Jürgen Deckert, Würzburg
Manfred Gerlach, Würzburg
Johannes Thome, Rostock

P1 Animal Models

P1.1 GRM8, the role of a metabotropic glutamate receptor in ADHD

Authors Lüffe T, D'Orazio A, Romanos M, Drepper C, Lillesaar C
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3402984

Introduction Attention-deficit-hyperactivity disorder (ADHD), the most common neurodevelopmental disorder, is characterized by an early childhood-onset and the core symptoms comprise inattention, hyperactivity and impulsivity. Profound research on the identification of potential causes revealed both environmental factors and a strong genetic component as contributors to an increased ADHD susceptibility (Biederman & Faraone, 2005) which helped to identify a number of potential risk genes (Demontis et al., 2019, Elia et al., 2015).

Methods As such, the gene for the metabotropic glutamate receptor 8 (GRM8/mGluR8), a member of the type III receptor family, was discovered. Type III mGlur receptors are G protein-coupled receptors (GPCR) that are predominantly situated at the presynapse where they are involved in regulation of transmitter release (Cartmell & Schoepp, 2000). Since a regulated release is required for balanced transmitter levels, GRM8 displays a relevant candidate with respect to molecular and functional circuits contributing to the pathophysiology of ADHD.

Results In the present study we use the well-established developmental model organism zebrafish (Danio rerio) to monitor the spatiotemporal expression of the GRM8 zebrafish paralogs grm8a and grm8b during embryonic development. Supported by different co-expression assays we show that grm8a/8b are expressed by GABAergic neurons among other cell types. In order to investigate its functional relevance we used a transient knockdown strategy and thereby reveal an influence of Grm8 on larval locomotion behavior.

Conclusion With the generation of several CRISPR/Cas9 knockout lines we have now established the basis to study the role of Grm8 in various cell populations and neuronal circuits to reveal how it may contribute to the pathophysiology of ADHD.

P1.2 Impact of different life histories on neuronal morphology in serotonin transporter deficient mice

Authors Schmitt-Böhrer A, Kolter JF, Kreis A, Hamann C, Bodden C, Sachser N, Asa E, Lesch K-P
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3402985

Introduction Stress is a risk factor for developing psychiatric disorders, e.g. anxiety disorders and depression. Several hypotheses postulate that the interaction between early and later life stress is crucial for the development of psychopathology. Two currently discussed hypotheses deal with that topic: the "allostatic load" and the "mismatch" hypothesis. The former considers the accumulation of environmental adversity over the lifetime as the major risk factor. The latter postulates highest vulnerability to diseases when there is a mismatch between the individual's experience during early and later phases of life.

Methods Moreover, variants of serotonergic system genes interact with life events moderating the susceptibility and/or resilience for psychiatric disorders. 5-HTT knockout (KO) mice already display increased anxiety-like behavior compared to wildtype (WT) mice.

Results Bodden and coworkers (2015) showed effects of four different life histories (with matching and mismatching situations of early and later life stress) on the behavior of mice varying in 5-Htt genotype.
Using Golgi-stained sections of these mice and with the help of the Neurolucida system (MicroBrightField) we analyzed the morphology of pyramidal-like neurons in the lateral amygdala (LA) and pyramidal neurons of the infralimbic cortex (IL).

Conclusion We revealed that 5-Htt genotype as well as early and late phases of life influence neuronal morphology in the LA, and in the IL, but in different ways. Whereas in the IL alterations of gross dendritic morphology such as dendritic length and nodes were prominent, in the LA spine density changes were most evident. In general, early adverse environment resulted in higher spine densities.

P1.3 Obese Zucker Rats after experiencing a Roux-en-Y gastric bypass surgery or calorie restriction: An expression study in the heart and various brain regions

Authors Hock A, Aria-Loza P, Heiser S, Ortega G, Deckert J, Seyfried F, Pelzer T, Warrings B, Schmitt-Böhrer A
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3402986
Introduction Obesity, which is associated with several comorbidities like diabetes type 2, cardiovascular disease and dementia, represents a major health burden. While conservative treatments often fail to improve, bariatric surgery is an effective weight-loss procedure. Although its positive effect is incompletely understood, hormonal and neuroendocrine changes are suggested to be causative.
Methods The "Wuerzburg Adipose Rodent Study" (WARS) uses the (fa/fa) Zucker rat as an animal model for obesity to study the effects of bariatric surgery (Roux-en-Y gastric bypass, RYGB) and calorie restriction on obesity and cardiac function. The study design comprises four experimental groups: Zucker lean rats sham treated; Zucker rats sham treated, Zucker rats RYGB treated, and Zucker rats sham treated with a calorie reduced diet. Applying an insulin signaling pathway RT2 profiler PCR array revealed expression differences of some of these investigated genes [such as insulin-like growth factor (Igf)1] in heart tissue of rats of different treatment groups of this study.
Results To investigate gene expression alterations of insulin signaling pathway-related genes in the brain of these rats, we performed quantitative real time PCRs (qPCR) using RNA extracted from hypothalamus, hippocampus, prefrontal cortex and striatum. Heart RNA was used as an additional control and to verify the originally obtained results.
Conclusion We detected significantly decreased expression levels of *Irs1*, *Igf1* and *Insr* in the heart of Zucker rats compared to Lean rats. RYGB and calorie restriction do not seem to have the potential to reverse effect. In the brain, only *Akt2* expression was increased in obese rats compared to lean controls. However, the investigation of other energy homeostasis-related genes like the adiponectin receptor 1 are still ongoing.

P1.4 Appetite-regulating hormones, alcohol dependence and craving in a rodent model

Authors Muschler M, Rhein M, Müschen L, Wieting J, Frieling H, Bleich S
Affiliation Medizinische Hochschule Hannover, Germany
DOI 10.1055/s-0039-3402987
Introduction Appetite-regulating hormones have long been the focus of research on alcohol dependence and craving. The leptin-melanocortin pathway, with its hormones leptin, alpha-melanocyte stimulating hormone (alpha-MSH) and the associated receptors, plays a central role. Could these peptide hormones be markers of craving in alcohol withdrawal?
Methods In a rodent model for alcohol addiction, we examined the plasma levels of the hormones alpha-MSH and leptin and their possible epigenetic regulation at various times during the six-day alcohol withdrawal.
Results In alcohol withdrawal, neither alcohol-consuming animals nor control animals showed changes in the leptin levels. In contrast, the alpha-MSH levels in alcohol withdrawal were significantly reduced, but remained unchanged in the control animals. The methylation of the leptin promoter was significantly reduced at the beginning of alcohol withdrawal compared to the controls. This difference disappeared within the six-day withdrawal.
Conclusion In the animal experiment presented, a significant decrease in the appetite-reducing hormone alpha-MSH was observed for the first time in alcohol withdrawal, despite free access to food. The upstream hormone leptin, which has an activating effect on the alpha-MSH precursor proopiomelanocortin, remained unchanged. Could alpha-MSH be a hormonal correlate of craving? Further investigation with changed withdrawal periods must follow to answer this question.

P1.5 Loss-of-function of foxp2 in zebrafish larvae leads to behavioural changes resembling ADHD-like pathology

Authors Drepper C, Lüffe T, Romanos M, Lillesaar C
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3402988
Introduction Attention-deficit/hyperactivity disorder (ADHD, OMIM #143 465) represents one of the most prevalent psychiatric disorders with 2–8 % affected children and adolescents worldwide. The characteristic symptoms are diverse, ranging from hyperactivity and impulsivity over inattention to emotional dysregulation. Previous studies claimed a genetic heritability of 60–90 % and thereby led to several genomic studies focusing on the identification of genetic variants contributing to ADHD susceptibility.
Making use of zebrafish (Danio rerio), a well-established model organism in genetic and (neuro-) developmental research with a rich behavioural repertoire, we aim to understand the genetic role as well as related neuro-developmental mechanisms of gene variants in the clinical picture of ADHD.
Methods Developmental expression analysis using RNA in situ hybridisation of foxp2, a forkhead box transcription factor present in the nervous system showing significant variability in ADHD patients (Demontis et al., 2019), is used to define foxp2 expression domains in the brain of zebrafish. In addition, genetic mutations are induced with CRISPR/Cas9 to generate a loss-of-function model. Using this model, various behavioural assays in zebrafish larvae are conducted to assess the developmental and functional role of foxp2.
Results foxp2 is already expressed during very early stages in the CNS of zebrafish larvae. Prominent domains of expression were seen in different brain regions, including parts of the forebrain, midbrain and hindbrain. Heterozygotic foxp2(±) larvae display a behavioural output in various assays which partly resembles human ADHD-like pathology. Currently, further characterisation of mutant animals is ongoing and will show, whether variability in foxp2 expression might affect downstream ADHD-specific gene networks.
Conclusion These results pave the way for the further characterisation of FOXP2 role in the development of ADHD.

P1.6 Impact of modified gut microbial composition on Alzheimer's disease pathology in 5 xFAD transgenic mice

Authors dos Santos GM, Endres K
Affiliation Universitätsmedizin Mainz, Germany
DOI 10.1055/s-0039-3402989
Introduction The human body hosts an enormous number of microbial commensals, mainly in the gut. Investigations especially regarding gut-microbiota and its impact on different diseases have come into focus. E. g. it has been shown that gut microbiota can regulate motor deficits in Parkinson's disease model mice. Via age-related loss of the integrity of the blood-brain and the gut barrier, microbiota and its metabolites probably can exert more systemic effects – e.g. on brain. This leads to the assumption, that gut-microbiota may have impact on age-related diseases such as Alzheimer's disease.
Methods 5 xFAD mice were treated chronically with antibiotics or probiotics for 14 weeks. Treatment efficiency was examined by plating representative bacteria: Enterobacteriaceae and Lactobacteriaceae. The impact of the gut-microbiome on AD was investigated e.g. by checking nest building ability of the mice and analysis of A-beta deposition in the brain.
Results We were able to reduce bacteria in antibiotics-treated and to induce them in probiotics-treated mice. Mice treated with antibiotics showed a better nest building ability compared to controls. Additionally, antibiotics treatment led to a reduction of A-beta deposition in the brain and interestingly to lower blood sugar levels in 5 xFAD mice.
Conclusion Impact of antibiotics-treatment on AD pathology in model mice has been described earlier1. However, long-term treatment with antibiotics might not be desirable for human patients. Our approach using probiotics theoretically has translational value but beneficial effects on pathology have to be proven in future investigations.

P1.7 Primary cilia structure is prolonged in enteric neurons of Alzheimer's Disease model mice

Author Nguyen VTT
Affiliation Universitätsmedizin Mainz, Germany
DOI 10.1055/s-0039-3402990
Introduction Neurodegenerative diseases such as Alzheimer's disease (AD) have long been acknowledged as disorders of the central nervous system (CNS). However, this dogma has been challenged in recent years with attention focusing on a more systemic perspective, which includes investigating pathophysiological changes in the gut. This association is intriguing since the gut contains the largest neuronal system outside the CNS – the enteric nervous system (ENS).
Methods The neurodegeneration mouse model 5 xFAD was used to analyze possible changes in gut functionality by organ bath measurement of peristalsis movement. Subsequently, we cultured primary enteric neurons from mutant mice and wild type littermate controls and assessed for cellular pathomechanisms. Neurite mass was quantified within transwell culturing experiments. Using different markers for the primary cilium, cilia number and length were determined using fluorescence microscopy.
Results Although we saw changes in gut motility and neurite mass in mutant mice, we were not able to detect a change in average cilia length or number of ciliated cells. However we did see a larger distribution of longer cilia in cultures generated from mutant mice, possibly suggesting a change in ciliary homeostasis.
Conclusion Our study indicates that although the gut of genetic AD model mice is affected by the disease-driving transgenes, general ciliary structure seems to be preserved in cultivated enteric neurons. Potential changes on the sub-organelle level require further investigations.

P1.8 Short- and long-term effects of chronic social stress on motor cortical neuroplasticity in mice

Author Gellner AK
Affiliation Universitätsklinikum Bonn, Germany
DOI 10.1055/s-0039-3402991
Introduction Chronic stress is a major cause of neuropsychiatric conditions such as depression, anxiety and post-traumatic stress disorder leading to a massive health burden worldwide. In contrast to well-studied affective and cognitive symptoms, motor retardation known to accompany many psychiatric conditions is not well understood yet. This longitudinal in vivo study discloses the alterations of neuroplasticity in mice with regards to individual stress vulnerability.
Methods Adult male Thy1-GFP M mice with a sparse fluorescent labelling of pyramidal cells were equipped with a chronic cranial window over M1 to enable repeated imaging of dendritic spines via in vivo 2-photon microscopy. The same regions of interest were visualized before and after 10 days of chronic social defeat stress (CSDS) following a resident-intruder paradigm or control conditions. This was followed by gross and fine motor skill learning. Imaging sessions were continued throughout and after the learning phase. Longitudinally and/or finally, plasma, CSF, feces, brain, adrenal glands and spleen were sampled for further analysis.
Results Chronic social defeat led to depression-like behavior with anhedonia, reduced sociability and self-care. A subgroup of animals showed signs of resilience. Stressed mice showed differently altered motor learning capabilities depending on their individual stress vulnerability. This was accompanied by a reduced spine density in the motor cortex shortly after the stress phase had ended. Spine dynamics remained altered compared to controls depending on their stress and motor phenotype. Stress vulnerability correlated with short- and long-term changes seen in the HPA axis.
Conclusion These data demonstrate short- and long-term dysfunctional effects caused by chronic social stress on the dynamics of motor cortical neuroplasticity and motor learning in a longitudinal in vivo approach. Function of the HPA axis was chronically altered which points to a potential underlying mechanism. This translational stress-motor model offers a broad range of biomarkers on the behavioral, humoral and organ/tissue level that can improve diagnostics and treatment for stress-related diseases.

P2 Biomarker

P2.1 Detecting motor function abnormalities in individuals with Autism Spectrum Disorder without intellectual impairment via visual-perceptive computing

Authors Cho AB, Otte K, Baskow I, Ehlen F, Maslahati T, Mansow-Model S, Schmitz-Hübsch T, Behnia B, Roepke S
Affiliation Charité Universitätsmedizin, Berlin, Germany
DOI 10.1055/s-0039-3402992
Introduction Beside the core symptoms, motor function abnormalities such as dyspraxia and abnormal gait are characteristics of individuals with autism spectrum disorder (ASD). However, detailed behavioral characterization of motor function abnormalities in adults with ASD is sparse. In this pilot study, we aim at more objectively assessing motor function abnormalities in adults with ASD without intellectual impairment using visual-perceptive motion capture and explore their association with symptom severity.
Methods 37 individuals with ASD and 45 healthy subjects with an IQ > 85 and aged 18 to 65 years were matched for sex, age, verbal IQ, height, and BMI. While performing nine movement tasks, participants were filmed by a 3D-infrared camera (Microsoft Kinect for Xbox One). Assessed anatomical models were quantified using custom-made software and resulting kinematic parameters were compared between individuals with ASD and HCs using independent t-tests and Cohen's D. Furthermore, the association between motor function abnormalities and severity of autistic symptoms assessed with the Autism Diagnostic Observation Schedule (ADOS-2) score module 4 severity was explored in adults with ASD via Pearson's correlation.
Results ASD individuals showed a reduced walking speed and cadence, and a greater mediolateral deviation while walking, greater sway during stance, tandem stance and single leg stance, a greater arrhythmicity during jumping jack tasks and an impaired manual dexterity during finger tapping tasks when compared to HCs ($p < .1$ and $|D| > .48$). Furthermore, some motor abnormalities correlated moderately to the ADOS score severity (Pearson's r up to .45).
Conclusion Our results show that adults with ASD display motor patterns different from HC. Adults with ASD moved slower, had a greater postural instability and reduced manual dexterity. The data reinforce knowledge of motor abnormalities shown in children and adolescents with ASD. Also, visual-perceptive computing analysis appears to be a feasible instrument for detection of subtle motor abnormalities in ASD and may be useful in the diagnosis of ASD.

P2.2 The effect of social influence on relief-learning

Authors Gründahl M, Retzlaff L, Andreatta M, Hein G
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3402993
Introduction Anticipation of pain triggers defensive responses such as startle potentiation, while its avoidance and termination result in positive sensations such as startle attenuation, called relief. These responses can become associated with and later elicited by other stimuli concurrently present. Importantly, social support reduces aversiveness of pain.
Methods We investigated the effect of social influence on relief responses and whether active relief (avoidance) differs from passive relief (pain termination) in 102 healthy females. During acquisition, the active group (N = 33) learned to actively oppress a painful stimulation (unconditioned stimulus, US), the social group (N = 35) believed that another participant oppressed the US, and the passive group (N = 34) had no influence. A visual stimulus (conditioned stimulus, CS+) followed US' termination. Subsequently (test phase), participants heard aversive startle probes presented with the CS+ or a novel visual stimulus (Control). Startle responses and fear ratings were collected as learning indices.
Results After acquisition, all participants rated CS+ as more frightening than Control, suggesting that on the explicit level, the relief-associated stimulus elicited fear in all groups. After test, fear ratings of CS+ further increased

but did not differ from Control. The same was evident for startle responses to CS+ and Control in both passive and active group. Thus, physiological responses indicate equal implicit valence for passive and active relief. In comparison, the social group showed overall lower startle responses. However, responses were higher to CS+ than Control.

Conclusion In sum, our results indicate that social influence reduces the physiological response to aversive events, but does not enhance relief learning.

P2.3 Cerebrospinal fluid findings in patients with severe mental disorders

Authors Meixensberger S, Tebartz van Elst L, Runge K, Endres D
Affiliation Universitätsklinikum Freiburg, Germany
DOI 10.1055/s-0039-3402994

Introduction Interest in the immunological pathways that play a role in the etiology and pathophysiology of a subgroup of patients with severe mental disorders has increased in recent years. Particularly, the association and detection of antineuronal autoantibodies and inflammatory changes in the cerebrospinal fluid (CSF) in a subgroup of patients have been a key research focus. As a result of this development, international consensus criteria for autoimmune psychosis have recently been published for the first time.

Methods We plan to analyze an unselected, retrospective cohort of patients with schizophrenia spectrum, and affective disorders who had a lumbar puncture to exclude a secondary, organic cause of their symptoms in the Department of Psychiatry and Psychotherapy of the University hospital in Freiburg. We will analyze alterations in CSF basic parameters (white blood cell count, protein concentration, albumin quotient, IgG index, and oligoclonal bands), several antineuronal antibody findings in the CSF and serum, and their association with cerebral magnetic resonance imaging and electroencephalographic findings.

Results The results should be presented descriptively and discussed with regard to the concept of autoimmune psychosis at the congress of the DGBP and AGNP 2020.

Conclusion The diagnostic clarification of underlying secondary autoimmune alterations in patients with schizophreniform and affective psychosis is of growing importance, as these new insights lead to new therapeutic anti-inflammatory treatment alternatives for a subgroup of patients. The limitations of the uncontrolled and retrospective study design will also be discussed.

P2.4 Olfactory function, transcranial sonography and fear generalization in patients with 22q11.2 deletion syndrome along the lifespan

Authors Radtke F, Holweck J, Geissler J, Strork T, Drepper C, Fouskova Z, Gerlach M, Fischer M, Romanos M
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3402995

Introduction The 22q11.2 deletion syndrome (22q11.2DS) is a rare chromosomal syndrome with a prevalence of approximately 0.025%. Affected individuals show a wide range of somatic features, most commonly congenital heart defects, immunodeficiency, hypoparathyroidism and palatal abnormalities. Furthermore, the syndrome is highly comorbid with psychiatric disorders. Among potential biomarkers in a range of modalities are substantia nigra (SN) hyperechogenity (reported in adult 22q11.2DS) and compromised olfactory function (reported in pediatric 22q11.2DS). Regarding fear conditioning and fear generalization, there is a scarcity of research despite the high number of comorbid anxiety disorders.

Methods We performed a multimodal assessment of olfactory function and transcranial sonography (TCS) on a sample of N = 39 22q11.2DS patients and N = 39 age and sex-matched healthy controls (age 4–44 years, m = 14.8 ± 8; N = 16 female). SN echogenicity was quantified with a planimetric measurement of the hyperechogenic signal at the location of the SN in mm^2. Olfactory sensitivity and discrimination was assessed with the Sniffin Sticks kit. For the assessment of fear learning and generalization, we used the paradigm established within the framework of SFB TRR58.

Results We found lower olfactory sensitivity ($p < .001$) and discrimination ($p < .001$) in 22q11.2DS compared to controls. ADHD symptoms correlated positively ($p = .034$) and symptoms of schizophrenia correlated negatively with olfactory discrimination ($p = .005$). There were no differences in SN echogenicity ($p = .316$). Preliminary data furthermore indicate altered fear generalization in 22q11.2DS.

Conclusion The results of our study point towards stable differences in olfactory functioning in 22q11.2DS, whereas we could not replicate previous findings of abnormal SN echogenicity. A combination of endophenotypes may be promising in characterizing the syndrome.

P2.5 Elevated interleukin-8 levels in the cerebrospinal fluid of patients with Schizophrenia Spectrum Disorders

Authors Runge K, Tebartz van Elst L, Kuzior H, Fiebich BL, Endres D
Affiliation Universitätsklinikum Freiburg, Germany
DOI 10.1055/s-0039-3402996

Introduction In recent years, immunological mechanisms have increasingly been discussed in the context of mental disorders. Schizophrenia, in particular, has become the focus of attention because of the discovery of autoimmune encephalitis with the presentation of psychotic symptoms. In addition, multiple studies have reported the associations of infections or autoimmune diseases with schizophreniform disorders. To identify potential immunological processes in the central nervous system, the analysis of cerebrospinal fluid (CSF) plays an important role. Therefore, this subproject of a larger study analyzed different cytokines, especially interleukin-8 (IL-8) levels, in the CSF of patients with schizophrenia spectrum disorders.

Methods The authors examined the CSF of 40 patients with schizophrenia spectrum disorders who were compared with a mentally healthy control group of 39 patients with idiopathic intracranial hypertension (IIH). A magnetic bead multiplexing immunoassay was used to retrospectively determine different cytokines in the CSF.

Results Significantly higher IL-8 levels in the CSF of the patient group with schizophrenia spectrum disorders were observed compared to the control group (Mean ± SD: 41.83 ± 17.50 pg/mL versus 21.40 ± 7.96 pg/mL; $p < 0.001$).

Conclusion The main finding of this study is the presence of significantly higher IL-8 concentrations in the CSF of patients with schizophrenia spectrum disorders compared to the control group. This supports the hypothesis that inflammatory processes may be involved in the pathophysiology of a subgroup of patients with schizophrenia spectrum disorders. The additional measurement of IL-8 might be helpful in a multimodal diagnostic work-up for the detection of secondary schizophrenic psychosis. However, the results of the study are limited by its retrospective design, methodological aspects, and the control group with IIH. Further research in this field is needed.

P2.6 Investigation of cross-section area of the vagus nerve, heart rate variability and inflammatory markers in major depression

Authors Schmidt FM, Wozniak D, Pelz JO, Scheller E, Boettcher E, Schreiber L
Affiliation Universitätsklinikum Leipzig, Germany
DOI 10.1055/s-0039-3402997

Introduction Major depression (MD) is a common affective disorder characterized by a low-grade inflammation as well as affections of the autonomous nervous system (ANS). The imbalance between the sympathetic and parasympathetic ANS may result in disruptions of the heart rate variability (HRV) as well as vegetative dysfunctions which are characterized by palpitations, impairment of sleep, appetite and gastrointestinal functioning. Affections of the vagus nerve (VN) could substantially participate in the pro-inflammatory state as well as the impairment of the ANS, as observed in Parkinson's Disease, in which the cross-section area of the VN is reduced.

To elucidate the role of the VN in MD, the research project focuses on the first-time ultrasonographic assessment of the VN in a cohort of depressed versus non-depressed subjects. Further, the association between the VN and the

HRV, markers of inflammation and the presence of autonomous dysfunction and depressiveness shall be explored.

Methods This trial is a naturalistic cross-sectional study for which 120 subjects (MD = 60, controls = 60) shall be enrolled. The measurements include the high-resolution ultrasonography of the cross-section area of both VN, determination of serum levels of inflammatory markers (IL-1/6/10, INF-g, TNF-a, Indoleamine 2,3-Desoxygenase), HRV measures, as well as electrophysiological (ProSiCard) and questionnaire-based assessment of ANS dysfunction and symptom load of MD.

Results and Conclusion This study could participate in understanding the neurobiological pathogenesis of MD and could provide a link between inflammation, neurophysiological alterations and the clinical picture for which the VN could be a key mediator.

P2.7 Breathomics for depressive disorders

Authors Lüno M, Meyer-Lotz G, Metzger C, Gescher D, Hoeschen C, Gbauoui L, Frodl T
Affiliation Otto von Guericke Universität Magdeburg, Germany
DOI 10.1055/s-0039-3402998

Introduction Especially for psychiatric disorders, there are no in vivo and easy-to-use biomarkers that could help in diagnosis or therapy. In severe depressive disorders (MDD), there is strong evidence that stress, particularly through the action of glucocorticoids, induces an increase in excitatory (glutamatergic) neurotransmission, leading to dendritic remodelling in some brain regions associated with behavioural changes. This hypothesis is called the stress-toxicity hypothesis of MDD. Since the lung acts as a gas exchanger between the internal and external environment, the effects of MDD could easily be assessed by analysing the exhaled breath. The aim of the study was to identify non-invasive markers that could indicate MDD in comparison to healthy subjects.

Methods 20 patients with severe depressive disorder according to DSM-V, as well as 20 healthy controls from the general population were initially used. Exclusion criteria are all other psychiatric, internal or neurological diseases that influence the functions of the central nervous system. Breathing air analysis is carried out using proton transfer reaction mass spectrometry (PTR-MS), whereby molecules (VOCs) of 1–500 amu can be detected with corresponding concentrations. From these data individual molecule patterns result, from which general rules can be derived, analogous to omics databases. The clinical applicability of respiratory gas analysis has already been demonstrated at our university using the example of diabetes mellitus using volatile organic compounds (VOC).

Results There are significant differences for the time-diagnosis effect between the two samples with respect to MDD. The pathological order of the molecular pattern known to us suggests that the biomarkers might be cyclic or aromatic hydrocarbons, and NO derivatives might also play a role.

Conclusion The exact classification of the VOCs and the pathophysiological mechanism is still pending. However, the current data situation is promising.

P2.8 The development of body mass index (BMI) in depressed patients during an antidepressant treatment and its effects on depressive symptomatology

Authors Engelmann J, Dreimüller N, Lieb K, Tadic A, Wollschläger D, Wagner S
Affiliation Klinik für Psychiatrie und Psychotherapy, Universitätsmedizin Mainz, Germany
DOI 10.1055/s-0039-3402999

Introduction Both depressed patients and also high-risk populations for developing depression have a high prevalence of obesity. A recent meta-analysis suggests that there may be an overlap in pathophysiology of both diseases. The aim of our study was to investigate the relationship between BMI and depressive symptomatology at baseline and during the course of an antidepressant treatment. Additionally we wanted to examine BMI as a potential predictor of antidepressant treatment response.

Methods 889 MDD patients were treated by a pre-defined antidepressant treatment algorithm within the Early Medication Change (EMC) study. Patients were divided in three BMI groups according to WHO criteria: low/normal weight (BMI < 25), overweight (BMI 25-<30) and obese (≥ 30). Depression severity (HAMD17) and BMI were assessed weekly from baseline to week 8. In linear regression models, BMI at baseline and the course of BMI during treatment were investigated as possible predictors of antidepressant response. Covariables like age, sex, comorbidities and plasma levels of antidepressant drugs were investigated.

Results 388 (48%) patients showed low or normal weight, 251 (31%) were overweight and 172 (21%) were obese. Patients with BMI between 25–30 showed a better response to antidepressant treatment than obese or normal weight patients. Also a weight gain during the course of treatment was associated with a better improvement of depressive symptomatology. BMI at baseline was correlated to an improvement in specific symptoms (neurovegetative and cognitive). Other co-variables were not able to explain the different response rates of the BMI subgroups.

Conclusion To our knowledge, this is the first study investigating the association between the course of BMI and the antidepressant treatment response during an antidepressant treatment. We could show that a decrease of depression severity is correlated to an increase of BMI. The underlying mechanisms remain unclear and require further investigations.

P2.9 Alzheimer's Disease biomarkers and cortical thickness in persons reporting subjective cognitive decline and healthy controls: Data derived from the DZNE DELCDODE-Study

Authors Meiberth D, Hu X, Schild AK, Spottke A, Brosseron F, Buerger K, Fliessbach K, Heneka MT, Kilimann I, Laske C, Peters O, Priller J, Schneider A, Teipel S, Wiltfang J, Wagner M, Duezel E, Jessen F, Study group DELCODE
Affiliation Klinikum der Universität zu Köln, Germany
DOI 10.1055/s-0039-3403000

Introduction Subjective cognitive decline (SCD) without objective performance deficits reflects in some individuals the earliest symptomatic manifestation of Alzheimer's Disease (AD) at the late preclinical stage1, 2. It is crucial to delineate the relationship between this syndrome, AD- specific biomarkers and the localization of early neurodegeneration.

Methods We investigated data from 293 individuals from the baseline-dataset of the DZNE-DELCODE-study3. In this subset, 39 AD-patients, 74 patients with mild cognitive impairment (MCI), 104 participants with SCD, and 76 healthy controls (CO) received biomarker assessment (Aβ-42, total-tau, phosphorylated-tau) through lumbar puncture as well as structural MRI. The cortical thickness values were estimated via FreeSurferV.6.0 in 135 subjects. Statistical analyses included one-way-ANCOVAs with a between-subject factor of diagnosis (covariates: age, sex and scanner-site) for the bilateral entorhinal cortices and bilateral parahippocampi defined as regions of Interest (ROI) reflecting regions of early AD pathology. Subsequently we calculated two-way-ANCOVAs for these ROIS with between-subject factors of diagnosis and CSF-biomarkers with the same covariates.

Results Our data show decreased bilateral entorhinal thickness in amyloid-positive persons reporting SCD compared to controls.

Conclusion This finding supports the assumption that SCD mirrors a late preclinical stage of AD in persons with amyloid pathology and is associated with mild neurodegeneration in brain regions affected early in AD. Our data confirm initial findings in independent samples4.

P2.10 Cortisol, aging and the influence on brain age

Authors Klinger-König J, Frenzel S, Wittfeld K, Van der Auwera S, Homuth G, Hannemann A, Bülow R, Völzke H, Grabe HJ
Affiliation Universitätsmedizin Greifswald, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Germany
DOI 10.1055/s-0039-3403001

Introduction A repeated and/or prolonged dysfunction of the HPA-axis (e.g. due to childhood maltreatment) has been associated with mental and physical diseases as well as biological aging. Glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) are fundamental regulators of these aging processes. The haplotype CA of the MR SNPs rs5522 and rs2070951 has been as-

sociated with lower basal cortisol levels, higher MR reactivity and enhanced stress resilience.

Methods Data of the general population based study of Health in Pomerania (SHIP) were analyzed. Age-dependent influences of childhood maltreatment (Childhood Trauma Questionnaire, CTQ) in interaction with a genetic disposition (rs5522 and rs2070951) on basal cortisol levels in blood samples were examined. Further, interaction effects of childhood maltreatment, cortisol, age and genetics o neuronal changes were investigated.

Results Childhood maltreatment was associated with lower basal cortisol levels in early and mid-adulthood. Additionally, cortisol effects on subcortical structure volumes and cortical thickness were observed, mediated by genotype effects of the SNP rs2070951.

Conclusion To improve the knowledge about the interaction between stressful life events, genetics, regulation of the HPA-axis and neuronal changes is essential to improve the knowledge about processes of healthy aging.

P2.11 No association between major depression with and without childhood adversity and the stress hormone copeptin

Authors Kaczmarczyk M, Spitzer C, Wingenfeld K, Wiedemann K, Kühl L, Schultebraucks K, Otte C

Affiliation Charité Universitätsmedizin, Berlin, Germany

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Introduction Major depressive disorder (MDD) is associated with adverse childhood experiences (ACE) and with hypothalamic-pituitary-adrenal (HPA) axis dysregulation. Copeptin, a cleavage product in the synthesis of arginine vasopressin, has been identified as a marker of the non-specific stress response. Children with ACE exhibit higher levels of copeptin compared to healthy controls (Krogh et al., 2013). In young adults, symptoms of depression and copeptin plasma concentrations were significantly associated (Thomsen et al., 2019). Our study aimed to disentangle the effects of MDD and ACE on copeptin in adults.

Methods We recruited 94 women (mean age: 34.03, SD: 10.9): 23 women with MDD and ACE, 24 women with MDD without ACE, 22 women with ACE without MDD, and 25 healthy controls. ACE was defined as repeated sexual or physical abuse at least once a month over at least one year before the age of 18. For MDD, all women had to meet MDD criteria according to DSM-IV. Copeptin plasma levels were measured with a radioimmunoassay.

Results The four groups did not differ in demographic variables. We found a significant effect of body mass index (BMI) on the plasma level of copeptin ($r = -.210$; $p < .045$), such that increasing BMI was associated with decreasing plasma levels of copeptin. After controlling for BMI, we found no significant main effect of MDD ($F(1,85) = .017$; $p = .895$) or of ACE ($F(1,85) = .490$; $p = .486$). The interaction between MDD and ACE was not significant, either.

Conclusion Neither MDD nor ACE were associated with altered plasma copeptin levels. Our results go in line with Krogh et al., 2013 and extend their findings by including ACE as an influencing factor. Our results contrast with Coelho et al., 2016 and Thomsen et al., 2019, indicating that altered copeptin levels after ACE or in MDD are predominantly found in children and young adults.

P2.12 Definition, detection and differentiation of acute emotional states using heart rate recording

Authors Hacke M[1,2], Signoret-Genest J[2], Tovote P[2], Romanos M[1]

Affiliations 1 Klinik und Poliklinik für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie, Universitätsklinikum Würzburg; 2 Institut für klinische Neurobiologie, Universitätsklinikum Würzburg

DOI 10.1055/s-0039-3403003

Introduction Anxiety and panic disorders are psychiatric disorders characterized by the occurrence of acute states, represented by short-term emotional, behavioral and cardiac responses. Dysregulation of the autonomic nervous system plays an important role in the pathogenesis of a majority of psychiatric disorders, including anxiety and panic disorders, and recording of Heart rate variability (HRV) is widely accepted as a peripheral measure for autonomic activity. Although heart rate analysis has been employed in clinical studies as a biomarker for diagnosis and therapy outcome for a multitude of diseases, there has been no reliable correlation between acute emotional and cardiac states in behavioral contexts to this date. This study investigates how heart rate variability can be used to define, detect and differentiate acute emotional states in a moment-to-moment resolution.

Methods For correlative analysis of acute cardiac and emotional states, 140 healthy participants and 30 participants with a confirmed anxiety diagnosis between the ages of 6 and 18 years were exposed to an established fear conditioning and generalization paradigm. In parallel, heart rate was recorded by electrocardiography during fear conditioning and generalization. Analysis of heart rate variability was performed in temporal correlation to the events of the behavioral paradigm in order to characterize acute states.

Results We were able to detect and define acute emotional states during a behavioral paradigm in children and adolescents. In the group of 140 healthy participants, largely similar situation-dependent cardiac dynamics were observed during the execution of a fear conditioning and generalization paradigm. In the group of 30 participants with a confirmed anxiety diagnosis, however, a significantly higher inter-individual variability in the anticipatory and reactive heart rate was observed. In addition, cardiac response of anxious and healthy participants could be categorized into distinct subgroups.

Conclusion Presented results indicate detectable patterns in the cardiac processing of acute emotional states induced by a fear conditioning and generalization paradigm. Different heart rate responses in healthy and anxious participants suggest the use of correlative heart rate analysis in detection and diagnosis of psychiatric diseases associated with acute emotional states. In summary, this suggests further investigation of moment-to-moment heart rate analysis for the detection and differentiation of acute emotional states for a variety of psychiatric disorders.

P2.13 Structural brain characteristics associated with appetitive aggression in martial artists

Author Seidenbecher S

Affiliation Universitätsklinikum Magdeburg, Germany

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Introduction Perception and practice of violence have hedonistic aspects that are associated with positive arousal (appetitive aggression). Earlier studies have primarily investigated the etiology of aggressive behavior in forensic and psychiatric samples. To deal with possible confounds (e.g. hospitalization, co-morbidities), the present study examined structural brain characteristics in healthy people inclined to violence (martial artists) in comparison to healthy controls not showing violent behavior.

Methods In an age-matched, healthy and male sample of 26 martial artists and 26 control subjects we measured different aggression parameters using a self-assessment test battery. All participants underwent structural T1-weighted Magnetic Resonance Imaging (MRI). Grey matter (GM) differences were analyzed with voxel-based morphometry using SPM12 and CAT12.

Results On whole brain level, martial artists compared to control subjects showed an increased mean GM concentration in four different clusters comprising the left superior frontal and middle gyrus, the left medial frontal cortex, the left anterior cingulate gyrus as well as the superior occipital gyrus ($p < .001$, uncorr.). Brain characteristics in two of these clusters were positively associated with appetitive aggression ($r = .308^*$, $p < .05$; $r = .351^*$, $p < .05$).

Conclusion The present study shows structural brain characteristics associated with aggression. A lateralization effect for the left hemisphere becomes evident. In contrast to earlier studies, confounds evoked by the presence of a psychiatric disorder or an incarceration were controlled. Further analyses of differences in the cortical thickness are planned.

P2.14 A proton magnetic resonance spectroscopy study in patients with major depression and overlapping anxiety disorder

Author Bonnekoh L
Affiliation Universitätsklinikum Magdeburg, Germany
DOI 10.1055/s-0039-3403005
Introduction It can be postulated that depression and anxiety disorders share common mechanisms. To improve our understanding of the co-occurrence, neurobiological investigations are required. In the current study we focused especially on metabolic alterations in MDD patients with overlapping anxiety disorder. The aim was to assess possible regional metabolic alterations in NAA, glutamate, glutamine, Glx, Creatine (Cr), Choline and Myoinositol levels and to investigate their association with clinical symptoms and childhood adversity.
Methods Groups consisted of 23 patients with major depression and overlapping anxiety disorder and 23 control subjects. Groups did not differ significantly by age (t-test), sex, (X2-Test) and education (X2-Test). Proton magnetic resonance spectroscopy (MRS) was performed with voxels placed in the pregenual ACC (pgACC) and dorsal ACC (dACC) (10 × 20 × 15 mm3) at a 3 T Siemens MAGNETOM (Prisma) scanner with a 64 channel receive array head coil.
Results A significant reduction of the NAA to Cr ratio ($p = 0.015$) in pgACC and a reduction of the NAA to Cr ratio ($p = 0.014$) were found in dACC in patients when age, sex, education and grey matter volume fraction were taken into account compared to the control group. Study participants who exceeded the cut-off in the subscale physical neglect of the childhood trauma questionnaire (CTQ) showed significantly higher glutamine levels ($p = 0.012$) in pgACC, significantly higher creatinine levels ($p = 0.047$) in dACC, significantly higher choline values ($p = 0.037$) in dACC and significantly higher Glx to Cr levels ($p = 0.035$) in dACC compared to study participants who did not exceed the cut-off: For study participants who exceeded the cut-off for emotional neglect, significantly lower white matter values in pgACC were found than for study participants who did not exceed the cut-off ($p = 0.040$). Moreover, significant positive correlations were shown between glutamine in pgACC with depression (HAM-D: $r = 0.270$; $p = 0.020$, BDI-II: $r = 0.275$; $p = 0.017$) and anxiety (BAI: $r = 0.248$; $p = 0.030$).
Conclusion The study provided a meaningful extension of the current state of research on brain metabolic changes in the key region ACC in depression and overlapping anxiety disorders. Furthermore, the study underlined the importance of a differentiated investigation of the subregions of the functionally heterogeneous ACC.

P3 Drug safety

P3.1 Drug-drug interactions between lithium and antihypertensive and anti-inflammatory drugs

Authors Unterecker S, Scherf-Clavel M, Treiber S, Deckert J, Hommers L
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403006
Introduction Lithium is the gold standard in treating bipolar disorders. As patients become increasingly older, drug-drug interactions leading to decreased excretion of lithium represent a key issue in lithium safety.
Methods To quantify the impact of potentially interacting drugs (diuretics, ACE inhibitors, AT1 antagonists and non-steroidal anti-inflammatory drugs) on lithium serum levels in addition to age, sex, sodium and potassium serum levels as well as renal function.
Patients and methods: Retrospective data of lithium serum levels were analyzed in 501 psychiatric inpatients (2008–2015) by means of linear regression modelling
Results The number of interacting drugs was significantly associated with serum levels of lithium in addition to the established factors age, renal function and sodium concentration. Additionally, absolute lithium levels were dependent on sex. However, only NSAIDs were identified to increase absolute lithium levels independently
Conclusion Routine clinical practice needs to focus especially on NSAIDs as over-the-counter medication that may lead to an increase in lithium serum concentration. Patients taking lithium should be informed about possible intoxications due to NSAIDs.

P3.2 Antipsychotics in routine treatment are minor contributors to QTc prolongation compared to genetics and age

Authors Hommers L, Scherf-Clavel M, Strempel R, Roth J, Hohner M, Pfuhlmann B, Mattheisen M, Deckert J, Gawlik M, Unterecker S
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403007
Introduction Drug-induced prolongation of cardiac repolarization is a limitation in the treatment of psychiatric disorders with many psychotropic drugs. Recently, the contribution of polygenic variation to the individual duration of the QT interval was identified.
Methods Drug-induced prolongation of cardiac repolarization is a limitation in the treatment of psychiatric disorders with many psychotropic drugs. Recently, the contribution of polygenic variation to the individual duration of the QT interval was identified.
Results Step-wise linear regression modelling revealed a significant association of age (beta = 0.314 ± 0.059; beta(std) = 0.184; $p < 0.001$), individual genetic duration of the QT interval (beta = 0.959 ± 0.196; beta(std) = 0.164; $p < 0.001$) and the number of QTc prolonging drugs applied (beta = 1.278 ± 0.582; beta(std) = 0.076; $p = 0.028$). In the subsample of patients with available electrolyte values (n = 615), an additional significant association was noted for potassium levels (beta = − 4.918 ± 2.318; beta(std) = − 0.082; $p = 0.034$) instead of the number of QTc prolonging drugs applied. No significant association was observed between drug serum concentration of aripiprazole (n = 55), clozapine (n = 125), haloperidol (n = 41), olanzapine (n = 33), perazine (n = 56), quetiapine (n = 108) or risperidone (n = 104) and QTc with and without correction for age, individual genetic duration of the QT interval, potassium levels and number of QTc prolonging drugs applied.
Conclusion In routine treatment, individual genetic factors and age determine the QTc interval. In the absence of individual risk factors, antipsychotic drug serum concentrations within the therapeutic range represent a low arrhythmogenic hazard.

P3.3 Sexuelle Funktionsstörungen nach Absetzen von Antidepressiva: Case Report von einem „Persistent Genital Arousal Disorder“ (PGAD)

Authors Seifert J, Bleich S, Grohmann R, Degner D, Toto S
Affiliation Medizinische Hochschule Hannover, Germany
DOI 10.1055/s-0039-3403008
Einführung Antidepressiva (AD), vor allem aus der Wirkstoffklasse der selektiven Serotonin-Wiederaufnahmehemmer (SSRI), zählen zu den am häufigsten verordneten Psychopharmaka in Deutschland (1). Sexuelle Funktionsstörungen können bereits nach der einmaligen Einnahme des Wirkstoffes auftreten (2) und gehen oft mit hohem Leidensdruck des Patienten einher. Diese können aber auch noch nach der Behandlung mit dem Wirkstoff persistieren („Post-SSRI sexual disorder“, z. B. als anhaltender Libidoverlust) (2) oder sich bei Absetzen des Wirkstoffes manifestieren als „persistent genital arousal disorder“ (PGAD) (3).
Methoden In 2019 wurde ein Fall eines „persistent genital arousal disorder“ während der Abdosierung von Sertralin erhoben. Der vorliegende Fall wurde im Projekt „Arzneimittelsicherheit in der Psychiatrie“ (AMSP) dokumentiert und im Rahmen des Auswertungsprozesses bei regionalen und überregionalen Konferenzen beurteilt. AMSP beobachtet seit 1993 systematisch das Auftreten schwerer, neuer und ungewöhnlicher unerwünschter Arzneimittelwirkungen (UAW) während und nach der Behandlung mit Psychopharmaka in der Behandlung stationärer Patienten (4).

Ergebnisse Wir berichten von einer Mitte 30-jährigen Patientin, die seit 2012 Sertralin erhielt, jedoch aufgrund subjektiv unzureichender Wirksamkeit eine medikamentöse Umstellung auf Milnacipran wünschte. Die Patientin gab an, dass sie unter starkem Libidoverlust litt. Bereits am Tag nach dem Abdosieren von Sertralin von 200 mg auf 100 mg entwickelte die Patienten ein ichdystones Gefühl der andauernden, unerwünschten sexuellen Erregung. Die Symptome wurden von der Patientin als sehr quälend empfunden und waren durch Maßnahmen wie z. B. Lorazepam, kalt duschen kaum oder nur kurzfristig zu beeinflussen. Dieses sogenannte „persistent genital arousal disorder" konnte durch die weitere Abdosierung des Sertralins in kleineren 25 mg-Schritten verbessert werden.

Zusammenfassung PGAD wurde erstmalig 2001 beschrieben (5) und im Verlauf ätiologisch u. a. als ein Absetzphänomen von AD erkannt (3). Am häufigsten werden Absetzphänomene nach Einnahme von AD unter dem SNRI Venlafaxin beobachtet. Paroxetin gilt unter den SSRI als Wirkstoff mit dem höchsten Risiko für Absetzphänomene, unter Sertralin und (Es-)Citalopram soll das Risiko geringer sein, jedoch auch möglich wie der vorliegende Fall einer raschen Dosisreduktion zeigt (1). Eine Behandlungsoption stellt „Tapering" – das schrittweise, langsame Ausdosieren des Antidepressivums – oder „Bridging" mit Fluoxetin (d. h. das SSRI mit der längsten Halbwertszeit) dar (6).

Die klinische Relevanz von Absetzphänomenen nach Einnahme eines Antidepressivums ist von zunehmender Bedeutung und wird entsprechend von Behandlern zunehmen ernst genommen (1). Die aktuelle S3-Leitlinie für die Behandlung der unipolaren Depression empfiehlt entsprechend einer Aufklärung von Absetzphänomenen bereits vor Beginn der medikamentösen Behandlung (7).

P4 Genetics

P4.1 Polymorphisms in CRYBB2 encoding alpha-B2-crystallin are associated with sensorimotor gating and memory function

Authors Hartmann A, Giegling I, Genius J, Konte B, Maul S, Straube A, Eggert T, Mulert C, Leicht G, Karch S, Hegerl U, Pogarell O, Hölter-Koch S, Möller H-J, Graw J, Rujescu D
Affiliation Universität Halle-Wittenberg, Halle (Saale), Germany
DOI 10.1055/s-0039-3403009

Introduction alpha-B2-crystallin (gene symbol: Crybb2/CRYBB2) was first described as a structural protein of the ocular lens before it was detected in various brain regions of the mouse, including the hippocampus and the cerebral cortex. Mutations in the mouse Crybb2 gene lead to alterations of sensorimotor gating measured as prepulse inhibition (PPI) and reduced hippocampal size, combined with an altered number of parvalbumin-positive GABAergic interneurons. Both are endophenotypes that typically occur in schizophrenia. The aim of this study was to investigate, whether CRYBB2 variants are associated with schizophrenia and schizophrenia related endophenotypes.

Methods 27 single nucleotide polymorphisms (SNPs) within the CRYBB2 gene and its flanking regions were genotyped using Matrix-assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) in a sample of 510 schizophrenia patients and 1322 healthy controls. CRYBB2 mRNA expression in lymphocytes, PPI, antisaccades, memory and working memory including functional magnetic resonance imaging were investigated. Association analyses between multimarker haplotypes and endophenotypes were calculated using the R software package "haplo.score".

Results In the case-control study, no association with schizophrenia was found. However, a haplotype at the 3′-end of CRYBB2 was associated with reduced sensorimotor gating, measured as P50-ratio. Two other haplotypes were associated with a decreased mRNA expression of CRYBB2, poorer antisaccade task performance, and altered working memory-linked functional magnetic resonance imaging signals. These results were not schizophrenia-specific, but could be detected in patients and healthy controls separately as well as in the combined group.

Conclusion This is the first study to demonstrate the importance of bB2-crystallin for sensorimotor gating and memory function in humans and therefore provides implications for bB2-crystallin function in the human brain. Replication and functional studies are needed to better understand the role of CRYBB2 in the human brain.

P4.2 Analysing schizophrenia risk variants in NRXN1 using functional and mature neuronal cultures from patient-derived iPS cells

Authors Jung M, Pfeifer J, Majer A, Reinsch J, Flegel N, Puls A, Hartmann A, Konte B, Giegling I, Rujescu D
Affiliation Universität Halle-Wittenberg, Halle (Saale), Germany
DOI 10.1055/s-0039-3403010

Introduction There is a growing interest in psychiatry to connect causal genetic variants to neurobiological dysfunction. Genomic studies indicate that copy number variants (CNVs) are related to the development of schizophrenia. Schizophrenia is a complex psychiatric disorder that affects nearly 1 % of the world's population. We previously described deletions in neurexin 1 (NRXN1) to be associated with schizophrenia. Neurexins are neuronal adhesion molecules. Disruption of the NRXN1 leads affects properties of synapses and leads to the disruption of neuronal networks. Especially, deletions in αneurexin 1 are involved in altered neural connectivity.

Methods For further analysis of NRXN1-related disease mechanisms, we used an in vitro cell culture model based on human induced pluripotent stem cells (iPS cells). Human iPS cells have been obtained from schizophrenia patients carrying CNVs in NRXN1. Patient derived induced pluripotent stem cells and healthy control cells were differentiated into mature and functional cortical neurons.

Results The analysis focused on gene expression regulating signaling pathways, which are part of the NRXN1 network. We applied transcript and protein analysis for identifying alterations in the expression of synaptic proteins. We verified the presence of NRXN1 and its interaction partners in differentiated neurons. We found differently regulated NRXN1 interaction partners in iPS cells carrying the CNV in NRXN1.

Conclusion In summary, the provided in vitro models represent promising models for applications using screening platforms enabling the identification of potential therapeutic targets in schizophrenia.

P4.3 Association of a schizophrenia risk variant with memory function

Authors Maul S, Konte B, Hartmann AM, Giegling I, Rujescu D
Affiliation Universität Halle-Wittenberg, Halle (Saale), Germany
DOI 10.1055/s-0039-3403011

Introduction Schizophrenia is a highly inherited severe psychiatric disorder characterized by disturbed intellectual abilities. In comparison to healthy controls, deficits in memory performance have been observed in schizophrenia patients, with verbal learning in particular, but also verbal and visual working memory being impaired. As memory deficits have also been found in non-affected first-degree relatives of schizophrenia patients, memory performance seems to be a suitable endophenotype for further investigations. Therefore, we conducted an association analysis of the 128 schizophrenia risk variants found in a genome-wide association study by Ripke et al. (2014) with memory performance.

Methods A cohort of 368 schizophrenia patients and a cohort of 633 healthy subjects were investigated in this study. The Structured Clinical Interview for DSM-IV (SCID 1 and SCID 2) was used to confirm the diagnosis of schizophrenia in patients and to rule out psychiatric disorders in healthy subjects. Healthy individuals with a positive family history of psychiatric disorders and subjects aged 60 years and older with evidence of cognitive impairment in the Mini Mental Status Examination (MMSE) were excluded. Memory function was assessed using the Wechsler Memory Scale revised (WMS-R; Wechsler, 1987). Genotype data was obtained using chip technology and imputation. For association analysis 128 variants associated with schizophrenia were selected. For each cohort and the total sample, an additive linear regression model was calculated with the 5 WMS-R indices using age, sex and education as covariates.

Results For rs13240464, which is an intronic variant within the IMMP2L gene, significant associations after correction for multiple testing were obtained for "Delayed Recall" in healthy subjects and for "Visual Memory" in the combined sample and in healthy controls. Nominally significant associations with 4 of the 5 WMS-R indices were detected for 2 variants in the total sample (rs12148337, rs7405404) and for 2 other variants in the patient cohort (rs7523273, rs6434928).

Conclusion The results of this study indicate an influence of schizophrenia-associated variations on memory performance in both schizophrenia patients and healthy controls. The most significant associations were found for a variant within the IMMP2L gene that encodes subunit 2 of the inner membrane peptidase (IMP2), which is part of a mitochondrial peptidase. An impact of IMMP2L on memory function is conceivable, as its knockout leads to mitochondrial dysfunction and genetic variants are implicated in autism spectrum disorders, Gilles de la Tourette syndrome and neurodevelopmental disorders. Further research is needed to validate the associations found and to determine their functional relevance.

P4.4 DNA methylation differences with respect to early life adversity and social anxiety disorder

Authors Wiegand A, Drohm S, Munk M, Fallgatter A, Kobor M, Kreifelts B
Affiliation Universitätsklinikum Tübingen, Germany
DOI 10.1055/s-0039-3403012

Introduction Social anxiety disorder (SAD) is a severe mental disorder characterized by an excessive fear of negative evaluation, being the focus of attention and embarrassing oneself. The etiology of anxiety is influenced by genetic as well as environmental factors, most importantly stressful life events. The contribution of early life adversities (ELA) to pathophysiological processes which lead to an increased risk for SAD later in life, has been consistently described. The underlying biological mechanisms are still poorly understood, but evidence is emerging that epigenetic regulation of gene expression like DNA methylation is involved in mediating this effect.

Methods For the present study, we investigated genome-wide whole blood DNA methylation of 143 participants of Caucasian descent. SAD status was determined by a Structured Clinical Interview for DSM-IV (SCID) and ELA was assessed using the Childhood Trauma Questionnaire (CTQ). Thus, four groups emerged: healthy controls with low (n = 47) and high (n = 30) levels of ELA and patients suffering SAD with low (n = 35) and high levels of ELA (n = 31).

Results Several differentially methylated regions (DMRs) were identified with respect to SAD and ELA as well as their interaction. Amongst others, these DMRs are associated with genes of the solute carrier (SLC) family.

Conclusion Our results support the idea that epigenetic mechanisms are involved in pathophysiological processes underlying psychiatric disorders but further studies are needed to increase power and to investigate the underlying pathways.

P4.5 SLC2A3 copy number variants in ADHD – from cellular to clinical correlates

Authors Ziegler G, Jansch C, Almos P, Conzelmann A, Hahn T, Weber H, Pauli P, Lesch KP
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403013

Introduction A duplication of the *SLC2A3* gene is associated with adult ADHD and leads to alterations of event-related potentials (ERPs) in executive tasks. *SLC2A3* is encoding the neuronal glucose transporter GLUT3 which is crucial for neuronal energy homeostasis. We hypothesize that copy number variants (CNVs) of the *SLC2A3* gene lead to a gene-dosage effect with consequences for cellular glucose uptake and promote changes on various endophenotypic levels in ADHD.

Methods *SLC2A3* expression levels and glucose uptake were assayed in peripheral cell models and iPSC-derived neuronal cell lines. Neuropsychological correlates of *SLC2A3 CN* were assessed by linear regression analysis of questionnaire data. To address possible alterations on the neural systems level, fMRI (ERPs to food cues) was performed.

Results Despite increased mRNA expression, the *SLC2A3* duplication did not lead to changes in GLUT3 protein levels and no effect on cellular glucose uptake was found. However, there is an inverse correlation of *SLC2A3 CN* with ADHD symptoms in the female subgroup. Furthermore, the *SLC2A3* duplication was associated with an altered multivariate neural response pattern towards high-caloric food stimuli.

Conclusion With iPSCs we have a powerful tool at hand to investigate the consequences of *SLC2A3 CNVs* beyond gene expression levels in the future. This will be helpful to disentangle molecular biologic consequences of *SLC2A3 CNVs*. *SLC2A3* plays a role in the neural processing of food cues which might be well in line with the known problem of impulsive overeating in ADHD. Our neuropsychologic data, however, speak against a strict categorical association of *SLC2A3 CNVs* with ADHD.

P4.6 Norepinephrine resets the clock of human dermal fibroblasts

Author Palm,D
Affiliation Medizinische Universität Rostock, Germany
DOI 10.1055/s-0039-3403014

Introduction Norepinephrine (NE) regulates important behavioural activities. Numerous studies linked the NE pathway with the pathophysiology of ADHD. Additionally, several animal studies demonstrated that alterations of the circadian clock are associated with the NE pathways. In this preliminary study we investigated the effect of NE stimulation on the circadian rhythm gene expression in human dermal fibroblasts (HDF).

Methods HDF were obtained via skin biopsy from healthy controls (HC) (3 men, 1 woman; 42.00 ± 15.38 years, mean ± SD; BMI: 29.10 ± 6.54 kg/m^2, mean ± SD) and volunteers suffering from ADHD (1 man, 3 women; 38.75 ± 8.15 years, mean ± SD; BMI: 24.97 ± 5.32 kg/m^2, mean ± SD). Cells were cultivated at 37 °C and 5% CO2. All participants completed the Multiple-Choice Word Test (IQ score: HC: 115.25 ± 10.04, mean ± SD; ADHD participants:110.25 ± 17.01, mean ± SD, n.s), German Morningness-Eveningness-Questionnaire (D-MEQ Score: HC: 50.00 ± 3.74, mean ± SD; ADHD participants: 53.50 ± 9.54, mean ± SD, n.s) and Wender Utah Rating Scale, German short-version (WURSk Score: HC: 13.75 ± 9.98, mean ± SD; ADHD participants: 31.75 ± 6.94, mean ± SD, p = 0.025). Synchronization was induced either with 1 µM NE or 0.1 µM dexamethasone (D) for 2 hours. Sampling was performed every forth hour starting after synchronization for a period of 28 hours. CLOCK, BMAL1, CRY1, PER1/2/3 gene expression was measured by qRT-PCR. Rhythmicity analysis was performed with CircWaveR software. Statistics were calculated using SPSSR.

Results HC presented an overweight BMI range, whereas the ADHD group had normal weight. Both groups showed a standard range IQ score. The WURSk score in the ADHD group is higher compared to the HC, like expected. Age and D-MEQ score of both groups are similar. Both groups showed an intermediate chronotype. Compared to D synchronization, NE induced CLOCK gene rhythms ($p < 0.05$, CircWave) whereas CRY1 and PER3 rhythms were dampened ($p > 0.05$, CircWave) in HC group.

In HC, gene expression was significantly different using NE compared to D, particularly, for time point ZT0 for CLOCK and BMAL1 ($p < 0.05$) and ZT16 for CRY1 ($p = 0.007$) and PER3 ($p = 0.001$). Additional, for NE synchronization in the ADHD group a phase advance was observed for CLOCK, BMAL1 and CRY1 · Furthermore, the expression of PER2 in ADHD group was different at ZT0 ($p = 0.01$) compared to HC.

Conclusion Our results suggest that NE stimulation may alter the circadian rhythm in HDF. Furthermore, both NE exposure and higher BMI might influence CLOCK gene rhythmicity.

P4.7 Genome-wide pleiotropy between depression and body mass index

Authors Garvert L, Roshchupkin GV, Völzke H, Nauck M, Milaneschi Y, Grabe J, Van der Auwera S
Affiliation Universitätsmedizin Greifswald, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Germany
DOI 10.1055/s-0039-3403015

Introduction Obesity and depression are public health problems with increasing prevalence worldwide. Previous studies indicate a phenotypic association between increased Body-Mass-Index (BMI) and higher rates of depression. However, it remains unclear how much of the association is due to environment or shared biological and genetic factors. In this study we apply a multilevel bioinformatics pipeline to summary statistics from recent GWASs of both traits to identify pleiotropic SNPs, genes and pathways. Moreover, we examined possible sex-specific pleiotropic effects. Finally, we could support some of our results using phenotype and genetic data from our general population sample from the SHIP study.

Methods Summary statistics of GWASs on MDD (Wray et al. 2018, cases: 135 458, controls: 344 901) and BMI (Locke et al. 2015, cases: 59 851, controls: 113 154) were used to identify pleiotropic SNPs employing a sum ranking method. Pleiotropic p-values for genes and pathways were calculated using the extended Simes test (GATES) and hybrid set-based test (HYST) as implemented in the software KGG (Knowledge-based mining system for Genome-wide Genetic studies). Regression analyses on the general population sample of the SHIP study (n = 5749) were performed to assess the association between the identified pleiotropic SNPs and BMI and MDD, respectively. Further regression analyses were performed to test the joint effect of SNPs and BMI on MDD status as well as the joint effect of SNPs and MDD status on BMI. All analyses were performed for the complete samples as well as for men and women separately.

Results We identified 243 SNPs with significant pleiotropic effect after correction for multiple testing. They were located in seven independent loci with lead SNPs rs7531118 (Chr 1), rs4714293 (Chr 6), rs1627536 (Chr 9), rs12411886 (Chr 10), rs11625397 (Chr 14), rs7243785 (Chr 18) and rs427943 (Chr 21). On gene-level we identified 16 pleiotropic genes with NEGR1 (Neuronal Growth Regulator 1) on chromosome 1 being the most significant ($p_{corrected} = 1.19 \times 10^{-6}$). Our analyses yielded 12 pathways with significant pleiotropic p-value, including the regulation of endogenous sterols and the purine metabolism. Of the seven pleiotropic loci, those around SNPs rs7531118, rs1627536 and rs11625397 also showed nominal significance in the association analyses on the SHIP study sample.

Conclusion The results of this study support the hypothesis that shared genetic factors play a relevant role in the frequent joint occurrence of obesity and depression. The identified pleiotropic genes and pathways indicate an important role of the HPA-axis, energy homeostasis and the endocrine system in the depression-obesity relationship and should be studied further to understand the biological mechanisms underlying this comorbidity.

P4.8 HLA-DQB1 6672 G>C is associated with the risk of clozapine-induced agranulocytosis in individuals of European ancestry

Authors Konte B, Walters JT, Giegling I, Legge S, Pardiña AF, Cohen D, Pirmohamed M, Tiihonen J, Hartmann AM, Bogers JP, van der Weide J, van der Weide K, Putkonen A, Repo-Tiihonen E, Hallikainen T, Silva E, Imgimarsson O, Sigurdsson E, Kennedy JL, Breen G, Sullivan PF, Rietschel M, Stefansson H, Collier DA, O'Donovan MC, Rujescu D
Affiliation Universität Halle-Wittenberg, Halle (Saale), Germany
DOI 10.1055/s-0039-3403016

Introduction The atypical antipsychotic drug clozapine is the only effective drug for treatment-resistant schizophrenia, but also bears the risk of inducing severe adverse drug responses including neutropenia and agranulocytosis. Agranulocytosis and neutropenia occurs in about 1% and 3% of treated individuals. The aetiology is largely unknown, but there is evidence for contributing genetic factors. Identifying biomarkers could decrease blood monitoring effort and enable a more widespread use of clozapine. Several studies identified HLA variants (e.g. Athanasiou et al. 2011) and especially a polymorphism located in HLA-DBQ1 (6672 G>C, rs113332494) as associated with clozapine-induced agranulocytosis or neutropenia. Our study was conducted to replicate previous findings on HLA-DBQ1 6672 G>C.

Methods The sample was comprised of individuals from sites of Finland, Germany, the Netherlands and the UK and was collected in the course of the CRESTAR project, which aimed at the development of pharmacogenetic biomarkers for schizophrenia. We analysed the risk allele distribution of rs113332494 in individuals of different ethnic background including 180 clozapine-induced neutropenia cases of which 61 developed agranulocytosis and 1396 controls treated with clozapine but not affected by this severe adverse drug response. We also performed association analyses and analysed local ancestry patterns in individuals of European ancestry, seeking replication and extension of earlier findings. This CRESTAR project was funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement #279 227.

Results HLA-DBQ1 (6672 G>C, rs113332494) was associated with neutropenia (OR = 6.20, P = 2.20E-06) and agranulocytosis (OR = 10.49, P = 1.83E-06) in individuals of European ancestry. The association signal strengthened after including local ancestry estimates (neutropenia: OR = 10.38, P = 6.05E-08; agranulocytosis: OR = 16.31, P = 1.39E-06).

Conclusion HLA-DBQ1 (6672 G>C, rs113332494) was associated with neutropenia (OR = 6.20, P = 2.20E-06) and agranulocytosis (OR = 10.49, P = 1.83E-06) in individuals of European ancestry. The association signal strengthened after including local ancestry estimates (neutropenia: OR = 10.38, P = 6.05E-08; agranulocytosis: OR = 16.31, P = 1.39E-06).

P4.9 Neural plasticity in an iPS-cell based model of Alzheimer's disease and schizophrenia

Authors Pfeifer J, Jung M, Hartmann C, Gutsfeld S, Xavier G, Giegling I, Rujescu D
Affiliation Universitätsklinik Halle, Klinik für Psychiatrie, Psychotherapie, Germany
DOI 10.1055/s-0039-3403017

Introduction Neurodegenerativ disease or psychiatirc disorders like Alzheimer's disease (AD) and schizophrenia (SCZ) are associated with a loss of neurons. Neurodegeneration is regulated by aging or a defect occuring during neural development. A loss of functional neurons affects the neural plasticity – the ability of the brain to adapt on stimuli of our environment. Additionally, from epidemological studies of the last years, we know many common genetic risk factors for both disease, leading to the question, if we can also find in iPS-cell derived neurons of AD and schizophrenia patients a changed neural plasticity compared to healthy controls.

Methods We established an iPS cell-based model, which allows us to analyze neural plasticity in a human in vitro model. We successfully differentiated the iPS cells to neural stem cells, neural progenitor cells, and finally to functional neurons.

Results The neural differentiation was verified by the expression of different markers by FACS, QPCR or immunofluorescence analysis. Gene expression analysis revealed in NSCs of AD patients compared to healthy controls show enhanced or increased expression of aging markers. Very interesting was the significant reduced FGF2 protein amount in AD-specific NSCs. FGF2 is not only described as an aging marker; more important for us FGF2 is a key protein during the neural development. Further, first results of proteome analysis, shows strong differences between the protein expression in neurons of SCZ compared to a healthy control. First pathway analysis demonstrate an association of the identified proteins with neural development.

Conclusion The introduced iPS-cell based model allows us to analyze cellular mechanisms of diseases that affect the neural network in a human in vitro model. With this model, we also get first hints, for changes in neural plasticity shared between AD and SCZ. In the future, we plan electrophysiological analysis and defined analysis of plasticity markers.

P4.10 Genetic variability of GLRB impact cognitive behavioral therapy response in panic disorder

Authors Weber H, Wittchen U, Lang T, Heinig I, Arolt A, Gerlach A, Kircher T, Rief W, Fehm L, Fydrich T, Ströhle A, Hamm A, Pané-Farré C, Alpers G, Pauli P, Reif A, Deckert J
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403018
Introduction A previous GWAS (N = 1370) on the Agoraphobic Cognition Questionnaire (ACQ) identified the genome-wide significant GLRB locus and evaluated its influence on agoraphobic behavior in two independent samples (N = 2547 and N = 3845). Functional analyses of GLRB risk variants showed modulated gene expression, increased startle reactivity and fear network activation. Since deletions in GLRB cause the neurological disorder hyperekplexia, characterized by generalized startle reaction and agoraphobic behavior, genetic variability in GLRB may predispose to panic disorder (PD) by increased startle response and fear network activation.
Methods Doing first steps towards genotype-based therapy, we examined the impact of 3 GLRB risk variants (rs17035816, rs191260602, rs7688285) on cognitive behavioral therapy (CBT) response in 411 PD/AG patients obtained from the multicenter Panic-Net. Treatment response was defined as baseline to post treatment percentage change and linear regressions were run, with percentage change of different anxiety relevant traits (HAMA, PAS, ASI, ACQ, MI) as dependent and genotypes, age and sex as independent variables.
Results In accordance with GWAS results two variants affected CBT response predominantly in regard to agoraphobic behavior, captured by the ACQ and MI. A nominal significant reduction of agoraphobic symptoms post CBT was found for rs17035816 (pACQ = 0.023; pMI = 0.026) which was mainly driven by females (Females: pACQ = 0.037; pMI = 0.091) and still present after 6 month follow-up (Total: pACQ = 0.067; pMI = 0.040; Females: pACQ = 0.058; pMI = 0.041). A significant reduction of agoraphobic symptoms for rs7688285 was restricted to the ACQ after 6 month follow-up (Total: pACQ = 0.063; Females: pACQ = 0.021).
Conclusion Altogether, our findings propose that genetic variability of GLRB impact CBT response in regard to agoraphobic behavior. As GLRB can be subjected to pharmacological interventions, its modulation may open new perspectives for personalized pharmacological and behavioral therapeutic approaches in PD/AG. Due to small sample size an independent replication to support the validity of the observed results is necessary.

P4.11 Biological relevance of a point mutation in the transcription factor LBX1 correlating with ADHD

Authors Elsenbach A, Lesch KP, Lillesaar C, Romanos M, Drepper C
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403019
Introduction Attention-deficit/hyperactivity disorder (ADHD, OMIM #143465) is a neurodevelopmental disorder primarily with symptoms of inattention, hyperactivity and impulsivity. Despite current research efforts, our understanding of the underlying biological processes is still limited. It is generally accepted that the heritability of ADHD lies somewhere between 60 to 90 percent. Recent family or large-scale genomic studies identified several gene variants contributing to ADHD susceptibility.
In a large local family with multigenerational instances of ADHD we have identified a point mutation in the neuronal homeodomain transcription factor LBX1. LBX1 has been linked to neuronal cell fate determination. Our objective is to investigate the possible role of this mutation in the development of ADHD.
Methods To analyse the potential impact of the family-specific point mutation we are using a cell culture system expressing wildtype and mutated versions of the LBX1 transcription factor in HEK293 cell lines. Expression of both variants is detected with qRT-PCR and Western Blot techniques. Total RNA is extracted and expression differences between wildtype and mutated conditions are characterised using RNAseq.
Results At the date of submission, we have identified potential downstream candidate genes with expression differences in the cell lines with the ADHD-family specific mutation with the RNAseq experiments. Currently, we are validating expression differences with qRT-PCR and we will present first results on ADHD-specific LBX1 dependent expression alterations during this congress.
Conclusion These results could give hints on potential pathways which might be involved in the pathogenesis of ADHD in this local family.

P5 Neuroimaging

P5.1 Brain network simulations indicate effect of neuregulin-1 genotype on excitation-inhibition balance in cortical dynamics

Authors Cosa Klein P, Ettinger U, Schirner M, Ritter P, Falka P, Koutsouleris N, Kambeitz J
Affiliation Klinikum der Universität zu Köln, Germany
DOI 10.1055/s-0039-3403020
Introduction Previous research indicates that patients with schizophrenia exhibit alterations in brain structure, brain function and neurochemistry. The high heritability of the disorder suggests that genetic factors play an important role in this pathophysiology. However, the specific factors driving the observed brain alterations remain unclear. Previous research indicates that single-nucleotide polymorphisms (SNPs) in the Neuregulin-1 (NRG1) gene could affect brain structure or brain function. Moreover, animal research suggests that NRG1 is a moderator of the excitatory-inhibitory (E–I) balance in cortical circuits with subsequent effects on cognition and potential relevance for the cognitive deficits observed in patients with schizophrenia.
Methods and Results For rs3924999 our results indicate that G-homozygotes exhibit effective connectivity in brain activity characterized by significantly lower local excitatory recurrence ($p = 0.038$) and significantly higher excitatory synaptic coupling ($p = 0.033$). Network-based statistics indicate no significant differences in structural connectivity between these groups, suggesting that these findings do not result from NRG1 effects on brain structural connectivity. There are no significant effects for the SNP rs35753505 (all $p > 0.05$).
Conclusion Our results suggest that NRG1 might be related to alterations in E–I balance in cortical circuits emphasizing the potential relevance of this genetic factor for the pathophysiology of schizophrenia. Moreover, we suggest the integration of imaging-genetics approaches with computational models of the brain, might be a promising way to investigate specific neurobiological pathways in psychiatric disorders.

P5.2 The role of emotion processing areas in children's face perception network: A functional magnetic resonance imaging pilot study in 7- to 9-year-old children

Authors Debus I, Hildesheim FE, Kessler R, Thome I, Zimmermann KM, Steinsträter O, Sommer J, Kamp-Becker I, Stark R, Jansen A
Affiliation Universität Marburg, Germany
DOI 10.1055/s-0039-3403021
Introduction Paediatric functional magnetic resonance imaging (fMRI) studies on face perception mainly focused on the location of regions in the so-called *core network* of face processing located in the occipito-temporal cortex. Little research has been done on the core network's counterpart, the *extended face processing network*. The present fMRI study seeks to close this research gap by examining activation patterns within the extended face processing network during emotional face processing in children. Regarding the localisation of the core network regions, recent literature points to an increasing specification of typical face-selective activation patterns (Aylward et al., 2005, Gathers et al., 2004, Paul et al., 2003) in the core network. Conversely, previous studies detected more wide-spread activation patterns in the extended part of the face system in children. Faces are rarely neutral, but convey

emotions – in everyday life, in fact, usually more than just one. The processing of the perceived emotions takes place in the extended part of the face network. This ability also develops with age, but so far it is unclear what the developmental differences look like at the neural level.

Methods Using functional Magnetic Resonance Imaging, we investigated brain activity in 7- to 9-year-old children (n = 8) during face processing (using faces with neutral, sad and fearful expression) and compared their neural response with an adult group (n = 10). In order to investigate the processing of the different facial expressions, the neural response of the groups was examined depending on the presented emotion category. Regions of interest were the amygdala, the *insula* and the *inferior frontal gyrus*, which were associated with emotion processing based on imaging studies with adults.

The experimental design is based on a face localizer paradigm which presented grey-scale photographs of faces (fearful, sad and neutral expression; Karolinska Directed Emotional faces (KDEF) dataset, http://www.emotionlab.se/resources/kdef) and houses. To capture the activity of smaller, subcortical regions, such as the amygdala, not the whole brain but only a brain section was measured. The area covered parts of the frontal and temporal lobe, as well as limbic structures and ranged up to the occipital lobe.

Results Our results were partly consistent with those of previous studies, since largely distributed neural activation patterns within the children's extended face perception network were active. Three different areas were identified to exhibit a significant heightened BOLD-response in 7- to 9-year-old children compared to adults: the left ventro-lateral prefrontal cortex and the bilateral medial temporal lobe which in the left hemisphere extended to the anterior insula. As reported by other studies, more wide-spread patterns compared to the adult group were found. The activation pattern particularly included the pre-defined ROIs amygdala, insula and inferior frontal gyrus. Notably, in contrast to adults, children showed a higher BOLD response within these ROIs and predominantly showed activation peaks in left frontal lobe.

Conclusion The observed activation differences indicate an important functional development in frontal and prefrontal regions and the limbic system in the course of emotional face perception across age. The data distribution of the children shows more variance in all three presented emotions than that of the adults, which illustrates the process of specialization of the face network that has not yet been completed in the children sample. The strong involvement of emotion-processing areas could be an indication that children are more emotionally stimulated by the presented faces than the adults. Moreover, an increased activity in the medial frontal cortex in children compared to adults, especially when processing neutral faces, points to more intensive evaluation processes and an ongoing acquisition of the ability to categorize emotions.

P5.3 "I spy with my little eye …": Connectivity analyses of the illusory face perception network

Authors Hohmann D, Thome I, Jansen A
Affiliation Universität Marburg, Germany
DOI 10.1055/s-0039-3403022

Introduction Face pareidolia is the illusory perception of non-existent faces. Putatively, it is caused by matching high-dimensional sensory input with internal face templates, achieved through a top-down mediated coupling between prefrontal regions and brain areas in the ventral temporal cortex, the so-called "core system of face perception". The objective of this study was to understand the coupling mechanisms between core and prefrontal regions in more detail.

Methods We conducted a functional magnetic resonance imaging study on face pareidolia. To trigger illusory face perception, subjects were shown pure noise images but were told that half of them contained a face. Network connectivity was assessed using psychophysiological interaction (PPI) analyses and Dynamic Causal Modeling (DCM).

Results Illusory face perception activated the bilateral core system, similar as for the processing of real faces. Contrary to the holistic processing ascribed to the right hemisphere when naturally perceiving a real face however, activity of the occipital face area (OFA) was atypically left-lateralized. Presumably, this arises due to the necessary and more fundamental feature-by-feature analysis of sensory input. Prefrontal activation was present within the inferior frontal gyrus (IFG), while the orbitofrontal cortex (OFC) was unexpectedly deactivated during the face perception condition, but activated when subjects could not detect a face. PPI analyses showed that the core system was stronger coupled with both prefrontal regions in the face detected compared to the no-face detected condition. DCM revealed in particular a stronger connectivity between OFA and OFC when subjects were unable to detect a face. This connectivity pattern was exhibiting a pronounced hemispheric asymmetry.

Conclusion Taken together, these findings suggest that while the IFG activity was face-sensitive, in line with current neuroanatomical models of face perception, the OFC served as a general, non-face specific matching point between external input and internal templates.

P5.4 Hemispheric lateralization of the face perception network

Authors Volk J, Thome I, Vogelbacher C, Jansen A
Affiliation Universität Marburg, Germany
DOI 10.1055/s-0039-3403023

Introduction Face perception plays an important role in the human visual system as it serves as the basis for communication and social interaction for the majority of people. At the neuroanatomical level, the processing of faces is mediated by a distributed hierarchical neural network, which is often divided into a core system and an extended system (e.g. Haxby, 2000). The core system consists of several brain regions in the occipito-temporal cortex: the fusiform face area (FFA), the occipital face area (OFA) and an area in the posterior superior temporal sulcus (pSTS). Each region plays a different role in face processing. Recently, other regions such as the anterior STS or the ventral anterior temporal cortex have also been described as face-specific.

Methods In the present project we evaluated the lateralization of face perception regions in a large sample of subjects (n ~ 500). Brain activity was assessed with functional magnetic resonance imaging (fMRI) during a face perception task. For each region, hemispheric lateralization was described by a lateralization index (LI) using a toolbox which provides multiple options to compute LIs. We also assessed the influence of ultra-high-risk (UHR) for schizophrenia on lateralization.

Results As expected, our results showed, that face perception is lateralized to the right hemisphere at the population level. The data also underlined the large variability of the lateralization patterns both between subjects and between face-sensitive regions, depending on age, sex and handedness.

Conclusion The variability of the lateralization of the face processing network both between subjects and different brain regions plays an important role in psychiatric research since atypical lateralization patterns have been reported in the context of schizophrenia.

P5.5 Dynamic causal modelling suggests impaired effective connectivity in schizophrenia spectrum disorders during gesture-speech integration

Authors Wroblewski A, He Y, Straube B
Affiliation Universität Marburg, Germany
DOI 10.1055/s-0039-3403024

Introduction Integrating visual and auditory information during gesture-speech integration (GSI) is important for successful social communication, which is often impaired in schizophrenia. Several studies suggested the posterior superior temporal sulcus (pSTS) to be a relevant multisensory integration site. However, intact STS activation patterns were often reported in patients. Thus, here we used Dynamic Causal Modelling (DCM) to analyze whether information processing in schizophrenia spectrum disorders (SSD) is impaired during GSI on network level.

Methods We investigated GSI in three different samples. First, we replicated a recently published connectivity model for GSI in a healthy subject group (n = 19). Second, we investigated differences between patients with SSD and a matched healthy control group (n = 17 each). Participants were presented videos of an actor performing intrinsically meaningful gestures accompanied by spoken sentences in German or Russian, or just telling a German sentence without gestures.

Results Across all groups, fMRI analyses revealed similar activation patterns, and DCM analyses resulted in the same winning model for GSI. This finding

directly replicates previous results. However, patients revealed significantly reduced connectivity in the verbal pathway (from left middle temporal gyrus (MTG) to left STS). The clinical significance of this connection is supported by its correlations with the severity of concretism and a subscale of negative symptoms (SANS).

Conclusion Our model confirms the importance of the pSTS as integration site during audio-visual integration. Patients showed generally intact connectivity during GSI, but revealed impaired information transfer via the verbal pathway. This might be the basis of interpersonal communication problems in patients with SSD.

P5.6 Time unpredictability increases BNST and amygdala activity during threat processing

Authors Herrmann MJ, Siminski N, Böhme S, Zeller JBM, Becker MPI, Bruchmann M, Hofmann D, Breuer F, Schiele MA, Weber H, Schartner C, Pauli P, Reif A, Domschke K, Deckert J, Mühlberger A, Straube T
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403025

Introduction Both animal studies and human studies suggest that the processing of aversive stimuli, from anticipation to confrontation, leads to an initial phasic response in the amygdala and an additional sustained response in the extended amygdala, in the bed nucleus of the stria terminalis (BNST). Furthermore, these effects seem to be modulated by the predictability of the aversive stimuli. However, there are few studies in humans that investigate these modulating effects of predictability in the confrontation with threatening stimuli on the activation of the amygdala and the BNST. In addition, no study has yet investigated a possible modulatory effect of the neuropeptide S receptor genotype (NPSR1) on susceptibility to temporal predictability.

Methods In this study, functional magnetic resonance imaging was used to investigate the anxiety network in 109 healthy subjects (37 males, age = 27.1 ± 6.3 years) during the anticipation and confrontation of a negative or neutral stimulus. An additional cue either signalled the exact time of the impending confrontation with the stimuli, or it signalled that the time is not predictable in time. ROI analyses with cluster-based permutations were used to identify significant clusters in the amygdala and BNST during threat prediction and confrontation. Genotype group differences in the significant clusters were analyzed.

Results The ROI analyses showed a higher activity during the announcement of an aversive stimulus compared to a neutral stimulus in the amygdala and the BNST. During the threat confrontation a main effect of predictability was shown in the right BNST and the right amygdala. Both regions showed a higher activation during the confrontation with unpredictable aversive stimuli. In addition, a significant major effect of valence during stimulus confrontation was observed in both the left BNST and the bilateral amygdala. Post-hoc analyses additionally showed that the valence effect of the left and right amygdala is modulated by the NPSR1 gene polymorphism. T-carriers showed a higher activity than homozygous A-carriers.

Conclusion A higher BNST activity during the valence information cue and during threat confrontation indicates that BNST activation is not limited to a persistent anticipatory response. A higher amygdala activity of AT/TT carriers of NPSR1 during threat confrontation is consistent with previous work and illustrates the risk potential of this allele. Future research will also use this study design in clinical samples to further investigate the modulation effects of temporal predictability and genotypes on anxiety-related brain activity.

P5.7 The impact from complications of pregnancy on gyrification

Authors Schmitt S, Meller T, Stein F, Brosch K, Meinert S, Grotegerd D, Dannlowski U, Krug A, Nenadíc I, Kirchner T
Affiliation Universität Marburg, Germany
DOI 10.1055/s-0039-3403026

Introduction Different complications of pregnancy like maternal stress, obstetric complications, maternal infections, prenatal exposure to nutritional deficiency and reduced fetal growth increase the risk for developing a major psychiatric disorder. This study aims to develop a better understanding of the impact from different childbearing periods on gyrification of the cortex from adults. Since gyrification is a relatively stable neurobiological marker we are able to detect antecedents from deviating cortical development during pregnancy.

Methods We investigated 441 healthy participants (65% women; average age 30 years (SD = 10.7) from the FOR2107 study and acquired T1-weighted structural MRI-data. Gyrification values were extracted with the CAT12-Toolbox and polynomial multiple Regressions were conducted using a threshold-free cluster enhancement (TFCE).

Results There was a significant positive association between weeks of pregnancy and gyrification in postcentral, precentral and superior frontal cortical areas. In the left hemisphere we found this association also in the insula and the supra marginal cortex, in the right hemisphere in paracentral and medial orbitofrontal regions.

Conclusion Large-scale effects demonstrate that deviating prenatal developmental processes considerably influence gyrification and that these deficits in cortical folding are not compensated during postnatal brain development. Grey matter volumes of the insula are transdiagnostically disturbed in main psychiatric diseases like schizophrenia, depression, bipolar disorder and anxiety disorder. Potentially, early acquired aberrations in gyrification in the insula ease later pathogenic mechanisms that lead to psychopathology. The insula is associated with recognition of deviations from expectations and interceptive functions. In psychiatric disorders disturbed behavioural adaptations which could be a result from structural changes in this brain anatomical region can be found transdiagnostically. Besides, a higher risk for developing a psychiatric disorder could also be moderated by reduced cognitive functioning that can be traced back to prenatally acquired changes in gyrification. Studies have already shown that deviated cortical folding in preterm newborns is associated with worse neurodevelopment outcome.

P5.8 The influence of recent stressful life events on brain structure

Authors Ringwald K, Meller T, Brosch K, Schmitt S, Stein F, Pfarr J, Waltemate L, Meinert S, Lemke H, Fingas S, Redlich R, Dannlowski U, Nenadic I, Kirch T
Affiliation Universität Marburg, Germany
DOI 10.1055/s-0039-3403027

Introduction According to the vulnerability-stress model stressful life events (SLEs) in adulthood can trigger mental disorders, such as depression, bipolar disorder, schizophrenia and others. The underlying neurobiological mechanisms are unclear.

Methods In this VBM study the association between grey matter volume, measured with 3 T MRI, and the total event score of the Life Events Questionnaire (LEQ) of 807 healthy subjects from the FOR2107 Cohort (Kircher et al., 2019) was examined. LEQ is an 82-item questionnaire in which subjects mark life events which occurred during the past six months and rate the subjective impact of the event on a 4-point scale. The sum of the impacts of all experienced events is the total event score.

Results There was a negative correlation between the total event score and grey matter volume in a cluster in the left mPFC (gyrus rectus and medial orbital gyrus) and, if corrected for subclinical depressive symptoms with BDI, in a second cluster in the right angular gyrus. Furthermore, the total event score was positively correlated with the scales PSS (chronic stress), CTQ (childhood abuse), STAIS (state anxiety) and negatively correlated with age and MWTB (IQ). After correcting for those factors the negative correlation between gray matter volume and total event score in both brain clusters remained significant.

Conclusion A previous study with a smaller sample size also found a negative correlation between the number of negative SLEs in the past year and grey matter volume in the mPFC and right insula (Ansell et al., 2012). SLEs are correlated with the grey matter volume in these regions and thereby might increase the vulnerability for mental disorders.

P5.9 Moderating effects of serum vitamin D on brain structure

Authors Bonk S, Van der Auwera S, Frenzel St, Wittfeld K, Hosten N, Nauck M, Völzke H, Grabe HJ
Affiliation Universitätsmedizin Greifswald, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Germany
DOI 10.1055/s-0039-3403028
Introduction The vitamin D level is known to affect a wide range of pathways in the human metabolism. As an example, vitamin D deficiency, which is common in the german population, has been linked to Alzheimer's disease and modifications of brain structures. Here, we investigate this association in the second cohort of the "Study of Health in Pomerania" (SHIP-TREND-0) study (Völzke et al., 2011). Head MRI and 25(OH)D serum values were collected from N = 1899 subjects. The brain data is characterized by hippocamus volumina, white matter hyperintensities and brain structure-based scores for Alzheimer's disease and brain age.
Methods We study the influence of vitamin D on FreeSurfer Brain Age (FSBA), FreeSurfer Alzheimer's disease and dementia (FSAD), hippocampus volumina and white matter hyperintensities using regression models. The data is adjusted for various confounders such as age, sex, season, calcium, cholesterin and depression.
Results Based on previous studies, we expect an association between vitamin D deficiency and reduced hippocampus volumina, increased brain age, increased Alzheimer's score and a higher amount of white matter hyperintensities.
Conclusion The possible relation of vitamin D levels to the brain structure might offer a simple path to positively influence the brain structure by applying vitamin D medication.

P5.10 Oxytocin attenuates nucleus accumbens-connectivity during alcohol cue presentation: Evidence from a recent randomized cross-over study

Authors Bach P, Reinhard I, Bühler S, Vollstädt-Klein S, Kiefer F, Koopmann A
Affiliation Zentralinstitut für Seelische Gesundheit Mannheim, Germany
DOI 10.1055/s-0039-3403029
Introduction The brain's oxytocin system is involved in a variety of addictive behaviors. In animal studies, the application of oxytocin led to a permanent decrease in the preference for alcoholic beverages and to a reduction in alcohol consumption. The effects of oxytocin have been linked to the modulation of neurotransmission and functional connectivity in the brain's reward system, the striatum and the nucleus accumbens (NAc). First human studies were able to demonstrate an effect of oxytocin on subjective alcohol cravings and neural cue-reactivity. However, the effects of oxytocin on functional connectivity during the presentation of alcohol-related stimuli have not been investigated in human studies.
Methods We investigated the effects of oxytocin on functional brain activation in a randomized cross-over trial in N = 15 participants with high alcohol consumption using functional magnetic resonance imaging (fMRI). 24 IU oxytocin vs. placebo (intranasal) were applied 40 minutes prior to the assessment of functional brain connectivity during the presentation of alcohol and neutral stimuli.
Results The fMRI results show a significant modulation of functional connectivity in the NAc, thalamus, and paracingular gyrus by oxytocin during the presentation of alcohol-related stimuli (all $p_{FDR} < 0.05$). This effect was specific to the alcohol condition and was not seen during the presentation of neutral images. The results also indicated a significant correlation between NAc-connectivity and subjective desire for alcohol ($r = 0.538$, $p = 0.024$).
Conclusion The results of the current study provide first evidence of a condition-specific and significant attenuation of NAc-connectivity by oxytocin, which was associated with a lower subjective alcohol craving. The oxytocin-induced modulation of NAc-connectivity was specific for the processing of alcohol stimuli and could reflect a reduction in the stimulus salience of alcohol stimuli by oxytocin.

P5.11 Non-invasive brain stimulation for modulating a consolidated fear memory

Authors Cybinski LM, Boehme S, Mühlberger A, Polak T, Herrmann MJ
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403030
Introduction Despite the high effectiveness of cognitive behavioural therapy in the treatment of anxiety disorders, not all patients show a satisfactory therapeutic success. Recently, studies have examined the additional benefit of non-invasive brain stimulation (NIBS) in combination with psychotherapy for anxiety disorders. To further optimise the effectiveness of NIBS, it has been suggested that the therapy-relevant learning processes involved should be examined in more detail. The present study, therefore, investigated the enhancing effect of tDCS stimulation of the ventromedial prefrontal cortex (vmPFC) on extinction learning in consolidated fear memory.
Methods In a two-day fear conditioning paradigm with female faces as conditioned stimuli and a 95-dB female scream as the unconditioned stimulus, skin conductance reactions and subjective fear ratings were examined. Sixty-one healthy subjects showed successful fear conditioning and were included in the statistical analyses. Participants were randomly and double-blinded assigned into a sham and verum stimulation group. The day after fear conditioning, brain stimulation and extinction learning took place under the same experimental conditions. The stimulation began ten minutes before extinction learning.
Results Results showed a significant time x condition x group interaction, $F(1.59) = 4.35$, $p < .05$. Post-hoc *t*-tests indicated that active stimulation enhances extinction learning with a significant loss of CS+/CS- discrimination. The discrimination loss was observed by a significant decrease in response to CS+ and an increase in response to CS- in the experimental group. During this period, the control group showed no significant reaction changes.
Conclusion Results showed that the stimulation protocol can be used to modulate a consolidated fear memory and thus to enhance therapy-relevant learning processes. Future studies should investigate the applicability of the paradigm to a clinical sample in the context of exposure therapy.

P5.12 Neural correlates of social inclusion in borderline personality disorder and non-suicidal self-injury

Authors Malejko K, Brown RC, Plener PL, Bonenberger M, Abler B, Graf H
Affiliation Universitätsklinikum Ulm, Institut für Psychiatrie, Germany
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Introduction Recent neuroimaging studies demonstrated a potential disorder-specific neural alteration during social inclusion in borderline personality disorder (BPD) by enhanced activations within the dorsomedial prefrontal cortex (dmPFC) and the posterior cingulate cortex (PCC) when compared to healthy controls (HC) and patients with major depression (MD) (1). To examine the specificity of these neural alterations, we now investigated a sample of patients with BPD and non-suicidal self-injurious behavior (NSSI) and patients with NSSI without BPD compared to HC. In addition, we examined potential neural commonalities during social inclusion considering the strong associations between these two disorders.
Methods A sample of 15 adults with BPD, 16 adults with NSSI and 17 HC were investigated with functional magnetic resonance imaging (fMRI) and the cyberball paradigm. According to our study aim, we focused on differential neural activations under social inclusion versus passive watching. Statistical inference was carried out at $p < 0.05$ (FWE-corrected on cluster-level). A conjunction analysis on differential neural activations was conducted to examine neural commonalities between these two clinical groups compared to HC under social inclusion ($p < 0.05$, FWE-corrected for search volume).
Results A significant increase in differential neural activation within the dmPFC was observed in BPD under social inclusion compared to both, NSSI and HC and enhanced activations within these regions were associated to individual borderline symptom severity. In contrast, differential neural activations within the PCC did not differ between BPD and NSSI. A conjunction analysis revealed a common increase in neural activation under social inclusion

within the pregenual anterior cingulate cortex (pgACC) and the anterior insula in both, BPD and NSSI compared to HC.

Conclusion Our study provides an evidence regarding a potential disorder-specific neural alteration within the dmPFC in BPD under social inclusion, whereas activations within the PCC may represent a rather unspecific neural alteration in BPD when compared to NSSI. However, both clinical groups revealed common neural increases in regions associated to the affective appraisal of social interaction condition (pgACC, anterior insula) as a potential early neural signature in NSSI without BPD.

P5.13 A bilateral model of congenital prosopagnosia – connectivity between FFA and ATL

Authors Kessler R, Albert I, Gracenea P, Zimmermann KM, Schmidt K, Jansen A
Affiliation Universität Marburg, Germany
DOI 10.1055/s-0039-3403032

Introduction Prosopagnosia is a condition, in which face perception or face recognition is affected (= "face blindness"). We differentiate between acquired prosopagnosia – caused by a lesion in a cerebral region related to face perception (e.g. OFA, FFA, ATL) – and congenital prosopagnosia (CP) – a quite heterogeneous disability affecting primarily identity recognition with no macroscopic structural lesions. There are two different opinions about the nature of CP. The pathological view sees clear differences between CPs and healthy subjects, whereas the normative view sees CP individuals as "just extremely bad" in the ability of face recognition. Consequently, CP individuals' face recognition abilities are supposed to reflect the lower tail of a normal-like distribution of this ability in the population. In the following, we work with the normative view of CP.

We asked whether alterations of connectivity between face regions are associated with CP. Recent studies have shown that there is reduced brain activation related to face perception in anterior temporal lobe face area (ATL) in CP. As part of the extended face perception system, ATL is connected to the core system most likely via fusiform face area (FFA). The reduced activation of ATL in CP may therefore be associated with disrupted connectivity between those regions. We hypothesized, that a reduction of ATL activation in CP (subjects with low face recognition scores) may result from a lack of face specific information transfer from FFA to ATL.

Methods We recruited 49 subjects. Individual face recognition ability was quantified using Cambridge Face Memory Test (CFMT). Participants with less than 58 % accuracy were classified as CPs (8 out of 49 subjects). Each of the 49 subjects underwent a face localizer paradigm in which we presented blocks of faces with different emotions and houses as a control condition. We identified brain regions related to face perception on a single-subject level for bilateral FFA & ATL. We then extracted the time series and constructed a 4-region dynamic causal model (DCM) for each subject. Regressor faces entered the model via bilateral FFA (C-matrix). Each FFA and ATL shared structurally reciprocal connections and interhemispheric reciprocal connections between homotopic brain regions (A-matrix). Furthermore, faces modulated all available structural connections (B-matrix).

To estimate a group model, we used Parametric Empirical Bayes (PEB, Friston et al., 2015). We included each subjects model, and inter-subjects effects such as [1 – CFMT score] (as a proxy for prosopagnosia), and alexithymia score, autism score, gender and age as covariates of no interest. By means of the PEB model, we will present A, B and C matrices, as well as the effect of prosopagnosia and gender.

Results Context-independent connection (A-matrix) became mostly positive in forward direction (FFA to ATL) and negative in backward direction (ATL to FFA), reciprocally positive between bilateral ATL, and reciprocally negative between bilateral FFA. Face perception excited the system positively via bilateral FFA (C-matrix). Furthermore, face perception increased the negative (inhibitory) connections from lFFA to rFFA, rATL to rFFA, lATL to lFFA, and flipped the sign at the connection from lATL to rATL to negative. PEB revealed just one significant effect of CP onto the model. That was, the inhibitory – face specific – backward connection from lATL to lFFA was slightly weakened by CP (parameter estimate of + 0.021). In contrast, gender had a very strong effect on the homologue connection in the right hemisphere, but with an effect of 50 times larger (parameter estimate of + 1.18).

Conclusion We saw a weak effect of CP on our bilateral model of face perception. However, this effect was factor 50 smaller than the effect of gender onto the homologue connection of the right hemisphere. Therefore we did not find support for our hypothesis, that CP or the individual ability of face recognition may be associated with alterations in connectivity between FFA and ATL. However, our study has several limitations: first of all, we recruited unobtrusive subjects of which only around 20 % were CP. Reliable diagnoses of prosopagnosia should also be supported by another questionnaire and another face recognition test. Furthermore, individual ATL was difficult to localize and shows high inter-subject variability. Therefore we may have used heterogeneous ATL subregions for different participants.

P5.14 Processing emotional ambiguity: When the prefrontal cortex jumps at a subtle smile

Author Thome I
Affiliation Universität Marburg, Germany
DOI 10.1055/s-0039-3403033

Introduction Reading other people's emotional facial expressions is a crucial aspect of social communication. What most people take for granted, is an insurmountable obstacle for patients suffering from an Autism-Spectrum-Disorder (ASD) or people affected with a condition called emotional blindness (Alexithymia). In the present study, we aimed to gain a deeper understanding of the underlying brain areas involved in such a complex task as the successful categorization of emotions. While most research on emotion categorization has been conducted with stereotypic emotions, real-life situations are more complex involving highly ambiguous emotional expressions. Hence, we set out to delineate the involvement of the prefrontal cortex (PFC) when subjects are confronted with pictures of ambiguous emotional faces.

Methods 30 healthy right-handed subjects were included in a functional magnetic resonance (fmri) study. Each subject perceived 480 morphed emotional face stimuli varying in their emotional content from prototypic emotions (happy, angry, sad, fearful) to complete ambiguity. For each emotional face stimulus, subjects indicated the predominant emotion in a two-alternative forced choice task.

Results When using the emotional intensity as a parametric modulator, we could show that the PFC together with the anterior insular gets increasingly activated while the emotional content is reduced to complete ambiguity. Task performance (steepness of the psychometric curve) was correlated with brain activity in the inferior frontal gyrus (IFG), indicating a central role of the IFG in top-down processing of ambiguous emotions.

Conclusion These preliminary results are an important groundwork to further investigate emotion categorization in patients with ASD and Alexithymia.

P5.15 Structural connectivity differences in patients with major depression and comorbid anxiety disorder compared to patients with major depression and healthy subjects, a DTI study

Author Knigge K
Affiliation Universitätsklinikum Magdeburg, Germany
DOI 10.1055/s-0039-3403034

Introduction Previous studies have shown that patients suffering from major depressive disorder (MDD) compared to healthy control subjects differ in white matter diffusivity, especially in the bilateral corticospinal tract, the bilateral posterior part of the internal capsule, the corona radiata (right superior) and the left external capsule. The aim of the present study is to investigate the influence of comorbid anxiety disorders on white matter diffusivity.

Methods So far 21 patients with MDD and anxiety disorder, eight patients with MDD and 23 healthy controls have participated in the MRI study and were measured with 3 Tesla MRI. Diffusion weighted EPI sequences have been used. DTI data will be pre-processed with FSL and statistically evaluated using Tract-Based Spatial Statistics (TBSS). Also of importance is the evaluation of rating questionnaires as well as stress parameters in saliva, hair and blood of the participants.

Results With the detection of connectivity differences in the brain of the participants, with special focus on the connections between hippocampus/

amygdala and the prefrontal cortex, in a group comparison we can gain new insights regarding patients with MDD and anxiety disorder and correlate these with stress parameters.

Conclusion Especially in the field of DTI measurements and this patient clientele there are currently only few scientific contributions. Here we want to further investigate the changes in the fibre course with a focus on anxiety and depression patients. For this purpose, the sample size of patients suffering from MDD will be increased in order to show differences between the groups related to the comorbid anxiety disorder.

P5.16 Childhood trauma and the reward system in patients with major depressive disorder

Author Jesse L
Affiliation Universitätsklinik Magdeburg, Germany
DOI 10.1055/s-0039-3403035

Introduction Early childhood trauma is one of the main risk factors for the development of psychiatric disorders, such as major depressive disorder (MDD). A consistent finding in MDD is a reduced neuronal activity in the ventral striatum during reward processing, however, the underlying causes of this finding are unclear. It is known that early childhood stress can have a negative effect on neuroplasticity and transmitter release and may lead to the development of depressions. The aim of our study was to find out to what extent early social conditions affect the neuronal reward system.

Methods We examined 19 patients with MDD and 18 control subjects using functional magnetic resonance imaging (3 Tesla MRI). Defined regions of the reward system in the brain (e.g. the prefrontal, orbitofrontal, anterior cingulate cortex and basal ganglia, especially the nucleus accumbens) were analyzed for changes in their activity during a reward task (reversal learning task). In addition, the Childhood Trauma Questionnaire (CTQ) was used to evaluate early childhood stress and to correlate it with neuronal activity.

Results The left nucleus n. accumbens showed in the contrast probabilistic errors versus correct answers lower activity in all test participants with childhood trauma compared to those without. In addition, there was a negative correlation between the severity of the childhood trauma and the activity of left n. accumbens in this contrast across all subjects. Moreover, controls showed stronger activity than in the patients.

Conclusion In the Reversal Learning task, a probabilistic error describes the situation where the respondent is given negative feedback on his selected answer, although it is correct. The altered activity of n. accumbens shows that subjects with childhood adversity react less strongly to negative feedback than subjects without. Thus, childhood adversity could explain in part the difference seen between patients and controls in the reward system.

P6 Neuropharmacology

P6.1 A Phase 3, double-blind, placebo-controlled trial of SAGE-217 in postpartum depression: Assessment of depressive symptoms across multiple measures

Author Junker H
Affiliation Zug, Switzerland
DOI 10.1055/s-0039-3403036

Introduction Postpartum depression (PPD) is a common complication during and after pregnancy. PPD and major depressive disorder (MDD) pathophysiology may involve dysregulation in GABAergic signaling. SAGE-217, an investigational, oral neuroactive steroid and GABAA receptor positive allosteric modulator, demonstrated improvements in depression versus placebo in a pivotal trial in MDD (NCT03000530). This double-blind, randomized, placebo-controlled Phase 3 trial (NCT02978326) evaluated SAGE-217 in women with PPD.

Methods Women, ages 18–45, ≤ 6 months postpartum, diagnosed with PPD, with a Hamilton Rating Scale for Depression (HAM-D) total score ≥ 26, were enrolled and randomized 1 : 1 to SAGE-217 30 mg or placebo capsules. Patients (n = 151) received study drug for 14 days, with follow-up through Day 45. HAM-D change from baseline (CFB) at Day 15 was the primary endpoint. The CFB in HAM-D total score at all other time points, Montgomery-Åsberg Depression Rating Scale (MADRS) score, and categorical HAM-D response (reduction ≥ 50%) and remission (score ≤ 7) rates were secondary endpoints. Adverse events (AEs) were recorded throughout the study.

Results At Day 15, SAGE-217 demonstrated significantly greater reductions in HAM-D versus placebo (− 17.8 vs. − 13.6, p = 0.0028) that were sustained through Day 45 (p = 0.0027). Compared with placebo, SAGE-217 showed significantly greater HAM-D response (72% vs. 48%, p = 0.0049) and remission (45% vs. 23%, p = 0.0110) rates at Day 15, with significance maintained through Day 45 (response p = 0.0216; remission p = 0.0091). At Day 15, SAGE-217 was associated with a significant CFB in MADRS score relative to placebo (− 22.1 vs. − 17.6, p = 0.0180). The most common (≥ 5%) AEs in the SAGE-217 group were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.

Conclusion SAGE-217 resulted in rapid (by Day 3), statistically significant, clinically meaningful, and sustained (through Day 45) reductions in depressive symptoms in women with PPD in this Phase 3 trial. SAGE-217 was generally well tolerated, supporting SAGE-217 as a potential PPD therapy.

P6.2 Pharmacotherapeutic management of acute alcohol withdrawal syndrome in critically ill patients

Authors Glahn A, Proskynitopoulos J, Bleich S, Hillemacher T
Affiliation Medizinische Hochschule Hannover, Germany
DOI 10.1055/s-0039-3403037

Introduction Alcohol withdrawal syndrome is a common and life-threatening condition in patients suffering from alcohol use disorder. Treatment of this syndrome is challenging, especially in patients that are critically ill, either because of withdrawal symptoms or underlying conditions. For the treatment, several pharmacological agents exist, such as benzodiazepines, barbiturates, or dexmedetomidine. Nonetheless, as alcohol withdrawal syndromes can occur in every clinical setting, it is necessary to provide a guideline for clinicians confronted with this syndrome in varying clinical contexts.

Methods The authors provide a systematic review of the literature found in PubMed and Embase following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Thereby we tried to obtain an overview of pharmacological options for the treatment of alcohol withdrawal syndrome in the critically ill. For the systematic research, we used the following research term and applied it to "all fields":(Alcohol withdrawal OR delirium tremens) AND (renal failure OR hepatic failure OR liver cirrhosis OR cardiac failure OR critical illness OR critical care OR intensive care)
Apart from this term, no other criteria were selected at this stage.

Results and Conclusion For the treatment of alcohol withdrawal syndrome, medications targeting the GABA system are preferred. Benzodiazepines are regarded as the gold standard. However, as many adjunct therapeutic options exist, it is essential to find symptom-triggered approaches and treatment protocols for the variety of clinical contexts. Apart from that, it is necessary to compare protocols towards clinical variables rather than investigating medications that are in use for the treatment of alcohol withdrawal syndrome.

P6.3 Cariprazine in the treatment of a long lasting psychosis in a female patient with Morbus Niemann-Pick Type B

Authors Eberlein C, Deest M, Das A, Bleich S, Frieling H
Affiliation Medizinische Hochschule Hannover, Germany
DOI 10.1055/s-0039-3403038

Introduction M. Niemann Pick type A and B is caused by an autosomal recessive inherited gene defect located on chromosome 11 and is a lysosomal disease. Due to the reduced activity of acid sphingomyelinase damage of liver, spleen and lungs occurs, especially in patients with type A the CNS is commonly affected. These affection of the CNS is uncommon in patients with type B. Nevertheless some descriptions of treatment resistant psychosis in patients with M. Niemann Pick type B can be found.

Methods We report on a 30 year old female patient with M. Niemann Pick type B who is treated in our specialized outpatient clinic for mental health in rare diseases since early 2018. She suffered from psychotic symptoms such as optic and acoustic hallucinations, delusion and periodic temper tantrums. Besides the mild mental retardation she was diagnosed with epilepsy and aortic valve insufficiency III.

Results and Conclusion Treatment was initialized using quetiapine as monotherapy, then in combination with aripiprazole, augmented with pipamperone. None of these did show any improvement, but dysphagia occurred as a side effect which had occurred in earlier years when she was treated with risperidone. After changing medication to cariprazine we observed a noticeable decrease of psychotic symptoms. Even regular visits at a day care center were possible.

P6.4 Medication in the elderly – data from the Vogel study Würzburg

Authors Haberstumpf S, Herrmann MJ, Deckert J, Polak T
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403039

Introduction The proportion of seniors (> 65 years old) in the population is rising steadily and will be 51 % in 2060 (2013: 38 %). Seniors often have several diseases, including chronic diseases, which means that in this age group the number of people taking medication in general, including psychoactive medication, is considerable. There are hardly any reliable statistics on this topic. Substance-related disorders in older age, as well as drug dependence, are rarely diagnosed and their extent is often underestimated; the number of representative studies on this topic is small.

Methods The Vogel study is a prospective long-term cohort study over 10 years to investigate the predictive validity of new electrophysiological methods in the early diagnosis of Alzheimer's dementia. Since 2011, 604 randomly selected residents of Würzburg, aged between 70 and 77 years, are thoroughly examined in 3-year intervals; data on medication and lifestyle habits are also collected.

Results Of 603 participants, 530 (87.9 %) took drugs at the time of the first cross-sectional survey. Most frequently, blood pressure medication was taken. 399 of 604 participants (66.1 %) took between one and five antihypertensives. 56 of 604 participants (9.3 %) regularly took 1–4 medications against pain. The use of analgetics decreased with age ($r = -0.09$, $p = 0.033$) and was higher in women than in men ($T = -2.8$, $p = 0.005$). Participants with a history of depression were more likely to take pain medication ($X^2 = 14.26$, $p = 0.007$). The number of drugs in general correlated weakly with the score of the anxiety sensitivity inventory (ASI; $r = 0.15$, $p = 0.01$). Out of 603 responses of participants at the time of the initial study, only 6 (< 1 %) stated that, in their own estimation, they had at some point in their lives taken more medication than prescribed by a doctor.

Conclusion Medication in old age is a relevant factor. The effect of current medication on the development of cognitive abilities in old age can only be shown after the completion of the long-term study.

P6.5 Impact of antidepressive drugs on regulatory mechanisms for the maintenance of cellular homeostasis

Authors Rohner H, Bajaj T, Philipsen A, Gassen NC
Affiliation Universitätsklinik Bonn, Abteilung für Psychiatrie und Psychotherapie, Germany
DOI 10.1055/s-0039-3403040

Introduction Through intensive research efforts over the past years Autophagy has been recognized as an important intracellular mechanism for the maintenance of homeostasis of cellular organelles and components. Thus, damaged cellular particles are degraded through lysosomal activity. Today we know that altered signaling pathways of autophagy can contribute to the genesis of all sorts of diseases which includes mental disorders. The focus of this project is on the so called "neuronal Autophagy" which plays a central role in diseases associated with stress. Previous studies point to the direction that psychotropic drugs alter signaling pathways important for neuronal autophagy regulation The aim of our study is to answer the important question 'how different psychotropic drugs influence the activity of neuronal cell cultures' in order to contribute to the understanding of the mode of action of pharmaceuticals for the efficient treatment of mental disorders. Our working model is that in the development of stress associated disorders there is a maladaptation of neuronal autophagy and that psychotropic drugs counteract this by re-establishment of autophagy modulation.

Methods Various pharmaceuticals with mostly antidepressive effects will be titrated on neuronal cell cultures in therapeutic dosages according to the AGNP-Guideline for drug monitoring. The autophagic flux will be measured with by using a fluorescent probe, called GFP-LC3-RFP- LC3ΔG. The cleavage products are only partly metabolized. Thus, we will be able to monitor induction and blocking of autophagic activity.

Results Performing a meta-analysis we observed that antidepressive drugs which are already tested on different levels of autophagy regulation show an overall autophagy-inducing effect. According to the research that has already been done the knowledge is still incomplete. It is important to include more substance classes to a standardized and established working protocol with a valid autophagic readout as a benchmark.

Conclusion Regarding the results we already obtained from the existing studies, the modulation of autophagic processes could be one opportunity for new approaches in the treatment of diverse diseases. Concerning mental disorders, drugs with psychotropic effects are of high relevance. With this study, we aim to examine the alteration of the different signaling pathways also on molecular level. Furthermore, we will focus on the effects of other psychotropic drugs such as antipsychotics, stimulants or mood stabilizers and also we will analyze the impact of illegal substances.

P6.6 Treating impulsivity with synbiotics in adults: a multicentre, double-blind, randomized, placebo-controlled trial

Authors Siegl A, Matura S, Reif A, Arteaga-Henríquez G, Rosales-Ortiz K, Arias-Vásquez A, Bitter I, Ginsberg Y, Kilencz T, Rethelyi J, Ramos-Quiroga JA
Affiliation Universitätsklinikum Frankfurt, Germany
DOI 10.1055/s-0039-3403041

Introduction Impulsivity and compulsivity are related to emotional and social maladjustment and often underlie psychiatric disorders. Alterations in microbiota composition demonstrated implications for brain development and social behaviour via the microbiota-gut-brain axis. Recent evidence suggests the modulatory effect of synbiotics on gut microbiota which could ameliorate symptoms of psychiatric diseases. No randomized-controlled trial has been performed yet to investigate effects of synbiotics on impulsivity and compulsivity.

Methods In a prospective, multicentre, double-blind, randomized-controlled trial patients receive either a synbiotic formula or placebo treatment. Primary outcomes include Clinical Global Impression-Improvement (CGI-I) score of 1 or 2 = very much or much improved, and Affective Reactivity Index (ARI-S) score reduction of minimally 30 % compared to baseline. N = 180 highly impulsive participants, 18–65 years old, diagnosed with attention deficit/hyperactivity disorder (ADHD) and/or borderline personality disorder (BPD), are screened at three study centres. Secondary outcome measures include changes in general psychopathology, ADHD symptoms, neurocognitive functions, somatic parameters, physical activity, nutritional intake and health-related quality of life. Intervention effects on microbiome, genetics and several blood biomarkers will be also assessed.

Results We hypothesize that the supplementation with synbiotics is an effective treatment in adults with high levels of impulsivity, compulsivity, and aggression, ameliorating these symptoms. Current stage of work: Data collection.

Conclusion This first randomized-controlled trial investigating synbiotics effects on reducing impulsive, compulsive and aggressive behaviour can help explain the crosstalk between intestinal microbiome and brain. If improvement effects are demonstrated, new cost-effective treatments might be available to these patients.

P6.7 Atomoxetine and clock gene expression in human dermal fibroblasts

Authors Palm D, Uzoni A, Thome J, Faltraco F
Affiliation Universität Rostock, Germany
DOI 10.1055/s-0039-3403042

Introduction Atomoxetine (ATO) is a substrate for ADHD medication. We propose that part of the therapeutic profile of ATO may be through circadian rhythm modulation. The aim of this study was to investigate the clock genes expression in human dermal fibroblasts (HDF) after ATO exposure.

Methods Four healthy controls (HC) participants (3 men, 1 woman; 42.00 ± 15.38 years, mean ± SD) and four volunteers suffering from ADHD (1 man, 3 women; 38.75 ± 8.15 years, mean ± SD) were included in the analysis. All participants completed the Multiple-Choice Word Test (IQ score: HC: 112.25 ± 9.32, mean ± SD; ADHD participants: 110.83 ± 13.27, mean ± SD, n.s), German Morningness-Eveningness-Questionnaire (D-MEQ Score: HC: 50.00 ± 3.74, mean ± SD; ADHD participants: 53.50 ± 9.54, mean ± SD, n.s) and Wender Utah Rating Scale, German short-version (WURSk Score: HC: 13.75 ± 9.98, mean ± SD; ADHD participants: 31.75 ± 6.94, mean ± SD, p = 0.025). HDF were obtained via skin biopsy and cultured under standard conditions (37 °C, 5 % CO2). HDF were incubated for 24 hours with 0.20 and 0.58 µM ATO. HDF without ATO incubation were used as negative control (NegControl). After dexamethasone synchronization, sampling was performed every forth hour for a period of 28 hours. CLOCK, BMAL1, CRY1, PER1/2/3 gene expression was measured by qRT-PCR and data was controlled for fitting in a time series model (CircWave). Statistics were calculated using SPSS.

Results ATO (0.58 µM) induced the rhythmicity of CLOCK in ADHD group (p = 0.009, CircWave) whereas this effect was not observed in HC. Moreover, ATO exposure damped the rhythmicity of PER1/2 in ADHD whereas normal rhythmicity of BMAL1, CRY1, PER1/2/3 was observed in HC.

PER1 (ZT4, p = 0.004) and PER2 (ZT8, p = 0.017) differ between HC and ADHD after 0.20 µM ATO exposure. Compared to NegControl, BMAL1 expression differs for ZT0 (p = 0.020) in HC. Similarly, in the ADHD group, 0.20 µM ATO phase shifted the expression of BMAL1 and CRY1 for ZT28 (p = 0.006; p = 0.011). Additionally, 0.58 µM ATO altered the expression of CRY1 (ZT16, p = 0.022) and PER2 (ZT0, p = 0.017) in ADHD. Moreover, PER3 differs for ZT8 (p = 0.015) between the two ATO concentrations.

Conclusion Our results suggest that ATO might influence clock gene expression in HDF. The number of participants will be increased.

P6.8 Metformin influences the expression of beta-actin in human dermal fibroblasts

Authors Palm D
Affiliation Medizinische Universität Rostock, Germany
DOI 10.1055/s-0039-3403043

Introduction Metformin is a drug used in diabetes mellitus type 2 (T2DM) therapy especially in case of Adipositas as a comorbidity. Furthermore, a molecular and cellular link between T2DM and Alzheimer's disease may exist. We showed in previous studies that drugs like Norepinephrine and Atomoxetine influence the circadian rhythm in human dermal fibroblasts (HDF). In this study, we investigate the influence of Metformin on circadian gene expression in HDF.

Methods HDF were obtained via skin biopsy from healthy controls (HC) (2 men, 1 woman; 39.00 ± 17.35 years, mean ± SD; BMI: 26.00 ± 4.38 kg/m^2, mean ± SD). Cells were cultivated at 37 °C and 5 % CO2. All participants completed the Multiple-Choice Word Test (IQ score: HC: 112.33 ± 10.01, mean ± SD), German Morningness-Eveningness-Questionnaire (D-MEQ Score: HC: 50.33 ± 4.51, mean ± SD) and Wender Utah Rating Scale, German short-version (WURSk Score: HC: 13.67 ± 12.22, mean ± SD). HDF were treated with either 0 mM, 2 mM or 20 mM Metformin. Synchronization was induced with 0.1 µM dexamethasone (D) for 2 hours. Sampling was performed every forth hour starting after synchronization for a period of 28 hours. CLOCK, BMAL1, CRY1, PER1/2/3, TAU, APP and Beta-Actin gene expression was measured by qRT-PCR. Rhythmicity analysis was perfomed with CircWaveR software. Statistics were calculated using SPSSR.

Results The middle-aged volunteers showed an overweight BMI and standard range IQ score as well as intermediate chronotype. Furthermore, the WURSk score presented no evidence for ADHD characteristics. Significant circadian oscillations were observed for BMAL1 and CRY1 (CircWave, p > 0.05) for all concentrations. Additionally, TAU expression was rhythmic after 2 mM Metformin.

CLOCK expression was significantly higher for 2 mM Metformin compared to 0 mM (p = 0.019) at ZT0. Moreover, BMAL1 expression differs at ZT8 for 20 mM Metformin compared to 0 mM (p = 0.016). Interestingly, APP expression for 2 mM Metformin is significantly lower at ZT12 (p = 0.006) compared to 20 mM Metformin. Additionally, TAU expression differs between the two metformin concentrations (2 mM and 20 mM) at ZT12 (p = 0.018). Interestingly, Beta-Actin, often used as a housekeeping gene, showed lower expression for 2 mM Metformin at ZT8 (p = 0.034) and ZT12 (p = 0.014) as well as for 20 mM Metformin at ZT8 (p = 0.032) compared to 0 mM.

Conclusion Our preliminary results suggest that Metformin may alter the circadian rhythm in HDF for CLOCK, BMAL1, APP and TAU, as well as Beta-Actin.

P6.9 Include me if you can!: Reasons for low enrollment of pediatric patients in a psychopharmacological trial

Authors Haege A, Mechler K, Niemeyer L, Buitelaar J, Durston S, Gooskens BR, Oranje B, Banaschewski T, Dittmann RW
Affiliation Zentralinstitut für Seelische Gesundheit Mannheim, Germany
DOI 10.1055/s-0039-3403044

Introduction Low recruitment in clinical trials is a common and costly problem which undermines medical research. This study aimed to investigate the challenges faced in recruiting children and adolescents with obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD) for a randomized, double-blind, placebo-controlled clinical trial and to analyze reasons for non-participation. The trial was part of the EU FP7 project TACTICS (Translational Adolescent and Childhood Therapeutic Interventions in Compulsive Syndromes (www.tactics-project.eu, FP7/2007-2013, grant agreement number 278948, EudraCT Number: 2014-003080-38).

Methods Demographic data on pre-screening patients were collected systematically, including documented reasons for non-participation. Findings were grouped according to content, and descriptive statistical analyses of the data were performed.

Results In total, n = 173 patients were pre-screened for potential participation in the clinical trial. Of these, only five (2.9 %) were eventually enrolled. The main reasons for non-inclusion were: failure to meet all inclusion criteria/meeting one or more of the exclusion criteria (n = 73; 42.2 % of pre-screened patients); no interest in the trial or trials in general (n = 40; 23.1 %); not wanting changes to current therapy/medication (n = 14; 8.1 %).

Conclusion The findings from this study add valuable information to the existing knowledge on reasons for low clinical trial recruitment rates in pediatric psychiatric populations. Low enrollment and high exclusion rates raise the question of whether such selective study populations are representative of clinical patient cohorts. Consequently, the generalizability of the results of such trials may be limited. The present findings will be useful in the development of improved recruitment strategies and may guide future research in establishing the measurement of representativeness to ensure enhanced external validity in psychopharmacological clinical trials in pediatric populations. Furthermore, researchers are encouraged to collect and publish detailed findings on recruitment difficulties and reasons for non-participation in clinical trials, in order to develop respective new tools and concepts based on sound data.

P6.10 OPTiMiSE: Können Blut-Metabolite den klinischen Verlauf einer paranoiden Schizophrenie bei einer Behandlung mit Amisulprid vorhersagen?

Author Hensel O
Affiliation Universität Halle-Wittenberg, Germany
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Einführung Die Schizophrenie ist eine schwere psychische Erkrankung, die die Lebensqualität der betroffenen Patienten stark einschränkt. Das Ansprechen auf eine antipsychotische Therapie ist aktuell nicht vorhersehbar, bei einem Drittel der Patienten ist die antipsychotische Medikation unwirksam. Ein frühes Ansprechen auf die Behandlung ist einer der Hauptfaktoren, der mit einer besseren Langzeitprognose einhergeht. Deswegen ist die Identifizierung von Prädiktoren für das Ansprechen auf eine antipsychotische Medikation. Das Metabolom im Ganzen stellt eine Art Fingerabdruck des Stoffwechsels zu einem bestimmten Zeitpunkt dar. Dies kann als ein Abbild eines Zustandes z. B. während einer Erkrankung angesehen werden. Bei Patienten mit Schizophrenie ist die Konzentration von Phosphatidylcholinen im Blut vermindert, während ein Lysophosphatidylcholin erhöht ist. Die Aminosäuren Alanin, Isoleucin und Leucin sind ebenfalls erhöht, während die Tyrosin-Konzentration vermindert ist. Das Frage der Studie „Optimization of Treatment and Management of Schizophrenia in Europe" (OPTiMiSE) ist unter anderen, ob Blut-Metabolite das Ansprechen auf eine 4-wöchige antipsychotische Medikation mit Amisulprid vorhersagen können.

Methoden In die Analyse eingeschlossen wurden 195 kaukasische, nüchterne Patienten (Alter 26.3 ± 6.3 Jahre, 130 Frauen, Symptomdauer 7,0 ± 6,5 Monate) mit einer ersten Episode einer schizophrenen, schizophreniformen oder schizoaffektiven Erkrankungen (definiert nach DSM-IV). Ihnen wurde vor und nach 4 Wochen antipsychotischer Medikation mit Amisulprid Blut entnommen. Im Plasma wurden Metabolite mit dem AbsoluteIDQ©-Kit der Firma Biocrates analysiert. Die Metabolite umfassen 21 Aminosäuren, 40 Acylcarnitine, 15 Sphingolipide, 21 biogene Amine, 90 (Lyso-)Phosphadidylcholine und eine Hexose. Zur Beurteilung der psychotischen Symptome wurde vor Behandlungsbeginn und nach 4 Wochen Medikation mit Amisulprid die klinisch-relevanten Symptome der PANSS (P1 Wahnideen, P2 formale Denkstörungen, P3 Halluzinationen, N1 Affektverarmung, N4 passiv-apathischer Rückzug, N6 mangelnde Spontanität und Gesprächsfähigkeit, G5 Manieriertheit und Posieren, G9 ungewöhnliche Denkinhalte) erhoben (Andreasen et al, 2005). Patienten mit geringen klinisch-relevanten PANSS-Werten (Summe der 8 PANSS-Werte ≤ 17 Punkte) bei Aufnahme wurden aus der Analyse ausgeschlossen. Die statistische Analyse erfolgte mittels einer linearen Regression (unabhängige Variable: Metabolitkonzentration vor Beginn der Medikation, abhängige Variable: absolute Änderung der klinisch-relevanten PANSS-Symptome nach 4 Wochen Amisulprid, Kovariablen Alter, Geschlecht, Body-Mass-Index und Land des Studienzentrums).

Ergebnisse 153 Metabolite waren nach der Qualitätskontrolle auswertbar. Die klinisch-relevanten PANSS-Symptome sanken nach 4 Wochen Amisulprid um 7,8 ± 6,5 Punkte. Die Konzentration der Aminosäuren Alanin, Isoleucin, Leucin und Tyrosin vor Beginn der Medikation sagte in der linearen Regression die Abnahme der klinisch-relevanten PANSS-Symptome voraus. Die Änderung dieser Symptome korrelierte mit der Konzentrationsänderung von Isoleucin, Leucin, Methionin und Tyrosin. Die Korrelation mit Alanin erreichte das Signifikanzniveau nicht.

Zusammenfassung Eine höhere Konzentration der 4 Aminosäuren Tyrosin, Alanin, Isoleucin und Leucin vor Beginn der Amisulprid-Medikation geht mit einer stärkeren Minderung der klinisch-relevanten PANSS-Symptome nach 4 Wochen einher. Diese Minderung korreliert bei 3 (Leucin, Isoleucin, Tyrosin) der 4 Aminosäuren direkt mit einer Konzentrationsabnahme. Die Ergebnisse legen nahe, dass die Konzentration spezifischer Aminosäuren für den klinischen Verlauf relevant sind und eventuell als Prädiktor in Frage kommen.

P7 Therapeutic drug monitoring

P7.1 Investigation of metabolite to parent compound ratios of venlafaxine and risperidone in minors

Authors Fekete S, Scherf-Clavel M, Gerlach M, Romanos M, Deckert J, Menke A, Egberts K, Unterecker S
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
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Introduction The Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) venlafaxine (VEN) and the atypical antipsychotic risperidone (RIS) are widely used in the treatment of psychiatric patients. VEN and RIS serum concentrations and the respective active metabolite (desmethylvenlafaxin (DVEN) and 9-hydroxyrisperidone (9OHRIS)) as well as their metabolite to parent compound ratio (MPR) reflect CYP2D6 activity. In the literature, age-related differences in CYP2D6 activity are discussed. Until now, no MPRs of VEN and RIS in minors have been described yet. The aim of the present study was to analyze and describe the MPR of VEN and RIS in order to investigate the impact of age on the serum concentration of VEN and RIS and their active metabolites.

Methods Serum level determinations of VEN and RIS were performed at the Center of Mental Health of the University Hospital of Wuerzburg, Germany, of the Departments Child and Adolescents Psychiatry and Psychiatry, Psychosomatics and Psychotherapy during the years 2015–2019 were retrospectively assessed. Serum concentrations of patients with CYP2D6 influencing comedication and patients demonstrating non-adherence such as no detectable serum concentrations were excluded from analysis.

Results First preliminary results in minors (n = 27) showed mean VEN daily dose of 140 mg/d ± 73 mg/d with a mean VEN serum concentration of 58.8 ng/ml ± 60.3 ng/ml and DVEN serum concentration of 125.3 ng/ml ± 61.5 ng/ml. Mean RIS daily dose (n = 79) was 2.0 mg/d ± 1.3 mg/d with a mean RIS serum concentration of 3.3 ng/ml ± 5.8 ng/ml and mean 9OHRIS serum concentration of 12.9 ng/ml ± 12.3 ng/ml. MPR in minors of VEN (age 12–17 years) was 4.69 (SD 5.02, range 0.28–25.0), MPR of RIS (age 8–17 years) was 8.82 (SD 12.35, range 0–69).

Conclusion The results of MPR might be helpful for laboratory interpretation of serum concentrations during treatment with VEN or RIS in minors by identifying CYP2D6 abnormalities or pharmacokinetic interactions. The determination of serum concentrations and the knowledge of MPR might predict and avoid adverse drug reactions in children and adolescents.

P7.2 Patterns of clozapine pharmacokinetics in patient subgroups with different body mass index

Authors Kuzin M, Haen E, Bochon B, Endres K, Ridders F, Hiemke C, Gründer G, Paulzen M, Schoretsanitis G
Affiliation Universitätsklinik für Psychiatrie und Psychotherapie, Universitäre Psychiatrische Dienste Bern, Switzerland
DOI 10.1055/s-0039-3403047

Introduction Obesity is associated with changes in pharmacokinetics such as alterations in cytochrome P450 activity or regional blood flow, which may affect the disposition of several medications. However, the impact of obesity on the pharmacokinetics of antipsychotics are poorly understood. The objective of this study was to investigate the impact of body mass index (BMI) on clozapine pharmacokinetics using therapeutic drug monitoring (TDM).

Methods A large TDM dataset with clozapine plasma concentrations was analyzed. Three patient subgroups were compared: a control group (CLZ0, 30 kg/m^2 BMI 20 kg/m^2, n = 266), a group with high- (CLZOB, BMI ≥ 30 kg/m^2, n = 162) and a group with low-BMI (CLZLOW, < 20 kg/m^2, n = 29). Comparisons were performed with the non-parametric Kruskal Wallis and the Mann-Whitney-U test (M–W-U) with a significance level of 0.05. Percentages were compared using the Pearson chi-square test (χ^2) and effects of confounders were assessed using analysis of covariance (ANCOVA).

Results Group differences regarding demographic parameters were significant only for sex distribution with more females in CLZLOW and CLZOB compared to CLZ0 (p = 0.002 for χ^2). The pairwise comparisons showed significant

differences for clozapine plasma concentrations and plasma concentrations corrected for the daily dose (C/D) of CLZ in CLZOB compared to CLZ0 ($p = 0.014$ and $p = 0.007$ respectively, M–W-U). After applying ANCOVA to control for the effects of sex, only differences for C/D values remained significant ($p = 0.02$), being higher in the CLZOB.

Conclusion Complex pathways including lower clearance, increased deposits of CLZ in fat tissue as well as changes in hepatic enzyme activity could lead to increased bioavailability of CLZ in obese patients.

P7.3 Drug-drug interaction between hydroxybupropion and venlafaxine: A pharmacokinetic study on CYP2D6

Authors Theisen S, Scherf-Clavel M, Deckert J, Menke A, Unterecker S
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403048

Introduction Venlafaxine and bupropion are common antidepressant drugs. A combination of both from a pharmacodynamic point of view makes sense, even if the drug-interaction potential of bupropion (as a CYP2D6 inhibitor) on venlafaxine metabolism is well known. Until now, no study has evaluated the pharmacokinetic influence of hydroxybupropion serum concentration on the metabolite to parent compound ratio of venlafaxine, yet.

Methods We examined retrospectively the serum concentrations of venlafaxine, o-desmethylvenlafaxine and hydroxybupropion in 42 patients, which were determined at the therapeutic drug-monitoring laboratory of the Department of Psychiatry, Psychosomatics and Psychotherapy of the University Hospital of Würzburg. We defined the ratio of o-desmethylvenlafaxine to venlafaxine as a measure for the CYP2D6 inhibiting effect of hydroxybupropion.

Results In a Spearman's Rho correlation, only a trend of an association between hydroxybupropion serum concentration and ratio o-desmethylvenlafaxine to venlafaxine was found ($p = 0.067$).

Conclusions This preliminary data did not show a significant relationship between the serum concentration of hydroxybupropion and the metabolic ratio of venlafaxine.

P7.4 Therapeutic Drug Monotoring: CYP2C19 genetic polymorphism and major depression

Authors Adamovic I, Michaelis S, Streit F, Binder L, Degner D
Affiliation Universität Göttingen, Germany
DOI 10.1055/s-0039-3403049

Introduction Several CYP2C19 genetic polymorphisms are described to be associated with ultrarapid (UM) or poor drug metabolism (PM), inducing treatment resistance and/or adverse drug events, and might therefore be related to pharmacoresistant severe mental health disease.This case report present a female 61-year old in-patient suffered from drug resistant severe major depression (ICD-10: F33.2). Antidepressive drugs like mirtazapine, duloxetine, were changed before. We start a treatment with sertraline, low serum levels of sertraline in stady-state were monitored during psychiatric care.

Methods Clinical course documentation, therapeutic drug monitoring with low-serum level concentration of sertraline in stady-state and dose related, medical imaging (cMRT, EEG).

Results Low-serum level sertraline were < 4.88 µg/ml (10–150 therapeutic range), desmethylsertraline 22.8 µg/l, ratio N.N (1.7–3.4) after four weeks, and two weeks later sertraline were 5.4 µg/l, desmethylsertraline 26.8, ratio 4.96 (1.7–3.4). In the clinical documentation patient suffered from resistent-symptoms of major depression like anhedonia and apathy.
Gene duplication associated with UM has been found at CYP2C19 (duplet of allels CYP2C19*17/*17).

Conclusion In this case report we demonstrate consequent therapeutic drug monitoring as an option to identify high-risk patients with genetic polymorphisms. Nevertheless, knowledge of individual metabolism and in particular CYP2C19 genotyping should be considered for clinical workup and treatment adjustment in resistant patients in psychiatry and might permit better treatment outcome, increased treatment adherence and diminished adverse drug events.

P8 Various

P8.1 Support vector machine? – not only for MRI-images

Authors Vasilevska V, Schlaaf K, Dobrowolny H, Meyer-Lotz G, Bernstein HG, Frodl T, Steiner J
Affiliation Universitätsklinik Magdeburg, Germany
DOI 10.1055/s-0039-3403050

Introduction Nowadays, the plethora of scientific data produced way exceeds the human's brain capacity, so automatic recognition tools may be used to avoid information loss and speed up data processing. Techniques like machine learning or deep learning are common in MRI-diagnostics, but their algorithms are also able to simplify the analysis of microscopic pictures.

Methods Using mentioned principle, Support Vector Machine (SVM) was developed as a part of the project "Occurrence and Spreading of TMEM-119-expriming Microglia in Schizophrenia and Affective Disorders". The tool is able to differentiate between microglia (TMEM-119-positive) and capillaries (Factor-VIII-positive), which can be used to study interactions between microglia and blood-brain barrier and measure distances between microglia and other microscopic objects.

Results The SVM algorithm uses four parameters, which accurately describe the morphology of microglia cells, including it's ramified and amoeboid form, for differing objects. These parameters can be calculated manually or received by image recognition and analysis tools like MatLab (3DMorph (York et al., 2014)) or Python.

Conclusion The performance of the tool was trained on 5000 samples of human microglial cells and 2000 samples of human brain capillaries. The sensitivity of recognition in test data set was 85 % and 82 % for microglia and capillary respectively, the specificity was 78 % for both objects. The SVM operation was improved by increasing the variety of different microglia staining, inclusive HLA-DR-staining and TMEM-119-staining and by including data from rat brain tissue.

P8.2 ADHS und Oligoantigene Diät – Verhaltensreaktionen auf unverträgliche Lebensmittel vor und nach der Diät

Authors Clement HW, Beiner L, Yorgidis E, Clement C, Schneider-Momm K, Schulz E, Fleichhaker C
Affiliation Universitätsklinikum Freiburg, Germany
DOI 10.1055/s-0039-3403051

Einführung Der Einfluss der Nahrung auf das Verhalten von Kindern mit ADHS wird bereits im frühen 20. Jahrhundert beschrieben. Eine Metaanalyse von Sonuga-Barke et al. (2013) vergleicht nicht-pharmakologische Interventionen bei ADHS bezüglich ihrer Wirksamkeit. Dabei wurden die Möglichkeiten der Ernährungsintervention, einschließlich restriktiver Eliminationsdiäten kritisch diskutiert. Ergebnisse aus der niederländischen Arbeitsgruppe von Buitelaar stechen hier durch besonders hohe Effektstärken hervor. Die Ernährungsumstellung aufgrund individueller Nahrungsunverträglichkeiten führte bei mehr als ⅔ der Patienten zur signifikanten Verbesserung von ADHS. Die vorliegende Studie prüft die Machbarkeit der Ernährungsintervention im ambulanten setting unter teilweise verblindeten Bedingungen.

Methoden Vierundzwanzig Kinder mit ADHS-Diagnose (18 m/6 f; Alter 7–14) gemäß ICD-10 wurden vor und nach vierwöchiger oligoantigener Diät getestet. Die ADHS Symptomatik wurde über den ADHD-Rating scale Elternbericht (ARS) und über die tägliche Beurteilung durch Conners Kurzfragebögen (CK) von Eltern und Lehrer bewertet. Die ARS Video-Befragungen wurden pseudonymisiert und verblindet bzw. unverblindet ausgewertet.

Ergebnisse Der ARS verbesserte sich unter Diät insgesamt auf etwa 44 % des Ausgangswerts und auch in den Subskalen (Hyperaktivität und Unaufmerksamkeit/Impulsivität) signifikant. Die Effekte der unverträglichen Nahrungskomponenten wurden mittels CK erfasst. Der CK zeigte einen Zusammenhang zwischen Nahrungsauswahl und ADHS nach, aber nicht vor der oligoantigenen Diät. Von 24 Patienten beendeten 22 die Diät, Bei 16 Patienten konnten in der Wiedereinführungsphase die Lebensmittel-Unverträglichkei-

ten identifiziert werden. Diese zeigten deutliche Verhaltensänderungen nach der Diät, aber nicht vor der Diät. Häufigste Auslöser waren Milch- und Milchprodukte.

Zusammenfassung Oligoantigene Diät ist ein valides Instrument zur Identifizierung individueller Nahrungsmittelunverträglichkeiten bei ADHS. Bei Einhaltung individueller Ernährungsempfehlungen können bei ⅔ der Kinder mit ADHS die Symptome nachhaltig verbessert werden.

P8.3 Differentiation of disease-specific induced pluripotent stem cells into a blood-brain barrier system analyzing the role of APOE4 in Alzheimer's disease

Authors Hartmann C, Haferkamp U, Gerhart A, Pfeifer J, Hartmann A, Giegling I, Schuldt B, Müller F-J, Pless O, Neuhaus W, Appelt-Menzel A, Jung M, Rujescu D
Affiliation Universität Halle-Wittenberg, Halle (Saale), Germany
DOI 10.1055/s-0039-3403052

Introduction Accumulation of amyloid-β (Aβ) peptides is one pathological hallmark of late-onset Alzheimer's disease (LOAD), the most common type of dementia. Dysregulation and later on breakdown of the blood-brain barrier (BBB) contributes and worsens the course of the disease. The ε4 allele of apolipoprotein E (APOE) was identified by GWAS as the most associated genetic risk factor for developing LOAD. APOE participates in several metabolic pathways including lipid transport, Aβ aggregation, and Aβ clearance. However, the molecular and cellular signaling pathways regulated by APOE4 are currently poorly understood. Therefore, we use patient-derived induced pluripotent stem cells (iPSCs) for the differentiation into BBB cells studying APOE, and in particular its role in AD disease mechanisms.

Methods First, we determined the APOE status of our AD patients and healthy matched controls. Secondly, B-lymphoblastoid cell lines of patients carrying the APOE4 allele and chosen controls with homozygous APOE3 alleles were used for reprogramming of iPSCs with episomal vectors. Then, subsequent to a successful verification of pluripotency and detailed characterization, the generated iPSCs lines were differentiated into cells of the BBB system. Expression levels of cell specific markers and barrier functionality were analyzed.

Results Following the generation of AD-specific and matched control iPSCs pluripotency was verified, inter alia, by alkaline phosphatase staining and a successful passed PluriTest microarray analysis. Then, characterized iPSCs were differentiated into brain microvascular endothelial-like cells and astrocytes. Existence of cell- and BBB-specific markers including TJP1, GLUT1 or GFAP, and GLAST confirmed efficient differentiation. Low volume quantitative RT-PCR analysis revealed significant differences in the expression level of BBB specific markers in AD-specific cells compared to healthy controls. Barrier functionality was demonstrated by transendothelial electrical resistance values > 1000 $\Omega^{*}cm^{2}$ and hindered permeability of the small molecule sodium fluorescein for both AD patients and matching controls. Co-culture with astrocytes strengthens barrier function for matched controls but not for LOAD-specific cells.

Conclusion Overall, we established a patient-specific BBB model suitable to research genetic risk variants (e.g. APOE4) and investigate underlying AD disease mechanisms. Co-culture with astrocytes seems to induce the observed pathogenic phenotype of the LOAD-specific BBB model compared to the control BBB model.

P8.4 Vitamin D level and depression in psychogeriatric patients

Authors Zech L, Herr A, Deckert J, Unterecker S
Affiliation Universitätsklinikum Würzburg, Zentrum für Psychische Gesundheit, Germany
DOI 10.1055/s-0039-3403053

Introduction Depression is a common psychiatric disorder among elderly people that decreases the quality of life and increases morbidity and mortality. The present study was conducted to evaluate the association between depressive syndromes and vitamin D level.

Methods 140 patients of a psychogeriatric day-care unit were included. GDS- and HDRS-Scores were assessed at the beginning and end of treatment. Vitamin D levels were measured at the beginning of treatment.

Results There was no association between the severity of depression and the level of vitamin D at the beginning of the treatment. Patients with a higher level of vitamin D, however showed a stronger decline of depressive symptoms measured by the GDS.

Conclusion According to the findings of this study there is no association between vitamin D-level and severity of depression. Nevertheless, Further investigation is needed to evaluate the neurophysiological association between vitamin D level and depressive symptoms.

P8.5 Untersuchungen zur kardialautonomen Dysfunktion als Endophänotyp der Schizophrenie

Author Refisch A
Affiliation Universitätsklinikum Jena, Germany
DOI 10.1055/s-0039-3403054

Einführung Kardiovaskuläre Erkrankungen tragen maßgeblich zu einer verkürzten Lebenserwartung von 15 Jahren bei Schizophrenie-Patienten bei. Ein offensichtlicher Zusammenhang besteht mit reduzierter kardial vagaler Modulation, die durch eine verminderte Herzratenvariabilität (HRV) charakterisiert ist. Diese Merkmale finden sich bei unmedizierten Ersterkrankten, chronischen Verlaufsformen und in milderer Ausprägung bei gesunden Erstgradverwandten, so dass alle wesentlichen Kriterien eines Endophänotpys erfüllt sind.

Methoden Neben der Genotypisierung von Genen innerhalb Schizophrenie-assoziierter Loci, die auch in die kardiale Funktion involviert sind, erfolgte bei allen eingeschlossenen Probanden (N = 93 unmedizierte Patienten, N = 96 Kontrollen) ein 30-minütiges autonomes Assessment. Patienten und Kontrollen wurden entsprechend ihres Genotyps in Risikogruppen eingeteilt und auf Unterschiede in den erhobenen CADF-Parametern untersucht.

Ergebnisse Patienten mit Risikovarianten in rs16902086 (HCN1, „funny channel"), rs4725982 (KCNH2, LQT2), rs8191992 + rs73158705 (CHRM2, muscarinerger Ach-Rezeptor), rs8042374 (CHRNA3, nikotinerger Ach-Rezeptor), rs9851724 (SCN5A-SCN10A, LQT3) zeigten signifikant erhöhte Herzfrequenzen und eine verminderte vagale Modulation im Vergleich zu Patienten ohne Risikoallel. Der Effekt war bei homozygoten Risikoallelträgern stärker.

Zusammenfassung Risikoallelträger in den selektierten SNPs sind hinsichtlich einer verminderten HRV prädisponiert, was mit einem erhöhten kardiovaskulären Risiko assoziiert ist. Gene in unmittelbarer Nähe tragen mgl. zu den HRV-Veränderungen der Schizophrenie-Patienten bei. Untersuchungen zur HRV sind eine reliable Möglichkeit für weiterführende hypothesengeleitete Untersuchungen zu etablierten Schizophrenie-Risikofaktoren. Untersuchungen zur Genetik der HRV können weitere Risikofaktoren aufdecken, die nicht im Fokus der Schizophrenieforschung stehen. Die hohe kardiale Sterblichkeit unter Schizophrenen erfordert die Identifizierung prädisponierende Marker, hierzu können weiterführende genetische Untersuchungen zur HRV einen elementaren Beitrag leisten.

P8.6 Der Einfluss verschiedener transkranieller Wechsel- und Gleichstromstimulationen auf die Leistung des visuellen Arbeitsgedächtnisses

Author Rauh J
Affiliation UKE Hamburg-Eppendorf, Germany
DOI 10.1055/s-0039-3403055

Einführung Das menschliche Arbeitsgedächtnis gehört zu den wichtigsten kognitiven Funktionen unseres Alltags. Defizite desselbigen werden häufig bei neuropsychiatrischen Erkrankungen wie der Schizophrenie beobachtet. Daher ist das Arbeitsgedächtnis ein interessantes Ziel für nicht-invasive Hirnstimulationsmethoden wie der transkraniellen elektrischen Stimulation. Während EEG-Studien eine Beteiligung der oszillatorischen Aktivität im Theta-Frequenzband bei Arbeitsgedächtnisprozessen gefunden haben, konnte mithilfe von fMRT-Studien hierbei die Aktivierung eines frontoparietalen Netzwerkes, u. a. des dorsalen präfrontalen Kortex (DLPFC) sowie des posterioren parietalen Kortex (PPC), gezeigt werden. Diese Arbeit vergleicht vorrangig den Einfluss

unterschiedlicher transkranieller elektrischer Stimulationsarten bezüglich Stromart (Wechsel- vs. Gleichstrom) oder Stimulationsort (frontal vs. parietal) auf die Leistung des visuellen Arbeitsgedächtnisses.

Methoden Es wurde eine „delayed-match-to-sample (DMTS)"-Aufgabe verwendet, bei der abstrakte, nicht-natürliche visuelle Stimuli mit niedriger (2 Objekte) oder hoher (4 Objekte) Arbeitsgedächtnisladung präsentiert werden und abgerufen werden müssen. 16 gesunden Probanden wurden an jeweils 4 Tagen währenddessen mit verschiedenen Setups stimuliert: Einer Wechselstromstimulation (tACS) mit einer Frequenz von 5 Hz (Thetaband) über dem linken DLPFC (Anode über EEG-Elektrodenposition F3) (1) oder über dem rechten posterioren Parietalkortex (Anode über P4) (2), einer Gleichstromstimulation (tDCS) über dem linken DLPFC (3) sowie einer Scheinstimulation (sham) (4). Bei allen Konfigurationen wurde ein high-density (HD) Setup mit 3-zu-1 Elektroden (Kathoden zu Anoden) und eine Stimulationsstärke von 1,5 mA (Spitze-Spitze bei Wechselstrom) verwendet.

Ergebnisse In der ANOVA zeigte sich ein signifikanter Effekt (Stimulationsart × Ladung) bei der Arbeitsgedächtnisleistung. Dies wurde durch eine signifikante Verbesserung der Arbeitsgedächtnisleistung bei hoher Ladung während einer Wechselstromstimulation über dem linken DLPFC im Vergleich zur Scheinstimulation qualifiziert.

Zusammenfassung Eine fokussierte HD-Wechselstromstimulation mit einer Frequenz von 5 Hz über dem linken DLPFC kann die Arbeitsgedächtnisleistung verbessern. Möglicherweise könnten auch Patienten, die aufgrund von neuropsychiatrischen Erkrankungen wie der Schizophrenie unter Arbeitsgedächtnisdefiziten leiden, von dieser Hirnstimulationsart profitieren.

P8.7 LAB–QA2GO: A free, easy-to-use toolbox for the quality assessment of magnetic resonance imaging data

Author Vogelbacher C
Affiliation Universität Marburg, Germany
DOI 10.1055/s-0039-3403056

Introduction In general, modern magnetic resonance imaging (MRI) systems show overall high technical quality, but image characteristics (e.g. signal-to-noise ratio, SNR) may change over the time course of a study. To monitor these changes a quality assurance (QA) protocol is necessary. In this project we present a light-weighted virtual machine (VM), called LAB–QA2GO, which provides scripts for fully automated QA analyses of phantom and human datasets and needs minimal setup and maintenance time. Due to the virtualization, LAB–QA2GO is already fully configured and easy to integrate in most hardware environments. Only few configuration steps have to be performed to adapt the QA pipeline to the own data. Additionally, we developed a user-friendly web interface to make the software easily accessible for inexperienced users. Nevertheless, everything (i.e. configuration, results and documentation) remains inside a portable VM. The usability and scope of QA is illustrated within a dataset that followed the QA protocol of our lab.

Methods We chose NeuroDebian as operating system for the VM as it provides a large collection of neuroscience software packages and is highly distributed within the neuroimaging community. To keep the machine small, i.e. the space required for the virtual drive, we included only packages necessary for the QA routines in the initial setup. To ensure transparency and reproducibility we decided to use only open source software. Users are also free to add packages according to their needs. In its present implementation, LAB–QA2GO provides two different types of QA analyses, a (gel and ACR) phantom and a (structural and functional) human data QA pipeline. LAB–QA2GO can receive MRI data either automatically ("network approach") or manually ("stand-alone approach"). To illustrate usability and the functions we developed a QA protocol for our lab which monitored the temporal stability of the MR scanner. Therefore, measurements of the gel phantom were performed.

Results The results of the analysis are presented on the integrated web based platform. The user can easily check the results from every workstation (if the network approach is chosen). We show an exemplary file for the analysis of gel phantom data. Furthermore, an overview page for each analysis type is generated. On this overview page the calculated parameters of all measurements of one data type are presented as a graph. An individual acceptance range can be defined using the configuration page, which is visible in the graph.

Conclusion LAB–QA2GO is a light-weighted tool to perform automated QA analysis. In general MR phantom QA protocols focus on the stability of the MR scanner and not the stability of the MR data, like MRIQC. After receiving the MRI data the VM performs the corresponding analysis method automatically. All results are presented in an easy readable and easy-to-interpret web based format. The simple access via web-browser guarantees a user friendly usage without any specific IT knowledge as well as minimalistic maintenance work. Results are presented in both tabular and graphical form. LAB–QA2GO can be used to assess the quality of MRI data sets acquired in neuroimaging studies, to monitor MRI scanners in multicenter imaging studies or to assess the long-term performance of MRI scanners.

P8.8 Electroconvulsive therapy induces changes in immune cell ratios

Author Maier H
Affiliation Medizinische Hochschule Hannover, Germany
DOI 10.1055/s-0039-3403057

Introduction Electroconvulsive therapy (ECT) is one of the most effective treatment options for pharmacotherapy resistant depressed patients. Alterations and the activation of the immune system during ECT were previously suggested. The underlying mechanism still remains elusive. Our hypothesis was that ECT modulates the immune system and influences the number and activity of certain immune cell subtypes. Additionally, we suggested that both effects are related with the clinical outcome.

Methods 21 inpatients with pharmacoresistant major depressive disorder (MDD) receiving ECT were included in the study. Blood was drawn directly before and 15 minutes after the first and the last ECT. Isolation of peripheral blood mononuclear cells (PBMC) was performed and defined populations of immune cells were analyzed by means of flow cytometry (FACS). Response was defined as a ≥ 50 % reduction and remission as a MADRS score below 10.

Results ECT remitters (n = 10) compared to non-remitters (n = 11) showed a significant difference in their relative proportion of CD56highCD16-/dim and CD56dimCD16+ natural killer cells (remitters = 0.064 ± 0.005), non-remitters = 0.047 (± 0.005), $p < 0.05$; linear mixed models). CD56highCD16-/dim and CD56dimCD16+ natural killer cells were also altered after a single single ECT session (before = 0.066 ± 0.005), after = 0.045 (± 0.005), $p < 0.001$; linear mixed models). Furthermore, the subtypes showed a correlation with long-term BDI-II rating changes ($r2 = 0.459$, $\beta = -0.726$, $p < 0.05$; linear regression analysis) and ECT parameters (maximum sustained coherence: $r2 = 0.389$, $\beta = -0.656$, $p < 0.001$; linear regression analysis).

Conclusion In conclusion, natural killer cell cytotoxicity might be involved in the acute effect of ECT and its clinical outcome.

P8.9 HPA-axis and insulin/Glucose levels during a course of electroconvulsive therapy

Author Maier H
Affiliation Medizinische Hochschule Hannover, Germany
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Introduction Electroconvulsive therapy (ECT) is one of the most effective treatment options for therapy resistant psychiatric disorders. Patients suffering from obesity seem to respond well to ECT and even weight loss was reported. In nondiabetic patients, an increase in blood sugar of about 10 % as well as an increase of insulin after one ECT treatment was reported. Chronic ECT was shown to be related with a decline in insulin levels in responders' only. The underlying mechanism is unknown and could be related with seizure-induced hormone secretion such as catecholamines or cortisol 4. The aim of our study was to assess cortisol, metanephrine, normetanephrine, glucose and insulin during a course of ECT in remitters and non-remitters.

Methods 12 men and 20 women receiving ECT were included in our study. Outcome analysis was performed for patients with pharmacoresistant major depressive disorder (n = 28). Remission was defined as a MARDS score below 10. Blood was withdrawn directly before and 15 minutes after the first and directly before the last ECT. Glucose levels were assessed using enzymatic reference method with hexokinase. Cortisol and insulin levels were assessed using electrochemiluminescence immunoassay (ECLIA). Metanephrine and normetanephrine were measured using HPLC.

Results At baseline, there were no significant differences between remitters and non-remitters to ECT. In remitters, normetanephrine levels differed significantly compared to non-remitters ($p = 0.049$). 15 minutes after ECT, glucose, cortisol and normetanephrine increased significantly, when compared to baseline (glucose: $p < 0.001$; cortisol: $p < 0.001$ normetanephrine: $p = 0.018$), but there was no chronic effect for glucose and normetanephrine (glucose: $p = 0.902$; normetanephrine: $p = 0.998$) Cortisol showed a significant difference between 15 minutes after the first ECT and before the last ECT ($p = 0.002$).15 minutes after the first ECT, there was a trend towards higher glucose and insulin levels in remitters ($n = 13$) to ECT compared to non-remitters ($n = 19$) (glucose: $p = 0.201$; insulin $p = 0.118$). Metanephrine did not differ between remitters and non-remitters (before and after first ECT $p = 0.291$). Correlation analysis revealed a positive correlation between duration of episode and cortisol level ($r = 0.639$; $p = 0.006$). Baseline Beck-Depressions-Inventar-II (BDI-II) was positively correlated with normetanephrine levels ($r = 0.389$; $p = 0.037$) and CRP ($r = 0.402$; $p = 0.031$) and we found a positive correlation between normetanephrine and baseline heart rate ($r = 0.506$; $p = 0.003$).

Conclusion Previous reports showed a reduction in urinary (nor-)metanephrine secretion in ECT patients. Our results show the acute effect in plasma rather than the effect during 24 hrs. The findings concerning glucose and insulin go in line with previous reports, even though we could not find significant differences but trends concerning response and glucose/insulin. It is possible, that the release of insulin reflects neural activation during ECT 4, since the pancreas underlies neural control of the right vagal nerve.

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