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ABSTRACTS

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Abstract Type:
Abstract in Keynote Lecture

Abstract Number:
27

Author:
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Abstract Title:
Fetal programming of brain development—role of intrauterine stress and stress biology in susceptibility for psychopathology

Abstract Text:
The origins of alterations in brain anatomy and connectivity, which may underlie cognitive impairment and mental illness, can be traced back to the fetal period of life when the developing embryo/fetus responds to suboptimal conditions during critical periods of brain development ("Fetal Programming"). Data from prospective longitudinal studies of pregnant mothers and their children will be presented that provide evidence for maternal gestational stress to be associated with alterations in their offsprings' brain anatomy and connectivity, which may underlie the higher prevalence of cognitive impairment and mental health problems in these children. Evidence is provided in support of alterations in maternal-placental-fetal endocrine an immune biology being likely biological mediators that provide cues about these maternal conditions to the fetus with the potential of altering the developmental trajectory of its brain. Furthermore, intrauterine pathways underlying the transmission of maternal preconceptional stress (i.e., childhood maltreatment) will be discussed. Advances in theory and methodology now afford an unprecedented opportunity to gain new and valuable insights into the developmental origins of human brain disorders with the aim to develop targeted interventions to prevent these.

Abstract Type:
Abstract in Keynote Lecture

Abstract Number:
174

Author:
Paz, Rony
Israel

Abstract Title:
Learning and generalization in primate networks: from behavioral advantage to psychopathology

Abstract Text:
I will describe several paradigms of mal-adaptive learning that can lead to anxiety, and point to the underlying neural circuits. These models will span extinction and spontaneous recovery, over-generalization and perceptual discrimination, and exploration–exploitation in aversive environments. The neural findings show that interactions between the amygdala and the prefrontal cortex underlie these forms of learning, and a slight imbalance can lead to anxiety. This will be demonstrated in single-neuron recordings in behaving primates and imaging in humans. The results suggest a framework in which several behaviors underlie the shift from normal adaptive learning to psychopathologies as in anxiety disorders.

Abstract Type:
Abstract in Satellite Symposium

Abstract Number:
178

Author:
Walter, Martin
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Abstract Title:
Stress modification as exemplified in irritated bowel syndrome

Abstract Text:
Objective: Neurexan®, a natural pharmaceutical product, is composed of passionflower, oats, coffee and zinc valerianate. It has been investigated in acute stressed subjects. Stress initiates changes in functional connectivity (FC) between amygdala and cortical regions. The functional integrity can be assessed via amygdala-centered

resting-state (rs) FC. Amygdala is involved in developing fear and emotions and its reactivity to negative stimuli associates with stress regulation. It can be assessed with the Hariri paradigm. Previous studies reported associations between ongoing variability in Autonomous Nervous System (ANS) tone measured by heart rate variability (HRV) and stress-induced changes in dACC and amygdala FC. In this study we investigated if Neurexan® affects emotional brain response to stress.

Methods: Thirty-nine healthy male subjects participated in a double-blind, randomized, placebo-controlled, within-subject cross-over fMRI study assessing Neurexan® effects at 3 Tesla. In each session, an 11 min rs-measurement was performed at baseline, after single dose of Neurexan® or placebo and after exposure to psychosocial stress. The emotional Hariri paradigm was measured after intake of verum or placebo. HRV was recorded continuously during the sessions. Data were preprocessed and analyzed in SPM12 and DPABI.

Results: Significant effect of Neurexan® was found on rs-FC between left centromedial amygdala and cortical regions. In the Hariri task, paired *t* test showed a drug effect in left amygdala, with stronger activations in placebo than Neurexan® condition. Comparing Neurexan® and placebo groups, Neurexan® improved variability in ANS tone in both conditions, prior and after psychosocial stress, compared to baseline.

Conclusion: We saw a beneficial effect of Neurexan® on stress-induced brain function. Neurexan® influenced rs-FC of the centromedial amygdala towards cortical regions involved in emotion regulation and reduced the emotional brain response to negative stimuli. The variability in ANS tone during stress task was also improved by Neurexan®.

Policy of full disclosure: This study was funded by Biologische Heilmittel Heel GmbH.

Abstract Type:
Abstract in Satellite Symposium

Abstract Number:
116

Author:
Schedlowski, Manfred
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Abstract Title:
Psychological Stress, Neuroendocrine Factors and Immunity

Abstract Text:
In the past decades, the interaction of cognitive, emotional, behavioral, neuroendocrine and immunological aspects of acute and chronic psychological stress have been analyzed in more details. Of particular interest is the understanding of how stress exposure is affecting health and the development and progression of immune-related diseases. Data from experimental animals, healthy human subjects and patients demonstrate that acute psychological stress is transiently elevating immune functions reflected by increased circulation of lymphocyte subpopulation and activity. These changes are mediated via activation of sympathetic nervous system (SNS) and the release of adrenaline and noradrenaline. In contrast, chronic psychological stress is suppressing humoral and cellular immune parameters, which is mediated via SNS and the activity of the Hypothalamus–Pituitary–Adrenal (HPA) axis and the release of cortisol. Depending on the individual capacity to cope with stress exposure, psychological stress effects are manifold, resulting in psychological disorders such as anxiety, depression, sleep disorders or somatic consequences, e.g. increased vulnerability to infections due to stress-induced suppression immune functions. Effective psychological, physical or pharmacological interventions are available to reduce stress and to prevent negative stress-induced consequences on psychological well-being and physical health.

Abstract Type:
Abstract in Satellite Symposium

Abstract Number:
118

Author:
Mönnikes, Hubert
Martin-Luther-Krankenhaus, Berlin, Germany

Abstract Title:
Stress—a key factor in the pathogenesis and clinical management of irritable bowel syndrome

Abstract Text:
Irritable bowel syndrome (IBS) is the most common gastrointestinal (GI) disorder in humans and characterized by chronic or recurrent pain associated with altered bowel motility. It significantly impairs quality of life, can be disabling and constitutes a major social and economic burden. IBS etiology is most likely multi-factorial involving biological, psychological and social factors.

Short- and long-term exposure to stress results in alterations of the brain–gut interaction (brain–gut and gut–brain axis). The major effects include alterations in GI motility and secretion, increase in visceral perception and intestinal permeability, negative effects on mucosal regeneration and blood flow, and alterations of intestinal microbiota. Mucosal mast cells (MC) translate stress signals mediated via brain–gut pathways into the release of various neurotransmitters, mediators and proinflammatory cytokines affecting the gastrointestinal physiology.

Clinical and experimental evidence suggests that IBS pathogenesis is a combination of irritable bowel and irritable brain, and psychological stress is an important factor for the development of IBS. In patients, alterations in GI sensitivity (due to visceral hyperalgesia and hypervigilance), motility, secretion, permeability and microbiota have been observed, which can be due by stress effects on neuro-endocrine-immune pathways along the gut–brain and microbiota–gut–brain axis. Furthermore, many patients also experience comorbid behavioral disorders, such as anxiety or depression.

IBS management is based on a multifactorial approach including pharmacotherapy, which targets predominant symptoms, psychological and behavioral intervention, dietary treatment and a positive patient-physician relationship. Since IBS is a stress-sensitive disorder, treatment should encompass managing stress and stress-induced responses. This includes non-pharmacological approaches, like stress management and coping strategies, as well as pharmacological treatment which targets on stress-related alterations.

Abstract Type:
Abstract in Symposium

Abstract Number:
104

Author:
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University of Münster, Münster, Germany

Co-Authors:
Blaesse, Peter; Pape, Hans-Christian; Jüngling, Kay

Abstract Title:
Opioids and receptors in synaptic networks of the amygdala

Abstract Text:
The amygdala is composed of a number of subnuclei with differential functional connectivity. In particular, the centromedial amygdala (CeM) mediates conditioned fear behavior via projections to brain stem and hypothalamic nuclei. CeM neuronal activity is further influenced by excitatory input from the basal nucleus of the amygdala (BA) and inhibitory projections from the centrolateral nucleus of the amygdala (CeL), among others. Interestingly, both CeL and BA receive afferent projections from the dorsal midline thalamus (dMT), a structure that has been implicated in mediating fear memory retrieval. The dense expression of μ-opioid receptors (MORs) in the dMT and its innervation by a vast array of neuropeptidergic fibers, containing e.g. enkephalin, suggest a neuromodulatory role for the μ-opioid system in the dMT and associated synaptic networks. In order to electrophysiologically characterize dMT-BA and dMT-CeL synaptic connections and to investigate how they are functionally modulated by MORs, we performed whole-cell patch clamp recordings in acute brain slices of mice in combination with retrograde tracing or optogenetics. We found that MORs mediate the hyperpolarization of both BA-projecting and CeL-projecting dMT neurons. In addition, we showed that both BA and CeL neurons receive excitatory input from dMT neurons and generate fast postsynaptic responses (eEPSCs). The activation of MORs attenuated transmission at both dMT-BA and dMT-CeL synapses. Interestingly, however, dMT-CeL and dMT-BA connections differed with regards to apparent synaptic connectivity, eEPSC amplitude, and modulatory influence of the MOR system. Furthermore, the activation of MORs reduced dMT-driven feedforward excitation of CeM neurons. Together, these results suggest that MORs are important negative modulators of synaptic transmission between the dMT and the amygdala, a circuit that is critically involved in the expression of emotional behaviors such as fear.

Abstract Type:
Abstract in Symposium

Abstract Number:
103

Author:
Richter, Helene
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Abstract Title:
Never replicate a successful experiment? Facing the reproducibility crisis in the life sciences

Abstract Text:
The scientific literature is full of publications discussing poor reproducibility of findings from animal experiments as well as failures to translate results from preclinical animal studies to clinical trials in humans. Critics even go so far as to talk about a "reproducibility crisis" in the life sciences, a novel headword that increasingly finds its way in numerous high-impact journals. So far, poor reproducibility and translational failures have mostly been discussed to result from biased animal data, methodological pitfalls, current publication ethics and animal welfare constraints. More recently, the concept of standardisation has also been identified as a potential source of these problems. By reducing within-experiment variation, rigorous standardisation regimes limit the inference to the specific experimental conditions. In this way, however, individual phenotypic plasticity is largely neglected, resulting in statistical significant, but irrelevant findings that are not reproducible under slightly different experimental conditions. By contrast, systematic heterogenisation has been proposed as a concept to improve representativeness of study populations, contributing to improved external validity and hence improved reproducibility. While some first heterogenisation studies are indeed very promising, it is still not clear how this approach can be transferred into practice in a logistically feasible and effective way. Thus, further research is needed to explore different heterogenisation strategies as well as alternative routes towards better reproducibility in animal experimentation.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Abstract in Symposium

Abstract Number:
105

Author:
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Co-Authors:
Lindström, Björn; Yi, Jonathan; Petrovic, Predrag; Olsson, Andreas

Abstract Title:
Neuropharmacological regulation of social fear learning

Abstract Text:
Objective: Many of our fearful expectations are shaped through observation of traumatic experiences in others. Yet, it is unknown if observational and direct fear learning engages similar neural networks. Moreover, the neuropharmacology regulating observational fear learning is unknown.
Methods: Here, we (1) formally compared neural responses during observational and direct fear conditioning and (2) tested if an opioidergic circuitry is regulating social threat learning through observation in humans.
Results: First, we could show a cross-modal (self/other) aversive learning network, centered on the amygdala, the anterior insula (AI), and the anterior cingulate cortex (ACC). Crucially, the information flow within this network differed between social and direct fear learning, as revealed by Dynamic causal modeling.

Second, we found that the blockade of opioid receptors enhanced observational learning through activity within the amygdala, midline thalamus and the PAG. In particular, temporal dynamics in PAG coding the observed aversive outcomes to other (observational US) predicted anticipatory responses to learned threat cues (CS), and were functionally connected to the superior temporal sulcus. Moreover, blockade of opioid receptors enhanced amygdala responses towards the observational US that correlated with the enhanced expression of threat responses 72 h after learning. A supervised machine-learning algorithm successfully classified individual endogenous opioid receptor function during the expression of conditioned threats with a kernel restricted to brain regions that were responsive to the observational US.

Conclusion: Our results reveal an overlapping aversive learning system engaged through direct, as well as observational fear learning. Moreover, we found that an opioidergic circuit codes the observed aversive outcomes to others into threat responses and long-term memory in the observer.

Given that vicarious experiences have been added as a diagnostic criterion for PTSD, but neuropharmacological studies of socially transmitted fear are missing, this provides a valuable starting point for neuropharmacological research on social fear learning.

Category/Topic:
4 Animal models of fear and anxiety

Abstract Type:
Abstract in Symposium

Abstract Number:
69

Author:
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Co-Authors:
Durairaja, Archana; König, Christian; Schleyer, Michael; Thöner, Juliane; Voigt, Anne; Yarali, Ayse

Abstract Title:
Timing-dependent valence reversal in flies, rodents and man

Abstract Text:
Objective: There two aspects worth learning about biologically salient, reinforcing events: What makes them happen? What makes them cease?
Methods: We use a combination of behavioral experiments and optogenetics to study thee learning processes.
Results: Typically in both animals and man, the established memories, respectively related to reinforcement onset and reinforcement offset, have opposite valence (reviewed in Gerber et al. 2014). For example, if subjects are trained such that first cue is presented and then an electric shock, learned avoidance of the odor is observed. If, however, timing is reversed such that shock is first and the cue is presented only upon the relieving cessation of shock, learned approach of the cue is observed. Such timing-dependent valence reversal is likewise observed in the appetitive domain (e.g. Hellstern et al. 1998): Cue-reward training establishes learned approach to the odor, while reward-cue training establishes learned avoidance.
Conclusion: Our contribution will briefly present the general principles of timing-dependent valence reversal in flies, rodents, and man, and will be specifically concerned with the sufficiency of optogenetic activation of single, identified dopaminergic neurons in this process.

Abstract Type:
Abstract in Symposium

Abstract Number:
44

Author:
Nievergelt, Caroline
USA

Co-Author:
Workgroup, PGC PTSD

Abstract Title:
Update on PGC-PTSD

Abstract Text:
Objectives: Development of post-traumatic stress disorder (PTSD) is influenced by both genetic and environmental factors. The Psychiatric Genomics Consortium (PGC) PTSD group has now accumulated over 50 multi-ethnic studies with genomic data from over 20,000 PTSD cases and 50,000 trauma-exposed controls. Here we present our findings from genome-wide association studies (GWAS) across ancestry groups and gender and present a genetic characterization of PTSD including SNP-based heritability analyses and genetic correlation across psychiatric disorders and other phenotypes/traits of interest.
Methods: Genotypes in the PGC PTSD freeze 2 were processed with the PGC-pipeline and GWAS were performed within European, African American, and Latino ancestry groups and meta-analyzed across studies and ancestries. Stratified analyses for gender were also conducted. Standard methods were used to estimate SNP-based heritability and genetic correlations with other psychiatric disorders and traits in European-ancestry subsets.
Results: Stratified analyses showed genome-wide significant hits in the European and African American data, and some evidence for association in the smaller Latino ancestry group. Trans-ethnic analyses did not result in genome-wide significant hits. We found that PTSD liability is significantly influenced by genetics, with SNP-based heritability being higher in European ancestry women than in men. Polygenic methods consistently show a significant overlap of PTSD with other psychiatric disorders.
Conclusions: Our current findings show that PTSD is significantly influenced by genetic factors, which vary between females and males and overlap with other psychiatric disorders. Unique challenges faced by the PGC PTSD group is the large number of studies contributing relatively small number of cases and the wide range of ancestry with high degree of admixed samples. Consistent with findings from other PGC disorders, much larger sample sizes are needed to fully characterize the genetic architecture of PTSD.

Abstract Type:
Abstract in Symposium

Abstract Number:
47

Author:
Hettema, Jack
USA

Abstract Title:
Multivariate anxiety disorder GWAS in the ANGST Consortium

Abstract Text:
Anxiety disorders, namely generalized anxiety disorder, panic disorder, and phobias, are common, etiologically complex conditions with a partially genetic basis. Despite differing on diagnostic definitions based upon clinical presentation, anxiety disorders likely represent various expressions of an underlying common diathesis of abnormal regulation of basic threat-response systems. We conducted genome-wide association analyses in nine samples of European ancestry from seven large, independent studies. To identify genetic variants contributing to genetic susceptibility shared across interview-generated DSM-based anxiety disorders, we applied two phenotypic approaches: (1) comparisons between categorical anxiety disorder cases and

super-normal controls, and (2) quantitative phenotypic factor scores derived from a multivariate analysis combining information across the clinical phenotypes. We used logistic and linear regression, respectively, to analyze the association between these phenotypes and genome-wide single nucleotide polymorphisms. Meta-analysis for each phenotype combined results across the nine samples for over 18,000 unrelated individuals. Each meta-analysis identified a different genome-wide significant region, with the following markers showing the strongest association: for case–control contrasts, rs1709393 located in an uncharacterized non-coding RNA locus on chromosomal band 3q12.3 ($P = 1.65 \times 10^{-8}$); for factor scores, rs1067327 within CAMKMT encoding the calmodulin-lysine N-methyltransferase on chromosomal band 2p21 ($P = 2.86 \times 10^{-9}$). Replication studies are underway in independent samples.

Abstract Type:
Abstract in Symposium

Abstract Number:
46

Author:
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Germany

Co-Authors:
Klauke, Benedikt; Ziegler, Christiane; Schartner, Christoph; Pauli, Paul; Zwanzger, Peter; Reif, Andreas; Deckert, Jürgen; Domschke, Katharina

Abstract Title:
Gene–environment coping interactions

Abstract Text:
Objectives: Genetic factors and environmental factors are assumed to interactively influence the pathogenesis of anxiety disorders and related phenotypes. However, protective influences such as functional coping ability may exert a buffering effect on the interplay of genetic disposition and environmental adversity in the conferral of risk or resilience to anxiety-related traits and the manifestation of disease.
Methods: Healthy subjects were assessed for childhood maltreatment (Childhood Trauma Questionnaire, CTQ) as well as coping-related properties (General Self-Efficacy Scale, GSE) and genotyped for functional variants in the serotonin transporter gene (5-HTTLPR/rs25531) and the neuropeptide S receptor gene (NPSR1 rs324981) in order to investigate their interactive effect on dimensional phenotypes of anxiety.
Results: A moderating effect of coping characteristics on the interaction of childhood trauma and genetic variants in the moderation of anxiety traits was observed, with higher coping ability serving as a potential buffer between the negative effects of childhood adversity and genetic susceptibility.
Conclusions: Results expand previous findings of gene-environment interactions underlying anxiety phenotypes by introducing protective elements related to functional coping as an additional dimension in an extended gene-environment-coping approach towards a better understanding of the mechanisms at the interface of risk or resilience to anxiety. These results provide new insights for clinical practice, particularly with regard to the development, improvement, and application of preventive therapeutic interventions.

Abstract Type:
Abstract in Symposium

Abstract Number:
48

Author:
Mehta, Divya
Australia

Abstract Title:
Epigenetic aging and resilience in a veteran cohort

Abstract Text:
Posttraumatic stress disorder (PTSD) is a common, debilitating disorder, yet the biology underlying PTSD remains unexplored. Given the interplay of genetic and environmental risk factors that contribute to the risk of PTSD, epigenetic mechanisms might be a molecular mechanism in the etiology of the disorder.

In the first study, we interrogated DNA methylation as biomarkers for PTSD including both risk and protective DNA methylation marks. While assessing DNA methylation study in a cohort of Australian combat-exposed veterans, we were able to identify significant DNA methylation changes associated with PTSD symptoms and also with resilience scores among several candidate genes previously identified to be associated with PTSD. In our genome-wide DNA methylation study in the veterans, we uncovered 5 novel risk loci for PTSD. Of these, we could independently validate the DOCK2 gene in a civilian population. The DOCK2 gene is also involved in Alzheimer's, giving some evidence of common genes involved in the etiology of neurodegenerative and stress-related disorders.

In the second study, we assessed epigenetic (biological) aging in combat-exposed Australian male veterans from the Vietnam War. The epigenetic clock was described by Steve Horvath and accelerated epigenetic (biological) aging has been found to be associated with a myriad of disorders. New data related to epigenetic aging and PTSD risk and protective factors as well as physical comorbidities associated with PTSD will be presented.

Abstract Type:
Abstract in Symposium

Abstract Number:
49

Author:
Entringer, Sonja
Germany

Abstract Title:
Telomere length and early adversity

Abstract Text:
Objective: Substantial evidence suggests conditions in intrauterine life may play a critical role in subsequent health and disease susceptibility (i.e., the concept of fetal or developmental programming of health and disease). The elucidation of biological mechanisms underlying these effects is an area of active investigation. We suggest that telomere biology may represent a novel mechanism underlying the effects of a disparate set of suboptimal intrauterine exposures on various health and disease risk phenotypes. Telomere biology is known to play a fundamental role in genomic integrity, cellular regeneration, physiology, aging, disease risk and mortality. The initial setting of telomere length (TL) in early life has major implications for telomere maintenance throughout the lifespan. Maternal stress and nutrition in pregnancy represent attractive candidate processes in the context of fetal programming of telomere biology. Our previous work

has established an important role for prenatal stress and stress-related processes in adult telomere biology. In our recent studies we use data from several longitudinal birth cohorts in which stress- and nutrition-related processes were assessed during pregnancy, and telomere length (TL) was subsequently measured in newborns (cord blood) and infants (buccal cells).

Results: Our results suggest that among the nutrition-related factors maternal lower folate levels (an essential methyl donor) and higher triglyceride concentrations in early pregnancy were significantly and independently associated with shorter newborn TL. Among psychosocial stress-related measures higher maternal pregnancy-specific stress was associated with shorter newborn TL. Maternal estrogen (E3) concentrations during early pregnancy seem to have a protective effect on infant telomere length because they were associated with longer infant TL.

Conclusion: Taken together, our findings provide evidence in humans that maternal nutrition and stress-related processes during pregnancy may exert a programming effect on the newborn and infant telomere biology system. In utero telomere biology represents a potential molecular mechanism whereby different exposures in this critical developmental period before birth could impact subsequent health and disease susceptibility over the life span, including aging and longevity.

Abstract Type:
Abstract in Symposium

Abstract Number:
52

Author:
Vinkers, Christiaan
The Netherlands

Abstract Title:
Longitudinal changes in glucocorticoid receptor exon 1F methylation in a military cohort

Abstract Text:
Background: Several cross-sectional studies have demonstrated the relevance of DNA methylation of the glucocorticoid receptor exon 1F region (GR-1F) for trauma-related psychopathology.

Objectives: We conducted a longitudinal study to examine GR-1F methylation changes over time in relation to trauma exposure and the development of post-deployment psychopathology.

Methods: GR-1F methylation (52 loci) was quantified using pyrosequencing in whole blood of 92 military men one month before and six months after a four-month deployment period to Afghanistan. GR-1F-wide methylation (mean methylation and the number of methylated loci) and functional methylation (methylation at loci associated with GR exon 1F expression) measures were examined. We first investigated the effect of exposure to potentially traumatic events during deployment on these measures. Subsequently, changes in GR-1F methylation were related to changes in mental health problems (total Symptom Checklist 90 score) and PTSD symptoms (Self-Report Inventory for PTSD).

Results: Trauma exposure during deployment was associated with in an increase in all methylation measures, but development of mental health problems six months after deployment was only significantly associated with increased functional methylation. Emergence of post-deployment PTSD symptoms was not related to increased functional methylation over time. Pre-deployment methylation levels did not predict post-deployment psychopathology.

Conclusion: This is the first study to prospectively demonstrate trauma-related increases in GR-1F methylation and it suggests that only increases at specific functionally relevant sites predispose for post-deployment psychopathology.

Abstract Type:
Abstract in Symposium

Abstract Number:
53

Author:
Jovanovic, Tanja
USA

Abstract Title:
Neurophysiological biomarkers of PTSD

Abstract Text:
Objective: Posttraumatic stress disorder (PTSD) is the fourth most common psychiatric disorder, and delineating risk and resilience factors is of great importance to the development of improved and personalized treatment approaches for this disorder. However, PTSD is frequently co-morbid with other mental disorders, such as depression, substance abuse, and related anxiety disorders. Neurophysiological measures of fear expression provide observable biomarkers of fear-related symptoms. Deficits in extinction of fear-potentiated startle due to high levels of fear (termed fear load) during the early phases of extinction have been observed in PTSD. The goals of the current work were to examine dimensional associations between fear-related symptoms of PTSD and fear load variables to test their validity as an intermediate phenotype. Based on previously reported findings, we hypothesized that fear load would be significantly associated with intrusion and fear memories of an index traumatic event.

Methods: We examined extinction of fear-potentiated startle in a cohort ($n = 269$) of individuals with a broad range of civilian trauma exposure (range 0–13 traumatic events per person, mean = 3.5). Fear-potentiated startle was measured using potentiation of the acoustic startle reflex assessed via electromyography recordings of the orbicularis oculi muscle during fear conditioning and extinction. PTSD symptoms were assessed using PSS.

Results: The results indicated that early extinction was correlated with intrusive thoughts ($p = 0.0007$) and intense physiological reactions to trauma reminders ($p = 0.036$). Degree of adult or childhood trauma exposure, and depression severity were not associated with fear load. After controlling for age, sex, race, income, level of prior trauma, and level of fear conditioning, fear load during extinction was still significantly predictive of intrusive thoughts ($p = 0.004$).

Conclusion: The significance of these findings is that they support dimensional associations with symptom severity rather than diagnostic category and, as such, fear load may emerge as a neurophysiological biomarker of PTSD.

Abstract Type:
Abstract in Symposium

Abstract Number:
56

Author:
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United Kingdom

Abstract Title:
Long Lasting epigenetic Signatures Associated with Enhanced Vulnerability for Depression by Using 'omics' and Cross Species Approaches

Abstract Text:
Stress and glucocorticoid hormones regulate hippocampal neurogenesis, but the molecular mechanisms mediating these effects are poorly understood. We focused the attention on an important player involved in the regulation of stress response: the Serum Glucocorticoid kinase-1 (SGK-1). I will show the long-lasting impact of early life stressful events on SGK-1 signaling pathway, which may be responsible for the increased vulnerability to psychopathology. I will present gene expression and epigenetic data involved in SGK-1 modulation by using a cross species and cross tissue approach.

We started with an animal model of depression, the prenatal stress model (PNS) where we found a significant increase in mRNA levels of SGK1 in association with PNS. Interestingly we found that SGK1 mRNA levels were significantly increased also in blood samples of subjects with a history of trauma as compared to those who had not experienced trauma and also in depressed patients, with a more pronounced effect in those patients exposed to childhood trauma.

As SGK-1 is altered later in life although the stressor occurred early in life, we have tested the possible role of epigenetic changes as possible underlying mechanism. When we looked at DNA methylation, we observed a hyper methylation within SGK1 gene both in animals exposed to PNS and also in subjects exposed to childhood trauma; moreover, a similar pattern of higher methylation within SGK1 gene was observed also in cord blood samples of babies exposed to maternal depression and also in a cohort of depressed patients. These data on DNA methylation indicated the presence of higher methylation as associated with exposure to stress or in association with depression and thus, did not explain the presence of long lasting higher expression in SGK1 that we observed in the same samples.

We thus looked at miRNAs as alternative epigenetic mechanism. Importantly, we found a down-regulation of a panel of miRNAs both in the hippocampus of PNS animals and in the blood of subjects exposed to childhood trauma. Interestingly, these miRNAs are involved in the modulation of TGF-beta signalling.

Our data indicate that an exposure to early life stressful event cause long lasting modulation in SGK1 signalling which are associated with enhanced vulnerability for depression development. Moreover, the persistence of changes over time in SGK1 is associated with changes in a panel of miRNAs rather than changes in DNA methylation.

Abstract Type:
Abstract in Symposium

Abstract Number:
55

Author:
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Abstract Title:
Neurobiology of attentional biases in anxiety disorders

Abstract Text:
Objective: Attentional biases are supposed to play a major role in the etiology and maintenance of anxiety disorders. The most prominent model to describe these biases is the hypervigilance-avoidance model which states that anxiety patients are hypervigilant towards threat cues but then tend to avoid them. Empirical studies partly supported this framework but also provided data that is inconsistent with this model.
Methods: A comprehensive approach will be provided that allows for a more fine-grained description of attentional biases in anxiety disorders. This approach will be linked to distinct neural networks that support these processes.
Results: Empirical studies on anxiety patients indicate biases regarding general hypervigilance, selective orienting, enhanced processing of stimuli that are in the focus of attention as well as difficulties in disengaging attention from threat cues. Active avoidance only seems to occur under specific circumstances and could not be observed in several laboratory studies. Most of these aspects can be linked to a dysregulation of subcortical structures centered on the amygdala.
Conclusion: An elaborated model of attentional biases in anxiety disorders improves the reliable description of symptoms, allows for specifying underlying neural mechanisms and might provide a starting point for novel interventions.

Abstract Type:
Abstract in Symposium

Abstract Number:
57

Author:
Drake, Amanda
United Kingdom

Abstract Title:
Translational approaches to epigenetics of early adversity Epigenetics and development

Abstract Text:
Epidemiological studies have demonstrated an association between low birth weight and an increased prevalence of neuropsychiatric and cardio-metabolic disorders in later life. One potential mechanism underpinning early life programming is early life exposure to excess glucocorticoids. The mechanisms are unclear but may include changes to the epigenome—with effects on development and gene expression, which last throughout life. In this talk I will present evidence from animal models and human studies in support of a role for early life stress in the programming of later disease risk.

Abstract Type:
Abstract in Symposium

Abstract Number:
60

Author:
Seymour, Ben
USA

Co-Author:
Norbury, Agnes

Abstract Title:
Reinforcement learning models of aversive learning and their translation to anxiety disorders

Abstract Text:
Computational neuroscience offers a relatively new way to approach the systems neuroscience of aversive learning, in which the goal is to try to reverse-engineer learning processes and understand how the

behaviour associated with them can be understood as a set of definable and quantifiable information processing operations. At the heart of this approach is the core computational model, which reflects a sort of 'source code' of punishment. If we can determine this then we have an understanding that in principle is sufficient to explain and quantify aversion in any situation, including clinical conditions such as anxiety disorder.

The central idea in models of aversive learning is that punishment commands a teaching signal that optimises behaviour (i.e. minimises harm) and can be described by models from Reinforcement Learning (RL). RL describes a general algorithmic (mathematical) method for learning from experience: predicting the occurrence of inherently salient events, and learning actions to exert control over them (maximising rewards, minimising punishment). In RL, an agent learns state or action value functions, or direct action policies, through interacting with the world. These functions can be learned by computing the error between predicted and actual outcomes, and using the error to improve future predictions and actions. I will review studies that show that these models offer a compelling account of many aspects of Pavlovian and instrumental learning, yielding a basic neural architecture of motivation and decision making that can be simulated (in autonomous agents) as an effective and efficient working aversive system.

However, the application of these models to clinical disorders relies on a plausible model of how the system might be abnormally structured or parameterised in susceptible people. An increasingly popular mechanistic model of anxiety disorder is that people overgeneralise across the continuum of incoming stimuli. Generalisation is well-studied for Pavlovian learning, but we don't understand whether and how it applies to instrumental behaviour i.e. avoidance. I will present a reinforcement learning model of generalisation in avoidance learning, and show how generalisation functions (over-and-above perceptual uncertainty) contribute to learned action values in behavioural and brain responses. I will also show how the parameters from this model can be used to predict trait anxiety in a large population of subjects, supporting the hypothesis that over-generalisation may be a key factor in the pathogenesis of anxiety disorder.

Abstract Type:
Abstract in Symposium

Abstract Number:
59

Author:
Provencal, Nadine
Max-Planck-Institut für Psychiatrie, München, Germany

Abstract Title:
Hippocampal progenitor cell models in deciphering the epigenomics of stress

Abstract Text:
Objective: Exposure to early life stress (ELS) is a well-known major risk factor for developing psychiatric and behavioural disorders later in life. A growing body of evidence indicates that exposure to ELS can lead to long lasting changes in a number of systems including the endocrine system, the immune system and brain structure and function. However, our understanding of the mechanisms underlying these effects is limited. One proposed mechanism that might lead to some of these long-lasting effects is that excessive glucocorticoids (GC) release after ELS exposure induces long-lasting epigenetic alterations in important regulatory genes. Indeed, accumulating evidences suggest that epigenetic mechanisms are in part responsible for the embedding of ELS where the type and timing of stress exposure are important moderating factors.
Methods: We used human hippocampal progenitor cells (HPCs) exposed to GCs during neurogenesis and multi-omic data analysis integrating gene expression and DNA methylation (5mC) at a genome-wide level to assess the long-lasting effects of GCs.
Results: We identified long-lasting 5mC alterations induced by GCs exposure during neurogenesis, where a significant portion of these marks were maintained after neuronal differentiation. Moreover, the sites showing GC-induced methylation changes are enriched in regulatory regions as well as in genes differentially methylated during fetal brain development as well as in genes previously associated with child abuse in human hippocampus and blood cells. To some extent, they also reflect epigenetic changes induced by acute GCs exposure in human blood cells.
Conclusion: Together, these results suggest that GC-induced epigenetic alterations in HPCs might reflect GC actions during ELS and be in part responsible for the increased risk for psychopathology.

Abstract Type:
Abstract in Symposium

Abstract Number:
30

Author:
Riemann, Dieter
Universitätsklinikum Freiburg, Psychiatrie und Psychotherapie, Freiburg im Breisgau, Germany

Abstract Title:
Chronic insomnia and hyperarousal—relevance for depressive disorders

Abstract Text:
Hyperarousal on a cognitive emotional and neurobiological level is assumed to characterize chronic insomnia. This is reflected by many psychophysiological investigations targeting emotions and cognitions and furthermore neurobiological variables like fast frequency EEG spectra, output of the HPA axis or data from neuroimaging studies. Insomnia is common to most mental disorders, especially in depression. Initially it was thought that changes in REM sleep, especially a shortened REM latency and an increase of REM density, are diagnostically specific for patients with severe depression. This turned out not to be the case, and present data suggested insomnia as a transdiagnostic mechanism for many mental disorders. Our own meta-analytic investigation into polysomnographic data revealed that changes in sleep continuity, i.e. increases in sleep latency and an increased number of nocturnal awakenings are typical for most of mental disorders apart from ADHD. The same applied to changes in sleep depth, i.e. slow wave sleep regulation.

We suggest that chronic insomnia may be an early predictor and risk factor for mental disorders, especially depressive disorders. Early and aggressive treatment of insomnia with cognitive behavioral treatment should be able to prevent mental sequelae, as indicated by a first pilot study, which suggests insomnia treatment as a preventive mechanism for mental disorders.

Abstract Type:
Abstract in Symposium

Abstract Number:
20

Author:
Derntl, Birgit
Klinik für Psychiatrie und Psychotherapie, Universität Tübingen, Tübingen, Germany

Abstract Title:
Stress and its regulation—insights from neuroimaging studies

Abstract Text:
Objectives: Although cognitive regulation of emotion has been extensively examined, there is a lack of studies assessing cognitive regulation in stressful achievement situations.
Methods: Therefore, in a first study we used functional magnetic resonance imaging in healthy female and males to investigate cognitive down-regulation of negative, stressful sensations during a frequently used psychosocial stress task. We also performed this paradigm with schizophrenia patients. Behavioral and functional data were analyzed with standard statistical approaches, i.e. ANOVAs and GLM.
Results: Subjective response supported the experimental manipulation by showing higher anger and negative affect ratings after stress regulation than after the mere exposure to stress. On a neural level sex differences were evident and cognitive regulation of stressful achievement situations seems to induce additional stress, recruiting regions implicated in sensory integration and working-memory and deactivating the memory system in women. In the second study, we performed a similar paradigm with schizophrenia patients and observed dysfunctional activation in the patient group indicating a deficit to disinhibit emotion-associated areas during psychosocial stress and the regulation phase. Interestingly, we did not see an increase in negative mood in patients.
Conclusions: Sex as well as group differences in cognitive regulation strategies merit further investigation that can guide sensitive interventions for stress-associated disorders.

Abstract Type:
Abstract in Symposium

Abstract Number:
22

Author:
Hegerl, Ulrich
Universitätsklinikum Leipzig, Klinik für Psychiatrie, Leipzig, Germany

Abstract Title:
Brain arousal dysfunction and psychiatric disorders

Abstract Text:
The human brain can take over different global functional states not only during sleep (sleep stages, e.g. slow wave sleep, REM sleep) but also during wakefulness (arousal levels). A variety of clinical and preclinical arguments indicate that dysfunctions in the regulation and adaptation of brain arousal play a pathogenetic role in major depression (MD), mania and ADHD. Within the arousal model of affective disorders the hyperactivity and sensation seeking observed in overtired children, ADHD and mania is interpreted as an autoregulatory attempt of the organism to stabilize brain arousal level by creating a stimulating environment. Correspondingly the withdrawal and sensation avoidance in MD is interpreted as a reaction to a state of tonically high brain arousal (1). A broadly validated EEG-based algorithm (Vigilance Algorithm Leipzig, VIGALL2.1; free download: http://research.uni-leipzig.de/vigall/) allows to objectively assess the level as well as the regulation of brain arousal. During a 15-min EEG recording under quiet rest, a hyperstable regulation of arousal is a robust finding in MD and the contrary is found during manic episodes (1). Furthermore, reduction of depressive symptoms after therapeutic sleep deprivation goes in line with a down-regulation of brain arousal and an upregulated arousal characterizes responders to antidepressants. Arousal regulation as a basic neurobiological dimension is helpful for separating fatigue with sleepiness and lack of drive, as found in the context of inflammatory or immunological disorders, from disease states with exhaustion and prolonged sleep onset latencies as well as inhibition of drive as found in MD (2).

Abstract Type:
Abstract in Symposium

Abstract Number:
32

Author:
Renner, Tobias
Julius-Maximilians-Universität, Kinder- und Jugendpsychiatrie, Würzburg, Germany

Abstract Title:
Recovery after sexual traumata—a German program for Yezidi girls

Abstract Text:
Objective: In the context of the war actions of the so called Islamic State Yezidi women and girls were systematically victimized and exposed to physical violence and sexual abuse. The federal state of Baden-Württemberg invoked a program, in which about 1000 traumatized Yezidi woman and girls from the area of northern Iraq and their family members were offered asylum in Germany. Specialized social care and intensified psychotherapy over a period of three years were installed. Here we focus on a Yezidi subgroup with a high ratio of children and report on the therapy program as well as on an ongoing study regarding the level of integration and the group's needs in terms of social care and mental health during the transition period at the end of the structured aid program.
Methods: The study applies a mixed methods design. To assess the mental health in children and adolescents SDQ, CGI-S, GAF. Further and own customized self-report and caregiver-reports questionnaires by self-reports and by caregivers. In a quantitative approach the children reflect in adapted focus groups on the transitions they experienced and on their view psychosocial and psychotherapeutic needs.
Results: In this group of Yezidi children and adolescents the interventions are successful regarding the social adaptation to the new German social context, in contrast to their mothers. Also the chosen psychotherapeutic approaches stabilized the children and adolescents, though the intensity of psychotherapeutic needs still fluctuate. The study is still ongoing.
Conclusion: In a subgroup with a high number of children, the specialized Baden-Württemberg program to aide traumatized Yezidi girls and women led to a good psychosocial adaptation for the included children and adolescents. The results of the ongoing study on the transition period will help to further validate the interventions and provide data for the improvement of future aide programs.

Abstract Type:
Abstract in Symposium

Abstract Number:
33

Author:
Gawrilow, Caterina
Germany

Abstract Title:
Stress related impairments in ADHD patients: influence of self-regulation and emotion-regulation

Abstract Text:
Inattention, hyperactivity, and impulsivity are the core symptoms of ADHD. Children, adolescents, and adults with ADHD show impairments in multiple domains of self-regulation and emotion-regulation. Thus, the ability to regulate and control one's own thoughts, emotions, and actions is altered in patients with ADHD and they often experience difficulties with respect to academic achievement, interpersonal relationships, and mental health. For instance, patients with ADHD are at risk for cognitive problems, show impaired physical and psychological functioning, and are prone to stress related impairments. To investigate the association between ADHD symptoms, self-regulation, emotion-regulation, and experienced stress in real life, it is important to take into account that the disorder is a highly heterogeneous condition. Two sources are assumed to contribute to this heterogeneity: between-person differences and within-person fluctuations in ADHD symptoms. This talk will discuss how self-regulation and emotion-regulation correlate in patients with ADHD from a cognitive, motivational, and neuronal perspective. Furthermore, the talk will present completed and ongoing studies on intraindividual variability in ADHD.

Abstract Type:
Abstract in Symposium

Abstract Number:
35

Author:
Walter, Martin
Klinik für Allgemeine Psychiatrie und Psychotherapie, Tübingen, Germany

Abstract Title:
Intrinsic network connectivity and affect dysregulation in depression

Abstract Text:
Intrinsic network connectivity shows typical abnormalities in depression, which predispose individuals to respond differently to external contexts. Importantly abnormal reactivity can be characterised both blunted positive affect and increased negative affect. The latter is also related to abnormal duration of specific neuronal states following negative information. More recent research investigates such mechanisms in the context of dynamic connectivity elicited in rest-task-rest designs. We have established different cognitive and affective challenges under which specific dynamic changes of functional network connectivity is induced. Results show distinct dynamic profiles of dorsal and ventral posterior cingulate cortex as a main hub of a core network orchestrating reallocation of attentional resources. These mechanisms were shown to depend on subject characteristics including coping style and personality markers. In a clinical group of depressed patients, we found increased tonic reactivity towards attachment related stressors and in both patients and controls, dynamic state trajectories were accompanied by dynamic changes in EEG signatures concurrently recorded during fMRI.

Abstract Type:
Abstract in Symposium

Abstract Number:
34

Author:
Hirsch, Etienne
Hôpital de la Salpêtrière, Research Unit UMR 679, Paris Cedex 13, France

Abstract Title:
Stress, glucocorticoids, neuroinflammation and Parkinson's disease

Abstract Text:
Parkinson's disease is characterized by motor symptoms due to a loss of dopaminergic neurons in the substantia nigra. From a pathological standpoint, this neuronal loss is associated with deposition of alpha-synuclein and a strong neuroinflammatory process. Indeed, we and others have reported a microglial activation and an infiltration of T lymphocytes in the substantia nigra in Parkinson's disease.

The symptoms of the disease are generally exacerbated by stress. One endogenous mechanism that is stimulated to restrict and terminate an inflammatory reaction is an activation of the hypothalamic–pituitary–adrenal (HPA) axis that results in a rise in the systemic level of glucocorticoids, which are produced and released by adrenal glands. As well as being released in response to an inflammatory reaction, glucocorticoids are released as a response to stress. Glucocorticoids exert their action by acting through ubiquitously expressed type II glucocorticoid receptors.

We have shown that cortisol levels are increased in the blood of patients with Parkinson's disease and post-mortem that glucocorticoid receptor levels are decreased in the substantia nigra and increased in the striatum (Ros-Bernal et al. 2011). This suggests a complex regulation of glucocorticoid response during the disease process. To get better insight into the molecular regulation of these mechanisms and to analyze its relation to neuroinflammation, we used mice in which glucocorticoid receptors were disabled in microglial cells or in the dopaminergic neurons and induced parkinsonism using the toxic MPTP. We found that in the absence of glucocorticoid receptors in the microglial cells the loss of dopaminergic neurons provoked by MPTP is exacerbated and that microglial activation and astrocytosis are increased. Furthermore, there was a decrease in the expression of anti-inflammatory cytokines and an increase in pro-inflammatory cytokines. While in wild-type animals inflammation was transient, it was long-lasting in the animals lacking glucocorticoid receptors in the microglial cells. None of these changes was observed in the animals lacking glucocorticoid receptors in the dopaminergic neurons.

These data suggest a tight regulation of the inflammatory processes by cortisol and glucocorticoid receptors and that this regulation is altered in Parkinson's disease.

Abstract Type:
Abstract in Symposium

Abstract Number:
36

Author:
Walter, Martin

Klinik für Allgemeine Psychiatrie und Psychotherapie, Tübingen, Germany

Abstract Title:
Multimodal pharmacological imaging of arousal fluctuations

Abstract Text:
Several psychiatric patient populations are characterised by typical abnormalities of vigilance measures. Neuronal changes which underlie, for example, a hyperarousal state in major depression, can nowadays be investigated via multimodal EEG-fMRI measurements. This allows not only to monitor the typically expected continuous drop of vigilance across continuous resting state assessments in one modality, but also to set their respective interdependence in context of time varying state changes and helps to unravel underlying causality of correlations. Next to spontaneous fluctuations of vigilance, such neurophysiological correlates can also be induced experimentally, may it be via noninvasive brain stimulation, pharmacological interventions or neurofeedback. Finally, hyperarousal patterns in vigilance measures can also be induced via social stress paradigms.
Neuronal correlates of intra- and interindividual variations of cerebral vigilance markers and peripheral arousal markers will be introduced and compared and finally, their prediction of individual stress resilience and their pharmacological modulation will be demonstrated.

Abstract Type:
Abstract in Symposium

Abstract Number:
37

Author:
Herrmann, Martin
Klinik für Psychiatrie, Würzburg, Germany

Co-Authors:
Böhme, Stephanie; Brinkmann, Leonie; Buff, Christine; Becker, Michael P.J.; Straube, Thomas

Abstract Title:
Phasic and sustained fear in humans: neural basis and implications for anxiety disorders

Abstract Text:
Objective: Several models suggest that the distinction of phasic and sustained fear has strong implications for the neural basis of anxiety responses and for the differentiation of pathological processes underlying different anxiety disorders. However, the transitions from phasic to sustained fear, the conditions for involvement of different brain areas, and the neural basis of abnormal levels of sustained fear in specific anxiety disorders are widely unclear.
Methods: We used fMRI to investigate the time course and functional connectivity of brain responses during threat anticipation in healthy subjects. Furthermore we investigated the neural basis of enhanced sustained fear in patients with panic disorder, posttraumatic stress disorder and generalized anxiety disorders (GAD) as compared to healthy controls.
Results: The results revealed that amygdala and BNST showed a rapid onset, but that BNST activation is both stronger and more sustained. With regard to anxiety disorders we found increased phasic neural activity in the amygdala and increased sustained activity in the bed nucleus of the stria terminalis (BNST) for the patients groups compared to the healthy controls. Furthermore, we found delayed-sustained BNST activity in GAD patients.
Conclusion: These studies underscore the hypersensitivity to uncontrollability and anticipatory anxiety in panic patients, PTSD and GAD patients and elucidate the role of sustained neural activation in BNST.

Abstract Type:
Abstract in Symposium

Abstract Number:
42

Author:
Alesch, Francois
Austria

Abstract Title:
Deep brain stimulation in psychiatry—lessons learned

Abstract Text:
Objective: The true success story of deep brain stimulation (DBS) is definitely its use in the treatment of movement disorders. Today, in Parkinson's disease (PD) DBS is an important compliment to medical treatment. In tremor and dystonia, DBS is often even superior to conservative treatment. Various studies have also been started to establish DBS as a standard treatment in psychiatric conditions, in a very similar way to the treatment of movement disorders. Depression, obsessive compulsive disorders, and Gilles de la Tourette Syndrome (GTS) were primarily addressed. Although very promising preliminary results have been published, even with spectacular results on a case level, we still lack larger studies confirming the efficacy and stability of DBS in the respective patient populations. Patient selection is crucial, unlike for movement disorders, the definition of the psychiatric pathologies is less sharp and depends on many nonbiological parameters. Up to now, we lack prognostic tests that support us in the definition of patients that may profit from DBS. Another important issue is the follow-up of these patients. Routine checkups of the stimulation parameters together with adaptation of the medication are important factors for a successful treatment. Particularly in psychiatric indications the surgical technique itself will further profit from the implementation of tractography in the planning procedure and from the use of directional leads allowing a more focussed stimulation, thus improving therapy while reducing side effect.
Conclusion: In conclusion, there is a potential for DBS in psychiatry in cases where medical treatment fails, however, today the decision for surgery has to be taken on a per case base and cannot rely on recommendations deducted from large scientific studies.

Abstract Type:
Abstract in Symposium

Abstract Number:
41

Author:
Lonsdorf, Tina
Germany

Abstract Title:
The impact of life adversity on fear generalization and the return of fear—mechanisms and implications

Abstract Text:

Objective: The efficacy of current treatments for anxiety disorders is limited by high relapse frequency. Exposure to adversity is known to promote relapse of anxiety disorders, but the underlying mechanisms remain unexplored.

Results: Results from a series of studies will be presented demonstrating the impact of life adversity and its developmental timing on fear and anxiety-related processes. Thereby, I will focus on experimental models of clinical relapse (i.e., return of fear). Data will be presented that show the impact of life adversity on anxiety, depression as well as brain morphology. Next, I will present data that demonstrate that individuals exposed to recent or childhood adversity show generalized (i.e. not stimulus specific) return of fear, while unexposed individuals showed differential return of fear (i.e. specifically to the stimulus that was previously predictive of an aversive event) in physiological responses despite of comparable fear acquisition and extinction. These group differences were accompanied by corresponding activation differences in brain areas known to be involved in fear processing and differentiability/generalization of return of fear (i.e. hippocampus, thalamus, amygdala). These results are complemented by a third study that reveals stronger generalization of fear responses in individuals exposed to childhood maltreatment.

Conclusion: Our results may provide first and novel insights into the possible mechanisms mediating enhanced relapse risk following exposure to adversity which may guide the development of effective pre- and intervention programs.

Abstract Type:

Abstract in Symposium

Abstract Number:

175

Author:

Domschke, Katharina
University of Freiburg, Freiburg, Germany

Abstract Title:

Epigenetics of anxiety—DNA methylation as a missing link in the missing heritability

Abstract Text:

Objective: The heritability of anxiety disorders ranges between 30 and 68%. However, only few candidate genes have relatively robustly been identified. Epigenetic mechanisms such as DNA methylation crucially influence gene function and have been shown to be temporally dynamic and responsive to environmental influences.

Results: Thus, DNA methylation could serve as a joint at the crossroads between risk and resilience and account for a considerable portion of the "missing heritability" in anxiety disorders. In the present talk, monoamine oxidase A (MAO-A), oxytocin receptor (OXTR) and corticotropin receptor (CRHR1) gene methylation will be reviewed with regard to its role in categorical panic disorder or social anxiety disorder and in dimensional phenotypes of anxiety, complemented by 'EpiG x E' interaction and 'imaging epigenetic' findings in anxiety. Also, the role of DNA methylation as a predictor or even correlate of pharmacotherapeutic and psychotherapeutic treatment response in anxiety and affective disorders will be discussed.

Conclusion: In sum, future molecular genetic studies in complex-genetic, temporally dynamic nosological entities such as anxiety disorders might greatly profit from taking into account epigenetic data as a possible major link in the attempt to unravel the "missing heritability". Furthermore, epigenetic studies could aid in establishing peripheral epigenetic biomarkers of treatment response and thereby contribute to the development of a more personalized treatment of anxiety and affective disorders.

Abstract Type:

Abstract in Symposium

Abstract Number:

176

Author:

Andreatta, Marta
University of Würzburg, Würzburg, Germany

Abstract Title:

Risk factors for contextual anxiety and its generalization

Abstract Text:

Objective: Anxiety patients show strong fear responses to cues, which share perceptual properties with a threat signal, but which have never been associated with the threat (i.e., fear generalization). Mechanisms underlying generalization of conditioned contextual anxiety are rarely investigated, despite their relevance in the etiology and maintenance of anxiety disorders. We investigated the role of risk factors for anxiety disorders in the generalization of contextual anxiety, such as being carrier of the met allele of the brain-derived neurotrophic factor (BDNF; Study 1) or having high trait anxiety scores (Study 2).

Methods: Sixty-five participants in Study 1 (33 were met carriers) and 60 participants in Study 2 underwent a context conditioning protocol during which they were guided into two virtual offices. One to three painful stimuli (unconditioned stimulus, US) were unpredictably delivered in one office (anxiety context, CTX+), but never in the other office (safety context, CTX−). During test, participants were guided into CTX+ and CTX− again as well as in additional offices, which created a continuum of similarity between CTX+ and CTX−.

Results: After learning, CTX+ was rated more negative, anxiogenic and arousing than CTX- and startle responses were potentiated indicating successful context conditioning. Neither BDNF-polymorphism nor trait anxiety modulated anxiety learning. Interestingly, these risk factors modulated the anxiety responses during test. Namely, met carriers, but not homozygous for the val allele showed generalization of conditioned anxiety as startle potentiation to the generalization context (G-CTX) indicates. Similarly, the more anxious individuals were, the more they generalized conditioned anxiety to safety contexts (i.e., CTX− and G-CTX, which was most similar to CTX−).

Conclusion: Risk factors for anxiety disorders did not modulate anxiety learning, but determined a greater generalization of the contextual anxiety.

Abstract Type:

Abstract in Symposium

Abstract Number:

180

Author:

Zwanzger, Peter
Medical Director, Wasserburg/inn, Germany

Abstract Title:
Modulation of neuronal activation in anxiety—is there hope for neurostimulation?

Abstract Text:
Objective: Anxiety disorders belong to the most frequent psychiatric disorders. With regard to treatment, both psychotherapeutic and pharmacologic interventions are recommended according to current treatment guidelines. However, still up to 30% of patients do not respond to first treatment offered or respond insufficiently. Thus, there is still a need for the development of new therapeutic strategies.
Methods: Repetitive transcranial stimulation (rTMS) is a well-established technique for focal cortical stimulation. In view of the large amount of publications, showing a deficit of cortical activity as well as disturbances in cortical limbic interaction in patients with anxiety and depression, the idea of focal brain stimulation as a treatment approach might represent a promising new avenue. The presentation aims to illustrate the potential therapeutic action by reviewing data from healthy volunteer studies on cognition and perception and treatment trials.
Results: Studies with healthy volunteers show a substantial impact of rTMS treatment on cognitive processes and affective perception. Moreover, also studies in patients show therapeutic action in small studies. Studies focusing on CBT-augmentation also show promising results.
Conclusion: Based on the current knowledge therapeutic brain stimulation with rTMS might represent a promising future strategy for the treatment of anxiety and anxiety disorders. With regard to inconsistent results and study limitations further research is however needed.

Abstract Type:
Abstract in Symposium

Abstract Number:
181

Author:
Okon-Singer, Hadas
Department of Psychology, University of Haifa, Israel

Co-Author:
Naor, Navot

Abstract Title:
Emotion–cognition interactions: cognitive biases in health, anxiety and depression

Abstract Text:
Cognitive biases are considered a hallmark characteristic of several psychiatric conditions, such as the expectancy of phobic individuals to encounter snakes, and the interpretation of neutral information as negative by depressed patients. In this talk, I will present recent evidence for a relation between expectancy and attention biases in spider phobia, discuss possible differences in cognitive biases between anxiety and depression, and present evidence for biased cognitive judgements in healthy participants following feelings of empathy to the pain of others. These findings will be discussed in the context of the neuro-cognitive systems underlying the interactions between emotion and cognition.

Abstract Type:
Abstract in Symposium

Abstract Number:
8

Author:
Desrivieres, Sylvane
Germany

Abstract Title:
Update on ENIGMA-Epigenetics: Epigenome-wide association studies of subcortical brain volumes

Abstract Text:
Objective: Epigenetic modifications are major aetiological factors in neuropsychiatric disorders such as depression. In particular, DNA methylation that is regarded as a potential link between environment and depression may serve as a biomarker for neuropsychiatric disorders, even when measured in easily accessible tissues, such as peripheral blood. In the past, associations between blood DNA methylation levels, disease-related brain phenotypes, and adverse health outcomes were discovered in small samples, focusing on candidate genes. We have now created the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) Epigenetics Working Group to make ultra-large scale imaging epigenetic studies possible.
Methods: Here we present an update from the ENIGMA Epigenetics Working Group that recently completed the first large epigenetic study of subcortical brain volumes relevant for depression. Structural T1-weighted brain magnetic resonance imaging scans from 3337 individuals were analysed with harmonized protocols at 11 sites around the world. Epigenome-wide association analyses of blood DNA methylation with volumes of the hippocampus, thalamus and nucleus accumbens were performed and statistical effects from sites meta-analysed.
Results: We detected 2 epigenome-wide differentially methylated positions (DMPs) where methylation significantly predicted hippocampal volumes. Analyses focusing on differentially methylated regions (DMRs) formed by clusters of neighboring CpG sites identified additional loci consistently associating with the volumes of the thalamus, hippocampus or nucleus accumbens in individual cohorts. Enrichment analyses of DMPs associated with hippocampal volumes revealed an overrepresentation of developmental genes associated high-CpG-density promoters bearing the repressive H3K27 histone tri-methylation mark in brain. Investigations of functional consequences of the top DMPs and DMRs in individual cohorts revealed correlations between DNA methylation, expression of nearby genes, brain volume and cognition.
Conclusion: While these findings await replication, they indicate that blood holds promises to identify epigenetic biomarkers that may be useful in stratifying neurological and psychiatric diseases, predicting clinical outcome, and as therapeutic targets, as they are in principle reversible.

Abstract Type:
Abstract in Symposium

Abstract Number:
11

Author:
Roelofs, Karin
Institute of Psychology, Leiden University, Leiden, The Netherlands

Abstract Title:
Primary defensive reactions: resilience or risk factors for anxiety?

Abstract Text:

Objective: The control over our automatic tendencies is often compromised in challenging situations when people fall back on automatic defensive reactions, such as 'freeze-fight-flight' (FFF) responses. Stress-induced lack of control over automatic defensive responses constitutes a problem endemic to high-risk professions, such as the police. Difficulties controlling automatic defensive responses may not only impair split-second decisions under threat, but may also increase the risk for and persistence of posttraumatic stress disorder (PTSD) symptoms.
Methods: I will introduce various methods by which we study neural control over FFF responses in humans, implicating a combination of decision tasks and cardiac and neuroimaging methods.
Results: Distinct areas in the prefrontal cortex are relevant for the regulation of automatic defensive reactions and to orchestrate the shift from passive freezing to active fight-or-flight. In addition, prolonged freezing is associated with increased levels of stress-related symptoms.
Conclusion: Control over automatic FFF tendencies may constitute a promising marker in longitudinal designs aiming to study resilience and risk factors for stress-related symptoms.

Abstract Type:

Abstract in Symposium

Abstract Number:

12

Author:

Tüscher, Oliver
Deutsches Resilienz-Zentrum (DRZ), Mainz, Germany

Co-Authors:

Müller, Marianne B.; Kalisch, Raffael

Abstract Title:

Mechanisms of resilience—a new framework

Abstract Text:

Objective: The majority of people experiencing severe psychological or physical adversity maintain mental health instead of developing stress-related mental illness. Intensive research efforts into the neurobiological mechanisms of stress-related mental illness such as anxiety disorder and depression have resulted in only few innovative therapy approaches. Moreover, research into resilience das recently also arrived in the neurobiological community, posing nontrivial questions about ecological validity and translatability. Hence, exploring neurobiological mechanisms of resilience is complimentary to pathophysiological investigations and represents a paradigm shift in clinical-psychological and psychiatric research that has great potential for the development of new prevention and treatment strategies.
Methods: Drawing on concepts and findings from transdiagnostic psychiatry, emotion research, and behavioral and cognitive neuroscience, we propose a unified theoretical framework for the neuroscientific study of general resilience mechanisms.
Results: The framework is applicable to both animal and human research and supports the design and interpretation of translational studies. The theory emphasizes the causal role of stimulus appraisal (evaluation) processes in the generation of emotional responses, including responses to potential stressors. On this basis, it posits that a positive (non-negative) appraisal style is the key mechanism that protects against the detrimental effects of stress and mediates the effects of other known resilience factors. Appraisal style is shaped by three classes of cognitive processes—positive situation classification, reappraisal, and interference inhibition—that can be investigated at the neural level.
Conclusion: Prospects for the future development of resilience research are discussed.

Abstract Type:

Abstract in Symposium

Abstract Number:

19

Presenter:

Skoluda, Nadine
University of Tübingen, Tübingen, Germany

Abstract Title:

Stress biomarkers and health

Abstract Text:

Objective: Stress may precipitate, exacerbate, and perpetuate psychological and physical symptoms. The assessment of stress biomarkers contributes to a better understanding of the underlying psycho-physiological mechanisms of the link between stress and health. What do we know so far? What does the future hold for stress biomarkers in health research? What are the promises and the challenges?
Methods: A brief overview is provided about the knowledge and future of the most prominent stress biomarkers in health research, focusing on the hypothalamic–pituitary–adrenal (HPA) axis, the autonomous nervous system (ANS), and the immune system.
Results: There are promising stress biomarkers which can be used in both laboratory and naturalistic settings. A better understanding of the role of biological systems in stress-related conditions will enable researchers and practitioners to have a more in-depth knowledge of cause and pathophysiology, which will, ultimately, lead to improved healthcare decisions regarding prevention, treatment, and rehabilitation.
Conclusion: Future research of psychological change using stress biomarkers should favour a multidimensional approach by concomitantly measuring HPA axis, ANS and immune system function within the same study. In addition, recent advances in the study of molecular mechanisms of the stress response (e.g. gene expression) or brain activation patterns should be implemented in these studies in order to better understand effects of altered stress biomarkers. This approach will help to discern differential stress reactivity patterns underlying the differences and commonalities between negative health outcomes, and hopefully lead to improved diagnostic tools, treatment options, and rehabilitation possibilities.

Abstract Type:

Abstract in Symposium

Abstract Number:

18

Author:

Raikkönen, Katri
Department of Psychology, University of Helsinki, Helsinki, Finland

Co-Authors:

Girchenko, Polina; Suarez, Anna; Lahti, Jari; Czamara, Darina; Lahti, Marius; Knight, Anna K.; Hämäläinen, Esa; Kajantie, Eero; Laivuori, Hannele; Villa, Pia M.; Reynolds, Rebecca M.; Jones, Meaghan J.; Kobor, Michael S.; Smith, Alicia K.; Binder, Elisabeth B.

Abstract Title:
Epigenetic age at birth an prenatal risk factors

Abstract Text:
Objective: A recent study demonstrated that it is possible to accurately estimate gestational age (GA) at birth. This novel epigenetic GA predictor, calculated of 148 CpG sites across the methylome of cord blood/newborn blood spots, showed a high correlation with the actual chronological GA (overall $r = 0.91$). The average absolute difference between DNA methylation GA and actual chronological GA was 1.49 weeks. It has been suggested that this epigenetic GA predictor may provide additional information relevant to developmental stage. One previous study using this novel GA biomarker has shown that epigenetic GA deceleration (GAD) (lower DNAm GA than actual chronological GA) was associated with maternal socioeconomic disadvantage and lower neonatal birth weight.
Conclusion: In this presentation we present data from the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) study ($n = 814$ mother-neonate pairs). These data extend the previous study findings by showing that variations in this novel biomarker of epigenetic GA measured from cord blood DNA are also associated with maternal pre-pregnancy risk factors of pre-eclampsia and intrauterine growth restriction, maternal pregnancy disorders and other perinatal complications and characteristics. We also present data suggesting that variations in this biomarker of epigenetic GA are associated with maternal prenatal stress. Future studies will unravel if this epigenetic GA variation is developmentally disadvantageous.

Abstract Type:
Abstract in Symposium

Abstract Number:
4

Author:
Wotjak, Carsten
Core Unit Verhalten und Physiologie, Max-Planck-Institut für Psychiatrie, München, Germany

Abstract Title:
Ethobehavioral assessment of innate fear and what endocannabinoids have got to do with it

Abstract Text:
Most of our current knowledge about the neuroanatomical, neurochemical and molecular basis of fear results from Pavlovian fear conditioning. Much less is known about the underpinnings of innate fear responses, which share higher face validity with human anxiety disorders such as agoraphobia, acrophobia and panic attacks. I will introduce our recently established new test paradigms, which allow us to study acrophobic/agoraphobic behavior and the transition between passive and active fear as a function of threat proximity. Using these paradigms, we could demonstrate differential contributions of the two endocannabinoids, anandamide and 2-AG, to fear regulation. With the help of conditional mutagenesis we start to ascribe the role of CB1 in controlling active vs. passive fear to different neuronal cell populations. Overall, our findings ascribe panicolytic characteristics to pharmacological enhancement of anandamide signaling, and suggest it as a promising strategy for pharmacoenhancement of exposure-based therapies.

Abstract Type:
Abstract in Symposium

Abstract Number:
5

Author:
Grünblatt, Edna
KJPD, Universität Zürich, Zürich, Switzerland

Abstract Title:
Oxidative stress parameters in a longitudinal aging population—the VITA study

Abstract Text:
Aging is related to various neurological and psychological alterations (e.g. brain plasticity, cognition, emotion etc.) resulting often in anxiety-, depressive-, cognitive- and movement-disorders. The Vienna Transdanube Aging (VITA) longitudinal birth cohort study was designed to investigate broad range of parameters that might correlate with aging in an interdisciplinary manner. All participants were inhabitants of the 21st and 22nd district of Vienna and aged 75 years at baseline. Follow-up investigations were conducted every 30 months up to 90 months (aged 82.5 years). In the current analysis, we investigated trajectories alterations observed in 585 non demented participants at baseline comparing between converters (possible, probable and postmortem confirmed pathology of dementia) and non-converters up to 90 months. MMSE-, UPDRS-, SGDS- and anxiety state and trait scores were significantly altered between converters and non-converters already at baseline, exacerbating with time. Serum cortisol and ferritin were altered at baseline and 30 months follow-up, while no significant difference between converters and non-converters was observed for plasma amyloid, HO-1, BDNF levels or platelet MAO-B and SOD activity. Nevertheless, BDNF levels, MAO-B and SOD activity increased with increased age. Since, converters demonstrated increased anxiety state and trait scores, correlation analysis were conducted, demonstrating significant correlations between STAI-X2 and MMSE (negative), UPDRS (positive), ferritin (negative), iron (negative at baseline), and MAO-B activity (positive). These findings suggest that the concomitant increase of stress and anxiety parameters might be a possible source for exacerbation of cognitive decline, depression and movement disorders in an aging population.

Abstract Type:
Abstract in Symposium

Abstract Number:
7

Author:
Kaess, Michael
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Abstract Title:
Hormonal changes after traumatic childhood experiences

Abstract Text:
Traumatic childhood experiences are among the most prominent risk factors for the development of psychiatric disorders across the life span. Understanding the biological pathways that mediate the association from early trauma to later psychiatric illness is critical but not yet achieved.
Traumatic childhood experiences commonly pose severe and enduring stress to an individual, which in turn is thought to activate hormonal systems, such as the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is a major stress system of the human body; thus,

one of the leading candidate systems for trauma-related alterations that contribute to the development of mental disorders.

The talk will summarize own and other's research on alterations of HPA axis functioning in the context of traumatic childhood experiences. Indices of HPA axis functioning are: cortisol awakening response, diurnal slope, hair cortisol, cortisol reactivity to stressors, and cortisol attunement in mother–child dyads. Direct effects as well as transgenerational effects of early adversity will be considered. Alterations across different age groups (ranging from toddlers to mid-adolescents) will be presented. Finally, the relationship of such alterations with mental health problems will be elucidated and discussed.

Abstract Type:
Abstract in Symposium

Abstract Number:
170

Author:
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Abstract Title:
Heart rate variability in sleep as indicator of hyperarousal in insomnia and depression

Abstract Text:
Objective: Heart rate variability (HRV) is an indicator of the activity of the autonomous nervous system (ANS). In rapid eye movement (REM) sleep, HRV is regulated predominantly by the central autonomous network (CAN). As the CAN is also involved in emotion regulation, HRV in REM-sleep may be an indicator of both, arousal and prefrontal limbic system regulation. The aim of this study was to examine biomarker properties of HRV in REM sleep in clinical samples of primary insomnia and major depressive disorder (MDD).
Methods: We examined three controlled clinical samples: (1) Ten women (mean age: 50 ± 8 years) with primary insomnia without any other physical or mental illness. (2) Thirty-four out-patients with MDD without antidepressant (AD) treatment (age: 28 ± 8 years; 55.6% females). (3) To examine if HRV would predict response to AD-treatment, we assessed thirty-three depressed in-patients under AD-treatment (age: 46 ± 16 years, 64% females) at week one and at week four. HRV frequency domain measures of REM, N2 and N3 sleep were compared between patients vs. controls and responders vs. non-responders.
Results: Blunted HRV discriminated primary insomnia from normal sleep with large effect sizes ($d > 1.3$). In REM-sleep there was a specific shift of relative HRV power from high to very low frequency band ($p < 0.05$). In MDD we found a similar pattern of results. HRV measures at week one did not predict response to antidepressants at week four, however blunted HRV at baseline did not recover with treatment response at week four.
Conclusion: HRV in REM sleep has properties of a biomarker: HRV discriminates patients with either primary insomnia or depression from healthy subjects with large effect sizes. Blunted HRV seems to be related to hyperarousal and REM sleep disinhibition, and may be a trait marker of depression.

Abstract Type:
Abstract in Symposium

Abstract Number:
171

Author:
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Co-Authors:
Gassen, Nils C.; Jia, Meiwen; Baumert, Jens; Hafner, Kathrin; Ködel, Maik; Haehle, Andreas; Iurato, Stella; Carrillo-Roa, Tania; Emeny, Rebecca T.; Lahti, Jari; Räikkönen, Katri; Eriksson, Johan; Drake, Amanda; Waldenberger, Melanie; Wahl, Simone; Kunze, Sonja; Lucae, Susanne; Bradley, Bekh; Gieger, Christian; Hausch, Felix; Smith, Alicia K.; Ressler, Kerry J.; Ludwig, Karl-Heinz; Müller-Myhsok, Betram; Rein, Theo; Binder, Elisabeth B

Abstract Title:
Aging- and stress-related epigenetic disinhibition of FKBP5 contributes to NF-κB-driven inflammation and cardiovascular risk

Abstract Text:
Objective: Aging and stress-related phenotypes are both associated with heightened inflammation and disease risk, including cardiovascular disease, but the underlying molecular mechanisms are unknown. Our objective was to examine the role of the stress-responsive immunophilin FKBP5 in these relations.
Methods: Peripheral blood DNA methylation was measured across the FKBP5 gene in four independent cohorts: the Grady Trauma Project (GTP, n = 393); the Cooperative Health Research in the Region of Augsburg (KORA; n = 1,727); the Max Planck Institute of Psychiatry (MPIP; n = 538); and the Helsinki Birth cohort study (n = 160). Genome-wide gene expression was assessed in peripheral blood in the GTP (n = 355). Functional protein interaction, reporter gene, and ELISA experiments were performed in cellular models of immune function.
Results: FKBP5 DNA methylation consistently decreased with age at selected CpGs, and this age-related demethylation was accelerated by childhood trauma ($p = 7.4 \times 10^{-3}$) and depressive symptoms (interaction $p = 3 \times 10^{-2}$) and was associated with increased FKBP5 mRNA ($p = 1.6 \times 10^{-2}$) and stronger cortisol-FKBP5 relationship (interaction $p = 1.4 \times 10^{-3}$). In peripheral blood, FKBP5 upregulation correlated with a proinflammatory profile and extensive changes in NF-κB-related gene networks. In accordance, FKBP5 overexpression in immune cells promoted chemokine secretion and strengthened the interactions of regulatory kinases of the NF-κB pathway. Notably, the same age-and stress-related CpGs associated with FKBP5 upregulation were also more demethylated in subjects with a history of myocardial infarction in both the KORA ($p = 4.4 \times 10^{-2)}$ and MPIP ($p = 3.1 \times 10^{-2}$).
Conclusion: These findings identify FKBP5 as mediator of stress-augmented peripheral inflammation with aging and potential contributor to cardiovascular risk.

Abstract Type:
Abstract in Symposium

Abstract Number:
164

Author:
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University of Wuerzburg, Wuerzburg, Germany

Co-Authors:
Weidner, Magdalena; Schraut, Karla-Gerlinde; Schmitt, Angelika; Lesch, Klaus-Peter

Abstract Title:
Prenatal stress-induced programming of genome-wide DNA methylation in 5-HTT-deficient mice: the road to resilience

Abstract Text:
Exposure to prenatal stress has been shown to have a profound impact on emotion regulation in adulthood, while the underlying molecular mechanisms remain somewhat diffuse. In recent years, epigenetic programming and changes in serotonin (5-HT) system function were pin-pointed as possible key mechanisms in the mediation of these effects.

To elucidate the role of 5-HT in early life programming, we used various gene-by-environment (GxE) designs in mouse lines with altered 5-HT system function. In one of our most recent studies, we exposed a cohort of wild-type C57/BL6 dams, which were impregnated by heterozygous serotonin transporter (5-HTT)-deficient C57/BL6 males, to restraint stress from embryonic day 13–17. Following birth, animals were allowed to grow up under normal conditions.

Subsequent behavioural analysis in the female offspring revealed several genotype-, stress- as well as GxE-specific effects, e.g. at the level of sociability/social anxiety. Follow-up molecular analysis furthermore revealed, amongst others, a cluster of myelin-associated genes to be regulated in a GxE dependent fashion. Moreover, these genes were differentially affected in animals resilient or vulnerable to developmental stress exposure. Recent evidence furthermore shows differential methylation of the gene encoding for Myelin-based protein (Mbp) in human offspring of mothers showing increased anxiety during pregnancy.

Category/Topic:
4 Animal models of fear and anxiety

Abstract Type:
Abstract in Symposium

Abstract Number:
162

Author:
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Abstract Title:
Rewrite or overwrite: identifying neuromolecular circuits of remote fear memory attenuation

Abstract Text:
Objective: How to attenuate traumatic memories has long been the focus of intensive research efforts, since traumatic memories are extremely persistent and heavily impinge on the quality of life. Yet, surprisingly few studies have investigated treatment options for remote, i.e., long-lasting forms of traumata in animal models. The few that have unanimously concluded that exposure therapy-based treatments, the most successful behavioral intervention for traumata in humans, fail to effectively reduce remote fear memories.

Methods: Recently, we have described a pharmacological approach by which even remote fear memories become amenable to attenuation: By combining exposure therapy-like approached with histone deacetylase inhibitors in mice, hippocampal neuroplasticity could be reinstated, which resulted in persistent fear reduction (Gräff et al., Cell, 2014).

Results: Notwithstanding, the physiological substrates of such persistent fear reduction still remain largely unknown. In particular, it is unclear whether successful attenuation of remote fear memories is the result of a new memory trace of safety or of a re-learning of the original memory trace of fear towards safety. In this talk, I will present our efforts how we investigate this question in a brain region and cell type-specific manner.

Abstract Type:
Abstract in Symposium

Abstract Number:
134

Author:
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Abstract Title:
Equipped to survive: adaptive response to acute threat

Abstract Text:
In response to acute environmental adversity, organisms rapidly shift into a state that is optimal to detect and react to imminent threat. Data is presented that supports a framework describing how stress-related neuromodulators trigger dynamic shifts in network balance prompting a reallocation of resources to a salience network, promoting fear and vigilance, at the cost of executive control. After stress subsides, resource allocation to these two networks reverses which normalizes emotional reactivity and enhances higher-order cognitive processes. To identify underlying neural network dynamics and neuromodulatory mechanisms we combined a series of human fMRI studies with thread based stress induction procedures and pharmacological manipulation. While this network reset has high adaptive value under aversive conditions, it might also constitute a critical mechanism for psychopathology.

Abstract Type:
Abstract in Symposium

Abstract Number:
135

Author:
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Cognitive Psychology, Hamburg, Germany

Abstract Title:
Stress-induced shift from 'cognitive' towards 'habit' memory: role of the mineralocorticoid receptor

Abstract Text:
For decades, research focused on the impact of stress and glucocorticoids on the modulation of consolidation and retrieval processes within a single (mainly hippocampus-dependent) memory system. More recent findings, however, show that stress modulates also the preferential engagement of multiple, anatomically and functionally distinct memory systems in a manner that favors dorsal striatal 'habit' memory over hippocampal 'cognitive' memory. Based on converging lines of evidence from rodent and human data, I will argue that the mineralocorticoid receptor (MR) plays a key role in this stress-

induced bias towards striatal memory. Moreover, I will provide evidence that the MR-dependent shift from hippocampal to striatal memory is beneficial for performance under stress, suggesting that this shift is crucial for behavioral adaptation to stressful events.

Category/Topic:
9 Genetics and epigenetics of anxiety and stress

Abstract Type:
Oral Presentation

Abstract Number:
137

Author:
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Co-Authors:
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Lesch, Klaus-Peter; Sachser, Norbert

Abstract Title:
Impact of varying social experiences during life history on behaviour, gene expression, and vasopressin receptor methylation in mice

Abstract Text:
Objective: Both negative and positive social experiences during sensitive phases of life profoundly shape brain and behaviour. Current research is therefore increasingly focussing on mechanisms mediating the interaction between varying life experiences and the epigenome.
Methods: Male mice, which grew up under either adverse or beneficial conditions until adulthood, were further subdivided into groups exposed to environmental variation in adulthood that either matched or mismatched the previous conditions, thus resulting in four different life histories. The impact of these life histories on anxiety-like behaviour as well as gene expression profiles of selected genes involved in anxiety and stress circuits and on arginine vasopressin receptor 1a (Avpr1a) gene methylation was investigated.
Results: Varying social experiences during life history profoundly modulated (1) anxiety-like behaviour; (2) hippocampal gene expression profiles of Avpr1a, serotonin receptor 1a (Htr1a), monoamine oxidase A (Maoa), myelin basic protein (Mbp), and glucocorticoid receptor (GR; Nr3c1); (3) hippocampal DNA methylation within the Avpr1a gene. Notably, mice experiencing early beneficial and later adverse conditions showed a most pronounced downregulation of Avpr1a expression, accompanied by low anxiety-like behaviour.
Conclusion: In summary, this study highlights the impact of interactive social experiences throughout life on the hippocampal epigenotype and associated behaviour.

Category/Topic:
11 Post-traumatic stress disorder

Abstract Type:
Oral Presentation

Abstract Number:
138

Author:
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Co-Authors:
Meliß, Stefanie; Simmons, Candice; Nothling, Jani; Seedat, Soraya

Abstract Title:
How childhood sexual abuse and posttraumatic stress disorder affect memory function in adolescents

Abstract Text:
Objective: Neuropsychological impairments are commonly observed in adults suffering from posttraumatic stress disorder (PTSD). However, attempts to generalize these results to children and adolescents lead to inconsistent results. Even less is known about the impact of childhood sexual abuse (CSA) on the relationship between PTSD and performance in neuropsychological tests. We hypothesized that participants with PTSD who have also suffered CSA would have the worst neurocognitive performance.
Methods: In a cross-sectional design, 105 traumatized South African adolescents, of which 52 fulfilled criteria of PTSD and 34 reported CSA, were tested with a broad neuropsychological battery that included tests of memory, executive functioning, and language to analyse the impact of PTSD diagnosis and CSA experiences thereon.
Results: Adolescents that had reported CSA performed significantly worse on the interference parameter of the Rey Auditory-verbal learning test and in the copy condition of the Rey Oesterreith Complex Figure Test, indicating impairments in attention and working memory. No independent effects of PTSD were found on neurocognitive performance.
Conclusion: The impact of PTSD on neurocognitive tests differs in adolescents compared to adults. Moreover, CSA seems to have an effect on parameters associated with working memory.

Category/Topic:
12 Adjustment disorders

Abstract Type:
Oral Presentation

Abstract Number:
142

Author:
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Co-Author:
Michalek, Silke

Abstract Title:
Stressor-induced conflicts in young males with ADHD: Implications for transition to mentalization and self-management

Abstract Text:
Objective: Attention deficit hyperactivity disorder (ADHD) is associated with a high rate of persistence into adulthood. This implies the need for a developmental approach toward treatment. Successful transfer of young people to an adult ADHD clinic requires anticipation of changing family roles for patients and their parents. These individuals are facing a significant number of personal and social demands, increasing the risk for internalizing and externalizing psychopathology at a time of increased vulnerability.

Psychodynamically, they may show difficulty in achieving autonomy and lack self-management skills. We report findings on young men with a childhood diagnosis of ADHD who disengaged from health services.

Methods: A feasibility study was conducted on 40 male outpatients (18–25 years) consecutively diagnosed with ADHD. Diagnosis (DSM-V) was evaluated with Conners' Adult ADHD Rating Scales (CAARS) and the Wender Utah Rating Scale (WURS). Psychiatric comorbidity was assessed clinically, psychological distress by use of the SCL-90-R Global Severity Index (GSI). Alexithymia was defined as a TAS-20 score >60 (Toronto Alexithymia Scale). OPD-2 (Operationalized Psychodynamic Diagnostic) was used for psychodynamic analysis of relationship patterns. The Mindful Attention Awareness Scale (MAAS) was applied initially and 6 months after restarting treatment with methylphenidate.

Results: 24 patients were of the combined ADHD subtype, 16 patients of the inattentive subtype. 83% of these individuals had received stimulant therapy as a child or adolescent, in most cases combined with behavioural psychotherapy (76%). (Self-)referral to our service was anteceded (88%) by a history of increasing distress (educational or work circumstances). Family relationships had become strained and experienced as unsupportive (90%). There was an interruption of ADHD specific treatment (median: 60 months) in 95% of cases. Comorbidity: depressive episode (15%), anxiety disorder (38%), history of substance use (45%), mainly cannabis. Psychological distress was high (mean GSI 1.23), as was the proportion of patients with alexithymia (70%). Most individuals (63%) showed dysfunctional relationship patterns (dependence vs. autonomy) and had a history of aggressive behaviour (53%). Low MAAS scores increased in most of the subjects after 6 months.

Conclusion: Current treatment strategies for adolescents with ADHD cannot prevent the interruption of treatment in the ´twilight zone´ from adolescence to adulthood. Our observations in a real-life adult healthcare setting may show that transition is poorly experienced and drop-out from services may be frequent and potentially disastrous. In a developmental framework, treatment should also focus on what makes young adults with ADHD vulnerable, such as compromised mindfulness and deficient mentalization abilities.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Oral Presentation

Abstract Number:
150

Author:
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Co-Authors:
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Abstract Title:
The neural correlates of fear generalization and its moderation by genetically determined risk for panic disorder

Abstract Text:
Objective: Generalization of associated fear is a likely mechanism involved in the pathoetiology of panic disorder (PD) and overgeneralization of conditioned fear is a prominent feature of PD. Meta-analyses of 23 SNPs associated to PD have confirmed the roles of TMEM132D and COMT in panicogenesis, and found several other SNPs to be nominally significant. As the exact way of how these SNPs moderate risk for PD is unknown, this study aimed to investigate the differences in neural correlates of the performance of a Fear Generalization and other anxiety-related tasks, associated with genetic risk for PD.

Methods: 160 healthy participants were measured with structural MRI, DTI, resting-state fMRI and several anxiety-related fMRI paradigms. The main focus was on the Fear Generalization (FG) paradigm, which was adapted from Lissek et al. (2009). Other tasks were related to intolerance of uncertainty (response to Unpredicted Threat and Feedback Response during Time Estimation), emotional face processing, and to cognitive bias during a Cognitive and Emotional Stroop task.

Results: The main effects of the FG paradigm showed generalization gradients of neural activity in fear-related regions such as the anterior insula, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), caudate nucleus and parietal cortex. Multiple regression with 4 TMEM132D SNPs showed a significant effect of the highly correlated rs879560 and rs900256 SNPs on the right inferior parietal cortex (PFWE = 0.007/0.002) in the CS+>CS− contrast. Cluster significant effects were seen in the same region on the left. This region was not part of the main effects seen in the CS+>CS− or the CS−>CS+ contrasts.

Conclusion: SNPs associated to PD indeed seem to moderate neural activity during fear generalization, although the exact influence is unclear as the affected brain region is not part of the activated network during the task main effect. The specificity of this genetic moderation will be further investigated by examining whether similar results are seen in the other paradigms. Additional SNPs and risk scores related to depression, schizophrenia and GR-receptor sensitivity will be investigated as well.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Oral Presentation

Abstract Number:
149

Author:
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Co-Authors:
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Abstract Title:
Cerebral mediation of attention biases in social anxiety: a near-infrared spectroscopy (NIRS) neurofeedback trial

Abstract Text:

Objective: Attentional biases towards threat signals have been linked to the etiology and symptomatology of social anxiety disorder (SAD). Dysfunction of the dorsolateral prefrontal cortex (dlPFC) is proposed to play a key role in the maintenance of attentional biases and symptomatology in anxious individuals. The aim of this study was to investigate the feasibility of NIRS neurofeedback (NF) training—targeting the dlPFC—and its effects on the attentional biases of SAD patients.

Methods: 12 social anxiety patients participated in the NIRS-NF training lasting 6–8 weeks and including a total of 15 sessions. Changes in attentional biases (i.e. response time interference and brain activation) before and after the NIRS-NF were assessed using an emotional counting Stroop (using fear-relevant word contents) and a task-irrelevant laughter perception experiment. Correlational analyses between NF performance, changes in symptomatology as well as behavioral measures and the neural activation betas of pre-defined ROIs were run to examine possible associations.

Results: Over the training period, NF performance increased significantly ($t(11) = 2.75$, p-value $= 0.02$), whereas psychopathology scores dropped significantly ($t(11) = 3.85$, $p = 0.002$). For the counting eStroop experiment, no significant changes on behavioral or neural levels were established. In the implicit laughter perception experiment, however, some promising links between the increase of neurofeedback performance as well as the decrease of psychopathology with NF-training-associated alterations in cerebral laughter processing in several regions of interest could be established ($|all\ r| > 0.53$, all p (one-tailed, uncorrected) ≤ 0.05).

Conclusion: This pilot study is the first to show that NIRS-based NF is feasible in SAD patients. Next to a general reduction in SAD symptoms, this decrease in symptomatology has also been linked to a decrease in alterations in cerebral laughter processing. Therefore, NIRS neurofeedback seems not only suitable to investigate the causal role of the dlPFC in the processing of attentional biases in SAD, but could also be a gateway to developing new, potentially effective treatment methods for anxiety disorders.

Category/Topic:

8 Neurobiology of anxiety and stress

Abstract Type:

Oral Presentation

Abstract Number:

161

Author:

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Co-Authors:

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Abstract Title:

Stress and neurovascular coupling: A new reciprocal mechanism for stress response regulation

Abstract Text:

Neurovascular coupling (NVC) links neuronal and metabolic processes in the brain, yet its role in stress-related neuropsychiatric disorders remains unclear. Here, we present data from a multimodal, human, psychosocial stress, fMRI study. We show that hemodynamic response peak latency, an NVC marker, is reversibly affected within seconds to minutes by acute stress in the limbic and prefrontal brain. The hippocampal NVC response predicted the subsequent cortisol response, and in turn, hippocampal baseline NVC features and stress-induced deflections were bound by an individual's glucocorticoid receptor (GR) sensitivity, as estimated from a validated polygenic marker. The hemodynamic response changes observed after stress were further validated to emerge from the NVC complex by genetic associations with KCNJ2, a potassium channel critically involved in NVC/stress interface. Taken together, our data suggest that, in humans, acute stress induces fast NVC adaptations that are interlinked to the systemic stress response. This proffers NVC markers as a new biomarker resource and endophenotype of stress-related disorders.

Category/Topic:

9 Genetics and epigenetics of anxiety and stress

Abstract Type:

Oral Presentation

Abstract Number:

153

Author:

Meier, Sandra
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Abstract Title:

Genome-wide association study of anxiety and stress-related disorders

Abstract Text:

Objective: In Europe, over 70 million people are annually suffering from anxiety and stress-related disorders and over 90% of patients with these disorders have another comorbid mental or somatic disorder. Therefore, it is of strong interest to identify the risk factors of these disorders. Heritability estimates vary between 30 and 50%, however first genome-wide association studies (GWAS) have been limited by their small sample sizes. As anxiety and stress-related disorders are likely to configure various expressions of abnormalities in the basic stress-response system, we aimed to conduct a GWAS aggregating a large number of cases with varying diagnoses of anxiety and stress-related disorders.

Methods: The study is making use of a Danish nation-wide population-based sample collected by the Lundbeck Foundation Initiative for Integrative Psychiatric Research including 14,711 cases with anxiety and stress-related diagnoses and 17,857 controls. Data were processed using the Ricopili pipeline; imputation is based on the 1000 genomes phase 3 as reference panel. GWAS was conducted using the imputed marker dosages and an additive logistic regression model. Analyses were supplemented by comparing severe mental disorder with comorbid anxiety and stress-related disorder to those without, using a propensity-score-matched design. SNP heritability and genetic correlation with other traits were computed using LD-score regression.

Results: In case–control design several SNPs located in the PDE4B gene achieved genome-wide significance. The analyses comparing mental disorders with and without comorbid anxiety and stress-related disorders revealed no significant signal. The SNP heritability estimate for anxiety was 14, 33% for stress-related disorders and 26% for the combined phenotype. Detailed comparisons/meta-analyses with previous efforts are ongoing and will be presented at the conference.

Conclusion: This is the first GWAS meta-analysis on anxiety and stress-related disorders demonstrating influences of common genetic variation in the etiology of these disorders and indicating PDE4B as a susceptibility locus.
This work is presented on behalf of the iPSYCH anxiety working group.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Oral Presentation

Abstract Number:
156

Author:
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Co-Authors:
Li, Meng; Demenscu, Liliana Ramona; Li, Shija; Muller, Iris; Richter, Anni; Seidenbecher, Constanze; Speck, Oliver; Schott, Bjorn; Stork, Oliver; Walter, Martin

Abstract Title:
Region specific metabolic correlates contribute to gene and sex relationship of anxiety endophenotypes

Abstract Text:
Objective: Anxiety disorders are typically prevalent in women, but the factors contributing to sex bias are unknown. Investigations have emphasized the role of the cortico–limbic circuit including the anterior cingulate cortex (ACC) in anxiety disorders. Pregenual ACC (pgACC) was highlighted as key region for successful affect regulation, and dysregulation of transmitter balance (GABA/Glu) was reported in anxiety disorders in this region. We therefore investigated whether a SNP in GABA synthesizing enzyme GAD65 and sex are associated with inhibitory/excitatory balance in ACC regions (pgACC and aMCC). Additionally, we explored the relationship between GAD65, sex, metabolites and harm avoidance (HA).
Methods: 107 healthy subjects (45 females, age = 27.07 ± 6.75) underwent a magnetic resonance spectroscopy in 7T. GABA and Glu levels were measured in aMCC and pgACC. Subjects completed TCI questionnaire and were genotyped for GAD65 promoter (40 G-carriers). Region by genotype by sex ANOVA was done including age as confound for GABA/Glu levels. Likewise, we tested differences for HA, and association to pgACC metabolism. Lastly, we performed an analysis of mediating effects of GABA/Glu on GAD65 to HA, moderated by sex.
Results: We found an interaction effect on GABA/Glu ($F_{1,63} = 8.69$, $p = 0.004$). Post-hoc analysis revealed that this interaction was driven by genotype difference in females in pgACC ($t(37) = -2.27$, $p = 0.029$). There was an effect of sex on HA and pgACC GABA/Glu levels (women: $\rho(25) = -0.552$, $p = 0.003$; men: $\rho(31) = -0.003$, $p = 0.98$). We also observed an effect for the moderated mediation (−1.17, −0.056).
Conclusion: Our results show that GABAergic gene polymorphisms and sex are factors contributing to anxiety endophenotypes in women via metabolic correlates in the pgACC. This interaction could be relevant for the observed sex bias in prevalence of anxiety disorders and possible sex specific treatment strategies.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Oral Presentation

Abstract Number:
70

Author:
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University of Maryland, College Park, MD, USA

Abstract Title:
Brain bases of individual differences in dispositional negativity

Abstract Text:
Objective: Dispositional negativity (DN)—the propensity to express more intense, frequent, or persistent negative affect—is a fundamental dimension of childhood temperament and adult personality. Elevated DN is a key risk factor for fear and anxiety disorders, depression, and co-morbid substance abuse, underscoring the need for a deeper understanding of the underlying neurobiology.
Methods: Here, I will highlight recent advances in our understanding of the neurobiology of DN, focusing on multimodal brain imaging studies (FDG-PET/fMRI) in human adults, children, and monkeys (n = 23–592). Human studies are essential for understanding the circuitry supporting subjective symptoms of fear and anxiety; for identifying the features of animal models that are conserved and, hence, most relevant to human disease; and for developing objective biomarkers. Nonhuman primates provide an ideal model for identifying the mechanisms underlying extreme DN. The brains of monkeys and humans are genetically, anatomically, and functionally similar. Homologous substrates, including a well-developed prefrontal cortex, endow the two species with a shared repertoire of defensive responses to threat, increasing the likelihood of successful translation.
Results: Individual differences in DN reflect elevated activity and aberrant connectivity in a network of brain regions that includes the central nucleus of the amygdala, bed nucleus of the stria terminalis (BST), and orbitofrontal cortex, ps < .05, corrected. More recent work suggests that the BST supports persistent anxiety following encounters with potential danger—a hallmark of pathological anxiety—and mediates the genetic transmission of DN from parents to offspring.
Conclusion: These observations provide new insights into the neurobiology of DN and a framework for developing improved diagnostic, treatment, and prevention strategies.

Category/Topic:
11 Post-traumatic stress disorder

Abstract Type:
Oral Presentation

Abstract Number:
72

Author:
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Co-Author:
Mkrtchyan, Gohar

Abstract Title:
Epigenetic alterations of the brain derived neurotrophic factor (BDNF) gene in combat veterans with posttraumatic stress disorder

Abstract Text:
Objective: Posttraumatic stress disorder (PTSD) is a disabling mental health condition that can develop following exposure to a traumatic event (DSM-V code: 309.81). Results of epidemiologic, clinical and experimental studies suggest implication of both environmental and genetic factors in pathomechanisms of PTSD and that, most probably, PTSD belongs to complex disorders with polygenic inheritance. Whereas the environmental factors triggering PTSD are well defined, less is known about PTSD-associated genetic variations and molecular etiopathomechanisms. PTSD is characterized by cognitive impairment, which may result from synaptic plasticity dysfunction. Brain derived neurotrophic factor (BDNF) is involved in the neural plasticity underlying the extinction of fear and recovery from stress, both disrupted in PTSD. Based on its role in hippocampal-dependent learning and the neurobiology of anxiety and depression, the aim of this study was to investigate the potential association of BDNF genetic polymorphism in relation to PTSD.
Methods: Study population includes 200 combat veterans with PTSD and an equal number of age- and sex-matched healthy controls. The experiments were performed using genomic DNA samples of study subjects. Methodological design was based on the polymerase chain reaction with sequence-specific primers (PCR-SSP). Data was evaluated using Hardy–Weinberg equilibrium, Pearson's Chi square test, Bonferroni multiple correction approach.
Results: According to the data obtained, the frequency of rs6265*A allele of the BDNF gene was significantly lower in patients compared to healthy controls ($p = 0.026$). Also, the number of carriers of rs6265*A minor allele was significantly lower in the group of patients compared to controls ($p = 0.02$). After Bonferroni correction, difference in allele frequency between the patient and control groups for these minor alleles remained significant.
Conclusion: In conclusion, our results demonstrate that BDNF rs6265 polymorphism has been implicated in the susceptibility to PTSD. However further research is required to provide the definitive evidence of BDNF rs6265 polymorphism association with BDNF level.

Category/Topic:
9 Genetics and epigenetics of anxiety and stress

Abstract Type:
Oral Presentation

Abstract Number:
75

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Abstract Title:
Identification of epigenetic and cerebral markers linking early life adversities and adult anxiety disorders

Abstract Text:
Objective: The contribution of early life adversities (ELA) to the pathophysiology of anxiety disorders has been consistently described, but the underlying biological mechanisms are still poorly understood. Evidence is emerging, that epigenetic processes might play a role. Furthermore, it has been demonstrated that both, anxiety disorders and ELA, are associated with distinct alterations of the brain, but the influence of epigenetic processes on brain properties and more importantly their potential mediating function between ELA and the occurrence of anxiety disorders remains to be elucidated.
Methods: We therefore aim to (i) identify epigenetic biomarkers which could predict the occurrence of anxiety disorders in individuals previously subjected to ELA and to (ii) evaluate the cerebral correlates of epigenetic influences of ELA on the occurrence of anxiety disorders and their potential function as mediators between epigenetic biomarkers and anxiety disorders.
Results: We intend to investigate early life adversity-responsive genes in a large cross-sectional cohort of adult anxiety disorder patients and healthy control individuals to identify whether those genes qualify as epigenetic biomarkers of anxiety disorders. Furthermore, in an imaging epigenetics approach, we aim to investigate the influence of the epigenetic regulation of those genes on brain properties to localize cerebral markers of epigenetic-driven effects of ELA on the development of anxiety disorders. First results of the project that started early 2017 will be presented.
Conclusion: Such a panel of peripheral biomarkers could be used to identify individuals at risk for anxiety disorders early after the exposure to ELA which in turn might contribute to the prevention of disease onset as protective strategies could be applied promptly.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Oral Presentation

Abstract Number:
74

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Co-Authors:
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Abstract Title:
Conditioned fear generalization and discrimination learning in children and adolescents

Abstract Text:
Objective: The generalization of conditioned fear is considered to represent a crucial mechanism underlying the disposition and development of pathological fear and anxiety disorders. The reversal of fear conditioning may be a novel therapeutic approach to treat anxiety disorders. The current study aimed to examine fear conditioning and generalization as well as its reversibility in typically developing children and adolescents. We used an aversive conditioning paradigm adapted from Lau and colleagues (2008).
Methods: The conditioned stimuli were two neutral female faces (CS+/CS−), whereas a fearful and screaming face was the unconditioned

stimulus. Fear acquisition was followed by a generalization phase presenting four generalization stimuli (GS1–GS4): The GS1 to GS4 were composite faces of CS+ and CS−, blended from CS+ to CS− in 20% steps. Following fear generalization we implemented a discrimination learning task. Its design was based on the hypothesis that discrimination training will result in de-generalization. The training was presented to half of the probands in an active (relevant) version or inactive (irrelevant) version in regard to fear generalization. The relevant training consisted of the pairwise presentation of two neutral faces (CS−, CS+, GS1–GS4), and the participants' task was to decide whether these faces are equal or different from each other. By providing instant feedback the participants learned to correctly discriminate all faces shown during fear conditioning and generalization. All three phases (acquisition, generalization, de-generalization) were accompanied by psychometric measures of arousal, valence and contingency. Additionally physiological data on skin conductance, heart rate and the activity of the corrugator muscle were collected.

Results: Until now 42 voluntary participants (22 female) participated in the study (M = 13.1 years; SD = 2.1 years).

The first preliminary results indicate successful fear conditioning. Discrimination training resulted in a nominal decrease in generalization for the group with the relevant discrimination training.

Conclusion: Our preliminary data suggest successful reversal of conditioned fear generalization by discrimination training. The sample size will be increased during the next months.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Oral Presentation

Abstract Number:
82

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Co-Authors:
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Abstract Title:
The influence of trait anxiety on structural and functional brain development

Abstract Text:
Objective: Anxiety disorders (AD) are the most prevalent group of mental disorders [F Jacobi et al. (2014) Int J Methods Psychiatr Res 23:304–319] and characterized by an early onset [RC Kessler et al. (2007) Curr Opin Psychiatry, 20:359–364] as well as prevalent persistence into adulthood [K Beesdo-Baum et al. (2015) Soc Psychiatry Psychiatr Epidemiol 50:851–866]. Since AD have long-term consequences for child maturation [DS Pine (1997) Curr Opin Pediatr 9:329–338] in general, advancing our understanding of these disorders is important. Because temperamental factors, e.g. high trait anxiety, predispose for AD [JA Chambers et al. (2004) J Anxiety Disord 18:587–607], they represents potential targets to investigate pathogenic factors and developmental trajectories of AD.

Methods: To address the influence of trait anxiety on structural and functional brain development, we examined subjects on an anxiety spectrum (aged: 8–15 years), comprising experimental groups of high (HA), low anxious (LA), and AD patients using the Hariri Face match Task [AR Hariri et al. (2002) Neuroimage 17:317–323].

Results: We found group-specific developmental trajectories in left middle frontal gyrus (MFG) brain activation in terms of a decrease with age in LA and an increase in HA. A decrease of activation in left frontal regions hints towards a normal maturation of (right-lateralized) frontal control, which, in return seemed to be impaired in HA. Structural development revealed a significant volume reduction in the left amygdala in HA children and patients with AD. In AD patients, this was combined with a volume increase in the right MFG hinting towards altered maturation of fronto-limbic pathways in HA and AD patients. Group-specific correlations between trait anxiety and brain activation revealed differences between LA and HA bilaterally in the MFG with LA showing an increase of right MFG activation with trait anxiety and a decrease with left MFG activation suggesting a heightened focus of relevant frontal activation. In HA the opposite pattern was found, indicating a compensatory additional recruitment of the left MFG.

Conclusion: The level of trait anxiety predominantly influenced fronto-amygdala pathways in terms of delayed frontal maturation in both, high and pathologically anxious children supporting the importance of trait anxiety on the manifestation of AD.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Oral Presentation

Abstract Number:
93

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Abstract Title:
Waiting impulsivity and anxiety-related traits

Abstract Text:
Objective: Attention deficit/hyperactivity disorder (ADHD) is often comorbid with anxiety disorders. Recent studies indicate that comorbid anxiety affects task performance on a variety of neuropsychological tests, while reporting both improvement or worsening of cognitive impairments in ADHD patients. In this study we address the influence of anxiety traits on waiting impulsivity (WI), which is defined as the ability to regulate a response in anticipation of reward. WI can be assessed via the 5-choice serial reaction time task (5-CSRTT), which has recently been used as part of a translational model of ADHD. Neural correlates of WI are the prefrontal cortex, the nucleus accumbens and mediotemporal regions such as the amygdala and the hippocampus.

Methods: 5-CSRTT-performance, neural activation and anxiety measures (sensitivity and trait) were compared between 27 typically developing (TD) boys and 24 male ADHD patients aged 8–18 years.

Results: Comparison of the behavioral performance revealed that ADHD patients committed more premature responses, the predominant behavioral parameter of WI, and had lower accuracy measures as TD children. On the neural level, ADHD patients showed reduced

prefrontal activation in inhibition phases. Self-report anxiety sensitivity was negatively correlated with task performance in TD children while there was no significant effect in the patient group. However with regard to impulsivity-related brain activation, we found that prefrontal areas as well as the amygdala and hippocampus correlated significantly with anxiety parameters in ADHD patients but not in TD children.

Conclusion: Reduced prefrontal recruitment during inhibition phases is a common sign of immature top-down control. Therefore, enhanced frontal-limbic activation in ADHD patients reporting higher anxiety traits may be interpreted as compensatory brain activation in order to optimize brain arousal. These results add to recent evidence that mildly elevated anxiety traits may exert a protective influence on cognitive impairments observed in ADHD patients [BM Ruf et al. (2017) J Clin Exp Neuropsychol 39:434–448].

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Oral Presentation

Abstract Number:
97

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Abstract Title:
Subcortical brain volumes as endophenotypes of social anxiety disorder—preliminary findings from the Leiden Family Study on Social Anxiety Disorder

Abstract Text:
Objective: Endophenotypes are measurable characteristics and reflective of genetically-based disease mechanisms. They are associated with the disorder, heritable, and co-segregate with the disorder within families of probands. Thereby, the endophenotype approach could shed more light on the genetic vulnerability for social anxiety disorder (SAD). Alterations in subcortical brain structures are candidate endophenotypes of SAD, as gray matter volumes of these structures are heritable and SAD-related changes in subcortical brain volumes have been reported. We investigated subcortical brain volumes in a sample of SAD-patients and their family-members, testing the assumption that volumetric changes in these structures co-segregate with social anxiety within these families.

Methods: Nine families with a genetic predisposition for SAD participated in the Leiden Family Study on Social Anxiety Disorder. Families contained at least two SAD-cases and family-members of two generations were included (total sample n = 117, age range 8.9–61.5 years). Structural T1-weighted MRI brain scans were analysed using Freesurfer. Focus was on differences in brain volume in the putamen and pallidum, based on the results of an international mega-analysis of SAD structural MRI scans (Bas-Hoogendam and van Steenbergen et al., in prep.). Explorative analyses were performed for the amygdala, hippocampus and caudate. Regression models were fitted in R (https://www.r-project.org) with (subclinical) SAD, age, gender and intracranial volume as independent variables, and volumes as dependent variables; correlations between family members were modeled by including random effects. Heritability was estimated for regions showing significant associations between volume and (subclinical) SAD using SOLAR-Eclipse (http://solar-eclipse-genetics.org).

Results: Preliminary results showed a positive association between left putamen volume and (subclinical) SAD ($p = 0.02$). Heritability of left putamen volume was moderate ($h2 = 0.25$, $p = 0.075$). No relationships between volume and (subclinical) SAD were present in the other regions.

Conclusion: These preliminary analyses suggest an association between left putamen volume and (subclinical) SAD in families genetically enriched for SAD; furthermore, left putamen volume was moderately heritable (significant at trend-level). However, further family studies using larger samples are warranted to determine whether subcortical brain volumes are SAD-endophenotypes.

Category/Topic:
13 Depression

Abstract Type:
Oral Presentation

Abstract Number:
98

Author:
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Co-Author:
Li, Jie

Abstract Title:
Brain-derived neurotrophic factor gene polymorphism (Val66Met) combined with adverse stressful life event increase susceptibility to major depressive disorder

Abstract Text:
Objective: Both genetic and environmental factors contribute to risk of major depressive depression (MDD), but estimates of their relative contributions are limited. This differs depending on the adverse stimuli, but also varies across individuals and may be influenced by genetic pre disposition. A gene polymorphism in the brain-derived neurotrophic factor (BDNF) gene (Val66Met) is a strong candidate in this regard. The current study aimed to replicate and extend previous research in a new independent sample of Han Chinese; to explore the effects of BDNF gene polymorphism (Val66Met) and the interaction of gene-environment interactions between gene BDNF rs6265 and stressful life events (SLEs) on risk of developing MDD.

Methods: A total of 500 Han Chinese, including 250 patients suffered from MDD aged from 18 to 60 and 250 age- and gender-matched controls that have no life time of any psychiatric disorders, were investigated in our study. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to determine BDNF (Val66Met) genotypes. Hamilton Depression Scale (HAMD-17) was used to evaluate the severity of depression; and SLEs in the previous 12 months were evaluated by Life Event Scale (LES) in all subjects. MDD cases reported the events experienced 12 months before their worst depressive episodes; controls reported the events experienced 12 months prior to their interview. All statistical analysis was performed using SPSS20.0 statistical software. The binary logistic regression model of gene-environment interaction was

established to analyze the association of the gene-environment interaction between BDNF (Val66Met) genotypes and SLEs with MDD.
Results: The distribution of BDNF (Val66Met) genotypes and alleles were not related to the onset of MDD and severity of depression. The impact of negative SLEs was moderated by the BDNF genotype for the onsets of MDD using a Met dominant model (adjusted risk difference = 0.13, 95% confidence intervals = 0.056–0.243, $p = 0.002$). The patients with Met/Met genotype had higher scores in retard factor, core factor and Maier factor ($p < 0.05$) than the Met carriers.
Conclusion: In conclusion, polymorphism Val66Met in the BDNF gene may not be independently associated with MDD risk, but the Met allele of BDNF increases susceptibility of MDD by interacting with environmental risk factors in the Han Chinese population.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Oral Presentation

Abstract Number:
85

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Co-Authors:
Niemeyer, Helen; Engel, Sinha; Cwik, Jan; Knaevelsrud, Christine

Abstract Title:
Biological markers in psychotherapeutic treatment evaluation: a systematic review on the effects of psychotherapeutic interventions on HPA axis function in posttraumatic stress disorder

Abstract Text:
Objective: The approach of integrating biological markers into the evaluation of psychotherapeutic interventions is gaining growing scientific interest. It promises deeper insights into the mechanisms, effects and stability of psychotherapy.
This study aimed at reviewing studies investigating measures of the hypothalamus–pituitary–adrenal (HPA) axis in the course of psychotherapeutic interventions for posttraumatic-stress disorder (PTSD).
Methods: The review is part of a larger meta-analysis focusing on HPA axis function in PTSD. Based on strategies recommended by Lipsey and Wilson (2001), various databases were screened for relevant published studies. Additionally, we searched for unpublished data. Studies investigating markers of the HPA axis, such as cortisol, dehydroepiandrosterone (DHEA), or dehydroepiandrosterone-sulfate (DHEA-S) during the course of a psychotherapeutic intervention for PTSD were eligible for inclusion. A rating of the primary studies was conducted with regard to study quality and risk of bias as well as to quality of hormone assessment.
Results: Six studies met the inclusion criteria, including data from 197 PTSD patients (57.87% female). All studies assessed cortisol as a HPA axis marker in either saliva (k = 5), blood plasma (k = 2), or urine (k = 1). Basal concentrations of cortisol were assessed (k = 4), as well as cortisol reactivity (k = 3), cortisol awakening responses (k = 2), and diurnal profiles (k = 1). DHEA (k = 2) and DHEA-S (k = 2) were also investigated.
Quality and risk of bias ratings as well as data analyses regarding changes in HPA markers due to psychotherapeutic treatment are still ongoing. Results will be presented in the poster.
Conclusion: The body of literature evaluating psychotherapeutic interventions by means of psychological and biological measures is still thin and methodologically heterogeneous. Development of guidelines for the inclusion of biological markers in intervention studies will be discussed.

Category/Topic:
10 Stress-related and anxiety disorders

Abstract Type:
Oral Presentation

Abstract Number:
86

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Abstract Title:
Mindfulness in elite unit: a pilot study on adaptation to military stress

Abstract Text:
Objective: The military population is exposed to repeated, chronic psychological and physical stressors that can be exacerbated during deployments on operational theatres (External Operations—OpEx). Those stressful situations are known to impact health status of military and can lead to the emergence of psychopathologies such as Post-Traumatic Stress Disorders (PTSD) and depression anxiety-related disorders. Mindfulness has been proposed as a protective factor for coping with this stress.
With respect to the specific training that includes cognitive and emotional stress control techniques, soldiers of elite unit are considered to be in good health and expert in the stress management.
The primary aim of this work is to assess these soldiers in (1) their psychobiological functioning and (2) the psychopathological impact of an OpEx with respect to their Mindfulness level.
Methods: 26 soldiers from the elite unit of the Intervention Group of the National Gendarmerie (GIGN) were involved in a prospective study during an OpEx deployment. Psychological (including Mindfulness, mental health functioning and psychopathological status) and physiological (parasympathetic activity, BDNF and oxidative status) assessments were conducted prior to departure and three months after return.
Results: These soldiers have a protective psychological profile and a high level of Mindfulness. Mindfulness plays a protective role on their health, before and after the mission. This psychological functioning is associated with an overall protective level of BDNF (>8 ng/L) and a protective heart rate variability at rest.
Conclusion: The GIGN population appears as a model population in understanding the psychobiological mechanisms of adaptation to stress. Its high level of Mindfulness helps to limit the impact of intense stressors (such as those faced during OpEx). Being mindful can therefore be considered as a behavior that protects health. These results should encourage the development of a positive approach to military health.

Category/Topic:
11 Post-traumatic stress disorder

Abstract Type:
Oral Presentation

Abstract Number:
88

Author:
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Abstract Title:
Dynamic of combat relates PTSD in war veterans with brain injury

Abstract Text:
Objective: A person, after a war, comes into contradictions with the society, based on the feeling of alienation and the need for adaptation to conditions of peace. It is suggested that combat-related mental disorders (related to the extraordinary stress) are very important among medical and sociological problems. The actuality of these disorders is determined by polygenic and multifactorial essence of combat trauma (the impact of psychogenic trauma, ecological factors, physical brain injury etc.) as well as by increasing prevalence of current disorders.
Methods: Karabakh war veterans were observed during 20 years with the use of the CAPS PTSD scale, the Mississippi scale (the military version), the BPAQ questionnaire, the SCL-90 questionnaire, "The patients-combatants examination card", and clinical-psychopathological, somatic-neurological investigations.
Results: All patients met all criteria of CAPS. The average Mississippi scale measurement in the study group was 120.6 ± 15.8, in the control group (100.6 ± 29.7; $p = 0.0034$).

A marked increase in "hostility" measure (2.5 ± 0.8) (compared to the previous years 2.24 ± 0.16 in 1994; 1.71 ± 0.14 since 1999), also a clear dominance of aggression (36.6 ± 7.4) and total BPAQ measure (92.4 ± 15.8) were observed.

The high level of somatization (2.2 ± 0.5) is explained by the absence of strong emotional experiences, the presence of unconscious "suppressed" anxiety, and long-term intractable existential, social and labor issues.
Conclusion: Psychiatric trauma and the clinical manifestations of PTSD undergo significant essential and formal changes during the long-term dynamics of the disease, leading to negative PTSD dynamics. First, a veteran's combat trauma, in certain socio-political and economic conditions, grows into moral injury. Second, PTSD transforms from socio-psychological phenomenon into clinical one.

Category/Topic:
10 Stress-related and anxiety disorders

Abstract Type:
Oral Presentation

Abstract Number:
90

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Co-Authors:
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Abstract Title:
Antianxiety effect of a combination of geniposide and *Panax notoginseng* saponins

Abstract Text:
Objective: Although there are many available medical and psychological approaches proved efficacious, a sizable subgroup of generalized anxiety disorder individuals fails to make sufficient treatment due to the untoward effects, such as sexual dysfunction, drowsiness, and weight gain. The combination of geniposide (GP) and Panax notoginseng saponins (PNS) (also called Tong Luo Jiu Nao in the clinic) has been proved to be efficacious in several brain disorders, such as acute stroke (clinical study) and Alzheimer's disease (animal study). In addition, in previous behavioral studies, we found this combination could influence emotional functions and accompanied with few side effect. Therefore, in order to explore if this drug enjoys an antianxiety effect, we administrated with both acute and persisting method to evaluate anxiety in behavioral tests (Vera Klenerova, et al. 2015).
Methods: Wistar male rats (250–280 g) were handled for 5 min for 10 days before medical administration. The combination was administered intragastrically during three successive days (days 1–3) and then, the double TLJN dose was given on day 7. For the evaluation of anxiety-related behaviors, the open field was tested on days 1, 2, 3, 4, 8, 14, and elevated plus maze was tested on day 23.
Results: Under the treatment of the combination, in the open field test, rats showed significantly longer exploratory activity compared with negative control. And the effect persisted up to day 14 and day 22. In the elevated plus maze, again, the treatment reduced anxiety-like behavior observed even after 16 days.
Conclusion: The combination of GP and PNS reduced anxiety-like behaviors observed in both open field test and elevated plus maze. And the effect can be maintained for almost 2 weeks.

Category/Topic:
10 Stress-related and anxiety disorders

Abstract Type:
Oral Presentation

Abstract Number:
108

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Co-Author:
Walitza, Susanne

Abstract Title:
Frozen in the calm amidst the storm—is there a link to sensory hypersensitivity and dissociative experiencing?

Abstract Text:
Objective: The aim of the study is to develop a new model for the development of selective mutism. In the model presented, selective mutism is primarily seen as a child's reaction to an overload of stimuli. The breakdown of its ability to speak in these contexts is only one significant symptom among others induced by the overload. The model assumes that patients who suffer from selective mutism have an extraordinary high sensitivity for external and internal sensory stimuli accompanied by a tendency toward strong affective reaction.

As a consequence, the contrast between familiar and thus "safe" and unfamiliar and thus "unsafe" situations is perceived as amplified to the extent that a critical threshold gets passed. Subsequently, in complex "unsafe" social situations this can result in a stress reaction with the symptoms of a transmarginal inhibition. The system "freezes" and speaking thus becomes impossible while other symptoms also may prevail. Repeated similar experiences may continuously reduce the threshold for dissociative experience and increase the habituation to the non-speaking behaviour. Safe and familiar situations, in contrast, do not lead to a comparable overload reaction.
Methods: In a pilot study a sample of children suffering from selective mutism and their respective mothers were compared to a normal sample of children and adolescents. Both groups were compared regarding sensitivity, dissociation and anxiety assessed by inventories.
Results: Preliminary results confirm the new model of selective mutism: Selective mutism is significantly associated with high sensitivity and dissociation.
Conclusion: Dissociation and sensitivity appear to be relevant constructs allowing a better understanding of selective mutism in children.

Category/Topic:
7 Panic disorder

Abstract Type:
Oral Presentation

Abstract Number:
114

Author:
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Abstract Title:
Experience of panic symptoms and related concepts of distress among patients with anxiety disorders in Northern India: a mixed-method study

Abstract Text:
Objective: Cultural concepts related to the mechanisms of mental and bodily events contribute to the experience of anxiety disorders by determining the meaning and importance of particular symptoms. Cross-cultural research has highlighted differences in the presentation of panic attacks and panic disorder in terms of symptom profiles, underlying beliefs, and causal explanations. This study was carried out with the purpose of exploring the phenomenology of panic attacks and understanding their culturally relevant characteristics which have implications for diagnosis and psychotherapeutic intervention.
Methods: This study adopted a two-phase, exploratory sequential mixed methods design. The first phase utilized qualitative methods to capture culturally relevant symptomatology, catastrophic cognitions, and pathophysiologies; and incorporated them in a standardized instrument. Focus groups and key informant interviews involving various stakeholders (patients, carers, mental health and other medical professionals) were conducted for this purpose. This adapted instrument was then applied on a clinical population presenting with complaints of episodic anxiety (panic attack-like episodes) with a myriad of somatic and behavioral symptoms to study phenomenology and correlates of panic attacks and panic disorder and to relate them to DSM-IV and ICD-10 descriptions.
Results: Four major themes emerged from the analysis: (1) Differential panic symptom endorsement and culture-specific symptoms, (2) idioms of distress with underlying unique ethnophysiological concepts, (3) possible existence of cultural variants of panic attacks across anxiety disorders not confirming to ICD-10 or DSM-5 classical descriptions, (4) causal attribution of illness and help seeking.
Conclusion: This is the first ethnographic study on panic disorder from India. It provides preliminary insights into the issues of diagnostic universality and cultural specificity which require further systematic investigation.

Category/Topic:
4 Animal models of fear and anxiety

Abstract Type:
Oral Presentation

Abstract Number:
109

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Abstract Title:
Environmental and metabolic therapeutic strategies improve anxiety-like behaviour in a rat model of sporadic Alzheimer's disease

Abstract Text:
Objective: Cognitive impairment has often been associated with anxiety in Alzheimer's disease (AD) seen both in AD patients and its animal models. Literature data indicate that social interactions, as well as physical and mental activities, might have beneficial effects on both cognitive and non-cognitive behavioural impairments in AD condition. We used streptozotocin-intracerebroventricularly treated rats (STZ-icv) as a model of sporadic AD to investigate possible beneficial effect of enriched housing and oral galactose treatment (might replace glucose as an energy source) on anxiety and cognitive deficits found in the model.
Methods: Adult male Wistar rats were given STZ-icv (3 mg/kg) while controls received vehicle only (CTRL). In one experiment half of STZ-icv and CTRL groups received oral galactose treatment (200 mg/kg/day) for 2 months, starting 4 month after icv injections. In the other experiment, half of STZ-icv and CTRl groups was rendered for 9 weeks to enriched housing (EH), starting 3 weeks after STZ-icv treatment. Behavioural assessment was done by Morris Water Maze Swimming (MWM) test, Dry maze (DM) and Open field test (OF). Data were analysed by Kruskal–Wallis and Mann–Whitney U-test ($p < 0.05$).
Results: STZ-icv treated rats demonstrated significant deficit in learning and memory functions associated with increased anxiety found both 3 (31%/MWM; 142%/DM) and 6 (58%/MWM; 395%/OF) months after icv treatment. STZ-icv induced anxiety behaviour was normalised both by EH and galactose treatment, while cognitive deficits were normalised only by EH.
Conclusion: Results indicate that the long-term mental activities/social interactions and nutrient-based treatment alleviate anxiety-like

behaviour in STZ-icv rat model of sAD, while their effect on the cognitive deficits depends probably both on the therapeutic approach and the underlying pathology stage at which the therapy has been introduced (irreversible pathology found previously in the later stage). Supported by MZOS, DAAD and HRZZ-IP-2014-09-4639.

Category/Topic:
10 Stress-related and anxiety disorders

Abstract Type:
Oral Presentation

Abstract Number:
126

Author:
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Abstract Title:
On the roles of emotional intelligence and metacognitive beliefs for coping with chronic heart failure

Abstract Text:
Objective: The meta-cognitive model of GAD proposed by Wells (2005) postulates that increased anxiety can result from reinforced beliefs about uncontrollability and danger due to ineffective coping strategies. The present study was aimed at investigating the role of emotional intelligence (EI) in coping with distress caused by chronic heart failure (CHF) and to identify metacognitions explaining ineffective coping despite high EI.
Methods: A cross sectional design was used to assess $N = 100$ chronic heart failure patients ($M = 53.79$ years, $SD = 13.77$) at CPE Institute of Cardiology Multan, Pakistan. In addition to socio-demographic data, standardized questionnaires were used to gather information on EI, coping strategies, meta-cognitive beliefs, depression, anxiety, worry and quality of life.
Results: High trait EI was significantly correlated with lower levels of generalized anxiety ($r = -0.52$), worry ($r = -0.50$), anxiety sensitivity ($r = -0.38$), depression ($r = -0.34$), negative coping mechanisms ($r = -0.49$) and meta-cognitive beliefs about uncontrollability and danger ($r = -0.45$) respectively (all $p \leq 0.05$). In contrast high trait EI was significantly correlated with high levels of cognitive self-consciousness (0.21), positive coping strategies (0.39), emotional well-being (0.62) and high levels of energy and low fatigue (0.37; all $p \leq .05$). Stepwise regression analysis indicated that meta-cognitive beliefs about uncontrollability and danger significantly predicted negative coping strategies and accounted for 55.2% of variance. Mediation analyses revealed that meta-cognitive beliefs about uncontrollability and danger accounted for the negative relationship between trait EI and negative coping styles ($p \leq 0.03$).
Conclusion: In line with the meta-cognitive model of GAD, the current findings support the hypothesis that the negative correlation between high trait EI and negative coping is fully mediated by meta-cognitive beliefs of Pakistani CHF-patients about uncontrollability and danger.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Oral Presentation

Abstract Number:
127

Author:
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Panitz, Christian; Rosso, Isabelle M.; Dillon, Daniel G.; Kumar, Poornima; Hermann, Andrea; Whitton, Alexis E.; Hermann, Christiane; Pizzagalli, Diego A.; Mueller, Erik M.

Abstract Title:
Fear extinction recall modulates human fronto-medial theta and amygdala activity during simultaneous EEG-fMRI

Abstract Text:
Objective: Translating insights from rodent threat processing studies to human brains is both challenging and important, as assumed functional and structural homologies are controversial. Human neuroimaging (fMRI) and electrophysiological (EEG) studies, as well as animal studies, indicate that the amygdala and fronto-medial brain regions—including fronto-medial theta oscillations—are critically involved in conditioned fear. However, few studies have used a multimodal approach to probe interactions among these key brain regions in humans. Here, our goal was to bridge the gap between prior human fMRI, EEG, and animal findings.
Methods: Twenty-one healthy participants underwent a 240-trial fear conditioning and extinction paradigm. Using simultaneous EEG-fMRI recordings during a recall test 24 h later, conditioned stimuli presented (CS+E, CS-E) and not presented during extinction (CS+N, CS−N) were compared to identify effects specific to extinction versus fear recall.
Results: Differential (CS+ vs. CS−) electrodermal, fronto-medial theta (EEG) and amygdala activity (fMRI) were reduced for extinguished vs. nonextinguished stimuli. Importantly, effects on theta power covaried with effects on the amygdala response. Fear and extinction recall as indicated by theta explained 60% of the variance for the analogous effect in the right amygdala ($R^2 = 0.60$, $pFWE = 0.015$).
Conclusion: This study demonstrated that simultaneous EEG-fMRI can capture oscillatory (theta) and subcortical (amygdala) fear-related activity at the same time in the human brain. Mirroring prior rodent data, our findings show for the first time the interplay of amygdala and fronto-medial theta activity during fear and extinction recall in humans and lay the foundation for studying abnormal fear processing in psychopathology.
Policy of full disclosure: The study was supported by a grant of Justus Liebig University Giessen (Germany) to Erik M. Mueller and by a PROMOS scholarship of the German Academic Exchange Service to Matthias F. J. Sperl.

Over the past three years, Dr. Pizzagalli received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Pfizer, and Posit Science, for activities unrelated to the current research. Dr. Pizzagalli was partially supported by NIH grant R37 MH068376. Dr. Rosso was partially supported by NIH grant R01 MH096987. In the last three years, Dr. Dillon has served as a consultant for Pfizer on unrelated projects. Dr. Dillon was supported by NIH grant 4R00MH094438-03. Mr. Sperl was supported by DFG grant

MU3535/2-3 and Mr. Panitz was supported by DFG grant MU3535/2-1. The remaining authors declare no competing financial interests.

Category/Topic:
13 Depression

Abstract Type:
Oral Presentation

Abstract Number:
133

Author:
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Abstract Title:
Glucocorticoid receptor challenge tests in major depression: Linking glucocorticoids and cytokines

Abstract Text:
Objective: Impaired glucocorticoid signaling has been repeatedly observed in depression, however, baseline hormone measurements do not reliably detect such alterations. In contrast, glucocorticoid receptor (GR) challenge tests like the dexamethasone suppression test (DST) and the dexamethasone/corticotropin-releasing hormone (dex-CRH) test are supposed to uncover alterations of GR sensitivity, however, a lack of sensitivity and specificity hamper the standardized clinical application. Recent evidence demonstrates the usefulness of dexamethasone-stimulated gene expression for detection of GR sensitivity alterations.
Results: GR-induced gene expression together with cortisol and ACTH was measured before and 3 h after ingestion of 1.5 mg dexamethasone in participants with major depression. Additionally, the impact of plasma dexamethasone concentrations on hormone levels and GR-induced gene expression was determined. These findings are combined with the analysis of GR-induced alterations of cytokines as well as accompanying alterations of the adrenergic nervous system measured by heart rate variability.
Conclusion: In the first approach GR-induced gene expression successfully outperformed the common tests using only hormone measurements. In fact, GR-induced gene expression detected an impaired GR-sensitivity in depressed patients which was supported by preliminary evidence of GR-induced alterations in cytokines.

Category/Topic:
11 Post-traumatic stress disorder

Abstract Type:
Oral Presentation

Abstract Number:
132

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Abstract Title:
Monoamine oxidase A gene hypermethylation and posttraumatic stress disorder—insights from the South Eastern Europe (SEE)-PTSD study

Abstract Text:
Objective: Posttraumatic Stress Disorder (PTSD) can occur after experiencing severe traumatic events. Prevalence rates in war-affected regions, i.e. Bosnian-Herzegovina and Kosovo, are estimated at 35 and 25%, respectively. Noradrenergic dysfunction, e.g. elevated noradrenaline concentrations in the cerebrospinal fluid of PTSD patients, is suggested to play a crucial role in the pathogenesis of PTSD. DNA methylation of genes involved in the noradrenergic system such as the monoamine oxidase A (MAOA) gene is known to mediate the interaction between environmental influences and a genetic predisposition and therefore might contribute to the biological basis of the dysregulated noradrenergic tone shaping PTSD risk.
Methods: DNA methylation at 13 CpGs of the MAOA exonI/intronI was analyzed in PTSD patients [N = 216; m = 157, age (mean ± S.D.): 50.08 ± 6.74 years], remitted PTSD patients [N = 151; m = 98, age (mean ± S.D.): 49.48 ± 8.20 years] and healthy controls [N = 349, m = 232, age (mean ± S.D.): 48.81 ± 8.50 years] via direct sequencing of sodium bisulfite-treated DNA. Severity of PTSD symptoms was assessed by Clinician-Administered PTSD Scale (CAPS).
Results: In males, MAOA methylation was significantly associated with symptom severity (CAPS scores; r = 0.206, p = 0.016) in current PTSD patients, but not in remitted patients (r = 0.182, p = 0.100). In addition, methylation at three CpGs was significantly increased in current PTSD patients as compared to healthy controls (ps = 0.040–0.004) and at five CpGs as compared to remitted patients (ps = 0.034–<0.001). A significant positive correlation between MAOA methylation and symptom severity (r = 0.294, p = 0.033), but not the categorical association, was also observed in females.
Conclusion: Results from this multicenter study for the first time indicate a possible role of MAOA hypermethylation in PTSD, which —resulting in decreased MAOA expression—might confer increased noradrenergic signalling and thus constitute a biological risk marker of PTSD. Given robust replication, the extended noradrenergic system including MAOA mediating noradrenergic turn-over might be a promising target for innovative and individualized treatment options in PTSD based on epigenetic markers.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
130

Author:
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Co-Authors:
Buff, Christine; Feldker, Katharina; Neumeister, Paula; Heitmann, Carina; Bruchmann, Maximilian; Herrmann, Martin J.; Straube, Thomas

Abstract Title:
Inter-individual differences in trait anxiety shape BNST-amygdala coupling during brief threat processing

Abstract Text:
Objective: There is an ongoing debate on whether the amygdala and the bed nucleus of the stria terminalis (BNST) are differentially involved in phasic and sustained responses to threat. Recent reviews suggest that the role of the BNST is not limited to sustained threat contexts. Amygdala and BNST seem to form a closely connected functional unit for the processing of briefly presented threat-related stimuli. However, this has not been tested in human research and it is unknown whether inter-individual differences in trait anxiety moderate phasic responses and functional connectivity of amygdala and BNST during threat processing.
Methods: Using functional magnetic resonance imaging, we investigated activation and functional connectivity of amygdala and BNST, as well as the influence of trait anxiety, during processing of briefly presented threat-related relative to neutral images in a large sample of 93 healthy participants.
Results: Both amygdala and BNST showed increased activation during presentation of threat-related relative to neutral images. Furthermore, functional connectivity between BNST and amygdala was positively associated with trait anxiety.
Conclusion: These findings suggest that amygdala and BNST form a functional unit during phasic threat processing and that their functional connectivity is shaped by inter-individual differences in trait anxiety.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
131

Author:
Buff, Christine
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Co-Authors:
Brinkmann, Leonie; Bruchmann, Maximilian; Becker, Michael P.I.; Tupak, Sara; Herrmann, Martin; Straube, Thomas

Abstract Title:
Temporal dissociation of the bed nucleus of the stria terminalis and amygdala during threat anticipation in patients suffering from generalized anxiety disorder

Abstract Text:
Objective: Sustained anticipatory anxiety is a core symptom in Generalized Anxiety Disorder (GAD), facilitating its development and maintenance. According to an influential neurobiological model, the bed nucleus of the stria terminalis (BNST) is ascribed a specific role during sustained responses to threat, while phasic responses are associated with amygdala activity. In GAD patients, it has been hypothesized that sustained anticipatory anxiety may be linked to alterations in BNST activity, but to date, no firm evidence was reported yet. With the present investigation we aimed to disentangle phasic and sustained responses during threat-anticipation in GAD patients relative to healthy individuals (HC).
Methods: For that purpose, participants underwent functional magnetic resonance imaging during a temporally unpredictable threat anticipation paradigm. In order to disentangle temporally dissociable involvement of BNST and amygdala, we implemented phasic and a systematic variation of sustained response models for blood oxygen level-dependent responses during threat-anticipation.
Results: The results show that GAD patients relative to HC responded to threat minus neutral anticipation with elevated phasic amygdala and with delayed-sustained BNST activity.
Conclusion: Overall, our findings suggest that amygdala and BNST activation was altered in GAD during threat anticipation, albeit with different time courses. Importantly, all findings survived strong statistical criteria based on permutation test statistics. Especially the BNST findings underline for the first time the role of the BNST in sustained response to threat in GAD, and contribute to a deeper understanding of pathological anticipatory anxiety in GAD.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
128

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Merz, Christian J.; Wolf, Oliver T.

Abstract Title:
Generalizing extinction memory using pre-extinction stress

Abstract Text:
Objective: Extinction learning, which creates new safety associations, is thought to be the mechanism underlying exposure therapy, commonly used for the treatment of anxiety disorders and post-traumatic stress disorder. The relative strength and availability for retrieval of both the fear and safety memories determine the response to a given situation. However, while the fear memory is often context-independent and may easily generalize, extinction memory is highly context-specific. 'Renewal' of the extinguished fear memory might thus occur following a shift in context. Pre-learning stress was previously found to impair memory contextualization. Thus, the aim of the current work was to create an enhanced and generalized extinction memory using stress exposure before extinction learning, thereby preventing renewal.
Methods: In our contextual fear conditioning paradigm, 40 healthy men acquired (day 1), retrieved and extinguished (day 2) the fear memories, with no differences between the stress and the control group.
Results: A significant difference between the groups emerged in the renewal test (day 3). A renewal effect was seen in the control group ($N = 20$), confirming the context-dependency of the extinction memory. In contrast, the stress group ($N = 20$) showed no renewal effect. Fear reduction was generalized to the acquisition context as well, suggesting that stress rendered the extinction memory more context-independent.

Conclusion: These results are in line with previous studies that showed contextualization disruption as a result of pre-learning stress, mediated by the rapid effects of glucocorticoids on the hippocampus. Our findings further support the use of glucocorticoids in exposure therapy and suggest the right timing of administration in order to optimize their effects.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
129

Author:
Silva, Bianca Ambrogina
EPFL, Brain Mind Institute, Lausanne, Switzerland

Co-Authors:
Kintscher, Michael; Schneggenburger, Ralf; Gräff, Johannes

Abstract Title:
A cortico-thalamic-hippocampal circuit for remote fear memory attenuation

Abstract Text:
Objective: The experience of strong traumata can lead to the formation of over-enduring fear memories that risk degenerating into a pathological state known as post-traumatic stress disorder (PTSD). When recalled, previously acquired memories can enter a labile state when new information can be incorporated. This memory updating is likely to form the basis of successful treatments for PTSD, during which subjects are repeatedly exposed to the trauma-inducing stimulus in a safe environment, resulting in an attenuation of the fearful component of trauma-related memories.

Traditionally, the recall of recently acquired fearful memories is thought to be dependent on the hippocampus, whereas remote memory storage is said to rely more on higher cortical areas such as the medial prefrontal cortex. Nevertheless, here we hypothesize that hippocampal reactivation is necessary for remote memory updating. In particular, we posit that a bisynaptic cortico-thalamic-hippocampal circuit, involving the anterior cingulate cortex, the nucleus reuniens of the thalamus, and hippocampal area CA1, is critically involved in this process.
Methods: To test this hypothesis, we are combining virus-based tracing and inducible chemogenetic tools for neuronal activity manipulation of the neuronal populations that constitute this bisynaptic pathway during remote fear memory attenuation.
Results: Preliminary results suggest a causal role of the nucleus reuniens of the thalamus (NRe) in remote fear memory attenuation.
Conclusion: The completion of this project may lead to the identification of a putative novel brain circuit involved in remote fear memory attenuation, which may serve as a substrate for innovative therapeutic approaches against PTSD.

Category/Topic:
4 Animal models of fear and anxiety

Abstract Type:
Poster

Abstract Number:
120

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Co-Authors:
Remmes, Jasmin; Goedecke, Lena; Pape, Hans-Christian

Abstract Title:
Impact of the Neuropeptide S system and NPS-receptor polymorphisms on fear and anxiety

Abstract Text:
Objective: The neuropeptide S-system, consisting of the 20 amino acid-long peptide neuropeptide S (NPS) and its G-protein coupled receptor (NPSR1) have been shown to be involved in variety of autonomous and cognitive functions (e.g. stress, fear and anxiety, fear extinction, sleep–wake-cycle, arousal). In our own previous work we have analyzed the facilitation of fear extinction of cue conditioned fear and the attenuation of stress-induced impairment of fear extinction in mice following local intra-amygdalar NPS injections (Jüngling et al. 2008; Chauveau et al. 2012). In humans, a single-nucleotide polymorphism (SNP) in the neuropeptide S receptor (NPSR1) gene that has been linked to panic disorders and increased stress levels. Here we use a novel mouse model that was generated by the use of CRISPR/Cas9 mediated gene editing inducing an amino acid substitution of isoleucine (I) by arginine (N) at position 107 in the NPSR1 protein analogue to the SNP found in humans. Whole-cell patch-clamp recordings from principal-neurons (PN) of the anterior basal amygdala (BAa) show that the NPSR1 107N variant shows decreased signaling compared to the 107I variant. Moreover, NPSR1 107N expressing PNs are depolarized to a lesser extent, resulting in a hypoactivation of the amygdalar excitatory network. This mouse model will be used to analyze the impact of the human-relevant SNP on information processing within fear-relevant circuits and to investigate possible behavioral alterations caused by the differential efficacy of the NPS-system.
Methods: In vitro electrophysiology, fear conditioning
Results: In vitro recordings from principal neurons of the basal amygdala expressing the NPSR1 receptor containing N107 show a reduced NPS-dependent inward current as compared to neurons expressing the NPSR1 I107. In addition, neurons with the NPSR1 N107 are less like depolarized above action-potential threshold upon NPS application.
Conclusion: On the cellular level NPSR1 N107 or I107 variants affect the excitability of basal amygdalar neurons and thus might alter information processing within the amygdala.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
121

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Co-Authors:
Rüdt von Collenberg, Cora; Blum, Robert

Abstract Title:
Context-dependent induction of cFOS in hippocampal Parvalbumin-positive interneurons

Abstract Text:
Objective: In the hippocampus, fast-spiking Parvalbumin-positive interneurons (Parv + INs) form inhibitory microcircuits and organize local network activity. Parv + INs are suggested to sample activity in the surrounding network to mediate feed-forward or feedback inhibition. Both mechanisms are involved in memory-related formation of network oscillations. In the CA3 microcircuit, feed-forward inhibition by Parv + INs is essential for the precise processing of contextual memory in fear conditioning paradigms. Here we asked whether Parv + INs in the hippocampus undergo activity-related plasticity during retrieval of learned fear and whether this plasticity correlates with the exploration of the conditioning context. To answer these questions, we investigated cFOS induction in different regions of the hippocampus in fear retrieval. cFOS is an activity-dependent transcription factor and its de novo synthesis correlates with previous activity and activity-related plasticity in individual neurons.
Methods: Contextual fear conditioning and fear retrieval were conducted with 8–12 weeks old male mice. 90 min after fear retrieval, immunohistochemical analysis of Parvalbumin, cFOS and the neuronal marker NeuN was performed. Quantitative analysis of cFOS + immunoreactivity in neurons in serial confocal z-stacks was done by a person blinded to the respective genotype or condition.
Results: Our data show that context exposure induced cFOS expression in pyramidal neurons of the hippocampal CA3 and CA1 regions, but not in granule neurons of the dentate gyrus. Notably, this context dependent effect on pyramidal neurons was accompanied by a pronounced cFOS induction in the local Parv + INs in CA3 and CA1, but not in the dentate gyrus.
Conclusion: These data suggest that hippocampal Parv + INs of CA3 and CA1 microcircuits undergo activity-related plasticity during exploration of a previously visited context, indicating their involvement in contextual memory processing.

Category/Topic:
3 Cognitive-behavioural therapy (cbt)

Abstract Type:
Poster

Abstract Number:
122

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Co-Authors:
Preiss, Andrea; Walitza, Susanne

Abstract Title:
Behavior therapy of social anxiety disorder in children and adolescence

Abstract Text:
The aim of this workshop is to present a German CBT program for children aged 8 to 12 years (Melfsen and Walitza 2012).

At first an overview of the guidelines for therapies of social phobia in childhood and adolescence will be given. In contrast to most common programs which focus on a group therapy the program which will be presented, uses a single setting. The therapy mainly focuses on expositions accompanied by games like "Angstopoly", stories and comics. A further emphasis of the therapy lies on cognitive strategies. The therapy materials may be used in an individualized order instead of a predetermined sequence. In the workshop ideas for the playful arrangement and child adapted presentation will be given.

Some room will be reserved for feedback and exchange of experiences.

Category/Topic:
4 Animal models of fear and anxiety

Abstract Type:
Poster

Abstract Number:
123

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Co-Authors:
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Abstract Title:
Ultra-high field fMRI neural activation correlates with c-Fos cell density in the amygdala of 5-HTT knockout mice after negative stimuli

Abstract Text:
Objective: The short (s) variant of the serotonin transporter-linked polymorphic region (5-HTTLPR), which results in reduced serotonin transporter (5-HTT) mRNA, 5-HTT protein and 5-HT re-uptake, is associated with several different psychiatric disorders including affective disorders and anxiety disorders. 5 HTT blocking by selective serotonin reuptake inhibitors (SSRIs) is a major target for the treatment of depression. 5 HTTLPR s-allele driven amygdala hyperactivity in response to negative stimuli is confirmed in humans with no psychiatric disorders. Therefore, this genotype effect in the amygdala, a brain region involved in fear processing, has to be examined in 5-HTT knockout (−/−) mice, which are the predominant model organism for the investigation of affective and anxiety disorders and have been shown to be significantly more anxious in behavioural tests compared to their wildtype (+/+) and heterozygous (+/−) littermates.
Methods: In this study, long term cerebral perfusion changes are measured by ultra-high field functional magnetic resonance imaging (fMRI) in a 17.6 Tesla Bruker Avance 750 WB system with continuous arterial spin labelling (CASL) and serve as indicator for neuronal activation. In several studies predator odours like rat soiled bedding have been used to evoke fear and are also applied in this experiment via a ventilation system. Amygdalar resting state (RS), stimulation state (SS) and post-resting state (PRS) of female and male 5 HTT WT, HET and KO are measured. Subsequently, 2 h after odor presentation, brains were dissected and immunohistochemically stained for c-Fos as marker for activation on neuronal level.
Results: 5-HTT+/+ animals show a lower RS activity, but comparable SS amygdala activity levels as 5-HTT+/− and −/− animals. The percental signal change from RS to SS is significantly higher in the

5-HTT+/+ compared to the 5-HTT+/− and −/− mice. The density of c-Fos-ir cells per μm^2 in 5-HTT+/+ is significantly higher than in 5-HTT+/− and −/− animals in all investigated amygdaloid nuclei (La, BL, Ce). The percental signal change from RS to SS correlates significantly with the density of c-Fos-ir per μm^2.
Conclusion: These genotype effects differ from previous studies in healthy humans and may result from different processing of visual and olfactory stimuli up to the amygdala. Hence the c-Fos-ir neurons have to be further characterized regarding their properties.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
125

Author:
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Abstract Title:
Magnetoencephalographic correlates of right dorsolateral prefrontal cortex inhibition on the interplay of contextual threat processing and emotion perception

Abstract Text:
Objective: Emotion regulation and cognitive control are supported by right dorsolateral prefrontal cortex (rDLPFC) function. Stronger rDLPFC activation is found in response to threat-irrelevant visual stimuli that are presented in threat-associated vs. safe contexts [167–287 ms (Klinkenberg et al. 2016)]. This may reflect stronger top-down control. Reduced rDLPFC excitability following rTMS enhances early emotion-specific and -unspecific temporo-parietal activation to fearful and neutral faces [<170 ms (Zwanzger et al. 2014)]. Here, we combine both aspects to investigate if and how rTMS-induced rDLPFC inhibition modulates emotional face perception in threat-associated compared to safe contexts.
Methods: We tested 40 healthy participants in a $2 \times 2 \times 2$ factorial design with the between-subject factor rDLPFC inhibition (rTMS vs. Sham) and the within-subject factors threat (safe vs threat) and emotion (fearful vs. neutral faces). Following inhibitory rTMS or Sham stimulation, participants viewed threat-irrelevant fearful and neutral faces in blocks that did or did not contain unpredictable threat-events (i.e. a video of a monster). Neural sources of event-related magnetic fields were reconstructed using minimum-norm approaches.
Results: In midlatency time intervals (170–253 ms), facial stimuli presented in threat-associated vs. safe contexts elicited stronger rDLPFC and parietal activation. Following rTMS but not Sham stimulation, we found enhanced parietal activation in response to faces presented in threatening contexts (260–257 ms) and enhanced temporal activation in response to fearful but not neutral faces (130–160 ms). Replicating previous studies, we found no evidence for an influence of threat-context on emotion perception.
Conclusion: First, we conclude that the rDLPFC differentially influences face-perception in threat-associated vs. safe contexts, irrespective of the facial emotion. Second, rDLPFC excitability modulates the differentiation of fearful vs. neutral faces—irrespective of the context. These findings suggest the existence of independent emotion-regulatory mechanisms for emotion perception and contextual threat processing, both of which rely on rDLPFC-driven mechanisms.

Category/Topic:
10 Stress-related and anxiety disorders

Abstract Type:
Poster

Abstract Number:
124

Author:
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Co-Authors:
Gromer, Daniel; Pauli, Paul

Abstract Title:
Transferring the elevated plus-maze to a human context: a virtual reality study

Abstract Text:
Objective: The Elevated Plus-Maze (EPM) is a widely used apparatus to test anxiety in rodents. Studies showed that rats instinctively prefer the closed arms in all cases but this effect can be manipulated by the application of anxiolytic substances e.g. diazepam. So far, the EPM has not been used in human research to test for any observations connected to anxiety related variables.
Methods: Therefore, we converted the EPM into a virtual environment using a five sided CAVE-System, adjusted to human proportions. Similar to the original animal studies, participants were given the opportunity to freely explore the EPM for five minutes. Additionally, questionnaires were used to establish different levels of acrophobia, claustrophobia and Trait-Anxiety (STAI, Spielberger et al. 2012) in participants. Moreover, motion-tracking data as well as subjective anxiety ratings on different areas of the EPM were recorded.
Results: The results reveal that there is no specific preference of alleys. Further analysis identified height anxiety as a crucial influence on exploration behavior i.e. avoidance of open arm alleys but no effect for Trait-Anxiety was found. Consequently, we assume that in exposing human participants to a virtual elevated plus-maze different anxiety-related networks are activated and a direct conceptual transfer to a human context is not practicable.
Conclusion: Future research may focus on more realistic and natural versions of a human plus-maze to extend existing anxiety models for a better understanding of anxiety-related factors.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
110

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Co-Authors:
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Abstract Title:
Y2 receptors in anteroventral BNST control fear memory independent of previous extinction

Abstract Text:
Objective: Over-sensitization to unpleasant threatening situations may lead to excessive stages of fear and anxiety, long time after the critical event, eventually resulting in pathological conditions like posttraumatic stress disorders (PTSD). Here we test the hypothesis that neuropeptide Y (NPY) Y2 receptors in the ventral sector of the anterior bed nucleus of the stria terminals (BNSTav) interfere with expression of fear at remote stages after conditioning.
Methods: Classical fear conditioning and extinction: C57BL/6NCrl adult mice were exposed to a fear conditioning and extinction paradigm, and Y2 receptor-specific agonist (NPY3-36) or antagonist (JNJ-5207787) was applied locally in BNSTav at 24 h after conditioning. Fear expression was assessed at remote stages 16 days after conditioning in groups of animals that had or had not received prior fear extinction training after Y2 receptor manipulation
Results: Single stimulation or blockade of Y2 receptors in BNSTav resulted in facilitation or impairment of subsequent fear extinction, respectively, and in a lasting effect on the expression of remote fear depending on previous extinction training. Prior fear extinction facilitated the decline of fear at remote stages, which was impaired in animals that had received Y2 blockade, whereas high levels of remote fear in the group with no extinction training were reduced after previous Y2 stimulation in BNSTav. Assessing neuronal activation patterns after remote fear examination through immediate early gene (c-Fos) mapping in BNSTav revealed a decrease in c-Fos expression in BNSTav neurons after NPY3-36 treatment. Whether the relevant Y2 receptors are located on local interneurons or on presynaptic terminals of BNST afferents remains to be verified.
Conclusion: These results indicate that pharmacological Y2 receptor manipulation in BNSTav interferes with expression of fear at remote stages and may be used as a pharmacological support to suppress fear recovery with or without exposure therapies

Category/Topic:
13 Depression

Abstract Type:
Poster

Abstract Number:
112

Author:
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Abstract Title:
Depressive and anxiety symptoms correlate with reduced metabolic rates of lactate in brain

Abstract Text:
Objective: The mechanism of lactate induced panic attacks is not clear. Nevertheless anxiety disorders are often associated with elevated lactate blood levels. 'Organic affective', anxious, dissociative, and emotionally labile (asthenic) symptoms (ICD 10: F06.3-06.7) were no longer corresponding as common syndromes in the category of Neurocognitive Disorders (DSM-IV-TR and 5). Is there a link between emotional lability and mood changes on the one side and abnormal levels of cerebral metabolic rates of lactate on the other?

Recently, there is great evidence from in vitro and in vivo experiments that lactate supports glucose as a fuel source on enhanced transport from blood into the brain. It may help energetically the neurons by oxidation. Lactate is known as relevant in situations of chronic stress. No question, depression and anxiety are producing enduring stress.
Methods: 155 patients with organic brain syndromes of degenerative, vascular, alcoholic, toxic and other etiologies were classified by cluster, principal component, and discriminant function analysis of AMDP system rating variables (English version). Blood flow was determined by a modification of Kety and Schmidt and enabled to measure CMRs lactate, glucose and oxygen. The metabolic brain results were compared with the syndromes found.
Results: Brain oxidative metabolism differed significantly within the classified syndromes ($p(u) = 0.001$).
CMR lactate was half of normal in the depressive/anxious patients. Delusional patients showed similar changes.
Conclusion: There is an obvious lack of energy based on deranged, probably exhausted glucose and lactate metabolism in the brain. These syndromes differed also from those as grouped as personality, behavioral disorders and dementia looking on both lines, i.e. psychopathology ($p(u) = 0.0000$) and cerebral rates of lactate (see above). Deleteriously decreased impaired lactate metabolism is not able to account for around 10%–12% in the adult human brain.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
111

Author:
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Jerusalem, Israel

Co-Authors:
Tsuk, Yuval; Golderberger, Sagi; Gendler, Tamar; Shechner, Tomer

Abstract Title:
The neuroscience of childhood risk for adolescent anxiety disorders: A behavioral observation and ERP study of the behavioral inhibition temperament

Abstract Text:
Objective: The behavioral inhibition (BI) temperament can be identified in early childhood and is an established risk-factor for the eventual the emergence of adolescent anxiety disorders (AD). During development, children with BI show heightened social reticence, rejection, and AD -related behaviors. Problems in fear learning and fear memory are implicated in the etiology of AD, however their associations with BI are not yet understood. The current study uses

paradigms of fear conditioning and extinction to examine behavioral and neurocognitive processes undergirding fear learning in a unique sample of children with BI temperament.
Methods: Stage I: In this novel laboratory-based interaction task are observed in a dyadic interaction with an unfamiliar female confederate for up to 9 min. The unfamiliar adult follows a predetermined script, and the interaction is recorded and then coded using a comprehensive coding system. Established questionnaires for assessing BI will also be used to measure preadolescent's temperament. The dyadic-interaction task provides an additional ecological laboratory-based method for BI assessment with high face-validity. Our preliminary data indicate that the behavioral observation procedure distinguishes impressively between BI and non-BI participants.
Stage II: Participants complete a fear memory task with ERPs, in order provide insight into associations between impaired fear processing and the BI temperament. This study uses an age-appropriate fear-memory task designed for use with children. Preadolescent participants complete a fear learning task in which they are presented pictures of bells, and taught to fear one of them. After one week, preadolescents return to the laboratory to complete a fear memory task. Participants view pictures of bells with various threat levels, while self-reports and ERPs are recorded. In order to classify the neural bases for the behavioral phenotypes associated with BI, behavioral and ERP measures of fear-memory performance are analyzed in light of observed BI status.
Results: Early data indicate that BI, as observed through behavioral observation, has unique behavioral and ERP fear-memory patterns. This poster presents trends observed in this ongoing investigation, as well as additional data on the neurocognitive underpinnings of BI during preadolescence.
Conclusion: This study focuses on two issues of concerning BI as a childhood antecedent of AD: (1) the need to identify BI in preadolescents via a novel in vivo behavioral observation procedure, and (2) the examination of potential associations impaired fear processing and the shy/reticent BI phenotype.

Category/Topic:
9 Genetics and epigenetics of anxiety and stress

Abstract Type:
Poster

Abstract Number:
115

Author:
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Presenter:
Mössner, Rainald

Abstract Title:
Obsessive–compulsive disorder and anxiety: a genetics perspective

Abstract Text:
Objective: Anxiety is part of the clinical symptom spectrum of Obsessive–compulsive disorder (OCD). OCD is characterized by persistent, intrusive thoughts and urges (obsessions) and repetitive, intentional behaviors (compulsions), typically performed to reduce anxiety caused by obsessions. Especially, the interruption of obsessions or compulsions leads to massive levels of anxiety. OCD is the fourth most common psychiatric illness with a lifetime prevalence of 1%–3%, with a very high proportion of serious cases, based on national surveys.
Methods: Our major genetic findings in OCD will be contrasted with findings in anxiety disorders, to assess the extent of a common genetic basis of OCD and anxiety.
Results: OCD genes and OCD genomic changes assessed for relevance in anxiety include the serotonin synthesizing enzyme in the brain (TPH2) and SLITRK1, Copy-number variants (CNVs) as well as findings from the largest OCD meta-analysis to date which will be published later this year.
Conclusion: This presentation will provide new insights into a possible shared aetiology of OCD and anxiety disorders.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
113

Author:
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Co-Authors:
König, Christian; Voigt, Anne; Durairaja, Archana; Thöner, Juliane; Weiglein, Alicé; Khalili, Afshin; Ganesan, Mathangi; Yarali, Ayse; Gerber, Bertram

Abstract Title:
Timing-dependent valence reversal by optogenetic control of dopamine neurons

Abstract Text:
Objective: Reinforcers are basic motivators of behavior, and learning to predict them is of essential importance, to animals and man. Such predictions are important not only regarding the beginning, but also regarding the end of a rewarding or punishing stimulus. The beginning of punishment has negative valence, while its termination can have positive valence (relief), and in turn the beginning and termination of a rewarding stimulus can have positive and negative valence (deprivation). We study the role of dopaminergic reinforcement neurons for these processes.
Methods: In adult and larval Drosophila, we use optogenetic activation of single (sic) dopaminergic neurons at various timings relative to an odour presentation. Depending on whether the odour cue precedes or follows the dopaminergic reinforcement signal it can be learned as a signal for the beginning or termination of reinforcement, respectively.
Results: In adult flies we use the PPL1-01 neuron. If the odour cue precedes the activation of PPL1-01, it is avoided in a subsequent test, suggesting punishment learning. If the odour follows the PPL1-01 signal, it is approached, suggesting relief learning. In larvae, in turn, we activate the DAN-i1 neuron. If the odour cue precedes the activation of DAN-i1, the odour is approached in a subsequent test, suggesting reward learning. If the odour follows the DAN-i1 signal, the odour is avoided, suggesting deprivation memory.
Conclusion: Our results show that single dopaminergic neurons can establish memories of opposite valence, depending on the relative timing between their activation and predictive cues. Given the deeply

conserved mechanisms of dopaminergic reinforcement signaling across multicellular organisms, these findings from flies may inspire investigating similar processes in vertebrates and humans.

Category/Topic:
10 Stress-related and anxiety disorders

Abstract Type:
Poster

Abstract Number:
106

Author:
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Armed Forces Hospital Southern, Abha, Saudi Arabia

Co-Author:
Arfaj, Ibrahim

Abstract Title:
Psychosocial determinants to glycemic control among diabetic adults attending armed forces hospital southern region

Abstract Text:
Objective: To find out the magnitude of depression, anxiety, stress symptoms and some social factors among diabetic patients with their predictions and association to glycemic control
Methods: Case–control study was implemented at Ahad Rufaidah, Southern Region, Saudi Arabia where the glycemic uncontrolled patients (cases) were compared to those who were controlled (controls) regarding the prevalence of psychological symptoms and other related social and demographic factors. A consecutive sample of adult diabetic patients registered at the diabetic centers in armed forces hospital was chosen. Participants were classified into two groups, i.e., glycemic uncontrolled patients group and controlled glycemic group. A self-administered questionnaire was developed and used for collection of data. It includes personal characteristics diabetes-related variables and the Arabic version of the Depression, Anxiety, and Stress Scale (DASS-21).
Results: The study included 395 patients. Their age ranged between 18 and 90 years with a mean ± SD of 53.9 ± 13.1 years Most of them were males (70.1%). Depression was reported among more than half of the participants (51.9%) whereas anxiety and depression were reported among 70.1 and 37.7% of them, respectively. Glycated hemoglobin level was not significantly associated with depression, anxiety or stress. Among studied demographic and social factors, only marital status and smoking history were significantly associated with glycemic control. Single patients were more likely to have uncontrolled diabetes compared to married patients (95.2 versus 65.3%), $p = 0.025$. Smokers were more likely to have uncontrolled diabetes compared to non-smokers (87.5 versus 65.6%), $p = 0.007$.
Conclusion: There is evidence of high co-morbidity of diabetes and depression, anxiety and stress symptoms in Saudi Arabia. However, glycemic control according to HBA1c level was not associated with psychological issues in diabetic patients

Category/Topic:
11 Post-traumatic stress disorder

Abstract Type:
Poster

Abstract Number:
107

Author:
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Electrophysiology Research Center, Neuroscience Institute, Tehran, Tehran, Islamic Republic of Iran
Presenter:
Mokhtari Hashtjini, Mina

Co-Authors:
Pirzad Jahromi, Gila; Sadr, S.S; Sahraei, Hedayat; Javidnazar, Danial

Abstract Title:
Crocin enhanced deep brain stimulation impact in alleviating post-traumatic stress disorder (PTSD) symptoms in male rats

Abstract Text:
Objective: Post-traumatic stress disorder (PTSD), one of the most devastating kinds of anxiety disorders, is the consequence of a traumatic event followed by an intense fear. Crocin as an active constituent of the *Crocus sativus* L., commonly known as saffron used traditionally for stress and anxiety.

The effects of peripheral administration of crocin joined with deep brain stimulation (DBS) on post-traumatic stress disorder (PTSD) model caused by contextual fear conditioning (electrical foot shock chamber) were examined in male Wistar rats.
Methods: Sixty-four rats (220–250 g) were divided into 8 groups ($n = 8$), undergone stereotactic surgery to implant the electrodes in the right-BLn of the amygdala. After 7 days, some animals were received the foot shock, followed by another 7-days of the treatment schedules [DBS and DBS + crocin(5 mg/kg,i.p)] then freezing behavior was measured as a predicted response in absence of the foot shock (re-exposure time). Blood serum corticosterone level and the amygdala c-fos protein expression were assessed using ELISA and Western blot, respectively. Further, dopamine- dependent behaviors (freezing) and general anxiety (elevated-plus maze test) were evaluated.
Results: PTSD decreased serum corticosterone level and increased both amygdala c-fos expression and dopamine-dependent behaviors. Peritoneal administration of crocin (5 mg/kg) combined with DBS treatment significantly ($P < 0.001$) raised the serum corticosterone level and reduced both c-fos expression and dopamine-dependent behaviors. Moreover, the general anxiety measured by EPM test indicated a significant ($P < 0.001$) change compare with another group.
Conclusion: We argue that these results might have potential in treatment-resistant PTSD patients as an alternative and completely therapeutic strategy.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
101

Author:
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Co-Authors:
Pape, Hans-Christian; Seidenbecher, Thomas

Abstract Title:
Contribution of CRF and 5-HT in the anterodorsal BNST to phasic and sustained fear in freely behaving mice

Abstract Text:
Objective: Sustained fear paradigms in rodents have been developed to model clinical situations in patients suffering from long-lasting anxiety disorders. Rodent data suggest that short-lasting (phasic) fear responses rely on the central amygdala, whereas more long-lasting (sustained) fear responses critically depend on the bed nucleus of the stria terminalis (BNST). Conditioned fear can be mediated by the amygdala via corticotropin-releasing factor (CRF), a stress hormone that acts on receptors in the BNST. CRF-containing cell bodies and CRF receptors were found in high concentrations in the BNST and CRF neurons co-localize with 5-HT (Serotonin) terminals in this brain region.
Methods: Therefore, in this study we used a pharmacological approach combined with fear behavioral protocols in a recently established phasic/sustained fear mouse model to reveal the critical involvement of CRF and 5-HT of the anterodorsal BNST in the modulation of sustained fear (long-lasting conditioned freezing).
Results: Bilateral local application of a CRF1-receptor agonist (Stressin I) before fear memory retrieval, 24 h after predictable CS-US training, induced a sustained component of fear (maintained freezing) indicating the critical contribution of the CRF1-receptor during sustained states of conditioned fear. Application of saline (control) revealed only phasic fear 24 h after predictable CS-US pairing as expected. Bilateral local application of a 5-HT2A-receptor antagonist (R-96544) either before unpredictable CS-US training or before fear memory retrieval, 24 h after unpredictable conditioning, blocked the sustained component of fear while phasic fear component was not affected, indicating the critical contribution of serotonergic transmission mediated by the 5-HT2A- receptor during sustained states of conditioned fear. Saline application as control revealed sustained fear 24 h after unpredictable CS-US pairing.
Conclusion: In summary, here we show the critical contribution of CRF and 5-HT in the anterodorsal BNST to phasic and sustained fear in freely behaving mice. In addition, this study will advance the understanding of clinical anxiety and its treatment strategies and will thus provide a putative perspective for pharmacological treatments that specifically target the BNST.
Supported by Deutsche Forschungsgemeinschaft SFB-TRR 58, TP A02

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
102

Author:
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Co-Authors:
Kühnel, Anne; Teckentrup, Vanessa; Colic, Lejla; Schultz, Myron; Fan, Yan; Walter, Martin

Abstract Title:
Effects of Neurexan® on emotional brain response

Abstract Text:
Objective: Neurexan®, a medicinal product sold over the counter (OTC), contains passionflower, oat, coffee and zinc valerianate. Neurexan® has been investigated in patients with symptoms related to acute stress, nervousness and insomnia. Amygdala is involved in the development of fear and emotional behavior. Acute stress sensitizes the amygdala, thereby increasing vigilance/anxiety, which in turn promotes the stress response. Amygdala reactivity to negative stimuli is a reliable phenotype that closely associates with stress regulation and can be assessed with Hariri paradigm. Furthermore, a linkage between an increased level of stress hormones and increased emotional response to angry faces has been shown in patients with social phobia. Previous investigation suggested an attenuated neuroendocrine stress response in healthy volunteers induced by Neurexan®. Thus, our aim was to further explore the effect of Neurexan® on the emotional brain response in the amygdala.
Methods: In a randomized, placebo-controlled, double-blind, two-period crossover trial brain response to the Hariri task, an emotional paradigm, of 39 healthy, moderate stressed males was measured after intake of a single dose of Neurexan® and placebo control via 3 Tesla functional magnetic resonance imaging. Data were preprocessed and analyzed in SPM12. Amygdala was anatomically defined by the AAL (Automated Anatomical Labelling Atlas).
Results: Hariri task was firstly validated for negative emotional faces response. Significant (peak level FWE corrected) bilateral activations of fusiform gyri, amygdalae and prefrontal cortex as well as unilateral activation in right thalamus were confirmed as previously reported. Paired t-test showed a treatment effect ($p < 0.05$) in the left amygdala, with stronger activations in placebo than in Neurexan® condition.
Conclusion: We found a significant reduction of BOLD response to negative faces in the left amygdala during the Neurexan® session as compared to placebo. Neurexan® reduced the emotional brain response to negative stimuli.
Policy of full disclosure: The study was funded by Biologische Heilmittel Heel GmbH, Baden-Baden, Germany.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
89

Author:
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Co-Authors:
Kneer, Katharina; Romanos, Marcel; Neufang, Susanne

Abstract Title:
Trait anxiety modulates fear learning and fear generalization in fronto-limbic pathways of the developing brain

Abstract Text:

Objective: Alterations in fear conditioning and generalization are considered to play an important role in the pathogenesis of anxiety disorders (AD). Since heightened trait anxiety is a risk factor for AD, we hypothesized a manifestation of this risk even at younger ages in terms of altered fear conditioning and generalization in combination with impaired fronto-limbic processing.
Methods: We investigated 32 typically developing volunteers (15 female), aged 10 to 15 years (12.0 ± 1.4 years) and screened for trait anxiety using the STAI-C, with a differential fear conditioning and generalization paradigm. Ratings of valence, arousal and contingency awareness as well as fronto-limbic activation were analyzed to indicate fear learning and generalization. Additional correlations with STAI-C scores quantified the impact of trait anxiety on experimental parameters.
Results: Successful conditioning was approved by (a) higher arousal ratings for the CS+ compared to CS− (b) higher contingency judgements for CS+ after conditioning and (c) CS+-induced brain activation bilaterally in fronto-temporal regions including the hippocampus. Additionally, fronto-hippocampal activation varied as a function of trait anxiety in terms of increased left middle frontal gyrus (MFG) activation and a decrease in hippocampal and right MFG regions.
Generalization processing was reflected by increased activation bilaterally in the MFG. Here, trait anxiety correlated positively with the left SFG and the amygdala as well as negatively with the right MFG and the hippocampus.
Conclusion: Given that right fronto-hippocampal activation reflects "cognitive" learning processes and amygdala activation represents the emotional fear component, we argue that higher trait anxiety seemed to impair learning processing during the conditioning phase and enhance amygdala activation and disturb learning processing during generalization.

Category/Topic:

4 Animal models of fear and anxiety

Abstract Type:

Poster

Abstract Number:

91

Author:

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Co-Authors:

Richter, S. Helene; Gamer, Matthias; Kaiser, Sylvia; Sachser, Norbert

Abstract Title:

What a difference a day makes—behaviour of female mice is less predictable near ovulation

Abstract Text:

Objective: While "animal personalities" have been shown to exist in many species, fluctuations in the stability of these inter-individual behavioural differences are not well understood. Against this background, we aimed to investigate whether the temporal stability of personality traits like anxiety is affected by the reproductive cycle.
Methods: Female mice were tested twice at an interval of eight weeks in four paradigms assessing anxiety-like behaviour and exploratory locomotion as well as social interest. Twenty-two individuals were tested repeatedly near ovulation, whereas another twenty-two were tested repeatedly in the non-receptive phase.
Results: While we found no major behavioural effects at the group level, the reproductive state indeed had profound effects on behavioural stability over time: anxiety-like behaviour and exploratory locomotion as well as social interest proved to be significantly less predictable near ovulation.
Conclusion: It is generally believed that phenotypic plasticity is limited due to the costs it brings about. In this context, our data indicate that females accept higher costs in the receptive phase, which is directly related to fitness maximization.

Category/Topic:

4 Animal models of fear and anxiety

Abstract Type:

Poster

Abstract Number:

92

Author:

Remmers, Floortje
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Co-Authors:

Lange, Maren Denise; Bartsch, Julia Constance; Pape, Hans-Christian; Lutz, Beat

Abstract Title:

Cell-type selective and brain-region specific knockout of the cannabinoid CB1 receptor using CRISPR/Cas9 to study its role in specific amygdala-BNST projections regulating sustained fear

Abstract Text:

Objective: The endocannabinoid system is involved in the regulation of many physiological processes via suppression of neurotransmitter release. Previously, cannabinoid CB1 receptor-containing projections from the basolateral amygdala (BLA) and central amygdala (CeA) to the anterodorsal part of the bed nucleus of stria terminalis (adBNST) were found to be necessary and sufficient for the transition from phasic to sustained fear. However, several cell types within the BLA and CeA contain the CB1 receptor and thus might be responsible for this effect.
Methods: In order to induce a cell-type and region-specific knockout of the CB1 receptor, adeno-associated virus (AAV) expressing CB1-gene-specific guideRNA will be injected bilaterally into the amygdala of mice that conditionally express Cas9 in distinct neuronal cell populations by using distinct Cre driver lines.
Results: Before administering the CB1-gene-specific guideRNAs in vivo, they were tested for efficacy and specificity in cell culture by T7 endonuclease mutation detection and by Tracking of Indels by Decomposition (TIDE). GuideRNAs with satisfactory efficacy and specificity were cloned into AAV plasmids, AAVs were generated, and injected into the hippocampus of mice that ubiquitously express Cas9 for in vivo verification. The resulting mutant mice will be characterized histologically, electrophysiologically, and behaviorally.
Conclusion: With the verified mouse model, we will study the role of CB1 in distinct receptor-containing neuronal projections in regulating the transition from phasic to sustained fear. Specifically, we will investigate the effects of ablation of CB1 from CeA/BLA-adBNST projections origination from neuronal populations positive for cholecystokinin, corticotropin releasing hormone, protein kinase Cδ, or somatostatin.

Category/Topic:
4 Animal models of fear and anxiety

Abstract Type:
Poster

Abstract Number:
87

Author:
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Co-Authors:
Klassen, Irene; Ossendorf, Edith; Kaiser, Sylvia; Sachser, Norbert; Richter, S. Helene

Abstract Title:
Assessment of cognitive judgement bias in laboratory mice: Utilising a tunnel-based discrimination task

Abstract Text:
Objective: Information processing in the brain can be influenced by emotional states, a phenomenon referred to as cognitive bias. Thus, an individual's appraisal of an ambiguous environmental cue can serve as an indicator of its underlying emotional state. A growing body of evidence suggests negative cognitive biases to be implicated in the aetiology of psychological disorders, such as anxiety disorders or depression in humans. Consequently, the development of appropriate methods to assess them in animal models has gained major importance. Since mice are the predominantly used animal model in biomedical research, the aim of this study was to develop a cognitive bias task for this species, based on ecologically relevant cues.
Methods: Initially, mice had to accomplish a discrimination task, in which they learned to associate two different tunnel lengths with an either high or low reward. In the consecutive judgement bias test, animals were confronted with three intermediate tunnel lengths, constituting ambiguous cues. One of the tunnels represented the exact intermediate length between the trained discriminatory cues, while the others resembled the positive or negative cue, respectively. The animals' response to the ambiguous cues was assessed and taken as a measure for their cognitive judgement bias.
Results: As expected, the animals' interpretation of the three intermediate tunnel lengths differed significantly. Tunnel lengths resembling either of the previously trained cues were judged accordingly, while choice scores in test trials with the exact intermediate tunnel length reflected highest degrees of ambiguity.
Conclusion: In summary, the here presented method constitutes a novel and promising approach to investigate cognitive bias in laboratory mice. Provided that the paradigm can be validated, it has the potential to considerably facilitate the assessment of animal emotion in neuropsychological research.

Category/Topic:
7 Panic disorder

Abstract Type:
Poster

Abstract Number:
99

Author:
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Abstract Title:
Exposure-based cognitive behavioral therapy is equally effective in panic disorder patients with and without a history of traumatic event exposure

Abstract Text:
Objective: Although cognitive behavioral therapy (CBT) is highly effective in the treatment of anxiety disorders, many patients still do not benefit. Traumatic events have been associated with neurobiological and psychological changes that might moderate the response to later treatment of mental disorders such as panic disorder. This study investigates whether a history of traumatic event experience is negatively associated with outcomes of CBT for panic disorder.
Methods: Post-hoc analysis of 301 (228 females) patients with panic disorder treated with 12 sessions of manualized exposure-based CBT in a multi-center study. Treatment outcome was assessed at post-treatment (Hamilton Anxiety Scale, Clinical Global Impression Scale, Panic and Agoraphobia Scale, Mobility Inventory).
Results: Among patients who completed CBT for panic disorder, traumatized and non-traumatized individuals did not differ regarding pre-post treatment effect size in any of the assessed outcome measures except for lower improvement in Panic and Agoraphobia Scale Scores in male patients ($b = -0.57$, 95% CI -1.02 to -0.12, $p = 0.014$). There was also a trend towards an association between trauma history and dropout among female patients (traumatized: 18.8%, non-traumatized: 10.5%; OR = 2.0, 95% CI 0.9–4.2, $p = 0.079$).
Conclusion: Findings suggest that exposure-based cognitive behavioral therapy is equally effective in panic disorder patients with and without a history of traumatic event exposure. The possibility of a somewhat lower treatment effects on specific panic symptoms in traumatized males and a higher risk for treatment dropout in traumatized female patients warrant further investigation. Future studies should focus on subgroups among traumatized individuals that might be less responsive to CBT.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
100

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Co-Authors:
Herrmann, Martin; Polak, Thomas

Abstract Title:
Modulation of extinction-processes by transcranial direct current stimulation

Abstract Text:

Objective: Although anxiety disorders are a widely spread mental disorder the effectiveness of their therapy is still unsatisfying. Transcranial direct current stimulation (tDCS) has already been used to improve psychotherapy but the underlying mechanisms have not been properly investigated yet. We hypothesized that tDCS could improve extinction processes, which happen to be the main functional factor of exposure based therapy for anxiety disorders.

Methods: To examine our hypothesis, we used a fear conditioning paradigm with female faces as conditioned stimuli and a 95-dB female scream as unconditioned stimuli. We aimed to stimulate the ventromedial prefrontal cortex with tDCS because this region is involved in extinction learning. For tDCS we applied two 4 × 4 cm electrodes approximately at the electrode positions F7 and F8 (anode right, cathode left) with a current of 1.5 mA. The stimulation was started after the acquisition phase, ran during a 10-min-break between acquisition and extinction and went on until the end of the experiment so that our subjects received 20 min of stimulation after all. 40 healthy subjects were randomly and double blinded assigned into a sham-stimulation and a real-stimulation group. To measure the fear reactions, we used skin conductance responses (SCR) and subjective ratings. SCR data were analyzed using a general linear model based approach (PsPM).

Results: We hypothesize that that tDCS will improve the extinction processes, so that our findings can be used to improve anxiety therapies more specifically in the future.

Category/Topic:

1 Fear conditioning, extinction and generalization

Abstract Type:

Poster

Abstract Number:

94

Author:

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Co-Authors:

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Abstract Title:

The effects of cannabidiol in fear memory generalization and its related behavioral outcomes

Abstract Text:

Objective: Fear memory generalization is a prominent feature of post-traumatic stress disorder. Animal studies investigating how to attenuate this maladaptive process could advance the mitigation of traumatic memories. Cannabidiol (CBD), the major non-psychotomimetic phytocannabinoid present in Cannabis sativa, is a potential candidate to achieve this goal. The objective of the present work is to evalate the CBD effect in fear memory generalization.

Methods: Male Wistar rats were submitted to a strong contextual fear conditioning (CFC) protocol that consisted of familiarization, conditioning, Test A (memory retrieval in the paired context) and Test B (generalization expression in the unpaired context). All sessions were conducted 24 h apart. After seven days, the animals were re-exposed to Test A and Test B. In each experiment the rats received CBD (3, 10 or 30 mg/kg ip) immediately after conditioning. On the following days they were exposed to TestA and to TestB. Freezing behavior was evaluated. Repeated measures ANOVA followed by Newman-Keuls test was used as statistical analysis.

Results: In experiment 1, no differences were found during Test A. During Test B, CBD-treated rats (10 and 30 mg/kg) presented less freezing than control in a long-lasting manner. Only in experiment 2, rats were subjected to a weaker CFC. During Test A, CBD-treated group (10 mg/kg) presented less freezing. In experiment 3, CBD-treated group (10 mg/kg) presented less resistance to fear extinction. In experiment 4, CBD-treated rats (10 mg/kg) presented less 22 kHz ultrasonic vocalizations during Test B. In experiment 5, the CBD effect in fear generalization was abolished by the systemic or hippocampal antagonism of CB1 (AM251 1.0 mg/kg or 50 pmol) or CB2 (AM630 0.3 mg/kg or 10 pmol) receptors. The inhibitor of anandamide catabolizing enzyme (URB597 1.0 mg/kg) impaired fear generalization.

Conclusion: Altogether, CBD given during a traumatic memory formation impairs fear memory generalization and its related behavioral outcomes. This effect depends on systemic or hippocampal CB1 and CB2 activation and is mediated by anandamide.

Category/Topic:

10 Stress-related and anxiety disorders

Abstract Type:

Poster

Abstract Number:

96

Author:

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Co-Authors:

Santl, Julia; Plab, Andreas; Kudielka, Brigitte; Wüst, Stefan; Shiban, Youssef

Abstract Title:

Trier social stress test in virtual reality: Does gender or social anxiety affect self-reported, physiological, and endocrine reactivity?

Abstract Text:

Objective: The Trier Social Stress Test (TSST) is commonly used to investigate stress reactivity in controlled laboratory settings by instructing participants to deliver a speech and to solve arithmetic problems in front of a committee. Its implementation in virtual reality (VR) enables an investigation of stress response under more easily controllable conditions. The aim of this study was to examine and compare stress responses depending on gender and social anxiety in a VR version of the TSST (VR-TSST).

Methods: Sixteen women and 16 men underwent a VR-TSST using a head-mounted display (HMD) setup. Sympathetic activity and cardiovascular activity were measured by recording electrodermal activity and heart rate. To investigate hypothalamic pituitary adrenal (HPA) axis activity, saliva cortisol samples were collected. Experienced stress levels were assessed during the TSST, whereas data concerning stress processing, judgment of the situation, and presence in VR were collected after the VR-TSST.

Results: The VR-TSST effectively induced an endocrine, physiological, and self-reported stress response, indicated by a significantly increase in cortisol, electrodermal activity, stress level, and negative affect. Half of the participants were classified as cortisol responders. Gender and social anxiety differences were found in the self-reported measures of stress levels and stress processing. Interestingly, gender did not predict cortisol response.
Conclusion: Our findings confirm earlier results that a VR-TSST is suitable to induce social stress. The similar cortisol response for both genders may hint on differences in processing a VR-TSST than an in vivo TSST. Further possibilities to enhance HPA responses should be investigated.
Policy of full disclosure: AM is stakeholder in a commercial company that develops virtual environment research systems. All other authors have no potential conflicts of interest.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
95

Author:
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Co-Authors:
Datunashvili, Maia; Lange, Maren; Verma, Dilip; Pape, Hans-Christian

Abstract Title:
Classification of neuropeptide y neurons in the BNST

Abstract Text:
Objective: The amygdala is known as a key area for integration of affective stimuli and formation of emotional memory. Recent studies implicate the anterior section of the bed nucleus of stria terminalis (BNST), as a key player in stress- and arousal-dependent modulation of fear memory expression. Neuropeptide Y (NPY) and its receptors can be found throughout the amygdala, the anterolateral (BNSTal) and anteroventral BNST (BNSTav). NPY is known to have an anxiolytic effect when applied systemically, while Y2 receptor (Y2R) agonism in the central Amygdala (CeA) seems to have an anxiogenic effect. Additionally, NPY and Y2R expression is upregulated in chronic restraint stress in the BNST in a stress-susceptible mouse line. Moreover, the deletion of Y2R in the CeA and basolateral amygdala (BA) results in an anxiolytic phenotype. Thus, NPY and Y2R may play a crucial role in the development of stress-related fear memory. Therefore, the present study was undertaken to characterize the critical role of NPY in the neuronal network of the extended amygdala, which may contribute to the previously observed behavioral phenotype.
Methods: Whole cell patch-clamp recordings were performed in acute brain slices from an NPY-GFP labeled mouse line.
Results: Upon cluster analysis, we identified different cell clusters in the BNSTal and –av, as well as distinctive electrotonic and electrogenic properties of NPY-positive and -negative neurons. Furthermore, we could show, that presynaptic Y2R activation reduces transmitter release onto both NPY-positive and –negative neurons. By combining optogenetic and electrophysiological approaches, we identified an input-specific Y2R-dependent modulation of synaptic transmission from CeA to BNSTav and BNSTal.
Conclusion: Taken together, our data contributes to the understanding of the cellular composition of the BNST and identifies a Y2R-modulated pathway from BA to BNST that might relate to stress-dependent modulation of fear processing.

Category/Topic:
11 Post-traumatic stress disorder

Abstract Type:
Poster

Abstract Number:
81

Author:
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Co-Authors:
Niemeyer, Helen; Cwik, Jan; Knaevelsrud, Christine; Schumacher, Sarah

Abstract Title:
HPA axis regulation in posttraumatic stress disorder: a meta-analysis

Abstract Text:
Objective: Posttraumatic stress disorder (PTSD) is a pathological response to a traumatic event involving exposure to actual or threatened death, serious injury or sexual violation. Among the most salient biological abnormalities that are associated with the development and maintenance of PTSD, is a complex dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis.
This meta-analysis aims at reviewing HPA axis regulation in PTSD that is reflected in concentrations of HPA axis markers such as cortisol, dehydroepiandrosterone (DHEA), and its sulfate form DHEA-S. Studies that investigate either basal alterations in hormone levels, or HPA axis reactivity (i.e. after exposure to a stressor) or changes due to psychotherapeutic treatment, are reviewed.
Methods: The literature search followed the search strategies recommended by Lipsey and Wilson (2001). Various databases were screened for relevant published studies. Additionally, we searched for unpublished data and a snowball search system was used for the identification of further potentially relevant studies. Both control group designs (healthy controls or controls with other mental disorders) and single group designs were suitable for inclusion. With regard to the PTSD group, studies examining subjects with clinical PTSD were eligible for inclusion. Both groups had to be diagnosed with standardized diagnostic criteria. With regard to biomarker assessment, studies using single as well as multiple time points of measurement were included. Moreover, all common forms of hormone assessment, that is, cortisol assessment in urine, blood, saliva and hair as well as studies measuring DHEA and DHEA-S in blood and saliva were eligible.

A rating of the primary studies was conducted with regard to study quality and risk of bias as well as to hormone assessment. For effect size estimation, studies were combined in separate data sets according to their design.
Results: Data analysis is still in progress. Results will be presented in the talk and discussed critically.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
83

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Co-Authors:
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Abstract Title:
Attentional mechanisms in combined context and cue extinction learning using the NPU-threat test

Abstract Text:
Objective: The NPU-paradigm is nicely suited to investigate threat cue vs. context conditioning. Three different context cues indicate safety (N), predictable (P) or unpredictable threat (U) while foreground cues reliably signal an upcoming shock in the P condition only. Previously, we used an adapted version of the NPU paradigm and recorded steady-state visual evoked potentials (ssVEPs) to quantify attention allocation during threat acquisition. In the present study, we followed up on these findings and investigated the temporal dynamics of extinction after cue-/context-conditioning in high (HA) vs. low anxious (LA) individuals.
Methods: To this end 30 LA and 30 HA participants completed a modified NPU-paradigm followed by an extinction phase. In addition to ssVEPs, we obtained subjective threat and shock contingency ratings of central and context cues.
Results: Results show increased threat and contingency ratings of context cues in the U-condition and of the central cues in the P-condition. HA participants showed in general higher threat- and contingency-levels for context cues. During extinction, HA participants showed a slower decrease of threat and contingency ratings for context cues in the U-condition. Preliminary ssVEP analysis showed that electrocortical responses to context and central cues differentiated between the conditions in the acquisition phase only.
Conclusion: The results support the view that HA participants are more sensitive to threat and extinguish more slowly - especially to contextual anxiety - than LA.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
84

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Abstract Title:
Can fear generalization be reversed by a discrimination training?

Abstract Text:
Objective: Current findings have shown that fear generalization gradients can depend on the stimuli's perceptual similarity to the conditioned cue. In two studies, we examined the reversibility of fear generalization in healthy people.
Methods: In each study, participants were randomly divided into two groups. One group (Study 1 and 2: N = 15, each) underwent a de-generalization task, where participants had to discriminate two facial stimuli presented simultaneously. The other group (Study 1 and 2: N = 14, each) underwent a control task, where animal pictures were compared. All participants went through a differential threat conditioning, during which a female face (conditioned stimulus, CS+) was associated to a desperate scream (unconditioned stimulus, US), but not a second face (CS−). During the generalization phase, CS+ and CS− were presented again and four additional morphs (GS1-GS4) of these faces. In Study 1, the discrimination training was conducted after generalization phase in order to reduce fear generalization, while in Study 2 before conditioning to prevent it.
Results: In both studies, CS+ elicited higher skin conductance response (SCR), arousal and probability ratings, as well as lower valence ratings than CS−. Conditioned fear was generalized to the stimulus most similar to the CS+ (GS1) visible in elevated SCR as compared to the CS−. All ratings showed fear generalization to GS1 and GS2, and for arousal and probability ratings in Study 1 also to GS3. The de-generalization task could neither reduce nor prevent fear generalization as no interactions including stimulus and group were found.
Conclusion: In conclusion, we found successful fear acquisition, which was then generalized to the perceptually most similar cues. However, the applied de-generalization task resulted ineffective, possibly because of little fear generalization or easiness of the tasks. For future studies, we suggest to improve discrimination learning by increasing the trial number or by involving working memory processes.

Category/Topic:
10 Stress-related and anxiety disorders

Abstract Type:
Poster

Abstract Number:
77

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Abstract Title:
Stress management and the role of Rhodiola rosea

Abstract Text:
Objective: Stress describes the physiological reaction to threat or pressure, which may be self-driven or external. The adaptogen Rhodiola rosea is reputed to have a dual mode of action: normalising the release of stress hormones and activating ATP synthesis. Thus, Rhodiola rosea can alleviate both psychological and physical symptoms of stress.

Here we present stress symptoms, their clinical relevance and their effect on health. Furthermore, we evaluate different stress management strategies, focusing on the role of Rhodiola rosea.
Methods: In December 2016, the authors met to discuss the health consequences of stress, stress management options and the role of Rhodiola rosea. They reviewed the current therapeutic options and reached a consensus in the form of a treatment scheme.
Results: If stress symptoms like exhaustion, lack of energy, irritability or tension are left untreated, they can lead to chronic stress states, burnout and secondary diseases. Coaching is the usual psychological form of care for work-related chronic stress, but if stress symptoms persist together with continuously demanding life circumstances, pharmacological intervention may become necessary to prevent serious mental and social sequelae. However, current medication therapy reveals a treatment gap: Many herbals, vitamin combinations or medicines like synthetic antidepressants, benzodiazepines, antihistamines and betablockers usually tend to target only either psychological or physical stress symptoms. Besides, chemical entities often have unacceptable side effects and may bear a risk of overtreatment. An ideal pharmacological therapy should offer a comprehensive treatment of all relevant stress symptoms combined with an excellent safety profile. Rhodiola rosea potentially fills the existing treatment gap: In clinical studies, it demonstrated positive effects on both physical and psychological symptoms of stress, burnout and chronic fatigue and was shown to be safe and well tolerated. Furthermore, it may play a role in the prevention of secondary diseases such as type 2 diabetes, cardiovascular diseases and depression by inhibiting the release of pro-inflammatory cytokines.
Conclusion: Due to its mode of action, Rhodiola rosea provides both physical and psychological stress symptom relief together with an excellent safety profile. It thus helps to close the treatment gap for clinically relevant stress symptoms.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
78

Author:
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Co-Authors:
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Abstract Title:
Context conditioning and generalization in panic disorder and comorbid major depression

Abstract Text:
Objective: Exaggerated reactivity to unpredictable aversive events and overgeneralization of conditioned fear have been proposed as crucial factors in the etiology and maintenance of panic disorder (PD). Although major depression disorder (MDD) is one of the most frequent comorbidities in PD, the modulating influence of this comorbid state on threat responding and generalization is still not well understood.
Methods: To investigate modulatory influences, 20 participants with PD, 20 with PD and comorbid MDD and 20 healthy controls underwent differential context conditioning followed by a generalization phase in virtual reality (VR). During acquisition, an electric stimulus (unconditioned stimulus, US) was delivered unpredictably in one virtual room (anxiety context, CTX+), but never in a second room (safety context, CTX−). During generalization, participants visited CTX+ and CTX− again as well as a generalization context (G-CTX) composed of features of both acquisition contexts, while no US was administered.
Results: We found successful context conditioning in all groups indicated by significant higher arousal, anxiety and contingency ratings, as well as fear potentiated startle and larger skin conductance level (SCL) to the CTX+ versus the CTX-. After generalization, individuals with PD generalized anxiety as both the CTX+ and the G-CTX were rated more arousing than the CTX−. On the contrary, startle responses were attenuated in the G-CTX compared to CTX+ and CTX−. Comorbid individuals, however, displayed attenuated responses in startle and skin conductance during the CTX+, but increasing responses in the generalization context. Interestingly, arousal ratings paralleled these physiological responses.
Conclusion: These results suggest that depressive comorbidity may alter the generalization of anxiety responses in individuals with panic symptoms. While both clinical groups may share the tendency to generalize anxiety on the verbal level, defensive response mobilization on the automatic level seems to be divergently modulated in dependence of symptomatology and sensitivity towards contextual threat.
Policy of full disclosure: PP is shareholder in a commercial company that develops virtual environment research systems for empirical studies in the field of psychology, psychiatry, and psychotherapy. No further potential conflicting interests exist.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
80

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Gamer, Matthias

Abstract Title:
How do attentional processes mediate acquisition of fear?

Abstract Text:
Objective: This study makes use of a novel multi-cue paradigm to examine how preferential attention toward threat and safety cues emerges during fear conditioning and contributes to learning and extinction. Specifically, participants are confronted with cues that are differentially predictive for an aversive electric shock (US). Two cues are ambiguous and paired with the shock in 50% of the trials. One cue serves as a threat cue (100% CS-US contingency) and one as a safety cue (0% CS-US contingency), respectively. After establishing these contingences in the first half of the experiment, they are switched in the second half (i.e., the previously ambiguous cues become predictive of threat or safety, respectively). In approximately 27% of trials, ambiguous cues are presented together with threat or safety predicting

cues to examine preferential attentional orienting toward predictive parts of these multi-cue displays. Altogether, this design allows for determining how fast and how reliable attention is captured by threat- or safety-predicting information, respectively, and how flexibly this pattern is adjusted after switching contingences.
Methods: Skin conductance, eye movements, and self-reported trait anxiety levels are acquired. Each trial results in the delivery or omission of the US. Shock intensity is individually adjusted with the aim of reaching a moderate level of pain. Participants accomplish a shock expectancy rating using a 5-point Likert scale (0 = no shock expected, 2 = uncertain, 4 = shock expected) after stimulus onset.
Results: Building upon our previous work with blocking paradigms (Eippert et al. 2012), we suppose that participants gradually learn CS-US contingencies and preferentially attend to predictive cues when being presented together with an ambiguous cue (multiple-cue displays). This pattern should be particularly pronounced for those subjects who quickly acquire knowledge of CS-US contingencies. Such pattern is indicated by a fast reduction of the associability (cp. Pearce & Hall, 1980) for threat- or safety predicting cues, respectively. We are going to contrast fast with slow learners by their associability decline and we expect fast learners to show an earlier gaze preference for the threat or safety predicting cue when being presented together with an ambiguous stimulus. On an explorative basis, we will also examine correlations of response patterns with anxiety trait measures.
Conclusion: Until now, 12 of 48 subjects have been acquired. We expect to be able to provide final results during the conference.
Policy of full disclosure: SFB-TRR 58

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
79

Author:
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Co-Author:
Andreatta, Marta

Abstract Title:
Effect of stress-induction on remote threat conditioning: translating an animal model to humans

Abstract Text:
Objective: More and more research is examining the effect of stress on threat conditioning, as important model for the etiology of anxiety disorders. An animal model found that stress-induction 10 days prior to threat conditioning impaired extinction learning. In the ongoing study, we want to translate this animal study and investigate in humans, whether stress experienced 10 days before learning might still affect the fear memory trace.
Methods: Twenty healthy participants were randomly divided into two groups. On Day 1, the stress-group (N = 13) underwent a socially evaluated cold pressor test (SECPT), while the other group (sham-group, N = 7) had to immerse the hand into lukewarm water. Ten days later, all participants underwent differential threat conditioning during which participants received a mild painful electric stimulus (unconditioned stimulus, US) at the offset of one geometrical shape (conditioned stimulus, CS+), but never at the offset of another shape (CS−). During extinction learning (24 h after conditioning) participants re-saw both CSs, without any US-delivery. Startle responses and subjective measures (valence, arousal and anxiety ratings towards CSs) were the learning indices.
Results: On an explicit level (ratings), threat acquisition (increased discriminative responses between CS+ vs. CS−) and extinction (decreased discriminative responses between CS+ vs. CS−) occurred. In valence ratings, the stress-group showed higher differentiation (CS+ vs. CS−) in extinction learning in comparison to the sham-group. Interestingly, on an implicit level (startle response) threat acquisition (startle potentiation to CS+ vs. CS−) and extinction learning (comparable responses to CS+ and CS−) were only found in the sham-group.
Conclusion: These results indicate that stress-induction ten days prior to threat conditioning may differently affect implicit and explicit conditioned fear responses: Implicitly, stress impaired threat acquisition, whereas it enhanced extinction learning explicitly. However, preliminary interpretations have to be considered with reservations due to small sample size and statistical power.

Category/Topic:
7 Panic disorder

Abstract Type:
Poster

Abstract Number:
73

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Abstract Title:
Characterizing the nature of emotional-associative learning deficits in panic disorder: Results from a fMRI study on fear conditioning and delayed extinction

Abstract Text:
Objective: Emotional-associative learning is used a translational model for the development, maintenance and treatment of panic disorder (PD). The exact nature of the underlying fear learning and extinction deficits however, still remains under debate. Using a three-day paradigm to clearly separate the distinct learning and consolidation processes, we aimed to gain insights into the neurofunctional substrates of altered fear conditioning and extinction as a function of PD.
Methods: In contrast to studies employing one-session fear conditioning paradigms, a delayed fear extinction task was conducted for the purpose of disentangling neural networks involved in fear acquisition, extinction and recall of fear-related memories. Using fMRI, quality-controlled datasets from 10 patients with PD and 10 healthy controls were available from 3 consecutive days (day 1: habituation and acquisition; day 2: extinction training; day 3: extinction recall) with human faces serving as CS's (CS+; CS−; reinforcement rate: 100%) and an aversive auditory stimulus (panic scream) as US.

Results: PD patients showed heightened bilateral amygdala and insula activation in response to the CS+ than the CS− during early acquisition, while they exhibited no differential activation during extinction training. Patients also showed stronger insula activation during late extinction recall than did healthy controls.
Conclusion: Stronger neural activation in fear-network structures during early acquisition can be interpreted as accelerated and stronger fear conditioning as a function of PD pathophysiology, while stronger insula activation during extinction recall could represent attenuated extinction recall. Future studies should investigate the predictive value of experimental measures of extinction recall for clinical relapse.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
76

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Abstract Title:
Fear generalization: new approaches of vagus nerve stimulation on fear relapse

Abstract Text:
Objective: Extinction learning might be the underlying mechanism of exposure therapy to treat anxiety patients. An animal study showed more stable extinction learning due to vagus nerve stimulation. We applied a combined cue in context conditioning paradigm in humans and investigated the effects of transcutaneous VNS (tVNS) on context-dependent fear generalization.
Methods: During acquisition on Day 1, all participants received sham tVNS and were guided through two offices in which two colored lights were alternately switched on. In one office (CTX+), a mildly painful electric stimulus (unconditioned stimulus, US) was administered at the offset of one light (conditioned stimulus, CS+) but not of the other (CS−). In the second office (CTX−), both CSs were presented, but no US was administered. Thirty minutes prior to extinction and between the two extinction phases, participants received either sham (N = 20) or real tVNS (N = 21). Extinction was identical to acquisition, but without US administration. Day 2 started with the application of sham tVNS and three USs for reinstatement. Afterwards, participants were guided through CTX+, CTX− and an additional generalization context (G-CTX), which consisted of 50% CTX+ and 50% CTX−. CSs were presented in all contexts and no further US was delivered.
Results: Analyses of startle responses indicated successful cue and context conditioning and extinction. On Day 2, startle responses were potentiated in CTX+ compared to CTX− and G-CTX. Interestingly, the tVNS group showed slightly lower startle responses to CS+ compared to CS- in G-CTX indicating reduced fear generalization. Sham stimulated participants showed potentiated startles for CS+ compared to CS− in G-CTX.
Conclusion: Current results underline the importance of a strong extinction memory to reduce context-dependent fear generalization. Therefore, tVNS might be a promising addition to exposure therapy.

Category/Topic:
7 Panic disorder

Abstract Type:
Poster

Abstract Number:
71

Author:
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Abstract Title:
Behavioral and neurofunctional effects of cognitive behavioral therapy on secondary social anxiety disorder in primary panic disorder: a longitudinal fMRI study

Abstract Text:
Objective: Social anxiety disorder (SAD) is a frequent comorbidity of panic disorder (PD) and agoraphobia (AG). Yet, there is little knowledge on the effect of comorbid SAD on the neural substrates of PD/AG and whether exposure-based treatment specifically tailored to primary PD/AG also targets behavioral and neurofunctional correlates of secondary SAD.
Methods: We conducted an exploratory post hoc functional magnetic resonance imaging analysis of 42 PD/AG patients from a randomized clinical trial ("Panic-Net") including 14 (33%) patients with comorbid SAD (PD/AG + SAD). A differential fear conditioning task served as the neurofunctional probe of interest. Patients were assessed before and after standardized exposure-based cognitive behavioral therapy (CBT).
Results: PD/AG + SAD patients showed a reduction in primary PD/AG as well as secondary SAD symptomatology following treatment. At baseline, PD/AG + SAD patients exhibited enhanced neural activation in the temporal lobe, inferior frontal operculum and amygdala during fear conditioning which attenuated after CBT to the level of PD/AG-SAD.
Conclusion: Exposure that is tailored to PD/AG bears potential to generalize to SAD symptomatology. On a neural level, specific signatures of secondary SAD affect the ventral object recognition pathway and defensive system network. This signature was effectively reduced following CBT. Future studies should more strongly consider comorbid anxiety disorders as potential confounders on behavioral and neural levels of analysis.

Category/Topic:
10 Stress-related and anxiety disorders

Abstract Type:
Poster

Abstract Number:
157

Author:
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Co-Authors:
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Abstract Title:
Neural changes in response to a home-based attention training in children with social phobia

Abstract Text:
Objective: Attentional biases (AB) towards threatening faces are a major feature of social anxiety disorder. At a neural level, AB have been indexed by enhanced amplitudes of P1, reflecting increased perceptual processing, and P2, indicating difficulties to remove attention from threatening information. According to Eysenck et al.'s theory (2007), AB would be due to an attention control deficit whose retraining has shown promising results in adults. The aims of this study were to evaluate the efficacy of a home-based attentional training on AB in children with clinical social phobia and to index the neural changes induced by this procedure.
Methods: After a first evaluation of AB, fifteen 8 to 12-year-old socially anxious children (mean = 10.12; SD = .76) completed 10 sessions of attentional retraining after what they completed a second evaluation of AB. AB were assessed by a visual dot-probe task in which children had to detect neutral targets cued by neutral or disgusted faces. During retraining sessions, the targets systematically followed the neutral faces to train children to engage their attention towards safety cues. Children completed the Social Phobia and Anxiety Inventory for Children, the State-Trait Anxiety Inventory and the Brief Fear of Negative Evaluation Scale before and after the training.
Results: Results showed that attentional training had no positive impact on AB in terms of response latencies or accuracy. However, the P100 amplitude was significantly decreased after the training for both disgusted and neutral faces, indexing a diminished perceptual processing of faces. No significant effect of the training was found on ERP components associated with targets processing. Finally, the protocol had a positive impact on the fear to be negatively evaluated by others which is a symptom of social anxiety.
Conclusion: These results indicate that a home-based attentional training may not seem sufficient to modulate the behavioural expressions of AB towards threat. However, positive effects observed at electrophysiological levels lead us to conclude that P100 can be considered as a neurobiological marker of treatment's efficacy.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
160

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Co-Authors:
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Abstract Title:
The effect of acute stress on working memory and impulsivity—a review and future directions

Abstract Text:
Objective: Experiencing acute stress is thought to affect cognition and behavior which are believed to be driven by underlying stress-related psychophysiological mechanisms. In this regard, working memory (WM) and impulsivity (IMP) constitute prominent and well-studied facets of cognition and behavior, respectively. There is an ongoing debate about whether stress actually enhances or impairs cognitive and behavioral performance. A narrative review addressing effects of acute stress on WM and IMP may contribute to this debate by summarizing previous knowledge and raising questions for future research.
Methods: Relevant publications were identified by using PubMed search (publications up to May 2017). We included only peer-reviewed English-language publications which investigated acute stress effects in healthy participants (overall age range: 9–77) by comparing performance in a WM task or IMP task (a) before and after stress induction or (b) after stress induction vs. after a control condition.
Results: Overall, 30 WM and 11 IMP studies fulfilled our inclusion criteria. For both WM and IMP, there was a heterogeneous picture, with acute stress having an enhancing, impairing, or no effect on performance. Findings further suggest that stress-induced effects were partly specific for sex, genotype, or cortisol stress responders.
Conclusion: The review of the current literature revealed (a) a smaller number of fitting studies than expected and (b) inconclusive findings. This inconsistency might be partly explained by methodological differences among studies (e.g., study design, type of stressor, cognitive/behavioral task, outcome measure, sample characteristics) which limit the comparability among findings. Future studies need to consider these limitations. For example, a stressor which elicits a reliable and valid stress response is essential for investigating stress-induced effects. A suitable task is mandatory to study reliable WM or IMP performance. Potential confounders and moderators such as sex differences, genetic contributions, or psychopathology related to cognition and behavior might be addressed in future studies.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
158

Author:
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Co-Authors:
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Abstract Title:
Effects of Neurexan® on brain regions associated with emotional expectancy

Abstract Text:
Objective: Neurexan® is a medicinal product containing four diluted plant and mineral ingredients, passionflower, oats, coffee and zinc valerianate. It has been shown to reduce nervousness, restlessness,

acute stress, and insomnia by modulating biological auto-regulating processes. Induced stress sensitizes the amygdala, which increases vigilance and in turn drives the stress response. This is mediated by an amygdala-prefrontal cortex (PFC) circuit, in which stress impairs the top-down cognitive functions of prefrontal regions, while strengthening the emotional bottom-up responses of the amygdala. We therefore hypothesized that Neurexan® may induce changes in amygdala activation during emotion processing elicited by an emotional expectancy task.

Methods: The drug effect was investigated in a randomized, placebo-controlled, double-blind, two-period-crossover clinical trial. The brain response of 37 male subjects (age range: 31–59) to the emotional expectancy paradigm was measured after intake of a single dose of Neurexan® or placebo by 3T functional magnetic resonance imaging. In the emotional expectancy task, negative, positive, and neutral IAPS pictures were presented, half of them preceded by visual cues. The visual cues before picture presentation were arrows pointing up (positive picture), down (negative picture) and to the right (neutral picture). The drug effect was assessed with paired t-test analysis comparing drug and placebo condition in the contrast expectancy positive > expectancy negative.

Results: We found amygdala activation in response to expected pictures, negative neutral, and positive. Furthermore, we observed significant differences in activation of the left amygdala during the expectancy task after the intake of Neurexan® as compared to the placebo condition. The differences in activation are explained by reduced changes in amygdala reactivity modulated by Neurexan®.

Conclusion: The intake of a single dose of Neurexan® effects emotional processing represented by left amygdala activation and decreases amygdala reactivity during expectancy of emotional pictures.

Policy of full disclosure: Research Support: This study was funded by Biologische Heilmittel Heel GmbH.

Category/Topic:
9 Genetics and epigenetics of anxiety and stress

Abstract Type:
Poster

Abstract Number:
152

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Abstract Title:
Investigating glucocorticoid receptor binding in lymphoblastoid cell lines with differing genetic risk profiles

Abstract Text:
Objective: The glucocorticoid receptor (GR) is a key regulator of the stress response system. Upon activation, the GR translocates to the nucleus where it regulates the transcription of specific genes. It has been demonstrated that functional variants in a subset of these GR responsive genes are associated with the risk of developing major depressive disorder and schizophrenia (Arloth et al. 2015). Therefore, the first objective of this project is to investigate whether high and low genetic risk profiles are associated with differential GR binding.

Methods: To investigate GR binding we used GR chromatin immunoprecipitation sequencing (ChIP-seq) in lymphoblastoid cell lines (LCLs). For this purpose, we activated GR by stimulating the cells with its agonist, dexamethasone. For the IP, chromatin fragments were required to be between 200 and 700 base pairs. To yield fragments within this range, three sonicators were compared: Covaris, Bioruptor and a Branson Probe Sonifier.

It is known that FKBP5 is a target of GR. Therefore, we used this locus to verify whether GR was activated with our stimulation condition. To assess enrichment, qPCR was performed using probes for FKBP5.

Results: Of the three shearing methods tested, the Branson 250 Probe Sonifier yielded fragments within the desired size range. Using a specific GR antibody, an IP was performed on these fragments. We found a sixfold enrichment compared to our control IP (IgG).

Conclusion: During this preliminary phase of the project, we successfully optimized the stringent conditions required for GR ChIP. Specifically, shearing the chromatin into a specific size range is crucial to ensure the specificity of the IP. GR ChIP-seq will provide valuable insight into how common variants in GR responsive loci contribute to the development of psychiatric disorders.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
154

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Co-Authors:
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Abstract Title:
Effects of natural medicinal on brain responses to deviant stimuli during an auditory oddball task

Abstract Text:
Objective: Neurexan®, a natural pharmaceutical product sold over the counter (OTC), contains diluted plant and mineral components: passionflower, oats, coffee and zinc valerianate. Neurexan® has been investigated in patients with symptoms related to acute stress and nervousness. It was shown that stress is associated with cognitive impairments, as for example during the oddball paradigm. Previous research suggested an attenuated neuroendocrine stress response in healthy volunteers induced by Neurexan®. This study further explores the effects of Neurexan® on cognitive performance. Expecting that Neurexan® reduces the stress level, we hypothesized that the subjects in the placebo group would be more susceptible to distraction compared to treatment group during an oddball paradigm coupled with an EEG measurement.

Methods: In a randomized, placebo-controlled, double-blind, two-period crossover trial, brain responses of 39 healthy, moderately stressed males were measured during an unattended auditory oddball paradigm via 64-channel electroencephalogram (EEG) after intake of a single dose Neurexan® or placebo. The paradigm consisted of 80%

standard tones and two types of deviant tones (10% frequency deviant; 10% duration deviant), presented in a pseudo-randomized order.
Results: RmANOVA with within-subject factors treatment (drug/-placebo) and deviant-type (frequency/duration) showed significant treatment by deviant-type interaction ($F(1, 37) = 8.828$, $p = 0.005$, $\eta^2 = 0.193$) on the latency of the mismatch negativity. The Wilcoxon-test confirmed that Neurexan® significantly reduced latency of the frequency deviant ($z(37) = -2.85$, $p = 0.004$).
Conclusion: We observed a difference between the placebo and Neurexan® for the latency of mismatch negativity to deviant tones (frequency deviant). Our findings suggest that Neurexan® induces subtle primary processing changes additionally to its postulated top-down effects.
Policy of full disclosure: The study was funded by Biologische Heilmittel Heel GmbH, Baden-Baden, Germany.

Category/Topic:
4 Animal models of fear and anxiety

Abstract Type:
Poster

Abstract Number:
151

Author:
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Abstract Title:
The categorization of facial fear expressions according EMFACS

Abstract Text:
Objective: Krippl (2013) showed a typical movement of fear according EMFACS (Friesen and Ekman, 1984) as being recognized as sadness by different groups of participants with different response formats. As the movement (Action Unit, AU 1 + 2 + 4 + 20) was only shown by one poser in pictures, a follow up study with several posers, pictures and videos, and a set of fear expressions according EMFACS was done.
Methods: 66 psychology students categorized stimuli from at least four posers for each AU-combination (FACS-coded by three coders). The intensity of nine emotion categories had to be rated from zero (not existent) to six (maximum).
Results: Whereas in the former studies sadness was the highest mean score for AU 1 + 2 + 4 + 20, disgust followed by surprise and despair (videos), and disgust, sadness and despair (pictures) where the highest scores. Whereas AU 1 + 2 + 4 did not show up a clear interpretation, AU 20 was clearly interpreted as disgust. AU 5 was interpreted as surprise and fear (pictures) or only as surprise (videos). AU 1 + 2 + 5 was categorized as surprise in pictures and videos. AU 1 + 2 + 4 + 5 was interpreted as surprise (videos) or surprise, fear or despair (pictures). In the most complete fear expression according EMFACS, AU 1 + 2 + 4 + 5 + 20 fear had the highest mean in pictures, in videos it was outperformed by disgust and surprise. For AU 1 + 2 + 5 + 20, surprise, disgust and fear were the highest mean scores.
Conclusion: Altogether the data show, that AU 1 + 2 + 4 + 20 is not categorized as fear as assumed in EMFACS. AU 20 is probably the reason that participants recognize disgust most often. AU 5 is recognized as surprise and fear, which is in line with EMFACS-assumptions. In summary one has to be very careful with the usually used interpretations of EMFACS. Further studies are needed to analyze in detail the recognition rates of specific AU-combinations.

Abstract Type:
Poster

Abstract Number:
165

Author:
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Abstract Title:
Validation of the Arabic version of the children illness attitudes scales

Abstract Text:
Objective: Health anxiety is an experience that we undergo when we misinterpret benign bodily sensations as being indicative of having a serious disease (Asmundson et al. 2010), being convinced of having a serious disease despite medical reassurance of having a good health is one of the features of having an excessive health anxiety condition that can lead to significant disorders such as phobia (Deacon and Abramowitz, 2008). The prevalence of excessive health anxiety was assessed in several studies around the world but very few were performed on children (Wright and Asmundson 2005). Assessment of the severity of health anxiety can be performed using questionnaires such as the Children Illness attitudes scales (CIAS) (Wright and Asmundson 2003), however no Arabic validated version of any of these tools is available. The CIAS measures fears, beliefs, and attitudes associated with health anxiety and abnormal illness behaviour in childhood. The Aim of this study is to validate the Arabic version of the CAIS questionnaire to provide a tool to measure the severity and prevalence of health anxiety among children in the Arabic speaking world.
Methods: The CIAS was translated from English to Arabic then back-translated by a different translator and the two versions were compared. Cognitive interviews were conducted with 60 children aged 9–16 years old to ensure that all questions were clear and can be understood by the children. The final version of the questionnaire was circulated to 597 children; of those 200 children were asked to re-take the questionnaire after (10–15 days) to evaluate test retest reliability. Confirmatory factor analysis (CFA) on the 4-factor model suggested by the original questionnaire version was performed, and the factor correlation matrix was evaluated to determine discriminant validity. Internal consistency for each subscale was evaluated by calculating Cronbach's alpha. Person correlation was performed to evaluate test–retest reliability.
Results: The CFA showed good fit (GFI = 0.92, CFI = 0.89, and RMSEA = 0.03), test–retest reliability was high (all above 0.5) and the model had good discriminant validity and internal consistency.
Conclusion: The Arabic version of the CFPQ provides a suitable tool to investigate childhood health anxiety in the Middle East region, which can be used to examine the prevalence and severity of childhood anxiety in the region.

Abstract Type:
Poster

Abstract Number:
169

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Abstract Title:
Resilience to developmental stress exposure in serotonin-transporter deficient female mice

Abstract Text:
Objective: Exposure to prenatal stress has been shown to have a profound impact on emotion regulation in adulthood (Alonso et al. 1991; van den Hove and Jakob et al. 2011; de Souza et al. 2013). In recent years, epigenetic programming (Weaver et al. 2004; Schraut et al. 2014) through changes in serotonin (5-HT) system function were pin-pointed as possible key mechanisms in the mediation of these effects (Marquez et al. 2013; van den Hove et al. 2014).
Methods: To elucidate the role of 5-HT in early life programming, we exposed a cohort of wild-type C57/BL6 dams, which were impregnated by heterozygous serotonin transporter (5-Htt)-deficient C57/BL6 males, repeatedly to restraint stress from embryonic day 13–17. Following birth, animals were allowed to grow up under normal conditions and behavioural analyses were performed in adulthood.
Results: In female offspring we observed several genotype-, stress- as well as GxE-specific effects, e.g. on the level of prosocial behaviour/social anxiety. Follow-up molecular analysis revealed, amongst other candidates, a cluster of myelination-associated genes to be regulated in a GxE dependent fashion. These genes were furthermore differentially affected in animals with a differential susceptibility to developmental stress exposure.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
146

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Abstract Title:
Effects of Neurexan® on amygdala-centered resting state functional connectivity

Abstract Text:
Objective: Stress initiates intricate changes in functional connectivity (FC) between amygdala and cortical regions that are associated with vigilance monitoring, salience processing and executive control. The functional integrity of these stress regulation circuitries can be assessed via amygdala-centered resting state functional connectivity (rs-FC). Previous studies have associated changes in amygdala rs-FC with state, trait and pathological anxiety. Neurexan®, a medicinal product sold over the counter (OTC), is composed of passionflower, oats, coffee and zinc valerianate. A recent study suggested that Neurexan® attenuates neuroendocrine stress response in healthy volunteers. Thus, in the present study, we aimed to explore the effect of Neurexan® on the amygdala-centered rs-FC.
Methods: Thirty-nine healthy male subjects (age = 43.7 ± 9.8) participated in an fMRI study of Neurexan® effects on resting state function using a double-blind, randomized, placebo-controlled, within-subject crossover design. In each scanning session, an 11-min resting state measurement was performed at baseline and after the intake of single dose of Neurexan® or placebo. Data were preprocessed and analyzed in SPM12 and DPABI. Using a seed-based approach, resting state functional connectivity maps of bilateral centromedial (CeA) and basolateral (BLA) subregions of amygdala were analyzed with whole–brain within–subject ANOVA (interaction: time by pharmaceutical, FWE cluster level corrected). Regions were created according to the probabilistic cytoarchitectonic maps provided by the Anatomy Toolbox.
Results: Significant effect of Neurexan® was found on rs-FC between left centromedial amygdala and cortical regions including posterior cingulate cortex, dorsomedial prefrontal cortex and bilateral inferior parietal lobule. This interaction was driven by a greater reduction of the left CeA rs-FC in Neurexan® compared to control condition after the intake of drug.
Conclusion: Our finding suggests that Neurexan® influences resting state functional connectivity of the centromedial amygdala towards cortical regions involved in emotion regulation and higher cognitive processes.

Category/Topic:
7 Panic disorder

Abstract Type:
Poster

Abstract Number:
148

Author:
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Abstract Title:
Bayesian analysis of fMRI resting-state functional connectivity of amygdala and bed nucleus of the stria terminalis in panic disorder

Abstract Text:
Objective: The role of amygdala and bed nucleus of the stria terminalis (BNST) in panic disorder is a topic of ongoing research. Up to now, there has not been an analysis of fMRI resting state functional connectivity (rsFC) of both these structures in panic disorder using Bayesian statistics. Whereas classical statistics is prone to high beta errors due to extensive multiple comparisons correction (MCC), Bayesian statistics eschews the need for MCC and thus provides better power for detecting smaller effect sizes.
Methods: 24 panic disorder patients (mean age: 25, SD: 6.57, 18 female) and 31 healthy controls (mean age: 24, SD: 2.98, 21 female) were analyzed. For every subject, a voxelwise multiple linear robust regression of the mean time course of left/right amygdala and BNST onto the residuals obtained from the preprocessed data was calculated. Subsequently, for the comparison of both groups, a Bayesian analysis was calculated and posterior probability maps (PPM) of a group effect greater than 0 were obtained. For the interpretation of the results, voxels showing a posterior probability of ≥95% were considered.
Results: Compared to controls, panic patients showed higher rsFC of amygdala/BNST between sensory, visuomotor regions as well as brainstem and lower rsFC between prefrontal regions.
Conclusion: Bayesian analysis of rsFC in panic disorder points towards heightened connectivity between amygdala/BNST and

sensory/visuomotor processing regions and reduced connectivity between prefrontal regions involved in emotional regulation during resting-state.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
143

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Co-Author:
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Abstract Title:
Functional heterogeneity of the human extended amygdala during phasic fear- and anxiety-related processes

Abstract Text:

Objective: Dissociable roles have been proposed for the two major subdivisions of the extended amygdala, the central amygdala and the bed nucleus of the stria terminalis (BNST), for phasic fear and sustained threat responding, respectively. However, a simple double-dissociation between amygdala-mediated 'fear' and BNST-mediated 'anxiety' has increasingly been challenged. The present work explores the recently acknowledged tight functional interconnection of both structures by means of differential behavioral, psychophysiological and neural responding towards explicit cue-related phasic fear as compared to context-related sustained anxiety.
Methods: We present data using a combined cue and context conditioning paradigm in healthy subjects (N = 49) while recording behavioral (ratings of fear), psychophysiological (skin conductance) and neural (functional magnetic resonance imaging) responding.
Results: Our results show a clear behavioral and psychophysiological dissociation between conditions of phasic cue-related fear and context-related sustained anxiety. Thereby, strong activation of the BNST is observed in cued fear but not sustained anxiety. This is extended by evidence for time-dependent involvement of the amygdala/hippocampus junction during contextual conditioning.
Conclusion: In sum, we provide further evidence for the functional heterogeneity of the human extended amygdala and, thus, challenging the notion of clearly distinct roles of amygdala and BNST in fear and anxiety processes respectively. Future studies need to explore the boundary conditions for a dissociable involvement of amygdala and BNST in more detail.

Category/Topic:
3 Cognitive-behavioural therapy (cbt)

Abstract Type:
Poster

Abstract Number:
145

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Abstract Title:
Targeting pathological personality traits as stress-causing factors in a novel psychoeducational group program

Abstract Text:

Objective: Pathological personality traits as accentuations of personality traits (ICD-10 Z 73.1) or personality disorders (ICD-10 F60/61) are a common phenomenon and strongly associated with (interpersonal) problems and stress in different life areas. As a result there is a high comorbidity between personality disorders and axis-I-disorders like depression or anxiety disorders. Moreover a comorbid personality disorder negatively influences therapy outcome for axis-I-disorders as well as dropout rates.
Patients with a personality disorder diagnosis often have a poor knowledge and understanding of their diagnosis. Nevertheless psychoeducation for patients with a personality disorder is only offered in a few hospitals and there are only a few therapy programs existing.
Methods: We developed a cognitive-behavioral psychoeducation program called the "Discovering personality" group therapy (DPG) which give patients information about (dysfunctional) personality traits, insight in their own personality traits, information about coping strategies and motivation for a further preoccupation with their own personality—and all that in a resource-oriented, non-confronting way. While existing psychoeducation programs inform about specific categories of personality styles and disorders, we developed a cross-categories approach which focuses on personality traits in general and their influence on mental well-being, referring to the alternative model of personality disorders in DSM-5.
We did a pilot-evaluation of 78 group sessions of the novel program in which 150 patients participated and filled in all in all 661 feedback-questionnaires. We evaluated not only the implementation process of the group program in a psychiatric hospital but also the outcome parameters increase in insight, coping strategies and motivation.
Results: The outcome of our pilot evaluation shows that by participating in the group therapy, patients describe an increase in insight in their own person and problems and in motivation for a further preoccupation with their own personality. We moreover evaluated each of the 15 modules of the group program concerning its prior outcome target and did an analysis of which subgroup of patients profits most from the group therapy.
Conclusion: Patients with a personality disorder or accentuation accept and can profit from a psychoeducational group program. Psychoeducation on pathological personality traits as risk factors for (interpersonal) problems and stress may help to motivate patients to target their own dysfunctional traits in further treatment—what in turn could reduce their negative influence on the development and maintenance of axis-I disorders.

Category/Topic:
1 Fear conditioning, extinction and generalization

Abstract Type:
Poster

Abstract Number:
144

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Co-Author:
Lonsdorf, Tina

Abstract Title:
Context dependency of the reinstatement-effect in humans

Abstract Text:
Objective: Return of fear (ROF) is highly context dependent as experimental manipulations to induce ROF involve context manipulations. Within fear conditioning models, ROF following a change in context after successful fear extinction is described as renewal, ROF after changes in temporal context as spontaneous recovery, and unexpected presentations of unconditioned stimuli (USs) in a context can be described as reinstatement. Specifically, the experimental conditions under which reinstatement occurs have been studied in single-cue protocols in rodents, and have suggested that reinstatement-effects are only observed when the context in which reinstatement USs are presented is either equal to the extinction or test context. The role of context in human ROF studies, and in particular in reinstatement protocols is not clear, even though reinstatement manipulations are frequently used. Aiming to translate rodent work, to humans and ultimately to the clinic, replication and investigation of the role of context in fear conditioning studies in humans is therefore eagerly awaited.
Methods: A differential fear conditioning experiment was conducted in which background colors of the computer screen differed for fear acquisition (context A), fear extinction (context A), reinstatement (context B), and test-phase (context A or B). Ratings, skin conductance responses (SCRs) and fear potentiated startle were measured.
Results: Repeated measures analyses with conditioned stimulus-type (cs+, cs−) and time (extinction, test-phase) as within, and context-group (AABA, n = 24; AABB, n = 27) as between subject variable revealed a trend-wise interaction between context and time only in SCRs, $F(1,49) = 3.76$, $p = 0.058$, $p\eta^2 = 0.071$. The AABA context-group, congruent to animal studies did not show (CS-unspecific) response enhancement after reinstatement, whereas the AABB context-group -equal test and reinstatement context- showed an (CS-unspecific; i.e., generalized) increase in responding.
Conclusion: We observed a trend-wise effect of context on the reinstatement-effect, and could thus not directly replicate animal findings. Even though our results suggest a similar direction of the ROF, the current finding asks for caution when translating ROF effects from rodent single-cue protocols to human differential conditioning.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
139

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Abstract Title:
Regulation of phasic and sustained fear via CB1 receptors in the extended amygdala: mediation by CRH neurons

Abstract Text:
Objective: While most studies assess fear as a transient state of apprehension in response to a discrete threat, such phasic states of fear can shift to a sustained anxious apprehension, particularly in face of diffuse cues with unpredictable environmental contingencies. We have recently demonstrated that cannabinoid type 1 (CB1) receptors on distinct amygdala inputs to neurons in the anterolateral BNST (alBNST) are necessary and sufficient for a shift to sustained fear. However, subpopulations of neurons driving the CB1 effect remain elusive. In light of previous evidence on the role of the corticotropin-releasing hormone (CRH) system in extended amygdala interactions, we hypothesize that CRH neurons are critically involved in regulating the fear profile.
Methods: Retrograde tracer studies combined with immunohistochemistry, optogenetic and electrophysiological approaches were performed ex vivo in CRH- and PKCδ-reporter mice. Next, CRH-cre mice were crossed with floxed-CB1 or floxed-STOP-CB1 mice, resulting in specific deficiency or rescue of CB1 in CRH neurons. By making use of Pavlovian fear conditioning with unpredictable CS-US pairings, phasic-sustained fear profiles were monitored in vivo.
Results: First results demonstrated that the projection from centrolateral amygdala (CeL) to alBNST is devoid of PKCδ, and that CRH is expressed in a large portion of this projection. CB1 receptors seem to reside on PKCδ-negative inputs from CeL to alBNST. Postsynaptic alBNST target neurons of CB1-regulated inputs are to a large part GABA-negative and CRH-positive. Behavioural results indicated that CB1-deficiency in CRH neurons is associated with rapidly declining fear, thereby resembling the phasic fear profile observed after constitutive CB1-deficiency or post pharmacological CB1-blockage in alBNST. Specific rescue of CB1 in CRH neurons resulted in reconstitution of the sustained fear phenotype in close resemblance to wildtype behavior.
Conclusion: This first evidence thereby suggests a causal role of CRH neurons in CeL to alBNST pathways, both at pre- and postsynaptic sites, for endocannabinoid regulation of phasic and sustained fear profiles.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
141

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Abstract Title:
The BDNF system modulates the extended amygdala network by inhibition of the ovBNST

Abstract Text:
Objective: The neurotrophin brain-derived neurotropic factor (BDNF) serves as a major growth factor and is mainly involved in the regulation of both neuronal differentiation and synaptic plasticity. Recently, in PVT expressed BDNF has been shown to be essentially

involved in memory formation and contributes to appropriate fear learning and extinction. However, the mechanism how BDNF modulates the PVT and the extended amygdala in the context of fear processing are still not yet fully understood.
Methods: Therefore, the present study was undertaken to investigate the effects of local BDNF deletion within the PVT by combining a homozygous floxed transgenic mouse line, local adeno-associated virus-mediated Cre expression and electrophysiological ex vivo whole cell patch clamp recordings in acute PVT slices.
Results: BDNF deletion in PVT resulted in significantly decreased frequency of both spontaneous and miniature inhibitory postsynaptic currents (IPSCs), indicating an impaired synaptic transmission. By performing retrograde and anterograde tracer studies we could reveal afferents innervating the oval nucleus of the BNST (ovBNST) originating from the PVT. Further, we were able to evoke excitatory postsynaptic currents (EPSCs) in ovBNST neurons upon light stimulation of ChR2, expressed in axon terminals of the PVT. To investigate whether BDNF also modulates ovBNST neurons electrophysiological in vitro patch clamp recordings were performed. Here, BDNF bath application induced a significant outward-directed current in ovBNST neurons compared to controls, evoked EPSCs were not affected.
Conclusion: In conclusion, we identified an excitatory connection from PVT neurons innervating the ovBNST. Further, the present findings indicate a critical role of BDNF in PVT and ovBNST modulation, which may correlate to previously observed changes in fear memory.

Category/Topic:
8 Neurobiology of anxiety and stress

Abstract Type:
Poster

Abstract Number:
140

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Abstract Title:
Role of ciliary neurotrophic factor in hippocampal synaptic plasticity

Abstract Text:
Objective: Ciliary neurotrophic factor (CNTF) is a potent survival factor for motor neurons. Based on previous results that CNTF rescues axon degeneration in a mouse model of motor neuron disease, recent studies by our group showed that this effect is mediated by a signaling cascade, involving STAT3/Stathmin, leading to increased microtubule dynamics. Microtubule dynamics also modulate hippocampal synaptic plasticity. Therefore, we investigated whether CNTF can induce synaptic plasticity in the hippocampus and modulate learning behavior through the STAT3-Stathmin pathway.
Methods: To address this question immunofluorescent stainings, electrophysiological analyses and behavioral experiments were performed.
Results: Electrophysiological analysis revealed that long-term potentiation (LTP) and long-term depression (LTD) are dramatically reduced at the Schaffer collateral CA1 synapse in organotypic slices from CNTF-deficient mice. Thus, CNTF modulates two prototypical cellular parameters for learning and memory. Notably, LTP can be rescued by acute exogenous CNTF application. Steady-state spine subtype composition and spine density is not altered in CNTF knockout mice. Next we investigated whether the deficit in LTP is reflected on a behavioral level. CNTF ko mice did not show a striking phenotype In the Morris Water Maze test which implies that spatial learning and memory retrieval are not affected. However in fear conditioning, CNTF ko mice showed an increased freezing response in a fear renewal paradigm. In contextual fear conditioning we observed a decreased freezing behavior in late phases of extinction learning. Furthermore, CNTF ko mice were not able to distinguish between a familiar and a novel object in a Novel Object Recognition task.
Conclusion: In conclusion, our observations indicate that CNTF is involved in hippocampal synaptic plasticity regulation and modulates fear processing. In humans about 3% of the population is deficient for CNTF, thus raising the question whether CNTF deficiency affects fear memory in these individuals.

Category/Topic:
4 Animal models of fear and anxiety

Abstract Type:
Poster

Abstract Number:
136

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Abstract Title:
Tph2 mutant mice as model for the role of serotonin in anxiety disorders

Abstract Text:
Objective: The amygdala is involved in the acquisition and expression of fear responses. Malfunctioning of these nuclear complexes may be due in part to dysfunctional serotonin (5-HT) neurotransmission. However the neural mechanisms involved are yet to be fully deciphered. Depletion of 5-HT through genetic inactivation of Tryptophanhydroxylase-2 (Tph2) during alters conditioned and unconditioned fear responses.
Methods: Inducible and constitutive Tph2 mutant mice were tested in paradigms for anxiety-like behaviour. After a fear-conditioning paradigm, functional histochemistry using cFos as immediate early marker of activation was conducted to assess amygdala-raphe network function.
Results: Tph2 mutant mice showed increased fear associated with hyperlocomotion and escape-like responses to inescapable foot shock and aversive environments, but no significant differences in the light–dark box transition test.
Conclusion: Inducible and constitutive Tph2 inactivation provides evidence for an acute effect of 5-HT on syndromal dimensions of anxiety disorders and agoraphobia.