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Tailored approach to a stepped mental care program for early intervention in the workplace: initial data and further research

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[2] Institute of Psychology, University of Hildesheim Foundation, Universitätsplatz 1, 31141, Hildesheim, Germany Psychological strain frequently occurs in the work context.

Psychological and psychotherapeutic consultation in the workplace has been shown to promote reachability of all genders and educational levels, early diagnosis (especially of subclinical mental disorders), integration of work- related topics into psychotherapeutic interventions, reduction of incapacity to work and sickness absence. The meaningful results of psychotherapeutic interventions in the workplace are now being investigated for efficacy in a nation-wide randomized controlled trial (RCT) implementing a tailored stepped care program for early intervention in the workplace (in German: Frühe Intervention am Arbeitsplatz – friaa). Recruitment is taking place at 5 sites, covering both urban and rural areas, starting September 2021. Baseline and follow-up data will be collected from a total of 520 participants (260 in intervention group, 1:1 allocation). The primary outcome is days of sick leave at work, the secondary outcome is workplace-related self-efficacy. The control group will receive a detailed clinical-psychological diagnosis and further treatment recommendation, while the intervention group will also receive a workplace-related psychotherapeutic intervention individually tailored with up to 16 additional sessions. The intervention in the workplace includes a basic diagnostic assessment on mental health, work-related diagnostic assessment, psychotherapeutic consultation or treatment with reference to the workplace and, if necessary, support in the return-to-work (RTW) process. The main objectives are (1) an improved prognosis of mental illness, (2) the reduction of the risk of reduced workability associated with mental illness, (3) a faster return to work after a longer period of incapacity, and (4) a reduction of costs for social insurance funds and companies. If the implementation and evaluation are successful, it could be possible to provide funding as part of standard care in cooperation with various payers. Accompanying the RTC, process evaluation studies will be conducted using sequential, multi-perspective interviews and group discussions with employees and health stakeholders, as well as health economic analyses. The concept of modular work-related psychotherapy combines early recognition and early intervention, work-related psychotherapy, psychotherapeutic assistance of the RTW process and work-related psychosomatic rehabilitation.

Development and evaluation of a novel ecological momentary intervention using monitoring, feedback, and positive refocusing of attention in patients with chronic musculoskeletal pain

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Musculoskeletal pain diseases affect between 13.5% and 47% of the general population constituting one of the most growing causes of disease burden globally, as they may become chronic. Pain diaries have long been a common tool in non-pharmacological pain-treatment in order to monitor and provide feedback on patients' symptoms in daily life. More recently, techniques for positive refocusing of attention have come to use, promoting pain-free episodes and positive outcomes rather than focusing on managing the pain. Embedded in a randomized controlled trial that compares three personalized treatment approaches for chronic musculoskeletal pain (CMSP), this study aims to optimize and evaluate the effects of a novel ecological momentary intervention (EMI) using a micro-randomized design in n=35 CMSP-patients over the course of 12 weeks. The EMI combines three micro-interventions targeted at positive refocusing of attention with experience sampling methodology (ESM) for digitalized monitoring of momentary outcomes, i.e. absence of pain, positive affect and subjective activity. Personalized daily and weekly feedback will be provided comparing two presentation modes (verbal vs. visual feedback) and a control condition (no feedback) at each time point. Additionally, the app will encourage participants to complete three micro-interventions that are based on techniques from positive psychology and cognitive-behavioural therapy. These micro-interventions are prompts to report joyful moments, everyday successes, or to plan pleasant activities. This EMI may offer a way to provide low-level accessible treatment to a broad target population promising significant public health implications by ultimately lowering disease burden of chronic pain.

Using mind control to modify cue-reactivity in AUD:
The impact of mindfulness-based relapse prevention on real-time fMRI neurofeedback to modify cue-reactivity in alcohol use disorder

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Despite the high prevalence of Alcohol Use Disorders (AUD) novel treatment options remain rather limited. In the context of the TRR SFB 265 C04 “Mindfulness-based relapse prevention as an addition to rtfMRI NFB intervention for patients with Alcohol Use Disorder (MiND)” study, two innovative interventions will be combined to a state-of-the-art intervention. The first intervention is a mindfulness-based relapse prevention (MBRP) that uses the traditional concept of mindfulness to help patients regain control of their feelings and decisions. The second intervention contains the use of real-time functional magnetic resonance imaging neurofeedback (rtfMRI NFB) to target the ventral striatum, which is a brain region centrally involved in cue-reactivity to alcohol-related stimuli. The MiND study will use MBRP to improve the efficacy of the rfMRI NFB intervention and thus reduce the participants’ relapses after treatment.

After inclusion, 88 participants will be randomly assigned to one of four groups. Two of those groups will receive mindfulness-based relapse prevention. All groups will receive two fMRI sessions and three real-time neurofeedback sessions in a double-blind manner and will regulate either the ventral striatum or the auditory cortex as a control region. Two groups will additionally receive five sessions of mindfulness-based relapse prevention prior to the neurofeedback intervention. After the last fMRI session, the participants will be followed-up monthly for a period of three months for an assessment of the relapse rate and clinical effects of the intervention.

The results of this study will give further insights into the efficacy of real-time functional magnetic resonance imaging neurofeedback interventions for the treatment of Alcohol Use Disorder. Additionally, the study will provide further insight on neurobiological changes in the brain caused by the neurofeedback intervention as well as by the mindfulness-based relapse prevention. The outcome might be useful to develop new treatment approaches targeting mechanisms of Alcohol Use Disorder with the goal to reduce relapse rates after discharge from the hospital.

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Living lab AI4U - artificial intelligence for personalized digital mental health promotion and prevention in youth

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Background: Youth are particularly affected by mental health problems, but their use of preventive interventions remains limited. The advances in Artificial Intelligence (AI) enable the development of digital interventions for mental health promotion and prevention. This applies to ecological momentary interventions (EMI), which offer adaptive training components in daily life. **Method:** In a preparatory phase, two focus groups (N=8, aged: 15-21 years) and a representative survey (N=666, aged: 16-24) with young individuals as well as expert interviews (N=5) with stakeholders in routine public mental health provision were conducted. **Results:** None of the stakeholders used digital interventions in their everyday work but were interested in their use. The importance of data protection and security, usability, and participation of the target population in all stages of the research process was emphasized. The risk of a digital divide, acceptance of used terminology, and difficulties of structural embedding were mentioned as important barriers for successful implementation. Young individuals had a positive attitude toward digitization and AI and their use in mental health promotion and prevention and underlined the importance of practical benefits for users. They had a pragmatic attitude toward data use policies. Around 70% of young individuals were already using mHealth apps. Psychological distress was associated with the use of, and positive attitude towards, mHealth apps. **Discussion:** Findings have contributed to the ongoing main phase. The living lab AI4U will be carried out in transdisciplinary projects involving direct participation of relevant stakeholders, users from the target population and an interdisciplinary research group. Each of these projects includes one or more real-world experiments. These will be embedded in a transdisciplinary infrastructure, which will ensure ongoing quality assurance, sustainability assessment, public relations, and networking.

5

A study of oxytocin effects within the medial entorhinal cortex-hippocampus domain in rats

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Oxytocin (OT) is the evolutionarily conserved hypothalamic neuropeptide involved in emotional behaviors, such as anxiety and fear, as well as complex social behaviors. In mammals OT is produced exclusively in the hypothalamic nuclei, which project to more than 50 brain regions, including the medial entorhinal cortex (MEC) and hippocampus (Hippo). Our project aims to explore the role of OT signaling within the MEC and reveal its possible role in regulation of spatial and goal-directed navigation. Employing cell-type specific recombinant adeno-associated viruses (AAVs), in adult rats we found profound innervation of all layers of MEC by OT. Utilizing newly generated OT receptor (OTR)-IRES-Cre knockin-rats in combination with Cre-dependent AAVs, we so far described two types of OTR+ neurons in the MEC: 1) principal cells (PCs) located predominantly in layer 3, and 2) parvalbumin-positive interneurons (INS) scattered throughout the extend of the MEC. Both cell types were highly sensitive to *ex vivo* application of selective OTR agonist TGOT. Analysis of target areas of MEC OTR+ PCs revealed their direct projections towards the CA1 region of the dorsal hippocampus. To tackle the functional role of MEC OTR+ neurons, we ablated them by Cre-dependent AAV expression of modified Caspase 3 injected in the MEC of OTR-IRES-Cre rats. After confirmed elimination of virtually all OTR+ MEC neurons, adult female rats were subjected to two sets of behavioral experiments: social recognition test and T-maze test. Our results suggest the involvement of the OT-sensitive MEC→CA1 pathway in modulation of spatial/goal-directed navigation of rats towards conspecifics.

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Effects of the COVID-19 pandemic on real-life affective well-being, social contact and roaming behavior in health, depression and schizophrenia

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Abstract

The COVID-19 pandemic has had and continues to have an immense impact on our daily lives [1], resulting in widespread mental health issues among large parts of the general population [2]. However, it remains unknown how the pandemic situation influences daily life experiences of particularly vulnerable people with a preexisting psychiatric diagnosis.

While the rising number of COVID-19 infection cases in mid-March 2020 was accompanied by a rapid increase in fear among the general population [3], many psychiatrists were concerned about a potential worsening of symptoms in psychiatric patients [4],[5]. Here, we therefore aimed to investigate whether patients with major depression or schizophrenia felt even more distress than healthy control subjects, using ecological momentary assessment (EMA) from two different samples before (preacute) and during (acute) the first and second waves of the COVID-19 pandemic in Germany (Fig1 A).

In this study, three groups (n=20 schizophrenia patients (SZ), n=24 major depression patients (MDD) and n=21 healthy controls (HC)) were subjected to an ambulatory assessment protocol including smartphone-based self-ratings and location tracking and repeated clinical interviews and psychological inventories across 24 weeks. Participants reported twice a day on their daily-life well-being (valence, energetic arousal, calmness), social context (lonely, alone) and anxiety level (fearful) using smartphone-based e-diaries from March to November 2020.

Despite the worldwide concern of many psychiatrists about a deterioration in the mental state of psychiatric patients due to the COVID-19 pandemic [4], [5], we could neither observe a worsening of symptoms nor a negative impact on the everyday well-being of patients. However, among healthy controls, we found a change in ratings during the acute phase of the first wave, which corresponds to the increase in fear, concern, and worry in the general population [3], [6]. Interestingly, during the second wave, calmness and anxiety ratings remained stable, indicating a potential habituation effect [7].

Unlike traditional measures, EMA provides unique insights into respondents' current experiences while they are engaged in their typical daily environment, reducing retrospective recall biases. Ecological momentary assessment may help to identify daily-life stress not only for healthy individuals, but also for psychiatric patients, and pave the path for individual mobile health interventions for mentally ill and at-risk populations. Nonetheless, further investigations are needed to better understand the effect of catastrophic circumstances, such as COVID-19 pandemic outbreak, on (perceived) mental health.

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Real-life affective implications of deficient amygdala habituation in community individuals with subclinical depression and anxiety

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Abstract

Successful prevention of internalizing disorders in the general population requires identification of daily-life psychological and neural affective markers in clinically at-risk individuals from naturalistic samples, but the biological underpinnings and everyday significance of risk states are unclear (1). We combined methods from epidemiology, psychology, ecological momentary assessment (EMA) and functional neuroimaging (fMRI) to study real-life and neural affective functions in clinically subthreshold individuals from a population-based cohort of young adults (2-4). We examined daily-life affective valence, fMRI amygdala habituation to negative emotional stimuli and the relevance of neural readouts for daily-life affective function in 132 non-help-seeking community individuals (2,4). We compared psychological and EMA measures of 61 unmedicated individuals at clinical risk for depression and anxiety to those of 48 non-risk individuals and 23 mood and anxiety patients. We studied risk-associated fMRI signals in subsamples with carefully balanced sociodemographic and image quality parameters (26 non-risk vs. 26 at-risk persons). Compared to non-risk persons, at-risk individuals showed a significant decrease in daily-life affective valence ($p = .038$), a blunted fMRI right amygdala habituation ($pFWE = .022$, region of interest [ROI] corrected) and a lacking association between amygdala habituation measures and real-life affective valence ($pFWE = .60$, ROI corrected). Comparisons to the clinical group point to a consistent, though mitigated, subclinical risk state.

Conclusions

Our data identify daily-life and neural markers for affective dysfunction in unmedicated community individuals at risk for depression and anxiety and highlight the significance of neuroimaging amygdala habituation measures for the daily-life affective experience in real-world environments.

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Figures

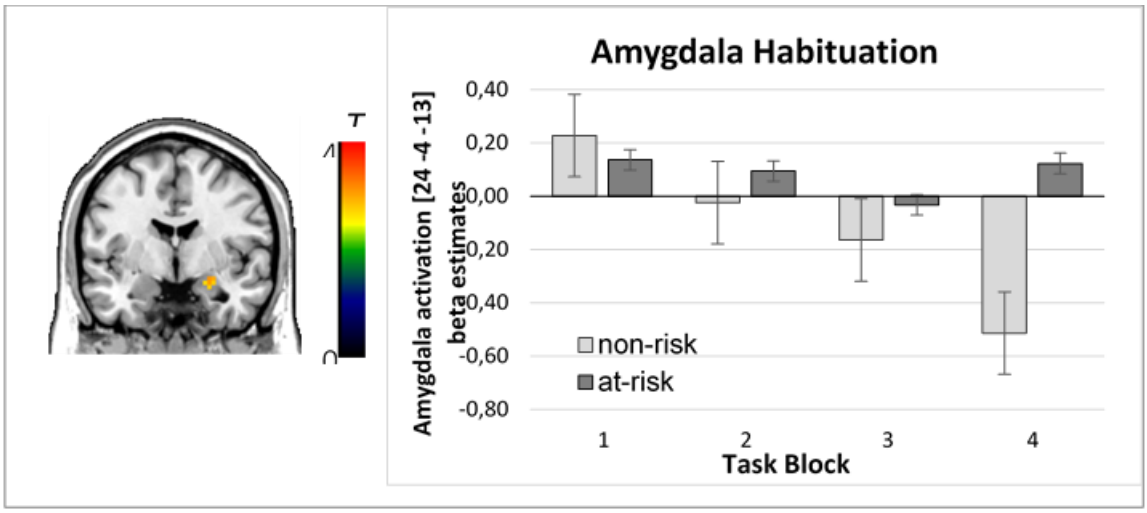

Figure 1. Group differences in Amygdala activation to threatening stimuli. Left: Decrease of amygdala activation for healthy non-risk group, whereas at-risk group showed delayed and overall reduced habituation (T=3,09, p_{FWE}-corr=,022) . For illustration purposes, a significance threshold of $p_{uncorr} < .005$ was applied and displayed on the coronal section.

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Social learning and person perception: current activities of the research group

Sabine Schellhaas, Niclas Willscheid, & Florian Bublatzky

The research group “Social learning and person perception” aims to better understand face and person perception as a function of individual learning history. A particular focus is on the different types of learning - based on own experiences, observations and instructions - and on how context and environment (e.g., knowledge about other people or situations) modulate self- and other-perception. The workings of the mechanisms and (dys)functions involved are examined from an experimental psycho(patho)logical perspective using combined social and neuroscientific methods (e.g., EEG/ERP, MEG, peripheral physiology). We take a dimensional transdiagnostic approach focusing on healthy and clinical populations, with implications for stress and anxiety-related disorders with interpersonal disturbances (e.g., anticipatory anxiety and social anxiety disorder). With this poster, we present exemplary studies from our research group that address how expectancy of threat and risk modulate our perception, cognition, and behavior toward others.

CHRONIC ETHANOL INTAKE INFLUENCES GENE EXPRESSION OF SARS-CoV2 INFECTION-RELEVANT GENES IN AN ORGAN-SPECIFIC MANNER

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Objectives: Since the end of 2019, the severe acute respiratory syndrome Corona-virus 2 (SARS-CoV2) has caused several millions of infections and deaths worldwide. It has been reported that certain risk factors like chronic lung disease, autoimmune dysfunction and diabetes are promoting SARS-CoV2 infection and worsening the course of disease. There is some evidence suggesting that chronic alcohol consumption might have an impact on SARS-CoV2 infection risk, but referring to this, there is little molecular data published so far. In this study, we obtained gene expression data following acute and chronic alcohol intake in the context of genes that are known to be involved in SARS-CoV2 infection. We hypothesize, that long-term alcohol intake causes a change in gene expression of SARS-CoV2 infection-relevant genes.

Material and Methods: We used three different animal models of chronic ethanol intake – repeated intermittent Ethanol IP injections, vapor exposure for seven weeks, and the post-dependent model - and measured gene expression of Ace2, Tmprss2 and Mas by qPCR in six different organs: lung, heart, liver, kidney, ileum, and brain. ACE2 and TMPRSS2 represent the virus entry point, whereas Mas is activating the anti-inflammatory response, once the cells are infected.

Results: Across the three animal models of chronic alcohol consumption, we found an organ-specific up-regulation of all three genes of interest. In the brain, Mas was down-regulated in both human postmortem and rat brain tissue, while Ace2 was too little expressed to obtain meaningful results.

Conclusion: This comparative study of three different animal models of chronic ethanol intake suggests that long-term ethanol intake might consistently up-regulate gene expression of SARS-CoV2 infection-relevant genes in an organ-specific manner. An up-regulated Ace2 gene expression might lead to an elevated stochastic probability of virus entry, but also to an enhanced anti-inflammatory response via the ACE2/Ang(1-7)/Mas axis.

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Introduction of a stress management training for leaders of small and medium sized enterprises

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Introduction

Small and medium-sized enterprises (SME) rarely offer stress management trainings (SMT) due to a lack of resources and evaluated programs. Leaders from SME in particular are confronted with a multitude of challenges and thus, high levels of stress. This gap is to be addressed by the project “KMU-GO”. The evaluation is aimed not only at the effects on the leaders but also on their subordinates. This a quite new and promising approach.

Material and Methods

The study aims to gather data from *N* = 200 leaders. The investigation uses a 2x3 mixed design. Group (intervention and waiting control group) serves as between factor and time (baseline, 6 and 12 months later) as within factor.

Based on an already successfully evaluated SMT and a previous needs analysis, 1.5 days of training were developed. The main contents of the SMT are a psychoeducation about effects of stress on the body, individual case work, different stress management tools including cognitive, emotional, physiological and behavioral approaches, individual stress analysis, and strategies on how to foster a health-oriented workplace.

The main outcomes of this study are the leaders´ stress reactivity, depression and anxiety scores, effort-reward imbalance, sick days and biological stress markers (hair cortisol, salivary alpha-amylase and heart rate variability). In addition, mental health of the employees is examined and a cost-benefit analysis is carried out.

We wish to present the design of our study, as well as report first practical experiences.

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Targeted Extinction of Drug Cues During Sleep

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Alcohol Use Disorder (AUD) is one of the most prevalent substance use disorders and globally millions of persons are affected by it. During the development of AUD, sensitization of the dopaminergic reward networks in the brain is thought to enhance “wanting” of alcohol, whereas “liking” of alcohol may stay the same or even decrease. Persons with substance use disorders experience an enhanced craving response towards drug related cues, i.e., cue reactivity that is related to the probability of relapse. In the cue reactivity task, enhanced activation of dopaminergic reward areas in the brain in response to alcohol stimuli, has been shown using fMRI measurements. We establish a cue reactivity task that uses olfactory stimulation in addition to the frequently used visual stimulation to enhance measurement precision.

Clozapine Pharmacokinetic Profiles of Patients with Schizophrenia treated with Clozapine in a Naturalistic Setting

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Background

Trough serum concentrations have been used to show differences in clozapine (CLZ) and Ndesmethylclozapine (NCLZ) levels in smoking and nonsmoking patients. Naturalistic studies often comprise patients under varying dose regimens. Single trough concentrations might then not optimally reflect patients drug exposure.

Methods

Clozapine pharmacokinetic (PK) profiles were assessed in a naturalistic sample of smoking (n=11) and nonsmoking (n=7) patients with schizophrenia. Capillary whole blood and venous serum samples were simultaneously drawn just before drug administration (trough levels, 8:30am) at steady state conditions. Three additional whole blood samples were collected from each patient at 10:37am, 20:30pm and 22:37pm. Serum concentrations of CLZ and NCLZ were quantified using liquid-chromatography-mass spectrometry (LC-MS/MS). Whole blood concentrations of CLZ were quantified using a Point-of-Care immunoassay test (MyCare® Insite). Dose-adjusted serum concentrations (ratio of the drug concentration and the applied daily dose, C/D, in [ng/mL]/[mg/day]) for CLZ, NCLZ, the metabolite-to-parent ratio (MPR; NCLZ/CLZ) and the fluctuation ratio for CLZ (FR; ratio of the highest and the lowest drug concentration measured by POC testing) were calculated. Two patients were excluded from analysis due to a confounding co-medication with a CYP1A2 inhibitor. Results were compared between both groups, smokers (S, n=10, age 41.7(±8.4), male sex 80%, dose (mg/d) 522.5 (±133.9)) and nonsmokers (NS, n=6, age 36.3(±12.5), male sex 67%, dose (mg/d) 400 (±190.9), using non-parametrical tests. Within-subject variances were calculated between whole blood and serum concentration for 16 subjects. Two patients' samples were eliminated from the analysis due to results >1390 ng/ml on the MyCare Insite. Additional clinical measures were eligible for 13 patients comprising of PANSS total score, clinical global impression severity (CGI-S) and the evaluation of medication side effects (UKU).

Results

Smoking patients had lower CLZ and NCLZ concentrations (ng/mL) (CLZ S= 337 (176-1430); NCLZ S = 198 (116-930); MPR = 0.75 (0.36-1.1)) compared to nonsmoking patients (CLZ NS= 547 (312-854); NCLZ NS= 356 (178-412); MPR = 0.54 (0.42-0.76)). Significant differences were detected between the two groupsfor doseadjusted serum concentrations of both, CLZ (p = 0.02; C/D S= 0.57 (0.35-1.97); C/D NS= 1.6 (1.2-1.8)) and NCLZ (p = 0.04; C/D S= 0.47 (0.20-1.28); C/D NS= 0.85 (0.59-1.19)). Our data indicates a decrease in peakto-trough fluctuation in patients when treated with a multiple dose regimen (FR; 1/d = 3.34 (2.11-3.65) (n=3), 2/d = 2.51 (1.91-3.19) (n=9), 3/d = 1.63 (n=1), 4/d = 1.75 (1.72-1.79) (n=2)) despite increasing trough concentrations. Notably, once daily dose regimens have been exclusively observed in smokers, whose overall fluctuation ratios are slightly higher than those of nonsmokers (FR S= 2.52; n=6, FR NS = 1.94; n=9). Mean PANSS total score (n=13) was 75.23 (21.81), mean CGI-S was 4.23 (0.97). Increased salivation was reported in all 13 patients. Increased fatigability, sleepiness/ sedation and increased duration of sleep were reported in 77%, 62% and 62% of patients. Passing-Bablok regression marks a shift towards serum concentrations when compared to whole blood (R = 0.94, slope = 1.06, intercept = -67.3). Discussion The applied blood sampling schedule provides valuable insight

in individual pharmacokinetics of patients treated with multiple CLZ dose regimens. The results from our preliminary analyses of the first patients indicate that smoking might not have a large impact on peak-to-trough fluctuationsin individuals. The effect of clinical measures, such as sleepiness and sedation, should be further explored in relation to individual PK profiles.

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Promoting stepped integrated mental healthcare by leveraging digital health interventions - the PROVIDE junior research group

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The research group PROVIDE (ImPROving cross-sectoral collaboration between primary and psychosocial care: An implementation study on VIDEo consultations, https://www.provide-project.de/ziel-konzept/?lang=en), funded by the German Federal Ministry of Education and Research, focuses on innovative modes for delivering primary care mental health.

Drawing on a comprehensive preimplementation needs assessment with the main stakeholders (patients, general practitioners, mental health specialists, and health policy experts), we have developed a video-based integrated mental healthcare model which provides (1) timely treatment engagement of primary care patients with depression and anxiety, (2) systematic diagnostics, follow-up, and, if indicated, triage to more intensive treatment modalities, and (3) seamless cooperation between general practitioners and mental health specialists.

Having evaluated the model in a randomised feasibility trial, we embarked on the multicentric, prospective, superiority, and assessor-blinded PROVIDE-C RCT (NCT04316572) to evaluate whether the proposed model is superior compared to treatment as usual in treating primary care patients with depression and anxiety. Currently, we have enrolled 370 patients from more than 20 primary care practices. Findings of the trial are still pending, but preliminary anecdotal feedback from patients and healthcare providers is promising.

Future work of the PROVIDE group will target the optimisation of integrated mental healthcare models. Specifically, we will incorporate clinical prediction models for a stepped care approach facilitating individualised treatment of patients. Moreover, we will continue to tailor, evaluate, and implement integrated mental healthcare models for a range of mental health disorders (e.g., somatic symptom disorder) and expand the portfolio of such models by leveraging new technologies (e.g., ecological momentary interventions or chat bots).

Modular mechanism-based psychotherapies

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Traumatized psychiatric patients do not sufficiently respond to disorder-specific psychotherapies due to broad and severe psychopathologies. Therefore, we dedicate our current psychotherapy research to developing modular psychotherapy programs for patients with severe functional impairments in daily life and a history of aversive childhood experiences (ACE). We will present innovative study designs that aim to test efficacy of modular psychotherapy programs that are composed in the way to target specific psychological and neurobiological mechanisms underlying psychiatric syndromes and functional impairments. One study design refers to a modular group psychotherapy that aims to reduce aggressive behavior with data from a feasibility study having been funded by the DFG. Subsequently, a confirmatory multicenter clinical trial has been designed whose application is currently in progress. A second DFG study (together with E. Schramm/Freiburg) on a modular psychotherapy was designed to compose single psychotherapy modules in the way to target individual domains of dysfunctioning related to ACE; this study is currently underway.

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A Neurofeedback Booster for Emotion Regulation Therapy: protocol of a randomized controlled clinical trial in Borderline Personality Disorder

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Background: Emotion dysregulation is one of the key symptoms in Borderline Personality Disorder (BPD) causing individual suffering and leading to social turbulence. Dialectical Behavioral Therapy (DBT) is an evidence-based treatment, however, more than half of BPD patients do not respond. Real-time fMRI amygdala-neurofeedback (amy-NF) targets amygdala-hyperactivity and weak top-down control of the amygdala by the prefrontal cortex. These biological targets have been strongly implicated in emotion regulation. During amy-NF, patients learn to voluntarily decrease amygdala activation in response to real time visual feedback.

Objectives: This study will test if amy-NF can augment the effects of DBT in people with BPD. Outcome measures will include affective instability in daily life, self-reported emotion regulation, BPD symptomatology, amygdala response to negative stimuli, and amygdala connectivity.

Methods: Patients demonstrating ongoing high levels of BPD symptomatology after six weeks of DBT were invited to participate in the study with random assignment to either neurofeedback or treatment as usual (22/group). fMRI amy-NF training involves three sessions scheduled in a two-week period. Outcomes are measured before intervention, immediately after intervention and at 3 and 6 month follow-up timepoints. Affective instability is monitored using Ecological Momentary Assessment over 4-day intervals, emotion regulation is assessed using an established fMRI task, and amygdala resting-state connectivity is measured. BPD symptoms are assessed using the BSL-23 questionnaire at all four timepoints.

Results: To date, we have recruited 13 patients, 9 of whom finished each of the scheduled sessions and tolerated the protocol well. One participant dropped out due to not tolerating the MRI. The other two participants who did not complete the protocol stopped because of therapy discontinuation.

Conclusions: This is the first time that amy-NF is used to boost DBT. If effective, the approach could significantly improve the effectiveness of the therapy and reduce suffering.

Keywords: neurofeedback, fMRI, BPD

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Comparing electroencephalographic and magnetoencephalographic data quality in healthy school-age children – a head-to-head race?

Anne Kaiser

Poster-Abstract – ZIHUb Mental Health Alliance Retreat and Kick Off 2021

INTRODUCTION

Electroencephalography (EEG) and magnetoencephalography (MEG) represent partly complementary measures of human brain function, have an excellent temporal resolution, and are easily to administer. Both neurophysiological methods have their pros and cons regarding data quality, with the MEG being probably more affected by head motion artifacts as a results of a fixed-sensor array not directly placed on the participant`s head requiring study participants to maintain their head in a fixed position. This might be especially difficult for childhood populations, compromising data quality despite correction attempts, and consequently the reliability and validity of study results and scientific conclusions. So far, no direct comparison between EEG and MEG data quality in healthy children has been conducted.

OBJECTIVES

Therefore, the aim of the current study is to explore EEG/MEG data quality in healthy, school-age children, directly compare the two methods, and identify factors that differentially affect EEG/MEG data quality.

METHODS

A group of healthy, school-age children between 6 and 11.11 years is explored using EEG and MEG (n=37 for EEG; n=17 for MEG). Resting-state data during an eyes open and eyes-closed condition, as well as during a Continuous Performance Task (CPT) are collected. A data quality index is calculated reflecting the percentage of segments/trials remaining after standard preprocessing. Data quality will be compared between methods using paired-samples t-tests. Further, for assessing effects of demographic and methodological variables, also regression models will be fitted.

RESULTS

Comparisons regarding data quality, replication of robust landmark effects from the EEG/MEG literature, and effects of demographic and methodological study-characteristics on EEG and MEG data quality in children will be reported.

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Virtual Doppelgangers as Movement Models in Chronic Back Pain

Kornelius Kammler-Sücker, Annette Löffler, Dieter Kleinböhl, and Herta Flor

Chronification of pain, e.g. back pain, is often promoted by changes in behavior, as e.g. avoidance behavior with respect to everyday movements. We present an experimental design to address the question whether virtual doppelgangers as movement models can increase participants' inclination to push their limits in a Virtual Reality Game in our ZIPP VR Lab. We hypothesize that personalization of virtual movement models will increase identification of participants with the models, and thereby increase the extent of their movements. We present data both from a pilot study with 33 healthy participants and from a study of 33 subjects with chronic back pain.

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Decoding Sequential Memory Replay from Human Resting State using MEG

Authors:

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Animal research suggests replay of memory traces during rest and sleep improves performance, but this research relies on highly invasive methods and only has access to simple behavior. Similarly, quantifying replay in humans has proven difficult, and up to this point, no study exists that is able to detect endogenous human memory replay during sleep. In this proof-of-principle study, we applied a recently developed method in healthy humans to record item-level human replay events and thereby uncover the processes occurring during quiet rest. In subsequent studies we hope to further develop this method to be able apply it to human sleep.

In this study we attempted to detect sequential memory replay in humans during rest. In a first step, sixteen items were presented multiple times in a pseudorandom order while brain activity (MEG) was recorded in order to extract the representational brain state activity for these items. Machine learning classifiers were trained to decode the brain states belonging to each item. In a second step, the participants learned an ordering of the previously presented items. Subsequently, in a resting state condition, we were able to detect preliminary evidence for time-compressed replay of the learned items. Our analysis confirmed previous findings, that items are replayed with a time-lag of around 40-50 milliseconds between individual items.

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Mein Kompass - Orientation in times of crisis. An online information platform on mental health for adolescents.

Authors
Leonie Kott, Prof. Dr. Harald Baumeister

Background
Only a small proportion of adolescents with mental health disorders are seeking care. Although the Internet is increasingly consulted by adolescents for questions around health, good websites are hard to find, often difficult to understand and usually present information in a rather passive way.

Project
The BMBF funded project „Mein Kompass“ is developing a health information platform, which guides adolescents through general information about mental disorders, scientific research, gives advice for further information and options for treatment using the potential of digital technology and persuasive design principles. This comprises for example a self-test and a dialogue inspired navigation aid.

Method
Research in the project includes a systematic review summarizing the status quo of web design principles, several studies further exploring adolescent’s help seeking strategy, general evaluation of websites, and health literacy as well as the integration of this information into a new framework.

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Oxytocin attenuates negative emotional valence to painful stimuli via its action in the insular cortex

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The hypothalamic neuropeptide oxytocin (OT) exerts not only prominent pro-social and anxiolytic effects, but has also garnered great attention for its analgesic actions. Recent studies demonstrated the existence of at least two OT sub-systems, which coherently mitigate the perception of physical pain and facilitate emotional coping with pain. In the present study we aimed to investigate effects of OT on pain perception and anticipation within the insular cortex (IC), which integrates pain processing and emotional valence. Utilising cell-type specific adeno-associated viruses (AAVs) in rats, we first demonstrated direct axonal projections from hypothalamic OT nuclei to the IC. Secondly, using newly generated OT receptor (OTR)-IRES-Cre knockin rats, we described types of OTR-positive neurons of the IC, revealing a high abundance of GABAergic neurons. Next, to study the functional role of OT signalling within the IC, we performed two behavioural experiments while manipulating OT fibre activity via a chemogenetic approach. We found that local chemogenetic stimulation of OT axons within the IC in rats with inflammatory pain resulted in a conditioned place preference, indicating a perceived alleviation of pain. In line, when presented with the choice to self-administer a sugar solution paired with a light foot-shock in an operant conditioning setup, chemogenetic activation of local IC OT axons increased lever pressing behaviour despite the delivery of a noxious stimulus. Notably, OT axon stimulation within the IC did not alter mechanical pain thresholds. Altogether, our results suggest that OT signalling in the IC might improve emotional coping with pain, while not being involved in physical sensing of pain.

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A new oxytocin-sensitive cortico-striatal circuit facilitates social interactions of virgin female rats

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Abstract:

The ventromedial prefrontal cortex (vmPFC) is the structure involved in modulation of social behaviors via its top-down control on various limbic regions, such as the amygdala and nucleus accumbens (NAcb). Using cell type specific viral vectors, we show that hypothalamic OT neurons directly project to the vmPFC and optogenetic stimulation of these OT axons increases social interaction time between two freely moving female rats. In conjunction, employing newly generated OT receptor (OTR)-IRES-Cre knock-in rats, we identified two types OTR+ GABA-ergic neurons within the vmPFC: 1) Layer (L) 2/3 Chandelier cells and 2) L5 Martinoti cells. Surprisingly, in the ventral pole of the vmPFC we discovered a small population of L5 OTR+ principal cells (PC). *Ex vivo* application of selective OT receptor agonist TGOT increases firing rates in all identified OTR+ cell types. The dual *ex vivo* recording revealed reciprocal connectivity between OTR+ L2 interneurons and L2 OTR- pyramids: pharmacologic or optogenetic activation of OTR+ neurons leads to simultaneous silencing of vast majority of L2 OTR- pyramids. On contrary, firing rates of L5 OTR+ PC is not affected by of OTR+ GABA-ergic neurons activation. At the behavioral level, we report that *in vivo* optogenetic stimulation or silencing of all types of vmPFC OTR+ neurons respectively increase or decrease interaction time between female rats. Further, using transsynaptic FLP/frt viral system we identified direct axonal projections from L5 OTR+ PC towards OTR+ cells located in the NAcb. The chemogenetic stimulation or inhibition of the NAcb OTR+ neurons, receiving synaptic input from L5 vmPFC OTR+ pyramids, respectively increase or decrease time spent during social interactions. Altogether, we identified a novel vmPFC→nAcb OTR+ pathway, which facilitates social motivation of virgin female rats, supporting our hypothesis on the existence of mutually connected OTR-sensitive circuits to coherently shape social behaviors.

Corticostriatal circuits in the transition to chronic back pain: the predictive role of reward learning

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Abstract: Fronto-striatal connectivity between the nucleus accumbens (NAc) and ventromedial prefrontal cortex (vmPFC) as well as reward learning predict the transition from acute to chronic pain. However, how these predictors are related, remains unclear.

Using functional magnetic resonance imaging, we investigated resting state functional connectivity and implemented an instrumental reward learning paradigm using money and pain relief as reinforcers in patients with subacute back pain and followed them over six months. To elucidate the role of reward learning in the chronic stage, a separate sample of chronic pain patients was compared to pain-free controls.

We found that the neural response to learning-related updating of the value of reinforcement (prediction error) for monetary reward predicted chronicity: patients with persistent pain at follow-up showed higher NAc responses and higher functional connectivity between NAc and vmPFC than recovering patients. Functional vmPFC-NAc connectivity at rest predicted the transition from subacute to chronic pain as well, but to a lesser degree. In patients with chronic pain, vmPFC responses to the prediction error signal were decreased, while the vmPFC response to a discriminative stimulus that signaled monetary reward was increased.

These data provide evidence, that functional alterations in fronto-striatal pathways represent learning-related prediction of chronic pain. It further reveals that different stages during the transition to chronic pain are characterized by distinct impairments in vmPFC- and NAc-dependent reward learning. These impairments should be targeted in the prevention of chronic pain accordingly.

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Assessment of immunometabolic alterations in stress-related mental diseases

M. Mack, A. Behnke, A. Gumpp, I.T. Kolassa

In our modern society, psychosocial stress is an omnipresent phenomenon and individual traumata during childhood and adulthood occur frequently. Stress-related mental diseases like major depressive disorder (MDD) or post-traumatic stress disorder (PTSD) cause enormous socio-economic costs and individual suffering. Especially early childhood adversity can have a major impact on the general health later in life. Stress-related mental diseases are often difficult to treat with consequently insufficient therapy success and a high rate of relapses after remission. These problems certainly originate from the disorders' heterogeneity, the lack of appropriate biomarkers as well as the insufficient understanding of biochemical mechanisms underlying the aetiology of disease. Therefore, our research targets immunocellular metabolic changes in psychiatric conditions and their potential reversibility after successful therapy. In particular, our transdisciplinary work previously revealed alterations in the mitochondrial energy metabolism and the DNA repair machinery in MDD and PTSD, respectively. Moreover, we could show that traumatic events during childhood already actuate metabolic changes constituting an organismal allostatic load. We aim to promote a holistic comprehension of stress-related mental disorders and identify novel targets for improvement of both diagnostic and treatment.

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Can Ecological Momentary Assessment (EMA) data predict changes in clinical states?

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To address the need of a more naturalistic assessment of psychopathological phenomena intensive longitudinal sampling schemes (e.g. Ecological Momentary Assessment (EMA; electronic diaries on smartphones) are gaining traction. The statistical methodology to analyze this intensive longitudinal data (ILD) is an intensively researched topic.

One of the promising approaches to capture the dynamic nature of psychopathology is grounded in the dynamical system theory, which is applied to analyze the behavior of complex systems like ecosystems, climate, and financial markets. It focuses on identifying a critical transition (change points) from one state to another (e.g. disease to health and vice versa). Here we present a methodological extension of Kernel change point detection (KCP) framework to extract information from the time series analysis of ILD and to predict clinical outcomes of participants of an ongoing multimodal observational study (INDICATE-N). In the first preliminary analysis, a fitted binary logistic model based on the extracted variables from KCP analysis of ILD (smartphone based electronic diaries) showed a remarkable predictive performance in an independent test sample. Based on the electronic diaries of the participants (N=59) a clinical change within the study period of 6 month could be detected with a sensitivity of 88% and the specificity of 90%. Further analysis with more participants and addition sensitivity analysis are needed to validate these findings.

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Methodological Challenges in Psychedelic Drug Trials:

Efficacy and Safety of Psilocybin in treatment-resistant major depression (EPIsoDE) – Rationale, Study Design and Current Status

Authors

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Background: Psychedelic drugs represent one of the most promising treatment approaches in contemporary psychiatry (Gründer, 2021; Gründer & Jungaberle, 2021). Specifically psilocybin, a partial serotonin (5-HT) 2A receptor agonist, has shown promising safety and efficacy results in the treatment of major depression and other psychiatric disorders (e.g. reviewed in Rucker et al., 2018; Mertens & Preller, 2021). While results from modern pilot studies on psilocybin in the treatment of major depression and other psychiatric disorders are promising, most of those trials lack randomization, double-blinding, and a sufficient sample size. The use of double-blinding and an appropriate placebo is particularly difficult in psychedelic trials, facing ethical issues as well as the problem of “expectation bias” and the risk of nocebo effects in patients in the comparator groups (Gründer & Mertens, in press). Accordingly, there is an immense need for additional, larger, well-designed randomized-controlled studies.

Objectives: The phase 2 EPIsoDE-Trial (NCT04670081) aims to investigate the efficacy and safety of a high psilocybin dose (25 mg, p.o.) administered in a psychotherapeutic context in treatment-resistant major depression in a randomized-controlled, bi-centric, parallel-group, double-blind design. We expect significant and stable treatment responses after a high (25 mg) dose of psilocybin in comparison to placebo (100 mg nicotinamide) and a low/supposedly inactive control dose (5 mg psilocybin), while provoking only mild and transient adverse events (AE). As a secondary objective the effect of a second high dose six weeks after the first dose will be assessed. Exploratory objectives are aimed at identifying potential neurobiological and psychological therapeutic mechanisms of psilocybin treatment.

Methods: 144 patients (25 – 65 years of age) diagnosed with treatment-resistant major depression of moderate to severe degree will be enrolled in the study, all of which will receive two dosing sessions six weeks apart. Treatment-resistance is defined as no improvement in depression despite two adequate courses of antidepressant treatment. After informed consent and potentially down-titration of their antidepressant medication, patients will be randomized to one of four treatment arms: 1) receiving placebo (100 mg nicotinamide)

first, 25 mg psilocybin second; 2) receiving the presumably sub-effective psilocybin dose (5 mg) first, the high dose (25 mg) second; 3a) receiving 25 mg psilocybin first, 5 mg psilocybin second; 3b) receiving the high psilocybin dose (25 mg) at both sessions. Dosing sessions will be accompanied by multiple psychotherapeutic preparation and integration sessions. The second dose takes place after assessment of the primary endpoint; the primary endpoint is treatment response, defined as a minimum of 50% reduction in symptoms as measured with the Hamilton Rating Scale for Depression (HAM-D), six weeks after the first dose.

Outlook: The trial is currently being conducted at the Central Institute of Mental Health (sponsor) in Mannheim as well as the Charité Universitätsmedizin Berlin, Campus Charité Mitte. The trial design, including the randomization, double blinding and comparator conditions, will allow valid conclusions on the efficacy and safety of psilocybin treatment in major depression.

The trial is funded by the German Federal Ministry of Education and Research (BMBF 01EN2006A and 01EN2006B); it has been approved by the Federal Institute for Drugs and Medical Devices (BfArM) and the responsible Ethics Committees.

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Effects of childhood maltreatment on distrust and emotion processing in daily life

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Abstract

Cross-sectional evidence suggests that childhood maltreatment (CM) is associated with interpersonal distrust and altered emotion processing. Whether individuals with CM experience these alterations in their daily lives, and in which contexts, remains unexplored. We measured momentary distrust and emotion perception using two novel experimental tasks implemented in an Ambulatory Assessment design, expecting both to be increased in the context of negative affect (NA). We recruited 61 individuals with varying levels of CM and psychopathology, who answered six daily semi-random prompts over 7 days, including self-reports and two experimental tasks on distrust and emotion processing. We found that CM and momentary NA were both associated with a negative evaluation of emotional faces in the moment. Momentary NA was also associated with increased momentary distrust and this effect was stronger in individuals with more CM. We suggest that interventions in populations with CM should target the effects of NA on social-cognitive functions.

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Resilience in light of the COVID-19 pandemic: Results from the Mannheim Study of Children at Risk

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Abstract

The COVID-19-pandemic led to unprecedented restrictions in social life, with the consequences of these social lockdowns on well-being are not yet fully understood. Social integration is a major resilience factor, whereas adaptive coping is particularly needed in response to such an ongoing stressor.

We longitudinally investigated the individual affective benefit from social interactions using a real-time, real-life ambulatory assessment once before and once during the initial lockdown of the pandemic in an at-risk birth cohort (N~6800 total observations). Moreover, we explored the predictive value of prefrontal affective and cognitive control on stress burden at three strategic time points during the COVID-19 crisis (N = 104).

Our results show that (I) social contacts were linked to higher momentary mood, demonstrating the protective role of social integration. Moreover, our findings indicate that (II) stress-buffering effects are predicted by the neural underpinnings of emotion regulation and cognitive regulation at different stages during the pandemic, highlighting the beneficial use of adaptive coping strategies in response to the COVID-19 pandemic.

These findings emphasize the importance of individual resilience factors on momentary well-being during the pandemic and may inform future prevention strategies seeking to foster stress coping.

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How do we learn to make good choices – a translational model of cognitive flexibility

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Cognitive flexibility is the ability to respond to changes of the environment in adaptive ways and deficits in this cognitive domain are observed in several major neuropsychiatric disorders. However, we lack a clear understanding how flexible decisions are identified. We developed a novel translational rule learning paradigm in rats and used movement tracking, reinforcement learning as well as multiple single-unit recording from the medial prefrontal cortex to show that rats use discrete behavioral strategies to sequentially test task features for relevance. Our behavioral model is able to explain salient features of rule learning such as sudden transitions in choice or transfer effects and offers a unifying link between competing concepts related to cognitive flexibility. First results from a pilot MEG study show that similar learning strategies in humans support flexible behavior.

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EMIcompass: A novel, transdiagnostic, hybrid ecological momentary intervention for improving resilience in youth

Isabell Paetzold, Anita Schick, Christian Rauschenberg, Dusan Hirjak, Tobias Banaschewski, Andreas Meyer-Lindenberg, Jan R Boehnke, Benjamin Boecking, Ulrich Reininghaus

Most mental disorders emerge in youth; they are the leading cause of overall disease burden in adolescents and young adults in high-income countries. Elevated stress reactivity is a widely studied putative mechanism underlying various mental health problems and is thus a promising target for preventing future adverse outcomes and enhancing resilience. Based on compassion-focused techniques, EMIcompass was developed as a hybrid intervention combining an ecological momentary intervention (EMI) and face-to-face sessions to offer a youth friendly and accessible real-time intervention for improving resilience in daily life. Initial support of beneficial effects, feasibility and safety of the intervention was provided by an uncontrolled phase I pilot study with *N*=10 help-seeking youths with depressive, psychotic, and/or anxiety symptoms, who were offered a pilot version of the EMIcompass intervention. We found decreased stress reactivity (e.g. b=-0.10, p=.005), momentary negative affect (e.g. b=-0.44, p<.001) and psychotic experiences (e.g. b=-0.25, p<.001) as well as increased positive affect (e.g. b=0.39, p=.001) and reduced symptom levels (r=0.30-0.65) at post-intervention and 4-week follow-up. No severe adverse events were observed. A randomised controlled trial is currently ongoing to establish feasibility and detect initial signals of efficacy of the EMIcompass intervention in help-seeking youth aged 14-25 with current distress, a broad Clinical High At Risk Mental State (CHARMS) or a first episode of severe mental disorder presenting to mental health services. If the trial indicates feasibility and initial signals of efficacy, EMIcompass has the potential to show beneficial effects for prevention and early intervention in youth in a future definitive trial.

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The psychedelic psilocin fosters neuroplasticity in iPSC-derived human cortical neurons

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The serotonergic plant-hallucinogen psilocybin is studied as innovative medication in anxiety, substance abuse and treatment-resistant depression. Animal studies show that psychedelics promote neuronal plasticity by strengthening synaptic responses and protein synthesis. However, the exact molecular and cellular changes induced in the patient's brain are not entirely understood. Here, we treated cortical neurons derived from human induced pluripotent stem cells with the psychoactive 5-HT2A receptor agonist psilocin. We analyzed pre - and postsynaptic markers, pathways related to neuroplasticity and 5-HT2A receptor localization. Acute exposure led to a decrease in axonal extracellular 5-HT2A receptor presentation which may indicate receptor complex formation or internalization. We further found the number of presynaptic BDNF, SV2A, Synaptophysin and postsynaptic PSD-95 puncta to be increased 24 hours after 10 *µM* psilocin exposure. Synaptophysin, BDNF, phosphorylated TrkB (activated BDNF receptor) and Akt (pro survival pathway) protein level was elevated as well. Modulation of the axon initial segment, reduction of resting state membrane potential and upregulation of activity-related immediate early genes, like *cFOS* were indicative for an altered excitability. PKC and vesicle invagination inhibition abrogate psilocin-induced BDNF increase suggesting a PKC - and endocytosis mediated process. Psilocin induced the expression of genes involved in the generation of plasmin that cleaves the precursor proBDNF into its mature form in the brain. Co-treatment with a selective 5-HT2A receptor antagonist blocked the BDNF puncta and plasmin associated gene set increase, indicating a receptor involvement. These data suggest that exposure of human neurons to psilocin might induce a state of enhanced neuronal plasticity. This neuroplasticity booster could explain why psilocin is beneficial in the treatment of neuropsychiatric disorders where synaptic dysfunctions are discussed.

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Investigating sense of agency under conditions of uncertain sensory outcomes

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Sense of agency is the experience of control over one's own action and its consequent outcomes. The perceived time between a motor action (e.g., a finger movement) and its consequent sensory outcomes (e.g., a flash of light) is shorter for a voluntary than involuntary action, a phenomenon known as intentional binding which has been used extensively as an implicit measure of sense of agency. We developed a novel task in which participants had to respond whether a flash appeared immediately or with a delay relative to their voluntary action. We found that under high, but not low, uncertainty about the perceived time between voluntary finger movement and a subsequent flash of light, a prediction signal was generated in the right inferior parietal lobule prior to motor action. This prediction signal was linked to the emergence of a sudden insight solution (colloquially referred to as "Aha!" moment) in the right superior temporal gyrus prior to response. Single-trial event-related potential analysis revealed a reliable correlation between amplitudes of pre-motor and pre-response activities. The results suggest the existence of a predictive mechanism under high uncertainty about the timing of the sensory consequences of a voluntary motor action. The results are in line with the optimal cue integration theory of sense of agency which states that both predictive and postdictive agency cues are crucial for the formation of sense of agency and the weight of each type of cue (predictive or postdictive) depends on their availability and reliability. Currently, we are planning a new study with an improved design to further investigate the existence of predictive mechanisms involved in the sense of agency when the uncertainty about the delay of sensory outcomes is high. Details of that project will be highlighted .

Keywords: consciousness awareness, event-related potentials, sense of agency, sensorimotor integration, synchrony judgment

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How to proof dopamine supersensitivity in humans using simultaneous PET/MR dopamine supersensitivity – a pilot study

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Text: Background After the first episode of schizophrenia, maintenance treatment with antipsychotic agents is the primary therapeutic regime recommended by international guidelines (NICE 2014, SIGN 2013, DGPPN 2019). However, long-term use of dopamine antagonists has been associated with an increasing risk of relapse after withdrawal and with treatment resistance. A possible underlying molecular mechanism might be dopamine supersensitivity (DS), an alteration of the dopaminergic system with upregulated dopamine receptor density and increased sensitivity of the dopaminergic system for dopamine agonists (Suzuki et al., 2015). Even though animal models could clearly show DS upon long-term treatment with dopamine antagonists (Sander, 2013), the phenomenon has not been investigated in humans, yet. Thus, we want to perform a human study with combined PET/MR-imaging in order to investigate DS. Methods We are piloting the use of combined PET/MR with a pharmacological intervention in healthy humans. We measure the average dopamine binding potential BPND (ND = non-displaceable) with [18F]fallypride, a selective dopamine D2/3 receptor-tracer, and analyze it with a simplified reference tissue model. Simultaneously, we quantify the change of cerebrovascular blood flow (CBF) in the striatum upon the administration of the dopamine agonist apomorphine with a pseudo-continuous arterial spin labelling sequence. Results The preliminary data of 6 healthy subjects shows an average dopamine BPND of 16.6 in the striatal areas. We show an average increase of cerebrovascular blood flow (CBF) upon the injection of apomorphine of 3.8±2.6 ml/100g/min in this region. The BPND and the increase of CBF show a linear correlation of r=0.07. Conclusion With our piloting study, we are able to show that the simultaneous investigation of dopamine BPND and CBF is feasible. The occurrence of DS will be further explored in our subsequent study including premedicated and unmedicated patients with schizophrenia.

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Oxytocin facilitates sexual behavior in male rats acting at the ventral hippocampus!accessory olfactory bulb pathway

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The hypothalamic neuropeptide oxytocin (OT) modulates a plethora of socio-sexual behaviors. In this study we focused on OT signaling in the ventral hippocampus (vHippo), a central social memory hub. In our preliminary experiments, implementing celltype specific adeno-associated viruses (AAVs) we first found substantial innervation of the vHippo from the hypothalamic OTergic nuclei. Next, using a combination of a newly generated OTRIRES-Cre knock-in rats and viral-based vectors, we identified 3 types of neurons expressing OT receptors (OTR) in the vHippo: 1) Parvalbumin-positive GABA-egic neurons, 2) Excitatory radiatum giant cells (RGS) and 3) Sub-population of pyramidal cells, residing in CA1 principal cell layer. External application of an OT agonist on acute vHippo slices resulted in generation of EPSCs in both types of OTR-expressing pyramidal neurons and simultaneous IPSPs in OTR-negative pyramidal cells. Anterograde and retrograde viralbased tracing revealed that OTR+ PCs predominantly project to the accessory olfactory bulb (AOB), which plays a critical role in processing social chemosensory information (detection of pheromones). We employed the transsynaptic FLP/frt AAV system to validate functional meaning of this pathway. By chemogenetic activation of AOB OTR+ cells, which receive synaptic input from CA1 PCs of the vHippo, we found that male rats spent significantly more time sniffing female urine compared to a neutral odor in a reference-based olfactory hole-board test. Our results suggest that OT in the vHippo is involved in female pheromone processing and hence in male socio-sexual behavior.

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Major Depressive Disorder and Bipolar Disorder Subtypes Differ in their Genetic Correlations with Physical Activity, Circadian Rhythm, and Sleep

Authors:

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Background: Disruptions in circadian processes, sleep patterns and physical activity are core features of mood disorders: for example, decreased locomotor activity levels are often observed in Major Depressive Disorder (MDD) and high variability in circadian patterns and lower relative amplitude is found in Bipolar Disorders (BIP). Relative amplitude is a circadian parameter characterizing activity and rest patterns; healthy people show higher values, with greater daytime activity and reduced nighttime activity. First reports have shown genetic associations between mood disorders, relative amplitude, and physical activity. Traits such as sedentary behavior and daytime sleepiness are highly related to depressive mood on the phenotypic level. Based on these findings we aim to explore the shared genetic etiologies between these traits and mood disorders.

Methods: Using the latest available GWAS summary statistics, we applied Linkage Disequilibrium Score Regression (LDSC) to calculate the genetic correlations of MDD and BIP, with continuous relative amplitude, overall physical activity, moderate activity, sedentary behaviour, daytime sleepiness, and sleep duration.

Results: MDD showed positive genetic correlations with sedentary behavior, and negative correlations with overall physical activity and moderate activity, while BIP-I showed associations in the opposite direction. MDD and BIP-II had negative genetic correlations with relative amplitude. All mood disorders were positively genetically correlated with daytime sleepiness.

Discussion: The correlational patterns show that MDD and BIP-I differ the most in their correlations with biological rhythms with BIP-II seemingly occupying a intermediate position. Furthermore, our results suggest that the clinically observed associations between mood disorders and biological rhythms have shared genetic underpinnings. Future research considering possible joint mechanisms may offer potential avenues for improving disease detection and treatment.

Multimodal MRI data fusion reveals distinct structural, functional and neurochemical correlates of heavy cannabis use

Authors:

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Abstract:

Heavy cannabis use (HCU) is frequently associated with a plethora of cognitive, psychopathological and sensorimotor phenomena. Although HCU is frequent, specific patterns of abnormal brain structure and function underlying HCU in individuals presenting without cannabis-use disorder or other current and life-time major mental disorders are unclear at present. The present multimodal magnetic resonance imaging (MRI) study examined resting-state functional MRI (rs-fMRI) and structural MRI (sMRI) data from twenty-four persons with HCU and sixteen controls. Parallel independent component analysis (p-ICA) was used to examine covarying components among gray matter volume (GMV) maps computed from sMRI and intrinsic neural activity (INA), as derived from amplitude of low-frequency fluctuations (ALFF) maps computed from rs-fMRI data. Further, we used JuSpace toolbox for cross-modal correlations between MRI-based modalities with nuclear imaging derived estimates, to examine specific neurotransmitter systems underlying HCU. We identified two transmodal components, which significantly differed between the HCU and controls (GMV: p=0.01, ALFF p=0.03, respectively). The GMV component comprised predominantly cerebello-temporo-thalamic regions, whereas the INA component included fronto-parietal regions. Across the HCU sample, loading parameters of both components were significantly associated with distinct HCU behavior. Finally, significant associations between GMV and the serotonergic system as well as between INA and the serotonergic, dopaminergic and μ-opioid receptor system were detected. This study provides novel multimodal neuromechanistic insights into HCU suggesting co-altered structure/function-interactions in neural systems subserving cognitive and sensorimotor functions.

The state-of-the-art MEG lab at the CIMH

Bankim Subhash Chander, Robert Becker, Matthias Ruf, Gabriele Ende

MEG-Unit, Center for Innovative Psychiatry and Psychotherapy Research (CIPP)

In 2019, the Central Institute of Mental Health (CIMH) started a new chapter with the Centre for Innovative Psychiatry and Psychotherapy Research (CIPP). In the coming years, the CIPP approach will yield fundamentally new insights and thus significantly improve the treatment and ultimately the lives of people suffering from mental illness. The CIPP will enable comprehensive and safe early-phase patient research integrated with multimodal neuroimaging.

As one of the key pillars for multimodal neuroimaging, the Magnetoencephalography (**MEG**) lab was setup with the state-of-the-art equipment. The MEG system inherits a whole head system equipped with 204 planar gradiometer, 102 magnetometer, 12 bipolar BIO channels and 16 trigger input/output channels. The entire MEG system is installed in a magnetically shielded room (MSR) that prevents interference from environmental magnetic noise and ensures signal quality. Additionally a 64-electrode electroencephalography (EEG) system for simultaneous recordings (64 monopolar electrodes, 2x32 head box, 3 EEG-caps) is available.

The MEG studies use the software packages “Presentation” (Neurobehavioral Systems Inc., Berkeley, US), PsychoPy3 (Peirce et al., 2019) or Psychtoolbox-3 for stimulus presentation and equipment for visual and auditory stimulation as well as somatosensory stimulation (Digitimer DS5). Audiovisual stimulation system consisting of a SXGA-beamer (Panasonic, Hamburg, Germany) with a 45deg mirror and a back-projection plane. Responses of the subjects are recorded with 4 and 2 digit-response-pads (Current Designs Inc., Philadelphia, US).

A 3D-Head digitization pen and software for digitizing the head shape and on scalp electrode locations of the subjects and a camera are also part of the equipment. Computational algorithms use the 3D-Head digitization information to attenuate artifacts not related to brain activity and allows co-registration of brain activity to individual brain anatomy acquired using MRI scans.

In addition to the above-mentioned equipment, there is a possibility to acquire additional equipment according to the requirements of the MEG user. Based on the feedback from the MEG users, the authors offer to provide support and endeavor to improve the MEG user experience. Furthermore, the authors would like to encourage our colleagues to utilize the MEG lab to address their research question and foster collaborations.

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DiSERVE@home - Innovative digital forms of service delivery for personalized crisis resolution and home treatment for people with severe mental health problems

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The rapid progress in the field of information and communication technology offers entirely new opportunities for innovative digital services in, and personalizing the delivery of, crisis resolution and home treatment for people with severe mental health problems. This poster will provide initial findings from DiSERVE@home, a translational research pilot study that aims to develop and evaluate digital forms of service delivery for personalizing crisis resolution and home treatment. In a first stage, interviews with service users and health professionals were carried out to identify and discuss promising digital forms of service delivery, including (1) channels for better communication, continuity of care, and flexibility; (2) monitoring of symptoms and behaviour in real-time through ESM; (3) use of multimodal ESM data to generate and offer personalized feedback on subjective experience and behavioural patterns as well as (4) ecological momentary interventions (EMIs) tailored to the person, moment, and context in daily life. Following principles of co-design, these findings were used to develop and evaluate a novel mHealth tool used in the context of home treatment by carefully investigating its quality from the user perspective, safety, feasibility, initial process and outcome quality as well as barriers and facilitators of implementation.

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Measuring the effect of reward on memory without the confounding influence of response bias

Tkotz, J., Morgan, D.P. & Feld, G.B.

If we want to draw strong conclusions in our research, it is important that the tasks we use can measure the concepts we are interested in, and are not biased by processes that are not of interest. The Motivated Learning Task is an important paradigm in reward and memory research, where participants memorise pictures associated with a reward (learning phase) that is paid out for later recognising the previously learned pictures among a set of new pictures (test phase). The task has been used to demonstrate the influence of reward on memory encoding, but with hit rate as its primary outcome measure, it is not able to distinguish between improved memory (sensitivity) and an increased response bias. We re-designed the task so it can separate the two concepts by adding either congruent or incongruent reward information to the test phase of the task. In a large online sample (N = 200), we validated our approach using a gamified version of the task. While we confirm that reward influences sensitivity, we also demonstrate that it increases response bias, which can lead to an overestimation of the reward effect on memory if not accounted for.

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Lifetime and Current Depression in the German National Cohort (NAKO)

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Here we present an overview of instruments for the assessment of depression and depressive symptoms in the German National Cohort (NAKO), report the distribution of the resulting depression measures and examine associations between these measures and with sociodemographic factors.

We report data from the first 101,667 participants (NAKO data freeze 100,000; total n = 204,000). The assessment included the Mini-International Neuropsychiatric Interview (MINI vs 5.0), self-reported physician's diagnosis of depression, and the depression scale of the Patient Health Questionnaire (PHQ-9).

15.0% of participants stated that they received a diagnosis of depression by a physician at some point in their lifetime; of these, 47.6% reported undergoing treatment for depression within the last year. In a subset of 26,342 participants assessed with the full MINI depression section, 15.9% fulfilled the criteria for lifetime depression. The PHQ-9 identified 5.8% of participants as currently having depression (major or other) using the diagnostic algorithm, while the dimensional assessment (score≥10) identified 7.8%. Women and participants with lower educational attainment or a family history of depression displayed an increased frequency of depression and higher depression scores.

We observed distributions of depression measures and associations with sociodemographic factors consistent with previous findings in depression research. The association with family history indicates a genetic contribution to the different depression phenotypes. The future availability of genotype data will enable detailed investigations using molecular genetic approaches.

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Multi-Omics Signatures of Alcohol Use Disorder in the Dorsal and Ventral Striatum

Running title: Multi-Omics Signatures of Alcohol Use Disorder

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Abstract

Alcohol Use Disorder (AUD) is a major contributor to global mortality and morbidity. The analysis of postmortem human brain tissue enables to investigate molecular mechanisms associated with AUD in brain regions. This study aimed to identify differentially expressed (DE) genes in the ventral and dorsal striatum between individuals with AUD and controls, and to integrate the results with findings from genome- and epigenome-wide association studies to identify functionally relevant molecular mechanisms of AUD. DNA-methylation and gene expression (RNA-seq) data was generated from human postmortem brain samples of 48 individuals with AUD and 51 controls from the ventral striatum (VS) and the dorsal striatal regions caudate nucleus (CN) and putamen (PUT). We identified DE genes using DESeq2, performed gene-set enrichment analysis (GSEA) with fgsea, and tested enrichment of DE genes in results of genome-wide association studies (GWAS) using MAGMA. Weighted correlation network analysis (WGCNA) was performed for both DNA-methylation and gene expression data and gene overlap was tested. Results showed DE genes at FDR < 0.05 in the dorsal striatum. In the VS, results at FDR < .25 were overrepresented in a recent GWAS of problematic alcohol use. *ARHGEF15* was upregulated in all three brain regions. GSEA in CN and VS results pointed towards cell-structure associated GO-terms and in PUT towards immune pathways. The WGCNA modules most strongly associated with AUD showed strong enrichment for immune response and inflammation pathways. Our integrated analysis of multi-omics data sets provides further evidence for the importance of immune-and inflammation-related processes in AUD.

Personalization applied to psychological PAIN management through mechanism-based interventions and targeted therapy assignments - the PerPAIN research network".

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Abstract:
Numerous musculoskeletal disorders are associated with chronic pain. For many of those affected, pain persists despite appropriate treatment. Although there has been substantial progress in understanding chronic pain in recent years, treatment outcomes are often unsatisfactory. Many studies report great heterogeneity in individual patient response to therapy. While some patients benefit relevantly from one treatment, others do not benefit or even experience adverse effects. Therefore, there is an urgent need to identify reliable predictors of response to psychological treatments and to develop new personalized therapeutic approaches for the treatment of chronic pain. The aim of the PerPAIN research network presented here is to identify relevant mechanisms of pain chronification based on psychological, psychophysiological and biological factors and, based on these, to develop and clinically test personalized allocation algorithms for patients with chronic musculoskeletal pain. By merging existing databases, the first step was to develop a preliminary stratification tool to cluster appropriately relevant psychological chronification mechanisms of patients with chronic musculoskeletal pain. A randomized proof-of-concept trial is now being conducted to evaluate the feasibility, safety, and efficacy of personalized pain psychotherapy allocation. Personalization is achieved by specific assignment to three therapies according to the mechanism-based stratification tool. Patients with high psychological distress receive EMDR-based treatment targeting emotionally distressing memories, patients with dysfunctional pain behaviors receive extinction retraining, and individuals with low psychological salience receive a low-threshold, smartphone-based minimal intervention.

Concomitantly, the underlying mechanisms in the development and treatment of chronic pain will be explored using data from ambulatory measurements in the daily lives of individuals using wearable devices, psycho-physiological profiles, and brain imaging data in a machine learning algorithm approach. The resulting data will be used to further develop mechanism-based algorithms for treatment prediction and personalized treatment assignment.

The interdisciplinary research network will enable exploration of underlying mechanisms about chronic musculoskeletal pain, development of clinical treatment allocation trees, and translation into personalized clinical care. In addition, improved biomarkers for prediction for therapy response using large-scale multi-system data and improved treatment outcomes through more effective treatment allocation and development of a novel outpatient smartphone-based positive activity diary as a novel first low-level intervention will be elaborated.

Abstract UBICA-II

Understanding and Breaking the Intergenerational Cycle of Abuse

Fabian Seeger, Mark Wenigmann, Corinne Neukel, Michael Kaess, Svenja Taubner, Sabine C. Herpertz

Background: Parental mental illness (MI) and parental history of early life maltreatment (ELM) are known to be risk factors for poor parenting behavior. In turn, poor parenting behavior may increase the risk for maltreatment and MI within the children of those parents and is therefore considered a crucial factor with respect to the intergenerational continuity of ELM and MI. Hence, there is an urgent need for prevention programs for families with an MI parent, which pay particular attention to experiences of parental ELM. Parental mentalizing was previously found to mediate successful parenting and interventions aimed at improving the parental mentalizing capacity reduced maltreatment risk in parents. As parents with a history of ELM or a current MI have been shown to exhibit impaired mentalizing capabilities, UBICA-II is aiming at investigating the effectiveness of a mentalization-based parenting-counselling (MB-PC) in acutely mentally ill parents who are currently treated psychotherapeutically or psychiatrically.

Methods: Within the bicentric randomized-controlled trial UBICA II (together with Charité) MB-PC is administered vs. enhanced standard clinical care. Patients with severe mental disorders currently in psychiatric treatment with children between 1.5-15 years will be included in the trial. Primary efficacy endpoint is self-reported parenting practices at follow-up. Two sub-studies using fMRI, psychophysiological and hormonal biomarkers additionally investigate social cognition and dyadic biobehavioral synchrony as mechanisms of change.

Discussion: The main goal of UBICA II is to investigate ways to break the intergenerational continuity of maltreatment by assessing the benefits of a prevention program which aims at improving parenting in mothers and fathers at high risk of child maltreatment. We hypothesize MB-PC to improve impaired parenting more than enhanced standard clinical care. MB-PC is a short, low-cost intervention which can be delivered by nurses and social workers and is applicable to MI patients with children with a broad range of diagnoses.

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Generalization of threat associations and reduced individualization of visual outgroup faces: An ERP study

Autors: Niclas Willscheid, Sabine Schellhaas, Florian Bublatzky

Abstract

Reduced perceptual individualization of faces of other visual phenotypes (outgroup homogeneity effect) is suggested to result from lower expertise. On a neural level, prior studies reported less identity-specific neural representations of other-phenotype faces, quantified by adaptation-based repetition suppression. Here, we examined whether instructed threat association related to a singular other-phenotype face generalizes over the visual group. A pilot sample of light-skinned German participants (*N* = 15) viewed 12 blocks of 40 pairs of consecutively presented light- or dark-skinned faces (i.e., visual in- and outgroup), serving as adaptor followed by the same or a different target (600 ms each, ISI 500 ms). Prior to each experiment block, one specific in- or outgroup face was instructed as threat-of-shock cue. Overall, results replicated threat-enhanced LPP amplitudes over parietal sensor sites (400–600 ms). Additionally, in blocks with an outgroup threat cue, outgroup safety cues elicited more positive LPP amplitudes compared to blocks with an ingroup threat cue. The reversed comparison for ingroup safety cues was less pronounced. On the contrary, exclusively for ingroup faces, identity-sensitive repetition suppression (i.e., more positive N170 amplitudes elicited by same compared to different targets) emerged over right lateralized occipito-parietal sensor sites (130–190 ms). Taken together, these results indicate a link between reduced individualization and generalization of threat associations for visual outgroup faces, potentially reflecting an early antecedent of stereotyping.

Key words: Adaptation and repetition suppression, threat-of-shock, outgroup homogeneity effect, other-race effect, event related potentials

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Neuroimaging markers for early recognition of at-risk states for major psychoses: recent findings from the BipoLife Consortium

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Previous studies suggest that patients suffering from psychiatric disorders, e.g., bipolar disorder (BD) or schizophrenia, exhibit alterations in reward processing in the brain (1, 2) and that these modifications are also detectable in healthy first-degree relatives of schizophrenic patients (3). Based on these findings we investigated the extended reward system in a multicenter study carried out by the BipoLife Consortium to develop neuroimaging markers for early recognition in persons at risk for the development of BD (4). In total, 180 youths and young adults (18-35 years), who were either seeking help at an early recognition center and show at least one risk factor for BD or were in-/outpatients with depressive syndrome or ADHD, respectively, were recruited. All participants performed the “desire-reason dilemma” (DRD) paradigm examining the neural correlates of reward gain processing while undergoing functional magnetic resonance imaging (fMRI). Based on predefined risk factors, the subjects were assigned to three risk groups: “no increased risk” (n = 22), “slightly increased risk” (n = 87) and “increased risk” (n = 71). By comparing the extreme groups in a factorial design, we found risk-dependent BOLD-responses to reward stimuli. More precisely, subjects with increased risk revealed reduced neural activity in the right ventral tegmental area, anteroventral prefrontal cortex, anterior insula and nucleus accumbens compared to the group with no increased risk. In summary, we found potential neuroimaging markers associated with reward processing and linked to the risk status of a person.

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Evaluation of digital interventions to enhance young people's mental health

Stephanie Bauer & Michael Kaess

The treatment gap, i.e. the disparity between those who need treatment and those who receive professional healthcare is a key driver of the disease burden related to mental illness. From a service research perspective, reducing this gap by facilitating access to mental healthcare is critically important. In two BMBF-funded projects we investigate the potential of digital interventions for health promotion, illness prevention as well as help-seeking intentions and treatment uptake.

Based on previous research on treatment barriers, the project INABI (2019-2022) evaluates two animated video interventions developed to improve intentions to seek professional help for various mental health problems (i.e., depression, non-suicidal self-injury, alcohol abuse, bulimia nervosa, generalized anxiety disorder). While intervention 1 aims at de-stigmatization and the improvement of participants' mental health literacy, intervention 2 seeks to induce positive outcome expectancies regarding the utilization of professional help. Intervention effects are investigated with an online, parallel group randomized controlled design in a sample of 1,200 adolescents and young adults (aged 14 to 25 years). The results promise to enhance existing and novel interventions for the promotion of help-seeking in young people with mental health problems.

In the project ProHEAD (2017-2022) the potential of digital interventions aimed at facilitating the uptake of professional treatment (sub-project 1), the selective prevention of common disorders (sub-projects 2-4), and counteracting the development of mental illness (sub-project 5) is investigated. Based on the results of a school-based online screening (current N > 8,000), high-school students aged 12 years or older are invited to register for one out of five RCTs. Across these RCTs, the potential of 14 digital interventions is studied (nine intervention groups, five active control groups). The results concerning the uptake, utilization, efficacy and cost-effectiveness of these interventions will draw a realistic picture of young people's interest and willingness to engage in such tools as well as their potential for the prevention, early identification and timely intervention in the field of child and adolescent mental health.

Help from the app stores? The results of 1,929 systematic quality ratings of mobile Health Applications in 15 indications – The MHAD project

Yannik Terhorst, Eva-Maria Messner, Lasse Bosse Sander, Harald Baumeister

Mobile Health Applications (MHA) have the potential to improve health care. Their applications reach from education, over monitoring to stand alone treatments. However, the MHA market is rapidly growing and unregulated, leading to an opaque market. Studies investigating the content, quality and scientific evidence of available MHA are highly needed.

The present poster summarizes the results of over 15 studies systematically investigating the quality and features of MHA available in the European app markets. In all studies MHA were rated by two independent researchers using the Mobile Application Rating Scale to assess the quality in terms of engagement, functionality, aesthetics and information quality. Furthermore, the underlying framework of the MHAD – a non-commercial project by the Ulm University - project will be presented.

Overall, the ratings of 1,929 MHA covering 15 diseases and symptom areas (e.g., depression, pain, etc.) showed a moderate quality. Information quality and engagement were discovered as the lowest quality subdimensions. Most striking less than 5% of the MHA were evaluated by randomized controlled trials. Objective expert ratings were not correlated to user ratings.

Currently, the potential of MHA is not exploited. Reliable information is highly needed to guide clinicians and patients to adequate MHA. While the BfArM and MDR regulations provide guidelines for the primary health market, the lack of guidelines and information remains in the secondary app markets (e.g., prevention). Information sites providing transparent expert ratings may help to foster the uptake of high-quality MHA and reduce the risk of patient harm. Innovative methods to investigate the effectiveness of MHAs seem to be of utmost importance to tackle the immense lack scientific evidence in the app markets. Smart-sensing will be discussed as a potential solution to achieve this.

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Social learning: Computational and neurobiological models for learning about the personality and preferences of others

Koen Frolichs, Christoph Korn

Introduction: Social learning underlies successful human interactions. In these situations humans learn about their own and other persons' character traits. Often such social learning processes go awry in persons with psychiatric symptoms. In recent studies, we have developed new computational models for conceptualizing and quantifying how humans learn about and from other persons across different categories.
Methods: In a series of behavioral studies, we tested participants on several variants of a social learning task (Frolichs, Rosenblau, Korn, 2020, preprint). We formalized social learning in so-called reinforcement learning models that hinge on prediction errors (i.e., the differences between initial expectations and received information about and from others) and combined these with social knowledge structures that capture some of the wealth of social information at our disposal.
Results: In general, participants used fine-grained representations combined with reference points of a specific social group to learn about others but they were able to flexibly adapt their strategies based on task demands.
Conclusions: Overall, our experiments demonstrate that variants of reinforcement learning algorithms, which incorporate social knowledge structures, describe crucial aspects of the dynamics at play when people interact with each other. Therefore, we believe, they also have potential to illuminate how and why these processes go awry in persons with psychiatric symptoms.

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Web-Based Computer-Adaptive Assessment in Clinical Health Care

Johannes Knauer, Yannik Terhorst, Selina Kallinger, Paula Philippi, Sandro Eiler, Prof. Dr. Harald Baumeister

A reliable diagnostic is key to design health care in needs-based manner. However, even if in place, a gap between diagnostic results and adequate treatment often remains. The integration of a web-based computer-adaptive patient reported outcome test (CAT) platform with persuasive design optimized features including recommendations for action into routine health care could provide a promising way to translate reliable diagnostic results into action. Furthermore, the ubiquitous presence of sensors (e.g., in smartphones) in our everyday life allows a constant real-time collection of data. This data has been successfully used in diagnosis and prediction of health outcomes and has the potential to improve health care. However, with data security and accountability as core requirements of medical applications, it remains a major challenge to integrate smart sensing information into the health care systems. One promising application is the integration into systems, in which smart sensing information is used to assist medical experts in their decisions. In a previous trial our system was implemented in three rehabilitation clinics with 12.785 participants completing baseline assessments. This corresponded to utilization rates between 74% and 85%. Acceptance was high for both patients and clinical staff. The current study RehaCAT+ aims to further evaluate the effectiveness of our diagnostic system with additional features in clinical routine health care.

Dopamine Transporter Silencing in the Rat: Systems-Level Alterations in Striato-Cerebellar and Prefrontal-Midbrain Circuits

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ABSTRACT

Silencing of the dopamine transporter (DAT), a main controlling factor of dopaminergic signaling, results in biochemical and behavioral features characteristic for neuropsychiatric diseases with presumed hyperdopaminergia including schizophrenia, bipolar disorder, attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). Investigation of DAT silencing thus provides a transdiagnostic approach towards a systems-level understanding of common underlying pathways. Using a high-field multimodal imaging approach and a highly sensitive cryogenic coil, we integrated structural, functional and metabolic investigations in tandem with behavioral assessments on a newly developed preclinical rat model, comparing DAT homozygous knockout (DAT-KO, N=14), heterozygous knockout (N=8) and wild-type male rats (N=14). We identified spatially distributed structural and functional brain alterations encompassing motor, limbic and associative loops that demonstrated strong behavioral relevance and were highly consistent across imaging modalities. DAT-KO rats manifested pronounced dorsal striatal volume loss, which anticorrelated with cerebellar volume increase. These alterations were associated with hyperlocomotion, repetitive behavior and loss of efficient functional small-world organization. Further, prefrontal and midbrain regions manifested opposite changes in functional connectivity and local network topology. These disturbances were corroborated by elevated myo-inositol levels and increased volume in the prefrontal cortex. To conclude, our imaging genetics approach provides multimodal evidence for prefrontal-midbrain decoupling and striato-cerebellar neuroplastic compensation as two key features of constitutive dopamine transporter blockade, proposing them as transdiagnostic mechanisms of hyperdopaminergia. Thus, our study connects developmental DAT blockade to systems-level brain changes, underlying impaired action inhibition control and resulting in motor hyperactivity and compulsive-like features relevant for ADHD, schizophrenia and OCD.