Aus dem Zentralinstitut für Seelische Gesundheit
Klinik Psychiatrie und Psychotherapie
AG Systemische Neurowissenschaften in der Psychiatrie
(Direktor: Prof. Dr. med. Andreas Meyer-Lindenberg)

Environmental influence on mental health - psychological, neural, and daily affective functions in at-risk populations

Inauguraldissertation
zur Erlangung des Doctor scientiarum humanarum (Dr. sc. hum.)
der
Medizinischen Fakultät Mannheim
der Ruprecht-Karls-Universität
zu
Heidelberg

vorgelegt von
Oksana Berhe
aus
Kiew, Ukraine
2022

Dekan: Prof. Dr. med. Sergij Goerdt

Referentin: Prof. Dr. med. Dr. phil. Heike Tost

PREFACE

This work is a publication-based cumulative dissertation, and several parts of the thesis have already been published in the peer-reviewed journals. Therefore, certain sections, tables, or figures of this thesis will be identical to these publications. The list of peer-reviewed publications:

Publication 1

Berhe O.*, Höflich, A.*, Moessnang, C., Reichert, M., Kremer, T., Gan, G., Ma, R., Braun, U., Reininghaus, U., Ebner-Priemer, U., Meyer-Lindenberg, A.*, Tost, H.* (2022). Reduced Real-life Affective Well-being and Amygdala Habituation in Unmedicated Community Individuals at Risk for Depression and Anxiety. Biol Psychiatry Cogn Neurosci Neuroimaging. 2022; S2451-9022(22)00153-7. ***These authors contributed equally**. Impact factor - 6.204. Original research paper.

Publication 2

Berhe, O., Moessnang, C., Reichert, M., Ma, R., Höflich, A., Tesarz, J., Heim, C., Ebner-Priemer, U., Meyer-Lindenberg, A., Tost, H. (in review). Dose-dependent changes in real-life affective well-being in healthy community-based individuals with mild to moderate childhood trauma exposure. Borderline Personal Disord Emot Dysregul. Impact factor 4.618. Original research paper.

Publication 3

Gerhardt, S.*, Berhe, O.*, Moessnang, C., Horning, M., Kiefer, F., Tost, H.*, & Vollstädt-Klein, S.* (2023). Lack of amygdala habituation to negative emotional faces in alcohol use disorder and the relation to adverse childhood experiences. Addict. Biol, 28(1), e13251 ***These authors contributed equally.** Impact factor 4.280. Original research paper.

The Publication 1 is presented in the corresponding chapter of the dissertation: '*Chapter 2.1: Study 1'*. The Publication 2 - in the '*Chapter 2.2: Study 2'*, and accordingly the Publication 3 - in the *'Chapter 2.3: Study 3'*.

The detailed description of the personal contribution to each of the publication:

Arbeitsschritte	**Publikation 1**	**Publikation 2**	**Publikation 3**
Konzeption (%)	50	100	50
Literaturrecherche (%)	50	90	40
Ethikantrag (%)	0	0	0
PTierversuchsantrag (%)	n/a	n/a	n/a
Datenerhebung (%)	80	90	0
Datenauswertung (%)	80	100	60
Ergebnisinterpretation (%)	70	70	45
Verfassen des Manuskripttextes (%)	40	80	40
Revision (%)	70	70	45
Geben Sie an, welche Abbildungen / Abbildungstafeln aus Ihrer Doktorarbeit entstanden sind	All figures of the main manuscript and supplement of this article arose from the dissertation work of O. Berhe	All figures of the main manuscript and supplement of this article arose from the dissertation work of O. Berhe	Figure 1 and Supplemental Figures S1, S2, S3 in this article arose from the dissertation work of O. Berhe
Geben Sie im Einzelnen an, welche Daten/Zahlen/Tabellen auf Forschungsergebnissen von anderen beruhen.	Parts of the clinical data presented in Table 1 and Supplemental Figure S2 were provided by Dr. A. Höflich	N/A	Table 1 arose from the dissertation work of S. Gerhardt

In both shared publications the expertise of both contributors was combined in order to answer the research question in the best possible way:

Publication 1: O. Berhe (data collection, data analysis, fMRI/EMA data interpretation), A. Höflich (at-risk population clinical diagnostic, clinical/psychological data interpretation).

Publication 3. A planned collaboration within the graduate school 2350 (Prof. C. Schmahl, ZI Mannheim);

S. Gerhardt: Conception of the evaluation presented here (50%), literature research for the introduction and discussion with a focus on alcohol use disorder (60%), ethics application (90%), data collection (100%), execution of the pre-processing and first-level analysis of the data as well Execution of the analysis of the psychometric and behavioral data as well as graphic processing (40%), interpretation of the results (total 45%), drafting of the manuscript text (45%), implementation of the revision (45%).

O. Berhe: Conception of the evaluation presented here (50% in total), literature research for the introduction and discussion with a focus on habituation processes (40%), ethics application (0%), data collection (0%), development of the analysis scripts and execution of the second -level analysis of the data and graphic preparation (60%), interpretation of the results (45%), drafting of the manuscript text (40%)

TABLE OF CONTENT

LIST OF FIGURES

Main Figures

Supplemental Figures

LIST OF TABLES

Main Tables

Supplemental Tables

ABBREVIATIONS

AAL	Automated Anatomical Labeling
ABF	Alltagsbelastungsfragebogen
ACC	Anterior cingulate cortex
ACE	Adverse childhood experience
ADS	Alcohol Dependence Scale
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
AUD	Alcohol use disorder
BCOPE	Brief- Coping Orientation to Problems Experienced
BF	Bonferroni corrected
BMI	Body mass index
BOLD	Blood-oxygen-level dependent
BPD	borderline personality disorder
BSSS	Berlin Social Support Scale
CHARMS	Clinical high at-risk mental state
CSSS	Chronic Stress Screening Scale
CT	Childhood trauma
CTQ	Childhood Trauma Questionnaire
CTS	Childhood Trauma Screener
df	degree of freedom
DSM	Diagnostic and Statistical Manual of Mental Disorders
EA	Emotional abuse
EMA	Ecological Momentary Assessments
EMI	Ecological momentary intervention
EN	Emotional neglect
ESPAD	European School Survey Project on Alcohol and other Drugs
FD	Framewise displacement
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
FWHM	Full-width at half-maximum
GAD	Generalized anxiety disorder
GSES	General Self-Efficacy Scale

HC	Healthy controls
HIS	history group
HPA	Hypothalamic–pituitary–adrenal
ICC	Intraclass correlation coefficient
ICD	International classification of diseases
LOT-R	Revised Life Orientation Test
M	Mean
MDBF	Mehrdimensionale Befindlichkeitsfragebogen
Mini-DIPS	Diagnostisches Kurz-Interview bei psychischen Störungen
MLM	Multilevel modeling
MNI	Montreal Neurological Institute
mPFC	Medial prefrontal cortex
MPRAGE	Magnetization-Prepared Rapid Acquisition Gradient-Echo
MRI	Magnetic resonance imaging
MSSD	Mean square successive difference
N/A	Not available
NEO-FFI	Neuroticism- Extraversion - Openness Five-Factor Inventory
OCD	Obsessive-compulsive disorder
PA	Physical abuse
PAT	clinical group
PFC	Prefrontal cortex
PN	Physical neglect
PTSD	Post-traumatic stress disorder
ROI	Region of interest
SA	Sexual abuse
SAB	Social affective benefit
SCID-IV	Structured Clinical Interview for DSM-IV
SD	standard deviation
SE	Standard error
SES	Socioeconomic status
SOC	Sense of Coherence Scale
SPM	Statistical Parametric Mapping
SPQ	Schizotypal Personality Questionnaire
SSCS	Chronic stress

STAI-T	State-Trait Anxiety Inventory
SUB	subclinical group
SWLS	Satisfaction with Life Scale
TE	Time to Echo
TI	Inversion time
TR	Repetition time
tSNR	Temporal Signal-to-Noise Ratio
UCLA	University of California Loneliness Scale
VS	Ventral striatum
WFU	Wake Forest University
WHO	World Health Organization

1. INTRODUCTION

1.1. Environmental influence and mental health

Mental health, including emotional, psychological, and social well-being, is a fundamental human right and essential at every stage of life, from childhood to adulthood. The prevalence of mental disorders have been on the rise since decades and continue to be among the top 10 causes of societal and economic burden worldwide, with depressive and anxiety disorders being among the leading causes, (Lancet, 2022). Nearly one billion people worldwide live with some form of mental disorder, according to the last WHO review (Freeman, 2022). Early recognition, early intervention and early prevention are essential key elements for minimizing this burden.

Mental health and environment are interconnected and interdependent. Environmental influence, in the broad sense, including ‘‘physical’’ as well as ‘‘social’’ exposures, shapes the developing and developed brain and behavior, be it good or bad. Epidemiological studies highlight the environmental risk factors of mental disorder (van Os, Rutten, & Poulton, 2008). These factors encompass a wide range of overlapping adverse exposures (**Figure 1.1**). The strongest evidence for an association with psychopathology are however for urban upbringing, migration, cannabis use, exposure to stressful life events, and early traumatic experiences (Lederbogen et al., 2011; van Os et al., 2008). Many of these factors increase the risk for a variety of mental disorders, such as anxiety, depression, in a nonspecific, dose-dependent manner. Furthermore, genetic variations make individuals selectively vulnerable for environmental risks, setting the stage for individual differences in vulnerability to stress experience and proclivity to mental disorders. Exposure to environmental adversities in childhood, during developmentally sensitive periods, has a particularly detrimental effect since it undermines the normal neural development, contributing thus to dysfunctional brain maturation (Danese & Baldwin, 2017; Holz et al., 2022; Tost, Champagne, & Meyer-Lindenberg, 2015).

1.1.1. Individuals at mental health risk - underresearched “gray area” between mental health and disorder

Meta-analysis reports up to 10% of all individuals suffer from subclinical symptoms in general population (Fusar-Poli, Bonoldi, et al., 2012; Shankman et al., 2009; Wolitzky-Taylor et al., 2014), referring to the phase between the appearance of some form of

daily function impairments and the manifestation of mental disorder. Approximately 36% of them will transition eventually to full-blown disorder (Fusar-Poli, Bonoldi, et al., 2012; McGorry, Hartmann, Spooner, & Nelson, 2018).

Over 25 years ago, criteria have been developed to identify individuals predisposed to the development of psychopathology (Yung & McGorry, 1996; Yung et al., 1998). These criteria, termed prodromal or at-risk mental states based on a combination of trait and state risk factors (Fusar-Poli et al., 2013; T. J. Miller et al., 2002; Yung & McGorry, 1996). In this work we adopted ‘at-risk mental states’, or just ‘at-risk’ to refer to this population group. As defined, the earliest subjective symptoms are nonspecific, a mixed set of affective and motivational alterations, anxiety states, sleep disturbances, social impairments, and other symptoms that dynamically affect each other, forming a causal network (Fusar-Poli et al., 2015). This is often accompanied by a deterioration in general functioning. The early symptoms usually persist before the individual comes to the attention of mental health services. Over time, these symptoms may gradually develop into distinct, but still largely overlapping, clinical syndromes.

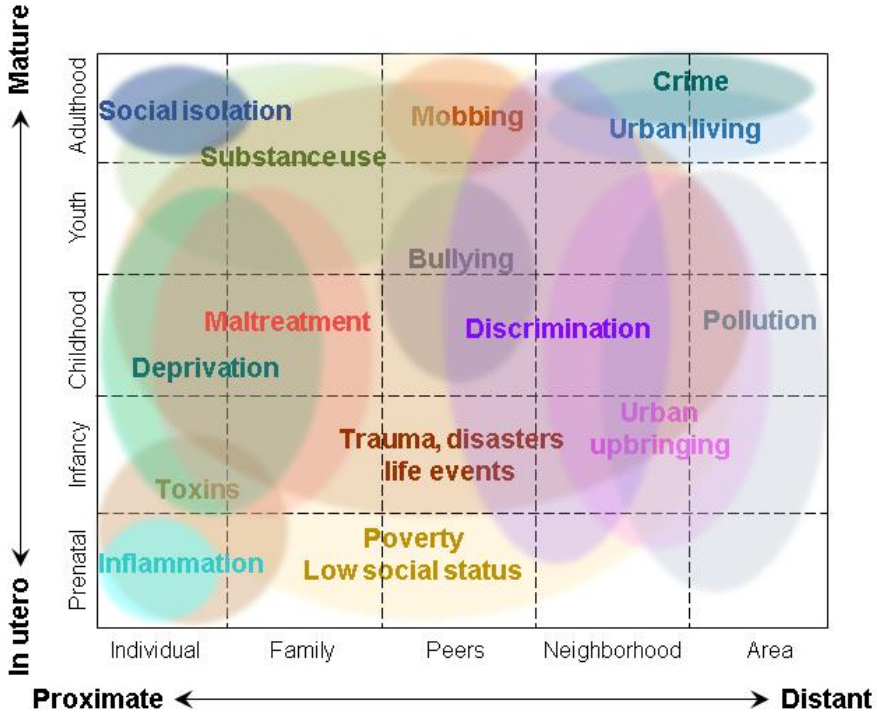


Figure 1.1: Early adverse exposures. Schematic representation of frequently named and often overlapping constructs studied in imaging research. Keywords are mapped to the approximate period of exposure during brain development (y-axis, from prenatal to early adulthood) and the spatial extent of exposure (x-axis, from person-level to area-level). The figure is adapted from Holz et al. (2022).

This widely used approach has rather low validity and specificity in identifying vulnerable population groups, in illuminating the risk factors and mechanisms underlying deteriorating mental health. Within this concept, at-risk mental states refer to help-seeking individuals with subthreshold symptoms, thus leaving unnoticed and unattended those who never present to clinical services. Retrospective assessment is inherent in this concept. Recall may be affected by a long delay between the actual experience and the screening interview. It may also be influenced by the current mental state or coping style of the individual. Furthermore, the symptoms manifestation is a dynamic process, involving a moment-to-moment changes in subjective experiences and behavior over time, rather than a list of symptoms.

The limitations of the conventional methods of risk identification call for the development of new, more progressive approaches. More accurate characterization of the non-specific symptoms and subjective experience can help to identify vulnerable individuals when they first show subtle changes in daily functioning and environmental risk-factors that may contribute to the symptoms development. Neuroimaging studies have the potentials to detect any abnormalities in brain function and structure to map the evolution of symptoms. Studying general population, rather than high-risk samples, can help to capture individuals earlier in the trajectory of a disorder, since mental distress experiences exist as a continuum within the population. These results may further aid the definition of reliable markers, i.e. features that may predict the subsequent development of disorder.

The studies in individuals at-risk are scares and rather heterogeneous and mainly focused on help-seeking individuals at ultra-high risk for developing mental health problems. On behavioral level, the high-risk states are characterized by significant and consistent impairments of daily functioning and reduction of quality of life (Lukow et al., 2021). Available fMRI studies indicate that the alterations in the brain function are traceable before the onset of disease, are qualitatively similar to but less pronounced than in a manifest disorder (Fusar-Poli, McGuire, & Borgwardt, 2012; Fusar-Poli et al., 2015). Aberrant activations in prefrontal regions as well as in limbic areas have been consistently reported for at-risk cohort, suggesting for emotional processing difficulties prior to the onset of florid disorder (Derntl et al., 2015; Seiferth et al., 2008; Tseng et al., 2016; van der Velde et al., 2015). It therefore remains critically important to further study the changes in brain function underlying the transition from at-risk state to full-blown disorder.

1.1.2. Childhood trauma - as a major risk factor for mental health impairments

Early adverse environmental exposures are well-established and well-documented risk factors for the increased physical and mental morbidity in adulthood (Felitti et al., 1998). While epidemiological studies indicate a wide range of overlapping early adverse environmental influences leading to poor health outcome later in life (Norman et al., 2012; Pietrek, Elbert, Weierstall, Muller, & Rockstroh, 2013)(**Figure 1.1.**), in this work I will focus on childhood trauma (or Adverse Childhood Experience (ACE)) as more consistently reported phenomenon antecedent to psychopathology and will use both terms interchangeably (Heim, Entringer, & Buss, 2019). Childhood trauma is commonly defined as "*all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment … resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power"* [(World Health Organization, 1999), p.15], and is operationalized as emotional, physical, or sexual abuse, and neglect before the age of 18 years (Butchart, 2006).

Childhood trauma has been consistently related to the development of a number of mental disorders such as anxiety, depression, bipolar or post-traumatic stress, substance use disorder, or schizophrenia (Heim & Nemeroff, 2001; McGrath et al., 2017; McKay et al., 2021). This is particularly relevant because population-based data show that up to 1 billion children globally, aged 2–17 years, experience at least some form of maltreatment, rates exceeded 50% in Africa, Asia, Northern America, 30% in Latin America, and 19,5% in Europa (Hillis, Mercy, Amobi, & Kress, 2016), thus constituting a major public health problem. Importantly, many incidents are still hidden and unreported due to fear, stigma, and societal norms (Pinheiro, 2006).

Early adversities reportedly cause dose-dependent effects on neurobiological, social, emotional, and cognitive development. On behavioral level, maltreated individuals show difficulties in social cognitive functioning (Crawford et al., 2022; Majer, Nater, Lin, Capuron, & Reeves, 2010) as well as social interactions (Mc Elroy & Hevey, 2014), sleep problems, decreased subjective well-being (Corcoran & McNulty, 2018; Oshio, Umeda, & Kawakami, 2013), and overall lead more disadvantaged lives (lower socioeconomic status (SES): education level, employment and earnings) (Boden, Horwood, & Fergusson, 2007; Currie & Widom, 2010). ACEs are also linked to heightened vulnerability to stressful life events (Mc Elroy & Hevey, 2014). Research

from psychology propose inflexible developmental personality patterns as vulnerability phenotype mediating the link between ACE and later manifestation of disorder (J. Kim, Cicchetti, Rogosch, & Manly, 2009; Kuzminskaite et al., 2021). Many studies indeed have linked ACE with maladaptive personality traits, like increased trait anxiety, neuroticism, negative self-associations, and lower optimism, and self-efficacy (Broekhof et al., 2015; A. X. Gorka, Hanson, & Radtke, 2014; Kuzminskaite et al., 2021; Mc Elroy & Hevey, 2014). Thus, experiencing early adversity may confer risk for psychopathology by creating a dispositional sensitivity to perceived daily hassles in adulthood.

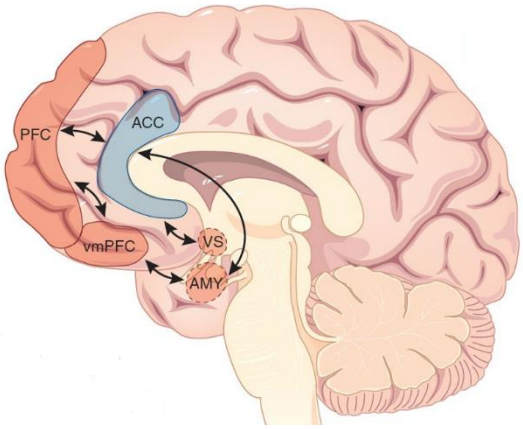


Figure 1. 2: Illustration of brain regions involved in the regulation of affective, social, and stress responses. In this circuitry, the anterior cingulate cortex (ACC) is influenced by higher-order cognitive processing areas such as the prefrontal cortex (PFC), and it provides top-down control of subcortical neural areas modulating stress response, salience and negative emotion, such as the amygdala and the ventral striatum (VS). The image is adapted from Meyer-Lindenberg and Tost (2012).

On the biological level, data from human and animal studies show enduring changes in the major stress system, namely, the hypothalamic-pituitary-adrenocortical axis (HPA) function, as a result of early adverse exposure (Danese & Baldwin, 2017; VanTieghem et al., 2021), including enduring alterations by chronical cortisol release, secretion of pro-inflammatory cytokines, and alterations of sympathetic and parasympathetic nervous system. This in turn is associated with altered plasticity processes during developmentally sensitive periods of increased neuroplasticity and affect the regular functional interaction of cortical and subcortical neural networks (such as amygdala, medial prefrontal cortex (mPFC), hippocampus) (Lupien, McEwen, Gunnar, & Heim, 2009; VanTieghem & Tottenham, 2018). In recent years imaging

research has accumulated new evidences to the neural basis of early adverse influence, with a number of brain function studied pointing to a convergence of the effects in frontal-limbic brain regions (Holz et al., 2022; Holz, Tost, & Meyer-Lindenberg, 2020; Meyer-Lindenberg & Tost, 2012; Tost et al., 2015)(**Figure 1.2**). Hyperresponsivity of amygdala and hypoactivity of the PFC to emotional stimuli are the most consistent findings in relation to ACE, suggesting for persistent vigilance to thread-related information and maladaptive prefrontal regulation (Kuzminskaite et al., 2021).

Cognitive and affective processes are also affected as a result of ACE-induced neurodevelopmental disturbances in the stress-/emotional brain circuits (Pechtel & Pizzagalli, 2011). Maltreated individuals show impairments in reward processing, in emotion regulation, show selective attention to and difficulty disengaging from threat-related information, which are thought to confer risks for later psychopathology (Pechtel & Pizzagalli, 2011).

To better understand who is at risk for disorder manifestation it is essential to identify the underlying mechanisms. Precise mechanisms through which childhood trauma impacts mental health are complex and heterogeneous, including psychological, environmental and biological domains (**Figure 1.3**), thus calling for multimodal integrative comprehensive characterizations.

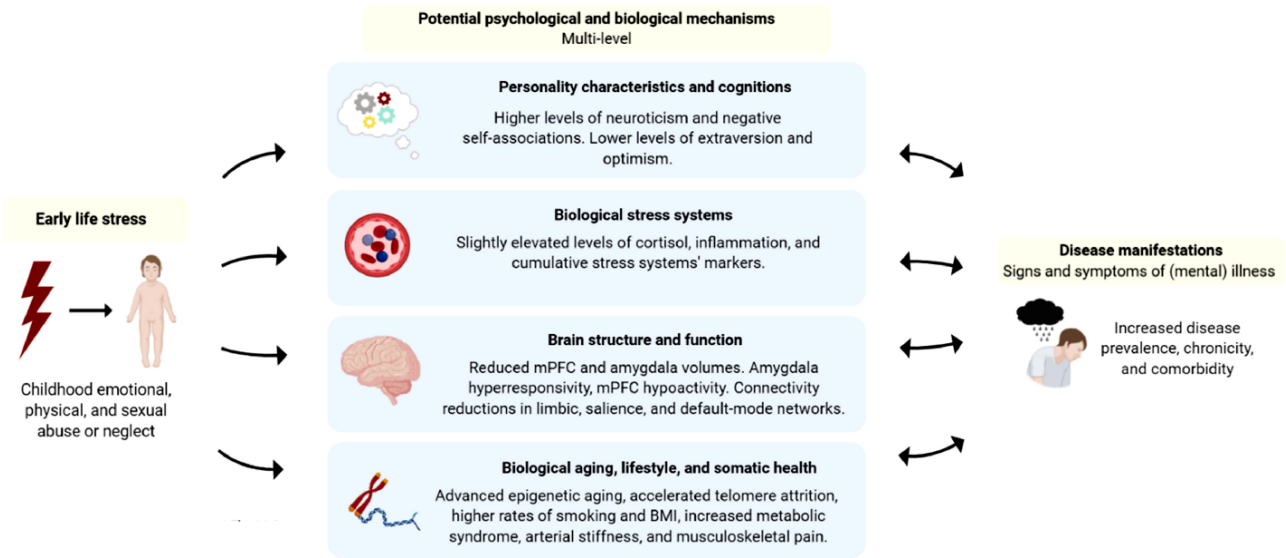


Figure 1.3: ACE-related psychological and biological changes involved in (mental) illness manifestations. Abbreviations: BMI, body mass index; CT, childhood trauma; mPFC, medial prefrontal cortex. The image is adapted from Kuzminskaite et al. (2021).

1.2. Modern approaches for early identification at-risk mental states

Efforts to identify at risk states, (i.e., early signs of affective and/or behavioral impairments indicating enhanced risk for mental illness) face a number of methodological challenges, due to unspecific nature of symptoms spanning multiple risk and environmental factors (see paragraph 1.1.2 for full review). Moreover, in real life psychiatric symptomatology as well as other affective experience are inherently dynamic and unstable, ebbing and flowing, emerging in a sporadic or gradual way, often as a result of contextual or environmental influence. To identify trajectories of risk leading to psychopathology it is important to capture momentary within-subject affective experience and its contextual influence. By now, however in clinical practice this is typically performed by screening or referral procedures still relying on traditional paper-and-pencil questionnaires and face-to-face clinical interviews.

1.2.1 Methodological challenges

These well-established methods have number of limitations. Traditional assessment requires individuals to reconstruct their symptoms over long periods of time. The time interval between the moment of experience and the recall may range from several days to several weeks or months, relying heavily on patients' retrospective self-report (Ebner-Priemer & Trull, 2009). Retrospective measures in turn are subject to memory distortions, rather revealing one's ability to reconstruct the past, rather than the real experience, highly influenced by current state/mood (Jurgen Margraf, Ehlers, & Roth, 1987; Trull & Ebner-Priemer, 2009). This applies to both disordered and healthy populations alike (Solhan, Trull, Jahng, & Wood, 2009). Moreover, retrospective methods are not able to capture the symptoms dynamic (e.g. variability and (in)stability) as well as interplay between the environment, personal experiences, and symptomatology (Ebner-Priemer, Eid, Kleindienst, Stabenow, & Trull, 2009). In addition, such approaches require the skill of the clinical interviewer, the greater amount of staff time, and the artificial setting of the assessment (the clinic). Given this, different, more refined approaches are important to study such complex dynamic processes.

1.2.2 Ambulatory Assessment as a promising tool

A rapid progress in the capability and affordability of digital technology over the past decades enables for intensive monitoring of psychosocial processes in real life (Malhi et al., 2017). The dramatic growth in smartphones ownership and its ubiquity offer

opportunities for simple, accessible, instantaneous and real-world context-sensitive measurements. Collecting intensive time series data using ecological momentary assessment (EMA) (Trull & Ebner-Priemer, 2013) opens new avenues for the assessment of the daily experience of complex dynamic psychological processes, enables investigating symptoms in settings where they evolve, i.e. in daily life, and offers a way to address (or at least minimize) the above limitations.

Known collectively as ambulatory assessment (Trull & Ebner-Priemer, 2013), this technology includes experience-sampling methods (e.g., paper-and-pencil diary (Csikszentmihalyi & Larson, 1987), ecological momentary assessment (e.g., electronic diaries on smartphones, (Stone & Shiffman, 1994), as well as real-time data capture (Stone & Broderick, 2007), among other. Though different, these methods commonly use digital devices (e.g., smartphone, accelerometer, electrocardiogram, respiration, or sleep actigraphy) to acquire ecologically valid data such as mood, behavior, affective states, physiology, subjective experience, location information, and environmental context in real-time and real-life settings (Trull & Ebner-Priemer, 2013). I adopted the term “ecological momentary assessment” in my dissertation, referring to technique typically using electronic diaries or mobile phones.

EMA has a number of important advantages over traditional methods (e.g., self-report retrospective questionnaires, or clinical and diagnostic interviews). First, EMA is ecological, enables a naturalistic daily assessments (can’t be recreated in artificial environment of the clinic, laboratory, or hospital), in the moment (not average over a long period of time - minimizing recollection bias, significantly higher accuracy of reports, reports (Schwarz, 2012; Solhan et al., 2009)), and in real-life settings (allowing to elucidate social and environmental influences). Second, EMA collects multiple assessments over time, capturing within-individual processes, allowing to study the dynamic patterns of symptoms. And lastly, EMA methods using electronic devices commonly show high compliance rates (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2002; Trull et al., 2008), eliminate inaccuracies in scheduled ratings (time-stamped reports) time), and significantly reduce amount of paper used (Trull & Ebner-Priemer, 2013).

EMA usually involves self-report e-diaries with predefined questions. Here, participants respond to queries that are either prompted (e.g., random prompts or prompts at set times) or self-initiated. Questions, response formats, and sampling strategies highly

depend on the research question or the clinical settings/needs (Ebner-Priemer & Sawitzki, 2007; Palmier-Claus et al., 2011). The most common sampling strategies are time- /, location or event-related, or mixed, e.g. a time- and location-based scheme. A time-based sampling sends questionnaire in a predefined time, random or at regular intervals (e.g., daily or hourly). The event-driven schema is triggered by the participant themselves only when a specific events occur (e.g., social contact (Fahrenberg, Myrtek, Pawlik, & Perrez, 2007)). The location-based algorithm monitors the distance between the current and previous locations of the respondent and triggers an e-diary assessment whenever distances larger than a predefined length. A mixed time- and location-based sampling strategy help to minimize the missed rare events, enhance the spatial coverage of assessments and increases the data variability within individuals (Ebner-Priemer, Koudela, Mutz, & Kanning, 2012). E-diary prompts usually are accompanied by acoustic, visual and vibration signal.

EMA assesses individuals repeatedly over time, includes multiple data points per individual, and has a hierarchical data-structure (e.g. the repeated assessments (level 1) nested within subjects (level 2), leading to a two-level model). An advanced statistical methods such as multilevel modelling is typically used that can handle a hierarchical data structure, unequally spaced time points, time-varying covariates, non-normal data, and missing data (Wilhelm, 2001). Also known as hierarchical linear models, linear mixed-effect models (Harville, 1977; Laird & Ware, 1982), mixed models, or random-effects models. This method includes ‘random effects’, which can be used to account for person-level differences (i.e., intercepts and slopes). Using multilevel models, we can then properly assess between-subject (fixed effect) variability in an outcome of interest (i.e., some individuals report higher/lower outcome measure overall) and within-subject (random) variability (i.e., the degree of variability in the moment-to-moment assessments of outcome measure).

1.2.3 Real-life measures of at-risk mental states

EMA is reliable, valid and ideally suited for clinical assessments (Myin-Germeys et al., 2018; Trull & Ebner-Priemer, 2013, 2020), e.g. depression- (Armey, Schatten, Haradhvala, & Miller, 2015), or anxiety-related symptoms (Robinaugh et al., 2020). Momentary mood, emotional experience, perceived stress, social experience (withdrawal, anhedonia) and general well-being and their fluctuation over time are the most relevant (and thus the most studied) constructs from the clinical prevention

perspective. The most widely used and well-established scale in EMA studies is Multidimensional Mood State Questionnaire (Mehrdimensionale Befindlichkeitsfragebogen, MDBF, (Steyer, Schwenkmezger, Notz, & Eid, 1997; Wilhelm & Schoebi, 2007). This three-dimensional scale is the first validated questionnaire for the measurement of within-subject fluctuations of daily mood affect (Gan et al., 2021; Tost et al., 2019), and has been shown a good reliability and sensitivity (Wilhelm & Schoebi, 2007). It covers: valence (with two bipolar items: “content/discontent” and “unwell/well”, calmness (”agitated/calm” and “tense/relaxed”), and energetic arousal (”full energy/without energy” and “awake/tired”) energy) (Matthews, Jones, & Chamberlain, 1990; Schimmack & Grob, 2000; Wilhelm & Schoebi, 2007).

To study social experience in real life using EMA, first a binary scale is offered to assess whether or not the participants have been in company since the last alert (Collip et al., 2011; Collip et al., 2014; Myin-Germeys et al., 2018; Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001). Then, in case if not alone, participants are asked to rate their social experience, using, as a rule, two items measuring how do they like they company, and the degree to which they would prefer to be alone (Collip et al., 2011; Collip et al., 2014; Myin-Germeys et al., 2001). Participants are also often asked to rate the intensity of the most important positive/negative event since the last beep (Wichers et al., 2009; Wichers et al., 2010). Several statistical indices of temporal instability have been used to assess the dynamic of affect in real life: the within-person variance or standard deviation, autocorrelation, and mean square successive difference (MSSD, (Jahng, Wood, & Trull, 2008)). MSSD is proved to be superior, because it takes into account both variability and temporal dependency in mood scores (Jahng et al., 2008; Trull et al., 2008).

1.3. Neural correlates of at-risk states

1.3.1 Brief introduction to functional magnetic resonance imaging (fMRI)

In the following section, I will provide the brief overview of the basis of fMRI by highlighting the most important aspects. fMRI methodology is complex and far beyond the scope of this thesis and can be found for example in (Ulmer & Jansen, 2013).

Magnetic resonance imaging (fMRI) is the most frequently used tool, providing researchers an opportunity to acquire in-vivo brain images. fMRI is noninvasive, low-risk, with no radiation involved, has high spatial resolution, and is easy to operate.

MRI exploits the magnetic properties of organic tissue and uses strong uniform static magnetic fields from the MRI scanner, magnetic gradients from gradient coils, and oscillating electromagnetic fields from radiofrequency coils to generate brain images. Specifically, the magnetic field aligns the atomic nuclei (typically within water molecules), that are normally randomly oriented, with the direction of the field. This alignment (or magnetization) is next disrupted by introduction of a magnetic pulses generated by radiofrequency coils. When the pulse is turned off, the nuclei return to their original equilibrium alignment producing energy and the emitted signals are measured. The amount of released energy depends on the different brain tissues. These physical characteristics are used to create high dimensional structural brain images, giving insight into the locations of different tissue types including gray matter, white matter, and cerebrospinal fluid.

The fMRI measurement is based on the concept that an increase in local neuronal activity requires an increased flow of oxygenated blood. Thus fMRI measures the change in blood oxygenation, defined as the blood-oxygen level–dependent (BOLD) signal (Ogawa, Lee, Kay, & Tank, 1990), resulting from changes in neuronal activity in active brain areas under particular task condition (Huettel, Song, & McCarthy, 2004). Advances in neuroimaging over the past 30 years have turned fMRI into the most frequently used tools for studying the biologic mechanisms of mental illness (Callicott & Weinberger, 1999; Rosen & Savoy, 2012)

1.3.2 The stress-regulatory circuitry in health and disorder

A wealth of preclinical and clinical research show that the amygdala, a region within the limbic system, is one of the critical mediators of emotion processing and stress response, given its roles in threat detection, stress reactivity, and memory for negative information (Herman & Cullinan, 1997; H. Kim, Somerville, Johnstone, Alexander, & Whalen, 2003; McEwen, Nasca, & Gray, 2016; Murty, Labar, & Adcock, 2012; Pessoa & Ungerleider, 2004).

The Amygdala, a structurally and functionally heterogeneous collection of nuclei, forms dense micro-circuits with amygdala subnuclei, as well as reciprocal connection with distant brain areas, e.g. the PFC, the anterior cingulate cortex (ACC), and Hippocampus (Zhang, Zhang, Holmes, & Pan, 2021) (**Figure 1.2)**. Receiving sensory inputs from visual, auditory, and somatosensory cortices, from the olfactory system (McDonald, 1998), the amygdala communicates it bidirectionally further to a wide

range of areas, including the PFC, the striatum, and other subcortical structures implicated in autonomic responses, hormonal responses, and startle (Davis & Shi, 2000). Amygdala exerts a strong regulatory influence over the HPA axis (Herman et al., 2016). The Amygdala acts thus as an integrative hub that converts relevant sensory information from the external and internal environment into emotional and physiological responses. The amygdala and other areas of the limbic system, particularly mPFC, Hippocampus, play fundamental role, as a dynamic player in regulating the effects of stress (Herman et al., 2016; Liu et al., 2020).

Top-down influence of mPFC over the amygdala (e.g. fear and anxiety, (Adhikari et al., 2015)) is believed to be affected by chronic stress, and other environmental adversities leading to aberrant amygdala function and associated emotional disturbances (Zhang et al., 2021). Supporting this view, fMRI has linked dysfunctional amygdala to different environmental risks (social stress, ACE, urbanicity, migration (Lederbogen et al., 2011; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015)), as well as mental health impairments (internalizing symptoms, (Swartz, Knodt, Radtke, & Hariri, 2015), posttraumatic symptoms (McLaughlin et al., 2014; Rauch et al., 2000), individuals at-risk mental state (Barbour et al., 2010; Kozhuharova, Saviola, Ettinger, & Allen, 2020; Lukow et al., 2021), anxiety symptoms (Rauch, Shin, & Wright, 2003)).

1.3.3 Amygdala habituation a reliable trans-diagnostic neural phenotype

Of particular relevance in the context of emotion regulation is neural habituation. Habituation, "response decrement as a result of repeated stimulation [p. 385] (Harris, 1943).", is a basic learning mechanism of the nervous system helping to rapidly and adaptively filter vast amount of familiar, predictable, and inconsequential signals in the environment (Ramaswami, 2014; Rankin et al., 2009; Thompson & Spencer, 1966). Animal studies suggest the homosynaptic depression of excitatory neurotransmission as the possible cellular mechanisms underlying habituation (Thompson & Spencer, 1966).

When novel information is encountered, all available attentional resources are immediately directed to assess whether it signals a potential threat or reward. As one learns that information is of no relevance, or safe and familiar, this leads to habituation at both neural and behavioral levels. In healthy population, habituation of amygdala response to repeated emotional presentation occurs very quickly, as many study document (Wright et al., 2001), enabling to selectively direct the attention and response

to salient signals of the environment. Deficits in habituation, on the other hand, may be considered maladaptive as it leads to inappropriate allocation of information processing resources to the stimuli with no potential relevance for survival, suggesting thus for deficit in neural plasticity.

This evolutionary conserved phenomenon is one of the most documented and fundamental forms of learning in animals as well as humans, individual differences have been reported as early as infancy though (Turk-Browne, Scholl, & Chun, 2008). In Autism spectrum disorder (ASD) patients, amygdala habituation to emotional faces is absent (Tam et al., 2017). Furthermore, very intense stimuli may yield no observable response decrease, comparing to weaker one (Rankin et al., 2009; Thompson & Spencer, 1966).

Aberrant amygdala habituation to emotional stimuli has been implicated in various mental disorders, such as social anxiety, borderline personality disorder (BPD), ASD, psychosis, and post-traumatic stress disorders (PTDS) (Hare et al., 2008; McDiarmid, Bernardos, & Rankin, 2017; Tam et al., 2017). It has also been linked to ACE, one of the strongest environmental risk factor for mental disorders (Bilek et al., 2019; Wang, Paul, Stanton, Greeson, & Smoski, 2013).

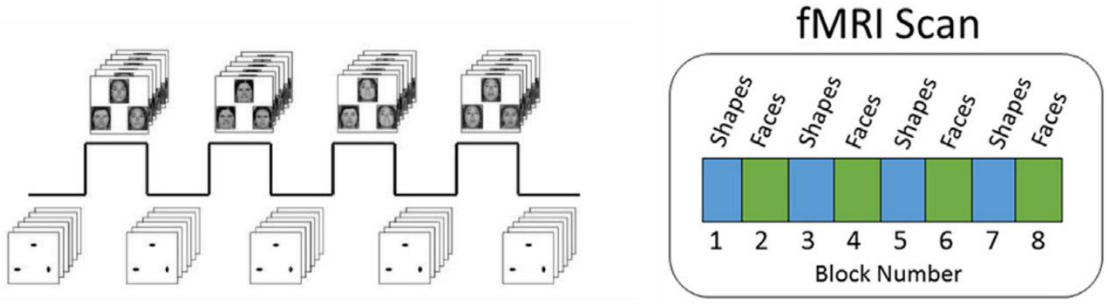


Figure 1.4: Face matching paradigm. Faces with fearful or angry faces, as well as shapes were presented in a block design. All stimuli were presented in black and white. Participants were instructed to select the corresponding face or form according to the target as quickly and precisely as possible. The image is adapted from Hariri Lab of Neurogenetics and Gerhardt et al. (2022).

While neural differences in habituation may occur across the whole brain, e.g. visual processing areas (Summerfield, Trittschuh, Monti, Mesulam, & Egner, 2008; Weigelt, Muckli, & Kohler, 2008), the prefrontal cortex (Wright et al., 2001; Yamaguchi, Hale, D'Esposito, & Knight, 2004), and the hippocampus (Blackford, Allen, Cowan, & Avery,

2013; Fischer et al., 2003), the amygdala would be a prime candidate due to its high relevance for clinical psychology, psychiatry and neuroscience (paragraph 1.3.2).

To consider amygdala function as a possible biomarker for emerging mental disorders, it is essential to have a reliable measure, that is stable over time and reflects individual' characteristics. Habituation in the amygdala reportedly has a stronger test-retest reliability than mean activation (Gee et al., 2015; Plichta et al., 2014), and robust to variations in neuroimaging methods (Bilek et al., 2019). In their paper, Plichta et al. 2012 report a stable response amplitudes in functional activation during emotion processing faces task (**Figure 1.4**), across all sessions and retest interval of two weeks (Plichta et al., 2012). They found however, a low within-subject reliability (ICC = −0.02–0.16). On the contrary, retest-reliability of amygdala habituation was significantly higher, comparing to the mean activation amplitude (Plichta et al., 2014).

There are at least three different amygdala habituation indices used so far: (1) the amplitude difference between stimulation blocks (Blackford et al., 2013), (2) modeling habituation by means of the (log-transformed) regression approach (Plichta et al., 2014), or parametric modulation (Preckel et al., 2019). While Plichta recommended a logarythmic regression index over block difference approach (Plichta et al., 2014), another studies found simple block difference model being more sensitive in explaining the relationship of amygdala habituation than linear or/and logarithmic parametric modulation (Preckel et al., 2019). These inconsistencies might suggest for a complex non-linear nature of neural response decrement, depending on number of factors (fMRI paradigm, brain area, underlying mechanisms, etc.) (Rankin et al., 2009).

1.3.4 Multimodal approach as a method of choice to study complex environmental influence

The complex, dynamic and unspecific nature of earliest expression of psychopathology as well as mechanisms underlying the transition to manifest disorder introduced above call for multimodal integrative characterizations generated in ecologically valid situations similar to what one usually experiences in daily life.

The neuro-epidemiological approach combining neuroimaging, ecological momentary assessments and the assessment of psychosocial trait-like measures in general population can take research outside the controlled laboratory environment, and may ultimately become a potent tool to study the dynamic relationship between the environmental influence and mental health (Tost et al., 2015). A few examples. Heller

et al., using a multimodal approach, was able to map a daily positive experience onto brain reward circuitry (Heller et al., 2015). Further, Tost and colleagues linked real-life green affective benefit to a neural risk marker of impaired human emotion processing (Tost et al., 2019). Reichert et al. (2021) established the neural mechanisms underlying the effect of physical activity on momentary affective well-being (Reichert et al., 2021). Another study suggested neural correlates for higher benefit in well-being from real-life social contact (Gan et al., 2021). Bakker et al., associated real-life engagement in pleasing activities alleviating depressive symptoms to brain reward processing (Bakker et al., 2019). Yet, another paper gave new insights about the neural bases of diverse daily activities (Urban-Wojcik et al., 2022). These studies cumulatively confirm the strong potential of a combined multimodal method.

1.4. Research Questions and Hypothesis

The reviewed studies revealed a noticeable progress in the current knowledge in the early identification of risk states and risk factors that predispose individuals to psychopathology and the intermediate phenotypes of brain function in recent years. However, the literature is still patchy and heterogeneous in terms of the intertwined adverse environmental influences and individual experiences and still lacks a few crucial points. The existing literature on at-risk states is still dominated by mechanistic diagnostic categories and traditional retrospective symptom measures, preferentially including help-seeking individuals. Multimodal ecological neuroscience community-based studies are needed to assess dimensional trans-diagnostic brain-behavior relationships by monitoring the dynamic emotional states in the flow of daily life under the influence of familial, environmental, emotional and cognitive factors and relating them to the reliable neural phenotype. Based on this theoretical background and to address the existing gap in the literature we have derived following research questions and hypothesis.

In the study 1 we investigated EMA and questionnaire data in 61 unmedicated individuals at clinical risk, 48 non-risk persons and 23 community-based individuals fulfilling the criteria for a current mood or anxiety disorder. We further compared fMRI readouts between carefully matched subsamples of 26 individuals at clinical risk and 26 non-risk individuals to identify alterations in neural affective habituation related to psychiatric risk. We hypothesized that (1) momentary affective valence in daily life would be significantly lower in the at-risk group and in the clinical group compared with

the non-risk group, and (2) amygdala habituation will be reduced in individuals at clinical risk reminiscent of that of clinical states. We further expected these neural affective signals to be related to the real-life affective experience.

In the Study 2 we explored the psycho-emotional functioning in healthy community-based individuals with milder forms of childhood adversities combining data from psychology and ecological momentary assessments. Given the non-specific nature of ACE effect, we studied the range of EMA and questionnaire measures to provide a comprehensive picture of the subclinical changes in everyday life and to better define the risk for and resilience against developing a mental disorder. We hypothesized that history of ACE, even in a healthy population, will predict decreased momentary affective valence in daily life and increased psychological risk for mental illness in a load-dependent manner.

In the third study we aimed to (1) probe the robustness of well-established habituation index in individuals with alcohol abuse, a well-known risk factor for psychopathology, and thus to (2) extend the prior knowledge to the examination of neural habituation patterns in another risk-population using fMRI and a facial emotion matching paradigm. To this end, we examined individuals with varying levels of severity of alcohol use as well as controls with no or minimal consumption of alcohol. We hypothesized that amygdala habituation will be reduced in alcohol-abused individuals compared to controls. This study was included for the validation purposes – to replicate the findings from the Study 1 in another risk-population and in the conceptually different unrelated sample.

Please note that several parts of this thesis have already been published (Study 1: Berhe, Höflich et al., 2021, Study 3: Gerhard, Berhe et al., 2022,) or are about to be published (Study 2: Berhe et al., in review) by the doctoral candidate as a first author. Therefore, certain sections, tables, or figures of this thesis will be identical to these publications.

2. EMPIRICAL STUDIES

2.1. Study 1: Reduced real-life affective well-being and amygdala habituation in unmedicated community individuals at risk for depression and anxiety[1]

2.1.1 Abstract

Background: Early identification of risk for depression and anxiety disorders is important for prevention, but real-life affective well-being and its biological underpinnings in the population remain understudied. Here, we combined methods from epidemiology, psychology, ecological momentary assessment (EMA) and functional magnetic resonance imaging (fMRI) to study real-life and neural affective functions in individuals with subclinical anxiety and depression from a population-based cohort of young adults.

Methods: We examined psychological measures, real-life affective valence, fMRI amygdala habituation to negative affective stimuli and the relevance of neural readouts for daily-life affective function in 132 non-help-seeking community individuals. We compared psychological and EMA measures of 61 unmedicated individuals at clinical risk for depression and anxiety (operationalized as subthreshold depression and anxiety symptoms or a former mood or anxiety disorder) to those of 48 non-risk individuals and 23 persons with a mood or anxiety disorder. We studied risk-associated fMRI signals in subsamples with balanced sociodemographic and image quality parameters (26 non-risk, 26 at-risk persons).

Results: Compared to non-risk persons, at-risk individuals showed significantly decreased real-life affective valence ($p = .038$), reduced amygdala habituation ($p_{FWE} = .024$, region of interest [ROI] corrected) and an intermediate psychological risk profile. Amygdala habituation predicted real-life affective valence in controls, but not in participants at risk ($p_{FWE} = .005$, ROI corrected).

[1] **Published as:** Berhe O*, Höflich, A.*, Moessnang, C., Reichert, M., Kremer, T., Gan, G., Ma, R., Braun, U., Reininghaus, U., Ebner-Priemer, U., Meyer-Lindenberg, A.*, Tost, H.* (2022). Reduced Real-life Affective Well-being and Amygdala Habituation in Unmedicated Community Individuals at Risk for Depression and Anxiety. Biol. Psychiatry Cogn Neurosci Neuroimaging. 2022; S2451-9022(22)00153-7.

Conclusions: Our data suggest real-life and neural markers for affective alterations in unmedicated community individuals at risk for depression and anxiety and highlight the significance of amygdala habituation measures for the momentary affective experience in real-world environments.

2.1.2 Introduction

Early diagnosis, treatment and ideally prevention of psychiatric disorders in the population is desirable, but the existing knowledge about daily-life psychological and neural affective alterations in community-based individuals at mental health risk is limited (Ruscio, 2019). Meta-analyses suggest that about ten percent of all individuals in the general population experience subclinical symptoms of anxiety (Witlox et al., 2021) and depression (Li et al., 2022), and a significant proportion of these individuals will eventually transition to manifest psychiatric disorder (Shankman et al., 2009; Wolitzky-Taylor et al., 2014) . However, many persons fall below the binary threshold of current diagnostic systems, which define the difference between mental health and disorder based on the presence of a predefined number and duration of psychiatric symptoms. Consequently, community-based individuals with daily-life subclinical symptoms often remain unnoticed and not sufficiently attended to, both in clinical and research settings (Rodríguez, Nuevo, Chatterji, & Ayuso-Mateos, 2012) .

From a community care and prevention standpoint, two groups of individuals are of particular relevance for the study of the underresearched “gray area” between mental health and disorder: Those who currently experience subthreshold symptoms but do not have a history of psychiatric illness, and those who have suffered from a psychiatric disorder in the past but do not currently experience any obvious clinical signs (Ruscio, 2019). In this work, we define these groups as *community-based individuals at mental health risk*. We derive this view from studies and discourses in the field that have critically addressed the clinical validity of diagnostic boundaries between normal and pathological mood and anxiety experiences (Markon, Chmielewski, & Miller, 2011; Watson et al., 2022). Here, evidence suggests that there is a smooth transition between pathological depression and anxiety and milder emotional experiences (Ruscio, 2019), and that subthreshold prodromal and residual states carry a substantial risk of progression to more severe states over the life course(Judd, 2012; Lee et al., 2019) . In our definition of mental health risk in the community, we thus put forward (and later explore) the notion that both risk groups map to a shared (subclinical) continuum of clinically relevant phenomena in between mental health and disease. At the biological level, the grouping of the two at-risk groups is supported by studies showing comparable abnormalities of subthreshold prodromal and residual states in social reward processing (Brinkmann & Franzen, 2017; Pechtel, Dutra, Goetz, & Pizzagalli, 2013), in cognitive domains such as cognitive control and executive function

(Hasselbalch, Knorr, & Kessing, 2011; Holmes & Pizzagalli, 2007; Rock, Roiser, Riedel, & Blackwell, 2014; Yang & Xiang, 2019) and resting-state functional connectivity (Dong et al., 2019; Gao et al., 2016). We further propose that the improved understanding of the daily-life psychological and neural characteristics of such risk states is important since the identification of salient risk markers can guide the development of novel early interventions at multiple, synergistic levels of influence, including in the areas of community mental health services, digital mental health and neurofeedback therapy (Reichert et al., 2021; Tost et al., 2015).

Important leads for this work came from the recent literature, which emphasizes the unspecific nature of symptoms at subclinical stages of psychiatric illness (McGorry & Mei, 2018; Ruscio, 2019; van Os, 2013). In addition, dimensional models of psychopathology such as the CHARMS (clinical high at-risk mental state) concept served as important conceptual influence, which promote the transdiagnostic investigation of subclinical risk markers and mechanisms to inform future preventive and predictive approaches (Hartmann et al., 2019; McGorry et al., 2018; McGorry & Mei, 2018). Indeed, the existing data suggest significant alterations in the daily-life experience in persons at clinical risk for mood and anxiety disorders (Al-Dajani & Uliaszek, 2021; Bakker et al., 2019; F. R. Goodman, Rum, Silva, & Kashdan, 2021). These include, among others, higher negative affect and lower hedonic capacity in real-world contexts, i.e., changes in daily experience that can be addressed with e-health based interventions. At the neural system level, altered habituation of the amygdala to threatening stimuli is a good candidate for mechanistic investigation. This view is supported by the demonstrated reliability of the phenotype (Plichta et al., 2014) as well as its documented role as an evolutionarily conserved neural mechanism for affective processing and behavioral adaptation (Bordi & LeDoux, 1992; Breiter et al., 1996). Altered amygdala habituation has further been associated with a range of psychiatric disorders and related risk constellations (Avery & Blackford, 2016; Bilek et al., 2019; Blackford et al., 2013; Demers, Drabant Conley, Bogdan, & Hariri, 2016; Kanske, Heissler, Schönfelder, & Wessa, 2012), including in community-based samples and across a dimensional range of symptom severity for anxiety, depression, and stress-related disorders (Hein et al., 2020; Y. J. Kim et al., 2019; Stevens et al., 2021; van den Bulk et al., 2016). However, studies in community-based individuals at clinical risk are still scarce and the interpretation of existing data is often complicated by concomitant, interfering factors such as the preferential inclusion of help-seeking

individuals or the contamination of neural readouts by confounding factors (e.g., treatment effects). Also, barely any study on this topic to date seized the opportunity of contemporary multimodal ecological neuroscience approaches, which allow for the coordinated inquiry of clinical, neural and daily-life psychological functions in naturalistic cohorts (Bakker et al., 2019).

In the present study, we combined methods from epidemiology, clinical psychology, ecological momentary assessment (EMA) and functional MRI (fMRI) to study affective functions in community-based persons at clinical risk for depression and anxiety disorders derived from a population-based cohort of young, non-help-seeking adults. We used EMA with smartphone-based e-diaries to study momentary affective responses in real-world environments (Tost et al., 2019), used fMRI and a well-established implicit emotion processing task (Hariri, Mattay, et al., 2002) (**Figure 1.4.**) to uncover alterations in amygdala signaling, and probed the significance of the identified neural phenotype for the affective experience in daily life.

We studied EMA and questionnaire data in 61 unmedicated individuals at clinical risk, 48 demographically similar non-risk persons and 23 community-based individuals identified as fulfilling the criteria for a current mood or anxiety disorder. We derived all study participants from the same naturalistic population by random selection. We hypothesized that momentary affective valence in daily life would be significantly lower in the at-risk group and in the clinical group compared with the non-risk group. We further compared fMRI readouts between carefully matched subsamples of 26 unmedicated persons at clinical risk and 26 non-risk individuals to identify alterations in neural affective signaling related to community psychiatric risk in the absence of demographic, medication and image quality confounds. Here, we expected to see a blunted amygdala habituation in community-based persons at clinical risk reminiscent of that of clinical states (Avery & Blackford, 2016; Bilek et al., 2019; Kanske et al., 2012). We further expected these neural affective signals to be relevant for the real-life affective experience of the non-risk individuals, the persons at clinical risk, or both groups. Beyond formal hypothesis testing, we further explored other EMA and questionnaire measures to yield novel insights into the nature and range of altered affective functions in community-based individuals at clinical risk.

2.1.3 Methods

Study participants and clinical assessment

The Psychoepidemiological Center at the Central Institute of Mental Health in Mannheim, Germany, recruited a total of 349 individuals for this study. Participants were young adults in the age range of 18 to 28 years, which we randomly drew from local population registries based on a two-stage proportionally layered procedure (see (Reichert et al., 2020; Tost et al., 2019) for details). General exclusion criteria were the presence of a relevant medical or neurological disorder. We assessed past and current psychiatric symptoms by screening forms and MINI-DIPS interviews (Hibell et al., 2009; J. Margraf, 1994; Jürgen Margraf, Cwik, Pflug, & Schneider, 2017) that were evaluated by two independent clinical raters (A.H., T.K.). The MINI-DIPS covers the most common mental disorders in adulthood according to ICD-10 and clarifies the presence of psychopathologically relevant experiences for the diagnostic categories. Based on these assessments, we defined four initial participants groups: *1)* individuals with current psychiatric symptoms above the diagnostic threshold (*clinical group*, n = 23, mean age: 23.17 ± 2.68 years, 20 females), *2)* individuals with one or more current symptoms on the mood-anxiety spectrum that did not qualify for the diagnosis of a psychiatric disorder (*subclinical group*, n = 40, mean age: 22.37 ± 2.55 years, 33 females), *3)* clinically remitted individuals with a personal history of relevant psychiatric symptoms in the past who denied the current presence of psychopathologically relevant experiences (*history group*, n = 21, mean age: 22.82 ± 3.01 years, 12 females), and *4)* healthy non-risk individuals that were free of any current or former psychiatric symptoms, diagnosis or treatment (*healthy non-risk group*, n = 48, 21.86 ± 1.56 years, 39 females) that we derived from a larger sample of non-risk individuals.

We later combined the individuals of the subclinical and history groups to a joint group of *community-based individuals at mental health risk* since we expected that both groups would map on a shared continuum of affective alterations in between mental health and disease (Hartmann et al., 2019) (see *Results* and *Supplemental Table S2.1*). None of the at-risk individuals had received psychotropic medication in the preceding 12 months of study and only one of the persons was currently in formal psychiatric care (*Supplemental Table S2.2*). We then drew a sample of 48 individuals from the total pool of 264 identified non-risk individuals using internal software to achieve a non-risk group with a comparable distribution of basic sociodemographic characteristics (i.e., age, gender, education) to the combined at-risk group.

After study inclusion, we first collected questionnaire measures on time-stable psychological constructs. Subsequently, we collected EMA data over 7 days in

everyday life. We performed the neuroimaging examination of the study participants immediately after the end of the EMA study week (i.e., 1.50 ± 1.36 (Min/Max=0/6) days after EMA completion). We compared the acquired questionnaire and e-diary measures between the groups to identify psychological and real-life indicators of community mental health risk (*Table 2.1*). For the ensuing neuroimaging analysis of risk indicators, we compared subgroups of 26 at-risk and 26 non-risk individuals with available neuroimaging data that we carefully matched for a broader panel of sociodemographic attributes and data quality indicators known for impacting mental health-related neural readouts (e.g., fMRI task performance, fMRI image quality metrics [including tSNR, spikes, translation/rotation metrics and frame-wise displacement], socioeconomic status, current urbanicity, adverse childhood experiences, see *Supplemental Table S2.3*) (Tost et al., 2015).

The fMRI at-risk group included 18 individuals from the *subclinical group* and 8 individuals from the *history group*. All enrolled study participants provided written informed consent for a protocol approved by the Medical Ethics Committee II of the Medical Faculty Mannheim at the Ruprecht-Karls-University in Heidelberg, Germany.

Psychological data acquisition and analysis

We acquired a battery of well-established psychological and demographic questionnaires quantifying socioeconomic status (Lampert, Kroll, Müters, & Stolzenberg, 2013), perceived social status (E. Goodman et al., 2001; Schweiger et al., 2021), degree of current urbanicity (Lederbogen et al., 2011), trait anxiety (Laux, Glanzmann, Schaffner, & Spielberger, 1981), loneliness (Döring & Bortz, 1993), self-efficacy (Jerusalem & Schwarzer, 1992), sense of coherence (Hannöver et al., 2004), optimism (Herzberg, Glaesmer, & Hoyer, 2006), perceived mental wellbeing (Topp, Østergaard, Søndergaard, & Bech, 2015), satisfaction with life (Glaesmer, Grande, Braehler, & Roth, 2011), perceived daily hassles (Traue, Hrabal, & Kosarz, 2000), chronic stress (P. Schulz, Schlotz, & Becker, 2004), coping strategies (Carver, 1997; Knoll, Rieckmann, & Schwarzer, 2005), perceived social support (U. Schulz & Schwarzer, 2003) and retrospective self-ratings of adverse childhood experiences (Glaesmer et al., 2013). We provide further details on the assessed questionnaires in *Supplemental Table S2.4*. We assessed group differences in SPSS (IBM, SPSS, version 25) using variable type and distribution appropriate tests (i.e., χ^2 test, classical

analysis of variance (ANOVA), Welch's ANOVA, Kruskal-Wallis H test, see *Table 2.1* for details).

E-diary data acquisition and analysis

We assessed e-diary-ratings for 7 consecutive days in daily life with study smartphones (Motorola Moto G, Motorola Mobility) and a flexible time and location-based sampling scheme with 9 to 23 prompts per day in between 7:30 AM and 22:30 PM (minimum/maximum interval: 40/100 minutes) as previously detailed (Gan et al., 2021; Reichert et al., 2020; Tost et al., 2019). Our primary interest was to capture potential alterations in real-life affective valence in clinically at-risk individuals. For this, we used a well-known short scale for EMA with established psychometric properties (Wilhelm & Schoebi, 2007) capturing within-subject fluctuations in real-life affective valence with the two bipolar items "content" to "discontent" (German translation: "zufrieden" – "unzufrieden") and "unwell" to "well" (German translation: "unwohl" – "wohl") presented at the edges of two computerized visual analogue scales with sliding locators (score range of 0 to 100). We instructed participants to place, upon each e-diary prompt, the locators at the scale positions representing their momentary affective state. We averaged the two item scores for use as dependent variable in our multilevel analyses.

For exploratory analysis, we further calculated an established EMA measure of daily-life affective (in)stability (i.e., the mean square of successive differences in valence, MSSD (Trull, Lane, Koval, & Ebner-Priemer, 2015)) and assessed e-diary items quantifying momentary calmness and energetic arousal, social contact (Gan et al., 2021), social anhedonia (Gan et al., 2021), and the appraisal of negative and positive events (Koval et al., 2015; Wichers et al., 2009). E-diaries and sampling strategy were implemented with the ambulatory assessment software movisensXS (version 0.6.3658, movisens GmbH, Germany). We used multilevel models in SAS (version 9.4., SAS Institute Inc., Cary, NC, USA) to test for group differences, thereby nesting within-subject e-diary assessments (level 1) within participants (level 2), and using a categorical group variable (level 2) (Bolger & Laurenceau, 2013). We provide further details on the EMA acquisition and analysis methods in the *Supplemental Information*. All participant groups surpassed an average compliance rate of 70% and we covaried for between-group differences in compliance in our multilevel analysis (*Table S2.5*).

fMRI data acquisition and preprocessing

We performed blood oxygen level–dependent fMRI on a 3T MRI scanner (Siemens Trio, Erlangen, Germany) using a well-established implicit emotion processing paradigm with two task conditions (emotional face matching, shapes matching, **Figure 1.4.**) (Hariri, Mattay, et al., 2002) providing reliable measures of amygdala habituation (Plichta et al., 2014). We processed and analyzed the fMRI data with SPM12 (www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (The MathWorks, Inc., Natick, MA). Data preprocessing consisted of standard procedures. We provide further methods details on the employed fMRI sequence, paradigm and preprocessing routines in the *Supplemental Information*.

Amygdala activation and habituation analysis

fMRI data analysis consisted of a two-level procedure. At the first level, we defined a general linear model (GLM) for each subject that included the boxcar reference vectors for the task blocks of the two conditions (convolved with the standard SPM hemodynamic response function) and the 6 head motion parameters from the realignment step (covariates of non-interest). During model estimation, we defined a high-pass filter with a cut-off frequency of 262*s* to remove low frequency signal components and used first-order autoregressive modeling to correct for temporal autocorrelations. We computed individual maps of voxel-wise habituation indices as previously described (Plichta et al., 2014) by calculating the mean response amplitude difference between the first and the last block of the face matching condition ([block 1 > block 4]. At the second level, we entered these maps into univariate ANOVA models with group (clinical at-risk, non-risk) as factor. Consistent with our previous work (Bilek et al., 2019), we defined a group contrast to test for the hypothesized amygdala habituation deficits in community-based individuals at clinical risk (clinical at-risk < non-risk). We further tested for general and group-specific associations between daily-life affective valence and amygdala habituation estimates. For this we used univariate ANOVA models with the mean individual EMA-derived valence measures and a corresponding interaction term (group x valence) as regressors of interest, respectively.

fMRI Statistical Inference

We assessed statistical significance at $p < 0.05$, peak voxel-level familywise error (FWE) corrected for multiple comparisons within an a priori defined anatomical region

of interest (ROI) mask of the right amygdala derived from the Wake Forest University (WFU) PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). As in our previous work (Bilek et al., 2019), we chose the right amygdala as a priori ROI for hypothesis testing since the literature suggests a different functional role and habituation rate for the right amygdala, with a specialization for the rapid and dynamical detection of affective stimuli (Baas, Aleman, & Kahn, 2004; Phillips et al., 2001; Wright et al., 2001) and a higher retest reliability of habituation estimates (Plichta et al., 2014).

2.1.4 Results

Psychological questionnaire data

Descriptive analysis of psychological data revealed a regular pattern across variables, with the group means of the at-risk group mapping in between those of the non-risk group and the clinical group, respectively. Inferential statistics revealed significant differences of the at-risk group for daily hassles, maladaptive coping and perceived loneliness compared to the non-risk group (all *p*s < .016, all reported *p* values are Bonferroni corrected for multiple group comparisons) but not the clinical group (all *p*s > .31). In contrast, in other psychological variables such as perceived mental well-being, satisfaction with life, optimism, self-efficacy and social support at-risk persons did not differ significantly from the non-risk group (all *p*s > .12) but differed significantly from the clinical group (all *p*s < .05). For trait anxiety and dispositional sense of coherence, the at-risk individuals displayed fully intermediate properties, in that they differed significantly from both the non-risk group and the clinical group (all *p*s < .001). We provide further statistical details in *Table 2.1*. There were no significant group differences in psychological questionnaire data between the community-based subgroups at mental health risk (i.e., *subclinical group* vs. *history group*, see *Supplemental Table S2.1* for details).

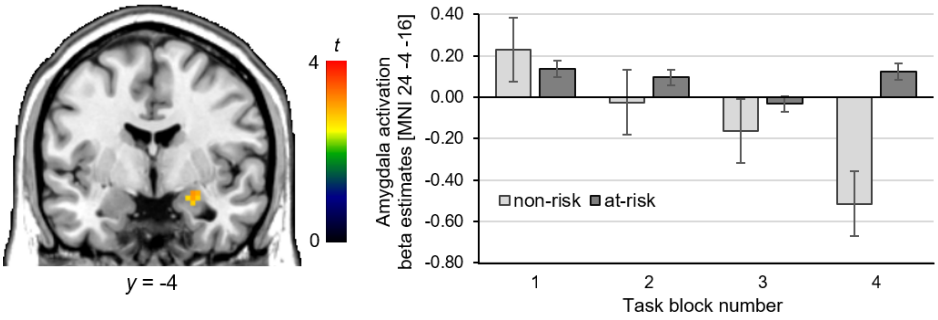


Figure 2.1. Group differences in amygdala reactivity changes to threatening stimuli over the course of the experiment. Significant difference in amygdala habituation manifesting as a rapid signal decrement to successive emotional stimulation blocks in the community-based individuals not at clinical risk (non-risk group) but not the community-based at clinical risk (at-risk group) (t = 3.03, p_{FWE} = .024). The functional map is thresholded at p = .005, uncorrected for illustration purposes, and is displayed on the coronal section of a structural-template magnetic resonance image. The plot shows habituation estimates (and standard errors of the mean) of the peak voxel in the right amygdala for each fMRI task block and group, respectively. FWE, family-wise error. MNI, Montreal Neurological Institute standard space.

Daily-life ecological momentary assessments

Daily-life affective valence in the at-risk individuals was significantly lower than that of the non-risk group (p = .038, all p values are Bonferroni corrected for multiple group comparisons) and significantly higher than that of the clinical group (p = .012) (*Figure 2.2B*). Exploratory analyses suggested no group differences in the frequency of social contacts and the appraisal of positive events (all reported ps > .67). We further did not detect any group differences between the at-risk group and the non-risk group for affective (in)stability, negative event appraisal, liking of social contact, preference of being alone and momentary feelings of calmness and energetic arousal (all ps > .11). In contrast to this, individuals in the clinical group exhibited widespread changes in these variables, which distinguished this group from both the at-risk and non-risk groups. We provide further statistical details in *Table 2.1* and *Supplemental Table S2.5*.

Table 2.1. *Sample description for community subject groups*

	Non-risk group (n=48)			**Clinical at-risk group (n=61)**			**Clinical group (n= 23)**			**ANOVA / χ^2/H-test/MLA[a]**		**Non-risk vs. Risk**	**Risk vs. Clinical**	**Non-risk vs. Clinical**
	M ± SD / count	min/max	n	M ± SD / count	min/max	n	M ± SD / count	min/max	n	*ß-value*	*p* value	*p* value[b]	*p* value[b]	*p* value[b]
Demographic data														
Age (year)	21.86 ±1.56	18.14/25.58	48	22.53 ±2.7	18.10/27.83	61	23.17 ±2.68	18.88/27.30	23	2.63	0.076	-	-	-
Sex (male/female)	9/39	N/A	48	16/45	N/A	61	3/20	N/A	23	2.01	0.366	-	-	-
Education (years)	12.48 ± 1.29	10/16	48	12.68±1.78	8/16	60	12.61±1.67	10/16	23	0.212	0.784	-	-	-
Socioeconomic status (SES)	12.80± 3.00	6.20/19.40	48	13.47± 3.31	6.90/20.20	61	11.20± 2.88	5.50/15.30	23	**4.40**	**0.014**	0.512	**0.009**	0.088
Psychological data														
Trait anxiety (STAI-T, sum)	33.00±6.78	20/50	47	39.82±9.60	21/66	60	52.09±10.71	34/71	23	**35.52**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Mental wellbeing (WHO-5, sum)	16.52±4.15	10/25	48	15.19±4.57	4/23	59	11.05±5.77	2/23	20	**9.91**	**<0.001**	0.259	**0.019**	**0.002**
Satisfaction with life (SWLS)	27.74±4.35	14/35	47	25.77±6.09	9/34	60	21.00±8.72	5/32	23	**9.95**	**<0.001**	0.128	0.057	**0.04**
BCOPE-adaptive coping	42.72±5.10	31/52	47	41.33±7.74	21/56	60	40.52±7.46	27/54	23	2.16	0.336	-	-	-
BCOPE-maladaptive coping	21.26±3.93	15/32	47	23.68±4.45	15/36	59	25.26±4.28	18/36	23	**7.28**	**0.001**	**0.012**	0.393	**0.001**
Self-efficacy (SWE, sum)	29.85 ±4.24	21/38	48	29.05 ±4.38	17/40	60	25.91 ±5.47	19/35	23	**6.04**	**0.003**	0.60	**0.049**	**0.012**
Loneliness (UCLA, mean)	29.37 ±6.94	20/48	48	34.32 ±11.22	20/76	60	39.91 ±16.74	20/87	23	**7.27**	**0.002**	**0.016**	0.314	**0.020**
Optimism (LOT-R, optimism sum)	16.98 ±3.47	9/23	48	15.60 ±4.48	4/23	60	12.04 ±5.44	0/22	23	**10.14**	**<0.001**	0.174	**0.023**	**0.001**
Perceived social support (BSSS, sum)	31.17 ± 1.63	25.00/32.00	48	29.85±3.16	19.00/32.00	60	27.69±5.76	15/32	23	**8.36**	**<0.001**	0.135	**0.030**	**0.001**
Sense of coherence (SOC, sum)	152.79 ± 17.73	115/189	48	138.76±20.90	88/181	59	114.95±23.17	64/152	22	**26.65**	**<0.001**	**0.001**	**<0.001**	**<0.001**
Daily Stress (ABF)	2.04±0.63	1.09/3.88	42	2.50±0.76	1.09/4.75	47	2.90±1.02	1.84/5.42	15	**8.36**	**<0.001**	**0.007**	0.360	**0.017**
Early adversity (CTS)	5.96±1.99	5/16	48	6.65±2.08	5/16	60	8.45±3.91	5/17	22	**7.83**	**0.001**	0.19	0.119	**0.023**
EMA[c]														
Valence (MDBF)[d]	75.82±11.63	48.99/99.14	47	69.04±10.18	47.88/89.59	61	60.10±14.85	28.19/84.32	22	**10.90**	**<0.001**	**0.038**	**0.012**	**<0.001**
Energetic arousal (MDBF)[d]	60.76±12.76	27.96/85.49	47	56.00±11.35	30.72/79.58	61	49.89±11.21	30.31/70.68	22	**4.30**	**0.016**	0.254	0.277	**0.014**
Calmness (MDBF)[d]	72.16±13.04	36.60/98.59	47	66.48±11.02	45.38/89.19	61	57.43±14.37	27.39/86.71	22	**8.47**	**<0.001**	0.164	**0.016**	**<0.001**
Alone (alone/not alone)	34/72	NA	47	31/64	NA	61	31/61	NA	22	0.40	0.673	-	-	**-**
Rather be alone[d]	11.20±9.59	0.73/38.43	47	16.32±14.34	1.57/65.14	61	25.7±20.34	1.21/63.92	22	**8.28**	**0.002**	0.315	**0.009**	**0.001**
Don't like the company[d]	10.70±12.99	0.63/77.17	47	14.14±14.34	0.70/65.80	61	17.81±14.09	2.91/59.92	22	**4.18**	**0.018**	0.39	0.199	**0.014**
Positive event appraisal[d]	23.14±11.31	2.54/48.68	47	24.97±14.29	1.39/56.04	61	23.35±10.69	2.36/44.84	22	0.26	0.771	-	-	-
Negative event appraisal[d]	8.91±6.18	0.67/33.22	47	12.78±7.36	0.68/32.56	61	17.16±11.45	6.32/56.63	22	**6.44**	**0.002**	0.119	0.110	**0.002**
Affective (in)stability (valence MSSD)	235,24±166,31	1.07/793.75	47	337.06±219.35	16.75/897.15	61	592.98±479.70	75.49/2141.76	22	**6.53**	**0.002**	0.887	**0.002**	**0.007**
E-diary prompts per day	12.56±1.32	9/15	47	12.29±1.07	10/15	61	12.56±1.29	10/15	22	0.744	0.453	-	-	-
E-diary Compliance (%)[f]	85.61±11.49	57.58/100	47	77.81±19.00	32.93/100	61	73.79±19.59	32.91/100	22	**4.271**	**0.011**	0.054	1.000	**0.022**

Broad-based changes in the clinical group on most outcome measures compared with limited changes in the at-risk group in areas involving stress experience, negative emotions, and personal coping skills. For details on the psychological questionnaires including acronyms, see *Supplemental Table S4*. Abbreviations: M = mean, SD = standard deviation, n = number of participants with available data, ANOVA = univariate analysis of variance, χ^2 = chi-squared test, H-test - Kruskal-Wallis Test. MLA = multilevel analysis controlling for time of the day and time of the day-squared (level 1); and controlling for differences in compliance (level 2), MSSD valence = mean square of successive differences of valence ratings.

[a]Employed tests: χ^2 tests for group comparisons with categorical variables, ANOVA and Tukey tests for group comparisons and variables with equal variance and normal distribution, Welch-ANOVA and Games-Howell tests for group comparisons with normally distributed variables with unequal variance (as identified by Levene-test), Kruskal-Wallis and Dunn tests for group comparisons with not-normally distributed variables with (un)equal variance.

[b]All *p*-values of post-hoc pairwise group comparisons are Bonferroni corrected for multiple group comparisons.

[c]Aggregation of EMA indices within and between subjects for use for sample description only.

[d]mean/day/participant

[e]number of prompts participants have been alone out of all prompts across 7 days of measurement

[f]Percent of answered prompts.

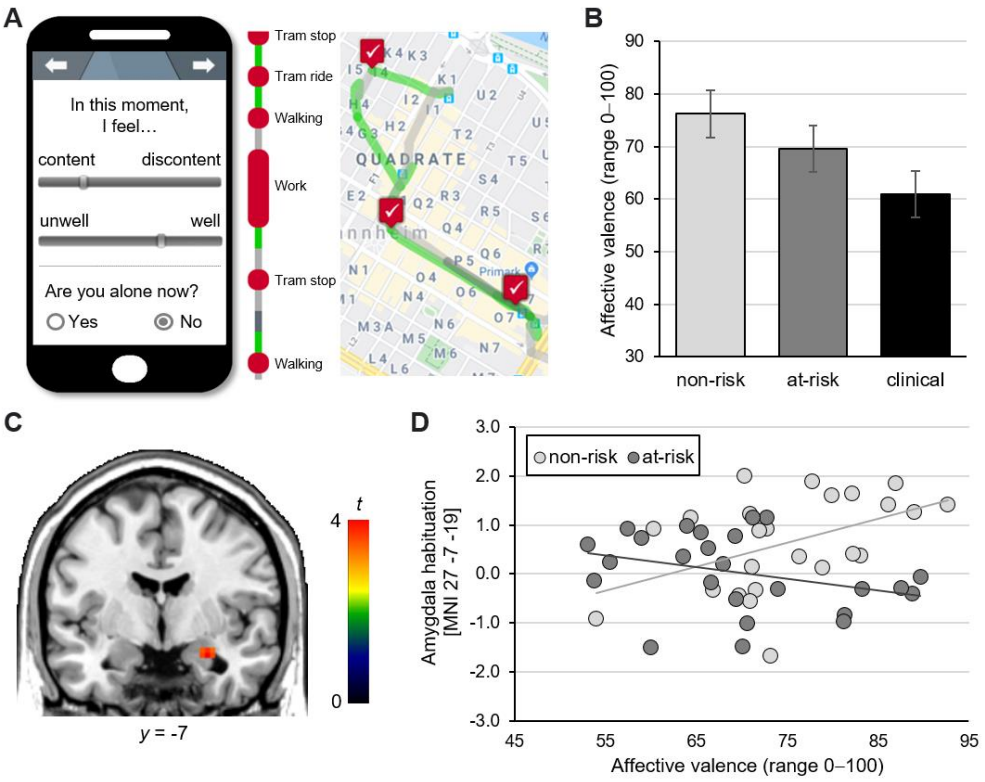


Figure 2.2. Study methods and amygdala habituation–affective valence associations. **(A)** Illustration of the smartphone-based assessment of affective valence in daily life in connection with a person's movement pattern in downtown Mannheim. Left: Visualization of the affective valence and social contact e-diary items. Smartphone image by ElisaRiva (http://www.pixabay.com). Right: White check marks on a red background displayed on the route symbolize positions where e-diary assessments were prompted (for illustration purposes, not real study participant). **(B)** Significant group differences in EMA valence between community-based individuals not at clinical risk, those at clinical risk, and those with a current mood or anxiety disorder. Community-based individuals at clinical risk display significantly lower valence levels than non-risk persons, and significantly higher valence levels than individuals in the clinical group; error bars display standard error (SE) from the MLM (for details see *Table 1*). **(C, D)** Differential association of amygdala habituation and affective valence in daily life in community persons at clinical risk compared to those not at risk (t = 3.70, p_{FWE} = .005). The functional map in panel (C) is thresholded at p = .005, uncorrected for illustration purposes, and is displayed on the coronal section of a structural-template magnetic resonance image. The scatterplot in panel (D) depicts the associations of the habituation estimates (extracted from the amygdala peak voxel) and valence values for the two groups. The reported interaction analysis finding in imaging space also survived FWE correction after excluding one outlier from the analysis. FWE, family-wise error. MNI, Montreal Neurological Institute standard space.

Amygdala habituation analyses

Comparison of the at-risk group and the non-risk group confirmed a significant reduction of right amygdala habituation to repeated negative affective stimuli in the at-risk individuals (t = 3.03, p_{FWE} = .024, all reported p values are peak-level corrected for region of interest) (*Figure 2.1B*). This finding also survived correction for a bilateral amygdala mask (t = 3.03, p_{FWE} = .047). In the non-risk individuals, data inspection suggested a high initial responsivity of the right amygdala followed by a rapid decline in activity with successive emotional block repetitions, whereas in the at-risk individuals the amygdala responsivity appeared blunted and uniform over time (*Figure 2.1C*). A regression analysis with daily-life affective valence scores as a predictor did not provide evidence for a significant association with amygdala habituation across all individuals (t = 1.96, p_{FWE} = .330). However, we detected a significant group by EMA valence interaction effect on right amygdala habituation (t = 3.70, p_{FWE} = .005; after correction for a bilateral amygdala mask: t = 3.70, p_{FWE} = .009) (*Figure 2.2*). Post-hoc regression analysis confirmed that higher right amygdala habituation was significantly related to higher daily-life affective well-being in the non-risk group (t = 3.33, p_{FWE} = .012; after correction for a bilateral amygdala mask: t = 3.33, p_{FWE} = .024) but not in the at-risk group (t = 0.96, p_{FWE} = 0.76).

2.1.5 Discussion

In this study, we took a multimodal ecological neuroscience approach to identify psychological, real world, and neural markers of altered affective function in unmedicated individuals at clinical risk for mood and anxiety disorders drawn from a population-based cohort of young adults. Specifically, we aimed to characterize the psychological profile of at-risk individuals in the community, determine the nature and extent of their current affective alterations in daily life, and examine the relevance of the neural signals examined to real-world affective experience. We obtained several interesting results, which we discuss below.

In terms of psychological profile, we posited that community-based individuals at clinical risk are on a continuum of change that spans between healthy non-risk individuals and individuals with a current manifest disorder. At the descriptive level, we observed just this: mean scores for the risk group were intermediate between those of the other two groups in all variables, and our supplemental analysis revealed no significant differences between the “history” and “subclinical” subgroups, which we combined into one risk group. At the same time, the areas in which at-risk persons differed *significantly* from the non-risk

individuals were relatively specific, while the group with a manifest disorder showed clear changes in almost all of the areas examined. Specifically, significant differences in risk individuals clustered around variables indicating heightened stress awareness, a tendency to negative emotions and a limited ability to use personal resources to cope with such experiences. These focal differences presented against a background of mostly unremarkable functions and resources, such as preserved satisfaction with life, optimism and social support. We conclude from these data that psychological alteration in the community is a gradual phenomenon, and that the psychological profile of individuals with subclinical mood and anxiety symptoms is comparable to that of fully remitted individuals with a previous mood or anxiety disorder. Further, the clearly salient psychological deficits of community-based individuals at clinical risk appear selective and involve the processing of stress and negative emotions.

Regarding the nature and extent of daily life impairments, we hypothesized that young community-based individuals with subclinical depression and anxiety would show a significant reduction in affective valence, and our study results confirmed this assumption. Although there are few comparable studies to date, this finding aligns well with our own findings on the impact of psychiatric risk and resilience factors on real-life affective valence (Gan et al., 2021; Tost et al., 2019) and changes in emotional experience of children and adolescents with subclinical symptoms reported in other community-based EMA studies (Frost, Hoyt, Chung, & Adam, 2015; Scott et al., 2015; Scott et al., 2017). In relative terms, our exploratory analysis of other EMA outcomes further suggests selective changes in the daily-life experience of community-based individuals at clinical risk. Precisely, while the clinical group differed significantly in almost all measures recorded, including those indicative of daily-life depressed mood, reduced drive, social anhedonia, affective instability, and increased stress experience, the decrease in affective valence in the at-risk subjects seemed to occur against a background of otherwise unremarkable real-life functions. Together with the psychological profile elaborated above, this suggests that community-based individuals at increased risk for mood and anxiety disorders exhibit selective risk phenotypes on the behavioral and experiential level, including limited personal resources to cope with stress-associated experiences and a reduction in affective valence in daily life. In addition to traditional psychotherapy, deficits in the daily-life experience can be addressed with targeted ecological moment interventions (EMI), especially when the real-world “risk marker” or target phenomenon is known, as in this case (Myin-Germeys, Klippel, Steinhart, & Reininghaus, 2016).

At the neural systems level, our results identify reduced amygdala habituation in community-based individuals with subclinical depression and anxiety. Specifically, whereas the non-risk group showed a decrease in estimated amygdala response of about 60%, it was only 1% for the risk subjects (emotional stimulation block 1 - 4). The amygdala plays an evolutionarily conserved role in threat processing (LeDoux, 2007) and the robust habituation phenotype studied (Plichta et al., 2014) reflects a basic neural plasticity mechanism that supports a basic and innate form of learning. Specifically, it protects the organism from repeatedly responding to threat-associated stimuli with no meaningful consequences for survival, thereby freeing up important neural and behavioral resources for more pressing tasks. The detected difference in habituation in community-based individuals at risk is thus suggestive of a neural plasticity-related alteration in the affective processing of environmental stimuli in this group. In our non-risk individuals, amygdala response habituated as expected and predicted increased momentary affective valence, indicating the relevance of this neurofunction in daily life. This link was not found in our community-based individuals at clinical risk whose diminished real-life affective well-being was unrelated to amygdala habituation. Although further experiments will be necessary to determine the origin of this dissociation, we speculate that reduced biological plasticity in the amygdala may require alternative regulatory strategies to deal with perceived threat (e.g., cognitive appraisal), which may disrupt the direct link of amygdala habituation to real-life affective well-being. Deficient amygdala habituation as such is unlikely specific to certain psychiatric disorders (Bilek et al., 2019; Tam et al., 2017) or sources of illness risk (Bilek et al., 2019; Holz et al., 2021; Perez-Rodriguez et al., 2017). However, since amygdala function can be directly targeted and modulated with neurofeedback-based interventions (Linhartová et al., 2019), this neural risk phenotype is an attractive candidate for novel multimodal treatment (and ideally prevention) concepts with multiple, synergistic starting points.

The results presented must be evaluated against the background of some limitations of our study, which we explain below. First, the size of the studied groups is limited. This is mainly because we obtained our participants from an epidemiological sample of young adults in the population, in which the prevalence of subclinical syndromes and full remissions of a previous disorder is finite. Second, we departed from a purely population-based approach by matching the composition of the non-risk comparison group using a set of predefined demographic and treatment-related variables. We consider both of these decisions important because we wanted to reflect as closely as possible the situation of

young, non-help-seeking, and clinically vulnerable individuals in the community, while minimizing bias in our results from confounding variables that are known to affect the outcomes we studied. Third, we could not consistently apply the three-group design of the questionnaire and EMA analyses in neuroimaging space because we did not have enough usable fMRI data from the clinical group. However, because our primary goal was to study a neuronal risk marker in individuals from the general population in the absence of treatment effects, the availability of sufficient patient data for this purpose would have been of limited help anyway. Fourth, beyond affective valence, the reported EMA results are based on exploratory analyses, and any interpretations based on these findings are therefore preliminary. However, we felt it was important to report these data and our opinions in this regard, as they may promote the formation of new hypotheses in future studies. Finally, the reported associations between neural and everyday affective measures are based on cross-sectional data and therefore do not allow for causal interpretations. We speculate that the relationship between brain function and everyday experience is a complex, reciprocal causal process, an assumption that should be further explored in future experimental studies.

2.1.6 Supplemental Information

Exploratory assessment of other e-diary outcomes

In addition to our main outcome variable momentary affective valence, we acquired, at each prompt, e-diary scales quantifying momentary calmness and energetic arousal (Wilhelm & Schoebi, 2007), momentary social contact, social (an)hedonia (Collip et al., 2011; Gan et al., 2021) and appraisals of positive and negative events (Wichers et al., 2009). We captured momentary calmness with the two bipolar items "*tense*" to "*relaxed*" and "*agitated*" to "*calm*", and momentary energetic arousal with the two bipolar items "*without energy*" – "*full of energy*" and "*tired*" – "*awake*" (Wilhelm & Schoebi, 2007). We presented the items at the edges of two computerized visual analogue scales with sliding locators (score range of 0 to 100) and later averaged the two item scores of the respective concepts for use as dependent variables. We assessed momentary social contact with a dichotomous item asking subjects whether they are currently alone or in the company of others. In the case of momentary social contacts, we additionally asked the participants to rate, via computerized visual analogue scales (score range of 0 to 100), the liking of the company (*"When you think about the people who surround you right now, to what extent is the following statement true? I don't like these people*!*"*), and the degree to which the subjects would prefer to be alone (*"When you think about the people who surround you right now, to what extent is the following statement true? I'd rather be alone!*") (Collip et al., 2011; Gan et al., 2021). We assessed positive and negative event appraisal with two coverage items *("Have you had one or more unpleasant experiences since the last query? How bad was your worst experience?"* and *"Have you had one or more pleasant experiences since the last query? How good was your best experience?"*) that the participants rated using visual analogue scales with score ranges of 0 – 100.

Multilevel modeling of e-diary assessments

For hypothesis testing, we estimated the effect of participant group (categorical variable: 0 = non-risk group, 1 = at-risk group, 2 = clinical group) on affective valence by conducting random-intercept multilevel model analysis in SAS (version 9.4., SAS Institute Inc., Cary, NC, USA), thereby nesting e-diary assessments (level 1) within participants (level 2) (Bolger & Laurenceau, 2013). Besides our main predictor group, we added the level-1 predictors time of the day and time of the day squared (transformed to the daily study start time at 7:30 AM) to the model to control for known time-of-day effects on affective valence (Reichert et al., 2017; Tost et al., 2019). We added compliance rate as a level-2 covariate.

Following established procedures (Bolger & Laurenceau, 2013), we incorporated random effects for both the intercept and each predictor and subsequently deleted non-significant random effects. Equation S1 details the full model below using a single equation representation.

Equation (S1):

$$Y(\boldsymbol{affective\ valence})_{ij} = \beta_{00} + \beta_{01} * \boldsymbol{group}_j + \beta_{02} * compliance_j + \beta_{10} * time\ of\ day_{ij} + \beta_{20} * time\ of\ day_{ij}^2 + u_{0j} + r_{ij}$$

Y_{ij} represents the level of affective valence in person *j* at time *i*. Within-subject effects are modeled on level 1, represented by each participant's (subscript *j*) value entries for every prompt (subscript *i*). Beta coefficients denote the intercept, the effect of our main predictor group, of compliance rate, and the effects of the level-1 covariates (time of the day, time of the day squared). Random effects, i.e., individual variation around the sample mean, are represented by u_{0j} for the intercept. For exploratory analysis, we computed analogous models for e-diary outcomes reflecting additional daily-life processes (for details, see section "exploratory assessment of other e-diary outcomes" above, and *Methods* and *Table 1* in the main text).

Emotional Face Matching Task

Participants completed a well-established implicit emotion processing paradigm during fMRI designed to reliably (Cao et al., 2014; Plichta et al., 2014; Plichta et al., 2012) engage the amygdala ("Hariri task" **Figure 1.4**. (Hariri, Mattay, et al., 2002)). We have described this paradigm in detail in our previous work (Bilek et al., 2019; Cao et al., 2016; Tost et al., 2019). Briefly, the block-designed task consists of two conditions, an emotional face condition (matching faces) and a control condition (matching shapes). In the emotional face condition, the participants are presented with trios of faces depicting fearful or angry expressions derived from a standard set of pictures of facial affect (Ekman & Friesen, 1976). In the control condition, the participants are presented with trios of simple geometric shapes (circles, vertical and horizontal ellipses). Participants were instructed to match the two stimuli illustrating the same individual, or the same geometric shape, respectively. The task consists of eight blocks (30 s) with alternating epochs of face- and shapes-matching conditions, comprised of six trials each (task duration: 4.3 min or 130 whole-brain scans).

fMRI data acquisition and preprocessing

We performed blood-oxygen-level-dependent (BOLD) fMRI on a 3 Tesla MRI scanner (Siemens Trio, Erlangen, Germany) using an echo-planar-imaging sequence with the following parameters: TR 2000 ms, TE 30 ms, 130 volumes, 28 oblique slices per volume, 4 mm slice thickness, 1 mm slice distance, 80° flip angle, 192 mm field of view, and 64 × 64 matrix. We processed and analyzed the data with SPM12 (www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (https://www.mathworks.com/products/matlab.html) using standard procedures (Bilek et al., 2019; Cao et al., 2016; Cao et al., 2018), in which the images were realigned to the mean image of the scan run using a 6-parameter rigid body spatial transformation, spatially normalized to the standard stereotactic space of the Montreal Neurological Institute (MNI) template, resampled to 3 mm isotropic voxels and smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel.

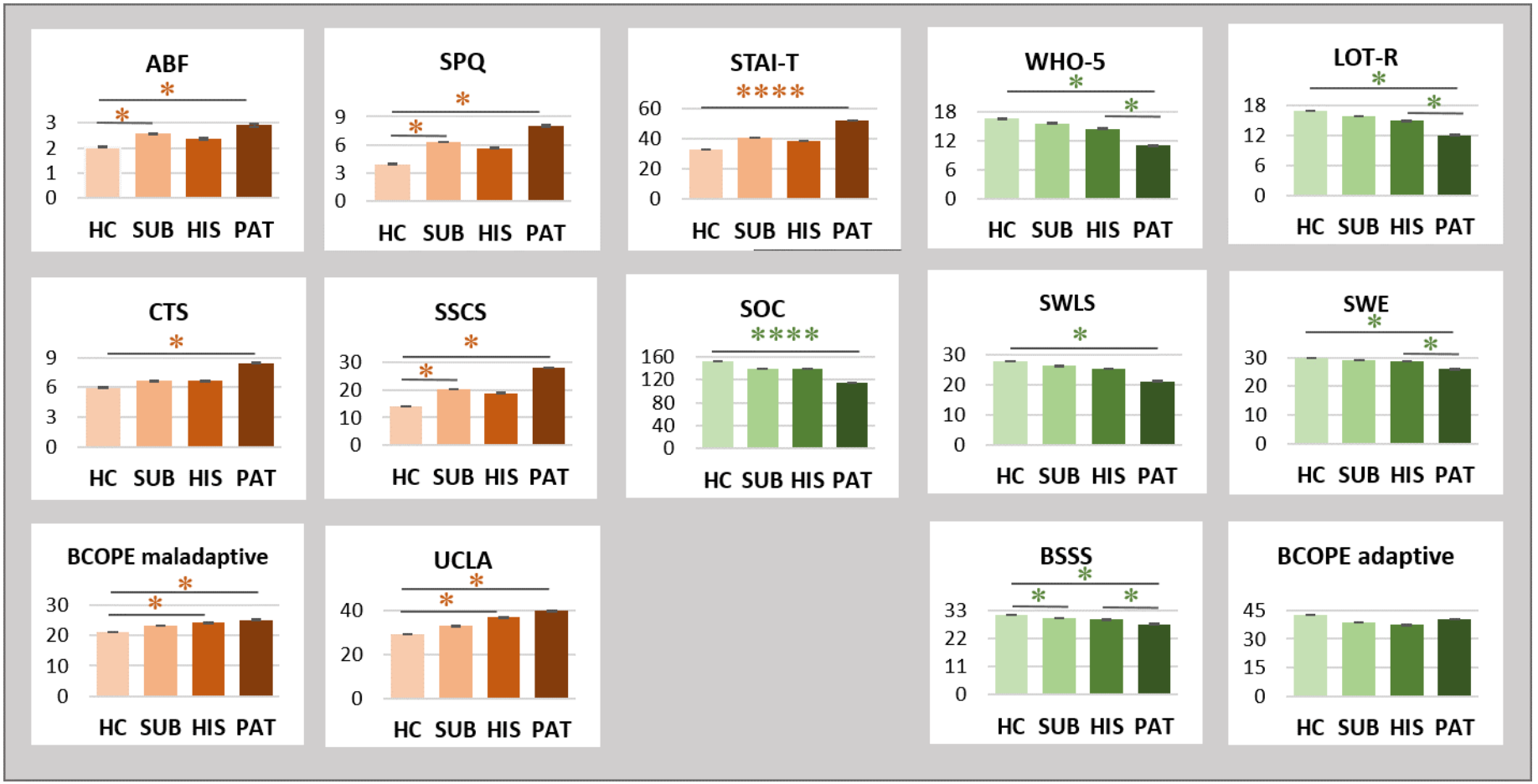
Supplemental Table S 2.1: Demographic and psychological sample description for community psychiatric risk groups

	Subclinical group (n=40)			History group (n=21)			t-test / χ^2 /U-test
	M ± SD / count	min/max	*n*	M ± SD / count	min/max	*n*	*p* value
Demographic data							
Age (year)	22.37 ± 2.55	18.10/27.20	40	22.82 ±3.01	18.18/27.83	21	0.539
Sex (male/female)	7/33	N/A	40	9/12	N/A	21	0.063
Education (years)	12.62± 1.65	10/16	39	12.81± 2.04	8/16	21	0.691
Body mass index (kg/m2)	22.98± 3.32	18.2/32.7	37	23.07± 3.69	17.00/31.50	21	0.924
Current urbanicity (Lederbogen et al., 2011)	2.47± 0.72	1/3	17	2.75± 0.71	1/3	8	0.371
Marital status (single/married)	3/36	N/A	39	3/18	N/A	21	0.417
Current employment (yes/no)	19/19	N/A	39	6/15	N/A	21	0.111
Household size (individuals)	2.46±1.25	1/5	39	2.71±1.74	1/7	21	0.519
Household income (€/month after taxes)	2195.70±1676.61	<250/>5599	30	2.506.24±1980.28	<250/>5599	21	0.549
Socioeconomic status (SES) (Lampert et al., 2013)	13.38±3.49	6.90/20.20	40	13.65±3.04	7.90/18.20	21	0.770
Perceived social status, self/current (Schweiger et al., 2021)	6.12±1.32	4/9	17	6.13±1.73	4/9	8	0.991
Perceived social status, parents/ infancy (Schweiger et al., 2021)	6.35±1.90	3/10	17	5.88±1.36	4/8	8	0.531
Psychological data							
Trait anxiety (STAI-T, sum) (Laux et al., 1981)	40.62±9.77	27/66	39	38.33±9.32	21/59	21	0.384
Mental wellbeing (WHO-5, sum) (Topp et al., 2015)	15.56±4.53	6/23	39	14.45±4.68	4/22	20	0.380
Satisfaction with life (SWLS) (Glaesmer et al., 2011)	26.08±6.29	10/34	39	25.19±5.81	9/34	21	0.595
BCOPE-adaptive coping (Carver, 1997; Knoll et al., 2005)	38.77±8.09	19/53	39	37.38±6.39	25/50	21	0.511
BCOPE-maladaptive coping (Carver, 1997; Knoll et al., 2005)	23.38±4.755	15/36	39	24.25±3.82	15/31	20	0.484
Self-efficacy (SWE, sum) (Jerusalem & Schwarzer, 1992; R. Schwarzer & Jerusalem, 1999)	29.21±4.35	17/36	39	28.76±4.53	21/40	21	0.712
Loneliness (UCLA, mean) (Döring & Bortz, 1993)	32.95±10.51	20/63	39	36.86±12.29	24/76	21	0.201
Optimism (LOT-R, sum score) (Herzberg et al., 2006)	15.92±4.57	8/23	39	15.00±4.34	4/23	21	0.451
Schizotypical traits (SPQ, sum) (Raine & Benishay, 1995)	6.30±3.37	0/13	30	5.68±3.99	0/15	16	0.585
Chronic stress (SSCS, sum) (P. Schulz et al., 2004)	20.35±9.15	4/41	17	18.87±4.97	10/26	8	0.675
Perceived social support (BSSS, sum) (U. Schulz & Schwarzer, 2003)	30.05±3.30	19/32	39	29.48±2.89	22/32	21	0.505
Sense of coherence (SOC, sum) (Hannöver et al., 2004)	138.87±22.34	88/181	38	138.57±18.54	99/177	21	0.959
Daily hassles (ABF) (Traue et al., 2000)	2.56±0.78	1.09/4.75	30	2.38±0.75	1.36/3.98	17	0.424
Adverse childhood experiences (CTS) (Glaesmer et al., 2013)	6.64±2.34	5/16	39	6.67±1.53	5/10	21	0.379

Study 1: Reduced real-life affective well-being and amygdala habituation in unmedicated community individuals at risk for depression and anxiety

For details on the psychological questionnaires including acronyms, see *Supplemental Table S4*. We assessed group differences in SPSS (IBM, SPSS, version 25) using variable type and distribution appropriate tests. Abbreviations: M = mean, SD = standard deviation, SUB – subclinical, n = number of participants with available data, t-test = t-test for independent samples, χ^2 = chi-squared test, U-test = Mann-Whitney U-test.

Supplemental Figure S 2.1: Bar plots showing similarities and differences of psychological characteristics of study groups



Abbreviations: HC – non risk group, SUB – subclinical group, HIS – history group, PAT – clinical group; ABF - Daily hassles, SPQ - Schizotypical traits, CTS - Adverse childhood experiences, SSCS - Chronic stress, BCOPE-maladaptive coping, UCLA – Loneliness, STAI-T - Trait anxiety, BCOPE-adaptive – BCOPE- adaptive coping, BSSS - Perceived social support, SOC – sense of coherence, SWE - Self-efficacy, SWLS - Satisfaction with life, LOT-R – Optimism, WHO-5 - Mental wellbeing.

**** HC ≠ PAT, HC ≠ SUB, PAT ≠ HIS, PAT ≠ SUB

Supplemental Table S2.2: Type and frequency of current psychiatric symptoms identified in community-based individuals by MINI-DIPS interviews

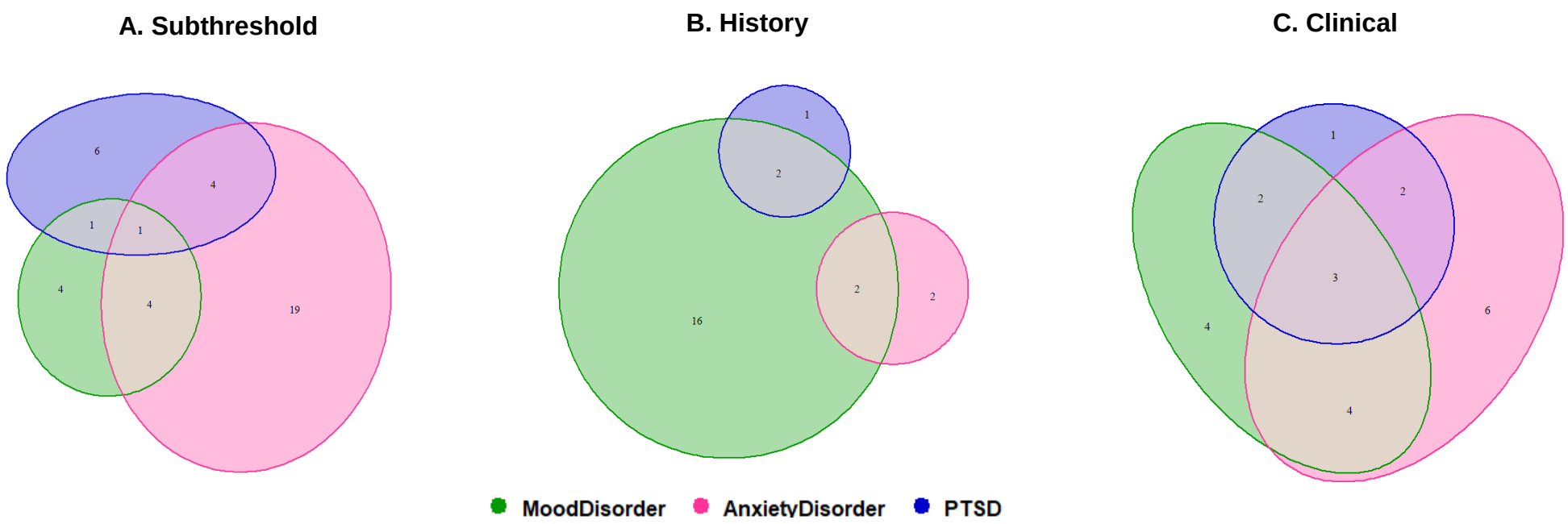
	Subthreshold group (n = 40)	History group (n = 21)[a]	Clinical group (n = 23)
	% (count)	% (count)	% (count)
Type of anxiety symptoms			
Panic disorder	32.5% (13)	9.52% (2)	34.78% (8)
Agoraphobia	20% (8)	4.76% (1)	4.35% (1)
Social anxiety	17.5% (7)	4.76% (1)	8.70% (2)
Generalized anxiety disorder	32.5% (13)	4.76% (1)	43.48% (10)
Type of affective symptoms			
Depressive symptoms	22.5% (9)	85.71% (18)	47.83% (11)
Mania/hypomania	5% (2)	4.76% (1)	8.70% (2)
Dysthymia	7.5% (3)	9.52% (2)	13.04% (3)
Other type of symptoms			
PTSD	30% (12)	14.29% (3)	39.13% (9)
OCD	5% (2)	0% (0)	4.35% (1)
Personality disorder	0% (0)	0% (0)	8.70 % (2)
Anorexia	0% (0)	0% (0)	4.35% (1)
Psychotic Symptoms	0% (0)	0% (0)	0% (0)
Symptoms of Addiction[b]	0% (0)	0% (0)	0% (0)
Number of symptom categories			
1	45% (18)	71.43% (15)	34.78% (8)
2	40% (16)	23.81% (5)	34.78% (8)
>2	15% (6)	4.76% (1)	30.43% (7)
Current psychiatric treatment			
Psychiatrist	0% (0)	4,76% (1)	21.73% (5)
Clinical psychologist	0% (0)	0% (0)	8.70% (2)
Psychotropic medication	0% (0)	0% (0)	17.39% (4)

Abbreviations: PTSD = posttraumatic stress disorder, OCD = obsessive-compulsive disorder.

[a]Community individuals with a history of psychiatric disorders were fully remitted at the time of the study. Retrospectively reported symptoms refer to the past experience.

[b] Symptoms of Addiction were assessed with the ESPAD (European School Survey Project on Alcohol and other Drugs) (Hibell et al., 2009).

Supplemental Figure S2.2: Type and frequency of current psychiatric symptoms identified in community-based individuals by MINI-DIPS interviews



Grouping: **Mood Disorder:** Depression, Personality disorder, Dysthymia, Mania;

Anxiety disorder: Social anxiety, GAD (Generalized anxiety disorder), OSD (Obsessive-compulsive disorder), Agoraphobia, Panic disorder;

Abbreviation: PTSD - Posttraumatic stress disorder.

Supplemental Table S 2.3: Demographic and data quality parameters for fMRI analysis groups

	Non-risk (n=26)			At-risk (n=26)			t-test / χ^2
	M ± SD / count	min/max	n	M ± SD / count	min/max	n	*p* value
Demographic data							
Age (year)	22.22 ±1.35	20.22/25.38	26	22.39 ±2.27	18.10/25.85	26	0.738
Sex (male/female)	6/20	N/A	26	4/22	N/A	26	0.482
Education (years)	12.65 ± 1.38	12/16	26	12.60±1.68	10.00/16.00	25	0.901
Body mass index (kg/m2)	23.54 ± 4.69	18.00/39.10	26	22.87 ± 3.77	17.00/32.7	24	0.577
Current urbanicity[a] (Lederbogen et al., 2011)	2.69 ±0.62	1/3	26	2.56 ±0.71	1.00/3.00	25	0.481
Marital status (single/married)	0/26	N/A	26	2/23	N/A	25	0.141
Current employment (yes/no)	9/17	N/A	26	10/15	N/A	25	0.691
Household size (individuals)	2.58 ± 1.10	1/5	26	2.24 ± 1.05	1/5	25	0.270
Household income (€/month after taxes)	2127.85 ± 1685.90	<50/>5000	20	1736.04 ± 1563.67	<50/>5000	23	0.434
Perceived social status, self/current (Schweiger et al., 2021)	6.46 ± 1.36	3/9	26	6.12 ± 1.42	4/9	25	0.386
Perceived social status, parents/ infancy (Schweiger et al., 2021)	6.19 ± 1.81	1/9	26	6.20±1.73	3/10	25	0.988
Socioeconomic status (SES) (Lampert et al., 2013)	12.97± 3.57	6.20/19.40	26	12.61± 3.52	6.90/20.20	26	0.720
fMRI task performance							
Correct ratio face (%)	99.36±1.53	95.83/100.00	26	99.04±1.79	95.83/100.00	26	0.534
Correct ratio form (%)	97.11±3.28	91.67/100.00	26	96.15±5.26	83.33/100.00	26	0.339
fMRI data quality							
Signal to noise ratio	86.29±13.14	44.78/112.00	26	92.03±17.32	52.93/127.00	26	0.221
Spikes	0.92±3.93	0/20	26	1.00±3.07	0/14	26	0.873
Sum motion translation (mm)	0.71±0.59	0.16/2.13	26	0.66±0.51	0.13/2.28	26	0.978
Sum motion rotation (degree)	0.51±0.36	0.15/1.45	26	0.54±0.42	0.15/2.04	26	0.666
Mean FWD (mm)	0.16±0.07	0.06/0.37	26	0.15±0.07	0.07/0.32	26	0.929

We assessed group differences in SPSS (IBM, SPSS, version 25) using variable type and distribution appropriate tests. Abbreviations: M = mean, SD = standard deviation, n = number of participants with available data, t-test = t-test for independent samples, χ^2 = chi-squared test, U-test = Mann-Whitney U-test, spikes = number of time points in which the signal intensity is larger than 10 *X* SD of the mean signal.

Supplemental Table S 2.4: Inventory measures

Name	Outcome measure(s)	Type	Details and references
Socioeconomic status assessment of the German Health Update 2009 (GEDA)	○ Socioeconomic status	Multidimensional aggregated index of status-constituting dimensions (education, occupation, income)	See (Lampert et al., 2013)
Perceived social status	○ Current perceived social status of the participant ○ Perceived social status of the parents at the time of the participant's birth	2 items, 10-rung visual analogue scales	Modification of the McArthur Scale of Subjective Social Status (Adler et al., 1994; Gianaros et al., 2007) (http://www.macses.ucsf.edu/) Adaptation as detailed in (Schweiger et al., 2021)
Chronic Stress Screening Scale (CSSS)	○ Perceived chronic stress	12 items, 5-point Likert scales	From the Trier Inventory for the Assessment of Chronic Stress (TICS) (P. Schulz et al., 2004)
Berlin Social Support Scale (BSSS)	○ Perceived social support	8 items, 4-point Likert scales	See (U. Schulz & Schwarzer, 2003)
Childhood Trauma Screener (CTS)	○ Retrospective self-rating of adverse childhood experiences	5 items, 5-point Likert scales	German short version of the Childhood Trauma Questionnaire (CTQ) Subscales: physical abuse, sexual abuse, emotional abuse, physical neglect, emotional neglect See (Glaesmer et al., 2013)
Current urbanicity	○ Degree of urbanicity of the current living environment	3-level ordinal scale index	Quantification as detailed in (Lederbogen et al., 2011)
State-Trait Anxiety Inventory (STAI-T)	○ Trait anxiety	20 items, 4-point Likert scales	See (Laux et al., 1981)
Schizotypal Personality Questionnaire (SPQ-Brief)	○ Schizotypal personality traits	22 items, yes/no response format	See (Raine & Benishay, 1995)
UCLA Loneliness Scale (UCLA)	○ Perceived loneliness	20 items, 4-point Likert scales	See (Döring & Bortz, 1993)
General Self-Efficacy Scale (GSES)	○ Generalized belief in the own ability to control environmental challenges	10 items, 4-point Likert scales	See (Jerusalem & Schwarzer, 1992; R. Schwarzer & Jerusalem, 1999)
Sense of Coherence Scale (SOC-29)	○ Dispositional sense of coherence	29 items, 5-point Likert scales	See (Hannöver et al., 2004)
Revised Life Orientation Test (LOT-R)	○ Dispositional optimism	10 items, 5-point Likert scales	See (Herzberg et al., 2006)
WHO-5 Well-Being Index	○ Perceived current mental well-being	5 items, 6-point Likert scales	See (Topp et al., 2015)
Satisfaction with Life Scale (SWLS)	○ Global cognitive judgments of satisfaction with life	5 items, 7-point Likert scales	See (Glaesmer et al., 2011)
Alltagsbelastungsfragebogen (ABF)	○ Daily hassles	58 items, 8-point Likert scales	Daily assessments at the end of the day See (Traue et al., 2000)
Brief-COPE	○ Maladaptive coping strategies ○ Adaptive coping strategies	28 items, 4-point Likert scales	See (Carver, 1997; Knoll et al., 2005)

Supplemental Table S2.5: Multilevel analysis results, main group comparison

Dependent variable	**Predictor** ***Fixed effects***	**Group**	**Beta coefficient**	**Standard Error**	***T value* (df)**	***P value***	***P value* BF**
Valence	Intercept		61.03	5.47	11.15 (131)	<0.001	
	Time (hours)		0.37	0.16	2.39(8552)	0.017	
(0-100)	Time-squared (hours^2)		-0.00	0.01	-0.47(8551)	0.643	
	Compliance rate (%)		0.14	0.06	2.38(129)	0.019	
	Group	Clinical	-14.05	3.03	-4.64(126)	<0.001	<0.001
		At-risk	-5.72	2.26	-2.53(125)	0.013	0.038
		Non-risk	Reference category	Reference category	Reference category	Reference category	Reference category

Abbreviations: Clinical = community-based individuals fulfilling the criteria for a current mood or anxiety disorder, At-risk = community-based individuals at mental health risk, Non-risk = community-based individuals not at clinical risk, df = degree of freedom, BF – Bonferroni corrected for multiple group comparisons. All reported *p* values for beta coefficients are two-sided and derived from the t-statistics of the multilevel model.

Supplemental Table S2.6: Multilevel analysis results, Exploratory group comparisons

Dependent variable	**Predictor** ***Fixed effects***	**Group**	**Beta coefficient**	**Standard error**	***T value* (df)**	***P value***	***P value BF***
Model 1: Energetic Arousal (0-100)	Intercept		38.31	5.71	6.71(133)	<0.001	---
	Time (hours)		5.04	0.19	26.33(8555)	<0.001	---
	Time-squared (hours^2)		-0.35	0.01	-28.49(8555)	<0.001	---
	Compliance rate (%)		0.13	0.06	2.03(130)	0.044	---
	Group	Clinical	-9.10	3.14	-2.89(126)	0.004	0.014
		At-risk	-4.08	2.34	-1.74(125)	0.085	0.254
		Non-risk	Reference category.	Reference category.	Reference category.	Reference category.	Reference category.
Model 2: Calmness (0-100)	Intercept		62.17	5.85	10.62(131)	<0.001	---
	Time (hours)		-0.87	0.16	-5.56(8551)	<0.001	---
	Time-squared (hours^2)		0.07	0.01	7.36(8550)	<0.001	---
	Compliance rate (%)		0.13	0.06	1.98(129)	0.050	---
	Group	Clinical	-13.34	3.24	-4.12(126)	<0.001	<0.001
		At-risk	-4.69	2.42	-1.95(126)	0.055	0.164
		Non-risk	Reference category.	Reference category.	Reference category.	Reference category.	Reference category.
Model 3: Affective Instability	Intercept		647.92	179.37	3.61(135)	<0.001	---
	Time (hours)		20.07	8.72	2.30(7674)	0.021	---
	Time-squared (hours^2)		-0.73	0.51	-1.41(7672)	0.158	---
	Compliance rate (%)		-2.06	1.40	-1.47(133)	0.144	---
	Valence (subject mean)		-4.49	1.97	-2.27(120)	0.025	
	Group	Clinical	256.16	72.46	3.54(119)	0.001	0.007
		At-risk	53.68	51.11	1.05(118)	0.30	0.887
		Non-risk	Reference category.	Reference category.	Reference category.	Reference category.	Reference category.
Model 4: Don't like the company (0-100)	Intercept		17.27	5.18	3.34(138)	0.001	---
	Time (hours)		0.16	0.25	0.64(4361)	0.523	---
	Time-squared (hours^2)		-0.04	0.01	-2.84(4358)	0.004	---
	Compliance rate (%)		-0.07	0.06	-1.31(132)	0.191	---
	Group	Clinical	8.06	2.80	2.88(123)	0.005	0.014
		At-risk	3.18	2.09	1.52(121)	0.131	0.392
		Non-risk	Reference category.	Reference category.	Reference category.	Reference category.	Reference category.
Model 5: Rather be alone (0-100)	Intercept		21.07	6.87	3.07(136)	0.003	---
	Time (hours)		0.45	0.30	1.48(4356)	0.139	---
	Time-squared (hours^2)		-0.06	0.02	-3.36(4353)	0.008	---
	Compliance rate (%)		-0.09	0.07	-1.23(131)	0.222	---
	Group	Clinical	15.14	3.73	4.06(123)	<0.001	0.001
		At-risk	4.55	2.78	1.63(121)	0.105	0.315
		Non-risk	Reference category.	Reference category.	Reference category.	Reference category.	Reference category.

Model 6: Positive Event Appraisal (0-100)	Intercept		15.27	6.22	2.46(137)	0.015	---
	Time (hours)		1.26	0.25	5.07(8496)	<0.001	---
	Time-squared (hours^2)		-0.02	0.02	-1.49(8495)	0.137	---
	Compliance rate (%)		0.00	0.07	0.04(132)	0.969	---
	Group	Clinical	0.06	3.40	0.02(126)	0.986	---
		At-risk	1.66	2.54	0.65(126)	0.515	---
		Non-risk	Reference category.	Reference category.	Reference category.	Reference category.	---
Model 7: Negative Event Appraisal (0-100)	Intercept		16.32	3.77	4.32(142)	<0.001	---
	Time (hours)		0.19	0.18	1.07(8569)	0.285	---
	Time-squared (hours^2)		-0.05	0.01	-1.34(8567)	0.181	---
	Compliance rate (%)		-0.09	0.04	-2.16(135)	0.032	---
	Group	Clinical	7.26	2.05	3.55(126)	0.000	0.002
		At-risk	3.17	1.53	2.08(125)	0.039	0.119
		Non-risk	Reference category.	Reference category.	Reference category.	Reference category.	Reference category.
Model 8: Being Alone (1/0)	Intercept		1.35	0.09	15.07(142)	<0.001	---
	Time (hours)		0.03	0.04	5.85(8568)	<0.001	---
	Time-squared (hours^2)		-0.00	0.002	-3.82(8566)	0.001	---
	Compliance rate (%)		-0.00	0.009	0.81(135)	0.417	---
	Group	Clinical	-0.04	0.05	-0.79(126)	0.429	---
		At-risk	0.00	0.04	0.01(125)	0.992	---
		Non-risk	Reference category.	Reference category.	Reference category.	Reference category.	---

Abbreviations: See legend *Supplemental Table 5*.

2.2. Study 2: Dose-dependent changes in real-life affective well-being in healthy community-based individuals with mild to moderate childhood trauma exposure[2]

2.2.1 Abstract

*Background***.** Adverse Childhood Experiences (ACEs) are frequent, well-established risk factors for the development of psychopathology. However, knowledge of the effects of ACEs in healthy individuals in a real life context, which is crucial for early detection and prevention of mental disorders, is incomplete. Here, we here use ecological momentary assessment (EMA) to investigate ACE load-dependent changes in daily-life affective function and psychosocial risk profile in n = 351 healthy, clinically asymptomatic, adults from the community with mild to moderate ACE exposure.

*Findings***.** EMA revealed significant ACE dose-dependent decreases in real-life affective valence ($p = 0.007$), energetic arousal ($p = 0.032$) and calmness ($p = 0.044$). Psychological questionnaires revealed a broad ACE-related risk profile with dose-dependent increases in mental health risk-associated features (e.g., trait anxiety, maladaptive coping, loneliness, daily hassles; p values < 0.003) and a corresponding decrease in psychological factors protective for mental health (e.g., life satisfaction, adaptive coping, optimism, social support; p values < 0.021). These results were not influenced by age, sex, socioeconomic status or education.

*Conclusions***.** Healthy community-based adults with mild to moderate ACE exposure exhibit dose-dependent changes in well-being manifesting in decreases in affective valence, calmness and energy in real life settings, as well as a range of established psychological risk features associated with mental health risk. This indicates an approach to early detection, early intervention, and prevention of ACE-associated psychiatric disorders in this at-risk population.

[2] **In Review:** Berhe, O., Moessnang, C., Reichert, M., Ma, R., Höflich, A., Tesarz, J., Heim, C., Ebner-Priemer, U., Meyer-Lindenberg, A., Tost, H. (in review) Dose-dependent changes in real-life affective well-being in healthy community-based individuals with mild to moderate childhood trauma exposure. *Borderline Personal Disord Emot Dysregul.*

2.2.2. Introduction

Adverse childhood experiences (ACEs) such as physical, sexual, and emotional abuse and physical and emotional neglect are recognized environmental risk factors for the development of a wide range of adverse health outcomes across the lifespan (Heim & Nemeroff, 2001; McGrath et al., 2017; McKay et al., 2021). For example, physical abuse, emotional abuse and neglect in childhood roughly double the likelihood of psychiatric disorders such as depression, anxiety disorders and substance abuse in adulthood (Norman et al., 2012), with a dose-dependent relationship between cumulative ACE exposure and severity of psychopathology (McKay et al., 2021; Pietrek et al., 2013). ACEs are further associated with a range of somatic conditions, including altered neuroendocrinological stress response, cardiovascular, inflammatory, and metabolic diseases and premature death (Brindle, Pearson, & Ginty, 2022). Given that up to 30% of the adult population have experienced some form of ACE (Sethi et al., 2013), this represents a massive public health burden.

At the same time, our knowledge of the effects of ACEs on mental health is still incomplete. First, our understanding of possible ACE-related affective changes in the general population is limited, especially when it comes to milder forms of adverse exposures and related subclinical changes in everyday life. Here, community-based studies and the availability of smartphone-based Ecological Momentary Assessment (EMA) in real life provide an opportunity for new insights (Berhe et al., 2022; Gan et al., 2021). Second, most studies on ACEs have focused on patient populations (Fritz, de Graaff, Caisley, van Harmelen, & Wilkinson, 2018). These results need to be complemented by information about the nature and extent of subclinical changes in healthy ACE-exposed individuals to define their risk for and resilience against developing a psychiatric disorder.

To fill this gap in knowledge, this study combined methods from psychology, epidemiology and EMA to investigate the psychosocial risk profile along with changes in daily-life affective function in ACE-exposed healthy individuals from the general population. Based on our previous work with at-risk populations (Berhe et al., 2022; Gan et al., 2021; Tost et al., 2019), we hypothesized that ACE exposure, even in a clinically healthy group, would predict reduced momentary affective valence in daily life and increased psychological risk for mental illness.

2.2.3. Methods

Study participants

We recruited 351 healthy young adults (mean age: 24.80 ± 6.54 years, 162 males) from local communities in the Rhine-Neckar metropolitan area in Germany for this study. We provide further demographic details in **Table 2.2** and **Table S2.7**. General exclusion criteria included the presence of a significant general medical disorder, neurological disorder, or a current or lifetime psychiatric disorder as determined by clinical interviews (First, Spitzer, Gibbon, & Williams, 2001; J. Margraf, 1994). None of the recruited subjects reported clinical psychiatric symptoms at the time of the study entry. Study participants gave written informed consent for a study protocol approved by the Medical Ethics Committee II of Heidelberg University.

Psychological data acquisition and analysis

Participants completed a battery of sociodemographic and psychosocial assessments aiming at quantifying established psychological risk factors for mental health. For retrospective assessment of ACEs we used the Childhood Trauma Screener (CTS), a validated instrument covering sexual, emotional and physical abuse and emotional and physical neglect (Glaesmer et al., 2013). (see sMethods for details). Other surveys assessed socioeconomic status (SES), trait anxiety, loneliness, self-efficacy, sense of coherence, optimism, mental well-being, life satisfaction, daily hassles, coping strategies and social support. We provide a full overview of the measures in **Table S2.8**. Because of the skewed distribution of CTS scores, we examined dose-dependent (linear) associations between cumulative ACE exposure (CTS sum score) and questionnaire scores in SPSS (IBM, SPSS, version 25) using nonparametric Spearman rank correlation analyses corrected for age, sex, education, and SES (see **FigureS2.3** and **Table2.2** for details).

EMA and analysis

We assessed e-diary-ratings of the momentary social affective experience with study smartphones (Motorola Moto G, Motorola Mobility). EMA ratings were collected on 7 consecutive days in daily life with a flexible time- and location-dependent sampling schedule with an average of 12.51 ± 1.79 prompts per day, as previously described (Gan et al., 2021; Reichert et al., 2020; Tost et al., 2019). We assessed momentary well-being using a validated EMA short scale with good reliability and sensitivity (Wilhelm & Schoebi, 2007) . The scale captures real-life *affective valence*, *calmness* and *energetic arousal* with

two bipolar items each, presented as computerized visual analog scales with sliding locators (score range: 0 – 100). At an exploratory level, we also evaluated e-diary scales quantifying momentary social contact, social anhedonia, the appraisal of negative and positive events, and computed an established EMA measure of affective instability in daily life (mean square of successive differences, MSSD) from momentary affective valence scores (Berhe et al., 2022; Gan et al., 2021). We nested within-subject e-diary assessments (level 1) within participants (level 2) and used multilevel models in SAS (version 9.4., SAS Institute Inc., Cary, NC, USA) to test for associations between cumulative ACE exposure (CTS sum score) and EMA outcome measures. Since the distribution of the CTS sum variable was skewed (see **Figure S2.3**) we log-transformed the variable using the natural logarithm. Furthermore, we examined the distribution of the residuals of the models to rule out any bias due to the structure of the data (**Figure S2.4**). We provide further methods details in the **sMethods**.

2.2.4 Results

Questionnaire data

As expected, the distribution of the CTS score in our sample was skewed to the left with the M= 6.29±1.97 (with a range of 5-25: '5' being the minimum value for selecting 'never true' for all 5 items), suggesting for a predominantly non-traumatized sample (**Figure S2.3**). A substantial proportion of individuals in our sample (N=259) reported no-to mild ACE; 93 participants reported moderate level of ACE (based on the CTS classification)(Glaesmer et al., 2013).

Higher severity of ACE-exposure was significantly associated with older age, lower SES, and fewer years of education (p values < 0.026. After adjustment for age, sex, SES, and education, higher ACE load was significantly associated with higher scores for trait anxiety, loneliness, perceived daily hassles, and use of maladaptive coping strategies, as well as significantly lower scores for psychological well-being, life satisfaction, optimism, sense of coherence, self-efficacy, and perceived social support (p values < 0.021). We provide further details of the results in **Table2.2** and **Figure 2.3**. Details of the statistical relationships of the five CTS subdomains to the psychosocial measures are presented in **Table2.9** for exploratory purposes.

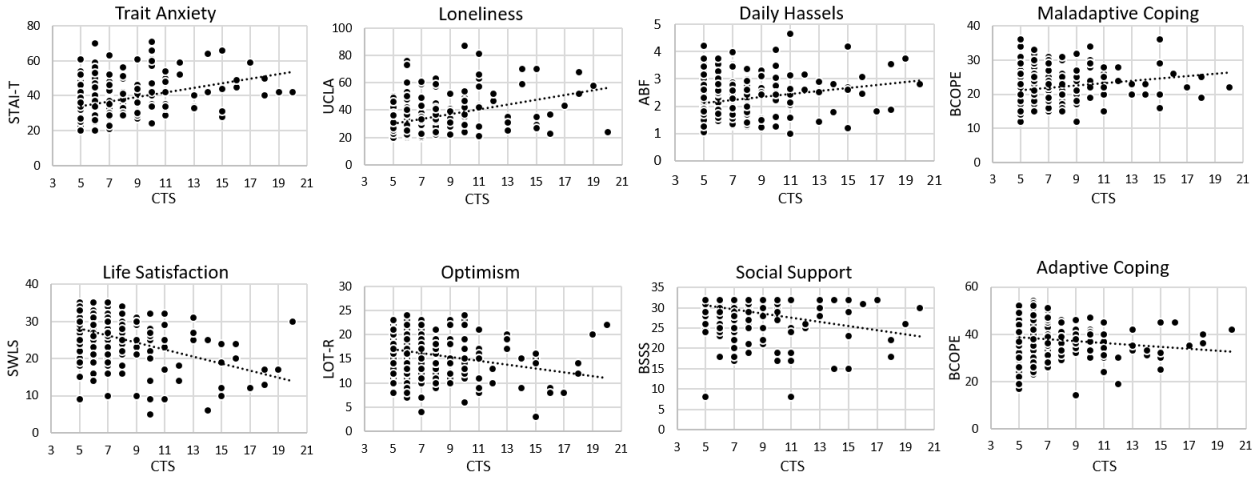


Figure 2.3. Relationship between ACE load and psychological risk and protective factors for mental health. Significant ACE dose-dependent increases in questionnaire measures capturing (upper row, from left to right) trait anxiety loneliness, daily hassles, and maladaptive coping (all *p* values < 0.003) and significant decrease in (bottom row, from left to right) life satisfaction, optimism, social support and adaptive coping (all *p* values < 0.021). X-axis: Childhood trauma screener (CTS) sum score; Y-axis: mean/sum values of questionnaire measures.

Ecological momentary assessments. Two datasets had to be excluded from the subsequent analysis due to low compliance (<30) (see **Table 2.2** in the main text and **Table S2.9** for more details). On average, participants responded to 12.51 prompts per day (SD = 1.79; range = 7/20), resulting in a high compliance rate of 81.59%.

As hypothesized, higher trauma exposure during childhood was significantly associated with lower momentary affective valence in daily life in adulthood (*p* = 0.007). In addition, higher ACE exposure related to lower momentary calmness and energetic arousal (p values < 0.044; see also **Table 2.2**, **Figure 2.4, and Table S2.10, S2.11**). Additional covariation for age, sex, SES, education and reported daily hassles did not change these results. In contrast, our exploratory analysis of EMA measures of affective instability, frequency and evaluation of momentary social contacts, and appraisal of positive and negative events in daily life revealed no significant associations with ACE burden. We provide further details of the EMA results in **Table 2.2**, **Figure 2.4, and Table S2.10, S2.11**.

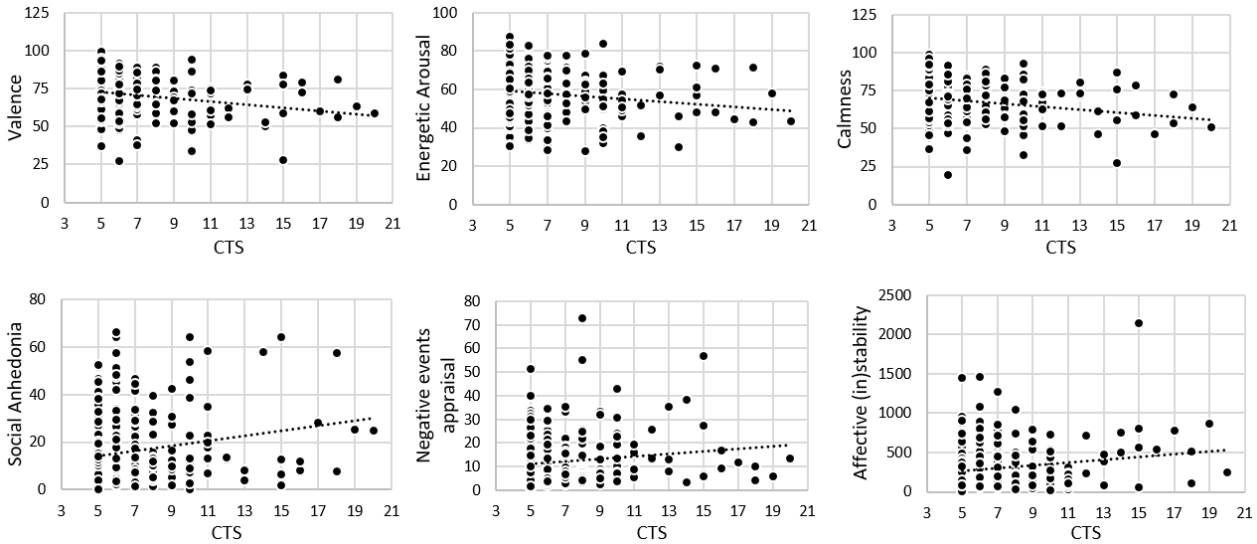


Figure 2.4. Relationship between ACE load and real-life affective well-being. Significant ACE dose-dependent decreases (upper row, from left to right) in real-life affective valence (p = 0.007), energetic arousal (p = 0.032,) and calmness (p = 0.044) in healthy community-based individuals with mild to moderate ACE exposure. Absence of such associations in social-affective EMA measures reflecting evaluation of (bottom row, from left to right) social anhedonia (p > 0.23), appraisal of negative events (p > 0.98) and affective (in)stability (valence MSSD, p > 0.50). X-axis: Childhood trauma screener (CTS) sum score; Y-axis: mean values of EMA indices across 7 days of measurement.

2.2.5 Discussion

In this study, we aimed to answer the question of whether there are dose-dependent changes in real-life affective function and psychosocial risk profile even in healthy asymptomatic individuals from the community with self-reported mild to moderate ACE exposure. Consistent with our hypothesis, we observed a significant ACE dose-dependent decrease in affective valence in everyday life. In addition, we found a significant negative association between ACE load and momentary energy and calmness. Notably, we have previously observed a similar sensitivity of these measures in relation to other established psychiatric risk and resilience factors, including in individuals with subclinical symptoms (Berhe et al., 2022) and healthy persons who benefited in well-being from social contact (Gan et al., 2021), physical activity (Reichert et al., 2020) and exposure to urban green space (Tost et al., 2019). Our study extends these data by showing that even clinically healthy, asymptomatic individuals from the community with milder forms of ACEs exhibit dose-dependent changes in real-life affective function as adults, and that these EMA scales are well suited to capture such risk-associated changes in naturalistic settings. Further longitudinal studies in healthy exposed individuals are needed to investigate the

value of these risk markers of the development of ACE-related mental disorders in adulthood.

Based on the collected questionnaire measures, we further identified a psychological risk profile in our ACE-exposed individuals consistent with our hypothesis. The profile consisted of a dose-dependent increase in several known psychological risk factors for mental health (e.g., trait anxiety, maladaptive coping, daily stress) and a corresponding decrease in factors known to reduce the odds of developing a psychiatric disorder (e.g., social support, adaptive coping, life satisfaction, optimism). Here, our data confirm and extend the existing knowledge by showing that, in addition to clinical populations with more pronounced ACEs (Kuzminskaite et al., 2021; Mc Elroy & Hevey, 2014) similar dose-dependent psychological associations can be found in healthy community-based individuals with milder forms of ACEs. Furthermore, they indicate potential psychological mechanisms through which ACEs reduce well-being in this population.

These results should be evaluated in light of several study limitations. First, although our study includes a comparatively large sample, we cannot draw any causal conclusions because of the cross-sectional design used. Second, as in many other studies, our measure of ACE burden is based on a retrospective self-report instrument. Although such surveys may be biased, previous data suggest that ACEs are underreported rather than overreported on such measures and that they are not crucially influenced by current emotional states (Spinhoven et al., 2014). Third, the distribution of ACE load was skewed in our population-based healthy sample, which was to be expected. Thus, we took special precautions to obtain robust results by using nonparametric methods, log-transforming predictors, and examining the distribution of model residuals.

In summary, we found that healthy, clinically asymptomatic individuals from the community with mild to moderate ACEs exhibit dose-dependent changes in well-being as adults. These changes manifest in a decrease in affective valence, calmness and energy in real life settings. We further identified a broad psychological risk profile, in which features detrimental to mental health accumulate. We hope that these data will contribute to a precision approach to early detection, early intervention, and prevention of ACE-associated psychiatric disorders in the general population

Table 2.2. ACE dose-dependent changes in real-life well-being and psychological metrics, well-known as risk and protective factors for mental well-being.

Characteristics	Sample (N=351)			Associations with trauma load (CTS sum score)	
	M ± SD / count	min/max	n	*Spearman's ρ / F value*[a]	*p* value
Demographic data[a]					
Age (year)	24.80 ±6.54	18.11/56.02	351	0.237	**<0.001**
Sex (male/female)	162/189	N/A	351	0.068	0.201
Education (years)	13.27 ± 1.89	8/16	350	-0.119	**0.026**
Socioeconomic status (SES)	14.53± 3.16	6.20/21.00	350	-0.179	**0.001**
Personality					
NEO-FFI Openess (mean)	14.94±4.89	1/24	347	0.017	0.751
NEO-FFI Agreeableness (mean)	17.67±3.92	5/24	346	-0.113	**0.038**
NEO-FFI Conscientiousness (mean)	18.04±3.63	6/24	346	-0.115	**0.033**
NEO-FFI Extraversion (mean)	15.08±3.61	1/24	347	-0.217	**<0.001**
NEO-FFI Neurotizismus (mean)	7.80±4.63	1/24	348	0.175	**0.001**
Risk Factors					
Early adversity (CTS, sum)	6.29±1.97	5/18	351	---	---
Trait anxiety (STAI-T, sum)	35.20±8.57	20/71	349	0.321	**<0.001**
Loneliness (UCLA, mean)	32.51 ±10.51	20/87	346	0.396	**<0.001**
Daily Stress (ABF)	2.21±0.68	1.00/4.66	319	0.174	**0.003**
BCOPE-maladaptive coping (sum)	21.37±4.22	12/36	343	0.164	**0.002**
Protective Factors					
Mental wellbeing (WHO-5, sum)	16.27±4.09	2/25	346	-0.166	**0.002**
Satisfaction with life (SWLS)	27.06±5.06	5/35	349	-0.310	**<0.001**
Optimism (LOT-R optimism, sum)	16.52 ±3.74	3/24	346	-0.279	**<0.001**
Sense of coherence (SOC, sum)	148.71±19.68	72/197	345	-0.342	**<0.001**
Self-efficacy (SWE, sum)	30.38±4.27	17/40	349	-0.147	**0.007**
Perceived social support (BSSS, sum)	29.83±3.61	8/32	350	-0.312	**<0.001**
BCOPE-adaptive coping (sum)	37.90±6.37	14/54	343	-0.120	**0.021**
EMA[b]					
Valence (MDBF)[c]	75.08±11.21	27.16/99.14	347	7.43	**0.007**
Energetic arousal (MDBF)[c]	58.80±11.14	27.96/87.45	347	4.65	**0.032**
Calmness (MDBF)[c]	69.55±11.55	19.73/98.59	347	4.09	**0.044**
Alone (alone/not alone)[d]	33/84	NA	347	0.83	0.363
Don't like the company[c]	10.54±9.74	0.24/69.12	347	1.40	0.237
Rather be alone[c]	14.96±13.58	0.17/66.17	347	2.48	0.117
Positive event appraisal[c]	23.64±13.84	1.5/75.71	347	1.86	0.174
Negative event appraisal[c]	11.29±7.97	0.67/55.00	347	0.00	0.982
Affective (in)stability (valence MSSD)	275.05±211.71	1.07/1448.43	347	0.44	0.508
E-diary prompts per day	12.51±1.79	7/20	347	-0.084	0.118
E-diary Compliance (%)[e]	81.59±14.26	32.93/100	347	-0.088	0.105

For details on the psychological questionnaires including acronyms, see *Supplemental Table S2*. Abbreviations: M = mean, SD = standard deviation, n = number of participants with available data, MSSD valence = mean square of successive differences of valence ratings.

[a]Spearman's correlation, partial spearman's correlation controlling for sex, age, SES, education; F-values from multilevel analysis (controlling for time of the day and time of the day-squared, level 1, and for sex, age, SES, education, and daily hassles, level 2, see Methods section and sMethods for details).

[b]Aggregation of EMA indices within and between subjects for use for sample description only;

[c]mean/day/participant, [d]number of prompts participants reported being alone out of all prompts across 7 days of measurement, mean;

2.2.6. Supplemental Information

Participants. The initial sample of young adults (N=310, 24.02 ±2.83 [mean ± SD]) was recruited via the local population registry from local communities in the Rhine-Neckar metropolitan area, taking into account stratification of the population according to age, sex and nationality. The study population was enriched for the presence of ACE. Additional 41 (38.26 ±10.12 [mean ± SD]) individuals were recruited from August 2019 to October 2020 via advertisement from the same neighborhoods using the same enrollment criteria over-sampling for ACE. (See Supplemental **Table S2.7** for sample overview).

Socio-demographic and psychological inventory measures. All participants that were admitted to the study completed a comprehensive battery of sociodemographic measures and psychosocial assessment comprising an established multidimensional aggregated index of socioeconomic status (SES (Lampert et al., 2013)), personality (Borkenau & Ostendorf, 2008), trait anxiety (Laux et al., 1981), loneliness (Döring & Bortz, 1993), perceived daily hassles (Traue et al., 2000), self-efficacy (Jerusalem & Schwarzer, 1992), sense of coherence (Hannöver et al., 2004), optimism (Herzberg et al., 2006), perceived wellbeing (Topp et al., 2015), satisfaction with life (Glaesmer et al., 2011), coping strategies (Carver, 1997), perceived social support (Ralf Schwarzer & Schulz, 2003). The detailed overview of the self-reported battery is published elsewhere and given in the Supplemental **Table S2.8** (Berhe et al., 2022).

To assess adverse childhood experiences we used Childhood trauma screener (CTS (Glaesmer et al., 2013)). The CTS is a short self-report retrospective inventory with a total of 5 items developed from the German version of the “Childhood Trauma Questionnaire” (CTQ, 28 items) (Bernstein, Fink, Handelsman, & Foote, 1998). Based on a large population sample on each of the 5 subscales of the CTQ was selected the item that best represented the dimension in terms of selectivity, explanation of variance and practicability. With high internal consistency (α=0.757), CTS is a reliable and economical screener for recording of adverse childhood experiences and recommended in diagnostic processes (Bernstein et al., 1998; Glaesmer et al., 2013). Thus, CTS is a 5-point Likert scale ranging from “Never true” to “Very often true”. The CTS contains five subscales, which measure three types of abuse and two types of neglect: namely emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN). The score for each scale is a sum of scores of specific items, and the total score of the CTS is a sum of scores on all scales (Glaesmer et al., 2013).

Ecological momentary assessments

Hardware. The 7-days EMA protocol included smartphone-based e-diary assessments (Motorola Moto G, Motorola Mobility), GPS-based location tracking, as well as accelerometry (movisens Move-II or movisens Move-III, movisens GmbH). We employed a flexible time and location-based sampling scheme for e-diary assessments. That is, each participants received between 9-23 prompts/day between 7:30 and 22:30 (fixed prompts at 8:00 and 22:20), with a minimum interval of 40 min and a maximum interval of 100min (Gan et al., 2021; Reichert et al., 2020; Tost et al., 2019). Assessments were done via a Smartphone App using the software movisensXS, version 0.6.3658 (movisens GmbH, https://xs.movisens.com).

Measures. In addition to our main outcome variables, measuring momentary affective wellbeing (indexed by valence, calmness and energetic arousal), we acquired, at each prompt, e-diaries quantifying momentary social contact, social (an)hedonia (Collip et al., 2011; Gan et al., 2021) and appraisals of positive and negative events (Wichers et al., 2009). We assessed momentary social contact with a dichotomous item asking subjects whether they are currently alone or in the company of others. In the case if in company, we additionally asked the participants to rate, via visual analogue scales (score range of 0 to 100), the liking of the company (*"When you think about the people who surround you right now, to what extent is the following statement true? I don't like these people*!*"*), and the degree to which the subjects would prefer to be alone (*"When you think about the people who surround you right now, to what extent is the following statement true? I'd rather be alone!*") (Collip et al., 2011; Gan et al., 2021). We assessed positive and negative event appraisal with two coverage items *("Have you experienced one or more negative events since the last query? How intense was the most important negative event? Have you experienced one or more pleasant events since the last query? How intense was the most important pleasant event?")* that the participants rated using visual analogue scales with score ranges of 0 – 100 ('no event'=0 to very intense' =100).

Multilevel modeling of e-diary assessments. To test our main hypothesis, we estimated the effect of adverse childhood experience (indexed by CTS) on affective valence by conducting random-intercept multilevel model analysis in SAS (version 9.4., SAS Institute Inc., Cary, NC, USA), thereby nesting e-diary assessments (level 1) within participants (level 2) (Bolger & Laurenceau, 2013). Besides our main predictor CTS (log-transformed), we added the level-1 predictors time of the day and time of the day squared (transformed to the daily study start time at 7:30 AM) to the model to control for known time-of-day effects

on affective valence (Reichert et al., 2017; Tost et al., 2019). Furthermore, we included age, gender, SES and years of education as level-2 covariates. Following established procedures (Bolger & Laurenceau, 2013), we incorporated random effects for both the intercept and each predictor and subsequently deleted non-significant random effects. Equation S1 details the full model below using a single equation representation.

Equation (S1):

$$Y(\boldsymbol{affective\ valence})_{ij} = \beta_{00} + \beta_{01} * \boldsymbol{CTS}_j + \beta_{02} * age_j + \beta_{03} * sex_j + \beta_{04} * SES_j + \beta_{05} * educ_j + \beta_{10} * time\ of\ day_{ij} + \beta_{20} * time\ of\ day_{ij}^2 + u_{0j} + u_{1j} * time\ of\ day_{ij} + r_{ij}$$

Y_{ij} represents the level of affective valence in person *j* at time *i*. Within-subject effects are modeled on level 1, represented by each participant's (subscript *j*) value entries for every prompt (subscript *i*). Beta coefficients denote the intercept, the effect of our main predictor CTS (log-transformed), of age, sex, SES, and education, and the effects of the level-1 covariates (time of the day, time of the day squared). Random effects, i.e., individual variation around the sample mean, are represented by u_{0j} for the intercept and u_{1j} – for time of the day. In the same vein, we set up two other separate models with calmness and energetic arousal as an outcome variable. For exploratory analysis, we further computed analogous models for e-diary outcomes reflecting additional daily-life processes (see above, and *Methods* and **Table 2.2** in the main text).

Supplemental Table S2.7: Sample overview

	Total Sample (N=351)			PEZ basic Cohort (N=310)			Enriched Sample (N=41)		
	M ± SD / count	min/max	n	M ± SD / count	min/max	n	M ± SD / count	min/max	n
Demographic data									
Age (year)	24.80 ±6.54	18.11/56.02	351	24.02 ±2.83	18.11/28.46	310	38.26 ±10.12	20.14/55.02	41
Sex (male/female)	162/189	N/A	351	141/169	N/A	310	21/20	N/A	41
Education (years)	13.27 ± 1.89	8/16	350	13.07 ± 1.85	8/16	310	14.84 ±2.96	7.20/19.20	40
Socioeconomic status (SES)	14.53± 3.16	6.20/21.00	350	14.49 ± 3.18	6.20/21.00	310	14.72 ±1.60	11.00/16.00	40

Supplemental Table S2.8: Inventory measures

Name	Outcome measure(s)	Details
Socioeconomic status assessment of the German Health Update 2009 (GEDA)(Lampert et al., 2013)	Socioeconomic status	Multidimensional aggregated index of status-constituting dimensions (education, occupation, income)
NEO Five-Factor Inventory(Borkenau & Ostendorf, 2008)	Measure of the five domains of personality (Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness)	60 items (12 per trait). 5-point Likert scale
Childhood Trauma Screener (CTS)(Glaesmer et al., 2013)	Retrospective self-rating of adverse childhood experiences	5 items, 5-point Likert scales
State-Trait Anxiety Inventory (STAI-T)(Laux et al., 1981)	Trait anxiety	20 items, 4-point Likert scales
UCLA Loneliness Scale (UCLA)(Döring & Bortz, 1993)	Perceived loneliness	20 items, 4-point Likert scales
Alltagsbelastungsfragebogen (ABF)(Traue et al., 2000)	Daily hassles	58 items, 8-point Likert scales
Brief-COPE(Carver, 1997)	Maladaptive coping strategies Adaptive coping strategies	28 items, 4-point Likert scales
WHO-5 Well-Being Index(Topp et al., 2015)	Perceived current mental well-being	5 items, 6-point Likert scales
Satisfaction with Life Scale (SWLS)(Glaesmer et al., 2011)	Global cognitive judgments of satisfaction with life	5 items, 7-point Likert scales
Revised Life Orientation Test (LOT-R)(Herzberg et al., 2006)	Dispositional optimism	10 items, 5-point Likert scales
Sense of Coherence Scale (SOC-29)(Hannöver et al., 2004)	Dispositional sense of coherence	29 items, 5-point Likert scales
General Self-Efficacy Scale (GSES)(Jerusalem & Schwarzer, 1992)	Generalized belief in the own ability to control environmental challenges	10 items, 4-point Likert scales
Berlin Social Support Scale (BSSS)(Ralf Schwarzer & Schulz, 2003)	Perceived social support	8 items, 4-point Likert scales

Supplemental Table S2.9: Relationships of the five CTS subdomains to the psychosocial measures

	Relation to CTS: emotional neglect		**Relation to CTS: physical abuse**		**Relation to CTS: emotional abuse**		**Relation to CTS: sexual abuse**		**Relation to CTS: physical neglect**	
	Spearman's ρ	*p* value	**Spearman's ρ**	*p* value	**Spearman's ρ**	*p* value	**Spearman's ρ**	*p* value	**Spearman's ρ**	*p* value
Demographic data[a]										
Age (year)	**0.158**	**0.003**	**0.182**	**0.001**	0.072	0.178	**0.121**	**0.023**	**0.165**	**0.002**
Sex (male/female)	**0.171**	**0.001**	0.055	0.303	-0.057	0.289	**-0.115**	**0.032**	0.048	0.367
Education (years)	0.052	0.336	0.091	0.090	0.040	0.452	0.085	0.112	0.009	0.870
Socioeconomic status (SES)	**-0.169**	**0.002**	-0.087	0.104	**-0.134**	**0.012**	-0.81	0.131	**-0.156**	**0.004**
Personality[b]										
NEO-FFI Openess (mean)	0.026	0.636	0.013	0.807	0.074	0.178	0.076	0.165	-0.049	0.368
NEO-FFI Agreeableness (mean)	**-0.153**	**0.005**	0.004	0.943	**-0.141**	**0.010**	-0.045	0.407	-0.011	0.840
NEO-FFI Conscientiousness (mean)	-0.063	0.246	**-0.121**	**0.026**	-0.075	0.170	-0.106	0.052	-0.052	0.344
NEO-FFI Extraversion (mean)	**-0.277**	**<0.001**	0.065	0.234	-0.080	0.143	-0.073	0.184	**-0.117**	**0.032**
NEO-FFI Neurotizismus (mean)	**0.151**	**0.006**	0.006	0.918	**0.210**	**<0.001**	0.041	0.455	0.060	0.270
Risk Factors										
Trait anxiety (STAI-T, sum)	**0.276**	**<0.001**	0.042	0.437	**0.251**	**<0.001**	0.081	0.129	**0.156**	**0.003**
Loneliness (UCLA, mean)	**0.374**	**<0.001**	**0.120**	**0.025**	**0.218**	**<0.001**	0.065	0.226	**0.278**	**<0.001**
Daily Stress (ABF)	0.096	0.099	0.036	0.533	**0.175**	**0.002**	0.044	0.454	-0.012	0.843
BCOPE-maladaptive coping	**0.126**	**0.019**	0.048	0.378	**0.208**	**<0.001**	0.062	0.252	**0.105**	**0.052**
Protective Factors										
Mental wellbeing (WHO-5, sum)	**-0.105**	**0.050**	-0.019	0.729	**-0.183**	**0.001**	-0.011	0.841	-0.046	0.397
Satisfaction with life (SWLS)	**-0.297**	**<0.001**	**-0.177**	**0.001**	**-0.208**	**<0.001**	**-0.139**	**0.010**	**-0.245**	**<0.001**
Optimism (LOT-R, optimism sum)	**-0.243**	**<0.001**	-0.038	0.487	**-0.161**	**0.003**	-0.077	0.154	**-0.146**	**0.007**
Sense of coherence (SOC, sum)	**-0.261**	**<0.001**	0.009	0.862	**-0.270**	**<0.001**	-0.007	0.897	**-0.203**	**<0.001**
Self-efficacy (SWE, sum)	**-0.109**	**0.043**	0.037	0.491	**0.098**	**0.067**	-0.031	0.558	**-0.107**	**0.046**
Perceived social support (BSSS, sum)	**-0.336**	**<0.001**	**-0.143**	**0.007**	**-0.224**	**<0.001**	0.012	0.828	**-0.230**	**<0.001**
BCOPE-adaptive coping	**-0.179**	**0.001**	**-0.120**	**0.026**	-0.048	0.379	-0.046	0.392	**-0.177**	**0.001**

For details on the psychological questionnaires including acronyms, see *Supplemental Table S2*.

[a] Spearman's correlation;

[b] Partial spearman's correlation controlling for sex, age, SES, education;

Supplemental Table S2.10: Multilevel analysis results, main models

Dependent variable	**Predictor** *Fixed effects*	**Beta coefficient**	**Standard Error**	***T value* (df)**	***P value***
Valence	Intercept	93.12	6.74	13.81 (337)	<0.001
	Time (hours)	0.61	0.08	7.19(11E3)	<0.001
(0-100)	Time-squared (hours^2)	-0.02	0.00	-4.09(24E3)	<0.001
	Gender: male	-3.34	1.25	-2.67(337)	0.008
	Age	0.11	0.12	0.95(336)	0.345
	SES	-0.23	0.21	-1.11(336)	0.269
	Education	-0.07	0.37	-0.19(336)	0.848
	Adverse childhood experience	**-22.44**	**5.81**	**-3.86(337)**	**<0.001**
Energetic Arousal	Intercept	51.24	8.50	6.03(335)	<0.001
	Time (hours)	5.35	0.13	41.86(2661)	<0.001
	Time-squared (hours^2)	-0.36	0.01	-54.31(24E3)	<0.001
(0-100)	Gender: male	-2.06	1.58	-1.31(335)	0.191
	Age	0.64	0.14	4.63(333)	<0.001
	SES	-0.32	0.26	-1.24(334)	0.217
	Education	0.26	0.47	0.55(334)	0.584
	Adverse childhood experience	**-21.20**	**7.32**	**-2.90(334)**	**0.004**
Calmness	Intercept	91.38	6.91	13.23(340)	<0.001
	Time (hours)	-0.61	0.09	-6.94(11E3)	<0.001
(0-100)	Time-squared (hours^2)	0.06	0.01	10.49(24E3)	<0.001
	Gender: male	-1.34	1.28	-1.05(339)	0.296
	Age	0.10	0.11	0.87(338)	0.383
	SES	-0.16	0.21	-0.75(338)	0.452
	Education	-0.28	0.38	-0.74(338)	0.462
	Adverse childhood experience	**-20.54**	**5.95**	**-3.45(339)**	**0.006**

Abbreviations: SES = socioeconomic status, df = degree of freedom, All reported *p* values for beta coefficients are two-sided and derived from the t-statistics of the multilevel model.

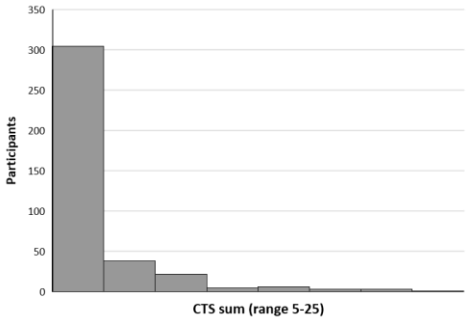
Supplemental Table S2.11: Multilevel analysis results, exploratory models

Dependent variable	**Predictor** ***Fixed effects***	**Beta coefficient**	**Standard error**	***T value* (df)**	***P value***
Model 1: Affective Instability	Intercept	714.06	149.15	4.79(331)	<0.001
	Time (hours)	7.71	4.51	1.71(19E3)	0.087
	Time-squared (hours^2)	-0.32	0.27	-1.23(22E3)	0.221
	Gender: male	-29.26	21.82	-1.34(322)	0.181
	Age	-0.47	1.92	-0.24 (318)	0.807
	SES	0.72	3.56	0.20(321)	0.840
	Education	-1.99	6.44	-0.31(320)	0.758
	Valence	-5.22	0.98	-5.31(325)	<0.001
	Adverse childhood experience	-36.81	103.13	-0.36(325)	0.721
Model 2: Don't like the company (0-100)	Intercept	-0.38	6.50	-0.06(297)	0.953
	Time (hours)	0.15	0.13	1.15(8626)	0.5248
	Time-squared (hours^2)	-0.04	0.01	-4.66(12E3)	<0.001
	Gender: male	2.21	1.19	1.86(295)	0.064
	Age	-0.09	0.11	-0.83(309)	0.405
	SES	0.15	0.20	0.78(294)	0.433
	Education	0.19	0.36	0.53(298)	0.597
	Adverse childhood experience	8.79	5.57	1.58(297)	0.116
Model 3: Rather be alone (0-100)	Intercept	-7.54	8.93	-0.84(319)	0.399
	Time (hours)	0.37	0.16	2.27(7795)	0.023
	Time-squared (hours^2)	-0.05	0.01	-5.32(12E3)	<0.001
	Gender: male	2.15	1.63	1.31(317)	0.190
	Age	0.08	0.15	0.51(332)	0.608
	SES	0.12	0.27	0.44(317)	0.662
	Education	0.38	0.49	0.77(320)	0.441
	Adverse childhood experience	15.24	7.66	1.99(319)	0.047
Model 4: Positive Event Appraisal (0-100)	Intercept	19.24	7.61	2.53(334)	0.012
	Time (hours)	1.40	0.15	9.39(13E3)	<0.001
	Time-squared (hours^2)	-0.05	0.01	-4.97(24E3)	<0.001
	Gender: male	-1.90	1.41	-1.34(333)	0.179
	Age	0.01	0.13	0.02(330)	0.988
	SES	0.21	0.23	0.90(334)	0.367
	Education	0.15	0.42	0.36(331)	0.716
	Adverse childhood experience	-6.65	6.56	-1.01(334)	0.312
Model 5: Negative Event Appraisal (0-100)	Intercept	4.17	4.39	0.95(319)	0.343
	Time (hours)	0.03	0.10	0.27(16E3)	0.783
	Time-squared (hours^2)	-0.01	0.01	-0.70(24E3)	0.485
	Gender: male	-0.30	0.81	-0.36(317)	0.716
	Age	0.11	0.07	1.58(313)	0.115
	SES	0.07	0.13	-0.53(317)	0.600
	Education	-0.10	0.24	-0.40(315)	0.688
	Adverse childhood experience	6.29	3.78	1.66(318)	0.098

Model 6:	Intercept	1.52	0.12	2.14(314.2)	<0.001
Being Alone	Time (hours)	0.03	0.00	10.36(10124)	<0.001
	Time-squared (hours^2)	-0.00	0.00	-7.33(23670)	<0.001
(1/0)	Gender: male	-0.03	0.02	-1.36(313.2)	0.176
	Age	0.00	0.00	-1.64(310)	0.102
	SES	0.00	0.00	0.23(311.8)	0.815
	Education	0.01	0.01	1.24(313.6)	0.218
	Adverse childhood experience	-0.15	0.11	-1.44(313.8)	0.151

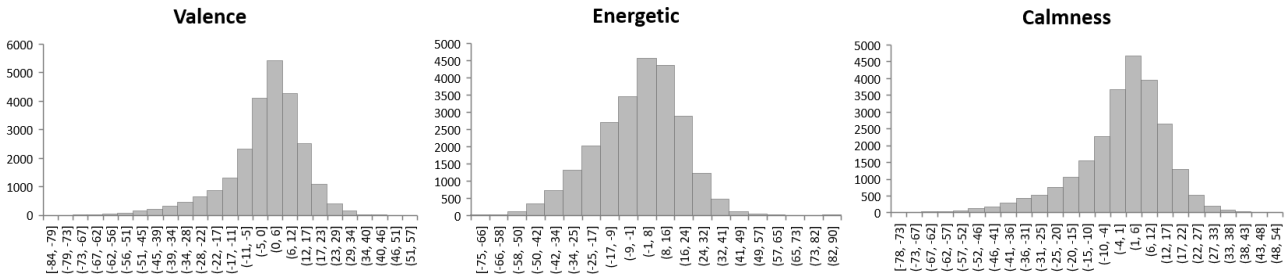
Abbreviations: See legend *Supplemental Table 2.10*.

Supplemental Figure S2.3: Distribution of childhood trauma experience measured by CTS.



The histogram depicts the distribution (y-axis - frequency) of childhood trauma experience (x-axis - CTS sum), indicating the skewed distribution of the measure.

Supplemental Figure S2.4: Distribution of level-1 residuals of the main hypothesis-testing multi-level models (valence, energetic, and calmness) (see Table S3)



The histogram depicts the distribution (y-axis shows the frequency) of level-1 residuals (x-axis), which measure deviations from the conditional mean (conditional residuals) derived from our multi-level models (see Methods, section “Data analysis – ambulatory assessment”). Visual inspection confirmed that there was no serious deviation from normal distribution, indicating that our multi-level model is well suited to deal with the given data structure in this sample.

2.3. Study 3: Lack of amygdala habituation to negative emotional faces in alcohol use disorder - and the relation to adverse childhood experiences[3]

2.3.1 Abstract

Introduction. Aberrant limbic circuit reactivity to negative stimuli might be related to alterations in emotion processing and regulation in alcohol use disorder (AUD). The current study tested for the first time in AUD the hypothesis of aberrant amygdala habituation to repeated aversive stimuli – a robust and reliable neuroimaging marker for emotion processing. We explored the link between deficits in habituation to adverse childhood experience (ACE), a common risk factor for impaired emotion regulation and AUD.

Methods. AUD individuals (N=36) and healthy controls (HC; N=26) participated in an observational case-control functional magnetic resonance imaging (fMRI) study. An established habituation index was used to investigate processing of aversive emotional faces of the amygdala.

Results. AUD individuals showed an overall deficit in amygdala habituation (right: t=4.26, p_{FWE}=0.004; left: t=4.79, p_{FWE}≤0.001). Amygdala habituation was significantly related to increased exposure to ACE in HC (t=3.88, p_{FWE}=0.012), whereas this association was not observed in AUD individuals (T=1.80, p_{FWE}=0.662). Further, a significant association between higher alcohol consumption and reduced amygdala habituation (right: R2=-0.356, F=8.736, p=0.004; left: R2=-0.309, F=6.332, p=0.015) was observed.

Conclusion. We found novel evidence for neural alterations in emotion processing in AUD individuals, indexed by deficient amygdala habituation to negative emotional content. We replicated a prior report on a link between ACE and amygdala habituation, a well-established environmental risk factor for mental disorders and emotion dysregulation, in our control sample. Additionally, deficient amygdala habituation related to the amount of alcohol consumption in the overall sample might indicate a short-term substance effect.

[3] **Published as**: Gerhardt, S.*, Berhe, O.*, Moessnang, C., Horning, M., Kiefer, F., Tost, H.*, & Vollstädt‐Klein, S*. (2023). Lack of amygdala habituation to negative emotional faces in alcohol use disorder and the relation to adverse childhood experiences. *Addict. Biol*, 28(1), e13251

2.3.2. INTRODUCTION

Alcohol use disorder (AUD) is a major health problem and socioeconomic burden (Peacock et al., 2018). Impairments in emotion processing and regulation play prominent roles in substance use disorders where negative emotional states, i.e., anxiety or dysphoria, might maintain the disorder through instances of relapse (Koob & Volkow, 2010). Impairments in emotion processing in AUD precede the development of the disorder (Kober, 2014; Le Berre, 2019; Petit et al., 2015) and compromise abstinence and treatment processes (Berking et al., 2011; Le Berre, 2019). The ability to tolerate negative emotions is one important predictor of relapse in AUD (Berking et al., 2011) and includes a process of habituation to such aversive experiences, e.g., via mindfulness-based practices (Witkiewitz, Bowen, Douglas, & Hsu, 2013). Negative urgency, the impulsive risk-taking during extreme negative emotional states, is positively related to alcohol craving and negative emotional reactivity, which consequently leads to increased alcohol consumption (VanderVeen et al., 2016). Additionally, not only intra- but also interpersonal emotional problems might further contribute to the maintenance of the disorder (Kopera et al., 2018).

Another line of research has shown that adverse childhood experiences (ACE) are associated with an increased likelihood of substance use in adulthood (Afifi, Henriksen, Asmundson, & Sareen, 2012; Afifi et al., 2020; Anda et al., 2006; Cutajar et al., 2010; Kirsch, Nemeroff, & Lippard, 2020; Oberleitner, Smith, Weinberger, Mazure, & McKee, 2015; Schückher, Sellin, Fahlke, & Engström, 2018; Turner & Lloyd, 2003). According to the stress coping model of addiction, high (early) life stress and lack of coping resources predispose an individual to use alcohol as a way of coping with negative emotions and traumatic events (Redman, 2008; Wills, 1990). Indeed, behavioral emotion dysregulation was observed to be a potential mediator between ACE and substance use disorder (Wolff et al., 2016). Further underlining the observed relation between ACE, emotion dysregulation, and SUD, attention and interpretation biases for negative emotional faces following ACE were reported (Gibb, Schofield, & Coles, 2009).

The amygdala as a central neural hub for the regulation of emotion perception and processing (Davis & Whalen, 2001; Gilpin, Herman, & Roberto, 2015; Swartz et al., 2015) is of particular relevance for both substance use disorder (Koob, 2003) and ACE. Reduced neural responses in the amygdala were not only reported in individuals with

AUD (Marinkovic et al., 2009), but also in offspring of individuals with AUD (Glahn, Lovallo, & Fox, 2007), which highlights the involvement of this brain region in AUD-driven emotion processing impairments. Likewise, neuroimaging studies in individuals with ACE have shown decreased amygdala volume, increased limbic connectivity at rest, hyperreactivity of the amygdala, and a deficit in amygdala habituation (Bilek et al., 2019; Dean, Kohno, Hellemann, & London, 2014; Hanson et al., 2015; Marusak, Martin, Etkin, & Thomason, 2015; Swartz et al., 2015; Tottenham et al., 2010).

Of particular interest in the context of emotion regulation is neural habituation – the rapid and adaptive decline of responsivity to repeated stimuli (Plichta et al., 2014). Habituation is a basic learning mechanism helping in rapidly and adaptively filtering irrelevant and repeated sensory information in the environment. Deficits to this end, however, lead to inappropriate allocation of processing resources to stimuli with no potential relevance for survival (Ramaswami, 2014). This trans-diagnostic risk factor for psychopathology further suggests a deficit in neural plasticity (Ramaswami, 2014). Aberrant amygdala habituation to emotional stimuli has been linked to various psychiatric conditions, such as social anxiety disorder, borderline personality disorder, autism spectrum disorder, schizophrenia, psychosis, and post-traumatic stress disorders (PTDS) (Avery & Blackford, 2016; Avery et al., 2021; Blackford et al., 2013; Hare et al., 2008; Y. J. Kim et al., 2019; Tam et al., 2017). It has also been linked to ACE (Bilek et al., 2019; Y. J. Kim et al., 2019), which facilitates the development and modulates the course subsequent mental disorders.

Despite the biological relevance of this phenomenon, this fundamental neural phenotype has not previously been studied in individuals with AUD, even though neural and neurobiological sensitization (Volkow, Wang, Fowler, & Tomasi, 2012) and failed habituation (Di Chiara, 2000) are known mechanisms in substance use disorder. Evidence of aberrant amygdala habituation in AUD could, however, provide an explanation of the biological underpinnings of disrupted emotion regulation in AUD and open an avenue to probe the link to environmental risk factors, such as ACE.

Consequently, this project aims (1) to examine neural habituation patterns in individuals with AUD when processing aversive emotional stimuli and (2) to investigate the potential relationship of the phenotype to ACE, a well-known risk factor for AUD. To this end, we examined individuals with varying levels of severity of AUD and ACE, as well as healthy controls (HC) with no or minimal consumption of alcohol and no or

minimal severity of ACE. We hypothesize (1) that amygdala habituation is reduced in individuals with AUD compared to HC. Additionally, we hypothesize (2) that this neural phenotype will be related to the severity of ACE in individuals with AUD.

2.3.3. Methods

Procedure and participants

Data was collected at the Central Institute for Mental Health (CIMH) in Mannheim, Germany between January 2019 and March 2021. The overall study of which this data derived from was pre-registered at ClinicalTrials.gov (identifier NCT03758053). The local Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, approved the study procedure (approval #2018-560N-MA). All participants provided written informed consent and received financial compensation.

HC and individuals with AUD were recruited via public announcements within the local community of Mannheim, Germany. Additionally, AUD patients from our clinic were examined. Following a short telephone screening to assess study eligibility, data was acquired at two time points: at the first baseline appointment, written informed consent was obtained, a drug and pregnancy screening was performed, breath alcohol was measured, sociodemographic data was collected, and the Structured Clinical Interview for the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (SCID-IV) (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) as well as a baseline drinking interview (FORM-90 interview) (W. R. Miller & Del Boca, 1994) were conducted. AUD-criteria were assessed according to DSM-5. Participants were between 18 and 65 years of age and. Individuals belonged to the AUD group if they fulfilled the clinical diagnosis of AUD or reported heavy drinking (alcohol/day ≥ 40 g (female), 60 g (male) on min. 5 days/week); a maximum of 28 days of abstinence was tolerated. Participants were excluded from the study if they reported MRI exclusion criteria, had a severe mental disorder (e.g., bipolar disorder, schizophrenia; currently severe depression, PTSD, anxiety or eating disorder), a neurological condition, or a history of severe head trauma. They were also excluded in case of pregnancy, severe somatic condition or withdrawal symptoms, treatment with psychotropic medication (except for withdrawal medication until 3 days max prior to study inclusion; antidepressants) or positive drug urine screening. HC were excluded if they reported a risky amount of alcohol consumption (alcohol/day ≥ 12 g (female), 24 g (male) on up to 5 days/week). Regarding ACE severity, a five-item screening questionnaire

representing all five subtypes of ACE (Grabe et al., 2012) was applied (range 5 – 25). HC were excluded if they reported more than minimal severity of ACE (cut-off score of 8 (2 *1 + 3*2)).

Participants completed several questionnaires using the web-based software EvaSys (Electric Paper Evaluationssysteme GmbH, Lueneburg, Germany). These included the Alcohol Dependence Scale (ADS) (Doyle & Donovan, 2009) and Childhood Trauma Questionnaire (CTQ), a 28-item self-report questionnaire (Bernstein et al., 1998). The reliable (0.87 < alpha < 0.95) CTQ assesses five sub scales of ACE, namely emotional, physical, and sexual abuse as well as emotional and physical neglect. Items are answered on a 5-point Likert scale (‘not at all’ to ‘very often’) leading to sum scores between 5 (none) and 25 (severe) for each sub scale, respectively (Wingenfeld et al., 2010). For the functional magnetic resonance imaging (fMRI) assessment, all smokers had to abstain from cigarettes for at least 90 minutes. Drinking data since the baseline appointment (maximum 14 days before the fMRI assessment) was assessed using a short version of the Form-90 (W. R. Miller & Del Boca, 1994).

Neuroimaging paradigm

Participants performed a well-established Face Matching paradigm that robustly recruits the cortico-limbic circuitry **Figure 1.4** (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002) and allows for reliable assessment of amygdala habituation (Plichta et al., 2014). In brief, participants were asked to match a face or a shape (e.g., rectangle) to one of two additional faces or shapes, respectively (Supplementary Figure S1). The participants were instructed to select the corresponding face or shape as quickly and precisely as possible. All stimuli were presented in black and white. The Presentation® software (Version 18.1.0, Neurobehavioral Systems, Inc., Albany, CA, USA) was used to implement and present the paradigm and all participants responded using a four-button response box (Current Designs, Philadelphia, PA, USA) by pressing left or right with the thumb of their dominant hand. The paradigm consisted of one run of 4:44 minutes. A block design of alternating form (4 blocks à 6 trials) and aversive faces (4 blocks à 6 trials) conditions with a preceding announcement was used.

fMRI acquisition and preprocessing

Functional neuroimaging data was collected using a 3T whole-body tomograph (Prisma Fit, Erlangen, Germany). A total of 88 T2*-weighted transversal echo planar images (EPI) were acquired, covering the entire brain (TR = 3.1 s, TE = 30 ms, flip angle = 90°, 51 slices, slice thickness: 2.5 mm, 0 mm gap, voxel size 2×2×2.5 mm, FOV 192×192 mm2, 96×96 in-plane resolution, 64-channel head coil). Fieldmaps were acquired to correct for geometric distortions due to magnetic field inhomogeneities (TR = 520 ms, TE =4.92 ms / 7.38 ms, flip angle = 60°, voxel size = 2×2×2.5 mm). Additionally, a 4:42 min anatomical scan was performed (T1-weighted 3D MPRAGE (Magnetization Prepared- Rapid Gradient Echo) dataset, 192 sagittal slices, TR = 2 s, TE = 3.03 ms, TI = 900 ms, flip angle = 9°, slice thickness: 1 mm, 0.5 mm gap, voxel size 1×1×1.5 mm, FOV 256×256 mm2, 256x256 in-plane resolution).

Preprocessing was performed using SPM12 (The Wellcome Centre for Human Neuroimaging, at University College, London, UK). The first 4 volumes of each run were excluded to avoid artefacts due to magnetic saturation effects. The remaining 84 scans were corrected for residual geometric distortion using the acquired magnetic field map. Slice timing, spatial realignment, and normalization to an MNI template (Montreal Neurological Institute, Quebec, Canada) were conducted. The resulting images were smoothed using an isotropic Gaussian kernel of 8 mm full width at half maximum. Quality checks were performed and individuals with excessive head movement or other artefacts were excluded from subsequent analyses.

Statistical analyses

In total, *N* = 69 participants participated in the study. Due to technical problems (*N* = 2), drop-outs (*N* = 3) and heavy movement in the scanner (*N* = 1), N = 27 healthy controls and N = 36 individuals with AUD were included in the final analyses. Psychometric data was analyzed with SPSS (Statistics for Windows, Version 27.0. IBM Corp., Armonk, NY). Sum scores were computed for all questionnaires according to their manuals. Descriptive analyses and chi square tests or t-test were applied to describe the sample and perform statistical analyses regarding group differences. Behavioral performance in the face matching task was assessed as response time and accuracy (percentage of correct hits) for each condition.

The analyses of MRI data consisted of a two-level procedure. As a first-level analysis, a general linear model was fitted for each participant for both experimental conditions,

faces and shapes, with each block as a regressor which was convolved with the standard SPM hemodynamic response function. Six head motion parameters from the realignment step were included as nuisance covariates. A high-pass filter with a cut-off frequency of 1/262 Hz was used and first-order autoregressive modeling was administered to correct for temporal autocorrelations. To estimate amygdala habituation, we employed an established habituation index, which is the difference between the first and the second half of the experiment for the faces condition ([block 1 + block 2] > [block 3 + block 4]) (Bilek et al., 2019; Wiggins, Swartz, Martin, Lord, & Monk, 2014).

The resulting contrast images were subjected to a second-level univariate analysis of variance (ANOVA) to assess the effect of group (HC, AUD) as a between-subject factor while correcting for sex. Further, we set up an analogous univariate ANOVA model with an additional interaction term (e.g., group x CTQ sum score) to test for potential group-specific associations between ACE and neural habituation. Based on our a priori hypothesis, we defined the bilateral amygdala as an a priori region of interest (ROI) by merging the left and right amygdala labels from the Automated Anatomical Labelling (AAL) (Tzourio-Mazoyer et al., 2002). Statistical significance was assessed using small volume correction at a threshold of $p < 0.05$, family-wise error (FWE) corrected for multiple comparisons within the ROI.

2.3.4. Results

Sample, sociodemographic and psychological data assessments

HC (N = 27) and individuals with AUD (N = 36) did not differ significantly regarding age ($T(61) = 1.05$, $p = 0.299$), however, the percentage of males was higher in the AUD group (67 %) than in the HC group (41%; $\chi^2(1) = 4.20$, $p = 0.040$). As expected, the AUD group had a higher overall score of the CTQ ($p = 0.007$) and higher scores in the severity of AUD and the amount of alcohol consumed 12 weeks prior to examination (see **Table 2.3** for details).

MRI

fMRI task performance. Participants' response data did not differ between conditions. No significant group differences were found in the percentage of correct responses ($p > 0.05$) and reaction time in the faces condition ($p > 0.05$) (see **Table 2.3** for details).

Table 2.3: Sample description of healthy individuals and individuals with AUD.

Characteristics	HC Mean/SD	AUD Mean/SD	Statistics
N	27	36	
Sex (male:female)	11:16	24:12	**$\chi^2(1) = 4.20$, p = 0.040**
Age (years)	36.9 (12.5)	40.3 (12.6)	T(61) = 1.05, p = 0.299
Marital status (married/divorced/single)	6:3:18	5:8:23	$\chi^2(2) = 1.72$, p = 0.423
Living (alone:together with others)	6:21	15:21	$\chi^2(1) = 2.63$, p = 0.105
Years of education	15.7 (2.3)	14.4 (3.0)	T(61) = -1.84, p = 0.071
Smoker (yes:no)	4:23	10:26	$\chi^2(1) = 1.50$, p = 0.221
CTQ			
Overall (sum score)	31.3 (7.7)	39.3 (14.4)	**T(56.1) = 2.82, p = 0.007**
ADS (sum score)	2.3 (2.4)	11.9 (6.6)	**T(46.4) = 7.97, p < 0.001**
FORM-90 at baseline			
Total amount of alcohol (g)	360 (367)	7231 (6690)	**T(35.3) = 6.15, p < 0.001**
fMRI emotional faces task			
Reaction-times faces (ms)	1089.2 (443)	1265.0 (308)	T(61) = 1.86, p = 0.068
Reaction-times forms (ms)	1212.8 (442)	1222.0 (265)	T(61) = 0.10, p = 0.919
Correct hits faces (%)	91.5 (27)	99.3 (2)	T(26.2) = 1.52, p = 0.139
Correct hits forms (%)	87.8 (24)	95.9 (5)	T(27.6) = 1.76, p = 0.090

Note: SD = Standard Deviation; g = grams; n = sample size; ms = milliseconds; AUD = alcohol use disorder; ADS = Alcohol Dependence Scale; CTQ = Childhood Trauma Questionnaire; FORM-90 = amount of alcohol consumption over the last 90 days. Significant group differences are highlighted in bold.

MRI results. Group comparison of AUD and HC revealed a lack of habituation in the AUD group within the right amygdala (t = 4.26, p_{FWE} = 0.004; **Figure 2.5A**) and the left amygdala (t = 4.79, $p_{FWE} \leq 0.001$). Specifically, we observed a rapid decline in amygdala activation across time within the ROI in the HC group (right amygdala: t = 3.97, p_{FWE} = 0.009, left amygdala t = 3.89, p_{FWE} = 0.011), whereas the AUD group failed to habituate (for left amygdala t = 1.31, p_{FWE} = 0.854, and right amygdala t = 0.56, p_{FWE} = 0.958). These opposing response patterns (see **Figure 2.5A**) were corroborated in an exploratory follow-up analysis in the AUD group using the inverse contrast ([block 1 + block 2] < [block 3 + block 4]; t = 3.43, p_{FWE} = 0.039). Inclusion of the CTQ sum score in an interaction model (Group x CTQ) as a predictor yielded a significant interaction effect within the right amygdala (T = 3.46, p_{FWE} = 0.037). The subsequent post hoc analysis revealed an association between CTQ and amygdala habituation within the HC group (T = 3.88, p_{FWE} = 0.012), but not in the AUD group (T = 1.80, p_{FWE} = 0.662; **Figure 2.5B**).

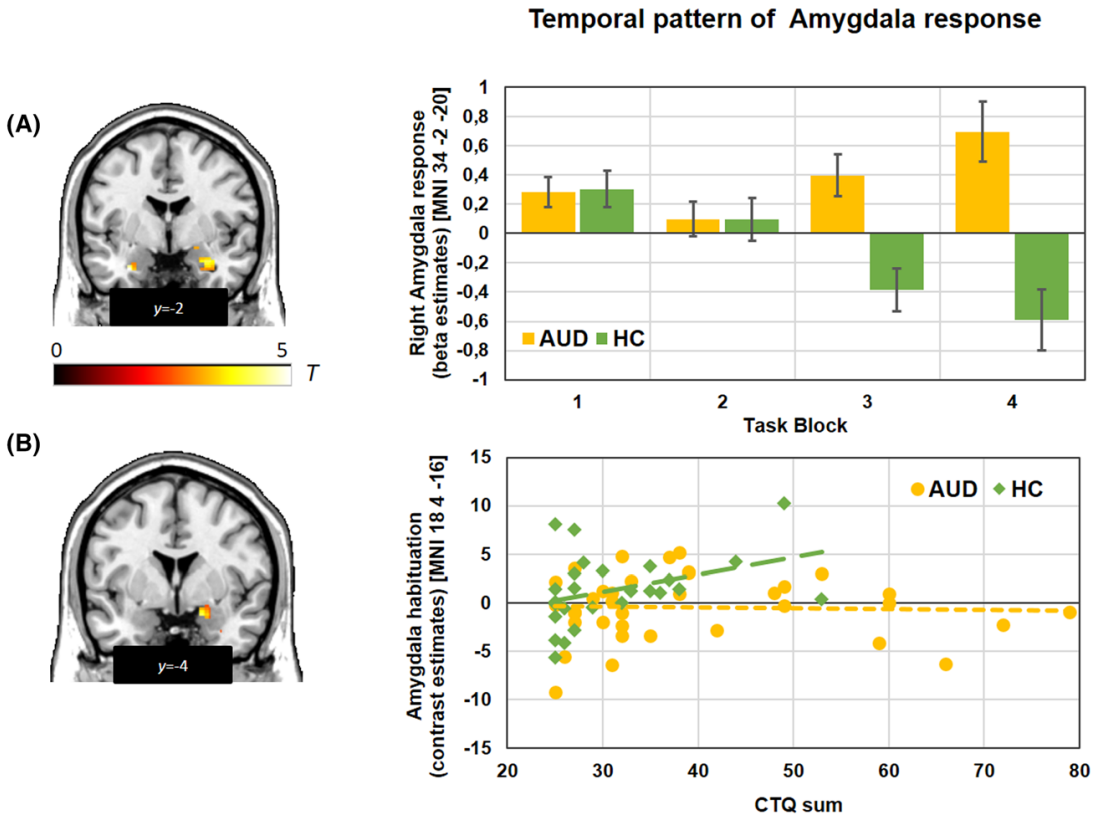


Figure 2.5. Group differences in Amygdala habituation to aversive stimuli. **A:** Decrease of amygdala activation over the course of the experiment for HC, whereas AUD group showed an increase (right amygdala (t = 4.26, p_{FWE} = 0.004) and left amygdala (t = 4.79, $p_{FWE} \leq 0.001$)). Right: Plotted habituation estimates of the peak voxel in the right amygdala. **B**: Amygdala habituation relates to ACE differently: increased amygdala habituation is associated with higher CTQ sum score in HC, but not in AUD group (Interaction: T = 3.46, p_{FWE} = 0.037; post hoc analysis: AUD: T = 1.80, p_{FWE} = 0.662, HC: T = 3.88, p_{FWE} = 0.012). For illustration purposes, a significance threshold of $p_{uncorr} < .005$ was applied and displayed on the coronal section. HC: healthy control participants, AUD: alcohol use disorder, ACE: adverse childhood experience; FWE: familywise error; MNI: Montreal Neurological Institute.

2.3.5 Discussion

Employing an established fMRI paradigm (Hariri, Tessitore, et al., 2002) and a reliable amygdala habituation index (Bilek et al., 2019; Wiggins et al., 2014), the current study provides novel evidence for a neural emotion processing mechanism promoting our understanding the AUD-related alterations in amygdala functioning. We report deficient amygdala habituation to repeated negative emotional stimuli in individuals with AUD relative to healthy controls. In our healthy sample, we replicated the finding of a link between amygdala habituation and ACE, an important environmental risk factor for mental disorders and deficient emotion regulation; however, this association was not observed in our AUD sample.

Alterations in amygdala activation in AUD are well documented (Koob, 2009). Some neuroimaging studies report blunted responses within the amygdala in relation to drinking or AUD (Glahn et al., 2007; Hur et al., 2018; Marinkovic et al., 2009; Stephens et al., 2005; Suzuki et al., 2020; Vollstädt-Klein et al., 2019). A positive relation between increased amygdala activation and AUD severity was also shown (Gowin et al., 2016). However, others observed no difference compared to healthy controls (Charlet et al., 2014; O'Daly et al., 2012). The (lack of) group difference in mean activation may be driven by either a dynamic or by sustained activation over time, and might therefore lead to false negative findings, and thus inferences (Phan, Wager, Taylor, & Liberzon, 2002; Plichta et al., 2014). Our data suggest a robust activation of both groups at the beginning of the experiment. However, repeated presentation of the stimuli resulted in habituation only in our HC group, while amygdala activation rather increased in individuals with AUD. This pattern resembles neural sensitization (Ramaswami, 2014) and might reflect changes in neurotransmission in the brain emotion regulatory systems with the development of AUD (Robinson & Berridge, 1993). Indeed, the process of neural sensitization, or kindling, has been reported in relation to AUD (Breese, Sinha, & Heilig, 2011; Gilpin & Koob, 2008), stress or negative affective stimuli (Heilig, Egli, Crabbe, & Becker, 2010), and can be discussed within the context of neural plasticity. However, due to experimental limitations (e.g., number of blocks, length of the paradigm), this interpretation needs further examination.

The observed deficit in habituation in individuals with AUD might reflect AUD-related alterations in fundamental neuroplasticity mechanisms (Lovinger & Kash, 2015; Seo & Sinha, 2015). These deficits and resulting inappropriate allocation of processing resources towards non-threatening or non-relevant stimuli (Ramaswami, 2014) might firstly indicate a failure in emotion regulation, and therefore, secondly maintain the AUD. They might further be driven by chronic and enduring stress during childhood through an impact on neurodevelopment and physiological changes (Dube et al., 2006). We specifically tested this hypothesis by probing the relationship of the established habituation phenotype to ACE, measured by CTQ sum. Interestingly, in our sample amygdala habituation towards negative emotional faces was positively related to the severity of ACE in healthy individuals, but not in AUD.

It might be that the impact of AUD or the consumption of high amounts of alcohol per se have masked the neurobiological effects of ACE, leading to the missing relationship between deficient amygdala habituation in the AUD group and ACE severity. Given

that both, ACE and drinking behavior are associated with neuroadaptive brain responses in emotion processing circuitry, especially the amygdala (Gilpin et al., 2015; Puetz et al., 2020), we may assume that the observed disrupted amygdala habituation in individuals with AUD could be an effect of both. ACE may serve as a predisposing and maintaining factor for AUD through emotion dysregulation (Berking et al., 2011; Wilcox, Pommy, & Adinoff, 2016). In turn, acute administration of alcohol (Hur et al., 2018) as well as chronic alcohol consumption (Stephens et al., 2005) reduce amygdala reactivity, and thus contribute further to the ACE-caused behavioral and neural alterations. Indeed, deficient amygdala habituation in AUD may reflect both, a risk factor predisposing individuals for the development of the disorder and/or a functional marker of the consequence of previous hazardous alcohol consumption. While it is generally difficult to disentangle the effect of both above mentioned factors, we consider the interpretation of a functional marker more likely, since our supplemental analysis did detect an association between amygdala habituation estimates and the quantity of recent alcohol consumption.

The observed deficit in habituation might also reflect alterations in amygdala functional connectivity across this brain circuitry, i.e., impaired prefrontal control function (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Wilcox et al., 2016), as the amygdala shows widespread connections within the emotion regulation network (Berboth & Morawetz, 2021). Previously, the acute consumption of alcohol (S. M. Gorka, Fitzgerald, King, & Phan, 2013) as well as having experienced ACE (Elton, Smitherman, Young, & Kilts, 2015; McLaughlin et al., 2015; van Harmelen et al., 2013) were related to altered fronto-limbic coupling. In the present study, mild to moderate depression was not an exclusion criterion - comorbid depression could also in part explain the deficit in habituation in AUD. In a study by (van den Bulk et al., 2016) participants with depression also demonstrated a lack of habituation. Further research is needed to reinforce this assumption.

The positive relationship between amygdala habituation and ACE severity in healthy controls could possibly be understood by the allostatic load and stress theory (Bower, Low, Moskowitz, Sepah, & Epel, 2008). Within the context of resilience, mild forms of ACE and a quick adaptation and habituation to repeated presentation of negative or aversive emotional cues could lead to a positive health outcome (McEwen, Gray, & Nasca, 2015). Previously, adaptive stress-dependent functioning of the amygdala has been discussed within the context of resilience towards psychopathologies (Holz et al.,

2020). However, the distribution of ACE severity in our low-risk healthy control group was highly (positively) skewed. Thus, any inferences about the observed relationship should be made with caution and require refinement in future work.

Limitations

Possibly due to the recruitment procedure and the corresponding in- and exclusion criteria, we examined only individuals with AUD that had mild to moderate levels of ACE. To overcome these methodological issues, future studies need to address the influence of ACE on amygdala habituation in individuals with AUD in larger study populations with a more normally distributed expression of ACE levels, while also including healthy controls with a wider range of ACE. Additionally, the proposed processes of sensitization need to be examined in a paradigm better suited for this purpose, e.g., by prolonging the current fMRI task. Lastly, longitudinal studies are needed to address amygdala habituation and causal relations of ACE as a major stressor in early life, the facilitating effect of ACE towards AUD, and finally the (neurotoxic) effect of alcohol.

Clinical implications

Following more recent developments in psychotherapy (i.e., modular, or process-based psychotherapy), emotion regulation is one of the core processes mediating symptom reduction and therapeutic outcome (Chambers, Gullone, & Allen, 2009; Kraiss, ten Klooster, Moskowitz, & Bohlmeijer, 2020; Pavlacic & Young, 2020). Our findings of a possible sensitization towards fearful and angry faces in individuals with AUD might serve as a neurobiological reinforcement for the fruitful use of interventions that aim to increase habituation to negative emotions (Berking et al., 2011; Garland, Froeliger, & Howard, 2014). Mindfulness-based relapse prevention as therapy add-on shows a positive effect on craving, which is mediated by acceptance, awareness, and nonjudgment (Witkiewitz et al., 2013). Berking et al. (2011) observed a negative relation between emotion regulation skills and alcohol use after standard treatment. In particular, tolerating negative emotions predicted alcohol consumption when controlling for other emotion regulation skills (Berking et al., 2011). Therefore, neural plasticity could also inversely be used to reduce sensitization and enhance habituation following before-mentioned interventions building a bridge from trans-diagnostic phenotypes to such therapeutic approaches.

CONCLUSION

The present study is the first to report a deficient amygdala habituation to repeated negative emotional stimuli in AUD. Our data suggests a lack of an association between amygdala habituation and adverse childhood experience in AUD. However, deficient amygdala habituation related to the amount of alcohol consumption in the overall sample might indicate a short-term substance effect. The findings of this study extend previous knowledge by suggesting a new neural mechanism for understanding the AUD-related alterations in amygdala functioning, and thus underlying emotion regulation, and thereby opening a new avenue for further research and treatment.

3 DISCUSSION

Early identification, intervention and prevention of mental disorder in general population is fundamental step to ensure emotional, psychological, and social well-being of every individual and can have a life-changing consequences for many. Despite all efforts, the modern literature on risk states is still dominated by mechanistic diagnostic categories and traditional retrospective measures of symptoms, and lacks research on brain-behavior interaction driven by dynamic emotional states and environmental influence in natural settings.

The primary aim of this work was to provide a comprehensive psychosocial characterization of at-risk mental states and relate it to the reliable daily-life and neural markers in community individuals with daily mental health challenges that often remain unnoticed and not sufficiently attended to, both in clinical and research settings. We took advantage of the modern multimodal environmental neuroscience approaches that enable the coordinated assessment of dimensional psychological, neural, and daily affective functions in naturalistic cohorts.

3.1. Identifying risk states in general population - subthreshold extended phenotype

In this work we deviated from the conventional definition of at-risk mental states that focuses on individuals with subthreshold symptoms who seek help at mental health services, and referred instead to the so-called subthreshold extended phenotype in the general population, which is conceptually different from the “at-risk mental state” populations (Keshavan, DeLisi, & Seidman, 2011; van Os, 2013). We built our approach on the evidence suggesting a trans-diagnostic and dimensional nature of the mental disorder (Markon et al., 2011; Watson et al., 2022) – a quantitative variation from health to disease, and with different illness risks (early and recent) if related to the time of exposure (Ruscio, 2019). Based on this, the study 1 investigated two at-risk populations - those who currently experience unspecific subclinical symptoms, and those who have suffered from a mental disorder in the past. We extended this definition further by including in the study 2 asymptomatic community individuals with early adverse experiences, a well-documented and well-replicated risk factor for psychopathology. Both samples were population-based cohort, i.e. without any inclusion bias, reflecting the real-life heterogeneity. Such unorthodox approach helped

us to identify individuals much earlier in the trajectory of the evolving disorder, manifesting subtle changes in mental state and in daily functioning.

3.2. Real-life affective function and psychosocial risk profile in community individuals at risk for mental disorder

3.2.1. Risk-related affective alterations in daily life

Both included studies on at-risk population (study 1 and study 2) report similar daily life impairments - a significant decrease in daily affective function, consistent with our hypothesis. Specifically, in the study 1 we observe the reduction in affective valence in categorical sample when comparing between groups with different risk-load. We further replicate it in a dimensional sample (study 2) by showing an ACE dose-dependent decrease in daily functioning (indexed by valence, calmness, and energetic arousal). Although there are only few comparable studies to date, our observations align well with changes in emotional experience of individuals at-risk reported in other community-based EMA studies (Frost et al., 2015; Infurna, Rivers, Reich, & Zautra, 2015; Scott et al., 2015; Scott et al., 2017).

Our exploratory analysis of other EMA variables, like social experience, affective (in)stability (the extended set of EMA scales harmonized between both studies), further revealed that almost all recorded measures remain unaffected in the at-risk population (both studies). However, these daily life experiences significantly differ in community individuals identified as fulfilling the criteria for a current mental disorder (study 1).

The observed findings cannot fully be considered as a pure replication, because the study participants were drawn from the same naturalistic sample. However, study 2 had a significantly larger sample size (N = 351) of unselected participants, whereas study 1 (N = 132) employed an established stratification method based on clinical interviews to categorize participants into three risk-groups. Thus, while samples were not fully independent, the consistently observed reduction in daily affective function across different populations at-risk and different sample sizes (against a background of unaffected other real-life functions), speaks for the trans-diagnostic relevance of this EMA measure. These results further corroborate that EMA as a screening tool in general, and employed EMA scales in particular, are especially suited to capture within-subject risk-associated changes in daily life emotional experiences in healthy community individuals (Stange, Kleiman, Mermelstein, & Trull, 2019). That is, the EMA scales are able to map daily symptoms of subclinical intensity below the sensitivity

threshold of traditional clinical scales. This is in line with previous reports, showing a high sensitivity of the EMA indices for other established psychiatric risk and resilience factors, such as benefit in well-being from social contact (Gan et al., 2021), physical activity (Reichert et al., 2020) and exposure to urban green space (Tost et al., 2019).

3.2.2. Psychological risk phenotype

Results from questionnaire measures derived from both studies showed that all studied at-risk populations share similar psychological risk profile. In both samples, with early and recent risk exposure, we observed analogous load-dependent difference in known psychological trait-like risk and protective factors, grouping around heightened stress perception, a tendency to negative emotions, and limited personal resources to deal with challenging daily hassles. While risk-related alterations in community individuals with subthreshold symptoms in the study 1 were observed only in selective variables (*selective risk phenotype*), individuals with ACE (study 2) showed psychological deficit in almost all of the examined areas (*extended risk phenotype*). We may conclude from these observations that psychological alterations in the community is a gradual phenomenon. And such alterations may be particularly pronounced in those who experienced adverse exposure early in life, during sensitive developmental periods. The developing brain internalizes experience of persisting stress, through the alterations in stress response system, brain development (Heim, Shugart, & Craighead, 2010; van Harmelen et al., 2010), this might lead to the formation of dispositional vulnerability (personality, attitudes, coping styles)(Segal, 1988; Williams, Watts, MacLeod, & Mathews, 1988). Together with the observed impairments in daily functioning, this might suggest a possible vulnerability mechanism linking early and recent risks to the manifest disorder by creating negative attitudes and dispositional sensitivity to minor stressors in daily life in adulthood.

3.3. Trans-diagnostic alterations in amygdala habituation

In the study 1 and study 3 we used an established fMRI paradigm (Hariri, Mattay, et al., 2002) and validated amygdala habituation estimates (Bilek et al., 2019; Plichta et al., 2014; Wiggins et al., 2014) to report the findings of maladapted amygdala habituation to repeated emotional stimulation in two risk populations, in individuals with subthreshold symptoms (study 1) and in individuals with excessive alcohol use (study 3). Two noteworthy messages to highlight here. First, we extend the prior scientific knowledge on amygdala habituation phenotype to two new vulnerable population

groups in the community. And secondly, we provide additional evidence about the reliability and sensitivity of the applied habituation estimate. The study 3 was used merely for replication purpose in a conceptually different at-risk population.

3.3.1. Aberrant amygdala habituation in at-risk states

In line with our expectations, in the study 1 we detected an aberrant amygdala habituation in community individuals with subthreshold symptoms. Employing the same fMRI paradigm and similar habituation index, in the study 3 we observed corresponding maladaptive habituation in amygdala response in a selected sample of individuals with alcohol abuse, a strong risk factor for psychopathology. Both reports are novel, and thus make a remarkable contribution to the existent knowledge in the field. Despite its ubiquity and biological relevance, this habituation phenotype surprisingly has not been previously studied in these risk populations.

Rapid habituation is a fundamental evolutionary preserved plasticity mechanism, aiming to conserve limited processing resources, is thought to signal safety and familiarity, and acts as a building block for normal 'affective' function (Ramaswami, 2014). The detected deficient habituation in the studied risk populations is thus suggestive of a neural plasticity-related alterations in the affective processing of the salient stimuli.

Abnormalities in the simplest form of learning, habituation, have been reported for numerous etiologically different neuropsychiatric disorders (McDiarmid et al., 2017), indicating a robust neural phenotype. With our results we provide further support for its trans-diagnostic relevance that reflects a sensitive biomarker for quantifying vulnerable states at the individual level. Furthermore, habituation is unspecific to certain mental disorder (McDiarmid et al., 2017), or sources of illness risk (Holz et al., 2021; Perez-Rodriguez et al., 2017), suggesting for diverse and complex underlying mechanisms. Given the amygdala's widespread connections with both inhibitory projections from PFC and bidirectional excitatory connections with sensory areas (as was detailed in the Introduction), the deficient habituation might result from imbalances in amygdala functional connectivity across the emotional brain circuitry. Some studies indeed provide evidence to support this hypothesis (Blackford et al., 2013; Dudas et al., 2017; Swartz, Wiggins, Carrasco, Lord, & Monk, 2013).

Aberrant amygdala habituation could be due to altered neuronal development (i.e. after chronic stress in childhood) (Pechtel & Pizzagalli, 2011). Some studies link deficient

amygdala habituation and genetic risk - serotonin receptor density and genetic variants modulating the neurotransmission, neuroplasticity, and psychiatric risk (Lonsdorf et al., 2011; Perez-Rodriguez et al., 2017; Wiggins et al., 2014), e.g., disease specific changes in synaptic gene expression. Very little is known about the cellular mechanisms underlying habituation. Some studies point to impaired ability to decrease excitatory neurotransmitter release (Armitage & Siegelbaum, 1998; Castellucci & Kandel, 1974; Weber, Schnitzler, & Schmid, 2002), another to a deficit in the ability to increase the firing of inhibitory neurons onto the circuit regulating behavior (Das et al., 2011; Glanzman, 2011). Further experiments are required to test all suggested above hypothetical mechanisms.

In light of our findings and existing literature on amygdala habituation, we may conclude that multiple sources of illness risk may converge on this neural phenotype and shape the vulnerability to the development of mental disorder, thus making it a trans-diagnostic neural phenotype. It may serve as a sensitive neural marker for affective integrity of mental state, wherein even moderate impairments in habituation may be able to signal clinical vulnerability.

Acknowledging this diversity of underlying mechanisms and its non-specificity, we may further conclude, that deficient habituation on its own can inform us very little about the underlying pathology. Only when integrated with other data modality, e.g., a specific knowledge about the behavioral and/or daily life manifestation of the disorder, it may shed light on the causes/mechanisms of maladaptive habituation. In study 1 we tested this hypothesis and found a link between rapid amygdala habituation and increased momentary affective valence in healthy community individuals, but not in at-risk group. Alongside observed psychological and daily life impairments, we may tentatively suggest that reduced biological plasticity in the amygdala may require alternative regulatory strategies to deal with perceived threat, which may disrupt the direct link of amygdala habituation to real-life affective well-being. This is the task for future studies.

3.3.2. Neural habituation – a well-validated measure

Notably, the explicit testing of the experimental design and/or analysis routine of habituation experiment in different clinical populations was beyond the scope of this work. Our work however makes in addition an important methodological contribution. Applying in the both included studies the well-validated habituation estimates (Bilek et al., 2019; Plichta et al., 2014; Wiggins et al., 2014), we prove the validity and sensitivity

of this index, being able to explain the relationship of amygdala habituation also in at-risk populations studied. By using the same well-established experimental paradigm in both studies, it makes the observed results more comparable and generalizable.

While normal habituation curve follows typically a negative exponential decrement, the trajectory and rate of decrement, as well as an initial sensitization, of altered habituation can vary representing a specific habituation phenotype in specific clinical population (McDiarmid et al., 2017). Although there is an attempt to classify the ways how habituation can be altered in each disorder (McDiarmid et al., 2017), literature is still sparse and rather inconsistent for a reliable disorder-specific taxonomy. As a result, despite the growing clinical relevance of the neural habituation phenotype, the methods to assess and interpret the alterations in habituation are still inconsistent. Beyond the diverse underlying mechanisms detailed above, the heterogeneity of methods further complicates making conclusions about the role of habituation in a specific mental condition. By validating the habituation measure in the new clinical population, we may bring the current knowledge one step forward to the reliable disorder-specific classification of the habituation phenotypes.

3.4. Critical reflection and limitations

Despite the obvious strength and novelty of the work, some critical points merit consideration.

3.4.1. Sample selection

The major challenge was the sample selection. While we were pre-determined to build our work on the population sample, as psychopathology was shown to exist on a continuum of symptoms severity, for some hypothesis however we couldn’t avoid categorical approach and selected samples due to certain reasons.

We are not aware of any study to date that has investigated multimodal measures (on psychological, daily-life, and neuroimaging level) for risk-populations in dimensional sample. Therefore, in order to more precisely isolate features uniquely associated with these at-risk populations, we investigated this question in a first step using an established categorization method, as for example in study 1. For the same reason we pursued the categorical approach in the study 3, although it has been shown that alcohol consumption is best conceptualized as a dimensional phenomenon (Fazzino, Rose, Burt, & Helzer, 2014).

In the study 1 we further diverged from a purely population-based approach by matching the composition of the non-risk comparison group using a set of predefined demographic variables. It was an important measure to minimize the effect from confounding variables that are known to affect the studied outcomes.

The size of the studied groups (especially study 1) was relatively small. This is mainly because the prevalence of these risk-groups (subclinical syndromes, full remissions of a previous disorder) is limited, they are not help-seeking and many do not relate themselves to the risk-population.

And lastly, we can't rule out completely the potential sample bias even in the large community-based epidemiological studies (study 2), because factors of interest might influence participation in the study (e.g., ACE) (Little, Lewitzky, Heeringa, Lepkowski, & Kessler, 1997).

3.4.2. Risk and symptoms assessments

As many other researchers, we relied on retrospective self-reports of early adverse experiences in study 2. However, while such surveys might be indeed influenced by recall bias, subjective interpretation, or current mental health (Shiffman, Stone, & Hufford, 2008), some evidence suggest that ACE is underestimated rather than overestimated by such measurements and is not significantly affected by current emotional states (Spinhoven et al., 2014). Literature further shows that the risk of psychopathology are more likely associated with the subjective rather than objective experience of early adverse experience (Danese & Widom, 2021). In study 1 to assess and categorize the community sample we used mini-DIPS, a brief and quick diagnostic interview for mental disorders, which is not well-suited for such purposes. Future studies should be based on the more appropriate standardized inventory.

3.4.3. Data structure.

Another challenge in this work was the data structure. The distribution of some variables of interest, e.g. ACE load, was skewed in our population-based samples (see study 2 for example), which was to be expected. In order to address this issue we used nonparametric methods, log-transforming predictors, and/or examined the distribution of model residuals.

3.4.4. Cross-sectional design

The cross-sectional study design used in this work limits any causal conclusions and does not allow to directly address the nature of established phenotypes during the transition phase, since multiple environmental factors (risk and protective) may implicate these phenotypes and affect the development of mental disorder. This should be addressed in future longitudinal studies.

3.5. Future directions

The results of this work improve current understanding of the behavioral, daily and biological features uniquely associated with studied at-risk populations, and lay thus a solid ground for future studies, some of which I highlight below.

3.5.1 Dimensional research

Future studies can a priori well position a dimensional investigation of mental disorder, including healthy individuals, various risk populations, and patients from the community. For the dimensional investigation to be functional, however, an appropriate (and standardized) inventory is needed to measure dimensional symptoms severity or risk burden. Disorder-specific measures alone, like BDI, or SPQ, might show low variance in general predominantly healthy population, and therefore will be less informative about the underlying shared or distinct mechanisms. The inclusion instead a broad psychological test battery, that incorporates state and trait measures, as we did in study 1 and 2, will be able to provide a comprehensive coverage of affected symptom domains.

3.5.2 Prospects to interventional research

The identified in this work daily and neural salient risk markers can motivate and guide the future tailored intervention studies at multiple levels of influence, such as Ecological Momentary Intervention, digital mental health (Myin-Germeys et al., 2016) or neurofeedback modulation (Reichert et al., 2021; Tost et al., 2015).

Ecological Momentary Intervention

Consistent with previous reports, in this work we also show the superiority of EMA measures over retrospective questionnaires in capturing mental states and psychopathological symptoms (Ebner-Priemer & Trull, 2009; van de Leemput et al., 2014). This work can be extended to the ambulatory interventions (or EMI), a real-time feedback (e.g. tailored intervention messages) to individuals in their everyday life at

predefined moments within their natural environment, using information gathered for example through EMA (Heron & Smyth, 2010). The established in this work daily risk markers in at-risk populations (i.e. affective valence) can be targeted in the intervention studies, in combination with other established environmental protective factors, such as green space exposure, or social contact (Gan et al., 2021; Tost et al., 2019). From other side, given its high sensitivity (Gan et al., 2021; Reichert et al., 2020; Tost et al., 2019), the studied EMA scales can be implemented in the real-life monitoring systems directed at risk-populations, aimed at daily life assessments of affective states as well as action steps, based on the reported symptoms and functioning or early warning signs (Myin-Germeys et al., 2016). Future intervention-based research, for example the experimental manipulation in everyday life, can give some insights about the causality of findings, e.g., whether changes in daily physical activity can impact gray matter volume (Reichert et al., 2020).

Neurofeedback modulation studies

Our findings on maladaptive function of amygdala in at-risk populations, opens a new avenue for intervention research, since amygdala function can be directly targeted and modulated with neurofeedback-based interventions (Linhartová et al., 2019). Real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback is a training method that builds on the ability to guide mental activity to selectively modulate brain response based on real-time feedback from the targeted brain region (Stoeckel et al., 2014). Although this line of research is still in its infancy, some studies have already demonstrated the successful feedback-guided regulation of amygdala in clinical and at-risk populations (Young, Misaki, et al., 2017; Young, Siegle, et al., 2017; Young et al., 2018; Young et al., 2014). Furthermore, rt-fMRI neurofeedback is a strong neurotherapeutic tool to drive plasticity in brain function. Some study indeed show that neurofeedback can be a promising procedure for neural plasticity modulation (Young, Misaki, et al., 2017), and thus may aid habituation deficits, and these changes might lead to improved functioning in those domains (Young, Misaki, et al., 2017). Amygdala-targeted neutofeedback can be further combined with ecological momentary interventions, such as smartphone-based training of mental strategies, creating thereby an intervention model on multiple, synergistic levels of influence to modulate affective function.

4. SUMMARY

The improved understanding of the daily-life psychological and neural characteristics of risk states in general population is important because the identification of salient risk markers can guide the development of novel early individually-tailored interventions at multiple levels of influence, such as mental health services, digital mental health and neurofeedback therapy. In this work we employed unorthodox definition of at-risk mental state - the extended subthreshold phenotype, by investigating three at-risk populations - community non-help-seeking individuals with subclinical symptoms, with childhood trauma history and those who suffered mental disorder in the past, the population groups that usually remain unnoticed and unattended from the clinical and research communities. We took advantage of the modern multimodal environmental neuroscience approach to investigate brain-behavior relationships in at-risk populations by monitoring the dynamic emotional states in the natural context under the influence of environmental, emotional and cognitive factors and relating them to the reliable neural phenotype.

Both presented studies (study 1 and study 2) consistently found reduced daily life affective well-being, indexed by affective valence, across all studied at-risk populations against a background of unnoticeable changes in other real-life functions. This observation provides further evidence suitability and sensitivity of EMA method and used EMA scales for mapping daily symptoms of subclinical intensity below the sensitivity threshold of traditional clinical scales.

We further identified a psychological risk profile for the investigated at-risk populations, reflecting features detrimental to mental health. While all demonstrated an analogous load-dependent alterations in known risk and protective factors, community individuals with recent risk (study 1) showed a selected risk phenotype, contrary to individuals with early adverse profile (study 2), who demonstrated psychological deficit almost in all studied measures - an extended risk phenotype. Together with the daily impairments, this suggests that community individuals at-risk for mental disorder exhibit risk phenotypes on the behavioral and experiential level, including limited personal resources to cope with stress-related experiences and a reduction in affective valence in daily life.

At the neural systems level, we observed deficient amygdala habituation in at-risk individuals (study 1) and replicated these findings in the independent at-risk sample

(study 3), thus suggesting of a neural plasticity-related alterations in the affective processing of emotional stimuli in at-risk population. These findings further point to a convergence of the multiple sources of illness risk in this neural phenotype, wherein even moderate impairments in amygdala habituation may signal clinical vulnerability. Alongside observed psychological and daily life impairments, we suggest that reduced biological plasticity in the amygdala in at-risk population may require alternative regulatory strategies to deal with perceived daily stress. We further speculate that the relationship between brain function and everyday experience is a complex, reciprocal causal process, an assumption that should be further explored in future experimental studies.

Future studies can be motivated and guided by these findings. First, large-scale multimodal community-based longitudinal studies that span the range from non-risk to high-risk individuals can enrich risk stratification allowing for more accurate prediction models and tailored interventions, and shed light on a complex causal relationship between brain function and daily experience. Further, these studies should include the dimensional psychological and real-life measures allowing for comprehensive coverage of affected symptom domains. And finally, I believe, the results of this work are novel and markedly improve our current understanding of the risk-associated psychological, real-life, and neural affective alterations in the population and can inform the future intervention studies at multiple levels of influence, such as ecological momentary intervention, or amygdala-neurofeedback modulation.

5. ZUSAMMENFASSUNG

Das verbesserte Verständnis der alltäglichen psychologischen und neuronalen Merkmale von Risikofaktoren in der Allgemeinbevölkerung ist wichtig, da die Identifizierung hervorstechender Risikomarker die Entwicklung neuartiger, früher, individuell zugeschnittener Interventionen auf mehreren Einflussebenen, wie z. B. psychiatrische Dienste, digitale psychische Gesundheit und Neurofeedback-Therapie leiten kann. In dieser Arbeit verwendeten wir eine unkonventionelle Definition der Risikopopulationen (at-risk mental status) – den erweiterten unterschwelligen Phänotyp –, indem wir drei Risikogruppen untersuchten – nicht hilfesuchende Personen aus der Allgemeinbevölkerung mit (I) subklinischen Symptomen und mit (II) traumatischer Erfahrung in der Kindheit und diejenigen, die in der Vergangenheit unter einer psychischen Störung gelitten haben (III) - die Bevölkerungsgruppen, die in Kliniken und in der Forschung normalerweise unbemerkt und unberücksichtigt bleiben. Wir nutzten den modernen multimodalen umweltneurowissenschaftlichen Ansatz, um Gehirn-Verhaltensbeziehungen in Risikopopulationen zu untersuchen, indem wir die dynamischen emotionalen Zustände im natürlichen Kontext unter dem Einfluss von Umwelt-, emotionalen und kognitiven Faktoren überwachten und sie mit dem verlässlichen neuronalen Phänotyp in Beziehung setzten.

Beide vorgestellten Studien (Studie 1 und Studie 2) stellten bei allen untersuchten Risikopopulationen, vor dem Hintergrund unbemerkter Veränderungen anderer Funktionen im realen Leben, durchweg ein verringertes affektives Wohlbefinden im Alltag fest, gemessen durch die affektive Valenz. Diese Beobachtung liefert weitere Belege für die Eignung und Sensitivität der EMA-Methode und der verwendeten EMA-Skalen zur Abbildung täglicher Symptome mit subklinischer Intensität unterhalb der Sensitivitätsschwelle traditioneller klinischer Skalen.

Wir haben außerdem ein psychologisches Risikoprofil für die untersuchten Risikopopulationen identifiziert, das Merkmale widerspiegelt, die sich nachteilig auf die psychische Gesundheit auswirken. Während alle Individuen analoge belastungsabhängige Veränderungen bekannter Risiko- und Schutzfaktoren aufwiesen, zeigten Personen mit aktuellem Risiko (Studie 1) einen selektiver Risikophänotyp, im Gegensatz zu Personen mit frühen negativen Erfahrungen (Studie 2), die bei fast allen untersuchten Variablen ein psychologisches Defizit zeigten - ein erweiterter Risikophänotyp. Zusammen mit den täglichen Beeinträchtigungen deutet

dies darauf hin, dass Personen aus der Allgemeinbevölkerung, bei denen das Risiko einer psychischen Störung besteht, Risikophänotypen auf Verhaltens- und Erfahrungsebene aufweisen, einschließlich begrenzter persönlicher Ressourcen zur Bewältigung stressbedingter Erfahrungen und einer Verringerung der affektiven Valenz im Alltag .

Auf neuronaler Ebene beobachteten wir eine mangelhafte Habituation der Amygdala bei Personen der Risikogruppe (Studie 1) und replizierten diese Ergebnisse in der unabhängigen Stichprobe in einer anderen Risikogruppe (Studie 3), was auf neuronale Plastizitätsbedingte Veränderungen in der affektiven Verarbeitung emotionaler Reize in der Risikopopulation hindeutet. Diese Ergebnisse deuten darüber hinaus auf eine Konvergenz der verschiedenen Krankheitsrisikoquellen bei diesem neuronalen Phänotyp hin, wobei selbst mäßige Beeinträchtigungen der Amygdala-Habituation auf eine klinische Anfälligkeit hinweisen können. Neben den beobachteten psychischen und alltäglichen Beeinträchtigungen vermuten wir, dass eine verringerte biologische Plastizität in der Amygdala bei Risikopopulation möglicherweise alternative Regulierungsstrategien erfordert, um mit dem wahrgenommenen Alltagsstress umzugehen. Wir spekulieren weiter, dass die Beziehung zwischen Gehirnfunktion und Alltagserfahrungen ein komplexer, reziproker Kausalprozess ist, eine Annahme, die in zukünftigen experimentellen Studien weiter untersucht werden sollte.

Zukünftige Studien können durch diese Erkenntnisse motiviert und geleitet werden. Zum einen können groß angelegte multimodale, gemeinschaftsbasierte Längsschnittstudien, die den Bereich von Nicht-Risiko- bis hin zu Hochrisiko-Personen abdecken, die Risikostratifizierung bereichern, was genauere Vorhersagemodelle und zugeschnittene Interventionen ermöglicht und Aufschluss über einen komplexen Kausalzusammenhang zwischen Gehirnfunktion und täglichen Erfahrungen gibt. Darüber hinaus sollten diese Studien die dimensional psychologischen und alltäglichen Maßnahmen umfassen, die eine umfassende Abdeckung der betroffenen Symptombereiche ermöglichen. Abschließend denke ich, dass die Ergebnisse dieser Arbeit neu sind und unser derzeitiges Verständnis der risikobedingten psychologischen, realen und neuronalen affektiven Veränderungen in der Bevölkerung deutlich verbessern und die zukünftigen Interventionsstudien auf mehreren Ebenen beeinflussen können, wie zum Beispiel bei ökologischen Momentinterventionen oder Amygdala-Neurofeedback-Modulation.

6. REFERENCES

Adhikari, A., Lerner, T. N., Finkelstein, J., Pak, S., Jennings, J. H., Davidson, T. J., . . . Deisseroth, K. (2015). Basomedial amygdala mediates top-down control of anxiety and fear. *Nature, 527*(7577), 179-185. doi:10.1038/nature15698

Adler, N. E., Boyce, T., Chesney, M. A., Cohen, S., Folkman, S., Kahn, R. L., & Syme, S. L. (1994). Socioeconomic status and health. The challenge of the gradient. *Am Psychol, 49*(1), 15-24. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8122813

Afifi, T. O., Henriksen, C. A., Asmundson, G. J., & Sareen, J. (2012). Childhood maltreatment and substance use disorders among men and women in a nationally representative sample. *Can J Psychiatry, 57*(11), 677-686. doi:10.1177/070674371205701105

Afifi, T. O., Taillieu, T., Salmon, S., Davila, I. G., Stewart-Tufescu, A., Fortier, J., . . . MacMillan, H. L. (2020). Adverse childhood experiences (ACEs), peer victimization, and substance use among adolescents. *Child abuse & neglect, 106*, 104504. doi:https://doi.org/10.1016/j.chiabu.2020.104504

Al-Dajani, N., & Uliaszek, A. A. (2021). The after-effects of momentary suicidal ideation: A preliminary examination of emotion intensity changes following suicidal thoughts. *Psychiatry Res, 302*, 114027. doi:10.1016/j.psychres.2021.114027

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., . . . Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur. Arch. Psychiatry Clin. Neurosci., 256*(3), 174-186. doi:10.1007/s00406-005-0624-4

Armey, M. F., Schatten, H. T., Haradhvala, N., & Miller, I. W. (2015). Ecological momentary assessment (EMA) of depression-related phenomena. *Curr Opin Psychol, 4*, 21-25. doi:10.1016/j.copsyc.2015.01.002

Armitage, B. A., & Siegelbaum, S. A. (1998). Presynaptic induction and expression of homosynaptic depression at Aplysia sensorimotor neuron synapses. *J Neurosci, 18*(21), 8770-8779. doi:10.1523/jneurosci.18-21-08770.1998

Avery, S. N., & Blackford, J. U. (2016). Slow to warm up: the role of habituation in social fear. *Soc Cogn Affect Neurosci, 11*(11), 1832-1840. doi:10.1093/scan/nsw095

Avery, S. N., McHugo, M., Armstrong, K., Blackford, J. U., Woodward, N. D., & Heckers, S. (2021). Stable habituation deficits in the early stage of psychosis: a 2-year follow-up study. *Transl, 11*(1), 20. doi:10.1038/s41398-020-01167-9

Baas, D., Aleman, A., & Kahn, R. S. (2004). Lateralization of amygdala activation: a systematic review of functional neuroimaging studies. *Brain Res Brain Res Rev, 45*(2), 96-103. doi:10.1016/j.brainresrev.2004.02.004

Bakker, J. M., Goossens, L., Kumar, P., Lange, I. M. J., Michielse, S., Schruers, K., . . . Wichers, M. (2019). From laboratory to life: associating brain reward processing with real-life motivated behaviour and symptoms of depression in non-help-seeking young adults. *Psychol Med, 49*(14), 2441-2451. doi:10.1017/s0033291718003446

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Phan, K. L. (2007). Amygdala–frontal connectivity during emotion regulation. *Soc Cogn Affect Neurosci, 2*(4), 303-312. doi:10.1093/scan/nsm029

Barbour, T., Murphy, E., Pruitt, P., Eickhoff, S. B., Keshavan, M. S., Rajan, U., . . . Diwadkar, V. A. (2010). Reduced intra-amygdala activity to positively valenced

faces in adolescent schizophrenia offspring. *Schizophr Res, 123*(2-3), 126-136. doi:10.1016/j.schres.2010.07.023

Berboth, S., & Morawetz, C. (2021). Amygdala-prefrontal connectivity during emotion regulation: A meta-analysis of psychophysiological interactions. *Neuropsychologia, 153*, 107767. doi:https://doi.org/10.1016/j.neuropsychologia.2021.107767

Berhe, O., Höflich, A., Mößnang, C., Reichert, M., Kremer, T., Gan, G., . . . Tost, H. (2022). Reduced real-life affective well-being and amygdala habituation in unmedicated community individuals at risk for depression and anxiety. *Biol Psychiatry Cogn Neurosci Neuroimaging*. doi:10.1016/j.bpsc.2022.06.009

Berking, M., Margraf, M., Ebert, D., Wupperman, P., Hofmann, S. G., & Junghanns, K. (2011). Deficits in emotion-regulation skills predict alcohol use during and after cognitive–behavioral therapy for alcohol dependence. *J Consult Clin Psychol., 79*(3), 307-318. doi:10.1037/a0023421

Bernstein, D. P., Fink, L., Handelsman, L., & Foote, J. (1998). Childhood trauma questionnaire. *Assessment of family violence: A handbook for researchers and practitioners.*

Bilek, E., Itz, M. L., Stossel, G., Ma, R., Berhe, O., Clement, L., . . . Tost, H. (2019). Deficient Amygdala Habituation to Threatening Stimuli in Borderline Personality Disorder Relates to Adverse Childhood Experiences. *Biol Psychiatry, 86*(12), 930-938. doi:10.1016/j.biopsych.2019.06.008

Blackford, J. U., Allen, A. H., Cowan, R. L., & Avery, S. N. (2013). Amygdala and hippocampus fail to habituate to faces in individuals with an inhibited temperament. *Soc Cogn Affect Neurosci, 8*(2), 143-150. doi:10.1093/scan/nsr078

Boden, J. M., Horwood, L. J., & Fergusson, D. M. (2007). Exposure to childhood sexual and physical abuse and subsequent educational achievement outcomes. *Child Abuse Negl, 31*(10), 1101-1114. doi:10.1016/j.chiabu.2007.03.022

Bolger, N., & Laurenceau, J.-P. (2013). *Intensive longitudinal methods: An introduction to diary and experience sampling research*. New York: The Guilford Press.

Bordi, F., & LeDoux, J. (1992). Sensory tuning beyond the sensory system: an initial analysis of auditory response properties of neurons in the lateral amygdaloid nucleus and overlying areas of the striatum. *J Neurosci, 12*(7), 2493-2503. doi:10.1523/jneurosci.12-07-02493.1992

Borkenau, P., & Ostendorf, F. (2008). *NEO-FFI : NEO-Fünf-Faktoren-Inventar nach Costa und McCrae* (2 ed.). Göttingen: Hogrefe.

Bower, J. E., Low, C. A., Moskowitz, J. T., Sepah, S., & Epel, E. (2008). Benefit Finding and Physical Health: Positive Psychological Changes and Enhanced Allostasis. *Soc. Personal. Psychol. Compass, 2*(1), 223-244. doi:https://doi.org/10.1111/j.1751-9004.2007.00038.x

Breese, G. R., Sinha, R., & Heilig, M. (2011). Chronic alcohol neuroadaptation and stress contribute to susceptibility for alcohol craving and relapse. *Pharmacol. Ther., 129*(2), 149-171. doi:https://doi.org/10.1016/j.pharmthera.2010.09.007

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., . . . Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron, 17*(5), 875-887. doi:10.1016/s0896-6273(00)80219-6

Brindle, R. C., Pearson, A., & Ginty, A. T. (2022). Adverse childhood experiences (ACEs) relate to blunted cardiovascular and cortisol reactivity to acute laboratory stress: A systematic review and meta-analysis. *Neurosci Biobehav Rev, 134*, 104530. doi:10.1016/j.neubiorev.2022.104530

Brinkmann, K., & Franzen, J. (2017). Blunted cardiovascular reactivity during social reward anticipation in subclinical depression. *Int J Psychophysiol, 119*, 119-126. doi:10.1016/j.ijpsycho.2017.01.010

Broekhof, R., Rius-Ottenheim, N., Spinhoven, P., van der Mast, R. C., Penninx, B. W., Zitman, F. G., & Giltay, E. J. (2015). Long-lasting effects of affective disorders and childhood trauma on dispositional optimism. *J. Affect. Disord, 175*, 351-358.

Butchart, A. (2006). *Preventing child maltreatment: a guide to taking action and generating evidence*: World Health Organization.

Callicott, J. H., & Weinberger, D. R. (1999). Neuropsychiatric dynamics: the study of mental illness using functional magnetic resonance imaging. *Eur J Radiol, 30*(2), 95-104. doi:10.1016/s0720-048x(99)00048-0

Cao, H., Bertolino, A., Walter, H., Schneider, M., Schafer, A., Taurisano, P., . . . Meyer-Lindenberg, A. (2016). Altered Functional Subnetwork During Emotional Face Processing: A Potential Intermediate Phenotype for Schizophrenia. *JAMA psychiatry, 73*(6), 598-605. doi:10.1001/jamapsychiatry.2016.0161

Cao, H., Harneit, A., Walter, H., Erk, S., Braun, U., Moessnang, C., . . . Tost, H. (2018). The 5-HTTLPR Polymorphism Affects Network-Based Functional Connectivity in the Visual-Limbic System in Healthy Adults. *Neuropsychopharmacology, 43*(2), 406-414. doi:10.1038/npp.2017.121

Cao, H., Plichta, M. M., Schafer, A., Haddad, L., Grimm, O., Schneider, M., . . . Tost, H. (2014). Test-retest reliability of fMRI-based graph theoretical properties during working memory, emotion processing, and resting state. *Neuroimage, 84*, 888-900. doi:10.1016/j.neuroimage.2013.09.013

Carver, C. S. (1997). You want to measure coping but your protocol's too long: consider the brief COPE. *Int J Behav Med, 4*(1), 92-100. doi:10.1207/s15327558ijbm0401_6

Castellucci, V. F., & Kandel, E. R. (1974). A quantal analysis of the synaptic depression underlying habituation of the gill-withdrawal reflex in Aplysia. *Proc Natl Acad Sci U S A, 71*(12), 5004-5008. doi:10.1073/pnas.71.12.5004

Chambers, R., Gullone, E., & Allen, N. B. (2009). Mindful emotion regulation: An integrative review. *Clin. Psychol. Rev., 29*(6), 560-572. doi:https://doi.org/10.1016/j.cpr.2009.06.005

Charlet, K., Schlagenhauf, F., Richter, A., Naundorf, K., Dornhof, L., Weinfurtner, C. E. J., . . . Heinz, A. (2014). Neural activation during processing of aversive faces predicts treatment outcome in alcoholism. *Addict. Biol., 19*(3), 439-451. doi:https://doi.org/10.1111/adb.12045

Collip, D., Oorschot, M., Thewissen, V., Van Os, J., Bentall, R., & Myin-Germeys, I. (2011). Social world interactions: how company connects to paranoia. *Psychol Med, 41*(5), 911-921. doi:10.1017/S0033291710001558

Collip, D., Wigman, J. T., van Os, J., Oorschot, M., Jacobs, N., Derom, C., . . . Myin-Germeys, I. (2014). Positive emotions from social company in women with persisting subclinical psychosis: lessons from daily life. *Acta Psychiatr Scand, 129*(3), 202-210. doi:10.1111/acps.12151

Corcoran, M., & McNulty, M. (2018). Examining the role of attachment in the relationship between childhood adversity, psychological distress and subjective well-being. *Child Abuse Negl, 76*, 297-309. doi:10.1016/j.chiabu.2017.11.012

Crawford, K. M., Choi, K., Davis, K. A., Zhu, Y., Soare, T. W., Smith, A., . . . Dunn, E. C. (2022). Exposure to early childhood maltreatment and its effect over time on social cognition. *Dev Psychopathol, 34*(1), 409-419. doi:10.1017/s095457942000139x

Csikszentmihalyi, M., & Larson, R. (1987). Validity and reliability of the Experience-Sampling Method. *J Nerv Ment Dis, 175*(9), 526-536. doi:10.1097/00005053-198709000-00004

Currie, J., & Widom, C. S. (2010). Long-term consequences of child abuse and neglect on adult economic well-being. *Child Maltreat, 15*(2), 111-120. doi:10.1177/1077559509355316

Cutajar, M. C., Mullen, P. E., Ogloff, J. R., Thomas, S. D., Wells, D. L., & Spataro, J. (2010). Psychopathology in a large cohort of sexually abused children followed up to 43 years. *Child Abuse Negl, 34*(11), 813-822. doi:10.1016/j.chiabu.2010.04.004

Danese, A., & Baldwin, J. R. (2017). Hidden Wounds? Inflammatory Links Between Childhood Trauma and Psychopathology. *Annu Rev Psychol, 68*, 517-544. doi:10.1146/annurev-psych-010416-044208

Danese, A., & Widom, C. S. (2021). The Subjective Experience of Childhood Maltreatment in Psychopathology. *JAMA psychiatry, 78*(12), 1307-1308. doi:10.1001/jamapsychiatry.2021.2874

Das, S., Sadanandappa, M. K., Dervan, A., Larkin, A., Lee, J. A., Sudhakaran, I. P., . . . Ramaswami, M. (2011). Plasticity of local GABAergic interneurons drives olfactory habituation. *Proc Natl Acad Sci U S A, 108*(36), E646-654. doi:10.1073/pnas.1106411108

Davis, M., & Shi, C. (2000). The amygdala. *Curr Biol, 10*(4), R131. doi:10.1016/s0960-9822(00)00345-6

Davis, M., & Whalen, P. J. (2001). The amygdala: vigilance and emotion. *Mol. Psychiatry, 6*(1), 13-34. doi:10.1038/sj.mp.4000812

Dean, A. C., Kohno, M., Hellemann, G., & London, E. D. (2014). Childhood maltreatment and amygdala connectivity in methamphetamine dependence: a pilot study. *Brain and Behavior, 4*(6), 867-876. doi:https://doi.org/10.1002/brb3.289

Demers, C. H., Drabant Conley, E., Bogdan, R., & Hariri, A. R. (2016). Interactions Between Anandamide and Corticotropin-Releasing Factor Signaling Modulate Human Amygdala Function and Risk for Anxiety Disorders: An Imaging Genetics Strategy for Modeling Molecular Interactions. *Biol Psychiatry, 80*(5), 356-362. doi:10.1016/j.biopsych.2015.12.021

Derntl, B., Michel, T. M., Prempeh, P., Backes, V., Finkelmeyer, A., Schneider, F., & Habel, U. (2015). Empathy in individuals clinically at risk for psychosis: brain and behaviour. *Br J Psychiatry, 207*(5), 407-413. doi:10.1192/bjp.bp.114.159004

Di Chiara, G. (2000). Role of dopamine in the behavioural actions of nicotine related to addiction. *Eur. J. Pharmacol., 393*(1), 295-314. doi:https://doi.org/10.1016/S0014-2999(00)00122-9

Dong, D., Ming, Q., Zhong, X., Pu, W., Zhang, X., Jiang, Y., . . . Yao, S. (2019). State-independent alterations of intrinsic brain network in current and remitted depression. *Prog Neuropsychopharmacol Biol Psychiatry., 89*, 475-480.

Döring, N., & Bortz, J. (1993). Psychometrische Einsamkeitsforschung: Deutsche Neukonstruktion der UCLA Loneliness Scale. *Diagnostica*.

Doyle, S. R., & Donovan, D. M. (2009). A Validation Study of the Alcohol Dependence Scale. *J Stud Alcohol Drugs, 70*(5), 689-699. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2741549/

Dube, S. R., Miller, J. W., Brown, D. W., Giles, W. H., Felitti, V. J., Dong, M., & Anda, R. F. (2006). Adverse childhood experiences and the association with ever

using alcohol and initiating alcohol use during adolescence. *J. Adolesc. Health, 38*(4), 444.e441-444.e410. doi:https://doi.org/10.1016/j.jadohealth.2005.06.006

Dudas, R. B., Mole, T. B., Morris, L. S., Denman, C., Hill, E., Szalma, B., . . . Voon, V. (2017). Amygdala and dlPFC abnormalities, with aberrant connectivity and habituation in response to emotional stimuli in females with BPD. *J Affect Disord, 208*, 460-466. doi:10.1016/j.jad.2016.10.043

Ebner-Priemer, U. W., Eid, M., Kleindienst, N., Stabenow, S., & Trull, T. J. (2009). Analytic strategies for understanding affective (in)stability and other dynamic processes in psychopathology. *J Abnorm Psychol, 118*(1), 195-202. doi:10.1037/a0014868

Ebner-Priemer, U. W., Koudela, S., Mutz, G., & Kanning, M. (2012). Interactive Multimodal Ambulatory Monitoring to Investigate the Association between Physical Activity and Affect. *Front Psychol, 3*, 596. doi:10.3389/fpsyg.2012.00596

Ebner-Priemer, U. W., & Sawitzki, G. (2007). Ambulatory assessment of affective instability in borderline personality disorder: The effect of the sampling frequency. *Eur J Psychol Assess, 23*(4), 238.

Ebner-Priemer, U. W., & Trull, T. J. (2009). Ecological momentary assessment of mood disorders and mood dysregulation. *Psychol Assess, 21*(4), 463-475. doi:10.1037/a0017075

Ekman, P., & Friesen, W. V. (1976). *Pictures of Facial Affect*. Palo Alto, CA: Consulting Psychologists Press.

Elton, A., Smitherman, S., Young, J., & Kilts, C. D. (2015). Effects of childhood maltreatment on the neural correlates of stress- and drug cue-induced cocaine craving. *Addict Biol, 20*(4), 820-831. doi:10.1111/adb.12162

Fahrenberg, J., Myrtek, M., Pawlik, K., & Perrez, M. (2007). Ambulatory Assessment - Monitoring Behavior in Daily Life Settings. *European Journal of Psychological Assessment, 23*(4), 206-213. doi:10.1027/1015-5759.23.4.206

Fazzino, T. L., Rose, G. L., Burt, K. B., & Helzer, J. E. (2014). Comparison of categorical alcohol dependence versus a dimensional measure for predicting weekly alcohol use in heavy drinkers. *Drug Alcohol Depend, 136*, 121-126. doi:10.1016/j.drugalcdep.2013.12.020

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., . . . Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med, 14*(4), 245-258. doi:10.1016/s0749-3797(98)00017-8

First, M., Spitzer, R., Gibbon, M., & Williams, J. (2001). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition with Psychotic Screen (SCID-I/P W/ PSY SCREEN).* New York: New York Psychiatric Institute.

Fischer, H., Wright, C. I., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2003). Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. *Brain Res Bull, 59*(5), 387-392. doi:10.1016/s0361-9230(02)00940-1

Freeman, M. (2022). The World Mental Health Report: transforming mental health for all. *World Psychiatry, 21*(3), 391-392. doi:10.1002/wps.21018

Fritz, J., de Graaff, A. M., Caisley, H., van Harmelen, A. L., & Wilkinson, P. O. (2018). A Systematic Review of Amenable Resilience Factors That Moderate and/or Mediate the Relationship Between Childhood Adversity and Mental Health in Young People. *Front Psychiatry, 9*, 230. doi:10.3389/fpsyt.2018.00230

Frost, A., Hoyt, L. T., Chung, A. L., & Adam, E. K. (2015). Daily life with depressive symptoms: Gender differences in adolescents' everyday emotional experiences. *J Adolesc, 43*, 132-141. doi:10.1016/j.adolescence.2015.06.001

Fusar-Poli, P., Bonoldi, I., Yung, A. R., Borgwardt, S., Kempton, M. J., Valmaggia, L., . . . McGuire, P. (2012). Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry, 69*(3), 220-229. doi:10.1001/archgenpsychiatry.2011.1472

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., . . . Yung, A. (2013). The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA psychiatry, 70*(1), 107-120. doi:10.1001/jamapsychiatry.2013.269

Fusar-Poli, P., McGuire, P., & Borgwardt, S. (2012). Mapping prodromal psychosis: a critical review of neuroimaging studies. *Eur Psychiatry, 27*(3), 181-191. doi:10.1016/j.eurpsy.2011.06.006

Fusar-Poli, P., Rocchetti, M., Sardella, A., Avila, A., Brandizzi, M., Caverzasi, E., . . . McGuire, P. (2015). Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. *Br J Psychiatry, 207*(3), 198-206. doi:10.1192/bjp.bp.114.157115

Gan, G., Ma, R., Reichert, M., Giurgiu, M., Ebner-Priemer, U. W., Meyer-Lindenberg, A., & Tost, H. (2021). Neural correlates of affective benefit from real-life social contact and implications for psychiatric resilience. *JAMA psychiatry, 78*(7), 790-792.

Gao, C., Wenhua, L., Liu, Y., Ruan, X., Chen, X., Liu, L., . . . Jiang, X. (2016). Decreased subcortical and increased cortical degree centrality in a nonclinical college student sample with subclinical depressive symptoms: a resting-state fMRI study. *Front Hum Neurosci., 10*, 617.

Garland, E., Froeliger, B., & Howard, M. (2014). Mindfulness Training Targets Neurocognitive Mechanisms of Addiction at the Attention-Appraisal-Emotion Interface. *Front. Psychiatr, 4*(173). doi:10.3389/fpsyt.2013.00173

Gee, D. G., McEwen, S. C., Forsyth, J. K., Haut, K. M., Bearden, C. E., Addington, J., . . . Cannon, T. D. (2015). Reliability of an fMRI paradigm for emotional processing in a multisite longitudinal study. *Hum Brain Mapp, 36*(7), 2558-2579. doi:10.1002/hbm.22791

Gerhardt, S., Berhe, O., Moessnang, C., Horning, M., Kiefer, F., Tost, H., & Vollstädt‐Klein, S. (2022). Lack of amygdala habituation to negative emotional faces in alcohol use disorder and the relation to adverse childhood experiences. *Addict. Biol., 28*(1), e13251.

Gianaros, P. J., Horenstein, J. A., Cohen, S., Matthews, K. A., Brown, S. M., Flory, J. D., . . . Hariri, A. R. (2007). Perigenual anterior cingulate morphology covaries with perceived social standing. *Soc Cogn Affect Neurosci, 2*(3), 161-173. doi:10.1093/scan/nsm013

Gibb, B. E., Schofield, C. A., & Coles, M. E. (2009). Reported History of Childhood Abuse and Young Adults' Information-Processing Biases for Facial Displays of Emotion. *Child Maltreatment, 14*(2), 148-156. doi:10.1177/1077559508326358

Gilpin, N. W., Herman, M. A., & Roberto, M. (2015). The Central Amygdala as an Integrative Hub for Anxiety and Alcohol Use Disorders. *Biol. Psychiatry, 77*(10), 859-869. doi:https://doi.org/10.1016/j.biopsych.2014.09.008

Gilpin, N. W., & Koob, G. F. (2008). Neurobiology of alcohol dependence: focus on motivational mechanisms. *Alcohol Res Health., 31*(3), 185-195.

Glaesmer, H., Grande, G., Braehler, E., & Roth, M. (2011). The German Version of the Satisfaction with Life Scale (SWLS): Psychometric Properties, Validity, and

Population-Based Norms. *Eur J Psychol Assess, 27*(4), 299-299. doi:10.1027/1015-5759/a000081

Glaesmer, H., Schulz, A., Hauser, W., Freyberger, H. J., Brahler, E., & Grabe, H. J. (2013). The childhood trauma screener (CTS) - development and validation of cut-off-scores for classificatory diagnostics. *Psychiatr Prax, 40*(4), 220-226. doi:10.1055/s-0033-1343116

Glahn, D. C., Lovallo, W. R., & Fox, P. T. (2007). Reduced Amygdala Activation in Young Adults at High Risk of Alcoholism: Studies from the Oklahoma Family Health Patterns Project. *Biol. Psychiatry, 61*(11), 1306-1309. doi:https://doi.org/10.1016/j.biopsych.2006.09.041

Glanzman, D. L. (2011). Olfactory habituation: fresh insights from flies. *Proc Natl Acad Sci U S A, 108*(36), 14711-14712. doi:10.1073/pnas.1111230108

Goodman, E., Adler, N. E., Kawachi, I., Frazier, A. L., Huang, B., & Colditz, G. A. (2001). Adolescents' perceptions of social status: development and evaluation of a new indicator. *Pediatrics, 108*(2), e31-e31.

Goodman, F. R., Rum, R., Silva, G., & Kashdan, T. B. (2021). Are people with social anxiety disorder happier alone? *J Anxiety Disord, 84*, 102474. doi:10.1016/j.janxdis.2021.102474

Gorka, A. X., Hanson, J. L., & Radtke, S. R. H., A.R. (2014). Reduced hippocampal and medial prefrontal gray matter mediate the association between reported childhood maltreatment and trait anxiety in adulthood and predict sensitivity to future life stress. *Biol Mood Anxiety Disord., 4*(1), 1-10.

Gorka, S. M., Fitzgerald, D. A., King, A. C., & Phan, K. L. (2013). Alcohol attenuates amygdala–frontal connectivity during processing social signals in heavy social drinkers. *Psychopharmacology, 229*(1), 141-154. doi:10.1007/s00213-013-3090-0

Gowin, J. L., Vatsalya, V., Westman, J. G., Schwandt, M. L., Bartlett, S., Heilig, M., . . . Ramchandani, V. A. (2016). The Effect of Varenicline on the Neural Processing of Fearful Faces and the Subjective Effects of Alcohol in Heavy Drinkers. *Alcohol Clin Exp Res., 40*(5), 979-987. doi:10.1111/acer.13046

Grabe, H. J., Schulz, A., Schmidt, C. O., Appel, K., Driessen, M., Wingenfeld, K., . . . Freyberger, H. J. (2012). Ein Screeninginstrument für Missbrauch und Vernachlässigung in der Kindheit: der Childhood Trauma Screener (CTS). [A Brief Instrument for the Assessment of Childhood Abuse and Neglect: the Childhood Trauma Screener (CTS)]. *Psychiatr Prax, 39*(03), 109-115.

Hannöver, W., Michael, A., Meyer, C., Rumpf, H.-J., Hapke, U., & John, U. (2004). Die Sense of coherence Scale von Antonovsky und das Vorliegen einer psychiatrischen Diagnose. *Psychother Psychosom Med Psychol, 54*, 179-186.

Hanson, J. L., Nacewicz, B. M., Sutterer, M. J., Cayo, A. A., Schaefer, S. M., Rudolph, K. D., . . . Davidson, R. J. (2015). Behavioral Problems After Early Life Stress: Contributions of the Hippocampus and Amygdala. *Biological psychiatry, 77*(4), 314-323. doi:https://doi.org/10.1016/j.biopsych.2014.04.020

Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biol Psychiatry, 63*(10), 927-934. doi:10.1016/j.biopsych.2008.03.015

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., . . . Weinberger, D. R. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297*(5580), 400-403. doi:10.1126/science.1071829

Hariri, A. R., Tessitore, A., Mattay, V. S., Fera, F., & Weinberger, D. R. (2002). The amygdala response to emotional stimuli: a comparison of faces and scenes. *Neuroimage, 17*(1), 317-323. doi:10.1006/nimg.2002.1179

Harris, J. D. (1943). *Habituatory response decrement in the intact organism* (Vol. 40).

Hartmann, J. A., Nelson, B., Spooner, R., Paul Amminger, G., Chanen, A., Davey, C. G., . . . McGorry, P. D. (2019). Broad clinical high-risk mental state (CHARMS): Methodology of a cohort study validating criteria for pluripotent risk. *Early Interv Psychiatry, 13*(3), 379-386. doi:10.1111/eip.12483

Harville, D. A. (1977). Maximum likelihood approaches to variance component estimation and to related problems. *JASA, 72*(358), 320-338.

Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect Disord., 134*(1-3), 20-31.

Heilig, M., Egli, M., Crabbe, J. C., & Becker, H. C. (2010). REVIEW: Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked? *Addict. Biol., 15*(2), 169-184. doi:https://doi.org/10.1111/j.1369-1600.2009.00194.x

Heim, C., Entringer, S., & Buss, C. (2019). Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health. *Psychoneuroendocrinology, 105*, 123-137. doi:10.1016/j.psyneuen.2018.12.011

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry, 49*(12), 1023-1039. doi:10.1016/s0006-3223(01)01157-x

Heim, C., Shugart, M., & Craighead, W. E. N., C. B. (2010). Neurobiological and psychiatric consequences of child abuse and neglect. *Dev. Psychobiol., 52*(7), 671-690.

Hein, T. C., Goetschius, L. G., McLoyd, V. C., Brooks-Gunn, J., McLanahan, S. S., Mitchell, C., . . . Monk, C. S. (2020). Childhood violence exposure and social deprivation are linked to adolescent threat and reward neural function. *Soc Cogn Affect Neurosci, 15*(11), 1252-1259. doi:10.1093/scan/nsaa144

Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci, 20*(2), 78-84. doi:10.1016/s0166-2236(96)10069-2

Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., . . . Myers, B. (2016). Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. *Compr Physiol, 6*(2), 603-621. doi:10.1002/cphy.c150015

Heron, K. E., & Smyth, J. M. (2010). Ecological momentary interventions: incorporating mobile technology into psychosocial and health behaviour treatments. *Br J Health Psychol, 15*(Pt 1), 1-39. doi:10.1348/135910709x466063

Herzberg, P. Y., Glaesmer, H., & Hoyer, J. (2006). Separating optimism and pessimism: a robust psychometric analysis of the revised Life Orientation Test (LOT-R). *Psychol Assess, 18*(4), 433-438. doi:10.1037/1040-3590.18.4.433

Hibell, B., Guttormsson, U., Ahlström, S., Balakireva, O., Bjarnason, T., Kokkevi, A., & Kraus, L. (2009). The 2007 ESPAD report. *Substance use among students in, 35*, 1-408.

Hillis, S., Mercy, J., Amobi, A., & Kress, H. (2016). Global Prevalence of Past-year Violence Against Children: A Systematic Review and Minimum Estimates. *Pediatrics, 137*(3), e20154079. doi:10.1542/peds.2015-4079

Holmes, A. J., & Pizzagalli, D. A. (2007). Task feedback effects on conflict monitoring and executive control: relationship to subclinical measures of depression. *Emotion, 7*(1), 68.

Holz, N. E., Berhe, O., Sacu, S., Schwarz, E., Tesarz, J., Heim, C., & Tost, H. (2022). Early social adversity altered brain functional connectivity and mental health. *Biol. Psychiatry*. doi:doi: https://doi.org/10.1016/j.biopsych.2022.10.019.

Holz, N. E., Häge, A., Plichta, M. M., Boecker-Schlier, R., Jennen-Steinmetz, C., Baumeister, S., . . . Brandeis, D. (2021). Early maternal care and amygdala habituation to emotional stimuli in adulthood. *Soc Cogn Affect Neurosci, 16*(10), 1100-1110. doi:10.1093/scan/nsab059

Holz, N. E., Tost, H., & Meyer-Lindenberg, A. (2020). Resilience and the brain: a key role for regulatory circuits linked to social stress and support. *Mol Psychiatry, 25*(2), 379-396. doi:10.1038/s41380-019-0551-9

Huettel, S. A., Song, A. W., & McCarthy, G. (2004). *Functional magnetic resonance imaging* (Vol. 1): Sinauer Associates Sunderland.

Hur, J., Kaplan, C. M., Smith, J. F., Bradford, D. E., Fox, A. S., Curtin, J. J., & Shackman, A. J. (2018). Acute alcohol administration dampens central extended amygdala reactivity. *Sci. Rep., 8*(1), 16702. doi:10.1038/s41598-018-34987-3

Infurna, F. J., Rivers, C. T., Reich, J., & Zautra, A. J. (2015). Childhood trauma and personal mastery: their influence on emotional reactivity to everyday events in a community sample of middle-aged adults. *PLoS One, 10*(4), e0121840. doi:10.1371/journal.pone.0121840

Jahng, S., Wood, P. K., & Trull, T. J. (2008). Analysis of affective instability in ecological momentary assessment: Indices using successive difference and group comparison via multilevel modeling. *Psychol Methods, 13*(4), 354-375. doi:10.1037/a0014173

Jerusalem, M., & Schwarzer, R. (1992). Self-efficacy as a resource factor in stress appraisal processes. In *Self-efficacy: Thought control of action* (pp. 195-213). Washington, DC: Hemisphere.

Judd, L. L. (2012). Dimensional paradigm of the long-term course of unipolar major depressive disorder. *Depress Anxiety, 29*(3), 167-171. doi:10.1002/da.21934

Kanske, P., Heissler, J., Schönfelder, S., & Wessa, M. (2012). Neural correlates of emotion regulation deficits in remitted depression: the influence of regulation strategy, habitual regulation use, and emotional valence. *Neuroimage, 61*(3), 686-693. doi:10.1016/j.neuroimage.2012.03.089

Keshavan, M. S., DeLisi, L. E., & Seidman, L. J. (2011). Early and broadly defined psychosis risk mental states. *Schizophr Res, 126*(1-3), 1-10. doi:10.1016/j.schres.2010.10.006

Kim, H., Somerville, L. H., Johnstone, T., Alexander, A. L., & Whalen, P. J. (2003). Inverse amygdala and medial prefrontal cortex responses to surprised faces. *Neuroreport, 14*(18), 2317-2322. doi:10.1097/00001756-200312190-00006

Kim, J., Cicchetti, D., Rogosch, F. A., & Manly, J. T. (2009). Child maltreatment and trajectories of personality and behavioral functioning: implications for the development of personality disorder. *Dev Psychopathol, 21*(3), 889-912. doi:10.1017/s0954579409000480

Kim, Y. J., van Rooij, S. J. H., Ely, T. D., Fani, N., Ressler, K. J., Jovanovic, T., & Stevens, J. S. (2019). Association between posttraumatic stress disorder severity and amygdala habituation to fearful stimuli. *Depress Anxiety, 36*(7), 647-658. doi:10.1002/da.22928

Kirsch, D., Nemeroff, C. M., & Lippard, E. T. C. (2020). Early Life Stress and Substance Use Disorders: Underlying Neurobiology and Pathways to Adverse Outcomes. *ARS, 1*(1), 29-47. doi:10.1007/s42844-020-00005-7

Knoll, N., Rieckmann, N., & Schwarzer, R. (2005). Coping as a mediator between personality and stress outcomes: a longitudinal study with cataract surgery patients. *Eur J Pers, 19*(3), 229-247.

Kober, H. (2014). Emotion regulation in substance use disorders. In *Handbook of emotion regulation, 2nd ed.* (pp. 428-446). New York, NY, US: The Guilford Press.

Koob, G. F. (2003). Neuroadaptive mechanisms of addiction: studies on the extended amygdala. *European Neuropsychopharmacology, 13*(6), 442-452. doi:https://doi.org/10.1016/j.euroneuro.2003.08.005

Koob, G. F. (2009). Brain stress systems in the amygdala and addiction. *Brain Res, 1293*, 61-75. doi:10.1016/j.brainres.2009.03.038

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of Addiction. *Neuropsychopharmacology, 35*(1), 217-238. doi:10.1038/npp.2009.110

Kopera, M., Trucco, E. M., Jakubczyk, A., Suszek, H., Michalska, A., Majewska, A., . . . Wojnar, M. (2018). Interpersonal and intrapersonal emotional processes in individuals treated for alcohol use disorder and non-addicted healthy individuals. *Addict. Behav., 79*, 8-13. doi:https://doi.org/10.1016/j.addbeh.2017.12.006

Koval, P., Brose, A., Pe, M. L., Houben, M., Erbas, Y., Champagne, D., & Kuppens, P. (2015). Emotional inertia and external events: The roles of exposure, reactivity, and recovery. *Emotion, 15*(5), 625-636. doi:10.1037/emo0000059

Kozhuharova, P., Saviola, F., Ettinger, U., & Allen, P. (2020). Neural correlates of social cognition in populations at risk of psychosis: A systematic review. *Neurosci Biobehav Rev, 108*, 94-111. doi:10.1016/j.neubiorev.2019.10.010

Kraiss, J. T., ten Klooster, P. M., Moskowitz, J. T., & Bohlmeijer, E. T. (2020). The relationship between emotion regulation and well-being in patients with mental disorders: A meta-analysis. *Compr Physiol, 102*, 152189. doi:https://doi.org/10.1016/j.comppsych.2020.152189

Kuzminskaite, E., Penninx, B., van Harmelen, A. L., Elzinga, B. M., Hovens, J., & Vinkers, C. H. (2021). Childhood Trauma in Adult Depressive and Anxiety Disorders: An Integrated Review on Psychological and Biological Mechanisms in the NESDA Cohort. *J Affect Disord, 283*, 179-191. doi:10.1016/j.jad.2021.01.054

Laird, N. M., & Ware, J. H. (1982). Random-effects models for longitudinal data. *Biometrics, 38*(4), 963-974.

Lampert, T., Kroll, L. E., Müters, S., & Stolzenberg, H. (2013). Measurement of the socioeconomic status within the German Health Update 2009 (GEDA) [Messung des sozioökonomischen Status in der Studie „Gesundheit in Deutschland aktuell“ (GEDA)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz, 56*, 131-146. doi:10.1007/s00103-012-1583-3

Lancet. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry, 9*(2), 137-150. doi:10.1016/s2215-0366(21)00395-3

Laux, L., Glanzmann, P., Schaffner, P., & Spielberger, C. D. (1981). Das state-trait-angstinventar [The state-trait anxiety inventory]. *Hogrefe, Göttingen (in German)*.

Le Berre, A. P. (2019). Emotional processing and social cognition in alcohol use disorder. *Neuropsychology, 33*(6), 808-821. doi:10.1037/neu0000572

Lederbogen, F., Kirsch, P., Haddad, L., Streit, F., Tost, H., Schuch, P., . . . Deuschle, M. (2011). City living and urban upbringing affect neural social stress processing in humans. *Nature, 474*(7352), 498-501.

LeDoux, J. (2007). The amygdala. *Curr Biol, 17*(20), R868-874. doi:10.1016/j.cub.2007.08.005

Lee, Y. Y., Stockings, E. A., Harris, M. G., Doi, S. A. R., Page, I. S., Davidson, S. K., & Barendregt, J. J. (2019). The risk of developing major depression among individuals with subthreshold depression: a systematic review and meta-analysis of longitudinal cohort studies. *Psychol Med, 49*(1), 92-102. doi:10.1017/s0033291718000557

Li, J., Zhang, G., Wang, J., Liu, D., Wan, C., Fang, J., . . . Zhu, W. (2022). Experience-dependent associations between distinct subtypes of childhood trauma and brain function and architecture. *Quant Imaging Med Surg. , 12*(2), 1172.

Linhartová, P., Látalová, A., Kóša, B., Kašpárek, T., Schmahl, C., & Paret, C. (2019). fMRI neurofeedback in emotion regulation: A literature review. *Neuroimage, 193*, 75-92. doi:10.1016/j.neuroimage.2019.03.011

Little, R. J., Lewitzky, S., Heeringa, S., Lepkowski, J., & Kessler, R. C. (1997). Assessment of weighting methodology for the National Comorbidity Survey. *Am J Epidemiol, 146*(5), 439-449. doi:10.1093/oxfordjournals.aje.a009297

Liu, W. Z., Zhang, W. H., Zheng, Z. H., Zou, J. X., Liu, X. X., Huang, S. H., . . . Pan, B. X. (2020). Identification of a prefrontal cortex-to-amygdala pathway for chronic stress-induced anxiety. *Nat Commun, 11*(1), 2221. doi:10.1038/s41467-020-15920-7

Lonsdorf, T. B., Golkar, A., Lindstöm, K. M., Fransson, P., Schalling, M., Ohman, A., & Ingvar, M. (2011). 5-HTTLPR and COMTval158met genotype gate amygdala reactivity and habituation. *Biol Psychol, 87*(1), 106-112. doi:10.1016/j.biopsycho.2011.02.014

Lovinger, D. M., & Kash, T. L. (2015). Mechanisms of Neuroplasticity and Ethanol's Effects on Plasticity in the Striatum and Bed Nucleus of the Stria Terminalis. *Alcohol research : current reviews, 37*(1), 109-124.

Lukow, P. B., Kiemes, A., Kempton, M. J., Turkheimer, F. E., McGuire, P., & Modinos, G. (2021). Neural correlates of emotional processing in psychosis risk and onset - A systematic review and meta-analysis of fMRI studies. *Neurosci Biobehav Rev, 128*, 780-788. doi:10.1016/j.neubiorev.2021.03.010

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci, 10*(6), 434-445. doi:10.1038/nrn2639

Majer, M., Nater, U. M., Lin, J. M., Capuron, L., & Reeves, W. C. (2010). Association of childhood trauma with cognitive function in healthy adults: a pilot study. *BMC Neurol, 10*, 61. doi:10.1186/1471-2377-10-61

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage, 19*(3), 1233-1239. doi:10.1016/s1053-8119(03)00169-1

Malhi, G. S., Hamilton, A., Morris, G., Mannie, Z., Das, P., & Outhred, T. (2017). The promise of digital mood tracking technologies: are we heading on the right track? *Evid Based Ment Health, 20*(4), 102-107. doi:10.1136/eb-2017-102757

Margraf, J. (1994). Diagnostisches Kurzinterview bei psychischen Störungen (MINI-DIPS). In. Berlin, Heidelberg, New York: Springer.

Margraf, J., Cwik, J. C., Pflug, V., & Schneider, S. (2017). Strukturierte klinische Interviews zur Erfassung psychischer Störungen über die Lebensspanne:

Gütekriterien und Weiterentwicklungen der DIPS-Verfahren. [Structured clinical interviews for mental disorders across the life span: Psychometric quality and further developments of the DIPS open access interviews.]. *Zeitschrift für Klinische Psychologie und Psychotherapie: Forschung und Praxis, 46*(3), 176-186. doi:10.1026/1616-3443/a000430

Margraf, J., Ehlers, A., & Roth, W. T. (1987). Case studies and clinical replication series: panic attack associated with perceived heart rate acceleration: a case report. *Behav. Ther., 18*(1), 84-89.

Marinkovic, K., Oscar-Berman, M., Urban, T., O'Reilly, C. E., Howard, J. A., Sawyer, K., & Harris, G. J. (2009). Alcoholism and Dampened Temporal Limbic Activation to Emotional Faces. *Alcoholism: Clinical and Experimental Research, 33*(11), 1880-1892. doi:https://doi.org/10.1111/j.1530-0277.2009.01026.x

Markon, K. E., Chmielewski, M., & Miller, C. J. (2011). The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review. *Psychol Bull, 137*(5), 856-879. doi:10.1037/a0023678

Marusak, H. A., Martin, K. R., Etkin, A., & Thomason, M. E. (2015). Childhood trauma exposure disrupts the automatic regulation of emotional processing. *Neuropsychopharmacology, 40*(5), 1250-1258. doi:10.1038/npp.2014.311

Matthews, G., Jones, D. M., & Chamberlain, A. G. (1990). Refining the measurement of mood: The UWIST Mood Adjective Checklist. *British Journal of Psychology, 81*(1), 17-42. doi:10.1111/j.2044-8295.1990.tb02343.x

Mc Elroy, S., & Hevey, D. (2014). Relationship between adverse early experiences, stressors, psychosocial resources and wellbeing. *Child Abuse Negl, 38*(1), 65-75. doi:10.1016/j.chiabu.2013.07.017

McDiarmid, T. A., Bernardos, A. C., & Rankin, C. H. (2017). Habituation is altered in neuropsychiatric disorders-A comprehensive review with recommendations for experimental design and analysis. *Neurosci Biobehav Rev, 80*, 286-305. doi:10.1016/j.neubiorev.2017.05.028

McDonald, A. J. (1998). Cortical pathways to the mammalian amygdala. *Prog Neurobiol, 55*(3), 257-332. doi:10.1016/s0301-0082(98)00003-3

McEwen, B. S., Gray, J. A., & Nasca, C. (2015). Recognizing Resilience: Learning from the Effects of Stress on the Brain. *Neurobiology of stress, 1*, 1-11. doi:10.1016/j.ynstr.2014.09.001

McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress Effects on Neuronal Structure: Hippocampus, Amygdala, and Prefrontal Cortex. *Neuropsychopharmacology, 41*(1), 3-23. doi:10.1038/npp.2015.171

McGorry, P. D., Hartmann, J. A., Spooner, R., & Nelson, B. (2018). Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. *World Psychiatry, 17*(2), 133-142. doi:10.1002/wps.20514

McGorry, P. D., & Mei, C. (2018). Ultra-high-risk paradigm: lessons learnt and new directions. *Evid Based Ment Health, 21*(4), 131-133. doi:10.1136/ebmental-2018-300061

McGrath, J. J., McLaughlin, K. A., Saha, S., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., . . . Kessler, R. C. (2017). The association between childhood adversities and subsequent first onset of psychotic experiences: a cross-national analysis of 23 998 respondents from 17 countries. *Psychol Med, 47*(7), 1230-1245. doi:10.1017/s0033291716003263

McKay, M. T., Cannon, M., Chambers, D., Conroy, R. M., Coughlan, H., Dodd, P., . . . Clarke, M. C. (2021). Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta Psychiatr Scand, 143*(3), 189-205. doi:10.1111/acps.13268

McLaughlin, K. A., Busso, D. S., Duys, A., Green, J. G., Alves, S., Way, M., & Sheridan, M. A. (2014). Amygdala response to negative stimuli predicts PTSD symptom onset following a terrorist attack. *Depress Anxiety, 31*(10), 834-842. doi:10.1002/da.22284

McLaughlin, K. A., Peverill, M., Gold, A. L., Alves, S., & Sheridan, M. A. (2015). Child Maltreatment and Neural Systems Underlying Emotion Regulation. *J Am Acad Child Adolesc Psychiatry, 54*(9), 753-762. doi:10.1016/j.jaac.2015.06.010

Meyer-Lindenberg, A., & Tost, H. (2012). Neural mechanisms of social risk for psychiatric disorders. *Nat Neurosci, 15*(5), 663-668. doi:10.1038/nn.3083

Miller, T. J., McGlashan, T. H., Rosen, J. L., Somjee, L., Markovich, P. J., Stein, K., & Woods, S. W. (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *Am J Psychiatry, 159*(5), 863-865. doi:10.1176/appi.ajp.159.5.863

Miller, W. R., & Del Boca, F. K. (1994). Measurement of drinking behavior using the Form 90 family of instruments. *J Stud Alcohol Suppl.*(12), 112-118.

Murty, V. P., Labar, K. S., & Adcock, R. A. (2012). Threat of punishment motivates memory encoding via amygdala, not midbrain, interactions with the medial temporal lobe. *J Neurosci, 32*(26), 8969-8976. doi:10.1523/jneurosci.0094-12.2012

Myin-Germeys, I., Kasanova, Z., Vaessen, T., Vachon, H., Kirtley, O., Viechtbauer, W., & Reininghaus, U. (2018). Experience sampling methodology in mental health research: new insights and technical developments. *World Psychiatry, 17*(2), 123-132. doi:10.1002/wps.20513

Myin-Germeys, I., Klippel, A., Steinhart, H., & Reininghaus, U. (2016). Ecological momentary interventions in psychiatry. *Curr Opin Psychiatry, 29*(4), 258-263. doi:10.1097/yco.0000000000000255

Myin-Germeys, I., van Os, J., Schwartz, J. E., Stone, A. A., & Delespaul, P. A. (2001). Emotional reactivity to daily life stress in psychosis. *Arch Gen Psychiatry, 58*(12), 1137-1144. doi:10.1001/archpsyc.58.12.1137

Norman, R. E., Byambaa, M., De, R., Butchart, A., Scott, J., & Vos, T. (2012). The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS Med, 9*(11), e1001349. doi:10.1371/journal.pmed.1001349

O'Daly, O. G., Trick, L., Scaife, J., Marshall, J., Ball, D., Phillips, M. L., . . . Duka, T. (2012). Withdrawal-Associated Increases and Decreases in Functional Neural Connectivity Associated with Altered Emotional Regulation in Alcoholism. *Neuropsychopharmacology, 37*(10), 2267-2276. doi:10.1038/npp.2012.77

Oberleitner, L. M., Smith, P. H., Weinberger, A. H., Mazure, C. M., & McKee, S. A. (2015). Impact of Exposure to Childhood Maltreatment on Transitions to Alcohol Dependence in Women and Men. *Child Maltreat, 20*(4), 301-308. doi:10.1177/1077559515591270

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A, 87*(24), 9868-9872. doi:10.1073/pnas.87.24.9868

Oshio, T., Umeda, M., & Kawakami, N. (2013). Impact of interpersonal adversity in childhood on adult mental health: how much is mediated by social support and socio-economic status in Japan? *Public Health, 127*(8), 754-760. doi:10.1016/j.puhe.2013.05.005

Palmier-Claus, J. E., Myin-Germeys, I., Barkus, E., Bentley, L., Udachina, A., Delespaul, P. A., . . . Dunn, G. (2011). Experience sampling research in

individuals with mental illness: reflections and guidance. *Acta Psychiatr Scand, 123*(1), 12-20. doi:10.1111/j.1600-0447.2010.01596.x

Pavlacic, J. M., & Young, J. (2020). Process-Based Cognitive Behavioral Therapy: A Framework for Conceptualization and Treatment. *Clinical Case Studies, 19*(6), 456-472. doi:10.1177/1534650120951858

Peacock, A., Leung, J., Larney, S., Colledge, S., Hickman, M., Rehm, J., . . . Degenhardt, L. (2018). Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. *Addiction, 113*(10), 1905-1926. doi:10.1111/add.14234

Pechtel, P., Dutra, S. J., Goetz, E. L., & Pizzagalli, D. A. (2013). Blunted reward responsiveness in remitted depression. *J Psychiatr Res, 47*(12), 1864-1869. doi:10.1016/j.jpsychires.2013.08.011

Pechtel, P., & Pizzagalli, D. A. (2011). Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology (Berl), 214*(1), 55-70. doi:10.1007/s00213-010-2009-2

Perez-Rodriguez, M. M., New, A. S., Goldstein, K. E., Rosell, D., Yuan, Q., Zhou, Z., . . . Hazlett, E. A. (2017). Brain-derived neurotrophic factor Val66Met genotype modulates amygdala habituation. *Psychiatry Res Neuroimaging, 263*, 85-92. doi:10.1016/j.pscychresns.2017.03.008

Pessoa, L., & Ungerleider, L. G. (2004). Neuroimaging studies of attention and the processing of emotion-laden stimuli. *Prog Brain Res, 144*, 171-182. doi:10.1016/s0079-6123(03)14412-3

Petit, G., Luminet, O., Maurage, F., Tecco, J., Lechantre, S., Ferauge, M., . . . de Timary, P. (2015). Emotion Regulation in Alcohol Dependence. *Alcohol Clin Exp Res, 39*(12), 2471-2479. doi:10.1111/acer.12914

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*(2), 331-348. doi:10.1006/nimg.2002.1087

Phillips, M. L., Medford, N., Young, A. W., Williams, L., Williams, S. C., Bullmore, E. T., . . . Brammer, M. J. (2001). Time courses of left and right amygdalar responses to fearful facial expressions. *Hum Brain Mapp, 12*(4), 193-202. doi:10.1002/1097-0193(200104)12:4<193::aid-hbm1015>3.0.co;2-a

Pietrek, C., Elbert, T., Weierstall, R., Muller, O., & Rockstroh, B. (2013). Childhood adversities in relation to psychiatric disorders. *Psychiatry Res, 206*(1), 103-110. doi:10.1016/j.psychres.2012.11.003

Pinheiro, P. S. (2006). Violence against children. *ATAR Roto Presse SA*.

Plichta, M. M., Grimm, O., Morgen, K., Mier, D., Sauer, C., Haddad, L., . . . Meyer-Lindenberg, A. (2014). Amygdala habituation: a reliable fMRI phenotype. *Neuroimage, 103*, 383-390. doi:10.1016/j.neuroimage.2014.09.059

Plichta, M. M., Schwarz, A. J., Grimm, O., Morgen, K., Mier, D., Haddad, L., . . . Meyer-Lindenberg, A. (2012). Test-retest reliability of evoked BOLD signals from a cognitive-emotive fMRI test battery. *Neuroimage, 60*(3), 1746-1758. doi:10.1016/j.neuroimage.2012.01.129

Preckel, K., Trautwein, F. M., Paulus, F. M., Kirsch, P., Krach, S., Singer, T., & Kanske, P. (2019). Neural mechanisms of affective matching across faces and scenes. *Sci Rep, 9*(1), 1492. doi:10.1038/s41598-018-37163-9

Puetz, V. B., Viding, E., Gerin, M. I., Pingault, J.-B., Sethi, A., Knodt, A. R., . . . McCrory, E. (2020). Investigating patterns of neural response associated with childhood abuse v. childhood neglect. *Psychol Med., 50*(8), 1398-1407. doi:10.1017/S003329171900134X

Raine, A., & Benishay, D. (1995). The SPQ-B: A brief screening instrument for schizotypal personality disorder. *J Pers Disord, 9*(4), 346-355.

Ramaswami, M. (2014). Network plasticity in adaptive filtering and behavioral habituation. *Neuron, 82*(6), 1216-1229. doi:10.1016/j.neuron.2014.04.035

Rankin, C. H., Abrams, T., Barry, R. J., Bhatnagar, S., Clayton, D. F., Colombo, J., . . . Thompson, R. F. (2009). Habituation revisited: an updated and revised description of the behavioral characteristics of habituation. *Neurobiol Learn Mem, 92*(2), 135-138. doi:10.1016/j.nlm.2008.09.012

Rauch, S. L., Shin, L. M., & Wright, C. I. (2003). Neuroimaging studies of amygdala function in anxiety disorders. *Ann N Y Acad Sci, 985*, 389-410. doi:10.1111/j.1749-6632.2003.tb07096.x

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., . . . Pitman, R. K. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry, 47*(9), 769-776. doi:10.1016/s0006-3223(00)00828-3

Redman, D. (2008). Coping-Related Substance Use Motives and Stressful Life Experiences Among People with a History of Incarceration. *J. Soc. Work Pract. Addict, 8*(4), 490-510. doi:10.1080/15332560802323956

Reichert, M., Braun, U., Gan, G., Reinhard, I., Giurgiu, M., Ma, R., . . . Meyer-Lindenberg, A. (2020). A neural mechanism for affective well-being: Subgenual cingulate cortex mediates real-life effects of nonexercise activity on energy. *Sci Adv, 6*(45). doi:10.1126/sciadv.aaz8934

Reichert, M., Gan, G., Renz, M., Braun, U., Brüßler, S., Timm, I., . . . Meyer-Lindenberg, A. (2021). Ambulatory assessment for precision psychiatry: Foundations, current developments and future avenues. *Exp Neurol, 345*, 113807. doi:10.1016/j.expneurol.2021.113807

Reichert, M., Tost, H., Reinhard, I., Schlotz, W., Zipf, A., Salize, H. J., . . . Ebner-Priemer, U. W. (2017). Exercise versus Nonexercise Activity: E-diaries Unravel Distinct Effects on Mood. *Med Sci Sports Exerc, 49*(4), 763-773. doi:10.1249/MSS.0000000000001149

Robinaugh, D. J., Brown, M. L., Losiewicz, O. M., Jones, P. J., Marques, L., & Baker, A. W. (2020). Towards a precision psychiatry approach to anxiety disorders with ecological momentary assessment: the example of panic disorder. *Gen Psychiatr, 33*(1), e100161. doi:10.1136/gpsych-2019-100161

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev, 18*(3), 247-291. doi:10.1016/0165-0173(93)90013-p

Rock, P. L., Roiser, J., Riedel, W. J., & Blackwell, A. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med., 44*(10), 2029-2040.

Rodríguez, M. R., Nuevo, R., Chatterji, S., & Ayuso-Mateos, J. L. (2012). Definitions and factors associated with subthreshold depressive conditions: a systematic review. *BMC psychiatry, 12*, 181. doi:10.1186/1471-244x-12-181

Rosen, B. R., & Savoy, R. L. (2012). fMRI at 20: has it changed the world? *Neuroimage, 62*(2), 1316-1324. doi:10.1016/j.neuroimage.2012.03.004

Ruscio, A. M. (2019). Normal Versus Pathological Mood: Implications for Diagnosis. *Annu Rev Clin Psychol, 15*, 179-205. doi:10.1146/annurev-clinpsy-050718-095644

Schimmack, U., & Grob, A. (2000). Dimensional models of core affect: a quantitative comparison by means of structural equation modeling. *European Journal of Personality, 14*(4), 325-345.

Schückher, F., Sellin, T., Fahlke, C., & Engström, I. (2018). The Impact of Childhood Maltreatment on Age of Onset of Alcohol Use Disorder in Women. *Eur Addict Res, 24*(6), 278-285. doi:10.1159/000494766

Schulz, P., Schlotz, W., & Becker, P. (2004). Trierer Inventar zum chronischen stress (TICS)[Trier inventory for chronic stress (TICS)].

Schulz, U., & Schwarzer, R. (2003). Soziale Unterstützung bei der Krankheitsbewältigung. Die Berliner Social Support Skalen (BSSS). *Diagnostica, 49*, 73-82.

Schwarz, N. (2012). Why researchers should think "real-time": A cognitive rationale. In (pp. 22-42).

Schwarzer, R., & Jerusalem, M. (1999). *Skalen zur Erfassung von Lehrer- und Schülermerkmalen. Dokumentation der psychometrischen Verfahren im Rahmen der Wissenschaftlichen Begleitung des Modellversuchs Selbstwirksame Schulen*. Berlin: Freie Universität Berlin.

Schwarzer, R., & Schulz, U. (2003). Soziale Unterstützung bei der Krankheitsbewältigung: Die Berliner Social Support Skalen (BSSS). *Diagnostica, 49*(2), 73-82.

Schweiger, J. I., Capraz, N., Akdeniz, C., Braun, U., Ebalu, T., Moessnang, C., . . . Tost, H. (2021). Brain structural correlates of upward social mobility in ethnic minority individuals. *Soc Psychiatry Psychiatr Epidemiol*. doi:10.1007/s00127-021-02163-0

Scott, L. N., Stepp, S. D., Hallquist, M. N., Whalen, D. J., Wright, A. G. C., & Pilkonis, P. A. (2015). Daily shame and hostile irritability in adolescent girls with borderline personality disorder symptoms. *Personal Disord, 6*(1), 53-63. doi:10.1037/per0000107

Scott, L. N., Wright, A. G. C., Beeney, J. E., Lazarus, S. A., Pilkonis, P. A., & Stepp, S. D. (2017). Borderline personality disorder symptoms and aggression: A within-person process model. *J Abnorm Psychol, 126*(4), 429-440. doi:10.1037/abn0000272

Segal, Z. V. (1988). Appraisal of the self-schema construct in cognitive models of depression. *Psychol. Bull., 103*(2), 147.

Seiferth, N. Y., Pauly, K., Habel, U., Kellermann, T., Shah, N. J., Ruhrmann, S., . . . Kircher, T. (2008). Increased neural response related to neutral faces in individuals at risk for psychosis. *Neuroimage, 40*(1), 289-297. doi:10.1016/j.neuroimage.2007.11.020

Seo, D., & Sinha, R. (2015). Neuroplasticity and predictors of alcohol recovery. *Alcohol Res., 37*(1), 143.

Sethi, D., Bellis, M., Hughes, K., Gilbert, R., Mitis, F., & Gauden, G. (Eds.). (2013). *European report on preventing child maltreatment*: World Health Organization. Regional Office for Europe.

Shankman, S. A., Lewinsohn, P. M., Klein, D. N., Small, J. W., Seeley, J. R., & Altman, S. E. (2009). Subthreshold conditions as precursors for full syndrome disorders: a 15-year longitudinal study of multiple diagnostic classes. *J Child Psychol Psychiatry, 50*(12), 1485-1494. doi:10.1111/j.1469-7610.2009.02117.x

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annu Rev Clin Psychol, 4*, 1-32. doi:10.1146/annurev.clinpsy.3.022806.091415

Solhan, M. B., Trull, T. J., Jahng, S., & Wood, P. K. (2009). Clinical assessment of affective instability: comparing EMA indices, questionnaire reports, and retrospective recall. *Psychol Assess, 21*(3), 425-436. doi:10.1037/a0016869

Spinhoven, P., Penninx, B. W., Hickendorff, M., van Hemert, A. M., Bernstein, D. P., & Elzinga, B. M. (2014). Childhood Trauma Questionnaire: factor structure,

measurement invariance, and validity across emotional disorders. *Psychol Assess, 26*(3), 717-729. doi:10.1037/pas0000002

Stange, J. P., Kleiman, E. M., Mermelstein, R. J., & Trull, T. J. (2019). Using ambulatory assessment to measure dynamic risk processes in affective disorders. *J Affect Disord, 259*, 325-336. doi:10.1016/j.jad.2019.08.060

Stephens, D. N., Ripley, T. L., Borlikova, G., Schubert, M., Albrecht, D., Hogarth, L., & Duka, T. (2005). Repeated ethanol exposure and withdrawal impairs human fear conditioning and depresses long-term potentiation in rat amygdala and hippocampus. *Biol Psychiatry, 58*(5), 392-400. doi:10.1016/j.biopsych.2005.04.025

Stevens, J. S., van Rooij, S. J. H., Stenson, A. F., Ely, T. D., Powers, A., Clifford, A., . . . Jovanovic, T. (2021). Amygdala responses to threat in violence-exposed children depend on trauma context and maternal caregiving. *Dev Psychopathol*, 1-12. doi:10.1017/s0954579421001085

Steyer, R., Schwenkmezger, P., Notz, P., & Eid, M. (1997). Der Mehrdimensionale Befindlichkeitsfragebogen MDBF [Multidimensional mood questionnaire]. *Göttingen, Germany: Hogrefe*.

Stoeckel, L. E., Garrison, K. A., Ghosh, S., Wighton, P., Hanlon, C. A., Gilman, J. M., . . . Evins, A. E. (2014). Optimizing real time fMRI neurofeedback for therapeutic discovery and development. *Neuroimage Clin, 5*, 245-255. doi:10.1016/j.nicl.2014.07.002

Stone, A. A., & Broderick, J. E. (2007). Real-time data collection for pain: appraisal and current status. *Pain Med, 8 Suppl 3*, S85-93. doi:10.1111/j.1526-4637.2007.00372.x

Stone, A. A., & Shiffman, S. (1994). Ecological Momentary Assessment (Ema) in Behavioral Medicine. *Annals of Behavioral Medicine, 16*(3), 199-202. doi:10.1093/abm/16.3.199

Stone, A. A., Shiffman, S., Schwartz, J. E., Broderick, J. E., & Hufford, M. R. (2002). Patient non-compliance with paper diaries. *Bmj, 324*(7347), 1193-1194. doi:10.1136/bmj.324.7347.1193

Summerfield, C., Trittschuh, E. H., Monti, J. M., Mesulam, M. M., & Egner, T. (2008). Neural repetition suppression reflects fulfilled perceptual expectations. *Nat Neurosci, 11*(9), 1004-1006. doi:10.1038/nn.2163

Suzuki, S., Mell, M. M., O'Malley, S. S., Krystal, J. H., Anticevic, A., & Kober, H. (2020). Regulation of Craving and Negative Emotion in Alcohol Use Disorder. *Biological psychiatry: cognitive neuroscience and neuroimaging, 5*(2), 239-250. doi:https://doi.org/10.1016/j.bpsc.2019.10.005

Swartz, J. R., Knodt, A. R., Radtke, S. R., & Hariri, A. R. (2015). A neural biomarker of psychological vulnerability to future life stress. *Neuron, 85*(3), 505-511. doi:10.1016/j.neuron.2014.12.055

Swartz, J. R., Wiggins, J. L., Carrasco, M., Lord, C., & Monk, C. S. (2013). Amygdala habituation and prefrontal functional connectivity in youth with autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry, 52*(1), 84-93. doi:10.1016/j.jaac.2012.10.012

Tam, F. I., King, J. A., Geisler, D., Korb, F. M., Sareng, J., Ritschel, F., . . . Ehrlich, S. (2017). Altered behavioral and amygdala habituation in high-functioning adults with autism spectrum disorder: an fMRI study. *Sci Rep, 7*(1), 13611. doi:10.1038/s41598-017-14097-2

Thompson, R. F., & Spencer, W. A. (1966). Habituation: a model phenomenon for the study of neuronal substrates of behavior. *Psychol Rev, 73*(1), 16-43. doi:10.1037/h0022681

Topp, C. W., Østergaard, S. D., Søndergaard, S., & Bech, P. (2015). The WHO-5 Well-Being Index: a systematic review of the literature. *Psychother Psychosom, 84*(3), 167-176. doi:10.1159/000376585

Tost, H., Champagne, F. A., & Meyer-Lindenberg, A. (2015). Environmental influence in the brain, human welfare and mental health. *Nat Neurosci, 18*(10), 1421-1431. doi:10.1038/nn.4108

Tost, H., Reichert, M., Braun, U., Reinhard, I., Peters, R., Lautenbach, S., . . . Meyer-Lindenberg, A. (2019). Neural correlates of individual differences in affective benefit of real-life urban green space exposure. *Nat Neurosci, 22*(9), 1389-1393. doi:10.1038/s41593-019-0451-y

Tottenham, N., Hare, T. A., Quinn, B. T., McCarry, T. W., Nurse, M., Gilhooly, T., . . . Casey, B. J. (2010). Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev. Sci., 13*(1), 46-61. doi:https://doi.org/10.1111/j.1467-7687.2009.00852.x

Traue, H. C., Hrabal, V., & Kosarz, P. (2000). AlltagsBelastungsFragebogen (ABF): Zur inneren Konsistenz, Validierung und Stressdiagnostik mit dem deutschsprachigen daily stress inventory. *Verhaltenstherapie und Verhaltensmedizin, 21*(1), 15-38.

Trull, T. J., & Ebner-Priemer, U. W. (2009). Using experience sampling methods/ecological momentary assessment (ESM/EMA) in clinical assessment and clinical research: introduction to the special section. *Psychol Assess, 21*(4), 457-462. doi:10.1037/a0017653

Trull, T. J., & Ebner-Priemer, U. W. (2013). Ambulatory assessment. *Annu Rev Clin Psychol, 9*, 151-176. doi:10.1146/annurev-clinpsy-050212-185510

Trull, T. J., & Ebner-Priemer, U. W. (2020). Ambulatory assessment in psychopathology research: A review of recommended reporting guidelines and current practices. *J Abnorm Psychol, 129*(1), 56-63. doi:10.1037/abn0000473

Trull, T. J., Lane, S. P., Koval, P., & Ebner-Priemer, U. W. (2015). Affective Dynamics in Psychopathology. *Emot Rev, 7*(4), 355-361. doi:10.1177/1754073915590617

Trull, T. J., Solhan, M. B., Tragesser, S. L., Jahng, S., Wood, P. K., Piasecki, T. M., & Watson, D. (2008). Affective instability: measuring a core feature of borderline personality disorder with ecological momentary assessment. *J Abnorm Psychol, 117*(3), 647-661. doi:10.1037/a0012532

Tseng, H. H., Roiser, J. P., Modinos, G., Falkenberg, I., Samson, C., McGuire, P., & Allen, P. (2016). Corticolimbic dysfunction during facial and prosodic emotional recognition in first-episode psychosis patients and individuals at ultra-high risk. *Neuroimage Clin, 12*, 645-654. doi:10.1016/j.nicl.2016.09.006

Turk-Browne, N. B., Scholl, B. J., & Chun, M. M. (2008). Babies and brains: habituation in infant cognition and functional neuroimaging. *Front Hum Neurosci, 2*, 16. doi:10.3389/neuro.09.016.2008

Turner, R. J., & Lloyd, D. A. (2003). Cumulative adversity and drug dependence in young adults: racial/ethnic contrasts. *Addiction, 98*(3), 305-315. doi:10.1046/j.1360-0443.2003.00312.x

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289. doi:10.1006/nimg.2001.0978

Ulmer, S., & Jansen, O. (2013). *fMRI (2nd ed.)*: Berlin Heidelberg: Springer-Verlag Berlin Heidelberg.

Urban-Wojcik, E. J., Lee, S., Grupe, D. W., Quinlan, L., Gresham, L., Hammond, A., . . . Schaefer, S. M. (2022). Diversity of daily activities is associated with greater

hippocampal volume. *Cogn Affect Behav Neurosci, 22*(1), 75-87. doi:10.3758/s13415-021-00942-5

van de Leemput, I. A., Wichers, M., Cramer, A. O., Borsboom, D., Tuerlinckx, F., Kuppens, P., . . . Scheffer, M. (2014). Critical slowing down as early warning for the onset and termination of depression. *Proc Natl Acad Sci U S A, 111*(1), 87-92. doi:10.1073/pnas.1312114110

van den Bulk, B. G., Somerville, L. H., van Hoof, M. J., van Lang, N. D., van der Wee, N. J., Crone, E. A., & Vermeiren, R. R. (2016). Amygdala habituation to emotional faces in adolescents with internalizing disorders, adolescents with childhood sexual abuse related PTSD and healthy adolescents. *Dev Cogn Neurosci, 21*, 15-25. doi:10.1016/j.dcn.2016.08.002

van der Velde, J., Opmeer, E. M., Liemburg, E. J., Bruggeman, R., Nieboer, R., Wunderink, L., & Aleman, A. (2015). Lower prefrontal activation during emotion regulation in subjects at ultrahigh risk for psychosis: an fMRI-study. *NPJ Schizophr, 1*, 15026. doi:10.1038/npjschz.2015.26

van Harmelen, A.-L., van Tol, M.-J., Demenescu, L. R., van der Wee, N. J. A., Veltman, D. J., Aleman, A., . . . Elzinga, B. M. (2013). Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Soc Cogn Affect Neurosci, 8*(4), 362-369. doi:10.1093/scan/nss007

van Harmelen, A.-L., van Tol, M.-J., van der Wee, N. J., Veltman, D. J., Aleman, A., Spinhoven, P., . . . Elzinga, B. M. (2010). Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. *Biol. Psychiatry, 68*(9), 832-838.

van Os, J. (2013). The dynamics of subthreshold psychopathology: implications for diagnosis and treatment. *Am J Psychiatry, 170*(7), 695-698. doi:10.1176/appi.ajp.2013.13040474

van Os, J., Rutten, B. P., & Poulton, R. (2008). Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr Bull, 34*(6), 1066-1082. doi:10.1093/schbul/sbn117

VanderVeen, J. D., Plawecki, M. H., Millward, J. B., Hays, J., Kareken, D. A., O'Connor, S., & Cyders, M. A. (2016). Negative urgency, mood induction, and alcohol seeking behaviors. *Drug Alcohol Depend., 165*, 151-158. doi:10.1016/j.drugalcdep.2016.05.026

VanTieghem, M., Korom, M., Flannery, J., Choy, T., Caldera, C., Humphreys, K. L., . . . Tottenham, N. (2021). Longitudinal changes in amygdala, hippocampus and cortisol development following early caregiving adversity. *Dev Cogn Neurosci, 48*, 100916. doi:10.1016/j.dcn.2021.100916

VanTieghem, M., & Tottenham, N. (2018). Neurobiological Programming of Early Life Stress: Functional Development of Amygdala-Prefrontal Circuitry and Vulnerability for Stress-Related Psychopathology. *Curr Top Behav Neurosci, 38*, 117-136. doi:10.1007/7854_2016_42

Volkow, N. D., Wang, G.-J., Fowler, J. S., & Tomasi, D. (2012). Addiction Circuitry in the Human Brain. *Annu Rev Pharmacol Toxicol., 52*, 321-336. doi:10.1146/annurev-pharmtox-010611-134625

Vollstädt-Klein, S., Bumb, J., Otto, A., Dinter, C., Karl, D. M., Koopmann, A., . . . Kiefer, F. (2019). The effects of nalmefene on emotion processing in alcohol use disorder – A randomized, controlled fMRI study. *Eur. Neuropsychopharmacol., 29*. doi:10.1016/j.euroneuro.2019.10.014

Wang, L., Paul, N., Stanton, S. J., Greeson, J. M., & Smoski, M. J. (2013). Loss of sustained activity in the ventromedial prefrontal cortex in response to repeated

stress in individuals with early-life emotional abuse: implications for depression vulnerability. *Front Psychol, 4*, 320. doi:10.3389/fpsyg.2013.00320

Watson, D., Levin-Aspenson, H. F., Waszczuk, M. A., Conway, C. C., Dalgleish, T., Dretsch, M. N., . . . Krueger, R. F. (2022). Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): III. Emotional dysfunction superspectrum. *World Psychiatry, 21*(1), 26-54. doi:10.1002/wps.20943

Weber, M., Schnitzler, H. U., & Schmid, S. (2002). Synaptic plasticity in the acoustic startle pathway: the neuronal basis for short-term habituation? *Eur J Neurosci, 16*(7), 1325-1332. doi:10.1046/j.1460-9568.2002.02194.x

Weigelt, S., Muckli, L., & Kohler, A. (2008). Functional magnetic resonance adaptation in visual neuroscience. *Rev Neurosci, 19*(4-5), 363-380. doi:10.1515/revneuro.2008.19.4-5.363

Wichers, M., Barge-Schaapveld, D. Q., Nicolson, N. A., Peeters, F., de Vries, M., Mengelers, R., & van Os, J. (2009). Reduced stress-sensitivity or increased reward experience: the psychological mechanism of response to antidepressant medication. *Neuropsychopharmacology, 34*(4), 923-931. doi:10.1038/npp.2008.66

Wichers, M., Peeters, F., Geschwind, N., Jacobs, N., Simons, C. J., Derom, C., . . . van Os, J. (2010). Unveiling patterns of affective responses in daily life may improve outcome prediction in depression: a momentary assessment study. *J Affect Disord, 124*(1-2), 191-195. doi:10.1016/j.jad.2009.11.010

Wiggins, J. L., Swartz, J. R., Martin, D. M., Lord, C., & Monk, C. S. (2014). Serotonin transporter genotype impacts amygdala habituation in youth with autism spectrum disorders. *Soc Cogn Affect Neurosci, 9*(6), 832-838. doi:10.1093/scan/nst039

Wilcox, C. E., Pommy, J. M., & Adinoff, B. (2016). Neural Circuitry of Impaired Emotion Regulation in Substance Use Disorders. *Am. J. Psychiatry, 173*(4), 344-361. doi:10.1176/appi.ajp.2015.15060710

Wilhelm, P. (2001). A multilevel approach to analyze ambulatory assessment data: An examination of family members' emotional states in daily life.

Wilhelm, P., & Schoebi, D. (2007). Assessing mood in daily life: Structural validity, sensitivity to change, and reliability of a short-scale to measure three basic dimensions of mood. *Eur J Psychol Assess, 23*(4), 258-267. doi:10.1027/1015-5759.23.4.258

Williams, J. M. G., Watts, F. N., MacLeod, C., & Mathews, A. (1988). *Cognitive psychology and emotional disorders*: John Wiley & Sons.

Wills, T. A. (1990). Stress and coping factors in the epidemiology of substance use. In *Research advances in alcohol and drug problems, Vol. 10.* (pp. 215-250). New York, NY, US: Plenum Press.

Wingenfeld, K., Spitzer, C., Mensebach, C., Grabe, H. J., Hill, A., Gast, U., . . . Driessen, M. (2010). [The German version of the Childhood Trauma Questionnaire (CTQ): preliminary psychometric properties]. *Psychother Psychosom Med Psychol, 60*(11), 442-450. doi:10.1055/s-0030-1247564

Witkiewitz, K., Bowen, S., Douglas, H., & Hsu, S. H. (2013). Mindfulness-based relapse prevention for substance craving. *Addict. Behav., 38*(2), 1563-1571. doi:https://doi.org/10.1016/j.addbeh.2012.04.001

Witlox, M., Garnefski, N., Kraaij, V., Simou, M., Dusseldorp, E., Bohlmeijer, E., & Spinhoven, P. (2021). Prevalence of anxiety disorders and subthreshold anxiety throughout later life: Systematic review and meta-analysis. *Psychol Aging, 36*(2), 268-287. doi:10.1037/pag0000529

Wittchen, H.-U., Wunderlich, U., Gruschwitz, S., & Zaudig, M. (1997). *SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Interviewheft und Beurteilungsheft. Eine deutschsprachige, erweiterte Bearb. d. amerikanischen Originalversion des SKID I*. Göttingen: Hogrefe.

Wolff, S., Holl, J., Stopsack, M., Arens, E. A., Hocker, A., Staben, K. A., . . . Group, C. S. (2016). Does Emotion Dysregulation Mediate the Relationship between Early Maltreatment and Later Substance Dependence? Findings of the CANSAS Study. *Eur Addict Res, 22*(6), 292-300. doi:10.1159/000447397

Wolitzky-Taylor, K., Dour, H., Zinbarg, R., Mineka, S., Vrshek-Schallhorn, S., Epstein, A., . . . Craske, M. G. (2014). Experiencing core symptoms of anxiety and unipolar mood disorders in late adolescence predicts disorder onset in early adulthood. *Depress Anxiety, 31*(3), 207-213. doi:10.1002/da.22250

World Health Organization, W. (1999). *Report of the consultation on child abuse prevention, 29-31 March 1999, WHO, Geneva*. Retrieved from

Wright, C. I., Fischer, H., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2001). Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport, 12*(2), 379-383. doi:10.1097/00001756-200102120-00039

Yamaguchi, S., Hale, L. A., D'Esposito, M., & Knight, R. T. (2004). Rapid prefrontal-hippocampal habituation to novel events. *J Neurosci, 24*(23), 5356-5363. doi:10.1523/jneurosci.4587-03.2004

Yang, T., & Xiang, L. (2019). Executive control dysfunction in subclinical depressive undergraduates: Evidence from the Attention Network Test. *J Affect Disord., 245*, 130-139.

Young, K. D., Misaki, M., Harmer, C. J., Victor, T., Zotev, V., Phillips, R., . . . Bodurka, J. (2017). Real-Time Functional Magnetic Resonance Imaging Amygdala Neurofeedback Changes Positive Information Processing in Major Depressive Disorder. *Biol Psychiatry, 82*(8), 578-586. doi:10.1016/j.biopsych.2017.03.013

Young, K. D., Siegle, G. J., Zotev, V., Phillips, R., Misaki, M., Yuan, H., . . . Bodurka, J. (2017). Randomized Clinical Trial of Real-Time fMRI Amygdala Neurofeedback for Major Depressive Disorder: Effects on Symptoms and Autobiographical Memory Recall. *Am J Psychiatry, 174*(8), 748-755. doi:10.1176/appi.ajp.2017.16060637

Young, K. D., Zotev, V., Phillips, R., Misaki, M., Drevets, W. C., & Bodurka, J. (2018). Amygdala real-time functional magnetic resonance imaging neurofeedback for major depressive disorder: A review. *Psychiatry Clin Neurosci, 72*(7), 466-481. doi:10.1111/pcn.12665

Young, K. D., Zotev, V., Phillips, R., Misaki, M., Yuan, H., Drevets, W. C., & Bodurka, J. (2014). Real-time FMRI neurofeedback training of amygdala activity in patients with major depressive disorder. *PLoS One, 9*(2), e88785. doi:10.1371/journal.pone.0088785

Yung, A. R., & McGorry, P. D. (1996). The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophr Bull, 22*(2), 353-370. doi:10.1093/schbul/22.2.353

Yung, A. R., Phillips, L. J., McGorry, P. D., McFarlane, C. A., Francey, S., Harrigan, S., . . . Jackson, H. J. (1998). Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry Suppl, 172*(33), 14-20.

Zhang, W. H., Zhang, J. Y., Holmes, A., & Pan, B. X. (2021). Amygdala Circuit Substrates for Stress Adaptation and Adversity. *Biol Psychiatry, 89*(9), 847-856. doi:10.1016/j.biopsych.2020.12.026

7. PUBLICATION LIST

Included publications

Berhe O*, Höflich, A.*, Moessnang, C., Reichert, M., Kremer, T., Gan, G., Ma, R., Braun, U., Reininghaus, U., Ebner-Priemer, U., Meyer-Lindenberg, A.*, Tost, H.* (2022). Reduced Real-life Affective Well-being and Amygdala Habituation in Unmedicated Community Individuals at Risk for Depression and Anxiety. *Biol. Psychiatry Cogn Neurosci Neuroimaging*. 2022; S2451-9022(22)00153-7.

Berhe, O., Moessnang, C., Reichert, M., Ma, R., Höflich, A., Tesarz, J., Heim, C., Ebner-Priemer, U., Meyer-Lindenberg, A., Tost, H. (**in review**) Dose-dependent changes in real-life affective well-being in healthy community-based individuals with mild to moderate childhood trauma exposure. *Borderline Personal Disord Emot Dysregul.*

Gerhardt, S.*, **Berhe, O.***, Moessnang, C., Horning, M., Kiefer, F., Tost, H.*, & Vollstädt‐Klein, S*. (2023). Lack of amygdala habituation to negative emotional faces in alcohol use disorder and the relation to adverse childhood experiences. *Addict. Biol*, 28(1), e13251

Other publications

Holz, N. E., **Berhe, O.,** Sacu, S., Schwarz, E., Tesarz, J., Heim, C., & Tost, H. (2022). Early social adversity altered brain functional connectivity and mental health. *Biol. Psychiatry*.

Schweiger, J. I., Capraz, N., Akdeniz, C., Braun, U., Ebalu, T., Moessnang, C., **Berhe, O.,** Zang, Z., Schwarz E., Bilek E., Meyer-Lindenberg, A. & Tost, H. (2022). Brain structural correlates of upward social mobility in ethnic minority individuals. *Soc Psychiatry Psychiatr Epidemiol.*, 57(10), 2037-2047.

Reichert, M., Gan, G., Renz, M., Braun, U., Brüßler, S., Timm, I., Ma, R., **Berhe, O.,** Benedyk, A., Moldavski, A., Schweiger J., Hennig, O., Zidda, F., Heim, C., Banaschewski, T., Tost, H., Ebner-Priemer, U., & Meyer-Lindenberg, A. (2021). Ambulatory assessment for precision psychiatry: Foundations, current developments and future avenues. *Exp. Neurol.*, 345, 113807.

Berhe O, Gerhardt S, Schmahl C. Clinical Outcomes of Severe Forms of Early Social Stress. *Curr Top Behav Neurosci*. 2022;54:417-438. doi:10.1007/7854_2021_261

Bayer, M., **Berhe, O.,** Dziobek, I., Johnstone, T. Rapid Neural Representations of Personally Relevant Faces, *Cerebral Cortex*, Volume 31, Issue 10, October 2021, Pages 4699–4708

Bilek, E., Itz, M. L., Stößel, G., Ma, R., **Berhe, O.,** Clement, L., Zang, Z., Robnik L., Plichta M., Neukel C., Schmahl C., Kirsch, P., Meyer-Lindenberg, A. & Tost, H. (2019). Deficient amygdala habituation to threatening stimuli in borderline personality disorder relates to adverse childhood experiences. *Biol. Psychiatry*, 86(12), 930-938.

***authors contributed equally**

8. CURRICULUM VITAE

PERSONAL INFORMATION

Name:	Oksana Berhe
Name of Birth:	Bezshchastna
Place of Birth:	Kyiv Ukraine
Nationality:	Ukrainian

ACADEMIC EDUCATION

07.2018 – till present	PhD student, Department of Psychiatry and Psychotherapy, research group Systems Neuroscience in Psychiatry; Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany Supervisor: Prof. Dr. Dr. Heike Tost
07.2018 – 06.2021	PhD Student, Research Training Group “Impact of Adverse Childhood Experiences on Psychosocial and Somatic Conditions Across the Lifespan” (GRK 2350)
10.2015 – 05.2018	Freie Universität Berlin, Germany Social, Cognitive and Affective Neuroscience Master Program (Grade 1,2) Thesis: “ERP effect of emotion and personal relevance”
09.2007 – 03.2020	Kyiv International University, Ukraine Diploma in Psychology
09.1995 – 05.1998	National University of Food Technologies, Kyiv, Ukraine Diploma in Food Technology (cum laude)

WORKING EXPERIENCE

08.2019 – 12.2019	Visiting researcher/Internship Cambridge University

	Research Project - Resilient Functioning after adversity
10.2016 – 06.2018	Visiting Researcher Berlin School of Mind and Brain | Humboldt-Universität zu Berlin; Social Cognition Lab; Master research project
04.2017 – 06.2018	Research Assistant Max Planck Institute for Human Development Center for Lifespan Psychology;

9. ACKNOWLEDGEMENTS

First and foremost, I would like to thank **Prof. Dr. Dr. Heike Tost** for giving me this great opportunity to do my doctoral thesis in the outstanding research projects - psycho-epidemiological center (PEZ) at the Central Institute of Mental Health in Mannheim (CIMH). I'm extremely grateful her for giving me the space and time to develop myself scientifically, for believing in my capabilities, and for the opportunity to acquire many new knowledge and skills. Her immense knowledge, plentiful experience and inspiring leadership have encouraged me all the time of my academic journey. I'm particularly grateful her for the extraordinary support in especially challenging personal situations.

I had the pleasure of working with **Carolin Mößnang** who inspired me throughout all this time with her profound methodological competence and experience and her invincible spirit and optimism to keep going in my goal.

Furthermore I would like to thank the rest of the **SNiP research team** for their collaborative effort, including many wonderful research assistants who worked for PEZ and helped with data collection. Furthermore I would like to thank my colleagues from the SNiP group, including many wonderful research assistants for their collaborative effort, constant support, and for making our work truly friendly and enjoyable. I would especially like to thank **Beate Hoechemer** for her committed and inspiring support of our research project. Thanks should also go to **Mirjam Melzer**, for being ‘’A und O’’ of this group and for helping to get through all disappointments and failures and reach the final destination.

I would also like to acknowledge the graduate program GRK2350 and **Prof. Dr. Christian Schmahl** for the opportunity to be part of the structured doctoral training, and for creating a supportive and encouraging research environment.

На завершення, найголовніше, я хочу подякувати моїм батькам, Анатолію та Катерині, а також сестрі Юлії за безумовну підтримку та віру в мене, особливо в цей дуже напружений період для нашої сімї. Зокрема хочу подякувати моїм батькам, які змалечку прищепили мені любов і повагу до знань та навчання, які багато пожертвували, щоб я могла отримати освіту.

Without all these people I would not have been able to made it through my doctoral degree!