Aus der Klinik für Psychosomatik und Psychotherapeutische Medizin
des Zentralinstituts für Seelische Gesundheit
der Medizinischen Fakultät Mannheim
der Universität Heidelberg
(Direktor: Prof. Dr. med. Christian Schmahl)

The neurobiology of early adversity in trauma- and stress-related mental disorders:

Timing, psychopathology, and reverse inference

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

vorgelegt von
Maurizio Sicorello
aus
Frankfurt a.M.
2022

Dekan: Prof. Dr. med. Sergij Goerdt
Referent: Prof. Dr. med. Christian Schmahl

Table of Contents

Abbreviations

ACE	Adverse Childhood Experiences
ACG	Anterior Cingulate Gyrus
BDI	Beck Depression Inventory
BOLD	Blood Oxygen Level Dependent
BMI	Body Mass Index
BPD	Borderline Personality Disorder
CAPS-5	Clinician Administered PTSD Scale for DSM-5
cPTSD	Complex Posttraumatic Stress Disorders
CRH	Corticotropin Releasing Hormone
CTQ	Childhood Trauma Questionnaire
DBT	Dialectical Behavioral Therapy
DERS	Difficulties in Emotion Regulation Scale
DTS	Davidson Trauma Scale
FDS	Questionnaire for Dissociative Symptoms
fMRI	functional Magnetic Resonance Imaging
HPA	Hypothalamic Pituitary Adrenal
HRF	Hemodynamic Response Function
IFOG	Inferior Fronto-Orbital Gyrus
IPDE	International Personality Disorder Examination
LEC-5	Life Events Checklist
MNI	Montreal Neurological Institute
MPRAGE	Magnetization-Prepared Rapid-Acquisition Gradient Echo
MTG	Middle Temporal Gyrus
PINES	Picture Induced Negative Emotion Signature
PFC	Prefrontal Cortex
ROI	Region of Interest
SAM	Sympathico-Adrenomedullary
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SFG	Superior Frontal Gyrus
SPM	Statistical Parametric Mapping
SNRI	Serotonin Noradrenalin Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
STAI	Stait-Trait Anxiety Inventory
RSQ-D	Response Style Questionnaire — German Version
ZAN	Zanarini Rating Scale

Preface

This cumulative dissertation is based on three research articles, published in peer-reviewed scientific journals. The publications are indicated below, together with a qualitative and quantitative (in percentages) approximate assessment of my contribution, confirmed by my supervisor Prof. Dr. med. Christian Schmahl.

Chapter II is based on "Siehl, S., Sicorello, M., Herzog, J. et al. (2022). Neurostructural associations with traumatic experiences during child- and adulthood. *Transl Psychiatry 12,* 515". First-authorship is shared between S. Siehl and myself, as both contributed equally on conceptualization, literature research, data analysis, interpretation, manuscript writing, and revisions (≈50%).

Chapter III is based on "Sicorello, M., Thome, J., Herzog, J., & Schmahl, C. (2021). Differential effects of early adversity and posttraumatic stress disorder on amygdala reactivity: The role of developmental timing. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 6*(11), 1044-1051". I performed most of the conceptualization of the study (≈95%) and was solely responsible for literature research, data analysis, interpretation, manuscript writing, and revisions (100%).

Chapter IV is based on "Sicorello, M., Herzog, J., Wager, T. D., Ende, G., Müller-Engelmann, M., Herpertz, S. C., ... & Niedtfeld, I. (2021). Affective neural signatures do not distinguish women with emotion dysregulation from healthy controls: A mega-analysis across three task-based fMRI studies. *NeuroImage: Reports, 1*(2), 100019". As for chapter III, I performed most of the conceptualization of the study (≈95%) and was solely responsible for literature research, data analysis, interpretation, manuscript writing, and revisions (100%).

All three studies tested novel hypotheses using existing data. I did not contribute to the ethics approval or the collection of these data (0%).

Theoretical Background

CHAPTER I

1.1 Early adversity and mental health

Early life adversities—such as abuse and neglect—are critical determinants of mental and physical health throughout the lifespan. They lead to a 20-year decrease in average life expectancy with a 5-fold higher mortality rate already apparent in early adulthood, accounting for over 400,000 annual deaths in the US alone (Brown et al., 2009; Grummitt et al., 2021; Rod et al., 2020). In Germany, around 8.9% of the population currently have a higher mortality risk due to adverse childhood experiences (ACE; Witt et al., 2019). This association is mediated by a broad range of health behaviors, including smoking, drug use, and sexually transmitted infections, resulting in a higher occurrence of heart diseases, strokes, cancer, and chronic respiratory diseases (Grummitt et al., 2021). However, the by far largest increase is observed for suicide risk, which can be up to 7-fold larger in people who experienced childhood adversities, highlighting the relevance of early adversity for mental health (Grummitt et al., 2021).

In the mental health sciences, early adversity is predominantly viewed as a causal transdiagnostic risk factor (Ball & Links, 2009), meaning it confers increased risk to develop mental disorders across diagnostic boundaries (Green et al., 2010). A representative German survey showed strong effects on depressiveness, anxiety, and overall life satisfaction (Witt et al., 2019). Conversely, similar prevalence of early adversity has been observed for different mental disorders like schizophrenia, major depressive and bipolar disorder, although rates appear to be particularly high for relatively persistent mental disorders with pronounced affective symptoms such as chronic depression and borderline personality disorder (BPD; de Aquino Ferreira et al., 2018; Frias et al., 2016; Struck et al., 2020). While the term *early adversity* has no formal definition and can vary in breadth (e.g., Nelson & Gabard-Durnam, 2020), a superordinate factor of maladaptive family functioning—including familial abuse, neglect—captures most variance in adverse experiences and confers the strongest risk for mental disorders, including PTSD

(Green et al., 2010; Kessler et al., 2017). This is especially alarming as these forms of childhood maltreatment are very common, with prevalence ranging between 9-30% dependent on the type of maltreatment (Sethi et al., 2013). In a representative German survey, up to 11% percent reported having experienced severe maltreatment during childhood (Häuser et al., 2011).

As early adversity is neither a necessary nor sufficient condition for any of the mental disorders mentioned above, there have been calls for additions to current taxonomies to close a potential nosological gap (Teicher et al., 2021). In 2019, the eleventh revision of the international classification of diseases was released by the world health organization, including a new diagnostic entity: complex posttraumatic stress disorder (cPTSD; World Health Organization, 2019). It incorporates all diagnostic criteria of PTSD (i.e., reexperience, avoidance, and threat sensitivity), but adds difficulties in affect regulation, self-concept, and interpersonal functioning (Brewin et al., 2017). While cPTSD was initially proposed to capture prolonged or repeated interpersonal childhood events as the antecedent traumatic experience, leading to complex constellation of symptoms, this definition has been broadened to include single events which might also occur during adulthood (Giourou et al., 2018). Still, critics point out that many victims of childhood maltreatment might not cross the threshold of cPTSD or any other mental disorder, while exhibiting distinct biopsychosocial deficits which require treatment (Teicher et al., 2021). Mechanistic insights into the consequences of childhood maltreatment and their relation to current diagnostic categories are direly needed to inform and refine psychopathological nosology, models, and treatments.

1.2 Stress physiology in body and brain

A cornerstone of neurodevelopmental theories of early adversity are aberrations in the psychoneuroendocrine stress response and their association with changes in brain structure and function (Juster et al., 2010). Acute (or anticipated) stressful experiences trigger a cascade of neuroendocrine events which facilitate an allostatic response. Allostasis describes a changed state

of physiological systems (e.g., heightened heart rate, increased sweating) which has evolutionarily developed to protect homeostasis of an organism by acting upon internal and external demands (McEwen & Lasley, 2002; Sterling, 2012). The allostatic stress response includes the activity of the hypothalamic pituitary adrenal axis (HPA), sympathicus, sympathico-adrenomedullary axis (SAM), as well as the central oxytocinergic system (Goldstein, 2010; Koss & Gunnar, 2018; Sapolsky et al., 2000). The release of catecholamines supports immediate physiological processes necessary for a 'fight-flight' response, such as changes in heartbeat and cardiac output, dependent on the specific characteristics of the stressor (Sapolsky et al., 2000). The HPA axis response is initiated by the release of corticotropin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. While CRH itself can function as a fast and direct facilitator of the stress response via metabolic, thermogenetic, and immunostimulatory processes, it is mainly known for triggering the release of adrenocorticotropin release hormone from the pituitary, which in turn stimulates the release of glucocorticoids from the cortex of the adrenal gland (Kovács, 2013)—in humans predominantly cortisol.

Cortisol has long been viewed as the major hormone to mediate the stress response and is among the most frequently investigated biological entities in research on basic stress and early adversity (Lupien et al., 2009; Selye, 1936). Cortisol can cross the blood-brain-barrier and bind to intracellular mineralo- and glucocorticoidreceptors within neurons (Joëls et al., 2018). While mineralocorticoid receptors have a high affinity to cortisol and are usually substantially occupied, glucocorticoid receptors are mostly occupied when cortisol concentrations, and therefore the HPA stress response, are markedly increased. The hippocampus and the amygdala are two brain regions which are particularly enriched with glucocorticoid receptors and play a central role in the stress response (Joëls et al., 2018; Lupien et al., 2009). The hippocampus contains neurons which inhibit the activity of CRH-secreting paraventricular neurons in the hypothalamus, therefore providing feedback inhibition to the HPA axis, i.e., cortisol inhibits its own secretion via hippocampal pathways (Lupien et al., 2009). In contrast, the amygdala contains

neurons which *increase* the activity of the HPA axis via the bed nucleus of the stria terminalis, while also facilitating a HPA-independent peripheral stress responses via CRH-based signaling to the locus coeruleus in the brain stem (Herman et al., 2005; Kovács, 2013). These feedback loops of the HPA-axis via hippocampus (inhibitory) and amygdala (excitatory) are essential to understanding brain changes following early adversity.

1.3 Neurodevelopmental theories of early adversity

Chronic, severe, or frequent activation of the HPA axis by stressors can lead to lasting neuro-structural alterations (Teicher & Samson, 2016). For the hippocampus, it has been well established that very high cortisol concentrations can lead to dendritic atrophy and reduced neurogenesis in rodents (Joëls et al., 2007; Sapolsky, 1996). These findings translate to studies in humans, where considerable reductions in hippocampal volumes following childhood maltreatment have been meta-analytically confirmed (Paquola et al., 2016). Similarly, cortisol levels prospectively predict hippocampus volume (Lupien et al., 1998). For the amygdala, however, animal and human studies are less convergent. While rodents exhibited dendritic *hyper*trophy after repeated stress or even a single dose of corticosterones (Mitra & Sapolsky, 2008; Patel et al., 2018; Zhang et al., 2019), childhood maltreatment in humans is associated with overall *reduced* amygdala volumes (Paquola et al., 2016). Still, these inconsistencies must be viewed in light of neurodevelopmental processes, as plasticity might differ dependent on species, individuals, brain systems, and, importantly, developmental timing.

Neurodevelopmental theories of brain alterations mostly bifurcate into two branches: A *neurotoxicity branch* primarily views brain changes as damage that can occur at different stages of the neurodevelopmental process, most influentially the life-cycle model of stress (Lupien et al., 2009). An *adaptivity branch* consists of several more recent theories, which argue that brain changes might be adaptive within the context of early adversity, but can lead to maladaptive behavior later on when the life context has changed (Frankenhuis & de Weerth, 2013).

For the neurotoxicity branch, Lupien and colleagues (2018) distinguish between three perspectives: First, brain changes might be the product of cumulative damage caused by enduring or severe stressors (cumulative damage hypothesis). Second, the damage to the brain might be more pronounced when it occurred at an earlier developmental stage. Third, the life-cycle model of stress posits that heighted glucorticoid concentrations in response to stress most strongly affect brain regions which are still under development at the time of adversity (Lupien et al., 2009). For example, the hippocampus shows rapid development extending into the first two life years, while the amygdala reaches its neurodevelopmental plateau much later during early adolescence (Silvers et al., 2017; Uematsu et al., 2012). The life-cycle model proposes that neurotoxic events could slow down neurodevelopment in these sensitive periods, having lasting effects. Hence, the timing of adversity is crucial to understand individual differences in brain volumes, with different sensitive time windows for different regions. Still, Lupien and colleagues (2009) also briefly state that the neurotoxicity hypothesis does not preclude that brain changes also function as vulnerability factors for psychopathology (instead of functional correlates). Rather, the stressful events could dysregulate the HPA-axis, leading to brain changes, which increase the risk to develop a mental disorder after stress exposure later in life (Lupien et al., 2018).

For the adaptivity branch, several evolutionary models posit that flexibility in developmental trajectories in response to environmental contexts might be in itself a conserved adaptive organismic feature favored by natural selection. Following this model, no single evolutionary strategy is likely to optimize evolutionary fitness across all contexts (Callaghan & Tottenham, 2016; Del Giudice et al., 2011). Therefore, evolution might have favored the emergence of adaptive developmental time windows, where organisms show increased plasticity (Frankenhuis & Walasek, 2020). Transition points between important developmental stages, for example the early postnatal years and the transition into puberty, are argued to be particularly susceptible to environmental contexts. These might shape the responsiveness of stress

systems, which is crucial for encoding and filtering survival-relevant environmental information (Frankenhuis & Walasek, 2020). Overall, there is compelling evidence that people with early adversity are tuned to perform well in cognitive tasks (e.g., improved detection, learning, memory) when the content of these tasks relates to their adverse experience (e.g., threat processing; Frankenhuis & de Weerth, 2013). This already highlights on a behavioral level that changes which seem maladaptive in one context might be viewed as adaptive in another.

In a similar vein, the stress acceleration hypothesis posits that instead of being "disrupted", neurodevelopment might be accelerated in response to adverse rearing environments to facilitate more autonomous coping, independent of the caregiver (Callaghan & Tottenham, 2016). Evidence for this hypothesis is largely based on animal research, which shows that evolutionarily conserved developmental transitions in behavior and physiology occur earlier when rat pubs were raised under adverse conditions, including impoverished environments, maternal separation, foot shocks, hypothermia, and restraint (Callaghan & Tottenham, 2016). Notably, research in humans is mixed and potentially highlights the importance of type of adversity (McLaughlin et al., 2019): The onset of the first menarche occurs earlier in women exposed to repeated threat-related events, but was unrelated to deprivation (Colich et al., 2020). In contrast, Keding and colleagues (2021) found that while neglect led to accelerated brain maturation, abuse led to a deceleration. Drobinin and colleagues (2021), in turn, reported generally increased brain age in individuals who experienced environmental adversity, corresponding to accelerated brain maturation.

Most of the discussed theoretical models from both branches assume the existence of sensitive developmental periods. Nevertheless, the brain is characterized by neuroplasticity across the lifespan (Lindenberger & Lövdén, 2019). Therefore, sensitive periods are hypothetical time frames of increased plasticity *relative* to other periods throughout an organisms lifespan, which tunes the brain to specific environmental inputs (Gabard-Durnam & McLaughlin, 2019). Here, the literature often distinguishes between *experience-dependent* and

experience-expectant mechanisms (Nelson & Gabard-Durnam, 2020). While experience-dependent mechanisms can induce plasticity throughout the lifespan, experience-expectant mechanisms posit genetically determined ontogenetic periods in which a certain kind of environmental input is expected, with further development depending on the specific characteristics of these inputs. One example is the critical period occurring in birds, where mere exposure to an individual accompanied by a quacking sound imprints that individual as "the mother" (Lorenz, 1937). Another example is the effect of early visual deprivation on perceptive development (Wiesel & Hubel, 1963). Nelson and Gabard Durnam (2020) go as far as to define early adversity as a violation of normatively expectable experiences, like a present and non-abusive parent.

In contrast, Frankenhuis and Walasek (2020) argue that such distinctions between experience-dependent and experience-expectant mechanisms are likely artificial and not useful across all scientific contexts, stating: "Nature rarely comes in two kinds" (p. 2). Based on information-theoretical ideas and mathematical models, they show the evolutionary emergence of sensitive periods can be favored as a function of differential cue reliability throughout ontogeny: The free energy principle posits that any adaptive change in the brain serves to minimize the amount of free energy, or *surprise* (Friston, 2009). Simply explained, organisms hold a prior model of their external and internal environment, which is both genetically prepared and further shaped through life experiences. From these prior models, predictions of the state of the world are made and then compared to perceptual input. The degree of mismatch between prediction and perceptive input determines the informational value, or surprise, of a cue. Surprise is maximized if (1) the prior prediction is made with high certainty, (2) the cue diverges from that prediction, and (3) the cue has high reliability (sometimes also referred to as cue validity), meaning it is highly indicative of the true state of the world, for example when it is more likely to occur in some specific situations than others. Ontogenetic time frames characterized by systematically higher surprise might lead to increased plasticity (Fawcett & Frankenhuis, 2015). Frankenhuis and Walasek (2020) argue that cue reliability varies across ontogeny. This can be

the case if background knowledge is necessary to interpret cues and/or cues only become indicative in a certain period. For example, the background knowledge that facilitates the validity of many cues related to romantic relationships might first emerge during adolescence. If cue reliability is constant or decreases throughout ontogeny, early sensitive periods are favored in terms of evolutionary costs versus benefits. If cue reliability increases throughout ontogeny, or first increased and then decreases again in a triangular shape, a second sensitive period during mid-ontogeny (e.g., adolescence) is favored as well. Organisms will build better models of their environment over time, reducing the average added informativeness of cues in later life, leading to a prediction of decreased plasticity (Fawcett & Frankenhuis, 2015).

Overall, compelling evidence has emerged to support the existence of sensitive periods in which early adversity has particularly strong long-lasting effects on hippocampal and amygdala structure: Socioeconomic status during pre-school prospectively predicted smaller amygdala and hippocampal volumes, while school-age socioeconomic status did not contribute significantly (Luby et al., 2019). In contrast, a cross-sectional study found that adolescent but not childhood socioeconomic status was associated with smaller amygdala volumes (Merz et al., 2018). The latter is further corroborated by a study identifying a sensitive period at early adolescence, associated with smaller volumes of both amygdala and hippocampus (Herzog et al., 2020). The same sensitive period in early adolescence was identified for the hippocampus by Andersen and colleagues (2008), but they additionally found another sensitive period during early childhood, with both periods being associated with decreased hippocampal volume. Notably, a relatively large study found that these effects might be largely dependent on gender (Teicher et al., 2018): While a mixed analysis indicates one sensitive period in early childhood and one in early adolescence, separate analyses revealed that the early period was only apparent for men who experiences neglect, while the late period was only apparent for women who experienced abuse. In sum, while there are some inconsistencies, these studies indicate periods of increased sensitivity to maltreatment in early childhood and early adolescence, which are both

characterized by developmental transitions, leading to smaller volumes of amygdala and hippocampus. Notably, another study identified early adolescence as a sensitive period for amygdala and hippocampus, but reported larger amygdala volumes and did not indicate the effect direction for the hippocampus (Pechtel et al., 2014). Recent studies also point towards a generalizability to amygdala *function*, with decreased and increased amygdala responses to emotional stimuli reported depending on the timing of adverse experiences (Zhu et al., 2019).

Taken together, neurodevelopmental theories elucidate neural alterations following early adversity and point towards the existence of sensitive periods characterized by heightened plasticity, which is largely corroborated by neuroimaging evidence in humans.

1.4 Structural limbic correlates of early adversity in psychopathology and health

A central question concerns the clinical implication of the neural alterations in amygdala and hippocampus following early adversity, as these alterations might be (1) risk factors, (2) clinically inconsequential byproducts, or (3) reflecting clinical traits. Based on basic biological theories, a case could be made for functional clinical relevance, as both regions are involved in forming fear-related memories, which in turn is associated with anxiety disorders and PTSD (Duits et al., 2015; Elzinga & Bremner, 2002). The amygdala is a central region for fear conditioning. It receives diverse sensoric inputs and forms new synaptic connections associating unconditioned with conditioned stimuli, which result in fear-like behavior in rodents (LeDoux, 2007). Optogenetic approaches have shown that conditioned fear memories can be inactived and activated by long-term depression and potentiation in the amygdala, respectively, supporting its causal role (Nabavi et al., 2014). The amygdala also receives afferent signals from the hippocampus, which encodes contextual information, and reciprocally modulates hippocampal memory consolidation via efferent connections (Barsegyan et al., 2014). These neurobiological

theories have been crucial in explaining cognitive deficits observed in PTSD, including impairments of memory, attention, and executive control (Durand et al., 2019; Elzinga & Bremner, 2002; Qureshi et al., 2011).

Based on empirical studies in humans, the clinical relevance of aberrations in these limbic regions is less clear. Smaller hippocampus volumes have been meta-analytically reported for trauma-related mental disorders like PTSD and BPD (Bromis et al., 2018; Logue et al., 2018; Schulze et al., 2016). Similarly, hippocampal atrophy is meta-analytically correlated to PTSD symptom severity and still apparent when patients are compared to trauma-exposed controls (Bromis et al., 2018; Nelson & Tumpap, 2017). Still, studies must control for the severity of traumatic events to strictly test the clinical significance of hippocampal atrophies. Despite matching attempts, PTSD samples often have more severe trauma histories than trauma-exposed healthy controls. Hence, a difference between these two groups might be due to the severity of antecedent trauma rather than clinical presentation. Substantial volume reductions were already found in trauma-exposed compared to trauma-naïve controls (Bromis et al., 2018) and chronic stress prospectively predicted hippocampal volume in healthy women, even when subclinical symptoms were controlled (Gianaros et al., 2007). This could imply either (a) hippocampal atrophies reflect early adversity rather than clinical symptoms or (b) trauma-exposed controls differ from trauma-naïve controls on symptom dimensions without crossing any diagnostic threshold. Early seminal studies in veteran twins with/without combat exposure suggested that smaller hippocampus volumes might be vulnerability factors predating PTSD (Gilbertson et al., 2002), but evidence is thus far limited by a small number of studies and sample size (for a broader review, see Szeszko et al., 2018).

The characteristics of traumatic experiences are likely important moderators in the assessment of clinical relevance. On a behavioral level, there is strong evidence for cognitive deficits in people suffering from PTSD compared to trauma-exposed healthy controls for most

traumatic experiences, while studies on PTSD following early adversity in particular are relatively inconclusive (Qureshi et al., 2011). Two well-powered prospective studies showed pronounced long-lasting cognitive deficits following maltreatment, but effects were largely independent of psychopathology (Geoffroy et al., 2016; Nikulina & Widom, 2013). Even in this area it remains a major challenge that many studies which focus on PTSD do not account for the severity of maltreatment and, in turn, many studies which focus on maltreatment do not account for clinical symptoms (Su et al., 2019).

On a neural level, the meta-analysis by Paquola and colleagues (2016) found that childhood maltreatment led to reduced hippocampus volumes regardless of mental health status. This provides substantial evidence that the byproduct hypothesis at least partially accounts for volume reductions. Still, this does not preclude that hippocampus atrophy can be a vulnerability factor or clinical feature as well. For example, early adversity might be a predisposing factor, affecting hippocampal integrity and immune function, which in turn become vulnerability factors to develop PTSD after a second hit later in life (Georgopoulos et al., 2018; Szeszko et al., 2018). Based on the current literature, hippocampus atrophy would be likely to be both (a) a consequence of severe stress such as childhood maltreatment and (b) a vulnerability factor for the development of PTSD, but (c) the causal association with psychopathology remains unclear in the study of maltreatment.

For the amygdala, there is compelling evidence for a symptom-related relevance of structural changes. Strong reductions are found in psychiatric cohorts which experienced childhood maltreatment, but not in healthy trauma-exposed cohorts (Paquola et al., 2016). This finding is supported by another meta-analysis on non-clinical and general population samples, which found no association between childhood maltreatment and amygdala volume, in contrast to a confirmed negative association with hippocampus volume (Calem et al., 2017). Moreover, PTSD patients have smaller amygdala volumes than healthy trauma-exposed controls while there is no further significant difference between trauma-exposed and trauma-naïve controls

(Bromis et al., 2018). Additionally, a recent study showed that amygdala volumetry following the 2011 Norwegian terror attack mediated PTSD symptom development from 4-5 months to 24-36 months after the incident (Ousdal et al., 2020).

1.5 Amygdala activity, complex patterns, and the reverse inference problem

A major question arises as brain structure is often only moderately correlated with brain function (Kalmar et al., 2009; Straathof et al., 2019). There is meta-analytic evidence for functional amygdala hyperreactivity to threat-related stimuli in people exposed to childhood maltreatment, but these studies could not quantitatively assess the role of psychopathology (Heany et al., 2018; Hein & Monk, 2017). While some studies implicate amygdala hyperreactivity as an intermediate biomarker in the etiology of anxiety-related symptoms after ACE (Fonzo et al., 2016), others suggest that amygdala hyperreactivity can also be observed in ACE-exposed individuals without mental disorders (Dannlowski et al., 2012). PTSD patients do show higher amygdala reactivity compared to trauma-exposed healthy controls, but this again could reflect a dose-response relationship, as PTSD groups usually still experienced more severe trauma than trauma-exposed controls in most studies (Stark et al., 2015).

There are two major research gaps which limit our functional understanding of brain changes following early adversity. First, while the importance of developmental timing is widely acknowledged in the maltreatment literature, these studies rarely account for psychopathology. This is exemplified by a recent large study, which identified sensitive developmental periods for both amygdala hypo- and hyperreactivity to emotional stimuli and draws explicit clinical conclusions, but does not include clinical features in statistical models (Zhu et al., 2019). Second, although amygdala reactivity is often taken to be an indicator of fear, or negative affect more generally, the interpretation of amygdala activity is likely much more ambiguous.

For a long time, the amygdala has been viewed as a center of fear and negative affect. In animal models, its role in fear conditioning has been firmly established by decades of evidence (LeDoux, 2007). Consequently, the amygdala was argued to be part of a "low-road" which forms coarse integrated representations of sensory stimuli, contextualized with threat-related episodic knowledge, leading to fear responses (LeDoux, 1996). Similarly, neuroimaging studies in humans show that the amygdala is highly responsive to threat-related stimuli (Vytal & Hamann, 2010). Still, the neuroimaging literature has largely focused on regions that are functionally *sensitive* to a process of interest, like fear, neglecting the limited *specificity* these regions might have.

Most neuroimaging studies employ *forward inference*, meaning that an experimental design is constructed to elicit a psychological process of interest to then study the neural responses. For example, a study on fear might use pictorial stimuli shown to elicit self-reported fear to then test for brain regions, which are significantly activated. Thus, forward inference describes inference from psychological concepts to biological measures. Still, a neural region that shows high sensitivity to a psychological concept such as fear might still be implicated in a broad range of other unrelated processes. This equates to low *specificity*. High specificity is necessary to perform *reverse inference*, i.e., observing brain activity and inferring a mental state from this activity. Thus, if a researcher observes heightened amygdala activity, can they infer someone is experiencing fear or has increased negative affect?

There is compelling evidence that the amygdala has insufficient specificity to be regarded as a center for fear or negative emotions and, consequently, perform reverse inference from its activity to these mental states. The amygdala is active in response to both positive and negative stimuli (Costafreda et al., 2008; Wager et al., 2003) and does not discriminate well between discrete emotions (Wager et al., 2015). Rather, there is support for the *affective workspace hypothesis*, which states that both positive and negative affect are supported by a flexible set of valence general regions, including the amygdala (Lindquist et al., 2016). Single studies

have even shown that the amygdala is responsive to salient but non-emotional events, like an oddball task (Camalier et al., 2019), granting support for the hypothesis that the amygdala is facilitating the neural processing of salient events, independent of valence (Ousdal et al., 2008; Sander et al., 2003). Additionally, a recent study demonstrated that the amygdala is not robustly involved in human fear learning, while it does distinguish between neutral faces and inanimate objects (Todorov, 2012; Visser et al., 2021). These observations of valence-independent salience-related activity is not only a result of the coarse resolution of functional magnetic resonance imaging (fMRI), but can even be found on the level of single neurons (Gothard, 2020).

Another theoretical account explains these findings by positioning the amygdala as a "body budgeting region" (Barrett, 2017a), instrumental in the coordination of physiological responses to meet organismic needs and facilitate allostasis (Barrett, 2017b). The amygdala has been found to be part of an intrinsic neural network supporting allostasis and interoception using a well-powered cross-species approach in macaque monkeys and humans (Kleckner et al., 2017). Moreover, amygdala is highly predictive of physiological arousal during fear conditioning tasks, but not of self-reported fear (Taschereau-Dumouchel et al., 2019). Similarly, deep brain stimulation appears to elicit peripheral physiological arousal, indicated by heightened heart rate and electrodermal activity, but did not systematically induce subjective experiences of negative emotions or fear (Inman et al., 2018). Importantly, the amygdala also facilitates the filtering and encoding of information through attentional processes (Jacobs et al., 2012). These processes are discussed as more general responsibilities of the stress systems, argued to be affected following early adversity (Del Giudice et al., 2011). Especially in light of these broad responsibilities, the question arises how neural markers can be safely interpreted as indicative of meaningful clinical features.

Multivariate neural signatures offer a promising approach to solve the problems of low specificity and, hence, interpretability of neural markers (Woo et al., 2017). Such neural signatures have been developed for many different states, such as physical pain (Wager et al., 2013),

social rejection (Woo et al., 2014), interpersonal guilt (Yu et al., 2020), sexual content (van 't Hof et al., 2020), and, most importantly, different emotion concepts (Chang et al., 2015; Kragel & LaBar, 2015; Zhou et al., 2021). Using machine learning models, different emotional states can be discriminated at relatively high accuracy from whole-brain data, while regions like the amygdala appear to be involved in most emotional states (Wager et al., 2015). Kragel and Labar (2015) developed neural signatures which discriminate between seven discrete emotions at an accuracy of 37.2% (chance = 14.3%) for both visual and auditory stimuli. Spontaneous activity of these signatures during resting state scans (i.e., fMRI measurements without a task) was correlated to individual differences in emotion-related traits (Kragel et al., 2016). Similarly, Chang and colleagues (2015) developed a neural signature which correlated with picture-induced self-reported negative affect to r = .92, maintaining its level of predictive utility in a relatively large hold-out sample. Recently, Zhou and colleagues (2021) developed a neural signature specifically for self-reported fear. They demonstrated that good prediction requires incorporating multiple brain systems across most parts of the brain, an observation that has been made before for physical pain (Kragel & LaBar, 2016). These studies also found that the amygdala is correlated with negative affect and fear, albeit with much lower sensitivity. Most importantly, besides their superior sensitivity, the neural signatures discussed above distinguish their concepts of interest from other similar but meaningfully different concepts (e.g., physical pain).

These studies on neural signatures make two important contributions to the field. First, they demonstrate that psychological concepts like "negative affect" and "fear" are best represented by brain-wide patterns of activation. Second, they provide these neural signatures for the broader scientific community, so they can be employed and validated in independent studies. This also offers the opportunity to use these innovative neural markers in clinical neuroimaging sciences.

1.6 Research Questions

Based on the literature reviewed above, several topics emerge which are important for a good theoretical understanding of the brain changes following early adversity. These can be framed as four research questions.

(I) Do brain alterations following adverse experiences differ qualitatively depending on whether they occur in child- or adulthood?

The literature points towards sensitive periods during early childhood and adolescence for structural changes in the amygdala and hippocampus. These sensitive periods have been theoretically embedded in frameworks highlighting the importance of experience-expectant plasticity, transition points, adaptive acceleration of maturation, and neurodevelopmental disruption. Still, there is some evidence that brain changes can also occur later in life in response to severe adverse experiences, supporting life-long experience-dependent plasticity. Based on the information theoretic approach to early adversity and the free energy principle, it is plausible that traumatic experiences can lead to highly plastic neural changes as they are characterized by high severity and low prior expectation.

(II) Do structural findings translate to functional alterations?

For the amygdala, alterations in both structure and function following maltreatment have been established. Nevertheless, most functional studies have so far not incorporated the influence of developmental timing of events, which has been demonstrated for structural measures. Only one study looked at amygdala function thus far (Zhu et al., 2019), identifying sensitive periods for responsivity to emotional faces for physical maltreatment during ages 3-6 and emotional abuse at ages 13 and15. Interestingly, experiencing adversity during these phases had opposite effects: childhood adversity was associated with decreased and adolescence adversity with increased amygdala reactivity. Still, these effects were found within a large search

space of different types of maltreatment and the study did not account for psychopathology, which is related to the next major question.

(III) How do brain changes relate to psychopathology versus exposure to adversity?

Brain changes can be the result of adverse experiences and/or reflect psychopathology. There are currently two branches of research: One investigates differences in neural markers in relation to both maltreatment and psychopathology but neglects the influence of timing of events. The other demonstrates that brain changes are highly dependent on the timing of events, but clinical consequences are usually restricted to post-hoc speculations. Studies must simultaneously account for psychopathology as well as the severity and timing of adverse experiences to inform the clinical relevance of biological alterations.

(IV) How can the clinical interpretability of neural alterations be facilitated?

Even if general clinical relevance is established, most brain alterations remain hard to interpret in the language of clinical psychology and psychiatry. This is largely due to the limited sensitivity and specificity of single regions as neural markers, as exemplified by the amygdala in the context of emotion processing.

In the following chapters, I present three studies, which address these four major questions. Study 1 contrasts the structural alterations following adverse experiences during child- and adulthood in 155 women (Research Question I). Extending the research on trauma timing to adulthood might offer important insights concerning plasticity and experience-expectant versus experience dependent learning. Study 2 extends previous structural work on sensitive periods during childhood and adolescence to functional amygdala reactivity in response to threatening scenes in 60 trauma-exposed women (Research Question II). Both studies 1 and 2 account for the role of psychopathology by including trauma-exposed groups with and without PTSD (Research Question III).

As described above, even if such approaches are informative to distinguish effects of maltreatment and psychopathology, these associations are still limited by ambiguous psychological interpretations due to the reverse inference problem and low specificity of region-based neural markers. Study 3 tests whether multivariate brain-wide functional neural signatures might be viable tools to better understand symptoms in trauma-related disorders (Research Question IV), focusing on the clinical feature *affective dysregulation*. To this end, 192 women from three studies (49 BPD, 62 cPTSD, 81 healthy controls) were shown pictures with negative content during fMRI and results aggregated using a mega-analytic approach.

Study I: Neurostructural associations with traumatic experiences during child- and adulthood

CHAPTER II

2.1 Abstract

Adverse experiences can lead to severe mental health problems such as PTSD throughout the lifespan. In individuals with PTSD, both global and local brain volume reductions have been reported—especially in the amygdala and hippocampus—while the literature on childhood maltreatment suggests strong dependency on the timing of adverse events. In the present study, we pooled data from two studies to contrast effects of reported trauma-exposure during neurodevelopmentally sensitive periods in early life with trauma-exposure during adulthood. A total of 155 women were allocated into one of six age-matched groups according to timing of traumatization (childhood vs adulthood) and psychopathology (PTSD vs trauma-exposed healthy vs trauma-naïve healthy). Volumes of amygdala and hippocampus were compared between these groups. Six additional exploratory regions of interest (ROI) were included based on a recent meta-analysis. Amygdala volume was strongly dependent on timing of traumatization: Smaller amygdala volumes were observed in the childhood sample, while larger volumes were observed in the adulthood sample. Hippocampal volume comparisons revealed no statistically significant differences, although the descriptive pattern was similar to that found for the amygdala. The remaining exploratory ROIs showed significant group effects, but no timing effects. Timing of traumatization was associated with amygdala volumes throughout the lifespan, with opposite effects dependent on age at trauma occurrence. The relevance of potential confounders like trauma-type and multiplicity is discussed.

2.2 Introduction

PTSD is a debilitating condition affecting about 3.9% of the global population during their lifetime (Koenen et al., 2017). It is characterized by intrusive re-experiencing of traumatic events, avoidance of trauma-related memories and external cues, alterations in cognition, mood, arousal, and reactivity (DSM-5; American Psychiatric Association, 2013). Motivated by its severe consequences for well-being, health, and mortality (Boscarino, 2006; Giesinger et al., 2020) and the extremely high prevalence of traumatic experiences worldwide (70% lifetime prevalence; Kessler et al., 2017), there have been major ongoing efforts to identify vulnerability factors and refine pathophysiological models of PTSD with a strong focus on neuroimaging.

Among the most consistent neuroimaging findings are lower regional and global white- and grey-matter brain volume in PTSD patients (Bromis et al., 2018; Kribakaran et al., 2020; Siehl et al., 2018). In terms of local regions, most research has been devoted to the amygdala and the hippocampus. Both regions are involved in cued and contextualized fear learning, show relative consistent volume reductions in PTSD samples, and exhibit stress-dependent alterations in animal studies (Brewin et al., 2010; Maren et al., 2013; Sapolsky, 1996; Shalev et al., 2017). Moreover, smaller local volumes have been reported for the insula and the medial prefrontal cortex (mPFC; Bromis et al., 2018), including alterations in interhemispheric white matter tracts in the PFC (Siehl et al., 2020). These regions play a key role in psychobiological models of PTSD (Liberzon & Abelson, 2016; Shalev et al., 2017).

For correct interpretation of these findings, it is crucial to distinguish which neural alterations are functionally related to PTSD symptoms and not a mere consequence of stress-exposure in the absence of mental or physical sequelae (Szeszko et al., 2018). A meta-analysis by Paquola and colleagues (2016) demonstrated that hippocampal atrophies can be found even in healthy stress-exposed samples, while amygdala atrophies were only present in samples with PTSD. Using a more complete approach, the meta-analysis by Bromis and colleagues (2018)

found that PTSD samples had smaller hippocampal volumes than trauma-exposed controls, which in turn had smaller volumes than trauma-naive controls, potentially reflecting a dose-response relationship of stress exposure. A similar pattern was descriptively found for the amygdala, but differences between groups were smaller and only statistically significant when the PTSD group was compared to the pooled control groups.

A major challenge for the field is the potential dependency of stress-brain associations on the timing of adverse experiences. This challenge has received substantial research attention during recent years in the literature on ACE, which is one of the strongest risk factors for PTSD (Kessler et al., 2017). Volume reductions following childhood maltreatment for both hippocampus and amygdala appear to be dependent on the developmental timing of events, supporting the existence of sensitive neurodevelopmental periods (Andersen et al., 2008; Herzog et al., 2020; Luby et al., 2019; Merz et al., 2018; Pechtel et al., 2014; Teicher et al., 2018). Moreover, first evidence indicates timing-effects generalize to amygdala function, revealing differential effects of trauma exposure and PTSD (Sicorello, et al., 2020; Zhu et al., 2019). These studies on trauma timing have added nuance to the interpretation of neural markers and contribute to theories of (mal-) adaptive neurodevelopment. Nevertheless, they have thus far focused on the period of childhood and adolescence, while studies on stress-exposed adults suggest volumetric alterations can still emerge later in life, although it is unclear whether these include the amygdala and hippocampus (Kühn et al., 2021).

In the present study, we aimed to contrast the neurostructural associations with early and late trauma-exposure, while also accounting for the role of psychopathology. We compared regional brain volumes of women who (a) either experienced traumatic events before or after entering adulthood (i.e., age 18) and (b) either developed PTSD or remained physically and mentally healthy. A trauma-naive healthy control group was included as well to assess the general effect of trauma exposure. All groups were matched for age to avoid confounding (Woon & Hedges, 2008). The main focus of our study was on the amygdala and the hippocampus,

which have by far the strongest theoretical and empirical basis for associations between trauma timing and psychopathology. For exploratory analyses, we further included all structures for which differences between PTSD and (combined) controls were reported in a previous meta-analysis (Bromis et al., 2018) to provide a first basis for the investigation of trauma timing effects on these regions. These exploratory regions included the inferior fronto-orbital gyrus (IFOG), anterior cingulate gyrus (ACG), anterior insula, posterior insula, middle temporal gyrus (MTG), and superior frontal gyrus (SFG).

2.3 Methods

Participants

The total sample of 156 adult women (mean age = 35.3; SD = 10.6; range 20-60 years) was pooled from two cross-sectional MRI studies on adverse experiences and psychopathology, conducted at the same scanner and facilities between 2010 and 2018 at the Central Institute of Mental Health in Mannheim, Germany. One participant had to be excluded from the analyses due to motion artifacts, resulting in an effective sample size of 155 participants. Sample 1 assessed adult women with traumatic experiences before the age of 18; sample 2 assessed adult women with traumatic experiences during adulthood. Both studies comprised three groups: patients with trauma-exposure and PTSD (PTSD), trauma-exposed healthy controls (TC), and trauma-naive healthy controls (HC). Hence, the pooled sample consists of six groups with 26 female participants in each group. Groups from the childhood sample are denoted with a subscripted "child" (e.g., $PTSD_{child}$); groups from the adulthood sample are denoted with a subscripted "adult" (e.g., $PTSD_{adult}$). Education levels, trauma characteristics, and clinical data can be found in Table 1 and Table S1. For further notable differences between the two samples, see the methods section on procedures and the discussion section on limitations.

All participants received reimbursement for participation (10€/h) and travel expenses. Patients were offered treatment in the outpatient clinics of the Central Institute of Mental Health

in Mannheim and the outpatient treatment center of Goethe University in Frankfurt. The study was carried out following the Code of Ethics of the World Medical Association (World Medical Association, Declaration of Helsinki, seventh revision, 2013). The study was approved by the Ethical Review Board of the Medical Faculty Mannheim (Heidelberg University) and the ethics committee of the Goethe University. All participants gave written informed consent including consent for data re-analysis.

Table 1

Demographic and clinical characteristics of the two PTSD groups

		$PTSD_{child}$				$PTSD_{adult}$							
		M	*SD*	*n*	%	*M*	*SD*	*n*	%	X^2	*t*	*df*	*p*
Education	No graduation/ Still at school			2				1		1.47		3	.69
	Junior High School [Hauptschule]			5				4					
	Junior High School [Realschule]			10				8					
	A-Level/American SAT [Abitur]			8				12					
Trauma													
Time since trauma (in years)		29.7	11.4	25		8.3	6.79	25			8.04	39.04	<.001
Age at index trauma (in years)		8.8	4.4	25		30.0	11.1	25			10.13	32.90	<.001
Type of traumatic event (index trauma)	**Total (caused voluntarily)**			**25**	**100.0**			**16**	**64.0**	**8.67**		**1**	**.003**
	(1) Imprisonment			-				-					
	(2) Physical violence			4				5					
	(3) Sexual abuse			21				-					
	(4) Rape			-				4					
	(5) Wartime experience			-				5					
	(6) Witness of sudden death/ serious injury of so.			-				2					
	(7) Other experience			-				-					
	Total (caused involuntarily)			**0**	**0**			**9**	**36.0**				
	(1) Natural disaster			-				-					
	(2) Fire or explosion			-				-					
	(3) Accident			-				7					
	(4) Sudden death of so.			-				1					
	(5) Other experiences			-				1					
Trauma diagnostics													
CAPS-4		-	-	-		57.0	18.9	26					
CAPS-5		42.6	9.15	25		-	-	-					
CTQ		85.1	21.9	16		44.4	19.0	25					
BSL		2.1	0.7	25		-	-	-					
Comorbidities													
Axis I disorder	**Yes/No**			**23/2**				**15/11**		**6.20**		**1**	**.013**
Type Axis I	Major Depressive Disorder			20	80.0			11	44.0				
	Anxiety			10	64.0			16	40.0				
	Substance Abuse/Addiction			3	8.0			2	12.0				
	Other			6	24.0			2	8.0				
Axis II disorder	**Yes/No**			**16/9**				**5/21**		**8.78**		**1**	**.003**
Borderline				16				-					
STAI-T		62.4	8.6	25		54.5	10.8	25			2.84	45.44	**.007**
Medication	**Total (yes)**			**20**	**76.9**			**13**	**52.0**	2.46		1	.12
	Psychopharmacological			20				1					
	Other			-				5					
	Total (no)			**6**	**23.1**			**12**	**48.0**				

Note. M = Arithmetic Mean, *SD* = Standard Deviation, *n* = sample size, CAPS = Clinician-Administered PTSD scale, CTQ = Childhood Trauma Questionnaire, BSL = Borderline Symptom List, STAI-T = State-Trait Anxiety Inventory (Trait Subscale).

Procedures

Sample 1: Trauma experience in childhood. Participants with PTSD after traumatic experiences in childhood ($PTSD_{child}$) were recruited from a larger randomized controlled psychotherapy study (Bohus et al., 2019, 2020). Inclusion criteria were the experience of physical or sexual abuse before the age of 18 as well as female sex and gender identity. Moreover, participants had to fulfill at least 3 criteria for BPD, including the criterion for affective instability. They underwent MRI measurements between randomization and the first therapy session. PTSD was assessed by trained diagnosticians using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Hans Ulrich Wittchen et al., 1997). Trauma exposure was measured by the Life Events Checklist (LEC-5; Weathers et al., 2013), which was also used to determine the index trauma. Additionally, the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Müller-Engelmann et al., 2020) and the BPD section of the International Personality Disorder Examination were administered (IPDE; Loranger et al., 1997). The CAPS-5 assesses the severity of 20 symptoms in relation to the index trauma. Symptoms are assessed on a 5-point scale ranging from 0 (no impairment) to 4 (extreme impairment). In addition to establishing PTBS diagnoses, the total CAPS-5 score, with a maximum of 80, gives an indication of clinical severity.

Further self-report measures included retrospective questionnaires on childhood trauma (Childhood Trauma Questionnaire [CTQ]; Bernstein et al., 2003), PTSD symptoms (PTSD checklist for DSM-5 [PCL-5]; Krüger-Gottschalk et al., 2017); Davidson Trauma Scale [DTS]; Davidson et al., 1997), and severity of depressive mood (Beck Depression Inventory 2 [BDI-II]; Beck et al., 2009). Healthy trauma-exposed controls (TC_{child}) who reported physical or sexual abuse before the age of 18 and healthy trauma-naive controls (HC_{child}) were recruited with advertisements in local newspapers, flyers and over the internet.

Exclusion criteria for all participants were age under 18 or over 65, metal implants, pregnancy, left-handedness, and claustrophobia. Exclusion criteria for PTSD participants specifically covered current and lifetime schizophrenia or bipolar-I disorder, mental retardation, or severe psychopathology requiring immediate treatment in a different setting (e.g., BMI<16.5), medical conditions contradicting exposure-based treatment (e.g., pregnancy), a highly unstable life situation (e.g., homelessness), a life-threatening suicide attempt within the last two months, and substance dependence with no abstinence within two months prior to the study. Exclusion criteria for the trauma controls were any current or previous mental disorder, any prior psychotherapy, or any intake of psychotropic medication.

Structural MRI analyses on a partially overlapping sample have been previously published (Herzog et al., 2020).

Sample 2: Trauma experience in adulthood. All participants were assessed by a trained psychologist for trauma exposure using a list of possible traumatic events, taken from the Posttraumatic Diagnostic Scale (Foa et al., 1997), followed by the SCID-I and II for DSM-IV-TR (American Psychiatric Association, 2000; Fydrich et al., 1997; Wittchen et al., 1997). Participants were assigned to the PTSD group, when the diagnostic criteria were fulfilled in the SCID-I interview. The index events reported by participants in sample 2 were not exclusively limited to interpersonal violence. Participants, reporting other traumatic events fulfilling DSM-V criteria A of the PTSD diagnostics, were also included. In addition, participants were assessed with the German version of the Clinician-Administered Posttraumatic Stress Scale for DSM-IV (CAPS; Blake et al., 1995; Schnyder & Moergeli, 2002) and had to fulfill criteria B through F. The CAPS score for symptom severity ranges from 0 to 100, assessed on a 5-point scale ranging from zero (“never”/ “none) to four “most or all the time”/ “extreme”).

For the sample of patients with trauma experience in adulthood ($PTSD_{adult}$) the following exclusion criteria were applied in the original studies: younger than 18 years, any traumatic experience (interpersonal or any other) before the age of 18 years, comorbid current or lifetime psychotic symptoms, current alcohol/ drug dependence or abuse, BPD, cardiovascular or neurological disorders, brain injury, acute pain, continuous pain or medication for attention deficit hyperactivity disorder, pregnancy and metal implants. Importantly, patients and trauma-exposed individuals in sample two had no traumatic experience before the age of 18 years (telephone screening with PDS and SCID). The healthy trauma-exposed individuals in this sample were trauma-exposed in adulthood (TC_{adult}) but did not fulfil any criteria for a current or past mental disorder as assessed with the SCID-Interview as well as the CAPS. Healthy trauma-naive individuals (HC_{adult}) did not fulfil any criteria for a mental disorder.

MRI Data Acquisition

For both samples, we acquired T1-weighted, magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) images using the same 3T Magnetom TRIO whole body magnetic resonance scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard 12-channel volume head coil. Slightly different acquisition parameters were used in each sample, for which we accounted in the preprocessing steps. In the sample of trauma experience in childhood (sample 1), the following parameters were applied: TR = 1570 ms, TE = 2.75 ms, flip angle 15°, FOV: 256 x256 mm^2, matrix size: 256 x 256, voxel size: 1.0 x 1.0 x 1.0 mm^3, 176 sagittal slices. In the sample of trauma experience in adulthood (sample 2), the following parameters were applied: TR = 2300 ms, TE = 2.98 ms, flip angle 9°, FOV: 256 x256 mm^2, matrix size: 256 x 256, voxel size: 1.0 x 1.0 x 1.1 mm^3, 160 sagittal slices.

Clinical Assessments for Both Samples

Traumatic childhood experience was assessed with the German version of the CTQ (Bernstein et al., 1994; Klinitzke et al., 2012). The self-report instrument assesses the severity of trauma exposure, such as emotional abuse and neglect, physical abuse and neglect as well as sexual abuse. The 25 items ask how often each event occurred during the participant's upbringing and each item is rated on a 5-point Likert scale ranging from 1 ("never at all") to 5 ("very often"). The overall sum score was calculated, which is calculated by the sum of the five subscales, ranging from 25 to 125. In sample two, the 40-item version of the CTQ was used, with additional two subscales and six items, in which participants could rate the age in which the childhood experiences occurred. However, for the purpose of this study, we only calculated the sum score of the same 25-items as for sample one.

Trait anxiety was assessed with the German version of the trait-version of the State-Trait-Anxiety-Inventory (STAI-T; Laux, 1981), a self-report questionnaire with 20 items, assessed on a 4-point Likert scale ranging from one ("not at all") to four ("very much"). The total STAI-T scores ranges from 20 to 80, with higher scores being associated with higher levels of trait anxiety.

Pooling and Matching of Data

The data of the two samples were pooled in a multi-step process. The original pool consisted of over 297 participants including 104 male participants. Male participants were excluded since the sample of traumatic experience in childhood consisted only of female participants. In a next step, data was assessed for completeness (excluding 10 participants). Patients from either of the two samples (childhood and adulthood) were age-matched and in a second step each group of patients was then age-matched to individuals from the TC and HC group (exclusion of 15 participants) manually minimizing the age difference between matched groups. If a pa-

tient could be age-matched equally well to a participant from either control group, the participant from the control group was taken with a total intracranial volume (TIV) more similar to the patient's TIV (exclusion of 12 participants, 1-3 participants from each group). After matching, an analysis of variance on age with group and sample as the independent variables indicated no significant age differences between groups (all $p > .60$; $PTSD_{child}$: $M = 38.5$, $SD = 9.9$; TC_{child}: $M = 32.4$, $SD = 12.0$; HC_{child}: $M = 33.8$, $SD = 7.6$; $PTSD_{adult}$: $M = 39.7$, $SD = 9.8$; TC_{adult}: $M = 34.0$, $SD = 11.2$; HC_{adult}: $M = 33.7$, $SD = 11.3$).

MRI Preprocessing

The T1-weighted images were preprocessed using the Computational Anatomy Toolbox (CAT12; http://www.neuro.uni-jena.de/cat) on Statistical Parametric Mapping version 12 (SPM12; Wellcome Department of Imaging Neuroscience, London, UK) implemented in customized scripts in MATLAB R2016a (The MathWorks Inc., Natick, MA, USA). The preprocessing steps included spatial registration, segmentation into gray and white matter and CSF as well as bias correction of intensity non-uniformities following our previous study (Siehl et al., 2020). We chose the Neuromorphometic atlas (provided by Neuromorphometrics, Inc., MA, USA; http://www.neuromorphometrics.com) for the definition of region of interests (ROIs). We then extracted gray matter volume (in cm^3) for eight predefined ROIs, following the results by a recent meta-analysis (Bromis et al., 2018): amygdala, hippocampus, IFOG, ACG, anterior insula, posterior insula, MTG, SFG. Data was assessed for head motion, excluding one participant (from the $PTSD_{child}$ group) moving more than the maximum translation of 1 mm in x-, y-, or z-direction and the maximum angular motion of 1° throughout the course of the scan.

Statistical Analyses

Statistical analyses were performed in R-Statistics (Team, 2013) using the packages dplyr (Wickham et al., 2019) for data processing, and rstatix and emmeans for the analyses and ggplot2 (Wickham, 2017) for plotting. We assessed all data for the appropriate assumptions, including normal distribution and outliers. Data was in line with these assumptions, if not stated otherwise below. For the socio-demographic data, two-sample t-tests as well as Chi-square tests of frequency distributions were applied. We then performed a mixed 3 ($group_{between\text{-}subject}$: PTSD, TC, HC) x 2 ($sample_{between\text{-}subject}$: childhood, adulthood) x 2 ($hemisphere_{within\text{-}subject}$: left, right) Analysis of Covariances (ANCOVAs) for each of the eight ROIs with total intracranial volume (TIV) as covariate. To counter inflation of Type I errors, Bonferroni corrections were applied ($\alpha/8 = .05/8 = .00625$). Post-hoc single-step multiple comparison t-tests were applied with Bonferroni corrections.

2.4 Results

Sample Descriptions

The two patient groups ($PTSD_{child}$, $PTSD_{adult}$) had similar education levels (Table 1). The age at index trauma was significantly lower in $PTSD_{child}$ than $PTSD_{adult}$. Similarly, CTQ scores differed strongly between the two groups (Table 1). There were significant differences in the types of traumatic events experienced in each patient group, with $PTSD_{child}$ experiencing significantly more interpersonal trauma (e.g., physical or sexual abuse) than $PTSD_{adult}$. Significantly more patients in the $PTSD_{child}$ group had comorbid mental disorders on axis-I as well as BPD (Table S1). In addition, patients in the $PTSD_{child}$ group reported significantly higher anxiety scores on the STAI-T. Finally, there was no difference in overall number of participants taking medication (dichotomous: yes/no) and kind of medication taken between the $PTSD_{child}$ and $PTSD_{adult}$ groups (Table 1, Table S1). Medication dosage was not assessed.

Amygdala

Comprehensive inferential statistics for all regions of interest are reported in Table 2. Region-wise means and standard deviations can be found in Table S2.

We found a significant interaction of group and sample (Figure 1; Table 2; Table S2). Post-hoc t-tests revealed an effect of trauma timing: Amygdala volume was significantly higher for participants with adult trauma compared to those with childhood trauma. This was also apparent in a time-series of index traumas in the PTSD groups with a finer time resolution (Figure *2*). In comparison to the trauma-naive healthy control groups, we found opposite effects dependent on timing: For childhood trauma, the $PTSD_{child}$ group exhibited significantly smaller amygdala volumes than the HC_{child} group. For adulthood trauma, both $PTSD_{adult}$ and TC_{adult} had significantly larger amygdala volumes compared to the HC_{adult} group.

We found a significant main effect of hemisphere, with the right amygdala showing significantly lower volume than the left amygdala. There were no further interactions between hemisphere and the other independent variables.

Hippocampus

We found a significant main effect of hemisphere, with larger volume in the right hippocampus (Figure 1; Table 2; Table S2). All remaining effects were not significant. Descriptively, similar to the pattern for the amygdala, only the $PTSD_{child}$ group had smaller hippocampal volumes than their reference groups, while both groups with adulthood trauma actually had slightly *higher* hippocampal volumes, opposite to the expected effect direction.

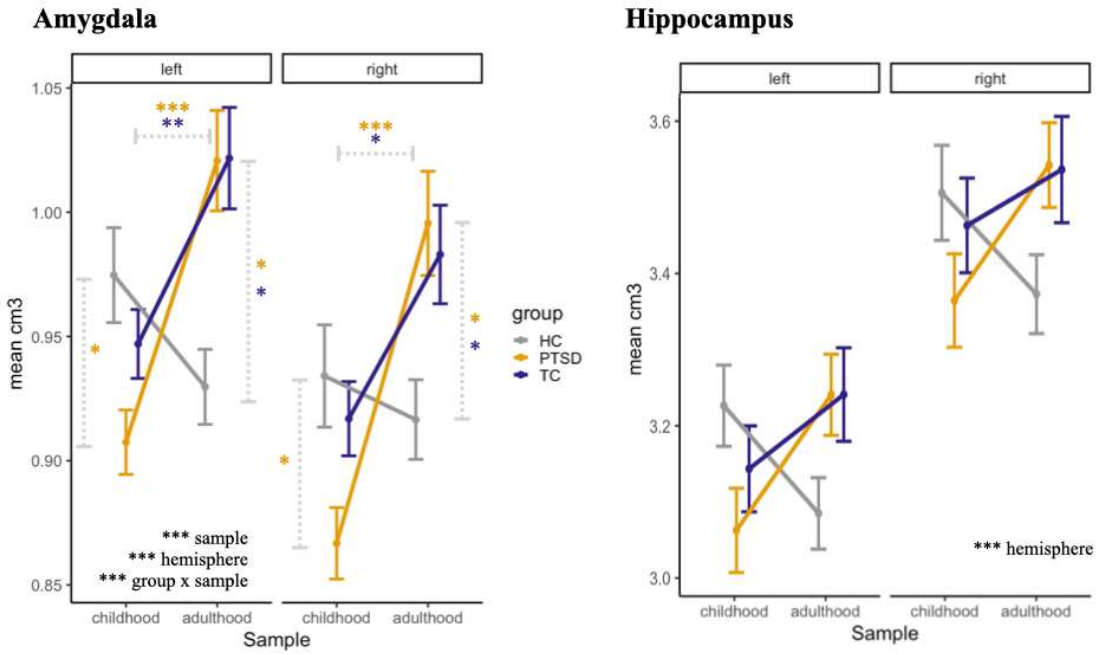

Figure 1. Volumetric differences in the amygdala and hippocampus between samples (childhood, adulthood), groups (PTSD, TC, HC) and hemispheres (left, right) in cm3.

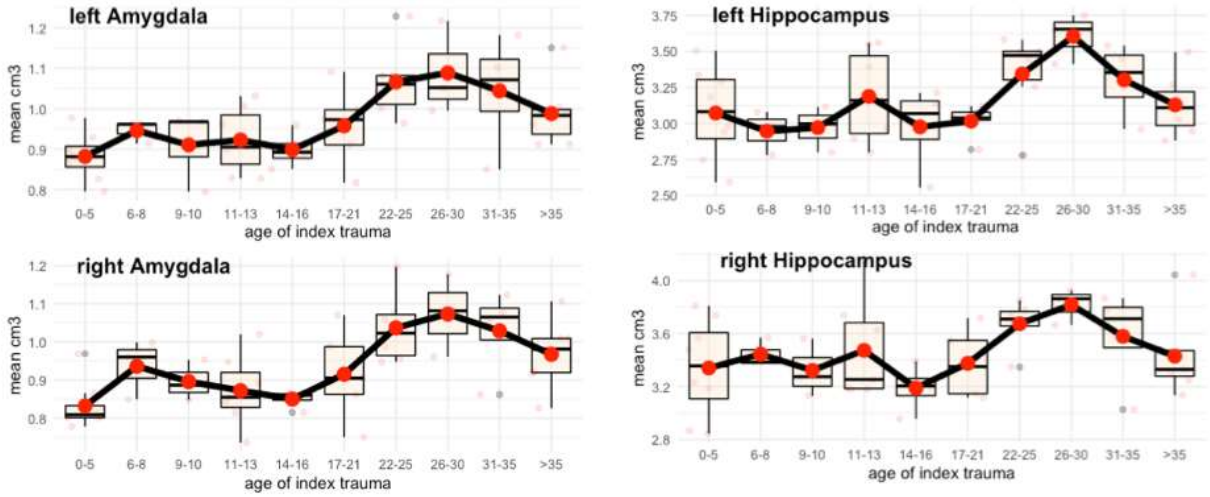

Figure 2. Volumetric differences in the amygdala and hippocampus for both patient groups (PTSDadult, PTSDchild) in time bins defined by the age of the index trauma separately for each hemisphere (left, right) in cm^3.

Exploratory Regions of Interest

Quantitative results and graphical representations for all exploratory ROIs can be found in Table 2 and Figures 3 and 4 (as well as Table S2).

IFOG. A significant main effect of group was found. Post-hoc tests revealed that within the childhood sample, both control groups had larger left IFOG volumes than the PTSD group.

Anterior insula. A significant main effect of group was found. Post-hoc test showed that within the adulthood sample, TCs had larger volumes than HCs.

Posterior Insula. There were significant main effects for group, sample, and hemisphere, as well as a significant interaction between sample and hemisphere. Only the post-hoc tests for hemisphere survived multiple comparison correction, confirming larger volumes of the right insula in all groups.

ACG. As for the posterior insula, we found a significant main effect of group, sample, and hemisphere, as well as a significant interaction between sample and hemisphere. Post-hoc effect indicated larger brain volumes in HC_{child} than $PTSD_{child}$ within the left ACG. There was also a significant difference between the two healthy control groups within the right ACG.

MTG. There was a significant interaction between sample and hemisphere, but post hoc tests did not survive correction for multiple comparisons. Descriptively, the significant interaction is most likely driven by the larger right volumes in the two trauma groups exposed during adulthood, with visual similarity to the disordinal pattern found for the amygdala.

SFG. Significant main effects for group, sample, and hemisphere were found, with no post-hoc contrasts surviving correction for multiple comparisons.

Table 2

ANCOVA results for volumetric data

Region	Main effects/interactions	Post-hoc *t*-tests									
		effect	group/ sample	hemisphere	contrast	M_{Diff}	95% CI	*t*	*df*	p_{bon_cor}	Hedges' *g*
Amygdala	**$F_{TIV}(1, 148) = 87.56, p<.001, \eta^2=.35$**	sample		left	adult > child	0.05	0.02; 0.08	3.13	147	.002	0.50
	$F_{group}(2, 148) = 2.33, p=.10, \eta^2=.03$			right	adult > child	0.06	0.03; 0.09	3.81	151	<.001	0.61
	$F_{sample}(1, 148) = 7.96, p<.001, \eta^2=.05$	hemisph.	$PTSD_{child}$		left > right	0.04	0.01; 0.05	2.10	47.5	.002	0.60
	$F_{hemisphere}(1, 148) = 79.44, p<.001, \eta^2=.05$	group x	PTSD	left	adult > child	0.11	0.07; 0.16	4.72	42.3	<.001	1.32
	$F_{group\ x\ sample}(2, 148) = 7.05, p<.001, \eta^2=.08$	sample		right	adult > child	0.13	0.08; 0.18	5.07	43.9	<.001	1.41
	$F_{group\ x\ hemisphere}(2, 148) = 0.56, p=.57, \eta^2<.01$		TC	left	adult > child	0.08	0.03; 0.13	3.03	44.0	.004	0.84
	$F_{sample\ x\ hemisphere}(1, 148) = 1.35, p=.25, \eta^2<.01$			right	adult > child	0.06	0.02; 0.12	2.66	46.5	.011	0.74
	$F_{group\ x\ sample\ x\ hemisphere}(2, 148) = 3.42, p=.035, \eta^2<.01$		adulthood	left	PTSD > HC	0.09	0.04; 0.14	3.61	46.3	.002	1.01
				right	PTSD > HC	0.08	0.03; 0.13	2.99	46.8	.013	0.83
			adulthood	left	TC > HC	0.09	0.04; 0.14	3.62	46.0	.002	1.01
				right	TC > HC	0.07	0.02; 0.11	2.61	47.9	.002	0.73
			childhood	left	HC > PTSD	0.07	0.02; 0.11	2.91	43.7	.017	0.81
				right	HC > PTSD	0.07	0.02; 0.11	2.68	44.3	.031	0.75
Hippocampus	**$F_{TIV}(1, 148) = 94.49, p<.001, \eta^2=.37$**	hemisph.	HC_{child}		right>left	0.28	0.12; 0.44	3.23	48.8	.002	0.95
	$F_{group}(2, 148) = 1.09, p=.34, \eta^2=.01$		HC_{adult}		right>left	0.29	0.15; 0.43	3.08	49.5	<.001	1.15
	$F_{sample}(1, 148) = 0.54, p=.47, \eta^2<.01$		$PTSD_{child}$		right>left	0.30	0.14; 0.47	3.06	47.5	<.001	1.04
	$F_{hemisphere}(1, 148) = 679.72, p<.001, \eta^2=.30$		$PTSD_{adult}$		right>left	0.30	0.15; 0.46	3.24	49.9	<.001	1.09
	$F_{group\ x\ sample}(2, 148) = 1.53, p=.22, \eta^2=.02$		TC_{child}		right>left	0.32	0.15; 0.49	3.14	49.5	.002	1.06
	$F_{group\ x\ hemisphere}(2, 148) = 0.34, p=.71, \eta^2<.01$		TC_{adult}		right>left	0.30	0.11; 0.48	3.24	49.2	<.001	0.89
	$F_{sample\ x\ hemisphere}(1, 148) = 0.26, p=.61, \eta^2<.01$										
	$F_{group\ x\ sample\ x\ hemisphere}(2, 148) = 0.41, p=.67, \eta^2<.01$										

Table 2
(continued)

Region	Main effects/interactions	Post-Hoc *t*-tests									
		effect	group/ sample	hemisphere	contrast	M_{Diff}	95% CI	*t*	*df*	p_{bon_cor}	Hedges' *g*
IFOG	**$F_{TIV}(1, 148) = 46.78, p < .001, \eta^2=.21$** **$F_{group}(2, 148) = 3.59, p = .03, \eta^2=.04$** $F_{sample}(1, 148) = 0.01, p=.94, \eta^2<.01$ $F_{hemisphere}(1, 148) = 0.01, p=.92, \eta^2<.01$ $F_{group\ x\ sample}(2, 148) = 2.45, p=.09, \eta^{2=}.03$ $F_{group\ x\ hemisphere}(2, 148) = 1.90, p=.15, \eta^2<.01$ $F_{sample\ x\ hemisphere}(1, 148) = 4.22, p=.04, \eta^2<.01$ $F_{group\ x\ sample\ x\ hemisphere}(2, 148) = 0.34, p=.71, \eta^2<.01$	group	childhood	left	HC>PTSD	0.19	0.06; 0.31	2.92	48.6	.016	0.82
				left	TC>PTSD	0.20	0.06; 0.34	2.96	48.9	.014	0.83
Ant. Insula	**$F_{TIV}(1, 148) = 61.90, p<.001, \eta^2=.28$** **$F_{group}(2, 148) = 12.74, p=.002, \eta^2=.08$** $F_{sample}(1, 148) = 2.74, p=.10, \eta^2=.02$ $F_{hemisphere}(1, 148) = 1.85, p=.18, \eta^2<.01$ $F_{group\ x\ sample}(2, 148) = 0.24, p=.79, \eta^2<.01$ $F_{group\ x\ hemisphere}(2, 148) = 2.94, p=.06, \eta^2<.01$ $F_{sample\ x\ hemisphere}(1, 148) = 2.98, p=.09, \eta^2<.01$ $F_{group\ x\ sample\ x\ hemisphere}(2, 148) = 0.83, p=.44, \eta^2<.01$	group	adulthood	left	TC>HC	0.44	0.13; 0.76	2.81	43.4	.022	0.78
Post. Insula	**$F_{TIV}(1, 148) = 83.39, p<.001, , \eta^2=.34$** **$F_{group}(2, 148) = 5.27, p=.006, \eta^2=.06$** **$F_{sample}(1, 148) = 6.72, p=.01, \eta^2=.04$** **$F_{hemisphere}(1, 148) = 671.70, p<.001, \eta^2=.32$** $F_{group\ x\ sample}(2, 148) = 0.15, p=.86, \eta^2<.01$ $F_{group\ x\ hemisphere}(2, 148) = 0.15, p=.86, \eta^2<.01$ **$F_{sample\ x\ hemisphere}(1, 148) = 15.46, p<.001, \eta^2=.01$** $F_{group\ x\ sample\ x\ hemisphere}(2, 148) = 0.06, p=.95, \eta^2<.01$	hemis.	HC_{child}		right>left	0.27	0.11; 0.44	3.34	49.6	.002	0.93
			HC_{adult}		right>left	0.26	0.21; 0.51	4.79	48.5	<.001	1.33
			$PTSD_{child}$		right>left	0.26	0.14; 0.38	4.33	46.2	<.001	1.23
			$PTSD_{adult}$		right>left	0.34	0.20; 0.51	4.70	48.0	<.001	1.31
			TC_{child}		right>left	0.26	0.10; 0.41	3.34	45.6	.002	0.93
			TC_{adult}		right>left	0.38	0.18; 0.58	3.77	49.0	<.001	1.05

Table 2

(continued)

Region	Main effects/interactions	Post-Hoc t-tests									
		effect	group/ sample	hemisphere	contrast	M_{Diff}	95% CI	*t*	*df*	p_{bon_cor}	Hedges' *g*
ACG	**$F_{TIV}(1, 148) = 74.10, p<.001, \eta^2=.29$** **$F_{group}(2, 148) = 3.56, p=.03, \eta^2=.04$** **$F_{sample}(1, 148) = 5.43, p=.02, \eta^2=.03$** **$F_{hemisphere}(1, 148) = 1924.18, p<.001, \eta^2=.69$** $F_{group\ x\ sample}(2, 148) = 1.03, p=.36, \eta^2<.01$ $F_{group\ x\ hemisphere}(2, 148) = 0.25, p=.78, \eta^2<.01$ **$F_{sample\ x\ hemisphere}(1, 148) = 5.43, p=.02, \eta^2=.01$** $F_{group\ x\ sample\ x\ hemisphere}(2, 148) = 0.50, p=.61, \eta^2<.01$	group sample	childhood HC	left right	HC>PTSD child>adult	0.45 0.40	0.09; 0.82 0.06; 0.74	2.52 4.24	44.1 47.0	.046 .021	0.71 0.66
MTG	**$F_{TIV}(1, 148) = 115.36, p<.001, \eta^2=.41$** $F_{group}(2, 148) = 1.56, p=.21, \eta^2=.02$ $F_{sample}(1, 148) = 1.48, p=.23, \eta^2=.01$ $F_{hemisphere}(1, 148) = 1.17, p=.28, \eta^2<.01$ $F_{group\ x\ sample}(2, 148) = 0.40, p=.68, \eta^2<.01$ $F_{group\ x\ hemisphere}(2, 148) = 0.38, p=.68, \eta^2<.01$ **$F_{sample\ x\ hemisphere}(1, 148) = 6.46, p=.01, \eta^2<.01$** $F_{group\ x\ sample\ x\ hemisphere}(2, 148) = 0.11, p=.90, \eta^2<.01$										
SFG	**$F_{TIV}(1, 148) = 102.79, p<.001, \eta^2=.38$** **$F_{group}(2, 148) = 4.60, p=.01, \eta^2=.05$** **$F_{sample}(1, 148) = 4.65, p=.03, \eta^2=.03$** **$F_{hemisphere}(1, 148) = 5.46, p=.02, \eta^2<.01$** $F_{group\ x\ sample}(2, 148) = 0.16, p=.85, \eta^2<.01$ $F_{group\ x\ hemisphere}(2, 148) = 0.35, p=.71, \eta^2<.01$ $F_{sample\ x\ hemisphere}(1, 148) = 0.11, p=.74, \eta^2<.01$ $F_{group\ x\ sample\ x\ hemisphere}(2, 148) = 2.25, p=.11, \eta^2<.01$										

Note. Inferential statistics of ANCOVA models predicting regional volume, separate for all ROIs. The second column shows main and interaction effects. The following columns show post-hoc comparisons. Abbreviations: ACG – Anterior Cingulate Gyrus; Ant. Insula – Anterior insula; IFOG – Inferior fronto-orbital gyrus; MTG – Middle temporal gyrus; Pos. Insula – Posterior Insula; SFG – Superior frontal gyrus

Significant tests are shown in bold if $p < .05$ (corrected for multiple comparisons; for correction procedure see methods section)

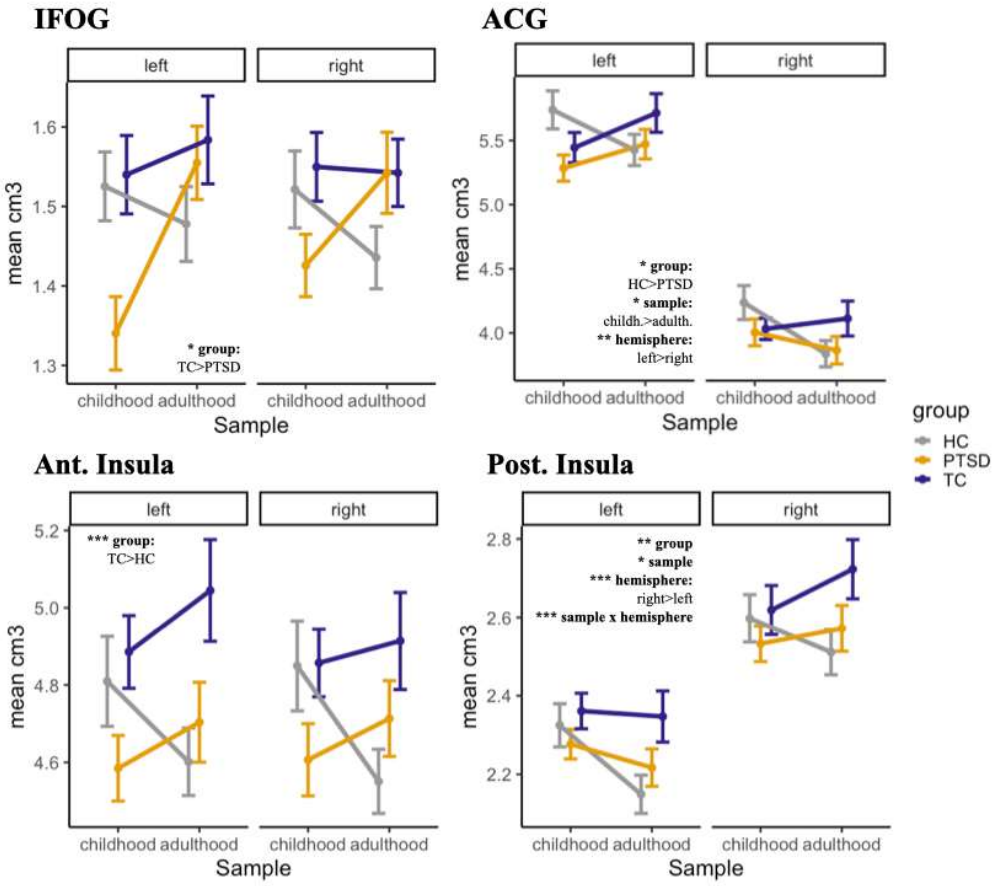

Figure 3. Volumetric differences in the inferior fronto-orbital gyrus (IFOG), anterior cingulate gyrus (ACG), anterior (ant.) and posterior (pos.) insulae between samples (childhood, adulthood), groups (PTSD, TC, HC) and hemispheres (left, right) in cm^3.

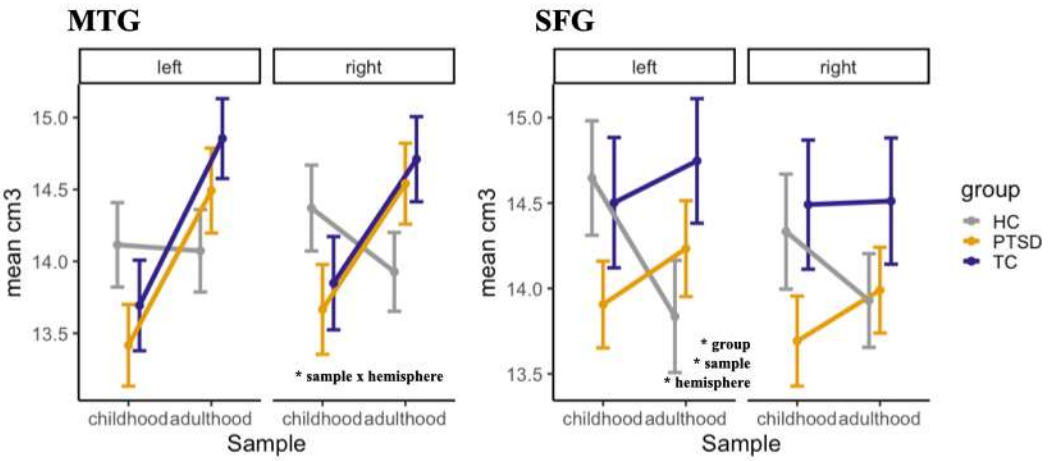

Figure 4. Volumetric differences in the middle temporal gyrus (MTG) and superior frontal gyrus (SFG) between samples (childhood, adulthood), groups (PTSD, TC, HC) and hemispheres (left, right) in cm^3.

2.5 Discussion

Discussion of Results

In the research literature on early adversity, trauma-induced differences in brain volume are increasingly viewed as largely dependent on the neurodevelopmental timing of events. Still, most studies on sensitive periods limited their scope to events occurring during childhood and adolescence. Extending research on sensitive periods to adverse events during adulthood may further help differentiate early neurodevelopmental processes from life-long plasticity.

The amygdala and the hippocampus play a key role in psychobiological models of PTSD and have been highlighted in research on sensitive periods during early childhood and early adolescence (Herzog et al., 2020; Shalev et al., 2017; Teicher & Samson, 2016). Building on this research, we found evidence that amygdala volumes strongly depended on the timing of events, revealing qualitative differences between individuals who were traumatized in childhood or adulthood (see the limitation section for a discussion of potential confounders). While participants with PTSD following childhood trauma had *lower* amygdala volumes compared to trauma-naive healthy controls, participants with adult trauma had *higher* amygdala volumes. These *higher* volumes were apparent in both trauma-exposed groups with- and without psychopathology, potentially indicating general neuroplastic events in response to exposure, rather than clinically meaningful differences.

We did not find significant timing effects on hippocampus volumes, which might be due to limited statistical power. Nevertheless, we find it notable that in the groups with trauma-exposure during adulthood, hippocampus volume was descriptively *larger* than in the trauma-naive controls for both hemispheres. This difference did not survive bonferroni-correction, albeit confidence intervals for this comparison were clearly separated. Qualitatively, this descriptive pattern did not show the often reported general reduction in hippocampus volume, but rather matched the pattern found for the amygdala.

In sum, these data agree with the notion that stress-dependent changes in the amygdala can occur even later in life and are dependent on timing. Most intriguing is the evidence that effect directions might be reversed dependent on timing, which has important implications for the interpretation of neurostructural alterations. Notably, even if these effects would be due to other differences between the two timing groups (e.g., trauma duration or multiplicity), these opposite effects would still reflect highly relevant nonlinearities as a function of these potential explanatory variables (see limitations for further discussion).

For the more exploratory regions, we did not find any interactions between group and sample, i.e., no indication for the relevance of trauma timing. As would be expected from the meta-analysis which motivated these ROI choices, we found significant main effects of group for all regions except for MTG. Visually, there was a tendency for lower volumes in the PTSD group, especially in the childhood sample. Still, post-hoc tests only confirmed this for the IFOG. Naturally, these non-significant post-hoc tests might be due to the decreased statistical power of the corrected p-values. Hence, while descriptively in line with previous research, we did not find evidence for timing effects in these regions.

We emphasize that the relationship between timing of first trauma experience and brain development is complex and we do not want to create a dichotomy between childhood and adult trauma experience. Many individuals with trauma experience in childhood do also experience aversive events in adulthood. Nevertheless, we think that our study is an important starting point to investigate differences in gray matter volumetry based on first exposure to traumatic experiences beyond childhood and adolescence.

Limitations

The study only included women, which limits the generalizability of results, especially as higher-order interactions between sex, adversity type, and timing have been previously observed (Teicher et al., 2018). Moreover, the studies were cross-sectional and relied on retrospective reports. A longitudinal design could differentiate between brain aberrations as vulnerability factors versus neuroplastic environment-contingent alterations. Still, such studies involve screening of at-risk cohorts with neuroimaging assessments at all time-points, which is thus far only feasible in limited settings, where healthy individuals have a very high prospective probability for trauma exposure, such as military deployment or first-aid workers. Even these studies are dependent on the differential occurrence of changes in psychopathology, a condition not always met (Kühn et al., 2021).

Importantly, we aggregated data from two different studies, one focusing on traumatic experiences during childhood and adolescence and one focusing on adulthood. These studies were conducted at the same facility, using the same scanner, but systematic differences might still occur, for example, due to different recruitment strategies. The samples had notable differences in the severity, type, duration, and multiplicity of traumatic events. Another notable difference is the higher prevalence of comorbid BPD in the childhood sample, which was facilitated by the study procedure. Therefore, it is possible that differences might be attributable to these confounders instead of trauma timing. Still, such differences on confounders might be inherent to realistic occurrences of traumatic events in feasible designs using human neuroimaging. For example, the whole childhood sample experienced maltreatment, a distinct trauma type without a direct counterpart in adulthood which usually coincides with higher multiplicity and duration. Even for singular and highly random adverse events that might seem comparable at first glance (e.g., certain cases of natural disasters and sexual assault), the meaning and impact is vastly different for affected children and adults. Hence, while our design cannot rule out many important confounders, suggesting careful interpretation of results, these confounders

might be inherent differences between typical trauma during child- and adulthood. Importantly, the opposite effects for amygdala volume in child- and adulthood are not compatible with a monotonic dose-response effect of variables like duration and multiplicity.

Conclusion

Our findings suggest that amygdala aberrations following adverse experience might be dependent on timing and could occur in response to traumatic events in both child- and adulthood. Adversity effects during child- and adulthood had opposing directions, highlighting the importance to differentiate between neurodevelopmental mechanisms and life-long plasticity. These findings add nuance to the interpretation of brain volumetric associations with adverse experiences. We did not observe such effects of timing for other predefined brain regions implicated in volumetric brain differences related to PTSD. Through our three-group design, our study might inform not only future studies on timing, but also help differentiate effects of psychopathology and trauma-exposure.

2.6 Supplemental materials

Table S1

Detailed clinical characteristics and eduction levels of the PTSD samples

		Childhood [*N* = 25]		Adulthood [*N* = 26]	
Comorbidities					
		Rem.	Rez.	Rem.	Rez.
	Depression	7	14	2	11
	Bipolar	1	6	1	0
	Abuse or Dependency	13	2	0	3
	Panic (with/without Agora)	4	3	0	3
	Agora (without Panic)	0	2	0	1
	Social phobia	11	10	0	0
	Specific Phobia	5	4	0	3
	Obsessive-Compulsive Disorder	4	4	0	0
	Generalized Anxiety Disorder	1	0	0	3
	Somatization	1	1	0	0
	Bulimia	3	2	1	2
	Binge	3	3	0	0
	Borderline	16		0	
	Other	0		5	
Medication					
	Antidepressant	16		9	
	Neuroleptics	9		6	
	Mood Stabilizer	0		0	
	Benzos	2		0	
	Other Psychotropic Medication	4		6	
	Other non-Psychotropic Medication	0		5	
Education					
	No graduation/ Still at school	2		1	
	Hauptschule	5		4	
	Realschule	10		8	
	Abitur	8		12	

Note. PTSD = Posttraumatic Stress Disorder

Table S2

Means and standard deviations of brain volume by group and hemisphere

Anatomical region	Hemisphere	Groups											
		Childhood						Adulthood					
		$PTSD_{child}$ [n=25]		TC_{child} [n=26]		HC_{child} [n=26]		$PTSD_{adult}$ [n=26]		TC_{adult} [n=26]		HC_{adult} [n=26]	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Amygdala	left	0.91	0.07	0.95	0.07	0.98	0.10	1.02	0.10	1.02	0.10	0.93	0.08
	right	0.87	0.07	0.92	0.08	0.93	0.11	1.00	0.11	0.98	0.10	0.92	0.08
IFOG	left	1.34	0.23	1.54	0.25	1.53	0.22	1.26	0.24	1.58	0.28	1.48	0.24
	right	1.43	0.20	1.55	0.22	1.52	0.25	1.54	0.26	1.54	0.22	1.44	0.20
Hippocampus	left	3.06	0.28	3.14	0.29	3.23	0.27	3.24	0.27	3.24	0.31	3.09	0.24
	right	3.36	0.31	3.46	0.32	3.51	0.32	3.54	0.28	3.54	0.36	3.37	0.26
Ant. Insula	left	4.59	0.42	4.89	0.48	4.81	0.59	4.70	0.53	5.05	0.67	4.60	0.45
	right	4.61	0.47	4.86	0.45	4.85	0.59	4.71	0.50	4.91	0.64	4.55	0.42
Pos. Insula	left	2.28	0.19	2.36	0.23	2.33	0.28	2.22	0.24	2.35	0.33	2.15	0.25
	right	2.53	0.23	2.62	0.32	2.60	0.31	2.57	0.30	2.72	0.38	2.51	0.30
ACG	left	5.28	0.51	5.45	0.60	5.74	0.76	5.47	0.59	5.72	0.77	5.43	0.62
	right	4.01	0.52	4.03	0.43	4.24	0.68	3.87	0.55	4.11	0.69	3.84	0.52
MTG	left	13.42	1.42	13.69	1.61	14.12	1.50	14.49	1.51	14.85	1.42	14.07	1.46
	right	13.67	1.56	13.85	1.65	14.37	1.52	14.54	1.44	14.71	1.51	13.93	1.40
SFG	left	13.91	1.27	14.50	1.95	14.65	1.71	14.23	1.43	14.75	1.86	13.84	1.68
	right	13.69	1.32	14.49	1.93	14.33	1.72	13.99	1.28	14.51	1.88	13.93	1.40

Note. PTSD = Posttraumatic stress disorder, TC = Trauma Controls, HC = Healthy Control, *M* = Arithmetic Mean, *SD* = Standard Deviation, IFOG = Inferior fronto-orbital gyrus, Ant. Insula = Anterior insula, Pos. Insula = Posterior Insula, ACG = Anterior Cingulate Gyrus, MTG = Middle temporal gyrus, SFG = Superior frontal gyrus

Study II: Differential Effects of Early Adversity and Posttraumatic Stress Disorder on Amygdala Reactivity: The Role of Developmental Timing

CHAPTER III

3.1. Abstract

PTSD is associated with altered processing of threat-related stimuli. Neurobiological models implicate right amygdala hyperreactivity in these alterations, but this potential biomarker has also been observed in individuals exposed to ACE (i.e., abuse and neglect) without psychopathology. Separating the differential contributions of PTSD and ACE to amygdala reactivity might benefit from incorporating the developmental timing of events.

We conducted comprehensive retrospective interviews assessing ACE for each life year between ages 1 and 17 in a sample of 60 trauma-exposed women (34 with PTSD, 26 healthy participants). FMRI was used to extract amygdala reactivity to threatening versus neutral scenes. Amygdala reactivity was predicted from PTSD diagnosis, total ACE severity, and ACE severity by life year using random forest regression.

PTSD and ACE significantly predicted reactivity in the right amygdala (R^2 = 7%) but explained no variance in the left amygdala. ACE during both a prepubertal (ages 3 & 4) and a postpubertal (ages 16 & 17) period emerged as particularly predictive, while total ACE severity did not contribute to prediction. Follow-up analyses revealed a positive relationship of amygdala activity with PTSD and a negative relationship with ACE during predictive life years.

The opposing effects of PTSD and ACE caution against simplistic etiological and diagnostic interpretations of amygdala function. The identification of potentially sensitive periods for ACE effects on amygdala reactivity to threat may help to uncover interactions between traumatization and development of PTSD.

3.2 Introduction

PTSD is a debilitating condition which affects hundreds of millions of people around the world (Koenen et al., 2017). It is characterized by the intrusive re-experience of traumatic events, avoidance of trauma-related stimuli, hyperarousal, and a view of the world as a generally dangerous place (American Psychiatric Association, 2013). The observation of characteristic structural and functional brain changes in PTSD have been essential to our understanding of the disorder as well as its recognition by the public (Pitman et al., 2012; Sapolsky, 2017). To refine pathophysiological models of PTSD, it is crucial to distinguish which neurobiological markers are functionally related to psychopathology and which are primarily the result of mere exposure to stressful events, apparent even in resilient trauma-exposed individuals without psychopathology (Dannlowski et al., 2012). This is especially relevant when PTSD is the consequence of ACE such as abuse and neglect. Both forms of adversity are among the strongest predictors of PTSD (Kessler et al., 2017) and may interfere with normal neurodevelopment, leading to a broad range of neurostructural alterations with often unclear clinical implications (Bick & Nelson, 2016; Hanson et al., 2015; Teicher & Samson, 2016).

The amygdala is a central structure in neurobiological models of PTSD (Rauch et al., 2006), mainly due to its prominent role in fear conditioning and the detection of relevant stimuli (LeDoux, 2007; Lindquist et al., 2016; Ousdal et al., 2008; Sander et al., 2003), which might contribute to aberrant threat processing in PTSD. Particularly the *right* amygdala is hyperreactive in PTSD patients during exposure to threat-related stimuli, which distinguishes the disorder from both healthy controls and patients with major depression (Patel et al., 2012; Schulze et al., 2019; Stark et al., 2015).

While some studies implicate amygdala hyperreactivity as an intermediate biomarker in the etiology of anxiety related symptoms following ACE (Fonzo et al., 2016), others suggest that amygdala hyperreactivity can also be observed in ACE-exposed individuals without mental disorders (Dannlowski et al., 2012). Therefore, ACE might represent an unrecognized confound

in neuroimaging studies on biomarkers for psychiatric disorders (Teicher & Samson, 2016). Two meta-analyses reported heightened amygdala reactivity in adults with ACE, again with a tendency towards more robust effects in the right amygdala, but did not quantitatively account for psychopathology (Heany et al., 2018; Hein & Monk, 2017). In contrast, another meta-analysis demonstrated that right amygdala hyperreactivity was detectable in PTSD patients even when compared to trauma-exposed healthy controls (Stark et al., 2015). This could support the relevance of psychopathology for amygdala hyperreactivity or reflect a dose-dependent effect of traumatic events, as more severe and frequent experiences increase the likelihood to develop PTSD (Schalinski et al., 2016). Resolving this question implies accounting for both PTSD and the intensity of adverse experiences in the same sample.

In the case of ACE, disentangling the contributions of PTSD and adverse experiences to amygdala function is complicated by the fact that the influence of adversity on brain biomarkers appears to be highly dependent on the developmental timing of the events (Lupien et al., 2009; Stevens et al., 2018; Teicher & Samson, 2016). Several brain morphological studies found that amygdala and hippocampal volume are influenced by the intensity of adverse experiences in sensitive life years instead of the total accumulated amount of adversity experienced throughout childhood and adolescence (Andersen et al., 2008; Herzog et al., 2020; Pechtel et al., 2014; Teicher et al., 2018). Extending morphological findings to brain function, a recent study reported that amygdala reactivity to emotional faces was actually *decreased* in individuals who experienced physical maltreatment in a prepubertal phase between ages 3 and 6, but *increased* for peer emotional bullying in a postpubertal phase between ages 13 and 15 (Zhu et al., 2019).

We aimed to disentangle the contributions of PTSD and ACE to amygdala function by accounting for the timing of adverse experiences. We measured blood oxygen level-dependent (BOLD) responses in meta-analytically predefined amygdala subregions (Stark et al., 2015),

while participants viewed negative versus neutral pictures during fMRI. We assessed the predictive utility of PTSD diagnostic status, total ACE severity, and ACE severity during single life years between the ages 3 and 17 using an established combination of a retrospective interview procedure and machine learning (Herzog et al., 2020; Khan et al., 2015; Teicher et al., 2018; Zhu et al., 2019). We tested how the relationship between PTSD and amygdala reactivity changes when accounting for the linear effect of total adversity versus adversity during predictive life years.

3.3 Methods

Participants

The sample comprised 60 trauma-exposed women between the ages of 19 and 63 (M = 35.0, SD = 12.8). All participants reported a history of sexual and/or physical abuse during childhood. Thirty-four women were diagnosed with current PTSD and 26 had no life-time diagnosis of any mental disorder. PTSD participants were recruited from a larger randomized controlled psychotherapeutic trial (Bohus et al., 2020). They underwent fMRI measurements between randomization and the first therapy session. Trauma control participants were recruited with advertisements in local newspapers, flyers and over the internet (Rausch et al., 2016). Further information on exclusion criteria and clinical assessment can be found in the supplements. See Table S3 for demographic and clinical sample characteristics by group.

The study was approved by the Ethical Board II of Heidelberg University (Nr.: 2013-635N-MA), Germany, and was conducted according to the Declaration of Helsinki at the Central Institute of Mental Health in Mannheim, Germany. Participants provided written consent after the procedures had been fully explained. All participants received monetary compensation of 12€/h for their participation.

Maltreatment History

We used a German adaptation of the Maltreatment and Abuse Chronology of Exposure (MACE) scale to retrospectively assess the occurrence of ten different types of adverse experiences by age at occurrence between the ages 3 and 17 in an interview setting (Isele et al., 2014). Types of adverse experiences included emotional neglect, physical neglect, parental physical abuse, siblings physical abuse, parental emotional abuse, siblings emotional abuse, sexual abuse, peer abuse, witnessing interparental violence, and witnessing violence to siblings. Scores for single life years are the sums across different ACE events at a given age. Total ACE severity was calculated as the average score across these life years.

Test-retest reliability has been found to be high over a period of 6 months in an US population (r = .91; Teicher & Parigger, 2015). Reliabilities for ACE severity during single life years is above r = .70 for all ages included in the present study. Convergent validity scores were found to be good as the MACE severity score correlated r = .74 with the CTQ in an US population (Teicher & Parigger, 2015) and r = 0.75 in a German population (Isele et al., 2014). As in previous studies (Herzog et al., 2020), life-years one and two were not included in the analyses due to their low reliability (Teicher & Parigger, 2015). The time-courses of total severity across childhood are depicted in Figure 5, separately for the PTSD and the trauma-control groups. Exclusion criteria for all participants were metal implants, pregnancy, left-handedness, and claustrophobia. Exclusion criteria for PTSD participants specifically covered current and lifetime schizophrenia or bipolar-I disorder, mental retardation, severe psychopathology, traumatic brain injuries or somatic illness that needs to be treated immediately in another setting (e.g., BMI<16), medical conditions making exposure-based treatment impossible, a suicide attempt within the last two months, and substance dependency with no abstinence within two months prior to the study. Exclusion criteria for the trauma controls were any current or previous mental disorder, any psychotherapeutic experience or any intake of psychotropic medication.

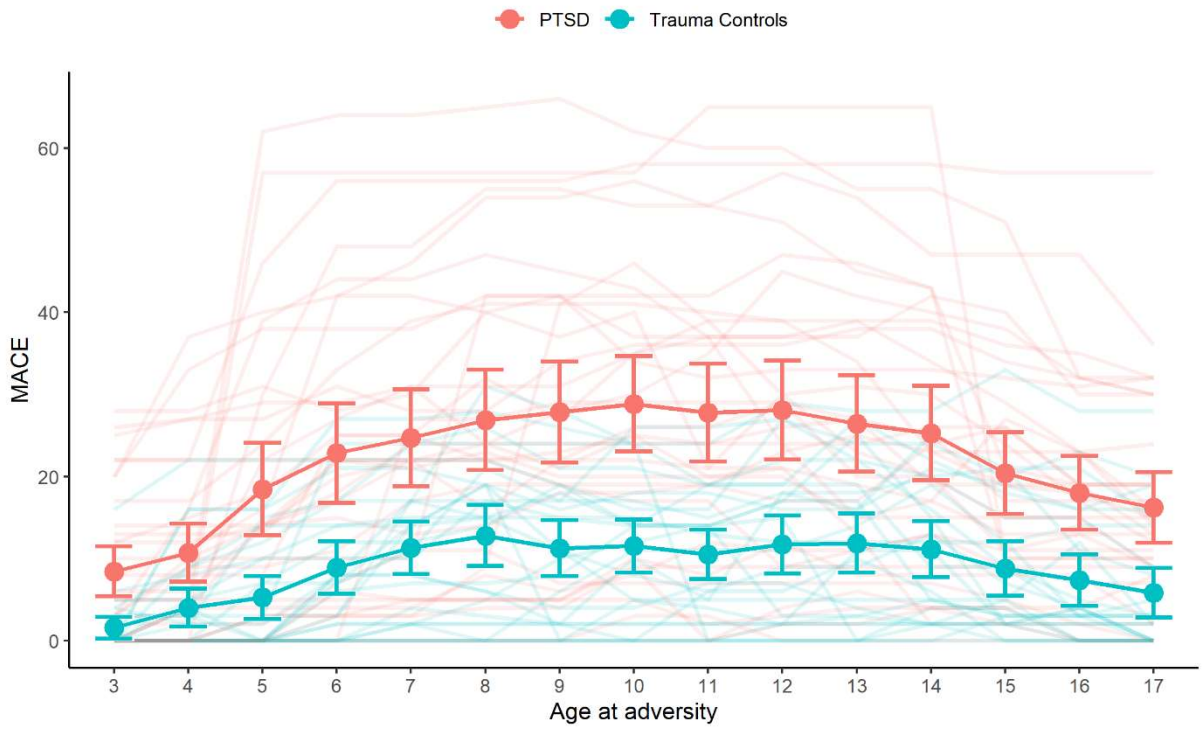

Figure 5. Intensity of adverse experiences by life year of event occurrence and group. Thin lines represent single participants and are smoothed for interpretability. Error bars represent 95% confidence intervals.

Image Acquisition and Preprocessing

Brain images were acquired using a 3 Tesla MRI scanner (TRIO, Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. Details on image acquisition and preprocessing can be found in the supplements.

fMRI Task

The activity of amygdala subregions was extracted from a contrast between viewing negative versus neutral pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008), which were presented within a Sternberg working memory task

(Krause-Utz et al., 2012). Participants saw sixteen pictures which were preselected as negative or neutral based on arousal and valence ratings in the general population. Pictures in the negative condition included negatively arousing interpersonal scenes on physical and sexual violence, emotional neglect, or mutilation. Neutral pictures were matched to negative pictures regarding the number of persons and complexity of the scene. Here, only the contrast between negative and neutral pictures was used, which induces a pronounced amygdala response. Detailed information on the task can be found in the supplements.

Amygdala Regions of Interest

The average amygdala response for the contrast between negative and neutral pictures was extracted from a ROI within the right amygdala, reported in a previous meta-analysis (Stark et al., 2015). An a priori ROI was chosen to prevent circularity, which can occur when ROIs are identified with a significance-based strategy and then used for further inferential tests in the same data (Kriegeskorte et al., 2009). As, to our knowledge, no recent meta-analysis on PTSD has reported differences in the left amygdala, the ROI in the right hemisphere was symmetrically reflected to the left hemisphere. Detailed information on the ROI procedure can be found in the supplements.

Statistical Analyses

Machine learning procedure. A common approach to detect sensitive life years for the effects of ACE is to predict an outcome of interest (here: amygdala reactivity) from the intensity of ACE during each life year, respectively. In our case, this means including at least 15 highly correlated predictors (ages 3–17) in the same statistical model. Conditional random forest regression and its variable importance measures are particularly suited for this task (Khan et al., 2015) and have been frequently used in previous studies on sensitive periods for early adversity (Herzog et al., 2020; Schalinski et al., 2016; Teicher et al., 2018; Zhu et al., 2019). We used conditional variable importance to quantify how much a predictor contributes to prediction,

which can be roughly interpreted like a multiple regression coefficient (Strobl et al., 2008), albeit predictors can also contribute to prediction through nonlinear or interaction effects. In addition to ACE scores during single life years, we included PTSD, total accumulated ACE, and current age of the participants in the model. We used the cforest function of the R package *party* to conduct conditional random forest regressions with 1000 trees and otherwise default hyperparameters (Hothorn et al., 2006; Strobl et al., 2007).

As performance measures, we report variance explained and variable importance based on the out-of-bag samples, which is a built-in cross-validation-like procedure in random forest regression where predictions from a model based on one part of the data (i.e., training set) is applied to another unseen part of the data (i.e., test set). This gives a more realistic estimate for the generalization of results. Additionally, variance explained and variable importance were tested for significance by randomly permuting the outcome 1000 times, creating a random distribution which reflects the null hypothesis of no effect (Altmann et al., 2010).

Linear models. After determining predictive life years with the random forest procedure, robust regressions were performed to disentangle the effects of PTSD and predictive ACE scores on amygdala reactivity using the rlm and f.robftest functions of the R packages *MASS* (Venables & Ripley, 2002) and *sfsmisc* (Maechler, 2020). This method provides more robust test statistics for regression weights in the presence of outliers, which might be particularly advantageous for fMRI data (Wager et al., 2005). If no outliers are present, robust regression leads to similar results compared to normal OLS regression. In all cases, *p*-values obtained with robust regression were larger and therefore more conservative compared to normal multiple regression analyses.

Relevant negative findings from linear models were supplemented with Bayes factors to provide a continuous measure of evidence for the alternative hypothesis versus the null hypothesis (Jarosz & Wiley, 2014). The functions lmBF and ttestBF of the R package *Bayesfactor* were used with default noninformative priors (Morey & Rouder, 2018). In the present study, a

BF_{01} value larger than one represents evidence in favor of the null hypothesis. Note that values between one and three are usually not considered sufficient evidence for either hypothesis (Jarosz & Wiley, 2014).

Reproducible analyses. The data and annotated R script to reproduce the main anlyses can be found on the open science framework (demographic information only used for sample description and original fMRI data are not provided):

https://osf.io/9vr8g/?view_only=987b630a6bf444ada123cae54b593f60

3.4 Results

Relationships between Amygdala Reactivity, PTSD and total ACE

The total ACE severity was higher in the PTSD group than in the trauma control group (Table S3).

Negative pictures induced a markedly increased response in both amygdala ROIs with similar effect sizes; right amygdala: $t(59) = 4.05$, $p < .001$, $d = .52$; left amygdala: $t(59) = 3.82$, $p < .001$, $d = .49$. Activities in the two ROIs were significantly correlated: $r(58) = .46$, $p < .001$. Although the right amygdala response was larger in the PTSD sample than in the TC sample, this effect was not statistically significant: $t(57.9) = 1.43$, $p = .157$, $d = .37$. A Bayes factor of $BF_{01} = 1.69$ slightly favored the null hypothesis (i.e., no effect of PTSD) but did not cross the common threshold of 3. This indicates that no confident conclusion can be reached in favor of either the null or the alternative hypothesis, given the effect and sample size. The group difference was smaller for reactivity in the left amygdala: $t(57.2) = 0.86$, $p < .392$, $d = .22$. Here, a Bayes factor of $BF_{01} = 2.80$ more clearly favored the null hypothesis, but still did not cross the threshold of 3. Amygdala responses by group are depicted in Figure S1.

The correlation between total ACE severity and right amygdala response was negative in the sample, but not statistically significant: $r(58) = -.11$, $p = .413$. The Bayes factor of $BF_{01} = 2.86$ was in favor of the null hypothesis, but still below the threshold of 3. There was no

correlation between total ACE severity and left amygdala response: $r(58) = .00$, $p = .983$, $BF_{01} = 3.81$.

Random Forest Regression

Amygdala reactivity was predicted by PTSD, age, overall ACE, and ACE scores by life year using random forest regression. The model explained a substantial and statistically significant amount of variance in the right amygdala ($R^2 = .07$, $p = .020$). PTSD as well as ACE at ages 3, 4, 16, and 17 significantly contributed to prediction (Figure 6, Table S4). The total MACE score, in turn, did not contribute to prediction.

In contrast, the model explained no variance in the left amygdala ($R^2 = .00$, $p = 1.00$). As the left functional amygdala ROI was a simple contralateral reflection of the right amygdala ROI, taken from a meta-analysis (Stark et al., 2015), we repeated the analysis with an anatomical ROI for the left amygdala (Tzourio-Mazoyer et al., 2002). The anatomical ROI was highly correlated with the functional ROI ($r(58) = .80$, $p < .001$) and yielded the same result ($R^2 = .00$, $p = 1.00$).

Follow-Up Analyses

Correlations and regression analyses were used to determine whether the contribution of significant variable importance measures for right amygdala reactivity was likely due to linear main effects or interactions.

ACE during single life years. ACE in single life years were all negatively correlated with right amygdala reactivity, with the significant life years from the random forest regression having the largest negative correlations (Figure 6). Hence, the life years 3, 4, 16, and 17 appeared to be largely predictive due to approximately linear main effects.

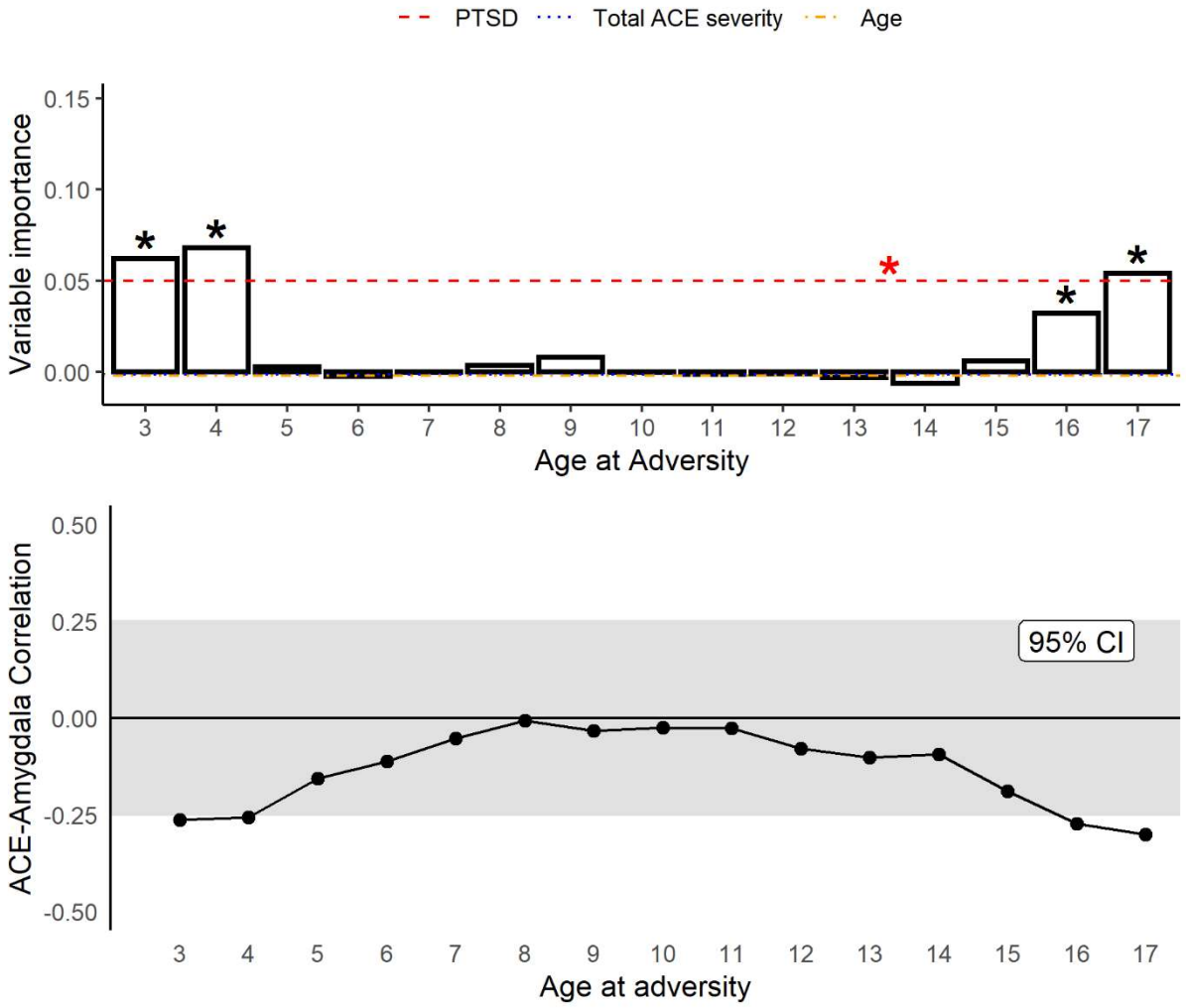

Figure 6. Predictors of right amygdala reactivity. Upper panel: Variable importances from random forest regression for ACE at different ages, as well as total ACE, group (PTSD versus trauma controls), and age. Asterisks indicate p-values smaller than .05. Lower panel: Bivariate correlations between right amygdala reactivity and ACE at different ages.

Contributions of PTSD and prepubertal ACE. We tested whether the ACE effects during predictive life years interacted with PTSD, which significantly contributed to prediction as well. We averaged ACE severity during the adjacent life years 3 and 4 into a "prepubertal" score and ACE during life years 16 and 17 into a "postpubertal" score following a previous approach (Zhu et al., 2019).

A robust regression analysis of right amygdala reactivity on prepubertal ACE and PTSD revealed significantly higher amygdala reactivity in the PTSD group compared to the trauma control group, but amygdala reactivity decreased with higher amounts of prepubertal ACE in both groups (Figure 7, Table 3). There was no significant interaction. This replicates both past meta-analyses on PTSD (Schulze et al., 2019; Stark et al., 2015) and the negative effects of prepubertal ACE (Zhu et al., 2019).

Notably, the standardized regression effect of PTSD on right amygdala reactivity ($\beta = .34$; Table 3) was substantially larger than their bivariate correlation ($r(58) = .18$), due to de-confounding the relationship for ACE during the predictive prepubertal years. This was not the case when total ACE severity was included, instead of prepubertal ACE (Table 3).

Contributions of PTSD and postpubertal ACE. The effect of postpubertal ACE was similar to the effect of prepubertal ACE. Figure 7 shows that the negative effect of postpubertal ACE was mainly driven by the PTSD group, although the interaction was not statistically significant (Table 3). This does not match the previously reported , positive effect of postpubertal ACE on amygdala reactivity. A possible explanation might be that early prepubertal adversity increases the chance to be victimized again during late adolescence for individuals with PTSD. We tested this possibility by calculating correlations between prepubertal ACE and ACE in later life years, separately for both groups. In the trauma control group, the correlation of prepubertal and later ACE decreased with larger age gaps between measurements, as should be expected when the environment changes over time (Figure S2; notably, this trend was not perfectly monotonous). In the PTSD group, however, the correlations initially decreased with larger age gaps between measurements, but then increased again, starting from age 14. As a result, the correlation between prepubertal ACE and ACE at age 17 was as large as the correlation with ACE at age 6 (Figure S2).

Table 3

Robust regression of right amygdala reactivity on PTSD and ACE severity

	Prepubertal ACE			Postpubertal ACE			Total ACE		
	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
ACE	**−.39**	**−2.29**	**.025**	**−.36**	**−2.29**	**.027**	−.09	−0.47	.637
PTSD	**.34**	**2.40**	**.019**	**.31**	**2.10**	**.040**	.21	1.24	.217
ACE×PTSD	.06	0.30	.767	−.14	−0.82	.418	−.13	−0.62	.539
R^2	16.84%			20.91%			9.11%		

Note. β = standardized regression coefficient. Significance tests had 56 degrees of freedom. *P*-values for pre- and postpubertal ACE should not be interpreted as independent significance tests, as they were preselected for significance by the machine learning-based search procedure. Instead, they represent a heuristic indicator for congruence between random forest and linear models.

Significant effects ($p < .05$) are indicated in bold.

Notably, *p*-values for pre- and postpubertal ACE should not be interpreted as independent significance tests, as they were preselected for significance by the machine learning-based search procedure. Instead, they represent a heuristic indicator for congruence between random forest and linear models.

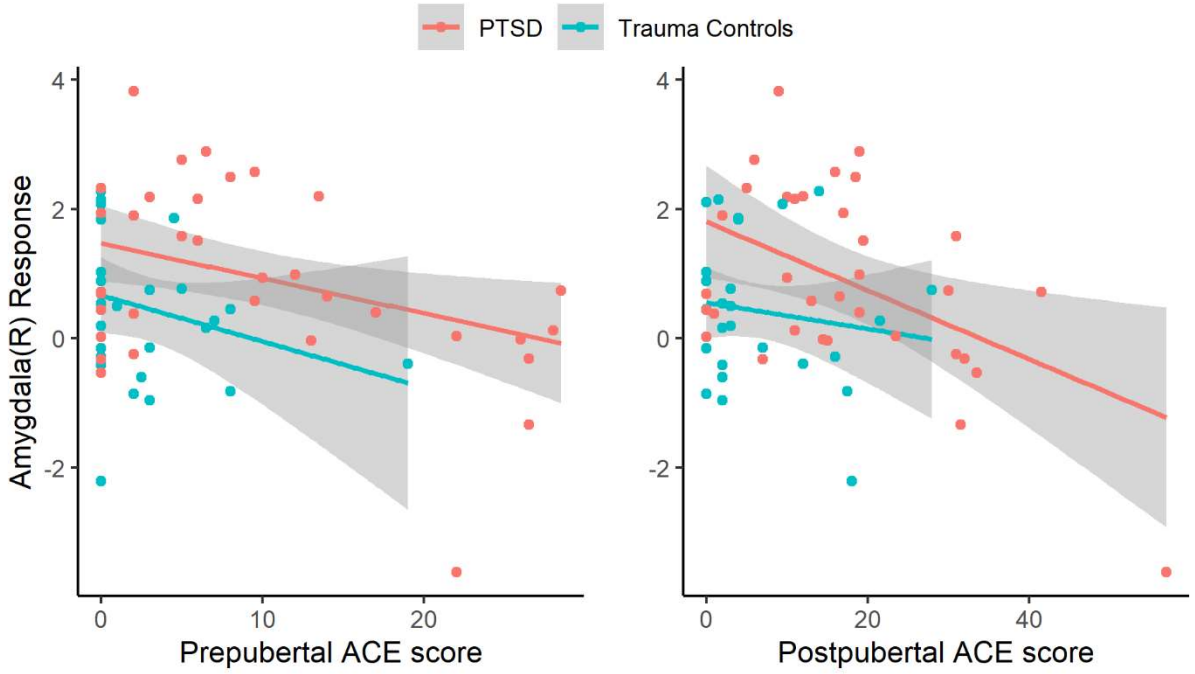

Figure 7. Robust regressions of right amygdala reactivity on PTSD and ACE severity. The prepubertal ACE score is an average of the predictive life years 3 and 4; the postpubertal ACE score is an average of the predictive life years 16 and 17. Grey areas represent 95% confidence bands.

Exploratory analyses on stimulus condition. The results could be distorted by a higher responsiveness to neutral baseline images in individuals with higher ACE severity or trauma-related psychopathology (Lischke et al., 2017). Both the PTSD and the trauma control group had similar amygdala responses in the neutral condition: $t(56.5) = -0.22$, $p = .827$, $d = -.06$, $BF_{01} = 3.71$ (Figure S3). While the correlation between ACE and amygdala response was positive in sign, the correlation was not significant and the Bayes factor favored the null hypothesis: $r(58) = .09$, $p = .512$, $BF_{01} = 3.17$. Moreover, the random forest regression did not explain any variance in the amygdala response during the neutral condition.

3.5 Discussion

Discussion of Results

Altered processing of threat-related stimuli is a central feature of PTSD with amygdala reactivity being one of the most promising neural substrates (Rauch et al., 2006). We tested to which degree amygdala hyperreactivity is a consequence of PTSD symptoms and the exposure to ACE, independent of psychopathology. This entails to account for the developmental timing of events.

We found differential effects of PTSD and ACE on amygdala reactivity by identifying sensitive periods for right amygdala reactivity in early childhood at the ages 3 and 4. In these life years, a higher severity of ACE was associated with a smaller amygdala reactivity to pictures with negative content. This conceptually replicates previous reports of Zhu and colleagues (2019) a negative effect of physical maltreatment at ages 3, 4, and 6 on bilateral amygdala reactivity. An explanation for this initially counterintuitive finding might be that a down-regulation of amygdala function could be adaptive during early childhood, as it maintains a vital attachment bond to a caregiver during a vulnerable phase in which an individual cannot yet sustain itself (Zhu et al., 2019). In both studies, the total severity of ACE did not contribute to the prediction of amygdala reactivity when single life years were included.

In contrast to the negative effects of prepubertal ACE, PTSD status was associated with higher reactivity of the right amygdala when prepubertal ACE was controlled, as would be expected from previous meta-analyses (Schulze et al., 2019; Stark et al., 2015). These meta-analyses only reported significant differences for the right amygdala, which is congruent with the result that our machine learning approach could only account for variance in the right amygdala as well. The variance explained of 7% is substantial, considering it is based on unseen observations and the typically modest test-retest reliability of fMRI measures (Elliott et al., 2019).

The ages 16 and 17 emerged as additional sensitive life years. Higher ACE severity led to attenuated amygdala reactivity, as for the prepubertal sensitive period. This does not match the previously reported pattern (Zhu et al., 2019) of a sensitive period for peer emotional bullying at ages 13 and 15 which resulted in heightened instead of decreased amygdala reactivity. Still, these findings concerned a specific ACE subtype. Moreover, our PTSD sample was characterized by many reoccurring experiences of adversity throughout childhood and adolescence, which represents an important difference. In our study, it appeared that the negative effect of prepubertal years might be driven by participants with both PTSD and prepubertal ACE also being more likely to experience postpubertal ACE. potentially pointing towards the relevance of repeated exposure in the development of PTSD (Kessler et al., 2017).

Notably, several previous studies reported heightened amygdala reactivity to negative faces in healthy individuals exposed to prepubertal ACE (Dannlowski et al., 2012, 2013; Ganzel et al., 2013; Suzuki et al., 2014; van Harmelen et al., 2013), which is inconsistent with the negative sign of ACE-Amygdala correlations observed here and previously (Zhu et al., 2019). Besides that these studies used faces as stimuli, which might tap into distinct processes, there is evidence that the combination of abuse and neglect leads to decreased amygdala reactivity, while their components alone lead to increased activity (Puetz et al., 2020). Our participants scored considerably on both ACE types. Hence, attenuated amygdala activity might be the result of nonlinearities introduced by overall ACE severity/multiplicity. Although the PTSD effect was of considerable size and in the same direction in all tests, its effect increased and only became statistically significant when the analyses simultaneously controlled for ACE during predictive periods. This is due to the stable positive association between PTSD and ACE: If two variables have opposing relationships with a third variable, but a positive relationship with each other, their relationships with the third variable will increase when they are both included as predictors in the same linear regression.

Our findings are of both theoretical and diagnostic interest: First, they contradict a simple etiological model where the effect of ACE on PTSD is mediated via amygdala hyperreactivity as a proximal endophenotype (Fonzo et al., 2016). Second, in our study amygdala *hyper*-reactivity appears to be a feature of psychopathology, rather than adverse experiences. Third, healthy individuals exposed to severe adversity during sensitive periods can also show neural alterations without clear clinical implications. Fourth, amygdala reactivity in general is not a simple straight-forward marker of psychopathology. In our data, it would be impossible to distinguish an individual with PTSD and severe ACE during sensitive periods from a healthy trauma-exposed control with no ACE during sensitive periods. Both individuals would be expected to have moderate amygdala reactivity (Figure 7). Last, our findings suggest that accounting for ACE during sensitive periods could represent a crucial moderator, enabling larger associations between brain biomarkers and psychopathology. Usually, ACE is measured in terms of a total accumulated score, which is likely not suited for this purpose.

Limitations

Retrospective designs are an efficient approach to assess ACE and detect sensitive periods in combination with machine learning approaches (Khan et al., 2015). Although the ACE measure we employed has sufficient test-retest reliabilities above age 2, the validity of retrospective self-report measures for ACE is still contested. A recent meta-analysis reported low agreement between prospective and retrospective measures of ACE, questioning whether the two measurement strategies capture the same construct (Baldwin et al., 2019). Nevertheless, while retrospective self-reports might be subject to psychological biases, the authors acknowledge that prospective studies likely have a lower sensitivity, only capturing the most severe cases. Moreover, they found that concordance was higher for interview procedures. In particular, comprehensive autobiographical interviews which assess ACE by life year, as used

in the present study, are relatively recent and have not yet been validated against prospective data, which is an important target for future research.

Another set of limitations pertains to the characteristics of our sample. First, we only measured women. The generalization of our results to men remains to be tested. Second, our PTSD sample was severely affected by ACE, which often extended over long periods of time. More variance within and between PTSD participants could potentially reveal nonlinearities in the effect of ACE severity on amygdala function. Also, more time-restricted ACE occurrence can likely be found in larger representative samples, which might aid the identification of sensitive periods and help distinguish between effects of brief but severe ACE episode versus long-lasting but less severe episodes (Herzog et al., 2018). Such data would have better structure and statistical power to reveal interactions between early and late ACE. Third, we could not account for the confounding effect of psychotropic medication due to the limited sample size and the diversity in pharmacological agents. Last, it is unclear whether the effect of psychopathology is specific to PTSD as no additional clinical control group was assessed and most individuals with PTSD had a broad range of comorbidities. A recent meta-analysis demonstrated that amygdala hyperreactivity can be observed in both PTSD and BPD, but not major depressive disorder (Schulze et al., 2019). This could imply that amygdala hyperreactivity is more generally related to a hyperactive negative valence system which is a central transdiagnostic dimension of the Research Doman Criteria (Kozak & Cuthbert, 2016).

Lastly, there was no objective measure of eye gaze to check whether participants equally attended to negative pictures or used avoidance strategies, which could potentially reduce the amygdala response (although this would not account for the amygdala hyperactivity in the PTSD group).

Conclusion

The present study demonstrated opposing relationships of right amygdala reactivity to PTSD and adversity during circumscribed developmental periods. This observation adds nuance to the interpretation of one of the most consistent biomarkers of PTSD and highlights the utility of incorporating neurodevelopmental aspects into research on psychopathology in adults.

3.6 Supplemental materials

Exclusion Criteria

Exclusion criteria for all participants were metal implants, pregnancy, left-handedness, and claustrophobia. Exclusion criteria for PTSD participants specifically covered current and lifetime schizophrenia or bipolar-I disorder, mental retardation, severe psychopathology, traumatic brain injuries or somatic illness that needs to be treated immediately in another setting (e.g., BMI<16), medical conditions making exposure-based treatment impossible, a suicide attempt within the last two months, and substance dependency with no abstinence within two months prior to the study. Exclusion criteria for the trauma controls were any current or previous mental disorder, any psychotherapeutic experience or any intake of psychotropic medication.

Clinical Assessment

Symptoms were assessed by trained diagnosticians using the Structure Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) and the BPD section of the IPDE (Loranger, Janca, & Sartorius, 1997). Additionally, the CAPS-5 (Weathers et al., 2013) was administered to the group prescreened for PTSD. Further self-report measures included retrospective questionnaires on childhood trauma (CTQ; Bernstein, 1998), PTSD symptoms (DTS; Davidson et al., 1997), and severity of depressive mood (BDI-II; Beck, Steer, & Brown, 2009).

Maltreatment History

Test-retest reliability has been found to be high over a period of 6 months in an US population (r = .91) (Teicher & Parigger, 2015). Reliabilities for ACE severity during single life years is above r = .70 for all ages included in the present study. Convergent validity scores were found to be good as the MACE severity score correlated r = .74 with the CTQ in an US population (Teicher & Parigger, 2015) and r = 0.75 in a German population (Isele et al., 2014). As

in previous studies 17, life-years one and two were not included in the analyses due to their low reliability. The time-courses of total severity across childhood are depicted in Figure 5, separately for the PTSD and the trauma-control groups.

Image Acquisition and Preprocessing

Using three-dimensional MPRAGE (T1-weighted contrast, voxel size 1×1×1 mm^3), a high-resolution anatomical scan was acquired for each participant as an individual template for the functional data. T2-weighted gradient echo planar imaging was used for measurement of the BOLD signal [EPI, T2-weighted contrast, field of view = 192×192 mm, voxel size 3×3×3 mm^3, 64×64 voxel matrix, flip angle 80°, echo time (TE) = 30 ms, repetition time (TR) = 2000 ms], with 36 transversal slices (3 mm, descending) covering the entire brain. The first four scans were discarded to minimize T1 effects. Head movement artefacts and scanning noise were restricted using head cushions and headphones.

Functional imaging data were processed using standard procedures implemented in SPM12 (Welcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm/). The EPI time series were pre-processed according to custom practice, including slice time correction, spatial realignment, segmentation of T1 scan, co-registration onto T1 scan, and normalization to the standard brain of the Montreal Neurological Institute (MNI) space. We did not have to exclude subjects due to excessive head motion (exclusion criterion for head motion was 3mm in each direction). The images were not smoothed, as we only analyzed average regression coefficients across multiple voxels defined from a priori functional masks within a small anatomically limited region. Smoothing might contaminate this measure with signal originating outside the ROI.

fMRI Task

The task consisted of 48 trials, each starting with the presentation of three uppercase letters (memoranda, 1000 ms). After a delay interval (1500 ms), again three letters (probe, 2000 ms) were presented, which participants had to compare with the memoranda. Participants had to press a "yes" button whenever they recognized a target, for example, a letter previously presented in the memorandum. In half of the trials, a target (one of the three memoranda) was present in the probe. During the delay interval, either a fixation cross or a picture stimulus (negative or neutral) was presented. The resting phase between the trials was jittered to prevent temporal correlation. We used the Software Presentation (Neurobehavioral Systems) to present stimuli and record behavioral data.

Region of Interest Procedure

The procedure to extract amygdala reactivity for each participant had three steps. First, whole-brain voxel-wise regression weights for the contrast between negative and neutral pictures were calculated using the first-level analysis procedure from SPM 12. We modelled the neural response with three regressors of interest (negative pictures, neutral pictures, fixation cross) and six motion regressors. The regressors were convolved with the canonical hemodynamic response function (HRF). A contrast image between negative and neutral pictures was calculated by subtracting the beta image of the negative picture regressor from the beta image of the neutral picture regressor.

Second, a mask was constructed from a fMRI meta-analysis to prevent potentially circular analyses. Circular analysis are the result of identifying ROIs with significance-based strategies and then using these ROIs for further inferential tests in the same sample (Kriegeskorte et al., 2009). We chose the meta-analysis from Stark and colleagues (2015) which reported differences between PTSD patients and healthy controls in the right amygdala for a contrast

between negative and neutral pictures, excluding specifically trauma-related material. The comparison between PTSD patients and trauma-naïve controls was chosen as it should capture effects of both adversity and psychopathology. A sphere with a radius of 6.46mm was centered on the reported peak voxel in the amygdala (x = 24, y = 0, z = −14) using MarsBaR 0.44 (Brett et al., 2002). The radius was calculated from the cluster size reported in the meta-analysis, assuming a spherical cluster. As a considerable portion of this sphere was outside the amygdala. To ensure anatomical precision, we created a mask from the overlap between the functionally defined sphere and an anatomical mask for the right amygdala based on an automatic anatomical labelling atlas (Tzourio-Mazoyer et al., 2002). As, to our knowledge, no recent meta-analysis on PTSD has reported differences in the left amygdala, we reflected our ROI to the left hemisphere.

Lastly, we extracted the average contrast values for the two masks (right and left amygdala) for each participant, which serve as the main outcomes.

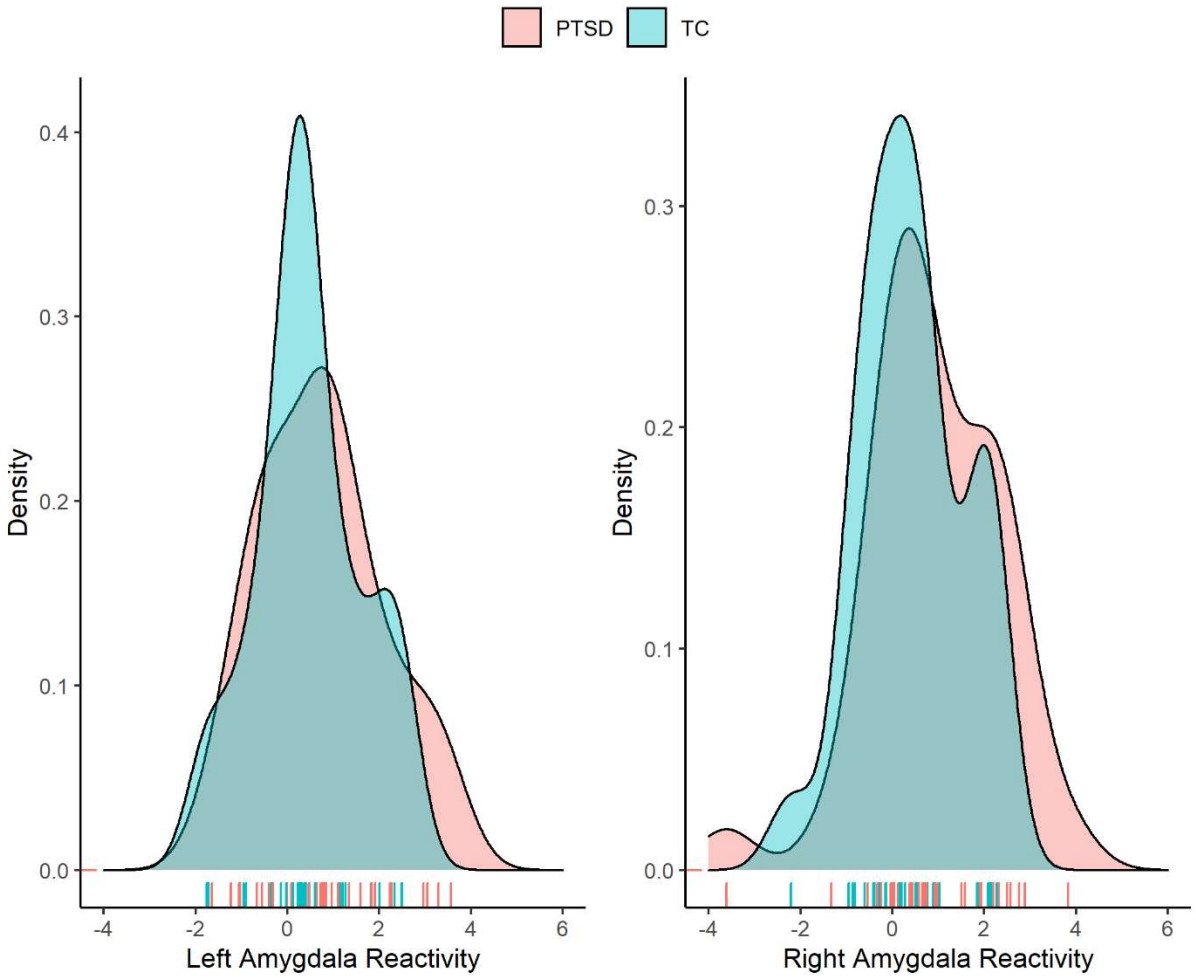

Figure S1. BOLD response to negative versus neutral pictures in the left and right amygdala by group.

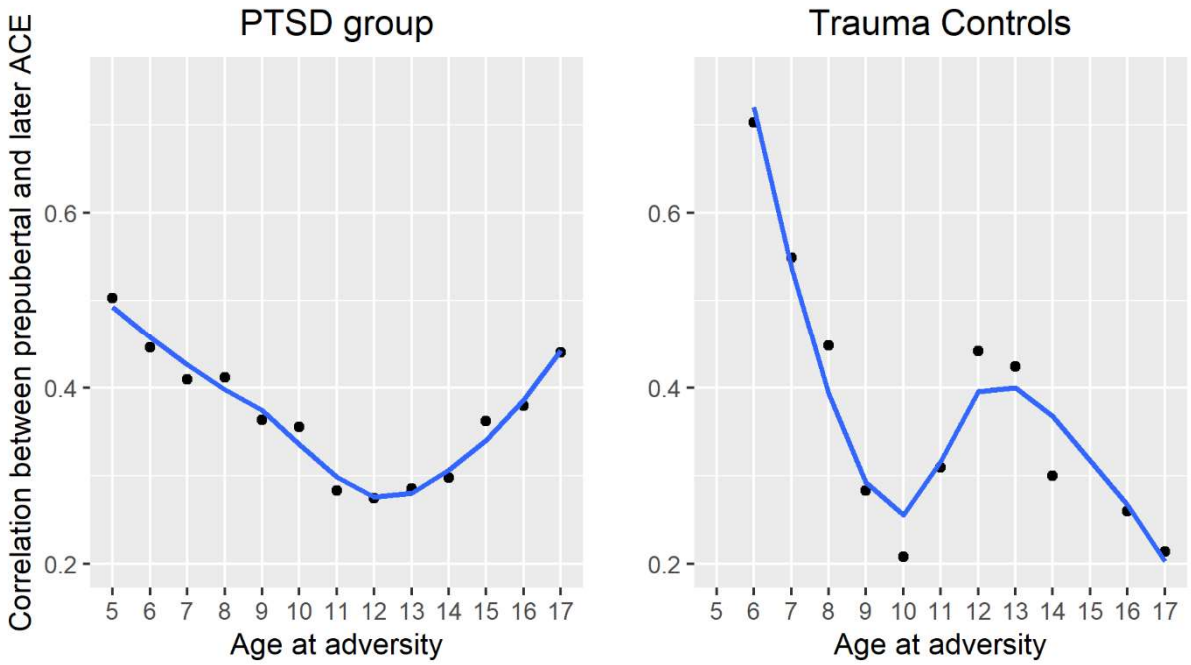

Figure S2. Pairwise correlations between prepubertal adversity (averaged over ages 3 and 4) and adversity at later ages, divided by group.

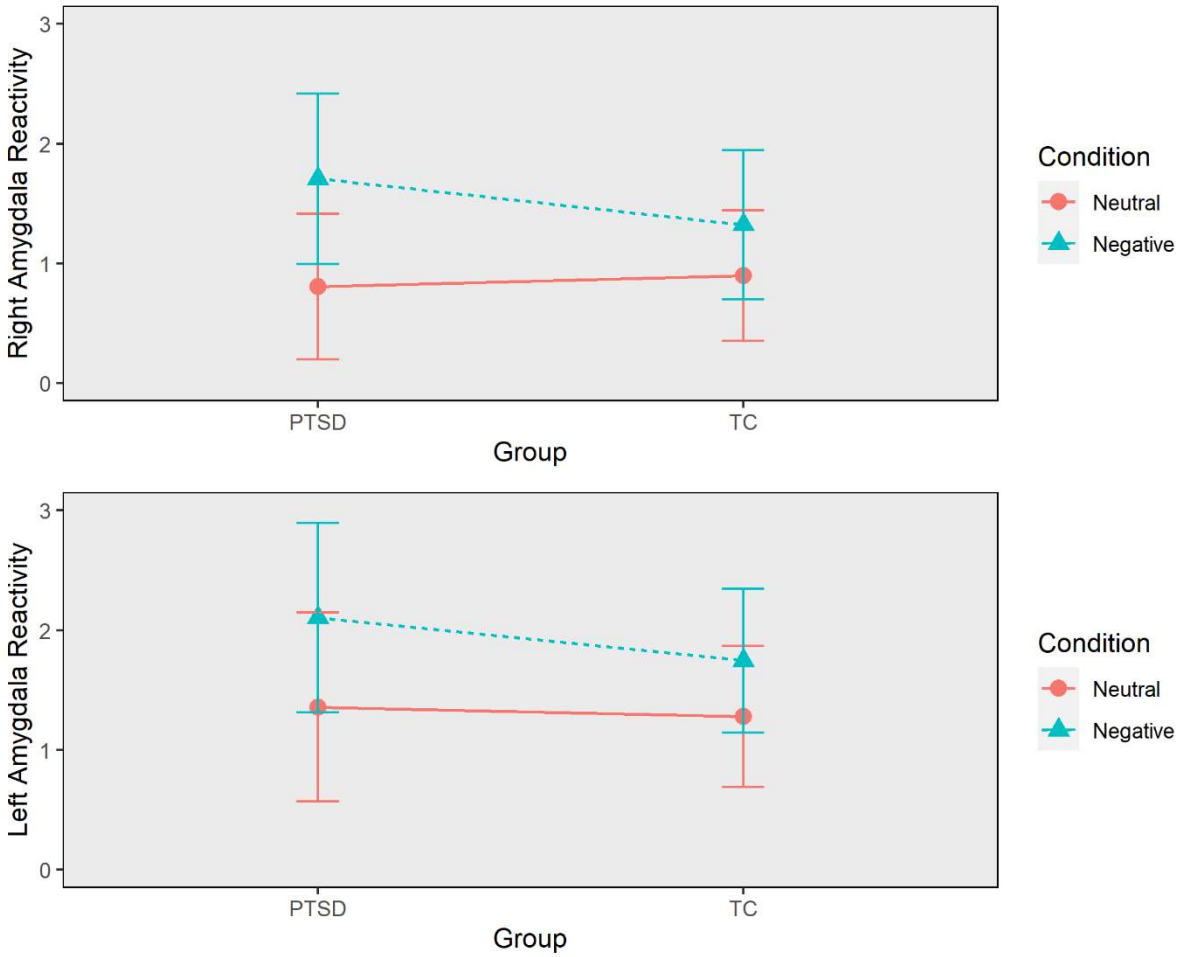

Figure S3. BOLD amygdala response to neutral or negative stimuli by group. Note, error bars show 95% confidence intervals for the estimated means and hence do not reflect significance of within-person effects (i.e., comparisons between neutral and negative stimuli).

Table S3

Demographic and clinical variables in PTSD and trauma controls

	PTSD		TC		Test-Statistics				
	N=34		N=26		*t*	*df*	*p*		
Demographics									
Age mean (SD)	37.88	(12.59)	31.23	(12.36)	2.05	54.46	0.045	*	PTSD>TC
Years of education (SD)	10.74	(1.31)	11.31	(0.97)	-1.94	57.96	0.057		TC>PTSD
Clinical Characteristics									
Childhood Trauma questionnaire (CTQ)									
Total (SD)	76.99	(22.55)	53.57	(12.75)	5.09	53.91	<.001	*	PTSD>TC
Abuse - total (SD)	28.1	(10.57)	20.08	(5.64)	3.77	52.54	<.001	*	PTSD>TC
Neglect - total (SD)	30.75	(9.43)	20.18	(6.38)	5.17	57.24	<.001	*	PTSD>TC
Emotional abuse (SD)	18.14	(5.67)	13.31	(4.51)	3.68	57.88	<.001	*	PTSD>TC
Physical abuse (SD)	11.56	(6.72)	9.81	(3.84)	1.27	54.13	.209		
Sexual abuse (SD)	16.54	(6.83)	10.27	(5.70)	3.87	57.52	<.001	*	PTSD>TC
Emotional neglect (SD)	18.59	(5.36)	12.88	(4.46)	4.50	57.54	<.001	*	PTSD>TC
Physical neglect (SD)	12.16	(4.46)	7.31	(2.65)	4.89	52.69	<.001	*	PTSD>TC
Davidson Trauma Scale (DTS)									
Total (SD)	78.15	(19.08)	12.04	(12.80)	15.76	55.29	<.001	*	PTSD>TC
Intensity (SD)	39.36	(10.3)	5.44	(6.43)	15.37	54.24	<.001	*	PTSD>TC
Frequency (SD)	38.79	(10.1)	6.73	(6.42)	14.83	54.78	<.001	*	PTSD>TC
Beck Depression Inventory 2 (BDI-II)									
Total (SD)	36.34	(9.84)	4.01	(5.35)	16.27	52.97	<.001	*	PTSD>TC
Maltreatment and Abuse Chronology of Exposure scale (MACE)									
Total (SD)	24.37	(15.22)	10.15	(6.89)	4.84	48.48	<.001	*	PTSD>TC
Abuse (SD)	4.97	(3.82)	2.31	(1.78)	3.58	49.20	.005	*	PTSD>TC
Neglect (SD)	7.37	(5.74)	2.36	(3.23)	4.28	53.80	<.001	*	PTSD>TC

Table S3
(continued)

	PTSD N = 34	
Current Comorbidities N (%)		
Affective Disorder	22	(64.7)
Substance Dependency	0	(0)
Substance Abuse	1	(2.9)
Anxiety Disorder	22	(64.7)
Obsessive Compulsive Disorder	5	(14.7)
Somatization Disorder	3	(8.8)
Eating Disorder	3	(8.8)
Borderline Personality Disorder	16	(47.1)
Psychotropic Medication N (%)		
SSRI	6	(17.6)
SNRI	9	(26.5)
Tricyclica	4	(11.8)
Other Antidepressants	5	(14.7)
Neuroleptics	6	(17.6)
Anticonvulsants	3	(8.8)
Unmedicated	16	(47.1)

Note. SD = standard deviation. *df* = degrees of freedom. Test statistics originate from two-sample t-tests for unequal variances.

* $p < .05$

Table S4

Variable importance and p-values for predictors of right amygdala reactivity

Predictor	Variable importance	*p*-value
PTSD	**0.05**	**.044**
Total ACE severity	0.00	.497
Age	0.00	.353
Age at adversity		
3	**0.06**	**.023**
4	**0.07**	**.016**
5	0.00	.257
6	0.00	.428
7	0.00	.331
8	0.00	.204
9	0.01	.144
10	0.00	.372
11	0.00	.416
12	0.00	.395
13	0.00	.495
14	0.01	.681
15	0.01	.201
16	**0.03**	**.038**
17	**0.05**	**.014**

Significant effects ($p < .05$) are indicated in bold.

Study III: Affective neural signatures do not distinguish women with emotion dysregulation from healthy controls: A mega-analysis across three task-based fMRI studies

CHAPTER IV

4.1 Abstract

Pathophysiological models are urgently needed for personalized treatments of mental disorders. However, most potential neural markers for psychopathology are limited by low interpretability, prohibiting reverse inference from brain measures to clinical symptoms and traits. Neural signatures—multivariate brain-patterns trained to be both sensitive *and* specific to a construct of interest—might alleviate this problem, but are rarely applied to mental disorders. We tested whether previously developed neural signatures for negative affect and discrete emotions distinguish between healthy individuals and those with mental disorders characterized by emotion dysregulation, i.e., BPD and cPTSD. In three different fMRI studies, a total sample of 192 women (49 BPD, 62 cPTSD, 81 healthy controls) were shown pictures of scenes with negative or neutral content. Based on pathophysiological models, we hypothesized higher negative and lower positive reactivity of neural emotion signatures in participants with emotion dysregulation. The expression of neural signatures differed strongly between neutral and negative pictures (average Cohen's d = 1.17). Nevertheless, a mega-analysis on individual participant data showed no differences in the reactivity of neural signatures between participants with and without emotion dysregulation. Confidence intervals ruled out even small effect sizes in the hypothesized direction and were further supported by Bayes factors. Overall, these results support the validity of neural signatures for emotional states during fMRI tasks, but raise important questions concerning their link to individual differences in emotion dysregulation.

4.2 Introduction

About 30% of the global population are estimated to suffer from a mental disorder during their lifetime, accompanied by significant human and societal costs (Steel et al., 2008; Whiteford et al., 2013). As for most physical maladies, biological explanations have a long history in this realm (Barondes, 1990). In the last 20 years, functional neuroimaging in particular has become a fundamental research strategy to improve our understanding of mental disorders. Most commonly, clinical researchers, practitioners, and patients are interested in features of the brain to infer clinical traits on a psychological level. For such *reverse inference*, neurobiological features must be both sensitive and specific, i.e., highly predictive of the psychological concept of interest, but not other distinct concepts (Poldrack, 2011). Unfortunately, with few exceptions, classic neural measures like average regional activity are not task-specific (Yarkoni et al., 2011) and have low test-retest reliability (Elliott et al., 2020), precluding reverse inference from brain activity to complex psychological constructs.

Neural signatures have been proposed as a solution to this problem (Woo et al., 2017). They can be defined as statistical models, which predict a psychological concept from brain data with great precision, but also distinguish it from similar but meaningfully different concepts (Kragel et al., 2018). For example, a machine learning-based multivariate neural signature of physical pain can be highly predictive of self-reported pain ratings, but distinguishes it from the concept of socio-emotional 'pain' following social rejection and vice versa (Woo et al., 2014). Hence, neural signatures ensure interpretability regarding psychological states above other brain-based approaches. Moreover, they might remedy the very low test-retest reliability of non-pattern brain measures (Gianaros et al., 2020; Kragel et al., 2020) as well as increase statistical power by limiting the number of statistical comparisons to a single neural indicator for the process of interest. Despite these advantages, validated neural signatures have rarely been applied to explain individual differences, particularly regarding clinical research questions on mental disorders.

Some mental disorders such as BPD and cPTSD are characterized by pervasive emotion dysregulation, comprising increased emotional reactivity and deficits in emotion regulation (American Psychiatric Association, 2013; Brewin et al., 2017; Carpenter & Trull, 2013; Linehan, 1993). For the reactivity component, dominant pathophysiological models posit that presumably emotion-generating brain regions are hyperactive in response to negative (or even neutral) stimuli (Brendel et al., 2005; Sicorello & Schmahl, 2021; Swartz et al., 2015). Especially for the amygdala, there is compelling evidence of hyperactivity in these disorders (Bryant et al., 2019; Schulze et al., 2019). Still, amygdala hyperactivity does not warrant reverse inference to heightened emotional reactivity, as it is not specific to negative emotions, but rather involved in a large spectrum of both valence-independent emotional and non-emotional processes (Cunningham & Brosch, 2012; Lindquist et al., 2016; Ousdal et al., 2008; Sander et al., 2003; Todorov, 2012; Wager et al., 2015). Hence, there is still no clear evidence demonstrating emotional hyperreactivity on a brain basis in these disorders.

Several neural signatures of emotions have been developed which are suitable to address this issue, which draw from sparse distributed information across the brain. The picture induced negative emotion signature (PINES; Chang et al., 2015) predicted one-item self-ratings of negative affect following negative pictures with a product-moment correlation above .90, outperforming single resting-state networks and regions, demonstrated dissociability from neural patterns of physical pain, and maintained its cross-validated accuracy in a hold-out sample. Complementary to this pattern for global negative affect, Kragel and LaBar (2015) developed seven patterns which distinguish discrete video-induced emotions from each other at an accuracy close to 40% (chance is ≈14%), including the emotions of fear, anger, sadness, surprise, amusement, contentment and a neutral reference state. Classification accuracy was also above chance when tested on music clips, supporting cross-modal validity. Moreover, in a large resting state fMRI sample of young healthy university students, spontaneous activity of the sadness pattern was associated with an epidemiological depression scale, while the fear pattern was associated

with trait anxiety (Kragel et al., 2016). This study provides first evidence that individual differences in the expression of neural emotion networks might map on traits related to the differential experience of emotions on a self-report level.

Expanding this approach to a clinical setting, we tested herein whether the activity of these previously developed neural signatures for general negative affect (i.e., PINES; Chang et al., 2015) and discrete emotions (Kragel & LaBar, 2015) in response to pictures of negative (versus neutral) scenes distinguished women with emotion dysregulation from healthy controls. Negative scenes are among the most common stimuli to study negative emotional reactivity in mental disorders (McDermott et al., 2018). Analyses were conducted across three datasets, each including a clinical group characterized by emotion dysregulation (2 BPD, 1 cPTSD), aggregating results with a mega-analytic approach based on individual participant data.

First, we tested whether neural signatures were differentially expressed in the two experimental conditions. When viewing negative pictures, we expected the pattern expression of negative affect (PINES signature) as well as fear, anger, and sadness (discrete emotion signatures) to be increased (hypothesis 1). Second, for the main research question, common models of the disorders predict heightened reactivity of negative emotions. Here, this translates to increased reactivity of the patterns for negative affect as well as fear, anger, and sadness in participants with emotion dysregulation (hypothesis 2).

Previously, we observed that naturalistic everyday life stressors are associated not only with higher negative affect, but also lower positive affect (Sicorello et al., 2020). Therefore, we included additional analyses on neural signatures for positive emotions as well. We predicted the pattern expression of amusement and contentment to be decreased in the negative condition. We predicted stronger deactivation of these patterns in the emotion dysregulation groups. For the surprise pattern, we expected a higher expression in the negative condition, but had no directional between-group hypothesis. Last, the neutral pattern indicates the presence (or absence) of any discrete emotional state. As the paradigm is designed to elicit negative emotions, we

expected neutral states to be decreased in the negatisve condition and more strongly so in the emotion dysregulation group.

4.3 Methods

Samples and Procedure

Three studies comprising a total of 192 women were included in the analyses of which 111 had a diagnosis of BPD or cPTSD. All participants were presented negative and neutral pictures during fMRI.

Study 1 comprised 57 women (29 with BPD, 28 healthy controls) who participated in a randomized controlled trial on BPD psychotherapy (German Clinical Trials Register: DRKS00000778). Only results from cross-sectional data collected before the intervention are reported here. Participants completed an fMRI experiment with three event-related runs, all with the same structure and number of trials. Each run involved a negative and a neutral condition presented after a "view" instruction. Either negative pictures or pictures of objects where shown, respectively. The experiment also involved regulate-conditions that were not analyzed here, where participants had to regulate their emotional response. Pictures were presented for 6s. Longitudinal results on therapy-effects in this sample have been published previously (Niedtfeld et al., 2017; Schmitt et al., 2016).

Study 2 comprised 40 women (20 with BPD, 20 healthy controls), who completed three runs of a picture viewing task with different designs: block-design (one picture per block, 18s), mixed-design (three pictures per block, 6s each), and event-related design (6s per picture). Participants viewed negative pictures (negative condition) and scrambled images (neutral condition). Data on the healthy group have been published previously (Paret et al., 2014).

Study 3 comprised 95 women (62 with cPTSD, 33 healthy controls), who were recruited from a larger randomized controlled psychotherapeutic trial (German Clinical Trials Register:

DRKS00005578), and therapy-effects were recently published (Bohus et al., 2020). Only results from cross-sectional data collected before the intervention are reported here. In addition to the DSM-5 criteria for PTSD, participants met at least three out of nine DSM-IV criteria for BPD, including criterion six for emotional instability. Negative pictures and neutral pictures were presented as distractors within a Sternberg working memory task for 1.5s and entered the analysis as negative condition and neutral condition, respectively. Neutral pictures matched with the negative pictures for complexity and content were used in the neutral baseline condition. FMRI data from 34 women of the cPTSD group have been published previously to test a different hypothesis against a trauma-exposed healthy control group (Sicorello et al., 2020). The trauma-exposed control group was not included in the analyses here.

Comprehensive descriptions of sample characteristics, designs, procedures, scanning parameters, and preprocessing for all three studies can be found in the supplemental material.

Pattern Expression

We downloaded the pattern-masks of each neural signature (PINES and the seven discrete emotion signatures) from the CANlab github repository: https://github.com/canlab. These pattern masks are freely available and consist of a brain image with a regression weight for each brain voxel. Pattern expression was calculated as the dot product between the pattern mask and an image containing beta weights from the first-level analysis for the respective regressor of interest (negative or neutral condition), separately for each picture condition, run, and participant. For the PINES, pattern expression reflects the predicted negative affect rating. For discrete emotions, pattern expression is a continuous indicator to what degree a given emotion category is more likely than the remaining categories. Notably, expression values cannot be directly compared between studies, as their scale depends on scanning parameters, scanner-specific gain and signal characteristics, and analysis choices. Expression values can, however, be compared across task conditions and participants if these values can be assumed to be constant across

participants. As an index of reactivity, pattern expression during the neutral condition was subtracted from pattern expression during the negative condition.

As an indicator of internal consistency, we calculated the reliability for the pattern responses as Cronbach's alpha between experimental runs when more than one run was available (studies 1 and 2). All runs occurred in the same fMRI session. For study 1, pattern responses had a mean reliability of α = .58, ranging from α = .48 for anger to α = .66 for the PINES and fear. As could be expected from previous reports (Gianaros et al., 2020; Kragel et al., 2020), the reliability was higher for pattern expression than for the mean response in an amygdala-hippocampal region-of-interest (ROI; α = .14), which was defined from the thresholded mask of a previous functional meta-analysis on emotion processing in BPD (Schulze et al., 2019; https://identifiers.org/neurovault.collection:3751). For study 2, pattern responses had a mean reliability of α = .64, ranging from α = .56 for amused to α = .72 for fear. Again, reliability of the amygdala-hippocampal ROI was substantially lower at α = .31. The correlation between pattern expressions in the event-related design and the two block designs was lower than between the two block designs, but not in a range indicating conclusive differences, given the sample size: *r*(event-related, block) = .26, *r*(event-related, mixed-block) = .37, *r*(block, mixed-block) = .57.

Statistical Analyses

Negative versus neutral condition. To test whether the expression of neural signatures differed between the negative and the neutral condition in studies 1-3, reflecting pattern reactivity, one-sample *t*-tests were conducted on the difference scores. Cohen's *d* was calculated as the mean difference score divided by the standard deviation of difference scores. The three runs of study 1 were averaged for this analysis, as the runs showed good compatibility in terms of sufficient internal consistency and only small differences in mean effects. Runs of study 2 were analyzed separately, to allow the inspection of design-dependent effects and as the three runs had large differences in mean activations, due to the different stimulus presentation parameters.

The corresponding within-person mega-analysis was conducted using a two-level multilevel analysis framework, with difference scores nested within participants (because of the multiple runs in studies 1 and 2). The difference score Δ_{ijk} of run *i* within participant *j* of study *k* was regressed on a fixed intercept γ_{000}, including random intercepts for study-participants ζ_{0jk}. as well as a residual term ε_{ijk}: $\Delta_{ijk} = \gamma_{000} + \zeta_{0jk} + \varepsilon_{ijk}$. Due to the low number of studies, the study-wise random intercept ζ_{00k} was not included. Moreover, Δ_{ijk} was scaled on the run-specific standard deviation $SD_{i \bullet k}$. With this scaling, γ_{000} is in the metric of the Cohen's *d* used for single study analyses and on a compatible scale between studies and runs, regardless of influences like design effects. All frequentist multilevel analyses were conducted using the lmer function of the lme4 package in R version 4.0.3 and restricted maximum likelihood estimation.

Group effects. For single studies, differences between the clinical and the healthy groups were tested with two-sample *t*-tests for unequal variances and pattern reactivity (Δ) as the dependent variable. Cohen's *d* was calculated as the difference in group means divided by the pooled standard deviation.

The mega-analysis was specified as $\Delta_{ijk} = \gamma_{100}(\text{group}) + \zeta_{0jk} + \varepsilon_{ijk}$, where γ_{100} represents the fixed effect of group. As for within-analysis, the corresponding random effect for group $\zeta_{10k}(\text{group})$ was not included due to the low number of studies. The group variable was recoded within runs, so that all intercepts (and their variance) are zero. Therefore, the fixed intercept γ_{000} and its variance between studies ζ_{00k} can be omitted from the model. For balanced group sizes (study 2), this can be achieved by coding groups as -0.5 and 0.5, with the regression weight representing the mean difference between groups. For unbalanced group sizes (studies 1 and 3), weighted effect coding was used (te Grotenhuis et al., 2017). Moreover, Δ_{ijk} was standardized within runs by subtracting the run-specific mean and dividing by the run-specific pooled standard deviation. With this standardization, γ_{100} is in the metric of Cohen's *d*, as used for single study analyses.

Bayes factors. Bayes factors were calculated for all models to quantify the relative evidence of the H_0 over the H_1 (e.g., effect = 0 versus effect ≠ 0), using the low information cauchy prior with a scale factor of 0.707, which is the default of the R package used here and was previously suggested for psychological applications (Wagenmakers et al., 2018). Bayes factors are a ratio between p(Data|H_1) and p(Data|H_0), with values above 3 (or below 1/3) often used as a minimum cutoff for claims of evidence in favor of one hypothesis over the other, although continuous interpretations are recommended as well (Jarosz & Wiley, 2014). BF_{10} denotes evidence for the H_1, divided by the evidence for H_0; BF_{01} denotes evidence for the H_0, divided by the evidence for H_1. BF_{10} equals $1/BF_{01}$ and vice versa.

To compute Bayes factor for tests in singles studies, the function ttestBF() of the Bayes factor package was used in R (Morey & Rouder, 2018). For mega-analyses, the multilevel models were refitted using the *brms* package, comparing models with (H_1) and models without (H_0) the effect of interest using the function bayes_factor().

In accordance with our hypotheses stated in the introduction, all Bayes factors reflected directional one-sided tests, except for the between-group effect of surprise. This was achieved by modelling a half-cauchy for the H_1 in the hypothesized direction. We argue this is appropriate here, as the Bayes factor should reflect evidence for/against the alternative hypothesis of interest, e.g., neural expression of fear is higher when viewing pictures with negative content (and neither zero *nor* lower).

Reproducible Analyses

Data and annotated R scripts to reproduce the main analyses can be found on: https://github.com/MaurizioSicorello/MVPAemoDys_Analyses.git.

Demographic information used for sample description and fMRI images are not openly provided. Requests for primary data should be addressed directly to the corresponding author.

4.4 Results

Comparison Between Negative and Neutral Pictures

In line with our hypothesis, both mega-analyses and single-study analyses indicated that neural signatures of negative affect and negative emotions were expressed more strongly while viewing negative pictures, except for the sadness pattern (Figure 8, Table 4). Likewise, neural signatures of positive emotions were expressed more strongly in the neutral conditions. Effect sizes were overall large, ranging between $d = 0.81$ (anger) and $d = 2.07$ (PINES/negative affect). Only the signature for sadness had a small effect of $d = -0.23$, which went in the opposite direction than expected, i.e., sadness was expressed more strongly in the neutral condition. The null hypothesis that the condition effect for sadness is zero or negative was 60 times more likely than the hypothesized positive effect, i.e., increased neural expression in the negative condition. Study 2 indicated that mixed-block design elicited the largest effects and the event-related design the smallest effects, as has been previously reported for the mass univariate ROI approach (Paret et al., 2014).

In the original validation study, the PINES distinguished the highest and the lowest negative affect ratings at an accuracy of 93.5% (Chang et al., 2015). A logistic regression of picture condition on PINES expression revealed mostly lower but compatible accuracies, with the highest accuracy in the mixed-block design of study 2 and the lowest accuracy in study 3, which had the shortest stimulus presentation duration: Study 1 = 82% [74.21%, 88.94%]; Study $2_{\text{Event-Related}}$ = 71.25% [60.05%, 80.82%]; Study 2_{Block} = 87.50% [78.21%, 93.84%]: Study 2_{Mixed} = 97.50% [91.26%, 99.70%]; Study 3 = 64% [56.41%, 70.52%].

In sum, these results overall support our first hypothesis that neural signatures of emotions are differentially expressed when viewing negative and neutral pictures in the hypothesized directions, except for the sadness pattern. The estimated effect sizes were very large, but also appeared to depend on design aspects of the studies.

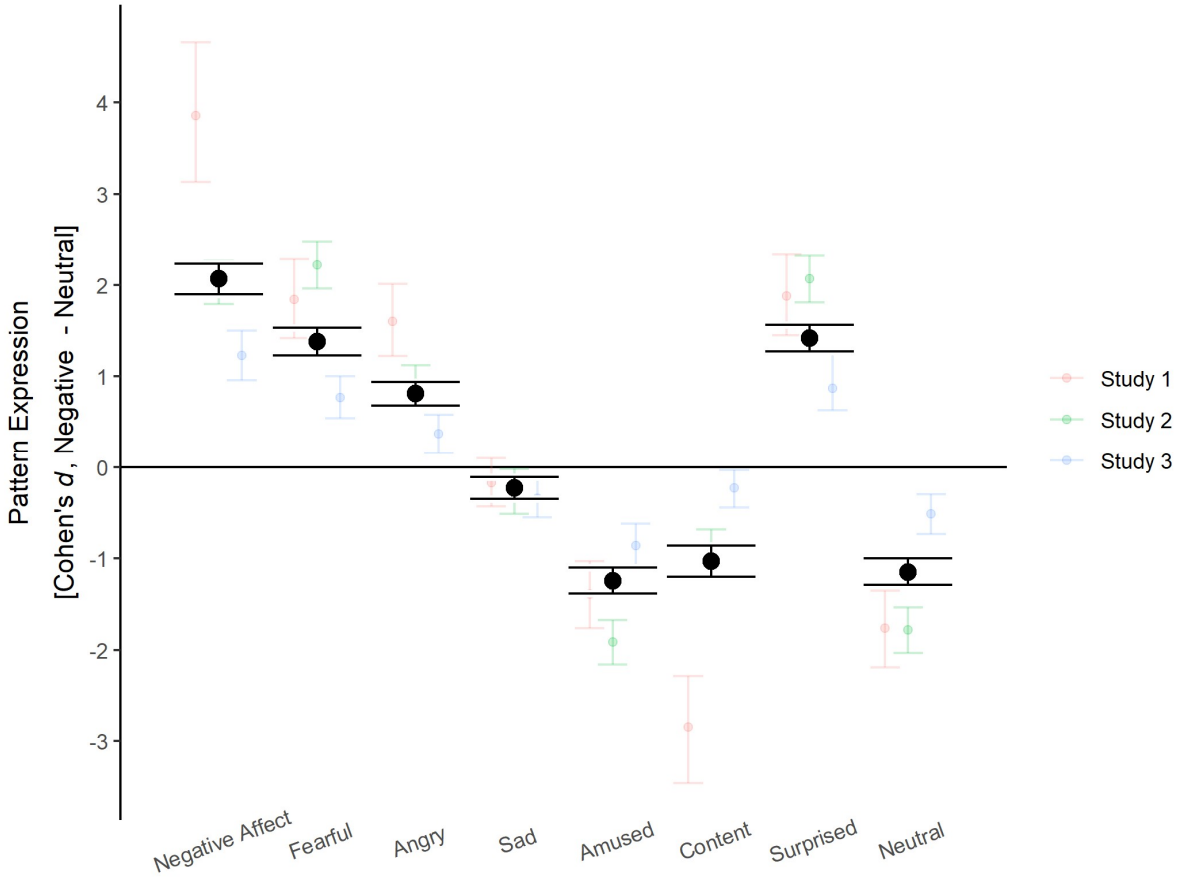

Figure 8. Differences in the expression of neural emotion signatures between the negative and the neutral condition. Error bars show 95% confidence intervals.

Table 4

Differences in neural pattern expression between negative and neutral condition

	Negative emotions				Positive emotions		Other emotions	
	Negative Affect	Fear	Anger	Sadness	Amusement	Contentment	Surprise	Neutral
Study 1	3.86 [3.13, 4.66] $BF_{10} > 100$	1.84 [1.42, 2.28] $BF_{10} > 100$	1.60 [1.22, 2.01] $BF_{10} > 100$	-0.17 [-0.43, 0.1] $BF_{10} = 0.07$	-1.39 [-1.76, -1.03] $BF_{10} > 100$	-2.85 [-3.46, -2.28] $BF_{10} > 100$	1.88 [1.45, 2.33] $BF_{10} > 100$	-1.76 [-2.19, -1.35] $BF_{10} > 100$
Study 2								
Event-related	1.45 [1.01, 1.91] $BF_{10} > 100$	1.26 [0.85, 1.69] $BF_{10} > 100$	0.49 [0.16, 0.83] $BF_{10} = 20.57$	-0.16 [-0.48, 0.16] $BF_{10} = 0.09$	-0.62 [-0.97, -0.28] $BF_{10} > 100$	-0.80 [-1.17, -0.44] $BF_{10} > 100$	1.10 [0.71, 1.51] $BF_{10} > 100$	-1.21 [-1.63, -0.80] $BF_{10} > 100$
Block	1.87 [1.36, 2.41] $BF_{10} > 100$	2.49 [1.88, 3.16] $BF_{10} > 100$	0.96 [0.59, 1.35] $BF_{10} > 100$	-0.32 [-0.65, 0.00] $BF_{10} = 0.06$	-2.28 [-2.91, -1.71] $BF_{10} > 100$	-0.82 [-1.19, -0.46] $BF_{10} > 100$	1.99 [1.47, 2.56] $BF_{10} > 100$	-1.47 [-1.94, -1.03] $BF_{10} > 100$
Mixed-Block	2.76 [2.10, 3.48] $BF_{10} > 100$	2.90 [2.21, 3.65] $BF_{10} > 100$	1.23 [0.82, 1.65] $BF_{10} > 100$	-0.32 [-0.65, 0.00] $BF_{10} = 0.06$	-2.84 [-3.58, -2.16] $BF_{10} > 100$	-1.19 [-1.61, -0.78] $BF_{10} > 100$	3.11 [2.38, 3.91] $BF_{10} > 100$	-2.66 [-3.36, -2.02] $BF_{10} > 100$
Study 3	1.23 [0.96, 1.5] $BF_{10} > 100$	0.77 [0.54, 1.00] $BF_{10} > 100$	0.37 [0.16, 0.58] $BF_{10} = 79.45$	-0.34 [-0.55, -0.13] $BF_{10} = 0.03$	-0.86 [-1.10, -0.62] $BF_{10} > 100$	-0.23 [-0.44, -0.03] 2.59	0.87 [0.63, 1.30] $BF_{10} > 100$	-0.51 [-0.73, -0.30] $BF_{10} > 100$
Mega-Analysis	2.07 [1.90, 2.23] $BF_{10} > 100$	1.38 [1.23, 1.53] $BF_{10} > 100$	0.81 [0.68, 0.94] $BF_{10} > 100$	-0.23 [-0.35, -0.11] $BF_{10} = 0.02$	-1.24 [-1.38, -1.10] $BF_{10} > 100$	-1.03 [-1.20, -0.86] $BF_{10} > 100$	1.42 [1.27, 1.56] $BF_{10} > 100$	-1.15 [-1.29, -1.00] $BF_{10} > 100$

Note. Estimates are Cohen's *d*. Numbers in brackets are 95% confidence intervals. BF_{10} = Bayes factor of the alternative hypothesis over the null hypothesis.

Comparison Between Clinical Groups and Healthy Controls

Most mega-analytic group effects were very small (all $|d| \leq 0.17$; Figure 9, Table 5). Contrary to hypothesis 2—i.e., higher neural pattern reactivity of negative emotions in participants with emotion dysregulation compared to healthy controls—the former actually showed lower reactivity of neural signatures for negative affect, fear, and anger. The upper confidence limit for these three emotions did not include values higher than $d = 0.12$ and Bayes factors favored the null hypothesis of equal or smaller neural signature reactivity in the emotion dysregulation groups. While the emotion dysregulation group did show the expected tendency of higher expression for sadness, the effect was very small ($d = 0.06$), confidence intervals covered zero and had an upper limit at a small effect size of $d = 0.31$, and the Bayes factor favored the null ($BF_{01} = 9.54$). Moreover, the condition-wise analyses indicated this emotion signature might not be a valid measure given the stimulus material. Group effects for neutral states, amusement, contentment, and surprise did not differ considerably from zero. These results were supported by Bayes factors, except for surprise, whose Bayes factor was relatively inconclusive ($BF_{01} = 2.15$). On a single study-basis, this pattern was overall present in studies 1 and 2. The descriptive effect directions in study 3 were more compatible with the theoretical predictions, albeit with miniscule effect sizes and inconclusive Bayes factors. These results were stable when a binary indicator for psychotropic medication was included as a covariate (Figure S4).

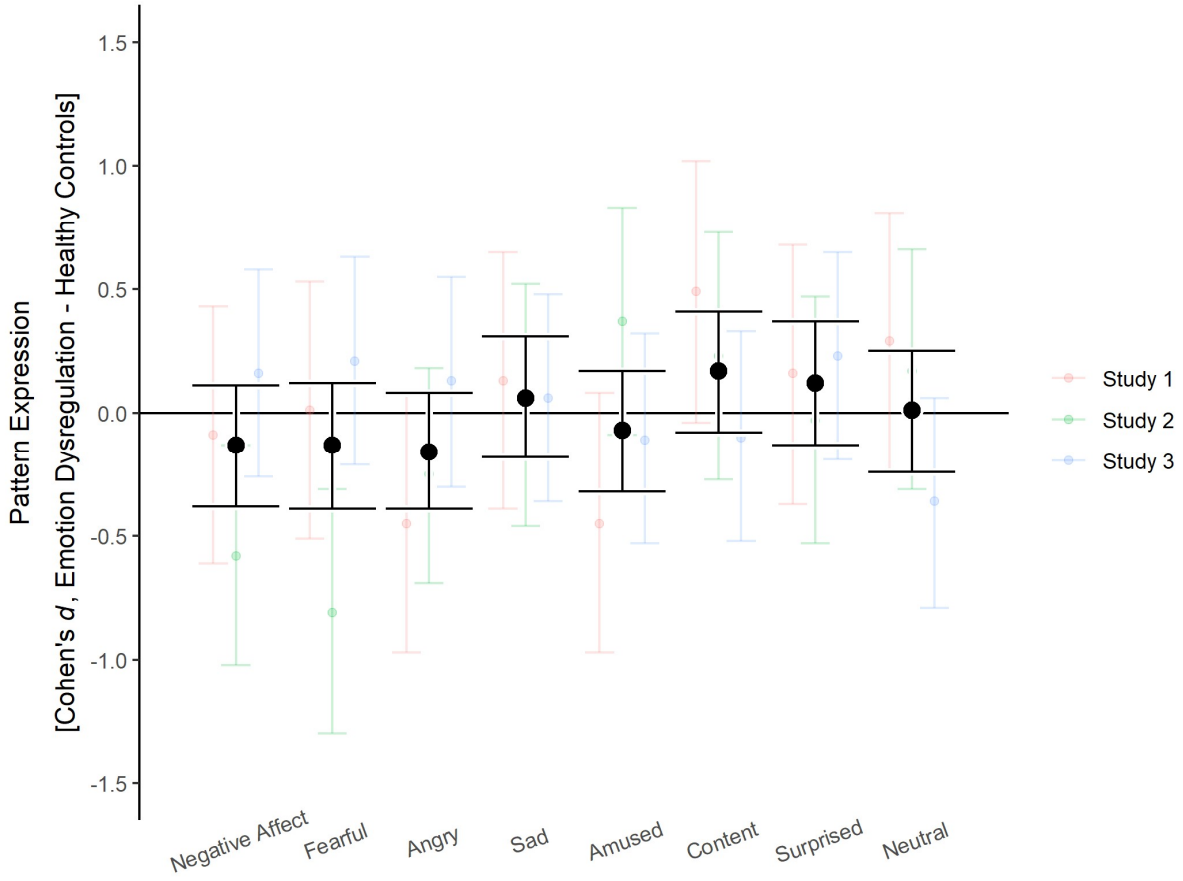

Figure 9. Group differences in the reactivity of neural emotion signatures between participants with emotion dysregulation and healthy controls. Error bars show 95% confidence intervals.

Table 5

Differences in neural pattern reactivity (negative – neutral condition) between emotion dysregulation and healthy control group

	Negative emotions				Positive emotions		Other emotions	
	Negative Affect	Fear	Anger	Sadness	Amusement	Contentment	Surprise	Neutral
Study 1	-0.09 [-0.61, 0.43] BF_{01} = 4.76	0.01 [-0.51, 0.53] BF_{01} = 3.57	-0.45 [-0.97, 0.08] BF_{01} = 9.09	0.13 [-0.39, 0.65] BF_{01} = 2.50	-0.45 [-0.97, 0.08] BF_{01} = 0.06	0.49 [-0.04, 1.02] BF_{01} = 10.0	0.16 [-0.37, 0.68] BF_{01} = 3.23	0.29 [-0.24, 0.81] BF_{01} = 7.14
Study 2								
Event-related	-0.37 [-0.99, 0.26] BF_{01} = 6.25	-0.36 [-0.98, 0.27] BF_{01} = 6.25	-0.20 [-0.82, 0.42] BF_{01} = 4.76	-0.39 [-1.01, 0.24] BF_{01} = 6.25	-0.08 [-0.70, 0.54] BF_{01} = 2.70	0.32 [-0.31, 0.94] BF_{01} = 5.88	0.15 [-0.47, 0.77] BF_{01} = 2.94	0.36 [-0.27, 0.98] BF_{01} = 6.25
Block	-0.99 [-1.64, -0.33] BF_{01} = 11.11	-0.95 [-1.60, -0.29] BF_{01} = 11.11	-0.34 [-0.96, 0.28] BF_{01} = 5.88	0.30 [-0.32, 0.93] BF_{01} = 1.41	0.68 [0.04, 1.31] BF_{01} = 9.09	0.20 [-0.43, 0.82] BF_{01} = 4.76	-0.23 [-0.85, 0.39] BF_{01} = 2.63	0.05 [-0.57, 0.67] BF_{01} = 3.57
Mixed-Block	-0.37 [-0.99, 0.26] BF_{01} = 6.25	-1.11 [-1.77, -0.44] BF_{01} = 12.5	-0.21 [-0.83, 0.41] BF_{01} = 5.00	0.18 [-0.44, 0.80] BF_{01} = 2.04	0.51 [-0.12, 1.14] BF_{01} = 7.14	0.17 [-0.45, 0.79] BF_{01} = 4.55	-0.01 [-0.63, 0.61] BF_{01} = 3.23	0.12 [-0.50, 0.74] BF_{01} = 4.17
Study 3	0.16 [-0.26, 0.58] BF_{01} = 2.27	0.21 [-0.21, 0.63] BF_{01} = 1.79	0.13 [-0.3, 0.55] BF_{01} = 2.70	0.06 [-0.36, 0.48] BF_{01} = 3.57	-0.11 [-0.53, 0.32] BF_{01} = 2.94	-0.10 [-0.52, 0.33] BF_{01} = 3.12	0.23 [-0.19, 0.65] BF_{01} = 2.70	-0.36 [-0.79, 0.06] BF_{01} = 0.69
Mega-Analysis	-0.13 [-0.38, 0.11] BF_{01} = 11.56	-0.13 [-0.39, 0.12] BF_{01} = 7.28	-0.16 [-0.39, 0.08] BF_{01} = 53.01	0.06 [-0.18, 0.31] BF_{01} = 9.54	-0.07 [-0.32, 0.17] BF_{01} = 4.79	0.17 [-0.08, 0.41] BF_{01} = 9.68	0.12 [-0.13, 0.37] BF_{01} = 2.15	0.01 [-0.24, 0.25] BF_{01} = 21.70

Note. Estimates are Cohen's *d*. Numbers in brackets are 95% confidence intervals. BF_{01} = Bayes factor of the null hypothesis over the alternative hypothesis.

Exploratory Analyses: Group Effects on the Neutral Baseline

There is some evidence that people with emotion dysregulation have a higher propensity to interpret neutral stimuli as negative (Daros et al., 2013; Mitchell et al., 2014), accompanied by heightened amygdala responses (Donegan et al., 2003; Lischke et al., 2017; Niedtfeld et al., 2010). As this might diminish group differences in the negative-neutral contrast, we repeated the between-group analyses of section 3.2 with activation in the neutral condition as the dependent variable, instead of the difference between negative and neutral conditions.

In these analyses, all confidence intervals contained zero by a considerable margin (Figure S5). Still, even statistically non-significant group effects on the neutral baseline might diminish group effects on the difference scores used to indicate neural reactivity. In the neutral condition, participants with emotion dysregulation had slightly increased responses for the fear pattern (d = 0.17, 95% CI = [-0.08, 0.43]) and decreased responses for the contentment pattern (d = -0.10, 95% CI = [-0.35, 0.15]). Hence, the hypothesized effects for these two patterns might be diminished by group differences in response to the neutral condition. All other effects were in the opposite direction of what would be expected if an increased responsiveness to neutral stimuli accounts for the null effects reported in section 3.2 (e.g., participants with emotion dysregulation had a lower expression of the PINES signature and a higher expression of the neutral signature).

To follow up on the potential attenuation effect for fear and contentment, we repeated the mega-analytic procedure on pattern expression in the negative condition against the implicit baseline (Figure S6). The estimates for the fear and contentment patterns were almost perfectly zero, although confidence intervals of the fear pattern still included small to moderate effect sizes (fear: d = 0.00, 95% CI = [-0.26, 0.26]; contentment: d = 0.01, 95% CI = [-0.24, 0.26]).

Coincidentally, we observed that the confidence interval of the effect of lower negative affect in the emotion dysregulation group vs. the healthy control group no longer contained zero (d = -0.32, 95% CI = [-0.57, -0.07]), which differs from the results for the negative-neutral contrast.

4.5 Discussion

Discussion of Results

To translate neurobiological models of mental disorders into the clinical language of traits and symptoms, neural markers have to be both sensitive *and* specific to the psychological concept of interest. This is rarely the case for properties of discrete anatomical brain regions like the amygdala, which nonetheless has been frequently used as an indicator of negative emotional processes in affect-related disorders, while it is also involved in a broad set of psychological phenomena other than emotions. Here, we used machine learning-based multivariate neural signatures for emotional states to test whether people with emotion dysregulation show signs of hyperreactive neuro-emotional systems. This assumption of leading psychopathological models was assessed in three independent studies from our lab, investigating participants diagnosed with either BPD or cPTSD and healthy controls.

Neural signatures of negative affect (Chang et al., 2015) and discrete emotions (Kragel & LaBar, 2015) showed strong differential expression between the negative and the neutral condition in the expected directions (hypothesis 1), supporting their validity and accuracy, even when transferred to a different lab, experimental design, and population than the initial validation studies. Effect sizes were very large and supported by very large Bayes factors in each of the three studies. Moreover, study 2 indicates that effect sizes might be partly related to stimulus presentation parameters such as exposure time. Notably, the effect observed with the sadness signature was in the opposite direction than expected (neutral > negative condition). As the stimuli were chosen based on valence and arousal ratings, it is possible that sadness-inducing

pictures were underrepresented or that sadness is harder to induce with briefly presented pictures.

Most importantly, the neural signatures did not differentiate between participants with and without emotion dysregulation, speaking against the main hypothesis of the present study (hypothesis 2). Except for the sadness and amusement signatures, all effects went in the opposite direction from the theoretical predictions, i.e., smaller negative emotional reactivity and positive emotional reactivity in the emotion dysregulation group vs. the healthy group. The corresponding confidence intervals ruled out even small effect sizes in the expected direction, below $|d| = 0.20$ and Bayes factors favored the null hypothesis for all signatures, except for surprise, which was inconclusive. Similar patterns emerged for separate analyses on studies 1 and 2, while the results in study 3 were less conclusive in terms of Bayes factors. These results could not be explained by a heightened response to the neutral condition in those with BPD and cPTSD, which has been observed previously for amygdala reactivity.

These findings are incompatible with the dominant pathological model of BPD and provide evidence against either the theoretical, experimental, or neurobiological assumptions of the present study, which we discuss below. Either way, important implications arise for future research. To discuss these potential explanations of the reported results, we mainly draw from the BPD literature, as the cPTSD literature is still relatively limited and the BPD criterion for emotional instability was the cardinal criterion for inclusion in study 3.

Showing participants pictures of scenes with negative content is among the most common tasks to experimentally investigate heightened emotional reactivity in mental disorders and affect-related traits. This approach rests on the implicit assumptions that (1) the clinical phenomenon of heightened emotional reactivity is not fully accounted for by more negative environments, a lower threshold for emotional responses, or difficulties in emotion regulation, (2) emotional reactivity can be observed outside of its naturalistic daily life context, and (3) the emotion-inducing effect of experimental stimuli is not limited to stimuli personalized according

to thematic relevance. If correct, these assumptions naturally lead to the conclusion that people with emotion dysregulation must have generally hyperresponsive emotion generating biological systems, whose exploration could aid the understanding and treatment of such disorders. Further, our aim to investigate these biological systems with neural signatures was based on the assumption that (4) neural signatures represent the best available neural markers for such systems, due to their high accuracy for emotional states.

Apart from qualitative clinical impression of therapeutic practitioners, there is empirical evidence for increased reactivity to discrete naturalistic everyday life stressors in BPD (Hepp et al., 2018). Notably, such studies cannot easily distinguish precisely which aspects of emotion processing are aberrant, due to their relatively low temporal resolution (assumption 1). Experimental settings offer higher control and better temporal resolution, but suffer from limited ecological validity, as stressors are presented outside of their natural context (assumption 2). A recent meta-analytic review found that the literature is surprisingly inconclusive concerning experimentally induced emotional reactions in BPD (Bortolla et al., 2020). While they did find moderate experimental group effects on affective self-ratings in their meta-analysis, many studies did not include a pre-measurement, potentially confounding tonic negative emotions and emotional reactivity, or only had pre- and post-task ratings, which might capture other processes than stimulus-contingent real-time responses. Moreover, peripheral-physiological effects were negligibly small and/or statistically not significant. Interestingly, there was no statistically significant difference in effect sizes dependent on whether stimuli were thematically related to BPD (assumption 3).

Taken together, it is possible that typical laboratory designs, as used in our studies, are not well-suited to probe individual differences in emotional reactivity which generalize to everyday life or that clinical subgroups with opposing phenomenology cancel each other's effects. Alternatively, it is possible that the neural signatures do not capture the psychological concept of interest well (assumption 4). If the concepts of interest are emotions as they are measured by

self-reports, this seems unlikely for the PINES, as it correlated with self-reports above $r = .90$ in both the training and the hold-out sample, which employed a design similar to ours. Still, it is possible that when asked for their mood directly after seeing a negative picture, participants partly rate the picture content, rather than exclusively their emotions, which could have impeded the construct validity of the PINES. Nevertheless, this argument does not hold for the discrete emotion signatures, which distinguish emotion categories and were associated with trait depressiveness and anxiety in a well-powered resting-state study.

Another neurobiological explanation of the null results might be the presence of stable physiological between-person noise (e.g., cerebrovasculature or hematocrit levels; D'Esposito et al., 2003; Yang et al., 2015). A recent meta-analysis demonstrated that test-retest reliability of resting state fMRI diminishes considerably after artefact correction, indicating the presence of such stable between-person noise (Noble et al., 2019). The neural signatures used here have been developed to explain variance without explicit differentiation of the within- or between-person level and their high accuracy might be preferentially due to variance within individuals. Notably, while machine learning-based approaches have been increasingly used to differentiate between clinical groups based on fMRI data (Gao et al., 2018; Woo et al., 2017), these approaches do not necessarily lead to interpretable neural markers, as groups might differ on many confounded dimensions.

Limitations and Future Directions

The mega-analyses did not include random slopes for studies, as the low number of studies does not allow a sensible estimate of between-study variance. Hence, the generalizability to other experimental investigations is limited and a wider range of effect sizes should be expected (Yarkoni, 2020). This limitation on generalizability is especially important, as studies included only female participants, due to potential gender-differences in symptom presentation (Sansone & Sansone, 2011). Study 2 indicated that stimulus presentation parameters might be one important influence on effect size differences, at least for within-person effects.

Another limitation to consider is the reliability of fMRI-based neural markers (Elliott et al., 2020). Testing the internal consistency for multi-run studies 1 and 2 indicated that reliability was considerably higher for neural signatures than for an amygdala-hippocampal cluster from a BPD meta-analysis, but still lower than desirable, ranging from $\alpha = .48$ to $\alpha = .72$. These estimates could be used in future studies to correct expected effect sizes for unreliability in power analyses.

As in most BPD studies which used fMRI designs with negative scenes, there were no affective self-ratings directly following pictures. Such ratings would be necessary to closely replicate the core assumption of the neural emotion signatures, that is, they predict momentary subjective affect ratings by means of BOLD responses to affective stimuli across different populations. More research is urgently needed to confirm the strict validity of neural signatures in clinical populations. Post-session valence ratings of negative pictures did not differ considerably between participants, as has been previously reported (Koenigsberg et al., 2009; Schulze et al., 2011), but are not necessarily a valid surrogate of *momentary* affect, immediately following negative trials. While these tasks have been frequently used, there has been to our knowledge no thorough psychometric validation to ensure their usefulness for research on individual differences on the psychological end. Therefore, we suggest a systematic assessment of their test-retest reliability and validity in terms of associations with clinically relevant traits, independent of neuroimaging techniques. As stated above, it is unclear whether valence ratings following the session should continue to replace self-ratings of affect immediately following image-exposure.

Conclusion

Neural signatures of emotions appear to be valid and transferable tools to investigate within-person relationships, but their utility to understand individual differences remains unclear. Contrary to theoretical expectations, we did not find differences between people with and without emotion dysregulation. We offer to share our analysis pipelines with other research

groups to reanalyze existing datasets. This could be done efficiently and lead to a more comprehensive picture of the relationship between neural signatures and emotion-related traits. Apart from neurobiological approaches, more research is needed concerning the psychometric properties and ecological validity of typical experimental tasks used to probe affective traits.

4.6 Supplemental material

Study 1: Supplemental Methods

Participants. The current sample of 29 patients with BPD and 28 HC was recruited within a larger project on alterations in neural correlates of emotion regulation in BPD after Dialectical Behavioral Therapy (DBT), which was registered as a clinical trial (German clinical trials register DRKS00000778). This project focused on longitudinal data, assessing on improvements after DBT versus treatment as usual, and several papers on alterations in structural and functional brain correlates were published before (Niedtfeld et al., 2017; Schmitt et al., 2016; Winter et al., 2017), suggesting normalization of emotion regulation via reappraisal, and a reduced effect of painful stimulation as a dysfunctional attempt to regulate negative affect after psychotherapy. However, previous analyses excluded participants that did not take part at both scanning sessions, pre and post 12 weeks of psychotherapy. In the current analysis, we included all complete datasets that were acquired at the first assessment point.

Patients were recruited at specialized DBT inpatient treatment units at the Central Institute of Mental Health Mannheim and at Heidelberg University Hospital, at local outpatient treatment units, and via email contact to local psychotherapists. Patients received DBT treatment, individual psychotherapy, residential crisis intervention, pharmacotherapy, self-help groups, or no specialized care. For more information on demographic and clinical characteristics, see Table S5. Study procedures were confirmed by the Ethics Board of the Medical Faculty Mannheim of the University of Heidelberg (Nr. 2010-243N-MA) and all subjects provided written informed consent before participation. All participants received monetary compensation of 12€/hour for their participation.

All BPD patients met DSM-IV diagnosis for BPD, including affective instability and NSSI during the last month prior to the first assessment. Diagnoses were assessed by trained clinical psychologists carrying out the German Versions of the SCID-IV (Wittchen et al., 1997), and the IPDE (Loranger et al., 1997). Symptom severity of BPD was assessed via the Zanarini

Rating Scale for BPD (Zanarini, 2003), and the Borderline Symptom List (Bohus et al., 2009). Additionally, BPD patients were either unmedicated or had a constant medication. HC did not meet any lifetime psychiatric disorder and received no psychotropic medication. We further excluded participants with left-handedness, traumatic brain injury, lifetime schizophrenia or bipolar I disorder, mental or developmental disorders, substance dependence during the last year, drug consumption in the last two months, current severe depressive episode, and benzodiazepine use.

Stimulus Material and Procedure. The fMRI task was a well-validated emotion regulation task (Ochsner et al., 2002) that were previously used in patients with BPD (Krause-Utz et al., 2012; Niedtfeld et al., 2010; Schulze et al., 2011). The paradigm was designed to incorporate two within-subject factors (picture valence, regulation condition). Within three different runs, we incorporated different emotion regulation conditions: distract versus look, reappraise versus look, and painful temperature versus look. In each run, 72 experimental trials were presented, consisting of negative or neutral picture stimuli (each presented for 6s), which were selected from two standardized picture sets, the Emotional Picture Set (Wessa et al., 2010) and the International Affective Picture System (Lang et al., 2005). We parallelized pictures with regard to valence and arousal between runs and conditions. For the current analysis, we extracted the look condition for each picture valence (i.e., 18 trials negative look, 18 trials neutral look, for each run), resulting in 108 trials for each participant. Between trials, participants saw a white fixation cross on a black screen, presented for a jittered time interval of 3 to 8 seconds. To monitor vigilance of the participants, 24 catch trials (i.e., the letter "O") were included between experimental trials that required an immediate button press response.

Data Acquisition and Preprocessing. Brain images were acquired using a 3 Tesla MRI scanner (TRIO, Siemens Medical Systems, Erlangen, Germany) with a 32-channel head coil and a T2*- weighted gradient echo-planar imaging sequence (repetition time=2000ms, echo time=30ms, voxel size =3x3x3mm, matrix = 64x 64, number of slices = 36). A high-resolution

T1-weighted structural scan was acquired for co-registration of functional images. Functional data were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom). The echo-planar imaging time series were pre-processed according to custom practice. Procedures comprised slice time correction, spatial realignment, segmentation of T1 scan, coregistration onto T1 scan, normalization to the standard brain of the MNI space, resampling to 3 mm3 voxels, smoothing with a Gaussian kernel with a full-width at half maximum of 6 mm.

First-level analysis. On the individual level, we modeled four regressors of interest (using a canonical HRF), resembling the 2x2 factor levels (i.e., negative regulate, negative look, neutral regulate, neutral look), and seven regressors of no interest (button presses, six movement parameters). To correct for low-frequency fluctuations and global signal intensity variation, a high-pass filter of 128s was applied. The contrasts images for this study (i.e., negative look, neutral look) were entered into the second level analyses.

Study 2: Supplemental methods

Participants. We tested 22 healthy female participants and 20 participants with BPD. One additional participant was measured in the BPD group after a phone screening but had to be excluded afterwards because she did not fulfill at least 5 DSM-IV BPD criteria. One healthy participant had to be excluded because of excessive movements (translation >3 mm) and another subject could not be included in the analysis due to an incidental finding. This resulted in N = 20 healthy subjects in the fMRI analysis. Healthy participants reported no current and past DSM-IV Axis I syndrome or family history of neurological or psychiatric disorders, as confirmed by a structured clinical interview (Wittchen et al., 1997). All participants were of Caucasian origin. Demographics and sample characteristics are provided in Table S6. Study procedures were confirmed by the Ethics Board of the Medical Faculty Mannheim of the University of Heidelberg (Nr. 2011-224N-MA) and all subjects provided written informed consent before participation. Compensation for expenses was 24 Euro.

Stimulus material and procedure. Participants underwent three fMRI-runs comprising the presentation of aversive pictures and scrambled versions of the same pictures as a baseline. All pictures were taken from standardized picture series (Lang et al., 2005; Wessa et al., 2010), where stimuli had been rated by representative samples using the Self-Assessment Manikin affective rating system on a 9-point scale. Stimuli were chosen to have high ratings of arousal and low ratings of pleasure referring to a high level of negative valence, respectively, and depicted scenes such as accidents, suffering people, or war. Each picture was presented only once to each participant during the whole experiment. Each scanning run used a different mode of stimulus presentation, subsequently referred to as different experimental 'designs'. Specifically, we employed an event related (ER) design (373 scans), an Single Picture Block (SPB) design (218 scans), and a multiple picture block (MPB) design (218 scans). In ER, 36 stimuli were presented for 2 s each with an adjacent inter-trial interval of 20 ± 1 s to allow partial recovery of the BOLD signal. During the ITI, participants viewed a white fixation cross on a black background. SPB and MPB used a trial duration of 18 s and an ITI of 12 ± 3 s. In SPB, one stimulus was presented for the whole 18 s, whereas in MPB, three stimuli were presented consecutively for 6 s each, resulting in a set of 14 pictures in the former and 42 in the latter design. The ITI was jittered within the given range to ensure reduced predictability of picture onset and optimized sampling of the BOLD signal. Picture assignment to design-type as well as design-type order was counterbalanced and randomized between subjects, as was trial order with the restriction of ≤2 consecutive stimuli of the same valence. A difference in affective intensity between design-types was prevented by matching the mean normative valence and arousal ratings of stimuli in the different runs. Before the first run, subjects were instructed to look directly at the pictures during the entire duration of presentation and not to distract themselves by thinking about other things. Each run started with a written instruction (6 s) introducing the upcoming design-type in German (e.g., for SPB: 'Now you will see 14 pictures for 18 s

each'). After every run, subjects were asked to rate their current level of aversive tension. Stimuli were presented using Presentation software (Neurobehavioral Systems, Inc, Berkeley, USA) via a 40″ monitor located in the back of the scanner which was visible for subjects through a mirror placed on top of the head coil. After completion of the experiment, subjects were asked to rate the negative stimuli with regard to valence and arousal outside the MRI suite.

Data acquisition and preprocessing. FMRI data were acquired on a 3 TeslaMRI Scanner (Magnetom Trio with TIM technology, Siemens Medical Service, Erlangen, Germany) equipped with a 32 channel head coil. Functional images of the BOLD contrast were acquired with gradient echo T2* weighted echo-planar imaging sequence (TE = 30 ms, TR = 2 s, FOV = 220 mm × 220 mm, matrix size=64 × 64, flip angle=80°). A volume comprised 36 slices in AC–PC orientation with a thickness of 3 mm and slice gap of 1 mm. Participants' heads were lightly restrained using soft pads to prevent head movement. A T1-weighted anatomical image was also recorded (TE = 3.03 ms, TR = 2.3 s, 192 slices and FOV = 256 mm × 256 mm, matrix size 256 × 256, slice thickness = 1 mm). FMRI data were analyzed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Before preprocessing of functional data, 5 initial volumes were discarded to avoid T1 effects. A slice timing correction of the functional scans was performed with reference to the 18th slice to correct for differences in acquisition time between slices. Realignment of functional images to the mean functional image was performed using a rigid body transformation. The required transformation matrix for the alignment of functional and anatomical (T1) images was estimated via the SPM12 coregister module. The T1 image was segmented into six tissue types using the ICBM template (MNI system) for the normalization. The received normalization parameters were used to transform the functional images into MNI space. Normalized functional images were finally smoothed with a kernel of 8 mm (FWHM).

First-level analysis. On the single-subject-level, we performed a separate General Linear Model (GLM) analysis for each run, resulting in one model for each design, i.e., ER, SPB, and MPB. In each analysis, 3 conditions were modeled: 'negative' (negative condition) as well as 'scrambled' (neutral condition) picture presentation, and the instruction (duration=6 s) at the beginning of the trial. The ITI period served as an implicit baseline. A high-pass filter (128 s) was added to the GLM to remove slow signal drifts and serial correlations were accounted for using an auto-regressive (AR(1)) model. All regressors were convolved with the HRF implemented in SPM12.

Study 3: Supplemental methods

Participants. The sample comprised 62 women with cPTSD and 33 healthy controls. cPTSD participants were recruited from a larger randomized controlled trial (German Clinical Trials Register: DRKS00005578) on the efficacy of dialectical behavior therapy and cognitive processing therapy in cPTSD after childhood abuse (Bohus et al., 2020). They underwent fMRI measurements between randomization and the first therapy session. All cPTSD patients met DSM-5 diagnosis for PTSD and met at least three criteria for BPD, including criterion six for emotional instability. Diagnoses were assessed by trained clinical psychologists carrying out the German Versions of the SCID for DSM-IV (Wittchen et al., 1997) and the IPDE (Loranger et al., 1997). Demographics and sample characteristics are provided in Table S7.

Healthy control participants were recruited with advertisements in local newspapers, flyers and over the internet. The study was approved by the Ethical Board II of Heidelberg University (Nr.: 2013-635N-MA), Germany, and was conducted according to the Declaration of Helsinki at the Central Institute of Mental Health in Mannheim, Germany. Participants provided written consent after the procedures had been fully explained. All participants received monetary compensation of 12€/h for their participation.

Stimulus material and procedure. Participants were shown negative versus neutral pictures from the International Affective Picture System (IAPS; Lang et al., 2005), which were presented within a Sternberg working memory task. Participants saw sixteen pictures which were preselected as negative or neutral based on arousal and valence ratings in the general population. Pictures in the negative condition included negatively arousing interpersonal scenes on physical and sexual violence, emotional neglect, or mutilation. Neutral pictures were matched to negative pictures regarding the number of persons and complexity of the scene to control for potentially confounding differences in visual information processing. In the present study, only the contrast between negative and neutral pictures was used.

The task consisted of 48 trials, each starting with the presentation of three uppercase letters (memoranda, 1000 ms). After a delay interval (1500 ms), again three letters (probe, 2000 ms) were presented, which participants had to compare with the memoranda. Participants had to press a "yes" button whenever they recognized a target, i.e., a letter previously presented in the memorandum. In half of the trials, a target (one of the three memoranda) was present in the probe. During the delay interval, either a fixation cross or a picture stimulus (negative or neutral) was presented. The resting phase between the trials was jittered to prevent temporal correlation. We used the Software Presentation (Neurobehavioral Systems) to present stimuli and record behavioral data.

Data acquisition and preprocessing. Brain images were acquired using a 3 Tesla MRI scanner (TRIO, Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. Using three-dimensional MPRAGE (T1-weighted contrast, voxel size 111 mm^3), a high-resolution anatomical scan was acquired for each participant as an individual template for the functional data. T2-weighted gradient echo planar imaging was used for measurement of the BOLD signal [EPI, T2-weighted contrast, field of view = 192192 mm, voxel size 333 mm^3, 6464 voxel matrix, flip angle 80°, echo time (TE) = 30 ms, repetition time (TR) = 2000 ms], with 36 transversal slices (3 mm, descending) covering the entire brain. The first four scans were discarded

to minimize T1 effects. Head movement artefacts and scanning noise were restricted using head cushions and headphones.

Functional imaging data were processed using standard procedures implemented in SPM12 (Welcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm/). The EPI time series were pre-processed according to custom practice, including slice time correction, spatial realignment, segmentation of T1 scan, co-registration onto T1 scan, and normalization to the standard brain of the MNI space. We did not have to exclude subjects due to excessive head motion (exclusion criterion for head motion was 3mm in each direction).

First-level analysis. Whole-brain voxel-wise regression weights of the regressors for negative and neutral pictures were calculated using the first-level analysis procedure from SPM 12. We modelled the neural response with three regressors of interest (negative pictures, neutral pictures, fixation cross) and six motion regressors. The regressors were convolved with the canonical HRF. A contrast image between negative and neutral pictures was calculated by subtracting the beta image of the negative picture regressor from the beta image of the neutral picture regressor.

Table S5

Sample descriptives for study 1

	BPD	HC
	N = 28	N = 29
Demographics		
Age mean (SD)	25.89 (6.82)	26.83 (8.21)
Memory span mean (SD)	15.11 (3.14)	16.62 (3.74)
School education N (%)		
School-leaving qualification	5 (17.9)	1 (3.4)
Secondary school-leaving qualification	9 (32.1)	15 (51.7)
General matriculation standard	12 (42.9)	13 (44.8)
Other	2 (7.1)	0
Profession N (%)		
None	12 (42.9)	11 (37.9)
Vocational Training	13 (46.4)	13 (44.8)
University/College	2 (7.1)	3 (10.3)
Missing	1 (3.6)	2 (6.9)
Clinical Characteristics M (SD)		
ZAN-BPD	15.64 (6.58)	0.48 (1.27)
DERS	125.59 (24.56)	61.10 (14.19)
BDI	27.67 (11.16)	1.90 (3.32)
STAI-State	56.58 (11.43)	29.75 (6.92)
STAI-Trait	60.35 (9.15)	29.69 (8.00)
BSL	1.89 (0.80)	0.21 (0.16)
RSQ-D	18.06 (7.24)	5.32 (3.15)
FDS	23.91 (15.22)	2.22 (2.21)
Current Comorbidities N (%)		
Posttraumatic Stress Disorder	12 (42.1)	
Major Depressive Disorder	8 (28.6)	
Anxiety Disorder	6 (21.4)	
Obsessive-Compulsive Disorder	4 (14.3)	
Bipolar II	1 (3.6)	
Somatoform Disorder	1 (3.6)	
Eating Disorder	13 (46.4)	
Substance Dependency	5 (17.9)	
Substance Abuse	4 (14.3)	
Other Current DSM-V Disorders	2 (7.1)	
Psychotropic Medication N (%)		
Total	4 (14.3)	
SSRI	4 (14.3)	
Atypical Neuroleptics	2 (7.1)	
Other	1 (3.6)	
Unmedicated	24 (85.71)	

Note. ZAN-BPD = Zanarini Rating Scale for BPD, DERS = Difficulties in Emotion Regulation Scale, BDI = Beck Depression Inventory, STAI = State-Trait-Anxiety Inventory, BSL = Borderline Symptom List, RSQ-D = Response Style Questionnaire - German Version, FDS = Questionnaire for Dissociative Symptoms (German).

Table S6

Sample descriptives for study 2

	BPD	HC
	N = 20	*N* = 20
Demographics		
Age mean (SD)	27.6 (6.43)	26.1 (4.53)
School education N (%)		
School-leaving qualification	0 (0)	0 (0)
Secondary school-leaving qualification	7 (35)	2 (10)
General matriculation standard	13 (65)	18 (90)
Picture Ratings M (SD)		
Valence	3.68 (0.31)	3.77 (0.50)
Arousal	2.91 (0.67)	3.03 (0.61)
Valence	3.68 (0.31)	3.77 (0.50)
Arousal	2.91 (0.67)	3.03 (0.61)
Clinical Characteristics M (SD)		
DERS	123.11 (15.04)	64.4 (17.32)
BDI	27.5 (9.29)	3 (3.61)
STAI-State	55.78 (7.46)	30.5 (7.80)
STAI-Trait	60.5 (7.76)	32.65 (9.50)
BSL	2.19 (0.72)	0.1 (0.12)
FDS	24.39 (15.39)	3.00 (2.01)
CTQ	61.06 (18.77)	32.7 (9.71)
ZAN-BPD	11.75 (4.87)	0.89 (1.91)
Current Comorbidities N (%)		
Posttraumatic Stress Disorder	5 (25)	
Depressive Disorder	13 (65)	
Anxiety Disorder	5 (25)	
Panic Disorder	2 (10)	
Obsessive-Compulsive Disorder	1 (5)	
Somatoform Disorder	3 (15)	
Eating Disorder	3 (15)	
Substance Abuse	2 (10)	
Psychotropic Medication N (%)		
SSRI	2 (10)	
Unmedicated	18 (90)	

Note. DERS = Difficulties in Emotion Regulation Scale, BDI = Beck Depression Inventory, STAI = State-Trait Anxiety Inventory, BSL = Borderline Symptom List, FDS = Dissociative Experiences Scale, CTQ = Childhood Trauma Questionnaire, ZAN-BPD = Zanarini Rating Scale for BDP. Picture ratings were only provided for images in the negative condition and not for scrambled images in the control condition.

Table S7
Sample descriptives for study 3

	cPTSD	HC
	N = 62	*N* = 33
Demographics M (SD)		
Age	35.15 (11.40)	32.30 (8.42)
School education in years	10.52 (1.40)	11.33 (1.05)
Picture Ratings M (SD)		
Valence Negative	4.47 (0.34)	4.38 (0.51)
Valence Neutral	2.70 (0.46)	2.57 (0.54)
Arousal Negative	3.80 (0.85)	3.31 (0.78)
Arousal Neutral	1.58 (0.48)	1.15 (0.20)
Clinical Characteristics M (SD)		
DTS	80.26 (18.16)	
ZAN-BPD	10.90 (5.40)	
DERS	126.26 (21.11)	60.12 (16.50)
BDI	34.42 (9.77)	4.32 (4.94)
STAI-State	58.10 (10.30)	29.85 (5.86)
STAI-Trait	62.32 (7.09)	29.79 (7.72)
BSI GSI	1.86 (0.65)	0.25 (0.24)
CTQ	14.86 (3.68)	6.09 (5.33)
GAF	50.58 (7.90)	91.13 (8.27)
FDS	22.56 (12.39)	2.65 (2.40)
Current Comorbidities N (%)		
Posttraumatic Stress Disorder	62 (100)	
Affective Disorders	40 (64.5)	
Anxiety Disorders	38 (61.3)	
Obsessive-Compulsive Disorder	6 (9.7)	
Bipolar II	0	
Somatoform Disorder	5 (8.1)	
Eating Disorder	17 (27.4)	
Substance Dependency	0	
Substance Abuse	0	
Borderline Personality Disorder	33 (53.2)	
Psychotropic Medication N (%)		
Total	26 (56.7)	
SSRI	15 (25.0)	
SNRI	13 (21.7)	
Other Antidepressants	10 (16.7)	
Atypical Neuroleptics	12 (20.0)	
Other Psychotropic Medication	3 (5.0)	
Unmedicated	34 (43.3)	

Note. DTS = Davidson Trauma Scale, ZAN-BPD = Zanarini Rating Scale for BDP, DERS = Difficulties in Emotion Regulation Scale, BDI = Beck Depression Inventory, STAI = State-Trait Anxiety Inventory, BSI GSI = Brief Symptom Inventory Global Severity Index, GAF = Global Assessment of Functioning, CTQ = Child Trauma Questionnaire, FDS = Dissociative Experiences Scale. Picture ratings were provided for pictures in both the negative and the neutral condition.

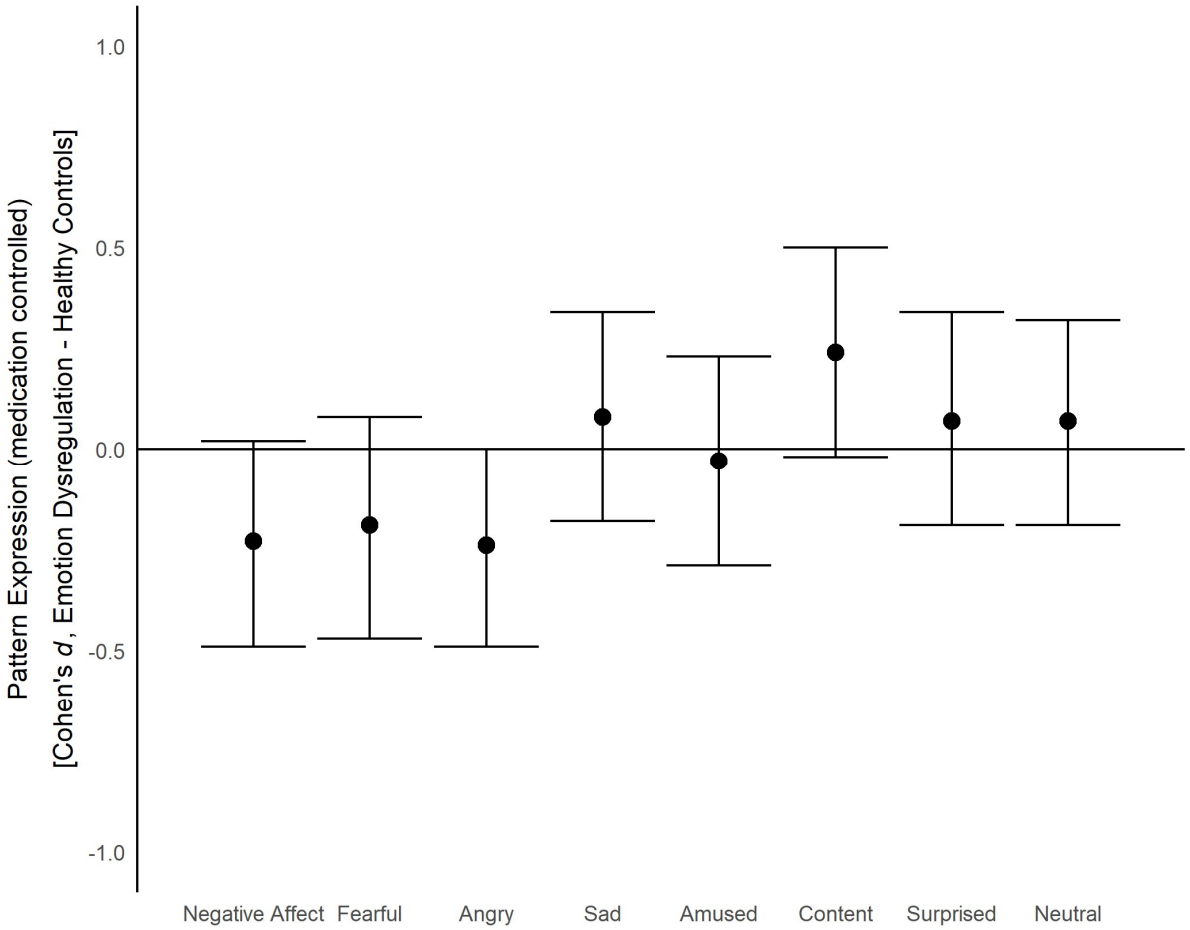

Figure S4. Mega-analytic group effects on pattern expression for the contrast negative versus neutral, controlling for medication status (medicated vs unmedicated). Error bars show 95% confidence intervals.

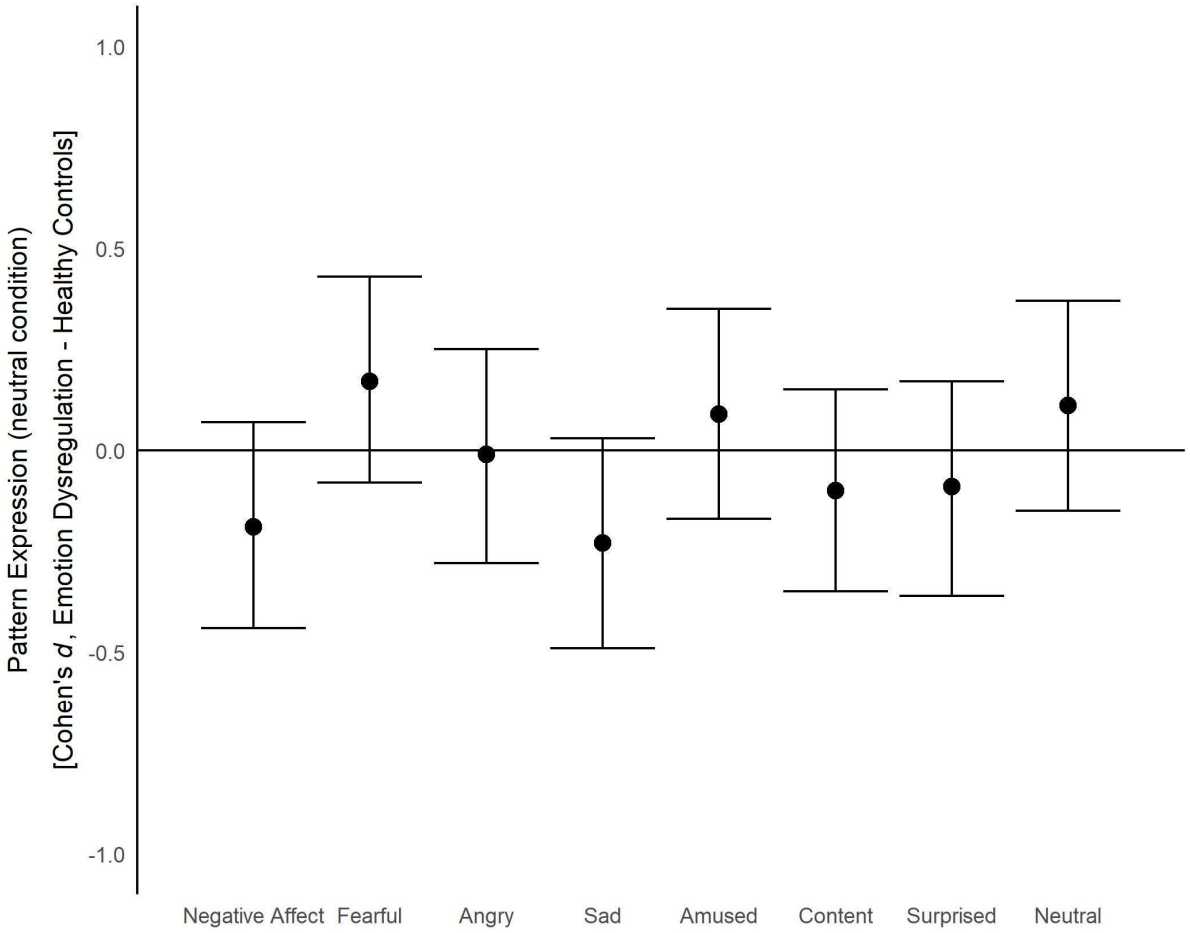

Figure S5. Mega-analytic group effects on pattern expression in the neutral baseline condition. Error bars show 95% confidence intervals.

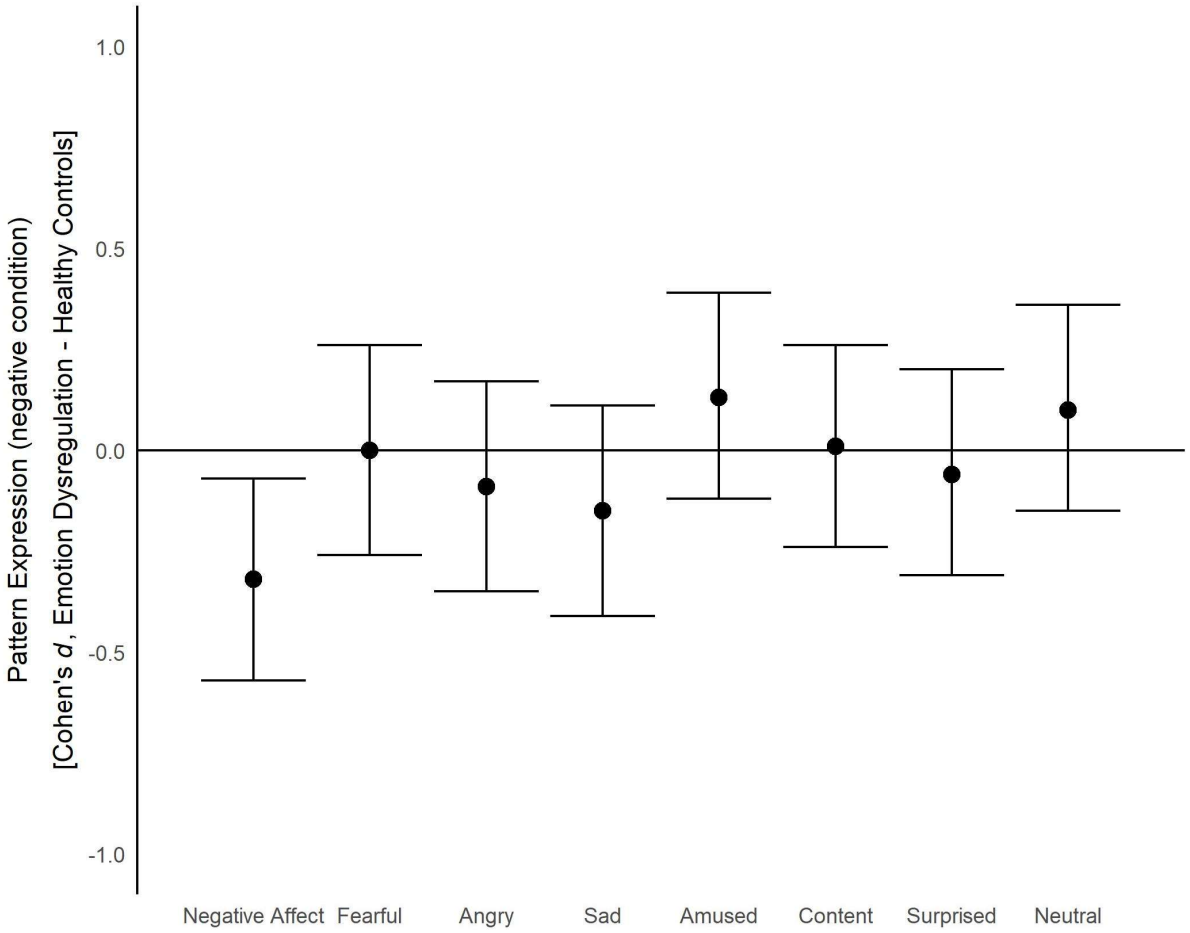

Figure S6. Mega-analytic group effects on pattern expression in the neutral baseline condition. Error bars show 95% confidence intervals.

Thesis Discussion

CHAPTER V

Early adversity is among the most impactful etiological factors across mental disorders (Green et al., 2010). A vast body of research exists, aiming to better understand the biological consequences of early adversity. Overall, there appear to be robust meta-analytic effects, including atrophy of the amygdala and the hippocampus (Paquola et al., 2016). For the amygdala, there is evidence that these findings generalize from structure to function during processing of aversive stimuli (Heany et al., 2018; Hein & Monk, 2017). Still, beyond these average results, there is considerable heterogeneity (Paquola et al., 2016). Increasingly, studies aim to elucidate the theoretical boundary conditions under which specific brain changes can be observed. Here, the neurodevelopmental timing of adversity is emerging as a crucial factor, moderating both the quality and quantity of such brain changes (Teicher & Samson, 2016).

For the amygdala and hippocampus, there is compelling evidence for the importance of trauma timing. Studies have been pointing towards sensitive periods for structural changes in early adolescence (Andersen et al., 2008; Herzog et al., 2020; Merz et al., 2018; Teicher et al., 2018), but also early childhood (Luby et al., 2020; Teicher et al., 2018), associated with smaller volumes. Still, there are many open questions regarding the neurodevelopmental, brain-functional, and psychological implications of these findings. Addressing these three levels is necessary to move from basic brain research to clinical application.

In study 1, I addressed the neurodevelopmental question whether brain changes differ dependent on whether adversity occurred during child- or adulthood (Question I). By pooling data from two studies, I found qualitative differences in amygdala aberrations, with hyper- or hypotrophy dependent on whether participants were screened for typical childhood or adulthood trauma.

A central axiom in neuroscience is that function follows structure (Pessoa, 2018). Still, this axiom does not necessarily hold on all levels of analysis (Question II). There is evidence

for a dissociation between structure and function on a macroscopic level of gross anatomical brain regions (Kalmar et al., 2009; Straathof et al., 2019). This is plausible, as a simple measure like amygdala volume might capture individual differences on some broad dimensions, but cannot capture more specific processes that are dependent on situational factors. Therefore, study 2 addressed whether previous findings of potential sensitive periods for early adversity generalize from brain structure to brain function—specifically, amygdala reactivity during the processing of threat-related stimuli, which is a central process in trauma-related disorders (Schulze et al., 2019). Here, I found that adverse events during early childhood and late adolescence are particularly predictive of amygdala reactivity.

Even if brain measures show aberrations in trauma-related disorders, it is often unclear whether these effects are due to psychopathology or the mere exposure to adversity, apparent even in healthy individuals (Question III). Therefore, studies 1 and 2 included both trauma-exposed groups with PTSD and trauma-exposed healthy controls. This approach revealed two major phenomena: First, structural amygdala hypertrophy in individuals screened for adulthood trauma is present in both clinical and healthy groups, with more ambiguous results in the childhood sample. Second, amygdala reactivity during threat-processing had *opposite* associations with PTSD and adversity.

The psychological interpretation of such functional amygdala aberrations remains a major challenge, largely due to the reverse inference problem (Question IV). Researchers are often interested in inference of mental phenomena from brain data, especially in mental health research. Such reverse inference is limited by incomplete knowledge on how mental events are implemented in the brain. This is exemplified by the limited sensitivity and very low specificity of the amygdala to infer constructs like negative affect and fear (Chang et al., 2015; Lindquist et al., 2016; Wager et al., 2015; Zhou et al., 2021). Despite these complications, it is common practice to infer emotion dysregulation from amygdala function in clinical studies on trauma-related disorders. In study 3, I leveraged multivariate brain patterns which are sensitive *and*

specific to negative affect and discrete emotions to provide a more severe test of whether people with trauma-related disorders are characterized by emotion dysregulation on a brain basis. Pooling data from three studies using a Bayesian mega-analytic approach, I found evidence against theoretically predicted difference in brain-based emotion responding between people with emotion dysregulation and healthy controls.

5.1 Summary and Integration of Study Findings

Multiple theories posit that timing is a crucial factor to understand adversity-contingent changes in brain and behavior (Callaghan & Tottenham, 2016; Fawcett & Frankenhuis, 2015; Lupien et al., 2018; Teicher & Samson, 2016). These accounts differ in the predicted time window of sensitive periods as well as the functional meaning of the hypothesized brain changes. Changes might be understood as pure "damage" that interferes with normal neurodevelopment (Lupien et al., 2009), but also as viable adaptations of the organism to harmful environments, which might lead to clinically relevant problems later in life (Callaghan & Tottenham, 2016; Teicher & Samson, 2016). Speaking of sensitive periods (or critical time windows) implies the effect of adversity within these periods differs from effects of adversity occurring outside these periods. Effects inside versus outside sensitive periods might differ quantitatively in size and qualitatively in direction. There are at least three potential explanations why differences might be qualitative: First, changes might be entirely experience-expectant, meaning they completely rely on early evolutionarily conserved ontogenetic time windows, similar to the development of basic vision and language processes (Nelson & Gabard-Durnam, 2020). Second, effects might be dependent on what is adaptive at the time of adversity, with systematic differences throughout the lifespan (Teicher & Samson, 2016). Third, there might be nonlinearities in the prolonged lifespan development of single regions (Russell et al., 2021).

So far, neurobiological studies on the timing of early adversity have restricted their time frame to childhood and adolescence. Still, depending on the theory, hypothesized sensitive periods might cover almost the entire time window until adulthood (Lupien et al., 2009). Therefore, inference to neurodevelopmental theories from such studies is impeded by the absence of participants who experienced their traumatic events during adulthood. Study 1 addressed this gap and found evidence that stress-related changes in the amygdala might also occur later in life, i.e., not only in early neurodevelopment. Both groups with adulthood trauma, whether with PTSD or healthy, showed equally large differences to their trauma-naïve healthy reference group. In size, their effect also matched that found in the childhood trauma group with PTSD, but most strikingly these effects differed *qualitatively* between the two samples: While the childhood PTSD group had smaller amygdala volumes than their trauma-naïve controls, both trauma-exposed adulthood groups had larger volumes.

These findings must be interpreted in light of the trajectory of amygdala development. At first, the amygdala shows considerable growth until early adolescence where it reaches a plateau (Uematsu et al., 2012; Zhou et al., 2021). Moreover, a recent longitudinal study reported decelerated amygdala growth in institutionalized children, followed by sustained lower volumes than the comparison group (VanTieghem et al., 2021). Hence, smaller amygdala volumes in the childhood trauma group are well in line with the idea of neurodevelopmental interference, proposed by the life-cycle model of stress (Lupien et al., 2009), but not the stress-acceleration hypothesis (Callaghan & Tottenham, 2016). But how can the increased volumes in the adulthood sample be explained?

A recent study suggests an inverted U-shaped developmental trajectory of the amygdala, with a similar peak to the studies reported above, followed by a volume decline (Russell et al., 2021). Given this trajectory, larger volumes in people with adulthood trauma would still be in line with the idea of decelerated neurodevelopment and the life-cycle model of stress: If the

developmental process is impeded in a phase of normative volume decrease, larger volumes are expected for the affected individuals.

The results in the adulthood sample support that stress-related changes in the amygdala are not strictly limited to small timeframes in childhood and adolescence. This is further corroborated by the fact that both trauma-exposed adulthood samples in study 1 showed similar structural differences to the trauma-naïve control group. Hence, volume differences are unlikely to be due to vulnerability factors or clinical consequences of psychopathology, leaving adverse experiences as the most plausible antecedent. This could only be tested by incorporating clinical and healthy trauma-exposed groups, which is a particular strength of study 1 and 2. Still, as the effects differed qualitatively in their direction, it cannot be ruled out that these differences can be attributed to experience-expectant versus experience-dependent neurodevelopment, reflecting qualitatively different ontogenetic processes.

A central and immensely complex question is whether these brain changes also might have adaptive value. Such interpretations are often made when associations between adversity and brain changes are found (Teicher & Samson, 2016; Zhu et al., 2019), but are extremely difficult to corroborate, as they necessitate theories that map brain measures to actual behavior, whether overt or covert. Amygdala volume, as for most brain measures, cannot easily be tied to interpretable individual differences in behavior. Meta-analyses tie amygdala volume to different affective and stress-related disorders (Schulze et al., 2016) and anxiety-related traits (Mincic, 2015). Still, often these studies do not correct for the confounding effect of early adversity, which could produce spurious correlations between brain measures and psychopathology. Moreover, most single studies have small sample sizes and recent large-scale studies revealed very small associations between regional brain volumes and complex traits (Marek et al., 2022; Schulz et al., 2022), leading some to argue that regional brain volume and complex traits might be on different conceptual levels (Brandt & Mueller, 2022; DeYoung et al., 2022).

Task-based fMRI is a viable option to further elucidate the functional implications of brain aberrations (DeYoung et al., 2022). A higher responsivity to threat is a cornerstone of many trauma-related disorders, including PTSD and BPD. While study 2 identified particularly predictive life periods for the effect of adversity on amygdala reactivity, these periods did not correspond to the periods found to be important for structural changes in the same sample (Herzog et al., 2020) and other structural studies employing a similar method (Andersen et al., 2008; Merz et al., 2018; but for an effect of early but not late socioeconomic status also see Luby et al., 2019). These prior structural studies identified potential sensitive periods in early adolescence, while study 2 pointed towards early childhood. This again highlights the dissociation between structure and function on the coarse temporospatial resolution of (f)MRI.

The time window in early childhood found in study 2 is compatible with the "earlier is worse" hypothesis (Lupien et al., 2018) and the predictions based on information-theoretic transition points (Frankenhuis & Walasek, 2020), but the latter would also predict a sensitive phase during early adolescence that was not present in the data. Most surprisingly, adversity led to *lower* amygdala responsivity. On the one hand, these effects are in contrast to two meta-analysis on childhood maltreatment and amygdala reactivity (Heany et al., 2018; Hein & Monk, 2017). On the other hand, similar results were published by a relatively large study, using a similar approach, which was published while our study was conducted (Zhu et al., 2019). The authors argue that a lower amygdala responsivity during very early adverse experiences might be adaptive, as the organism is particularly dependent on the caregiver during that phase and a lower amygdala responsivity could potentially help maintain the adverse relationship in favor of a higher risk of complete abandonment. Another study found that amygdala responsivity was higher in samples which either experienced abuse or neglect, but was *lower* in samples which experienced both to a considerable degree (Puetz et al., 2020). This might also explain results in study 2, as most participants fit the latter profile.

Importantly, the previous meta-analyses on early adversity did not control for the effect of psychopathology (Heany et al., 2018; Hein & Monk, 2017). This is problematic, as clinical meta-analyses suggest amygdala hyperreactivity in trauma-related disorders such as PTSD and BPD (Schulze et al., 2019), which could be driving the results found in the meta-analysis on early adversity. Similarly, the study on adversity timing by Zhu and colleagues (2019), which reported negative effects of early adversity on amygdala reactivity, did not investigate the influence of psychopathology. Study 2 not only found that higher adversity in early childhood was associated with lower amygdala reactivity, in line with Zhu and colleagues (2019), but also matches the previous meta-analytic finding of higher amygdala reactivity in PTSD. This study highlights the importance to include psychopathology in studies on early adversity as well as consider the moderating effect of timing.

A crucial question is what can be inferred from this differential amygdala reactivity during processing of threatening stimuli? In the literature, there has been a tendency to interpret higher amygdala reactivity as a stronger tendency to experience negative emotions, especially fear (Zhou et al., 2021). Study 3 suggests this interpretation is probably not warranted.

In contrast to the amygdala, multivariate brain patterns can predict affect and emotion with very high precision in a generalizable manner. This was confirmed in study 3. Most strikingly, there were no differences in the expression of neural signatures for affect and emotion in participants with trauma-related disorders and clinical emotion dysregulation during the most common fMRI paradigm to study threat processing: exposure to pictures of negative/threatening scenes. The evidence from this study is particularly strong, as it combined three samples using both frequentist and Bayesian mega-analysis, granting higher statistical precision compared to most previous studies. Bayesian analyses are often used to grant evidence of absence, i.e., the null hypothesis that an effect does not exist. All evidence-of-absence procedures have in common that they must form a reasonable alternative hypothesis of effect sizes (Rouder et al., 2009). In case of Bayesian analyses with default priors, the alternative hypothesis reflects a

reasonable distribution of effect sizes that can be expected in psychological science (Rouder et al., 2009). It always remains hard to falsify that a very small effect in the expected direction exists, but study 2 at least grants evidence *against* even a range of small effect sizes. Hence, even if amygdala hyperreactivity is meta-analytically confirmed in these disorders, the strongest current basis for inference from brain measures to emotions suggests no differences in brain-based emotional reactivity between these disorders in the same fMRI paradigms.

According to the theory of constructed emotion, emotions are multi-component phenomena (Barrett, 2017b). This is supported by the fact that only a large array of brain-wide cortical and subcortical regions together are sufficient to create precise and specific predictions of emotional events (Wager et al., 2015). The amygdala is usually still an integral part of emotion networks, but does not distinguish well between discrete emotions. This raises the question what it means if the amygdala—but not brain signatures of emotions—show differences between healthy controls and people with trauma-related disorders characterized by emotion dysregulation.

The amygdala has long been posited to be more broadly involved in the preferential processing of salient stimuli and modulates activity in sensory brain regions (Cunningham & Brosch, 2012; Ousdal et al., 2008). It also elicits peripheral allostatic responses through efferent connections via the basal nucleus of the stria terminalis, the hypothalamus, and the periaqueductal grey (Keifer et al., 2015; Kleckner et al., 2017). Consequently, the amygdala is a good predictor of physiological arousal, but not subjective emotions (Inman et al., 2018; Taschereau-Dumouchel et al., 2019). This gives rise to possible interpretations concerning the dissociation of findings for the amygdala and neural signatures of emotion: If emotions are multi-component processes, involving attention, physiology, and subjective experience, the amygdala is most likely to reflect the first two components. Both the two-factor theory of emotion (Schachter & Singer, 1962) and the theory of constructed emotion (Barrett, 2017b) posit that without emotional attributions for stimuli and context, neither changes in attention nor peripheral physiology

will lead to a conscious emotional experience. Such emotional attributions might lack in artificial laboratory contexts, where participants are shown pictures of threatening scenes. Participants might be aware that pictures by themselves are not threatening, but dependent on the content of the pictures, participants with trauma-related disorders might still engage more physiological and attentional resources.

5.2 Limitations and Research Implications

While many limitations concerning specific studies have been already discussed in the individual chapters, there are some more general limitations, which also highlight opportunities for future research.

Sensitive Periods

Many neurodevelopmental theories propose the existence of sensitive periods in which the impact of environmental influences is particularly strong. The hypotheses concerning these periods are often grounded in evolutionary theories (Ellis et al., 2022), normative brain development (Lupien et al., 2009), or information theoretic accounts (Frankenhuis & Walasek, 2020). Studies which target their identification, like studies 1 and 2, aim to test whether effect sizes differ quantitatively or qualitatively dependent on the timing of exposure to adversity. Nevertheless, such effect size differences could also be due to primarily non-biological factors. Study 2 showed that the probability to experience adversity is not uniformly distributed across childhood and adolescence. The same observation has been made in similar studies (Herzog et al., 2020; Teicher et al., 2018). If the probability to experience adverse events differs by age, this might affect effect sizes for statistical reasons. For example, if there is a relatively low probability to experience adversity in a given life year, this might lead to a skewed distribution of ACE scores with low variance for that year. This, in turn, might attenuate effect sizes, given the appearance of a relatively insensitive period. In this case, apparent sensitive periods would emerge due to societal rather than biological factors. Similarly, when a person discloses they

have been hit by a parent in a questionnaire or interview, this act of violence could have very different severity and implications dependent on that person's age, without invoking complex biological explanations.

In future research, biologically based hypotheses might be tested more rigorously if sociological, statistical, and contextual factors are controlled, but also if hypothesized periods are strongly guided by basic biological processes. The life-cycle model attempts this by proposing that brain regions still under development are particularly prone to adversity-effects (Lupien et al., 2009). For the hippocampus, this is a relatively short period in the first two life years. Generally, a more precisely stated hypothesis is more falsifiable. As a result, it can be clearly stated this particularly hypothesis is currently not supported by human neuroimaging evidence: In women, potential sensitive periods have only been found for early adolescence, while the earlier sensitive periods found in men extended well beyond the proposed phase of accelerated hippocampal neurodevelopment (Herzog et al., 2020; Teicher et al., 2018). In contrast, the proposed sensitive periods for the amygdala are so large that falsifying this hypothesis is extremely difficult. Similarly, the hypothesis that changes are experience-expectant (rather than experience-dependent) is strengthened by positing time windows as precisely as possible. In general, deriving predictions for sensitive periods from well-researched biological mechanisms makes it more likely that confirmatory findings reflect biological rather than societal influences. Regardless of the factors creating apparent sensitive periods in data patterns, studies 1 and 2 have shown that neglecting timing as a factor in biological psychiatry studies can lead to imprecise or even wrong interpretations of neural markers, especially for amygdala structure and function.

Causality

All three studies are cross-sectional in nature. Especially studies 1 and 2 rely on retrospective reports of childhood adversity. The effect of adversity is assumed to be causal, which cannot be strictly tested outside of natural experiments (e.g., adotoption studies; Rutter et al.,

2012). The influential causal theory by Judea Pearl posits that aiming to infer causality is necessary in most areas of empirical research (Pearl, 2009). Such causal inference can be valid even in cross-sectional designs, if it rests on correct assumptions, which must be transparently communicated and subject to theoretical critique (Grosz et al., 2020).

One causal assumption in the summarized studies is that self-reported adversity precedes the outcome of interest (e.g., amygdala volume), which is likely to be the case. Nevertheless, both self-reported adversity and amygdala features might share a common cause, including genetic or familial confounds. For example, if lower amygdala volumes are a feature of a mental disorder, and further that disorder is transgenerationally transmitted and increases the risk for childhood maltreatment by the affected parent, then a spurious correlation between maltreatment and amygdala features would emerge. Still, there is an established neuroendocrine theory concerning how brain changes in the amygdala can be causally influenced by adverse experiences through glucocorticoid feedback loops (Lupien et al., 2009). Causal assumptions are also partially supported by the observation of larger amygdala volumes in both trauma-exposed adulthood samples in study 1. Here, larger brain volumes in traumatized individuals cannot be explained by the confounding effect of psychopathology, as this effect was also apparent in healthy but trauma-exposed individuals. Genetic or socioeconomic confounders that predispose to adulthood trauma and larger amygdala volumes might still be a possible explanation but would need to accommodate the differential effects in the childhood and adulthood sample of study 1 (i.e., smaller versus larger volumes compared to their healthy trauma-naïve reference group).

Retrospective reports are also subject to response biases, for example mood-congruent memory effects (Gaddy & Ingram, 2014). In theory, amygdala aberrations might at least partially reflect such response biases (Ramel et al., 2007), affecting the causal assumption of temporal order. Still, if these response biases are a systematic part of mental disorders, this would

again not be easily reconciled with the results from studies 1 and 2 for the same reasons discussed in the previous paragraph.

The low concordance between prospective and retrospective measures of adversity raises essential questions concerning optimal measurement strategies of adverse experiences (Baldwin et al., 2019). Prospective measures often consist of official records, likely only capturing a subset of very severe environments, and might be preferable for the comparison of extreme groups. In contrast, assessing the effects of adversity on a continuous scale likely offers important complementary information, e.g., on nonlinear effects. Here, subjective self-reports are still the preferential mode of measurement. The dimensional assessment of adversity was crucial in study 2 to identify opposite effects of adversity and psychopathology.

Generalizability

All studies only included female participants. Focusing on female participants likely helps increase statistical precision by reducing systematic variance introduced by gender, but on the cost of untested generalizability to male samples. An easy suggestion for future research is to repeat the analyses reported here on male samples, but generalizability might also be addressed more broadly by a different approach: While the three studies used mainly categorical conceptualizations of mental disorders, assigning labels like “PTSD” and “BPD”, clinical research is increasingly moving towards dimensional taxonomies of psychopathology based on fundamental traits and processes (Clark et al., 2017; Kotov et al., 2017; Kozak & Cuthbert, 2016). Reasons for this are the large comorbidities between and marked heterogeneity within mental disorders, the negligence of subthreshold phenomena, as well as etiological multi- and equifinality (Clark et al., 2017). Gender is just one factor that can introduce heterogeneity in symptom presentations within a diagnostic category. Hence, generalizability might not only be aided by the inclusion of male participants, but more fundamentally by decomposing trauma- and affect-related disorders into their underlying dimensions. This allows testing which individual dimensions, behaviors, and processes map most strongly on brain measures of interest

(e.g., amygdala responses). If a stable and specific association with a clinical dimension is found, this makes generalizability more likely across a broader range of selection factors beyond gender. Still, this suggestion would only address the generalizability of brain-psychopathology associations. Adverse experiences might still have different associations with brain measures, for example, due to hormonal or cultural influences (Chaloner & Greenwood-Van Meerveld, 2013; Shear et al., 2007).

Another layer of generalizability is added when focusing on task-based fMRI. The tasks in studies 2 and 3 target the processing of threatening stimuli but cover merely one possible paradigm that can be used to study this construct. Generalizability affords to look at different operationalizations to warrant inference to the target construct as a whole (Čeko et al., 2022). For example, both a stroop test and a specifically developed clinical questionnaire can be said to measure the construct *impulsivity*, but might be relatively unrelated with each other, as they might target very different facets (Strasser et al., 2016; Yarkoni, 2020). Construct validity of brain measures from different tasks will be an important challenge for future studies (Enkavi & Poldrack, 2020). For activity in single regions like the amygdala this is especially complicated by its low test-retest reliability (Elliott et al., 2020): If the correlation of amygdala activity with itself at a different time point is very low, its correlation with itself at different time points in different experimental tasks must be extremely low (Noble et al., 2021). Study 3 showed that even when participants perform three matched runs of an fMRI tasks in the same session, the average amygdala response of a participant differs greatly between runs, as indicated by low internal consistency. Descriptively, study 3 also suggested that correlations between block designs might be higher than between block and event-related designs. This could mean that even very similar tasks, which only differ in stimulus timings, have limited convergent validity.

Study 3 also demonstrated much stronger internal consistency for multivariate signatures than for the amygdala ROI. Similar observations have been made recently for test-retest

reliability (Han et al., 2022). Nevertheless, multivariate signatures at least partly gain their improved reliability through massive averaging over large parts of the brain for the price of lost spatial specificity. It will still remain of interest how regions like the amygdala, which are subsumed in many of these signatures, work together to create mental states and traits. Here, structural equation modelling might be a viable option for future research.

Structural equation models can be used to decompose measured signals into hypothetical latent true score variables and random noise (Steyer et al., 1999). These latent true scores, in turn, can be correlated to external variables (e.g., depression scores) to produce larger noise-disattenuated correlations (Hancock, 1997). Especially when such a latent factor is modelled from different tasks which all capture the same construct, both sensitivity and generalizability of results might benefit greatly.

From this line of reasoning, another challenge emerges: The design of suitable fMRI tasks which target clinically meaningful concepts. Most fMRI tasks currently used in clinical research were adapted from basic research (Elliott et al., 2020). Therefore, they were often not designed with clinical reasoning in mind. They are also prone to the reliability paradox, which describes the fact that tasks which elicit few individual differences are particularly suited for research on basic within-person processes, but not suited to investigate associations and differences *between* people (Hedge et al., 2018).

Theory-driven approaches in computational psychiatry might be a particularly fruitful path for the improvement of fMRI tasks (Huys et al., 2016). In this approach, researchers aim to develop mathematical models that predict (and are hypothesized to generate) observed task-related data. Parameters of the mathematical model can have psychologically meaningful interpretations, for example, the learning rate in Rescorla-Wagner models for classical conditioning. If clinical and healthy groups differ in task behavior, this should be reflected in differences of model parameters. These model parameters, in turn, might be better correlates of brain measures than observed behavior.

Using the Brain to Understand the Mind

Study 3 highlighted many of the challenges when inferring mental states and traits from brain data: Valid reverse inference is only possible when brain measures are sensitive *and* specific. This is currently not the case for the amygdala, where several competing accounts exist, many suggesting the amygdala has a very broad function (i.e., low specificity). Hence, a stronger basic theory of the amygdala in stimulus processing and allostasis is necessary to make significant effects more meaningful for clinical practice. So far, only multivariate neural signatures that aggregate data from large parts of the brain have fulfilled the precision criteria of reverse inference in a satisfactory manner. Still, the multivariate approach is facing several challenges as well. First, neural signatures must be validated well, as they might be prone to confounds of the task used for building them (Kohoutová et al., 2020). A recent study showed that different tasks which elicit negative affect can be decomposed in task-specific and task-general patterns, with the latter being more likely to provide a strong fundament for psychological interpretations concerning negative affect (Čeko et al., 2022).

Second, another recent study has shown that for the same decoding task predictive accuracy can be extremely similar for different brain patterns (Jabakhanji et al., 2022). This casts some doubt on the simple spatial interpretability of the brain regions that together constitute a neural signature. It also raises more fundamental questions concerning how mental states are generated by the brain: The classic brain mapping approach aims to disaggregate the brain into modules, which implement different aspects of a mental event. For example, emotion is viewed as a multi-component phenomenon, consisting of appraisals, physiological arousal, behavioral tendencies, and subjective experiences. Therefore, it seems plausible that complex emotion patterns in the brain can be decomposed into individual (sub-)regions which are responsible for a respective component. Such a decomposition of emotion patterns would be extremely valuable to better understand mental disorders. For example, some studies suggest that amygdala activity

might be important for physiological arousal, while other regions were more important for conscious emotional valuations (LeDoux, 2012; LeDoux & Pine, 2016; Taschereau-Dumouchel et al., 2019). Distinguishsing these facets on a neural level might improve our understanding of clinical phenomena where single facets or their interactions are impaired (e.g., dissociation or alexithymia).

A contrasting view posits that complex brain states can only be understood on a system level (Pessoa, 2017). Here, the function of no single region can be understood without its network interactions with other regions. Cognition and emotion become emergent properties of the brain that cannot be explained by the sum of their parts. Yet another explanation for the difficult spatial interpretability of neural signatures is the idea that the brain is a *degenerate system*, where multiple regions can implement the same computation, making the localization of an emotion to only one single region futile (Barrett, 2017b).

A third challenge for multivariate neural signatures are individual differences. Study 3 did not indicate any differences in affective signatures between women with and without clinical emotion dysregulation. There might be many reasons for this result, such as a limited ecological validity of the experimental task. Still, neural signatures generally perform worse when predicting between-person differences, compared to within-person differences (Jabakhanji et al., 2022). This suggests the existence of between-person confounds that must be identified and controlled to increase the precision of between-person fMRI. Here, a very important factor that receives increasing attention is spatial heterogeneity between individuals: Even if there is a specific voxel in each individual that is dedicated to a task feature, this voxel would not necessarily be at exactly the same brain coordinate for everyone. This heterogeneity has been shown for representations of painful stimuli in the PFC, while representations in somatosensory regions were more similar between individuals (Kohoutová et al., 2022). Hyperalignment is a promising new method which aligns brain voxels between people according to their function (e.g., by leveraging complex connectivity patterns while watching a movie; Haxby et al., 2020).

This technique can profoundly increase effect sizes of brain-behavior associations but is yet underused in clinical studies.

Dissociation

Both studies 2 and 3 contained surprising findings concerning brain function: Study 2 revealed a negative effect of adversity on amygdala reactivity, while study 3 provided evidence against theoretic associations between emotion dysregulation and affective neural signatures. However, both studies did not test for a crucial confound that might explain counterintuitive physiological findings in trauma-related disorders: Dissociation.

Dissociation can be defined as a disconnect from present sensory experiences or an inability to access information and control mental functions that would usually be available (Carlson et al., 2012). It is especially common in trauma-related disorders such as PTSD and people who experienced childhood maltreatment (Vonderlin et al., 2018). Hence, childhood adversity can lead not only to hyperarousal, but also to a dampening of experience, potentially explaining the negative results of study 3. Barnow and colleagues (2012) demonstrated such an effect of dissociation for skin conductance response in BPD patients by collecting state measures of dissociation during an experimental task. Such real-time assessments of *state* dissociation might be a particularly effective approach as *trait* measures of dissociation and hyperarousal are highly correlated, suggesting that both are present at different time points in the same individuals (Carlson et al., 2012). Therefore, future studies should control for the time-dependent effects of dissociation and hyperarousal when investigating brain function in regions related to salience processing and allostasis.

5.3 Clinical implications

The translation of biological findings to clinical practice can occur on multiple levels, including psychoeducation, nosology, therapy, and prediction, which I will discuss in turn.

Psychoeducation

Substantial parts of the psychiatric research community and the broad public view mental disorders as disorders of the brain (Corrigan & Watson, 2004; Schomerus et al., 2006). While the validity and consequences of this perspective are still heavily debated (e.g., Banner, 2013), it is already part of therapeutic practice in the form of biological models in psychoeducation. For example, BPD patients are often educated on the apparent role of the PFC and the limbic system in the pathophysiology of their disorders (Linehan, 1993). Biological explanations can affect how patients deal with their disorders and, as a result, therapeutic outcomes (Lebowitz, 2019). Therefore, from an ethical perspective, basic biological psychiatry research has an obligation to build pathophysiological models that strike a balance between being sufficiently simple and communicable, while also being sufficiently valid for a given patient.

All three studies presented here demonstrate that while the amygdala remains an important target region for research on trauma- and stress-related disorders, its clinical role is still unclear. Study 1 demonstrated that the direction of changes in amygdala structure can differ depending on features of the adverse experience, such as developmental timing and its confounds. Moreover, in the adulthood sample, even trauma-exposed healthy individuals showed similar aberrations as the PTSD group. While there is more research to be done, both observations speak against the validity of simple explanations in the form of: “Smaller amygdala volumes explain clinical phenomenon X”.

At first glance, study 2 has more clear implications for pathophysiology models, namely: As expected, people with PTSD have larger amygdala responses to threatening stimuli. Still, as amygdala reactivity was *negatively* associated with trauma severity, which in turn increases the risk of PTSD, these effects can cancel each other. As a result, a patient with PTSD

and high trauma severity could exhibit amygdala reactivity to threatening stimuli similar to those found in healthy controls. Factors like dissociation and subthreshold symptoms in healthy controls might help resolve this ambiguity in future studies, but until then, study 2 suggests that knowing a person's amygdala reactivity can currently not be safely used to explain clinical phenomena without controlling for type and timing of adverse experiences. This is further supported by study 3: Often, amygdala activity during threat-processing has been used to explain emotional hyperreactivity and hyperarousal in trauma-related disorders (Patel et al., 2012; Sicorello & Schmahl, 2021). This explanation is limited by several findings concerning the relative domain generality of the amygdala and the main finding of study 3: Neural signatures with relatively high precision and interpretability do not show the proposed effects of affective hyperreactivity in BPD and cPTSD on a brain basis. Therefore, practitioners should be cautious when providing patients with simple biological explanations of complex affective phenomena.

Nosology

Teicher and colleagues (2021) argue that childhood maltreatment should become a distinct nosological entity as it is associated with different biological correlates, symptom presentations, and treatment implications within disorders. This is partly supported by studies 1 and 2. Study 1 showed different effects for people with typical childhood versus adulthood trauma. In theory, effects could also be explained by non-linear effects of severity, duration, multiplicity or type. In practice, these confounding factors often co-occur as a correlated cluster in maltreated individuals. This highlights the importance of this finding for a large patient group, despite the limited internal validity to attribute these effects to timing specifically. Similarly, study 2 suggests that the biology of psychopathological categories cannot be understood without controlling for the effect of early adversity.

Therapy

Mental disorders can be viewed, researched, and treated on several different levels, including social, psychological, and biological interventions. Currently, the most promising biological pathways towards better treatment are psychotropic medication, (non-) invasive brain stimulation (Drobisz & Damborská, 2019; Polanía et al., 2018), and neurofeedback (Paret & Hendler, 2020). The long-term success of new interventions in these areas becomes much more likely if they are based on good biological theories of mental disorders. If we do not want to rely on serendipity or trial-and-error, as has historically often been the case in the discovery of new psychotropic medication (Cobb, 2020), we have to ask which biological entities pharmacological agents, brain stimulation, or neurofeedback should target.

Currently, the amygdala is an important target in neurofeedback for trauma- and stress-related disorders (Linhartová et al., 2019; Zaehringer et al., 2019). Similarly, a recent pharmacological trial focused on the potential of the antidepressant citalopram to reduce affective symptoms in BPD by regulating amygdala function (Paret et al., 2021). In the long run, such endeavors are more likely to succeed if we understand the complex role of the amygdala in these disorders. Furthermore, through ecologically valid tasks and dimensional approaches to psychopathology, brain-wide neural signatures might still turn out to be better biological descriptors of mental disorders than single regions, representing better targets for biological interventions like neurofeedback (Woo et al., 2017).

Prediction

Machine learning has seen an unparalleled advent in biological psychiatry in recent years, promising models for precision medicine to improve the diagnosis and treatment-allocation in mental disorders without the need for a complete theory of their etiology and pathophysiology. This innovation has led to promising but also sobering results: Even complex brain

markers only led to insufficient diagnostic precision (Marek et al., 2022; Schulz et al., 2022), while large-scale trials predicting psychiatric treatment outcomes are still needed.

Machine learning models can benefit greatly from human guidance based on domain knowledge. This pertains to the choice of a suitable algorithm, but also feature selection: If a machine learning model is fed a smaller number of reliable and meaningful predictors, it is more likely to succeed (Khalid et al., 2014). The studies presented here show that a model of the relation between psychopathology and the brain is likely incomplete if the influence of adversity and its timing is neglected. Incorporating such insights from basic research can have great impact on clinical prediction.

Summary

Early adversity is a major etiological factor for the understanding of trauma- and stress-related disorders. A large body of research points towards changes in brain volume and function following stressful events, especially for the amygdala and the hippocampus. Still, many boundary conditions of these effects and their precise relation to clinical phenomena are unexplored. In recent years, neurodevelopmental timing emerged as a potential moderator of adversity-contingent brain changes in limbic regions.

This dissertation addresses the role of adversity timing, psychopathology, and reverse inference in the neurobiology of trauma- and stress related mental disorders. Study 1 tested structural brain changes in 155 women screened for childhood and adulthood trauma as well as posttraumatic stress disorder (PTSD) versus healthy trauma-exposed and trauma-naïve controls. The data was pooled from two separate studies at the same facility and tested eight regions of interest identified in a previous meta-analysis, with emphasis on amygdala and hippocampus. The results suggest that effects of traumatic experiences on amygdala volume might differ between typical instances of childhood and adulthood trauma: In the childhood sample with PTSD amygdala volumes were smaller compared to trauma-naïve healthy controls; in both adulthood samples with trauma-exposure amygdala volumes were *larger* compared to trauma-naïve healthy controls. These findings might suggest that structural changes in the amygdala could occur in response to both child- and adulthood trauma and are apparent even in healthy individuals exposed to trauma during adulthood. These results highlight the relevance of trauma-timing as a moderator. Importantly, the timing effects were confounded by other trauma characteristics, which often coincide with childhood maltreatment, such as type, multiplicity, and duration. Nevertheless, the qualitatively different effects found in both samples caution against simple clinical interpretations of structural aberrations in the amygdala, while corroborating their association to adverse experiences.

Study 2 expanded previous structural findings to amygdala *function* while accounting for the role of PTSD. Sixty trauma-exposed women (34 PTSD, 26 healthy) were shown pictures of threatening scenes during fMRI and underwent comprehensive retrospective interviews for early adversity at a time resolution of single years. The study confirmed the role of developmental timing as a moderator for the effect of adversity on amygdala reactivity to threatening stimuli. Moreover, study 2 revealed opposite effects of adversity exposure and psychopathology, highlighting similar interpretational caveats for amygdala function as study 1 revealed for structure.

Study 3 addressed the ambiguous interpretation of regional functional brain measures by employing neural signatures previously developed to be highly sensitive *and* specific to affective processes. A mega-analysis of three studies was conducted, comprising 192 women (49 Borderline Personality Disorder, 62 complex PTSD, 81 healthy controls), using both frequentist and Bayesian multilevel analyses. Both patient groups are characterized by an extremely high prevalence of childhood maltreatment as well as emotion dysregulation on a psychological level. As in study 2, all participants were shown pictures of threat-related scenes during fMRI, which is among the most common tasks to probe affective processing in mental disorders. The neural signatures distinguished extremely well between negative and neutral pictures on a within-person level. In contrast, there was evidence against even small group differences in the hypothesized direction, meaning patients did not exhibit higher affective reactivity on a brain basis, as confirmed by Bayesian analyses and confidence intervals.

Taken together, the three studies confirm an association between early adversity and both amygdala structure and function. Still, they caution against simple clinical interpretations in terms of affective symptoms and emphasize the importance to incorporate timing as a moderator. In future studies, a focus on dissociation and novel tasks designed to address specific dimensional clinical phenomena might be promising additions to the line of research presented here.

References

Altmann, A., Toloşi, L., Sander, O., & Lengauer, T. (2010). Permutation importance: A corrected feature importance measure. *Bioinformatics*, *26*(10), 1340–1347. https://doi.org/10.1093/bioinformatics/btq134

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* (Vol. 1). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890423349

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th ed.* (5th ed.). American Psychiatric Association.

Andersen, S. L., Tomada, A., Vincow, E. S., Valente, E., Polcari, A., & Teicher, M. H. (2008). Preliminary Evidence for Sensitive Periods in the Effect of Childhood Sexual Abuse on Regional Brain Development. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *20*(3), 292–301. https://doi.org/10.1176/jnp.2008.20.3.292

Baldwin, J. R., Reuben, A., Newbury, J. B., & Danese, A. (2019). Agreement between prospective and retrospective measures of childhood maltreatment: A systematic review and meta-analysis. *JAMA Psychiatry*, *76*(6), 584–593. https://doi.org/10.1001/jamapsychiatry.2019.0097

Ball, J. S., & Links, P. S. (2009). Borderline personality disorder and childhood trauma: Evidence for a causal relationship. *Current Psychiatry Reports*, *11*(1), 63–68. https://doi.org/10.1007/s11920-009-0010-4

Banner, N. F. (2013). Mental disorders are not brain disorders. *Journal of Evaluation in Clinical Practice*, *19*(3), 509–513. https://doi.org/10.1111/jep.12048

Barnow, S., Limberg, A., Stopsack, M., Spitzer, C., Grabe, H. J., Freyberger, H. J., & Hamm, A. (2012). Dissociation and emotion regulation in borderline personality disorder. *Psychological Medicine*, *42*(4), 783–794. https://doi.org/10.1017/S0033291711001917

Barondes, S. H. (1990). The biological approach to psychiatry: History and prospects. *Journal of Neuroscience*, *10*(6), 1707–1710. https://doi.org/10.1523/jneurosci.10-06-01707.1990

Barrett, L. F. (2017a). *How emotions are made: The secret life of the brain*. Houghton-Mifflin-Harcourt.

Barrett, L. F. (2017b). The theory of constructed emotion: an active inference account of interoception and categorization. *Social Cognitive and Affective Neuroscience*, *12*(1), 1–23. https://doi.org/10.1093/scan/nsw154

Barsegyan, A., McGaugh, J. L., & Roozendaal, B. (2014). Noradrenergic activation of the basolateral amygdala modulates the consolidation of object-in-context recognition memory. *Frontiers in Behavioral Neuroscience*, *8*(MAY), 1–8. https://doi.org/10.3389/fnbeh.2014.00160

Beck, A. T., Steer, R. A., & Brown, G. K. (2009). *BDI-II: Beck Depressions-Inventar: Revision (Deutsche Ausgabe von M. Hautziger, F. Keller und C. Kühner)* (2nd Editio). Pearson.

Bernstein, D. P., Fink, L., Handelsman, L., & Foote, J. (1994). Childhood Trauma Questionnaire (CTQ). *APA PsycTests.*, 297–298. https://doi.org/10.1037/t02080-000

Bernstein, David P. (1998). *Childhood Trauma Questionnaire: A Retrospective Self-report : Manual*. Psychological Corporation.

Bernstein, David P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., & Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse and Neglect*, *27*(2), 169–190. https://doi.org/10.1016/S0145-2134(02)00541-0

Bick, J., & Nelson, C. A. (2016). Early adverse experiences and the developing brain. *Neuropsychopharmacology*, *41*(1), 177–196. https://doi.org/10.1038/npp.2015.252

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress*, *8*(1), 75–90. https://doi.org/10.1002/jts.2490080106

Bohus, M., Kleindienst, N., Hahn, C., Müller-Engelmann, M., Ludäscher, P., Steil, R., Fydrich, T., Kuehner, C., Resick, P. A., Stiglmayr, C., Schmahl, C., & Priebe, K. (2020). Dialectical Behavior Therapy for Posttraumatic Stress Disorder (DBT-PTSD) Compared With Cognitive Processing Therapy (CPT) in Complex Presentations of PTSD in Women Survivors of Childhood Abuse. *JAMA Psychiatry*, *77*(12), 1235. https://doi.org/10.1001/jamapsychiatry.2020.2148

Bohus, M., Kleindienst, N., Limberger, M. F., Stieglitz, R.-D., Domsalla, M., Chapman, A. L., Steil, R., Philipsen, A., & Wolf, M. (2009). The Short Version of the Borderline Symptom List (BSL-23): Development and Initial Data on Psychometric Properties. *Psychopathology*, *42*(1), 32–39. https://doi.org/10.1159/000173701

Bohus, M., Schmahl, C., Fydrich, T., Steil, R., Müller-Engelmann, M., Herzog, J., Ludäscher, P., Kleindienst, N., & Priebe, K. (2019). A research programme to evaluate DBT-PTSD, a modular treatment approach for Complex PTSD after childhood abuse. *Borderline Personality Disorder and Emotion Dysregulation*, *6*(1), 1–16. https://doi.org/10.1186/s40479-019-0099-y

Bortolla, R., Cavicchioli, M., Fossati, A., & Maffei, C. (2020). Emotional reactivity in borderline personality disorder: Theoretical considerations based on a meta-analytic review of laboratory studies. *Journal of Personality Disorders*, *34*(1), 64–87. https://doi.org/10.1521/pedi_2018_32_382

Boscarino, J. A. (2006). Posttraumatic stress disorder and mortality among U.S. Army veterans 30 years after military service. *Annals of Epidemiology*, *16*(4), 248–256. https://doi.org/10.1016/j.annepidem.2005.03.009

Brandt, A., & Mueller, E. M. (2022). ScienceDirect Negative affect related traits and the chasm between self-report and neuroscience. *COBEHA*, *43*, 216–223. https://doi.org/10.1016/j.cobeha.2021.11.002

Brendel, G. R., Stern, E., & Silbersweig, D. A. (2005). Defining the neurocircuitry of borderline

personality disorder: Functional neuroimaging approaches. *Development and Psychopathology*, *17*(4), 1197–1206. https://doi.org/10.1017/S095457940505056X

Brett, M., Anton, J., Valabregue, R., & Poline, J. (2002). Region of interest analysis using an SPM toolbox [Abstract presented at the 8th International Conference on Functional Mapping of the Human Brain, June2-6, 2002, Senda Japan]. *Neuroimage*, *16*(2).

Brewin, C. R., Cloitre, M., Hyland, P., Shevlin, M., Maercker, A., Bryant, R. A., Humayun, A., Jones, L. M., Kagee, A., Rousseau, C., Somasundaram, D., Suzuki, Y., Wessely, S., van Ommeren, M., & Reed, G. M. (2017). A review of current evidence regarding the ICD-11 proposals for diagnosing PTSD and complex PTSD. *Clinical Psychology Review*, *58*(September), 1–15. https://doi.org/10.1016/j.cpr.2017.09.001

Brewin, C. R., Gregory, J. D., Lipton, M., & Burgess, N. (2010). Intrusive images in psychological disorders: Characteristics, neural mechanisms, and treatment implications. *Psychological Review*, *117*(1), 210–232. https://doi.org/10.1037/a0018113

Bromis, K., Calem, M., Reinders, A. A. T. S., Williams, S. C. R., & Kempton, M. J. (2018). Meta-Analysis of 89 Structural MRI studies in posttraumatic stress disorder and comparison with major depressive disorder. *American Journal of Psychiatry*, *175*(10), 989–998. https://doi.org/10.1176/appi.ajp.2018.17111199

Brown, D. W., Anda, R. F., Tiemeier, H., Felitti, V. J., Edwards, V. J., Croft, J. B., & Giles, W. H. (2009). Adverse Childhood Experiences and the Risk of Premature Mortality. *American Journal of Preventive Medicine*, *37*(5), 389–396. https://doi.org/10.1016/j.amepre.2009.06.021

Bryant, R. A., Felmingham, K. L., Malhi, G., Andrew, E., & Korgaonkar, M. S. (2019). The distinctive neural circuitry of complex posttraumatic stress disorder during threat processing. *Psychological Medicine*, *May*. https://doi.org/10.1017/S0033291719003921

Calem, M., Bromis, K., McGuire, P., Morgan, C., & Kempton, M. J. (2017). Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-

clinical and general population samples. *NeuroImage: Clinical, 14,* 471–479. https://doi.org/10.1016/j.nicl.2017.02.016

Callaghan, B. L., & Tottenham, N. (2016). The Stress Acceleration Hypothesis: Effects of early-life adversity on emotion circuits and behavior. *Current Opinion in Behavioral Sciences*, *7*, 76–81. https://doi.org/10.1016/j.cobeha.2015.11.018

Camalier, C. R., Scarim, K., Mishkin, M., & Averbeck, B. B. (2019). A Comparison of Auditory Oddball Responses in Dorsolateral Prefrontal Cortex, Basolateral Amygdala, and Auditory Cortex of Macaque. *Journal of Cognitive Neuroscience*, *31*(7), 1054–1064. https://doi.org/10.1162/jocn_a_01387

Carlson, E. B., Dalenberg, C., & McDade-Montez, E. (2012). Dissociation in posttraumatic stress disorder part I: Definitions and review of research. *Psychological Trauma: Theory, Research, Practice, and Policy*, *4*(5), 479–489. https://doi.org/10.1037/a0027748

Carpenter, R. W., & Trull, T. J. (2013). Components of emotion dysregulation in borderline personality disorder: A review. *Current Psychiatry Reports*, *15*(1), 335. https://doi.org/10.1007/s11920-012-0335-2

Čeko, M., Kragel, P. A., Woo, C.-W., López-Solà, M., & Wager, T. D. (2022). Common and stimulus-type-specific brain representations of negative affect. *Nature Neuroscience*, *25*(6), 760–770. https://doi.org/10.1038/s41593-022-01082-w

Chaloner, A., & Greenwood-Van Meerveld, B. (2013). Early Life Adversity as a Risk Factor for Visceral Pain in Later Life: Importance of Sex Differences. *Frontiers in Neuroscience*, *7*. https://doi.org/10.3389/fnins.2013.00013

Chang, L. J., Gianaros, P. J., Manuck, S. B., Krishnan, A., & Wager, T. D. (2015). A sensitive and specific neural signature for picture-induced negative affect. *PLoS Biology*, *13*(6), 1–28. https://doi.org/10.1371/journal.pbio.1002180

Clark, L. A., Cuthbert, B., Lewis-Fernández, R., Narrow, W. E., & Reed, G. M. (2017). Three Approaches to Understanding and Classifying Mental Disorder: ICD-11, DSM-5, and the

National Institute of Mental Health's Research Domain Criteria (RDoC). *Psychological Science in the Public Interest*, *18*(2), 72–145. https://doi.org/10.1177/1529100617727266

Cobb, M. (2020). *The idea of the brain*. Hachette UK.

Colich, N. L., Platt, J. M., Keyes, K. M., Sumner, J. A., Allen, N. B., & McLaughlin, K. A. (2020). Earlier age at menarche as a transdiagnostic mechanism linking childhood trauma with multiple forms of psychopathology in adolescent girls. *Psychological Medicine*, *50*(7), 1090–1098. https://doi.org/10.1017/S0033291719000953

Corrigan, P. W., & Watson, A. C. (2004). At Issue: Stop the Stigma: Call Mental Illness a Brain Disease. *Schizophrenia Bulletin*, *30*(3), 477–479. https://doi.org/10.1093/oxfordjournals.schbul.a007095

Costafreda, S. G., Brammer, M. J., David, A. S., & Fu, C. H. Y. (2008). Predictors of amygdala activation during the processing of emotional stimuli: A meta-analysis of 385 PET and fMRI studies. *Brain Research Reviews*, *58*(1), 57–70. https://doi.org/10.1016/j.brainresrev.2007.10.012

Cunningham, W. A., & Brosch, T. (2012). Motivational salience: Amygdala tuning from traits, needs, values, and goals. *Current Directions in Psychological Science*, *21*(1), 54–59. https://doi.org/10.1177/0963721411430832

D'Esposito, M., Deouell, L. Y., & Gazzaley, A. (2003). Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. *Nature Reviews Neuroscience*, *4*(11), 863–872. https://doi.org/10.1038/nrn1246

Dannlowski, U., Kugel, H., Huber, F., Stuhrmann, A., Redlich, R., Grotegerd, D., Dohm, K., Sehlmeyer, C., Konrad, C., Baune, B. T., Arolt, V., Heindel, W., Zwitserlood, P., & Suslow, T. (2013). Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. *Human Brain Mapping*, *34*(11), 2899–2909. https://doi.org/10.1002/hbm.22112

Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D.,

Domschke, K., Hohoff, C., Ohrmann, P., Bauer, J., Lindner, C., Postert, C., Konrad, C., Arolt, V., Heindel, W., Suslow, T., & Kugel, H. (2012). Limbic scars: Long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological Psychiatry*, *71*(4), 286–293. https://doi.org/10.1016/j.biopsych.2011.10.021

Daros, A. R., Zakzanis, K. K., & Ruocco, A. C. (2013). Facial emotion recognition in borderline personality disorder. *Psychological Medicine*, *43*(9), 1953–1963. https://doi.org/10.1017/S0033291712002607

Davidson, J. R. T., Book, S. W., Colket, J. T., Tupler, L. A., Roth, S., David, D., Hertzberg, M., Mellman, T., Beckham, J. C., Smith, R. D., Davison, R. M., Katz, R., & Feldman, M. E. (1997). Assessment of a new self-rating scale for post-traumatic stress disorder. *Psychological Medicine*, *27*(1), 153–160. https://doi.org/10.1017/S0033291796004229

de Aquino Ferreira, L. F., Queiroz Pereira, F. H., Neri Benevides, A. M. L., & Aguiar Melo, M. C. (2018). Borderline personality disorder and sexual abuse: A systematic review. *Psychiatry Research*, *262*(December 2017), 70–77. https://doi.org/10.1016/j.psychres.2018.01.043

Del Giudice, M., Ellis, B. J., & Shirtcliff, E. A. (2011). The Adaptive Calibration Model of stress responsivity. *Neuroscience and Biobehavioral Reviews*, *35*(7), 1562–1592. https://doi.org/10.1016/j.neubiorev.2010.11.007

DeYoung, C. G., Sassenberg, T. A., Abend, R., Allen, T., Beaty, R., Bellgrove, M., Blain, S. D., Bzdok, D., Chavez, R. S., Engel, S. A., & others. (2022). *Reproducible between-person brain-behavior associations do not always require thousands of individuals*.

Donegan, N. H., Sanislow, C. A., Blumberg, H. P., Fulbright, R. K., Lacadie, C., Skudlarski, P., Gore, J. C., Olson, I. R., McGlashan, T. H., & Wexler, B. E. (2003). Amygdala hyperreactivity in borderline personality disorder: Implications for emotional dysregulation. *Biological Psychiatry*, *54*(11), 1284–1293. https://doi.org/10.1016/S0006-

3223(03)00636-X

Drobinin, V., Van Gestel, H., Helmick, C. A., Schmidt, M. H., Bowen, C. V., & Uher, R. (2021). The Developmental Brain Age Is Associated With Adversity, Depression, and Functional Outcomes Among Adolescents. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 1–9. https://doi.org/10.1016/j.bpsc.2021.09.004

Drobisz, D., & Damborská, A. (2019). Deep brain stimulation targets for treating depression. *Behavioural Brain Research*, *359*, 266–273. https://doi.org/10.1016/j.bbr.2018.11.004

Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., Van Den Hout, M. A., & Baas, J. M. P. (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and Anxiety*, *32*(4), 239–253. https://doi.org/10.1002/da.22353

Durand, F., Isaac, C., & Januel, D. (2019). Emotional Memory in Post-traumatic Stress Disorder: A Systematic PRISMA Review of Controlled Studies. *Frontiers in Psychology*, *10*. https://doi.org/10.3389/fpsyg.2019.00303

Elliott, M. L., Knodt, A. R., Ireland, D., Morris, M. L., Poulton, R., Ramrakha, S., Sison, M. L., Moffitt, T. E., Caspi, A., & Hariri, A. R. (2019). What is the test-retest reliability of common task-fMRI measures? New empirical evidence and a meta-analysis. *BioRxiv*. https://doi.org/https://doi.org/10.1101/681700

Elliott, Maxwell L., Knodt, A. R., Ireland, D., Morris, M. L., Poulton, R., Ramrakha, S., Sison, M. L., Moffitt, T. E., Caspi, A., & Hariri, A. R. (2020). What Is the Test-Retest Reliability of Common Task-Functional MRI Measures? New Empirical Evidence and a Meta-Analysis. *Psychological Science*, *31*(7), 792–806. https://doi.org/10.1177/0956797620916786

Ellis, B. J., Sheridan, M. A., Belsky, J., & McLaughlin, K. A. (2022). Why and how does early adversity influence development? Toward an integrated model of dimensions of environmental experience. *Development and Psychopathology*, 1–25.

https://doi.org/10.1017/s0954579421001838

Elzinga, B., & Bremner, J. D. (2002). Are the neural substrates of memory the final common pathway in posttraumatic stress disorder (PTSD)? *Journal of Affective Disorders*, *70*(1), 1–17. https://doi.org/10.1016/S0165-0327(01)00351-2

Enkavi, A. Z., & Poldrack, R. A. (2020). Implications of the lacking relationship between cognitive task and self report measures for psychiatry. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/10.1016/j.bpsc.2020.06.010

Fawcett, T. W., & Frankenhuis, W. E. (2015). Adaptive explanations for sensitive windows in development. *Frontiers in Zoology*, *12*(1), 1–14. https://doi.org/10.1186/1742-9994-12-S1-S3

Foa, E. B., Cashman, L., Jaycox, L., & Perry, K. (1997). The validation of a self-report measure of posttraumatic stress disorder: The Posttraumatic Diagnostic Scale. *Psychological Assessment*, *9*(4), 445–451. https://doi.org/10.1037/1040-3590.9.4.445

Fonzo, G. A., Ramsawh, H. J., Flagan, T. M., Simmons, A. N., Sullivan, S. G., Allard, C. B., Paulus, M. P., & Stein, M. B. (2016). Early life stress and the anxious brain: Evidence for a neural mechanism linking childhood emotional maltreatment to anxiety in adulthood. *Psychological Medicine*, *46*(5), 1037–1054. https://doi.org/10.1017/S0033291715002603

Frankenhuis, W. E., & de Weerth, C. (2013). Does Early-Life Exposure to Stress Shape or Impair Cognition? *Current Directions in Psychological Science*, *22*(5), 407–412. https://doi.org/10.1177/0963721413484324

Frankenhuis, W. E., & Walasek, N. (2020). Modeling the evolution of sensitive periods. *Developmental Cognitive Neuroscience*, *41*(April 2019), 100715. https://doi.org/10.1016/j.dcn.2019.100715

Frias, A., Palma, C., Farriols, N., Gonzalez, L., & Horta, A. (2016). Anxious adult attachment may mediate the relationship between childhood emotional abuse and borderline personality disorder. *Personality and Mental Health*, *10*(4), 274–284.

https://doi.org/10.1002/pmh.1348

Friston, K. (2009). The free-energy principle: a rough guide to the brain? *Trends in Cognitive Sciences*, *13*(7), 293–301. https://doi.org/10.1016/j.tics.2009.04.005

Fydrich, T., Renneberg, B., Schmitz, B., & Wittchen, H. (1997). Strukturiertes Klinisches Interview für DSM-IV Achse II: Persönlichkeitsstörungen (SKID-II) [Structured clinical interview for DSM-IV. Axis II: Personality disorders]. In *Göttingen: Hogrefe*.

Gabard-Durnam, L. J., & McLaughlin, K. A. (2019). Do Sensitive Periods Exist for Exposure to Adversity? *Biological Psychiatry*, *85*(10), 789–791. https://doi.org/10.1016/j.biopsych.2019.03.975

Gaddy, M. A., & Ingram, R. E. (2014). A meta-analytic review of mood-congruent implicit memory in depressed mood. *Clinical Psychology Review*, *34*(5), 402–416. https://doi.org/10.1016/j.cpr.2014.06.001

Ganzel, B. L., Kim, P., Gilmore, H., Tottenham, N., & Temple, E. (2013). Stress and the healthy adolescent brain: Evidence for the neural embedding of life events. *Development and Psychopathology*, *25*(4pt1), 879–889. https://doi.org/10.1017/S0954579413000242

Gao, S., Calhoun, V. D., & Sui, J. (2018). Machine learning in major depression: From classification to treatment outcome prediction. *CNS Neuroscience and Therapeutics*, *24*(11), 1037–1052. https://doi.org/10.1111/cns.13048

Geoffroy, M.-C., Pinto Pereira, S., Li, L., & Power, C. (2016). Child Neglect and Maltreatment and Childhood-to-Adulthood Cognition and Mental Health in a Prospective Birth Cohort. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(1), 33-40.e3. https://doi.org/10.1016/j.jaac.2015.10.012

Georgopoulos, A. P., James, L. M., Christova, P., & Engdahl, B. E. (2018). A Two-Hit Model of The Biological Origin of Posttraumatic Stress Disorder (PTSD). *Journal of Mental Health & Clinical Psychology*, *2*(5), 9–14. http://www.ncbi.nlm.nih.gov/pubmed/6446559

Gianaros, P. J., Jennings, J. R., Sheu, L. K., Greer, P. J., Kuller, L. H., & Matthews, K. A.

(2007). Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. *NeuroImage*, *35*(2), 795–803. https://doi.org/10.1016/j.neuroimage.2006.10.045

Gianaros, P. J., Kraynak, T. E., Kuan, D. C.-H., Gross, J. J., McRae, K., Hariri, A. R., Manuck, S. B., Rasero, J., & Verstynen, T. D. (2020). Affective brain patterns as multivariate neural correlates of cardiovascular disease risk. *Social Cognitive and Affective Neuroscience*, *March*, 1–12. https://doi.org/10.1093/scan/nsaa050

Giesinger, I., Li, J., Takemoto, E., Cone, J. E., Farfel, M. R., & Brackbill, R. M. (2020). Association between Posttraumatic Stress Disorder and Mortality among Responders and Civilians following the September 11, 2001, Disaster. *JAMA Network Open*, *3*(2), 1–14. https://doi.org/10.1001/jamanetworkopen.2019.20476

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience*, *5*(11), 1242–1247. https://doi.org/10.1038/nn958

Giourou, E., Skokou, M., Andrew, S. P., Alexopoulou, K., Gourzis, P., & Jelastopulu, E. (2018). Complex posttraumatic stress disorder: The need to consolidate a distinct clinical syndrome or to reevaluate features of psychiatric disorders following interpersonal trauma? *World Journal of Psychiatry*, *8*(1), 12–19. https://doi.org/10.5498/wjp.v8.i1.12

Goldstein, D. S. (2010). Adrenal responses to stress. *Cellular and Molecular Neurobiology*, *30*(8), 1433–1440. https://doi.org/10.1007/s10571-010-9606-9

Gothard, K. M. (2020). Multidimensional processing in the amygdala. *Nature Reviews Neuroscience*, *21*(10), 565–575. https://doi.org/10.1038/s41583-020-0350-y

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood Adversities and Adult Psychiatric Disorders in the National Comorbidity Survey Replication I. *Archives of General Psychiatry*, *67*(2),

113. https://doi.org/10.1001/archgenpsychiatry.2009.186

Grosz, M. P., Rohrer, J. M., & Thoemmes, F. (2020). The Taboo Against Explicit Causal Inference in Nonexperimental Psychology. *Perspectives on Psychological Science*, *15*(5), 1243–1255. https://doi.org/10.1177/1745691620921521

Grummitt, L. R., Kreski, N. T., Kim, S. G., Platt, J., Keyes, K. M., & McLaughlin, K. A. (2021). Association of Childhood Adversity with Morbidity and Mortality in US Adults: A Systematic Review. *JAMA Pediatrics*. https://doi.org/10.1001/jamapediatrics.2021.2320

Han, X., Ashar, Y. K., Kragel, P., Petre, B., Schelkun, V., Atlas, L. Y., Chang, L. J., Jepma, M., Koban, L., Losin, E. A. R., Roy, M., Woo, C.-W., & Wager, T. D. (2022). Effect sizes and test-retest reliability of the fMRI-based neurologic pain signature. *NeuroImage*, *247*, 118844. https://doi.org/10.1016/j.neuroimage.2021.118844

Hancock, G. R. (1997). Correlationvalidity Coefficients Disattenuated for Score Reliability: A Structural Equation Modeling Approach. *Educational and Psychological Measurement*, *57*(4), 598–606. https://doi.org/10.1177/0013164497057004006

Hanson, J. L., Nacewicz, B. M., Sutterer, M. J., Cayo, A. A., Schaefer, S. M., Rudolph, K. D., Shirtcliff, E. A., Pollak, S. D., & Davidson, R. J. (2015). Behavioral problems after early life stress: Contributions of the hippocampus and amygdala. *Biological Psychiatry*, *77*(4), 314–323. https://doi.org/10.1016/j.biopsych.2014.04.020

Häuser, W., Schmutzer, G., Brähler, E., & Glaesmer, H. (2011). Maltreatment in Childhood and Adolescence. *Deutsches Ärzteblatt International*. https://doi.org/10.3238/arztebl.2011.0287

Haxby, J. V., Guntupalli, J. S., Nastase, S. A., & Feilong, M. (2020). Hyperalignment: Modeling shared information encoded in idiosyncratic cortical topographies. *ELife*, *9*, 1–26. https://doi.org/10.7554/eLife.56601

Heany, S. J., Groenewold, N. A., Uhlmann, A., Dalvie, S., Stein, D. J., & Brooks, S. J. (2018). The neural correlates of Childhood Trauma Questionnaire scores in adults: A meta-

analysis and review of functional magnetic resonance imaging studies. *Development and Psychopathology*, *30*(4), 1475–1485. https://doi.org/10.1017/S0954579417001717

Hedge, C., Powell, G., & Sumner, P. (2018). The reliability paradox: Why robust cognitive tasks do not produce reliable individual differences. *Behavior Research Methods*, *50*(3), 1166–1186. https://doi.org/10.3758/s13428-017-0935-1

Hein, T. C., & Monk, C. S. (2017). Research Review: Neural response to threat in children, adolescents, and adults after child maltreatment - a quantitative meta-analysis. *Journal of Child Psychology and Psychiatry*, *58*(3), 222–230. https://doi.org/10.1111/jcpp.12651

Hepp, J., Lane, S. P., Wycoff, A. M., Carpenter, R. W., & Trull, T. J. (2018). Interpersonal stressors and negative affect in individuals with borderline personality disorder and community adults in daily life: A replication and extension. *Journal of Abnormal Psychology*, *127*(2), 183–189. https://doi.org/10.1037/abn0000318

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: Hypothalamo-pituitary- adrenocortical axis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*(8), 1201–1213. https://doi.org/10.1016/j.pnpbp.2005.08.006

Herzog, J. I., Thome, J., Demirakca, T., Koppe, G., Ende, G., Lis, S., Rausch, S., Priebe, K., Müller-Engelmann, M., Steil, R., Bohus, M., & Schmahl, C. (2020). Influence of Severity of Type and Timing of Retrospectively Reported Childhood Maltreatment on Female Amygdala and Hippocampal Volume. *Scientific Reports*, *10*(1), 1–10. https://doi.org/10.1038/s41598-020-57490-0

Herzog, S., D'Andrea, W., DePierro, J., & Khedari, V. (2018). When stress becomes the new normal: Alterations in attention and autonomic reactivity in repeated traumatization. *Journal of Trauma & Dissociation*, *19*(3), 362–381. https://doi.org/10.1080/15299732.2018.1441356

Hothorn, T., Bühlmann, P., Dudoit, S., Molinaro, A., & Van der Laan, M. (2006). Survival

ensembles. *Biostatistics*, *7*(3), 355–373. https://doi.org/10.1093/biostatistics/kxj011

Huys, Q. J. M., Maia, T. V, & Frank, M. J. (2016). Computational psychiatry as a bridge from neuroscience to clinical applications. *Nature Neuroscience*, *19*(3), 404–413. https://doi.org/10.1038/nn.4238

Inman, C. S., Bijanki, K. R., Bass, D. I., Gross, R. E., Hamann, S., & Willie, J. T. (2018). Human amygdala stimulation effects on emotion physiology and emotional experience. *Neuropsychologia*, *February*, 106722. https://doi.org/10.1016/j.neuropsychologia.2018.03.019

Isele, D., Teicher, M. H., Ruf-Leuschner, M., Elbert, T., Kolassa, I. T., Schury, K., & Schauer, M. (2014). KERF - Ein Instrument zur umfassenden Ermittlung belastender Kindheitserfahrungen: Erstellung und psychometrische Beurteilung der deutschsprachigen MACE (Maltreatment and Abuse Chronology of Exposure) Scale. *Zeitschrift Fur Klinische Psychologie Und Psychotherapie*, *43*(2), 121–130. https://doi.org/10.1026/1616-3443/a000257

Jabakhanji, R., Vigotsky, A. D., Bielefeld, J., Huang, L., Baliki, M. N., Iannetti, G., & Apkarian, A. V. (2022). Limits of decoding mental states with fMRI. *Cortex*, *149*, 101–122. https://doi.org/10.1016/j.cortex.2021.12.015

Jacobs, R. H. A. H., Renken, R., Aleman, A., & Cornelissen, F. W. (2012). The amygdala, top-down effects, and selective attention to features. *Neuroscience & Biobehavioral Reviews*, *36*(9), 2069–2084. https://doi.org/10.1016/j.neubiorev.2012.05.011

Jarosz, A. F., & Wiley, J. (2014). What Are the Odds? A Practical Guide to Computing and Reporting Bayes Factors. *The Journal of Problem Solving*, *7*(1), 1–9. https://doi.org/10.7771/1932-6246.1167

Joëls, M., Karst, H., & Sarabdjitsingh, R. A. (2018). The stressed brain of humans and rodents. *Acta Physiologica*, *223*(2), 1–10. https://doi.org/10.1111/apha.13066

Joëls, Marian, Karst, H., Krugers, H. J., & Lucassen, P. J. (2007). Chronic stress: Implications

for neuronal morphology, function and neurogenesis. *Frontiers in Neuroendocrinology*, *28*(2–3), 72–96. https://doi.org/10.1016/j.yfrne.2007.04.001

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, *35*(1), 2–16. https://doi.org/10.1016/j.neubiorev.2009.10.002

Kalmar, J. H., Wang, F., Chepenik, L. G., Womer, F. Y., Jones, M. M., Pittman, B., Shah, M. P., Martin, A., Constable, R. T., & Blumberg, H. P. (2009). Relation between amygdala structure and function in adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(6), 636–642. https://doi.org/10.1097/CHI.0b013e31819f6fbc

Keding, T. J., Heyn, S. A., Russell, J. D., Zhu, X., Cisler, J., McLaughlin, K. A., & Herringa, R. J. (2021). Differential Patterns of Delayed Emotion Circuit Maturation in Abused Girls With and Without Internalizing Psychopathology. *American Journal of Psychiatry*, *178*(11), 1026–1036. https://doi.org/10.1176/appi.ajp.2021.20081192

Keifer, O. P., Hurt, R. C., Ressler, K. J., & Marvar, P. J. (2015). The Physiology of Fear: Reconceptualizing the Role of the Central Amygdala in Fear Learning. *Physiology*, *30*(5), 389–401. https://doi.org/10.1152/physiol.00058.2014

Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Benjet, C., Bromet, E. J., Cardoso, G., Degenhardt, L., de Girolamo, G., Dinolova, R. V., Ferry, F., Florescu, S., Gureje, O., Haro, J. M., Huang, Y., Karam, E. G., Kawakami, N., Lee, S., Lepine, J. P., Levinson, D., … Koenen, K. C. (2017). Trauma and PTSD in the WHO World Mental Health Surveys. *European Journal of Psychotraumatology*, *8*. https://doi.org/10.1080/20008198.2017.1353383

Khalid, S., Khalil, T., & Nasreen, S. (2014). A survey of feature selection and feature extraction techniques in machine learning. *2014 Science and Information Conference*, 372–378. https://doi.org/10.1109/SAI.2014.6918213

Khan, A., McCormack, H. C., Bolger, E. A., McGreenery, C. E., Vitaliano, G., Polcari, A., & Teicher, M. H. (2015). Childhood maltreatment, depression, and suicidal ideation: Critical importance of parental and peer emotional abuse during developmental sensitive periods in males and females. *Frontiers in Psychiatry*, *6*(MAR), 1–30. https://doi.org/10.3389/fpsyt.2015.00042

Kleckner, I. R., Zhang, J., Touroutoglou, A., Chanes, L., Xia, C., Simmons, W. K., Quigley, K. S., Dickerson, B. C., & Feldman Barrett, L. (2017). Evidence for a large-scale brain system supporting allostasis and interoception in humans. *Nature Human Behaviour*, *1*(5). https://doi.org/10.1038/s41562-017-0069

Klinitzke, G., Romppel, M., Häuser, W., Brähler, E., & Glaesmer, H. (2012). Die deutsche Version des Childhood Trauma Questionnaire (CTQ) – psychometrische Eigenschaften in einer bevölkerungsrepräsentativen Stichprobe. *PPmP - Psychotherapie · Psychosomatik · Medizinische Psychologie*, *62*(02), 47–51. https://doi.org/10.1055/s-0031-1295495

Koenen, K. C., Ratanatharathorn, A., Ng, L., McLaughlin, K. A., Bromet, E. J., Stein, D. J., Karam, E. G., Meron Ruscio, A., Benjet, C., Scott, K., Atwoli, L., Petukhova, M., Lim, C. C. W., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Bunting, B., Ciutan, M., De Girolamo, G., … Kessler, R. C. (2017). Posttraumatic stress disorder in the World Mental Health Surveys. *Psychological Medicine*, *47*(13), 2260–2274. https://doi.org/10.1017/S0033291717000708

Koenigsberg, H. W., Siever, L. J., Lee, H., Pizzarello, S., New, A. S., Goodman, M., Cheng, H., Flory, J., & Prohovnik, I. (2009). Neural correlates of emotion processing in borderline personality disorder. *Psychiatry Research: Neuroimaging*, *172*(3), 192–199. https://doi.org/10.1016/j.pscychresns.2008.07.010

Kohoutová, L., Atlas, L. Y., Büchel, C., Buhle, J. T., Geuter, S., Jepma, M., Koban, L., Krishnan, A., Lee, D. H., Lee, S., Roy, M., Schafer, S. M., Schmidt, L., Wager, T. D., & Woo, C.-W. (2022). Individual variability in brain representations of pain. *Nature*

Neuroscience, *25*(6), 749–759. https://doi.org/10.1038/s41593-022-01081-x

Kohoutová, L., Heo, J., Cha, S., Lee, S., Moon, T., Wager, T. D., & Woo, C.-W. (2020). Toward a unified framework for interpreting machine-learning models in neuroimaging. *Nature Protocols*, *15*(4), 1399–1435. https://doi.org/10.1038/s41596-019-0289-5

Koss, K., & Gunnar, M. (2018). Annual research review: Early adversity, the HPA axis, and child psychopathology. *Molecular Ecology*, *59*(4), 327–346. https://doi.org/10.1111/jcpp.12784.Annual

Kotov, R., Waszczuk, M. A., Krueger, R. F., Forbes, M. K., Watson, D., Clark, L. A., Achenbach, T. M., Althoff, R. R., Ivanova, M. Y., Michael Bagby, R., Brown, T. A., Carpenter, W. T., Caspi, A., Moffitt, T. E., Eaton, N. R., Forbush, K. T., Goldberg, D., Hasin, D., Hyman, S. E., … Zimmerman, M. (2017). The hierarchical taxonomy of psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology*, *126*(4), 454–477. https://doi.org/10.1037/abn0000258

Kovács, K. J. (2013). CRH: The link between hormonal-, metabolic- and behavioral responses to stress. *Journal of Chemical Neuroanatomy*, *54*, 25–33. https://doi.org/10.1016/j.jchemneu.2013.05.003

Kozak, M. J., & Cuthbert, B. N. (2016). The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics. *Psychophysiology*, *53*(3), 286–297. https://doi.org/10.1111/psyp.12518

Kragel, P. A., Knodt, A. R., Hariri, A. R., & LaBar, K. S. (2016). Decoding Spontaneous Emotional States in the Human Brain. *PLoS Biology*, *14*(9), 1–19. https://doi.org/10.1371/journal.pbio.2000106

Kragel, P. A., Koban, L., Barrett, L. F., & Wager, T. D. (2018). Representation, Pattern Information, and Brain Signatures: From Neurons to Neuroimaging. *Neuron*, *99*(2), 257–273. https://doi.org/10.1016/j.neuron.2018.06.009

Kragel, P. A., & LaBar, K. S. (2015). Multivariate neural biomarkers of emotional states are

categorically distinct. *Social Cognitive and Affective Neuroscience*, *10*(11), 1437–1448. https://doi.org/10.1093/scan/nsv032

Kragel, P. A., & LaBar, K. S. (2016). Decoding the Nature of Emotion in the Brain. *Trends in Cognitive Sciences*, *20*(6), 444–455. https://doi.org/10.1016/j.tics.2016.03.011

Kragel, P., Han, X., Kraynak, T., Gianaros, P., & Wager, T. (2020). fMRI can be highly reliable, but it depends on what you measure (v2). *PsyArXiv*. https://doi.org/10.31234/osf.io/9eaxk

Krause-Utz, A., Oei, N. Y. L., Niedtfeld, I., Bohus, M., Spinhoven, P., Schmahl, C., & Elzinga, B. M. (2012). Influence of emotional distraction on working memory performance in borderline personality disorder. *Psychological Medicine*, *42*(10), 2181–2192. https://doi.org/10.1017/S0033291712000153

Kribakaran, S., Danese, A., Bromis, K., Kempton, M. J., & Gee, D. G. (2020). Meta-analysis of Structural Magnetic Resonance Imaging Studies in Pediatric Posttraumatic Stress Disorder and Comparison With Related Conditions. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(1), 23–34. https://doi.org/10.1016/j.bpsc.2019.08.006

Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S., & Baker, C. I. (2009). Circular analysis in systems neuroscience: The dangers of double dipping. *Nature Neuroscience*, *12*(5), 535–540. https://doi.org/10.1038/nn.2303

Krüger-Gottschalk, A., Knaevelsrud, C., Rau, H., Dyer, A., Schäfer, I., Schellong, J., & Ehring, T. (2017). The German version of the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): Psychometric properties and diagnostic utility. *BMC Psychiatry*, *17*(1), 1–9. https://doi.org/10.1186/s12888-017-1541-6

Kühn, S., Butler, O., Willmund, G., Wesemann, U., Zimmermann, P., & Gallinat, J. (2021). The brain at war: effects of stress on brain structure in soldiers deployed to a war zone. *Translational Psychiatry*, *11*(1). https://doi.org/10.1038/s41398-021-01356-0

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2005). *International Affective Picture System (IAPS): Digitized Photographs, Instruction Manual and Affective Ratings. (Technical*

Report a-6 Ed.). University of Florida.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8. University of Florida, Gainesville, FL.*

Laux, L. (1981). *Das State-Trait-Angstinventar (STAI) : theoretische Grundlagen und Handanweisung*.

Lebowitz, M. S. (2019). The Implications of Genetic and Other Biological Explanations for Thinking about Mental Disorders. *Hastings Center Report*, *49*, S82–S87. https://doi.org/10.1002/hast.1020

LeDoux, J. (2007). The amygdala. *Current Biology*, *17*(20), 868–874. https://doi.org/10.1016/j.cub.2007.08.005

LeDoux, J. (2012). Rethinking the Emotional Brain. *Neuron*, *73*(4), 653–676. https://doi.org/10.1016/j.neuron.2012.02.004

LeDoux, J. E. (1996). *The Emotional Brain*. Simon & Schuster.

LeDoux, Joseph E., & Pine, D. S. (2016). Using neuroscience to help understand fear and anxiety: A two-system framework. *American Journal of Psychiatry*, *173*(11), 1083–1093. https://doi.org/10.1176/appi.ajp.2016.16030353

Liberzon, I., & Abelson, J. L. (2016). Context Processing and the Neurobiology of Post-Traumatic Stress Disorder. *Neuron*, *92*(1), 14–30. https://doi.org/10.1016/j.neuron.2016.09.039

Lindenberger, U., & Lövdén, M. (2019). Brain Plasticity in Human Lifespan Development: The Exploration–Selection–Refinement Model. *Annual Review of Developmental Psychology*, *1*(1), 197–222. https://doi.org/10.1146/annurev-devpsych-121318-085229

Lindquist, K. A., Satpute, A. B., Wager, T. D., Weber, J., & Barrett, L. F. (2016). The Brain Basis of Positive and Negative Affect: Evidence from a Meta-Analysis of the Human Neuroimaging Literature. *Cerebral Cortex*, *26*(5), 1910–1922.

https://doi.org/10.1093/cercor/bhv001

Linehan, M. M. (1993). *Cognitive-behavioral Treatment of Borderline Personality Disorder*. Guilford Press. https://books.google.de/books?id=UZim3OAPwe8C

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

Lischke, A., Herpertz, S. C., Berger, C., Domes, G., & Gamer, M. (2017). Divergent effects of oxytocin on (para-)limbic reactivity to emotional and neutral scenes in females with and without borderline personality disorder. *Social Cognitive and Affective Neuroscience*, *12*(11), 1783–1792. https://doi.org/10.1093/scan/nsx107

Logue, M. W., van Rooij, S. J. H., Dennis, E. L., Davis, S. L., Hayes, J. P., Stevens, J. S., Densmore, M., Haswell, C. C., Ipser, J., Koch, S. B. J., Korgaonkar, M., Lebois, L. A. M., Peverill, M., Baker, J. T., Boedhoe, P. S. W., Frijling, J. L., Gruber, S. A., Harpaz-Rotem, I., Jahanshad, N., … Morey, R. A. (2018). Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia. *Biological Psychiatry*, *83*(3), 244–253. https://doi.org/10.1016/j.biopsych.2017.09.006

Loranger, A. W., Janca, A., & Sartorius, N. (1997). *Assessment and diagnosis of personality disorders: The ICD-10 international personality disorder examination (IPDE)*. Cambridge University Press.

Lorenz, K. Z. (1937). The Companion in the Bird's World. *The Auk*, *54*(3), 245–273. https://doi.org/10.2307/4078077

Luby, J. L., Baram, T. Z., Rogers, C. E., & Barch, D. M. (2020). Neurodevelopmental Optimization after Early-Life Adversity: Cross-Species Studies to Elucidate Sensitive Periods and Brain Mechanisms to Inform Early Intervention. *Trends in Neurosciences*, *43*(10), 744–751. https://doi.org/10.1016/j.tins.2020.08.001

Luby, J. L., Tillman, R., & Barch, D. M. (2019). Association of Timing of Adverse Childhood Experiences and Caregiver Support with Regionally Specific Brain Development in Adolescents. *JAMA Network Open*, *2*(9). https://doi.org/10.1001/jamanetworkopen.2019.11426

Lupien, S. J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N. P. V., Thakur, M., McEwen, B. S., Hauger, R. L., & Meaney, M. J. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience*, *1*(1), 69–73. https://doi.org/10.1038/271

Lupien, S. J., Juster, R. P., Raymond, C., & Marin, M. F. (2018). The effects of chronic stress on the human brain: From neurotoxicity, to vulnerability, to opportunity. *Frontiers in Neuroendocrinology*, *49*(February), 91–105. https://doi.org/10.1016/j.yfrne.2018.02.001

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445. https://doi.org/10.1038/nrn2639

Maechler, M. (2020). *sfsmisc: Utilities from "Seminar fuer Statistik" ETH Zurich. R package version 1.1-5.* https://cran.r-project.org/package=sfsmisc

Marek, S., Tervo-Clemmens, B., Calabro, F. J., Montez, D. F., Kay, B. P., Hatoum, A. S., Donohue, M. R., Foran, W., Miller, R. L., Hendrickson, T. J., Malone, S. M., Kandala, S., Feczko, E., Miranda-Dominguez, O., Graham, A. M., Earl, E. A., Perrone, A. J., Cordova, M., Doyle, O., … Dosenbach, N. U. F. (2022). Reproducible brain-wide association studies require thousands of individuals. *Nature*, *603*(7902), 654–660. https://doi.org/10.1038/s41586-022-04492-9

Maren, S., Phan, K. L., & Liberzon, I. (2013). The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*, *14*(6), 417–428. https://doi.org/10.1038/nrn3492

McDermott, T. J., Kirlic, N., & Aupperle, R. L. (2018). Roadmap for optimizing the clinical

utility of emotional stress paradigms in human neuroimaging research. *Neurobiology of Stress*, *8*(November 2017), 134–146. https://doi.org/10.1016/j.ynstr.2018.05.001

McEwen, B. S., & Lasley, E. N. (2002). *The end of stress as we know it*. Dana Press.

McLaughlin, K. A., Weissman, D., & Bitrán, D. (2019). Childhood Adversity and Neural Development: A Systematic Review. *Annual Review of Developmental Psychology*, *1*(1), 277–312. https://doi.org/10.1146/annurev-devpsych-121318-084950

Merz, E. C., Tottenham, N., & Noble, K. G. (2018). Socioeconomic Status, Amygdala Volume, and Internalizing Symptoms in Children and Adolescents. *Journal of Clinical Child & Adolescent Psychology*, *47*(2), 312–323. https://doi.org/10.1080/15374416.2017.1326122

Mincic, A. M. (2015). Neuroanatomical correlates of negative emotionality-related traits: A systematic review and meta-analysis. *Neuropsychologia*, *77*, 97–118. https://doi.org/10.1016/j.neuropsychologia.2015.08.007

Mitchell, A. E., Dickens, G. L., & Picchioni, M. M. (2014). Facial emotion processing in borderline personality disorder: A systematic review and meta-analysis. *Neuropsychology Review*, *24*(4), 166–184. https://doi.org/10.1007/s11065-014-9254-9

Mitra, R., & Sapolsky, R. M. (2008). Acute corticosterone treatment is sufficient to induce anxiety and amygdaloid dendritic hypertrophy. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(14), 5573–5578. https://doi.org/10.1073/pnas.0705615105

Morey, R. D., & Rouder, J. N. (2018). *BayesFactor: Computation of Bayes Factors for Common Designs. R package version 0.9.12-4.2*. https://cran.r-project.org/package=BayesFactor

Müller-Engelmann, M., Schnyder, U., Dittmann, C., Priebe, K., Bohus, M., Thome, J., Fydrich, T., Pfaltz, M. C., & Steil, R. (2020). Psychometric Properties and Factor Structure of the German Version of the Clinician-Administered PTSD Scale for DSM-5. *Assessment*, *27*(6), 1128–1138. https://doi.org/10.1177/1073191118774840

Nabavi, S., Fox, R., Proulx, C. D., Lin, J. Y., Tsien, R. Y., & Malinow, R. (2014). Engineering a memory with LTD and LTP. *Nature*, *511*(7509), 348–352. https://doi.org/10.1038/nature13294

Nelson, C. A., & Gabard-Durnam, L. J. (2020). Early Adversity and Critical Periods: Neurodevelopmental Consequences of Violating the Expectable Environment. *Trends in Neurosciences*, *43*(3), 133–143. https://doi.org/10.1016/j.tins.2020.01.002

Nelson, M. D., & Tumpap, A. M. (2017). Posttraumatic stress disorder symptom severity is associated with left hippocampal volume reduction: A meta-analytic study. *CNS Spectrums*, *22*(4), 363–372. https://doi.org/10.1017/S1092852916000833

Niedtfeld, I., Schmitt, R., Winter, D., Bohus, M., Schmahl, C., & Herpertz, S. C. (2017). Pain-mediated affect regulation is reduced after dialectical behavior therapy in borderline personality disorder: A longitudinal fMRI study. *Social Cognitive and Affective Neuroscience*, *12*(5), 739–747. https://doi.org/10.1093/scan/nsw183

Niedtfeld, I., Schulze, L., Kirsch, P., Herpertz, S. C., Bohus, M., & Schmahl, C. (2010). Affect regulation and pain in borderline personality disorder: A possible link to the understanding of self-injury. *Biological Psychiatry*, *68*(4), 383–391. https://doi.org/10.1016/j.biopsych.2010.04.015

Nikulina, V., & Widom, C. S. (2013). Child maltreatment and executive functioning in middle adulthood: A prospective examination. *Neuropsychology*, *27*(4), 417–427. https://doi.org/10.1037/a0032811

Noble, S., Scheinost, D., & Constable, R. T. (2019). A decade of test-retest reliability of functional connectivity: A systematic review and meta-analysis. *NeuroImage*, *203*(August), 116157. https://doi.org/10.1016/j.neuroimage.2019.116157

Noble, S., Scheinost, D., & Constable, R. T. (2021). A guide to the measurement and interpretation of fMRI test-retest reliability. *Current Opinion in Behavioral Sciences*, *40*, 27–32. https://doi.org/10.1016/j.cobeha.2020.12.012

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. E. (2002). Rethinking Feelings: An fMRI Study of the Cognitive Regulation of Emotion. *Journal of Cognitive Neuroscience*, *14*(8), 1215–1229. https://doi.org/10.1162/089892902760807212

Ousdal, O. T., Jensen, J., Server, A., Hariri, A. R., Nakstad, P. H., & Andreassen, O. A. (2008). The human amygdala is involved in general behavioral relevance detection: Evidence from an event-related functional magnetic resonance imaging Go-NoGo task. *Neuroscience*, *156*(3), 450–455. https://doi.org/10.1016/j.neuroscience.2008.07.066

Ousdal, Olga Therese, Milde, A. M., Hafstad, G. S., Hodneland, E., Dyb, G., Craven, A. R., Melinder, A., Endestad, T., & Hugdahl, K. (2020). The association of PTSD symptom severity with amygdala nuclei volumes in traumatized youths. *Translational Psychiatry*, *10*(1), 288. https://doi.org/10.1038/s41398-020-00974-4

Paquola, C., Bennett, M. R., & Lagopoulos, J. (2016). Understanding heterogeneity in grey matter research of adults with childhood maltreatment—A meta-analysis and review. *Neuroscience and Biobehavioral Reviews*, *69*, 299–312. https://doi.org/10.1016/j.neubiorev.2016.08.011

Paret, C., & Hendler, T. (2020). Live from the "regulating brain": Harnessing the brain to change emotion. *Emotion (Washington, D.C.)*, *20*(1), 126–131. https://doi.org/10.1037/emo0000674

Paret, C., Kluetsch, R., Ruf, M., Demirakca, T., Kalisch, R., Schmahl, C., & Ende, G. (2014). Transient and sustained BOLD signal time courses affect the detection of emotion-related brain activation in fMRI. *NeuroImage*, *103*, 522–532. https://doi.org/10.1016/j.neuroimage.2014.08.054

Paret, C., Niedtfeld, I., Lotter, T., Wunder, A., Grimm, S., Mennes, M., Okell, T., Beckmann, C., & Schmahl, C. (2021). Single-Dose Effects of Citalopram on Neural Responses to Affective Stimuli in Borderline Personality Disorder: A Randomized Clinical Trial. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *6*(8), 837–845.

https://doi.org/10.1016/j.bpsc.2021.02.002

Patel, D., Anilkumar, S., Chattarji, S., & Buwalda, B. (2018). Repeated social stress leads to contrasting patterns of structural plasticity in the amygdala and hippocampus. *Behavioural Brain Research*, *347*(November 2017), 314–324. https://doi.org/10.1016/j.bbr.2018.03.034

Patel, R., Spreng, R. N., Shin, L. M., & Girard, T. A. (2012). Neurocircuitry models of posttraumatic stress disorder and beyond: A meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *36*(9), 2130–2142. https://doi.org/10.1016/j.neubiorev.2012.06.003

Pearl, J. (2009). *Causality*. Cambridge University Press.

Pechtel, P., Lyons-Ruth, K., Anderson, C. M., & Teicher, M. H. (2014). Sensitive periods of amygdala development: The role of maltreatment in preadolescence. *NeuroImage*, *97*(August), 236–244. https://doi.org/10.1016/j.neuroimage.2014.04.025

Pessoa, L. (2017). A Network Model of the Emotional Brain. *Trends in Cognitive Sciences*, *21*(5), 357–371. https://doi.org/10.1016/j.tics.2017.03.002

Pessoa, L. (2018). Understanding emotion by unraveling complex structure– function mappings. In A. S. Fox, R. C. Lapate, A. J. Shackman, & R. J. Davidson (Eds.), *The nature of emotion* (pp. 84–87). Oxford University Press.

Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., Milad, M. R., & Liberzon, I. (2012). Biological studies of post-traumatic stress disorder. *Nature Reviews Neuroscience*, *13*(11), 769–787. https://doi.org/10.1038/nrn3339

Polanía, R., Nitsche, M. A., & Ruff, C. C. (2018). Studying and modifying brain function with non-invasive brain stimulation. *Nature Neuroscience*, *21*(2), 174–187. https://doi.org/10.1038/s41593-017-0054-4

Poldrack, R. A. (2011). Inferring Mental States from Neuroimaging Data: From Reverse Inference to Large-Scale Decoding. *Neuron*, *72*(5), 692–697.

https://doi.org/10.1016/j.neuron.2011.11.001

Puetz, V. B., Viding, E., Gerin, M. I., Pingault, J.-B., Sethi, A., Knodt, A. R., Radtke, S. R., Brigidi, B. D., Hariri, A. R., & McCrory, E. (2020). Investigating patterns of neural response associated with childhood abuse v. childhood neglect. *Psychological Medicine*, *50*(8), 1398–1407. https://doi.org/10.1017/S003329171900134X

Qureshi, S. U., Long, M. E., Bradshaw, M. R., Pyne, J. M., Magruder, K. M., Kimbrell, T., Hudson, T. J., Jawaid, A., Schulz, P. E., & Kunik, M. E. (2011). Does PTSD Impair Cognition Beyond the Effect of Trauma? *Journal of Neuropsychiatry*, *23*(1), 16–28. https://doi.org/10.1176/appi.neuropsych.23.1.16

Ramel, W., Goldin, P. R., Eyler, L. T., Brown, G. G., Gotlib, I. H., & McQuaid, J. R. (2007). Amygdala Reactivity and Mood-Congruent Memory in Individuals at Risk for Depressive Relapse. *Biological Psychiatry*, *61*(2), 231–239. https://doi.org/10.1016/j.biopsych.2006.05.004

Rauch, S. L., Shin, L. M., & Phelps, E. A. (2006). Neurocircuitry Models of Posttraumatic Stress Disorder and Extinction: Human Neuroimaging Research-Past, Present, and Future. *Biological Psychiatry*, *60*(4), 376–382. https://doi.org/10.1016/j.biopsych.2006.06.004

Rausch, S., Herzog, J., Thome, J., Ludäscher, P., Müller-Engelmann, M., Steil, R., Priebe, K., Fydrich, T., & Kleindienst, N. (2016). Women with exposure to childhood interpersonal violence without psychiatric diagnoses show no signs of impairment in general functioning, quality of life and sexuality. *Borderline Personality Disorder and Emotion Dysregulation*, *3*(1), 13. https://doi.org/10.1186/s40479-016-0048-y

Rod, N. H., Bengtsson, J., Budtz-Jørgensen, E., Clipet-Jensen, C., Taylor-Robinson, D., Andersen, A. M. N., Dich, N., & Rieckmann, A. (2020). Trajectories of childhood adversity and mortality in early adulthood: a population-based cohort study. *The Lancet*, *396*(10249), 489–497. https://doi.org/10.1016/S0140-6736(20)30621-8

Rouder, J. N., Speckman, P. L., Sun, D., Morey, R. D., & Iverson, G. (2009). Bayesian t tests

for accepting and rejecting the null hypothesis. *Psychonomic Bulletin & Review*, *16*(2), 225–237. https://doi.org/10.3758/PBR.16.2.225

Russell, J. D., Marsee, M. A., & Weems, C. F. (2021). Developmental Variation in Amygdala Volumes: Modeling Differences Across Time, Age, and Puberty. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *6*(1), 117–125. https://doi.org/10.1016/j.bpsc.2020.08.006

Rutter, M., Kumsta, R., Schlotz, W., & Sonuga-Barke, E. (2012). Longitudinal Studies Using a "Natural Experiment" Design: The Case of Adoptees From Romanian Institutions. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(8), 762–770. https://doi.org/10.1016/j.jaac.2012.05.011

Sander, D., Grafman, J., & Zalla, T. (2003). The Human Amygdala: An Evolved System for Relevance Detection. *Reviews in the Neurosciences*, *14*(4), 303–316. https://doi.org/10.1515/REVNEURO.2003.14.4.303

Sansone, R. A., & Sansone, L. A. (2011). Personality disorders: A nation-based perspective on prevalence. *Innovations in Clinical Neuroscience*, *8*(4), 13–18.

Sapolsky, R. M. (1996). Why stress is bad for your brain. *Science (New York, N.Y.)*, *273*(5276), 749–750. http://www.ncbi.nlm.nih.gov/pubmed/8701325

Sapolsky, R. M. (2017). *Behave: The biology of humans at our best and worst (p.78)*. Penguin.

Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, *21*(1), 55–89. https://doi.org/10.1210/er.21.1.55

Schachter, S., & Singer, J. (1962). Cognitive, social, and physiological determinants of emotional state. *Psychological Review*, *69*(5), 379–399. https://doi.org/10.1037/h0046234

Schalinski, I., Teicher, M. H., Nischk, D., Hinderer, E., Müller, O., & Rockstroh, B. (2016). Type and timing of adverse childhood experiences differentially affect severity of PTSD, dissociative and depressive symptoms in adult inpatients. *BMC Psychiatry*, *16*(1), 295.

https://doi.org/10.1186/s12888-016-1004-5

Schmitt, R., Winter, D., Niedtfeld, I., Herpertz, S. C., & Schmahl, C. (2016). Effects of Psychotherapy on Neuronal Correlates of Reappraisal in Female Patients With Borderline Personality Disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *1*(6), 548–557. https://doi.org/10.1016/j.bpsc.2016.07.003

Schnyder, U., & Moergeli, H. (2002). German version of clinician-administered PTSD scale. *Journal of Traumatic Stress*, *15*(6), 487–492. https://doi.org/10.1023/A:1020922023090

Schomerus, G., Matschinger, H., & Angermeyer, M. C. (2006). Public beliefs about the causes of mental disorders revisited. *Psychiatry Research*, *144*(2–3), 233–236. https://doi.org/10.1016/j.psychres.2006.05.002

Schulz, M.-A., Bzdok, D., Haufe, S., Haynes, J.-D., & Ritter, K. (2022). Performance reserves in brain-imaging-based phenotype prediction. *BioRxiv*, 2022.02.23.481601. https://www.biorxiv.org/content/10.1101/2022.02.23.481601v1%0Ahttps://www.biorxiv.org/content/10.1101/2022.02.23.481601v1.abstract

Schulze, L., Domes, G., Krüger, A., Berger, C., Fleischer, M., Prehn, K., Schmahl, C., Grossmann, A., Hauenstein, K., & Herpertz, S. C. (2011). Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. *Biological Psychiatry*, *69*(6), 564–573. https://doi.org/10.1016/j.biopsych.2010.10.025

Schulze, L., Schmahl, C., & Niedtfeld, I. (2016). Neural Correlates of Disturbed Emotion Processing in Borderline Personality Disorder: A Multimodal Meta-Analysis. *Biological Psychiatry*, *79*(2), 97–106. https://doi.org/10.1016/j.biopsych.2015.03.027

Schulze, L., Schulze, A., Renneberg, B., Schmahl, C., & Niedtfeld, I. (2019). Neural Correlates of Affective Disturbances: A Comparative Meta-analysis of Negative Affect Processing in Borderline Personality Disorder, Major Depressive Disorder, and Posttraumatic Stress Disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *4*(3), 220–232. https://doi.org/10.1016/j.bpsc.2018.11.004

Selye, H. (1936). A Syndrome Produced by Diverse Nocuous Agents. *Nature*, *138*, 32. http://psychiatryonline.org/doi/abs/10.1176/jnp.10.2.230a

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

Shalev, A., Liberzon, I., & Marmar, C. (2017). Post-Traumatic Stress Disorder. *New England Journal of Medicine*, *376*(25), 2459–2469. https://doi.org/10.1056/NEJMra1612499

Shear, K., Halmo, K. A., Widiger, T. A., & Boyce, C. (2007). Sociocultural factors and gender. In W. E. Narrow, M. B. First, P. J. Sirovatka, & D. A. Regier (Eds.), *Age and gender considerations in psychiatric diagnosis: A research agenda for DSM-V* (pp. 65–79). American Psychiatric Publishing.

Sicorello, M., Dieckmann, L., Moser, D., Lux, V., Luhmann, M., Neubauer, A. B., Schlotz, W., & Kumsta, R. (2020). Highs and lows: Genetic susceptibility to daily events. *PLoS ONE*, *15*(8 August), 1–17. https://doi.org/10.1371/journal.pone.0237001

Sicorello, M., & Schmahl, C. (2021). Emotion dysregulation in borderline personality disorder: A fronto–limbic imbalance? *Current Opinion in Psychology*, *37*, 114–120. https://doi.org/10.1016/j.copsyc.2020.12.002

Sicorello, M., Thome, J., Herzog, J., & Schmahl, C. (2020). Differential Effects of Early Adversity and Posttraumatic Stress Disorder on Amygdala Reactivity: The Role of Developmental Timing. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *16*, 1–8. https://doi.org/10.1016/j.bpsc.2020.10.009

Siehl, S., King, J. A., Burgess, N., Flor, H., & Nees, F. (2018). Structural white matter changes in adults and children with posttraumatic stress disorder: A systematic review and meta-analysis. *NeuroImage: Clinical*, *19*(May), 581–598. https://doi.org/10.1016/j.nicl.2018.05.013

Siehl, S., Wicking, M., Pohlack, S., Winkelmann, T., Zidda, F., Steiger-White, F., King, J.,

Burgess, N., Flor, H., & Nees, F. (2020). Structural white and gray matter differences in a large sample of patients with Posttraumatic Stress Disorder and a healthy and trauma-exposed control group: Diffusion tensor imaging and region-based morphometry. *NeuroImage: Clinical*, *28*(May), 102424. https://doi.org/10.1016/j.nicl.2020.102424

Silvers, J. A., Insel, C., Powers, A., Franz, P., Helion, C., Martin, R., Weber, J., Mischel, W., Casey, B. J., & Ochsner, K. N. (2017). The transition from childhood to adolescence is marked by a general decrease in amygdala reactivity and an affect-specific ventral-to-dorsal shift in medial prefrontal recruitment. *Developmental Cognitive Neuroscience*, *25*, 128–137. https://doi.org/10.1016/j.dcn.2016.06.005

Stark, E. A., Parsons, C. E., Van Hartevelt, T. J., Charquero-Ballester, M., McManners, H., Ehlers, A., Stein, A., & Kringelbach, M. L. (2015). Post-traumatic stress influences the brain even in the absence of symptoms: A systematic, quantitative meta-analysis of neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *56*, 207–221. https://doi.org/10.1016/j.neubiorev.2015.07.007

Steel, P., Schmidt, J., & Shultz, J. (2008). Refining the Relationship Between Personality and Subjective Well-Being. *Psychological Bulletin*, *134*(1), 138–161. https://doi.org/10.1037/0033-2909.134.1.138

Sterling, P. (2012). Allostasis: A model of predictive regulation. *Physiology & Behavior*, *106*(1), 5–15. https://doi.org/10.1016/j.physbeh.2011.06.004

Stevens, J. S., van Rooij, S. J. H., & Jovanovic, T. (2018). Developmental contributors to trauma response: The importance of sensitive periods, early environment, and sex differences. In E. Vermetten, D. G. Baker, & V. B. Risbrough (Eds.), *Behavioral Neurobiology of PTSD* (pp. 1–22). Springer International Publishing.

Steyer, R., Schmitt, M., & Eid, M. (1999). Latent state-trait theory and research in personality and individual differences. *European Journal of Personality*, *13*(5), 389–408. https://doi.org/10.1002/(SICI)1099-0984(199909/10)13:5<389::AID-PER361>3.0.CO;2-

A

Straathof, M., Sinke, M. R. T., Dijkhuizen, R. M., & Otte, W. M. (2019). A systematic review on the quantitative relationship between structural and functional network connectivity strength in mammalian brains. *Journal of Cerebral Blood Flow and Metabolism*, *39*(2), 189–209. https://doi.org/10.1177/0271678X18809547

Strasser, E. S., Haffner, P., Fiebig, J., Quinlivan, E., Adli, M., & Stamm, T. J. (2016). Behavioral measures and self-report of impulsivity in bipolar disorder: no association between Stroop test and Barratt Impulsiveness Scale. *International Journal of Bipolar Disorders*, *4*(1), 16. https://doi.org/10.1186/s40345-016-0057-1

Strobl, C., Boulesteix, A.-L., Kneib, T., Augustin, T., & Zeileis, A. (2008). Conditional variable importance for random forests. *BMC Bioinformatics*, *9*(1), 307. https://doi.org/10.1186/1471-2105-9-307

Strobl, C., Boulesteix, A. L., Zeileis, A., & Hothorn, T. (2007). Bias in random forest variable importance measures: Illustrations, sources and a solution. *BMC Bioinformatics*, *8*. https://doi.org/10.1186/1471-2105-8-25

Struck, N., Krug, A., Yuksel, D., Stein, F., Schmitt, S., Meller, T., Brosch, K., Dannlowski, U., Nenadić, I., Kircher, T., & Brakemeier, E. L. (2020). Childhood maltreatment and adult mental disorders – the prevalence of different types of maltreatment and associations with age of onset and severity of symptoms. *Psychiatry Research*, *293*(May), 113398. https://doi.org/10.1016/j.psychres.2020.113398

Su, Y., D'Arcy, C., Yuan, S., & Meng, X. (2019). How does childhood maltreatment influence ensuing cognitive functioning among people with the exposure of childhood maltreatment? A systematic review of prospective cohort studies. *Journal of Affective Disorders*, *252*, 278–293. https://doi.org/10.1016/j.jad.2019.04.026

Suzuki, H., Luby, J. L., Botteron, K. N., Dietrich, R., McAvoy, M. P., & Barch, D. M. (2014). Early Life Stress and Trauma and Enhanced Limbic Activation to Emotionally Valenced

Faces in Depressed and Healthy Children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *53*(7), 800-813.e10. https://doi.org/10.1016/j.jaac.2014.04.013

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. https://doi.org/10.1016/j.neuron.2014.12.055

Szeszko, P. R., Lehrner, A., & Yehuda, R. (2018). Glucocorticoids and Hippocampal Structure and Function in PTSD. *Harvard Review of Psychiatry*, *26*(3), 142–157. https://doi.org/10.1097/HRP.0000000000000188

Taschereau-Dumouchel, V., Kawato, M., & Lau, H. (2019). Multivoxel pattern analysis reveals dissociations between subjective fear and its physiological correlates. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-019-0520-3

te Grotenhuis, M., Pelzer, B., Eisinga, R., Nieuwenhuis, R., Schmidt-Catran, A., & Konig, R. (2017). When size matters: advantages of weighted effect coding in observational studies. *International Journal of Public Health*, *62*(1), 163–167. https://doi.org/10.1007/s00038-016-0901-1

Team, R. (2013). *R: A language and environment for statistical computing*.

Teicher, M. H., Anderson, C. M., Ohashi, K., Khan, A., McGreenery, C. E., Bolger, E. A., Rohan, M. L., & Vitaliano, G. D. (2018). Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus. *NeuroImage*, *169*(October 2017), 443–452. https://doi.org/10.1016/j.neuroimage.2017.12.055

Teicher, M. H., Gordon, J. B., & Nemeroff, C. B. (2021). Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Molecular Psychiatry*, *October*. https://doi.org/10.1038/s41380-021-01367-9

Teicher, M. H., & Parigger, A. (2015). The 'Maltreatment and Abuse Chronology of Exposure' (MACE) Scale for the Retrospective Assessment of Abuse and Neglect During

Development. *PLOS ONE*, *10*(2), e0117423. https://doi.org/10.1371/journal.pone.0117423

Teicher, M. H., & Samson, J. A. (2016). Annual Research Review: Enduring neurobiological effects of childhood abuse and neglect. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *57*(3), 241–266. https://doi.org/10.1111/jcpp.12507

Todorov, A. (2012). The role of the amygdala in face perception and evaluation. *Motivation and Emotion*, *36*(1), 16–26. https://doi.org/10.1007/s11031-011-9238-5

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & 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. https://doi.org/10.1006/nimg.2001.0978

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., & Nishijo, H. (2012). Developmental Trajectories of Amygdala and Hippocampus from Infancy to Early Adulthood in Healthy Individuals. *PLoS ONE*, *7*(10), e46970. https://doi.org/10.1371/journal.pone.0046970

van ’t Hof, S. R., Van Oudenhove, L., Klein, S., Reddan, M. C., Kragel, P. A., Stark, R., & Wager, T. D. (2020). The Brain Activation-based Sexual Image Classifier (BASIC): A sensitive and specific fMRI activity pattern for sexual image perception. *BioRxiv*.

van Harmelen, A.-L., van Tol, M.-J., Demenescu, L. R., van der Wee, N. J. A., Veltman, D. J., Aleman, A., van Buchem, M. A., Spinhoven, P., Penninx, B. W. J. H., & Elzinga, B. M. (2013). Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Social Cognitive and Affective Neuroscience*, *8*(4), 362–369. https://doi.org/10.1093/scan/nss007

VanTieghem, M., Korom, M., Flannery, J., Choy, T., Caldera, C., Humphreys, K. L., Gabard-Durnam, L., Goff, B., Gee, D. G., Telzer, E. H., Shapiro, M., Louie, J. Y., Fareri, D. S., Bolger, N., & Tottenham, N. (2021). Longitudinal changes in amygdala, hippocampus and

cortisol development following early caregiving adversity. *Developmental Cognitive Neuroscience*, *48*, 100916. https://doi.org/10.1016/j.dcn.2021.100916

Venables, W. N., & Ripley, B. D. (2002). *Modern Applied Statistics with S* (Fourth Edi). Springer.

Visser, R. M., Bathelt, J., Scholte, H. S., & Kindt, M. (2021). Robust BOLD Responses to Faces But Not to Conditioned Threat: Challenging the Amygdala's Reputation in Human Fear and Extinction Learning. *The Journal of Neuroscience*, *41*(50), 10278–10292. https://doi.org/10.1523/JNEUROSCI.0857-21.2021

Vonderlin, R., Kleindienst, N., Alpers, G. W., Bohus, M., Lyssenko, L., & Schmahl, C. (2018). Dissociation in victims of childhood abuse or neglect: A meta-Analytic review. *Psychological Medicine*, *48*(15), 2467–2476. https://doi.org/10.1017/S0033291718000740

Vytal, K., & Hamann, S. (2010). Neuroimaging support for discrete neural correlates of basic emotions: A voxel-based meta-analysis. *Journal of Cognitive Neuroscience*, *22*(12), 2864–2885. https://doi.org/10.1162/jocn.2009.21366

Wagenmakers, E.-J., Love, J., Marsman, M., Jamil, T., Ly, A., Verhagen, J., Selker, R., Gronau, Q. F., Dropmann, D., Boutin, B., Meerhoff, F., Knight, P., Raj, A., van Kesteren, E.-J., van Doorn, J., Šmíra, M., Epskamp, S., Etz, A., Matzke, D., … Morey, R. D. (2018). Bayesian inference for psychology. Part II: Example applications with JASP. *Psychonomic Bulletin & Review*, *25*(1), 58–76. https://doi.org/10.3758/s13423-017-1323-7

Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C.-W., & Kross, E. (2013). An fMRI-Based Neurologic Signature of Physical Pain. *New England Journal of Medicine*, *368*(15), 1388–1397. https://doi.org/10.1056/NEJMoa1204471

Wager, T. D., Keller, M. C., Lacey, S. C., & Jonides, J. (2005). Increased sensitivity in neuroimaging analyses using robust regression. *NeuroImage*, *26*(1), 99–113.

https://doi.org/10.1016/j.neuroimage.2005.01.011

Wager, T. D., Phan, K. L., Liberzon, I., & Taylor, S. F. (2003). Valence, gender, and lateralization of functional brain anatomy in emotion: A meta-analysis of findings from neuroimaging. *NeuroImage*, *19*(3), 513–531. https://doi.org/10.1016/S1053-8119(03)00078-8

Wager, T., Kang, T. D., Johnson, J. D., Nichols, T. D., Satpute, T. E., & Barrett, A. B. (2015). A Bayesian Model of Category-Specific Emotional Brain Responses. *PLoS Comput Biol*, *11*(4), 1004066. https://doi.org/10.1371/journal.pcbi.1004066

Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013). *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*. www.ptsd.va.gov.

Wessa, M., Kanske, P., Neumeister, P., Bode, K., Heissler, J., & Schönfelder, S. (2010). Subjektive und psychophysiologische Evaluation neuen Bildmaterials für die klinisch-bio-psychologische Forschung. *Zeitschrift Für Klinische Psychologie Und Psychotherapie*, *39*, 77.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., Charlson, F. J., Norman, R. E., Flaxman, A. D., Johns, N., Burstein, R., Murray, C. J. L., & Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *The Lancet*, *382*(9904), 1575–1586. https://doi.org/10.1016/S0140-6736(13)61611-6

Wickham, H. (2017). ggplot2 - Elegant Graphics for Data Analysis (2nd Edition). *Journal of Statistical Software*, *77*(Book Review 2), 3–5. https://doi.org/10.18637/jss.v077.b02

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L., François, R., Grolemund, G., Hayes, A., Henry, L., Hester, J., Kuhn, M., Pedersen, T., Miller, E., Bache, S., Müller, K., Ooms, J., Robinson, D., Seidel, D., Spinu, V., … Yutani, H. (2019). Welcome to the Tidyverse. *Journal of Open Source Software*, *4*(43), 1686. https://doi.org/10.21105/joss.01686

Wiesel, T. N., & Hubel, D. H. (1963). SINGLE-CELL RESPONSES IN STRIATE CORTEX OF KITTENS DEPRIVED OF VISION IN ONE EYE. *Journal of Neurophysiology*, *26*(6), 1003–1017. https://doi.org/10.1152/jn.1963.26.6.1003

Winter, D., Niedtfeld, I., Schmitt, R., Bohus, M., Schmahl, C., & Herpertz, S. C. (2017). Neural correlates of distraction in borderline personality disorder before and after dialectical behavior therapy. *European Archives of Psychiatry and Clinical Neuroscience*, *267*(1), 51–62. https://doi.org/10.1007/s00406-016-0689-2

Witt, A., Sachser, C., Plener, P. L., Brähler, E., & Fegert, J. M. (2019). The Prevalence and Consequences of Adverse Childhood Experiences in the German Population. *Deutsches Ärzteblatt International*. https://doi.org/10.3238/arztebl.2019.0635

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 Bearbeitung der amerikanischen Originalversion des SKID I*. Hogrefe.

Wittchen, Hans Ulrich, Wunderlich, U., Gruschwitz, S., & Zaudig, M. (1997). SKID-I: Strukturiertes klinisches Interview für DSM-IV, Achse I: Psychische Störungen. [Structured clinical interview for DSM-IV. Axis I: Mental disorders]. *Göttingen: Hogrefe*.

Woo, C.-W., Koban, L., Kross, E., Lindquist, M. A., Banich, M. T., Ruzic, L., Andrews-Hanna, J. R., & Wager, T. D. (2014). Separate neural representations for physical pain and social rejection. *Nature Communications*, *5*(November), 5380. https://doi.org/10.1038/ncomms6380

Woo, C. W., Chang, L. J., Lindquist, M. A., & Wager, T. D. (2017). Building better biomarkers: Brain models in translational neuroimaging. *Nature Neuroscience*, *20*(3), 365–377. https://doi.org/10.1038/nn.4478

Woon, F. L., & Hedges, D. W. (2008). Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: A meta-analysis.

Hippocampus, *18*(8), 729–736. https://doi.org/10.1002/hipo.20437

World Health Organization. (2019). *International Statistical Classification of Diseases and Related Health Problems* (11th ed.).

Yang, Z., Craddock, R. C., & Milham, M. P. (2015). Impact of hematocrit on measurements of the intrinsic brain. *Frontiers in Neuroscience*, *8*. https://doi.org/10.3389/fnins.2014.00452

Yarkoni, T. (2020). The generalizability crisis. *Behavioral and Brain Sciences*. https://doi.org/10.1017/S0140525X20001685

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, *8*(8), 665–670. https://doi.org/10.1038/nmeth.1635

Yu, H., Koban, L., Chang, L. J., Wagner, U., Krishnan, A., Vuilleumier, P., Zhou, X., & Wager, T. D. (2020). A Generalizable Multivariate Brain Pattern for Interpersonal Guilt. *Cerebral Cortex*, *30*(6), 3558–3572. https://doi.org/10.1093/cercor/bhz326

Zaehringer, J., Ende, G., Santangelo, P., Kleindienst, N., Ruf, M., Bertsch, K., Bohus, M., Schmahl, C., & Paret, C. (2019). Improved emotion regulation after neurofeedback: A single-arm trial in patients with borderline personality disorder. *NeuroImage: Clinical*, *24*(October), 102032. https://doi.org/10.1016/j.nicl.2019.102032

Zanarini, M. C. (2003). Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. *Journal of Personality Disorders*, *17*(3), 233.

Zhang, J. Y., Liu, T. H., He, Y., Pan, H. Q., Zhang, W. H., Yin, X. P., Tian, X. L., Li, B. M., Wang, X. D., Holmes, A., Yuan, T. F., & Pan, B. X. (2019). Chronic Stress Remodels Synapses in an Amygdala Circuit–Specific Manner. *Biological Psychiatry*, *85*(3), 189–201. https://doi.org/10.1016/j.biopsych.2018.06.019

Zhou, F., Zhao, W., Qi, Z., Geng, Y., Yao, S., Kendrick, K. M., Wager, T. D., & Becker, B. (2021). A distributed fMRI-based signature for the subjective experience of fear. *Nature*

Communications, *12*(1), 1–16. https://doi.org/10.1038/s41467-021-26977-3

Zhou, Q., Liu, S., Jiang, C., He, Y., & Zuo, X. N. (2021). Charting the human amygdala development across childhood and adolescence: Manual and automatic segmentation. *Developmental Cognitive Neuroscience*, *52*. https://doi.org/10.1016/j.dcn.2021.101028

Zhu, J., Lowen, S. B., Anderson, C. M., Ohashi, K., Khan, A., & Teicher, M. H. (2019). Association of Prepubertal and Postpubertal Exposure to Childhood Maltreatment With Adult Amygdala Function. *JAMA Psychiatry*, *76*(8), 843–853. https://doi.org/10.1001/jamapsychiatry.2019.0931

List of Tables

List of Supplementary Tables

List of Figures

List of Supplementary Figures

Curriculum Vitae

Maurizio Sicorello
born 20th January 1990 in Frankfurt, a.M.

Address
Department of Psychosomatic Medicine and Psychotherapy
Central Institute of Mental Health Mannheim
C4, 11, Room 406
68159 Mannheim (Germany)
(+49) (0) 621 1703 4461
maurizio.sicorello@zi-mannheim.de

Education

Since November 2017	**Doctoral Studies, Heidelberg University** Central Institute of Mental Health Clinic for Psychosomatic Medicine and Psychotherapy Supervisor: Prof. Dr. Christian Schmahl
Oct. 2015 – Nov. 2017 *24.10.2017*	**M.Sc. Psychology, Heidelberg University** Program: Developmental and Clinical Psychology Final Grade: 1.0 [GPA: 4.0] Master's Thesis: "Demand-Resource Imbalance and Stress Appraisal: A Response Surface Analysis of EMA Data" (Grade: 1.0 [GPA: 4.0])
Oct. 2010 – Sept. 2015 *10.09.2015*	**B.Sc. Psychology, Johannes Gutenberg University of Mainz (JGU)** Final Grade: 1.3 [GPA: 3.7] Bachelor's Thesis: "Sexual and Physical Victimization of University Students in Context of Committed Relationships, Dating Relationships, and One-Night Stands" (Grade: 1.0 [GPA: 4.0])
Sept. 2014 – Dec. 2014	**Nihon University Tokyo, Exchange program of JGU Mainz**
Aug. 2000 – June 2010 *18.06.2010*	**Main-Taunus-Schule Hofheim** Abitur (Grade: 1.5 [GPA: 3.5])

Teaching Experience

April 2022 – July 2022	**Quantitative Research Methods (Heidelberg University)** Master level seminar Title: "Neurobiology of Emotion: Methods & Insights"
April 2015 – July 2015	**General Experimental Psychology (JGU Mainz)** Teaching Assistant: Dr. Jasmina Stevanov
Oct. 2012 – Aug. 2014	**Methods & Statistics (JGU Mainz)** Teaching Assistant: Dr. habil. Malte Persike

Research Experience

Feb. – April 2017	**Psychological and Brain Sciences, Dartmouth College** Visiting Scholar: Prof. Tor D. Wager
Feb. – April 2017	**Genetic Psychology, Ruhr-University Bochum** Research Internship: Prof. Robert Kumsta
May 2016 – May 2017	**Quantitative Research Methods, Heidelberg University** Student Research Assistant: Prof. Andreas Voss
Nov. 2015 – Jan. 2016	**General Experimental Psychology, JGU Mainz** Student Research Assistant: Prof. Heiko Hecht
Jan. 2014 – April 2014	**Graduate School of Letters, Kyoto University** Research Internship: Prof. Hiroshi Ashida
Oct. 2012 – Aug. 2014	**General Experimental Psychology, JGU Mainz** Student Research Assistant: Prof. Heiko Hecht

Scholarships, Grants & Awards

G.-A.-Lienert Scholarship for the promotion of early career researchers in biological methodology (3000€)

Grant of the German Psychological Association (Section: Biopsychology and Neuropsychology) for the validation of a German version of the State Difficulties in Emotion Regulation Scale (1000€)

PROMOS scholarship of the DAAD as a visiting student at Nihon University, Tokyo (2000€)

Poster Award of the German Psychological Society (Section: Biopsychology and Neuropsychology) for the contribution: "Affective neural signatures do not distinguish women with emotion dysregulation from healthy controls" (300€)

Service

Since January 2022	**Social media team of the German Psychological Association (Section: Biological and Neuropsychology) and the German Association for Psychophysiology and its Application**
Since June 2021	**Science communication team of the European Society for the Study of Personality Disorders**
Since Nov. 2021	**Elected early career researcher representative at the department for Psychosomatic Medicine and Psychotherapy**
Jan. 2019-Dec. 2021	**Elected early career researcher representative of the German Society for Psychophysiology and its Application** Organizational duties the annual German biopsychological conference "Psychologie und Gehirn" and other events throughout the year, including workshops on reproducibility, career development, as well as political and social events.

Societies

Associate Member of the Society for Ambulatory Assessment
Associate Member of the German Psychological Society
Full member of the German Society for Psychophysiology and its Application
Invited member of the European Society for the Study of Personality Disorders

Publications

*shared first-authorships

Siehl*, S., **Sicorello*, M.**, Herzog, J., Nees, F., Kleindienst, N., Bohus, M., Müller-Engelmann, M., Steil, R., Priebe, K., Schmahl, C., & Flor, H. (*under review at Translational Psychiatry*). Neurostructural associations with traumatic experiences during child- and adulthood. *Preprint available at medRxiv*

Mueller, S.*, **Sicorello, M.***, Moser, D. A., Frach, L., Limberg, A., Gumpp, A. M., ... & Kolassa, I. T. (*under review at Translational Psychiatry*). The DNA methylation landscape of the human oxytocin receptor gene (OXTR): Recommendations for future research. *Preprint available on bioRxiv*

Hummel, E., Elgizouli, M., **Sicorello, M.**, Beygo, J., Giuranna, J., Leitão, E., ... & Kumsta, R. (2022). No evidence for intervention-associated DNA methylation changes in monocytes of patients with posttraumatic stress disorder or anorexia nervosa. *Scientific Reports, 12,* 17347

Meier, M., Lonsdorf, T. B., Lupien, S. J., Stalder, T., Laufer, S., **Sicorello, M.**, ... & Puhlmann, L. M. (2022). Open and reproducible science practices in psychoneuroendocrinology: opportunities to foster scientific progress. *Comprehensive Psychoneuroendocrinology*, 100144.

Paret, C., Unverhau, N., Feingold, F., Poldrack, R. A., Stirner, M., Schmahl, C., & **Sicorello, M.** (2022). Survey on Open Science Practices in Functional Neuroimaging. *NeuroImage*, 119306.

Nebe, S., Hermann, A., Herrmann, M. J., Mier, D., & **Sicorello, M.** (2022). On behalf of the Board of Directors of the German Society for Psychophysiology and its Application eV (DGPA) The Potential of Biopsychological and Neuroscientific Teaching for Teaching Open Science Practices. *Psychologische Rundschau, 73*(1), 33.

Kaess, M., Hooley, J. M., Klimes-Dougan, B., Koenig, J., Plener, P. L., Reichl, C., Robinson, K., Schmahl, C., **Sicorello, M.**, Westlund Schreiner, M., Cullen, K. R. (2021). Advancing a Temporal Framework for Understanding the Neurobiology of Nonsuicidal Self-Injury: An Expert Review. *Neuroscience & Biobehavioral Reviews, 130,* 228-239.

Sicorello, M., Janine, T., Herzog, J., & Schmahl, C. (2021). Differential effects of early adversity and PTSD on amygdala reactivity: The role of developmental timing. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 6*(11), 1044-1051.

Sicorello, M., Herzog, J., Wager, T. D., Ende, G., Mueller-Engelmann, M., Herpertz, S. C., ... & Niedtfeld, I. (2021). Affective neural signatures do not distinguish women with emotion dysregulation from healthy controls: A mega-analysis across three task-based fMRI studies. *Neuroimage: Reports, 1*, 100019.

Sicorello, M., Neubauer, A. B., Stoffel, M., Koehler, F., Voss, A., & Ditzen, B. (2021). Psychological structure and neuroendocrine patterns of daily stress appraisals. *Psychoneuroendocrinology, 105198*.

Sicorello, M., Schmahl, C. (2021). Emotion Dysregulation in Borderline Personality Disorder: A Fronto-Limbic Imbalance? *Current Opinion in Psychology, 37,* 114-120.

Beyer, F., Flannery, J., Gau, R., Janssen, L., Schaare, L., Hartmann, H., ..., **Sicorello, M.**, … & Panagoulas, E. (2021). A fMRI pre-registration template. *PsychArchives.*

Sicorello, M., Dieckmann, L., Moser, D., Lux, V., Luhmann, M., Schlotz, W., & Kumsta, R. (2020). Oxytocin and the stress buffering effect of social company: A genetic study in daily life. *Social Cognitive and Affective Neuroscience, 15*(3), 293-301.

Sicorello, M. & Schmahl, C. (2020). Borderline personality disorder in development. In Kadosh K.C., *Handbook of developmental cognitive neuroscience*. Oxford: University Press.

Sicorello, M., Dieckmann, L., Moser, D., Lux, V., Luhmann, M., Neubauer, A. B., Schlotz, W., & Kumsta, R. (2020). Highs *and* lows: Genetic susceptibility to daily events. *PloS one, 15*(8).

Sicorello, M., Stevanov, J., Ashida, H., & Hecht, H. (2018). Effect of gaze on personal space: A japanese-german cross-cultural study. *Journal for Cross–Cultural Psychology, 50*(1), 8-28.

Sicorello, M., Hölle, M., Baranowski, A. M., & Rettenberger, M. (2016). [Sexual and physical victimization of university students in context of committed relationships, dating relationships, and one-night stands]. *RPsych Rechtspsychologie, 2*(4), 411-428

Acknowledgments

I would like to thank my supervisor Prof. Dr. Christian Schmahl for supporting me throughout my time as a PhD student. In my opinion, a good supervisor gives people what they need to thrive. Christian did exactly this. He gave me autonomy, trust, and—most importantly—always made me feel that he believes in me. Without all these ingredients, I do not think I would have been able to put together this body of work over the last few years. Needless to say, he gave me plenty of scientific guidance, support, and initiated exciting projects I am grateful to have worked on, but the by far biggest gift was: He made me feel proud of my work.

I would also like to thank apl. Prof. Dr. Inga Niedtfeld and Prof. Dr. Robert Kumsta for being great mentors over the last years. More than once, Inga saved my life and sanity with her incredible pragmatism when large projects or my overall career felt chaotic and unpredictable. I deeply appreciate the kind, warm-hearted and caring person she is. The latter is also true for Robert, who was and is such an important person in my life. He is all an outstanding mentor, friend, dancer, and cook. From the first moment we met during my master's studies, I have always felt his genuine support and guidances. He is much more than any intern could have hoped for.

Throughout my time as a PhD student, I learned that the most important thing about any job is the people who surround you. I am incredibly happy to have spent time with so many great people in C4. From the moment I joined the office of Dr. Janine Thome there was always mutual support and a lot of laughter. And the laughter kept on coming with my next office roommates Dr. Julia Herzog and Dr. Jenny Zähringer. The laughter culminated with my last office roommate Sabine Schellhaas, who is simply the best person to lock down with in a remote Airbnb with nothing but a rogue cat and the intention to write a thesis. Also, she always knew when to throw something at me and how heavy I deserve it to be thrown. Her aim

was immaculate, except if it turns out she actually wanted to hit me. In that case, it was very bad.

I never quiet shared an office with Maria Gligorijevic, but it was assuring to know that she was there when I yell moderately loud. She would probably hate me saying this and argue why it is not true, but she is both an amazingly funny and wise person. Talking to her often reminded me of what is important in life, which was a real gift during my dissertation.

It was probably a good idea that I have never shared an office with Dr. Johanna Hepp, because we would not have gotten any work done. Johanna, you are a kindred spirit to a degree that almost feels spooky. Still, I cannot I claim I can match you on your positive attributes, because you are just mind-bogglingly intelligent, effective, reflected, deep, creative, funny, lively, and caring. s

During the last few years, I was privileged to work with so many great student research assistants which both brightened many moments and often took a great weight off my shoulders. Thank you, Beate Martensen, Pauline Schnell, Marlene Schweizer, Elena Buck, Lena Neunerdt, Marlene Schweizer, Svenja Bellmann, Ricarda Natus, and Alina Bruhns.

I would like to thank my parents for patiently supporting me throughout my multiple degrees, even if it seems everything always took longer than expected. I would also like to apologize to my grandmother, who rightfully asked me repeatedly over the last few years, whether I can manage to get my PhD while she is still alive. This was a very effective motivator. I would also like to thank Claudio for being a great big brother and teaching me math.

I would like to thank Lenny and Henning for the great people they are and the many adventures I could not have had without them, as well as my first real PhD friends Dr. Maria Meier, Dr. Stephan Nebe, and Dr. Anne Gärtner. They all were irreplaceable in stressful work phases.

I am especially grateful for Nikolai Jungk, who taught me so much about the nature of emotion.

Last but not least, I would like to thank Clemens for being my best friend and all the support in work and life that comes with this job description.