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How adverse childhood experiences get under the skin: A systematic review, integration and methodological discussion on threat and reward learning mechanisms.

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## Author note

## Conflict of Interest

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### Abstract

Adverse childhood experiences (ACEs) are a major risk factor for the development of multiple psychopathological conditions, but the mechanisms underlying this link are poorly understood. Associative learning encompasses key mechanisms through which individuals learn to link important environmental inputs to emotional and behavioral responses. ACEs may impact the normative maturation of associative learning processes, resulting in their enduring maladaptive expression manifesting in psychopathology. In this review, we lay out a systematic and methodological overview and integration of the available evidence of the proposed association between ACEs and threat and reward learning processes. We summarize results from a systematic literature search (following PRISMA guidelines) which yielded a total of 81 articles (threat:  $n=38$ , reward:  $n=43$ ). Across the threat and reward learning fields, behaviorally, we observed a converging pattern of aberrant learning in individuals with a history of ACEs, independent of other sample characteristics, specific ACE types, and outcome measures. Specifically, blunted threat learning was reflected in reduced discrimination between threat and safety cues, primarily driven by diminished responding to conditioned threat cues. Furthermore, attenuated reward learning manifested in reduced accuracy and learning rate in tasks involving acquisition of reward contingencies. Importantly, this pattern emerged despite substantial heterogeneity in ACE assessment and operationalization across both fields. We conclude that blunted threat and reward learning may represent a mechanistic route by which ACEs may become physiologically and neurobiologically embedded and ultimately confer greater risk for psychopathology. In closing, we discuss future directions for the research field, including methodological and ACE assessment considerations.

*Keywords:* Fear Conditioning, Reward Learning, Adverse Childhood Experiences,  
Literature Review

*Word count:* 9351

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## Introduction

Adverse childhood experiences (ACEs) are defined as “experiences that are likely to require significant adaptation by an average child and that represent a deviation from the expectable environment” (cf. McLaughlin et al., 2016), which in turn impacts a typical (neuro-) developmental trajectory. This definition of ACEs covers a wide range of adverse experiences, such as sexual and physical abuse, emotional abuse and/or neglect, physical neglect, witnessing domestic violence, peer victimization and institutional rearing (e.g., Anda et al., 2006; McLaughlin et al., 2016). For a recent overview of the assessment and operationalization of ACEs in the literature, see Koppold et al. (2023). ACEs confer a heightened risk for developing severe and enduring behavioral, somatic and psychopathological conditions McLaughlin et al. (2012), which incur not only substantial individual suffering but also significant societal costs (Hughes et al., 2021), and are associated with considerable mortality and morbidity. As approximately 60% of all children and adolescents are exposed to at least one adverse event (Madigan et al., 2023), understanding the mechanisms altered by ACEs is crucial for developing theory-guided prevention and intervention approaches (McLaughlin et al., 2019; e.g., Romeo et al., 2018). Early work on ACEs typically focused on single adversity types, such as neglect (Crouch & Milner, 1993) or sexual abuse (Heim et al., 2013) or considered the total number of events experienced as cumulative risk (e.g., allostatic load hypothesis, McEwen, 2003). Over time, the latter approach has been criticized, as different types of experiences are simply ‘lumped’ into a single general adversity category, implicitly assuming a common and equally

powerful, additive impact of different ACE types (Smith & Pollak, 2021). In contrast, the specificity model (e.g., McMahon et al., 2003; Pollak et al., 2000; Pollak & Tolley-Schell, 2004) posits that different types of adverse events impact distinct mechanisms, leading to distinct negative outcomes. Alongside distinct adversity types, research has begun to examine the impact of ACE characteristics on developmental trajectories and outcomes, such as chronicity and intensity, environmental context, or developmental timing of exposure (for a detailed overview see Smith & Pollak, 2021).

Recently, the dimensional model of adversity and psychopathology (DMAP) has emerged as a model of ACE that extends the cumulative and specificity approaches by specifically implicating heightened environmental threat and deprivation as two primary adverse experience dimensions that impact distinct neurobiological systems and lead to differential clinical outcomes (Berens et al., 2017; Kuhlman et al., 2017; Machlin et al., 2019; McLaughlin et al., 2016, 2014; Sheridan & McLaughlin, 2016, 2014; Smith & Pollak, 2021; for an extension see Ellis et al., 2022). In the DMAP, threat has been conceptualized as “the presence of an atypical (i.e. unexpected) experience characterized by actual or threatened death, injury, sexual violation, or harm to one’s physical integrity”, while deprivation has been conceptualized as “the absence of expected environmental inputs in cognitive (e.g. language) and social domains, as well as the absence of species- and age-typical complexity in environmental stimulation” (cf. Sheridan & McLaughlin, 2014). Accordingly, DMAP suggests a specific impact of threat-related experiences on emotional functioning whereas deprivation experiences are hypothesized to affect cognitive functioning (Sheridan & McLaughlin, 2014). A conceptually appealing advantage of DMAP is that threat and deprivation are considered distinct adversity dimensions with specific and distinct effects on developmental mechanisms that can supposedly be examined in parallel. Although there is still an ongoing scientific debate in which the DMAP has been discussed controversially

(McLaughlin et al., 2021; Pollak & Smith, 2021; Smith & Pollak, 2021), a common emphasis placed by all models is on the impact of adversity on the development of associative learning processes in mediating the enduring effects of ACE on later functioning (McLaughlin, 2016; McLaughlin et al., 2019). Associative learning describes implicit learning processes through which environmental cues gain predictive value of positive or negative outcomes. Specifically, threat learning entails an initially neutral stimulus becoming associated with an aversive outcome, while reward learning involves environmental cues becoming predictive of a positive outcome. Being able to identify environmental threats and associated cues and rapidly mobilize adequate defensive responses is essential to ensure survival of the organism. Likewise, interpreting the predictive value of environmental cues or actions that are associated with or are reinforced by rewards is central to guiding motivated behavior and decision-making (Cisek, 2019; Dranias et al., 2008; LeDoux, 2012). Crucially, a considerable amount of cross-species research suggests that the neurobiological circuitry contributing to threat and reward learning is particularly malleable and undergoes substantial maturation and shaping during childhood and adolescence (McLaughlin et al., 2014; Somerville et al., 2010; Tottenham & Galván, 2016). Given this developmental vulnerability, ACEs have been suggested to exert their enduring deleterious effects by impacting the normative development of the circuitry underlying implicit threat and reward learning (Oltean et al., 2022), which is thought to represent an adaptation to unpredictable or fast changing environments (McLaughlin et al., 2019, 2014). For example, growing up in a household with a high probability of physical violence may impact patterns of threat learning: Growing up in a volatile and uncertain environment where incidences of threatening events cannot be predicted and seemingly occur at random disrupt associative learning processes in the long term. Enduring disruptions in associative learning processes may then manifest as persistently maladaptive emotional, cognitive, and behavioral responses, and thereby constitute

an important mechanism underlying the onset and persistence of psychopathology (McLaughlin et al., 2019; McLaughlin & Sheridan, 2016). Aberrant threat learning manifesting in reduced discrimination between threat and safety signals has consequences for survival of the organism and the efficient allocation of energy. Furthermore, while the generalization of fear responses to similar cues is adaptive to ensure survival in the potential presence of threat (“better safe than sorry”), excessive or context-inappropriate overgeneralization can be very costly for the organism and depriving it from benefits (Duits et al., 2015; McCrory et al., 2017). However, not only threat learning but also reward learning is central to an organism’s adaptive functioning. For instance, aberrant patterns of reward learning such as reduced reward anticipation and reduced sensitivity to rewarding feedback, are characteristic of anhedonia-like symptoms typical for mood disorders (Gerin et al., 2017; Oltean et al., 2022). Of note, also other mechanisms, that are, however, not the focus of this work, are of potential relevance including emotion regulation and executive control (McCrory et al., 2017) as well as the quality of the social network (McCrory et al., 2022). Thus, early adverse experiences have enduring consequences due to the heightened neural plasticity during development (Kolb & Gibb, 2014) and are considered to convey an adaptation to the environment in which the child develops (i.e., experience-dependent plasticity, McCrory et al., 2017).

In order to paint a coherent picture of the influence of ACEs on associative learning processes, it is essential to provide a systematic and methodological investigation and integration of the relatively insulated fields of threat and reward learning. Improving our understanding of how reward and threat learning may be impacted by ACEs could inform the mechanistic link between childhood adversity and psychopathology. Further, it holds promise to improve existing and develop novel avenues in targeted prevention and intervention approaches for psychopathology associated with a history of ACE (McLaughlin et al., 2019; Odriozola & Gee,



2021). In addition, this systematic investigation serves to identify key methodological considerations and challenges in the study of ACEs and can be expected to spark discussion for future research.

## Methods

The systematic literature search was conducted according to the PRISMA guidelines (Moher et al., 2015; Page et al., 2021). Studies published before December 2022 were included if tasks involved a threat or reward learning element (instructed or uninstructed) and investigated associations with ACEs using terms related to “fear or threat conditioning”, “aversive anticipation”, “threat of shock” in the threat learning field and “reward or reinforcement learning or anticipation” in the reward learning field, as well as the terms “adversity”, “maltreatment”, “abuse”, “neglect”, “stress”, “trauma”, “deprivation”, “institutionalization”, “orphanage”, “adoption”, “harassment”, “bullying”, “household violence”, “domestic violence”, “poverty”, “low SES”, “food insecurity” and “adverse childhood experiences” in “children”, “childhood”, “early”, “youth” or, “adolescents”. Articles were excluded, if they were reviews or meeting abstracts, or if they used non-human samples, if they did not include a learning element or if they assessed general life-time trauma or adversity instead of ACEs (see **Supplementary Material** for details). ”

A threat or reward learning element was defined as physiological or behavioral adaptation over time to the repetitive or prolonged presentation of a cue. While fear conditioning and reinforcement learning tasks can obviously be categorized as learning tasks, the view on the monetary incentive delay (MID) task is more nuanced. The MID can also be understood as a learning task because participants show a response modulation by the reward amount (Dhingra et

al., 2020). More precisely, the task induces changes in sensory processing over time (Krugliakova et al., 2019), providing evidence of instrumental or reinforcement learning, where the presentation of a specific cue triggers an action that is rewarded. Likewise, the learned, anticipatory response (Wilson et al., 2018) - as assessed through BOLD fMRI - to a reward is conceptually comparable to BOLD fMRI responses during presentation of CS+ vs. CS- in threat learning (see **BOX 1** for information on the paradigm), that is the anticipation of threat vs. safety. We used a likelihood heuristic (Lakens & Etz, 2017) as an indicator of the (relative) evidence for either the alternative (H1) or the null hypothesis (H0) in sets of studies that yield mixed results. In fact, it is highly unlikely that a given set of studies will all yield significant effects. To this end, we calculated the probability of the observed ratio of statistically significant results, and null effects or results pointing in the opposite direction under the assumption that either the null or the alternative hypothesis is true (based on code provided by Lakens & Etz, 2017). The likelihood ratio is a comparison of how well the two hypotheses (in this case, H0 and H1) predict the observed data (given  $\alpha = 0.05$  and a power of 0.8). Of note, the likelihood ratios are neither intended to serve as quantitative, meta-analytic metrics, nor do they provide any information on effect sizes of the studies or weight the included studies by quality measures (as typically done in a meta-analysis). The likelihood ratios rather provide a heuristic estimation of whether the overall pattern of results across the included studies is in favor of the H0 or the H1. For data analyses and visualizations as well as for the creation of the manuscript, we used the following R packages <sup>1</sup>.

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<sup>1</sup> R (Version 4.2.3; R Core Team, 2023) and the R-packages *ade4* (Bougeard & Dray, 2018; Chessel et al., 2004; Dray et al., 2007; Version 1.7.22; Dray & Dufour, 2007), *citr* (Version 0.3.2; Aust, 2019), *data.table* (Version 1.15.2; Dowle & Srinivasan, 2023), *dplyr* (Version 1.1.4;

## Results

We identified a total of 3,127 publications, and after screening of title, abstract, and full text, 81 articles investigating associations between ACEs and threat (n= 38 publications) and reward learning (n=43 publications) were retained and included in analyses (see **Supplementary Material** for details). A breakdown of sample and ACE characteristics as well as experimental specifications of these studies are detailed in the following section and illustrated in **Figure 1** and **Figure 2**, respectively.

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Wickham, François, et al., 2023), *forcats* (Version 1.0.0; Wickham, 2023), *ggplot2* (Version 3.5.0; Wickham, 2016), *ggpubr* (Version 0.6.0; Kassambara, 2023), *here* (Version 1.0.1; K. Müller, 2020), *knitr* (Version 1.45; Xie, 2015), *lubridate* (Version 1.9.3; Golemund & Wickham, 2011), *papaja* (Version 0.1.2; Aust & Barth, 2022), *patchwork* (Version 1.2.0; Pedersen, 2022), *psych* (Version 2.4.3; William Revelle, 2023), *purrr* (Version 1.0.2; Wickham & Henry, 2023), *qgraph* (Version 1.9.8; Epskamp et al., 2012), *RColorBrewer* (Version 1.1.3; Neuwirth, 2022), *readr* (Version 2.1.5; Wickham, Hester, et al., 2023), *readxl* (Version 1.4.3; Wickham & Bryan, 2023), *reshape2* (Version 1.4.4; Wickham, 2007), *stringr* (Version 1.5.1; Wickham, 2022), *tibble* (Version 3.2.1; K. Müller & Wickham, 2023), *tidyr* (Version 1.3.1; Wickham, Vaughan, et al., 2023), *tidyverse* (Version 2.0.0; Wickham et al., 2019), *tinylabls* (Version 0.2.4; Barth, 2022), *viridis* (Garnier et al., 2022; Version 0.6.5; Garnier et al., 2023), and *viridisLite* (Version 0.4.2; Garnier et al., 2022)

### Summary of sample characteristics

Studies in the threat and reward learning fields were compared across several dimensions. First, in terms of participant age, studies in the threat field relied on roughly similar proportions of pediatric samples (i.e. children/adolescents) and samples of adults who report that they have experienced adverse events as children (**Figure 1A,B**), while in the reward field slightly more studies were conducted in children or adolescent samples. Second, across both fields, studies typically recruited healthy individuals who were screened for psychiatric disorders or community samples (i.e. participants drawn from the general population with little or no exclusion criteria for psychiatric symptoms or diagnoses). Only very few studies recruited clinical samples (**Figure 1C,D**), although in the threat field participants were often recruited from populations with high risk of experiencing trauma (e.g., low socioeconomic status regions, agencies that work with families exposed to violence or food banks). Third, while most studies across both research fields did not specifically aim to study specific ACE types (**Figure 1E,F**), threat-learning studies investigated predominantly samples reporting experience of threat-related adverse events (**Figure 1E**), as assessed mostly through self-reported questionnaires (**Figure 1G**). In contrast, studies from the reward learning field also used official records and diagnostic criteria for medical conditions as well as customized questions not part of a validated questionnaire for the assessment of ACEs (**Figure 1H**). Further, some studies from the reward learning field specifically focused on parental substance abuse (category “nonspecific”, **Figure 1F**) and reduced neighborhood quality or socioeconomic status. Fourth, studies from the threat learning field assessed mostly subjective adverse experiences rather than exposure to potentially adverse events or environments, whereas this ratio was more balanced across the reward learning studies (**Figure 1I, J**).

### Summary of paradigm characteristics

In the threat learning field, the majority of studies used a fear conditioning paradigm (71.05%) with varying experimental phases (e.g. acquisition training, extinction training, generalization, return of fear), and the remaining studies employed different forms of threat anticipation tasks (**Figure 2A** and see **BOX 1** for details on other paradigms such as threat of shock task, the NPU threat task or an aversive avoidance task) which involved learning by direct experiences or instructions. The paradigms employed in the reward-learning field were more heterogeneous spanning 15 different paradigms which illustrates that there is no prototypical reward learning task in the field (see **BOX 1** for an overview). The most commonly applied task was the MID task (19/43 studies). Other more common reward tasks included for example instrumental reward learning (3/43 studies), and probabilistic learning (3/43 studies) while other tasks were only employed in individual studies (see **Figure 2B**). As such, studies in the threat learning field used primary reinforcers (e.g., aversive stimuli), while the reward learning field used exclusively secondary reinforcers such as monetary reward (**Figure 2C,D**). In addition, while the threat learning field mainly employed subjective ratings and psychophysiological outcome measures (mainly skin conductance response (SCR) and fear potentiated startle (FPS)) to assess learning-driven changes, the reward learning field focused primarily on task behavior metrics, such as reaction time, accuracy, points earned, learning rates, and reward prediction error in addition to fMRI (**Figure 2, E,F**).

### Study quality evaluation

**Supplementary Tables 6 and 7** show the assessments of study quality. The quality assessment tool used in the meta-analysis by Oltean et al. (2022) was adapted to the present review and focuses on sample characteristics and ACE assessment methods. Paradigm specifications were not evaluated, because objective criteria for assessing the quality of e.g. fear conditioning

paradigms are not available. The quality assessment showed that, in both the threat and reward learning field, sample sizes were very small (less than 30 subjects per group) in a substantial amount of studies (33.3 %). However, 50 % of studies had large sample sizes of 60 participants or more speaking for enhanced interpretability of results (see Supplementary Figure 1 for a distribution of sample sizes) . In addition, the samples were at least somewhat representative and subjects were screened for psychopathologies in the majority of the studies (88.9 %). In 50 % of the studies only very few or even single ACE types were assessed (e.g. institutional rearing or low SES) - 38.9 % using non validated assessment instruments or composite scores from different instruments.

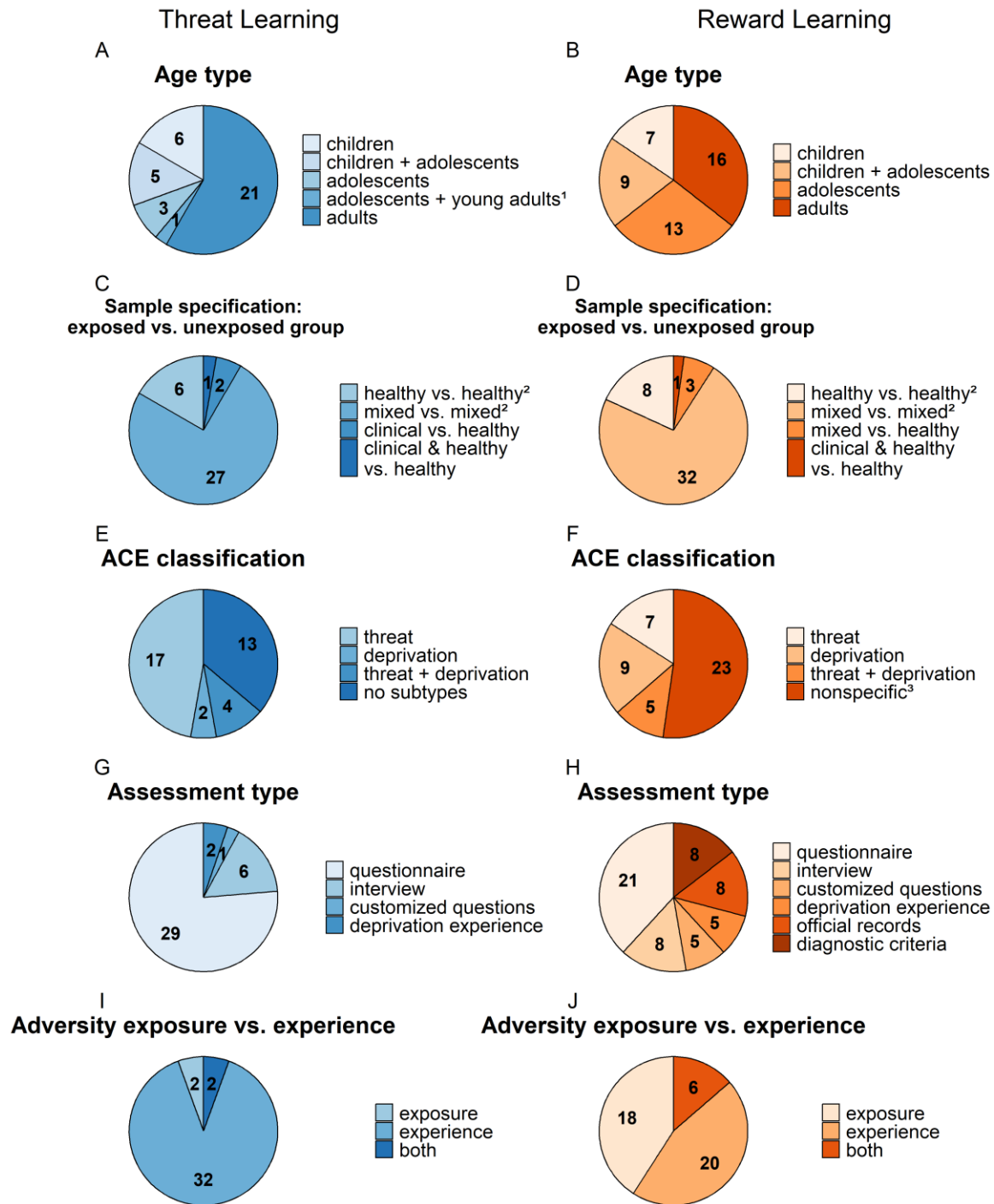


Figure 1: Sample characterization and ACE assessment instruments used in the studies included in the review on an association between ACEs and threat (n=38; A, C, E, G, I in blue) and reward (n=43; B, D, F, H, J in orange) learning processes. Numbers represent the number of studies to

which a specific characteristic applies (note that these do not add up to the total number of studies as multiple characteristics may apply to a single study). Total sample sizes of the individual studies range from  $N = 19$  to  $N = 11360$  (see **Supplementary Figure 1** for details). <sup>1</sup> Refers to participants aged 17-19 years; <sup>2</sup> Includes studies that assess ACEs dimensionally across all participants as well as studies that excluded participants with psychological disorders. <sup>3</sup> Includes studies that assess ACEs that cannot be classified as either threat or deprivation.

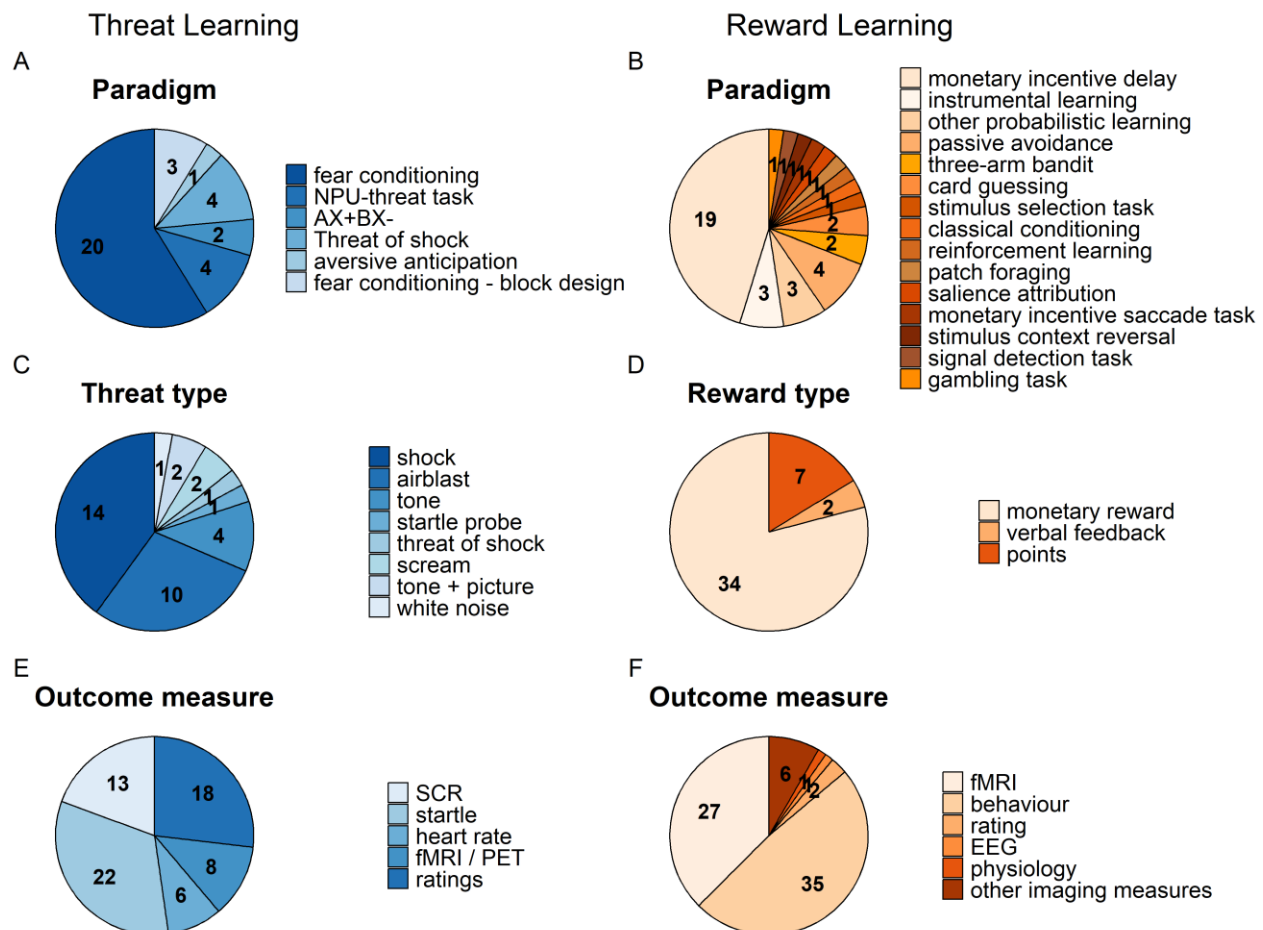




Figure 2: Paradigm specifications as well as outcome measures used in the studies included in this review for threat- (A, C,E, in blue) and reward-related learning (B, D, F, in orange) including paradigm type (A, B), type of threat or reward (C, D), and outcome measures used (E, F).

Numbers represent the number of studies to which a certain specification applies (note that these do not add up to the total number of studies as multiple specifications may apply to a single study).

### **Associations between exposure to ACEs and threat-related learning**

The following results are structured according to the phases of a typical classical fear conditioning paradigm. During fear acquisition training, a neutral cue is repeatedly paired with an aversive stimulus (e.g., electrotactile stimulation; unconditioned stimulus, US). This pairing turns the previously neutral cue into a conditioned stimulus (CS+), which triggers conditioned fear responses (CRs), while a second neutral cue (CS-) is never paired with the US, serving as a safety stimulus. In a fear generalization phase, additional stimuli, perceptually similar to the CS+ and CS-, are presented (generalization stimuli; GSs) to assess generalization of the conditioned fear response. During a subsequent fear extinction training phase, both CS+ and CS- are presented without the US, leading to a gradual decrease in CRs. For details on the paradigm and the different variations employed in the studies included in this review, see **BOX 1**.

*Acquisition.* Across a number of threat-related learning paradigms (n=21 studies), a consistent finding emerged of reduced discrimination between signals of threat and safety (i.e., CS+ and CS-) in individuals reporting ACEs. Reduced discrimination was rather consistently driven by blunted responding to cues signaling threat (i.e., CS+, anticipation of a negative image) in psychophysiological fear responses as measured with SCR (Harnett et al., 2019; Klingelhöfer-

Jens et al., under review; Kuehl et al., 2020; Machlin et al., 2019; McLaughlin et al., 2016), FPS (Lis et al., 2020; Stout et al., 2021; Thome et al., 2018), as well as self-reported fear ratings (Qiu et al., 2022); see **Figure 2E** for outcome measures used across studies. These results originate from samples of adults reporting ACEs as children (6 out of 10 studies) as well as children and adolescents (3 out of 5 studies; see **Supplementary Material** for details). However, three additional studies reported enhanced rather than reduced discrimination between signals of threat and safety in exposed individuals reporting a history of ACEs in SCRs (Marusak et al., 2021) and FPS (Zoladz et al., 2022) in females, but not males (Morrison et al., 2022). Of note, methodological challenges (use of unorthodox SCR scoring windows (Marusak et al., 2021); reporting of exclusively within-CS or within-group statistics (Morrison et al., 2022; Zoladz et al., 2022) without providing the crucial statistical test for an interaction effect (Gelman & Stern, 2006; Nieuwenhuis et al., 2011)) render the claims of these studies difficult to interpret unambiguously. At the same time, however, similar methodological challenges were also evident in some studies that do show reduced threat discrimination in individuals reporting ACEs (Machlin et al., 2019; Thome et al., 2018, see discussion for details), highlighting the need for consistent methodological approaches in the fear conditioning field. Furthermore, although only rarely analyzed, severity of ACEs was also negatively correlated with responsiveness to danger signals (McLaughlin et al., 2016; Qiu et al., 2022; but see Estrada et al., 2020).

A substantial number of studies also report no effects of ACEs on fear acquisition for at least one out of several outcome measures, including SCR (Bremner et al., 2005; Estrada et al., 2020; Huskey et al., 2022; Morrison et al., 2022; Scharfenort et al., 2016), FPS (Deslauriers et al., 2018; Huskey et al., 2022; Jovanovic et al., 2009; Kuehl et al., 2020; Morrison et al., 2022; Rowland et al., 2022; Stenson et al., 2021; Thome et al., 2018; Zoladz et al., 2022), heart rate (Huskey et al., 2022), ratings of valence and arousal (Klingelhöfer-Jens et al., under review; Qiu et al., 2022;

Schellhaas et al., 2022), fear (McLaughlin et al., 2016; Scharfenort et al., 2016), expectancy/contingency (Huskey et al., 2022; Klingelhöfer-Jens et al., under review; Zoladz et al., 2022) as well as null findings also during re-acquisition (Bremner et al., 2005) and behavioral distance (Marusak et al., 2021).

In addition, two studies suggest developmental effects of ACEs on threat learning in which successful CS discrimination at an earlier than typical age (i.e., already at 4-5 years, Machlin et al., 2019) and more adult-like functional connectivity between the hippocampus and prefrontal regions (Silvers et al., 2016) was observed.

*Generalization.* Patterns of reduced discrimination between signals of threat and safety following threat learning in individuals reporting ACEs also emerges in generalization phases (Klingelhöfer-Jens et al., under review; 5 out of 7 studies: Lange et al., 2019; Qiu et al., 2022; Thome et al., 2018; Zoladz et al., 2022). This was, however, again mostly driven by blunted CS+ responding in SCRs (Klingelhöfer-Jens et al., under review), lower US expectancy ratings (Qiu et al., 2022), blunted valence and arousal ratings to the CS+ as well as enhanced ratings to the CS- (Lange et al., 2019) rather than differences in generalization gradients. A single study reported enhanced startle to the CS- in females reporting ACEs only (Zoladz et al., 2022), although no statistical results for males or females that do not report ACEs were provided. Of note, these effects matched the direction of effects for the same study during preceding acquisition training phase in Klingelhöfer-Jens et al. (under review) but were in the opposite direction in Zoladz et al. (2022) while no acquisition results were reported in Lange et al. (2019).

No study reported enhanced CS discrimination during generalization, but a number of null findings emerged (ratings of US expectancy/contingency: Lange et al. (2019); Klingelhöfer-Jens et al. (under review); Zoladz et al. (2022), valence and arousal: Klingelhöfer-Jens et al. (under review), risk: Lis et al. (2020) and fear: Lange et al. (2019), startle Lis et al. (2020)).

Interestingly, generally no differences in generalization gradients were observed in these studies, even though one study (Zoladz et al., 2022) claims enhanced generalization in exposed females. As this study, however, did not observe any statistically significant differences between any of the conditioned and generalization stimuli, these results are difficult to interpret. On a behavioral level, trauma-exposed individuals reported highest threat uncertainty (longer reaction times) to highly-ambiguous GSs, while healthy controls reported most uncertainty when rating GSs that were most similar to the CS+ (Thome et al., 2018).

In sum, a converging pattern emerged across studies whereby individuals reporting a history of ACEs show reduced discrimination between learned signals of danger and safety, primarily driven by blunted responding to signals of danger during fear acquisition training and generalization.

*Extinction.* For the extinction phase (N=12, whereof six do not report acquisition results), most studies report no effects of ACEs on extinction learning (Bremner et al., 2005; Huskey et al., 2022; Kuehl et al., 2020; SCR: Marusak et al., 2021; McLaughlin et al., 2016; Scharfenort et al., 2016; Susman et al., 2021), FPS: France et al. (2022); Huskey et al. (2022); Kuehl et al. (2020), ratings of fear: Scharfenort et al. (2016); McLaughlin et al. (2016), and expectancy: Huskey et al. (2022), as well as heart rate: Bremner et al. (2005); Huskey et al. (2022), or behavioral distance: Marusak et al. (2021)].

Of the three studies that observed a significant association between ACEs and fear extinction, one reports higher US expectancy to the CS- with an increasing number of experienced traumatic events. The same study demonstrated an enhanced behavioral distance to the CS+ as compared to the CS- during extinction recall (but not extinction) for children reporting a history of ACEs compared to children reporting no history of ACEs (Marusak et al., 2021). Two other studies report enhanced SCR to the CS+ in children with a history of ACEs during extinction (Jenness et

al., 2019; Milojevich et al., 2020). The results, however, are inconsistent across the two publications reporting results from the same experiment using the same sample: McLaughlin et al. (2016) and Machlin et al. (2019) report the results from a preceding fear acquisition training to the extinction phase referred to in Jenness et al. (2019) and Milojevich et al. (2020), respectively (outlined in detail in the discussion).

*General reactivity.* In addition to the overall pattern of blunted threat-learning, a number of studies also report heightened general (physiological) reactivity in ACE exposed individuals in FPS (Jovanovic et al., 2009; Kreutzer & Gorka, 2021; Pole et al., 2007; Rowland et al., 2022; Wolitzky-Taylor et al., 2014), interaction effects (Young et al., 2019; Zoladz et al., 2022), descriptive evidence (Morrison et al., 2022), SCRs (Estrada et al., 2020, i.e. decreased habituation), interaction effects (Jovanovic et al., 2020; Scharfenort et al., 2016; Young et al., 2019) and risk ratings (Lis et al., 2020; Thome et al., 2018). Of note, Kreutzer and Gorka (2021) observed generally enhanced startle reactivity in individuals that have experienced interpersonal trauma (and higher trauma load), but blunted responding in individuals exposed to other trauma types (and lower trauma load) as compared to controls. In addition, Jovanovic et al. (2022) report a negative correlation of startle reactivity towards the CS+ and trauma exposure, but only in participants aware of experimental contingencies, while they report the opposite pattern for unaware participants. Decreased general reactivity, however, is only reported by one study using SCR (Klingelhöfer-Jens et al., under review) and some studies report null findings (all outcome measures: Young et al. (2018); Huskey et al. (2022); Jovanovic et al. (2022); startle and contingency ratings: Jovanovic et al. (2009); valence, arousal, contingency ratings: Klingelhöfer-Jens et al. (under review), heart rate: Young et al. (2019)).

*Neuroimaging.* Neuroimaging results are presented separately and across all experimental phases, as only few studies report such findings. Results (see **Figure 2E**) for both amygdala and

hippocampus activation during acquisition training were inconsistent across studies. For the amygdala, blunted CS discrimination and learning slopes (DeCross et al., 2022) as well as enhanced (Bremner et al., 2005) or reduced reactivity in individuals reporting ACEs (Harnett et al., 2019) and null findings (Silvers et al., 2016) are reported. For the hippocampus, higher activation for CS+ vs. CS- in individuals reporting ACEs (Silvers et al., 2016) or a negative association with ACEs (Harnett et al., 2019) and null findings (DeCross et al., 2022; Scharfenort et al., 2016) are reported. Negative associations of neural activation with ACEs are further reported for the dorsolateral and ventromedial prefrontal cortex (Harnett et al., 2019). During fear generalization, no associations between ACEs were observed with (re-)activation of the amygdala, vmPFC (Lange et al., 2019), insula, dorsal anterior cingulate cortex (dACC), hippocampus, or vmPFC (Morey et al., 2015). During extinction recall, children reporting ACEs showed stronger (re-)activation in the dACC and the insula (but not in other regions of interest (ROIs)) to the extinguished CS+ as compared to controls in absence of group differences for the CS- (Marusak et al., 2021).

*Summary of results.* For fear acquisition, a total of 21 studies reported results. Of these studies, 9 studies reported blunted responses to the threat cue in individuals with a history of ACEs (in any outcome measure), yielding a likelihood ratio of 520.90 . This indicates that the likelihood that the alternative hypothesis (i.e., there is an effect) is true is 521 times higher than the likelihood that the null hypothesis is true. In contrast, 3 studies report enhanced responding to the threat cue in individuals with a history of ACEs (even though methodological challenges hamper a clearcut interpretation of these results, see introduction and discussion for details) which yields a likelihood ratio of 369,934,661.74 in favor of the null hypothesis. For threat generalization, a total of 7 studies reported results for a generalization phase. Of those, 5 reported blunted responding to threat cues in individuals reporting ACEs compared to controls, yielding a

likelihood ratio of 46,474.28 in favor of the alternative hypothesis . Together, these results can be taken to infer that the cumulative evidence provides support for the interpretation that ACEs are indeed linked to blunted responding to threat cues during (experimental) threat acquisition and generalization. As likelihood ratio tests do not provide quantitative meta-analytic evidence and are not weighted by study quality, these results should be interpreted as heuristic estimates of the overall pattern.

### **Associations between exposure to ACEs and reward-related learning**

The systematic literature search for reward learning revealed a mix of null findings alongside the same amount of studies showing attenuated reward (learning) performance. Here, attenuated reward performance serves as an umbrella term describing a plethora of outcome measures across the different tasks (see **Figure 2B**) that share a common element of deficient behavior during probabilistic, reward-related reinforcement learning.

*Behavioral results.* 14 out of 28 studies reporting behavioral results show blunted responding to rewarding feedback following adverse experiences during childhood (see **Figure 2F**). The most commonly employed indicators of reward learning performance in these studies are measures of task performance (i.e, number of correct responses, points or reward earned) and speed of learning (i.e, reaction time or learning rate (H. Delgado et al., 2022; Dennison et al., 2019; Harms et al., 2018; Patterson et al., 2013; Pechtel & Pizzagalli, 2013; Sheridan et al., 2018; Weiss et al., 2019; White et al., 2022; Wilkinson et al., 2021; Wismer Fries & Pollak, 2017)). Deficient reward expectation or the violation thereof (i.e., prediction error) in the ACE group was restricted to studies employing reinforcement learning models (Hanson et al., 2017; Letkiewicz et al., 2022). Furthermore, in an exploration-exploitation task, reduced exploration and learning rate in exposed individuals is interpreted as a less optimal strategy to maximize rewards (Lloyd et al.,

2022). In addition, in an incentive saccade task, exposed individuals show reduced responsiveness to rewarding feedback and less improvement of error performance under positive reinforcement (Mueller et al., 2012). One study (Dillon et al., 2009) reports that exposed participants rated rewarding cues as less positive in a MID task.

*Behavioral null results.* Importantly, the same number of studies (n=14) report null results for the association between ACEs and reward learning performance. Outcome measures were comparable between studies reporting significant and null findings (e.g., response times, success rate or number of errors (Bjork et al., 2008; Boecker-Schlier et al., 2016; Cisler et al., 2019; Dennison et al., 2016; Dillon et al., 2009; Gonzalez et al., 2016; Mehta et al., 2010; Morris et al., 2015; K. U. Müller et al., 2015; Smith & Pollak, 2022; Weiland et al., 2013), measures of reward expectation and prediction error (Cisler et al., 2019)). A more unique set of outcome measures – commission and omission errors - obtained from passive avoidance tasks was used in two studies with null findings (Blair et al., 2022; Gerin et al., 2017), which might suggest that while active reward learning seems to be affected by ACEs, reinforcement learning in the context of passive avoidance may not be.

*Neuroimaging results.* In addition to these behavioral measures, 17 studies additionally or exclusively used neuroimaging (i.e., fMRI) to compare brain activity elicited during reward anticipation or feedback in participants with and without a history of ACEs. Ten of these studies provide evidence for reduced neural (re)activation during the anticipation of a rewarding outcome following ACEs in distributed areas Morelli et al. (2021) as well as in dedicated reward-processing circuitry including the ventral striatum and the insula (Boecker-Schlier et al., 2016; Gerin et al., 2017; Martz et al., 2022; Mullins et al., 2020; Yau et al., 2012). In contrast, six studies show enhanced (re)activation (e.g. in the thalamus, midbrain, insula, ventral striatum, inferior and medial frontal gyrus, dorsolateral prefrontal gyrus) during reward anticipation



(Casement et al., 2014; DelDonno et al., 2019; Gonzalez et al., 2016; Hendrikse et al., 2022; Kwarteng et al., 2021; Romens et al., 2015).

Three studies show ACE-related enhanced brain (re)activation (i.e. inferior frontal, cingulate and superior temporal gyrus as well as, prefrontal cortex, thalamus, putamen) during loss feedback or prediction errors (Birn et al., 2017; Gerin et al., 2017; Yang et al., 2021) including a linear relationship between number of traumatic events and ventral ACC activation (Eckstrand et al., 2019). An additional four studies show no difference between exposed participants and an unexposed control group during reward anticipation (Bjork et al., 2008; K. U. Müller et al., 2015; Weiland et al., 2013) and delivery (Boecker-Schlier et al., 2016).

*Summary of results.* Together, the current systematic literature review suggests evidence for reduced learning associated with rewards in participants with a history of ACEs. This finding is consistent with a recent meta-analysis (Oltean et al., 2022) that included 14 of the 43 studies reviewed here but had a broader focus on reward processing in general. The current review extends such general findings by focusing specifically on reward learning mechanisms and specifically including experiences of deprivation - which was in the studies included here operationalized for instance as low SES or institutional rearing. The observed pattern of results is further supported by likelihood ratio tests (Lakens & Etz, 2017). A total of 28 studies obtained and reported behavioral measures of reward learning performance. Of those studies, 14 studies reported a significant reduction in reward learning or the valuation of rewarding outcomes. Fourteen studies reported no significant group differences or associations with ACEs in reward learning. This pattern of findings yields a likelihood ratio of 24,208,574.79 implying that - given the data - the alternative hypothesis is 24208575 times more likely to be true than the null hypothesis. From these results we can infer that similar to threat learning, reward learning in individuals reporting ACEs seems to be blunted. A more inconsistent pattern of results could be

detected for fMRI activation patterns: 10 out of 17 studies suggest reduced (re-)activation in (not only) reward-related brain regions during the anticipation of a rewarding outcome. At the same time, seven studies showed the opposite result pattern with enhanced activation in midbrain regions and the activation of a wider brain network during reward anticipation.

## **Discussion**

Here we provide a systematic literature review on associations of ACEs with threat and reward learning while also focusing on general experimental and assessment practices in the field. The results paint a rather converging picture of blunted threat and reward learning (but no effect on safety learning or generalization) across different samples, ACE types and behavioral outcome measures.

### **ACEs are linked to blunted threat learning**

Blunted threat learning manifested primarily as reduced discrimination between learned signals of threat and safety, consistently driven by reduced responding specifically to the threat signal. Thus, reporting a history of ACEs appears to be associated with enduring effects on the capacity to differentiate environmental cues for aversive and safe outcomes. Of note, this pattern is distinct from what is typically observed in patients suffering from anxiety and stress-related disorders - enhanced responding specifically to the learned safety signal (e.g., Duits et al., 2015), which likewise results in reduced CS discrimination. Yet, it is important to note that not all patient samples in the threat learning field are characterized by exposure to adverse events, even though this is a strong risk factor associated with the development of psychopathologies. As most of the studies included in this review were conducted in non-clinical samples, it could be speculated that blunted conditioned threat responding may reflect a potential resilience factor,

since participants were generally healthy despite a history of ACEs. Yet, this interpretation seems rather implausible in the light of blunted CS+ responding also in studies including at-risk and patient samples (i.e., patients suffering from PTSD following childhood sexual abuse (Lange et al., 2019; Lis et al., 2020; Thome et al., 2018)). Hence, we suggest that threat learning processes in individuals with a history of ACEs are distinct from those generally observed in anxiety patients.

As ACEs are considered a potent risk factor for the development of psychopathology (e.g., Teicher et al., 2022), we speculate that individuals with a history of ACEs may represent a distinct sub-group of patients which has so far been understudied due to a strong focus on group level inferences (patients vs. controls) and a lack of studies aiming to identify and utilize individual-level heterogeneity in response pattern.

### **ACEs are linked to blunted reward learning**

Reduced reward learning performance presented itself as reduced accuracy or reward earned and speed of learning in individuals with a history of ACEs which can be interpreted as blunted responding to, and integration of, reinforcing reward information. This finding is in line with a recent meta-analysis demonstrating a medium-sized association between ACEs and reward learning (in addition to other aspects of reward processing, Oltean et al., 2022). In contrast to the results presented in the meta-analysis, the current work has a much broader understanding of ACEs that includes adversity ranging from specific threatening experiences (e.g. sexual abuse) to long-lasting exposure to potentially adverse events for which the individual experience is less clear and may differ substantially between individuals (e.g., growing up in a low SES environment, parental substance abuse). The fact that we observe a similar pattern of results with a much broader definition of ACEs compared to the previous meta-analysis should be considered a strength of the current work and can be taken as evidence for the robustness of the identified

effects. Our systematic investigation of the literature additionally revealed a mix of blunted ( $n=10$ ) and enhanced ( $n=7$ ) responding at the level of the brain during reward anticipation in a distributed set of brain regions. Further, evidence from several studies indicates that individuals with a history of ACEs show hyperresponsivity to losses, suggesting that the differences in reward anticipation are not due to diminished hedonic value (Birn et al., 2017) but rather reflect reduction in incentive salience (Olney et al., 2018). This interpretation is further supported by a study showing that individuals that report ACEs rate rewarding cues - not the reward itself - as less positive than unexposed individuals (Dillon et al., 2009). A more far-reaching interpretation would be that ACEs might have affected the development of the dopaminergic system, which has been discussed as a consequence of childhood adversity more broadly (for a discussion see Smith & Pollak, 2022). It would, however, be premature to draw strong conclusions about such neurobiological mechanisms without more conclusive evidence. From a neuropathological perspective, the collected findings are in line with findings in anhedonia which is similarly characterized by selective impairments in reinforced actions rather than reward responsiveness (Pizzagalli, 2014).

### **Robustness of blunted threat and reward learning in light of heterogeneity in samples, procedures and operationalizations**

Integrating the results from two research fields, we can conclude that the pattern of blunted behavioral responding to threat or rewards emerges independent of diverse sample or paradigm choices. Hence, we suggest that our conclusions hold for both research fields in general. For instance, this pattern of results is observed in pediatric samples (i.e., children or adolescents) versus adults, and regardless of whether individuals were exposed to only potentially adverse events or whether they had experienced severe threat or harm.

Furthermore, our systematic literature review highlights the existence of rather homogeneous

threat but quite heterogeneous reward learning paradigms. It is hence noteworthy that a rather converging pattern was observed not only in the threat learning field - in which similar paradigms are applied across studies - but also in the reward learning field despite diversity of the employed paradigms and hence the specific sub-processes investigated. We thus conclude that ACEs seem to be linked to generally blunted learning from threat and reward.

From an evolutionary perspective, it is generally adaptive to quickly learn to link environmental cues to threats and rewards to promote survival and thriving of the organism in normative environments. The often unpredictable nature of environments featuring adverse conditions may render it more adaptive to dampen behavioral modification by the erratic and infrequent signals of threat and reward. This pattern of responding, potentially resembling ‘emotional numbness’ (Litz & Gray, 2002), may be understood as a behavioral and neural recalibration to an ever-changing environment (Gerin et al., 2017) and thus as a coping strategy. It can hence be speculated that the pattern of blunted threat and reward learning in individuals reporting a history of ACEs may represent a coping strategy to environmental demands.

From a therapeutic perspective, blunted threat and reward learning constitutes a potentially modifiable experience-dependent plasticity process that is at the core of many well established clinical interventions such as cognitive behavioral therapy and hence holds promise to be targeted in clinical interventions. More specifically, discrimination training may enhance the ability to discriminate between signals of threat and safety which may prevent overgeneralization. While successful clinical translation is based on individual level effects, the studies reviewed here nearly exclusively focus on group level inferences. It is hence an important next step for future work to disentangle whether these associations observed on average also map onto response patterns at the individual level.

In addition, it is important to note that the scope of effects due to perturbed maturation of threat

and reward learning processes following ACE might extend beyond simple associative learning to other experience-dependent domains. For example, ACE-driven blunted reward or threat signals during intricate social situations may interfere with the ability to acquire normative social cognition capacities that are based on accurate reinforcement, and impair social functioning as individuals grow up (Leblanc & Ramirez, 2020). Indeed, social learning has been shown to be malleable in children and affected by environmental factors such as caretaker education (Bulgarelli & Molina, 2016). Similarly, a recent meta-analysis demonstrated that children and adolescents with a history of ACE, and particularly deprivation, show executive functioning difficulties, such as poor inhibitory control (Johnson et al., 2021). Given that the extent of such capacities is believed to depend on the availability and presence of rewards (which affords experiences of inhibition, Burton et al., 2021), an environment of early-life deprivation may result in diminished ability to acquire adequate inhibitory control capacity that is required for general executive functioning. Given such potential links, future research is encouraged to examine the role of associative learning deficits due to ACE in perturbed development of cognitive and emotional functions that extend beyond simple threat and reward responding.

**No evidence from the literature for a link between specific ACE types and reward and/or threat learning**

Importantly, our systematic literature review does not find evidence for distinct effects of specific ACEs with either reward or threat learning performance. In the threat learning field, four out of nine studies focusing exclusively on threat-related ACEs show blunted responding to threat-cues in individuals with a history of ACEs (Kuehl et al., 2020; Lis et al., 2020; McLaughlin, 2016; Thome et al., 2018) while three studies report null-findings (Jovanovic et al., 2009; Rowland et al., 2022; Stenson et al., 2021) and two studies enhanced threat responding (Marusak et al., 2021; Morrison et al., 2022). A likelihood ratio test indicates that - given this pattern of results - an

association between threatening experiences and blunted threat responding is 27.10 times more likely than the null hypothesis. The pattern of results from the two available studies focusing exclusively on deprivation-related ACEs is comparable: One study investigating the relationship between deprivation-related ACEs and threat learning reports reduced CS discrimination driven by blunted responding to cues signaling threat in self-reported fear ratings in individuals with a history of ACEs as compared to controls (Qiu et al., 2022). The second study reports higher hippocampus (but not amygdala) (re)activation for the CS+ as compared to the CS- in individuals reporting a history of ACEs as well as a more “adult-like” connectivity pattern in previously institutionalized individuals (Silvers et al., 2016). The latter study does not report results from psychophysiological measures or ratings rendering the interpretation of brain imaging data somewhat difficult. Since there are only two such studies we could not calculate a likelihood ratio for threat learning. The pattern of results in the seven studies investigating associations between deprivation-specific experience and behavioral indices of reward learning also seem to match the general pattern of results reported here. Four studies (H. Delgado et al., 2022; Sheridan et al., 2018; White et al., 2022; Wismer Fries & Pollak, 2017) show reduced behavioral reward learning performance in the group exposed to deprivation experiences while three studies show no differences at the behavioral level (Gonzalez et al., 2016; Mehta et al., 2010; Smith & Pollak, 2022). Two additional studies did not provide behavioral measures of reward learning (Mullins et al., 2020; Romens et al., 2015). A likelihood ratio test provides further evidence for this qualitative assessment suggesting that - given the data - an association between deprivation and blunted reward responding is 611.50 times more likely than a null result. Of the studies focusing on threat-only experiences, four studies (Hanson et al., 2017; Harms et al., 2018; Letkiewicz et al., 2022; Pechtel & Pizzagalli, 2013) showed blunted responding, while only one study (Cisler et al., 2019) revealed a null result. Based on these findings, the likelihood ratio test suggests that an

association between threat-only experiences and blunted responding is 13797.1 times more likely than a null result. Hence, results from the systematic literature search provides evidence for a uniform association between reporting a history of ACEs and blunted reward and threat learning - irrespective of the specific type of ACE (i.e., threat vs. deprivation). Yet, most studies included in this review did not differentiate explicitly between adversity subtypes which does not allow us to draw firm conclusions on this from the literature. This observed pattern of results, however, stands in contrast to predictions by prominent theoretical accounts in the field (DMAP, Sheridan and McLaughlin (2014); McLaughlin et al. (2014)) that posit distinct (neuro-) biological effects of different ACE types. Yet, while such ‘splitting approaches’ (Smith & Pollak, 2021) are theoretically appealing and currently represent the dominant view in the field of threat learning (McLaughlin et al., 2019), this is a matter of ongoing debate. In brief, one challenge that has been highlighted is that certain aspects of ACEs are inseparable and can be conceptualized as different sides of the same coin. While co-occurrence of different dimensions are considered to be statistically controlled within the DMAP framework, it has been argued that this is impossible when different dimensions root in an identical event (e.g., a criminal neighborhood comes with threat of physical harm but most probable also with deprivational experiences such as the lack of safety and material resources). Additional criticism includes that there is little evidence for the core DMAP dimensions (i.e., deprivation and threat) mapping indeed onto specific neurobiological systems (Carozza et al., 2022; Smith & Pollak, 2021) or clinical outcomes (Witt et al., 2016). In addition a wealth of research suggests that the effects of experiences of early life adversity are cumulative, non-specific and rather unlikely to be tied to specific types of adverse events (Danese et al., 2009; Danese & Widom, 2020; Gehred et al., 2021; Smith & Pollak, 2022; Young et al., 2019).



**No evidence for an impact of developmental timing of ACEs on behavioral threat and reward learning** Another factor potentially influencing the association of learning patterns and childhood experiences is the age distribution of the sample and particularly the developmental timing of ACEs. More precisely, when investigating pediatric samples vs. adults who report ACEs, it is challenging to distinguish the effect of recency of the experiences from the developmental timing effects (discussed in Gee, 2021). In the current literature search, studies from the threat field relied approximately equally often on pediatric samples (i.e., children or adolescents), and adults with a history of ACEs (see **Figure 1A** and **1B**) and the ratios of studies reporting blunted threat responding during fear acquisition vs null findings were similar across pediatric (3 out of 5) and adult samples (6 out of 10). In contrast, studies from the reward field relied more often on children or adolescents ( $n=29$ ) than adult ( $n=16$ ) samples. However, the ratios of children/adolescent to adult samples did not differ between studies who report blunted behavioral responding (12:5) vs null results (11:5) in the reward field. Thus, our literature review provides no evidence that the reported associations between ACEs and either threat or reward learning processes, or their direction may vary as a function of developmental timing of ACEs or recency of the experiences. However, these behavioral findings stand in contrast to a recently published meta-analysis reporting adversity-related alterations in amygdala and PFC BOLD activation in emotion processing, memory processing, inhibitory control, and reward processing tasks only in adult samples (having experienced adversity recently or during childhood), but not in children or adolescents (Gee, 2021; Hosseini-Kamkar et al., 2023). In sum, we do not find evidence for an impact of development timing of ACEs on threat and reward learning for behavioral outcome measures across the studies included in the current review. At the same time, there is evidence in the literature that such an effect might exist at the neural level (Hosseini-Kamkar et al., 2023).

**No evidence for specificity of an association between different outcome measures and the association between ACEs and threat or reward learning** Across the studies included in this work, a variety of different outcome measures has been used to study associations between ACEs and threat (e.g. SCR, FPS, ratings, fMRI BOLD response) as well as reward learning (e.g. behavioral measures, fMRI). Even though it is well known that different outcome measures tap into different underlying processes (e.g., Lonsdorf et al. 2017), the pattern of results observed does not seem to differ depending on the outcome measure. It should be noted though that these different outcome measures might be differentially sensitive to individual differences vs. group effects. Recently, the reliability of different outcome measures (i.e., SCRs, fear ratings and BOLD fMRI) was compared (Klingelhöfer-Jens et al., 2022; see also Flournoy et al., 2024 for BOLD fMRI only) with the conclusion that there is no universally objectively most reliable measure, even though some specifications led to more reliable estimates. Yet, too little is known on this topic to meaningfully compare the studies accordingly.

**General Challenges of investigating ACE type specific associations with threat and reward learning** Our systematic inventory of ACE operationalization in the field of threat and reward learning (see **Figure 3** and **4** as well as **Supplementary Material** for a list of questionnaires used in the included studies) highlights substantial heterogeneity in assessment tools and operationalization as a general challenge for cross-study comparison and drawing broad inference across this field (Koppold et al., 2023; Smith & Pollak, 2022). Likewise, the operationalization of ACEs varied greatly between studies (e.g., dimensional vs. categorical and specific vs. general adversity types) and often involved the generation of (artificial) groups from a continuous variable (Cohen, 1983) by median-split dichotomization (Jovanovic et al., 2020; Lange et al., 2019) or by applying cut-offs - that may vary even for a single questionnaire (Bernstein et al., 1997; e.g., CTQ, Bernstein & Fink, 1998). These data reduction approaches may

obscure meaningful variability (Gee, 2021) and render the composition of adequate control groups challenging. Relatedly, it is a challenge that a number of studies focus exclusively on a specific ACE subtype without screening for other experiences (of no interest to this study). More precisely, studies focusing on deprivation-related ACEs oftentimes did not assess potential additional threat-related experiences. Further the studies focusing on threat-related ACEs typically did not assess potential additional deprivation-related experience. As a consequence, control and ACE groups may be characterized by similar overall levels of ACEs and may only differ with regard to one specific ACE (Kuehl et al., 2020; Marusak et al., 2021; McLaughlin et al., 2016; Morrison et al., 2022). In other words, participants assigned to the control group might have had severe adverse experiences not screened for (e.g., Jovanovic et al. (2020); Zoladz et al. (2022); Stout et al. (2021). This lack of broad screening might be particularly problematic as there is little support for distinct neuro-biological effects of different adversity types as discussed above.

**Navigating methodological challenges** Taken together, we echo a recent call for “a basis for classifying adversity” (Koppold et al., 2023; Pollak & Smith, 2021) and highlight that improving and potentially standardizing assessment, measurement and classification is urgently needed to improve comparability, replicability, and cumulative knowledge generation. For future research, data-driven approaches could be considered to address this problem of heterogeneity and co-occurrence of ACEs (Brieant et al., 2023). We also call for a more comprehensive in-depth phenotyping and characterization of the adverse childhood experiences (i.e., onset, developmental timing, controllability, e.g., Cloitre et al., 2009; Cowell et al., 2015), including subjective evaluations (Baldwin et al., 2019; Danese & Widom, 2020; Pollak & Smith, 2021), rather than simply screening for the exposure to events or environments that are potentially experienced as adverse (e.g., parental substance abuse), as well as for longitudinal studies in

humans and complementary cross-species translational work that could aid to improve understanding about underlying mechanisms (see **BOX 2** for further topical and methodological directions). In addition to mastering assessment challenges, the field would profit from a generally increased focus on precision in reporting (e.g., sample and specification, methods) and adhering to published guidelines for processing psychological data Blumenthal et al. (2005), experimental procedures (Lonsdorf et al., 2017).

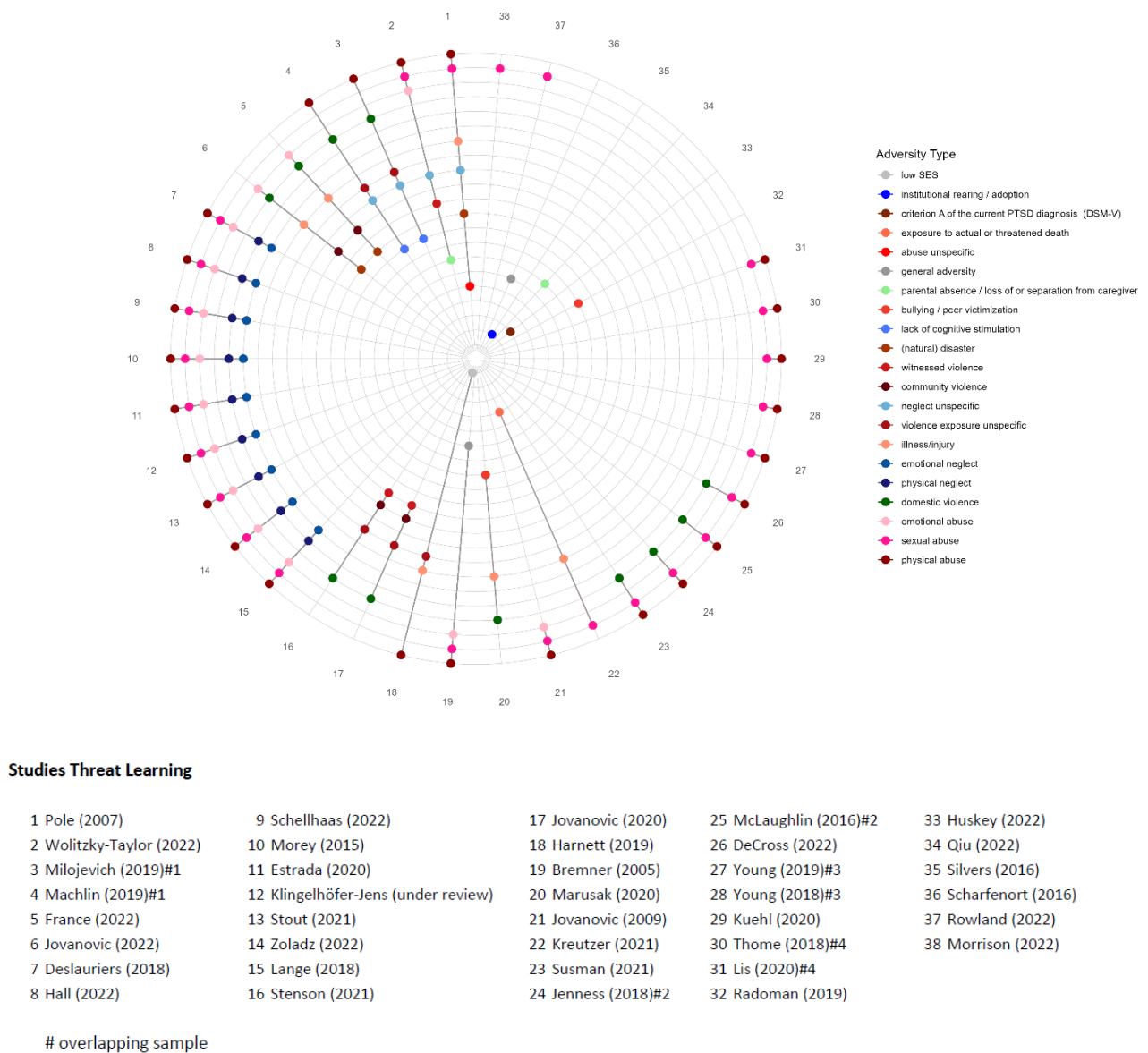


Figure 3. Distinct adversity types that were assessed in the 38 articles from the threat learning field. Numbers refer to the studies listed below the figure. The colored dots represent the adversity types listed in the legend on the right. Shades of red correspond to threat-related experiences, while blue dots correspond to deprivation-related experiences and green dots correspond to household dysfunction. Adversity types that did not fit into any of these categories were colored in gray. We included all adversity types that were considered as early adversity according to the studies and were assessed accordingly. The adversity types are being captured

rather roughly as they represent the content of the assessment instruments as a whole or its subscales but not individual items.

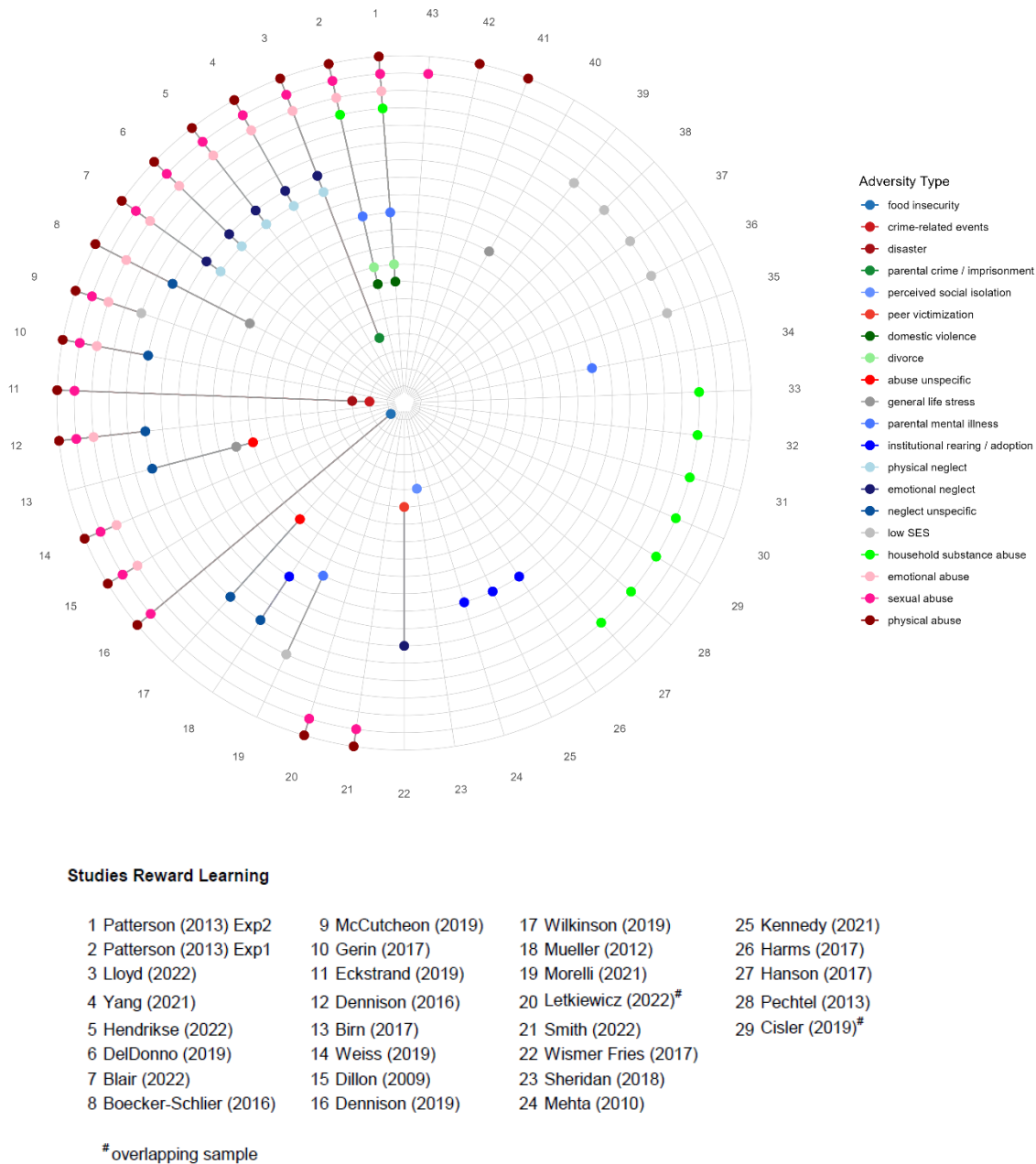


Figure 4. Distinct adversity types that were assessed in the 43 studies from the reward learning field. Numbers refer to the studies listed below the figure. The colored dots represent the adversity types listed in the legend on the right. Shades of red correspond to threat-related

experiences, while dots in shades of blue correspond to deprivation-related experiences and dots in shades of green correspond to household dysfunction. Adversity types that did not fit into any of these categories were colored in gray. We included all adversity types that were considered as early adversity according to the studies and were assessed accordingly. The adversity types are being captured rather roughly as they represent the content of the assessment instruments as a whole or its subscales but not individual items.

Further, we emphasize the need to report results of all (particularly preceding) experimental phases and stimuli rather than splitting them up into different publications (e.g., scientific salami slicing; Nature Materials 2005). Even though hypotheses may be specific to extinction, group differences can only be meaningfully interpreted in light of the results during acquisition training. More precisely, differences observed during extinction training may not represent differences in extinction learning, but differences during threat learning that are transferred to later experimental phases. Unfortunately, this is not always common practice in the reviewed studies (e.g. Jenness et al., 2019; McLaughlin et al., 2016 and Machlin et al., 2019; Milojevich et al., 2020). In this context, we also highlight that the experimental paradigm and response quantification approaches need to be tailored to the outcome measures used. A mismatch may render results uninterpretable and may bias results if it goes undetected. For instance, skin conductance responses are slow physiological responses with the onset of a stimulus-bound peak typically occurring 1-4s after stimulus onset and the peak occurring even later than that. As a consequence, this makes a minimum inter-stimulus-interval of at least 5-6s necessary to avoid overlapping and hence confounded responses (unless model-based approaches are employed). If the inter-stimulus interval, however, is shorter, the SCR response to the CS+ will be specifically confounded by the SCRs to the US (which co-terminates typically with CS offset) and render data uninterpretable. For instance, using CS specific scoring windows in an

attempt to circumvent this problem (Marusak et al., 2021), or, when SCR scoring windows are longer than the stimulus presentations, a single “score” may include SCRs to several successive trials including the US (Machlin et al., 2019; Milojevich et al., 2020).

**Summary and Outlook** In sum, this work summarizes and integrates evidence from two potential mechanistic routes on how ACEs, a potent risk factor for psychopathology, lead to blunted responding to environmental cues supporting reward and threat-related learning processes. Differences in samples (children vs. adults, clinical vs. healthy), different paradigms, and considerable variance in the operationalisation and assessment of ACEs as well as different subtypes or dimensions of ACEs do not appear to have a systematic influence on this pattern of results. The fact that blunted responding to threat and reward following early adversity is such a robust finding in the existing literature, underscores that these altered learning mechanisms are a promising target for tailored clinical prevention and intervention programs. Yet, we also identify a number of challenges - foremost with respect to ACE assessment and methodological precision - that hamper cumulative knowledge generation as well as progress in the field. We call for an increased focus on measurement (homogenization) as well as studies in larger cohorts, cross-lab collaboration as well as increased data sharing practices to achieve the statistical power or leveraging replicable and robust insights. Such large scale studies hold promise to shed light on the substantial heterogeneity in individual risk and resilience trajectories and will allow moving beyond group averages and capitalizing on individual differences (see **BOX 2**). It should be noted that threat and reward learning are certainly not the only potential mechanistic routes that link ACEs and psychopathology. Other potentially relevant mechanistic routes that involve adaptation to adverse environments may be linked to the risk to psychopathology, such as social cognition, executive functions, emotion regulation and the quality of an individuals’ social network McCrory et al. (2022). While addressing all these diverse potential mechanisms is beyond the



scope of this work, future research should consider these factors in the study of associations between psychopathology and ACEs.

### **Box 1. Paradigms employed to study threat – and reward-related learning processes**

#### **THREAT LEARNING PARADIGMS**

##### **Fear conditioning paradigms<sup>2</sup>**

- The Fear Conditioning paradigm consists of a number of successive experimental phases. During fear acquisition training, an initially neutral stimulus (i.e. conditioned stimulus, CS+) is repeatedly paired with an unconditioned aversive stimulus (US) and as a consequence the CS+ acquires the ability to elicit conditioned responses (CRs). Typically a second stimulus (i.e., CS-) is never paired with the US and hence serves as a control stimulus which has also been suggested to signal safety. Following fear acquisition a generalization phase can take place, during which the potential generalization of CRs to new stimuli, perceptually resembling the CSs (generalization stimuli, GS) can be observed. In a subsequent (optional) extinction training phase, both CSs are presented without the US, which leads to a gradual waning of the CRs (Milad & Quirk, 2012; Vervliet et al., 2013). While fear acquisition training serves as a laboratory model for the acquisition of fear, extinction serves as a model for the active ingredient of exposure based treatment. Relapse phenomena have been modeled experimentally in return of fear phases such as renewal (Vervliet et al., 2013) or reinstatement (Haaker et al., 2014).

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<sup>2</sup> Marusak et al. (2021); Jovanovic et al. (2022); Qiu et al. (2022); France et al. (2022); McLaughlin (2016); Jenness et al. (2019); Susman et al. (2021); Lange et al. (2019); Zoladz et al. (2022); Scharfenort and Lonsdorf (2016); Lis et al. (2020); Thome et al. (2018); Bremner et al. (2005); Kuehl et al. (2020); Morrison et al. (2022); Klingelhöfer-Jens et al. (under review); Jovanovic et al. (2020); Stenson et al. (2021); Rowland et al. (2022); Estrada et al. (2020); Morey et al. (2015); Deslauriers et al. (2018); Harnett et al. (2019)

**Fear conditioning paradigms in pediatric samples<sup>3</sup>**

- Typical fear conditioning paradigm has also been modified in different ways to be applicable in samples of (young) children and hence differ partly substantially from those employed in adults (see Shechner et al. (2014)] for recommendations). The paradigms specifically tailored to children samples often rely on a block design with blocks of reinforced and unreinforced CS+ as well as blocks of CS- trials (Machlin et al., 2019; Milojevich et al., 2020; Silvers et al., 2016), following the reasoning that this facilitates learning in young cohorts. Yet, these paradigms have also been applied in older children and adolescents and also non-block designs for fear acquisition and generalization have been successfully applied in samples of children (Qiu et al., 2022; Schiele et al., 2016). Typically the use of aversive electrotactile stimulation is precluded for ethical reasons and hence aversive tones, human screams or airblasts delivered at the larynx are typically used.

**AX+BX- task<sup>4</sup>**

- The AX+BX- task, also referred to as the conditional discrimination paradigm, is a variant of the fear conditioning paradigm used to study fear inhibition (Jovanovic et al., 2005; Myers & Davis, 2004) It was designed to allow for the systematic comparison of excitatory and inhibitory learning. Two different cues (A and B) provide the information whether a third stimulus (X), presented in compound with either A or B, is paired with an aversive stimulus or not. More precisely, stimuli A and X are presented simultaneously and paired with aversive shock, and stimuli B and X were presented simultaneously without any aversive shock being presented. Typically, startle responses are used as the main outcome measure and typically, higher startle responses are seen in the presence of A and AX as compared to B and AB because B serves as a conditioned inhibitor.

**Aversive Anticipation Task<sup>5</sup>**

- In the aversive anticipation task, colored circles are presented. The color of the circles predicts the presentation of either positive or negative images. Participants are asked to anticipate the type of image they are about to see, while the cue (i.e. the colored circle) is

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<sup>3</sup> Machlin et al. (2019); Milojevich et al. (2020); Silvers et al. (2016); DeCross et al. (2022)

<sup>4</sup> Jovanovic et al. (2009); Huskey et al. (2022)

<sup>5</sup> Stout et al. (2021)

presented. Participants learn the association between cue and valence of the image, which can be observed in the anticipatory-potentiated startle responses.

#### **NPU-threat test<sup>6</sup>**

- The NPU-threat test (Schmitz & Grillon, 2012) was developed to assess short-duration (fear) and long-duration (anxiety) aversive states in human participants - both adult and pediatric samples. The experiment typically consists of three conditions with threat contingencies being explicitly instructed (i.e, instructed learning): a safe condition (neutral (N)), during which no aversive stimuli are presented, and two threat conditions. In the predictable threat condition (P), aversive events are administered predictably and are signaled by a cue. In the unpredictable conditioning (U), the aversive stimuli are administered unpredictably. Typically, the main outcome measure is the human startle reflex.

#### **Threat of Shock paradigm<sup>7</sup>**

- The Threat of Shock Paradigm typically involves explicit verbal information (i.e, instructed learning) that participants may receive aversive shock with different probabilities in different experimental conditions such as high threat, medium threat and low or no threat. The different conditions are typically explicitly indicated through visual cues.

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<sup>6</sup> Wolitzky-Taylor et al. (2014); Kreutzer and Gorka (2021); Hall et al. (2022); Radoman et al. (2019)

<sup>7</sup> Pole (2007); Schellhaas et al. (2022); Young et al. (2018); Young et al. (2019)

## REWARD LEARNING PARADIGMS

### Monetary Incentive delay task<sup>8</sup>

- The monetary incentive delay (MID) task is a widely used decision-making task in humans embedded in the framework of reward processing (see e.g. (Wilson et al., 2018) which also contains a learning element (see below). Typically, the task is implemented as an fMRI task for the investigation of neural mechanisms underlying motivational salience processes. Importantly, the MID contains two phases allowing to differentiate between two distinct aspects of reward processing: anticipation and feedback. A typical task contains three different types of stimuli presented in fixed order. First, a visual cue representing gain, loss or a neutral outcome is presented allowing to assess brain activation during the anticipation period. Second, a target cue is presented representing a prompt to perform a certain action (e.g. pressing a button as fast as possible). Of note, this learned, anticipatory response (as assessed through BOLD fMRI) to a reward in a monetary incentive delay (MID) task is conceptually comparable to BOLD fMRI responses during presentation of CS+ vs. CS- in threat learning, that is the anticipation of threat vs. safety. Likewise the MID can be understood as a learning element, because participants decrease response time to the rewarded cue over the course of the experiment providing evidence of instrumental or reinforcement learning where the presentation of a specific cue triggers an action that is rewarded. Following the anticipation phase, feedback about the outcome of the trial, i.e. (financial) gain, loss or neutral dependent on anticipation and performance is presented. Behavioral outcome measures of interest include reaction time, differences in gain vs loss trials, as well as the total amount of rewards earned. For neuroimaging, a recent meta-analysis shows robust activation of the striatum, the anterior cingulate cortex, as well as the insula during anticipation of both gains and losses (Wilson et al., 2018). A child friendly version of the MID, that was designed to be visually appealing and engaging, requires children to virtually beat pinatas with variable numbers of stars as quickly as possible (Helfinstein et al., 2013). They are instructed that the number of stars determine the reward they receive at the end of the task.

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<sup>8</sup> Birn et al. (2017); Boecker-Schlier et al. (2016); DelDonno et al. (2019); Dennison et al. (2016); Dennison et al. (2019); Dillon et al. (2009); Hendrikse et al. (2022); Mehta et al. (2010); Morelli et al. (2021); Sheridan et al. (2018); Yang et al. (2021)

**Monetary incentive saccade task<sup>9</sup>**

- In the monetary incentive saccade task, a cue indicates whether the participant is supposed to make an eye movement toward (prosaccade) or away from (antisaccade) a target presented subsequently. The cue further informs the participants, whether they would win, lose or not receive reward or punishment upon correct eye movement. Participants learn to adapt their behaviour (i.e. direction and speed of saccade) in response to the different cues. Feedback indicating win or loss was displayed after each completed trial in the location of the correct eye movement target.

**Passive avoidance task<sup>10</sup>**

- In the probabilistic passive avoidance task (White et al., 2013), participants learn which of four different stimuli are associated with a (higher) chance of winning or losing. In each trial, participants have to decide whether they want to actively approach (i.e. respond) or passively avoid (i.e. withhold) a response to a stimulus. In the subsequent feedback phase participants are then informed whether they lost or gained points and how much. Two of the four stimuli lead to a reward (high vs. low) in 70 – 80 % of all trials and the other two lead to punishment (high vs. low) in 70 – 80 % of all trials when responded to. Passive avoidance results in no feedback and no reward or punishment.

**Three-arm bandit task<sup>11</sup>**

- Participants have to choose one out of three different stimuli to allocate money to. They have to learn that those stimuli have varying probabilities of a positive outcome and vary in the amount of the return ranging from more money than invested to no return at all. Besides the choices made and the reaction time during the decision phase, brain activation during the decision, anticipation (waiting for outcome) and feedback phase are of interest.

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<sup>9</sup> Mueller et al. (2012)

<sup>10</sup> Gerin et al. (2017); Blair et al. (2022); White et al. (2022)

<sup>11</sup> Cisler et al. (2019); Letkiewicz et al. (2022)

**Stimulus selection task<sup>12</sup>**

- A stimulus selection task is a version of a reinforcement learning task with a phase during which contingencies are learned and a test phase during which decisions have to be made based on previously learned contingencies. During the learning phase participants are presented with different stimulus pairs with different probabilities of being rewarded. For example, stimulus pairs A-B, C-D and E-F might have probabilities of 80 vs. 20%, 70 vs. 30 % and 60 vs. 40 % chance of being rewarded when choosing one stimulus or the other. Participants are informed that they made the correct choice when they choose the stimulus that has a higher chance of leading to a reward for any given stimulus pair. The learning phase is completed when a certain performance criterion is reached. In the subsequent test phase, the familiar stimulus pairs from the learning phase are mixed with novel combinations of all stimuli presented before. No feedback is given during the test phase to prevent further learning. Instead the focus is on decision making based on previously learned information that needs to be employed here in a novel context.

**Card-guessing task<sup>13</sup>**

- During a reward-based card-guessing task (M. R. Delgado et al., 2000), participants are presented with a card in every trial and have to guess whether the card when revealed has a value higher or lower than 5. Their guess does not influence the actual outcome of the trial, which results in four different experimental conditions (i.e. win trials – expected win and actual win, loss trials – expected and actual loss, mixed trials – mismatch between expectation and outcome, neutral trials – no expectation and no change during outcome) and allows to evaluate brain activation patterns in anticipation of the outcome and during the feedback phase. Such decision-making processes are thought to be modulated by reinforcement learning processes because the decision in each trial is affected by previous rewards and punishments (Dong et al., 2014).

**Probabilistic (reinforcement) learning task<sup>14</sup>**

- Participants are presented with two stimuli (e.g. everyday objects) and are told to choose one of them via button press (van den Bos et al., 2012). This decision phase was followed by positive or negative feedback. Feedback is dependent on the unknown reinforcement

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<sup>12</sup> Pechtel and Pizzagalli (2013)

<sup>13</sup> Eckstrand et al. (2019); Romens et al. (2015)

<sup>14</sup> Hanson et al. (2017); Kennedy et al. (2021); Wilkinson et al. (2021)

schedule of each stimulus pair and has to be learned through trial and error. For example, in AB stimulus pairs, choosing stimulus A leads to positive feedback on 80% of trials (as opposed to 20% for stimulus B), whereas in CD pairs positive feedback is received in 70% and 30% of trials. The goal of the participants is to receive as much positive feedback as possible in order to maximize the reward earned.

### **Probabilistic reversal learning task<sup>15</sup>**

- In the probabilistic reversal learning task (Cools et al., 2002), participants have to choose between rich and lean patterns in order to maximize points. The rich stimulus is rewarded in 80% of all cases, the lean stimulus in 20%. After a certain number of correct choices, contingencies are reversed. Measures of interest are win-stay probability which describes the probability that a participant chooses the same stimulus again if they just won with that stimulus and vice versa for lose-shift probability. Additionally, the number of rule changes that a participant reached is assessed. Moreover, a reinforcement learning model can be used to model learning rate as well as degree of choice variability. It further allows comparing an individual's performance to an optimal performance.

### **Signal detection task<sup>16</sup>**

- Participants are presented with two stimuli (e.g. short and long line), one of which was rewarded more often when chosen. A response bias or successful reward learning was indexed by a higher proportion of choices made that would lead to a reward.

### **Stimulus context reversal paradigm<sup>17</sup>**

- In this task (Levy-Gigi et al., 2014), stimuli (e.g. everyday objects) are shown in boxes overlaid on a neutral or salient (e.g. drug-related) context. In each trial, the participant has to decide whether to open the box or not. During the acquisition phase, the participant has to learn which combination of object in the box and background is associated with a positive and which with a negative outcome with the overarching goal to maximize the reward earned. After reaching a certain number of correct responses, the participant moves on to the retention phase during which the combinations from the acquisition phase are presented alongside new combinations with old boxes but new backgrounds (neutral or drug-related). In the trials with the changed background, the reward associated with a

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<sup>15</sup> Wilkinson et al. (2021)

<sup>16</sup> Morris et al. (2015)

<sup>17</sup> Weiss et al. (2019)

box is reversed such that previously rewarded boxes are no longer rewarded and vice versa. The participant is expected to learn that the change in the background indicates a change in the reward contingencies but that box - background combinations from the acquisition phase are not affected. The proportion of correct answers in the different phases relative to each other is used as the main outcome measure.

### **Children's gambling task<sup>18</sup>**

- Participants were presented with two decks of cards that could be differentiated visually by their back. One of the card decks was advantageous over the course of the experiment because more net reward could be earned while the other one was disadvantageous. Thus, the aim of the gambler is to make relatively more advantageous than disadvantageous choices.

### **Patch foraging task<sup>19</sup>**

- A patch foraging task is a sequential decision-making task in which participants have to optimize an explore/exploit trade-off (Lloyd et al., 2021). During this task a participant is set at a patch and can choose to exploit the patch and collect rewards there or move to a different patch instead. Importantly, the longer the participant remains within the same patch, the fewer rewards are available. This is called the depletion rate. When choosing to forage and move to a different patch the participant has to consider that the travel time between patches is not rewarded. Thus throughout this task the participant has to learn when it is best to explore and when to exploit. The initial richness of the new patch is based on the number of rewards on the first patch. The experimenter can further vary the richness of the environment. In a poor quality environment an optimal forager would exploit each patch more whereas a high quality environment would require a higher degree of exploration in order to maximize rewards.

### **Salience attribution test<sup>20</sup>**

- The salience attribution test is employed to measure aberrant and adaptive salience (Roiser et al., 2009). In this task in each trial one stimulus of 4 different categories is presented (e.g. blue animal, red animal, blue household object, red household object) spanning two dimensions (here type of objects and colour). Stimulus presentation is

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<sup>18</sup> H. Delgado et al. (2022)

<sup>19</sup> Lloyd et al. (2021)

<sup>20</sup> McCutcheon et al. (2019)



followed by a probe to which participants have to respond to as quickly as possible to maximize potential reward. At any given point, one dimension is relevant for the reward probability. One of the two stimuli of the relevant dimension has a high chance of being rewarded, the other stimulus has a low probability. The irrelevant dimension does not affect reward probability. Adaptive salience encompasses that participants learn to expect a higher reward for and respond with faster reaction times to a stimulus of the relevant dimension relative to the irrelevant dimension.

### **Mixed appetitive and aversive conditioning<sup>21</sup>**

- In a mixed Pavlovian conditioning paradigm (Metereau & Dreher, 2015), participants are exposed to different stimuli that are either followed by an appetitive or an aversive reinforcer. A neutral reinforcer can further be integrated as a control condition. In a typical trial, participants are presented with a stimulus and either after a certain delay or a button press, the reinforcer is presented. Often stimulus ratings of e.g. goodness or likeability are completed before and after conditioning or throughout in order to measure how the association with the reinforcer changed the subjective experience of the stimulus. If a button press was required or encouraged, response times can be used to model learning rates using the Rescorla and Wagner reinforcement learning framework (1972). Here, learning is understood as an adaptive process in which expectations are updated on a trial-by-trial basis based on expected and actual outcome.

### **Associative learning task<sup>22</sup>**

- A visually cued reward schedule task is designed to test children's ability to learn associative connections with rewards in their environment and adapt their behaviour (Liu et al., 2000). Each trial is initiated by the child keeping a button pressed, which in turn triggers the presentation of a stimulus on the screen. The stimulus is either a coloured circle (in the colour discrimination version) or a geometric shape (in the shape discrimination version). As soon as those stimuli change to a different colour or shape in the respective version of the task, the child is instructed to release the button. Reaction time to the change as measured by the release of the button, is recorded. Children have to complete 1, 2 or 3 consecutive trials correctly before receiving a reward.

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<sup>21</sup> Smith and Pollak (2022)

<sup>22</sup> Wismer Fries and Pollak (2017)

**Instrumental learning<sup>23</sup>**

- In an instrumental learning task a participant learns that an action such as a simple button press in response to a stimulus (Finger et al., 2008) or the execution of a certain sequence of button presses (Vogel-Sprott, 1967) leads to a reward. The reward schedule might indicate that all correctly performed actions are rewarded, or a partial reinforcement schedule might determine that a certain percentage of correctly performed actions is rewarded. A purely reward-based task can also be mixed with a component of punishment in which the response to a different stimulus or the performance of an incorrect action might lead to the loss of points to be maximized. Variations of an instrumental learning task might further involve a reversal condition in which the association between action and reward or punishment is reversed, i.e. actions that were previously rewarded are now punished and vice versa.

**Box 2. Future Directions to advance research on the association between ACEs and threat as well as reward learning processes**

**Methods-focused future directions****Assessment of ACEs**

- More attention to assessment tools: avoid assessment modifications (e.g., adding or dropping items) which threaten construct validity Flake & Fried (2019) and replicability. If modifications are unavoidable, these need to be reported with sufficient detail, ensuring construct validity, original factor structure, and profound scientific reasoning as outlined in Flake et al. (2017).
- Adhere to validated cut-offs and preferably report cut-off details rather than merely referring to previous publications.
- Consider (additional) assessment tools which allow for a fine-grained evaluation of potentially relevant ACE characteristics including onset and duration of exposure and controllability (e.g., MACE (Teicher & Parigger, 2015) although following Zorowitz and Tuominen (2022) it lacks subscale specificity) as well as social aspects (e.g., social support).
- Consider making materials openly available (e.g., questionnaires, interviews used) to facilitate cumulative knowledge generation.

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<sup>23</sup> Patterson et al. (2013); Harms et al. (2018)

- Consider significant sample differences based on retrospective or prospective assessment of early life adversity and related implications on measurement selection (e.g., questionnaire or interview; as mentioned in Baldwin et al. (2019)).
- Include subjective evaluations as there is converging evidence that risk for psychopathology develops based on subjective rather than objective evaluations (Baldwin et al., 2019; Danese & Widom, 2020; Pollak & Smith, 2021).

### **General methodological recommendations**

- Provide sufficient details on the sample, paradigm, data recording and processing (consider supplementary material in case of space restraints) and avoid referring exclusively to previous work which can result in reference chains ending with implausible or ambiguous information.
- Adhere to published methodological guidelines for data recording, experimental design and terminology. For instance, short CS-US intervals and a failure to account for these in SCR response quantification may result in artificially enhanced CS+ responses due to the US and CS+ response being inseparable Milojevich et al. (2020)
- Avoid common statistical errors (as e.g., Makin & Orban de Xivry, 2019) such as inferring group differences from a significant within-group effect in one group and a non-significant within-group effect in a second group (the same applies for within-CS effects).
- Provide statistics not only for significant effects but also for non-significant results as well as post-hoc tests to avoid ambiguity and support cumulative knowledge generation.
- Consider providing single-trial data and individual-level data in visualizations (Weissgerber et al., 2015); potentially in supplementary material] to allow for a more comprehensive interpretation including habituation processes.
- Avoid “salami-slicing” and report results for all experimental phases. If results need to be published separately for different experimental phases, clearly highlight this as well as explicitly refer to the results reported previously. It hampers cumulative knowledge generation if publication 1 reports a significant effect for fear acquisition training but not extinction while publication 2 in the same sample publishes no differences in the last trial of acquisition (without referring to the previous work) and a significant effect on extinction in an outcome measure not included in publication 1 (Jenness et al., 2019; Machlin et al., 2019 ; as in McLaughlin et al., 2016; Milojevich et al., 2020).
- In case results include higher-order interactions, consider discussing whether the study has acceptable power for interpreting them.
- Differences in responding to unconditioned stimulus such as threat and reward signals themselves should be considered.
- Tasks vary substantially and may not tap into the same processes even though they claim so (e.g. in the blocked fear conditioning design, the learning blocks with unreinforced CSs might rather be extinction learning (Machlin et al., 2019; Milojevich et al., 2020)).

- Progress will be supported and facilitated by increasing data sharing practices (Ehlers & Lonsdorf, 2022) as only ten out of 81 studies provided open data (see **Supplementary Table 3 and 4**). include information on potential group differences to reinforcers (e.g., unconditioned threat and reward cues) as these may underlie group differences in learning

### Topical directions

- Provide a more comprehensive sample characterization of ACEs beyond a specific study focus to support cumulative knowledge generation and cross-study integration (e.g., provide a comprehensive experience profile for participants including control groups even though the study focus is specifically on household violence).
- Longitudinal developmental samples may aid the identification of mechanisms. Increased focus on variability between ACEs (e.g., developmental timing, protective factors) may aid the identification of mechanisms (Gee, 2021).
- Investigate potential mediators including epigenetics, neuroendocrine as well as immunological and neurobiological aspects.
- Increased focus on psychometric properties and reliability of the used measures is key for individual-level investigations and different from those suitable for group-level inferences.
- Furthermore, as ethical considerations restrict research in humans to observational studies, complementary cross-species translational work, including animal models in which life histories can be actively generated, will be important for testing mechanistic hypotheses on risk and resilience in the future.

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## Supplementary Methods

### 1.1. Systematic literature Search

The literature search was conducted collaboratively with help of the free online tool ‘rayaan’ (<https://www.rayyan.ai/>) by J.R., A.Ka., M.R.E. and T.B.L. using search terms outlined in Supplementary Table 1, which also provides an overview of the number of publications identified, retained and excluded. We retained a total of 81 publications that were included in the systematic literature review with 38 and 43 publications investigating an association between ACEs and threat as well as reward learning processes, respectively. We decided to exclude conference papers as well as gray literature as the results from these kinds of publications might still change and did not yet undergo a structured review process. Note that five additional studies, that were not identified through the systematic literature search, were included as a recent meta-analysis (Oltean et al., 2022) included them and we considered them relevant. In addition, in the threat field, the results from the acquisition and extinction training phase of one study were reported in two different publications in two cases ((Jenness et al., 2019; McLaughlin et al., 2016; and Machlin et al., 2019; Milojevich et al., 2020)). Therefore, it should be noted that we only show methodological results for the 36 distinct studies from the total of 38 publications in the respective figures. It was challenging to reconcile the respective results as these were not entirely consistent across these publications deriving from the same study. More precisely, one publication reports a significant effect during acquisition training but not extinction (McLaughlin et al., 2016) and the second study reports a significant effect during extinction training but not during the last trial of acquisition (Jenness et al., 2019). In addition, in two cases, two publications rely on an overlapping sample reflecting different timepoints during data collection (Lis et al., 2020; Thome et al., 2018; Young et al., 2019; as well as Young et al., 2018). We

further included one unpublished study from our group (Klingelhöfer-Jens et al., under review) in the review. Our literature search focused on associations between ACE's and threat as well as reward-related learning processes. Some of the identified studies focused additionally or even primarily on higher order interactions or used learning performance as predictor. These findings will not be described in detail here as they are beyond the focus of our work. These additional results include for instance higher-order interactions (e.g., 3- or 4- way interactions) with childhood adversity and a number of variables such as specific genotypes (COMTval148met, BDNFval66met, ADCYAP1R1 (Deslauriers et al., 2018; Jovanovic et al., 2020; Young et al., 2018)), volume in specific brain regions such as the hippocampus and corpus callosum (Young et al., 2019), stimulus intensity and the modulation of activation in certain brain areas (e.g. insula, LC and thalamus, Morey et al. (2015)) as well as interactions between threat-related reactivity and childhood adversity on symptom scores (e.g., problematic alcohol, anxiety and depression Hall et al. (2022); Radoman et al. (2019)) or interactions with subsequent memory tasks (Schellhaas et al., 2022).

**PRISMA Flow Chart**

Associations between exposure to ACEs and	threat learning processes	reward learning processes
date search conducted	2022-12-08	2022-12-09
search terms pubmed	(("fear conditioning"[All Fields] OR "threat conditioning"[All Fields] OR "conditioned inhibition"[All Fields] OR "conditioned inhibition"[All Fields] OR ("fear learning"[All Fields] OR "threat learning"[All Fields] OR "extinction learning"[All Fields]) OR ("return of fear"[All Fields] OR "extinction retention"[All Fields] OR "fear generalization"[All Fields] OR "threat generalization"[All Fields] OR "aversive anticipation"[All Fields] OR "threat of shock"[All Fields] OR "fear-potentiated"[All Fields] OR "fear inhibition"[All Fields])) <b>AND</b> (((("childhood"[All Fields] OR "early"[All Fields] OR "youth"[All Fields] OR "adolesc*"[All Fields]) <b>AND</b> ("adversity"[All Fields] OR "adversities"[All Fields] OR "maltreatment"[All Fields] OR "abuse"[All Fields] OR "neglect"[All Fields] OR "stress"[All Fields] OR "trauma"[All	("childhood" OR "early" OR "youth" OR "adolesc*") AND ("advers*" OR "maltreatment" OR "abuse" OR "neglect" OR "stress" OR "trauma" OR "deprivation" OR "institutionalization" OR "orphanage" OR "adoption" OR "harassment" OR "bullying" OR "household violence" OR "domestic violence" OR "poverty" OR "low SES" OR "food insecurity") AND ("reward" OR "reinforcement" OR "probabilistic") AND ("learning" OR "anticipation" OR "performance") NOT ("mice" OR "mouse" OR "rodents" OR "rabbits")

	Fields] OR "deprivation"[All Fields] OR "institutionalization"[All Fields] OR "orphanage"[All Fields] OR "adoption"[All Fields] OR "harassment"[All Fields] OR "bullying"[All Fields] OR "household violence"[All Fields] OR "domestic violence"[All Fields] OR "poverty"[All Fields] OR "low SES"[All Fields] OR "food insecurity"[All Fields])) OR "adverse childhood experiences"[MeSH Terms] OR "early childhood"[All Fields])) <b>AND</b> (humans[Filter])	
search terms Web of Science	ALL= ( "fear conditioning" OR "threat conditioning" OR "conditioned inhibition" OR "fear learning" OR "threat learning" OR "extinction learning" OR "return of fear" OR "extinction retention" OR "fear generalization" OR "fear generalization" OR "threat generalization" OR "aversive anticipation" OR "threat of shock" OR "fear-potentiation" OR "fear-potentiated" OR "fear inhibition") <b>AND</b> ALL= ("childhood" OR "early" OR "youth" OR "adolesc*") <b>AND</b> ALL= ("advers*" OR "maltreatment" OR "abuse" OR "neglect"	ALL=("childhood" OR "early" OR "youth" OR "adolesc*") <b>AND</b> ALL= ("advers*" OR "maltreatment" OR "abuse" OR "neglect" OR "stress" OR "trauma" OR "deprivation" OR "institutionalization" OR "orphanage" OR "adoption" OR "harassment" OR "bullying" OR "household violence" OR "domestic violence" OR "poverty" OR "low SES" OR "food insecurity" ) <b>AND</b> ALL= ("reward" OR "reinforcement" OR "probabilistic") <b>AND</b> ALL= ("learning" OR "anticipation" OR "performance") <b>NOT</b> ALL= ("mice" OR

	OR "stress" OR "trauma" OR "adverse childhood experiences" OR "early childhood" OR "deprivation" OR "institutionalization" OR "orphanage" OR "adoption" OR "harassment" OR "bullying" OR "household violence" OR "domestic violence" OR "poverty" OR "low SES" OR "food insecurity"))	"mouse" OR "rodents" OR "rabbits")
number of identified publications	1222 PubMed: 281 Web of Science: 941)	1905 PubMed: 761 Web of Science: 1144
number of publications after exclusion of duplicates	1110	1543
Number of publications after title and abstract screening	105	99
Number of publications after full text screening	37+1*	38 + 5**

\*An additional unpublished study was included (Klingelhöfer-Jens et al., under review).

\*\*An additional 5 publications were included based on a recent meta-analysis on childhood adversity and reward processing (Oltean et al., 2022)

that were, however, not identified through the systematic literature search.

## 1.2 List of Questionnaires used in the included Studies

**Table 5. List of Questionnaires used in the included studies**

	Full name	No. items	Subscales	Reference	Comments
CECA.Q	Childhood Experiences of Care and Abuse Questionnaire	36	Mother / Father	personal communication with Antonia Bifulco & AKo, 06.11.2022	
CTQ-SF	Childhood Trauma Questionnaire - Short Form	28	physical abuse, emotional abuse, sexual abuse, physical neglect, emotional neglect	personal communication with Vanessa Freund & AKo,, 18.11.2022	
ETISR -SF	Early Trauma Inventory Self Report-Short Form	29	General Traumas, Physical Punishment, Emotional Abuse, Sexual Events	personal comm. with Douglas Bremner & AKo, 14.11.2022, MAPI platform (online portal)	
JVQ	Juvenile Victimization Questionnaire	34	Conventional Crime, Child Maltreatment, Peer and Sibling Victimization, Sexual Victimizations, Witnessing and Indirect Victimization	Finkelhor et al. (2005)	
LEC-5	Life Events Checklist for DSM-V	17	-	Weathers et al. (2013)	
LSC-R	Life Stressor Checklist - Revised	30	-	personal comm. with Terence Keane, Michelle Bovin & AKo, 16.11.2022	

Life events checklist	Life events checklist	27	-	Caspi et al. (1996)	modified version
THS	Trauma History Screen	14	-	Carlson et al. (2005)	
UCLA-PTSD RI	UCLA Child/Adolescent PTSD Reaction Index for <i>DSM-5</i>	15	-	personal comm. with Alan Steinberg & AKo, 14.11.2022	
VEX-R	Violence Exposure Scale for Children-Revised	25	-	personal comm. with Ariana Shahinfar & AKo, 14.11.2022	
ACE-Q	Adverse Childhood Experiences Questionnaire	19	-	Felitti et al. (1998)	
CLES	Coddington life events scale	40	-	personal communication with Karen Smith & AKo, 14.01.2023	modified version
ELSQ	Early Life Stress Questionnaire	19	-	personal communication with Wojciech Dragan & AKo, 13.01.2023	
GHQ	Generalized Harassment Questionnaire	21	passive, verbal, physical, cyberbullying	personal communication with Kathleen Rospenda & JR, 25.01.2023	school version
TAQ	Traumatic Antecedents Questionnaire	40	-	Luxenberg et al. (2001)	

THQ	Traumatic History Questionnaire	24	Crime Related Events, General Disaster and Trauma, Physical and Sexual Experiences	Hooper et al. (2011)	
PC-CTS	Conflict Tactics Scale	30	Nonviolent Discipline, Psychological Aggression, Physical Assault (minor /severe/ very severe),, Neglect	Straus et al. (1996)	parent questionnaire
TEI	Traumatic Events Inventory	15	-	personal comm. with Jennifer Stevens & JR, 24.01.2023	modified version
CAPI	Child Abuse Potential Inventory	160	-	Milner (1986)	
MNBS - CR	The Multidimensional Neglectful Behavior Scale	51	Emotional, Cognitive, Supervision, Physical, Abandonment, Exposure to Conflict, Alcohol use, General appraisal	Straus et al. (1995)	modified version
HSQ	Home Screening Questionnaire	34	-	Frankenburg and Coops (1986)	modified version
Mac Arthur SSS	MacArthur Scale of subjective social status	2	-	Hoebel et al. (2015)	
PEQ	Peer Experiences Questionnaire	9	Peer Victimization, Bullying	Vernberg et al. (1999)	customized by Giovazolias et al. (2010)



**References Questionnaires**

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## Supplementary Material

### 2.1. Summary of samples sizes across the included studies

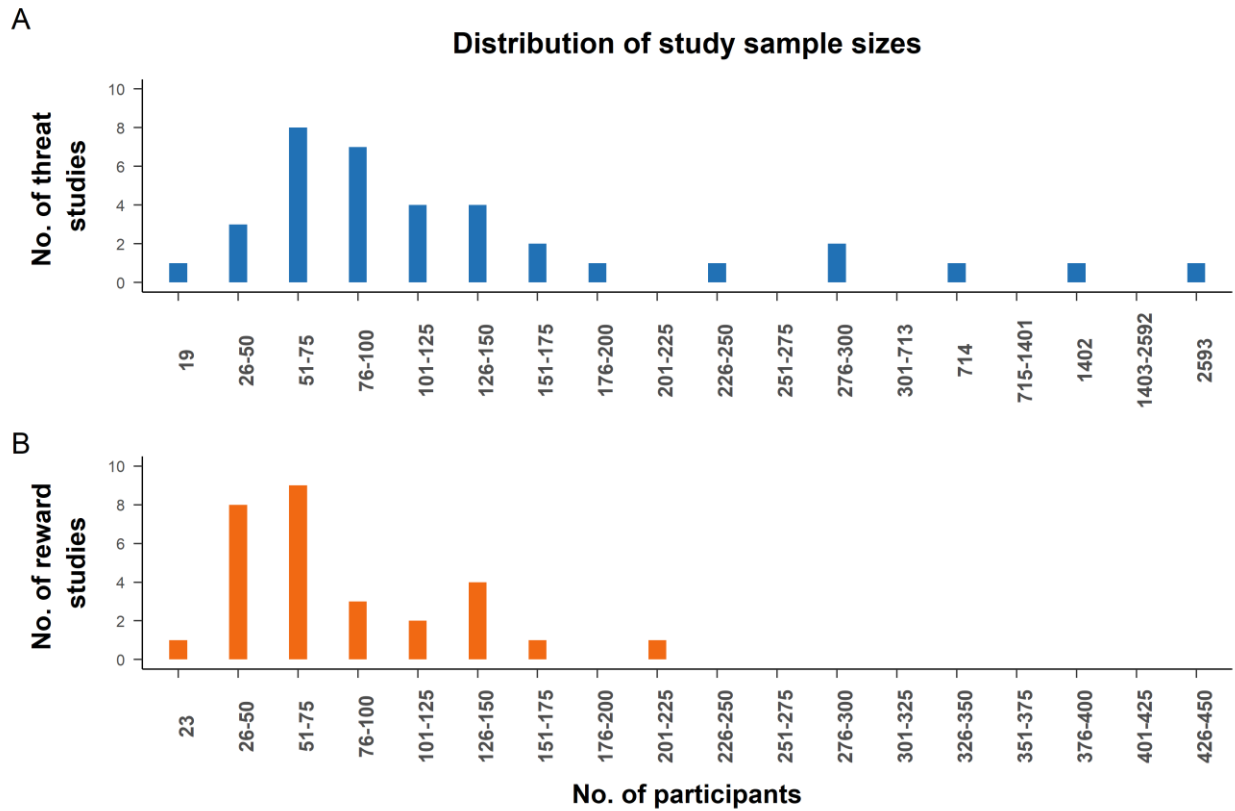


Figure S1: Total sample sizes of the individual studies range from  $n = 19$  to  $n = 2593$  and  $n = 23$  to  $n = 11360$ , for threat and reward related studies, respectively, with the number of exposed individuals as low as  $n = 8$  and as high as  $n = 1670$ .

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Supplementary Table 1: Sample Information\_Threat

No.	Author (year)	Sample information									Childhood adversity							
		N	N male/female	Age mean in years	Age range	Recruitment strategy	Exclusion criteria	Assesment of general or recent adversity	Handling of psychiatric disorders	Psychopathology screening	N exposed	N unexposed	Categorical or dimensional analyses	Exposure severity considered	Adversity type considered or recruited  blue = adverse experience green = exposure to potentially adverse events	Adversity types explicitlynot considered	Assessment instrument	Cut-off used
1	Machlin (2019) same sample as Milojevic (2020)	64	27/36	6.2	4 - 7	oversampling for at risk and diversity: low SES families, racial or ethnic minorities, low education of caregiver, or parents met a clinical cut-off for concern in the CAPI	none	no	included	no	not applicable (dimensional scores used)		dimensional	yes	neglect, cognitive stimulation, violence exposure, domestic violence, physical abuse		VEX-R, CTS-2, CAPI, MNBS-CR (subset), HSQ (subset), MacArthur SSS	z-transformed sum-score across measures
2	Milojevic (2020) same sample as Machlin (2019)	64	27/36	6.2	4 - 7	oversampling for at risk and diversity: low SES families, racial or ethnic minorities, low education of caregiver, or parents met a clinical cut-off for concern in the CAPI	none	no	included	no	not applicable (dimensional scores used)		dimensional	yes	neglect, cognitive stimulation, violence exposure, domestic violence, physical abuse		VEX-R, CTS-2, CAPI, MNBS-CR (subset), HSQ (subset)	z-transformed sum-score across measures
3	Marusak (2021)	44	22/22	8.8	6 - 11	recruited from local healthcare providers	nonnative English speakers, history of brain injury with loss of consciousness or a neurological condition (e.g., epilepsy), OCD, psychotic disorder, or significant learning disorder	no	included	PTSD, anxiety disorders, depression	20	24	categorical	no	domestic violence, witness, bullying/peer victimization, victim, illness/medically-related trauma		parent and/or child report, JVQ	criterion A trauma listed on the UCLA PTSD RI (DSM-IV)
4	Jovanovic (2022)	62	33/29	9	9	recruited from a longitudinal study of trauma exposure, community sample in Detroit, Michigan.	autism spectrum disorder, hearing loss as assessed by an audiometer, and cognitive disability via parent report	no	included	PTSD, anxiety disorders	not applicable (dimensional scores used)		dimensional	no	domestic and community violence, injuries, natural disasters, and verbal abuse (experienced or witnessed)		TESI-C	number of events
5	Qiu (2022)	72	36/36	10.6	not provided	recruited at a primary school	not reported	no	not explicitly reported	depression	31	41	categorical and dimensional	no	parent being away for work for at least 6 consecutive month per year		one question	parent being away for work for at least 6 consecutive month per year
6	France (2022)	29	14/15	9.55	9	recruited through an ongoing study of childhood trauma exposure conducted by the Detroit Trauma Project, in Detroit, Michigan.	hearing loss, neurological disorder, developmental impairment, or autism spectrum disorder	no	not explicitly reported	anxiety disorders	not applicable (dimensional scores used)		dimensional	no	domestic and community violence, injuries, natural disasters, and verbal abuse (experienced or witnessed)		TESI-C	number of events
7	Silvers (2016)	89	34/55	12	7 - 16	recruitment from a larger study (no details, no reference); no information how healthy individuals or previously institutionalized children were recruited	not reported	no	not explicitly reported	anxiety disorders	46	43	categorical	not applicable	institutionalization andadoption age 3-120month	anything that is not prevoius institutionalization in an orphanage and subsequent adoption	not applicable	not applicable
8	DeCross (2022)	147	74/73	12.65	8 - 16	recruited at schools, and adoption / food bannk / after school programs, parenting programs, shelters, preventing programs and general community	IQ < 80, pervasive developmental disorder, psychosis, mania, substance abuse, safety concerns	no	included	PTSD, anxiety disorders, depression, externalizing disorders	77	70	categorical	no	physical and sexual abuse, direct witnessing of domestic violence (i.e. towards a caregiver)		CTQ, CECA, UCLA PTSD-RI, JVQ, VEX-R	CTQ: Bernstein '97
9	McLaughlin (2016) same sample as Jenness (2018)	90	47/43	13.5	6 - 18	oversampling for at risk: recruited from schools, medical clinics, and the general community, neighborhoods with high levels of violent crime, clinics that serve predominantly low-SES clients, agencies that work with families exposed to violence	none	no	included + robustness analyses	PTSD, anxiety disorders, depression, externalizing disorders	35	55	categorical	yes	physical and sexual abuse, witnessing domestic violence	accidents, injuries and witnessing community violence; other scales than physical and sexual were not considered	CTQ + CECA composite score	CTQ: Bernstein '97
10	Jenness (2018) same sample as McLaughlin (2016)	94	48/46	13.5	6 - 18	oversampling for at risk: recruited from schools, medical clinics, and the general community, neighborhoods with high levels of violent crime, clinics that serve predominantly low-SES clients, agencies that work with families exposed to violence	none	no	not explicitly reported	PTSD	38	56	categorical	no	(a) physical abuse, sexual abuse, or witnessing more than 2 incidents of domestic violence during the CECA interview or (b) scores on the CTQ physical and sexual abuse subscales that exceed a validated threshold	accidents, injuries and witnessing community violence; other scales than physical and sexual were not considered	CTQ + CECA composite score	criterion A trauma listed on the UCLA PTSD RI (DSM-IV), CTQ: Bernstein '97
11	Susman (2021)	165	86/79	12.65	9 - 17	recruited from neighborhoods with high levels of violent crime, clinics that served a predominantly low SES catchment area, and agencies that work with families who have been victims of violence	IQ < 80, pervasive developmental disorder, psychosis, mania, substance abuse, safety concerns	no	included	PTSD, anxiety disorders, depression, externalizing disorders	86	79	categorical	no	physical and sexual abuse, direct witnessing of domestic violence		CTQ, CECA, UCLA PTSD-RI, JVQ, VEX-R	CTQ: Bernstein '97

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		Sample information									Childhood adversity							
No.	Author (year)	N	N male/female	Age mean in years	Age range	Recruitment strategy	Exclusion criteria	Assesement of general or recent adversity	Handling of psychiatric disorders	Psychopathology screening	Nexposed	Nunexposed	Categorical or dimensional analyses	Exposure severity considered	Adversity type considered or recruited  blue = adverse experience green = exposure to potentially adverse events	Trauma types explicitly not considered as exposure	Assessment instrument	Cut-off used
12	Wolitzky-Taylor (2022)	127	44/83	17	baseline: ~ 17 startle protocol completed: 16 - 18	high school juniors from Los Angeles and Chicago, oversampling for high neuroticism	current clinically significant Axis I psychiatric disorder at the baseline assessment	no	current diagnoses excluded	PTSD, anxiety disorders, depression, externalizing disorders	not applicable (dimensional scores used)		dimensional	yes	separations from or loss of a caregiver, caregiver neglect, emotional abuse, physical abuse, witnessing violence, and sexual abuse and assault		CTI	sum of adversity severity scores for each domain of adversity
13	Kreutzer (2021)	112	36/76	18.5	17 - 19	recruited through advertisements on social media and in the local community	serious medical condition, psychotropic medication use, deafness, pregnancy, lifetime and/or current alcohol or substance use disorder, and psychosis.	no	included	PTSD, anxiety disorders, depression	57	55	categorical	no	exposures to actual or threatened death, serious injury, or sexual violence; divided into interpersonal and non-interpersonal trauma		SCID-5	criterion A trauma listed on the UCLA PTSD RI (DSM-V)
14	Lange (2018)	113	22/91	21	16 - 25	recuited via posters in schools, public places and newspaper ads	<b>HC:</b> history of psychiatric diagnosis or treatment, or a current DSM-IV axis I disorder; subclinical group: current psychiatric treatment or a significant need for care; <b>both groups:</b> lefthandedness, alcohol and substance dependence, current use of psychotropic drugs, a history of neurological disease, severe head trauma, organic brain disease and MRI contraindications	no	included	PTSD, anxiety disorders, depression	58	55	categorical	yes	emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect		CTQ	median split
15	Zoladz(2022)	291	156/135 low CA: 133/87 high CA: 71/48	19.37	> 18	healthy undergraduate students	PTSD, skin diseases, history of syncope or vasovagal response to stress, heart condition/ cardiovascular issues, severe head trauma, current treatment with narcotics, beta-blockers, steroids; substance use disorder,hearing loss, regular nightshift worl, recreational drugs	no	life time diagnoses excluded	PTSD, anxiety disorders, depression	71	220	categorical (high vs. low exposure)	no	emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect		CTQ	CTQ: Bernstein '98
16	Pole (2007)	90	76/24	28.5	not reported	incoming police academiyl cohort in San Francisco	no exclusion criteria, but controlled for potentially confounding medication and past major depression	no	current diagnoses excluded	PTSD, anxiety disorders, depression	25	65	categorical	yes	disaster, physical assault, serious illness / accident, serious abuse, serious neglect, sexual assault	events that were merely witnessed, happend to some else and were not associated with intense peritraumatic distress	LSC-R	0 events or 1 and more
17	Scharfenort (2016)	76	41/35	25	not reported	recruited from a screening sample (mainly students)	current or prior psychiatric / neurological disorders	recent	life time diagnoses excluded	PTSD, anxiety disorders, depression	35	41	categorical and dimensional	yes	general exposure (no subtypes)		life events checklist	1 events or 1 and more
18	Lis (2020) overlapping sample with Thome (2018)	PTSD: 64; HC: 30	all female	app. 35	18 - 65	PTSD patients were recruited from a longitudinal treatment study (before they started treatment), HC recruited through the database at the Department for Psychosomatic Medicine and Psychotherapy, CIMH Mannheim, and public advertisements	<b>PTSD:</b> lifetime diagnosis of schizophrenia or Bipolar I disorder, current substance dependence, a body mass index <16, or intake of the following psychotropic drugs: tricyclic antidepressants, neuroleptics, trazodon, benzodiazepines, anxiolytic drugs, as well as beta adrenergic blocking agents. suicide attempt within the last 2 months; <b>HC:</b> no axis I disorder or borderline, no life time psychotherapy experience	no	explicitly clinical sample	PTSD, anxiety disorders, depression	64	30	categorical	yes	physical and sexual abuse		CTQ, LEC-5	CTQ: Bernstein '98
19	Thome (2018) overlapping sample with Lis (2020)	PTSD: 30; TC: 30 HC: 30	0/30 each	app. 31	18 - 65	PTSD patients were recruited from a longitudinal treatment study (before they started treatment), TC & HC recruited through the database at the Department for Psychosomatic Medicine and Psychotherapy, CIMH Mannheim, and public advertisements	<b>PTSD:</b> lifetime diagnosis of schizophrenia or Bipolar I disorder, current substance dependence, a body mass index <16, or intake of the following psychotropic drugs: tricyclic antidepressants, neuroleptics, trazodon, benzodiazepines, anxiolytic drugs, as well as beta adrenergic blocking agents. suicide attempt within the last 2 months; <b>HC:</b> no axis I disorder or borderline, no life time psychotherapy experience, <b>TC &amp; HC:</b> lifetime diagnosis of any axis - I or borderline personality disorder, the intake of psychotropic drugs or experiences of psychotherapeutic interventions	no	explicitly clinical sample	PTSD, anxiety disorders, depression	60	30	categorical	yes	physical and sexual abuse		CTQ, LEC-5	CTQ: Bernstein '98
20	Jovanovic (2009)	60	32/28	app. 45	18 - 63	recruited from a larger study investigatng genetic and environmental factors contributing to PTSD , primarily African-American, low SES, inner-city population	active psychosis and severe medical illness	no	included	PTSD, anxiety disorders, depression	20	40	categorical	yes			CTQ	CTQ: Bernstein '98
21	Stout (2021)	2593	2593/0	22.7	not reported	recruited from First Marine Division infantry battalions preparing to deploy to either Iraq or Afghanistan	none	recent	included	PTSD, anxiety disorders, depression	1312	1145	categorical and dimensional	yes	emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect		CTQ	CTQ: Bernstein '98

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No.	Author (year)	N	N male/female	Age mean in years	Age range	Recruitment strategy	Exclusion criteria	Assesement of general or recent adversity	Handling of psychiatric disorders	Psychopathology screening	N exposed	N unexposed	Categorical or dimensional analyses	Exposure severity considered	Adversity type considered or recruited  blue = adverse experience green = exposure to potentially adverse events	Trauma types explicitly not considered as exposure	Assessment instrument	Cut-off used
22	Huskey (2022)	42	7/35	20.4	18 - 50	recruited via social media and flyers - resulting in mainly (psychology) students	cardiorespiratory and cardiovascular conditions, history of seizures, epilepsy, neurological conditions, or brain disorders, Hearing impairments	recent	not expclicitly reported	PTSD, anxiety disorders	17	9	categorical and dimensional	no	traumatic events that comprise Criterion A of the current PTSD diagnosis as defined by the DSM-V		THS	criterion A trauma listed on the UCLA PTSD RI (DSM-V)
23	Bremner (2005)	19	0/19	37	not mentioned	newspaper advertisement	major medical illness, substance abuse, medication, organic mental disorders or co-morbid psychotic disorders, retained metal, a history of head trauma, loss of consciousness, cerebral infectious disease, or dyslexia	no	life time diagnoses excluded	PTSD, anxiety disorders, depression	8	11	categorical	no	physical,emotional, and sexual abuse, as well as general traumatic events		ETI-SR	sum score
24	Kuehl (2020)	118	54/64	app. 35	not mentioned	recruited through public potings and via affective disorder unit at the Charité Berlin	CNS relevant diseases, neurological diseases, severe somatic diseases, diabetes type 1 and 2, diseases of steroid hormones, hypertonia, tinnitus, hearing impairments, current infections, pregnancy as well as the intake of psychotropic medication. <b>HC:</b> current mental disorder. <b>Depressed patients:</b> schizophrenia, schizoaffective disorder, bipolar disorder, depr. with psychotic features, dementia, panic disorder, alcoool or drug dependence	no	current diagnoses excluded	PTSD, anxiety disorders, depression, externalizing disorders	50	68	categorical	no	repeated physical or sexual abuse at least once a month over one year or more		CTQ, ETI	physical or sexual abuse at least once a month over one year or more until the age of 18
25	Morrison (2022)	110	all female	no access to information	18 - 45	Blood plasma samples were selected from a biobank generated by a larger study of risk factors for PTSD - participants were recruited through waitingrooms of a large urban tertiary care center serving low income populations with high trauma load	not reported	no	included	PTSD, depression	74	27	categorical	no	sexual abuse or assault (and different age of exposure gruops)		TEI (subset)	sum score
26	Klingelhöfer-Jens (2023)	1402	557/845	exposed: 26.8, unexposed: 25.1	18 - 50	recruited via online platforms within a Collaborative Research Center on fear and anxiety (SFB-TRR58) at the Universities of Würzburg, Münster, and Hamburg	left-handedness, non-Caucasian descent, current or lifetime diagnosis of psychiatric and neurological disorders, intake of illegal drugs or psychoactive medication, excessive consumption of alcohol, nicotine or caffeine, pregnancy	recent and general	current + lifetime diagnoses excluded	German version of the Mini International Psychiatric Interview	203	1199	both	yes	emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect		CTQ	CTQ: Bernstein '98, Häuser 2011
		Studies with a slightly different focus or with ACEs only included in higher order interaction																
27	Jovanovic (2020)	63	34/29	10	8 - 13	Mothers were recruited from an ongoing study of PTSD and trauma exposure.	diagnosis of autism spectrum disorder, bipolar disorder, psychotic disorder, or cognitive disability	no	included	PTSD	36	21	categorical (high vs. low exposure)	no	minor and severe violence victimization and witnessing violence at home, school, and neighborhood.		VEX-R	median split
28	Stenson (2021)	78	38/40	10.2 (first visit)	8 - 13	recruited from a larger study of African-American primary caregivers and children from a low-income, urban population with high trauma exposure (J	autism spectrum disorders, bipolar or psychotic disorders, and cognitive disability	no	included	PTSD, anxiety disorders	not applicable (dimensional scores used)		included as covariate	yes	minor and severe violence victimization and witnessing violence in the home, school, and neighborhood.		VEX-R, TESI	not mentioned
29	Radoman (2019)	70	21/49	181.4	17-19	recruited through flyers social media neaby a highschool an college campus (all were students)	major active medical or neurological illness, lifetime history of manic/psychotic symptoms or active suicidal ideation, deafness, traumatic brain injury, psychotropic medication use (past 4 months), lifetime history of alcohol or substance use disorder, positive drug screen, and pregnancy.	no	partly excluded/partly included	PTSD, anxiety disorders, depression	not applicable (dimensional scores used)		dimensional	yes	bullying only (past year, aged 16-18)	any events earlier than the last 12 month and anything except for bullying	GHQ	sum score (includes frequency and intensity)
30	Rowland (2022)	FPS paradigm: 285; fMRI: 95	all female	mid 30ies (unclear for subsample) see supplement	18-65	recruited through waiting rooms of general medical clinic with a low income black population visiting typically	history of bipolar disorder, schizophrenia, other psychotic disorder, pregnancy, or illegal drug use (cocaine, marijuana, opiates, amphe-tamines, and methamphetamines)	general	included	PTSD	not applicable (dimensional scores used)		included as covariate	yes	sexual abuse by an older teenager or adult a) between age 0 and 13, b) between 14 and 17 or after the age of 17 (the latter would not qualify as childhood really)		TEI (subset), CTQ	sum score
31	Estrada (2020)	164	114/50	40.24	18-75	recruited through flyers in a high crime region	insufficient reading, IQ < 70; schizophrenia, bipolar disorder, or psychosis, history of auditory impairment, loss of consciousness >30 min, seizures	general	included + robustness analyses	PTSD, anxiety disorders, depression, externalizing disorders	not mentioned	not mentioned	included as covariate	yes	emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect		CTQ, ETV	not mentioned
32	Morey (2015)	67	51/16	42	not mentione	veterans from a repository	major Axis I diagnosis (other than depression), contraindication to MRI, substance dependence, traumatic brain injury, and neurological disorders	no	included	PTSD, anxiety disorders, depression, externalizing disorders	not applicable (dimensional scores used)		dimensional	yes	emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect		CTQ	sum score

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No.	Author (year)	N	N male/female	Age mean in years	Age range	Recruitment strategy	Exclusion criteria	Assesement of general or recent adversity	Handling of psychiatric disorders	Psychopathology screening	N exposed	N unexposed	Categorical or dimensional analyses	Exposure severity considered	Adversity type considered or recruited  blue = adverse experience green = exposure to potentially adverse events	Trauma types explicitly not considered as exposure	Assessment instrument	Cut-off used
33	Schellhaas (2022)	64	5/59	32	19-60	recuitment of individuals with diverse range of childhood maltreatment	acute and/or chronic physical diseases (e.g. cardiovascular, respiratory, or neurological diseases), psychotic disorders, use of psychotropic drugs (except selective serotonin and norepinephrine reuptake inhibitors [SSRIs and SNRIs]), and current (past 12 months) substance dependence and/or abuse	no	partly excluded/partially included	PTSD, anxiety disorders, depression, externalizing disorders	all	0	included as covariate	yes	emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect: in a pre-screening, one item of every subscale was presented with an overall value of >=1		CTQ	sum score
34	Young (2018) overlapping sample with Young 2019	226		44.8	not reported	gulf war veteran, recruited from larger study	severe physical impairment or medical illness, current or lifetime history of psychosis or of suicidal or homicidal ideation, and a history of neurological or systemic illness affecting central nervous system functioning	general	included	PTSD	70	156	categorical	no	childhood physical or sexual abuse prior to the age of 16	all that are not sexual or physical abuse	THQ	none (likely single item yes sufficient)
35	Young (2019) overlapping sample with Young 2018	147	115/32	50	not reported	gulf war veteran, recruited from larger study	severe physical impairment or medical illness, current or lifetime history of psychosis or of suicidal or homicidal ideation, and a history of neurological or systemic illness affecting central nervous system functioning	general	included	PTSD	45	102	categorical	no	childhood physical or sexual abuse prior to the age of 16	all that are not sexual or physical abuse	THQ	none (likely single item yes sufficient)
36	Hall (2022)	131	97/34	25.7	18-65	sample was taken from a larger study with HC and individually with depression, anxiety or both	major active medical or neurological problem; lifetime history of mania or psychosis; current OCD; intellectual disability or pervasive developmental disorder; current psychiatric treatment; psychoactive medication (past 4 months); a history of traumatic brain injury; pregnancy	no	explicitly clinical sample	anxiety disorders, depression	45	86	categorical	no	emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect		CTQ	CTQ: Bernstein '98
37	Deslauriers (2018)	714	714/0	app. 22	not mentioned	US Marines from infantry battalions at bases in Southern California that were deployed to Afghanistan	All ancestries other than European-American were excluded to reduce population stratification, PTSD diagnosis before deployment	general	not explicitly reported	PTSD, depression	264	450	categorical	no	emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect		CTQ	CTQ: Bernstein '98
38	Harnett (2019)	198	98/100	20.73	one school cohort	initially recruited from 5th grade classrooms in local public schools as part of a larger study	not reported	no	not explicitly reported	no	not reported	not reported	categorical	no	within the 12 months before each assessment: victimized or witnessed: 1) threat of violence, 2) physical violence, and 3) threat or physical violence involving a weapon; Victimized: 4) violent injury requiring medical treatment; family income , neighborhood disadvantage	traumatic events that happened outside the three 1-year time windows of assessment	customized questions	average scores for witnessing and victimization for each timepoint, the average score of all four time points was used as an index of violence exposure in the present study

Supplementary Table 2: Sample Information\_Reward

		Sample information									Childhood adversity							
No.	Author (year)	N	N male/female	Age mean in yrs	Age range	Recruitment strategy	Exclusion criteria	Assesment of general or recent adversity	Handling of psychiatric disorders	Psychopathology screening	N exposed	N unexposed	Categorical or dimensional analyses	Exposure severity considered	Exposure type considered or recruited blue = adverse experience green = exposure to potentially adverse events	Trauma types explicitly not considered as exposure	Assessment instrument	Cut-off used
1	Birn (2017)	54	26/28	20.5	19-23	recruited from larger study, stress assessment at age 10 and 10 year follow-up, highest and lowest quintiles re-contacted	none	recent	not explicitly reported	depression	29	25	dimensional	yes	neglect, abuse, general life stress		YLSI	> 4.0 for early life stress, < 2.5 for controls on a 10-point scale
2	Bjork (2008)	26	16/10	13.9	12-16	Recruitment through parent undergoing treatment + community	Axis I disorders, probable fetal alcohol exposure	no	exclusion	Axis I disorders	13	13	categorical	no	Parental alcoholism		DSM-IV criteria for alcoholism (SSAGA assessment)	One or two parents with alcohol use problem
3	Blair (2022)	142	91/51	16.4	14-18	care facility for behavioral and mental health problems, community via flyers or social media	none	no	not explicitly reported	MDD, GAD, PTSD, ADHD, CD	91	51	dimensional	yes	emotional/physical neglect, emotional/sexual/physical abuse		CTQ	CTQ: Walker et al., 1999
4	Boecker-Schlier (2016)	168	71/97	24.5	25	large epidemiological study, children born between 1986-1988; first borns; German-speaking parents	handicap, MRI contraindications, current psychopathology, psychotropic medication	no	not explicitly reported	psychiatric disorders incl. ADHD; YASR	not applicable (dimensional scores used)		dimensional	yes	emotional, sexual abuse, neglect, general adversity		parent interview	Rutter&Quinton, 1977: childhood family adversity compound score over childhood period
5	Casement (2014)	120	0/120	NA	16	recruited from larger longitudinal study (Pittsburg Girls Study); screened at age 8 for high depressive symptoms + matched controls; invited back at age 16	Eligible for scanning	no	included	depression	not applicable (dimensional scores used)		dimensional	yes	Low parental warmth; peer victimization		Items from parent-child rating scale; items from peer experiences scale	
6	Cisler (2019) same sample as Letkiewicz (2022)	60	0/60	not provided	11-17	community sample, half exposed to assault that could be remembered, half not; balance in PTSD diagnoses in assaulted sample	controls: mental health disorders, trauma exposure, and psychiatric treatment; all: histories of psychotic symptoms, developmental disorders, neurocognitive disorders, MRI contraindications, pregnancy, history of traumatic brain injury, loss of consciousness greater than 10 min, and major medical disorders	no	included	PTSD, mood, anxiety disorders	30	30	categorical and dimensional	yes	physical, sexual assault		interview for assault, CTQ	1 or more assaults, CTQ only used dimentionally
7	DelDonno (2019)	50	11/39	27	18-55	community sample: roughly half of participants have MDD	psychotic symptoms, bipolar disorder or mania, family history of psychosis, suicidal attempts in the past 6 months, chronic or serious medical conditioning, smoking, alcohol or substance abuse	no	included	MDD; comorbid anxiety, BISBAS	50	0	dimensional	yes	emotional, physical or sexual abuse, emotional or physical neglect		CTQ	
8	Delgado (2022)	227	115/112	75.28 months	5-7	Recruited from nine public schools in Uruguay	none	no	not explicitly reported	NA	108	119	categorical	no	Low SES		Socioeconomic level index (SLI), questionnaire	
9	Dennison (2016)	59	23/36	17	13-20	recruited from larger community-based study	psychiatric medication, braces, claustrophobia, active substance dependence, pervasive developmental disorder, non-English speaking, safety concerns	no	included	depression, externalizing and internalizing disorders	21	38	categorical	no	neglect, emotional, sexual and physical abuse		CTQ + CECA	report during CECA interview or CTQ cut-off (Walker et al., 1999)
10	Dennison (2019)	94	48/46	13.6	6-19	community sample: schools, prevention programs, medical clinics, general community	MRI contraindication and younger than 7 years of age for MRI portion	no	included	depression	38	56	categorical	no	physical or sexual abuse, neglect, food insecurity		CTQ + CECA + 4 questions about food insecurity	abuse: reported in CECA interview or CTQ subscale threshold (Walker et al., 1999); neglect: CECA cutoff (Bifulco et al., 2005)
11	Dillon (2009)	44	20/24	33.8	not provided	maltreated recruited from other study; community sample for controls	both: left-handedness, history of neurological or medical conditions, MRI contraindications; controls only: psychopathology, psychotropic medication,	no	included	MDD, anxiety disorders, PTSD	11	31	categorical	yes	emotional, physical or sexual abuse		adult attachment interview, conflict tactics scale, traumatic stress schedule (TSS)	multimodel assessment of whether or not abuse was present or not
12	Eckstrand (2019)	111	33/78	22	18-25	counseling service for mental healthcare, community ads, participant registry	all: left handedness, not fluent in English; controls: present psychological distress, personal history of psychiatric illness	no	included	anhedonia, depression, anxiety	50	61	dimensional	yes	crime-related events, general disaster, unwanted physical/sexual experience		THQ	no, dimensional approach
13	Gerin (2017)	37	11/26	13	10-15	via social services department; via schools/advertisements for controls	presence of pervasive developmental disorder, neurological abnormalities, MRI contraindications, IQ below 70	no	included	anxiety, depression, PTSD, conduct problem, hyperactivity	18	19	categorical	yes	neglect, emotional, sexual and physical abuse		adversity history and severity reported by social worker or adoptive parent	severity rated from 0-4 (Kaufmann et al., 1994); subtype estimated based on file information
14	Gonzalez (2016)	83	42/41	24.4	NA	Recruited from larger, longitudinal study (Virginia Institute for Development in Adulthood)	If participants couldn't bring opposite sex partner to testing session (due to ongoing relationship study); MR safety criteria not met	no	not explicitly reported	no	NA	NA	dimensional	yes	Low neighborhood quality		Initially: Neighborhood Quality Questionnaire (NQQ), controlled for parental SES and current income	no, dimensional approach

### Supplementary Table 2: Sample Information\_Reward

[illegible]



Supplementary Table 2: Sample Information\_Reward

		Sample information									Childhood adversity							
No.	Author (year)	N	N male/female	Age mean in yrs	Age range	Recruitment strategy	Exclusion criteria	Assesment of general or recent adversity	Handling of psychiatric disorders	Psychopathology screening	N exposed	N unexposed	Categorical or dimensional analyses	Exposure severity considered	Exposure type considered or recruited  blue = adverse experience green = exposure to potentially adverse events	Trauma types explicitly not considered as exposure	Assessment instrument	Cut-off used
25	Mehta (2010)	23	12/11	16	not provided	Romanian adoptees living close to London; controls: local schools	MRI contraindications	no	not explicitly reported	quasi-autism, hyperactivity, cognitive impairment, disinhibited attachment	12	11	categorical	no	adoption (global deprivation)		deprivation experience + self report	
26	Morelli (2021)	46	21/25	7.3	6-8	flyers, mailing list, oversampling for parents w depression	developmental or physical disability, non-fluent English, lifetime history of psychotic or bipolar disorder in parent	recent	included + robustness analyses	depression, anxiety	not applicable (dimensional scores used)		dimensional	yes	low family income, low parental education, single parent household, parental depression, parental hostility, four additional events of early life stress		composite score: low family income, low parental education, single parent household, exposure to parental depression, parental hostility, min. 4 stressful life events from preschool age psychiatric	sum of scores
27	Morris (2015)	204	103/101	12.3	8-19	Children of participants from previous study with either childhood onset depression or control group	Participants with low rewards	recent	included	Depression, anxiety	86	118	categorical	no	Parental depression			Parent with history of childhood onset depression assessed in previous study
28	Mueller (2012)	46	20/26	16	not provided	larger ongoing study (Infant Caregiver Project), controls: local newspapers	all: IQ below 80, controls: adopted, medical or psychiatric problems, history of maltreatment	no	included	anxiety, depression, bipolar	17	29	categorical	no	adoption, neglect		deprivation experience + self report	1 or more experience
29	Müller (2014) Sample 1	412	NA	NA	13-15	Participants were part of a large longitudinal European multi-center study (IMAGEN); recruitment via high schools	Serious medical conditions (e.g. diabetes, rheumatologic disorders, neurological conditions, developmental conditions), previous head trauma with unconsciousness and MRI contra-indications as well as heavy maternal alcohol use during pregnancy (>14 bottles of beer or nine glasses of wine per week) were exclusion criteria.	no	not explicitly reported	Psychiatric disorders	206	206	dimensional	yes	Alcoholism in first or second degree relative		Diagnosis by medical doctor/psychologist or in treatment for it	
30	Müller (2014) Sample 2	154	NA	NA	13-15	Participants were part of a large longitudinal European multi-center study (IMAGEN); recruitment via high schools	Serious medical conditions (e.g. diabetes, rheumatologic disorders, neurological conditions, developmental conditions), previous head trauma with unconsciousness and MRI contra-indications as well as heavy maternal alcohol use during pregnancy (>14 bottles of beer or nine glasses of wine per week) were exclusion criteria	no	not explicitly reported	Psychiatric disorders	77	77	categorical	no	Parental alcoholism		Diagnosis by medical doctor/psychologist or in treatment for it	
31	Mullins (2020)	6396	NA	NA	9-10	Data from publicly available data from larger study (ABCD study, recruited at age 9-10); screened for parental substance use and matched controls	Participants who didn't complete the MID, had missing CBCL scores, were scanning on scanner not from Siemens or GE	no	included	Internalizing and externalizing symptoms			dimensional	yes	Neighborhood deprivation		Area deprivation index (ADI) via US census data	
32	Patterson (2013) Exp1	73	14/59	19.8	18-23	undergrads at UCLA	none	no	not explicitly reported	anxiety, depression	36	37	categorical	no	emotional/physical/sexual abuse, domestic violence, divorce, household substance abuse/mental illness/criminal		ACEQ	
33	Patterson (2013) Exp2	212	50/162	20.2	18-39	undergrads at UCLA oversampled for ELS	none	no	not explicitly reported	anxiety, depression	126	86	categorical	yes	emotional/physical/sexual abuse, domestic violence, divorce, household substance abuse/mental illness/criminal		ACEQ	0, 1-2 or 3+ experience for no, moderate and high ELS
34	Pechtel (2013)	49	0/49	29	not provided	online, printed ads	left handedness, significant medical or neurological conditions, current mood disorder, current or past psychotic symptoms, somatoform disorders, personality disorders, lifetime substance dependence, substance abuse within past 6 months, seizures, antidepressant medication in the past 2 months	no	included	MDD	31	18	categorical	no	childhood sexual abuse (min 3 episodes, age 7-12)	other physical or emotional abuse	self report	
35	Romens (2016)	123	0/123	NA	16	recruited from larger longitudinal study (Pittsburg Girls Study); screened at age 8 for high depressive symptoms + matched controls; invited back at age 16	Eligible for scanning	no	included	depression	not applicable (dimensional scores used)		dimensional	yes	Low SES		Number of years of household receipt of public assistance	
36	Sheridan (2018)	136	67/69	12	11-14	BEIP longitudinal study: recruited from child rearing institutions; controls: pediatric clinics, three groups: never institutionalized (NIG), foster care (FCG), prolonged institutional care (CAUG)	none	no	included	depression, social functioning	48/43	47	categorical/dimensional	yes	institutional rearing to varying degrees		deprivation experience	



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No.	Author (year)	N	N male/female	Age mean in yrs	Age range	Recruitment strategy	Exclusion criteria	Assesment of general or recent adversity	Handling of psychiatric disorders	Psychopathology screening	N exposed	N unexposed	Categorical or dimensional analyses	Exposure severity considered	Exposure type considered or recruited <small>blue = adverse experience green = exposure to potentially adverse events</small>	Trauma types explicitly not considered as exposure	Assessment instrument	Cut-off used
37	Smith (2022)	72	29/43	8.4	8-9	from Midwestern city	none	no	not explicitly reported	anxiety, depression	not applicable (dimensional scores used)		dimensional	yes	perceived social isolation		CLEC	number of stressful events, perception of social isolation as additional measure
38	Weiland (2014)	70	46/24	20.1	18-22	Recruited from ongoing study of families with parental alcoholism (MLS study)	Mother drinking during pregnancy or signs of fetal alcohol spectrum disorder, any neurological, acute, uncorrected or chronic medical illness; any current or recent (within six months) treatment with centrally active medications, including sedative hypnotics; and history of psychosis or schizophrenia in first-degree relatives. The presence of most Axis I psychiatric or developmental disorders was exclusionary	no	exclusion	Axis I disorders	49	21	categorical	no	Parental alcoholism		DSM-IV criteria for alcoholism	One or both parents with a lifetime history of alcoholism
39	Weiss (2019)	51	33/18	51.7	not provided	addiction clinic: all participants have opiod addiction, in treatment for 3+ months	none	no	not explicitly reported	self harm, drug use	32	19	categorical	no	physical, verbal or sexual abuse or rape		self report	
40	White (2022)	172	59/113	13.94	12-15	Recruitment from Chicago area	Not in 8 <sup>th</sup> grade, not English-speaking, not in good health, fMRI contraindications; history of serious medical illness or axis I psychiatric disorder, medication on previous 3 months, hospitalization in previous 12 months	no	exclusion	Axis I disorders	not applicable (dimensional scores used)		dimensional	yes	Low SES		MacArthur Network Sociodemographic Questionnaire; income-to-poverty ratio as main measure	
41	Wilkinson (2021)	129	53/76	37.6	25-65	screening through online platform Prolific	not fluent in English, mild cognitive impairment or dementia, mental health disorder, Parkinson's	recent and general	included	social status, depression, anhedonia, stress	64	65	categorical	no	abuse, neglect		ELSQ	3 or more adverse experiences
42	Wismer Fries (2017)	52	27/25	6.3	not provided	exposed: from Easter European orphanages; controls: always resided with their birth parents	developmental disorder, known or suspected fetal alcohol exposure or fetal alcohol syndrome	no	not explicitly reported	indiscriminate behaviour	26	26	categorical	no	caregiving neglect (adoption, foster care)		deprivation experience	
43	Yang (2021)	45	22/23	14.9	11-19	group 1: treatment seeking for trauma related CBT; group 2: treatment seeking for anxiety/depression related CBT	MRI contraindications, major medical problems, problems understanding the procedure	no	included + robustness analyses	depression, anxiety	not applicable (dimensional scores used)		dimensional	yes	emotional, physical or sexual abuse, emotional or physical neglect		CTQ	CTQ: Bernstein et al., 1998
44	Yau (2012)	40	24/16	20.3	18-22	Recruited from ongoing study of families with parental alcoholism (MLS study)	Mother drinking during pregnancy or signs of fetal alcohol spectrum disorder, any neurological, acute, uncorrected, or chronic medical illness; any Axis I psychiatric or developmental disorders; any current or recent (within 6 months) treatment with centrally active medications; a history of psychosis or schizophrenia in first-degree relatives; and a positive urine drug screen on the day of the study	no	exclusion	Axis I disorders	20		20	categorical	Parental alcoholism		DSM-IV criteria for alcoholism	One or both parents with a lifetime history of alcoholism

Supplementary Table 3: Paradigm Information\_Threat

No.	Author (year)	Open data	Paradigm information I			Paradigm information II									Outcome measures					
			Paradigm type	Experimenal phases	Instruction	Reinforcement rate %	Stimulus (CS) type	Stimulus (CS) duration	ITI duration in s	Number of trials per CS (acquisition)	Number of trials per CS (extinction)	Number of trials per CS and GS (generalization)	US type	US calibration	Psycho-physiological measures	Min. amplitude SCR in us	SCR non-responder	Ratings	Neuroimaging	Other measures
1	Machlin (2019) same sample as Mилоjevič (2020)	no	Fear conditioning (block design)	pre-cond, acq, immediate ext	information not provided by authors	80%	geometric	1.5	0.5	40	40	not applicable	tone	fixed level	SCR	0.05	excluded (N=3)	contingency (after each exp. phase)	none	none
2	Mилоjevič (2020) same sample as Machlin (2019)	no	Fear conditioning (block design)	pre-cond, acq, immediate ext	information not provided by authors	80%	geometric	1.5	0.6	40	40	not applicable	tone	not reported	SCR	0.05	not reported by authors	contingency (after each exp. phase)	none	none
3	Marusak (2021)	no	Fear conditioning	acq, immediate ext, 24h-ext recall (included but not reported: re-ext, renewal, CS+ unextinguished)	information not provided by authors	80%	VR avatar	4	4-9	8	8	not applicable	scream	fixed level	SCR	0.02	not reported by authors	fear, expectancy (intermittend)	fMRI (only during extinction recall for a subsample; ROI: AI, dACC, exploratory: amygdala, hippocampus, vmPFC)	distance to CS (VR)
4	Jovanovic (2022)	no	Fear conditioning	hab, acq, immediate ext	information not provided by authors	100%	geometric	6	9-22	9	12	not applicable	airblast	fixed level	startle	not applicable	not applicable	contingency (intermittend during extinction)	none	none
5	Qiu (2022)	upon request	Fear conditioning	acq, gen	threat contingencies not explicitly provided	75% (acq), 50% (gen)	faces	3	3+1	16	not applicable	6	white noise	individually calibrated for being scary/annoying/unpleasant (range 90-110dB)	none	not applicable	not applicable	fear, valence, arousal, expectancy (after each exp. phase)	none	none
6	France (2022)	no	Fear conditioning	acq, immediate ext	information not provided by authors	100%	geometric	6.5	9-22	9	12	not applicable	airblast	fixed level	startle	not applicable	not applicable	expectancy (after each exp. block and phase)	none (fMRI only in a memory face viewing paradigm)	none
7	Silvers (2016)	no	Fear conditioning (block design)	acq (included but not analyzed: CS+ reinforced trial blocks)	threat contingencies not explicitly provided	no information provided (likely different between participants due to escape component)	geometric	min. 1s (variation due to escape component)	no ITI between CSs	8 times 37s blocks (3 reinforced CS+, 3 non-reinforce CS+, 2 CS-), trial number differed between participants as block lenght was fixed but due to	none (even though the non-reinforced CS+ would be extinction)	not applicable	tone	individually calibrated to be annoying but not painful (max. 65 dB)	none	not applicable	not applicable	none	fMRI (ROI: amygdala, hippocampus)	reaction time for escape, connectivity
8	DeCross (2022)	yes	Fear conditioning (block design)	acq (to do: bei den block designs kann man ja irgendwie nicht unterscheiden was acq und ext ist...)	information not provided by authors	80%	geometric	1.5	500ms	40	not applicable	not applicable	tone	fixed level	none	not applicable	not applicable	none	fMRI (ROI: right amygdala (amygdala, insula, and dorsal ACC) and default mode network (hippocampus, PHG and vmPFC))	none
9	McLaughlin (2016) same sample as Jenness (2018)	no	Fear conditioning	pre-cond, acq, immediate ext	some threat contingencies provided	80%	items	8	8-12	10	8	not applicable	tone+ picture	fixed level	SCR	0.02	included + robustness check	fear, liking, unpleasantness (after each experimental phase)	MRI (subsample)	none
10	Jenness (2018) same sample as McLaughlin (2016)	no	Fear conditioning	pre-cond, acq, immediate ext	some threat contingencies provided	80%	items	8	8-12	10	8	not applicable	tone+ picture	fixed level	SCR, respiratory sinus arrhythmia (ECG)	0.02	excluded + robustness check	none	none	none

Supplementary Table 3: Paradigm Information\_Threat

			Paradigm information I			Paradigm information II									Outcome measures					
No.	Author (year)	Open data	Paradigm type	Experimenal phases	Instruction	Reinforcement rate %	Stimulus (CS) type	Stimulus (CS) duration	ITI duration in s	Number of trials per CS (acquisition)	Number of trials per CS (extinction)	Number of trials per CS and GS (generalization)	US type	US calibration	Psycho-physiological measures	Min. amplitude SCR in us	SCR non-responder	Ratings	Neuroimaging	Other measures
11	Susman (2021)	yes	Fear conditioning	pre-cond, acq, immediate ext	some threat contingencies provided	80%	items	8	8-12	10	8	not applicable	tone+ picture	fixed level	SCR, vagal tone (ECG)	0.02	excluded (N=11, whereof N=8 from violence-exposed group)	none	none	none
12	Wolitzky-Taylor (2022)	no	NPU threat task	startle hab, predictable, unpredictable and safe condition	explicit contingency instructions	not applicable	NPU instructions	55	22	not applicable	not applicable	not applicable	shock	fixed level	startle	not applicable	not applicable	none	none	none
13	Kreutzer (2021)	no	NPU threat task	startle hab, predictable, unpredictable and safe condition	explicit contingency instructions	100%	NPU instructions	6	15-21	not applicable	not applicable	not applicable	shock	individually calibrated to be annoying but not painful	startle	not applicable	not applicable	none	none	none
14	Lange (2018)	no	Fear conditioning	pre-cond, acq, gen	some threat contingencies provided	66% (acq), 50% (gen)	geometric	4. 4	either 2.2 or 4.4	12	not applicable	12	shock	individually calibrated to be highly uncomfortable but not painful	none	not applicable	not applicable	fear, valence, arousal (after each phase), US expectancy (trial-by-trial, during)	fMRI (ROI: amygdala, vmPFC)	none
15	Zoladz(2022)	yes	Fear conditioning	startle hab, pre-cond, acq, 24h delayed gen	information not provided by authors	100% (acq), 0% (gen)	geometric	7	CS- : 6.25	9-22	12	not applicable	3	airblast	fixed level	startle	not applicable	not applicable	expectancy (trial-by-trial, during trial)	none
16	Pole (2007)	no	Threat of shock	startle hab, low, medium and high threat conditions	explicit threat of shock instructions	not applicable	treat of shock instruction													
				startle hab, low, medium and high threat conditions	explicit threat of shock instructions	not applicable	5 stimuli per threat-level, order of medium and high level counterbalanced	0.4	30-50	not applicable	not applicable	not applicable	shock	fixed level	SCL, startle, heart rate (ECG)	not applicable	N=11 excluded due to lacking valid responses	fear, anxiety, danger, anger, stress, annoyance, helplessness, safety, pleasure, calmness, contentment (after	none	none
17	Scharfenort (2016)	no	Fear conditioning	pre-cond, acq, 24-delayd ext, reinstatement	threat contingencies not explicitly provided	100%	geometric	6-8, mean: 7	10-16, mean: 13	14	14	not applicable	shock	individually calibrated to be painful but tolerable	SCR	0.02	N=1 (day 1) and N= 5 (day 2) excluded due to insufficient data quality	fear (after each exp. phase)	fMRI (ROIs; amygdala, vmPFC, hippocampus, anterior insula cortex (AI), ACC and thalamus)	none
18	Lis (2020) overlapping sample with Thome (2018)	no	Fear conditioning	startle hab, pre-cond, acq, gen	some threat contingencies provided	75% (acq) 25% (gen)	geometric	8	1.5 - 4	12	not applicable	CS+/CS-: 8; GSs: 4	shock	individually calibrated to be highly uncomfortable but not painful	startle	not applicable	not applicable	risk (trial-by-trial, during trial)	none	reaction time (for ratings)
19	Thome (2018) overlapping sample with Lis (2020)	no	Fear conditioning	startle hab, pre-cond, acq, gen	some threat contingencies provided	75% (acq) 25% (gen)	geometric	8	1.5 - 4	12	not applicable	CS+/CS-: 8; GSs: 4	shock	individually calibrated to be highly uncomfortable but not painful	startle	not applicable	not applicable	risk (trial-by-trial, during trial)	none	reaction time (for ratings)
20	Jovanovic (2009)	no	AX+BX-	startle hab, acq, inhibition test	some threat contingencies provided	100%	geometric	6	9-22	12	not applicable	not applicable	airblast	fixed level	startle	not applicable	not applicable	risk, contingency (trial-by-trial, during trial)	none	none

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No.	Author (year)	Open data	Paradigm type	Experimenal phases	Instruction	Reinforcement rate %	Stimulus (CS) type	Stimulus (CS) duration	ITI duration in s	Number of trials per CS (acquistion)	Number of trials per CS (extinction)	Number of trials per CS and GS (generalization)	US type	US calibration	Psycho-physiological measures	Min. amplitude SCR in us	SCR non-responder	Ratings	Neuroimaging	Other measures
21	Stout (2021)	no	aversive anticipation	anticipation, image viewing	threat contingencies explicitly provided	100%	geometric	8	8s cue + 2 s picture	10	not applicable	not applicable	picture	fixed level	startle	not applicable	not applicable	none	none	none
22	Huskey (2022)	no	AX+BX-	startle hab, pre-cond, acq, test1, re-acquiston, test2, immeddate ext	some threat contingencies provided	100%	geometric	7	not mentioned exactly,but probably 3 seconds	12	7	not applicable	airblast	fixed level	startle, heart rate variability (ECG)	not applicable	not applicable	expectancy (trial-by-trial, during trial)	none	none
23	Bremner (2005)	no	Fear conditioning	pre-cond,acq, immediate ext, 24h delayed unpredictable US phase, 24h delayed ext	some threat contingencies provided	100%	geometric	4	6	16	16	not applicable	shock	individually calibrated to be annoying	SCR, heart rate	not reported by authors	not reported by authors	none	PET (ROI: amygdala)	none
24	Kuehl (2020)	no	Fear conditioning	pre-cond, startle hab, acq, immediate ext	information not provided by authors	75%	geometric	7.5	8.5	8	8	not applicable	shock	individually calibrated to be clearly aversive but not painful	SCR, startle	0.01	not mentioned	none	none	none
25	Morrison (2022)	no	Fear conditioning	acq	information not provided by authors	100%	geometric	CS+: 6.5 CS- : 6	9-22	3 blocks with 4 trials each CS+, CS-, Noise alone	not applicable	not applicable	airblast	fixed level	SCR, startle	none	included	none	none	none
26	Klingelhöfer-Jens (2023)	no	Fear conditioning	acq, gen	not instructed threat contingencies	acq: 83.3%; gen: 50%	faces	6	9-12	12	not applicable	12	scream	fixed level	SCR	0.02	included + robustness check	arousal, valence, contingency, (intermittend)	none	none
			Studies with a slightly different focus or with ACEs only included in higher order interaction																	
27	Jovanovic (2020)	no	Fear conditioning	startle hab, acq	information not provided by authors	100%	geometric	6.5	9-22	12	not applicable	not applicable	airblast	fixed level	startle	not applicable	not applicable	none	none	none
28	Stenson (2021)	no	Fear conditioning	pre-cond, acq	information not provided by authors	100%	geometric	6.5	9-22	9	not applicable	not applicable	airblast	fixed level	startle	not applicable	not applicable	none	none	none
29	Radoman (2019)	no	NPU threat task	predictable, unpredictable and safe condition	explicit contingency instructions	not applicable	NPU instructions	4	15-21	not applicable	not applicable	not applicable	shock	individually calibrated to be highly annoying but not painful	startle	not applicable	not applicable	none	none	none
30	Rowland (2022)	no	Fear conditioning	acq, immediate ext	some threat contingencies provided	100%	geometric	6	9-22 (randomized)	4	8	not applicable	airblast	fixed level	startle	not applicable	non-applicable	none	none (fMRI only in an emotinoal face viewing paradigm)	none

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			Paradigm information I			Paradigm information II									Outcome measures						
No.	Author (year)	Open data	Paradigm type	Experimenal phases	Instruction	Reinforcement rate %	Stimulus (CS) type	Stimulus (CS) duration	ITI duration in s	Number of trials per CS (acquisition)	Number of trials per CS (extinction)	Number of trials per CS and GS (generalization)	US type	US calibration	Psycho-physiological measures	Min. amplitude SCR in us	SCR non-responder	Ratings	Neuroimaging	Other measures	
31	Estrada (2020)	no	Fear conditioning	baseline phase, hab, acq, post-acq check	information not provided by authors	100%	sounds	1	10-20	6	not applicable	not applicable	startle probe	fixed level	SCR, startle	0.01	not excluded	none	none	none	
32	Morey (2015)	no	Fear conditioning	pre-cond, acq, gen	information not provided by authors	acq + gen: 30%,	faces	pre-cond: 4s; acq: 6s, gen: 4	pre-cond: 5-8 (mean 6.5); acq: 10-15 (mean 12.5), gen: 9-15 (mean 12)	12 CS-, 18 CS+		not applicable	8CS-, 12 CS+, 16 each GS	shock	individually calibrated to be highly annoying but not painful	none	not applicable	not applicable	expectancy (trial-by-trial, during trial)	fMRI (ROI: (amygdala, calcarine, IFG, insula, locus coeruleus, thalamus)	none
33	Schellhaas (2022)	yes	Threat of shock	theat and safety context during memory task after observational fear conditioning or threat instructions	explicit threat of shock instructions or contingencies acquired by observation	not applicable	treat of shock instruction after observational fear learning or threat instructions	not reported by authors (for video)	not reported by authors (for video)	not applicable	not applicable	not applicable	shock (but fake electrode)	no calibration and no shock delivered (only threat of shock)	none	not applicable	not applicable	valence, danger, arousal	none	none	
34	Young (2018) overlapping sample with Young 2019	no	Threat of shock	low, medium and high threat conditions	explicit threat of shock instructions	not appliccable	treat of shock instruction	4min per conditiong	1 minute	5 startle probes (for safe condition 10 but only last 5 analyzed)		not applicable	not applicable	shock	fixed level	SCR, startle, heart rate	none	excluded (at least four (of five) valid responses with a trial for all three physiological measures required for inclusion)	none	MRI	none
35	Young (2019) overlapping sample with Young 2018	no	Threat of shock	low, medium and high threat conditions	explicit threat of shock instructions	not appliccable	treat of shock instruction	4min per conditiong	1 minute	5 startle probes (for safe condition 10 but only last 5 analyzed)	not applicable	not applicable	shock	fixed level	SCR, startle, heart rate	none	excluded (at least four (of five) valid responses with a trial for all three physiological measures required for inclusion)	none	MRI	none	
36	Hall (2022)	no	NPU threat task	startle habituation, predictable, unpredictable and safe condition	explicit contingency instructions	100%	NPU instructions	4	15-21	not applicable	not applicable	not applicable	shock	individually calibrated to be highly annoying but not painful	startle	not applicable	not applicable	none	none	none	
37	Deslauriers (2018)	no	Fear conditioning	acq, immediate ext	some threat contingencies provided	75%	geometric	6	8-13	8	16	not applicable	airblast	fixed level	startle	not applicable	not applicable	none	none	none	
38	Harnett (2019)	upon request	Fear conditioning with US alone trials	acq (only US responses), not reported: responding to CS+ and CS-	information not provided by authors	100%	sounds	10	18	24	not applicable	not applicable	tone	fixed level	SCR	0.05	not mentioned	expectancy (trial-by-trial, during trial)	fMRI (ROIs: dlPFC, dmPFC, vmPFC, hippocampus, amygdala)	none	

Supplementary Table 4: Paradigm Information\_Reward

			Paradigm information I			Paradigm information II					Outcome measures				
No.	Author (year)	Open data	Paradigm type	Paradigm name	Reward type	Reinforcement rates/reward values	Stimulus type	Total number of trials	Phases of interest	ITI duration in s	Outcome measure I	Outcome measure II	Outcome measure III	fMRI	other imaging measures
1	Birn (2017)	no	probabilistic learning task	monetary incentive delay task	monetary	-5 to + \$5	geometric symbols	90	anticipation, feedback	2-6	no behavioral measures for MID task			yes	
2	Blair (2022)	No	probabilistic learning task	passive avoidance	monetary	20 vs 80 %	shapes	108	learning	1-4	omission errors			commission errors	
3	Bjork (2008)	no	probabilistic learning task	monetary incentive delay task	monetary	-5 to + \$5	geometric symbols	108	anticipation		Hit rate	Reaction time	Omission errors	yes	
4	Boecker-Schlier (2016)	No	reward learning task	monetary incentive delay task	monetary or verbal	60%	smiley	100	anticipation, reward delivery	3-5	reaction time	number of win trials		yes	
5	Casement (2014)	No	probabilistic learning task	Reward-guessing task	monetary	Loss, no change, win	cards	24	anticipation	9				yes	
6	Cisler (2019)	No	probabilistic learning task	three-arm bandit task	monetary	20, 50 or 80 %	faces, houses	90	decision, anticipation, feedback	1.5-3	prediction error	learning rate	value expectations	yes	
7	DelDonno (2019)	No	reward learning task	monetary incentive delay task	monetary	-5 to + \$5	visual	100	anticipation	4	total reward	accuracy		yes	
8	Delgado (2022)	No	reward learning task	Children's gambling task	points	-6 to 6	cards	60	Learning/decision-making		Number of advantageous choices			no	
9	Dennison (2016)	No	probabilistic learning task	monetary incentive delay task	monetary	-5 to + \$5	geometric symbols	208	response	2-2.375	reaction time			no (for reward)	
10	Dennison (2019)	No	probabilistic learning task	monetary incentive delay task	monetary	0-4 stars	cartoon faces	132	anticipation, response, feedback	1-2	reward earned	reaction time		no	white matter microstructure
11							geometric								

Supplementary Table 4: Paradigm Information\_Reward

	Dillon (2009)	No	probabilistic learning task	monetary incentive delay task	monetary	-2.19 to + \$2.34	symbols	120	anticipation	3-7.5	reaction time	affective ratings		yes	
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Supplementary Table 4: Paradigm Information\_Reward

			Paradigm information I			Paradigm information II					Outcome measures				
No.	Author (year)	Open data	Paradigm type	Paradigm name	Reward type	Reinforcement rates/reward values	Stimulus type	Total number of trials	Phases of interest	ITI duration in s	Outcome measure I	Outcome measure II	Outcome measure III	fMRI	other imaging measures
12	Eckstrand (2019)	No	probabilistic learning task	card-guessing task	monetary	win, loss, mixed, neutral	cards	96	feedback	2-6	reward prediction error (RPE)			yes	connectivity
13	Gerin (2017)	No	probabilistic learning task	passive avoidance	points	70 %	animals	56	decision, feedback	0-4	omission errors	commission errors	total errors	yes	
14	Hanson (2017)	No	probabilistic learning task	probabilistic learning task	points	20 vs 80 % and 30 vs 70%	everyday objects	200	NA	1-6	decision weights	variability of choice	reward expectation	no	
15	Harms (2017)	O	probabilistic learning task	instrumental learning	points	50 %	everyday objects	96	acquisition, reversal	0.2	accuracy	learning rate		yes	
16	Gonzalez (2016)	No	reward learning task	monetary incentive delay task	monetary	-5 to + \$5	geometric symbols	144	anticipation, feedback	2-2.5s	reaction time			yes	
17	Hendrikse (2022)	No	reward learning task	monetary incentive delay task	monetary	50%	emoticons	60	anticipation, feedback		reaction time			yes	
18	Kennedy (2021)	No	reward learning task	probabilistic learning task	points	70% or 80%	everyday objects	200	decision, feedback	1-6	prediction error	feedback sensitivity parameter		no	quantitative anisotropy
19	Kwarteng (2021)	Yes	probabilistic learning task	monetary incentive delay task	monetary	-5 to + \$5	geometric symbols	100	anticipation	3.5-4.15	no behavioral measures for MID task			yes	
20	Letkiewicz (2022)	no	reward learning task	social reinforcement learning task	monetary	20, 50 or 80 %	faces	90	(decision, anticipation,) feedback	1.5-3	prediction error	learning rate		yes	
21	Lloyd (2022)	no	exploration-exploitation task	patch foraging task	monetary	variable	apples as tokens	NA	decision, harvest time		reaction time	time spend in poor and rich environments		no	
22	Martz (2022)	no	probabilistic learning task	monetary incentive delay task	monetary	-5 to + \$5	geometric symbols	100	anticipation		no behavioral measures for MID task			yes	



Supplementary Table 4: Paradigm Information\_Reward

			Paradigm information I			Paradigm information II					Outcome measures				
No.	Author (year)	Open data	Paradigm type	Paradigm name	Reward type	Reinforcement rates/reward values	Stimulus type	Total number of trials	Phases of interest	ITI duration in s	Outcome measure I	Outcome measure II	Outcome measure III	fMRI	other imaging measures
23	McCutcheon (2019)	no	probabilistic learning task	salience attribution test	monetary	50, 90 %	everyday objects	128	NA		probability ratings	reaction time		yes	connectivity
24	Mehta (2010)	no	probabilistic learning task	monetary incentive delay task	monetary	0 to \$2	geometric symbols	144	anticipation, feedback	variable	accuracy	reaction time		yes	
25	Morelli (2021)	no	reward learning task	monetary incentive delay task	monetary	50 %	pinatas	60	anticipation, feedback	2.5-5.5	none			yes	
26	Morris (2015)	no	Reward learning task	Signal detection task	monetary	25 vs 75 %	smileys	300	learning		Response bias	discriminability	accuracy		
27	Mueller (2012)	no	probabilistic learning task	monetary incentive saccade task	monetary	-1 to + \$1	asterisk	144	NA		accuracy of saccades	latency		no	
28	Müller (2014)	No	probabilistic learning task	passive avoidance	monetary	-5 to + \$5	geometric symbols	66	anticipation	3.5-4.15	success	Reaction time	Errors	yes	
29	Mullins (2020)	yes	reward learning task	monetary incentive delay task	monetary	-5 to + \$5	geometric symbols	100	anticipation	3.5-4.15	Reaction time			yes	
30	Patterson (2013) Exp1	no	instrumental learning task	instrumental learning task	monetary	50% and 100%	sequence of button presses	variable	acquisition, extinction	5	number of trials	expectancy rating	correct responses	no	
31	Patterson (2013) Exp2	no	instrumental learning task	instrumental learning task	monetary	50% and 100%	sequence of button presses	variable	acquisition, extinction	2	number of trials	correct responses		no	
32	Pechtel (2013)	no	probabilistic learning task	stimulus selection task	verbal feedback	20 vs 80 %, 30 vs 70%, 40 and 60%	Snodgrass images	120	learning, test	0.35-0.55	accuracy	reaction time		no	
33	Romens (2016)	no	probabilistic learning task	Reward-guessing task	monetary	Loss, no change, win	cards	24	anticipation	9				yes	
34	Sheridan (2018)	no	reward learning task	monetary incentive delay task	monetary	0-4 stars	pinatas	132	anticipation, feedback		accuracy			no	

Supplementary Table 4: Paradigm Information\_Reward

			Paradigm information I			Paradigm information II					Outcome measures				
No.	Author (year)	Open data	Paradigm type	Paradigm name	Reward type	Reinforcement rates/reward values	Stimulus type	Total number of trials	Phases of interest	ITI duration in s	Outcome measure I	Outcome measure II	Outcome measure III	fMRI	other imaging measures
35	Smith (2022)	yes	Pavlovian conditioning	mixed appetitive and aversive conditioning	points/pictures (pos), sound/pictures (neg)	20 vs 80 %	coloured shapes	70	acquisition, approach/avoidance w CS	2.5-5.5	VAS ratings	learning rate (RT)	heart rate reactivity	no	
36	Weiland (2014)	no	probabilistic learning task	monetary incentive delay task	monetary	5 to + \$5	geometric symbols	100	anticipation		Succession rate	Amount won		yes	
37	Weiss (2019)	no	probabilistic learning task	stimulus context reversal paradigm	points	NA	everyday objects	40-64	acquisition, retention, reversal		correct responses			no	
38	White (2022)	no	probabilistic learning task	Passive avoidance task	monetary	-50 to + \$50	geometric symbols	96	Anticipation, Feedback	0.5-2.5	accuracy			yes	
39	Wilkinson (2021)	yes	reward learning task	probabilistic reversal learning task (PRLT), probabilistic reward task (PRT)	monetary	20, 80 % / 20, 60%	patterns/cartoon faces	unclear/300			accuracy	learning rate	latency	no	
40	Wisner Fries (2017)	no	probabilistic learning task	associative learning task	monetary	33, 66, 100%	colours or shapes	147	learning	1	reaction time			no	
41	Yang (2021)	no	reward learning task	monetary incentive delay task	monetary	50 %	pinatas	60	anticipation, feedback	2.5-5.5	none			yes	
42	Yau (2012)	no	probabilistic learning task	monetary incentive delay task	monetary	5 to + \$5	geometric symbols	100	anticipation		Reaction time			yes	

## QUALITY ASSESSMENT TOOL

*Adapted from Oltean, L. E., Șoflău, R., Miu, A. C., & Szentágotai-Tătar, A. (2023). Childhood adversity and impaired reward processing: A meta-analysis.*

### Sample

1) Was the sample size adequate?

0 = < 30 per group

0,5 = < 50 per group

1 = 50 or more per group

2) Was the sample representative or not?

0 = No (e.g. female psychology students), also if not mentioned

0,5 = Somewhat (e.g. recruited from university campus/community etc.)

1 = Yes (e.g. both sexes, large age range, from community etc.)

3) Were the drop-outs described sufficiently?

0 = No description

1 = Described adequately

4) Controlled for psychopathology?

0 = no, not explicitly reported

1 = yes, excluded or controlled for

### ACE assessment

5) ACE types considered

0 = only exposure (e.g. institutionalization, low SES) or only very specific/ few types considered, no control for other experiences

1 = broad range of experiences considered

6) Quality of ACE measure(s):

0 = non validated "composite score" or customized questionnaires

1 = validated questionnaire(s) or interview or official records

7) Analysis of ACEs: Continuous or dichotomous score of ACEs? And if a dichotomous score was used, was there a control group?

0 = dichotomous score and no control group

1 = dichotomous score WITH control group

1 = continuous score

Supplementary Table 6: Quality Assessment\_Threat learning studies

Authors	1) Sample size	2) Representative Sample	3) Drop-out	4) Psycho-pathology	5) ACE types	6) ACE measures	7) Two groups, continuous	Sum
Machlin (2019) same sample as Milojevic (2020)	0,5	1	1	0	1	0	1	4,5
Milojevic (2020) same sample as Machlin (2019)	0,5	1	1	0	1	0	1	4,5
Marusak (2021)	0	1	1	1	1	1	1	6
Jovanovic (2022)	0,5	0,5	1	1	1	1	1	6
Qiu (2022)	0,5	0,5	0	0	0	0	1	2
France (2022)	0	0	1	0	1	1	1	4
Silvers (2016)	0,5	0	0	0	0	0	1	1,5

DeCross (2022)	1	1	1	1	0	1	1	6
McLaughlin (2016) same sample as Jenness (2018)	0,5	1	1	1	0	0	1	4,5
Jenness (2018) same sample as McLaughlin (2016)	0,5	1	1	1	0	0	1	4,5
Susman (2021)	1	1	1	1	0	1	1	6
WolitzkyTaylor (2022)	1	0,5	0	1	1	1	1	5,5
Kreutzer (2021)	1	1	1	1	1	1	1	7
Lange (2018)	1	1	0	1	1	0	0	4
Zoladz(2022)	1	0	0	1	1	1	0	4
Pole (2007)	0	0,5	1	1	1	0	1	4,5

Scharfenort (2016)	0,5	0,5	1	1	1	0	1	5
Lis (2020) overlapping sample with Thome (2018)	0,5	1	1	1	0	1	1	5,5
Thome (2018) overlapping sample with Lis (2020)	0,5	1	1	1	0	1	1	5,5
Jovanovic (2009)	0	0,5	0	1	0	1	1	3,5
Stout (2021)	1	0,5	0	1	1	1	1	5,5
Huskey (2022)	0	0	1	0	1	1	1	4
Bremner (2005)	0	0	0	1	1	1	1	4
Kuehl (2020)	1	0,5	1	1	0	0	1	4,5
Morrison (2022)	0,5	0,5	0	1	0	0	1	3

Klingelhöfer-Jens (2023)	1	0,5	1	1	1	1	1	6,5
Jovanovic (2020)	0	0	1	1	1	1	0	4
Stenson (2021)	0,5	0,5	1	1	1	1	0	5
Radoman (2019)	0,5	0,5	1	1	0	1	1	5
Rowland (2022)	1	1	1	1	0	0	1	5
Estrada (2020)	1	1	0	1	1	1	1	6
Morey (2015)	0,5	0,5	0	1	1	1	1	5
Schellhaas (2022)	1	1	1	1	1	1	1	7
Young (2018) overlapping sample with Young 2019	1	0,5	0	1	0	1	1	4,5

Young (2019)  
overlapping sample with  
Young 2018

0,5

0,5

0

1

0

1

1

4

Hall (2022)

0,5

0,5

1

1

1

1

1

6

Deslauriers (2018)

1

0,5

1

0

1

1

1

5,5

Harnett (2019)

1

0,5

1

0

1

0

1

4,5



Supplementary Table 7: Quality Assessment\_Reward learning studies

Authors	1) Sample size	2) Representative Sample	3) Drop-out	4) Psycho-pathology	5) ACE types	6) ACE measures	7) two groups, continuous	Sum
1.Birn (2017)	0	0	1	1	1	1	1	5
2. Blair (2022)	1	1	1	1	1	1	1	7
3. Boecker-Schlier (2016)	1	1	1	1	1	1	1	7
4. Cisler (2019)	0	0,5	1	1	1	1	1	5,5
5. DelDonno (2019)	0	1	1	1	1	1	1	6
6. Dennison (2016)	0	1	1	1	1	1	1	6
7.Dennison (2019)	0,5	1	1	1	1	1	1	6,5
8. Dillon (2009)	0	0,5	1	1	1	1	1	5,5
9. Eckstrand (2019)	1	1	1	1	1	1	1	7
10. Gerin (2017)	0	1	1	1	1	1	1	6
11. Hanson (2017)	0,5	1	0	0	1	1	1	4,5
12. Harms (2017)	0	1	1	0	1	1	1	5
13. Hendrikse (2022)	1	0,5	1	1	1	1	1	6,5

14. Kennedy (2021)	0,5	1	0	0	1	1	1	4,5
15. Letkiewicz (2022)	0	0,5	1	1	1	1	1	5,5
16. Lloyd (2022)	0,5	1	1	0	1	1	1	5,5
17. McCutcheon (2019)	0	0,5	0	1	1	0	1	3,5
18. Mehta (2010)	0	0,5	1	0	0	0	1	2,5
19. Morelli (2021)	1	1	1	1	1	0	1	6
20. Mueller (2012)	0	1	1	1	0	0	1	4
21. Patterson (2013) Exp 1	1	0,5	1	1	1	1	1	6,5
22. Patterson (2013) Exp 2	1	0,5	1	1	1	1	1	6,5
23. Pechtel (2013)	0	0,5	1	1	0	0	1	3,5
24.Sheridan (2018)	1	0,5	1	0	0	0	1	3,5
25. Smith (2022)	0,5	1	1	1	0	0	1	4,5
26. Weiss (2019)	0	0,5	1	0	1	0	1	3,5
27. Wilkinson (2021)	1	1	0	1	1	1	1	6
28. Wismer-Fries (2017)	0	0,5	1	1	0	0	1	3,5
29. Yang (2021)	0,5	0,5	1	1	1	1	1	6

30. Kwarteng (2021)	1	1	1	0	0	1	1	5
31. Weiland (2014)	0	0,5	1	1	0	1	1	4,5
32. Martz (2022) sample 1	1	1	0	0	0	1	1	4
33. Martz (2022) sample 2	1	0,5	1	1	0	1	1	5,5
34. Bjork (2008)	0	1	0	1	0	1	1	4
35. Müller (2014) sample 1	1	1	1	1	0	1	1	6
35. Müller (2014) sample 2	1	1	1	1	0	1	1	6
36. Yau (2012)	0	0,5	1	1	0	1	1	4,5
37. Morris (2015)	1	0,5	1	1	0	0	1	4,5
38. Casement (2014)	1	0,5	1	1	0	1	1	5,5
39. Gonzalez (2016)	1	0,5	1	1	0	0	1	4,5
40. Mullins (2020)	1	1	1	1	0	0	1	5
41. Delgado (2022)	1	1	0	0	0	0	0	2
42. Romens (2016)	1	0	1	1	0	0	1	4
43. White (2022)	1	1	0	1	0	0	2	5