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Extinction learning in childhood anxiety disorders, obsessive compulsive disorder and posttraumatic stress disorder: implications for treatment

Joseph F. McGuire[1], **Scott P. Orr**[2], **Joey K.-Y. Essoe**[3], **James T. McCracken**[1], **Eric A. Storch**[4,5,6,7,8], and **John Piacentini**[1]

[1]Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles

[2]Massachusetts General Hospital and Harvard Medical School, Boston, MA

[3]Department of Psychology, University of California Los Angeles

[4]Department of Pediatrics, University of South Florida

[5]Departments of Psychiatry and Behavioral Neurosciences, University of South Florida

[6]Department of Health Policy and Management, University of South Florida

[7]Rogers Behavioral Health – Tampa Bay

[8]All Children's Hospital, Johns Hopkins Medicine, St. Petersburg, FL

Abstract

Introduction—Threat conditioning and extinction play an important role in anxiety disorders, obsessive compulsive disorder (OCD), and posttraumatic stress disorder (PTSD). Although these conditions commonly affect children, threat conditioning and extinction have been primarily studied in adults. However, differences in phenomenology and neural architecture prohibit the generalization of adult findings to youth.

Areas covered—A comprehensive literature search using PubMed and PsycInfo was conducted to identify studies that have used differential conditioning tasks to examine threat acquisition and extinction in youth. The information obtained from this review helps to clarify the influence of these processes on the etiology and treatment of youth with OCD, PTSD and other anxiety disorders. Thirty studies of threat conditioning and extinction were identified.

Expert Commentary—Youth with anxiety disorders, OCD, and PTSD have largely comparable threat acquisition relative to unaffected controls, with some distinctions noted for youth with PTSD or youth who have suffered maltreatment. However, impaired extinction was consistently observed across youth with these disorders and appears to be consistent with deficiencies in inhibitory learning. Incorporating strategies to improve inhibitory learning may improve extinction

Corresponding Author: Joseph F. McGuire, Ph.D., Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, 760 Westwood Plaza, 48-228B, Los Angeles, CA, 90095. Phone: 310-794-5609, Fax: 310-206-4446, jfmcguire@mednet.ucla.edu.

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learning within extinction-based treatments like cognitive behavioral therapy (CBT). Strategies to improve inhibitory learning in CBT are discussed.

Keywords

conditioning; extinction; threat; fear; anxiety disorders; obsessive compulsive disorder; posttraumatic stress disorder; adolescence; inhibitory learning; exposure therapy

Introduction

Psychiatric conditions previously classified as anxiety disorders in the Diagnostic and Statistical Manual (DSM)-Fourth Edition (Text Revision) include specific phobia, panic disorder, separation anxiety disorder, social anxiety disorder, generalized anxiety disorder, obsessive compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) [1]. Although OCD and PTSD were reclassified separately due to phenomenological distinctions in the DSM-5 [2], these psychiatric conditions are collectively characterized by clinically significant fear, anxiety, and distress in response to stimuli and/or situational cues perceived as threats (collectively referred to as fear-based psychiatric disorders). These fear-based psychiatric disorders affect up to 29% of the population [3], and serve as a leading cause of disability [4,5]. Notably, some fear-based psychiatric disorders predominantly develop in childhood [3], and serve as strong risk factors for adult anxiety disorders [6]. Thus, the efficient and effective treatment of fear-based psychiatric disorders during childhood and adolescence has the potential to reduce their prevalence, impairment, morbidity, and disability across the lifespan.

Evidence-based treatments for fear-based psychiatric disorders in youth primarily include cognitive behavioral therapy (CBT) and serotonin reuptake inhibitors (SRIs) [7-9]. For many of these psychiatric conditions, exposure-based CBT is recommended as a first-line intervention for youth with mild-to-moderate symptom severity and in combination with SRI medication for those with severe symptoms [10,11]. While CBT, SRIs, and their combination have demonstrated considerable efficacy in reducing symptom severity [7,9,12,13], a considerable portion of youth remain symptomatic after receiving a typical course of treatment with a limited number achieving symptom remission [7-9]. Moreover, naturalistic follow-up suggest that relapse occurs in up to 50% of initial treatment responders [14]. Thus, there is a need to improve therapeutic outcomes for existing evidence-based treatments in order to effectively extinguish pathological fear and its associated morbidity.

Several approaches have been explored to improve treatment outcomes for youth with fear-based psychiatric disorders. These approaches include increasing SRI dosage, augmenting existing evidence-based treatment with additional pharmacological agents (e.g., clomipramine, antipsychotics) [10,11], or using cognitive enhancers to augment therapeutic learning in CBT [15]. Although augmentation of CBT with SRI medications is recommended for youths with severe symptoms [10,11], SRI medications are not a preferred treatment option by their parents [16,17].

Several studies have examined the benefit of augmenting CBT with medications referred to as cognitive enhancers. Broadly, cognitive enhancers are pharmacological compounds that influence signaling pathways involved in synaptic plasticity of brain regions associated with threat acquisition and thereby enhance the neurocircuity of extinction learning [19]. Several cognitive enhancers have been examined across fear-based psychiatric disorders [15]. Findings suggest that cognitive enhancers do not universally expedite and/or enhance CBT outcomes. The most well-studied cognitive enhancer, d-cycloserine (DCS), has demonstrated the most consistent benefit for augmenting CBT in anxiety disorders [15,20,21]. However, evidence suggests that its effects may be influenced by specific characteristics (e.g., comorbid psychiatric conditions, psychiatric medication) [20] and/or therapeutic mechanisms (e.g., extinction learning, extinction retention) [22-24]. However, most of these trials have been conducted in adults. Additional research is needed to better understand the nuances of augmenting CBT with cognitive enhancers in youth [25,26].

Translational research provides an opportunity to increase insight into the mechanisms underlying fear-based psychiatric disorders that may help to identify avenues for maximizing therapeutic learning and improving treatment outcomes [27-29]. Accordingly, laboratory tasks can be used to investigate potential neurobiological phenotypes of clinical phenomena [30]. While the etiology of fear-based psychiatric disorders is undoubtedly influenced by multiple factors (for review see [31]), threat conditioning[1] and extinction learning play an important role in the development, persistence, and treatment of such disorders [33,34]. Indeed, threat acquisition and extinction procedures serve as a laboratory analogue for exposure therapy [35], which is the principle component of CBT for fear-based psychiatric disorders. Although there has been considerable research on threat conditioning and extinction in adults [29,34], there has been a relatively small, but increasing, amount of research in youth. Translational research has highlighted developmental differences in threat conditioning and extinction between juvenile, adolescent, and adult rodents [36,37], with particular deficits in extinction learning identified during adolescence. Similarly, in humans, there are distinctions in disorder phenomenology [38,39] and neural architecture [40,41] that strongly challenge the generalization of adult findings to youth. Moreover, neuroimaging research on emotion regulation in adolescents has led to the development of an “imbalance” model, which suggests that early-maturing subcortical structures (i.e., amygdala and hippocampus) are hyperactive, while late-maturing cortical structures (i.e., prefrontal cortex) are hypoactive [42,43]. Thus, an improved understanding of threat conditioning and extinction in youth with fear-based psychiatric disorders can clarify whether specific impairments are present, and identify factors that may facilitate and/or impair extinction learning. This information is critical to developing CBT exposures that maximize extinction learning, which in turn may lead to improved treatment outcomes.

This paper serves as a comprehensive literature review on threat conditioning and extinction in unaffected youth and youth with fear-based psychiatric disorders. The goal of this review

[1]Ledoux has recently made the compelling argument that the process of “fear conditioning” can be explained solely in terms of associations created and stored in amygdala circuits and that, consequently, there is no need to infer that conscious feelings of “fear” are necessary for this associative learning process [32]. Ledoux has suggested that “threat conditioning” is a more precise term for describing what has traditionally been referred to as “fear conditioning” and that the concept of “fear” be used when referencing what individuals subjectively report as fear. We will follow this suggested convention throughout the manuscript [32].

is to identify acquisition and extinction impairments in youth, and provide recommendations to improve extinction learning. PubMed and PsycInfo were searched in February 2016 using the key phrases “fear conditioning” or “fear extinction,” and either “child” or “adolescence.” Identified abstracts were evaluated for appropriateness and the references of eligible review articles were searched as well. Studies were included if they met the following criteria: (1) used a differential conditioning procedure, (2) included youth less than 18 years of age, and (3) included either unaffected youth or youth with anxiety disorders, OCD, or PTSD and/or related conditions. When comparisons with adult populations and/or populations “at risk” of developing one of these psychiatric conditions were included within these studies, this information was also included in our review. This literature search identified 30 studies on threat (“fear”) conditioning and/or extinction in youth (16 studies of unaffected youth, 10 studies of youth with anxiety disorders, 1 study of youth with OCD, and 3 studies of youth with PSTD and/or related conditions). Seven of these studies included comparisons with adult populations, and only one examined youth “at risk” of developing anxiety disorders. Youth who participated in these 30 studies ranged in age from 2-17 years. First, we provide a brief overview of the multiple mechanisms implicated in fear-based psychiatric disorders that are assessed with conditioning tasks: threat acquisition, threat generalization, context conditioning, extinction learning, and extinction retention (also called extinction recall). Although other factors (e.g., reinstatement, memory consolidation, memory reconsolidation) may be of interest, investigation of these processes in children has been very limited and the concepts recently discussed by Britton et al. [44]. Next, we summarize the findings of published studies that examine these mechanisms in unaffected youth and those with fear-based psychiatric disorders. This serves to identify impairments within these mechanisms across fear-based psychiatric conditions. Finally, based on identified impairments, we offer recommendations for maximizing extinction learning during exposures conducted within CBT for youth with fear-based psychiatric disorders.

2. Mechanism Implicated in Fear-based Psychiatric Disorders and CBT

2.1

Threat conditioning (also referred to as *fear conditioning* or *fear acquisition*) refers to the process of learning that something is dangerous. It occurs when an emotionally neutral stimulus (a conditioned stimulus, CS) is paired with an aversive unconditioned stimulus (US). Subsequent exposures to the CS become capable of producing a conditioned response (CR) that includes defensive behaviors (e.g., freezing behaviors, avoidance, compulsions) and/or psychophysiological changes (e.g., changes in electrodermal activity, heart rate, respiration, etc.). Conditioning is observed across anxiety disorders such as phobia (e.g., being bitten by a dog and experiencing worry about harm from animals), OCD (e.g., having obsessional thoughts about harming a loved one and experiencing fear when seeing any sharp objects), and PTSD (e.g., getting into a car accident and subsequently experiencing fear or anxiety when in a car). When encountering a CS and experiencing its associated CR, youth with fear-based psychiatric disorders commonly engage in defensive behaviors such as avoidance and/or ritualized behaviors (e.g., safety behaviors, compulsions) to alleviate the distress. This reduction in worry or fear serves to reinforce the actions, thereby supporting their maintenance and enhancement [33]. In studies of humans, threat conditioning is

commonly evaluated using a differential conditioning task, with conditioned threat responses frequently being assessed using psychophysiological measures (e.g., skin conductance response, SCR; fear potentiated startle, FPS; heart rate, HR), subjective report (e.g., self-report ratings of fear, valence, arousal), and behavioral observation (e.g., study attrition, avoidance).

2.2

Threat generalization occurs when a conditioned threat response generalizes to stimuli that share similar characteristics to the CS. This is clinically observed across several fear-based psychiatric disorders. For example, if a child is attacked by an animal, the perceived threat may generalize to other animals with similar characteristics (e.g., similar color, appearance, animal class). Similarly, individuals with OCD have been found to generalize perceived threat across successive degrees of contact with contaminated stimuli [46]. Threat generalization is expressed by increasingly large CRs as stimuli more closely approximate the CS previously paired with the US, and increasingly smaller CRs as stimuli become less similar to the CS [47].

2.3

While cue-specific threat conditioning and threat generalization has been used to examine and explain transient fear, *contextual conditioning* has been used to explain the occurrence of more generalized and/or sustained threat response [48,49]. Contextual features constitute the background in which specific threat cues are encountered, and play an important role in the acquisition and extinction of CRs [50]. For example, if a child has been attacked by a pet during a visit to a friend's house on one occasion but not others, the child may experience fear when visiting the friend's house again even in the absence of the pet. Context conditioning is evidenced by responses to the cues that provided the context within which the threat CS and/or US were presented.

2.4

Extinction learning is a process whereby the response to a threat CS declines through repeated exposures of the threat cue in the absence of the US and/or the defensive behaviors (e.g., compulsions, avoidance). This process does not eradicate the CS-US association formed during conditioning; rather, a new association between the CS and no US is formed that competes with the original CS-US association for expression [53]. Over repeated exposures to the threat cue, the new CS-no US association becomes stronger and thereby inhibits the CR previously generated by the CS-US association [53]. For example, a child who was attacked by an animal might be exposed to other animals without any negative consequences in order to establish a new learned association. As the new association (i.e., “animals do not always attack me”) is strengthened through repetition, the previously learned association and the CR generated by the association becomes inhibited. Importantly, when youth engage in defensive behaviors, these behaviors prevent new learning from taking place that is needed to establish and strengthen a competing threat-inhibitory association.

Although the terms "*habituation*" and "*extinction learning*" are sometimes used interchangeably in the clinical literature, there are conceptual distinctions between these terms that should be recognized. *Habituation* refers to the decrease of a natural response that is automatically elicited by a US; whereas, *extinction learning* refers to the decrease of an acquired or conditioned response.

2.5

Extinction retention (also called *extinction recall*) refers to the extent to which the inhibitory response previously learned during an extinction procedure is retained over time. Thus, extinction learning focuses on the ability to acquire and strengthen the CS-no US association during non-reinforced exposures; whereas, extinction retention measures the ability to retain and/or recall the learned CS-no US association at a later time (e.g., between sessions). Extinction retention is reported to be highly context dependent in translational animal research [50,54] and is commonly assessed 1-7 days following extinction learning.

3. Threat Conditioning and Extinction In Unaffected Youth

Table 1 presents differential threat conditioning and extinction studies of unaffected youth. Differential threat conditioning is consistently observed across studies of unaffected youth as evidenced by larger skin conductance response (SCR), fear potentiated startle (FPS), and/or self-report (SR) to a CS+ (a CS that is paired with the US) compared to a CS- (a CS that is explicitly not paired with the US) [36,40,55-68]. Differential conditioning has been reliably observed in children starting at around six years of age [56], with SCR and FPS magnitudes increasing with age [59,61] and peaking during adolescence [40]. Although gender [59] and neuroticism [63] do not appear to be associated with differential conditioning in unaffected youth, several other influential factors have been identified. These include the type of conditioned stimuli [62], contingency awareness [61], attention bias [60], parental clinical psychopathology [64], and youth subclinical psychopathology [65,66]. When examining threat generalization across stimuli, evidence suggests that unaffected youth exhibit greater threat generalization than adults [61,68]. For example, youth (aged 8-10) were found to exhibit larger SCRs and greater SR arousal to some generalization stimuli compared to adults (aged 18-50) [68]. Additionally, in a related study of 8-13 year olds, there was a larger FPS response to generalization stimuli among older youth compared to younger participants. Notably, threat generalization may likely be impacted by age and/or developmental stage; adolescents exhibit diminished differential conditioning, but greater SC reactivity overall, compared to adults [40]. Despite the hippocampus being implicated in the neural architecture of threat conditioning in youth [40], there has been only one examination of context conditioning in youth [66]. This study provided two relevant findings. First, unaffected youth with high trait anxiety had less contingency awareness compared to low trait anxiety youth [66]. Second, larger FPS responses were observed to threat cues, compared to context stimuli, when contingencies were predictable rather than unpredictable. Taken together, findings suggest that youth are capable of differential conditioning starting around 6 years of age and that threat conditioning peaks in adolescence. Youth experience some difficulty recognizing CS-US associations, and generalize threat across stimuli sharing similar characteristics with the CS+.

When considering extinction learning, there are mixed findings across psychophysiological and SR measures. For example, several reports indicate that extinction is achieved for SCR, FPS, and SR measures among youth [36,57,63,67]; whereas other studies indicate that the CRs persists for SCR and SR measures after extinction [36,58,60,62-64,67]. With regard to examining extinction retention and generalization, 9-10 year olds reported greater SR fear to stimuli resembling the CS+, compared to 5-8 year olds [67]. However, 9-10 year olds also recalled the CS-US association better than the 5-6 year olds when assessed across generalization stimuli [67]. Thus, there is conflicting evidence regarding whether extinction of the CR is achieved or tends to persist in unaffected youth. Notably, when extinction learning is not achieved, it is best characterized by a deficiency in inhibitory learning, i.e., difficulty inhibiting the CR produced by the initial CS-US association following extinction trials (CS-no US pairings). Additionally, these findings suggest that older youth may acquire greater threat discrimination due to better CS-US association recognition, but also experience more persistent SR fear. Different conditioning procedures can influence conditioning outcomes [69], and procedural differences may explain, at least in part, discrepant findings among studies of unaffected youth. Alternatively, given the poor contingency awareness reported among youth, insight may be gained by examining within-individual discrepancies between psychophysiological and SR outcomes during extinction learning. Indeed, examining such discrepancies has provided important information among phobic youth [70], and may help to identify specific characteristics of youth who appear to achieve extinction on one outcome measure, but not another.

4. Threat Conditioning and Extinction In Youth with Anxiety Disorders

Table 2 presents differential threat conditioning and extinction studies of youth with anxiety disorders that include: social phobia, specific phobia, panic disorder, separation anxiety disorder, and generalized anxiety disorder. In these studies, differential conditioning is [71,76,77]. Although, some studies suggest that anxious youth show larger SCR and SR fear to both the CS+ and the CS-, a larger differential response is not reported [41,72,74,75]. Consistent with clinical evidence, anxious youth have been found to exhibit greater behavioral avoidance, as evidenced by higher rates of study attrition when confronted with an aversive US [41,73]. Additionally, anxiety symptom severity was found to be associated with greater SR fear of stimuli [73]. As noted above for unaffected youth, several factors have been found to influence threat conditioning, including gender [78] and age-related neurobiological distinctions [75]. Unfortunately, there has been no examination of threat generalization or context conditioning in anxious youth. Thus, available findings indicate that youth with anxiety disorders exhibit differential threat conditioning, with no strong evidence that differential conditioning is greater among anxious, compared to unaffected, youth. Rather, anxious youth exhibit greater reactivity to conditioned stimuli (CS+ and CS-) and are more likely to exhibit behavioral avoidance relative to unaffected controls.

When examining extinction learning, there is mixed evidence for group differences. Although some studies found extinction to be achieved in unaffected controls [74] and/or across affected and unaffected groups [76], other studies found that youth with anxiety disorders exhibited deficits in extinction learning [72-74,76]. Specifically, group differences during extinction were found for youth with anxiety disorders on SCR and SR measures

[41,72,74]. Also, poorer extinction retention was found among anxious youth [72,73] and youth at-risk for anxiety disorders [72]. When exploring potential differences within a group of anxious youth, one study found that threat-avoidant anxious youth had greater unconditioned response and less extinction compared to threat-vigilant anxious youth [64]. When testing extinction retention, anxious youth were found to exhibit a difference in activated neural structures [41]. Extinction learning in anxious youth has been linked with changes in child-reported anxiety symptoms following group CBT; non-responders were found to have greater SR fear to stimuli during conditioning [79]. Taken together, variable findings exist regarding extinction learning and retention among youth with anxiety disorders across psychophysiological and SR outcomes. When extinction learning deficits were identified, they were predominantly characterized by deficits in inhibitory learning (i.e., difficulty inhibiting the CR, produced by the initial CS-US pairings, following extinction trials). Notably, these findings may be influenced by neural architecture activated during extinction learning [41], and/or specific study design considerations [69].

5. Threat Conditioning and Extinction In Youth with OCD

To date, there has only been one examination of threat conditioning and extinction in youth with OCD (see Table 3). In this study, SCR differential conditioning was observed in both youth with OCD and unaffected controls [80], with no significant group difference in the magnitude of the CRs. Across youth, anxiety symptom severity and OCD symptoms had moderate associations with magnitude of the SCRs to the CS+ and/or CS-. To date, there has been no examination of threat generalization or context conditioning among youth with OCD.

Initial evidence suggests that youth with OCD have impaired extinction learning, compared to unaffected youth [80]. Similar to some aforementioned studies, unaffected controls exhibited a differential CR throughout extinction. In contrast, youth with OCD exhibited an initial reversal of conditioned threat to the CS+ and CS- in early extinction likely reflecting an anticipated contingency shift [81], followed by a persistent CR to the CS+ throughout extinction [80]. Across youth, greater OCD severity and anxiety sensitivity were moderately associated with a smaller differential response to the CS+ and CS-. We are not aware of any examination of extinction retention among youth with OCD.

Taken together, findings suggest that youth with OCD acquire a conditioned threat response similarly to unaffected controls, but experience a different pattern of extinction learning. This may be attributed, in part, to an anticipated contingency shift in early extinction, but more likely is accounted for by impaired inhibitory learning, as the initial CR to the CS+ persists throughout extinction. OCD symptom severity and anxiety sensitivity have been found to be associated with differential conditioning and, thus, may be relevant constructs to examine further in youth with OCD.

6. Threat Conditioning and Extinction In Youth with PTSD, Trauma, and/or Maltreatment

To date, there have been three studies of threat conditioning and extinction in youth with PTSD, trauma exposure, and/or maltreatment (see Table 3). Across studies, differential conditioning has been observed in these groups of youth [81-83], with some differences emerging for maltreated youth and those with PTSD. Youth who experienced maltreatment exhibited slower differential conditioning as evidenced by a blunted SCR to the CS+ [83]. Additionally, youth with PTSD did not exhibit a differential conditioned SCR when compared to youth without PTSD [83]. In contrast, another study found PTSD symptom severity to have a small-to-moderate association with larger SCRs to the CS+ [82]. Furthermore, youth from a high trauma-exposure population and with high anxiety were found to exhibit greater FPS to the CS+ and CS- during conditioning, compared to youth from the same population who had low anxiety [81]. Gender [82] and age [81] were found to influence threat conditioning within trauma-exposed youth. Boys from a highly trauma-exposed population were found to exhibit greater differential conditioning, compared to girls [82], and younger children exhibited poorer discrimination between CS+ and CS-, compared to older youth [81]. When examining the neurobiology of threat conditioning within this population, findings suggested that the amygdala and hippocampus volume were negatively associated with SCR and/or SR fear to the CS+ during early conditioning, but that the ventromedial prefrontal cortex thickness was positively associated with SR fear to the CS- [83]. To date, there has been no examination of threat generalization or context conditioning among youth with PTSD, trauma exposure, and/or maltreatment. Taken together, these findings suggest that many youth with PTSD symptoms, trauma exposure, and/or maltreatment exhibit differential threat conditioning. However, for those youth meeting criteria for a PTSD diagnosis, differential conditioning may be impaired. Across youth with PTSD, trauma exposure, and/or maltreatment, the magnitude of conditioning was associated with gender, age, and/or co-occurring psychiatric symptom severity (e.g., anxiety symptom severity, PTSD symptom severity).

Extinction learning was observed across groups of youth with PTSD, trauma exposure, and/or maltreatment for psychophysiological [81,83], but not for SR [83], measures. Additionally, younger children with high anxiety showed reduced FPS to the CS+ [81]. Furthermore, there was an increase in SCR and FPS to the CS- from late conditioning to early extinction, which may reflect the anticipation of a shift in the CS-US relationships [81]. To date, we are unaware of any examination of extinction retention in youth with PTSD, trauma exposure, and/or maltreatment. The limited available evidence collectively suggests that these groups of youth show intact extinction learning for psychophysiological measures, but not for SR outcomes.

7. Summary of Conditioning and Extinction Findings Across Disorders, Gender, and Age

Youth with anxiety disorders, OCD, and/or trauma-exposure exhibited differential conditioning across studies; whereas, youth who experienced maltreatment or had PTSD

demonstrated slower or impaired differential conditioning, respectively. Interestingly, psychiatric symptom severity was often positively associated with the magnitude of differential conditioning across studies. In regards to extinction learning, youth with anxiety disorders and OCD exhibit impairments in extinction on psychophysiological and SR outcomes that are consistent with deficiencies in inhibitory learning. Youth with PTSD, trauma-exposure and maltreatment exhibited deficiencies in inhibitory learning for SR, but not psychophysiological, outcomes.

To date, there has been minimal examination of gender and age in conditioning studies of youth, which is somewhat surprising given the dramatic changes that take place during childhood and adolescence. While gender was not found to be an influential factor in unaffected youth, there are some gender differences in fear-based psychiatric disorders. Among trauma-exposed youth, boys exhibited larger differential conditioning relative to girls. Additionally, among youth with anxiety disorders, boys had longer FPS latency compared to girls during extinction. However, there were no other gender differences reported across studies. With regard to age, differential conditioning is evident at about 6 years of age in unaffected youth and increases with age. However, adolescents have been found to show diminished differential conditioning compared to adults. Older, compared to younger, children were reported to have better threat discrimination and contingency recognition across studies. Additionally, older youth were reported to have greater persistence of SR fear following extinction. Interestingly, while age was not associated with greater SR fear in anxious youth, it was associated with greater activation in prefrontal brain regions in response to the CS+, compared to unaffected controls.

8. Implications for Treatment Based on Impaired Threat Conditioning and Extinction

Although there are clear differences between threat conditioning laboratory tasks and CBT, the tasks serve as analogues for the exposure interventions that comprise CBT. When considering the evidence across conditioning and extinction studies, it is challenging to draw definitive conclusions due to conflicting findings. The mixed results are likely influenced by study differences in methodology, outcome measures, and demographic characteristics [69]. However, a few broad themes are evident across unaffected youth and youth with fear-based psychiatric disorders. First, multiple factors have been found to influence threat conditioning and extinction. These include (but are not limited to) developmental stage (childhood versus adolescence), age, gender, contingency awareness, attention bias, parental psychopathology, and youth psychopathology. These factors should be taken into consideration during the assessment and treatment of youth with fear-based psychiatric disorders to better understand their relationship with CBT treatment outcome.

Second, there are considerable discrepancies between psychophysiological and SR measures between and within studies of threat conditioning and extinction in youth. Notably, discrepant findings across measures are relatively common among studies of childhood psychopathology [85]. Discrepancies suggest that youth may report fear to be “extinguished” via a SR measure, but may continue to show psychophysiological reactivity

to threat cues. Conversely, youth may no longer experience psychophysiological reactivity to threat cues or contexts, but may not become consciously aware, and thereby are unable to report, that their fear has diminished or extinguished. Thus, these youth will continue to report persistent fear on SR measures. There may be some benefit to better understanding youth who display differential outcomes between psychophysiological and SR measures, as these same youth may be the ones who do not adequately respond to CBT. For these youth, emotion recognition strategies prior to, and/or alongside, exposure-based CBT may prove useful to help strengthen the connection between thoughts (self-report awareness) and somatic feelings (physiological arousal).

Third, studies identified that children, compared to adolescents (or adults), exhibit impairment in their ability to discriminate threats during differential cued tasks and generalization tasks. Moreover, youth in several studies exhibited poor awareness of the CS-US contingency [61,66,80,81]. While this may be potentially influenced by inattention during conditioning, many of these studies conducted interviews to assess for, and rule-out, other psychiatric illness such as attention deficit hyperactivity disorder (ADHD). Threat discrimination and contingency awareness are important components of extinction learning; their consideration provides a new direction for interventions targeting children with fear-based psychiatric disorders. Specifically, there may be some benefit to improving threat discrimination during early CBT to facilitate later extinction learning during treatment exposures. Efforts to promote accurate threat discrimination may be facilitated by attention bias modification tasks adapted for this purpose. As attention can be a critical aspect of threat acquisition, taking into account inattention and/or poor threat discrimination during CBT is important. Indeed, it may be that youth who have difficulty accurately discerning threats may not fully benefit from exposures conducted during CBT because they cannot identify the primary threatening stimulus that should be targeted.

Finally, there are clear deficits in extinction learning in youth, which may be greater in adolescence and/or those with fear-based psychiatric disorders. When present, these deficits suggest impaired *inhibitory learning* (i.e., difficulty inhibiting the initial CS-US association with the new CS-no US association learned during extinction). However, there is inconsistent evidence linking extinction and/or extinction retention with CBT outcomes. Waters and Pine [79] found that greater pre-treatment psychophysiological extinction learning predicted greater reductions in child-rated anxiety after group CBT. However, there has been mixed evidence regarding SR extinction and extinction retention (via subjective units of distress, SUDS) predicting treatment outcome in individual CBT [86,87]. Thus, further research is needed to understand whether extinction learning and extinction retention of psychophysiological and SR measures both predict CBT treatment outcome. Moreover, these examinations should include diagnostic group comparisons, as well as examinations at the individual participant level.

The predominant rationale guiding exposures in CBT for the past two decades has been Emotion Processing Theory [88], which emphasizes self-reported extinction and/or extinction retention via SUDS as the key measures of therapeutic exposure. The extinction deficits observed across youth are consistent with impairments in inhibitory learning. Thus, CBT exposures that emphasize inhibitory learning principles may improve extinction

learning and retention and thereby lead to improved clinical outcomes. Several strategies that focus on enhancing inhibitory learning, retention, and retrieval have been suggested to improve extinction during exposures among adults [27,28,89,90], and may be beneficial for youth when implemented in a developmentally appropriate manner. There are a handful of articles that describe the theoretical rationale for inhibitory learning strategies in detail, and clarify more fully how these strategies differ from prior theoretical approaches [27,28].

First, e*xpectancy violation* is a strategy that focuses exposures on whether the expected negative outcome occurred or not. For example, a clinician has the youth identify the specific threatening outcome (e.g., “the dog will bite me if I stand close to it”), and conducts the exposure until the expectation is violated. Notably, a reduction in SUDS is not needed for the expectation to be violated and the exposure to be completed. Following each exposure trial, the clinician will ask the youth about the learning that occurred regarding the non-occurrence of the feared outcome and discrepancies between initial predictions and actual outcomes [28]. Using this strategy, exposures can still progress in a graduated manner whereby expectancy violations are driving the progression of exposures rather than a reduction in SUDS. Thus, youth learn to tolerate fear and uncertainty rather than waiting for a reduction in subjective distress.

Second, *intermittent reinforced extinction* is a related strategy that uses intermittent encounters with feared outcomes during exposures. This approach may serve to violate the patient's expectancy that no negative outcomes will ever occur in response to the exposure. Thus, a clinician may have a youth with social anxiety experience occasional mild social rejection during social exposures within the treatment session.

Third, employing s*timulus variability* is another strategy that can improve inhibitory learning. This approach introduces variability into the stimuli, duration, intensity, and/or progression of exposures. Accordingly, exposures would proceed in a non-linear fashion rather than continue an exposure until within-session extinction via SUDS is achieved. In this case, a clinician might develop an exposure hierarchy and begin with the least distressing item, in order to avoid treatment dropout. After initial mastery of expectancy violation, the clinician would begin to vary exposures within the same domain by varying the duration, intensity, and/or stimuli.

Fourth, clinicians may consider the *elimination of “safety signals”* to improve inhibitory learning. Safety signals (i.e., parents, therapists, medications, food, drink, cell phones) and/or safety behaviors (i.e., ritualized behaviors) can serve as “safe” stimuli that impede the violation of expectancies. Accordingly, this strategy targets the reduction and/or elimination of youth's reliance on them. For example, when treating a youth with emetophobia (fear of vomiting), a clinician may encourage the patient not to take sips of water after every bite of food (i.e., a safety signal/behavior). Although gradual removal of safety signals is suggested to minimize treatment attrition (i.e., decreasing sips of water during eating), more immediate removal is preferred (i.e., discontinuation of drinking water during eating).

Fifth, clinicians may consider using *compound extinction (*also referred to as *deepened extinction)* to improve inhibitory learning [91]. Compound extinction involves conducting

exposures to individual threatening stimuli and/or situations, and combining these stimuli/situations in later exposures. It may also include combining previously extinguished stimuli with new threatening stimuli and/or situations. For example, when treating a youth with OCD who has harm obsession symptoms, a clinician might initially conduct three separate exposures (i.e., imagined exposure of stabbing a loved one, being in a room with a loved one and a knife present, and holding a knife) and later combine all three exposures to deepen extinction (i.e., holding a knife while sitting next to a loved one).

Sixth, clinicians may also wish to use *multiple contexts* to promote inhibitory learning. Thus, when conducting interoceptive, imaginal, and in vivo exposures, these exposures should vary across contexts. For example, a clinician treating a youth with social anxiety might have the patient practice exposures initially with the clinician, but later by themselves. As the youth continues to practice throughout the week, he/she would practice exposures in different settings, and/or at varying times throughout the week.

Seventh, clinicians may consider using *retrieval cues* for patients to enhance inhibitory learning, as such cues can facilitate extinction recall across contexts. Thus, a patient might carry a retrieval cue (i.e., wristband, pin, small toy) and/or have it in their room (i.e., certificate on the wall) to remind them of extinction learning during exposure sessions. Alternatively, the patient may be asked to remind themselves of (or rehearse) extinction learning each time they encounter a previously feared stimulus or situation. Some experts suggest that this approach may be best integrated as a relapse prevention strategy [28], as there could be some concern that a patient might initially view the retrieval cue that they carry (i.e., wristband, pin) as a safety signal.

Eighth, *reconsolidation of extinction learning* is an inhibitory learning strategy that capitalizes on the retrieval and modification of individual threat memories during the period of reconsolidation. Reconsolidation occurs when a memory is activated, and thereby becomes destabilized and subject to modification, and then is restabilized into long term memory (i.e., reconsolidated). Accordingly, a clinician may introduce a patient with a specific phobia of dogs to a dog briefly prior to conducting repeated exposure trials. For example, the child might view a dog from afar and then wait 10 minutes before actually conducting the repeated exposure trials. Two additional strategies that may improve inhibitory learning include *affect labeling (*identifying and labeling emotions during exposures) [92], and *increased time intervals between sessions* (gradually increasing the time and duration between exposure sessions during relapse prevention and booster sessions) [28,89].

It is important to note that these inhibitory learning strategies are intended to enhance extinction learning and are primarily extrapolated from laboratory studies of threat conditioning and extinction. There has been minimal evaluation of these strategies in controlled clinical research trials [93]. Although many of these strategies have been used by CBT experts in clinical practice, they warrant evaluation in clinical trials before being fully promoted and adopted into clinical practice by front-line clinicians.

9. Discussion

This paper reviewed threat conditioning and extinction studies of unaffected youth and youth with fear-based psychiatric disorders in order to better understand threat conditioning, extinction learning, and retention deficits in youth. In doing so, our goal was to provide recommendations for improving extinction learning and retention that can ultimately lead to enhancements of CBT. Despite discrepant findings and a limited amount of available research, four broad themes emerged. First, several factors were found to influence threat conditioning and extinction among unaffected youth and youth with fear-based psychiatric disorders. Second, discrepancies between objective (SCR, FPS) and subjective (SR) outcome measures were noted between and within studies. Third, children, compared to adolescents (or adults), were found to exhibit impairment in threat discrimination and/or contingency awareness. Finally, identified deficits in extinction appear to be consistent with impairments in inhibitory learning.

Taken together, these findings highlight several directions for future clinical treatment research. First, as threat conditioning and extinction studies serve as analogues to exposure-based CBT, studies should examine whether the factors influencing conditioning and extinction learning impact CBT outcomes in youth with fear-based psychiatric disorders. This is particularly relevant for the findings regarding age and developmental stage, as questions remain whether extinction learning may be impaired during adolescence [36,84]. Second, there is a need to better understand the discrepant findings between psychophysiological and SR outcome measures, and determine their respective relationships with CBT outcome. As treatment response in clinical research studies is typically determined by an amalgamation of patient, parent, and clinician perspectives; youth who exhibit a disconnection between psychophysiological and SR outcomes may be accounting for a number of CBT non-responders. Indeed, it may be that a subset of youth exhibit impairment in extinction on either physiological or SR outcomes, which could impede therapeutic progress (or conscious recognition of therapeutic progress) in exposure-based CBT. Third, as children were identified as having deficits in threat discrimination and/or contingency awareness compared to adolescents, it may be that the exposures conducted with youth having these deficits are not as efficacious due to an inability to correctly select threatening stimuli and appropriately forming inhibitory CS-no US associations.

Fourth, deficits in extinction learning may benefit from the use of inhibitory learning strategies to maximize extinction. Although expert CBT clinicians have employed several of these strategies in clinical practice, conceptualizing the deficits in terms of inhibitory learning provides a new perspective in which to understand the role of exposures in CBT, and suggests potentially beneficial therapeutic strategies. Although showing initial promise [93], there is a need for clinical research evaluating developmentally appropriate adaptation of these strategies in youth with fear-based psychiatric disorders.

In summary, translational research on threat conditioning, extinction learning, and extinction retention holds considerable promise for understanding and improving therapeutic outcomes for youth with fear-based psychiatric disorders. Our review of published conditioning and extinction studies in youth suggests the presence of deficits in extinction learning and

extinction retention, which highlights new directions for interventions. Despite the growing number of studies, further research is needed to advance this important field. First, given the context dependent nature of extinction learning, future research should examine extinction learning across contexts among unaffected youth and youth with fear-based psychiatric disorders, as it may be associated with symptom relapse after CBT. Second, prospective treatment studies are needed to examine whether pre-treatment extinction learning and/or retention predicts CBT treatment response [79]. This information could clarify the degree to which pre-treatment extinction learning and retention might serve as indicators for a positive response to CBT. Third, inhibitory learning strategies warrant testing within clinical trials to determine whether they actually enhance extinction learning and lead to improved CBT outcomes. Finally, as initial evidence suggests that self-reported extinction learning and/or extinction retention via SUDS does not account for therapeutic outcomes in exposure-based CBT among youth [86,87], a detailed examination is needed to understand the mechanisms by which CBT responders achieve therapeutic improvement and the degree to which extinction learning is implicated.

10. Expert Commentary

Threat conditioning and extinction studies in unaffected youth and youth with fear-based psychiatric disorders were reviewed with the goal of using this information to inform and improve the exposures that comprise CBT. As noted above, findings offer several new directions for clinical research and CBT practice. From a clinical perspective, these findings encourage the consideration of factors that influence threat conditioning and extinction into treatment planning, as these same factors may impact CBT outcomes. These factors can be assessed within the context of an evidence-based assessment [94], which uses psychometrically validated rating scales to assess symptom severity and monitor severity throughout treatment. While there may be some concern regarding the use of extinction-based treatments for adolescents [36,84], more research is needed to better understand the relationship between adolescence, extinction learning, extinction retention, and exposure-based CBT. For younger patients that may have impairments in threat discrimination and/or contingency awareness (relative to adolescents and adults), it may prove useful for clinicians to assess a youth's awareness of threat associations and spend time facilitating contingency awareness and/or threat discrimination. As youth learn to recognize associations and discriminate threats appropriately, subsequent extinction learning will be facilitated. Finally, these findings support the use of inhibitory learning strategies within exposure-based CBT. While the various strategies warrant testing in clinical trials, several of them have been used in clinical practice by expert CBT clinicians. Before attempting to incorporate inhibitory learning strategies into exposure-based treatments, it is important to provide developmentally appropriate psychoeducation to patients and families to ensure that they understand the rationale underlying these strategies. As suggested by leading CBT experts, psychoeducation should include a discussion of the nature of associative learning and avoidance in the context of fear-based psychiatric disorders and acknowledge that short-term distress may be experienced before longer-term improvement [28]. This is a notably different approach than focusing on immediate and/or short-term reduction in subjective distress, as measured by SUDS. As the incorporation and implementation of inhibitory

learning principles can be challenging, it may prove useful for clinicians interested in using these strategies to seek out consultation from CBT experts with first-hand experience in their application.

11. Five-Year View

There has been considerable growth in the number of threat conditioning and extinction studies among unaffected youth and youth with fear-based psychiatric disorders over the past five years. The next five years hold promise for the continuation of this work and production of important new findings. The next five years will likely bring several changes and improvements to threat conditioning and extinction research. First, there is likely to be an increase in the number of studies among youth, especially those with OCD and PTSD. Second, along with an increase in the number of studies, there will likely be a more consistent application and standardization of methodology. Indeed, there is already a trend towards the use of standardized unconditioned stimuli (i.e., a loud female scream, loud alarm sound) and tasks with comparable designs to facilitate comparison across studies. Third, there will likely be more translational research focused on examining the differences in extinction learning and retention between children, adolescents, and adults—with an emphasis on understanding the specific nature of extinction learning deficits in adolescence. The information provided by this research will help to identify specific strategies for improving extinction and CBT outcomes in adolescent youth with fear-based psychiatric disorders. Fourth, there will likely be an increase in the examination of pre-treatment extinction learning as a potential predictor of exposure-based CBT outcomes. One study has recently provided support for a relationship between conditioning and extinction learning with group CBT treatment response [79], and other studies are on the horizon [95]. Finally, there will likely be several studies examining the benefit of inhibitory learning strategies on extinction learning and retention in unaffected youth and youth with fear-based psychiatric disorders. Although expert clinicians have been using several of these strategies in clinical practice for some time, empirically based investigation will prove critical to updating existing CBT protocols and disseminating reliable and useful therapeutic approaches to front-line treatment providers.

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Reference annotations

*Of interest

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Key Issues

- Fear-based psychiatric disorders predominantly develop in childhood, affect up to 29% of the population, and serve as a leading cause of disability.
- Although exposure-based cognitive behavior therapy (CBT) is efficacious in reducing symptom severity for youth with fear-based psychiatric conditions, few youth experience symptom remission with as many as 50% of initial treatment responders experience a relapse of symptoms.
- Threat conditioning, extinction learning, and extinction retention play important roles in the etiology and treatment of fear-based psychiatric disorders.
- Translational studies of threat conditioning, extinction learning, and extinction retention serve as an analogue to CBT, and thus, can offer insight into approaches that may improve treatment outcomes.
- A comprehensive literature review identified 30 studies of threat conditioning, extinction learning, and extinction retention in youth that were included in this review (16 studies of unaffected youth, 10 studies of youth with anxiety disorders, 1 study of youth with obsessive compulsive disorder, and 3 studies of youth with posttraumatic stress disorder, trauma, and/or maltreatment).
- Conditioning studies in unaffected youth and youth with fear-based psychiatric disorders revealed that several factors (e.g., age, gender, developmental stage, contingency awareness, attention bias, parental psychopathology, youth psychopathology) influence threat conditioning and extinction.
- Across conditioning and extinction studies of unaffected youth and youth with fear-based psychiatric disorders, discrepancies were observed between psychophysiological and self-report outcomes.
- Children compared to adolescents (and adults) exhibited an impaired ability to discriminate between conditioned stimuli and/or poor contingency awareness, which are important components for extinction learning.
- Across conditioning and extinction studies, youth fear-based psychiatric disorders had deficits in extinction learning. These deficits were best characterized by deficiencies in inhibitory learning.
- Based on these deficits in extinction learning and retention, strategies to improve inhibitory learning may maximize extinction and improve CBT outcomes. These strategies include: expectancy violation, intermittent reinforced extinction, stimulus variability, elimination of safety signals, compound extinction, using multiple contexts, using retrieval cues, and reconsolidation of extinction learning.
- Although expert CBT clinicians have been using several of these strategies for some time, further research is needed to evaluate the actual benefit of

inhibitory learning strategies in promoting extinction learning and improving CBT outcomes.

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Table 1

Summary of Threat Conditioning and Extinction Studies in Unaffected Community Control Youth

Study	N	Age	CS	US	DV	Phases	Conditioning and Extinction Results	Additional Comparisons
Morrow et al. [55]	12	10-12	2 sets of 3 circular white lights arranged either vertically or horizontally for 5 s	2.5 mp electric shock for 0.1 s	SCR	PRE-CON: 4 CS+, 4 CS-, 3 separate US CON: 20 CS+, 20 CS-, 20 US GEN: N/A CXT: N/A EXT: N/A ER: N/A	PRE-CON: No difference between CS on SCR. CON: Differential CON (CS+ > CS-) observed on SCR	Comparison w/ young (n = 12) and older (n =10) adults. Age: Children exhibited greater SCR to CSs relative to both adult groups, but no differences in the magnitude of differential CON between groups.
Block et al. [56]	50 (22 2-4 year olds, 17 4-6 year olds, 38 6-11 year olds)	2-11	Two 55 dB tones (400 and 1000 Hz) for 5 s	95 dB horn for 1 s	HR	PRE-CON: N/A CON: 10 CS+, 10 CS-, 10 US GEN: N/A CXT: N/A EXT: N/A ER: N/A	CON: 2-4 year olds failed to display differential CON. 4-6 year olds demonstrated partial evidence of differential CON. Meanwhile, 6-11 year olds exhibited evidence of differential CON (CS+ > CS-)	N/A.
Neumann et al. [57]	15 (7 boys, 8 girls)	13-17	2 shapes for 8 s	US < 83 dB sound of garden fork scrapping against slate for 3 s Startle 100 dB white noise for 50 ms	SCR, FPS, SR	PRE-CON: N/A CON: 8 CS+, 8 CS-, 8 US GEN: N/A CXT: N/A EXT: 8 CS+, 8 CS- ER: N/A	CON: Differential CON (CS+ > CS-) observed for SCR and FPS. SR expectancy ratings increased for CS+ across trials, and decreased for CS-. EXT: No differences between CS+ and CS- on SCR, FSP, but some evidence of increased SR expectancy ratings for the CS+ during early EXT trials.	N/A.
Neumann et al. [58]	16	8-11	2 shapes for 8 s	< 83 dB sound of metal scrapping against slate for 3 s	SCR, SR	PRE-CON: 2 CS+, 2 CS- CON: 12 CS+, 12 CS-, 12 US GEN: N/A CXT: N/A EXT: 12 CS+, 12 CS- ER: N/A	PRE-CON: No differences between CSs on SCR, SR expectancy, SR pleasantness, or SR arousal. CON: Differential CON (CS+ > CS-) observed on SCR, SR expectancy, SR pleasantness, and SR arousal. EXT: Initial difference between CS+ and CS- during early EXT on SCR and SR expectancy that became non-significant over later trials. No differences between CSs on SR pleasantness, or SR arousal.	N/A.
Gao et al. [59]	172 (tested annually over 5 years)	3-8	Two 60 dB tones (500 or	95 dB sound of tin can with	SCR	PRE-CON: 3 1000 Hz and 3 1211 Hz	CON: Differential CON (CS+ > CS -) evident on SCR 3 and 8 years of age across averaged	Age: SCR magnitudes increased with age.

Study	N	Age	CS	US	DV	Phases	Conditioning and Extinction Results	Additional Comparisons
			1000 Hz) for 12 s	metal jangling for 4 s		tones at 75 dB for 1 s CON: 9 CS+, 3 CS-, 6 US GEN: N/A CXT: N/A EXT: N/A ER: N/A	responses, but only significant at 8 years for second interval response.	Gender: No difference on SCR between gender across time.
Haddad et al. [60]	42	12-15	3 neutral faces for 1-3 s	US: CS_{neg} = angry face+ critical comment, CS_{pos} = happy face + compliment, CS_{neu} = neutral face + neutral comment	SR	PRE-CON: 2 CS_a, 2 CS_b, 2 CS_c for 3 s. CON: 9 CS_a, 9 CS_b, 9 CS_c for 1 s with, 6-7 CS_{neg}, 6-7 CS_{pos}, 15-17 CS_{neu} for 2 s. GEN: N/A CXT: N/A EXT: 8 CS_a, 8 CS_b, 8 CS_c for 3 s. ER: N/A	PRE-CON No differences between CS on SR scariness or pleasantness. CON: Differential CON present, with CS_{neg}> CS_{neu}> CS_{pos} on SR scariness, with a reverse relationship for SR pleasantness. EXT: Differential CON present, with CS_{neg}> CS_{neu}> CS_{pos} on SR scariness, with a reverse relationship for SR pleasantness.	Attention bias: Youth with greater SR scariness to CS_{neg} had greater attentional bias for the CS_{neg} on a dot-probe task. No
Lau et al. [40]	21	*Mn* = 13.1	2 neutral female faces for 5 s	Fearful face for 3 s + 90 dB scream for 1 s	SCR, SR	PRE-CON: 8 CS+, 8 CS- CON: 10 CS+, 10 CS-, 8 US GEN: N/A CXT: N/A EXT: N/A ER: N/A	PRE-CON: No difference between CSs on SCR. CON: Differential CON present (CS+ > CS-) on SCR or SR.	Comparison with adults: Adolescents exhibited greater SCR relative to adults during CON across CSs.
Lau et al. [40]	15	10-17	2 neutral female faces for 6 s	Fearful face + 90 dB scream for 1 s	SR, fMRI	PRE-CON: 3 CS+, 3 CS- CON: 60 CS+, 60 CS-, 30 US GEN: N/A CXT: N/A EXT: N/A ER: N/A	PRE-CON: No difference between CSs on SR. CON: Differential CON present (CS+ > CS-) on SR.	Comparison with adults: Adolescents exhibited smaller differential fear CON relative to adults. fMRI results identified differences between adults and adolescents in the right amygdala and bilateral hippocampus. Additionally in adults DLPFC positive associated with greater fear SR to CS-, but negatively associated with CS- in adolescents.
Glenn et al. [61]	40	8-13	CS 2 neutral faces for 6 s GS 1 blended neutral face for 6 s	US Fearful face for 3 s + 80 dB scream for 1 s Startle 95 dB white noise for 50 ms	FPS, SR	PRE-CON: 1 CS+, 1 CS-, 1 GS, 1 US CON: 8 CS+, 8 CS-, 6 US GEN: 8 CS+, 8 CS-, 8 GS, 6 US CXT: N/A EXT: N/A ER: N/A	CON: No Differential CON on SR measures, however differential CON (CS+ > CS-) on FPS. GEN: Differential CON present (CS+. CS-) on FPS, but no difference between CS- and GS.	Contingency Awareness: 80% of youth correctly aware of contingency. Youth with contingency awareness exhibited larger FSP to CS+ than CS- during CON. Age: Positive associated between child age and FSP during CON. Additionally, larger FSP to GS compared to CS- among older children.

Study	N	Age	CS	US	DV	Phases	Conditioning and Extinction Results	Additional Comparisons
Pattwell et al. [36]	77 (43 children, 44 adolescents)	5-17	2 colored shapes for 3 s	85 -107 dBwhite noise with a 1,000 Hz tone for 1 s	SCR	PRE-CON: N/A CON: 24 CS+, 24 CS-, 12 US (Day 1) GEN: N/A CXT: N/A EXT: 24 CS+, 24 CS- (Day 2) ER: N/A	CON: Differential CON (CS+ > CS-) observed on SCR across groups. EXT: Adolescents showed diminished differential CON (CS+ > CS-) via SCR relative to children	Comparison with adults (n = 38): Adolescents showed diminished differential CON (CS+ > CS-) relative to adults via SCR, but no difference between children and adults for EXT.
Chauret et al. [62]	117 (56 boys, 61 girls)	10-17	2 neutral male faces or 2 neutral female faces for 3 s	Fearful face for 1 s + 90 dB scream for 1 s (matched for gender of face)	SCR, SR	PRE-CON: N/A CON: 28 CS+, 28 CS-, 14 US GEN: N/A CXT: N/A EXT: 14 CS+, 14 CS- ER: N/A	CON: Greater SR fear to male versus female CSs. However, SCR revealed that differential CON (CS+ > CS-) present only when gender of CSs matched participant's gender. EXT: Differential CON (CS +> CS-) in SR ratings, but not in SCR. Additionally, greater SR fear to male versus female CSs.	Gender: Girls showed had greater SR fear to CS- relative to boys during EXT. Meanwhile, boys exhibited differential CON (CS+ > CS-) in SCR to male faces only during EXT.
Tzschoppe et al [63]	47	14	2 neutral male faces for 6 s	80 dB female scream for 1 s	SCR, SR, fMRI	PRE-CON: 10 CS+, 10 CS-, 10 US CON: 30 CS+, 30 CS-, 15 US GEN: N/A CXT: N/A EXT: 10 CS+, 10 CS- ER: N/A	PRE-CON: No differences between CSs on SCR and SR arousal, unpleasantness, and expectancy. CON: Differential CON on SCR and SR for arousal, unpleasantness, and expectancy. EXT: Although EXT observed on all SR measures, differential CON still present on SCR.	Neuroticism: No association observed between neuroticism and SR and SCR to CS+ or CS- during CON or EXT. However, during CON, greater neuroticism associated with stronger interaction between right amygdala and both the right hippocampus and prefrontal cortical regions.
Waters et al. [64]	55 (31 Low Risk, 26 High Risk)	7-14	2 colored shapes for 8 s	100 dB tone (1000 Hz) for 1 s	SCR, SR	PRE-CON: 1 CS+, 1 CS-, 2 control shapes CON: 8 CS+, 8 CS-, 8 US GEN: N/A CXT: N/A EXT: 4 CS+, 4 CS- ER: N/A	CON: Across groups, youth exhibited differential CON (CS+ > CS-) on SR valence, SR arousal, and SCR. EXT: Differential CON (CS +> CS-) persisted on arousal SR, but not on other measures across groups.	Depressed parent, Anxious parent, and HC parent: During CON, youth with DEP parents had smaller SCR differential CON and smaller SCR to CS+ relative to youth with ANX parents and HC parents. During EXT, youth with ANX parents exhibited larger differential SCR during orienting response relative to youth with DEP or HC parents.
Den et al. [65]	59	12-17	2 neutral female faces for 8 s	Fearful female face + 75 dB scream for 3 s	SR, ET	PRE-CON: 4 CS+, 4CS- CON: 7 CS+, 7 CS-, 5 US GEN: N/A CXT: N/A EXT: 5 CS+, 5 CS- ER: N/A	PRE-CON TO CON: 10 HC dropped out due to aversive US, with SR scary ratings higher in CON relative to PRE-CON. CON TO EXT: Reduction in SR scary and expectancy ratings from CON to EXT.	AGE: Adolescents exhibited stronger ET orienting response to CS+ compared to adults. Adults had greater SR expectancy scores than adolescents reflecting worse stimuli discrimination. Depression: Increased depression score associated with faster orienting response to CS+ after CON.

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Study	N	Age	CS	US	DV	Phases	Conditioning and Extinction Results	Additional Comparisons
								Increased depression also associated with greater scary and expectancy SR after EXT, suggesting that fear retained and expectancy unchanged.
Kadosh et al. [66]	60 (30 Low ANX, 30 High ANX)	*Mn* = 14	3 neutral female faces (cues) that appear for 2 s within one of 3 distinct background images of rooms for 10 s (context)	US Fearful face + 95 dB scream for 0.75 s Startle Air puffs for 40 ms	FPS, SR	PRE-CON: 3 Contexts (no cues), 1 US CON: N/A GEN: N/A CXT: 24 CS+, 24 US, 24 CS_u- but US in same context, 24 CS_{ns}- EXT: N/A ER: N/A	CXT: CS+ =Predictable condition (US paired with cue), CS_u- = Unpredictable condition (US presented in context independent of cue), CS_{ns}- = No US presented. Across participants, greater FPS to cued stimuli (face) compared to context (room) stimuli in Predictable and No Scream conditions, but no difference in cued versus context for Unpredictable condition. No difference in FPS in context background.	HIGH/LOW ANX: First, HA had greater FPS than LA across conditions. Second, LA discriminated between cued and context better than HA group. Third, HA had greater FPS to no scream CON, but lower FPS to unpredictable CON relative to LA. Fourth, LA had greater contingency awareness in no scream condition.
Michalska et al. [67]	59 (20 5-6 year olds, 20 7-8 year olds, 19 9-10 year olds)	5-10	2 colored bells (blue and yellow) for 7-8 s	Red bell + 95 dB alarm for 1 s	SCR, SR	PRE-CON: 4 CS+, 4CS- CON: 10 CS+, 10 CS-, 8 US GEN: N/A CXT: N/A EXT: 8 CS+, 8 CS- GEN ER: 3 CS+, 3 CS-, 27 GG	PRE-CON: No differences between CSs on SCR or SR. CON: Differential CON on SCR and SR (CS+ > CS-). EXT: Differential CON on SR (CS+ > CS-), but no difference on SCR. GEN ER: Average 19 days after EXT. Older age group exhibited better discrimination and greater contingency recall compared to younger age group and middle age group. However, younger age groups reported less SR fear to GG CS resembling CS+ relative to older age group.	Age: 9-10 year olds reported highest SR fear relative to other age groups (6-7, and 7-8) across all phases.
Schiele et al. [68]	267	8-10	CS 2 neutral female faces for 6 s GS 4 blended images for 6 s	Fearful face + 95 dB scream for 1.5 s	SCR SR	PRE-CON: 4 CS+, 4CS- CON: 12 CS+, 12 CS-, 10 US GEN: 12 CS+, 5 US, 12 CS-, 12 of each GEN CS CXT: N/A EXT: N/A ER: N/A	PRE-CON: No differences in SCR or SR for stimuli. CON: Differential CON (CS+ > CS-) observed in SCR and SR. GEN: Youth exhibited greater SCR to ambiguous GEN CSs, but quadratic trend (suggesting good discriminate learning) was not significant.	Comparison with 285 adults (aged 18-50). Age: Youth rated CS as more pleasant than adults during PRE-CON. During CON and GEN, SCR in youth greater than adults across CSs. Youth had greater fear toward some GEN CSs compared to adults on SR and SCR. Contingency awareness greater in adults than youth in both CON and GEN.

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Note: ANX = Anxious, CON = Conditioning, CS = conditioned stimulus, CXT = Context Conditioning, dB = decibel, DEP = Depressed, DLPFC = dorsolateral prefrontal cortex, DV = Dependent variable, ER = Extinction Retention, ET = Eye tracking, EXT = Extinction, fMRI = functional magnetic resonance imaging, FPS = Fear potentiated startle, GEN = Generalization, GS = Generalization Gradient Stimulus, HC = Healthy Controls, HR = Heart rate, Hz = hertz, Mn = Mean, ms = millisecond, N/A = Not applicable, PRE-CON = Pre-Conditioning, s = second, SCR = Skin conductance response, SR = Self-report, US = unconditioned stimulus, HA = High Anxiety, LA = Low Anxiety.

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Table 2

Summary of Threat Conditioning and Extinction Studies in Youth with Anxiety Disorders

Study	Diagnosis	N	Age	CS	US	DV	Phases	Conditioning and Extinction Results	Additional Comparisons
Pliszka et al. [71]	ANX, ADHD, HC	56 (11 ANX, 23 ADHD, 22 HC)	6-12	2 squares paired with a different loud tone (500-1000 Hz) for 4 s	White notes for 200 ms at 110 dB	SCR, HR	PRE-CON: N/A CON: 8 CS+, 8 CS-, 8 US GEN: N/A CXT: N/A EXT: 4 CS+, 4 CS- ER: N/A	CON: Differential CON (CS+ > CS-) observed in SCR and HR across participants. No group differences. EXT: EXT observed in HR across groups, with no difference between CS+ and CS-. However, differential CON still present in SCR across groups (CS+ > CS-).	N/A.
Liberman et al. [78]	ANX (SoP, GAD, SP, SAD), HC	83 (53 ANX, 30 HC)	7-14	4 neutral cartoons for 5 s	US 105 dB tone (1000 Hz) for 500 ms Startle 105 dB white noise for 50 ms	SCR, FPS, SR	PRE-CON: 4 stimuli CON: 6 CS+, 6 CS-, 6 US GEN: N/A CXT: N/A EXT: 8 CS+, 8 CS- ER: N/A	PRE-CON: No sig differencesbetween groups in FPS, SCR, or SR. CON: Differential CON observed in HC group using SR arousal' rating, but not ANX group. No differential CON in FPS or SCR. No group differences. EXT: Differential CON observed in ANX group using SR fear' rating and FPS, but not in HC group.	Gender: (only in ANX group). Latency of FPS was greater in boys than girls during PRE-CON. During EXT, shorter FPS latency in girls than boys.
Craske et al. [72]	ANX (SoP, GAD, SP, PD, SAD), ANX-AR, HC	49 (23 ANX, 15 ANX-AR, 11 HC)	7-12	4 shapes for 8 s	107 dB tone (1000 Hz) for 1 s	SCR, SR	PRE-CON: 4 shapes CON: 8 CS+, 8 CS-, 8 US GEN: N/A CXT: N/A EXT: 4 CS+, 4 CS- ER: 4 CS+, 4 CS-	CON: Differential CON observed across all groups on SCR. ANX exhibited greater anticipatory SCR relative to HC and AR groups across stimuli. EXT: ANX exhibited greater anticipatory SCR relative to HC group across stimuli. ANX reported lower valence toward CS + post CON compared to HC. No differencesin EXT between ANX and AR groups. ER: Average 12 days ER. ANX and AR exhibited greater anticipatory SCR relative to HC group across stimuli.	N/A.
Lau et al. [73]	ANX (SoP, GAD, SAD), HC	54 (16 ANX, 38 HC)	*Mn* = 13.5	2 neutral female faces for 8 s	Fearful face + 95 dB scream for 3 s	SR	PRE-CON: 4 CS+, 4 CS- CON: 16 CS +, 16 CS-, 12 US GEN: N/A CXT: N/A EXT: 3 CS+, 3 CS-	CON: Differential CON exhibited across groups (CS+ > CS-), however ANX group had higher ratings to the CS+ (but not the CS-) compared to HC group. Anxiety symptoms associated with fear ratings of CS+ across groups.	Stability: Magnitude of correlations within stimulus time across EXT to ER demonstrated strong stability for CS+ (r=.57) and CS= (r=.55). Additionally strong association of differential fear CON across visits (r=.51).

Study	Diagnosis	N	Age	CS	US	DV	Phases	Conditioning and Extinction Results	Additional Comparisons
							ER: 12 CS+, 12 CS-	EXT: Differential CON exhibited across groups (CS+ > CS-). ER: Average 16 days ER. Attrition at ER associated with males and higher levels of fear to CS+ following EXT. Both groups continued to rate CS+ > CS-.	
Waters et al. [74]	ANX (SoP, GAD, SP), HC	35 (17 ANX, 18 HC)	8-12	4 shapes for 8 s	10 dB tone (1000 Hz) for 1 s	SCR, SR	PRE-CON: 4 shapes CON: 8 CS+, 8 CS-, 8 US GEN: N/A CXT: N/A EXT: 4 CS+, 4 CS- ER: N/A	PRE-CON: No group or stimuli difference. CON: ANX group exhibited differential CON (CS+>CS-) on self-report arousal and SCR, but HC group only on SCR. ANX group also had larger SCR to CS, compared to HC group during orienting response. EXT: No group difference on self-report, but ANX group exhibited greater SCR to both stimuli compared to HC group. Differential CON in ANX group observed in SCR orienting response, but not other aspects or in HC group.	N/A.
Britton et al. [41]	ANX (SoP, GAD), HC	65 (23 ANX, 42 HC)	8-19	CS 2 neutral female faces for 7-8 s GS 9 blended images for 7-8 s	US Fearful face + 95 dB scream for 1 s Startle 10 psi air puff for 40 ms	FPS, SCR, SR, fMRI	PRE-CON: 4 CS+, 4 CS- CON: 10 CS+, 10 CS-, 8 US GEN: N/A CXT: N/A EXT: 8 CS+, 8 CS- GEN ER: 3 CS+, 3 CS-, 27 GS	PRE-CON: No difference in SCR or FPS. CON: ANX group more likely to discontinue participation. Differential CON observed (CS+ > CS-) across groups for FPS, SCR, and SR. ANX group had greater SR to stimuli compared to HC group. EXT: ANX group had impaired EXT to CS+ compared to HC group. Additionally, ANX group had similarly high SR ratings of CSs compared to HC group. GEN ER: Average 20 days after EXT. During threat appraisal questions, ANX group exhibited lower sub-genual anterior cingulated activation compared to HC group. Additionally, ANX group had greater activation to CSs and not gradient stimuli in vmPFC.	Compared data with 49 adults (18 ANX, 31 HC) Age Differences: Youth have greater SCR during CON and EXT than adults. Less EXT in youth FPS compared to adults. Additionally, ANX adults had hypoactivation in vmPFC during threat appraisal compared to other groups.
Haddad et al. [75]	ANX, HC	26 (15 ANX, 11 HC)	11-17	CS 2 neutral female faces for 6 s	Fearful face + 95 dB scream for 1 s	SR fMRI	PRE-CON: 5 CS+, 5 CS-, 5 CC	PRE-CON: ANX group had higher nervous SR to CS+ than HC group. No within group difference to CSs.	AGE: Age was not associate with nervous SR ratings of stimuli during PRE-CON or CON. Age-related activation increases to CS+ relative to CC

Study	Diagnosis	N	Age	CS	US	DV	Phases	Conditioning and Extinction Results	Additional Comparisons
				Control cue (CC) Grey oval for 6 s			CON: 30 CS +, 15 CS-, 15 CC, 15 US GEN: N/A CXT: N/A EXT: NR ER: N/A	CON: Differential CON (CS+> CS- > CC) across groups, with the ANX group reporting greater nervousness to both stimuli compared to CON group. CON group exhibited greater activation in amygdala, right hippocampus, and vmPFC compared to ANX group to threat cue (CS+ relative to CC).	observed in the insula and DLPFC across the sample. ANX and AGE: In HC group, greater response with to CS- > CC in DLPFC, bilateral insula and striatum, but not in ANX group.
Shechner et al. [76]	ANX (SoP, GAD, SP, SAD), HC	32 (15 ANX, 17 HC)	*Mn* = 11.5-13.0	2 neutral female faces for 7-8 s or 2 colored bells for 7-8 s	US 95 dB scream + fearful face for 1s or 95 dB alarm + red bell for 1 s Startle 10 psi air puff for 40 ms	SCR, FPS, SR	PRE-CON: 4 CS+, 4 CS- CON: 10 CS +, 10 CS-, 8 US GEN: N/A CXT: N/A EXT: 8 CS+, 8 CS- ER: N/A	PRE-CON: No stimuli or group difference in SR or SCR. CON: 6 youth (3 ANX, 3 HC) discontinued task. Differential CON (CS+ > CS-) in SR, FPS, and SCR observed across groups. EXT: Differential CON (CS+> CS-) observed in SR across groups, but no differences in SCR or FPS.	Task Comparison: “Screaming Lady” and Bell CON task had moderate to strong ICC for SR and SCR CON and EXT (r=. 42-.65), but only modest association for FPS CON (r=. 34-36). However, some task specific differences were observed. Age: Compared data with 52 adults (22 ANX, 30 HC). Youth exhibited higher overall SCR, FPS, and differential CON compared to adults who had lower SCR and did not exhibit differential CON.
Waters & Kershaw [77]	ANX (SoP, GAD, SP, SAD)	34 ANX (18 TVB, 16 TAB)	7-12	2 colored shapes for 8 s	107 dB tone (1000 Hz) for 1 s	SCR, SR	PRE-CON: NR CON: 8 CS+, 8 CS-, 8 US GEN: N/A CXT: N/A EXT: 4 CS+, 4 CS- ER: N/A	CON: Greater orienting response in TAB compared to TVB in first trial block, with larger unconditioned response to US in TAB across blocks. However no group difference in anticipatory response (i.e., CON). EXT: SR anxiety to CSs decreased across groups after EXT. However, TAB had higher SR anxiety ratings compared to TVB, with greater orienting responses across CS to the first trial block. No group differences in SR or SCR.	N/A
Waters & Pine [79]	ANX (SoP, GAD, SP, SAD), HC	76 (44 ANX: 26 RESP, 18 NON-RESP; 32 HC)	7-13	2 colored shapes for 8 s	107 dB tone (1000 Hz) for 1 s	SCR, SR	PRE-CON: NR CON: 8 CS+, 8 CS-, 8 US GEN: N/A CXT: N/A EXT: 4 CS+, 4 CS- ER: N/A	CON: Differential CON in SCR exhibited across groups, but no group differences. NON RESP had higher unpleasant SR of CSs after CON compared to PRE-CON or EXT. However, this was not observed in RESP or HC groups. EXT: RESP and HC exhibited decreased SCR over trial blocks. Additionally, SCR to the CS+	Change In Anxiety: Change in child-reported anxiety associated with initial EXT response to CS+ trials (r=.48)

Study	Diagnosis	N	Age	CS	US	DV	Phases	Conditioning and Extinction Results	Additional Comparisons
								during first trial block were larger than NON RESP, but neither RESP or NON RESP differed from HC group.	

Note: ANX = Anxious, SoP = Social Phobia, GAD = Generalized Anxiety Disorder, SP = Specific Phobia, PD = Panic Disorder, SAD = Separation Anxiety Disorder, ANX AR = Anxiety At-Risk, CON = Conditioning, CS = conditioned stimulus, CXT = Context Conditioning, dB = decibel, DEP = Depressed, DV = Dependent variable, ER = Extinction Retention, ET = Eye tracking, EXT = Extinction, fMRI = functional magnetic resonance imaging, FPS = Fear potentiated startle, GEN = Generalization, GEN ER = Generalization Extinction Retention, GS = Generalization Gradient Stimulus, HC = Healthy Controls, HR = Heart rate, Hz = hertz, Mn = Mean, ms = millisecond, N/A = Not Applicable, PRE-CON = Pre-Conditioning, psi = pounds per square inch, s = seconds, SCR = Skin conductance response, SR = Self-report, US = unconditioned stimulus, vmPFC = ventralmedial prefrontal cortex.

Table 3

Summary of Threat Conditioning and Extinction Studies in Youth with Obsessive Compulsive Disorder, Posttraumatic Stress Disorder, Trauma Exposure, and/or Maltreatment

Study	Diagnosis	N	Age	CS	US	DV	Phases	Conditioning and Extinction Results	Additional Comparisons
McGuire et al. [80]	OCD	41 (19 OCD, 22 HC)	7-17	2 neutral faces for 8 s	Fearful face + 95 dB scream for 3 s	SCR	PRE-CON: 4 CS+, 4 CS- CON: 10 CS+, 10 CS-, 8 US GEN: N/A CXT: N/A EXT: 8 CS+, 8 CS- ER: N/A	PRE-CON: No stimuli or group difference. CON: Differential CON (CS+ > CS-), no group difference. EXT: 3-way interaction. HC exhibited differential CON (CS+ > CS-). OCD exhibited stimulus × trial block interaction where CS- = CS+ in early trials. In later trials, CS- declined to HC level, but fear to CS+ persisted.	CON: Anxiety severity (r=.36) and OCD symptoms (r=.34) associated with SCR to CS+, with anxiety severity associated with CS- (r=.41). EXT: CS differential associated with OCD severity (r=-.33) and anxiety sensitivity (r=-.46)
Jovanovic et al. [81]	HC *	60	8-13	2 colored shapes for 6.54 s	US 80 psi air blast for 0.5 s Startle 106 dB broadband noise for 40 ms	SCR, FPS	PRE-CON: N/A CON: 9 CS+, 9 CS-, 9 US GEN: N/A CXT: N/A EXT: 12 CS+, 12 CS- ER: N/A	ACQ: Differential CON (CS+ > CS-). EXT: Main effect for trial block. Initial increase to CS-, but both CS+ and CS- decreased over later trials. No sig. difference between CS+ and CS- during EXT.	Age & Anxiety: Younger children have worse discrimination between CS+ and CS- relative to older youth, and exhibited greater CON to CS+. High anxiety younger children also had reduced FPS to CS+ during EXT. Older children w/ high anxiety have greater FPS to CS+ and CS- in CON. FSP to CS- in CON associated with anxiety.
Gamwell et al. [82]	PTSD, HC *	105 (14 PTSD, 91 HC)	8-13	2 colored shapes for 6.54 s	US 50 psi air blast for 0.1s Startle 106 dB broadband noise for 40 ms	SCR, FPS	PRE-CON: 3 CS+, 3 CS- CON: 9 CS+, 9 CS-, 9 US GEN: N/A CXT: N/A EXT: N/A ER: N/A	PRE-CON: No difference in response to stimuli. CON: Differential CON (CS+ > CS-).	Gender: Differential CON greater in males relative to females. PTSD: PTSD severity was associated with SCR to the CS+ (r=.24) Gender & PTSD: SCR to CS+ associated with intrusive symptoms in males (r=.37), but self-blame (r=.40) and fear of repeated trauma in trauma (r=.43). Differential CON associated with avoidance symptoms in females (r=.46)
McLaughlin et al. [83]	TE, HC *	90 (35 TE, 55 HC)	6-18	2 colored bellsfor 7-8 s	Different colored bell + 95 dB alarm noisefor 1 s	SCR, SR, MRI	PRE-CON: 4 CS+, 4 CS- CON: 10 CS+, 10 CS-, 8 US GEN: N/A CXT: N/A EXT: 8 CS+, 8 CS- ER: N/A	PRE-CON: No difference in response to stimuli. CON: Differential CON (CS+ > CS-) across groups. Maltreatment associated with blunted SCR to CS+, increase to both stimuli in early CON, and differential CON only emerging in late CON. EXT: Across groups, no difference in response between stimuli in SCR, but persistent differential CON (CS+ > CS-) evidenced in SR.	Maltreatment: Youth with maltreatment exhibited delayed differential CON. PTSD & EP: Youth with PTSD or EP did not exhibit differential CON. MRI: Amygdala and Hippocampus negative associated with CS+, with vmPFC positively associated with CS-.

* healthy controls were recruited entirely or in part from a low-income urban population with high trauma exposure.

Note: CON = Conditioning, CS = conditioned stimulus, CXT = Context Conditioning, dB = decibel, DV = Dependent variable, EP = Externalizing Psychopathology, ER = Extinction Retention, EXT = Extinction, FPS = Fear potentiated startle, GEN = Generalization, GEN ER = Generalization Extinction Retention, HC = Healthy Controls, HR = Heart rate, Hz = hertz, MRI = magnetic resonance imaging, ms = millisecond, N/A = Not Applicable, OCD = Obsessive Compulsive Disorder, PRE-CON = Pre-Conditioning, psi = pounds per square inch, PTSD = Posttraumatic Stress Disorder, s = second, SCR = Skin conductance response, SR = Self-report, TE = Trauma Exposure, US = unconditioned stimulus, vmPFC = ventralmedial prefrontal cortex.