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Pavlovian Learning Processes in Pediatric Anxiety Disorders: A Critical Review

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Abstract

Deficits in associative and Pavlovian learning are thought to lie at the center of anxiety related disorders. However, the majority of studies have been carried out in adult populations. The aim of this paper is to critically examine the behavioral and neuroimaging literature on Pavlovian learning in pediatric anxiety disorders. We conclude that, although there is evidence for deficits in Pavlovian processes (e.g., heightened reactivity to safety cues in anxious samples), the extant literature suffers from key methodological and theoretical issues. We conclude with theoretical and methodological recommendations for future research in order to further elucidate the role of Pavlovian learning in the etiology, maintenance, and treatment of pediatric anxiety disorders.

Keywords

fear learning; Pavlovian learning; conditioning; extinction; pediatric anxiety disorders; fear generalization

The ability to learn associations among stimuli, contexts, and outcomes, and to flexibly adapt one's behavior in response to changes in these associations, is an essential aspect of navigating one's environment. However, deficits in associative learning are thought to be at the core of several psychiatric disorders. Indeed, it is arguably the sine qua non of anxiety related disorders (which includes post-traumatic stress disorder and obsessive-compulsive disorder) (1). We use the term associative learning to broadly refer to the formation of associations in memory between stimuli, contexts, outcomes, and behaviors (e.g., Pavlovian, operant learning). Pavlovian learning refers to the specific formation of predictive associations (e.g., tone leads to shock, social interactions lead to social rejection, etc.).

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In a typical Pavlovian experiment a neutral stimulus (conditional stimulus or CS+) is repeatedly paired with a biological significant outcome (unconditional stimulus or US) while another stimulus (CS−) is not. The CS+ then elicits conditional responding (e.g., fear) as it becomes a strong predictor of the US (CS-US association). Following memory consolidation, repeatedly presenting the CS+ in the absence of the US leads to extinction learning and a reduction in the conditional response. Extinction learning does not result in the erasure of the original fear association but rather entails the formation of a new association (CS-noUS association). Thus, conditional responding can return following the passage of time (spontaneous recovery), with a context change (context renewal), or following additional presentations of the US (reinstatement) (2).

The overwhelming majority of studies examining Pavlovian learning in anxiety related disorders have been conducted in adults. A wealth of evidence suggests that, although individuals with anxiety and trauma related disorders demonstrate comparable differential fear learning (CS+ > CS−), they also demonstrate greater reactivity to safety cues during fear acquisition, enhanced fear generalization, and reduced extinction of conditional responses compared to healthy controls (1, 3–6). In addition, deficits in extinction predict the emergence of anxiety and trauma related disorders (e.g., PTSD) (7), predict response to exposure-based treatments (8), and change as a result of exposure therapy (9). However, given the dearth of treatment studies, additional research is need to further elucidate the role of extinction learning as potential mechanism of change.

These findings are supported by neuroimaging studies which have mapped differences in key neurobiological structures associated with fear learning and extinction learning including hyperactivation in the amygdala in social anxiety and post-traumatic stress disorder, along with hypoactivation in the ventromedial cortex (vmPFC) and anterior cingulate cortex (ACC) in post-traumatic stress disorder (10).

However, analogous studies of Pavlovian learning in pediatric samples are scarce. This is unfortunate, given that a considerable number of anxiety disorders begin in childhood or adolescence (11). In addition, developmental changes in neurobiology may differentially impact Pavlovian learning. For instance, during typical development from ages four to twenty-three, resting-state functional connectivity of the bilateral amygdala tends to increase with the medial prefrontal cortex and decrease with the insula (12). Likewise, when viewing fearful faces, functional connectivity between the amygdala and the medial prefrontal cortex shifts from positive to negative throughout typical development from childhood into adulthood, although interpretations vary regarding the precise relationship (e.g. excitatory or inhibitory) between these regions during development (13). Similarly, the association between brain structure (i.e. cortical thickness of insular, mid-cingulate, or middle frontal gyrus cortices, as well as grey matter volume of the hippocampus) and physiology (i.e. skin conductance response during fear conditioning) tends to exhibit a positive-to-negative shift from ages eight to 50 (14). The emergence of anxiety disorders, and developmental changes in neural pathways responsible for the regulation of fear, highlight the importance of studying Pavlovian learning in pediatric samples.

Fewer than a dozen studies have examined Pavlovian learning processes in pediatric samples with anxiety disorders. The aim of the present paper is to critically examine the extant behavioral and neuroimaging literature on Pavlovian learning in pediatric anxiety disorders. We focus on several core Pavlovian processes including differential fear conditioning, fear generalization, extinction learning, and renewal (see Table 1). We conclude with theoretical and methodological recommendations for future research in order to further elucidate the role of Pavlovian learning in the etiology, maintenance, and treatment of pediatric anxiety disorders.

Differential Fear Conditioning

The results of a recent meta-analysis (15) indicated that anxious youths, as compared to healthy controls, demonstrate increased reactivity to both a CS+ and CS− across fear acquisition with no differences in differential learning. A recent study spanning ages eight to 50 identified a similar pattern of increased SCR across conditional stimuli among anxious participants compared with healthy controls (averaging both acquisition and extinction phases of the fear conditioning task) (14). These results differ slightly from the most recent meta-analysis which indicated heightened reactivity to the CS− but not to the CS+ in adults with anxiety disorders (1). However, drawing comparisons across studies of children and adults is complicated given the use of different unconditional stimuli. For example, the intensity of the US has a profound impact on fear acquisition (16), and differential intensities may well exist between studies with children versus adults. As such, comparisons across studies with children and adults should be tentative.

Only a few neuroimaging studies have examined differential fear learning in pediatric anxiety disorders and the results are mixed. Chauret and colleagues (17) examined differential fear learning and extinction in adolescents with an anxiety disorder, healthy controls, and at-risk youth (defined as having a parent with an anxiety disorder). Anxious youths demonstrated decreased activation in the left dorsal anterior cingulate cortex (dACC; BA24) and left ventrolateral prefrontal cortex (vlPFC; BA47) compared to healthy and at-risk youths. This did not appear to be a result of increased reactivity to the CS−, but rather reduced activation to the CS+ in the anxious group. This is interesting, given that the dACC is a purported homologue of the rodent prelimbic cortex which demonstrates increased reactivity to threat cues during fear conditioning (18). Furthermore, at least one study has found that, compared to healthy controls, adolescents with anxiety disorders demonstrate *decreased* activation in the amygdala to the CS+ compared with a control cue during fear acquisition (19). Given the relevance of the dACC and amygdala in fear expression, one interpretation suggests a blunting of neural reactivity to conditional stimuli in pediatric anxiety disorders.

Taken together, the results of behavioral studies suggest heightened reactivity to both threat and safety cues in pediatric anxiety disorders during fear acquisition although the neuroimaging findings are mixed.

Fear Generalization

Heightened fear generalization is purported to be a central feature of anxiety related disorders, and offers an explanatory model for the spread of fears following aversive events (20). Generalization can occur along perceptual (4,20) or categorical dimensions (21). A common method for examining generalization is to first conduct differential conditioning, and then to examine reactivity to generalization stimuli that parametrically vary between the CS+ and CS− (4).

Only a few studies have examined fear generalization processes in healthy children and adolescents. For example, children (ages 8-10) demonstrated increased arousal ratings and SCR to generalization stimuli compared to adults (22). Neuroimaging of adolescents and adults during fear acquisition revealed that subcortical structures (e.g., amygdala and hippocampus) activated more strongly in adolescents when differentiating CS+ and CS− cues, whereas increased activation of the dorsolateral prefrontal cortex to the CS− compared to CS+ tended to correspond with greater self-reported fear to the CS− among adults (23). Threat and safety discrimination has been associated with functional connectivity between subcortical structures, such as the amygdala or hippocampus, with the dorsomedial and ventromedial prefrontal cortex (24,25). Deficits in engaging prefrontal areas during stimulus discrimination in adolescents, consistent with developmental differences in the maturation of cortical structures (13), may suggest a heightened vulnerability to fear generalization during this developmental period.

Unfortunately, we are unaware of any studies that have intentionally examined perceptual or categorical fear generalization in pediatric anxiety disorders by examining stimulus generalization prior to extinction. Inasmuch as the adult literature has consistently found heightened fear generalization among individuals with anxiety disorders, this is a notable gap in the pediatric literature.

Several studies claiming to measure extinction retention and generalization may best be characterized as instances of fear generalization. These studies in children and adolescents have employed the “screaming lady paradigm” in which fear is differentially conditioned to two pictures of female faces (one of which, the CS+ is followed by a scream) and then extinguished. Extinction generalization is then examined several weeks later through reactivity to generalization stimuli that parametrically vary between the CS+ and CS−. However, closer examination of the methodology indicates that the number of extinction trials may be insufficient to generate extinction learning. Extinction trials need to greatly outnumber those during acquisition to ensure the formation of an extinction memory (26). If the number of trials during extinction were insufficient to generate extinction learning, then these studies may best be characterized as an examination of fear generalization rather than extinction generalization.

Results from these studies indicate that children and adolescents with anxiety disorders demonstrate decreased activation in the subgenual anterior cingulate cortex (sgACC) across a range of generalization stimuli (27). The extant literature on fear generalization in adults has established an important role for the sgACC in discriminating between threat and

safety cues (24,28). For example, there is increased activity in the sgACC when viewing generalization stimuli that resemble the CS− (28). Thus, these results would seem to indicate deficient safety signal processing or stimulus discrimination in anxious youths.

In addition, a few of these studies have highlighted a crossover effect, wherein anxiety-related differences in functional brain connectivity are inverted for children compared with adults. For instance, anxious youth exhibited *more negative* connectivity between the amygdala and vmPFC during threat appraisal and memory ratings, compared with visual discrimination of image components, whereas anxious adults exhibited *more positive* connectivity between these regions (29). A recent study highlighted a similar crossover effect, whereby anxious youth exhibited *greater* functional connectivity between the amygdala and ventromedial prefrontal cortex, whereas anxious adults tended to exhibit *lower* functional connectivity between these regions (30). This study examined average functional connectivity across the recall task, rather than comparing specific task components.

Therefore, whereas studies have highlighted the developmental importance of connectivity between the left amygdala and the vmPFC during fear generalization, future studies are needed to clarify the specific associations of this pathway.

Extinction

The term “extinction” can refer to 1) a specific phase of the task paradigm, in which the CS+ is presented in the absence of the US, 2) reductions in conditional responding that occur during this phase of the task paradigm, or 3) the proposed mechanism by which individuals form a CS-noUS association. Unfortunately, the extant literature often fails to specify the manner in which they are discussing extinction. For the remainder of this manuscript, we will use the term “extinction” to refer to the phase of the experiment, “extinction of…” to refer to the decrease in conditional responding often seen during extinction (e.g., “extinction of SCR”), and “extinction learning” to refer to the formation of a CS-noUS association (see Table 1).

Across numerous studies, youth with anxiety disorders demonstrate reduced extinction learning on self-report and psychophysiological indices (e.g. SCR) compared to healthy controls (31). The extant literature suggests that adolescence in particular may correspond with a reduced capacity for extinction learning to punctate cues. In an interesting parallel translational study with rodents and humans, Pattwell and colleagues (32) first demonstrated that healthy adolescents showed attenuated extinction of SCR compared to both children and adults. Similarly, adolescent mice maintained heightened freezing behavior across extinction compared to preadolescent and adult mice. The effect was speculated to be due to increased dendritic spine formation in excitatory fear circuits (i.e., prelimbic-amygdala) found in adolescent mice (33).

Neurobiological processes of extinction learning in adolescents with anxiety disorders are understudied. Chauret and colleagues (17) found that adolescents with anxiety disorders demonstrated increased activation in the left amygdala to an average of both CS+ and

CS− cues across extinction compared to healthy controls. Anxious youth also failed to demonstrate significant reduction in their SCR across extinction.

In addition, at least two studies have reported that deficits in extinction of SCR were associated with poorer response to exposure based therapy, evidenced by no reduction in SCR among children with anxiety disorders(34) and poor discrimination between the CS+ and CS− among children with obsessive-compulsive disorder(35). Importantly, in both studies, responders and non-responders each demonstrated comparable differential learning during fear acquisition. Thus, it appears that deficits in extinction of SCR, rather than fear acquisition, are predictive of response to exposure-based therapy, although additional research is needed to further elucidate the role of associative learning as a predictor of response to cognitive-behavioral therapy in pediatric samples.

That being said, these results should be interpreted with caution. The number of extinction trials used in several of these studies may be insufficient to generate extinction. As noted previously, successful extinction requires significantly more trials than used during fear acquisition, particularly with partial reinforcement schedules, and extant studies may have failed to provide a sufficient number of extinction trials (26). Thus, the current results may be consistent slower acquisition of extinction learning during early extinction in pediatric samples rather than deficits in the formation of extinction learning with sufficient trials.

In addition, the majority of studies conducted conditioning and extinction on the same day. Although cellular consolidation begins soon after a learning episode, sleep appears critical in the formation of long-term memories (36,37). It is debatable whether one can measure “extinction learning” if the original fear association has not first been consolidated into long-term memory. Similarly, there is a dearth of neuroimaging studies examining extinction learning in anxious youths making conclusions regarding potential development differences or between anxious youths and adults difficult.

Renewal

As discussed previously, extinction learning does not result in the erasure of the original fear association but rather entails the formation of a new association (CS-noUS association). This new association is contextually dependent and conditional responding can renew under various circumstances (e.g., following a context shift) (2). The ability to generalize extinction across contexts, stimuli, and time frames can be adaptive, while differences in the degree of fear renewal may be an important risk factor for anxiety disorders.

Unfortunately, there is a paucity of research examining fear renewal processes in pediatric anxiety disorders. One study found higher orienting and anticipatory SCR to both conditional stimuli among anxious youth compared to controls during extinction recall, but no differences between youth with anxiety disorders and at-risk youth (defined as having a parent with an anxiety disorder (31).

Reinstatement, in which the US is presented alone following extinction, is another renewal phenomenon. We are unaware of any studies that have examined reinstatement in anxious

youth. However, at least two studies in healthy samples have found no differences in reinstatement between adolescents and adults (38,39).

Retention and retrieval of extinction learning is known to rely, in part, on vmPFC activity and connectivity (40). Given that maturation of cortical areas occurs later in development (13), it is possible that children and adolescents display broad deficits in extinction recall regardless of anxiety diagnosis. In support of this possibility, healthy adolescents demonstrate reduced activation in the vmPFC and dorsolateral prefrontal cortex (dlPFC) during extinction recall compared to adults (41).

Given the evidence of impoverished vmPFC-amygdala connectivity in pediatric anxiety disorders (13), it is possible that extinction recall is particularly impoverished in anxious youths. Indeed, in one study state anxiety among adolescents was correlated with negative functional connectivity between the dorsolateral prefrontal cortex and the amygdala as well as the hippocampus (42).

The lack of behavioral and neuroimaging studies examining extinction retention, context renewal, and reinstatement in pediatric anxiety disorders prevents any conclusions. In addition to the dearth of research, many studies of renewal processes in both children and adults fail to conduct proper tests of fear renewal (43).

Recommendations for Future Research

The extant literature examining Pavlovian learning in pediatric samples suffers from methodological shortcomings that mitigate the ability to examine associative learning processes. Below, we offer several suggestions to better elucidate Pavlovian learning processes in pediatric anxiety disorders. These recommendations are broadly applicable across pediatric and adult samples. However, given the comparative scarcity of research focusing on clinically anxious pediatric samples, these recommendations will be especially useful for efforts to elucidate how Pavlovian processes correspond with the emergence, maintenance, and treatment of anxiety disorders during childhood and adolescence.

Conduct Acquisition, Extinction, and Renewal on Separate Days

Although cellular consolidation begins soon after learning, sleep appears critical in the formation of long-term memories (36,37). Unfortunately, the majority of studies conduct fear conditioning and extinction on the same day. From an organism’s perspective, conducting acquisition and extinction on the same day, even when separated by a short time period to complete rating scales, can be construed as a single learning episode with a variable rate of reinforcement. Similar arguments can be made for renewal processes. Although there are logistical advantages to conducing conditioning, extinction, and renewal on the same day (e.g., reduced drop-out), allowing associative learning to be consolidated into long-term memory is essential. Therefore, we recommend that conditioning, extinction, and renewal should be separated by at least 24 hours.

Utilize More Nuanced and Ecological Valid Paradigms

A common misconception is that Pavlovian learning is confined to directly experienced stimuli and outcomes. On the contrary, Pavlovian learning simply refers to the formation of predictive associations among stimuli, contexts, and outcomes. Indeed, evidence suggests that Pavlovian associations can be formed via observation and verbal instruction, and these methods of acquisition engage similar neural structures and operate via similar processes (e.g., error correction) as directly experienced conditioning (44,45). Employing diverse methods of acquisition will enhance the ecological validity of fear learning in children and adolescents with anxiety disorders.

We also advise researchers to consider using lower reinforcement rates during acquisition. High reinforcement rates result in a “strong situation” in which aversive events are relatively well predicted and potentially obscure clinical differences in fear acquisition (46). High reinforcement rates may also obscure potential differences in extinction learning. Reduction in conditional responding during extinction can either result from a generalization decrement, in which the organism stops responding as they have determined that the context differs from that during acquisition, or extinction learning, in which the organism learns that the CS is no longer the best predictor of the US(2). Generalization decrement does not involve new learning whereas extinction learning involves changes in associative learning. Higher reinforcement rates during conditioning may lead to the appearance of faster “extinction learning” via a generalization decrement as the conditions differ greatly from acquisition (48). However, this can mask potential group differences between clinical and healthy samples in extinction learning. Reduction in response rate due to determining the context differs from that during acquisition is fundamentally different from acquiring a new association in which the CS is no longer the best predictor of the US.

Acquisition has been obtained with low reinforcement rates in fear conditioning studies (49,50), human contingency learning studies[48], as well as one-trial learning in phobic samples (51). Lower reinforcement rates more closely approximate clinical reality where unconditional stimuli occur infrequently (with the exception of repeated traumatization). Lower reinforcement rates (below 50%) also increase stimulus generalization in healthy controls (47) and therefore are important in determining whether there truly exists group differences in fear generalization between clinical and control samples.

Although reducing the rate of reinforcement offers several advantages, there are also potential downsides. For example, the “strong situation” results in a robust learning rate whereas more ambiguous learning paradigms may result in a higher number of individuals failing to learn the CS-US contingencies (52). However, given the potential advantages to conducting fear conditioning with lower reinforcement rates we advise researchers to consider using lower reinforcement rates during acquisition.

Increase the Number of Extinction Trials

As mentioned previously, the majority of the studies reviewed implemented relatively few extinction trials. For example, in several of the “screaming lady” paradigms (27,29,30) there were 10 trials of the CS+ (80% reinforcement rate) during acquisition and only 8

trials of the CS+ during extinction. This may be insufficient to generate extinction (26). Animal studies routinely employ a greater number of extinction trials (e.g., 60 trials of extinction compared to 8 trials of acquisition) (53). Extinction proceeds at a slower rate than acquisition due to differences in learning parameters (54). Although individuals may demonstrate within session decreases in conditional responding, this may be due to factors other than extinction learning (e.g., generalization decrement). Any potential group differences in pediatric samples may reflect slightly delayed acquisition of extinction rather than deficits in the formation of extinction learning with sufficient trials. Researchers should consider significantly increasing the number of trials during extinction in order to ensure extinction learning is acquired and to elucidate group differences in extinction learning.

Utilize Diverse Associative Learning Paradigms

All of the studies reviewed employed relatively standard differential fear conditioning and extinction paradigms. However, there are numerous other Pavlovian learning paradigms including occasion setting (55), context conditioning (56), transfer of inhibition (6), context renewal (57), reinstatement (58), and rapid reacquisition(2). Inasmuch as anxiety disorders are characterized by deficits in aversive and appetitive learning, it may also be important to include appetitive conditioning and extinction paradigms in future research (59). Given the biobehavioral differences in pediatric and adult fear learning, studies across a full range of associative learning paradigms will likely highlight how specific deficits emerge and correlate with developmental processes.

Utilize Trial-by-Trial US Expectancy Ratings

The development of predictive associations is at the core of Pavlovian learning. This is best indexed via measurement of US expectancy ratings during each trial. However, less than 20% of studies in pediatric samples utilize US expectancy ratings (60). While fear potentiated startle and SCR are important dependent variables, they represent aspects of the conditional response rather than the CS-US relationship. We concur with other researchers who recommend trial-by-trial US expectancy in a developmentally appropriate manner (60).

Conduct Treatment Prediction and Mediational Studies

Elucidating the role of Pavlovian learning in the maintenance and treatment of pediatric anxiety will require both treatment prediction and mediational studies. Unfortunately, we are aware of only two studies examining Pavlovian learning as a predictor of treatment (34,35). We are unaware of any studies that have examined Pavlovian conditioning and extinction as a mediator of exposure-based treatment in pediatric samples. There are logistical challenges in examining associative learning as a mediator or mechanisms of treatment. Ideally, the paradigms should be conducted several times across treatment to examine changes in Pavlovian learning prior to symptom change. Multiple paradigms will require different sets of stimuli, as repeating the same stimuli results in rapid reacquisition and re-extinction rather than new conditioning and extinction.

Finally, future research should employ disorder relevant CSs and USs when possible. The majority of studies employ neutral stimuli (e.g., geometric shapes, faces) in order to reduce the impact of any previous associations. However, exposure based procedures are targeted

to disorder specific stimuli (e.g., social interactions in social phobia, physical sensations in panic disorder). While overall threat learning may change as a result of exposure therapy, it is possible that only specific associations are targeted. For example, paradigms that employ socially relevant USs in social anxiety disorder (61) or interoceptive conditioning for panic disorder (62) should be used. Of course, there are ethical considerations in employing certain unconditional stimuli in youth. Employing human contingency learning paradigms with disorder relevant stimuli may be useful. Human contingency learning operates via the same process as Pavlovian learning (63), and therefore may be useful when there are ethical concerns with delivering unconditional stimuli.

Summary

In sum, there is a dearth of studies examining Pavlovian learning processes in anxious youth. This represents a significant barrier to elucidating its role in the genesis, maintenance, and treatment of anxiety related disorders. The results of the few behavioral and neuroimaging studies suggest that pediatric anxiety disorders are associated with heightened reactivity to both safety and threat cues across conditioning and extinction, and there is evidence for reduced activation in key excitatory and inhibitory fear circuitry.

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Table 1

Definition of Key Terms

Context Conditioning	Paradigm in which conditioning occurs to a complex array of contextual features (e.g., visual background, spatial location) rather than to a discrete, punctate cue.
Context Renewal	Paradigm in which the context at test differs from that during extinction. Conditional responses often renew following a context shift.
Differential Conditioning	Conditioning paradigm in which one cue (CS+) is repeatedly paired with the US whereas another cue (CS−) is not.
Discrimination	The ability to accurately differentiate between perceptually related cues.
Extinction	Experimental phase in which the CS+ is repeatedly presented in the absence of the US.
Extinction of…	Decrease in conditional responding during extinction. For example, extinction of SCR.
Extinction Learning	Proposed mechanism of action during extinction. Formation of a CS-noUS association.
Fear Generalization	Generalization of fear to a stimulus that is perceptually or categorically related to the CS+.
Generalization Decrement	Decrease in responding when an organism recognizes that the context differs from the previous experimental phase. Generalization decrement does not involve new learning.
Occasion Setting	Experimental paradigm in which a stimulus modulates (e.g., sets the occasion for) the relationship between the CS-US.
Rapid Reacquisition	Re-pairing the CS+ with the US following extinction.
Reinstatement	Presenting the US alone following extinction. Results in a renewal of fear to the CS+.
Safety Signal	Stimulus that predicts the non-occurrence of the US.
Spontaneous Recovery	Renewal of conditional responding following the passage of time.
Transfer of Inhibition	Conditioning paradigm in which a compound stimulus (AX+) is paired with a US while another compound stimulus (BX−) is not. Subsequent test of AB compound examines the transfer of inhibition from B to A.