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Fear conditioning and extinction across development: Evidence from human studies and animal models☆

Tomer Shechner[a,*], **Melanie Hong**[b], **Jennifer C. Britton**[c], **Daniel S. Pine**[d], and **Nathan A. Fox**[b]

[a]Department of Psychology, University of Haifa, Israel

[b]Department of Human Development and Quantitative Methodology, University of Maryland, USA

[c]Psychology Department, University of Miami, USA

[d]The National Institute of Mental Health, MD, USA

Abstract

The ability to differentiate danger and safety through associative processes emerges early in life. Understanding the mechanisms underlying associative learning of threat and safety can clarify the processes that shape development of normative fears and pathological anxiety. Considerable research has used fear conditioning and extinction paradigms to delineate underlying mechanisms in animals and human adults; however, little is known about these mechanisms in children and adolescents. The current paper summarizes the empirical data on the development of fear conditioning and extinction. It reviews methodological considerations and future directions for research on fear conditioning and extinction in pediatric populations.

Keywords

Classical conditioning; Fear conditioning; Extinction Development; Animal models; Human studies

1. Introduction

The ability to identify danger emerges early in life and develops in a similar way across cultures. Young children tend to fear strangers or separation. When these fears diminish during school-age, they typically are replaced by fears of animals or other natural dangers. In adolescence, fears arise of social circumstances and abstract dangers, such as the fear of humiliation. While extensive research charts developmental patterns of human fear in response to such intrinsically threatening events, far less research examines developmental aspects of learned fears. Because considerable basic research examines fear conditioning and extinction, particular interest has arisen in the development of these forms of learning.

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*Corresponding author. Tel.: +972 4 824 9660. tshechner@psy.haifa.ac.il (T. Shechner).

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This paper summarizes findings from developmental research on fear conditioning and extinction. It unfolds in four stages. Section 2 defines major concepts relevant to fear conditioning and extinction. Because few studies examine fear conditioning and extinction in children, Section 3 attempts to extrapolate to children and adolescents from data in animals and human adults. Section 4 details findings from the few available conditioning and extinction studies in children and adolescents, emphasizing the unique ethical and methodological considerations that complicate such work. The paper concludes by summarizing directions for future studies.

2. Studying fear conditioning and extinction developmentally

Fear conditioning, a form of associative learning, is a widely used experimental paradigm for investigating the psychophysiological processes and neural mechanisms sub-serving learning about danger cues in a range of mammalian species. In classical fear conditioning, a neutral conditioned stimulus (CS, e.g., tone) is repeatedly paired with an aversive stimulus (UCS, e.g., shock), yielding a CS-UCS association. Discrimination conditioning uses two CSs, one that is paired with the UCS (CS+) and another that is not (CS−). A conditioned response (CR, e.g., freezing behavior) is produced in response to the CS+, thus enhancing the organism's ability to respond to similar events in the future. This paradigm allows for the rapid induction of a learned fear state and the expression of learned fear-related behaviors. Conditioned fear responses have been found across multiple species and include various responses such as changes in autonomic activity (e.g., heart rate, blood pressure, skin conductance), defensive behaviors (e.g., freezing), endocrine response (e.g., hormone release), pain sensitivity (e.g., analgesia), and modulation of reflex expressions, like fear potentiated startle and eye blink response (LeDoux, 2000).

Extinction is a process during which the CS+ is presented in the absence of the UCS, leading the conditioned response (CR) to decline across repeated presentations. Based on numerous studies, extinction does not eradicate the initial CS+-UCS association but rather creates new learning, where the CS+ is associated with the absence of the UCS (for review see Bouton, 2002, 2004; Quirk & Mueller, 2008). Following successful extinction, the initial CS+-UCS association competes with the newer CS+-no-UCS association. When presentation of the extinguished CS triggers the no-UCS memory, it inhibits the original CR. Retrieval of extinction, also known as extinction recall, occurs when the extinguished CS+ is re-presented at a later time. Low levels of the fear expression (i.e., CR) indicate successful extinction recall, whereas high levels of fear expression indicate poor extinction recall (Quirk & Mueller, 2008). Fear responses may also reappear spontaneously with passage of time (i.e., spontaneous recovery), following contextual manipulations (i.e., renewal) or presentation of the UCS even in the absence of the CS+ (i.e., reinstatement) (Bouton, 2002).

Interactions between fear conditioning and extinction shape behavior, mainly during development, when the effects of learning can be particularly profound. Hence, understanding the developmental changes of these processes and the underlying neural correlates that support them informs a mechanistic understanding of fear and safety learning. In rodents, fear conditioning emerges early in life and involves subcortical areas, predominantly the amygdala; whereas the maintenance of extinction, as expressed in

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extinction recall, appears to emerge later in development and involves the prefrontal cortex and hippocampus (Kim & Richardson, 2010). Thus, when studying these learning-related processes, a developmental perspective examining maturation of brain regions supporting fear conditioning and fear extinction may explain the emergence of individual differences in fear and anxiety.

3. The neural circuitry underpinning fear conditioning and extinction

Most neuroscience research on fear conditioning uses animal models. Nonetheless, translating these findings to human studies is feasible due to the strong cross-species similarities in the physiology of fear (LeDoux, 2000). Animal models are particularly important for studying the emergence of fear conditioning across development as some of the procedures are less feasible in humans and particularly in children and adolescents. Therefore, findings from animal models can be translated to research in human adults, which in turn can be applied to pediatric populations.

3.1. Animal models

3.1.1. Fear conditioning—Fear conditioning involves processing sensory information about the CS and the UCS. Typically, the CS and UCS are presented in different sensory modalities (e.g., auditory tone and tactile shock) and thereby activate different sensory cortices as well as the thalamus and hypothalamus and the brainstem periaqueductal gray region. Ultimately, information about the CS and the paired UCS is thought to first converge in the basolateral nucleus of the amygdala. Initially, the neutral CS will produce weaker amygdala stimulation than produced by the UCS. Following CS-UCS pairings, the initially weak amygdala stimulation produced by the CS becomes stronger, reflecting a CS-UCS association. After this association is formed, the weak stimulus, presented on its own without the UCS, has the capacity to elicit a stronger amygdala response, thus influencing behavior and physiology through efferent projections from the central nucleus of the amygdala. This region of the amygdala sends projections to brainstem and motor areas that control the expression of fear responses across a variety of domains expressed via behavioral, autonomic nervous system, and endocrine responses (LeDoux, 2000).

The amygdala appears to mediate learning by influencing cortical plasticity via changes in synaptic connection. Once a CS-UCS association has been acquired, a decline in amygdala activation may occur (Buchel & Dolan, 2000), unless later-appearing changes in the CS-UCS association take place. For example, mounting evidence implicates a portion of the medial prefrontal region (mPFC), the so-called “pre-limbic” cortex, in enhancement of amygdala activity and its importance for expression of conditioned fear. Specifically, it is proposed that this region integrates input from other brain structures to enhance the expression of fear conditioning via excitatory projections to the amygdala (Corcoran & Quirk, 2007; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011; Sotres-Bayon & Quirk, 2010).

Relative to the considerable work on fear conditioning in mature rodents and primates, far less work examines developmental aspects of fear conditioning using animal models (Kim & Richardson, 2010). Research investigating the emergence of fear conditioning in infant

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rats has identified a sensitive period in which amygdala activation to aversive stimuli is inhibited. During early stages of postnatal development, newborns are equipped with innate abilities for appetitive learning (Landers & Sullivan, 2012). For instance, infant rats acquire the ability to orient toward their mother's odor to facilitate mother-infant attachment. In contrast, during the first 10 days, amygdala activation in response to threats is attenuated due to low neonatal cortisol levels, resulting in an approach response to the aversive stimuli (Moriceau & Sullivan, 2004). At postnatal day 10, stress-induced cortisol in young rats increases to adult-like levels, which in turn facilitates amygdala activation allowing fear conditioning to emerge. This plasticity in rats continues to develop into adolescence (for review see Landers & Sullivan, 2012).

The ability to learn CS-UCS associations may change during development, as the organism acquires new capacities to encode details of stimuli in particular sensory modalities. For example, associative learning of olfactory and gustatory CS occurs earlier than auditory and visual CS in the rodent as these modalities mature differentially with development (for review see Richardson & Hunt, 2010). Additionally, the expressions of learned associations may continue to change as further development supplies the maturing organism with an increasingly complex behavioral repertoire. For instance, rats as young as 16 days can express learned associations between olfactory or visual CSs and a shock-UCS via freezing behavior and heart rate; however, the presence of such associations are not expressed at this age using fear potentiated startle, but do manifest at 23 days of age (for review see Richardson & Hunt, 2010). These complex processes influence the inferences that can be drawn about development and fear conditioning. The degree to which fear conditioning might appear mature or immature may depend on the particular stimuli used during learning and the behavioral modality through which learning is probed.

3.1.2. Extinction—Animal research on the neural mechanisms underpinning extinction learning and extinction recall highlight the importance of three neural structures: the amygdala, the ventromedial pre-frontal cortex (vmPFC), and the hippocampus. All three structures play a major role in extinction learning with differential involvement over time and across contexts. Inhibitory circuits comprised of intercalated neurons in the amygdala, relay inhibitory outputs to the central nucleus in the amygdala preventing neuronal excitation to the same brain regions that control fear (Royer & Pare, 2002). Additionally, "infra-limbic" cortex, which lies ventral to the prelimbic cortex in the rodent, appears to attenuate the expression of fear responses through connections with these so-called intercalated inhibitory cells within the amygdala (Quirk & Mueller, 2008). Lastly, findings also suggest that the hippocampus plays a role in mediating context-specific learning and recall of fear extinction (Corcoran & Maren, 2001, 2004).

The amygdala plays a role in fear extinction processes across development. In adult rats undergoing extinction, the amygdala supports forming of the initial CS-no-UCS association. However, once this association is formed, the amygdala is no longer needed for subsequent extinction processes (Laurent, Marchand, & Westbrook, 2008). Unlike at older ages (24-day-old rats), these re-extinction processes continue to be dependent on the amygdala in younger animals (i.e., 17-day-old rats) (Kim & Richardson, 2008). Thus, development results in a shift from amygdala-dependent to amygdala-independent extinction.

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Likewise, developmental findings emerge for the involvement of vmPFC in extinction recall. In adult rats, vmPFC damage does not affect within-session extinction, but impacts extinction recall 24 h after extinction (Lebron, Milad, & Quirk, 2004; Quirk, Russo, Barron, & Lebron, 2000). These results further emphasize the difference between the process of extinction learning and extinction recall in both the neural and the behavioral levels. Similarly, no developmental differences emerge in extinction learning between 23-day-old (preadolescent), 35-day-old (adolescent) and 70-day-old (adult) rats. However, adolescent rats elicited greater freezing behavior compared to their younger and older counterparts when tested 24 h following extinction, indicating that adolescents failed to retrieve the extinction memory of the CS (Kim, Li, & Richardson, 2011; McCallum, Kim, & Richardson, 2010). These findings may reflect a non-linear developmental trajectory of the PFC function during extinction recall. Some controversy exists concerning the presence of such non-linearity, which may also manifest in changes in PFC volume during adolescence, in both rats and humans (Casey & Durston, 2006; Pattwell, Casey, & Lee, 2013; Shaw et al., 2008). Other work more consistently finds linear changes in brain volume and behavior during adolescence, without clear evidence of nonlinear discontinuities (Steinberg, 2005). Regardless, development influences extinction recall within the infralimic cortex.

Finally, developmental differences also emerge for the hippocampus, a region involved in context learning and context modulation of extinction (Corcoran, Desmond, Frey, & Maren, 2005). During fear conditioning and extinction, spatial aspects of the surroundings are also integrated in the learning processes to form a long-term contextual memory (Maren, 2011). Although evidence of long-term contextual memories emerges in preadolescent rats between 18 and 23 days after birth, young rats are impaired in forming these long term contextual memories (Rudy & Morledge, 1994). Extinction learning in the younger rats might be context-independent (Gogolla, Caroni, Luthi, & Herry, 2009; Kim & Richardson, 2007a, 2007b; Storsve & Richardson, 2009). For example, 24-day-old rats show renewal and reinstatement effects following extinction; whereas, 17-day-old rats do not. If extinction learning in young rats is indeed context-independent, they may fail to express successful extinction recall even if within-session extinction was observed because retrieving context information may be necessary for extinction recall (Delamater, 2004). Alternatively, the hippocampus could mediate within-session extinction even before it reaches full maturation, but is not involved in retrieving extinction memory at later assessments (Corcoran et al., 2005; Delamater, 2004; Kim & Richardson, 2010).

Taken together, the available developmental data from research in animal models suggest an essential difference in the neural architecture underlying fear extinction across development. More specifically, fear extinction during early development may depend primarily on the amygdala, whereas joint roles for the amygdala, vmPFC and the hippocampus may occur at later ages. These findings may reflect neural processes that are undergoing maturation (amygdala and hippocampus) as well as structural changes (PFC) across the developing rodent.

Developmental differences in rat models have also emerged from pharmacological studies. Studies using adult rats examining the formation of long-term extinction memory have implicated N-methyl-D-asparate (NMDA) involvement in fear conditioning and extinction

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(Lattal, Radulovic, & Lukowiak, 2006; Miserendino, Sananes, Melia, & Davis, 1990). Interestingly, a strong NMDA antagonist (MK-801) impairs long-term extinction in pre-adolescent (23-day-old), as indicated by higher freezing behavior (CR) during extinction retention, but not in younger (16-day-old) rats (Langton, Kim, Nicholas, & Richardson, 2007). Moreover, differential alterations of inhibitory neurotransmission mechanisms involved in fear extinction have been associated with increased γ-aminobutyric acid (GABA) binding in the amygdala (Chhatwal, Myers, Ressler, & Davis, 2005). Similar to NMDA results, GABA antagonist (FG7142) has been shown to attenuate extinction in adult rats (Harris & Westbrook, 1998), and in pre-adolescent rats (23-day-old) as indicated by higher levels of freezing when exposed to the extinguished CS in the same context, but not in younger rats (16-day-old) (Kim & Richardson, 2007b). These pharmacological findings further support the differences in extinction learning processes and the underpinning mechanisms across development.

3.2. Human studies

Functional magnetic resonance imaging (fMRI) studies in human adults have used classical fear conditioning paradigms to examine fear responses to discrete CSs (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998), extinction learning (Milad et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004), and context conditioning (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Lang et al., 2009). In addition, data from lesions studies on patients complement imaging data (LaBar, LeDoux, Spencer, & Phelps, 1995; Weike et al., 2005). Consistent with animal models, this literature highlights the importance of the amygdala, vmPFC, and hippocampus as the primary brain regions involved in fear conditioning and extinction in humans.

3.2.1. Fear conditioning—Similar to findings in animal models, the amygdala has also been implicated in fear conditioning in human adults (Costafreda, Brammer, David, & Fu, 2008; Delgado, Olsson, & Phelps, 2006; Sehlmeyer et al., 2009; Sergerie, Chochol, & Armony, 2008). Lesion studies in humans support the central role of the amygdala in fear conditioning and extinction. This line of research could potentially elucidate the causal contribution of the amygdala and other relevant brain structures by determining if damage to these brain areas affects fear conditioning. Studies conducted on patients with amygdala lesions report impairments in fear conditioning (LaBar et al., 1995; Weike et al., 2005). For instance, amnestic patients with damage to the hippocampus, but an intact amygdala, show increased skin conductance response (SCR) during fear conditioning paradigms despite their inability to explicitly report the CS-UCS contingency (Fried, MacDonald, & Wilson, 1997). In contrast, patients with damage to the amygdala demonstrate awareness of the CS+-UCS contingencies but fail to show elevated physiological arousal when presented only with the CS+ (Phelps, 2006). Finally, a study in war veterans found that damaged amygdala was associated with reduced levels of fear symptoms manifested in post-traumatic stress disorders (Koenigs et al., 2008). fMRI studies examining amygdala activation during fear conditioning paradigms have found increased amygdala activation to CS+ relative to the CS − during fear acquisition (Buchel, Dolan, Armony, & Friston, 1999; LaBar et al., 1998; Sehlmeyer et al., 2009). Taken together, lesion studies and brain imaging studies in humans

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converge with data from animal models demonstrating the conserved functionality of the amygdala in fear conditioning across species.

Some have suggested that early in life, the amygdala plays an even stronger role in fear learning (LaBar et al., 1998). For example, human amygdala lesions early in life impair the processing of fearful facial expression (Adolphs, Tranel, Damasio, & Damasio, 1994; Shaw et al., 2005) more strongly than similar lesions occurring later in life (Hamann & Adolphs, 1999; Shaw et al., 2005). These findings may allude to the role of the amygdala in learning during development, a role that diminishes once these associations have been created (Tottenham, Hare, & Casey, 2009).

To date, only one fMRI study has been published examining adolescent fear circuitry during fear conditioning (Lau et al., 2011; see Table 1). This study found that adolescents were more likely than adults to recruit early-maturing subcortical regions (i.e., amygdala and hippocampus) when discriminating CS+ and CS−. In addition, only adults' engagement of late-maturing prefrontal cortex regions (i.e., dorsolateral prefrontal cortex) correlated positively with fear ratings during the task. These findings may imply that shifts between the development of subcortical and prefrontal regions may account for age-related differences in CS+/CS− discrimination.

In addition to the amygdala, a recent review of fMRI and PET imaging studies on human fear conditioning suggests that the insula and the anterior cingulate (ACC) are implicated in fear conditioning independent of the specific fear conditioning paradigm used (Sehlmeyer et al., 2009). The hippocampus, cerebellum, thalamus, striatum, and sensory cortices have also been associated with fear conditioning. Heterogeneity in neuroimaging results across studies is not surprising given the vast methodological differences in conditioning paradigms, contingency rate, the type of CS and UCS used, and the outcome measures indicating successful fear conditioning (for review see Sehlmeyer et al., 2009).

3.2.2. Extinction—Although the amygdala is most know for its role in fear conditioning, several studies examining extinction have demonstrated increased amygdala activation to CS-no UCS association (Knight, Smith, Cheng, Stein, & Helmstetter, 2004; LaBar et al., 1998; Milad et al., 2007). For instance, successful fear extinction has been found to be correlated with increased amygdala activation (Phelps et al., 2004). Additionally, other data suggest that specific activation of the lateral amygdala and the orbitofrontal cortex during extinction may be subserved by the modulation of the amygdala-orbitofrontal circuitry in the expression of fear responses (Gottfried & Dolan, 2004). A large body of human studies has implicated the medial prefrontal cortex (mPFC) including the anterior cingulate cortex (ACC) in extinction learning (Gottfried & Dolan, 2004; Phelps et al., 2004). Similarly, findings from neuroimaging studies have shown a significant increase in vmPFC activation during extinction recall (Kalisch et al., 2006), as well as a positive correlation between signal change in vmPFC activation and degree of extinction retention (Milad et al., 2007). Further evidence from structural imaging indicates that vmPFC thickness is correlated with extinction recall (Hartley, Fischl, & Phelps, 2011; Milad et al., 2005). These data allude to the similar function of the human vmPFC and the rodent infra-limbic cortex in fear extinction (Milad & Quirk, 2012).

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Finally, these studies have also implicated the hippocampus in contextual extinction learning in humans (Kalisch et al., 2006; Milad et al., 2007). More recently, connectivity between dorsal anterior cingulate cortex (dACC), left posterior hippocampus, and right amygdala was exhibited during extinction (Lang et al., 2009). As a result, the interaction between the mPFC and the hippocampus may reflect context-specificity of extinction learning.

4. Fear conditioning and extinction studies in children and adolescents

One of the first documented classical conditioning studies in infants was conducted by Watson and Rayner (1920). In their early studies, they demonstrated that fear can be learned through conditioning presented through repeated pairings of a neutral stimulus (e.g., white rat) with a loud noise (Watson & Rayner, 1920). In another study, 12 full-term infants as young as 3 months of age showed greater response magnitude to the CS+ compared to the CS− as indexed by skin conductance response (SCR) (Ingram & Fitzgerald, 1974). Results from these studies were among the first to demonstrate the effects of simple fear conditioning in infants at early stages of development.

While in the past decade there has been a rekindling of interest in research examining the emergence of fear conditioning in children, there are still relatively few fear conditioning studies in child and adolescent populations. Following these early studies on fear conditioning in children, research in this field has been hindered by ethical and methodological considerations. Questions in regard to the aversive nature of the UCS required to produce fear responses in developmental populations or the appropriate measures of fear conditioning and extinction, have always been an integral part in the scientific effort to study fear conditioning developmentally. In the following sections, we will review the most commonly used UCS and CR in these fear conditioning studies, after which we will summarize the major findings for fear conditioning and extinction in children and adolescents. A summary of sixteen fear conditioning studies conducted in normative and anxious samples of children and adolescents using a discrimination fear conditioning paradigm is presented in Table 1.

4.1. Unconditional stimuli (UCS)

Successful fear conditioning and fear extinction in humans and rodents is highly dependent on the selection of a strong, potent, and biologically relevant UCS, usually electric shock (Britton, Lissek, Grillon, Norcross, & Pine, 2011; Neumann & Waters, 2006). However, electrical shock presents the risk of causing pain or increased levels of anxiety and generally cannot be used with child populations (Neumann, Waters, & Westbury, 2008; Neumann, Waters, Westbury, & Henry, 2008; Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009). As a result, one of the major limitations in examining fear conditioning in children is the selection of a developmentally appropriate UCS while still preserving its potency and novelty.

As described in Table 1, 6 out of the 16 studies used ecologically valid UCS such as loud car horns (Block, Sersen, & Wortis, 1970), loud sounds of metal jangling objects (Gao, Raine, Venables, Dawson, & Mednick, 2010), aversive noises (e.g., metal scraping on slate) (Neumann, Waters, & Westbury, 2008; Neumann, Waters, Westbury, et al., 2008), and negatively-associated comments (Haddad, Lissek, Pine, & Lau, 2011). The use of one

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specific ecologically valid UCS (e.g., a 83 dB sound of a three-pronged garden tool being scraped across slate) yielded reliable fear acquisition and extinction effects across 8–11 year old children (Neumann, Waters, Westbury, et al., 2008), 13–17 year old adolescents (Neumann, Waters, & Westbury, 2008), and adults (Neumann & Waters, 2006). Five studies used stimuli such as pure tones (1000 Hz) or tones combined with white noise (105–110 dB), in various duration ranging from 200 ms to 4000 ms (Craske et al., 2008; Liberman, Lipp, Spence, & March, 2006; Pliszka, Hatch, Borcherding, & Rogeness, 1993; Waters, Henry, & Neumann, 2009). One potent fear conditioning paradigm that was tested successfully with children and adolescents used social stimuli (images of human faces) paired with an aversive scream (Britton et al., 2013; Glenn, Klein, et al., 2012; Lau et al., 2011, 2008). This UCS was found to be comparable to an alarm, a loud tone, and white noise as measured by subjective self-report (Britton et al., 2011). Further, a recent study found that although subjects reported shock to be more aversive than the “screaming lady”, both paradigms yielded similar differential conditioning effects as evidenced by larger FPS magnitudes to the CS+ relative to the CS− (Glenn, Lieberman, & Hajcak, 2012).

4.2. Conditioned response (CR)

Various methodologies have been used to measure CR in fear conditioning paradigms. In human studies, fear acquisition is often indexed using implicit measures of physiological arousal, such as skin conductance response (SCR) and fear potentiated startle (FPS). Additionally, most studies with human subjects use explicit self-reported measures of fear and anxiety levels. As shown in Table 1, SCR (***n*** = 11) and self-report (***n*** = 11) are used with similar frequency to measure CR, where the majority of studies use more than one dependent variable. Studies in children show that both SCR and self-report are reliable measures of fear conditioning during fear acquisition (Britton et al., 2013; Gao et al., 2010; Lau et al., 2011; Morrow, Boring, Keough, & Haesly, 1969; Neumann, Waters, Westbury, et al., 2008).

Although self-reported measures are common in the adult literature, the use of self-report in younger children raises concerns regarding whether children are able to provide reliable explicit judgments concerning CS-UCS contingencies. Thus, the addition of physiological measures may provide converging information regarding differences among autonomic and subjective measures of learning. Nevertheless, it is important to highlight that the overall physiological measures may also reflect changes in both physiology and brain regions as a function of age. For instance, one possible account for SCR differences in fear conditioning may result from sweat physiology across various developmental periods (e.g., childhood vs. puberty); however, difference between CS+ and CS−should not be affected.

To date, very few developmental studies have reported using FPS (***n*** = 4), EKG (***n*** = 2), or fMRI (***n*** = 2) in conjunction with either SCR or self-report. In particular, the use of FPS as a measure of CR is advantageous in that it is able to capture cross-species (e.g., human and non-human animals) physiological responses to valence-specific states (Grillon, Ameli, Woods, Merikangas, & Davis, 1991). While the inclusion of multiple psychophysiological measures may hinder the feasibility of fear conditioning studies in children, findings from these studies can provide converging evidence on the interplay between different autonomic

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measures of fear conditioning. In summary, SCR and self-report are the most widely used measures in fear conditioning studies with children. However, more studies are needed to determine how these measures are related to the developmental processes involved in the emergence of fear conditioning in children.

4.3. Fear conditioning

Across all fear conditioning studies (see Table 1), pediatric samples (healthy and anxious) show differential fear conditioning to the CS+ relative to the CS− (i.e., discrimination paradigm) as indexed by psychophysiological measures and/or subjective ratings. Results from these studies show that fear acquisition is present in typically developing children as early as 2 years of age (Ingram & Fitzgerald, 1974) with older children showing increased CR (e.g., CS+ > CS−) compared to younger children (Gao et al., 2010; Glenn, Klein, et al., 2012). More specifically, children between the ages of 5 and 6 years show 36% greater stimulus discrimination between CS+ and CS− in a fear conditioning task compared to younger children (2–4 year olds)(Block et al., 1970), as well as differences in SCR, particularly in response to the onset and absence of CS+ (Gao et al., 2010).

Differences in fear conditioning and associated behaviors may be a function of changes in the brain networks subserving fear conditioning that occur across development (Lau et al., 2011). In one study, adolescents (10–17 year olds) subjectively reported less differential fear, suggesting reduced discrimination between the CS+ and the CS− compared to adults (18–50 year olds)(Lau et al., 2011). In addition, imaging data allude to neural differences underlying the recruitment of brain regions in adolescents and adults. Lau et al. (2011) propose that subcortical regions (e.g., amygdala and hippocampus) play a large role in fear conditioning in adolescents; however with cortical maturity, adults showed greater recruitment of regions in the prefrontal cortex (e.g., dlPFC) during differential learning.

The six studies comparing anxious and non-anxious children have yielded mixed findings regarding differences in fear conditioning. Results based on subjective ratings showed that anxious children rated the CS+ as more unpleasant than the CS−; whereas, non-anxious children did not report differences in CS ratings during fear acquisition (Craske et al., 2008; Waters et al., 2009). However, in a different study, both anxious and non-anxious children showed differential learning to the CS+ and CS−, although anxious children reported greater overall fear ratings to CS+ (Britton et al., 2013; Lau et al., 2008). Yet in another study, anxious children failed to report differential learning to the CS-UCS contingency (i.e., no differences between CS+ and CS−) while non-anxious children reported expected learning effects (Liberman et al., 2006).

Given the variability in the selection of UCS across studies, it may be possible that these methodological differences produced inconsistencies in CR magnitudes rather than capture developmental processes in fear conditioning. For example, it is unclear whether disparities among adolescents and adults in fear conditioning (Pattwell et al., 2012) result from cortical maturation or, if these differences stem from variability in the aversive properties of the UCS (e.g., loud sounds vs. shock) (Pine et al., 2001). The UCS potency (e.g., weak vs. strong UCS) may also explain variability in fear conditioning studies (Britton et al., 2011). While some studies use loud sounds as the UCS, the potency of the stimulus (i.e., sound

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pressure levels) varies across paradigms. For instance, two separate studies used a 1000 Hz pure tone as the UCS but in one study it was administered at 107 dB for 1 s (Craske et al., 2008) while in another study it was presented at 105 dB for 500 ms (Liberman et al., 2006). Another example of this issue can be exemplified in studies using the fearful face and scream as the UCS where audio stimuli have been presented at 80 dB (Glenn, Klein, et al., 2012), 90 dB (Lau et al., 2011), and 95 dB (Lau et al., 2008; Britton et al., 2013). Therefore, the aversive properties of the UCS can ultimately impact the magnitude of the CR and the degree of fear conditioning across paradigms using different UCS.

Despite the differences in UCS, the aforementioned studies demonstrate that children are generally capable of fear conditioning from an early age. Nevertheless, some debate in the literature exists in regard to the comparability of evaluative measures of the CSs, expectancy learning, contingency awareness, and subjective fear ratings (For review based on human adult literature see Lissek et al., 2005). Finally, it is still unclear how these processes may be related to the vast neural changes associated with this period of development and whether differences in fear conditioning would emerge by using longitudinal designs.

4.4. Extinction

Numerous studies using self-report indicate that normative fears generally subside with age (Field & Davey, 2001). One possibility is that as children mature they are better able to extinguish previously learned associations thus resulting in more effective regulation of their emotions. As a result, developmental differences in the ability to extinguish fear may be more pronounced throughout childhood and adolescence (Pattwell et al., 2012). However, few studies examine the differences in extinction of learned fear behaviors in typically developing children. Four studies that examined fear extinction found expected patterns of extinction in paradigms that utilized geometric shapes (CS) and aversive tones (UCS) in both SCR and self-reported ratings (Neumann, Waters, & Westbury, 2008; Neumann, Waters, Westbury, et al., 2008). Extinction learning was less strong in paradigms that have used social stimuli such as affective faces (Haddad et al., 2011). In one study, adolescents were presented with gender and age matched photographs of neutral expressions (CS) that were followed by three socially-valenced UCS (e.g., happy face with auditory “you are nice”, angry face with auditory “I don’t like you”, and neutral face with auditory “I live in Bristol”) (Haddad et al., 2011). Extinction results showed less self-reported fear to negative CS+ relative to the neutral and positive CS+, although results did not return to pre-acquisition baseline levels. As evidenced in these findings, poor extinction of CR may be associated with social stimuli such as affective faces that unlike other stimuli used in fear conditioning paradigms could not be considered neutral (Britton et al., 2011, 2013; Pine et al., 2009).

Six studies compared anxious and non-anxious children in extinction. In 4 studies, anxious children showed resistance to within-session extinction as indicated by higher levels of CR to the CS+ than the CS− (Craske et al., 2008; Liberman et al., 2006; Pliszka et al., 1993; Waters et al., 2009). In another study both anxious and non-anxious children showed extinction (Britton et al., 2013), however in yet a different study both groups failed to show extinction (Lau et al., 2008). In addition, anxious children showed higher levels of fear to

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both CS+ and CS− relative to non-anxious children, as indicated by self-report (Britton et al., 2013) and SCR (Craske et al., 2008). Finally, some differences in brain activation were reported, with anxious children showing lower sub-genual anterior cingulate (sgACC) activation compare to their healthy counterpart while performing an extinction recall task (Britton et al., 2013).

Some studies have found inconsistencies between physiological results and subjective verbal ratings, primarily within anxious pediatric samples. For instance, one study reported discrepancies during initial phases of extinction between self-reported measures of UCS expectancies and physiological measures of SCR and FPS (Neumann, Waters, Westbury, et al., 2008). Findings have also revealed that anxious children show resistance to extinction, as measured by SCR, and no differences on self-reported measures of arousal relative to controls (Waters et al., 2009). Finally, Britton et al. (2013) found anxious adolescents report more fear to the CS+ and CS− during conditioning and extinction phases while no differences emerged in SCR or FPS when compared to non-anxious adolescents.

5. Insights for future developmental research on fear conditioning

There is a need for research on fear conditioning and extinction processes in children to gain additional understanding of the underlying behavioral, physiological, and neural mechanisms associated with normative and pathological fear learning across development. The majority of studies conducted on this topic have primarily focused on fear conditioning and extinction during late childhood and adolescence but rarely have they focused on infancy or early childhood. Given the developmental changes children undergo throughout these crucial periods, behavioral and neural differences in fear conditioning and extinction are expected to emerge as a function of age. A translational developmental neuroscience approach is particularly advantageous given the strong behavioral and neurological conservation of underlying fear circuits and learning processes across human and nonhuman species. The use of well-controlled fear conditioning paradigms may offer insights into these developmental trajectories by enabling a systematic examination of basic fear related mechanisms and associative learning processes.

Research in animal models conducted in parallel with human studies has identified developmental differences among cortical and subcortical brain regions at certain ages. Findings from these studies indicate that the neural circuits underlying fear conditioning and fear extinction are mediated by different brain regions. In addition, changes in functional connectivity among different brain regions are also expected to change with age and thereby to affect behavior (Gee et al., 2013; Guyer et al., 2008; Kim, Hamlin, & Richardson, 2009). And indeed, fear conditioning emerges early in development but extinction, in particular the ability to retrieve extinction memory, emerges later in development. These results highlight the need for further translational work that will examine the emergence of these learning processes in human children, adolescents, and adults via cross-sectional and longitudinal designs.

Fear conditioning can be an adaptive and beneficial form of associative learning that aids in signaling the presence of a danger. However, this form of learning can become a source of

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pathology when fear becomes pervasive and interferes with normal functioning. In particular, perturbations in fear learning can occur when fear conditioned responses are triggered in the absence of the CS-UCS contingency (Lissek et al., 2005). In recent years research on information processing in anxiety shifted its focus from fear conditioning to fear extinction processes. Specifically, pathological anxiety involves deficient capacity to recognize safe cues, particularly ones that closely resemble threat cues (Lissek, 2012; Lissek et al., 2005).

Anxiety disorders are among the most prevalent forms of childhood psychopathology (Verhulst, van der Ende, Ferdinand, & Kasius, 1997). While some anxiety disorders are transient throughout development, recent studies suggest that pediatric anxiety disorders commonly persist into adulthood (Bruce et al., 2005; Hasler et al., 2005; Perkonigg et al., 2005). Because anxiety disorders are costly and debilitating conditions that are very often associated with other severe psychopathology (Achenbach, 1995; Pine, Cohen, Gurley, Brook, & Ma, 1998), there is an imperative need to identify early risk and resilience factors that moderate pediatric anxiety to chronic illness. For example, exposure therapy which is one of the most effective treatment for pediatric and adults anxiety disorders relies heavily on extinction learning processes mediated by the vmPFC. Based on the available data reviewed in the paper, future research should focus primarily on differences in extinction, extinction recall, and children's ability to differentiate between threatening and non-threatening stimuli (i.e., danger vs. safety) as potential targets for prevention and treatment strategies. The increasing learning capabilities along with the brain plasticity that occurs throughout early development provide a unique opportunity to alter anxiety trajectories and prevent long-term psychiatric morbidity.

References

Achenbach TM. Diagnosis, assessment, and comorbidity in psychosocial treatment research. Journal of Abnormal Child Psychology. 1995; 23(1):45–65. [PubMed: 7759674]

Adolphs R, Tranel D, Damasio H, Damasio A. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature. 1994; 372(6507):669–672. [PubMed: 7990957]

Alvarez RP, Biggs A, Chen G, Pine DS, Grillon C. Contextual fear conditioning in humans: Cortical-hippocampal and amygdala contributions. Journal of Neuroscience. 2008; 28(24):6211–6219. [PubMed: 18550763]

Block JD, Sersen EA, Wortis J. Cardiac classical conditioning and reversal in mongoloid, encephalopathic, and normal child. Child Development. 1970; 41(3):771–785.

Bouton ME. Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. Biological Psychiatry. 2002; 52(10):976–986. [PubMed: 12437938]

Bouton ME. Context and behavioral processes in extinction. Learning and Memory. 2004; 11(5):485–494. [PubMed: 15466298]

Britton JC, Lissek S, Grillon C, Norcross MA, Pine DS. Development of anxiety: The role of threat appraisal and fear learning. Depression and Anxiety. 2011; 28(1):5–17. [PubMed: 20734364]

Britton JC, Grillon C, Lissek S, Norcross M, Szuhany KL, Chen G, et al. Response to learned threat: An fMRI study in adolescent and adult anxiety. American Journal of Psychiatry. 2013; 170(10): 1198–1204.

Bruce SE, Yonkers KA, Otto MW, Eisen JL, Weisberg RB, Pagano M, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic

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disorder: A 12-year prospective study. American Journal of Psychiatry. 2005; 162(6):1179–1187. [PubMed: 15930067]

Buchel C, Dolan RJ. Classical fear conditioning in functional neuroimaging. Current Opinion in Neurobiology. 2000; 10(2):219–223. [PubMed: 10753800]

Buchel C, Dolan RJ, Armony JL, Friston KJ. Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. Journal of Neuroscience. 1999; 19(24):10869–10876. [PubMed: 10594068]

Casey BJ, Durston S. From behavior to cognition to the brain and back: What have we learned from functional imaging studies of attention deficit hyperactivity disorder? American Journal of Psychiatry. 2006; 163(6):957–960. [PubMed: 16741192]

Chhatwal JP, Myers KM, Ressler KJ, Davis M. Regulation of gephyrin and GABAA receptor binding within the amygdala after fear acquisition and extinction. Journal of Neuroscience. 2005; 25(2): 502–506. [PubMed: 15647495]

Corcoran KA, Maren S. Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction. Journal of Neuroscience. 2001; 21(5):1720–1726. [PubMed: 11222661]

Corcoran KA, Maren S. Factors regulating the effects of hippocampal inactivation on renewal of conditional fear after extinction. Learning and Memory. 2004; 11(5):598–603. [PubMed: 15466314]

Corcoran KA, Quirk GJ. Activity in prelimbic cortex is necessary for the expression of learned, but not innate, fears. Journal of Neuroscience. 2007; 27(4):840–844. [PubMed: 17251424]

Corcoran KA, Desmond TJ, Frey KA, Maren S. Hippocampal inactivation disrupts the acquisition and contextual encoding of fear extinction. Journal of Neuroscience. 2005; 25(39):8978–8987. [PubMed: 16192388]

Costafreda SG, Brammer MJ, David AS, Fu CH. Predictors of amygdala activation during the processing of emotional stimuli: A meta-analysis of 385 PET and fMRI studies. Brain Research Reviews. 2008; 58(1):57–70. [PubMed: 18076995]

Craske MG, Waters AM, Lindsey Bergman R, Naliboff B, Lipp OV, Negoro H, et al. Is aversive learning a marker of risk for anxiety disorders in children? Behaviour Research and Therapy. 2008; 46(8):954–967. [PubMed: 18539262]

Delamater AR. Experimental extinction in Pavlovian conditioning: Behavioural and neuroscience perspectives. Quarterly Journal of Experimental Psychology. B, Comparative and Physiological Psychology. 2004; 57(2):97–132. [PubMed: 15204112]

Delgado MR, Olsson A, Phelps EA. Extending animal models of fear conditioning to humans. Biological Psychology. 2006; 73(1):39–48. [PubMed: 16472906]

Field, AP.; Davey, GCL. Conditioning models of childhood anxiety. In: Silverman, WK.; Treffers, PA., editors. Anxiety disorders in children and adolescents: Research, assessment and intervention. Cambridge: Cambridge University Press; 2001. p. 187-211.

Fried I, MacDonald KA, Wilson CL. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. Neuron. 1997; 18(5):753–765. [PubMed: 9182800]

Gao Y, Raine A, Venables PH, Dawson ME, Mednick SA. The development of skin conductance fear conditioning in children from ages 3 to 8 years. Developmental Science. 2010; 13(1):201–212. [PubMed: 20121876]

Gee DG, Humphreys KL, Flannery J, Goff B, Telzer EH, Shapiro M, et al. A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. Journal of Neuroscience. 2013; 33(10):4584–4593. [PubMed: 23467374]

Glenn CR, Klein DN, Lissek S, Britton JC, Pine DS, Hajcak G. The development of fear learning and generalization in 8–13 year-olds. Developmental Psychobiology. 2012; 54(7):675–684. [PubMed: 22072276]

Glenn CR, Lieberman L, Hajcak G. Comparing electric shock and a fearful screaming face as unconditioned stimuli for fear learning. International Journal of Psychophysiology. 2012; 86(3): 214–219. [PubMed: 23007035]

Gogolla N, Caroni P, Luthi A, Herry C. Perineuronal nets protect fear memories from erasure. Science. 2009; 325(5945):1258–1261. [PubMed: 19729657]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Gottfried JA, Dolan RJ. Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. Nature Neuroscience. 2004; 7(10):1144–1152. [PubMed: 15361879]

Grillon C, Ameli R, Woods SW, Merikangas K, Davis M. Fear-potentiated startle in humans: Effects of anticipatory anxiety on the acoustic blink reflex. Psychophysiology. 1991; 28(5):588–595. [PubMed: 1758934]

Guyer AE, Monk CS, McClure-Tone EB, Nelson EE, Roberson-Nay R, Adler AD, et al. A developmental examination of amygdala response to facial expressions. Journal of Cognitive Neuroscience. 2008; 20(9):1565–1582. [PubMed: 18345988]

Haddad AD, Lissek S, Pine DS, Lau JY. How do social fears in adolescence develop? Fear conditioning shapes attention orienting to social threat cues. Cognition & Emotion. 2011; 25(6): 1139–1147. [PubMed: 21895575]

Hamann SB, Adolphs R. Normal recognition of emotional similarity between facial expressions following bilateral amygdala damage. Neuropsychologia. 1999; 37(10):1135–1141. [PubMed: 10509835]

Harris JA, Westbrook RF. Evidence that GABA transmission mediates context-specific extinction of learned fear. Psychopharmacology. 1998; 140(1):105–115. [PubMed: 9862409]

Hartley CA, Fischl B, Phelps EA. Brain structure correlates of individual differences in the acquisition and inhibition of conditioned fear. Cerebral Cortex. 2011; 21(9):1954–1962. [PubMed: 21263037]

Hasler G, Lissek S, Ajdacic V, Milos G, Gamma A, Eich D, et al. Major depression predicts an increase in long-term body weight variability in young adults. Obesity Research. 2005; 13(11): 1991–1998. [PubMed: 16339131]

Ingram E, Fitzgerald HE. Individual differences in infant orienting and autonomic conditioning. Developmental Psychobiology. 1974; 7(4):359–367. [PubMed: 4425337]

Kalisch R, Korenfeld E, Stephan KE, Weiskopf N, Seymour B, Dolan RJ. Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. Journal of Neuroscience. 2006; 26(37):9503–9511. [PubMed: 16971534]

Kim JH, Richardson R. A developmental dissociation in reinstatement of an extinguished fear response in rats. Neurobiology of Learning and Memory. 2007a; 88(1):48–57. [PubMed: 17459734]

Kim JH, Richardson R. A developmental dissociation of context and GABA effects on extinguished fear in rats. Behavioral Neuroscience. 2007b; 121(1):131–139. [PubMed: 17324057]

Kim JH, Richardson R. The effect of temporary amygdala inactivation on extinction and reextinction of fear in the developing rat: Unlearning as a potential mechanism for extinction early in development. Journal of Neuroscience. 2008; 28(6):1282–1290. [PubMed: 18256248]

Kim JH, Richardson R. New findings on extinction of conditioned fear early in development: Theoretical and clinical implications. Biological Psychiatry. 2010; 67(4):297–303. [PubMed: 19846065]

Kim JH, Hamlin AS, Richardson R. Fear extinction across development: The involvement of the medial prefrontal cortex as assessed by temporary inactivation and immunohistochemistry. Journal of Neuroscience. 2009; 29(35):10802–10808. [PubMed: 19726637]

Kim JH, Li S, Richardson R. Immunohistochemical analyses of long-term extinction of conditioned fear in adolescent rats. Cerebral Cortex. 2011; 21(3):530–538. [PubMed: 20576926]

Knight DC, Smith CN, Cheng DT, Stein EA, Helmstetter FJ. Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. Cognitive, Affective, & Behavioral Neuroscience. 2004; 4(3):317–325.

Koenigs M, Huey ED, Raymont V, Cheon B, Solomon J, Wassermann EM, et al. Focal brain damage protects against post-traumatic stress disorder in combat veterans. Nature Neuroscience. 2008; 11(2):232–237. [PubMed: 18157125]

LaBar KS, LeDoux JE, Spencer DD, Phelps EA. Impaired fear conditioning following unilateral temporal lobectomy in humans. Journal of Neuroscience. 1995; 15(10):6846–6855. [PubMed: 7472442]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. Neuron. 1998; 20(5):937–945. [PubMed: 9620698]

Landers MS, Sullivan RM. The development and neurobiology of infant attachment and fear. Developmental Neuroscience. 2012; 34(2–3):101–114. [PubMed: 22571921]

Lang S, Kroll A, Lipinski SJ, Wessa M, Ridder S, Christmann C, et al. Context conditioning and extinction in humans: Differential contribution of the hippocampus, amygdala and prefrontal cortex. European Journal of Neuroscience. 2009; 29(4):823–832. [PubMed: 19200075]

Langton JM, Kim JH, Nicholas J, Richardson R. The effect of the NMDA receptor antagonist MK-801 on the acquisition and extinction of learned fear in the developing rat. Learning and Memory. 2007; 14(10):665–668. [PubMed: 17909101]

Lattal KM, Radulovic J, Lukowiak K. Extinction: [corrected] Does it or doesn't it? The requirement of altered gene activity and new protein synthesis. Biological Psychiatry. 2006; 60(4):344–351. [PubMed: 16919523]

Lau JY, Lissek S, Nelson EE, Lee Y, Roberson-Nay R, Poeth K, et al. Fear conditioning in adolescents with anxiety disorders: Results from a novel experimental paradigm. Journal of the American Academy of Child and Adolescent Psychiatry. 2008; 47(1):94–102. [PubMed: 18174830]

Lau JY, Britton JC, Nelson EE, Angold A, Ernst M, Goldwin M, et al. Distinct neural signatures of threat learning in adolescents and adults. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108(11):4500–4505. [PubMed: 21368210]

Laurent V, Marchand AR, Westbrook RF. The basolateral amygdala is necessary for learning but not relearning extinction of context conditioned fear. Learning and Memory. 2008; 15(5):304–314. [PubMed: 18463174]

Lebron K, Milad MR, Quirk GJ. Delayed recall of fear extinction in rats with lesions of ventral medial prefrontal cortex. Learning and Memory. 2004; 11(5):544–548. [PubMed: 15466306]

LeDoux JE. Emotion circuits in the brain. Annual Review of Neuroscience. 2000; 23:155–184.

Liberman LC, Lipp OV, Spence SH, March S. Evidence for retarded extinction of aversive learning in anxious children. Behaviour Research and Therapy. 2006; 44(10):1491–1502. [PubMed: 16360117]

Lissek S. Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: The case for conditioned overgeneralization. Depression and Anxiety. 2012; 29(4):257–263. [PubMed: 22447565]

Lissek S, Powers AS, McClure EB, Phelps EA, Woldehawariat G, Grillon C, et al. Classical fear conditioning in the anxiety disorders: A meta-analysis. Behaviour Research and Therapy. 2005; 43(11):1391–1424. [PubMed: 15885654]

Maren S. Seeking a spotless mind: Extinction, deconsolidation, and erasure of fear memory. Neuron. 2011; 70(5):830–845. [PubMed: 21658578]

McCallum J, Kim JH, Richardson R. Impaired extinction retention in adolescent rats: Effects of D-cycloserine. Neuropsychopharmacology. 2010; 35(10):2134–2142. [PubMed: 20592716]

Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: Ten years of progress. Annual Review of Psychology. 2012; 63:129–151.

Milad MR, Quinn BT, Pitman RK, Orr SP, Fischl B, Rauch SL. Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102(30):10706–10711. [PubMed: 16024728]

Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biological Psychiatry. 2007; 62(5):446–454. [PubMed: 17217927]

Miserendino MJ, Sananes CB, Melia KR, Davis M. Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. Nature. 1990; 345(6277):716–718. [PubMed: 1972778]

Moriceau S, Sullivan RM. Unique neural circuitry for neonatal olfactory learning. Journal of Neuroscience. 2004; 24(5):1182–1189. [PubMed: 14762136]

Morrow MC, Boring FW, Keough TE, Haesly RR. Differential Gsr conditioning as a function of age. Developmental Psychology. 1969; 1(4):299–302.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Neumann DL, Waters AM. The use of an unpleasant sound as an unconditional stimulus in a human aversive Pavlovian conditioning procedure. Biological Psychology. 2006; 73(2):175–185. [PubMed: 16698165]

Neumann DL, Waters AM, Westbury HR. The use of an unpleasant sound as the unconditional stimulus in aversive Pavlovian conditioning experiments that involve children and adolescent participants. Behavior Research Methods. 2008; 40(2):622–625. [PubMed: 18522074]

Neumann DL, Waters AM, Westbury HR, Henry J. The use of an unpleasant sound unconditional stimulus in an aversive conditioning procedure with 8- to 11-year-old children. Biological Psychology. 2008; 79(3):337–342. [PubMed: 18822341]

Pattwell SS, Duhoux S, Hartley CA, Johnson DC, Jing D, Elliott MD, et al. Altered fear learning across development in both mouse and human. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109(40):16318–16323. [PubMed: 22988092]

Pattwell SS, Casey BJ, Lee FS. The teenage brain: Altered fear in humans and mice. Current Directions in Psychological Science. 2013; 22(2):146–151. [PubMed: 25937708]

Perkonigg A, Pfister H, Stein MB, Hofler M, Lieb R, Maercker A, et al. Longitudinal course of posttraumatic stress disorder and posttraumatic stress disorder symptoms in a community sample of adolescents and young adults. American Journal of Psychiatry. 2005; 162(7):1320–1327. [PubMed: 15994715]

Phelps EA. Emotion and cognition: Insights from studies of the human amygdala. Annual Review of Psychology. 2006; 57:27–53.

Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: Role of the amygdala and vmPFC. Neuron. 2004; 43(6):897–905. [PubMed: 15363399]

Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Archives of General Psychiatry. 1998; 55(1):56–64. [PubMed: 9435761]

Pine DS, Helfinstein SM, Bar-Haim Y, Nelson E, Fox NA. Challenges in developing novel treatments for childhood disorders: Lessons from research on anxiety. Neuropsychopharmacology. 2009; 34(1):213–228. [PubMed: 18754004]

Pine DS, Fyer A, Grun J, Phelps EA, Szeszko PR, Koda V, et al. Methods for developmental studies of fear conditioning circuitry. Biol Psychiatry. 2001; 50(3):225–228. [PubMed: 11513822]

Pliszka SR, Hatch JP, Borcherding SH, Rogeness GA. Classical conditioning in children with attention deficit hyperactivity disorder (ADHD) and anxiety disorders: A test of Quay's model. Journal of Abnormal Child Psychology. 1993; 21(4):411–423. [PubMed: 8408987]

Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology. 2008; 33(1):56–72. [PubMed: 17882236]

Quirk GJ, Russo GK, Barron JL, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. Journal of Neuroscience. 2000; 20(16):6225–6231. [PubMed: 10934272]

Richardson, R.; Hunt, PS. Ontogeny of fear conditioning. In: Blumberg, MS.; Freeman, JH.; Robinson, SR., editors. Oxford handbook of developmental behavioral neuroscience. New York: Oxford University Press; 2010.

Royer S, Pare D. Bidirectional synaptic plasticity in intercalated amygdala neurons and the extinction of conditioned fear responses. Neuroscience. 2002; 115(2):455–462. [PubMed: 12421611]

Rudy JW, Morledge P. Ontogeny of contextual fear conditioning in rats: Implications for consolidation, infantile amnesia, and hippocampal system function. Behavioral Neuroscience. 1994; 108(2):227–234. [PubMed: 8037868]

Sehlmeyer C, Schöning S, Zwitserlood P, Pfleiderer B, Kircher T, Arolt V, et al. Human fear conditioning and extinction in neuroimaging: A systematic review. PLoS ONE. 2009; 4(6):e5865. [PubMed: 19517024]

Sergerie K, Chochol C, Armony JL. The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies. Neuroscience and Biobehavioral Reviews. 2008; 32(4):811–830. [PubMed: 18316124]

Shaw P, Bramham J, Lawrence EJ, Morris R, Baron-Cohen S, David AS. Differential effects of lesions of the amygdala and prefrontal cortex on recognizing facial expressions of complex emotions. Journal of Cognitive Neuroscience. 2005; 17(9):1410–1419. [PubMed: 16197694]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, et al. Neurodevelopmental trajectories of the human cerebral cortex. Journal of Neuroscience. 2008; 28(14):3586–3594. [PubMed: 18385317]

Sierra-Mercado D, Padilla-Coreano N, Quirk GJ. Dissociable roles of pre-limbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology. 2011; 36(2):529–538. [PubMed: 20962768]

Sotres-Bayon F, Quirk GJ. Prefrontal control of fear: More than just extinction. Current Opinion in Neurobiology. 2010; 20(2):231–235. [PubMed: 20303254]

Steinberg L. Cognitive and affective development in adolescence. Trends in Cognitive Sciences. 2005; 9(2):69–74. [PubMed: 15668099]

Storsve AB, Richardson R. A developmental dissociation in compound summation following extinction. Neurobiology of Learning and Memory. 2009; 92(1):80–88. [PubMed: 19445009]

Tottenham, N.; Hare, TA.; Casey, BJ. A developmental perspective on human amygdala function. In: Whalen, PJ.; Phelps, EA., editors. The human amygdala. New York: Guilford Press; 2009.

Verhulst FC, van der Ende J, Ferdinand RF, Kasius MC. The prevalence of DSM-III-R diagnoses in a national sample of Dutch adolescents. Archives of General Psychiatry. 1997; 54(4):329–336. [PubMed: 9107149]

Waters AM, Henry J, Neumann DL. Aversive Pavlovian conditioning in childhood anxiety disorders: Impaired response inhibition and resistance to extinction. Journal of Abnormal Psychology. 2009; 118(2):311–321. [PubMed: 19413406]

Watson JB, Rayner R. Conditioned emotional reactions. Journal of Experimental Psychology. 1920; 3:1–14.

Weike AI, Hamm AO, Schupp HT, Runge U, Schroeder HW, Kessler C. Fear conditioning following unilateral temporal lobectomy: Dissociation of conditioned startle potentiation and autonomic learning. Journal of Neuroscience. 2005; 25(48):11117–11124. [PubMed: 16319311]

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Table 1

Summary of developmental fear conditioning and extinction studies in healthy and anxious youth. The first part of the table reviews studies on healthy youth followed by studies examining anxious youth.

Authors	Dx	N	Age (years)	CS	UCS	DV	Pre-exposure		# of Trials			Main results
							CS	UCS	ACQ	EXT	ER	
Healthy youth												
Block et al. (1970)	Hv	77	2–11	400 Hz tone or 1000 Hz tone for 5 s (55 dB)	Loud sound for 1 s: auto horn (95 dB)	EKG	0	0	CS+:10 CS−:10	NA	NA	Two-to-4 year olds failed to display cardiac discrimination (i.e., lack of conditioning). Four-to-6 year olds showed partial evidence for conditioning. Six-to-11 year olds showed evidence for conditioning.
Gao et al. (2010)	Hv	200	3, 4, 5, 6, 8	1000 Hz or 500 Hz for 12.5 s (60 dB)	Loud sound for 4.5 s: white noise in tin can with metal jangling objects (95 dB)	SCR	Neutral tones: 6	0	CS+:9 CS−:3	NA	NA	Children as young as 3years old showed fear conditioning (CS+ > CS−). Differential SCR responses increased with age, particularly in 5–6 year olds.
Glenn, Klein, et al. (2012)	Hv	40	8–13	2 neutral female faces for 6 s	Fearful face (3 s) + scream for 1 s (80 dB)	FPS S.R.	CS+:4 CS−:4	0	CS+:8 CS−:8	0	CS+:8 CSCS−:8 GS:8	Self-report ratings revealed marginally significant differences from pre- to post-task (increase in CS + and decrease in CS−). During acquisition, FPS results revealed larger startle

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Authors	Dx	N	Age (years)	CS	UCS	DV	Pre-exposure		# of Trials			Main results
							CS	UCS	ACQ	EXT	ER	
												magnitudes (CS+ > CS
												magnitudes (CS+ > CS
												Older children were better able at discriminating threat from safety cues.
Haddad et al. (2011)	Hv	42	12–15	3 neutral faces for 3 s	CSnegative: angry face + criticism CSpositive: happy face + compliment CSneutral: neutral face + neutral comment for 2 s	S.R.	CSnegative:2 CSpositive:2 CSneutral:2	0	CS+:9 CS−:9 CS−:9	CS+:8 CS−:8 CS−:8	NA	Adolescents reported greater subjective fear to the CSnegative compared to CSpositive and CSneutral post-acquisition. After extinction, differences across CSs persisted with subjects reporting less pleasantness to CSnegative compared to CSpositive and CSneutral.
Lau et al. (2011)	Hv	Total:42 21 adolescents and 21 adults	***M***adolescents = 13.09 ***M***adults = 27.10	2 neutral female faces for 5 s	Fearful face for 3 s + scream for 1 s (90 dB)	SCR S.R.	CS+:8 CS−:8	0	CS+:10 CS−:10	NA	NA	During fear acquisition, all subjects showed greater SCR to the CS + than CS−; adolescents showed greater overall SCR than adults. All subjects reported greater subjective fear to the CS+ than CS−.
	Hv	Total:35 15 adolescents and 20 adults	10–17; 18–50	2 neutral female faces for 6 s	Fearful face + scream for 1.1 s (90 dB)	S.R. fMRI	CS+:3 CS−:3	0	CS+:60 CS−:60	NA	NA	Both groups showed differential learning (CS+

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Authors	Dx	N	Age (years)	CS	UCS	DV	Pre-exposure		# of Trials			Main results
							CS	UCS	ACQ	EXT	ER	
												> CS−), but adolescents re
												), but adolescents reported
												), but adolescents reported
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												), but adolescents reported
												Adolescents showed increased amygdala and hippocampal activation to the CS+ versus CS− trials than adults. Age differences were also found in subjective fear ratings of the CS− and dorsolateral prefrontal cortex (dlPFC) activation.
Morrow et al. (1969)	Hv	42	10–12; 19–21; 62–75	3 horizontally or 3 vertically arranged white lights for 5.1 s	Electric shock for 100 ms	SCR	CS+:4 CS−:4	3	CS+:20 CS−:20	NA	NA	Children and young adults showed increased SCR to the CS+ and overall decline to the CS− during conditioning. No learning differences were found between the age groups.
Neumann et al. (2008a)	Hv	15	13–17	2 geometric shapes for 8 s: diamond or triangle	Loud sound for 3 s: three-pronged garden fork	FPS SCR S.R.	0	0	CS+:8 CS−:8	CS+:8 CS−:8	NA	Adolescents showed fear conditioning (CS+ > CS−) and extinction

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Authors	Dx	N	Age (years)	CS	UCS	DV	Pre-exposure		# of Trials			Main results
							CS	UCS	ACQ	EXT	ER	
					scrapping slate (83 dB) scrapping slate (83 dB) scrapping slate (83 dB)							across all three DVs.
Neumann et al. (2008b)	Hv	16	8–11	Two geometric shapes for 8 s: white 10-cm square or black 30-cm square	Loud sound for 3 s: metal scrapping slate (83 dB)	SCR S.R.	CS+:2 CS−:2	0	CS+:12 CS−:12	CS+:12 CS−:12	NA	Eight-to-11-year olds showed fear acquisition (CS+ > CS−) and extinction as evidenced by SCR and self-report of arousal and unpleasantness.
Pattwell et al. (2012)	Hv	83	5–11; 12–17; 18–28	2 colored squares: blue or yellow presented for 3 s	White noise combined with 1000 Hz (85–107 dB) for 1 s	SCR	0	0	CS+:24 CS−:24	CS+:24 CS−:24	NA	Participants across all age groups showed differential fear learning (CS+ > CS−) during fear acquisition. Age differences emerged during extinction with adolescents showing dampened extinction compared to children and adults.
Anxious youth												
Britton et al. (2013)	Hv, GAD, SOC, SAD	Total:65 Hv:42 ANX:23	8–19	2 neutral female faces for 7–8 s	Fearful face + Scream for 1 s (95 dB)	FPS SCR S.R. fMRI	CS+:4 CS−:4	0	CS+:10 CS−:10	CS+:8 CS−:8	***M*** = 20 days CS+:1 CS−:1 GS:9	During acquisition and extinction, relative to healthy youth, anxious youth reported greater fear to both CSs. All groups showed similar fear conditioning (CS+ > CS−) and extinction across all three

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Authors	Dx	N	Age (years)	CS	UCS	DV	Pre-exposure		# of Trials			Main results
							CS	UCS	ACQ	EXT	ER	
												DVs. During extinction re displaying a U-shaped pattern of activation.
Craske et al. (2008)	Hv, SAD, PD, GAD, SOC	Total:49 Hv:11 ANX:23 At risk:15	7–12	4 geometric shapes for 8 s: trapezoid (CS+), triangle (CS−), circle, rectangle	1000 Hz pure tone for 1 s (107 dB)	SCR S.R.	CS+:1 CS−:1 Circle:1 Triangle: 1	0	CS+:8 CS−:8	CS+:4 CS−:4	***M*** = 12 days CS+:4 CS−:4	All groups showed conditioning effects (CS+ > CS−) reflected in SCR. During extinction and extinction recall, anxious children showed elevated levels of SCR to CS+ and CS− compared with non-anxious children. Anxious children showed resistance to within-session extinction and extinction

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Authors	Dx	N	Age (years)	CS	UCS	DV	Pre-exposure		# of Trials			Main results
							CS	UCS	ACQ	EXT	ER	
												retest at 2-week follow-up
												retest at 2-week follow-up
												retest at 2-week follow-up
Lau et al. (2008)	Hv GAD, SOC, SAD	Total:54 Hv:38 ANX:16	***M*** = 13.64	2 neutral female faces for 8 s	Fearful face + scream for 3 s (95 dB)	S.R.	CS+:4 CS−:4	0	CS+:16 CS−:16	CS+:3 CS−:3	***M*** = 16 days CS+:12 CS−:12	During acquisition, all subjects rated the CS+ as more fearful than CS−, however anxious adolescents' ratings to the CS+ were greater compared to healthy subjects. During extinction, both groups rated the CS+ as more aversive compare to the CS−, indicating stability even post-extinction.
Liberman et al. (2006)	Hv, SOC, GAD, SAD, SP	Total:83 Hv:30 ANX:53	7–14	4 neutral cartoons for 5 s: 4 cartoons during pre-exposure and 2 cartoons during acquisition (CS+ = 1; CS− = 1)	1000 Hz Pure tone for 500 ms (105 dB)	FPS SCR S.R.	CS+: 1 CS−: 1 Cartoons:2	0	CS+:6 CS−:6	CS+:8 CS−:8	NA	During acquisition, healthy children rated the CS+ as more arousing than CS−, but no differences were found in anxious children. After extinction, healthy children showed no differences in fear ratings between CS+ and CS− whereas anxious children rated

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Authors	Dx	N	Age (years)	CS	UCS	DV	Pre-exposure		# of Trials			Main results
							CS	UCS	ACQ	EXT	ER	
												the CS+ as more fearful th the CS+ as more fearful th the CS+ as more fearful th During acquisition, SCR and FPS did not reveal conditioning effects in both groups. However, anxious children showed increased FPS during extinction to the CS+ compare to the CS−, whereas healthy children showed no difference.
Pliszka et al. (1993)	Hv, ANX, ADHD	Total:56 Hv:22 ANX:11 ADHD:23	6–12	2 geometric shapes + tone for 4 s: red square + 1000 Hz tone or blue square + 500 Hz tone	White noise for 200 ms (110 dB)	SCR EKG	0	0	CS+:8 CS−:8	CS+:4 CS−:4	NA	During acquisition, subjects showed differential conditioning (CS+ > CS−) in both SCR and EKG, with no group differences. Extinction was observed only in EKG but not it SCR.
Waters et al. (2009)	Hv, SOC, GAD, SP	Total:35 Hv:18 ANX:17	8–12	4 geometric shapes for 8 s: CSs were trapezoid or triangle and two additional shapes of a circle and a rectangle	1000 Hz Pure tone for 1 s (107 dB)	SCR S.R.	CS+:1 CS−:1 Circle:1 rectangle:1	0	CS+:8 CS−:8	CS+:4 CS−:4	NA	Compared to healthy subjects, anxious children showed increased SCR to both CSs and reported the CS+ to be more arousing compared to the CS− during

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Authors	Dx	N	Age (years)	CS	UCS	DV	Pre-exposure		# of Trials			Main results
							CS	UCS	ACQ	EXT	ER	
												acquisition. At the extinct
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Note: All reported studies used a discrimination fear conditioning paradigm. Dx, disorder; Hv, healthy volunteers; ANX, anxiety disorder; ADHD, attention deficit hyperactivity disorder; SOC, social anxiety disorder; GAD, generalized anxiety disorder; SAD, separation anxiety disorder; SP, specific phobia; PD, panic disorder; ***N***, number of subjects; CS, conditioned stimuli; UCS, unconditioned stimulus; GS, generalization stimuli; DV, dependent variable; EKG, electrocardiogram; SCR, skin conductance response; S.R., self-report; FPS, fear potentiated startle; fMRI, functional magnetic resonance imaging; ACQ, acquisition phase; EXT, extinction phase; ER, extinction re-recall/test; NA, not applicable.

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