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Mechanisms Linking Childhood Adversity with Psychopathology: Learning as an Intervention Target

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Abstract

Exposure to childhood adversity is common and a powerful risk factor for many forms of psychopathology. In this opinion piece, we argue for greater translation of knowledge about the developmental processes that are influenced by childhood adversity into targeted interventions to prevent the onset of psychopathology. Existing evidence has consistently identified several neurodevelopmental pathways that serve as mechanisms linking adversity with psychopathology. We highlight three domains in which these mechanisms are well-established and point to clear targets for intervention: 1) threat-related social information processing biases; 2) heightened emotional reactivity and difficulties with emotion regulation; and 3) disruptions in reward processing. In contrast to these established pathways, knowledge of how childhood adversity influences emotional learning mechanisms, including fear and reward learning, is remarkably limited. We see the investigation of these mechanisms as a critical next step for the field that will not only advance understanding of developmental pathways linking childhood adversity with psychopathology, but also provide clear targets for behavioral interventions. Knowledge of the mechanisms linking childhood adversity with psychopathology has advanced rapidly, and the time has come to translate that knowledge into clinical interventions to prevent the onset of mental health problems in children who have experienced adversity.

Keywords

childhood adversity; early-life stress; learning; development; psychopathology; early intervention

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Exposure to childhood adversity is a potent risk factor for psychopathology in childhood, adolescence, and adulthood. Although prior research has identified a variety of developmental processes that are altered following exposure to adversity that increase risk for psychopathology, little progress has been made in translating those mechanisms into interventions to prevent psychopathology among children exposed to adversity. In addition, although emotional learning mechanisms are involved in the etiology and maintenance of many forms of psychopathology and represent the targets of the most effective behavioral interventions, remarkably little research has investigated how childhood adversity influences these learning mechanisms.

In this opinion piece, we argue for greater translation of knowledge about the developmental processes that are influenced by childhood adversity into interventions to prevent the onset of psychopathology. Existing evidence has converged on several neurodevelopmental pathways that serve as mechanisms linking adversity with psychopathology, and the time has come to translate that knowledge into interventions to prevent mental health problems in children who have experienced adversity. In addition, the investigation of basic learning mechanisms is a critical next step for the field that will not only advance understanding of developmental pathways linking childhood adversity with psychopathology, but also provide clear targets for behavioral interventions. We first review the existing literature on developmental mechanisms linking childhood adversity with psychopathology, and highlight interventions that could target these mechanisms. We highlight promising areas for future research on learning mechanisms and the value that greater understanding of these mechanisms would have for developing interventions to prevent psychopathology in children who have encountered adversity.

Defining Adversity

Here we use the term childhood adversity to refer to negative environmental experiences that are likely to require significant adaptation by an average child and that represent a deviation from the expectable environment (McLaughlin, 2016). Deviations from the expectable environment often reflect either the presence of an unexpected input that represents a threat to the physical integrity or well-being of the child (e.g., exposure to violence) or an absence of some type of expected input (e.g., the presence of a primary caregiver, exposure to complex language) (Humphreys & Zeanah, 2015; McLaughlin, Sheridan, & Lambert, 2014). Population- based studies show that these forms of childhood adversity are common, with approximately half of all children experiencing at least one form of adversity by the time they reach adulthood in the U.S. (Green, et al., 2010; McLaughlin, et al., 2012) and globally (Kessler, et al., 2010).

We conceptualize adversity as a multi-dimensional construct. Adversity can involve multiple underlying dimensions of experience that may have distinct associations with neuro-developmental processes (McLaughlin & Sheridan, 2016; McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014). Two such dimensions are *threat*, which encompasses experiences involving harm or threat of harm to the child, and *deprivation*, which involves an absence of expected inputs from the environment during development, such as support, nurturance, and cognitive and social stimulation. Many forms of adversity

involve threat of harm to the child, including physical and sexual abuse, witnessing domestic violence, and exposure to violence in the school or community. In contrast, deprivation involving low levels of social and cognitive stimulation is a core feature of neglect, institutional rearing, other forms of parental absence, and occurs more often in families with low socio-economic status (SES), though not universally (Bradley & Corwyn, 2002; Bradley, Corwyn, McAdoo, & Coll, 2001).

Childhood Adversity and Psychopathology

Exposure to childhood adversity is associated with many forms of psychopathology. Converging evidence from population-based and longitudinal studies indicates that children exposed to adversity are more likely to develop anxiety disorders, depression, externalizing problems, substance abuse, and psychosis than children who have never experienced adversity, and this risk increases as the degree of adversity increases (Fergusson, Horwood, & Lynskey, 1996; McGrath, et al., 2017; McLaughlin, et al., 2012). Heightened risk for psychopathology occurs not only in childhood and adolescence (McLaughlin, et al., 2012), but persists into adulthood (Clark, Caldwell, Power, & Stansfeld, 2010; Green, et al., 2010). Childhood adversity is also associated with heightened persistence and severity of mental disorders once they emerge and greater resistance to treatment (McLaughlin, Green, et al., 2010a, 2010b; Nanni, Uher, & Danese, 2012). Approximately one-third of all mental disorder onsets in the population are attributable to exposure to childhood adversity (Green, et al., 2010; Kessler, et al., 2010; McLaughlin, et al., 2012). These sobering findings underscore the importance of developing more effective early interventions for children exposed to adversity, which has driven a search for mechanisms linking these experiences with risk for psychopathology.

Developmental Processes Linking Adversity and Psychopathology

A growing body of research has identified neurodevelopmental mechanisms linking childhood adversity with risk for psychopathology. Existing work has focused largely on three domains: threat-related social information processing biases; altered patterns of emotional reactivity and emotion regulation; and reward processing. We briefly review prior work in these areas and highlight existing evidence-based interventions that could be used to target each of these mechanisms (Figure 1). Different underlying dimensions of environmental experience may have divergent influences on development, and understanding these distinct pathways is critical for identifying mechanisms linking adversity with psychopathology. Below, we highlight whether the developmental mechanisms identified in prior research have been observed broadly across multiple adversity types or are specific to a particular dimension of adverse experiences. We then examine the relevant learning mechanisms that are likely to play a role in the onset and persistence of psychopathology among children who have experienced adversity.

Threat-Related Social Information Processing Biases.

Altered patterns of social and emotional information processing that facilitate the rapid identification of environmental threats have consistently been observed among children who have experienced threat-related adversity, such as physical abuse or exposure to violence.

These biases include heightened perceptual sensitivity to anger, attention biases to threatening social information, and hostile attributions of neutral or ambiguous social situations. Specifically, children who have experienced violence require less perceptual information to identify anger in other people (Pollak, Cicchetti, Hornung, & Reed, 2000; Pollak & Sinha, 2002), classify a wider range of negative emotions as anger (Pollak & Kistler, 2002), and exhibit altered neural responses reflecting attentional allocation when viewing angry faces, but not other types of emotion, than children who have not experienced violence (Pollak & Tolley-Schell, 2003). Children exposed to violence also exhibit attention biases to threatening social information (Shackman & Pollak, 2014), including faster attentional engagement and slower disengagement from angry facial expressions (Pollak & Tolley-Schell, 2003; Shackman, Shackman, & Pollak, 2007). When presented with ambiguous social situations, children exposed to violence generate more hostile attributions about others' intentions and have greater difficulty identifying prosocial responses than children who have not experienced violence (Dodge, Bates, & Pettit, 1990; Dodge, Petit, Bates, & Valente, 1995).

Biases that facilitate threat identification can interfere with other aspects of information processing. For example, children who have experienced violence exhibit difficulties remembering contextual information in the presence of threat cues (Lambert, Sambrook, et al., 2017). This could contribute to psychopathology by making it difficult to discriminate between safe and dangerous environments, leading to fear even in safe contexts. Indeed, these threat- related information processing biases have been associated with risk for anxiety and post- traumatic stress disorder (PTSD) (Briggs-Gowan, et al., 2017; Shackman, et al., 2007). Hostile attribution biases predict the onset of externalizing psychopathology and mediate the link between violence exposure and externalizing problems (Dodge, et al., 1995; Shackman & Pollak, 2014; Weiss, Dodge, Bates, & Petit, 1992).

Biases in information processing that prioritize threat-related stimuli have generally not been observed among children exposed to deprivation. Children exposed to neglect do not exhibit perceptual sensitivity to anger, but rather have difficulty discriminating among different emotions (Pollak, et al., 2000). Attention biases towards threat have not been observed in children reared in deprived institutional settings early in life (Silvers, Goff, et al., 2016; Troller- Renfree, McDermott, Nelson, Zeanah, & Fox, 2015; Troller-Renfree, et al., 2016).

Proposed Translational Targets.—Attention-bias modification treatment (ABMT) explicitly targets the attentional biases towards threat that characterize anxiety. ABMT utilizes the dot probe task used to measure attention biases, but trains people to orient their attention *away* from threatening cues (e.g., angry faces) to a neutral or positive cue (Bar-Haim, 2010). This type of attention retraining leads to meaningful reductions in attention biases towards threat and symptoms of anxiety in both children and adults (Eldar, et al., 2012; See, MacLeod, & Bridle, 2009). Meta-analyses of ABMT demonstrates significant reductions in anxiety symptoms of small to medium effect size, with significant heterogeneity across studies (Cristea, Kok, & Cuijpers, 2015; Hakamata, et al., 2010). Because ABMT effects on anxiety are larger in samples that do not yet meet criteria for an anxiety disorder (Cristea, et al., 2015), this intervention may be more effective as a preventive approach than a treatment for anxiety. Given that attention biases towards threat

are common in children who have experienced trauma, ABMT is a potentially promising clinical approach to preventing the emergence of anxiety disorders in this group. To our knowledge, ABMT has not been evaluated in children who have experienced trauma, particularly as a preventive approach.

Intervention techniques have also been developed to target the threat-related social information processing biases commonly observed in children exposed to violence, such as hostile attributions and difficulty generating prosocial responses in ambiguous social situations. These techniques have been used in interventions designed to prevent the onset of externalizing problems, such as the Fast Track intervention (Conduct Problems Prevention Research Group, 1992). This intervention teaches social cognitive skills to prevent antisocial behavior and is effective at reducing hostile attributions, increasing socially competent responses, and reducing the valuation of aggression as an appropriate response; these changes in social information processing mediate intervention effects on antisocial behavior during adolescence (Dodge, Godwin, & The Conduct Problems Prevention Research Group, 2013). This type of social cognitive training has clear value as a target for intervention among children who have experienced trauma, many of whom exhibit these types of social information processing biases.

Emotional Reactivity and Regulation.

A consistently identified pattern among children who have experienced violence is heightened emotional reactivity to negative stimuli that could signal the presence of threat. Magnified emotional reactions to threat cues have been observed at multiple levels including physiological responses to laboratory-based stressors (Heleniak, McLaughlin, Ormel, & Riese, 2016; McLaughlin, Sheridan, Alves, & Mendes, 2014), trait-level measurements (Heleniak, Jenness, Van der Stoep, McCauley, & McLaughlin, 2016), affective responses to daily stressors (Glaser, van Os, Portegijs, & Myin-Germeys, 2006; Wichers, et al., 2009), and amygdala reactivity to threatening or negative cues (McCrory, et al., 2013; McCrory, et al., 2011; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). Similar patterns have also been observed in children exposed to deprivation, including institutional rearing (Gee, et al., 2013; Tottenham, et al., 2011), neglect (Maheu, et al., 2010), and poverty (Javanbakht, et al., 2015). Associations between child maltreatment and elevated amygdala reactivity have been confirmed in meta-analysis (Hein & Monk, 2016).

Children exposed to both threat and deprivation-related adversities also exhibit numerous difficulties with emotion regulation, including challenges with modulating emotional reactions (Kim & Cicchetti, 2010; McLaughlin, et al., 2015) and disengaging from negative emotional content (Lambert, King, Monahan, & McLaughlin, 2017; Marusak, Martin, Etkin, & Thomason, 2015; Tottenham, et al., 2010). Children exposed to trauma engage in high levels of maladaptive emotion regulation strategies, such as rumination (Heleniak, Jenness, et al., 2016; Heleniak, King, Monahan, & McLaughlin, 2018). Together, these findings suggest that heightened emotional reactivity and difficulties with emotion regulation are developmental processes impacted by multiple dimensions of adversity exposure, including both threat and deprivation.

Heightened emotional reactivity and difficulties with emotion regulation are transdiagnostic mechanisms that have strong links with both internalizing and externalizing problems (Aldao, Nolen-Hoeksema, & Schweizer, 2010), predict the onset of psychopathology in prospective studies (McLaughlin, Hatzenbuehler, Mennin, & Nolen-Hoeksema, 2011; Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013), and serve as a mechanisms linking multiple forms of adversity with the onset of psychopathology (Heleniak, Jenness, et al., 2016; Kim-Spoon, Cicchetti, & Rogosch, 2013; McLaughlin, Kubzansky, et al., 2010; Michl, et al., 2013). Heightened amygdala response to negative stimuli and difficulties with emotion regulation predict the onset of PTSD symptoms following a traumatic event (Jenness, et al., 2016; McLaughlin, Busso, et al., 2014) and increases in internalizing symptoms after stressful life events (Swartz, Knodt, Radtke, & Hariri, 2015). Together, these emotional processing pathways are clear mechanisms linking childhood adversity to psychopathology risk.

Proposed Translational Targets.—Heightened emotional reactivity and difficulties with emotion regulation are relatively non-specific mechanisms that manifest at multiple levels (i.e., affect, physiology, neural responses) and increase risk for psychopathology transdiagnostically. Numerous evidence-based treatments for youth psychopathology include elements that target these mechanisms. For example, trauma-focused cognitive behavior therapy (TF–CBT)—an empirically-supported treatment for children exposed to trauma (Dorsey, et al., 2017)—includes modules focused on relaxation, identifying and labeling emotions, and developing effective skills for modulating emotions (Cohen, Mannarino, & Deblinger, 2006). TF-CBT can be administered in an individual or group format and is effective with children as young as three years of age (Scheeringa, Weems, Cohen, Amaya-Jackson, & Guthrie, 2011). Perhaps most promising for early intervention, techniques targeting emotional reactivity and regulation feature prominently in recently developed transdiagnostic treatment approaches that are designed to flexibly and efficiently treat a wide range of internalizing and externalizing problems, such as the FIRST protocol developed by John Weisz and colleagues (2017). Training in calming skills (e.g., relaxation) and cognitive reappraisal represent core elements of the treatment designed to reduce emotional reactivity and improve emotion regulation skills. FIRST also includes elements, such as problem solving training, that may be effective at reducing social information processing biases common in children exposed to violence that predict externalizing problems.

Reward Processing.

Alterations in reward processing have frequently been observed among children exposed to deprivation, including institutional rearing and neglect. Children raised in institutions are less likely than children raised in families to modify their behavior in response to increasing values of a reward (Sheridan, et al., 2018). A similar pattern has been observed among maltreated children—defined as either abuse or neglect (Guyer, et al., 2006), and children who experienced food insecurity, a form of material deprivation (Dennison, et al., 2019), although not among adolescents or adults who experienced child abuse (Dennison, et al., 2016; Pechtel & Pizzagalli, 2013). These findings indicate that early deprivation is associated with reductions in approach motivation, or the regulation of behaviors that result in reward achievement. In addition, blunted response in the ventral striatum to reward

anticipation and receipt and positive social cues has been observed following both neglect and institutional rearing (Goff, et al., 2013; Hanson, Hariri, & Williamson, 2015; Mehta, et al., 2010), indicating reductions in reward responsiveness following deprivation. In contrast, adolescents exposed to abuse exhibit enhanced responses in the ventral striatum to positive social cues (Dennison, et al., 2016). Children exposed to deprivation associated with institutional rearing and food insecurity also exhibit reduced white matter integrity in fronto-striatal tracts (Bick, et al., 2015; Dennison, et al., 2019). Together, these findings indicate altered reward processing in children exposed to adversity, though the pattern varies across specific reward processes and adversity types.

Alterations in reward processing are associated with risk for depression. Low modulation of behavior based on prior reinforcement is a risk factor for depression in prospective studies (Forbes, Shaw, & Dahl, 2007; Pizzagalli, Jahn, & O'Shea, 2005). Differences in behavioral measures of approach motivation (Sheridan, et al., 2018), neural measures of reward responsiveness (Goff, et al., 2013; Hanson, et al., 2015), and structural measures of fronto-striatal connectivity (Bick, Fox, Zeanah, & Nelson, 2017; Dennison, et al., 2019; Fareri, et al., 2017) have all been identified as mechanisms linking early deprivation with depression.

Proposed Translational Targets.

Behavioral activation (BA) is an evidence-based treatment for depression that focuses on the importance of experiencing positive reinforcement to maintain normal mood (Dimidjian, et al., 2006; McCauley, et al., 2016). BA aims to increase engagement with personally meaningful sources of positive reinforcement to reduce anhedonia and withdrawal and increase motivation, activity, and feelings of mastery and pleasure. By increasing behaviors designed to achieve positive reinforcement that are often reduced among children exposed to deprivation, BA represents a potentially promising clinical approach for preventing depression in this group. In addition to BA, other approaches have been recently developed to target similar reward-related mechanisms. These include training in positive mental imagery (Linke & Wessa, 2017) and positivity training to alter approach-avoid tendencies (Becker, et al., 2016), which have produced improvements in reward sensitivity, motivation to pursue rewards, stress reactivity, and depression symptoms in adults. Although greater research is needed to evaluate these strategies in children, these strategies also represent promising approaches for targeting reward mechanisms in early interventions for children who have experienced adversity.

Although BA and positive mental imagery techniques target the specific reward processing mechanisms that have been demonstrated to be influenced by exposure to adversity, particularly deprivation, we are unaware of published research examining BA or other techniques designed to increase positive reinforcement with children who have experienced adversity. However, BA is currently being examined as a treatment for depression among adolescents exposed to maltreatment in a research study at the University of Washington led by Jessica Jenness in collaboration with the first author (KM) and Elizabeth McCauley. This study examines whether BA alters the reward processing mechanisms that are altered following adversity and associated with risk for depression. This ongoing study will provide important information about the feasibility of BA as an intervention approach for increasing

motivation to pursue rewards and reducing depression among children who have experienced adversity.

Learning Mechanisms

Although the intervention approaches reviewed above may have translational value, we argue that greater knowledge of emotional learning mechanisms influenced by childhood adversity is needed to stimulate progress in intervention development. These learning mechanisms represent a promising area for future research on childhood adversity and psychopathology for several reasons. First, an extensive literature in animal models demonstrates that early-life adversity produces enduring differences in both aversive and reward-based learning and underlying neurobiology (Patwell & Bath, 2017; Perry & Sullivan, 2014; Sasagawa, et al., 2017). Second, normative variation has been observed in emotional learning across development. Pronounced developmental differences in fear and reward learning processes and associated neurobiological mechanisms have been demonstrated in both animal and human studies (Bath, et al., 2012; Li, Kim, & Richardson, 2012; Patwell, et al., 2012). Finally, learning mechanisms represent the targets of behavioral interventions for many forms of psychopathology, including anxiety, depression, behavior problems, and substance abuse (Chorpita & Daleiden, 2009). These behavioral approaches represent some of our most effective approaches for treating psychopathology and can be leveraged to develop more effective early interventions once the underlying learning mechanisms involved are better understood.

Fear Learning.

Despite the therapeutic targeting of learning in clinical practice and the wide use of fear learning paradigms in animal models of early-life stress, surprisingly little research has examined how childhood adversity influences aversive learning in humans. Fear conditioning refers to the acquisition of a fear response after multiple pairings of a neutral conditioned stimulus (CS) with an aversive unconditioned stimulus (US). Differential conditioning involves two stimuli, one that is paired with the US (CS+) and one that is not (CS-); discrimination between conditioned threat and safety signals can be measured by comparing fear responses to the CS+ vs. CS-. Extinction occurs after repeated presentations of the CS+ without the aversive stimulus, forming a new association of the CS+ with an absence of threat.

Recent work using a classical differential fear conditioning and extinction paradigm has shown that children exposed to trauma show blunted skin conductance response (SCR) to the CS+ during conditioning and take longer than children without trauma histories to acquire a differential CS+ vs. CS- response, suggesting poor discrimination between threat and safety cues (McLaughlin, et al., 2016). This pattern of altered fear conditioning mediated the association between trauma and externalizing psychopathology. Another study used an escape-from-threat paradigm to examine the effects of institutional rearing on fear conditioning (Silvers, Lumian, et al., 2016). Both previously institutionalized (PI) children and children raised by their biological parents learned to discriminate the CS+ from the CS-, and there were no differences in amygdala activation or behavioral responses during fear

conditioning. PI children recruited a more adult- like, distributed neural network during the task, including greater hippocampal activation and increased functional connectivity of the prefrontal cortex with the amygdala and hippocampus (Silvers et al, 2016). These initial studies suggest that learning about threat and safety cues may be differentially influenced by experiences of threat versus deprivation. Other fear learning processes like generalization, reinstatement, and renewal are relevant mechanisms closely tied to clinical phenomena that have not yet been studied in children exposed to adversity.

The study of aversive learning processes in children is challenging. It is difficult to create tasks that are sufficiently aversive to elicit biological and behavioral responses but do not result in high attrition, particularly among children exposed to adversity. This may explain the relative dearth of research in this area. Clearly, greater research is needed in order to better delineate how experiences of adversity influence aversive learning processes in children.

Reward Learning.

Reward learning involves the acquisition of reward contingencies that must be learned over time through active feedback. Poor reward learning, or reductions in the strength of associative learning following positive reinforcement, has been documented in children exposed to multiple forms of adversity, including deprivation associated with institutional rearing (Wismer Fries & Pollak, 2017) and threat involving abuse (Hanson, et al., 2017; Harms, Shannon Bowen, Hanson, & Pollak, 2018). Altered reward learning in children exposed to adversity is reflected in weak reward contingency associations, slower rates of reward contingency acquisition, and less adaptation to changing contingencies (Hanson, et al., 2017; Harms, et al., 2018; Wismer Fries & Pollak, 2017), consistent with the notion that reward contingencies are less consistent and more unpredictable for children exposed to both threat and deprivation. Although blunted ventral striatum activity during reward processing tasks has been found in children who had experienced institutional deprivation (Mehta, et al., 2010) and emotional neglect (Hanson, et al., 2015), few studies have examined neural responses during reward *learning* following childhood adversity. In a recent study, the association between expected value of cues paired with reward and striatal activation was weaker in adolescents with trauma exposure relative to controls (Gerin et al., in press). Together, evidence is relatively consistent in finding impaired associative learning of reward contingencies among children exposed to adversity. Though greater research is needed in this area, these findings point to the potential utility of intervention approaches that directly target reward learning, described below.

Changes in Learning Across Development

It has been argued that human brain development is designed to maximize opportunities for learning (Tottenham, 2014). Consistently, we see significant change in learning and associated neurobiology during adolescence. Importantly, the systems are often those influenced by early-life adversity and implicated in psychopathology. As reviewed extensively elsewhere (Crone & Dahl, 2012; Somerville, Jones, & Casey, 2010; Tottenham & Galvan, 2016), the second decade of life is characterized by continued development of

cortical-subcortical circuit structure, function, and connectivity in regions like the amygdala, hippocampus, striatum, and medial prefrontal cortex (mPFC), and with these changes come changes in emotional learning.

There are numerous examples of adolescent changes in both fear and reward-based learning paradigms. For example, the ability to discriminate threat and safety cues strengthens between childhood and adolescence (Haddad, Lissek, Pine, & Lau, 2011; Jovanovic, et al., 2014; A. M. Waters, Theresiana, Neumann, & Craske, 2017), which has been linked to a decreasing reliance on subcortical structures (i.e., the amygdala), and an increasing recruitment of the PFC as age increases (Lau, et al., 2011). And yet, adolescents are also more likely than adults to retain their negative evaluations of aversive associations following extinction training (Waters, et al., 2017). This resistance to re-evaluate aversive associations may be related to strong fear recall (Ganella, Drummond, Ganella, Whittle, & Kim, 2017) and poor extinction in adolescence (Baker, Bisby, & Richardson, 2016; Ganella, et al., 2017; Pattwell, et al., 2012), corresponding to the weaker connectivity between the amygdala and mPFC in adolescents relative to adults (Ganella, et al., 2017). However, if extinction training occurs during a period of reconsolidation—when the consolidated memory has been reactivated by exposure to a CS, then extinction is as successful in adolescents as in adults (Johnson & Casey, 2015). This is an example of how learning mechanisms can inform intervention; reconsolidation relies less on the maturing adolescent prefrontal cortex (Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013), and is potentially more effective than traditional approaches for reducing fear during adolescence.

Adolescent brain development has also been associated with changes in reward learning (Tottenham & Galvan, 2016). Enhancements in reward learning for both monetary and social rewards are commonly found during adolescence, which are associated with increases in activity and connectivity in the ventral striatum, medial PFC, and anterior insula (Cohen, et al., 2010; Hauser, Iannaccone, Walitza, Brandeis, & Brem, 2015; van den Bos, Cohen, Kahnt, & Crone, 2012). Taken together, these developmental changes in learning systems point to the relevance of learning mechanism in the increased risk for adversity-related psychopathology, but also suggest that interventions targeting these learning mechanisms may be particularly effective when delivered during adolescence.

Learning and Psychopathology

Disruptions in fear- and reward-related associative learning processes are mechanisms underlying the onset and persistence of numerous forms psychopathology, including anxiety, depression, externalizing problems, and substance abuse. For example, atypical patterns of fear learning are thought to underlie the onset and maintenance of PTSD (Jovanovic & Ressler, 2010; Milad & Quirk, 2012). According to these models, exposure to a traumatic event serves as the US, and neutral stimuli present at the time of the trauma (CS's) acquire the ability to elicit fear that can be triggered when the person subsequently encounters similar stimuli. Supporting this line of thinking, emotional and physiological reactivity to stimuli associated with the traumatic event, even years later, is common in PTSD (Pitman, Orr, Forgue, de Jong, & Claiborn, 1987). PTSD is associated with heightened fear to the CS–(i.e., safety signal) in conditioning paradigms (Duits, et al., 2015; Jovanovic, et al.,

2010; Jovanovich & Norrholm, 2011). People with PTSD also show deficits in extinction learning (Norrholm, et al., 2011; Orr, et al., 2000; Peri, Ben- Shakhar, Orr, & Shalev, 2000) and extinction recall (Milad, et al., 2008; Milad, et al., 2009). These learning difficulties are thought to underlie the persistence of fear to trauma-related cues over time; indeed, difficulty inhibiting fear is related to re-experiencing and hyper-arousal symptoms of PTSD (Gamwell, et al., 2015; Glover, et al., 2011; Norrholm, et al., 2015).

Although other disorders do not have a clear onset event in the same manner as PTSD, abnormalities in fear learning have been observed in adults across the anxiety disorders (Lissek, et al., 2005) and in antisocial behavior (Birbaumer, et al., 2005), and obsessive-compulsive disorder (OCD) (Milad, et al., 2013). Greater generalization of fear to cues similar to those that previously associated with threat has been observed in adults with panic disorder (Lissek, et al., 2009), generalized anxiety disorder (Cha, et al., 2014; Lissek, et al., 2014), social anxiety (Ahrens, et al., 2016), and schizophrenia (Tuominen, et al., 2017). Altered fear generalization is thus a transdiagnostic factor contributing to many forms of psychopathology. While most studies have been conducted in adults, increasing evidence documents alterations in fear learning in youth with anxiety (Craske, Waters, et al., 2008; Lau, et al., 2008; Waters, Henry, & Neumann, 2009), PTSD (Gamwell, et al., 2015; McGuire, et al., 2016), and externalizing problems (Fairchild, van Goozen, Stollery, & Goodyer, 2008; McLaughlin, et al., 2016).

Abnormalities in reward learning are also associated with psychopathology. This has most commonly been studied in relation to depression, as reduced responsiveness to pleasurable stimuli (i.e., anhedonia) is a primary symptom of depression. For example, depression has been associated with reduced modulation of behavior in response to rewards, stemming from a failure to integrate the history of prior reward reinforcements (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008); this reduced reward responsiveness is associated with anhedonia. Reduced reward learning is also associated with poor treatment response among adults with depression (Vrieze, et al., 2013). Disruptions in reward learning and associated fronto-striatal circuitry feature prominently in conceptual models of substance disorders (Hyman, Malenka, & Nestler, 2006) and are thought to play a major role in features of substance disorders, such as craving, elicited by environmental stimuli previously associated with the substance (Grant, et al., 1996). Atypical reward learning has also been observed in adults with antisocial personality disorder, where typical responses are observed in response to prediction errors, but this information is not incorporated effectively into decision-making (Von Borries, et al., 2010). Existing work on reward-related learning and psychopathology comes from adult studies, pointing to the critical importance of examining these mechanisms in the development of psychopathology in children and adolescents.

Relevance of Learning Mechanisms to Intervention

Behavioral interventions targeting emotional learning mechanisms represent some of the most effective evidence-based treatment approaches for treating anxiety, depression, and externalizing problems (Chorpita & Daleiden, 2009). These approaches have been evaluated and refined for decades and represent some of the most powerful tools for treating psychopathology. Greater knowledge of the learning mechanisms underlying the link

between childhood adversity and psychopathology would allow these evidence-based treatment approaches to be harnessed in early interventions aimed at preventing the onset of mental health problems in children who have experienced adversity. For example, if difficulties with extinction learning or retention of extinction learning emerge as mechanisms linking trauma exposure with anxiety or other forms of psychopathology, techniques designed to maximize inhibitory learning during exposure could be used to target these learning mechanisms (Craske, Kircanski, et al., 2008; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). Approaches that integrate techniques designed to reduce attention biases towards threat (e.g., ABMT) along with exposure techniques (Waters & Craske, 2016) may ultimately be the most effective approach for preventing anxiety following adversity.

Extensions of these behavioral techniques could be used to address other relevant emotional learning mechanisms. For example, if heightened generalization of fear emerges as a mechanism linking childhood adversity to psychopathology, discrimination training may be a useful approach. Discrimination training produces decreases in fear generalization and reduced avoidance of cues resembling the threat cue in adults (Ginat-Frolich, Klein, Katz, & Shechner, 2017; Lommen, et al., 2017). If reward learning mechanisms prove to be important, a recent extension of behavioral activation—Positive Affect Treatment—was designed to enhance approach motivation, responsiveness to reward, and reward learning (Craske, Meuret, Ritz, Treanor, & Dour, 2016). This intervention not only encourages increased engagement with sources of positive reinforcement, but aims to increase reward learning through activities designed to facilitate the savoring of positive experiences along with attention retraining to shift attention to positive stimuli rather than away from negative ones, and activities designed to cultivate appreciation, generosity, and gratitude (Craske, et al., 2016).

Although behavioral approaches targeting emotional learning mechanism are effective treatment strategies, remarkably little research has examined their utility in early interventions to prevent the onset of psychopathology following childhood adversity. However, a recent study examining a brief modular behavioral intervention including elements focused on relaxation, guided imagery, behavioral activation, and problem solving, among others for children exposed to trauma suggests that these types of strategies may be able to prevent the onset of psychopathology. Children randomized to the intervention were less likely to develop anxiety and PTSD following a traumatic event than a control group (Berkowitz, Stover, & Marans, 2011). Examining the efficacy of brief behavioral interventions in preventing psychopathology among children who have experienced adversity represents a critical next step for the field.

Conclusion

Substantial progress has been made in identifying developmental mechanisms underlying the strong association between exposure to childhood adversity and the onset of psychopathology. Many of these mechanisms are well-replicated across studies and point to clear translational targets for intervention to prevent the emergence of psychopathology in children who have experienced adversity. Developing and evaluating psychosocial

interventions that target these mechanisms using the strategies proposed here (Figure 1) is a critical next step for the field. These efforts will be bolstered by greater research into the emotional learning mechanisms that are influenced by childhood adversity and increase risk for psychopathology given the well-established behavioral techniques that have been developed to target these mechanisms. Evaluating whether such behavioral interventions are particularly effective during adolescence, a period of substantial plasticity in the neural circuits that underlie emotional learning, or during other developmental periods when the effects of adversity are particularly pronounced may help to identify sensitive windows for intervention. Translating the increasing knowledge of developmental mechanisms that confer risk for psychopathology following childhood adversity into intervention strategies and testing the efficacy of those approaches is, in our view, the most important next step for the field.

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Highlights

- Several clear developmental pathways link childhood adversity with psychopathology
- These include threat and reward processing and emotional reactivity and regulation
- We suggest intervention approaches to target these mechanisms
- Knowledge of learning mechanisms linking adversity and psychopathology is limited
- Emotional learning mechanisms provide clear targets for behavioral interventions

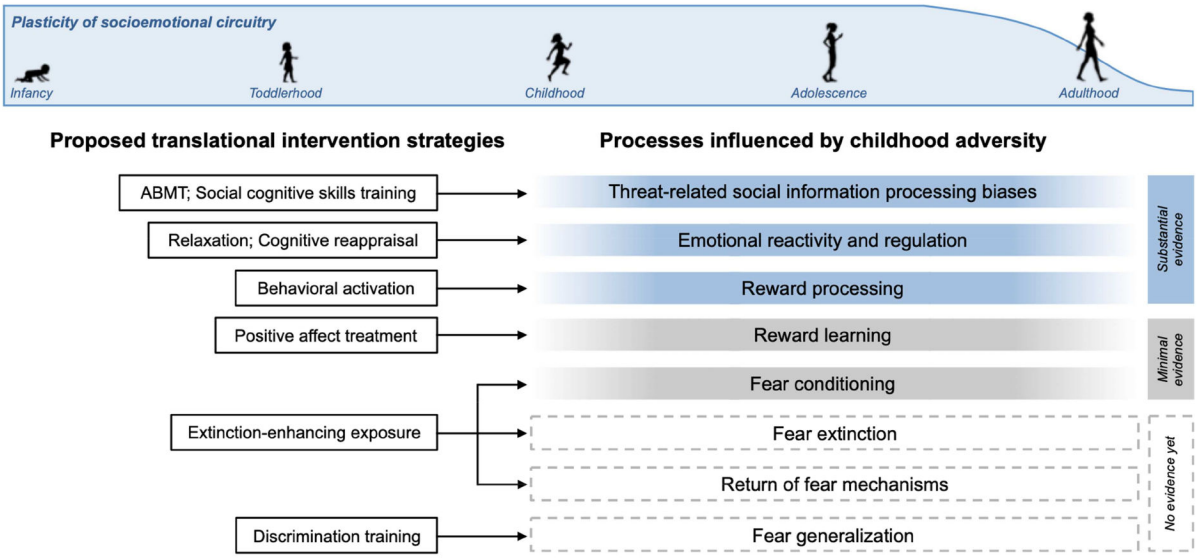

Figure 1.

Transdiagnostic mechanisms linking childhood adversity with psychopathology across the life span and proposed interventions. Blue bars indicate extensively studied processes known to be influenced by childhood adversity, spanning the stages of life throughout which such processes have been studied. Gray bars indicate processes for which initial evidence demonstrates an influence of childhood adversity but remain understudied, and dashed lines represent processes that are hypothesized to be influenced by childhood adversity across life stages, but have rarely been studied. Intervention strategies targeting each of these mechanisms are depicted in boxes on the left side of the figure. The curved line at the top of the figure is a graphical schema of the relative neural plasticity within socioemotional learning circuits across the lifespan. The coincidence between high plasticity and prevalence of processes influenced by childhood adversity during childhood and adolescence make this period an ideal time to implement interventions. ABMT: Attention-bias modification treatment.