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Review

A window of vulnerability: Impaired fear extinction in adolescence

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ABSTRACT

There have been significant advances made towards understanding the processes mediating extinction of learned fear. However, despite being of clear theoretical and clinical significance, very few studies have examined fear extinction in adolescence, which is often described as a developmental window of vulnerability to psychological disorders. This paper reviews the relatively small body of research examining fear extinction in adolescence. A prominent finding of this work is that adolescents, both humans and rodents, exhibit a marked impairment in extinction relative to both younger (e.g., juvenile) and older (e.g., adult) groups. We then review some potential mechanisms that could produce the striking extinction deficit observed in adolescence. For example, one neurobiological candidate mechanism for impaired extinction in adolescence involves changes in the functional connectivity within the fear extinction circuit, particularly between prefrontal cortical regions and the amygdala. In addition, we review research on emotion regulation and attention processes that suggests that developmental changes in attention bias to threatening cues may be a cognitive mechanism that mediates age-related differences in extinction learning. We also examine how a differential reaction to chronic stress in adolescence impacts upon extinction retention during adolescence as well as in later life. Finally, we consider the findings of several studies illustrating promising approaches that overcome the typically-observed extinction impairments in adolescent rodents and that could be translated to human adolescents.

1. Introduction

Adolescence is often described as a developmental window of vulnerability in which the majority of psychological disorders emerge (Paus, Keshavan, & Giedd, 2008; Spear, 2000). Anxiety disorders are the most common class of psychological disorder in adolescence (Kessler et al., 2012). Further, it has been estimated that approximately 75% of adults with fear-related disorders met diagnostic criteria as children or adolescents (Kim-Cohen et al., 2003). As noted by McNally (2007), exposure-based treatments for anxiety disorders have been an undeniable success within psychology. An important component of these therapies is the process of extinction, which involves repeatedly exposing the individual to the feared stimulus/situation in the absence of any danger. As noted in several recent reviews (e.g., Milad & Quirk, 2012), substantial progress has been made in the past decade on understanding the processes mediating extinction of learned fear. Although there are over a thousand publications on fear extinction in animals and humans since 2000 (Milad & Quirk, 2012), very few of these studies have examined fear extinction during development. There have been a few recent studies in infants (for review see Kim & Richardson, 2010), but scarcely any in adolescents. In this paper, we first review this relatively small body of research on fear extinction in adolescent rodents and humans. A major finding of this work has been that adolescents, both humans and rodents, exhibit a marked impairment in extinction compared to both younger (e.g., juvenile) and older (e.g., adult) groups. We then move onto a consideration of various factors/mechanisms that could mediate this pronounced impairment in extinction in adolescence. We conclude that changes in the functional connectivity within the fear extinction circuit, particularly between prefrontal cortical regions and the amygdala, may be the neurobiological basis for the impaired extinction observed during adolescence. We then describe work examining the impact of chronic stress on fear extinction in adolescence; this research shows that stress may increase the likelihood of resistance to extinction earlier or later in life, depending on the age at which the stressor is experienced. We also briefly describe another body of research – on emotional regulation and attentional processes – for additional clues as to potential cognitive mechanisms that may mediate the observed impairments in extinction in adolescence. Finally, we describe several recent studies that provide evidence for approaches that overcome extinction impairments in adolescent rodents, and that could be translated to treating adolescent humans with an anxiety disorder.

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2. Fear extinction in adolescent rodents

Those studies that have examined extinction of fear in adolescence have all used Pavlovian procedures to first condition fear. This involves pairing an initially neutral conditioned stimulus (CS; e.g., a tone or a light) with a naturally aversive unconditioned stimulus (US; e.g., a shock or a loud noise). At some point following this, the CS is presented by itself, and over repeated trials the fear elicited by the CS diminishes. Before describing those studies, however, it is important to define adolescence given that there are some disagreements about exactly when adolescence begins and ends, in both rodents and humans (Spear, 2000). In this review we will be very inclusive and define adolescence in rodents as being between postnatal (P) day 28 to P50, and in humans as being 12–17 years of age.

In perhaps the first study on fear extinction in adolescent rodents, Hefner and Holmes (2007) examined differences in conditioned fear acquisition and extinction between early adolescent (P28), mid-adolescent (P42), and young adult (P56) mice. Early adolescent mice showed enhanced fear acquisition as well as higher levels of freezing during extinction training compared to mid-adolescent and young adult mice. However, there were no age differences in the rate of within-session extinction. Further, extinction retention was not tested in that study. Two subsequent studies replicated this finding in rats, demonstrating that adolescents (P35) did not differ in rates of within-session extinction compared to juvenile (P24) and adult (P70) rats, and these studies also found a marked impairment in extinction retention in the adolescents (Kim, Li, & Richardson, 2011; McCallum, Kim, & Richardson, 2010). That is, although adolescent rats expressed the same low-level of CS-elicited freezing at the end of the extinction training session as did juvenile and adult rats, when tested the following day they exhibited a striking return of fear, relative to the other two age groups (see Fig. 1A; redrawn from McCallum et al., 2010). A more recent study did not detect any age-related differences in extinction retention between adolescent and adult rats (Broadwater & Spear, 2013). Although adolescent (~P35) rats in that study showed a remarkable recovery of fear when extinction retention was tested, so too did adult (~P71) rats (i.e., rats of both ages exhibited ~80% CS-elicited freezing at test). This high level of fear at test makes it nearly impossible to detect any potential extinction retention impairment in the adolescents. In contrast to those results, another study reported impaired extinction learning and retention in adolescent mice (Pattwell et al., 2012). Specifically, when extinction training was spread over several days (with 5 trials per day over 4 days), adolescent mice (P29) displayed impaired extinction learning and retention compared to juvenile (P23) and adult (P70) mice. These deficits in fear extinction in adolescent rodents do not seem to be due to differences in fear conditioning. Although Hefner and Holmes (2007) observed enhanced fear acquisition (as reflected by higher levels of CS-elicited freezing) in adolescents, such a difference was not observed in the three studies that reported impaired extinction retention in adolescents. In addition, there are other studies that have reported similar acquisition of fear in adolescent compared to adult rats (Brasser & Spear, 2004). Taken together, these studies demonstrate a marked deficit in fear regulation in adolescence, but clearly more research needs to be done in this area.

3. The study of fear extinction in adolescent humans

Neumann, Waters, and Westbury (2008) gave 13–17 year old participants pairings of a geometric shape (CS+) with the unpleasant sound of metal scraping on a slate (US). Across a number of dependent variables (including potentiated startle, skin conductance, and self-report measures), robust fear conditioning and within-session extinction was observed. Contrary to this finding of robust within-session extinction, Haddad, Lissek, Pine, and Lau (2011) reported that adolescents were resistant to extinction. A social threat cue task was used in that study; this type of task was chosen because negative social relationships are highly salient during adolescence and may contribute to the etiology and maintenance of anxiety disorders. Of course, the level of conditioned fear in this type of study is going to be much less than what occurs in studies where painful stimulation (e.g., shock or loud noise) is used as the US. Nonetheless, the participants in the study by Haddad and colleagues were 12–15 years of age and were given pairings of three different neutral face CSs with three different USs: (1) CS-positiveUS (i.e., a neutral face CS was paired with a US that was the same face displaying a positive facial expression and a positive comment), (2) CS-negativeUS (i.e., a neutral face CS was paired with a US that was the same face with a negative facial expression and negative comment), and (3) CS-neutralUS (i.e., a neutral face CS was paired with the same neutral face and a neutral comment). After conditioning, participants rated the CS that was paired with the negative expression and comment as more unpleasant and scary than both of the other two CSs. More importantly, this difference persisted after extinction trials in which the CS that had been paired with the negative expression was repeatedly presented alone. This finding supports the claim that adolescents show impaired within-session extinction. In both of the

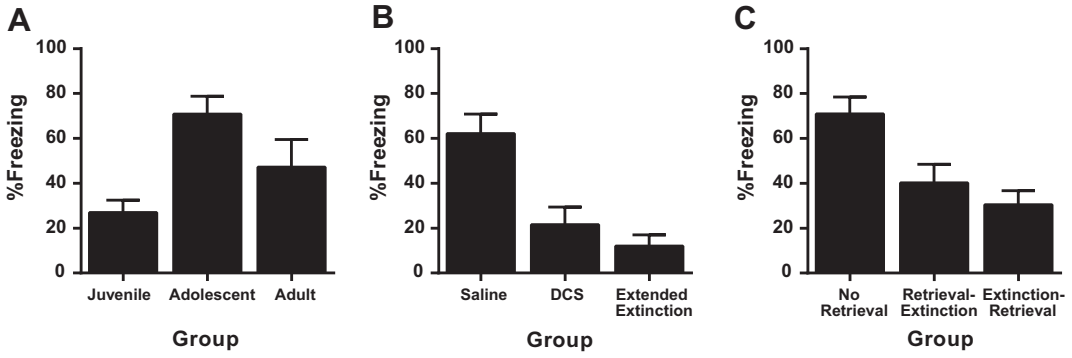

Fig. 1. Adolescent rats show impaired extinction retention at test compared to juvenile and adult rats (Panel A). D-cycloserine (DCS) and extended extinction training improved extinction retention in adolescent rats (Panel B). Memory retrieval 10 min before or after extinction augmented extinction retention in adolescent rats (Panel C). The data shown in Panels A and B were taken from McCallum, Kim, and Richardson (2010) and the data shown in Panel C were taken from Baker, McNally, and Richardson (2013).