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Adolescent Transitions in Reflexive and Non-Reflexive Behavior: Review of Fear Conditioning and Impulse Control in Rodent Models

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Abstract

Adolescence is a time of critical brain changes that pave the way for adult learning processes. However, the extent to which learning in adolescence is best characterized as a transitional linear progression from childhood to adulthood, or represents a period that differs from earlier and later developmental stages, remains unclear. Here we examine behavioral literature on associative fear conditioning and complex choice behavior with rodent models. Many aspects of fear conditioning are intact by adolescence and do not differ from adult patterns. Sufficient evidence, however, suggests that adolescent learning cannot be characterized simply as an immature precursor to adulthood. Across different paradigms assessing choice behavior, literature suggests that adolescent animals typically display more impulsive patterns of responding compared to adults. The extent to which the development of basic conditioning processes serves as a scaffold for later adult decision making is an additional research area that is important for theory, but also has widespread applications for numerous psychological conditions.

Keywords

rat; mouse; delay; trace fear; context; impulsivity; reward; inhibition; decision-making

Introduction

Characterized by novel alterations in behavior, growth, and structural remodeling of the brain (Brenhouse & Andersen, 2011; Caballero & Tseng, this volume; Juraska et al., 2013; Stevens, this volume; Smith et al., 2015; Spear, 2000), adolescence may represent a unique period in cognitive development, different from prior and later life stages. This can be contrasted to a view of adolescence as reflecting a more linear transition to adulthood, when learning and other cognitive processes become progressively, and monotonically, more mature. However, isolating and characterizing adolescent-unique patterns of development is made complex given that there are many distinct components to learning and memory (e.g.,

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encoding, maintenance, retrieval), as well as different forms of learning ranging, for example, from simple reflexive classical conditioning to more complex non-reflexive processes of complex choice behavior and decision-making. The present review brings focus to these latter different dimensions of cognitive function and behavior, namely, classical conditioning and decision making.

Although not well integrated in the literature there are important connections between these two areas. Many processes recognized as critical to more complex aspects of cognition such as decision making are also known to be affected by classical conditioning, including attention (Pearce & Hall, 1980), learning (Rescorla & Wagner, 1972), value representation (Holland & Rescorla, 1975), response selection (Bolles, 1970; Fanselow, 1994; Miller & Matzel, 1988) and inhibition (Pavlov, 1927; Rescorla, 1969). Our review of classical conditioning and decision making in adolescents will be presented in separate sections. As we suggest later, a significant future research area is how variation in the development of basic associative learning processes affects decision making. The first section of this review considers behavioral plasticity, specifically learning, involved in classical fear conditioning. The second section considers more complex aspects of cognition, specifically, impulse control in decision making. Thus, the two sections of review span reflexive and non-reflexive dimensions of behavior in adolescence. It is noteworthy that the extensive and analytical review of adolescence by Spear (2000) in this journal over 15 years ago acknowledged and cited the limited nature of available evidence for adolescent-unique performance in basic fear learning tasks (the first section of the present review; in Spear, 2000, see p. 423 “Cognitive development” section). Since that time there have important advances we highlight in this review. We equally highlight significant remaining gaps in current literature. Our review expands upon basic findings on adolescence from conditioning experiments to also include issues of impulse control in decision making. Given the paucity of data available on these topics from studies comparing adolescent animals to other age groups our review will be intentionally focused. An overall summary of the literature discussed in this review is presented in Table 1 which is intended as a useful aggregate of available findings.

Defining Adolescence in Rodent Models

In its broadest sense, adolescence refers to a transitional period between the parental dependence of childhood and the independence and sexual maturity of adulthood. Adolescence can be considered in many ways (e.g., social, emotional, cognitive, hormonal and neural) and, depending upon the specific question being asked, adolescence may be defined in a more restrictive sense that is based upon the observation of a specific behavior or measure (Adriani & Laviola, 2004; Juraska et al., 2013; Spear, 2000). Within the adolescent period there can be further distinctions spanning early, middle-, to late-adolescence.

In rodents (rats and mice), this transitional period between maternal dependence and adulthood occurs between the time of typical laboratory weaning (postnatal day [PD] 21) and the attainment of sexual maturity (PD 60 or even up to approximately PD 70, cf. Smith et al., 2015). Many researchers, however, may use a more limited range of ages, based on the

age-specific behavior of interest, to define adolescence (e.g. Juraska et al., 2013; Smith et al., 2015; Spear, 2000), sometimes discriminating between early (PD 24-35, Adriani et al., 2002; centered around PD 30, Juraska et al., 2013) middle, (PD 37-48, Adriani et al., 2002) and late adolescence (PD 50-61, Adriani et al., 2002) although it is recognized there are no strict age-limits defining these phases (Adriani & Laviola, 2004). Thus the operational age range of PD 21 to PD 60 includes the adolescent period. However, given our desire to capture more of the limited available literature characterizing adolescent performance in basic conditioning and decision making (i.e., operant choice tasks), some papers reviewed vary from this range. As seen throughout this journal volume, the specific age range used to capture a rodent adolescent period also varies across laboratories. Nonetheless, most investigators would agree that PD 30-35 is part of the adolescent period and the majority of studies in this review include animals in this age range. We will also include discussion of data from younger and older subjects, when available, placing the adolescent within broader developmental context.

Defining Fear: Procedures for Induction and Measurement

Fear is a central emotional state that confers advantage in the face of threat. The fear state elicits reflexive behaviors that are protective and enhance survival and has been preserved both phylogenetically and ontogenetically (Bolles, 1970; Bolles & Fanselow, 1980; Hunt & Campbell, 1997). Decades of animal research, primarily with rodents (rats and mice), together with more recent human neuroimaging data, serve to highlight the fact that the neural systems regulating fear, and the variety of ways in which fear is expressed, have also been conserved (Cain et al., 2013; Craske et al., 2006; Davis et al., 2010; Debiec & LeDoux, 2009). There is also a clear similarity between fear studied in animals and human anxiety (Craske et al., 2006; Perusini & Fanselow, 2015). Both humans and animals show conditioned fear potentiation of the startle reflex (in rats, Davis et al., 1993; in humans, Grillon & Davis, 1997), contextual modulation of startle (in rats, McNish et al., 1997; in humans, Ameli et al., 2001), conditioned fear modulation of heart rate (in rats, Hunt et al., 1997; Iwata & LeDoux, 1988; in humans, Hamm et al., 1993), and blood pressure (in rats, LeDoux, 2000; in humans, De Leon, 1972, see also Reiff et al., 1999). Other common measures related to fear and anxiety include conditioning of skin conductance in humans (Hamm et al., 1993; Öhman, 1974) and freezing in rodents (Bolles, 1970; Fanselow, 1994). Thus, findings and conclusions based on research with animal subjects can, to some extent, generalize to human fear and anxiety. Furthermore, fear conditioning can be used to address fundamental questions regarding the mechanisms underlying learning and memory formation across species and ages (e.g. Dumas & Rudy, 2010; LeDoux, 2000; Pattwell et al., 2012; Powell et al., 1997; Richardson & Hunt, 2010; Sullivan et al., 2010).

Fear can be studied in the lab using well-controlled experiments employing classical conditioning paradigms (Cain et al., 2013; Davis et al., 2010; Maren, 2001; Perusini & Fanselow, 2015). In classical conditioning, a neutral stimulus (conditioned stimulus, CS) such as a tone or light is followed by the onset of an aversive stimulus (unconditioned stimulus, US) such as a brief footshock or loud noise. During this training procedure, the subject learns not only about the predictive nature of the CS, but also about the context in which the CS-US pairings occur. Upon presentation of the CS or context during test, animals

display a variety of observable or measurable changes in physiology and behavior. Some of the more common measures of fear are freezing/immobility (Blanchard & Blanchard, 1972; Fanselow, 1994), changes in heart rate or blood pressure (LeDoux et al., 1988; Powell et al., 1997; Richardson & Hunt, 2010), and the potentiation of startle reflexes (Barnet & Hunt, 2006; Davis et al., 2010). There is generally wide agreement that the study of classically conditioned fear can inform mechanisms responsible for fear and anxiety including those in humans (Bouton et al., 2001; Cain et al., 2013; Davis et al., 2010; Fanselow & Gale, 2003; Grillon & Davis, 1997; Mineka & Zinbarg, 2006; Perusini & Fanselow, 2015). However, at least one review suggests the contribution of classical fear conditioning to anxiety disorders in human clinical populations may be more modest or depend on conditioning paradigm (Lissek et al., 2005).

The adolescent period is a time of intense and fluctuating emotional reactions, compounded by a lack of regulatory control (Dreyfuss et al., 2014; Guyer et al., this volume; Hare et al., 2008; Mills et al., 2014; Somerville et al., 2010; Steinberg, 2004). Certain classes of emotional states, particularly negative, increase sharply during adolescence (Hare et al., 2008). Thus, examination of the mechanisms underlying fear and anxiety in adolescence is crucial for understanding the etiology of fear-associated disorders. Fear in adolescents is particularly critical to understand because it may differ dramatically with respect to that observed in children or adults (Gee et al., 2013; Hare et al., 2008; Pattwell et al., 2011; Pattwell et al., 2012; Somerville et al., 2010). To the extent that adolescents and adults differ in patterns of emotional expression mediated by underlying regulatory circuits, strategies for prevention or treatment of fear and anxiety disorders, which are commonly based upon understanding of these processes in adults, may not adequately translate to effective strategies for use with adolescents (Baker et al., this volume; Baker & Richardson, 2015; Casey et al., 2015; Pattwell et al., 2012).

Learning and expression of fear behaviors requires several neural structures embedded in a network, including the amygdala, hippocampus and medial prefrontal cortex (mPFC). These brain regions and connectivity between them continue to undergo functional maturation during adolescence (Giedd, 2004; Goddings et al., 2014; Koss et al., 2014; Mills et al., 2014; Rubinow & Juraska, 2009; Saul et al., 2013; Smith et al., 2015; Wierenga et al., 2014). The amygdala, located in the medial temporal lobe, is necessary for acquisition of fear as well as the organization of its expression (Davis et al., 2010; Debiec & LeDoux, 2009; LeDoux, 2000; Perusini & Fanselow, 2015; Quinn & Fanselow, 2006). Learning-related plasticity occurs in the basolateral nucleus (BLA; Romanski et al., 1993) which in turn projects both directly and indirectly to the central nucleus (CeA). Neurons in the CeA project to midbrain and brainstem areas, such as the periaqueductal grey, the lateral hypothalamus, and the pontine nuclei, each of which is responsible for the expression a specific fear response (freezing, changes in blood pressure, fear-potentiated startle, respectively; Davis et al., 2010; Debiec & LeDoux, 2009; Perusini & Fanselow, 2015).

Another structure involved in fear learning is the hippocampus. The hippocampus increases in overall volume during the adolescent period (Godings et al., 2014), and connectivity with the amygdala and mPFC increases in functionality during this time (Hare et al., 2008). The hippocampus has been well-studied for its role in learning and memory (Bliss & Lomo,

1973; Clark et al., 2005; Dumas & Rudy, 2010; Milner, 1970; Morris et al., 1982; O'Keefe & Nadel, 1978; Squire, 2004; Zeamer et al., 2010). In fear conditioning, this structure plays a vital role in processing information about the context of learning and integrating cues separated in time (Fanselow, 2000; Kitamura et al., 2005; Rodriguez & Levy, 2001; Rudy, 2009). Increased sophistication of hippocampal function during adolescence can result in age-unique patterns of processing of temporally and spatially disparate cues, contexts and situations.

The frontal lobes undergo extensive maturation and re-organization through adolescence (Giedd, 2004). Unique frontal functioning during adolescence has been linked to the emotionally volatile, impulsive, and sensation-seeking behavior often observed during adolescence (e.g. Dreyfuss et al., 2014; Steinberg, 2004). Subregions of the medial prefrontal cortex (mPFC), especially the infralimbic (IL) and prelimbic (PL) regions, are important for acquisition, behavioral expression and extinction of learned fear (Baker et al., this volume; Marek et al., 2013; Sotres-Bayon & Quirk, 2010). The mPFC is additionally important to complex aspects of cognition and executive function including decision making (Grafman et al., 1995) implying a potential relationship between mechanisms underlying basic conditioning and decision making behavior. Of consideration throughout this volume and beyond the scope of our current review of behavioral findings, advances in understanding conditioning and more complex aspects of behavior in adolescents benefits from consideration of how connectivity within the fear circuit changes over time as different contributing neural structures become functionally mature.

Adolescent Fear Conditioning and Expression in Rodent Models

There is a paucity of developmental data for which fear conditioning in adolescents is directly compared with that in both younger *and* older subjects. This makes it particularly difficult to assess whether there are adolescent-specific peculiarities in emotional learning. Developmental researchers are primarily interested in the first emergence of learning and memory capacities (e.g. Dumas & Rudy, 2010; Freeman, 2010; Hunt & Campbell, 1997; Richardson & Hunt, 2010; Stanton, 2000; Sullivan et al., 2010). Pre- and weanling-age subjects are typically the target age groups in these studies. Adolescents, when included, are viewed as the end-point of that developmental trajectory and memory expression often is assumed to be adult-like at that time. As we will discuss below, this may be an incorrect assumption. In contrast, other lines of research, such as investigations of impulsivity, drug sensitivity, and risk-taking behaviors, compare adolescents with adults, but do not often include younger ages (e.g. Doremus-Fitzwater, et al., 2012; Hefner & Holmes, 2007; Hunt & Barnett, 2016; Ito et al., 2009; Meyer & Bucci, 2014). Thus, there are significant gaps in the literature, specifically studies that directly compare the adolescent group with both younger and older ages in order to assess non-monotonic transitional trends and age-dependent discontinuities. The present review attempts to bridge that gap by highlighting what is currently known about adolescent-unique behavioral effects in adolescent classical conditioning.

Shortly after laboratory weaning, by about 23 days of age, the basic fear system is sufficiently functional to afford learning to CSs of all stimulus modalities (Richardson &

Hunt, 2010). Moreover, animals of this age are able to express fear in a manner similar to that of adults, being evident in terms of immobility/freezing, changes in heart rate, and fear-potentiation of the startle reflex (Barnet & Hunt, 2006; Hunt, 1999; Richardson & Hunt, 2010). There is some evidence that, in certain circumstances, adolescent rodents show either exaggerated or diminished fear responding, relative to both younger and older subjects. The published studies have focused on assessing adolescent learning in delay, trace and contextual fear conditioning procedures.

Delay Conditioning

Delay fear conditioning is a procedure in which a discrete CS is presented contiguously with an aversive US. The amygdala is critical for acquisition and expression of delay conditioned fear (Cain et al., 2013; Davis et al., 2010). Most fear conditioning studies that include adolescent animals report no differences across age in delay fear conditioning after about PD 23 (Barnet & Hunt, 2005; Pattwell et al., 2011; Richardson & Hunt, 2010; Rudy & Morledge, 1994). One study however, found that delay fear conditioning was stronger in adolescent animals than in adults. Hefner & Holmes (2007) compared mice that were 4 (early adolescence), 6 (middle adolescence) or 8 weeks of age (late adolescence) at the time of fear conditioning. Animals were given tone-shock pairings and were tested 24 h later. Freezing to the CS at test was significantly higher in the 4-week-old mice compared with 6- and 8-week-old mice. The 6-week-olds also showed more freezing than the 8-week-olds. Thus, fear conditioning was strongest in the early adolescent animals and thereafter showed a decrease across this age range (4-8 weeks). Ito et al. (2009) examined *generalization* of fear in adolescent (4-5 weeks) and adult (9-10 weeks) mice. Animals were given tone-shock pairings and were then tested in a novel context for freezing to the training CS and to a different auditory cue. Ito et al. reported that the adolescent animals (4-5 weeks) showed greater generalization of fear than the adults; that is, greater freezing to the novel auditory cue, despite equivalent levels of freezing to the training CS. Another finding was that the 4-5 week old mice showed greater generalization of fear to the novel test context. Mice younger than 4 weeks were not included in this study, and therefore it is unknown if the particularly high level of fear and fear generalization exhibited by 4-5-week-old mice is greater than what would be evident in younger animals.

Using neuroimaging methods, some studies have reported that human adolescents exhibit heightened amygdala activity and greater negative emotional reactivity in the presence of learned and unlearned threat cues (e.g. fearful facial expressions), compared to children or adults (Dreyfuss et al., 2014; Hare et al., 2008; Lau et al., 2011). These exaggerated responses may be due to an age-specific inefficiency in recruiting frontal regions involved in fear regulation (Somerville et al. 2010). In adolescents the progressing but incomplete maturity of frontal regions results in an imbalance between mPFC and amygdala activity (Mills et al., 2014). This imbalance could contribute to the emotional volatility and disproportionate emotional responses that are characteristic of adolescence and to the vulnerability to develop fear and anxiety disorders in this age group (Dreyfuss et al., 2014; Hare et al., 2008).

Trace Conditioning

Another type of conditioning that has been used to examine learning and memory across different developmental stages is trace conditioning (Barnet & Hunt, 2005; Den & Richardson, 2013; Ivkovich et al., 2000; Moye & Rudy, 1987). Trace conditioning involves the hippocampus (Czerniawski et al., 2012; Kitamura et al., 2015; McEchron et al., 1998; Misane et al., 2005; Quinn et al., 2002, 2005; Rodriguez & Levy, 2001), as well as the mPFC (Beeman et al., 2013; Gilmartin & McEchron, 2005; Kalmbach et al., 2009; McLaughlin et al., 2002; Raybuck & Gould, 2010; Runyan et al., 2004; Song et al., 2015) for acquisition and retention. The procedure is very similar to delay conditioning, except that the US is presented sometime after the offset of the CS. This gap between CS offset and US onset is known as the trace interval. The longer the trace interval, the more difficult it is to acquire the CS-US association (Beylin et al., 2001; Chowdhury et al., 2005).

For many years we have observed that adolescent-age rats (PD 30-35) exhibit a particular propensity for trace fear conditioning (Barnet & Hunt, 2005; Hunt & Barnet, 2016; Hunt et al., 2006, 2009; Schreiber & Hunt, 2013). These animals express just as much conditioned freezing to a CS that was trained with Trace conditioning trials as when trained with Delay conditioning trials, which is commonly superior. Barnet & Hunt (2005) examined the ontogenetic emergence of trace and delay fear conditioning. A flashing light CS (10 s) was followed by a brief footshock US after 10 s (Trace) or 0 s (Delay) intervals. Unpaired controls were also included. We demonstrated that trace conditioning to a visual CS (see Barnet & Hunt, 2005 for additional data with an auditory CS) was virtually nonexistent in preweaning (PD 18) animals, and showed a progressive increase in magnitude up to PD32 in adolescence (see also Moye & Rudy, 1987). Delay conditioning was equivalent in strength at all ages tested. Some of these results are shown in Figure 1. This figure also includes data (right panel) from an unpublished study that compared adolescent and adult animals in Trace conditioning using the same procedures as Barnet and Hunt (2005). These data highlight the fact that adolescent animals show greater trace conditioned responding relative to both younger *and* older animals. The finding that younger animals are impaired in acquiring trace fear has been attributed to immaturity of the hippocampus (Dumas & Rudy, 2010; Moye & Rudy, 1987). Why adult animals also show a trace conditioning deficit, a common finding in the literature, has not been delineated, except to say that it is a more difficult task compared to delay (Beylin et al., 2001; Chowdhury et al., 2005; Kaplan & Hearst, 1982; see also Burman & Gewirtz, 2004; see Cole et al., 1995 for an alternative explanation).

Den and Richardson (2013) directly compared delay and trace fear conditioning in weanling (PD 23), adolescent (PD 35) and adult (PD 90) rats in the same experiment. Animals were given six pairings of a 10 s auditory CS with a footshock US. Trace groups were trained with either a 20- or 40-s trace interval, longer than those used by Barnet and Hunt (2005). Despite high and equivalent levels of freezing to the delay-conditioned CS at all ages, there was no trace conditioning evident in PD 23 and PD 90 subjects with these procedures. Noteworthy was the finding that the adolescent PD 35 animals showed strong trace conditioning with both the 20- and 40-s trace intervals, exhibiting just as much freezing to the trace conditioned CS as to the delay conditioned CS. These data are consistent with those of Figure 1 in revealing behaviorally defined developmental transitions into and out of

adolescence. Collectively, these findings verify that adolescent animals seem to be, uniquely, predisposed to acquiring fear in a trace conditioning procedure, even in situations where younger and older animals do not.

Long-delay conditioning

In studies comparing delay and trace conditioning, the duration of the training CS has typically been maintained across training procedures. However, this leads to group differences in the length of the Inter-Stimulus Interval (ISI), defined as the time from CS onset to US onset. This confound thus makes it difficult to determine the nature of a trace learning impairment, if observed (Ivkovich & Stanton, 2001). As described above, young and adult rodents typically show a deficit in trace conditioning, relative to delay, and this has traditionally been viewed as a function of the imposed trace interval. In an attempt to further explore the role of the trace interval versus the ISI in the relatively late ontogenetic emergence of trace conditioning, Barnet and Hunt (2005) included a long-delay group in this developmental study. The long-delay group was matched to the trace group in terms of the ISI, but maintained the CS-US contingency of delay conditioning. Specifically, the long-delay group was trained with a 20 s CS immediately followed by shock. We observed that learning in the trace and long-delay procedures was developmentally time locked and emerged in parallel. As with trace conditioning, long-delay conditioning was nonexistent at PD 18 and increased in strength up to adolescence (PD 32). Of note is that this parallel emergence was seen with both auditory and visual CSs. These findings suggest that the later developmental emergence of trace compared with delay conditioning through the adolescent period may be the result of the longer ISI, rather than the stimulus-free trace interval *per se*.

The correspondence between the ontogeny of trace and long-delay conditioning raises the possibility that both types of learning require identical neural systems. However, evidence from Hunt and Richardson (2007), showing a pharmacological dissociation between trace and long delay conditioning, indicates that these forms of learning are not based upon entirely overlapping neural circuits. Animals (PD 25-32) were administered a cholinergic agonist (physostigmine) or antagonist (scopolamine) prior to trace or long-delay CS-US pairings. Training was identical to that of Barnet and Hunt (2005). Animals were tested for CS-elicited freezing 24 h later, in a drug-free state. Physostigmine enhanced, and scopolamine reduced, trace conditioned responding, but neither had an effect on long-delay conditioning. Collectively, these results indicate that, while learning of both forms of conditioning occurs at an older age than standard short-delay conditioning, trace and long-delay fear conditioning differ in their neural underpinnings in adolescent animals. Ivkovich et al. (2000) similarly observed a later-emerging but parallel development of trace and long-delay eyeblink conditioning, compared with short-delay, and Ivkovich and Stanton (2001) further showed that hippocampal lesions on PD 10 impaired trace conditioning on PD 30 to a greater extent than long-delay conditioning. These results highlight the similar developmental onset of trace and long delay learning across different aversive conditioning preparations (fear and eyeblink), and indicate a dissociation between their underlying neural mechanisms.

Context Conditioning

Ontogenetic changes in context conditioning, another hippocampus-dependent task (Anagnostaris et al., 2001; Fanselow, 2000; Matus-Amat et al., 2007; Rudy, 2009), have been examined using a variety of training and testing procedures. For this discussion we will separately consider the results of studies using standard context conditioning (also called *foreground conditioning*; Phillips & LeDoux, 1992), background context conditioning, and the context pre-exposure facilitation effect (CPFE).

Standard context conditioning—While the term *context* broadly consists of all cues and events surrounding a training episode, the vast majority of researchers studying context conditioning use this term synonymously with the experimental chamber. In standard context conditioning experiments an animal is placed into a chamber with a grid floor and allowed to explore the environment (the context) for a brief period of time, usually 2-3 min. This exploration period allows the animal to construct a configural representation of the features of the context referred to as a *conjunctive* representation (Rudy 2009; Rudy & O'Reilly, 1999). The exploration period is necessary for context conditioning to occur, as shown by the lack of context conditioning when shock is delivered immediately upon placement into the chamber (Fanselow 1990). After this exploration period one or more shocks are delivered and the animal is then removed from the chamber. The test of context fear involves recording fear behavior such as the amount of freezing in the context when animals are returned at some later time, for example, after 24 h.

The ability to express context freezing following a standard context training procedure emerges by about 23 days of age in rats (Rudy, 1993; Rudy & Morledge, 1994) and by about 14 days in mice (Akers et al., 2012). Furthermore, extrapolating across studies, there does not appear to be further ontogenetic development of this learning. For example, Rudy (1993) reported similar levels of context freezing in 23- and 27-day old rats, and Hunt & Barnett (2016) reported equal levels of context freezing in 30- and 75-day old rats. Akers et al. (2012) also found equivalent levels of freezing in mice ranging from 15 to 60 days.

Background context conditioning—When animals are given CS-US pairings in a fear conditioning procedure, they not only learn about the predictive nature of the CS, but also acquire fear to the context in which the CS-US pairings occur. There are some interesting differences between rats and mice that have recently been reported using this type of context conditioning procedure. In rats, background context conditioning emerges by about 23 days of age (Raineke et al., 2010; Rudy, 1993). Whether background conditioning has an early developmental trajectory in mice as it does for standard context conditioning (Akers et al., 2012; Pattwell et al., 2011) is unclear although it is clearly present in mice by at least 23 days of age (the youngest age tested; Pattwell et al., 2011). As with standard context conditioning, there is little evidence that the strength of background context conditioning changes with increasing age (Hunt & Barnett, 2016), although there are some reports of the CS overshadowing the context in adults, resulting in lower levels of context freezing (Brasser & Spear, 2004; Esmoris-Arranz et al., 2008; Odling-Smee, 1978; see Grillon et al., 2006 for a related example in humans).

An important finding that seems to oppose the accounts of equivalent or in some cases exaggerated fear learning in adolescents was reported by Pattwell et al. (2011) in which contextual freezing was *suppressed* in adolescent mice compared to younger and older ages. In these experiments mice ranging in age from PD 23 to PD 70 were given three tone-shock pairings and were assessed for freezing to the context 24 h later. Pre-adolescent (PD 23, 25 or 27), late adolescent (PD 49) and adult (PD 70) mice exhibited substantial and equivalent freezing to the context whereas PD 29-39 adolescent mice froze substantially less. In fact, in PD 29, 31 and 33 mice context freezing was virtually nonexistent. High and similar levels of freezing to the discrete tone CS were observed across all ages. Because younger (e.g., PD 23, 25) but not adolescent (e.g., PD 29, 31, 33) animals did express context learning, this pattern of impaired adolescent suppression of contextual fear cannot be explained by reference to simple (progressive) maturation of neural structures required for learning, but rather reveals an age-specific discontinuity in fear expression. Interestingly, the commonly reported *anatomical* dissociation seen in hippocampus dependency of context but not CS conditioning, namely that the hippocampus is required for context but not CS conditioning (Phillips & LeDoux, 1992) is parallel to this *developmental* dissociation of CS and context conditioning (Pattwell et al., 2011; Rudy & Morledge, 1994; Stanton, 2000). That is, these findings reveal another way in which CS and context conditioning are dissociated. Hippocampus lesions impair performance in context but not CS conditioning (Phillips & LeDoux, 1992) and the adolescent period of development is similarly associated with performance impairments in context but not CS conditioning (Pattwell et al., 2011).

This adolescent-unique suppression of context fear was further revealed in electrophysiological correlates of the reported behavioral differences (Pattwell et al., 2011). The deficit in context conditioning during the transition into early adolescence (PD 29) was associated with reduced synaptic potentiation in the basal amygdala and hippocampus as well as reduced PI3K and MAPK signaling in the hippocampus. Pattwell et al. (2011) also found that the diminution of contextual fear conditioning in adolescence was not the result of a failure to learn, but was rather an inability to express this learning by the adolescent subjects. Animals that were trained on PD 29, but not tested until 2 weeks later (on PD 43), exhibited substantial freezing to the context, indicating that the young adolescent animals did in fact acquire the context-US association.

The Pattwell et al. (2011) findings with mice are important in showing that transitions into and out of adolescence can produce behaviors that differ quantitatively from those observed in younger and older subjects. They further indicate a qualitative difference in mechanisms underlying this learning (see Pattwell et al., 2011, 2012 for further discussion) and the suppression of expression that is unique to adolescents. Their findings, nonetheless, are difficult to reconcile with the many reports employing rats showing strong contextual fear conditioning in adolescents, up to PD 32 (Hunt & Barnet, 2016; Rudy & Morledge, 1994; Schiffrino et al., 2011). Developmental differences between rats and mice, with mice exhibiting earlier maturation of many brain regions important to learning (Clancy et al., 2001) and entering puberty earlier (Korenbrod et al., 1977; Pinter et al., 2007) may underlie this species difference. This hypothesis predicts that rats tested at an age for which brain maturation is comparable to the PD 29 mice, would similarly exhibit an adolescent suppression of context freezing. Data from a study employing the context pre-exposure

facilitation effect that includes age ranges across pre-adolescent, adolescent, and post-adolescent animals, however, do not support this conjecture.

Context pre-exposure facilitation effect (CPFE)—The CPFE is a variant of standard context conditioning in which no CSs are presented. In the CPFE procedure, context conditioning and testing occur during three separate phases that are separated by periods of 24 h or longer (Fanselow, 1990, 2000; Jablonski et al., 2012; Schiffino et al., 2011). During the first phase of the CPFE, the animals are exposed to the context for 2–3 min and then removed. This allows the animal the opportunity to form the requisite conjunctive representation of the context (Rudy, 2009). During Phase 2 the animals are placed back into the context and are given an immediate shock, which by itself is insufficient for context conditioning (Fanselow, 1990). Finally, in Phase 3 the animals are again returned to the context and conditioned freezing is measured. Thus, each component of context conditioning (forming a representation, associative learning, expression) occurs on different days, and thus each can be examined independently.

Robinson-Drummer and Stanton (2015) employed the CPFE procedure in order to study the retention for Phase 1 learning in rats. For our purposes, we will describe only two of their findings. Animals were pre-exposed to the context on PD 24 or 31 (Ph 1) and were trained (immediate shock, Phase 2) following retention intervals of 1, 8, 15 or 22 days. All animals were tested 24 h after training. They found that animals pre-exposed at both ages (PD 24 or 31) exhibited context freezing when shock training occurred after retention intervals of up to 15 days. In other words, in animals given context-shock pairings on days 25, 32, 39 or 46, all expressed freezing 24 h later. Notwithstanding the fact that different conditioning procedures were used, these findings with rats are not consistent with the findings reported by Pattwell et al. (2011) with mice. There was no evidence that rats between the ages of 25 and 46 days show any developmental tendency toward context fear suppression as was observed in mice. Thus it appears that the Pattwell et al. (2011) findings may be unique to mice, and are not accounted for simply by species differences in maturation rate. Furthermore, the results of Akers et al. (2012) using standard context conditioning procedures did not find such a suppression effect in their adolescent mice (PD 30), and thus the Pattwell et al. findings may also be specific for *background* contextual fear conditioning. An important feature of the Pattwell (2011) study with mice was inclusion of preadolescent, early and late adolescent, and adult aged animals permitting evaluation of developmental discontinuities arising from transitions both into and out of adolescence. The Robinson-Drummer and Stanton (2015) experiment with rats is similarly important by its inclusion of animals spanning the preadolescent (PD 25), early adolescent (PD 32) and late adolescent (PD 39, 46) periods. Despite including this wider range of ages which should better permit observation of an *adolescent*-unique suppression of context conditioning, no evidence for age-dependent suppression of context conditioning was found.

Extinction of acquired fear

A full discussion of fear extinction is beyond the scope of this review, and is presented elsewhere in this volume (Baker et al., current volume). Nonetheless, a few important points about fear extinction that relate to some of the research described above will be made.

Examination of extinction processes during adolescence is highly relevant for developing treatment approaches for fear and anxiety disorders that target this age group. Exposure-type therapies that are based on the principles of extinction learning in adults may not be effective for alleviating fear and anxiety in the adolescent (Baker et al., 2014; Liberman et al., 2006).

Pattwell et al. (2012) expanded on their findings of contextual fear expression failure in adolescent mice and reported a somewhat parallel impairment in CS fear extinction. Adolescent mice (PD 29) showed impaired fear extinction compared to either younger or older subjects and indeed showed no evidence of extinction even across 4 days of training. Immunohistochemistry revealed developmental dissociations in mPFC activity that was related to extinction learning. Specifically, c-Fos protein levels in the infralimbic (IL) division of the mPFC, which is involved in extinction learning and retention (Sotres-Bayon & Quirk, 2010), was *increased* in pre-adolescent (PD 23) and adult (PD 70) mice, but not in adolescent (PD 29) mice. Correspondingly, c-Fos protein levels in the prelimbic (PL) division of the mPFC, a region linked to fear acquisition and behavioral expression (Sotres-Bayon & Quirk, 2010), *decreased* in pre-adolescent and adult mice but not in adolescents, which could explain the exaggerated fear conditioning in adolescents described previously (trace conditioning: Barnett & Hunt, 2005; Den & Richardson, 2013; delay conditioning: Hefner & Holmes, 2007)). Further, electrophysiological measures in these areas following CS extinction suggested enhanced IL synaptic potentiation in pre-adolescent and adult mice. No such variation in IL plasticity measures following extinction were observed in adolescent mice indicating an adolescent-unique variation in functional cortical circuitry associated with fear learning and expression.

Richardson and colleagues (e.g. Baker et al., 2014; Baker & Richardson, 2015; Kim et al., 2009) have been assessing extinction learning and extinction retention in developing rats, with an emphasis on adolescence. Baker and Richardson (2015) reported that pre-adolescent (PD 24), adolescent (PD 34) and adult (PD 70) rats exhibited comparable rates of within-session extinction, but that 24 h retention of extinction learning was significantly impaired in the adolescents. However, this was true only when fear acquisition also occurred in adolescence. Animals that were fear conditioned at PD 23 and extinguished at PD 34 showed good retention of fear extinction, as did animals that were trained at PD 34 and extinguished at PD 70. These data indicate that when both fear acquisition and extinction occur during adolescence, extinction retention is poor. Additional results assessing extinction-dependent MAPK activity in the IL and PL revealed age differences as well. There was less MAPK activity in both regions when fear conditioning and extinction occurred in adolescence (Baker & Richardson, 2015). Kim et al. (2009) observed a similar effect that MAPK activity in the IL of adolescent rats is not enhanced by extinction training, whereas it is in PD 23 and PD 75 animals. In sum, both quantitative and qualitative differences in behavior and mechanisms responsible for adolescent learning and retention of extinction have been observed. This suggests unique vulnerabilities and opportunities for treatment of anxiety and affective disorders that emerge during adolescence.

Summary of Adolescent Fear Conditioning

Alterations in learning and behavior uniquely associated with adolescence can be revealed by consideration of developmental changes in the wider distributed circuitry which regulates fear learning and expression. Furthermore, examination of critical *transitions* into and out of adolescence, as opposed to viewing adolescence as merely an intermediate step in a linear progression to maturity (King et al., 2014), is likely to better clarify both constraints and affordances of adolescent learning. The former section reviewing findings in classical conditioning tasks with adolescents reveals clear evidence for adolescent-unique patterns of conditioning within learning systems traditionally viewed as reflexive. In the next section, we extend that review by examining findings from adolescents in non-reflexive (operant) tasks used to explore aspects of decision making.

Choice Behavior and Impulsivity in Adolescence

Paradigms used to assess more complex decision-making processes in rodents typically employ operant conditioning procedures. In operant conditioning, the organism engages in behavior that can be rewarded or punished, altering the frequency of the behavior occurring in the future. Many features of operant conditioning are presumed to be developed by the end of adolescence and in some cases by early adolescence. Literature in classical fear conditioning is similar to that of operant conditioning in that there is little research directly examining whether the transition into and out of adolescence is in fact continuous with earlier developmental stages or whether there are adolescent-unique patterns of behavioral change. Moreover, there is a poor understanding about whether or to what extent in adolescents and adults the same brain mechanisms contribute to motivational systems that drive decision making and other forms of learning (Simon & Moghaddam, 2015). However, some brain systems (i.e., PFC) that contribute to more complex aspects of decision making are known to be functionally immature during adolescence (Giedd, 2004; Mills et al., 2014) and studies described below have shown a greater likelihood of impulsive behavior in adolescents compared with adults, potentially implying monotonic maturation of these systems (see Ordaz et al. 2013 for recent fMRI human longitudinal data).

Neural basis for impulsive behavior during adolescence

The prefrontal cortex has been the significant focus of research trying to understand brain differences that lead to increased impulsive behavior during adolescence (e.g, Silveri et al., 2013). Puberty onset is associated with synaptic pruning in the prefrontal cortex in male and female rats (Drzewiecki et al., 2016). This synaptic pruning has been proposed to support greater response inhibition, although dissociating the contributions of hormonal changes in puberty from neural reorganization is needed (Juraska & Willing, 2016). A considerable amount of research has provided information about the neural mechanisms underlying performance in measures of impulsivity. However, one limitation is that studies typically employ adolescent or adult rats, but do not directly compare the two ages to assess if any brain changes are unique to adolescence. One experiment did provide evidence of differences in the laterality of norepinephrine, as measured by microdialysis, with adolescents showing higher levels in the left ventral prefrontal cortex and adults having

higher norepinephrine levels in the right ventral prefrontal cortex (Staiti et al., 2011). Interestingly, norepinephrine transporter density decreases, from PD40 to PD60, in the prelimbic cortex and in the lateral orbitofrontal cortex, regions associated with cognitive flexibility and reversal learning, respectively (Bradshaw et al., 2016). Finally, impulsive subpopulations of rats have been shown to have lower NE levels in the medial frontal cortex (Adriani et al., 2004). Thus, normative development of the regulation of the noradrenergic system may be critical in the transition to adult-like regulation of impulsive behavior.

Another approach to glean information about relevant neurotransmitter systems is to examine the effects of drugs that act upon specific neurotransmitter systems on measures of impulsivity. Burton & Fletcher (2012) trained adolescent rats in a two-choice reaction time task when animals were required to nose poke to a port which was signaled by a visual stimulus. Any nose pokes during the inter-trial interval (the time between a nose poke on a previous trial and the initiation of the subsequent trial) were considered impulsive responses. Compared to male adult rats, male adolescent rats that were given amphetamine, but not nicotine or the NMDA NR2B subunit antagonist, Ro 63-1908, showed more impulsive behavior in this task (Burton & Fletcher, 2012). The authors concluded that dopaminergic regulation is different in adolescent male rats compared with adult male rats. Differences in dopaminergic activity during adolescence is consistent with differences in reward processing at this age (Simon & Moghaddam, 2015) and with literature related to the implications of impulsive behavior, such as drug use and addiction (Crews & Boettiger, 2009; de Wit, 2009).

Framework for Tasks Assessing Decision-Making and Impulsive Behaviors

A number of processes affected by classical conditioning, including attention, learning and memory, value representation, goal-directed behavior and response selection also contribute importantly to decision making (Blakemore & Robbins, 2012). Impulsive decisions have been characterized by a lack of inhibitory control. Bari and Robbins (2013) have conceptualized several subdivisions of inhibitory control that serve as a useful guide for this section. Specifically, they describe cognitive inhibition (e.g., memories, thoughts) and behavioral inhibition, the latter of which will be the focus here. Behavioral inhibition consists of three components: response inhibition, deferred gratification, and reversal learning. The emphasis of this section will be on describing these three components, the tasks that tap into these processes and the available literature with respect to comparing the performance of adolescent and adult animals in these tasks. Other reviews have thoroughly discussed the translational potential of studying these different forms of impulsivity in animal models for a variety of human conditions, including drug addiction, gambling and attention deficit hyperactivity disorder (Winstanley, 2011).

Response Inhibition

Response inhibition is the ability to inhibit a pre-potent response and includes action restraint and action cancellation (Bari & Robbins, 2013). Extinction in operant tasks involves the reduction of a previously-rewarded response when the reward is omitted. Compared to adults, adolescent rats show slower extinction rates (Andrzejewski et al., 2011), consistent with some of the data on extinction of conditioned fear (above). Response inhibition also can be evaluated in Differential Reinforcement of Low rates of responding

(DRL) procedures. A DRL schedule requires the animal to withhold responding for a particular duration in order to receive the reward; a premature response during this interval resets the waiting time and increases the delay to reward. Adolescent rats respond more frequently during the non-rewarded time interval compared with adult rats (Andrzejewski et al., 2011), which is interpreted as a more impulsive behavioral pattern. Other tasks for assessing response inhibition include go/no go tasks, action restraint or withholding, and stop signal tasks, requiring action cancellation (Bari & Robbins, 2013). To our knowledge, no studies have compared performance of adolescents with other age groups in go/no go or stop signal tasks. Collectively, the available research in this area suggests that adolescents are slower to learn under conditions that require response inhibition, and therefore show more impulsive behavior.

Deferred Gratification

Impulsivity is also a component of deferred gratification, often studied using discounting tasks. Deferred gratification is an organism's ability to withhold responding for a small reward in order to gain a larger reward. This aspect of inhibition can be assessed with different procedures, including delay discounting, probability discounting and effort discounting. In these tasks, a choice is available between a small reward and a larger reward. To receive the larger reward, the animal must (a) wait for a longer time, (b) receive the large reward with a certain probability, or (c) must engage in additional work (e.g., press a lever more often). Impairments in deferred gratification are considered impulsive choice (Bari & Robbins, 2013).

One challenge with this research area is that the amount of time required to train animals in these tasks (several weeks to months) typically exceeds the brief adolescent period in rats. However, Adriani et al. (2003) developed procedures for testing adolescent rats in a delay discounting task (see also Adriani et al., 2010). The primary changes that facilitated the rate of task acquisition were the use of nose pokes as the operant response (as opposed to lever presses) and overnight training sessions. This group reported that adolescent rats (PD 30-46) showed a shift in preference for a large, delayed reward to a small, immediate reward when the delay to receive access to the large reward was changed from 15 to 30 sec (Adriani & Laviola, 2006), indicating a reduced ability to delay gratification for the larger reward outcome. In the same manuscript, Adriani and Laviola (2006) reported that adolescent rats preferred a large, unpredictable reward compared with a smaller, certain reward, suggesting that these rats selected the riskier option. However, there was no group of adult rats compared directly with the adolescents in these experiments. Doremus-Fitzwater et al. (2012) did compare adolescent and adult rats in a delay discounting task and found that the adolescent rats were more likely than adults to select the smaller, immediately available reward, again suggesting adolescent's reduced ability to delay gratification in favor of a larger reward.

McClure et al. (2014) innovated a procedure which allows the contribution of the delay component in the discounting procedure to be uniquely assessed (as opposed to reward magnitude) by offering the same sucrose reward to adolescent rats in either of two response options. These investigators had one lever for which the time to receive reward was variable

and another lever for which the delay to receive reward after a press was stable. Adolescent rats initially preferred pressing the variable lever. The delay on the stable lever was then systematically reduced until the animals showed no preference for the two levers. The final delay on the stable lever at which responding to the two levers was similar then served as a measure of delay discounting (i.e., only delay, and not reward, was varied). These authors additionally measured time perception using a peak interval task. Rats that demonstrated more precise time perception were less likely to exhibit impulsive-like behavior in the delay discounting task. The McClure et al. (2014) procedure is interesting because it uniquely isolates one of the key variables (delay) known to affect impulsive action in adolescents. Its further exploit could critically inform how impulsive action varies as a function of delay over development. Notably, however, McClure et al. (2014) reported adolescent animals exhibited a small but significant reduction in delay discounting compared to adults when testing the same group of animals at different ages; though the authors acknowledge this pattern cannot be uniquely attributed to age-specific traits in impulsivity and could be the result of experience (re-testing).

In summary, with limited exception the available literature suggests that adolescent rats are more likely to make impulsive and riskier decisions compared with adult animals. Also, some important individual differences that may influence impulsive choice behavior, such as time perception, are beginning to be investigated. For example, a recent experiment reported that adolescent male rats expressing individual differences of high activity, but low preference for novelty, were more likely to exhibit impulsive patterns of responding, by preferring a small, immediate reward in a delay discounting task (Lukkes et al., 2016). A rich area for future investigation will be to better understand whether variables that are correlated with the presence of impulsive behavior can be manipulated to probabilistically influence the likelihood (i.e., are critical influences) of impulsive behavior.

Reversal Learning

Reversal learning is a further metric of behavioral inhibition because it requires the ability to respond flexibly following changes in reinforcement contingency or discrimination rules (i.e., to inhibit former response patterns when new contingencies are encountered). Deficits in reversal learning are associated with increases in inflexible, compulsive behaviors (Bari & Robbins, 2013). Set shifting tasks are one class of procedures for assessing flexible changes in response learning. Newman and McGaughy (2011) used a procedure in which rats learned to dig in sand within small pots in order to obtain a reward. The rats were trained to discriminate between stimuli based upon different dimensions: the texture of the pots, the digging media, or the scent of the sand. After learning an initial discrimination, rats were exposed to either an intradimensional or extradimensional shift. In the intradimensional shift condition, identifying the rewarded pot was still based upon the same cues (dimension) that had previously been relevant, for example, the scent of the sand, but the specific scent that signaled reinforcement was changed. In the extradimensional shift condition, a new dimension, for example, the digging media became the relevant feature signaling availability of reward. Typically, extradimensional shifts require more trials to reach criterion because the animal must stop responding based upon the previously relevant dimension, determine which dimension is now relevant, and learn the discrimination rules based upon the new

relevant dimension and contingency. Newman and McGaughy (2011) reported that adolescent rats required more trials to reach criterion when there was an extradimensional shift compared to adult rats. Importantly, adolescent rats were able to learn the initial discrimination as quickly as adult rats, and performed comparably to adults when there was an intradimensional shift. Moreover, adolescent rats were slower to reach criterion learning when a second, irrelevant (distracting) dimension was included. Thus, the adolescents show less flexibility in adjusting and inhibiting old patterns of responding when contingencies change and more susceptibility to distraction than do adults.

Summary of Decision-making Section

Decision making is multi-faceted and served by numerous cognitive processes. The available literature strongly indicates that critical aspects of decision making processes change from adolescence into adulthood. Largely, adolescent animals display a more impulsive pattern of responding and engage in riskier decisions than adults, something that occurs in human adolescents as well (e.g. Green et al., 1994; Humphreys et al., 2016). At least in tasks described, there are no studies that have included pre-adolescent, adolescent, as well as adult animals permitting direct comparison. We also note that, for other tasks used to examine aspects of choice behavior (e.g. go/no go task, stop signal task), there are no studies to our knowledge that directly compare adolescent and adult animals. Thus, there is a clear need to expand upon the available literature to more comprehensively assess decision making in adolescence.

Conclusions and Future Directions

Adolescence is a time of numerous transitions in brain connectivity that impact learning and choice behavior. The available literature suggests that mechanisms responsible for classical conditioning are largely functional by early stages of adolescence (~ PD 30). However, the scarcity of research on developmental transitions in conditioning, before, through adolescence, and into adulthood makes it difficult to fully characterize the extent to which basic reflexive conditioning processes change during and after adolescence and the relevance of such alterations to the ontogenetic vectors of more flexible, complex, memory and behavioral competencies. For example, generalization gradients relevant to how environmental stimuli are perceived and control behavior, or the ability to form associations between greater varieties of stimuli including one associations' ability to modulate activation or inhibition of other associations (Baker et al., this volume; Bouton, 1993; Holland, 1992) may change during or after adolescence. The literature has established that basic conditioning processes are intact by early adolescence, but transitional changes in these processes remain poorly investigated.

One further direction for research is to better understand how basic reflexive learning processes, such as conditioning, that develop relatively early in life, impact later-developing and more complex processes such as decision making. These two aspects of behavior overlap in terms of cognitive components (attention, learning, representation of stimulus or reinforcer value, response selection, and inhibition), as well as critical components of underlying neural circuitry (hippocampus, mPFC) which is, at a minimum, suggestive of

developmental interplay. For example, environmental experiences including early life stress or exposure to toxins, which can alter the trajectory of normal development of conditioning might impact decision making processes later in life (Kosten et al., 2006; Nakao et al., 2013). Wright et al. (2015) exposed adolescent (PD 26-35) rats to a variety of stressors (e.g., restraint, tail pinch) and later evaluated acquisition of Pavlovian fear conditioning to a CS that differed in probability of US (shock) occurrence. During the learning phase, a CS was 100% predictive of US presence, 100% predictive of US absence, or 25% probabilistically predictive of US presence. Control rats that did not receive stressors in adolescence accurately adjusted fear behavior measured as a suppression ratio based on the different contingencies over sessions, coming to suppress most to the CS that reliably predicted US presence, suppress minimally to the CS that reliably predicted US absence, and suppress at intermediate levels to the uncertain 25% predictive CS. Rats exposed to stressors as adolescents, however, were slower to reduce fear to the 25% predictive CS and displayed comparatively protracted fear suppression to the CS that predicted US absence. Wright et al. (2015) argued that stress during adolescence alters and impairs development of the ability to use negative prediction errors in order to adjust associative strength later in adulthood. This implies that experiences during adolescence can alter fundamental underlying mechanisms responsible for associative learning (cf. Rescorla & Wagner, 1972). Moreover, Wright et al. (2015) suggest that alterations in the capacity to use negative prediction errors was produced by their experimental manipulation affecting the dorsal raphe nucleus that shares projections with the PFC whose function overlaps critically in complex choice behavior (Amat et al., 2005; L. Clark et al., 2004). Though speculative, it is reasonable to assume that fundamental alterations in the ability to adjust predictions of environmental threat would affect risk assessment and subsequent decision making. Our point is simply that how alterations in normative development of learning processes engaged in conditioning paradigms affects more complex aspects of behavior, even independent from any assessment or manipulation of underlying neural systems, is not well-understood. The field would benefit from data that inform how environmental experiences that alter behavior by facilitating or inhibiting development of basic learning processes during adolescence (i.e., ‘conditioning’) impact the capacity for normative and adaptive regulation by ‘top down’ learning processes associated with decision making during later adulthood. Moreover, translational and early intervention studies are needed to assess the extent to which *ameliorating* experience-produced alterations in the development of basic learning processes can be a therapeutic target for improving developmental outcomes in later life for complex cognitive processes. This approach may be particularly relevant for conditions characterized by broader and widespread changes in neural connectivity, where the development of targeted pharmacotherapies is challenging.

The present review highlights some key transitions and discontinuities in the developmental period associated with adolescence. However, the corpus of available literature has focused on the day (i.e., postnatal day) since birth when defining “adolescence” and assigning subjects to different age-grouped experimental conditions. Different insights may emerge by examining specific transitions in neural or behavioral markers to designate developmental conditions, rather than birth date per se (current age). An important problem, or at least constraint, emerges when studies of conditioning and decision making reveal deficits of

performance in adolescents of a specific age compared to adults because they encourage a view of simple monotonic development in relevant neural and behavioral systems. This kind of view is not supported by findings that, in some situations, younger (preadolescent) and older (adult) animals express similar learning patterns, whereas adolescents exhibit a quite different pattern (Den & Richardson, 2013; Kim et al., 2009; Pattwell et al., 2011, 2012). There are additional complexities. When learning in two highly related tasks (e.g. trace and long-delay fear conditioning) is ontogenetically time-locked and emerges in parallel during development, it would be reasonable to assume that they are both mediated by attainment of progressive functional maturity in the same neural system. Yet, there is clear evidence to the contrary (Barnet & Hunt, 2005; Hunt & Richardson, 2007; Ivkovich & Stanton, 2001). Analysis of mechanisms responsible for learning in different tasks including variation in ontogenetic vectors for learning in those tasks, before as well as after adolescence, is likely to further inform unique and normative aspects of adolescent development.

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Highlights

- Fear conditioning during adolescence is greater than at other ages
- Adolescent rodents show exaggerated fear and less fear extinction
- Adolescent rodents are more impulsive and choose riskier options
- Conditioning and decision making reveal nonlinear features during adolescence

Figure 1.

Left panel. Rats ranging in age from 18 to 32 days of age at training. Animals were given 10 light CSs (25-W bulb, flash rate 250ms on/off, 10 s duration) and 10 USs (0.5mA, 1 s duration) during a 60-min training session. Delay subjects were given trials in which the CS was immediately followed by the US. Trace subjects were given pairings of the CS followed by a 10-s trace interval. Unpaired animals were given the CSs and USs in an alternating but explicitly unpaired manner. All animals were tested for CS-elicited freezing 24 h later in a novel context. Data are mean $\pm$ SEM and based on 8-10 subjects per group. Freezing was measured using a time-sampling procedure. Change Freezing (%) = % CS freezing - % pre-CS freezing (from Barnet & Hunt, 2005). *Right panel.* Adolescent (35 days old) and adult (75 days old) animals were given 5 CS-US pairings in a 30-min session. CS, US and test procedures were identical to those of Barnet & Hunt (above). Importantly, adolescent animals (PD 32-35) exhibited the same high levels of freezing after 5 or 10 training trials,

and older and younger animals showed less trace conditioned responding than adolescents. Delay conditioned responding was equivalent at all ages for both studies.

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Table 1

Published findings on conditioning and decision making during adolescence

Nature of Task	Subjects/Ages	Findings	Reference
Delay conditioning	C57BL/6J mice 4 vs. 6 vs. 8 weeks old	stronger delay conditioning but similar extinction in adolescents (4-wk)	Hefner & Holmes (2007)
Delay/Trace conditioning	Sprague Dawley rats PD 18 through PD 32	equivalent delay but stronger trace conditioning in adolescents than preadolescents	Barnet & Hunt (2005); see also Moye & Rudy (1987)
Delay/Trace conditioning	Sprague Dawley rats PD 35 vs. PD 75	equivalent delay but stronger trace conditioning in adolescents than adults	Hunt (unpublished data)
Delay/Trace conditioning	Sprague-Dawley rats PD 23 vs. PD 35 vs. PD 90	Equivalent freezing to delay CS. PD 23 and 90 fail to show trace conditioning. PD 35 express high and equivalent freezing to delay and trace CS	Den & Richardson (2013)
Context conditioning	Long Evans Rats PD 18 vs. PD 23 vs. PD 32	No differences in context conditioning across ages	Rudy & Morledge (1994); see also Rudy (1993)
Context conditioning	C57Bl/6 × 129Svev mice PD 13-17, 30, 60	Context conditioning seen in PD 14 mice. Context freezing equal in PD 15, 30 and 60 mice.	Akers et al. (2012)
Context conditioning	Long Evans Rats PD 17 vs. PD 24 vs. PD 31	High and similar context conditioning in PD 24 and PD 31 compared to PD 17	Schiffinio et al. (2011)
Context conditioning	Long-Evans rats PD 17 vs. PD 24 vs. PD 31 vs. PD 52	Using the CPFE procedure, demonstrated equivalent levels of context freezing in rats trained at PD 25, 32, 39, 46, or 75. No context freezing in PD 17 rats.	Robinson-Drummer & Stanton (2015)
Context conditioning	Sprague-Dawley rats PD 17 vs. PD 28-31 vs. PD 50-70	PD 17 and adolescents (PD 28-31) show background context conditioning but adults do not	Esmoris-Arranz, Méndez, & Spear (2008)
Delay and context conditioning	B6/129 F1 hybrid mice 4-5 vs. 9-10 weeks old	equivalent delay and context conditioning at both ages but greater generalization of delay and context conditioning in 4-5 week olds	Ito et al., (2009)
Delay and context conditioning	C57BL6/J mice PD 23 through PD 70	equivalent delay conditioning at all ages but impaired context fear expression in PD 29-33 adolescents	Patwell et al. (2011)
Extinction of delay conditioning in mice; extinction of differential (CS+/CS-) conditioning in humans	C57BL6/J mice PD 23 through PD 70; and approx. 9-yrs vs. 14-yrs vs. 23-yrs old humans	impaired extinction in both adolescent mice and humans, compared to preadolescents and adults	Patwell et al. (2012)
Extinction of delay conditioning	Sprague Dawley rats PD 24 vs. PD34 vs. PD 70	similar within-session extinction across ages but impaired 24-hr retention of extinction in adolescents	Baker & Richardson (2015)
Response inhibition/differential reinforcement of low (DRL) rates schedules	Sprague Dawley rats/ begin testing at PD 28 or PD 83 (± 3 days)	Adolescents were less sensitive than adults in	Andrzejewski et al. (2011)

Nature of Task	Subjects/Ages	Findings	Reference
		adapting responding to DRL schedule	
Response inhibition/5-choice serial reaction time	Sprague Dawley rats/ begin testing at PD 21 or PD 70	Adolescent rats show more impulsive responding during inter-trial interval compared to adults	Burton & Fletcher (2012)
Deferred gratification/delay discounting	Wistar rats/begin testing at PD 30	Adolescent rats show intolerance for delay	Adriani & Laviola (2006)
Deferred gratification/delay discounting	Sprague Dawley rats/ begin PD 25-27 or PD 68-71	Adolescent rats more impulsive than adult rats	Doremus-Fitzwater et al. (2012)
Deferred gratification/delay discounting	Wistar rats/begin pretraining at PD 23	Adolescent rats with more precise discrimination of timing were less impulsive	McClure et al. (2014)
Deferred gratification/probability discounting	Wistar rats/begin testing at PD 30	Adolescent rats show greater risk taking for large reward	Adriani & Laviola (2006)
Set shifting	Long Evans rats/begin testing at PD 39 or PD 66	Adolescent rats more cognitively rigid than adults	Newman & McGaughy (2011)