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Author: Tamara L. Doremus-Fitzwater PhD Linda P. Spear PhD

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Reward-centricity and attenuated aversions: An adolescent phenotype emerging from studies in laboratory animals

Running Head: Adolescent Rats and Reward

Tamara L. Doremus-Fitzwater, PhD & Linda P. Spear, PhD

Affiliation:
Developmental Alcohol Exposure Research Center
Center for Development and Behavioral Neuroscience
Department of Psychology
Binghamton University
Binghamton, New York 13902-6000
USA

*Address Correspondence to:
Dr. Tamara L. Doremus-Fitzwater
Department of Psychology, Williams Hall
Ithaca College
953 Danby Road
Ithaca, NY 14850
Email: tlfitzwater@gmail.com
phone: 607-777-2449
Fax: 607-777-4890

Highlights

- Brain reward circuits and behaviors change similarly across species in adolescence
- Data suggest adolescence is characterized by a heightened sensitivity to rewards
- Conversely, adolescents exhibit attenuated sensitivity to many aversive stimuli
- Mesocorticolimbic DA and endocannabinoid changes may contribute to these behaviors
- Adolescent behaviors promote adaptive achievements, but also impart vulnerability

Abstract

Adolescence is an evolutionarily conserved developmental period, with neural circuits and behaviors contributing to the detection, procurement, and receipt of rewards bearing similarity across species. Studies with laboratory animals suggest that adolescence is typified by a "reward-centric" phenotype—an increased sensitivity to rewards relative to adults. In contrast, adolescent rodents are reportedly less sensitive to the aversive properties of many drugs and naturally aversive stimuli. Alterations within the mesocorticolimbic dopamine and endocannabinoid systems likely contribute to an adolescent reward-sensitive, yet aversion-resistant, phenotype. Although early hypotheses postulated that developmental changes in dopaminergic circuitry would result in a "reward deficiency" syndrome, evidence now suggests the opposite: that adolescents are uniquely poised to seek out hedonic stimuli, experience greater "pleasure" from rewards, and consume rewarding stimuli in excess. Future studies that more clearly define the role of specific brain regions and neurotransmitter systems in the expression of behaviors toward reward- and aversive-related cues and stimuli are necessary to more fully understand an adolescent-proclivity for and vulnerability to rewards and drugs of potential abuse.

Keywords: Adolescent, Rat, Reward, Aversion, Neurobiology, Behavior

Introduction

Reward-related behaviors guide organisms toward environmental stimuli that are necessary for individual, as well as species survival. As individuals need to forage for food and fluids, engage in social interactions with conspecifics, locate safe habitats, and find a mate for sexual reproduction, natural rewards provided by procurement of these goals steer attention toward appropriate stimuli and reinforce behaviors leading to these goals. While some of these survival goals begin at birth, others gain importance over the course of development. During adolescence, many of these goals and behaviors take on new significance, with the gradual transition from dependence on adults and the family unit to relative independence and a focus on peer interactions (for review see Crone and Dahl, 2012; Spear, 2000). Thus, the adolescent transition between childhood and adulthood represents a unique ontogenetic niche during which adolescents often behave quite distinctly from their younger and older counterparts. This may be especially true with regards to reward-related neural systems and behaviors.

The goals of survival and reproduction are conserved across species, and thus it is not surprising that neural circuits and behaviors related to finding and consuming the necessary rewards to attain these goals likewise bear similarity across mammalian species. Indeed, research both with human subjects (e.g., Delgado, 2007; Haber and Knutson, 2010; O'Doherty, 2004; Sescousse et al., 2013) and in laboratory animals (e.g., McBride et al., 1999; Schultz, 2010; Sesack and Grace, 2010; Spanagel and Weiss, 1999) has demonstrated notable concordance across species regarding the neural substrates contributing to the detection, procurement, and receipt of rewards, as well as the behaviors promoted by these brain circuits. Moreover, the ontogenetic transition of adolescence itself has been shown to be an evolutionarily conserved developmental phase that is characterized by similar neural, hormonal, physiological, and behavioral alterations in a wide variety of mammals. In particular, the rodent appears to be a well-suited medium for investigating neural and behavioral transformations of

adolescence, as adolescent rats and mice recapitulate elevations in peer-directed social interactions, risk-taking/novelty seeking, and drug and alcohol use that are observed in their human counterparts. Additionally, adolescent rodents have been reported to exhibit significant changes in motivational and reward-related behaviors (as reviewed below), as well as marked transformations in reward-relevant neural regions and related neurocircuitry, with similarity in these fundamental neural alterations again evident between human adolescents and laboratory animals (for reviews see Spear, 2000; 2011; Wahlstrom et al., 2010). The exact beginning and end of adolescence are equally imprecise events in both humans and rodents that are determined by a combination of neural, biological, behavioral, and social factors. Given these transitional "gray zones," research studies have determined the approximate timing of adolescence to conservatively occur from postnatal days (P) 28 to 42 (see Spear, 2000 for review), but with broader definitions identifying the six-week period from P28 to 55 as a more all-encompassing (early adolescence through late adolescence/emerging adulthood) categorization of adolescence in rats (e.g., see Vetter-O'Hagen and Spear, 2012).

This review is guided by the hypothesis that adolescence is characterized by a reward-sensitive phenotype, where goal-directed behavior is dominant and receipt of rewards is particularly reinforcing. Such "reward-centricity" may not only favor a focus on primary rewards such as food, water, social, and, eventually, sexually attractive stimuli, but may direct behavior towards other rewarding stimuli as well. In many individuals, positive experiences and opportunities provide the scaffolding for adolescents to focus on rewards related to academic pursuits, sports, and other constructive activities that lead to immediate or future success (Telzer, 2016). Yet, the reward-sensitive phenotype of adolescence may also impart a liability at this age. Reward-centricity may promote sensation-seeking and risk taking behaviors directed toward the attainment of other, potentially detrimental rewards including drugs and alcohol. While some expression of these behaviors is normative during adolescence, in the presence of

difficult and stressful environments or other vulnerabilities (e.g., risk-prone peers), the "reward-sensitive" phenotype of adolescence may prove maladaptive, leading for example to patterns of binge drinking and escalated drug use (e.g., D'Amico and McCarthy, 2006; Roberts et al., 2015; Simantov et al., 2000). Such propensities for alcohol/drug use during adolescence may not only be encouraged by an adolescent reward-sensitive phenotype, but also by (as we shall see) an attenuated sensitivity to aversive stimuli, including the aversive properties of alcohol, nicotine, and illicit drugs. This pattern of increased rewarding but decreased aversive sensitivities may help to promote high levels of alcohol/drug use among susceptible adolescents—elevated use that has the potential to impact normative developmental changes in brain structure and function during this critical period, thus altering neural processes and behaviors occurring within adolescence, as well as into adulthood (see reviews by Silveri et al. and Spear in this Issue).

Adolescent sensitivity to rewards

Adolescents differ notably from younger and older organisms in the ways in which they respond to meaningful stimuli in their environment. Sensitivity to rewarding stimuli often appears to peak in adolescence, an effect that is evident in both studies with humans (see van Duijvenvoorde et al., this issue) and in work with laboratory animals (e.g., Doremus-Fitzwater et al., 2010). Among human adolescents, for example, peer interactions and social rewards are of particular importance given that they interact more with peers than at other developmental periods (Hartup and Stevens, 1997), find peers to be a major source of positive experiences (e.g. Brown, 2004), and are more influenced by peers in their decision-making than adults (Gardner and Steinberg, 2005). When using self-reports to assess reward-related behavior across age, a peak in reward seeking was observed at 12-15 years of age, and at levels higher than seen at younger or older ages (Steinberg et al., 2009). When reward sensitivity was indexed via the Behavioral Approach System (BAS) scale, a developmental rise was observed

in the BAS through early to late adolescence, followed by a decline in the early twenties (Urosĕvić et al., 2012). Likewise, reward seeking in a gambling task was reported to peak beginning at 14-15 years of age, while declining after 21 years – a notably different pattern of ontogenetic sensitivity than seen with avoidance behaviors that were low early in adolescence and only increased gradually over age (Cauffman et al., 2010). Even the preference for a natural reward—sweet tastes—was found to be greater early in adolescence (11-15 years) than during late adolescence/emerging adulthood (19-25 years) (Desor and Beauchamp, 1987). A multitude of other studies have demonstrated enhanced sensitivity to rewarding stimuli in human adolescents for both decision-making/risk taking behaviors, as well as for cognitive control and learning behaviors, data that have been recently reviewed by van Duijvenvoorde and colleagues (in this Issue).

Similar age-related enhancements in sensitivity to a variety of rewarding stimuli are evident in studies using rodents to examine the adolescent transition, which ranges from approximately postnatal days (P) 28-42 (early/mid adolescence) to P43-55 (late adolescence) (see Vetter-O'Hagen and Spear, 2012). Like their human counterparts, adolescent rodents are more sensitive to palatable foods and tastes than adults (Friemel et al., 2010; Wilmouth and Spear, 2009). They additionally have been found to engage in higher overall levels of social behavior than adults, while displaying a different pattern of social interactions that emphasizes play, rather than more adult-typical social investigation (e.g., Vanderschuren et al, 1997; Varlinskaya and Spear, 2002; 2008). Adolescent rodents also exhibit enhanced novelty seeking (Adriani et al., 1998; Philpot and Wecker, 2008; Stansfield and Kirstein, 2006) relative to their more mature counterparts. The incidence of such behaviors may be especially high during adolescence because adolescents find these stimuli to be particularly reinforcing. Indeed, adolescents have been found to be more sensitive than adults to the rewarding effects of social peers (Douglas et al., 2004), as well as to novelty (Douglas et al., 2003), when indexed via conditioned place preferences (CPP)–i.e., the development of a preference for a place

previously paired with social or novel stimuli relative to an equally familiar place where no such pairings were given (Bardo and Bevins, 2000). When drugs were paired with one of the chambers of the CPP apparatus, adolescents have been shown to be more sensitive than adults to the rewarding consequences of drugs such as nicotine (Ahsan et al., 2014; Dannenhoffer and Spear, 2016; Shram et al., 2006; Torres et al., 2008) and cocaine (Brenhouse and Andersen, 2008; Brenhouse et al., 2008; Zakharova et al., 2008; but see Aberg et al., 2008), as they exhibit significant CPP (i.e., spend more time on the drug-paired side) at lower doses than do adults. Likewise, numerous laboratories have observed that under a variety of circumstances adolescent rats exhibit greater intravenous (i.v.) self-administration than adults for cocaine (Anker and Carroll, 2010; Wong et al., 2013), amphetamine (Shahbazi et al., 2008), methamphetamine (Anker et al., 2012), and nicotine (Ahsan et al., 2014; Levin et al., 2011; Natividad et al., 2013), although it should be mentioned that some negative findings have emerged (e.g., for cocaine: Harvey et al., 2009; for nicotine: Schassburger et al., 2016; Schram et al., 2008a; 2008b). Critical variables influencing age differences in drug self-administration may include age of initiation during adolescence (with early adolescence perhaps being a particularly sensitive period – Levin et al., 2011), length of access period (Anker et al., 2012), dose and operant schedule (Schram et al., 2008a; and 2008b), dependent measure of focus (e.g., self-administration per se versus drug-seeking behavior – Doherty and Frantz, 2012), and whether animals were group- or isolate-housed (the latter has been reported to increase drug/alcohol abuse vulnerability in adolescent rodents – Butler et al., 2016). Furthermore, and as is reminiscent of human adolescents and demonstrated in Figure 1, adolescent rats and mice have been observed to drink more alcohol per drinking occasion than adults in many test circumstances (e.g., Doremus et al., 2005; García-Burgos et al., 2009; Schramm-Sapyta et al., 2014; Tambour et al., 2008; Vetter et al., 2007; Walker et al., 2008). For the data sets shown in Figure 1, human adolescents drank 88% more alcohol than adults during a drinking occasion. In rodents, the difference was even greater, with adolescents drinking 156% more than adults.

Such differences have not been ubiquitous (e.g., Siegmund et al., 2005), however, and perhaps especially when alcohol access was not provided until late adolescence (as in Doherty and Gonzales, 2015; Schramm-Sapyta et al., 2010). Adolescent rats seem to find ethanol to be more rewarding than adults when indexed via second order conditioning (Pautassi et al., 2008) and the heart-rate response to ethanol consumption (Ristuccia and Spear, 2008), whereas adolescent mice exhibit this via a greater locomotor stimulant effect to acute challenge with ethanol during the rise in blood alcohol levels shortly after administration (Quoilin et al., 2010). Yet, evidence for greater reward sensitivity during adolescence was not seen in mice when indexed via CPP (Song et al., 2007; Dickinson et al., 2009), perhaps due to induction of conditioned activity that may compete with expression of CPP (see Camarini and Pautassi, 2016, for discussion). Thus, under a variety of (but not all) circumstances, adolescent rodents join their human counterparts in exhibiting a "reward-sensitive endophenotype" (see Stolyarova and Izquierdo, 2015), often displaying an enhanced sensitivity relative to adults to positive rewarding properties of a variety of stimuli, ranging from natural stimuli to alcohol and drugs of abuse. The precise circumstances under which this adolescent-typical reward-sensitivity phenotype is and is not expressed, however, require further study.

Rewards and goals

The reward sensitive endophenotype of adolescence in rodents is evident in their goal-directed responding and how hard adolescents are willing to work for rewards. For instance, Stolyarova and Izquierdo (2015) examined performance of adolescent and adult rats on choice trials where they were able to choose between: 1) a large reward requiring substantial effort (i.e., crawling over a high barrier wall to reach 2 "Froot Loops"); 2) a medium reward with moderate effort (1 Froot Loop; a shorter wall); or 3) a small reward with little effort (1/2 Froot Loop; no barrier). Relative to adults, adolescents demonstrated a rightward shift in their preference for the moderate and larger rewards, as indexed by significant increases in the number of times they chose the more effort-requiring medium and large rewards compared to

the small reward (and low-effort option) (Stolyarova and Izquierdo, 2015). Ontogenetic differences were additionally observed in a study where mid- (P40) and late- (P50) adolescents were compared with adults (P90) in their performance on a progressive ratio task. In this task, the number of lever presses required to receive a bit of sweetened condensed milk was increased by two responses over subsequent trials (i.e., response requirements of 2, 4, 6, 8, etc. lever presses). Using this procedure, late adolescent animals completed significantly higher response requirements than did adults (as well as younger adolescents) (Friemel et al., 2010). Both of these data sets form a nice contrast with evidence that adolescents exhibit greater impulsivity compared to adults when indexed via delay discounting (i.e., greater responding for a more immediate smaller reward than a delayed greater magnitude reward) (Doremus-Fitzwater and Spear, 2012). Collectively these findings highlight that adolescents may find higher magnitude rewards sufficiently motivating such that they will *expend greater effort* than adults to attain them (Stolyarova and Izquierdo, 2015; Friemel et al., 2010). Yet, at the same time, the more impulsive nature of adolescence renders them *unlikely to wait* as long as adults in order to attain a larger reward when a smaller reward is more immediately available (Doremus-Fitzwater and Spear, 2012).

In other rodent studies, adolescents have been shown to not only work harder for rewards, but to be unusually reward- (goal-) directed under some circumstances. Serlin and Torregrossa (2015) gave adolescent and adult animals extended training on an operant lever press schedule for a sweetened alcohol solution that was designed to promote development of habitual behavior. Formation of habits was then indexed via an insensitivity to contingency degradation. Using this procedure, response declines during a test where reinforcers are still given, but are unrelated to lever pressing, is thought to reflect goal-directed behavior, whereas an insensitivity to removing the response/reinforcer contingency is used to index habitual behavior. In this test, adults were found to be unaffected by the degradation procedure, suggesting that their lever pressing had become habitual. In contrast, adolescents' response

rates declined during degradation—a pattern of behavior consistent with expression of goal-directed responding. Even with more extended training that was designed to promote stronger habit formation, adolescent animals remained goal-directed (Serlin and Torregrossa, 2015). Similar evidence for greater goal-directed responding by adolescent rats, and more rapid habit formation by adult rats, has recently been obtained in our laboratory. In this study, an operant task for food reward was used, with responding after reinforcer devaluation measuring goal-directed responding (indexed via attenuated responding following pre-session massed access to the operant reinforcer) and maintenance of responding despite pre-test devaluation assessing habitual behavior (Fager and Spear, in preparation). Reminiscent of the Serlin and Torregrossa (2015) study, the adolescents in the Fager and Spear study remained goal-directed at a point in training where the adults displayed evidence of habitual behavior. Consistent with a potential increased focus on goals and rewards during adolescence, adolescents also have been reported to be more resistant to extinction than adults (Andrzejewski et al., 2011; Brenhouse et al., 2010; Spear and Brake, 1983; Sturman et al., 2010). Such age differences are not always evident (Hammerslag and Gulley, 2014; Naneix et al., 2012), however, and may depend, in part, on the nature of the reward and other test variables.

Incentive salience in adolescence

One useful distinction that has been drawn in the reward literature in adult animals is that characterized by Robinson and Berridge (2008) between “wanting” (the seeking of rewarding stimuli), and “liking” (the hedonic response to the reward per se). Wanting refers to the incentive salience ascribed to cues associated with desired rewarding stimuli, including both natural stimuli and alcohol/drugs (Berridge and Robinson, 1998). The attribution of incentive salience to reward-predictive cues is a process that can sensitize with repeated pairings, especially in response to cues associated with drugs of abuse, thereby increasing wanting behaviors. Indeed, repeated drug exposure has often been shown to enhance responsiveness to the locomotor stimulating effects of drugs. Such behavioral sensitization is typically stronger

in the presence of discrete or contextual cue(s) associated with drug exposure, and is thought to be associated with cue/context-dependent increases in incentive salience and motivation for the drug, thereby increasing propensity for drug abuse (e.g., Robinson and Berridge, 1993). Incentive salience also has been studied via assessment of sign-tracking, which is defined as an induction of behavior towards a cue predictive of an upcoming appetitive reward. Using a Pavlovian conditioned approach (PCA) procedure involving the repeated pairing of a cue followed some seconds later by receipt of a reward, some rats typically develop into "sign trackers," whereby they approach and contact the reward-predictive cue during the lag period between cue presentation and reward delivery (e.g., Flagel et al., 2008; Robinson and Flagel, 2009; Tomie et al., 2012). In contrast, "goal trackers" exhibit an opposite strategy and approach the location where the reward will be given.

When examining incentive salience during adolescence using both assessment of context-dependent drug sensitization as well as emergence of sign-tracking behavior, adolescents have been found to show less evidence of incentive motivation than adults. For instance, when examining ethanol-induced locomotor sensitization in mice, adolescents did not exhibit a context-dependent sensitization that was evident in adults (Faria et al., 2008). Moreover, in another study, adolescents required higher doses than adults in order to exhibit sensitization to ethanol, although once adolescents were given sufficiently high doses to express sensitization, they expressed greater sensitization than adults (Quoilin et al., 2012). Interestingly, whereas adolescents did not show context-dependent sensitization in the Faria et al. (2008) study, they did express sensitization of the locomotor stimulant response when ethanol was given in the home cage rather than being paired with the test context—data which suggest that adolescents may find it difficult to show increased incentive salience to reward-predictive cues. A similar conclusion emerged from the study of sign-tracking behavior in a food-motivated PCA task, where adolescent rats often showed notably weaker sign-tracking (Doremus-Fitzwater and Spear, 2011) and enhanced goal tracking (Anderson et al., 2013;

2011) when compared to their adult counterparts. Thus, although adolescents often appear notably motivated and directed towards rewards, they seem less prone to link these rewards to predictive cues in their environment, and may instead attribute more incentive salience to the goals themselves under certain testing circumstances. While one could alternatively interpret reduced cue-associated behavior among adolescents as an immaturity of associative cognitive processes, other data from conditioning based studies (e.g., latency to approach the goal delivery area) would suggest that adolescents do develop associations between cues and rewards similarly to adults (e.g., see Anderson and Spear, 2011).

These findings are reminiscent of fMRI studies reporting that under some circumstances the ventral striatum of human adolescents is recruited less than that of adults during a cued reward anticipation period (Bjork et al., 2004; Geier et al., 2010), but not in response to receipt of rewards where enhanced ventral striatal activation has sometimes (e.g., Galvan et al., 2006; van Leijenhorst et al., 2010) although not always (e.g., Bjork et al., 2004; Forbes et al., 2010) been reported in adolescents relative to adults. Additional evidence for an attenuated sensitivity of adolescents to reward-predictive cues is provided by work showing less cue-induced reinstatement of cocaine and morphine self-administration in adolescent versus adult rats (Doherty et al., 2009; Li and Frantz, 2009). In an aversively motivated passive avoidance task, adolescent rats were likewise found to be less disrupted by a change in a redundant discriminative cue when their task performance was compared to that of either adults or pre-adolescent animals (Barrett et al., 1984). Such adolescent-typical attenuations in sign-tracking, context-dependent drug sensitization, and other indications of potentially weaker associations between cues and rewards may be related, at least in part, to ontogenetic alterations in brain regions known to be critical for developing reward associations such as the amygdala, prefrontal cortex (PFC), nucleus accumbens (nAc) and their connectivity (Everitt et al.,1999), a topic to which we later turn.

Synergistic effects on adolescent reward-related behaviors

Adolescents seem to be unusually sensitive to the consequences of variations in internal state and the environment on expression of reward-related behaviors. For instance, adolescents subjected to a schedule of food restriction that modestly tempered weight gains during this developmental period of accelerated growth exhibited a synergistic increase in operant responding during extinction when in the presence of the cue light that previously signaled reward availability (Sturman et al., 2010). In adults, however, this combination of internal and external motivational factors did not interact synergistically to increase extinction responding. Adolescent sign-tracking and goal-tracking behaviors are unusually sensitive to synergisms provided by motivational state. Anderson et al. (2013) found that, whereas food restriction elevated goal-tracking in normal, socially housed, adolescents relative to non-restricted adolescents, a combination of food restriction and isolate housing instead led to marked increases in sign-tracking behavior. Again, these effects were not evident in adults, with food restriction only inducing a mild increase in both behaviors, and isolate housing having no effect.

Social stimuli have been reported to synergize with other rewarding stimuli during adolescence. For example, adolescent rats failed to exhibit a CPP for a low dose of nicotine or a few pairings of a social stimulus (Thiel et al., 2009). Yet, when the two rewards were combined, robust CPP was observed. Evidence was presented to suggest that this effect was not merely due to the additive combination of two sub-threshold rewards, but rather was synergistic. More specifically, when the low dose of nicotine was paired with both sides of the apparatus, but the social stimulus was provided on only one side during the pairings, CPP emerged to the combined side, seemingly reflecting a synergistic effect of the social stimulus on nicotine's rewarding effects. Similar findings of social context facilitation of drug reward have been reported with cocaine (Thiel et al., 2008). Interestingly, both cocaine and nicotine suppressed social behavior during conditioning sessions, which suggests that direct increases in social/physical interactions cannot explain the synergistic effects of social and drug rewards (Thiel et al., 2009; 2008). Indeed, social CPP can be produced even when adolescent rats are

separated from each other during conditioning trials by a mesh barrier (Peartree et al., 2012). Studies of this nature generally have not included comparably tested adult animals, and hence is it is unclear as to the degree to which the enhancement of the rewarding properties of other stimuli by social rewards is specific to the adolescent period. These findings are, however, reminiscent of behavioral and fMRI data from human adolescents demonstrating that the presence of peers enhances the rewarding properties of stimuli during risky decision making among adolescents, but not adults (Albert et al., 2013; Chein et al., 2011; Smith et al., 2015).

Social stimuli may not only enhance the efficacy of other rewarding stimuli, but may also attenuate the negative properties of aversive stimuli as well. For instance, the presence of a social peer buffers against the aversive properties of alcohol in a conditioned taste aversion (CTA) paradigm in adolescent but not adult male rats (Vetter-O'Hagen et al., 2009), further reducing the innate attenuated sensitivity of adolescents to aversive stimuli – a topic to which we turn in the next section. Thus, a social context appears to further strengthen the already notable reward/aversion bias of adolescents toward greater sensitivity to rewards, in combination with attenuated sensitivity to aversions.

Adolescent sensitivity to aversive stimuli

Studies in rodents have shown that adolescents differ markedly from adults in how they respond to aversive stimuli, including both natural and drug-related stimuli. In particular, substantial research has now accumulated to suggest that adolescents are less sensitive than adults to the negative consequences of drug and alcohol exposure. While nearly all drugs of potential abuse are initially consumed in anticipation of their rewarding properties, most of these drugs have some negative consequences that can emerge during or following acute or repeated administration (e.g., nausea, motor impairment, sedation, anxiety, disruptions in social behavior). Adolescents are often relatively resistant to these effects. There is, for instance, an extensive literature demonstrating that adolescents are less sensitive to the sedative (e.g.,

Acevedo et al., 2013; Ramirez and Spear, 2010), motor-impairing (Silveri and Spear, 1999; 1998), and social inhibitory (e.g., Varlinskaya and Spear, 2006; 2002) effects of acute ethanol exposure when compared to older adult rats. Additionally, adolescents have demonstrated reduced sensitivity to the aversive effects associated with drug withdrawal, with adolescents less sensitive than adults to withdrawal-related anxiogenesis that occurred following a large binge-like dose of ethanol (e.g., Brasser and Spear, 2002; Doremus et al., 2003; Varlinskaya and Spear, 2004). Adolescent rats likewise exhibited an attenuated withdrawal response after cessation of nicotine exposure relative to withdrawing adults (O'Dell et al., 2004).

In addition to attenuated withdrawal sensitivity, adolescents are less sensitive to aversive effects of alcohol and drugs that emerge during the period of intoxication per se. In rodent studies, these aversive effects have been most often examined using conditioned place aversion (CPA) or CTA paradigms. In such tests, avoidance of a taste (for CTA) or chamber (for CPA) that was previously paired with the target drug is thought to index an aversive state induced by that drug. Studies have consistently demonstrated that adolescents exhibit marked reductions in sensitivity to the aversive effects of drugs across most drug classes. Relative to their adult counterparts, adolescents display a weaker CTA and/or CPA to nicotine (Shram et al., 2006; Torres et al., 2008), amphetamine (Infurna and Spear, 1979), tetra-hydrocannabinoid (THC; one of the major cannabinoids in marijuana) (Quinn et al., 2008; Schramm-Sapyta et al., 2007), cocaine (Schramm-Sapyta et al., 2006), morphine (Hurwitz et al., 2013), 3,4-Methylenedioxymethamphetamine (MDMA; commonly known as "ecstasy") (Cobuzzi et al., 2014), and methylenedioxypyrovalerone (MDPV: the active component in "bath salts") (Merluzzi et al., 2014). The attenuated sensitivity of adolescents to aversive drug effects extends to alcohol as well, with reports consistently demonstrating that adolescent rats or mice require higher doses than adults in order to exhibit a CTA to ethanol (e.g., Anderson et al., 2010; Holstein et al., 2011; Saalfield and Spear, 2016; Schramm-Sapyta et al., 2014; 2010; 2008; Vetter-O'Hagen et al., 2009), and are more resistant than adults to the formation of conditioned

aversions to an odor paired with ethanol administration (Pautassi et al., 2015). This attenuated sensitivity to ethanol is most marked early in adolescence in both male and female rats, and declines over the course of adolescence, gradually reaching the accentuated aversive sensitivity seen in adulthood (Saalfield and Spear, 2015). An example of the adolescent-associated insensitivity to ethanol-induced CTA reported by Vetter-O'Hagen et al. (2009) is shown in Figure 2. In that study, adolescent and adult rats were examined across a wide range of low-to-moderate ethanol doses, with adolescent rats exhibiting significant avoidance of the saccharin solution only when a dose of 2.0 g/kg ethanol was reached. In contrast, adults demonstrated avoidance of the saccharin solution with doses as low as 1.0 and 1.5 g/kg (Vetter-O'Hagen et al., 2009). Interestingly, in that study, administration of the US – ethanol – in a social context following CS exposure (saccharin) eliminated the significant CTA to 2.0 g/kg ethanol that was observed in adolescents who were challenged with ethanol under non social testing circumstances. Adults, however, did not show this social buffering effect on the expression of ethanol-induced CTA to any of the doses examined (Vetter-O'Hagen et al., 2009). Whereas adolescents have been shown to be more resistant than adults to the aversive effects of low-to-moderate doses of ethanol, these results are not evident at higher doses, with for instance, both adolescents and adults found to be equally sensitive to the aversive consequences of higher doses of ethanol (3.0 and 3.5 g/kg) using a second-order conditioning paradigm (e.g., see Pautassi et al., 2011).

Although receiving far less attention, adolescent-associated attenuated sensitivities to aversive stimuli may extend from drugs to natural stimuli as well. For example, when reflexive taste reactivity responses were used to examine sensitivity to aversive stimuli in adolescent and adult rats, adolescents demonstrated fewer negative reactions (i.e., gaping and forepaw wiping) than adults in response to passive intraoral infusion of the aversive tastant, quinine (Wilmouth and Spear, 2009). Using a CTA procedure, adolescents also were significantly less sensitive to the aversive effects of lithium chloride (LiCl) when paired with a naturally appetitive tastant,

0.2% saccharin, as they required a higher dose of LiCl in order to fully express a conditioned suppression of saccharin intake on the test day (Schramm-Sapyta et al., 2006). Clasen and colleagues (2016) replicated this decreased sensitivity among adolescents to LiCl-induced CTA, and further demonstrated that they were less sensitive to alterations in acquisition/expression of LiCl CTA by LiCl pre-exposure. Thus, studies in laboratory animals have convincingly demonstrated that adolescents are often less sensitive to the aversive effects of a wide variety of stimuli than are adults.

The neurobiology of rewards and aversions during adolescence

As described above, studies using animal models have revealed compelling evidence that adolescence is a time of reward-centricity when rewards appear particularly reinforcing, as well as a time of a relative attenuated sensitivity to aversive stimuli. How these age-specific differences may be linked to developmental changes occurring in the brain with the transitions through adolescence into adulthood are hence of considerable interest, a topic to which we now turn.

The mesocorticolimbic dopamine system

An evolutionarily conserved network of brain structures has been recognized as directing reward- and motivationally-related behaviors across a variety of species. The canonical view of this reward neurocircuitry describes midbrain dopaminergic neurons in the ventral tegmental area (VTA) projecting to dopamine (DA) receptors of the nAc located within the ventral striatum as the nexus of this circuitry (Berridge, 2004; Spanagel and Weiss, 1999). Frontocortical connections between and from orbitofrontal (OFC) and PFC provide additional critical inputs to both the nAc and VTA, with the VTA also projecting to frontolimbic regions including the PFC, hippocampus and amygdala (Berridge, 2004). Dopaminergic cells of the substantia nigra

projecting to the dorsal striatum additionally play a role in certain reward-associated processes (e.g., see Simon and Moghaddam, 2015; Voorn et al., 2004).

As discussed throughout this Special Issue, the adolescent brain differs from that of the adult neuroanatomically, neurophysiologically, and in terms of its molecular biology (e.g., see Bava and Tapert, 2010; Casey and Jones, 2010; Giedd et al., 1999; Sturman and Moghaddam, 2011). Particularly notable among these changes are alterations in the mesocorticolimbic DA system and the afferent targets of these projections, with a wealth of studies having now demonstrated dramatic transformations within mesocorticolimbic DA systems during adolescence (Marinelli and McCutcheon, 2014). Dopamine activity within the nAc traditionally has been emphasized for its importance in reward-related behaviors, and was one of the first neural systems shown to undergo remodeling during adolescence. The concentration of DA receptors, including both D1-like (D1R) and D2-like (D2R) receptors within the nAc follows an inverted U-shaped pattern, with the majority of studies demonstrating a peak occurring in mid-adolescence, followed by modest pruning thereafter (e.g., Andersen et al., 2000; Andersen, 2002; Tarazi and Baldessarini, 2000). Pharmacological modifications by dopaminergic drugs of the electrophysiological properties of D1Rs and D2Rs on medium spiny neurons in the nAc to NMDA- and AMPA-related stimulation also have been shown to differ in adolescent rats relative to their adult counterparts (Benoit-Marand and O'Donnell, 2008; Huppe-Gourgues and O'Donnell, 2012a;b). Indeed, there are critical changes in connectivity between the PFC and nAc throughout adolescence, as afferent projections from the PFC to nAc increase in number during adolescence, along with a late-adolescent elevation in the percentage of these cells expressing D1Rs (Brenhouse et al., 2008). Alterations in DA projections to the nAc include developmental increases in levels of the rate-limiting enzyme for production of DA, tyrosine hydroxylase (TH) (Mathews et al., 2009), and elevations in basal DA levels in the nAc septi during mid-adolescence (Philpot et al., 2009). Developmental increases in DA content in the

nAc over the course of adolescence have been reported (Naneix et al., 2012), although in that study no significant alterations were observed in this brain region in TH fiber density or rates of DA turnover indexed by the ratio of DA metabolites to DA (e.g., homovanillic acid/DA and 3,4-dihydroxyphenylacetic acid [DOPAC]/DA ratios). While measurement of DA transients in the nAc additionally revealed no differences between adolescents and adults in basal DA release, adolescents exhibited a unique response to a social stimulus. When presented with a social stimulus on two different occasions, DA transients habituated across the exposures in adults, but persisted through both presentations in adolescents (Robinson et al., 2011). Collectively, such data indicate that the nAc and its DA input system change from adolescence into adulthood, although as we shall later see, these changes may sometimes be less pronounced than those observed in other regions such as the dorsal striatum and medial PFC (mPFC) (see Naneix et al., 2012).

Currently, research primarily involving mature subjects has led to many hypotheses regarding the involvement of DA function in the nAc to several aspects of reward-related behavior, including high-effort responding to collect rewards (Floresco et al., 2008; Phillips et al., 2007), invigoration of behavioral responding and goal-directed behavior toward rewards (Berridge and Robinson, 1998; Robbins and Everitt, 2007), Pavlovian conditioning of reward-predictive cues (Berridge and Robinson, 1998; Nicola, 2007; Robbins and Everitt, 2007), and "flexible approach" behavior (Nicola, 2010). Under some circumstances, the adolescent nAc has been reported to be highly sensitive to activation by salient rewards and reward-related stimuli (e.g., Badanich et al., 2006; Robinson et al., 2011; for review see Simon and Moghaddam, 2015). Given the normative course of development of this region throughout adolescence, it is not surprising that adolescents exhibit ontogenetic alterations in many aspects of reward-related behavior that are thought to be influenced by dopaminergic activity in the nAc such as enhanced goal-directed behavior (e.g., Anderson et al., 2013; Serlin and Torregrossa, 2015), expending

more effort for larger rewards (e.g., Friemel et al., 2010; Stolyarova and Izquierdo, 2015), and altered responding to drug- and reward-associated cues (e.g., Anderson et al., 2013; Doherty et al., 2009; Li and Frantz, 2008). Furthermore, the responsiveness of dopaminergic activity in the nAc to drug-related rewards (for review see Volkow and Morales, 2015) is consistent with evidence that this region may be especially vulnerable to lasting modification by adolescent exposure to drugs of abuse (e.g., Catlow and Kirstein, 2007; Smith et al., 2015; Zandy et al., 2015), as well as to natural rewards, such as sucrose overconsumption (e.g., Naneix et al., 2016).

Until recently, the dorsal striatum had received considerably less attention relative to its more ventral neighbor (the nAc) when assessing potential neural contributors to adolescent reward-related behavior. This seeming neglect now appears unfounded, with reports of developmental alterations in this region throughout adolescence, and evidence suggesting the importance of these alterations for responding in reward-relevant tasks during adolescence. Ontogenetic patterns of DA receptor expression and densities in dorsal striatum appear to peak at a higher relative level, and later in adolescence, when compared to patterns seen in nAc, although with a timing and intensity that is similar to the PFC (see below) (Naneix et al., 2012; Tarazi and Baldessarini, 2000; Teicher et al., 2003). Dramatic increases in DA content in dorsal striatum in combination with reductions in DA turnover were apparent across adolescence into adulthood, findings consistent with typical inverse ontogenetic relationships between these measures (Naneix et al., 2012). These researchers, though, observed no significant change in TH fiber density in dorsal striatum during adolescence, whereas Matthews et al. (2013) measured TH content in dorsal striatum and showed lower levels of this enzyme during adolescence than in adulthood. Functionally, evidence is beginning to accumulate that the dorsal striatum may be uniquely responsive to rewards during adolescence. Moghaddam and colleagues have used single-unit extracellular recordings to measure activity of multiple neurons

in awake behaving animals during performance of a simplified instrumental learning task, and recorded task-evoked activity in neurons within several reward-related brain structures including OFC, nAc, dorsal striatum, and VTA (for review see Simon and Moghaddam, 2015). Unexpectedly, the dorsal striatum, and not the nAc, exhibited pronounced age differences during the learning task, with adolescent neurons increasing activity prior to reward-seeking action and again in anticipation of reward. In contrast, adult neurons responded after completion of the reward action, and they were actually inhibited during retrieval of the reward (Sturman and Moghaddam, 2012). Such data have been used to implicate the often over-looked dorsal striatum—and in particular the dorsal medial striatum—in alterations in reward-associated behaviors seen during adolescence, especially with respect to learning and expression of goal-directed behaviors, flexibility in response patterns with changing cue-response contingencies, and linking actions to rewarding outcomes (Simon and Moghaddam, 2015).

Another critical component of mesocorticolimbic DA projection systems for the processing of rewards in adolescence is the PFC. At approximately P20 in the rat, dopaminergic inputs to the mPFC were shown to begin to increase, and continue to do so throughout the adolescent transition to adulthood (Benes et al., 2000). TH immunoreactivity likewise significantly increased from early adolescence into adulthood in multiple subregions of the mPFC (Mathews et al., 2009; Naneix et al., 2012), with these increases more pronounced in anterior portions of this structure (Naneix et al., 2012). Not surprisingly given the developmental rises seen in TH through adolescence, DA content was lower in mPFC during adolescence than in adulthood (Benes et al., 2000; Naneix et al., 2012). Levels of DA turnover (Naneix et al., 2012) were higher in adolescence compared to adulthood, findings consistent with the inverse ontogenetic relationship between DA content and DA turnover seen in dorsal striatum. Electrophysiological studies have indicated enhanced sensitivity of inhibitory interneurons in the PFC to dopaminergic inputs during adolescence (Tseng and O'Donnell, 2007), with

developmental increases in postsynaptic protein kinase A (PKA) activity likely driving augmented L-type Ca^{++} channels critical for maturation of PFC function (Heng et al., 2011). Ontogenetic alterations in expression of D1Rs and D2Rs across adolescence within the PFC also have been reported using a variety of methods (mRNA expression, protein expression, binding studies). Despite some subtle differences in the timing of the these developmental changes across studies, the majority of experiments indicate that both D1Rs and D2Rs in PFC rise across adolescence to exhibit peak expression late in adolescence, and then decline substantially into adulthood (e.g., Anderson, 2000; Anderson et al., 2002; Naneix et al., 2012; Weickert et al., 2007) – a delayed ontogenetic time course relative to that seen in the nAc.

Developmental alterations in DA receptor expression within the PFC may be of considerable significance. Converging evidence from a number of sources has led to the suggestion that elevations in D1R expression in frontal cortex may impart a vulnerability for drug-associated cues, while also contributing to adolescent-motivated behaviors (Brenhouse and Andersen, 2008; Brenhouse et al., 2008; Kota et al., 2011; Leslie et al., 2004). One recent approach providing data consistent with the suggestion of an involvement of D1Rs in expression of adolescent-typical behaviors comes from work assessing consequences of lentivirus-induced overexpression of D1Rs in the prelimbic PFC of adult rats. These D1R over-expressing adults exhibited an adolescent-like behavioral phenotype that included increased impulsivity, enhanced intake of sweet solutions, and greater addictive behavior for drugs and drug-associated cues (Sonntag et al., 2014). Although not studied as extensively as the PFC, the OFC appears to show a developmental pattern of D1R expression similar to the PFC, with an adolescent-associated over-expression of D1Rs that are subsequently pruned into adulthood (Garske et al., 2013). Interestingly, an adolescent-related deficit in odor-guided associative learning paralleled developmental changes in OFC D1R expression, with pharmacological

manipulation of the dopamine system attenuating these associative deficits in adolescents (Garske et al., 2013).

Suggestions for the involvement of DA projections to frontal regions in the reward-directed behavior of adolescents have emerged using other approaches. For instance, Naneix et al. (2012) observed an adolescent-associated deficit in goal-directed behavior that was characterized by a failure to adapt behavior based on a change in the contingency between the response and outcome. Interestingly, the ontogenetic timing of the decline in this behavioral deficit was found to parallel late adolescent maturation of the mesocortical DA pathway (Naneix et al., 2012). Further indirect evidence for the importance of PFC to reward behaviors comes from developmental investigation of polysialylated neural cell adhesion molecule (PSA-NCAM) expression within the PFC. PSA-NCAM is considered to be a marker of structural plasticity and remodeling, and also has been shown to be related to DA signaling within this structure (as reviewed in Stolyarova and Izquierod, 2015). Stolyarova and Izquierod (2105) demonstrated developmental alterations in PSA-NCAM concentrations in the PFC, which, only in the case of adolescents, was highly correlated with a propensity to expend greater effort for a larger reward in a behavioral task. Thus, DA projection systems in the PFC join those of the dorsal striatum and the nAC in undergoing considerable developmental transformation during adolescence, thus providing changing neural substrates likely to alter the significance and impact of rewards on behavior and cognition in the adolescent.

The endogenous cannabinoid system

Our focus thus far has been primarily on the DA system's role in reward-related behaviors during adolescence. Of course, other neurotransmitter systems undergo alterations during this developmental period, and may impact expression of adolescent behavioral phenotypes and reward sensitivity. Of particular interest is the cannabinoid system, which has

been shown to undergo changes that likely influence adolescent behavior, including reward-related behaviors (Schneider et al., 2008). The cannabinoid system is predominantly a retrograde neurotransmitter system, with presynaptic cannabinoid receptors (CB1Rs) shown to regulate both excitatory glutamatergic and inhibitory GABAergic activity, thereby functioning as a “protective mechanism” to prevent over-stimulation of excitatory activity, perhaps especially during critical periods of development (Bossong and Niesink, 2010). Within prefrontal cortical regions in particular, endocannabinoids appear to play an important role in modulating GABA/glutamate interactions with the DA system (Cohen et al., 2008). Via CB1Rs that are extensively located throughout the mesocorticolimbic and nigrostriatal DA systems, cannabinoids seem to indirectly impact DA transmission (for review see Fitzgerald et al., 2012). Endocannabinoid activation of CB1Rs can inhibit both GABAergic and glutamatergic modulation of DA activity, which can lead to either potentiated or attenuated DA release in midbrain VTA and nAc neurons. This allows for an indirect “fine tuning” of dopaminergic activity in these pathways (Fitzgerald et al., 2012) and allows the endocannabinoid system to be uniquely positioned to influence reward-related and motor behaviors governed by these DA pathways.

There is ample evidence that this system undergoes notable ontogenetic change during adolescence. For example, using Western blot analyses, levels of the major cannabinoid receptor in brain, CB1R, were found to be higher in the striatum and PFC of adolescents than adults (Klugmann et al., 2011). Moreover, when CB1Rs in the striatum, limbic forebrain, and ventral mesencephalon were measured by radioligand binding, binding was found to increase ontogenetically in all areas from P10 to the time of puberty (approximately P30 or P40 for females and males, respectively), and then to decline substantially into adulthood (by P70) (Rodriguez de Fonseca et al., 1993). In a similar study that examined CB1R binding in the PFC in female rats, binding was reported to increase from P46 to P60, before decreasing slightly but significantly by P75 (Rubino et al., 2015). When assessing CB1 mRNA expression, Van Waes

et al. (2012) observed higher expression levels at P25 across multiple striatal subregions, with expression levels declining from P25 to P40, and even more so by P70. Furthermore, CB1 mRNA expression was reported to follow a parallel developmental pattern in corticolimbic areas—ontogenetic changes in PFC expression that were mirrored by electrophysiological measures of CB1R function in these brain regions (Heng et al., 2011).

In addition to developmental changes in CB1Rs during the adolescent transition, research has demonstrated notable ontogenetic transformations in levels of the endogenous cannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Whereas Ellgren et al. (2008) reported an inverted U-shaped pattern in AEA levels from early (P29), to mid (P38), to late (P50) adolescence in the nAc of male rats, a gradual increase across these ages was observed in the PFC. In contrast, these authors reported an inverted U-shaped pattern at these three ages in 2-AG in the PFC, with a gradual decrease in 2-AG from early to late adolescence in the nAc (Ellgren et al., 2008). Slightly different patterns of developmental alterations in endogenous cannabinoids were observed in the PFC in a recent report (Rubino et al., 2015), however, females were examined in this study and at different ages (P46, P60, and P75). Despite such differences, taken together, the receptor binding and endogenous substrate data support the conclusion that the broad adolescent period is characterized by dramatic alterations in both endogenous ligands for the CB1R, as well as expression and functionality of the receptor itself.

In sum, the majority of available data point to elevated cannabinoid receptor expression, increased levels of the CB1R, and greater levels of endogenous cannabinoid ligands during early-mid adolescence in regions implicated in processing and responding to rewards. Given these data, it is hypothesized that adolescence would thus be characterized by an overall pattern of enhanced endocannabinoid signaling that could be a major contributor to adolescent-typical behaviors, particularly those that involve risk-taking and reward-directed behaviors. In

support of this notion, Schneider et al. (2015) created a mutant animal for the Cnr1 gene, which resulted in a gain of function in CB1Rs in dorsal striatum. When these Cnr1 mutant adults were tested in a battery of behavioral assays, they exhibited an adolescent-like phenotype in terms of elevated risk-taking, novelty-seeking, reward consumption, and cocaine-related reward. Results such as these serve as indirect evidence that enhanced endocannabinoid signaling during adolescence may contribute to the reward-centric phenotype characteristic of this age. Interestingly, these mutant Cnr1 mice also exhibited increases in peer-directed social behavior, potentially implicating the endocannabinoid system in the expression and rewarding aspects of social behavior during this developmental window as well (for further discussion see Vanderschuren and colleagues, in this Issue).

Neural substrates of aversions in adolescence

Most stimuli offer a mix of both appetitive and aversive properties. Although as we have seen, this is particularly apparent in the case of alcohol and other drugs, it holds for other stimuli as well. For instance, even a highly palatable sucrose solution can be concentrated so much that is becomes unpleasant to drink, while quinine (which is usually found to be unpleasant tasting) is viewed by some as pleasurable in very low concentrations (such as in the case of tonic water). It should not be surprising then that the neural circuitry responsible for the processing of aversive stimuli and their conditioned cues overlap considerably with brain regions and neurotransmitter systems that have been shown to govern behavior directed towards rewarding stimuli and the cues that become associated with them.

As previously discussed, DA projections to limbic regions such as the nAc and dorsal striatum are heavily implicated in reward processing and goal-directed behaviors (Frank, 2011; Nicola, 2010; Wise, 2004) and undergo considerable ontogenetic change during adolescence (Marinelli and McCutcheon, 2014). Yet, research has now consistently shown that this mesolimbic DA system also impacts processing of aversive information and guides adaptive

behaviors in response to aversive stimuli (e.g., Faure et al., 2008; Zweifel et al., 2011). As reviewed by Wenzel at al. (2014), the more canonical view of the mesolimbic DA system's role in aversive behavior involves attenuation of midbrain neuronal dopaminergic activity, which decreases DA activity within the nAc. In doing so, indirect inhibition of pallidal neurons via D2Rs on medium spiny neurons is decreased, thus allowing expression of avoidance behavior. The midbrain DA cells have been argued to act as a "teaching signal," where hedonic and unexpected rewards stimulate their activity, and cues that become associated with these positive stimuli alter the timing and activity of DA neurons. In contrast, aversive stimuli and unexpected negative events (including reward omission) are thought to diminish the activity of mesolimbic DA neurons. Several types of studies have supported enhanced DA activity in nAc by hedonic stimuli, but suppressed activity with aversive events/cues using procedures ranging from passive infusion of sucrose versus quinine (Roitman et al., 2008), examination of a positive versus negative auditory stimulus (22 versus 50 kHz ultrasonic vocalizations) (Willuhn et al., 2014), presentation of a cue that was either predictive of illness or not (McCutcheon et al., 2012), or a shock-predictive cue (Oleson et al., 2012). Although studies such as these provide convincing evidence that mesolimbic DA neurons seem to code the valence of rewarding/aversive stimuli, recent advances are revealing that this is likely oversimplified (e.g., see Hu, 2016). Activity of DA projection systems in response to hedonic/aversive events may be much more complicated than previously thought, with for instance, heterogeneous subpopulations of neurons within DA terminal regions (i.e., nAc shell versus core) uniquely responding to appetitive versus aversive events (for review see Lammel et al., 2014; Wenzel et al., 2015). Notably, there appear to be certain neurons within both the VTA and nAc that are activated in response to aversive stimuli (Lammel et al., 2014; Wenzel et al., 2015).

Additionally, another circuit of structures has been shown to markedly influence responding to aversive stimuli via inhibition of midbrain DA neurons. The rostromedial tegmental nucleus (RMTg), or "tail of the VTA" (Kaufling et al., 2009), receives input from the extended

amygdala, as well as afferents from the lateral habenular nucleus. The GABAergic neurons of the RMTg have been shown to integrate signals from these inputs to increase inhibition of midbrain VTA DA neurons in response to negative events such as presentation of aversive stimuli or their associated cues, as well as reward omissions (Jhou et al., 2009). Yet, these GABAergic VTA-projecting RMTg neurons have been reported to respond to appetitive stimuli through suppression of inhibition upon DA neurons of the VTA. Taken together, data such as these indicate that, while important advancements are being made in our understanding of this circuitry, more research is needed to fully elucidate the nuanced neuronal processes within the mesolimbic DA system that respond to aversive stimuli and their cues.

There are certainly other brain regions and neurotransmitter systems that have been discovered to be important for determining adolescent sensitivity to aversions. Especially in the case of events that are categorized as fear-provoking, associated with fearful events, and/or emotionally aversive in nature, the PFC-amygdala-dorsal periaqueductal gray circuit is known to be of particular importance (e.g., Cole and McNally, 2009; Lee et al., 2013; Toyoda et al., 2011). These regions and their interconnections are critical for learning about fearful stimuli, acquisition and expression of associative fear conditioning, as well as extinction of fear-related behaviors, with both this circuitry and fear conditioning/extinction undergoing considerable modification during adolescence (as recently reviewed by Baker et al., in this Issue). Moreover, there is evidence to support involvement of the Dynorphin/Kappa opioid receptor (Dyn/KOR) system in the neural processing of and responding to aversive stimuli and their cues. For instance, the Dyn/KOR system has been implicated in the negative effects of stressors and the aversive properties of many drugs of abuse, including alcohol (for review see Wee and Koob, 2010). In a recent developmental study, KOR agonist-induced CTAs and CPAs were examined in both adolescent and adult male rats. Using both conditioning paradigms, adults exhibited robust aversions to all doses of the KOR agonist, U62,066, whereas adolescents did not (Anderson et al., 2014). These results suggest the possibility that adolescent-associated attenuations in the

dysphoric properties of alcohol and other drugs may be related in part to ontogenetic differences in activation of the Dyn/KOR system.

Elucidating critical differences in the neural substrates that mediate the attribution of reward versus aversion is an area of active investigation, and is of considerable importance as researchers continue to identify neural contributors to vulnerabilities for drug addiction and other psychological disorders. Such studies to dissect the neural mechanisms of rewards versus aversions may benefit from examination of these systems as they are naturally elaborated during ontogenetic shifts in their relative expression, rather than solely through use of more invasive pharmacological, optogenetic, or electrophysiological approaches in adult animals. Thus, discovering the neural underpinnings of the adolescent phenotype of reward-centricity and attenuated aversions may provide not only critical information regarding functioning of the adolescent brain per se, but also data useful in the search for distinct neural contributors to reward/aversion valences more generally.

Conclusions and comments

More than a decade and a half ago, Spear (2000) published an often-cited review that coalesced the available literature on the adolescent brain and behavior and made a number of testable hypotheses and predictions. These included the “tentative speculation that adolescents may generally attain less positive impact from stimuli with moderate to low incentive value… [and] display a mini-’reward deficiency syndrome’“ that may encourage them to “seek out additional appetitive reinforcers via pursuit of new social interactions and engagement in risk taking or novelty seeking behaviors“ (Spear, 2000, p.446). Studies conducted over the last decade and a half by Spear and colleagues and many others have conclusively demonstrated that this speculation was incorrect. Compelling evidence has instead emerged to suggest that adolescents find the hedonic effects of many stimuli, including drugs of potential abuse, to be *more* rewarding than do adults, while they are conversely often less sensitive to aversive

consequences. This adolescent phenotype ultimately results in an adolescent who is uniquely poised to seek out and "consume" these stimuli, to do so excessively, and to experience fewer negative interoceptive repercussions from such behavior.

As discussed earlier, studies using rodent models of adolescence are only useful to the degree that the data produced are relevant to human adolescents. The evidence is strong for notable cross-species consiliences in the neural substrates underlying reward and aversions, and in the neural alterations that occur in these and other regions during adolescence. There is additionally cogent evidence for an accentuated sensitivity to rewards in adolescent humans and laboratory animals, at least during receipt of rewards, and possibly also during reward anticipation/cuing of reward. Less clear are the data regarding aversions, however, with compelling data indicating an attenuated aversion sensitivity in adolescent rodents relative to their adult counterparts contrasting with mixed evidence in human adolescents. Under certain circumstances, signs of aversion insensitivities reminiscent of those seen in adolescent rodents have been reported in human adolescents (e.g., Moutsiana et al., 2013), whereas other studies have failed to observe this type of an age difference (e.g., Barkley-Levenson et al., 2013). It is not clear why the overwhelming evidence for attenuated aversive sensitivity observed during adolescence in rodent studies is inconsistently observed in human studies. The nature of the tasks used may be key—assessment of losses during a risk-taking task under conditions where gains are also possible may yield a different pattern of findings than when focusing on aversions in a context with no alternative possibility of rewards (as is used in much of the rodent literature). Work in this area continues, and hence rapid advances are expected in understanding the circumstances under which youth through adolescence are and are not resistant to adverse consequences and negative feedback, and the degree to which there are across-species concordance in these findings.

An adolescent phenotype of reward-centricity and attenuated aversions could have numerous consequences. On the one hand, enhanced rewarding proclivities could help promote educational, athletic, and/or other pursuits with beneficial outcomes (Telzer, 2016). Heightened incentive motivational processes during adolescence have been hypothesized to encourage the "seeking of experience," and to provide the drive to "get up and go" that allows adolescents to pursue and achieve productive goals within their social and environmental context (see Luciana commentary, in this Issue; Luciana et al., 2012; Luciana and Collins, 2012). On the other hand, increased reward sensitivities could help to promote the initiation of alcohol/drug use, and the consumption of relatively high quantities (e.g., "binge drinking" in the case of alcohol). Indeed, at least in the case of alcohol, greater sensitivity to alcohol's stimulatory and rewarding effects, in combination with an attenuated sensitivity to its aversive effects, reflects a known risk factor for alcohol use disorders and is evident in individuals with a family history of alcoholism and in rodent populations selectively bred for high levels of alcohol consumption (Schuckit, 1991; Green and Grahame, 2008; Trim et al., 2009; Quinn and Fromme, 2011). Propensity to engage in risky behaviors when pursuing novel and exciting rewards could be encouraged by such a reward/aversion shift. To the extent that attenuated sensitivity to aversions is similarly evident in human adolescents, this might suggest that framing advice and feedback in terms of positive benefits for adolescents may be more useful than emphasizing potential negative outcomes. Evidence additionally supports the suggestion that the reward-centric, aversion-insensitive behaviors of adolescents may be exacerbated further in the presence of peers, with social stimuli not only being particularly rewarding to adolescents, but also synergizing to enhance the rewarding value of other stimuli. Although the power of peers for adolescents has long been known, peer influences likely have not been fully harnessed to date for promotion of pro-educational and other pursuits of immediate or longer-term benefit for the individual.

Now that basic science studies have convincingly characterized a reward-centric and attenuated aversion phenotype of adolescence, research is critically needed to determine the

neural underpinnings of these converse adolescent-typical sensitivities. That is, while developmental changes during adolescence have been documented in a diversity of reward/aversion-relevant mesocorticolimbic DA projections and associated neural systems, few studies have yet been designed to explore which of these many alterations contribute to observed adolescent-associated sensitivities to rewarding and aversive stimuli. It is not even known whether these converse increased and decreased developmental sensitivities have similar underlying neural substrates – a feasible, yet unexplored, possibility given overlapping neural contributors to processing, learning about, and responding to appetitive and aversive stimuli. A number of techniques that move beyond correlational associations have potential utility in this quest, including targeted pharmacological, optogenetic, and conditional knock-out/knock-in gain or loss of function genetic approaches to explore the involvement of specific neural systems and neural projections in these developmental alterations. The challenge, as is often the case when using rodent models of adolescence, is to adapt such procedures for testing during this brief developmental period, particularly given that adolescent-related alterations in appetitive/aversive effects often appear most marked during early to mid-adolescence (i.e., the 2 week period from approximately P28-42). It is also time perhaps to further widen the focus beyond DA to include other neurotransmitters and neuromodulatory systems, including the endocannabinoid system.

In addition to defining the role of specific brain regions, projections and neurotransmitter/neuromodulatory systems in the expression of behaviors toward reward- and aversive-related stimuli, more research is needed to investigate environmental and genetic contributors to these adolescent-typical phenotypes and how these phenotypes are expressed in the disposition of motivated behaviors among adolescents with different vulnerabilities and in different contexts. Ultimately, it is the hope that findings from animal models of adolescence will prove useful for developing scaffolding approaches at the therapeutic, family, educational, and

community level to help adolescents benefit maximally as they navigate this ontogenetic transition.

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Figure Captions

Figure 1. Data representing alcohol consumption in both humans and rats are shown. When reporting number of drinks per drinking occasion (A), a developmental decline in alcohol intake from adolescence (12-20 years), to late adolescence (21-26), to adulthood (26+) was observed. Data are collapsed across gender and are adapted from the report to Congress on the "Prevention and Reduction of Underage Drinking," U.S. Department of Health and Human Services, 2011. (B) When examining average daily alcohol (ethanol) consumption (as measured using a continuous-access, 2-bottle choice between water and sweetened ethanol) in adolescent (postnatal day 23-33) and adult (postnatal day 60-70) Sprague-Dawley rats, adolescents, similar to their human counterparts, were found to drink significantly more ethanol than adults. The data shown in panel B are collapsed across sex, as well as across 10 days of ethanol access, and are adapted from Doremus et al. (2005).

Figure 2. Using a conditioned taste aversion (CTA) paradigm, the aversive properties of acute ethanol exposure were examined in both adolescent and adult male Sprague-Dawley rats across a dose range from 0 - 2.0 g/kg in adolescents and 0 - 1.5 g/kg in adults. When tested in a non-social context (A), adolescents exhibited significant CTA to the saccharin test solution only at the highest dose of 2.0 g/kg ethanol. Testing in a social context (B), however, eliminated the acute ethanol-induced CTA to even this dose of ethanol among adolescents. Adults demonstrated significant CTA to ethanol at doses that were insufficient to induce ethanol CTA in adolescents, with adults receiving ethanol exposure in both a non-social (C) and social (D) context showing significant ethanol CTA after 1.0 and 1.5 g/kg ethanol. Data represent the mean for each experimental group, plus and minus the standard error of the mean (SEM). Asterisks denote a significant difference from the saline control group (0 g/kg ethanol) within each Age and Testing Context condition. Data are adapted from Vetter-O'Hagen et al. (2009).

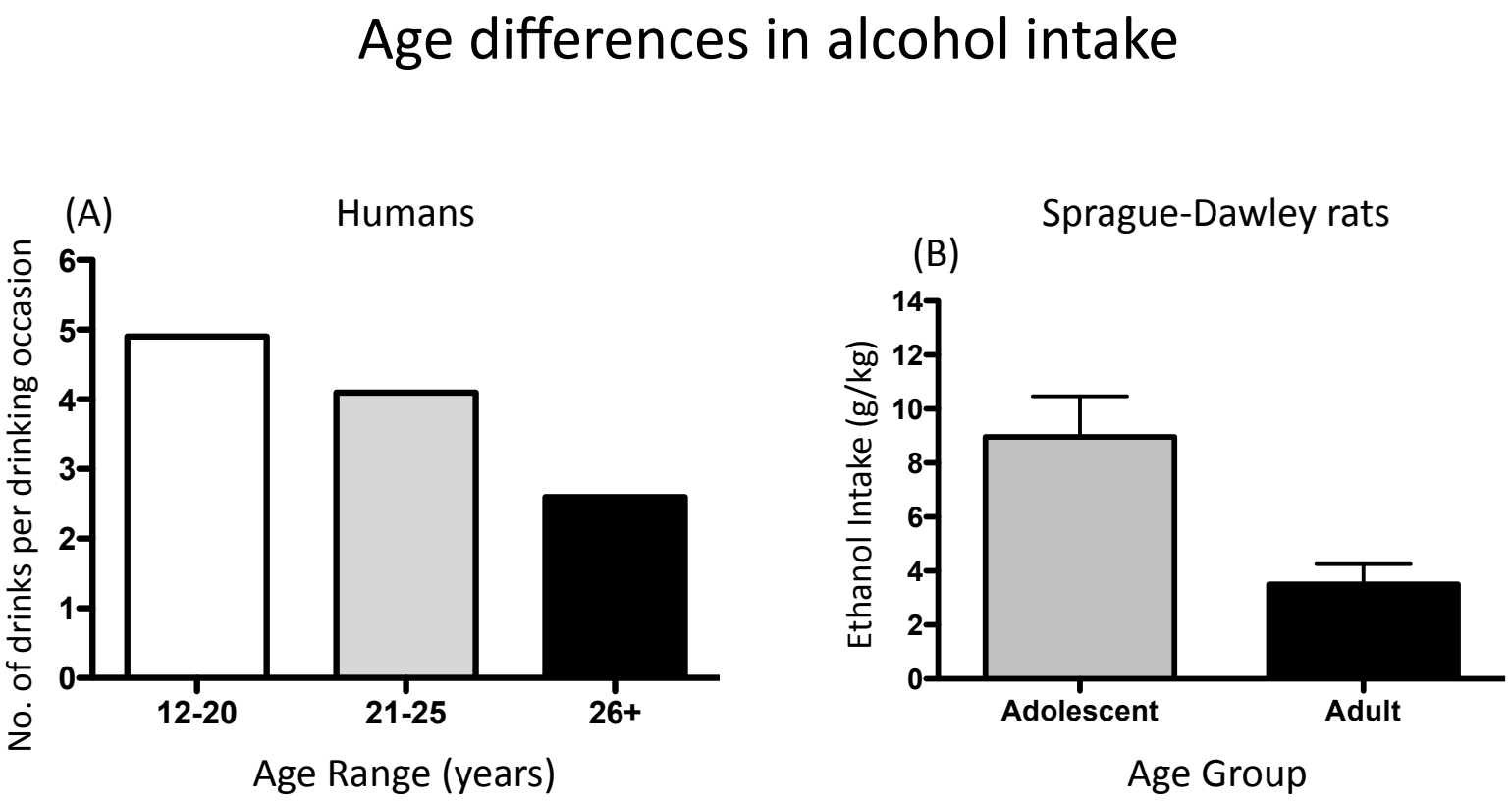

Figure 1.

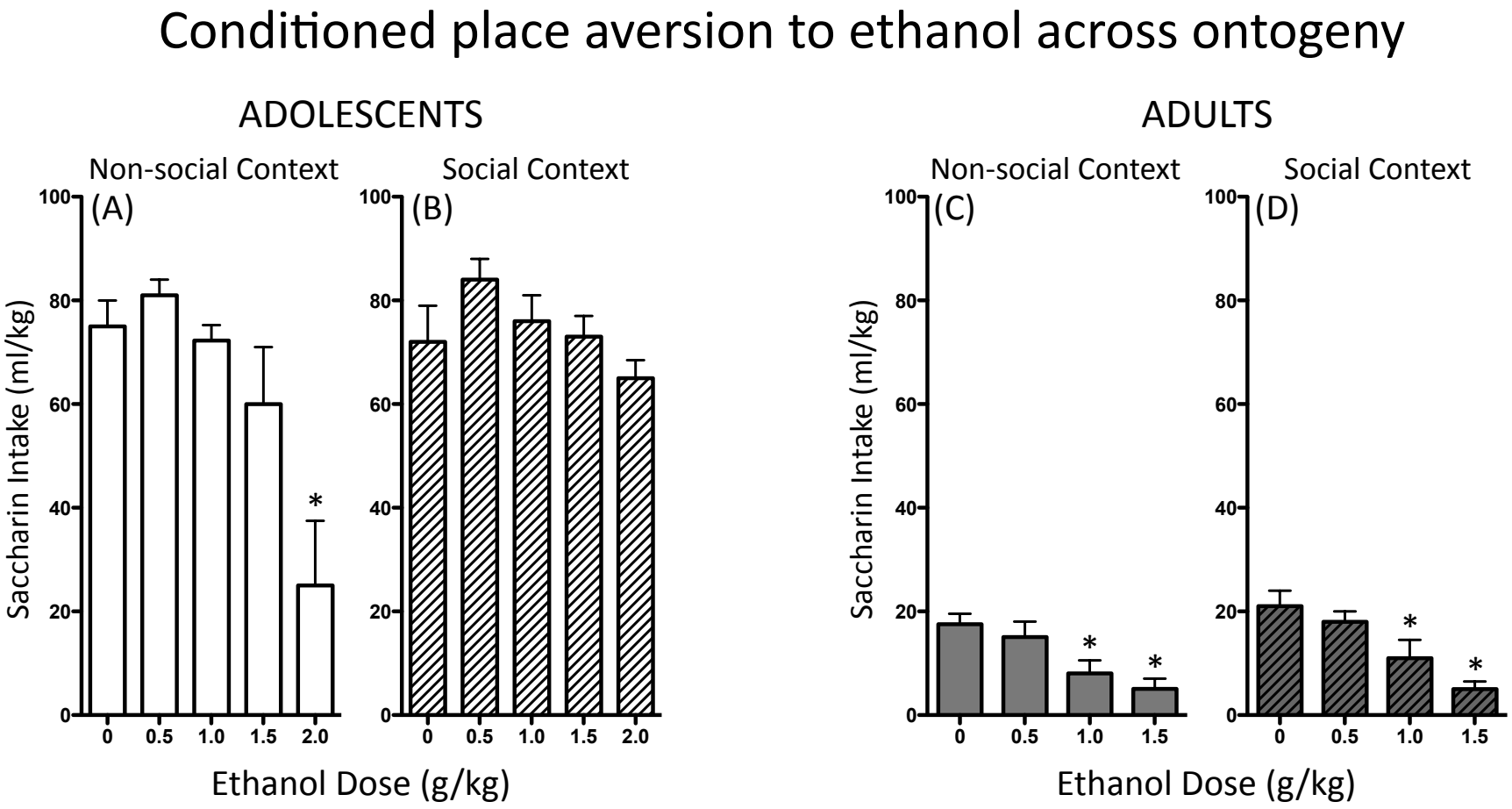

Figure 2.