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Motivational systems in adolescence: Possible implications for age differences in substance abuse and other risk-taking behaviors

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Abstract

Adolescence is an evolutionarily conserved developmental phase characterized by hormonal, physiological, neural and behavioral alterations evident widely across mammalian species. For instance, adolescent rats, like their human counterparts, exhibit elevations in peer-directed social interactions, risk-taking/novelty seeking and drug and alcohol use relative to adults, along with notable changes in motivational and reward-related brain regions. After reviewing these topics, the present paper discusses conditioned preference and aversion data showing adolescents to be more sensitive than adults to positive rewarding properties of various drugs and natural stimuli, while less sensitive to the aversive properties of these stimuli. Additional experiments designed to parse specific components of reward-related processing using natural rewards have yielded more mixed findings, with reports of accentuated positive hedonic sensitivity during adolescence contrasting with studies showing less positive hedonic affect and reduced incentive salience at this age. Implications of these findings for adolescent substance abuse will be discussed.

Keywords

Adolescence; animal model; motivation; reward; drug use

Adolescence is a time of rapid physical change, along with sometimes striking alterations in mood and behavior. Although adolescence is sometimes thought of as a unique phase of human development, developing organisms of all mammalian species go through a similar transition from dependence to independence. Indeed, human adolescents and their counterparts in other species share numerous similarities in hormonal changes, behavioral characteristics and brain transformations (Spear, 2000), including alterations in reward-related circuitry (Ernst & Spear, 2008), suggesting that these adolescent-typical characteristics may reflect in part hard-wired, evolutionarily sculpted systems.

Adolescent-characteristic behavioral changes, including enhanced interactions with peers and increases in risk taking, sensation and/or novelty seeking are evident across a variety of species, and seemingly have evolved in part to facilitate emigration by providing the impetus to search

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for new territories, sexual partners, and new sources of food (Spear, 2000, 2007a). To the extent that common evolutionary pressures have led adolescents of a number of species to exhibit certain shared behavioral attributes, these behavioral commonalities may reflect similar underlying biological substrates, with brain regions undergoing particularly marked changes during adolescence highly conserved. Alterations during adolescence in evolutionarily ancient brain motivational systems and reward-related neurocircuitry may play a particularly critical role in the expression of adolescent-typical behavioral characteristics.

While the rich complexity of human adolescence can be at best only partially modeled in laboratory animals, neural regions modulating pleasure and reward-motivated behavior bear considerable similarity between humans and other mammalian species (Berridge & Kringlebach, 2008). These similarities provide reasonable face and construct validity for the use of animal models to explore reward-related behaviors, including drug and alcohol use during adolescence.

I. Reward-Related Behaviors of Adolescence

Adolescents often differ notably from younger or older individuals in the ways they respond to and interact with meaningful stimuli in their environment. Such adolescent-typical characteristics include marked elevations in interactions with peers, novelty seeking/risk taking, and consummatory behaviors (Spear, 2000, 2007a). Interactions with peers become particularly important during adolescence, with these interactions beginning to exert a greater influence over decision-making and behavior than they do among adults (Gardner & Steinberg, 2005; Grosbras et al., 2007; Steinberg, 2005). During adolescence, humans spend more time interacting with peers than at any other developmental period (Hartup & Stevens, 1997), and these relationships provide a significant source of positive experiences for adolescents (Brown, 2004; LaGreca et al., 2001; Steinberg & Morris, 2001). Similarly, during the age interval from postnatal days (P) 28 to 42, which has been conservatively defined as adolescence in the rat (for review see Spear, 2000), rats demonstrate higher levels of social activity than younger and older animals. These high levels of social interactions are particularly characterized by play fighting in adolescence, in contrast to social investigation which predominates the more moderate amounts of social interaction seen in adults (see Vanderschuren et al., 1997 for references and review; Varlinskaya & Spear, 2002, 2008). Adolescents not only engage in more social interactions than adults, but they find these social interactions unusually rewarding (Douglas et al., 2004).

Increases in risk-taking and novelty seeking are other relatively conserved behavioral characteristics of adolescence. Notable increases in risk-taking behavior are seen between childhood and adolescence, with adolescents engaging in more risk-taking activities than adults (Steinberg, 2008). These increases in risk-taking behavior among human adolescents are associated with the motivation to experience multiple new and intense stimuli to attain potential rewards (Arnett, 1994; Trimpop et al., 1999; Steinberg, 2005). This motivation to seek out new experiences, i.e., novelty seeking behavior, has been identified as a significant contributor to current and future drug use, multiple drug use, and later abuse (Hittner & Swickert, 2006; Kelly et al., 2006).

Enhanced novelty responding has been demonstrated as well in adolescent rodents relative to their more mature counterparts in a number of experimental paradigms (Adriani et al., 1998; Adriani & Laviola, 2000; Beluzzi et al., 2004; Caster et al., 2007; Collins & Izenwasser, 2004; Douglas et al., 2003; Philpot & Wecker, 2008; Spear & Brake, 1983; Stansfield & Kirstein, 2006, but also see Cao et al., 2007; Caster et al., 2005). Given that adolescence is a time of acquiring new skills for survival away from parents, enhanced novelty seeking may have been evolutionally conserved for its adaptive value during this developmental period,

contributing to exploration of novel areas and providing the opportunity to find new sources of food, water, and mates (Spear, 2000).

Social factors play an important role in responsiveness to novelty in human adolescents, as well as adolescents of other species. In humans, social conformity, peer deviance, and social support influence novelty-seeking and risk-taking in adolescence (Martin et al., 1995), with peer effects on risk taking and risky decision making being stronger among adolescents than adults (Gardner & Steinberg, 2005). Rewarding properties of novelty are influenced by social deprivation in adolescent-specific (and sex-specific) ways in rodent studies of reward as well (Douglas et al., 2003).

At least some experimental use of alcohol and other drugs is also common during adolescence, with this use perhaps reflecting an example of risk-taking behavior. For example, in the Monitoring the Future study of 2007, approximately 50% of high school seniors reported having used an illicit drug during their lifetime (Johnston et al., 2008). Frequent and excessive use of alcohol is particularly widespread among adolescents, with approximately 25% of 12th graders reporting an episode of binge drinking within the past month. Importantly, drug and alcohol use during adolescence has been shown to correlate with an increased incidence of drug and alcohol problems in adulthood (DeWit et al., 2000; Grant et al., 2001). Similarly, using a simple animal model of adolescence in the rat, we have demonstrated that adolescents drink 2–3 times more ethanol than do adults (Brunell & Spear, 2005; Doremus et al., 2005, Vetter et al., 2007), in part seemingly due to their insensitivity to some of the adverse and incapacitating effects of ethanol (see Spear & Varlinskaya, 2005 for references and review). It is likely that the behavioral traits typical of adolescence partly contribute to this initiation of drug and alcohol use, with peer pressure (Segal & Stewart, 1996) and the desire for more relaxed social interactions (Smith et al., 1995) likely contributing to alcohol intake among human adolescents during this developmental period. Adolescent rodents as well show a unique relationship between ethanol and social behavior, with adolescents exhibiting a robust increase in social interactions following moderate doses of ethanol, ethanol-induced social facilitation that is not seen among adults (Varlinskaya & Spear, 2002, 2006, 2007).

Taken together, these findings demonstrate that a number of fundamental reward-related behaviors observed in a simple animal model of adolescence in the rat bear similarity to those seen among human adolescents. These robust motivated behaviors of adolescence likely reflect, in part, developmental transformations in evolutionarily conserved brain areas regulating motivational and reward processes, a topic to which we now turn.

II. Neurobiology of Motivational and Reward Systems

Relatively ancient brain regions mediate the basic, survival-dependent activities of desiring, seeking out, locating, and enjoying natural rewards such as food, novelty, and social stimuli. These reward systems are also activated by alcohol and other drugs used for their rewarding effects, perhaps abnormally so, with repeated exposures to such “supranormal” drug stimuli contributing to the development of drug dependence. A core element of such reward-related neurocircuitry has long been attributed to the nucleus accumbens (NAc) and the dopamine (DA) input it receives from DA cell bodies in the ventral tegmental area (VTA) of the midbrain. Additional critical components of the reward circuitry include other forebrain targets of DA projections from VTA, including the amygdala, hippocampus, and prefrontal cortex (PFC), along with the dorsal striatum and the input it receives from DA cell bodies in the midbrain substantia nigra (SN) (i.e., the nigra-striatal DA system), with these mesolimbic and mesocortical brain regions closely interconnected (e.g., see Berridge, 2004).

Lesion studies in laboratory animals have revealed that motivationally oriented behaviors towards natural rewards and drugs can be partitioned into a diversity of psychological

components, each with complex, sometimes overlapping, and incompletely understood neural representations (e.g., Baxter & Murray, 2002; Cardinal et al., 2002). There is continuing controversy, however, as to the nuances of how reward-related processes should be parsed, the roles of specific neural components in these separable processes, and the identification of the constituents that become dysfunctional during the development of addiction (e.g., see Berridge, 2007). For instance, one influential theory views DA projections to forebrain as critical for mediating the hedonic impact of rewards, with repeated drug use inducing a hypo-DA state, leading to a decrease in sensitivity to natural and drug rewards that in turn promotes elevations in drug use to counter this insufficiency (e.g., Volkow et al., 2007). This hypothesis is wildly different from another prominent perspective that views these DA projections as critical for the attribution of incentive salience, and hence motivational drive, to reward-related stimuli; this theory posits that repeated drug use increases DA sensitivity, leading to increased “wanting” behavior or drug craving (Robinson & Berridge, 2003). According to this perspective, DA is not critical for mediating the hedonic, affective reaction (i.e., “liking” response) to a rewarding stimulus. Instead, such “liking” reactions are coordinated by other neurochemical systems in various small, opioid and cannabinoid-sensitive “hot spots” of positive hedonic affect within portions of the NAc and ventral pallidum (Smith & Berridge, 2005).

Others have focused on the importance of mesolimbic DA projections in circuitry involved with learning about rewards, citing research suggesting that DA is critical for “stamping in” reward learning, or for detecting errors in reward prediction, with the resulting DA release serving as a “teaching signal” for new learning when a predicted reward is not received (see Hollerman et al., 2000; Berridge, 2007, for review and references). Such reward-based learning is thought to involve neurocircuitry that includes afferents and efferents from both ventral parts of the striatum (i.e., the NAc) and from dorsal striatum (e.g., nigrostriatal DA system) (Meredith et al., 2008), along with the amygdala, hippocampus, and regions of frontal cortex (e.g., see Berridge & Kringelbach, 2008).

III. Adolescent brain transformations in motivational and reward systems

Given the ongoing controversy as to how different components of forebrain reward systems are functionally organized into systems that serve to attribute hedonic value, incentive salience, learning and relative motivational significance to reward-relevant stimuli in adults, it should not be surprising that even less is known about functions of these reward-based systems during adolescence. What is clear, however, is that reward-related regions of the brain and their neurocircuitry undergo particularly marked developmental changes during adolescence.

Recent data have shown that connections among these reward-relevant regions continue to be elaborated during adolescence. Consistent with the relatively delayed development of frontal cortical regions that continues through adolescence and into young adulthood (see Spear, 2007b), neurocircuitry connecting the PFC and subcortical reward-related regions likewise continues to develop through this period. For instance, glutaminergic projections from the basolateral amygdala to PFC continue to be elaborated in adolescence (Cunningham et al., 2008), even though overall synaptic density and excitatory drive to PFC decline notably during adolescence (see Spear, 2007b, for review and references). The number of DA fibers terminating in PFC also increases into adolescence (Benes et al., 2000), as does the inhibitory control of PFC activity by these DA afferents from VTA (Tseng & O'Donnell, 2007). Levels of the rate-limiting enzyme in the synthesis of DA, tyrosine hydroxylase, likewise increase through adolescence and into adulthood in the medial PFC and the NAc of rats (Mathews et al., 2009).

Connections from PFC to the NAc continue to rise during adolescence as well, with developmental increases in the number of PFC pyramidal cells that project to NAc, along with a transient increase in the proportion of these projection neurons that express DA D1 receptors (D1-Rs). As a result, the percentage of accumbal-projecting pyramidal cells containing D1-Rs peaks at levels notably higher late in adolescence (>40%) than at younger or older ages (<4–5%) (Brenhouse et al., 2008). These findings are intriguing, given evidence for the importance of PFC projections to NAc in drug seeking (e.g., Kalivas et al., 2005) and for a potential role of PFC D1-Rs in increasing the reinforcing efficacy of drugs (see Brenhouse et al., 2008). The pruning of these PFC DA receptors does not occur until early adulthood, with substantial declines in D1- and D2-R density evident between P60 and P80 (Andersen et al., 2000).

In contrast, the marked developmental peaks in DA receptor density seen in dorsal striatum during adolescence is followed by substantial pruning of these receptors during the adolescent transition, characterized by a loss of 1/3 – 1/2 of the DA receptor population between early adolescence and young adulthood, a loss evident in both human autopsy material and in studies using animal models (e.g., Seeman et al., 1987; Tarazi & Baldessarini, 2000; Teicher et al., 2003). The NAc likewise shows peak D1- and D2-R levels during adolescence, although the subsequent pruning there seems relatively modest, with reports of significant declines of 20–35% or so between early adolescence and young adulthood (e.g., Andersen, 2002; Tarazi & Baldessarini, 2000;) contrasting with a lack of significant pruning in other studies (e.g., see Andersen et al., 2000).

Developmental alterations in DA tone have also been reported in these reward-related regions. For instance, the elevation in DA tone (“hyperdopaminergic” state) postulated to be reached during late adolescence in NAc and dorsal striatum based on forskolin-induced cAMP accumulation data (Andersen, 2002) and estimated turnover rates (see Spear, 2000 for review) contrasts markedly with the (perhaps compensatory) blunting of the cAMP response to DA D1- and D2-R stimulation (suggestive of DA “hyposensitivity”) that is also seen in these areas during late adolescence (Andersen, 2002). Such compensatory responses have been long known to be rampant within DA systems (e.g., Zigmond et al., 1990) and even across systems. For an example of the latter, signs of increased DA transmission during adolescence were associated with compensatory changes in the cholinergic neurons to which they project in striatum, resulting in a functionally hyposensitive DA system (Bolanos et al., 1998), along with the blunted psychomotor stimulant response to DA agonists frequently (e.g., Bolanos et al., 1998; Frantz et al., 2007; Mathews et al., 2009; Spear & Brake, 1983; Zombeck et al., 2008) but not always (Collins & Izenwasser, 2002; Niculescu et al., 2005; Smith & Morrell, 2008) seen when adolescent rats are compared with adults. Environmental variables (such as the amount of pretest manipulation or handling) may contribute to these different psychopharmacological findings across studies (Maldonado & Kirstein, 2005a,b; Doremus-Fitzwater & Spear, under revision), perhaps via their influence on mesocorticolimbic DA systems (Brake et al., 2004) adding further complexity.

How developmental alterations in these DA projections to reward-relevant forebrain regions might influence reward-related behavior during adolescence is unclear. Should these changes reflect a hyposensitivity of DA systems, a disruption in the attribution of incentive salience or expression of goal-directed behavior during adolescence might result (e.g., see Berridge, 2007). Alternatively, any adolescent-associated DA hyposensitivity could be hypothesized to lead to an attenuated sensitivity to natural or drug rewards, intensifying drug use to compensate for this reward deficiency (akin to theories of addiction as representing reward deficiencies -- e.g., Volkow et al., 2007). Yet, there are many other potential “players” in reward-associated regions that also change during adolescence. Consider, for example, the cannabinoid system, with receptors (CB1-Rs) that are largely localized to presynaptic endings where they serve as important regulators of neural inputs to DA target regions (Cohen et al., 2008). CB1-Rs peak

developmentally in striatum and limbic regions during adolescence (P30–40 in rats), before declining significantly to reach adult levels (Rodriguez de Fonseca et al., 1993). Notable developmental transformations in endocannabinoid levels also are evident during adolescence, with, for instance, developmental increases in anandamide, but declines in 2-Arachidonoylglycerol (2-AG) seen throughout adolescence in PFC (Ellgren et al., 2008). Thus, although much of the focus to date has been on alterations in DA-related systems in adolescence, these are embedded within other transformations in reward-related circuitry that have yet to be extensively explored but that are likely to contribute critically to adolescent-typical responding to rewarding stimuli.

IV. Adolescent motivation for natural rewards and drugs of abuse

Given developmental alterations discussed above in reward-related brain regions, it is not surprising that adolescents differ from their younger and older counterparts in the ways that they respond to rewarding stimuli. For example, findings in laboratory animals using the conditioned place preference (CPP) paradigm suggest that motivation for many natural rewards, including social stimuli and novelty, may be enhanced during adolescence compared to adulthood. The place conditioning procedure essentially pairs the presence of a stimulus (e.g., administration of a drug, presence of a novel object, or social partner) with a distinct chamber, while pairing the absence of the stimulus with another distinct chamber on separate trials. On the test day, animals are allowed simultaneous access to both chambers, without the training stimulus being present. More time spent on the side previously paired with the training stimulus is used as an index of preference for that stimulus (i.e., the stimulus was rewarding), with more time spent on the alternative side indexing an aversion for the stimulus (i.e., a conditioned place aversion). Using this procedure, socially reared adolescent male rats were shown to exhibit CPP for novel stimuli, conditioning that was not evident in their adult counterparts (Douglas et al., 2003). Similarly, when expression of social CPP was assessed within our laboratory using a same-sex, unfamiliar partner as the social stimulus, both male and female adolescents in general exhibited more robust CPP than adults (Douglas et al., 2004). These rewarding properties of social interactions were enhanced by prior social deprivation in both adolescents and adults, although social stimuli were still rewarding to adolescents even without prior deprivation of social contact (Douglas et al., 2004). Relatively short-term social deprivation (5–7 days of isolate housing) of adolescent rats has likewise been reported to increase social behavior, particularly in terms of play fighting (Holloway & Suter, 2004; Panksepp, 1981; Takahashi & Lore, 1983; Varlinskaya et al., 1999), effects that are particularly marked early in adolescence (Varlinskaya & Spear, 2008).

Similar to the rewarding effects of natural stimuli, the rewarding properties of drug stimuli may also vary between adolescents and adults. Many of these ontogenetic studies have focused on nicotine and traditional stimulants, particularly cocaine, with findings to date generally showing enhanced preference for these drugs among adolescents relative to adults. In a study from our laboratory, adolescent male and female rats were found to exhibit significant nicotine-induced CPP to a relatively low dose of nicotine (0.6 mg/kg), whereas their adult counterparts failed to express CPP under these circumstances (Vastola et al., 2002). Adolescents have been reported to exhibit stronger nicotine-induced CPP than adults in other studies as well (e.g., Shram et al., 2006; Torres et al., 2008).

Greater expression of CPP to cocaine likewise has been reported among adolescents relative to adults. For example, adolescent male rats showed CPP at lower doses of cocaine than did adult males (Badanich et al., 2006; Brenhouse & Andersen, 2008; Brenhouse et al., 2008; Zakharova et al., 2008a), with this age difference in sensitivity to cocaine CPP also reported for females (Zakharova et al., 2008b). Cocaine-induced CPP was shown to develop not only at lower doses during adolescence, but also to extinguish more slowly and show greater

propensity for reinstatement among adolescents compared to adults (Brenhouse & Andersen, 2008). Reports of enhanced CPP to cocaine among adolescents are not ubiquitous, however, with some studies failing to observe age-related differences (Aberg et al., 2007; Campbell et al., 2000).

Developmental investigations of the rewarding properties of ethanol have proved challenging, in part because of difficulties in establishing CPP for ethanol in rats, with mice, in contrast, demonstrating reliable ethanol-induced CPP (see Green & Grahame, 2008 for references and review). Rats, however, typically show ethanol-induced conditioned place aversion (CPA), with ethanol CPP being reported in animals following prior exposure to ethanol (see Fidler et al., 2004 for references). The frequent emergence of ethanol-induced CPA (rather than CPP) in ethanol-naïve adult rats is likely to be related to enhanced sensitivity of adult rats to aversive postabsorptive effects of ethanol (Fidler et al., 2004). Using other strategies for assessment of ethanol reward, however, a couple of recent reports have provided some initial evidence that adolescent rats may find ethanol to be more reinforcing than adults. In work examining second-order conditioning, experimental (paired) rats received intragastric infusions of ethanol (the unconditioned stimulus [US]) paired with intra-oral infusions of sucrose (CS1) during phase 1, whereas unpaired control animals were exposed to the sucrose CS1 four hours prior to administration of the ethanol US (Pautassi et al., 2008). In the second conditioning phase, animals in both paired and unpaired groups were exposed to the sucrose CS1 in a discrete environment (CS2). At test, when adolescent and adult rats were then given the opportunity to explore a 3-chamber apparatus that contained the CS2 environment, adolescents in the paired condition showed greater preference for the CS2 than their unpaired controls, suggesting that the CS2 had attained positive reinforcing properties through a CS1-mediated association with the ethanol US. Such second order conditioning was not evident in adults, with adults receiving paired exposure to the CS1/US in phase 1 not differing from unpaired adults when examining CS2 preference at test.

Additional evidence for greater rewarding effects of ethanol among adolescents than adults was recently obtained through the assessment of ethanol-induced tachycardia, an autonomic measure shown to be positively correlated with DA release in the ventral striatum (Boileau et al., 2003), and with subjective measures of ethanol's rewarding effects in human studies (Conrod et al., 1998; Holdstock & de Wit, 2001; Holdstock et al., 2000). Ristuccia & Spear (2008) used ethanol-induced tachycardia to index the hedonic value of ethanol in both adolescent and adult male rats during a 2-hr limited-access, oral self-administration session. Under these conditions, adolescent rats not only consumed more ethanol than adults, an age difference in ethanol intake that has been repeatedly observed (Brunell & Spear, 2005; Doremus et al., 2005; Vetter et al., 2007), but they also showed a significantly greater increase in heart rate when drinking the ethanol relative to the saccharin control solution—a difference not observed among adults. To the extent that the tachycardic responses to self-administered ethanol represent a valid index of its rewarding/positive hedonic effects, these results suggest that adolescents are more likely than adults to voluntarily consume sufficient amounts of ethanol to gain its rewarding benefits.

Recent human and animal studies suggest that the rewarding value of drugs of abuse may be influenced by social context, with this interaction being more pronounced in adolescence than in adulthood. The impact of social context on drinking during adolescence is viewed as particularly important (Read et al., 2005), with drinking rates highest among adolescents who strongly endorse social motives for drinking (Mohr et al., 2005). Social influences are among the most robust predictors of adolescent substance use, with drug use of peers and friends being a major risk factor for adolescent drug use (Epstein et al., 2007; Skara & Sussman, 2003). The propensity for elevated drug use and the particular relevance of social context during adolescence may be, in part, biological. Reminiscent of their human counterparts, adolescent

rats are notably more sensitive to the social facilitating effects of ethanol than adults (Varlinskaya & Spear, 2002). Moreover, drug exposure in a social context has been shown to enhance the rewarding value of cocaine (Thiel et al., 2008) and nicotine (Thiel et al., 2009) in adolescent rats when tested in the CPP paradigm, although no age comparisons have been done in these studies. This social enhancement of nicotine and cocaine reward seen in adolescent animals may be related to activation of the endogenous mu opioid system by social stimuli, since this system is implicated in both social behavior and drug reward (Van Ree et al., 2000; Gianoulakis, 2004).

In contrast to the often enhanced sensitivity to the rewarding properties of natural rewards and drugs of abuse seen in adolescents relative to adults, their sensitivity to the aversive consequences of drugs (and perhaps even to some natural rewards) appears to be attenuated. For instance, separate studies within the same experimental series found that, relative to adults, adolescents exhibited both greater sensitivity to nicotine-induced CPP, but weaker aversive responses to nicotine when indexed either via conditioned taste aversions (CTA) to nicotine (Shram et al., 2006) or via conditioned place aversions to higher nicotine doses (Torres et al., 2008). Adolescents may show not only enhanced positive rewarding effects but also attenuated aversive consequences with other drugs as well. Recently, we have used CTA procedures to assess the aversive consequences of ethanol, with adolescents requiring much higher doses than adults in order to establish a significant ethanol-induced CTA to a paired CS solution (Anderson et al., 2008a, b; Varlinskaya et al., 2006). Furthermore, Infurna & Spear (1979) showed an attenuated efficacy of amphetamine in inducing CTA in adolescence, which contrasts with the often reported enhanced CPP for psychomotor stimulants during adolescence discussed earlier (e.g. Badanich et al., 2006; Brenhouse & Andersen, 2008; Brenhouse et al., 2008; Zakharova et al., 2009a, b). The social context may not only enhance drug reward in adolescent animals, but also attenuate aversive consequences of ethanol exposure. For instance, exposure to a social context during intoxication decreases sensitivity to the aversive effects of ethanol as indexed by CTA, an effect observed in adolescent but not adult male rats (Vetter-O'Hagen et al., 2009).

Although exact neural mechanisms of this adolescent-associated insensitivity to aversive drug consequences are still unknown, there is some evidence that dynorphyn/kappa opioid receptor systems located within reward-related neurocircuitry may be involved in sensitivity to negative consequences of drugs, including cocaine and ethanol (Chefer et al., 2005; Zapata & Shippenberg, 2006). Increases in the activity of this endogenous opioid system oppose cocaine- or ethanol-induced activation of the mesolimbic DA system, thereby either decreasing positive rewarding effects of these drugs or even producing dysphoria (see Shippenberg et al., 2007). Our recent studies have shown that adolescent rats are relatively insensitive to social anxiogenic effects not only of ethanol (Varlinskaya & Spear, 2002), but also of the selective kappa agonist, U60,622E, with both drugs decreasing social investigation and transforming social preference into social avoidance (Varlinskaya & Spear, 2009). Work is ongoing to explore further the impact of ontogenetic differences in the kappa opioid system to adolescent insensitivities to adverse consequences of alcohol.

Together, studies of this nature provide increasing evidence that adolescence may be an ontogenetic period of unique motivational sensitivity for natural rewards, as well as for drugs and alcohol, with social context enhancing the rewarding effects of drugs (Thiel et al., 2008, 2009), and attenuating their aversive properties (Vetter-O'Hagen et al., 2009). During adolescence, an increased sensitivity to drug reward, combined with a relative resistance to aversive drug consequences, could increase not only the likelihood of continuing use due to initial pleasant drug experiences, but also the magnitude of subsequent use due to a decreased sensitivity to the aversive components of that use.

Although useful for revealing general rewarding and aversive properties of meaningful stimuli, CPP has been argued to reflect multiple components of reward, such as affective attribution, goal-directed behavior, and learning processes (Berridge & Robinson, 2003). Thus, age differences in CPP findings could reflect any of a composite of reward-related processes. Hence, in our work we have begun to focus on more discrete aspects of reward processes across ontogeny to better characterize motivational differences between adolescents and adults. One such strategy is to focus on assessing ontogenetic differences in the presumed hedonic affect of naturally rewarding stimuli (assuming, of course, that hedonic affect represents a valid construct in non-human mammalian species). Among the traditional methods for indexing hedonic state in studies in laboratory animals is examination of sucrose consumption, given that intake of a palatable solution is attenuated under a variety of anhedonic states in rodents (e.g. Papp & Moryl, 1996; Willner et al., 1987). When this method was used to determine possible age differences in sucrose intake between adolescent and adult rats, adolescents were found to exhibit greater sucrose consumption on a ml/kg basis relative to their adult counterparts (Wilmouth & Spear, 2009).

Assessment of taste reactivity has also been used to index the hedonic properties (or “liking”) of taste stimuli, with this response highly conserved across species (for reviews see Berridge, 2007; Grill & Berridge 1985). For instance, rhythmic or lateral tongue protrusions are exhibited in response to delivery of a palatable taste (positive responses), whereas aversive tastes elicit other responses such as a gaping reaction (Berridge & Treit, 1986; Grill & Norgren, 1978). The number and intensity of the positive responses to palatable solutions has been suggested to index the positive hedonic properties attributed to the solution by the test subject (Grill & Berridge, 1985). In a series of experiments examining taste reactivity among adolescents and adults to various concentrations of sucrose and other solutions delivered through intraoral cannulae, adolescent rats have been consistently shown to exhibit greater positive taste responses (e.g. more rhythmic and lateral tongue protrusions) than adults (Wilmouth & Spear, 2009). Such increases in positive taste reactivity and sucrose intake among adolescents are reminiscent of the greater motivation for natural, drug and alcohol rewards revealed in the CPP, second-order conditioning and tachycardia studies described earlier. The enhanced effects seen during adolescence using these presumptive measures of positive hedonic affect are also evocative of human imaging studies suggesting greater recruitment of NAc during receipt of rewards in adolescents than adults (e.g., Ernst et al., 2005; Galvan et al., 2006), although these findings are not ubiquitous (e.g., Bjork et al., 2004).

In addition to showing greater positive responses to sucrose solutions in the taste reactivity paradigm, adolescent rats also have been found to exhibit reduced negative taste reactions relative to adults to an aversive solution, such as quinine (Wilmouth & Spear, 2009), a pattern of findings reminiscent of the enhanced rewarding, but attenuated aversive properties of drugs of abuse during adolescence described previously. Somewhat similar findings are emerging in recent imaging work where the dorsolateral prefrontal cortex has been reported to show greater recruitment to positive than negative feedback during the pre-/early adolescent period, with a gradual switch to greater recruitment by negative than positive feedback by late adolescence/early adulthood (van Duijvenvoorde et al., 2008). Crone and colleagues (2008) likewise have evidence of delayed development of adult-typical increases in activation to negative feedback across a variety of frontal brain regions during the adolescent period.

In contrast to the results of sucrose consumption and taste reactivity studies, however, some evidence of an adolescent-related attenuation in the hedonic response to a rewarding social stimulus has been observed when using emissions of 50 KHz ultrasonic vocalizations (USVs) as an index of positive affect (Blanchard et al., 1993; Fu & Brudzynski, 1994). In previous research, rats have been shown to emit USVs in the range of 22 KHz under a variety of aversive circumstances (see Brudzynski, 2001), including foot shock (Tonoue et al., 1986) and the

presence of predator odor (Blanchard et al., 1991). Expression of USVs in the 50–55 KHz range, however, was associated with circumstances inducing a positive affective state, such as play fighting (Knutson et al., 1998), experimenter “tickling” (Panksepp & Burgdorf, 2000), and electrical stimulation of the reward pathway (Burgdorf et al., 2000). When production of these 50 KHz USVs was assessed during a 10-min period of social interaction with an age- and sex-matched conspecific, adolescents were found to produce significantly fewer positive calls than adults during this “consummatory” period, even though the adolescents engaged in significantly more social behavior during the test than adults (Willey et al., 2009). These results are highly replicable and are not due to a competition between production of 50 KHz USVs and expression of social behavior, given that social deprivation is positively correlated with both frequency of social behavior and 50 KHz USVs (Knutson et al., 1998; Willey et al., 2007). Thus, results of these USV experiments suggest a developmental dissociation between social behavior and 50 KHz USVs emitted in that context – a presumptive index of the hedonic value of social interactions.

Using the arguable assumption that 50 kHz USVs reflect positive affect, the Willey et al. (2009) data provide evidence for reduced positive affect to social stimuli during adolescence relative to adulthood, perhaps leading the adolescents to a compensatory increase in “consumption” of this natural reward (i.e. increased social interactions) in order to achieve the desired amount of hedonic pleasure. Yet, the sucrose intake and taste reactivity data discussed above conversely provide evidence in support of an increased positive hedonic impact of palatable solutions during adolescence, with this increased hedonic pleasure perhaps precipitating increased reward consumption for its pleasurable aspects during this developmental transition. Thus, the data to date do not lead to a simple conclusion as to whether adolescence is a period of enhanced or attenuated hedonic responses to natural rewarding stimuli, nor to clear predictions regarding age-related alterations in sensitivities to drug-related rewards as well. Clearly, more research is needed to resolve these issues, with perhaps particular attention directed toward need state, as well as modality and relative intensity of reward. Indeed, when using fMRI to compare NAc activation to rewards in human adolescents and adults, Galvan and colleagues (2006) found the relationship between NAc activation and reward magnitude normally seen in adults to be exaggerated during adolescence, with adolescents showing more dramatic increases in NAc recruitment with larger rewards than adults, but tending to show weaker recruitment in response to small rewards. Together, fMRI studies of reward sensitivity of human adolescents, combined with further studies using basic animal models of adolescence, may provide important information as to the affective significance of potentially rewarding stimuli and their impact on reward-directed behaviors during adolescence compared to adulthood.

Other clues regarding possible adolescent-peculiar responsiveness to rewards may be gleaned from focusing on how adolescents are motivated by rewards – i.e., by investigating potential age differences in the process of incentive salience. The concept of incentive salience, or “wanting,” has been greatly popularized by Robinson & Berridge (Robinson & Berridge, 2003, 1993, 2008), with “wanting” referring to goal-directed behavior towards relevant environmental stimuli. Organisms need a process to recognize and seek rewarding stimuli in the environment, such as food and water, to ensure survival. According to this hypothesis, the process of incentive salience is responsible for attributing motivational value to cues associated with natural rewards and drugs (Robinson et al., 1998). Importantly, it has been hypothesized that drugs of abuse are capable of hi-jacking the processes responsible for attribution of incentive salience, which were originally in place for the purpose of obtaining natural rewards (for review see Robinson & Berridge, 2003, 1993, 2008). Specifically, when repeated encounters with drugs induce behavioral sensitization, sensitization of incentive salience for drugs and drug-associated cues (through neural alterations in reward-related brain circuitry) is

also thought to occur—a phenomenon termed “incentive sensitization” (Robinson & Berridge, 1993, 2008).

Work in our laboratory (Doremus-Fitzwater & Spear, 2008) has begun to explore potential age differences in incentive salience for natural rewards using assessment of sign-tracking behavior (Flagel et al., 2007, 2008, 2009). Sign-tracking occurs when a cue associated with an appetitive reward elicits approach and goal-directed behavior towards the cue itself, a cue-directed behavior that can become excessive over time (Tomie, 1995). Flagel and colleagues have hypothesized that expression of approach and goal-directed behavior to such cues (rather than to the spatial location of impending reward delivery) is indicative of enhanced incentive salience for the cue (for review see Flagel et al., 2009).

To the extent that greater consumption of natural and drug rewards during adolescence is associated with enhanced incentive salience for reward-related cues, adolescents would be expected to exhibit greater sign-tracking behavior relative to adults. In initial work to examine this hypothesis, adolescent and adult male rats (with 12 animals per age group) were placed into an autoshaping situation, with an 8-sec presentation of an illuminated retractable lever preceding response-independent delivery of a banana pellet. Rats were given 25 lever-pellet pairings each day, for a total of 5 days. Over time, some rats approached and contacted the lever CS upon its presentation (“sign-trackers”), whereas other rats approached and entered the food trough when the lever was inserted into the chamber (“goal-trackers”), even though contacts with neither the lever nor the food trough impacted delivery of the food reward. Although the adolescent and adult age groups both contained certain animals that displayed evidence of sign-tracking, adolescents overall showed significantly weaker sign-tracking than their adult counterparts (see Fig. 1). This adolescent-associated reduction in sign-tracking behavior is also evident in female rats (Doremus-Fitzwater & Spear, 2008; Doremus-Fitzwater & Spear, under revision) and has been confirmed by additional work in our laboratory as well (Anderson & Spear, 2009). This attenuation in sign-tracking among adolescent animals when compared to adults was surprising, and opposite to what we had hypothesized. It instead supports the suggestion that incentive salience for a discrete cue predicting food reward may be lower during adolescence than at maturity. To the extent sign tracking represents a valid index of incentive motivation and generalizes to cues predicting other rewards, the findings could be interpreted to suggest that adolescents may not be more vulnerable to cue-induced craving for drug rewards. Although counter to our original hypothesis, these data are reminiscent of findings from human fMRI work showing adolescents to exhibit less recruitment of the NAc than adults when anticipating a reward, while responding similarly to reward receipt, data interpreted to suggest that “adolescents selectively show reduced recruitment of motivational but not consummatory components of reward-directed behavior” (Bjork et al., 2004, p.1793).

It is also possible that the markedly attenuated sign tracking seen in adolescents relative to adults could reflect in part age differences in stimulus selection and cue learning propensities. For instance, in a passive avoidance task, an older study found that adolescent rats were less disrupted by a change in a redundant discriminative cue, while more disrupted by a contextual change than younger or older rats (Barrett et al., 1984). In recent work, less cue-induced reinstatement of drug intake was seen in rats trained to self-administer cocaine or morphine in adolescence compared to animals that initiated drug use as adults (Doherty et al, 2009, Li & Frantz, 2009), data also commensurate with the suggestion that adolescents may perhaps attribute motivational salience to stimuli differently than do adults. Clearly, more research is needed to resolve the issue of how adolescents differ from adults in their attribution of incentive salience for rewards and for cues predicting those rewards, as well as to determine the potential implications of these developmental differences for the adolescent-associated propensity to use and sometimes abuse drugs and alcohol.

Summary and Conclusions

Adolescence is a developmental phase that is characterized by unique transformations in brain and behavior. Adolescents across a variety of species not only show increases in risk-taking and novelty seeking behaviors, but also demonstrate elevated social interactions with their peers. Brain alterations in regions implicated in mediating motivational and reward-related behaviors likely contribute to expression of these adolescent-typical behaviors. An early maturing or exaggerated reward system, perhaps associated with an augmented responsiveness of the NAc, may lead to an enhanced sensitivity to the positive hedonics of potential rewards during this developmental phase. Additional behavioral evidence suggests that adolescents may conversely exhibit an attenuated sensitivity to aversive properties of stimuli, perhaps in part through developmental alterations in neural components of these same motivational systems, although the neural mechanisms underlying such aversive properties have not been systematically explored in adolescence. Ultimately, this adolescent-typical combination of enhanced positive/attenuated aversive biases toward drugs and other stimuli may contribute to elevated drug use during adolescence. Upon first use of a novel drug, adolescents may experience positive effects in the absence of notable aversive effects (e.g. nausea, light headedness), increasing the probability that this initial use will be repeated. With continued use, these patterns of sensitivity permit relatively high levels of use and the emergence of abusive patterns of use among vulnerable individuals. Given the developmental differences in brain circuitry between adolescents and adults, a different path to abuse patterns may be present in adults, with perhaps repeated use leading to sensitization of drug “craving” (e.g., Robinson & Berridge, 2003) or to augmentation of post-use aversive consequences that prompt continued use for their relief (e.g., see Koob, 2001). In order to better understand risky and drug-related behaviors during adolescence, more research is needed to characterize reward-related processing among adolescents, as well as the impact of developmental alterations in associated reward-relevant neurocircuitry on these processes.

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Figure 1.

Adolescent (black circles) and adult (white circles) male rats were exposed to an autoshaping procedure in which an 8-sec presentation of an illuminated lever (the conditioned stimulus) was followed by response-independent delivery of a banana pellet. Rats were given 25 lever-pellet pairings each day, for a total of 5 days. The total number of times the lever was pressed was recorded for each session, with the mean ($\pm$ standard error) number of lever presses for each group shown across the 5 conditioning days.