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Reward processing in adolescent rodents

Nicholas W Simon and **Bita Moghaddam**

University of Pittsburgh, Department of Neuroscience

Abstract

Immaturities in adolescent reward processing are thought to contribute to poor decision making and increased susceptibility to develop addictive and psychiatric disorders. Very little is known; however, about how the adolescent brain processes reward. The current mechanistic theories of reward processing are derived from adult models. Here we review recent research focused on understanding of how the adolescent brain responds to rewards and reward-associated events. A critical aspect of this work is that age-related differences are evident in neuronal processing of reward-related events across multiple brain regions even when adolescent rats demonstrate behavior similar to adults. These include differences in reward processing between adolescent and adult rats in orbitofrontal cortex and dorsal striatum. Surprisingly, minimal age related differences are observed in ventral striatum, which has been a focal point of developmental studies. We go on to discuss the implications of these differences for behavioral traits affected in adolescence, such as impulsivity, risk-taking, and behavioral flexibility. Collectively, this work suggests that reward-evoked neural activity differs as a function of age and that regions such as the dorsal striatum that are not traditionally associated with affective processing in adults may be critical for reward processing and psychiatric vulnerability in adolescents.

Keywords

Adolescent; reward; electrophysiology; striatum; dopamine; rat

1. Introduction

Current research on psychiatric disorders has placed a strong emphasis on early detection and treatment. Many symptoms of schizophrenia, mood disorders and addiction first manifest during the adolescent period (Adriani and Laviola, 2004; Casey et al., 2008; Schramm-Sapyta et al., 2009; Mitchell and Potenza, 2014). Accordingly, it is critical to elucidate the biological and environmental risk factors that render adolescents highly

Address correspondence to: Bita Moghaddam, University of Pittsburgh, Department of Neuroscience, A210 Langley Hall, Pittsburgh, PA 15260, tel: 412 624-2653, fax: 412 624-9198, bita@pitt.edu.

4. Conflicts of Interest

The authors declare that there are no conflicts of interest.

vulnerable to these disorders. Such mechanistic knowledge is necessary for the development of interventions to prevent or attenuate the emergence of disease.

Previous preclinical research on brain development and disease has primarily assessed morphological changes or alterations at the receptor level. These studies have yielded critical information about adolescent biology and behavior. There is little known, however, about real-time dynamics of neuronal activity during behavior. This information is particularly relevant in light of recent theories positing that dysfunctional neuronal network activity is a critical contributor to the etiology of disease (Uhlhaas and Singer, 2012; Moghaddam and Wood, 2014). To fully understand how behaviorally relevant neuronal network activity is altered in vulnerable individuals, we must first understand how individual neurons and neural ensembles encode salient events in healthy adolescents and adults.

Changes in affect, motivation, and motivational processing during adolescence are among the first observed behaviors predictive of schizophrenia and other psychiatric illnesses in high risk individuals (Ernst et al., 2006; Gladwin et al., 2011; Juckel et al., 2012). To understand the development of symptoms during this vulnerable developmental period, it is essential to quantify the basic neural mechanisms underlying adolescent reward processing. Recent data accumulated in our lab using adolescence rats suggest substantial age-related differences in reward-induced neuronal activity. These differences are manifested even when 1) measurable behavior is equivalent between adolescent and adult subjects, and 2) baseline levels of neuronal activity are equivalent between age groups. Thus, reward-evoked neuronal activity may, in some instances, be more effective than behavioral measures of motivation or **baseline** activity as a marker of early vulnerability to disease. In this review, we summarize adolescent reward-processing data acquired from a rat model across multiple brain regions, and discuss the implications of these differences for adolescent behavior and disease vulnerability.

2. Adolescent reward processing differs from adults across multiple regions

The technique focused in this review is single-unit extracellular recording where neuronal activity of multiple neurons can be measured in real-time in behaving animals (Sturman and Moghaddam, 2011b). For this method, multiwire electrode arrays are implanted in specific brain regions and electrical signals are amplified and high pass filtered to isolate high frequency neuronal activity, such as action potentials or local field potential oscillations (Buzsaki, 2004; Sturman and Moghaddam, 2011b; Wood et al., 2012). Measuring neural activity in awake-behaving adolescent rats is a challenging endeavor, as the adolescent window only spans approximately between postnatal days 28 – 55 (Spear, 2000). After accounting for the required time for electrode implantation surgery, recovery and habituation, the brief remaining time window precludes the use of complex behavioral paradigms with electrophysiology. Therefore, behavioral tasks that do not require long training times must be used to measure reward processing in adolescent rats. Our lab utilizes a rewarded instrumental task in which rats learn to nose poke into a lit port to receive a single sugar pellet, while neural activity is recorded from electrode arrays implanted into

specific brain regions (Figure 1). Importantly, the task is simple enough that learning and performance of the primary components of the task are comparable between adults and adolescents (Sturman et al., 2010), thus any differences in neuronal activity are indicative of reward processing differences, rather than a product of behavioral asymmetry between groups. Each of these behavioral events can be synchronized with measures of neural activity with sub-second long temporal resolution, allowing assessment of neural activity associated with reward-related cues, goal-directed actions, and reward anticipation and delivery. Using variants of this task, we recorded from orbitofrontal cortex, dorsal and ventral striatum, and ventral tegmental area in adult and adolescent rats. We then discuss how these differences in reward-processing may be related to reward-related cognitive traits observed during adolescence, including impulsivity, risk taking and behavioral flexibility.

2.1. Prefrontal cortex

Prefrontal cortex (PFC) undergoes substantial development throughout adolescence, and this development has been implicated in adolescent behavioral tendencies, particularly the ability to regulate and inhibit motivated behaviors (Brenhouse et al., 2010; Geier et al., 2010; Sturman and Moghaddam, 2011a; Ernst, 2014). PFC is divided into multiple functionally distinct subregions with different implications for adolescent behavior and disease vulnerability. Orbitofrontal cortex (OFC) is a lateral prefrontal-cortical region that receives input from sensory regions and is extensively connected with limbic areas (Price, 2007; Rolls and Grabenhorst, 2008). Accordingly, OFC is ideally suited to integrate physical aspects of rewarding and aversive outcomes with emotional information, and then utilize this affective information to guide behavior. Neuronal activity in OFC has been associated with the representation of rewarding outcomes (van Duuren et al., 2007; Balleine et al., 2011; Schoenbaum et al., 2011), and has been implicated in multiple facets of impulsive behavior (Berlin et al., 2004; Winstanley et al., 2010; Zeeb et al., 2010), which is elevated in humans and rats during adolescence (Green et al., 1994; Adriani and Laviola, 2003; Burton and Fletcher, 2012; Doremus-Fitzwater et al., 2012; Mitchell and Potenza, 2014). Because OFC (along with other prefrontal regions) has been shown to be underdeveloped in **human** adolescents (Sowell et al., 1999; Galvan et al., 2006), OFC is a logical target for probing for age-related differences in reward processing.

Single unit extracellular recording was used to measure task-evoked activity in individual neurons. In adults, OFC population neuronal activity decreased during **reward retrieval (Figure 1B)**. In contrast, the adolescent OFC population activity was increased **during retrieval** (Sturman and Moghaddam, 2011b). This profound difference in activity occurred despite similar baseline firing rate between groups, and comparable neuronal inhibition during the performance phase of the instrumental action that lead to reward delivery. These data suggest that reward processing in OFC can be an effective biomarker of age-related differences, even when baseline neuronal activity and behavior are equivalent between groups.

Although baseline firing rate was similar between age groups, an alternate analysis of firing patterns revealed further distinctions. Adolescent OFC showed increased variability compared to adults in firing rate across multiple trials, as assessed by fano factor

(Churchland et al., 2010). This variability may be indicative of inefficient neural coding of reward-related events, as spike variability undermines effective inter-regional communication through spike-field coherence (Fries, 2005; Churchland et al., 2010). Importantly, this finding suggests that measures beyond simple firing rate may be necessary to detect functional differences in neural processing between age groups, and possibly between healthy controls and diseased or at-risk patients.

OFC plays a modulatory role in impulsive choice, defined as a preference for immediate rewards/gratification (Winstanley, 2007). Adolescent humans and rats have increased preference for immediate gratification compared to adult humans and rats, and this has been implicated in adolescent drug abuse and maladaptive behavior (Adriani and Laviola, 2003; Doremus-Fitzwater et al., 2012; Mitchell and Potenza, 2014; Stanis and Andersen, 2014). Impulsive decision-making is associated with several psychiatric disorders (Bechara et al., 2001; Ahn et al., 2011; Nolan et al., 2011), and is both a predictor of drug abuse and a consequence of long-term exposure to drugs of abuse (Simon et al., 2007; Perry et al., 2008; Anker et al., 2009; de Wit, 2009; Mendez et al., 2010). Thus, a feed forward condition may develop in which individuals with psychiatric vulnerabilities involving aberrant impulsive regulation are highly likely to abuse drugs, which then exacerbates trait impulsivity (Garavan and Stout, 2005; Setlow et al., 2009). Our data suggest that age differences in impulsivity may be, in part, due to neuronal processing differences in the OFC, as OFC encodes information about reward-associated delays (Roesch and Olson, 2005; Roesch et al., 2006). The highly variable neural processing throughout task performance (as assessed by fano factor) and hyperactive reward-evoked response observed in adolescent OFC may, therefore, be related to unstable representations of reward-related events. Our observation may also be related to a suboptimal ability to bridge long delays between actions and outcomes, a function associated with OFC neurons (Roesch et al., 2006). This in turn would facilitate persistent choice of immediate over delayed gratification.

Age-related differences also are observed in infralimbic and prelimbic regions of the medial PFC , which are implicated in behavioral planning and feedback, attention, and response inhibition (Goldman-Rakic, 1995; Fuster, 2001; Killcross and Coutureau, 2003; Magno et al., 2006; Peters et al., 2008; Burgos-Robles et al., 2013; Pezze et al., 2014). While neuronal activity has not yet been recorded in these regions in behaving adolescent animals, developmental correlates of reward processing have been revealed by quantifying immediate early genes. After heroin self-administration, adolescents showed an attenuated increase in Fos positive neurons in prelimbic and infralimbic cortices compared to adults, indicative of reduced activation of adolescent medial PFC by drug reward seeking (Doherty et al., 2013). Reports of nicotine-evoked activity are conflicting, demonstrating either enhanced increase in Arc or similar changes in cfos in adolescent compared to adult medial PFC (Leslie et al., 2004; Schochet et al., 2005). Finally, cocaine exposure caused increase c-fos expression in adolescent PFC (Cao et al., 2007). While these studies provide useful data, direct measurements of neural processing of both drug and natural rewards in adolescent medial PFC will yield temporally specific information about adolescent medial PFC function.

Dopamine receptor expression in prelimbic cortex peaks during adolescence (Andersen et al., 2000). D1 dopamine receptors, in particular, have been linked to adolescent motivated

behavior. Adolescent rats demonstrate increased vulnerability to drug-associated cues compared to adult rats (Leslie et al., 2004; Brenhouse and Andersen, 2008; Brenhouse et al., 2008; Kota et al., 2011); blocking D1 receptors in adolescent prelimbic cortex decreases sensitivity to these cues (Brenhouse et al., 2008). In addition, overexpressing D1 receptors in adult prelimbic cortex recapitulated adolescent behavioral tendencies, including impulsivity and increased sensitivity to drug-associated cues (Sonntag et al., 2014). D1 receptor manipulation also modulates behavioral sensitivity to amphetamine to a greater degree in adolescents than adults (Mathews and McCormick, 2012).

2.2. Striatum

Neural development during adolescence is ongoing in the striatum (Sowell et al., 1999; Ernst et al., 2006; Casey et al., 2008; Geier et al., 2010; Somerville et al., 2011). Striatum is involved with learning, reward processing and movement, and has been strongly implicated in psychiatric disorders including schizophrenia and addiction (Kalivas and Volkow, 2005; Everitt et al., 2008; Horga and Abi-Dargham, 2014). Both ventral and dorsal striatum receive dense dopaminergic projections from the midbrain, and dopamine transmission has repeatedly been shown to differ between adulthood and adolescence (Adriani and Laviola, 2004; Volz et al., 2009; McCutcheon et al., 2012). While there is a wealth of data from animal models describing neuroanatomical and pharmacological differences in striatum between adolescent and adult rodents (Andersen et al., 1997; Bolanos et al., 1998; Tarazi et al., 1998), there are considerably less data describing age-related differences in neural activity. The majority of the neural imaging studies performed in human adolescent subjects have focused on ventral striatum (VS) in particular the nucleus accumbens (NAc), which is implicated in motivation, learning and cue processing (Robbins and Everitt, 1996; Kelley, 2004; Ernst et al., 2006; Galvan et al., 2006; Geier et al., 2010; Hart et al., 2014). However, dorsal striatum (DS), which is implicated in learning, action-selection and habit formation (Packard and White, 1990; Balleine et al., 2007; Kimchi et al., 2009), has been largely overlooked as a locus of developmental differences. To quantify and compare neural correlates of reward processing in both striatal regions, our lab recorded single-unit **extracellular** activity in both DS and NAc of adult and adolescent rats during goal-directed behavior.

Somewhat surprisingly, task-evoked activity in NAc did not differ substantially between adult and adolescent rats (Sturman and Moghaddam, 2012). Robust age-related differences, however, were observed in DS. Adolescent neurons were activated just prior to a reward-seeking action, whereas adult neurons did not respond until after action completion **(Figure 1B)**. Adolescent neurons in DS also were activated prior to reward **retrieval**, while adult neurons were inhibited by reward **(Figure 1B)**. This demonstrated that the adolescent brain recruits DS circuitry both earlier and to a greater degree than adults during reward-retrieval.

While adolescent DS neurons are hyper-responsive to rewards, amphetamine-evoked dopamine release is attenuated compared to adults in this region. Lower levels of amphetamine-evoked dopamine efflux in the DS, but, again, not the NAc of adolescent rats compared to adults (Matthews et al., 2013). Interestingly, the opposite effect has been observed with dopaminergic drugs that act as uptake inhibitors, such as cocaine and

methylphenidate, which cause enhanced dopamine efflux in adolescent compared to adult DS (Walker and Kuhn, 2008; Walker et al., 2010). As with amphetamine, this age-related cocaine effect was more pronounced in DS than NAc (Frantz et al., 2007; Walker and Kuhn, 2008). This difference between DS dopamine release may be a function of baseline dopamine availability, as reduced dopamine availability in projection dopamine neurons would likely affect drugs that facilitate dopamine release (such as amphetamine) to a greater degree than drugs that maintain dopamine in the synapse (such as cocaine). Accordingly, tyrosine hydroxylase, an enzyme involved with the synthesis of dopamine, was reduced in adolescent DS but not NAc (Matthews et al., 2013). This reduction in evoked-dopamine neurotransmission **suggests** that dopamine projections to DS, which arise from substantia nigra pars compacta (Ungerstedt, 1971; Lynd-Balta and Haber, 1994), may be hypoactive during adolescence. Dopamine has an inhibitory influence on medium spiny neurons in the striatum (Kreitzer and Malenka, 2008). A hypoactive dopamine neurotransmission in adolescence DS may, therefore, contribute to our observed enhanced reward-evoked activity in DS neurons. Future studies recording from dopamine projections to the adolescent DS will directly address this mechanism.

The area of striatum traditionally associated with attributing value and motivation to cues and rewards is VS (Robbins and Everitt, 1996; Kelley, 2004; Cooper and Knutson, 2008; Flagel et al., 2011). Accordingly, many theories of adolescent illness and behavioral vulnerability hinge on aberrant reward-related motivated behavior and responsivity of reward-related brain circuitry (Bjork et al., 2004; Galvan et al., 2006; Geier et al., 2010; Van Leijenhorst et al., 2010). The previous data, on the other hand, suggest that age-related differences to rewards may be even greater in DS (Sturman and Moghaddam, 2012; Matthews et al., 2013). While these do not preclude the role of the developing VS in adolescent behavioral and disease vulnerability, they suggest that DS may also play a substantial role in adolescent behavioral tendencies.

The DS is strongly associated with learning and the physical manifestation of locomotive behavior (Robbins and Everitt, 1992; Packard and Knowlton, 2002; Gittis and Kreitzer, 2012). In particular the dorsomedial striatum (DMS), or associative striatum region of the DS is implicated in linking actions to rewarding outcomes, as lesions of DMS abolish the learning and expression of goal-directed behavior (Yin and Knowlton, 2004; Ragozzino, 2007), and DMS activity also has been implicated in the encoding of flexible response patterns (Kimchi and Laubach, 2009). Conversely, dorsolateral striatum (DLS) is involved with the consolidation and expression of habitual behavior, during which actions are no longer dependent on outcome representation (Yin et al., 2004; Yin et al., 2009). The studies of adolescent neuronal activity and dopamine release detailed in this review (Sturman and Moghaddam, 2012; Matthews et al., 2013) were both localized to DMS, underscoring the importance of this region in development toward the adolescent behavioral phenotype and illness vulnerability. In line with this idea, several differences have been observed in instrumental behavior between adult and adolescent rats, with adolescents demonstrating differences in instrumental behavior, including differences in appetitive motivation, reduced extinction, attenuated response inhibition and impaired ability to adjust to changes in action-outcome contingencies (Friemel et al., 2010; Sturman et al., 2010; Andrzejewski et al.,

2011; Spear, 2011; Burton and Fletcher, 2012; Naneix et al., 2012). In addition, adolescents exhibit reduced ability to quickly initiate an appropriate response after a stop signal (Simon et al., 2013), similar to the effect observed after lesions of DMS (Eagle and Robbins, 2003).

In contrast to adolescent DMS, the presence of developmental differences in DLS is less clear. During the expression of goal-directed behavior, actions are initially tightly linked to outcome representation. After overtraining, however, actions become less influenced by outcome representation, and more automated ("habitual") (Dickinson, 1985). Plasticity related to this habit learning occurs in DLS (Yin et al., 2009; Balleine and O'Doherty, 2010; Thorn et al., 2010), and the shift from goal-directed to habitual behavior is mediated in part by dopamine transmission in DS (Packard and White, 1991; Belin and Everitt, 2008). There are conflicting data on the development of habit formation in adolescent vs. adult rats. Adolescent rats demonstrate an inability to adjust responding to changes in contingency, as well as increased habitual behavior in a reinforcer devaluation task (Naneix et al., 2012; Hammerslag and Gulley, 2014). There is evidence for either behavioral rigidity or flexibility in adolescent rats on a set shifting task compared to adults, based on task design and parameters (Leslie et al., 2004; Newman and McGaughy, 2011; Snyder et al., 2014). More complex tasks appear to consistently yield greater levels of flexibility in adolescents. A four-choice reversal task, which requires a greater cognitive load than the standard two-choice set shifting design, revealed greater flexibility in adolescent compared to adult mice (Johnson and Wilbrecht, 2011). In addition, recent data demonstrate that, after learning to withhold an action in the presence of a cue, adolescent rats acquire that cue more quickly as a Pavlovian-conditioned stimulus predictive of reward, as assessed by an increase in reward approach behavior. This suggested that adolescents are able to rapidly adjust the value of a cue that was previous salient (which differs from reversal tasks, which typically involve attributing value to a previously unrewarded cue). A recent experiment in our lab tested this ability to adjust to changes in cue identity further by training rats in a cued instrumental paradigm, during which a 10 second cue (light or tone) was presented, and a nose poke into a lit port resulted in food pellet delivery. No difference in correct responses between adults and adolescents was observed in this task ($F(1,12)=.23$, $p = .64$; n=7/age group; Figure 2). In the second phase of this experiment, the instrumental cue was shifted in modality to a 10 second Pavlovian cue. After the shift in cue-outcome relationship, adolescents showed a higher percentage of Pavlovian approach during this cue than adults, as assessed by time spent in the food trough during the cue ($F(1,12) = 6.96$, $p = .023$; Figure 2). In a control experiment, adolescent and adult rats acquired Pavlovian approach to a novel cue at an equal rate, indicating that this effect was not related to an age related difference in the general ability to learn or perform Pavlovian conditioning ($F(1,12)= .26$, $p = .62$). These data, therefore, indicate that, when a cue acts as either a stop or go signal within an instrumental context, changes in cue-outcome relationships can be flexibly acquired by adolescent rats more quickly than adults. This characteristic of the adolescent brain would allow it to adjust to changes in value of previously salient cues or environments more efficiently than an adult brain. This is an interesting finding because much of the research on adolescents focuses on maladaptive behaviors, whereas behavioral flexibility is generally suggested to be an advantageous characteristic.

The summarized data suggest that adolescent rats may encode relationships between cues and outcomes in which cues were previously meaningful more flexibly than adults (Simon et al., 2013; Figure 2), or in situations with a higher cognitive load (Johnson and Wilbrecht, 2011). The hyper-responsivity observed in adolescent DMS during reward-related events (Sturman and Moghaddam, 2012) may promote increased ability to alter behavioral strategies (Kimchi and Laubach, 2009). It would be of interest to record from adolescent DLS, which is involved with the learning and expression of habitual behavior, to observe if this region is hypoactive compared to adults. Accelerated habit formation is proposed to promote addiction, as habitual drug seeking behavior is less sensitive to the negative consequences of drug abuse and addiction (Everitt et al., 2008; Hogarth et al., 2013). Thus, ongoing study of the role of the developing DS in habit formation is highly relevant toward the preponderance of adolescent drug addiction.

Both DS and VS are involved with risky decision-making (Cardinal, 2006; Simon et al., 2011; Kohno et al., 2013; Mitchell et al., 2014), defined as a preference for risky over safe rewards. Risky behavior is a hallmark of adolescence, and is linked to drug abuse (Bornovalova et al., 2005; Balogh et al., 2013). Moreover, recent evidence from a rat model of risky decision-making demonstrates that risky behavior in adolescents predicts cocaine self-administration (Mitchell et al., 2014), which may facilitate the drug abuse and addiction vulnerability during adolescence (Adriani and Laviola, 2004; Merline et al., 2004; Doremus-Fitzwater et al., 2010). Reduced dopamine receptor availability in both striatal regions is predictive of higher levels of risky decision-making in rats, and local infusion of selective dopamine agonists either systemically or into adolescent striatum reduces risky behavior (Simon et al., 2011; Mitchell et al., 2014). Accordingly, adolescent rats demonstrate reduced dopamine responsivity and TH expression in DS (Matthews et al., 2013), which may provide a partial mechanism for adolescent risky behavior. Risky decision-making also is associated with neuronal activity and dopamine receptor expression in OFC (Eshel et al., 2007; Van Leijenhorst et al., 2010; Simon et al., 2011; O'Neill and Schultz, 2013). It is possible that the hyperactive reward responses in both OFC and DS (Sturman and Moghaddam, 2011b, 2012) are related to the excessive and occasionally maladaptive risky decision-making during adolescence. Further study of this circuitry could yield interesting data and therapeutic options for the early stages of diseases characterized by risky behavior that manifest during adolescence, including addiction, schizophrenia and depression (Ludewig et al., 2003; Bornovalova et al., 2005; Taylor Tavares et al., 2007).

2.3. Ventral tegmental area

Dopamine neurons, especially those localized in ventral tegmental area (VTA), are involved with reward processing, associative learning, and the pathophysiology of addiction, mood disorders, and schizophrenia (Wise and Bozarth, 1985; Schultz, 1998; Wise, 2004; Sesack and Grace, 2010; Howes et al., 2012). The dopamine system has been implicated in adolescent behavioral and illness vulnerabilities (Luciana et al., 2012; Matthews et al., 2013; Niwa et al., 2013), and aspects of dopamine transmission and VTA activity are different in adults and adolescents (Robinson et al., 2011; McCutcheon et al., 2012; Matthews et al., 2013). In addition, dopamine neurons in VTA project to prefrontal cortex and ventral striatum, regions undergoing development during adolescence. Little is known, however,

about how adolescent VTA neurons process reward related events compared to adults. Recent preliminary recording of extracellular activity from VTA neurons in adult and adolescent rats indicates that these neurons have similar basal firing rate and responding to reward related cues (Kim and Moghaddam, 2012), and work is ongoing that will assess adolescent reward processing in this, and other, dopaminergic regions.

2.4. Reward processing circuitry summary

Adolescents demonstrate enhanced impulsive behavior, risk taking, cue salience, drug and reward seeking, and behavioral flexibility compared to adults. As detailed above, single unit electrophysiology revealed age-related differences in reward processing that are likely involved with these behavioral tendencies. Adolescents demonstrate hyper-activation to reward relative to adults in both OFC and DS (Figure 3). The OFC directly projects to the DS, at least in adult rodents, suggesting that immature OFC-DS connectivity also may contribute to these observed effects (Berendse et al., 1992; Reep et al., 2003). Dopaminergic neurons projecting from the substantia nigra also project to DS (Voorn et al., 2004), and aberrant reward-evoked activity in these neurons may contribute to hyperactive DS reward processing in adolescence. The reduced dopamine efflux observed in DS following amphetamine exposure suggests that these neurons may indeed be hyperactive compared to adults, although further experiments are necessary to confirm this functional difference. Reward-evoked activity in DLS, which receives the strongest dopaminergic input from substantia nigra (Groenewegen, 2003; Voorn et al., 2004), also is likely to differ between adults and adolescents, as the development of behavioral habits varies across the lifespan (Johnson and Wilbrecht, 2011; Newman and McGaughy, 2011; Simon et al., 2013; Snyder et al., 2014).

Interestingly, no substantial age-related differences were observed in NAc reward processing, despite VS being a prominent factor in models of adolescent behavioral vulnerability (Ernst et al., 2009; Geier et al., 2010). This similar neural activity between age groups is consistent with reports of no age related differences in drug-evoked dopamine efflux in NAc (Frantz et al., 2007; Matthews et al., 2013), although studies about dopamine receptor expression in NAc are conflicting (Teicher et al., 1995; Tarazi and Baldessarini, 2000). The lack of differences in NAc reward-processing does not preclude the influence of the developing adolescent NAc on behavioral and psychopathology vulnerabilities; however, the observed differences in motivational processes during adolescence (Spear, 2011) may arise from functional neural activity in DS and PFC regions to a greater extent than NAc. Collectively, these finding suggest that the traditional brain reward circuitry should be modified for adolescents (Figure 3).

3. Conclusion

The findings reviewed here inform future adolescent research in two ways: (1) Baseline activity or response to sensory stimuli such as reward predicting cues are unaffected, or less affected, than neuronal processing around the time of reward. Thus, a focus on reward response may provide the ideal biomarker for early vulnerability to disorders of motivation and affect. (2) Robust neuronal responses were observed in regions that are not typically

associated with reward processing in adults. Thus, the dynamic circuitry of motivated behavior may be different than our adult models and involve cortical and basal ganglia regions that are not classically associated with reward processing. Future emphasis on regions such as the DS may greatly enhance our knowledge of this dynamic circuitry and its contribution to disease vulnerability in at-risk individuals.

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Highlights

- The adolescent brain processes rewards differently than in adults
- These differences occur even when behavior is similar between age groups
- DS was the locus of substantial developmental differences in reward activity
- Surprisingly, differences were not as pronounced in VS
- These differences may have implications for adolescent psychiatric vulnerability

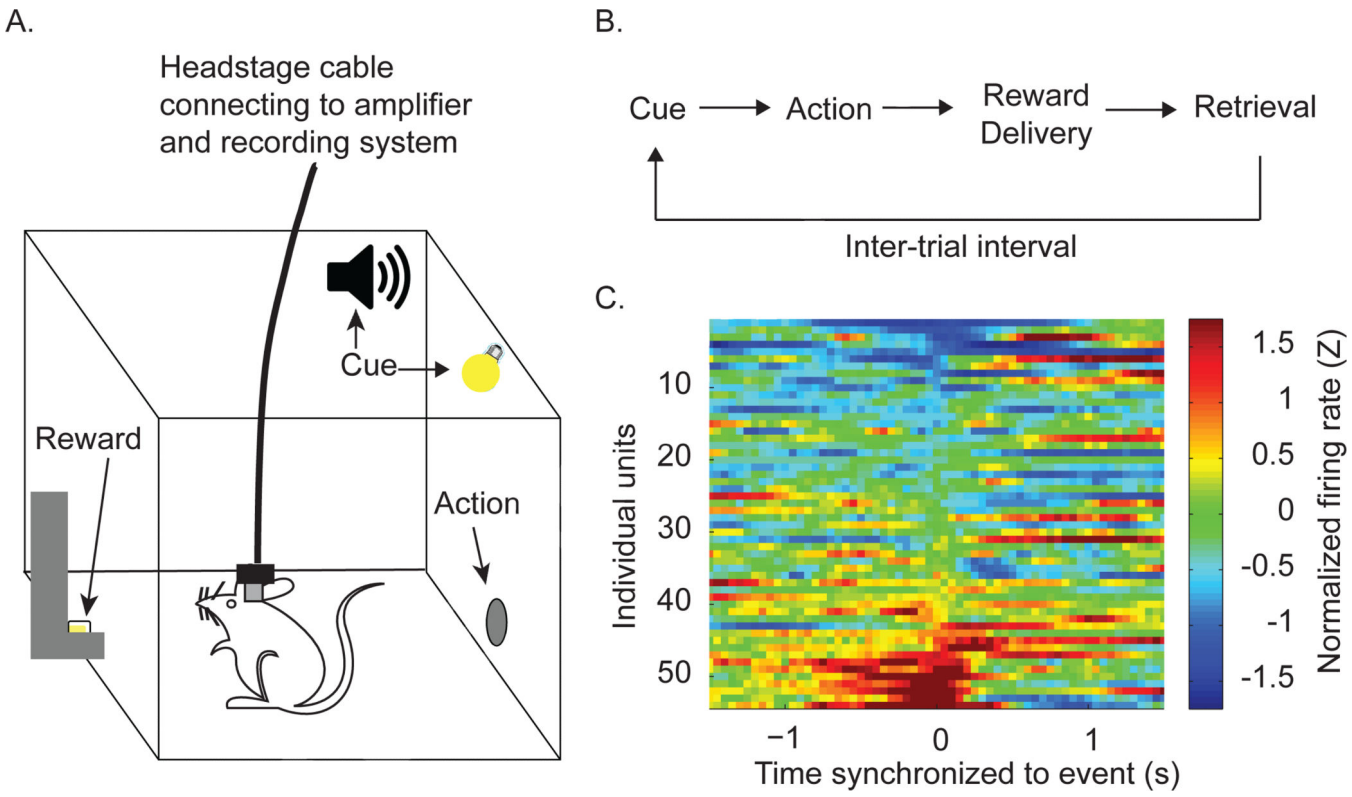

Figure 1.

A. Single unit electrophysiology was performed with awake-behaving adolescent and adult rats during reward-related behavior. Rats were implanted with microwire arrays and placed into an operant chamber equipped with a nose poke port, food trough that delivered sugar pellet rewards, and a cue light used to signal reward availability. It should be noted that the identity of the cue was a light, a tone, or a compound cue consisting of both. B. The instrumental tasks utilized began with illumination of the light cue, during which performance of a nose-poke (action) caused delivery of a pellet reward. After the rat collected the reward, a variable inter-trial interval was initiated, then the next trial began. C. This heat plot shows sample data demonstrating the typical response of individual neurons to a reward-associated event. A subset of neurons demonstrate increased firing rate surrounding the event (bottom), others demonstrate suppressed firing rate during the event (top), and others are unresponsive (middle).

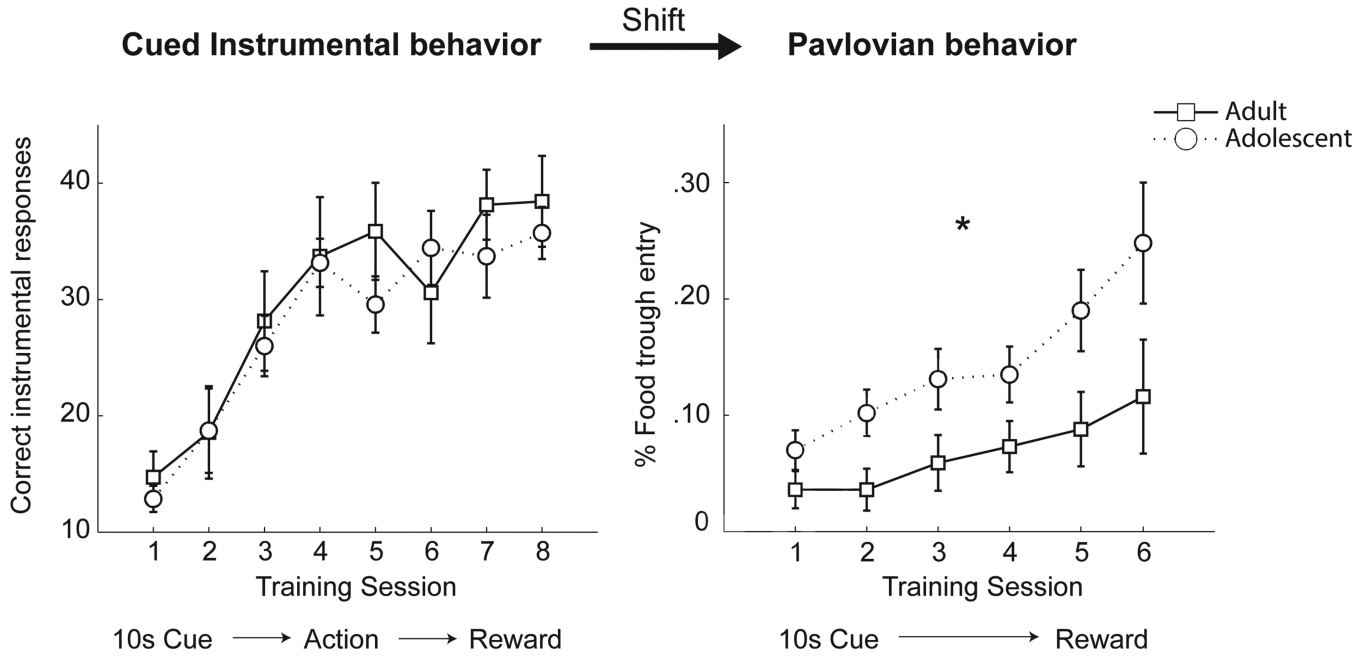

Figure 2.

Adult and adolescent rats learned to perform an instrumental action for reward following cue presentation. B. The same cue was shifted to a Pavlovian cue, during which reward was no longer contingent on a response, but was always delivered as the cue terminated. Adolescent rats acquired a Pavlovian response to the cue (defined as time spent in the food trough anticipating reward during the cue) more quickly than adults.

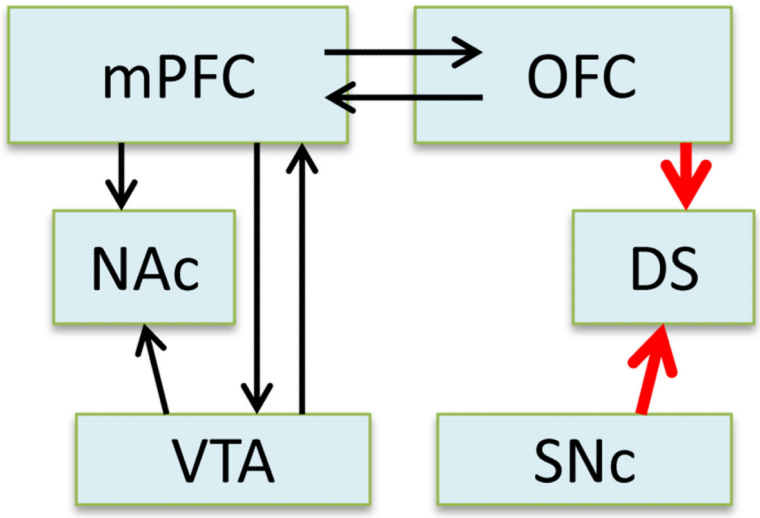

Figure 3.

A modified reward circuit for the adolescent brain. Connections of the common "reward circuits" are depicted in black and involve nucleus accumbens (NAc), ventral tegmental area (VTA), and medial prefrontal cortex (mPFC). Our findings in adolescents identify a complementary reward processing pathway depicted in red. We find that dopamine projections to the dorsal striatum (DS), which arise from substantia nigra (SNc) may be hypoactive in adolescents (Matthews et al., 2013) while orbitofrontal cortex (OFC) and DS neurons of adolescents are hyper-responsive to reward compared to adults (Sturman & Moghaddam 2011, 2012). On the other hand, NAc dopamine release and reward-evoked activity, and baseline firing of dopamine neurons in the ventral tegmental area (VTA) are comparable between adults and adolescents (Kim et al., 2012; Matthews et al., 2013).