

# Neurobiology of the Adolescent Brain and Behavior: Implications for Substance Use Disorders

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**Objective:** Adolescence is a developmental period that entails substantial changes in risk-taking behavior and experimentation with alcohol and drugs. Understanding how the brain is changing during this period relative to childhood and adulthood and how these changes vary across individuals are key in predicting risk for later substance abuse and dependence. **Method:** This review discusses recent human imaging and animal work in the context of an emerging view of adolescence as characterized by a tension between early emerging “bottom-up” systems that express exaggerated reactivity to motivational stimuli and later maturing “top-down” cognitive control regions. Behavioral, clinical, and neurobiological evidences are reported for dissociating these two systems developmentally. The literature on the effects of alcohol and its rewarding properties in the brain is discussed in the context of these two systems. **Results:** Collectively, these studies show curvilinear development of motivational behavior and the underlying subcortical brain regions, with a peak inflection from 13 to 17 years. In contrast, prefrontal regions, important in top-down regulation of behavior, show a linear pattern of development well into young adulthood that parallels that seen in behavioral studies of impulsivity. **Conclusions:** The tension or imbalance between these developing systems during adolescence may lead to cognitive control processes being more vulnerable to incentive-based modulation and increased susceptibility to the motivational properties of alcohol and drugs. As such, behavior challenges that require cognitive control in the face of appetitive cues may serve as useful biobehavioral markers for predicting which teens may be at greater risk for alcohol and substance dependence. *J. Am. Acad. Child Adolesc. Psychiatry, 2010;xx(x):xxx.* **Keywords:** adolescence, brain, development, alcohol, risk-taking

Adolescence is a transitional period of development when there are many changes experienced concomitantly, including physical maturation, drive for independence, increased salience of social and peer interactions, and brain development.<sup>1-3</sup> This developmental period is also a time characterized by an inflection in risky behaviors including experimentation with drugs and alcohol, criminal activity, and unprotected sex. Understanding the neural basis of these risky behaviors is key in identifying which teens may be at risk for poor outcomes, such as substance dependence and abuse.

Different hypotheses have been postulated for why adolescents may engage in impulsive and risky behaviors. Traditional accounts of adolescence suggest that it is a period of development associated with progressively greater efficiency

of cognitive control capacities. This efficiency in cognitive control is described as dependent on maturation of the prefrontal cortex as evidenced by imaging<sup>4-7</sup> and postmortem studies<sup>8-10</sup> showing continued structural and functional development of this region well into young adulthood.

Improved cognitive control with development of the prefrontal cortex is consistent with a linear increase in this ability from childhood to adulthood. Yet suboptimal choices and actions observed during adolescence represent an inflection in development<sup>11</sup> that is unique from childhood or adulthood, as evidenced by the National Center for Health Statistics on adolescent behavior and mortality.<sup>12</sup> If cognitive control and an immature prefrontal cortex were the basis for suboptimal choice behavior alone, then children should look remarkably similar or presum-

ably worse than adolescents, given their less developed prefrontal cortex and cognitive abilities.<sup>2</sup> This review addresses the primary question of how the brain is changing during adolescence that may explain inflections in risky and impulsive behavior. In addition, examples are provided of how alcohol and drug use during this period of development may further exacerbate these changes and can lead to subsequent abuse and dependence.

First, to accurately capture cognitive and neurobiological changes during adolescence, this period must be treated as a transitional one rather than a single snapshot in time.<sup>3</sup> In other words, to understand this developmental period, transitions into and out of adolescence are necessary for distinguishing distinct attributes of this period compared with other time points in development. Therefore, empirical data that establish developmental trajectories from childhood to adulthood for cognitive and neural processes are essential in characterizing these transitions and, more importantly, in constraining any interpretations about changes in brain or behavior in adolescence.

Second, accurate depictions of adolescence require a refinement in the phenotypic characterization of this period. For example, on a behavioral level, adolescents are often characterized as impulsive and greater risk-takers, with these constructs used almost synonymously. Yet, these constructs are distinct and appreciating this distinction is important for describing their developmental trajectories and neural underpinnings. We provide behavioral, clinical, and neurobiological evidences that suggest that risk-taking is

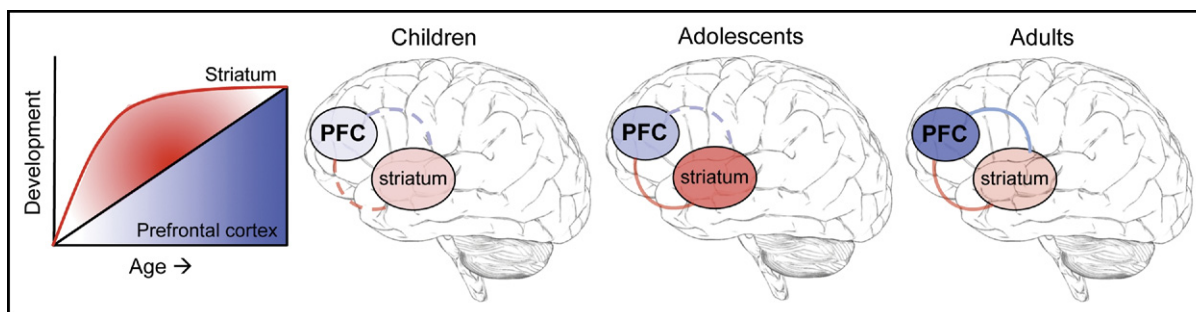
more tightly coupled with sensitivity to environmental incentives (sensation-seeking), whereas impulsivity is associated with poor top-down cognitive control.

To theoretically ground the empirical findings, we provide a plausible neurobiological model for adolescence and suggest how development during this time may lead to an enhancement in vulnerabilities for alcohol and drug abuse. The intention of this review is not to “psychopathologize” adolescence, but rather to explain why some teens but not others are vulnerable to substance abuse. As such, we attempt to identify potential biological and behavioral markers for early identification and for outcome assessments of interventions.

## NEUROBIOLOGICAL MODEL OF ADOLESCENCE

A neurobiological model of adolescent development<sup>2</sup> that builds on rodent models<sup>13,14</sup> and recent imaging studies of adolescence<sup>6,7,15-20</sup> is depicted Figure 1.<sup>21</sup> This model illustrates how subcortical and prefrontal top-down control regions must be considered together as a circuit. The cartoon shows different developmental trajectories for signaling of these regions, with limbic projections developing sooner than prefrontal control regions. According to the model, the adolescent is biased by functionally mature subcortical relative to less mature cortical circuitry during adolescence (i.e., imbalance in reliance of systems) compared with children for whom this frontolimbic circuitry is still developing and compared with adults for whom these systems

**FIGURE 1** Cartoon model of ventral striatal cortex and prefrontal cortex (PFC) interactions across development. Note: Deeper color indicates greater regional signaling. Line represents functional connectivity, with solid line indicating mature connection and dotted line indicating immaturity. Reprinted from *Current Opinion in Neurobiology*, Vol. 20, Somerville LH, Casey BJ. Developmental neurobiology of cognitive control and motivational systems, 236-241. Copyright 2010, with permission of Elsevier.<sup>21</sup>



are fully mature. With development and experience, the functional connectivity between these regions is strengthened and provides a mechanism for top-down modulation of the subcortical systems.<sup>7</sup> Thus, it is the frontostriatal circuitry and functional strengthening of connections within this circuitry that may provide a mechanism to explain changes in impulsivity and risk-taking observed across development.

This model is consistent with previous ones<sup>22-25</sup> in that it provides a basis for nonlinear inflections observed in behavior from childhood to adulthood, due to earlier maturation of subcortical projections relative to less mature top-down prefrontal ones. Specifically, the triadic model<sup>22</sup> proposes that motivated behavior has three distinct neural circuits (approach, avoidance, and regulatory). The approach system is largely controlled by the ventral striatum, avoidance system by the amygdala, and the regulatory system by the prefrontal cortex.<sup>26</sup> The present model differs largely from others in that it is grounded in empirical evidence for brain changes not only in the transition from adolescence to adulthood, but also the transition *into* adolescence from childhood and later *out of* adolescence into adulthood. Moreover, the model does not suggest that the striatum and amygdala are specific to approach and avoidant behaviors given recent studies showing valence independence of these structures,<sup>27</sup> but rather are systems that are important in detecting motivationally and emotionally relevant cues in the environment that can bias behavior. In this review, we describe the most recent evidence from behavioral and human imaging studies of adolescence in the context of our model that illustrates the transition from childhood to adulthood.

## PHENOTYPIC CHARACTERIZATION OF ADOLESCENCE

The ability to resist temptation in favor of long-term goals is a form of cognitive control. Lapses in this ability have been suggested to be at the very core of adolescent risky behavior.<sup>28</sup> Cognitive control, which includes resistance from temptation or delay of immediate gratification, has been studied in the context of social, developmental, and cognitive psychology. Developmentally, this ability has been measured by assessing how long a toddler can resist an immediate reward (e.g., a cookie) in favor of a larger

reward later (e.g., two cookies).<sup>29</sup> Although individuals vary in this ability even as adults, developmental studies have suggested windows of development when an individual may be particularly susceptible to temptations. This ability has been described as a form of impulse control<sup>30</sup> and it is multifaceted<sup>31,32</sup> but can be operationally defined as the ability to accomplish goal-directed behavior in the face of salient, competing inputs and actions.<sup>33</sup>

Historically, developmental studies have shown a steady improvement in cognitive control capacity from infancy to adulthood.<sup>34</sup> This observation is supported by a wealth of behavioral evidence from experimental paradigms in controlled laboratory settings including paradigms such as the go/no-go task, Simon task, and task-switching paradigms that require participants to override a prepotent response to achieve a correct one.<sup>33,35</sup> However, when it is advantageous to suppress a response to incentive-related cues, cognitive control suffers.<sup>20</sup> This decreased control is especially evident during the period of adolescence, when suboptimal choices in sexual and drug-related behaviors peak.<sup>3,11,12,14</sup> These observations imply that developmental trajectories in cognitive control are complex and can be modulated by emotionally charged or reinforcing contexts (e.g., social and sexual interactions), in which cognitive control demands interact with motivational drives or processes.

Motivation can modulate cognitive control in at least two ways. First, being rewarded for performance on a given task can make people work harder and ultimately perform better than when not rewarded.<sup>17</sup> Second, the capacity to exert control can be challenged when required to suppress thoughts and actions toward appetitive cues.<sup>20</sup> Recent studies of adolescent development have begun to compare cognitive control capacity in relatively neutral versus motivational contexts. These studies have suggested a change in sensitivity to environmental cues, especially reward-based ones at different points in development, and have suggested a unique influence of motivation on cognition during the adolescent years.

In the following section, we highlight some of the most recent studies of how adolescent behavior is differentially biased in emotionally charged contexts compared with adults.

For example, Hardin et al.<sup>36</sup> and Jazbec et al.<sup>37</sup> examined performance on an antisaccade task with a promise of financial reward for accurate performance on some trials but not others. Results showed that promise of a reward facilitated adolescent cognitive control behavior more than for adults, a finding that has been replicated<sup>17</sup> and recently been extended to social rewards (e.g., happy faces<sup>20</sup>).

Although the previous examples provide instances of enhanced performance in teens with incentives, rewards can also diminish performance when suppressing responses to rewards that lead to high gain. For example, using a gambling task in which reward feedback was provided immediately during decision-making (“hot” trials that heightened task-elicited affective arousal) or withheld until after the decision (“cold” deliberate decision making trials), Figner and colleagues<sup>38</sup> showed that adolescents made disproportionately more risky gambles compared with adults but only in the “hot” condition. Using a similar task, the Iowa Gambling Task, Cauffman and colleagues<sup>39</sup> showed that this sensitivity to rewards and incentives actually peaks during adolescence, with a steady increase from late childhood to adolescence in a tendency to play with more advantageous decks of cards and then a subsequent decrease from late adolescence to adulthood. These findings illustrate a curvilinear function, peaking roughly from 13 to 17 years and then declining.<sup>28</sup> Although prior findings with the Iowa Gambling task have shown a linear increase in performance with age,<sup>40</sup> these studies did not look at age continuously nor did they examine only trials with advantageous decks of cards.

Recent studies have suggested that social contexts, particularly peers, may also serve as a motivational cue and can diminish cognitive control during adolescence. It has been shown that the degree to which an adolescent’s peers are using substances is directly proportional to the amount of alcohol or illegal substances that the adolescent will use.<sup>41</sup> Using a simulated driving task, Gardner and colleagues<sup>42</sup> showed that adolescents make riskier decisions in the presence of peers than when alone and that these risky decisions decrease linearly with age.<sup>24,41</sup>

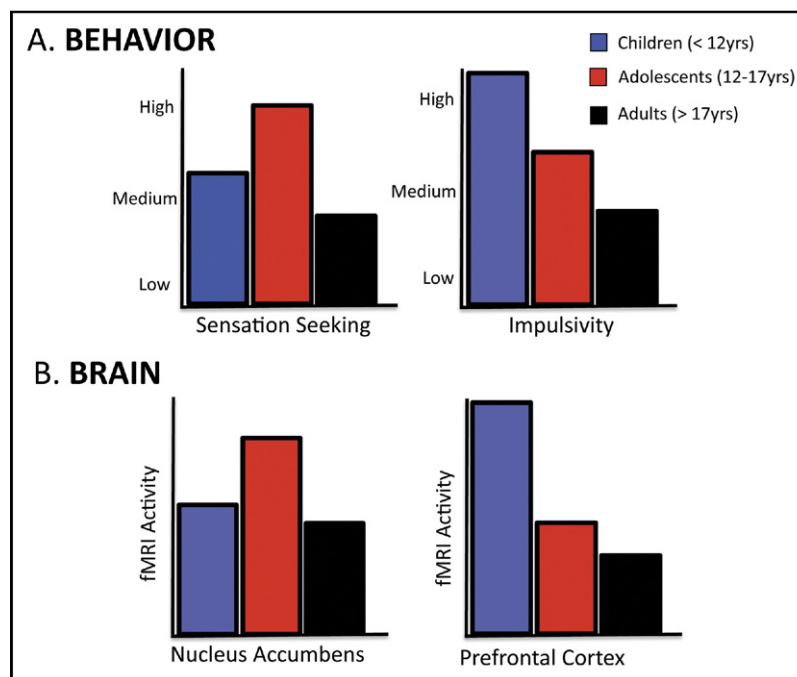
Taken together, these studies suggest that during adolescence, motivational cues of potential reward are particularly salient and can lead to improved performance when provided as a rein-

forcer or rewarded outcome, but to riskier choices or suboptimal choices when provided as a cue. In the latter case, the motivational cue can diminish effective goal-oriented behavior. Furthermore, these studies suggest that sensitivity to rewards and sensation-seeking behavior are distinct from impulsivity with very different developmental patterns (curvilinear function versus a linear function, respectively). This distinction is further evident in a recent study by Steinberg et al.<sup>43</sup> using self-report measurements of sensation-seeking and impulsivity. They tested whether the often-conflated constructs of sensation-seeking and impulsivity develop along different timetables in nearly 1,000 individuals 10 to 30 years old. The results showed that differences in sensation-seeking with age followed a curvilinear pattern, with peaks in sensation-seeking increasing from 10 to 15 years and decreasing or remaining stable thereafter. In contrast, age differences in impulsivity followed a linear pattern, with decreasing impulsivity with age in a linear fashion (Figure 2A<sup>6,16,43</sup>). These findings and the laboratory-based findings suggest heightened vulnerability to risk-taking in adolescence that “may be due to the combination of relatively higher inclinations to seek excitement and relatively immature capacities for self-control that are typical of this period of development.”<sup>43</sup>

## NEUROBIOLOGY OF ADOLESCENCE

As denoted in our model of adolescence, two key regions implicated in cognitive and motivational behaviors are the prefrontal cortex, known to be important for cognitive control,<sup>44</sup> and the striatum, critical in detecting and learning about novel and rewarding cues in the environment.<sup>45</sup> We highlight recent animal and human imaging work on neurobiological changes supporting these motivational and cognitive systems across development in the context of the previous behavioral findings on the development of sensation-seeking and impulsivity. We use the previously described imbalance model of linear development of top-down prefrontal regions compared with a curvilinear function for development of bottom-up striatal regions involved in detecting salient cues in the environment to ground the findings. The importance of examining circuitry rather than specific regional change, especially within frontostriatal circuits that underlie different forms of goal-oriented behavior, is key. This

**FIGURE 2** Illustration of different developmental courses for sensation-seeking and impulsivity. Note: (A) Plot of sensation-seeking and impulsivity as a function of age (adapted from Steinberg et al.<sup>43</sup>). (B) Plot of patterns of activity in brain regions sensitive to reward outcomes during a cognitive control task across development (adapted from Galvan et al.<sup>6</sup> and Galvan et al.<sup>16</sup>). fMRI = functional magnetic resonance imaging.



perspective moves the field away from an examination of how each region matures in isolation to how these regions may interact in the context of interconnected circuits.

Seminal animal and human works have shown how striatal and prefrontal cortical regions shape goal-directed behavior.<sup>7,28,38,39,45</sup> Using single-unit recordings in monkeys, Pasupathy and Miller<sup>46</sup> demonstrated that when flexibly learning a set of reward contingencies, very early activity in the striatum provides the foundation for reward-based associations, whereas later, more deliberative prefrontal mechanisms are engaged to maintain the behavioral outputs that can optimize the greatest gains; these findings have been replicated in lesion studies.<sup>47-49</sup> A role for the striatum in early temporal coding of reward contingencies before the onset of activation in prefrontal regions has also been extended to humans.<sup>50</sup> These findings suggest that understanding the interactions between regions (and their component functions) within the frontostriatal circuitry is critical for developing a model of cognitive and motivational control in adolescence.

Frontostriatal circuits undergo considerable elaboration during adolescence<sup>51-54</sup> that is partic-

ularly dramatic in the dopamine system. Peaks in the density of dopamine receptors D<sub>1</sub> and D<sub>2</sub> in the striatum occur early in adolescence, followed by a loss of these receptors by young adulthood.<sup>55-57</sup> In contrast, the prefrontal cortex does not show peaks in D<sub>1</sub> and D<sub>2</sub> receptor density until late adolescence and young adulthood.<sup>58,59</sup> Similar developmental changes have been shown in other reward-related systems including cannabinoid receptors.<sup>60</sup> It remains unclear how changes in the dopamine systems may relate to motivated behavior because controversy remains as to whether reward sensitivity is modulated by dopamine systems (e.g.,<sup>61,62</sup>) and whether it is a result of less active or hypersensitive dopamine systems (e.g.,<sup>63,64</sup>). However, given the dramatic changes in dopamine-rich circuitry during adolescence, it is likely to be related to changes in sensitivity to rewards distinct from childhood or adulthood.<sup>51,65,66</sup> Beyond the significant changes in dopamine receptors, there are dramatic hormonal changes that occur during adolescence that lead to sexual maturity and influence functional activity in frontostriatal circuits<sup>66</sup>; however, a detailed discussion is beyond the scope of

this review; see Romeo<sup>67</sup> and Forbes and Dahl<sup>68</sup> for detailed reviews on the subject.

Human imaging studies have begun to provide support for strengthening in the connections of dopamine-rich frontostriatal circuitry across development. Using diffusion tensor imaging and functional magnetic resonance imaging, Liston et al.,<sup>69</sup> Casey et al.,<sup>70</sup> and Asato et al.<sup>71</sup> have shown greater strength in distal connections within these circuits across development and have linked connection strength between prefrontal and striatal regions with the capacity to effectively engage cognitive control in typically and atypically developing individuals.<sup>69,70</sup> These studies illustrate the importance of signaling within the corticostriatal circuitry that supports the capacity to effectively engage in cognitive control.

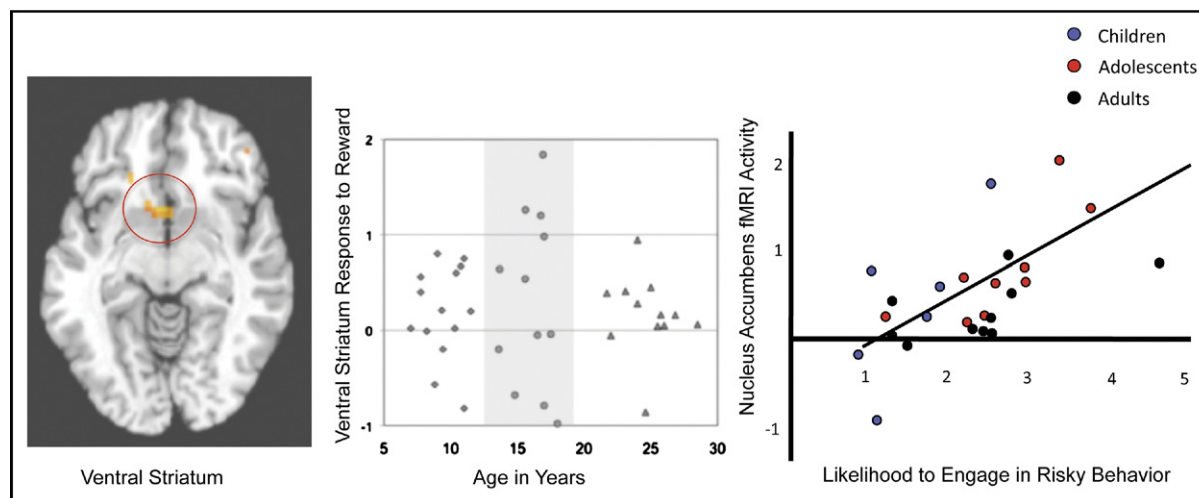
Likewise, there is mounting evidence from human functional neuroimaging studies on how subcortical systems such as the striatum and prefrontal cortex interact to give rise to risky behavior observed in adolescents.<sup>72</sup> Most imaging studies have focused on one or the other region showing that the prefrontal cortex, thought to subserve age-related improvement in cognitive control,<sup>73-79</sup> undergoes delayed maturation,<sup>4,80,81</sup> whereas striatal regions sensitive to novelty and reward manipulations develop sooner.<sup>75,82</sup> Several groups have shown that adolescents show heightened activation of the ventral striatum in anticipation and/or receipt of rewards compared

with adults,<sup>6,15,17,18</sup> but others have reported a hyporesponsiveness.<sup>83</sup>

One of the first studies to examine reward-related processes across the full spectrum of development from childhood to adulthood was completed by Galvan and colleagues<sup>6</sup> in 6- to 29-year-olds. They showed that ventral striatal activation was sensitive to varying magnitudes of monetary reward<sup>50</sup> and that this response was exaggerated during adolescence compared with children and adolescents<sup>6</sup> (Figure 3<sup>6,16</sup>), indicative of signal increases<sup>6</sup> or more sustained activation.<sup>84</sup> In contrast to the pattern in the ventral striatum, orbital prefrontal regions showed protracted development across these ages (Figure 2B<sup>6,16,43</sup>).

How does this enhancement of signaling in the ventral striatum relate to behavior? In a follow-up study, Galvan and colleagues<sup>16</sup> examined the association between activity in the ventral striatum to large monetary reward and personality trait measurements of risk-taking and impulsivity. Anonymous self-report rating scales of risky behavior, risk perception, and impulsivity were acquired in their sample of 7- to 29-year-olds. Galvan et al. showed a positive association between ventral striatal activity to large reward and the likelihood of engaging in risky behavior (Figure 3). These findings are consistent with adult imaging studies showing ventral striatal activity with risky choices.<sup>85,86</sup>

**FIGURE 3** Ventral striatal activity to reward and association with risk-taking. Note: Localization of the ventral striatum in the axial plane (left) is activated with reward (middle) and correlated with risk-taking (right) (adapted from Galvan et al.<sup>6</sup> and Galvan et al.<sup>16</sup>). fMRI = functional magnetic resonance imaging.



To further support an association between adolescents' risky behavior and sensitivity to reward as indexed by an exaggerated ventral striatal response, Van Leijenhorst and colleagues<sup>18</sup> tested this association using a gambling task. The task included low-risk gambles with a high probability of obtaining a small monetary reward and high-risk gambles with a smaller probability of obtaining a larger monetary reward. The functional magnetic resonance imaging results confirmed that high-risk choices were associated with ventral striatal recruitment, whereas low-risk choices were associated with activation in the ventral medial prefrontal cortex. These findings are consistent with the hypothesis that risky behavior in adolescence is associated with an imbalance caused by different developmental trajectories of subcortical reward and prefrontal regulatory brain regions consistent with our neurobiological model of adolescence.

Although there appears to be an association between risk-taking behavior and ventral striatal activation, in the study by Galvan et al.,<sup>16</sup> no correlation was reported between ventral striatal activity and impulsivity. Rather, impulsivity ratings were correlated with age, consistent with numerous imaging studies showing linear development with age in prefrontal cortical recruitment during impulse control tasks<sup>7,76,78</sup> (and see reviews by Casey et al.<sup>35,87</sup>). Moreover, recent studies have shown that impulsivity ratings inversely correlate with volume of the ventral medial prefrontal cortex in a sample of healthy boys (7 to 17 years old).<sup>88</sup> Studies of clinical populations characterized by impulsivity problems such as attention-deficit/hyperactivity disorder have shown impaired impulse control and decreased activity in prefrontal regions compared with controls<sup>89,90</sup> but not heightened responses to incentives.<sup>91</sup>

These findings provide neurobiological empirical support for a dissociation of the constructs related to risk-taking and reward sensitivity from that of impulsivity, with the former showing a curvilinear pattern and the latter a linear pattern (Figure 2B). Thus, adolescent choices and behavior cannot be explained by impulsivity or protracted development of the prefrontal cortex alone. Rather, motivational subcortical regions must be considered to elucidate why adolescent behavior is not only different from adults but also from children. Thus, the ventral striatum appears to play a role in levels of excitement<sup>83,92</sup>

and positive affect<sup>15</sup> when receiving rewards and the propensity for sensation-seeking and risk-taking.<sup>16,92</sup> More importantly, these findings suggest that during adolescence some individuals may be more prone to engage in risky behaviors due to developmental changes in concert with variability in a given individual's predisposition to engage in risky behavior, rather than to simple changes in impulsivity.

A scientific area that has received less attention is determining how cognitive control and motivational systems interact over the course of development. Ernst and colleagues<sup>36,37</sup> showed that the promise of a monetary reward facilitated adolescent cognitive control behavior more than for adults. Geier et al.<sup>17</sup> recently identified the neural substrates of this cognitive upregulation using a variant of an antisaccade task during functional brain imaging. In adolescents and adults, trials for which money was at stake speeded performance and facilitated accuracy, but this effect was larger in adolescents. After a cue that the next trial would be rewarded, adolescents showed exaggerated activation in the ventral striatum while preparing for and subsequently executing the antisaccade. An exaggerated response was observed in adolescents within prefrontal regions along the precentral sulcus, important for controlling eye movements, suggesting a reward-related upregulation in control regions.

Rewards can enhance and diminish goal-directed behavior. The observation that adolescents take more risks when appetitive cues are present versus absent during gambling tasks makes this point (e.g.,<sup>38</sup>). In a recent imaging study, Somerville et al.<sup>20</sup> identified the neural substrates of downregulation of control regions with appetitive cues. Somerville et al. tested child, adolescent, and adult participants while they performed a go/no-go task with appetitive social cues (happy faces) and neutral cues. Task performance to neutral cues showed steady improvement with age on this impulse control task. However, on trials for which the individual had to resist approaching appetitive cues, adolescents failed to show the expected age-dependent improvement. This performance decrement during adolescence was paralleled by enhanced activity in the striatum. Conversely, activation in the inferior frontal gyrus was associated with overall accuracy and showed a linear pattern of change with age for the no-go versus go trials. Taken

together, these findings implicate exaggerated ventral striatal representation of appetitive cues in adolescents in the absence of a mature cognitive control response.

Collectively, these data suggest that, although adolescents as a group are considered risk-takers,<sup>42</sup> some adolescents will be more prone than others to engage in risky behaviors, putting them at potentially greater risk for negative outcomes. These findings underscore the importance of considering individual variability when examining complex brain-behavior relations related to risk-taking and impulsivity in developmental populations. Further, these individual and developmental differences may help to explain vulnerability in some individuals to risk-taking, which is associated with substance use and, ultimately, addiction.<sup>65</sup>

## SUBSTANCE USE AND ABUSE IN ADOLESCENTS

Adolescence marks a period of increased experimentation with drugs and alcohol,<sup>93</sup> with alcohol being the most abused of illegal substances by teens.<sup>11,94,95</sup> Early use of these substances, such as alcohol, is a reliable predictor of later dependence and abuse.<sup>96</sup> Given the surge in alcohol dependence between adolescence and adulthood that is unequalled at any other developmental stage,<sup>97</sup> we focus predominantly on a select review of its use and abuse in adolescents and motivational properties.

Alcohol and other substances of abuse, including cocaine and cannabinoids, have been shown to have reinforcing properties. These substances influence mesolimbic dopamine transmission with acute activations of neurons in frontolimbic circuitry rich in dopamine, including the ventral striatum.<sup>98-100</sup> As suggested by Hardin and Ernst,<sup>93</sup> the use of these substances may exacerbate an already enhanced ventral striatum response resulting in heightened or strengthening of reinforcement properties to the drug. Robinson and Berridge<sup>62,64,101</sup> have suggested that these drugs of abuse can “hijack” the systems associated with drug incentives, such as the ventral striatum, thus downregulating top-down prefrontal control regions.

The majority of empirical work on adolescent use of alcohol has been done in animals, given ethical constraints in performing such studies in human adolescents. Animal models of ethanol also provide the most evidence for differential

effects of alcohol in adolescents compared with adults and are consistent with human findings of adolescents having relative insensitivity to ethanol effects. Spear and colleagues have shown that adolescent compared with adult rats are less sensitive to the social, motor, sedation, acute withdrawal, and “hangover effects” of ethanol.<sup>102-104</sup> These findings are significant because many of these effects serve as cues to limit intake in adults.<sup>11</sup> Likewise, at the same time when adolescents are insensitive to cues that may help to limit their alcohol intake, positive influences of alcohol such as social facilitation may further encourage alcohol use.<sup>105</sup> Most risky behaviors in humans—including alcohol abuse—occur in social situations,<sup>24</sup> potentially pushing adolescents toward greater use of alcohol and drugs when this behavior is valued by their peers.

How is the brain altered with alcohol use and abuse in adolescents compared with adults? Whereas adolescents may be less sensitive to some behavioral effects of alcohol, they appear to be more sensitive to some of the neurotoxic effects.<sup>95</sup> For example, physiologic studies (e.g.,<sup>106</sup>) have shown greater ethanol-induced inhibition of N-methyl-D aspartic acid-mediated synaptic potentials and long-term potentiation in hippocampal slices in adolescents than in adults. Repeated exposure of intoxicating doses of ethanol also produces greater hippocampal-dependent memory deficits,<sup>107,108</sup> and prolonged ethanol exposure has been associated with increased dendritic spine size.<sup>109</sup> These latter findings of dendritic spine changes are suggestive of modification of brain circuitry that may stabilize addictive behavior.<sup>95</sup>

Data from brain imaging studies have provided parallel evidence in humans of neurotoxic effects of alcohol on the brain. Many studies have reported altered brain structure and function in alcohol-dependent or -abusing adolescents and young adults compared with healthy individuals. These studies have reported smaller frontal and hippocampal volumes, altered white matter microstructure, and poorer memory.<sup>110-114</sup> Moreover, these studies have reported positive associations between hippocampal volumes and age of first use,<sup>110</sup> suggesting that early adolescence may be a period of heightened risk to alcohol's neurotoxic effects. Duration, which was negatively correlated to hippocampal volume, may compound this effect.

Currently, only a few studies have examined



functional brain activity to drug- or alcohol-related stimuli (i.e., pictures of alcohol) in adolescents,<sup>115</sup> although this is an area of future research (see Pulido et al.<sup>116</sup>). Studies of high-risk populations (e.g., familial load of alcohol dependence) have suggested that impairments in frontal functioning are apparent before drug-use exposure (e.g.,<sup>117,118</sup>) and can predict later substance use.<sup>119,120</sup> However, in an early behavioral study of the effects of alcohol in 8- to 15-year-old boys of low and high familial risk,<sup>121</sup> the most significant finding was little if any behavioral change or problem on tests of intoxication—even after given doses that had been intoxicating in an adult population were observed. These neurotoxic effects and an increased sensitivity to the motivational effects of alcohol and evidence of poorer top-down prefrontal control apparent even before drug-use exposure<sup>117</sup> may set up a long-term course of alcohol and drug abuse well beyond adolescence.<sup>119,120</sup>

Together, the studies described support a view of adolescent brain development as characterized by a tension between early emerging “bottom-up” systems that express exaggerated reactivity to motivational stimuli and later maturing “top-down” cognitive control regions. This bottom-up system, which is associated with sensation-seeking and risk-taking behavior, gradually loses its competitive edge with the progressive emergence of “top-down” regulation (e.g.,<sup>2,7,15,24,65,122-124</sup>). This imbalance between these developing systems during adolescence may lead to heightened vulnerability to risk-taking behaviors and an increased susceptibility to the motivational properties of substances of abuse.

This review provides behavioral, clinical, and neurobiological evidences for dissociating these subcortical-cortical systems developmentally. Behavior data from laboratory tasks and self-report ratings administered to children, adolescents, and adults (e.g.,<sup>18,20,38,43</sup>) have suggested a curvilinear development of sensation-seeking, with a peak inflection roughly from 13 to 17 years, whereas impulsivity decreases across development in a linear fashion from childhood to young adulthood. Human imaging studies have shown patterns of activity in subcortical brain regions sensitive to reward (ventral striatum) that parallel the behavioral data. Specifically, they have shown a curvilinear pattern of development in these regions and the magnitude of their response is associated with risk-taking behaviors.

In contrast, prefrontal regions, important in top-down regulation of behavior, have shown a linear pattern of development that parallels those seen in behavioral studies of impulsivity. Moreover, clinical disorders with impulse-control problems have shown less prefrontal activity, further linking neurobiological substrates with the phenotypic construct of impulsivity.

The tension between subcortical regions compared with prefrontal cortical regions during this period may serve as a possible mechanism for the observed heightened risk-taking, including use and abuse of alcohol and drugs. Most adolescents have tried alcohol,<sup>94</sup> but this does not necessarily lead to abuse. Individuals with less top-down regulation may be particularly susceptible to alcohol and substance abuse as suggested by studies of high-risk populations showing impairments in frontal functioning before alcohol and drug exposure (e.g.,<sup>117,118</sup>). In the context of our neurobiological model of adolescence, these individuals would have an even greater imbalance in cortico-subcortical control. These findings are also in accordance with clinical findings in attention-deficit/hyperactivity disorder populations who show decreased prefrontal activity and are four times as likely to develop a substance use disorder compared with healthy controls.<sup>125</sup> This imbalance in cortico-subcortical control would be further compounded by the insensitivity of adolescents to the motor and sedative effects of alcohol that otherwise may help to limit intake and the positive influences of alcohol in social facilitation that may further encourage alcohol use.<sup>105</sup> As shown by Steinberg<sup>24</sup> and Gardner and Steinberg,<sup>42</sup> most risky behaviors—including alcohol and substance abuse—occur in social situations. Thus use of alcohol and drugs may be encouraged and maintained by peers when this behavior is valued.

One of the challenges in addiction-related work is the development of biobehavioral markers for early identification of risk for substance abuse and/or for outcomes assessments for interventions/treatments. Our findings suggest that behavioral challenges that require cognitive control in the presence of tempting appetitive cues may be useful potential markers. Examples of such behavioral assays include gambling tasks with high and low risk or “hot” and “cold” conditions described in this review<sup>18,38</sup> or simple impulse control tasks that require suppressing a response to an appetitive/tempting cue.<sup>20</sup> These tasks are reminiscent of the delay of the gratifi-

cation task developed by Mischel and Underwood.<sup>126</sup> In fact, performance on simple impulse control tasks such as these in adolescents and adults has been associated with their performance as toddlers on the delay of gratification task.<sup>29,30</sup> Mischel and colleagues<sup>127</sup> have shown the high level of stability and predictive value of this task in later life. Relevant to substance abuse, they showed that the ability to delay gratification as a toddler predicted less substance abuse (e.g., cocaine) later in life.<sup>127</sup> In our current work, we are beginning to use a combination of these tasks to identify the neural substrates of this ability to further understand potential risk factors for substance abuse.

Collectively, these data suggest that, although adolescents as a group are considered risk-takers,<sup>42</sup> some adolescents will be more prone than others to engage in risky behaviors, putting them at potentially greater risk for negative outcomes. However, risk-taking can be quite adaptive in the right environments. So rather than trying to eliminate adolescent risk-taking behavior that has not been a successful enterprise to date,<sup>24</sup> a more constructive strategy may be to provide access to risky and exciting activities (e.g., after school programs with in-door wall climbing) under controlled settings and limit harmful risk-taking opportunities. Because the adolescent

brain is a reflection of experiences, with these safe risk-taking opportunities, the teenager can shape long-term behavior by fine-tuning the connections between top-down control regions and bottom-up drives with maturity of this circuitry. Other successful strategies are cognitive behavioral therapies that focus on refusal skills, or cognitive control, to decrease risky behaviors.<sup>128</sup> The findings underscore the importance of considering individual variability when examining complex brain-behavior relations related to risk-taking and impulsivity in developmental populations. Further, these individual and developmental differences may help explain vulnerability in some individuals to risk-taking associated with substance use and, ultimately, addiction. &

Accepted August 30, 2010.

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This work was supported in part by NIDA R01 DA018879, NIDA Pre-Doctoral training grant DA007274, the Mortimer D. Sackler family, the Dewitt-Wallace fund, and the Weill Cornell Medical College Citigroup Biomedical Imaging Center and Imaging Core.

Disclosure: Dr. Casey and Ms. Jones report no biomedical financial interests or potential conflicts of interest.

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DOI: 10.1016/j.jaac.2010.08.017

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