

# Could the link between drug addiction in adulthood and substance use in adolescence result from a blurring of the boundaries between incentive and hedonic processes?

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**Abstract:** There is a broad consensus that the development of drug addiction in adulthood is closely linked to the onset of drug use in adolescence. However, the relationship between drug exposure during adolescence and subsequent vulnerability to addiction is yet to be fully understood. This review will first use evidence from adult studies on reward and addiction to give an up-to-date reference point of normal reward-circuitry and the maladaptive changes that later occur in addiction. This will then be compared with current evidence from adolescent studies on reward-circuitry. Similarities between the reward processes governing characteristic behavioral traits in adolescence and the reward profile in adult addiction could help to explain why the risk of later developing addiction is increased when substance use is initiated in adolescence. We argue that the age of onset is a major risk factor in the development of substance use disorder due to a blurring of the boundaries between incentive and hedonic processes, which occurs during adolescence. A deeper understanding of the processes that mediate this blurring could open new avenues for the prevention and treatment of adult drug addiction.

**Keywords:** addiction, dopamine, impulsive, compulsive, opiate

## Introduction

In the US, 75% of high-school students have reportedly used illegal drugs, drunk alcohol or smoked tobacco.<sup>1</sup> Given that brain structures during adolescence are highly plastic,<sup>2</sup> this figure is alarmingly high. Adolescence is a developmental period that is (mostly) agreed to commence with puberty at age 10 and end when sexual and physical maturation is complete at around age 20.<sup>3,4</sup> Behaviorally, adolescence is characterized by rapid changes in social functioning brought about by increased impulsivity, reward-sensitivity and sensation-seeking.<sup>5,6</sup> Exposure to drugs during this sensitive developmental period could lead to maladaptive changes in brain structures that persist into adulthood and increase the risk of developing mental health disorders such as addiction.

Addiction is defined as a maladaptive pattern of drug use that persists despite negative consequences.<sup>7</sup> It is characterized by a strong desire to take drugs, difficulty in controlling drug use and physiological or psychological dependence.<sup>8</sup> Given that, on average, only one in six cocaine users develop dependency,<sup>9</sup> it is evident that some individuals are more vulnerable to developing drug addiction

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than others. This individual vulnerability has been found to be associated with the presence or absence of behavioral traits such as sensation-seeking, which predicts initiation of cocaine use,<sup>10</sup> impulsivity, which predicts compulsive cocaine seeking<sup>10</sup> and anxiety, which predicts escalation of cocaine use.<sup>11</sup>

Substance use disorder in adolescence is also a major risk factor for the development of addiction in adulthood.<sup>1</sup> A deeper understanding of the underlying neurocircuitry that governs the motivation to take drugs in adolescence could elucidate what confers risk to some and resilience to others. This understanding may also highlight protective mechanisms that could be extrapolated and used to prevent and effectively treat addiction in adulthood.

This review aims to parse the underlying neurocircuitry of reward in adolescence to better understand the etiology of adult addiction when substance use is commenced at this age. Brain mechanisms of reward can be categorized as either preparatory or consummatory in nature; these aspects of reward are thought to rely on dissociable incentive and hedonic processes, respectively.<sup>12</sup> We address the question “could the link between drug addiction in adulthood and substance use in adolescence result from a blurring of the boundaries between incentive and hedonic processes?” A summary of the key findings of the review can be found in [Table 1](#).

Since we draw on evidence from animal as well as human studies (see [supplementary materials](#)), we must acknowledge that there are factors which limit the usefulness and reliability

of data from both. These factors include: legal differences as to the point at which adulthood is reached,<sup>13</sup> leading to different permissible social activities being tied to this developmental period;<sup>1</sup> inter-individual variability as to when puberty is reached<sup>2</sup> (individuals at the same age may not be at the same developmental stage); and inter-individual variability in the presence of traits that are known to increase the chances of substance use disorder<sup>10</sup> (described above). These factors are often not controlled for in human studies, explaining why many produce conflicting results. Although animal models may not fully explain the complexity of adolescence and the development of drug addiction in adulthood, they allow for better operationalization of and to some extent control over variables, allowing for a better assessment of causality.<sup>14</sup>

Importantly, a failure in the wider research field to reach a consensus on the definition of key terms, which are related to reward, means that studies on the same construct often study different things and studies on “different” constructs study the same thing. Therefore, for the purposes of this review, key terms are defined in [Table 2](#).

## Adult reward circuitry

In order to understand why drug use in adolescence increases the risk of developing substance use disorder as an adult,<sup>1</sup> it is first important to tease apart the ways in which adolescent reward processing differs from adult reward processing. A brief overview of adult reward processing will provide a “baseline” which this paper will use as a reference point to compare with studies investigating the nature of reward processing in adolescents. Notable differences will be later highlighted and used to address the link between adolescent onset of drug taking and later developing substance use disorder.

## A brief history of adult reward processing: the dopamine hypothesis of reward

In 1978, Roy Wise proposed the dopamine hypothesis of reward, which stated that dopamine transmission mediated all forms of reward.<sup>15</sup> At the time, the hypothesis appeared to be supported by evidence implicating the mesolimbic dopamine pathway in motivated behavior. The mesolimbic pathway connects the ventral tegmental area (VTA) to the nucleus accumbens (NaC).<sup>16</sup> Activation of this pathway leads to increased dopamine release into the NaC. This increased dopamine release increases the salience of

**Table 1** Key findings of the review

- In adolescence, both dopamine and opioids play a role in incentive and hedonic processes; the dissociation between the roles of these two neurotransmitters is less concrete than once thought.
- This finding may inspire new pharmacological approaches to the treatment of substance use disorder.
- The blurring between incentive and hedonic processes that is seen neurobiologically is also seen behaviorally; there is a blurring of the boundaries between the behavioral traits sensation-seeking and impulsivity.
- These traits both have links to the later development of drug addiction in adulthood.
- An altered reward-learning process along with reduced cognitive control may also add to the increased risk of developing drug addiction when substance use is initiated in adolescence.
- Promising outcomes have been noted from interventions based on improving cognitive control in the brain of adults with substance use disorder and adolescents at high risk of developing substance use disorders.

**Table 2** Definitions of key terms used throughout this review

<b>Sensation-seeking:</b> the seeking out of novel experiences. <sup>2</sup>
<b>Impulsivity:</b> the tendency to act out on behavioral impulses without consideration of consequences. <sup>5</sup>
<b>Reward-sensitivity:</b> sensitivity to the rewarding properties of stimuli, "liking". <sup>18</sup>
<b>Incentive processes:</b> psychological and neural mechanisms of wanting/approach behavior. <sup>12</sup> These processes are not solely tied to drive reduction but instead desires and incentive motivation.
<b>Hedonic processes:</b> psychological and neural mechanisms of pleasure. <sup>12</sup>
<b>Reward:</b> the rewarding effects of a stimulus or drug describes the subjective pleasure attributed to that stimulus or drug. Subjective pleasure is a composite of changes to sensory processing (positive feelings) and/or any changes to the salience of the environment. <sup>79</sup>
<b>Reinforcement:</b> the strengthening of an association between: a conditioned and unconditioned stimulus, a stimulus and a response, or an action and an outcome. <sup>15</sup> Positive reinforcers increase the probability of a contingent response and negative reinforcers, when omitted, increase the probability of contingent response. <sup>79</sup>
<b>Drug addiction:</b> maladaptive pattern of drug use that persists despite negative consequences. <sup>80</sup>
<b>Reward circuitry:</b> neural structures that are responsible for wanting/approach behavior; associative learning and pleasure. <sup>12,81</sup>
<b>Cognitive control:</b> the controlling of thoughts and actions in order to achieve a goal. <sup>82</sup>
<b>Dopaminergic transmission:</b> a process involving the release of dopamine from pre-synaptic terminals, the activity of this dopamine on other neurons and re-uptake of this dopamine by other cells. <sup>83</sup>

rewards and reward-related stimuli to facilitate reinforcement, goal-directed and habitual behavior.<sup>17</sup> The nigrostriatal pathway connects the substantia nigra with the dorsal striatum. This pathway controls the production of movement, which is also implicated in habitual behavior.<sup>18</sup> The mesocortical pathway connects the VTA to the prefrontal cortex (PFC). This pathway is involved in cognitive control and is thus closely associated with the mesolimbic pathway.<sup>19</sup> In addition, dopamine in the basolateral amygdala (BLA) mediates wanting and incentive learning.<sup>20</sup>

Olds & Milner found that adult rats with electrodes implanted into various sites within their brains would press a lever to self-stimulate, a phenomenon known as intra-cranial self-stimulation (ICSS).<sup>21</sup> Subsequent studies discovered that electrodes implanted along the mesolimbic dopamine pathway facilitated the greatest increase in ICSS. The stimulating electrodes were found to increase extracellular dopamine within this pathway,<sup>22</sup> which appeared to reinforce lever-pressing in the rats. Thus, ICSS data linked dopamine to the reinforcing properties of rewards.

Wise's theory was also supported by brain microdialysis studies. In adult male rats, Di Chiara & Imperato<sup>23</sup> found that dopamine levels increased before and during sexual behavior in the NaC. In addition, Pfaus et al found that drugs commonly involved in substance use disorders such as opiates, alcohol and amphetamine also increased extracellular dopamine in the NaC of adult rats.<sup>24</sup> This evidence showed that accumbal dopamine was correlated with reward.

Self-administration studies also supported Wise's theory. For example, when Hoebel et al implanted cannulas into the NaC of adult rats and measured self-administration rates of amphetamine and saline, the rats maintained higher rates of lever pressing to self-administer amphetamine.<sup>25</sup> In addition, Yokel & Wise found that neuroleptics (D<sub>2</sub> R antagonists) decrease rates of amphetamine self-administration in adult rats.<sup>26</sup> Under low doses of neuroleptics, rats increased their lever-pressing to overcome the antagonism (a right-ward shift in the dose-response curve). But, under high doses of neuroleptics, rats greatly reduced their rates of responding. The neuroleptics, therefore, appeared to reduce the rewarding properties of amphetamine and thus reduce its self-administration. Taken together, this evidence suggested that dopamine mediated the reinforcing effects of amphetamine.

However, there were several limitations to Wise's dopamine hypothesis of reward. Firstly, dopamine was not found to be necessary for the self-administration of all drugs. Dopamine receptor antagonism did not cause dose-dependent compensatory increases in heroin self-administration, while MOR (mu-opioid-receptor) antagonism with naltrexone did,<sup>27</sup> suggesting that the primary reinforcing effects of heroin were not mediated by dopamine signaling, but rather by opiate signaling.

Secondly, it was not possible to dissociate mechanisms of wanting and liking during ICSS and self-administration experiments, making it invalid to conclude that dopamine mediated all aspects of reward. Subsequent studies have managed to dissociate mechanisms of wanting from liking for food in rats.<sup>28</sup> New-born humans and rodents make characteristic affective reactions to sweet and bitter tastes: positive reactions to sweet stimuli include paw licking and tongue protrusion, while negative reactions to bitter tastes include gapes and head shaking.<sup>21</sup> These orofacial measures have been widely used to study the neurocircuitry that governs liking for food rewards. Pecina et al gave rats pimozone, a dopamine receptor antagonist, and found that the rats showed no changes in orofacial responses to palatable

food.<sup>29</sup> This suggested that dopamine does not control the hedonic valuation of food reward. Instead, opiate signaling appears to play a role, as evidenced by the fact that MOR agonism enhances orofacial reactions to palatable food in rats.<sup>30</sup> However, it is important to note that orofacial reactions are expressed in new-borns with no cortex and decerebrated animals.<sup>12</sup> Therefore, these data alone cannot be used to make conclusions about subjective pleasure in humans as these behaviors do not rely on higher cognitive functions.

In humans, wanting and liking can be dissociated using subjective reports. For example, L-Dopa is a drug, which enhances levels of dopamine in the brain, yet, human patients given L-Dopa to treat Parkinson's disease do not self-report increases in pleasure.<sup>31</sup> This indicates that dopamine is not always correlated with reward, challenging the strength of the relationship between dopamine and reward, which Wise attempted to establish.

## Current views of adult reward circuitry

Further findings from human patients have helped to shape our current view of the adult reward system. Significantly, patients suffering from substance use disorders often describe an intense wanting for drugs without the subjective feelings of pleasure,<sup>32</sup> indicating a clear dissociation between incentive and hedonic processes.

## Incentive processes in adults

Dopamine does not seem to be involved in the pleasurable aspects of reward, but it may indeed encode the salience and incentive motivational value that is attributed to rewards and reward-predictive cues.<sup>32</sup> Considerable evidence supports dopamine's role in incentive processes.

Firstly, ICSS is now thought to be a measure of reinforcement. The increase in extracellular dopamine in the NaC caused by ICSS appears to increase the salience of the lever, which reinforces lever pressing.<sup>12</sup> Adult rats therefore increase their rates of responding because of increased desire to press the lever as opposed to increased pleasure from doing so.

There is also convincing evidence that dopamine mediates incentive processes in adult humans. Deep brain stimulation in patients with depression in sites such as the NaC increases their desire to take up specific activities.<sup>33</sup> Moreover, when patients with Parkinson's disease are treated with dopamine agonists, many indicate experiencing a side effect of intense desires, which include wanting for drugs, gambling and sex.<sup>34</sup>

Secondly, incentive processes may also be mediated by recruitment of dopaminergic transmission within the nigrostriatal pathway. DiFeliceantonio & Berridge trained rats to respond for sucrose under a second-order schedule of reinforcement, in which reward-associated conditioned-reinforcers maintained sucrose seeking over a delay period before access to sucrose.<sup>35</sup> Some rats displayed seeking behavior towards the conditioned stimulus (CS)-lever whilst others displayed seeking behavior towards the goal dish. These rats were termed sign-trackers and goal-trackers, respectively. Amphetamine injections into the dorsolateral striatum (DLS) of the rats increased sign-tracking in sign-trackers and goal-tracking in goal trackers. They also found that sign-trackers would work to gain access to presentations of the CS-lever and that they would follow the lever to new locations during the experiment. This shows that dopamine in the DLS increases the salience of reward-predictive cues to increase conditioned approach. However, the authors tenuously concluded that the enhancements in cue attraction seen were due to stronger goal-directed behavior and not stronger habits. This evidence does not suggest that; rather, it tells us that the lever itself had become a conditioned reinforcer. To test whether dopamine in the DLS brings about habitual behavior, devaluation experiments, in which the goal outcome is devalued, are required. If the behaviors were indeed habitual, they would be resistant to goal devaluation as habits are governed by stimulus-response associations.

Overall, experiments have shown that incentive processes, which govern the appetitive stage of motivated behavior, are mediated primarily through dopamine transmission in the mesolimbic pathway. Since dopaminergic increases in wanting for rewards can occur without changes in hedonic valuation, as sometimes seen in Parkinson's disease and adult drug addiction, there appears to be a dissociation between incentive and hedonic processes. But what governs these hedonic processes?

## Hedonic processes in adults

Endogenous opiates appear to play a significant role in hedonic processes. Injections of MOR and DOR (delta-opioid-receptor) agonists into the rostradorsal quadrant of the NaC medial shell enhance orofacial reactions to sweet tastes in rats, while KOR (kappa-opioid-receptor) agonism in the same region causes aversion.<sup>17</sup> Additionally, MOR agonism within rats' posterior ventral pallidum (VP), a major output structure of the NaC, blocks the normal increases seen in sucrose liking in hungry states.<sup>36</sup> Taken together, these data show that the rostradorsal quadrant of

the NaC medial shell and the posterior VP are hedonic hotspots and that opioid neurotransmission within these hotspots encodes liking for food.

There are two hedonic hotspots within the brain. The NaC medial shell hotspot, approximately one millimeter cubed in volume in rats, is located in the rostradorsal quadrant of the shell. The second hotspot is in the posterior ventral pallidum. MOR and DOR and signaling within these hotspots increases liking whereas KOR stimulation produces aversion.<sup>17</sup> Conversely, hedonic coldspots exist; MOR and DOR signaling within these coldspots suppress liking. The coldspots are located within the caudal NaC shell and the anterior ventral pallidum.<sup>37</sup> The hotspots in the VP and NaC are connected; if opiate signaling is blocked in one area then increases in liking cannot be produced.<sup>17</sup> Opiate neurotransmission across the NaC and VP either enhances or suppresses liking depending on where exactly the stimulation occurs; in this way an affective keyboard is produced across these sites.<sup>28</sup> Furthermore, the glutamatergic circuit from the lateral hypothalamus (LH) to the VTA is modulated by orexin.<sup>38</sup> Orexin from the LH works here to increase subjective liking during periods of hunger.

The findings that link opiates to hedonic processes have also been replicated in human subjects. Ziauddeen et al gave binge eaters aged 18–60 MOR antagonist GSK1521498.<sup>39</sup> Compared to controls, binge-eaters on the drug showed significant decreases in their self-reported hedonic reactions to sweetened foods.

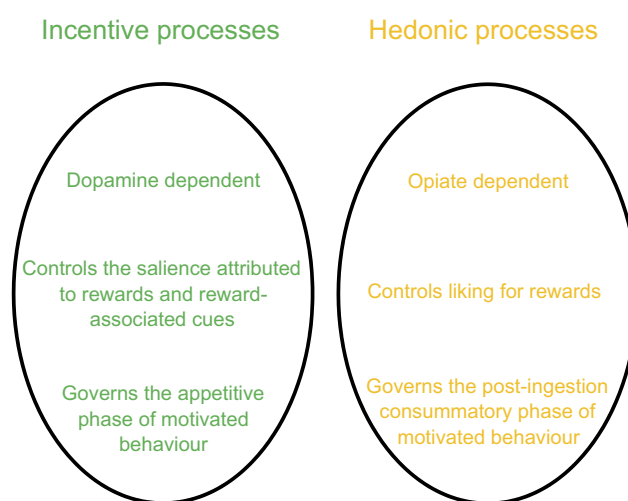
Taken together, there is evidence for a dissociation between incentive and hedonic processes, with dopamine controlling the former and opiates the latter (Figure 1). However, this does not explain why cocaine users often self-report feelings of highs and euphoria when cocaine's primary action is to increase extracellular dopamine levels.<sup>40</sup> Hence, a closer look at this dissociation is needed.

## The dissociation explored further

On closer examination, the dissociation between the role of opiates and the role of dopamine in incentive and hedonic processes seems too simplistic. Subtle and not-so-subtle nuances exist.

## Subtle nuances

Firstly, evidence suggests that subtle nuances exist in the hedonic processes that govern the reinforcing effects of psychostimulant drugs. It appears that the reinforcing effects of psychostimulant drugs are mediated at least in



**Figure 1** The dissociation between incentive and hedonic processes. Incentive processes govern the appetitive “wanting” stage of motivated behavior. It is widely recognized that incentive processes are mediated by dopaminergic signaling. On the other hand, hedonic processes govern the consummatory phase of motivated behavior. They control liking for rewards and are thought to be mediated by opioid signaling.

part through dopamine signaling and not opiate signaling. This presents a special scenario where dopamine appears to play a role in hedonic processes. Giuliano et al trained rats to self-administer cocaine or heroin.<sup>41</sup> MOR antagonists GSK1521498 or naltrexone (NTX) were given. GSK1521498 has a more complete antagonist profile whereas NTX has been reported to have partial agonist activity at MORs.<sup>42</sup> Under a continuous reinforcement schedule, neither drug influenced the self-administration of cocaine; however, doses of both drug increased heroin-self administration (the rats increased their responding to overcome the antagonism). The fact that the MOR antagonists had no effect on cocaine self-administration indicates that MOR-stimulation does not mediate the primary reinforcing effects of cocaine. Stimulant drugs, such as cocaine, lead to increases in extracellular dopamine levels in the NaC. Imaging studies have shown that these increases are associated with self-reported euphoria.<sup>43</sup> This evidence, combined with the evidence from Giuliano et al, adds weight to the theory that dopamine mediates liking for stimulant drugs.

However, dopamine-receptor antagonism in humans does not consistently reduce the highs associated with stimulant drugs. For example, pimozide, a dopamine-receptor antagonist, does not block amphetamine-induced euphoria in humans.<sup>44</sup> An alternative explanation which accounts for this is that stimulant drugs secondarily recruit the endogenous opioid system in the NaC, leading to the generation of pleasure as a secondary effect.<sup>45</sup> However,



this recruitment is often downregulated with continuous drug-taking and so cannot explain why addicts self-report euphoria when taking psychostimulant drugs. Instead, it is more likely that the intense wanting, generated by increases in dopamine, is reappraised subjectively as pleasure in humans.<sup>12</sup> Therefore, separating liking from wanting is a difficult process. This means that there is a subjective overlap between incentive and hedonic processes when it comes to psychostimulant drugs. This has important implications when considering pharmacological treatments for adult drug addiction as perhaps drugs which work on both systems are required.

## Not-so-subtle nuances

Dopamine signaling currently dominates theoretical frameworks on incentive processes. However, a growing body of work suggests that opiate signaling also plays a part. Under a second-order schedule of reinforcement, rats given MOR antagonist GSK1521498 greatly reduced their food-seeking behavior before food presentation.<sup>46</sup> Second-order schedules of reinforcement are measures of cue-controlled seeking. Cue-controlled seeking behavior is thought to be controlled by dopamine neurotransmission but in this experiment GSK1521498 managed to reduce this behavior. This shows that opiates play a role in anticipatory mechanisms. The reduction in seeking behavior could be brought about by GSK1521498's action on MORs on GABAergic interneurons in the VTA or changes to the influence that conditioned-stimuli have on instrumental responding.

Opioid activity at MORs on GABAergic interneurons in the VTA indirectly leads to increases in dopamine release in the NaC culminating in an increase in incentive motivation. Opiates inhibit the GABAergic interneurons, which disinhibits VTA dopamine neurons.<sup>47</sup> Opiates also directly act on MORs on NaC neurons and in many other regions. The opiate receptors and dopamine receptors on NaC neurons signal via Gi; thus, signaling is enhanced.<sup>47</sup>

GSK1521498 therefore works by inhibiting the indirect and direct action of opiates at MORs in this pathway. There is however an alternative explanation to the reduction in seeking behavior that GSK1521498 brings about. MORs in the BLA are needed for incentive learning.<sup>22,36</sup> Incentive learning is a process whereby the positive effects of a reward are encoded as incentive value to guide future reward-seeking behavior. Hence, antagonism in the BLA could weaken the encoding of instrumental associations leading to a reduction in seeking behavior. A study

comparing the effects of localized and systemic MOR antagonist action would help to better parse the effects of opiates on seeking behavior.

There are other sites where opioid neurotransmission can mediate incentive processes. Firstly, evidence supports the role of opiates in incentive processes in the DLS. In an autoshaping experiment where MOR agonist DAMGO was injected into the DLS of rats, seeking behavior was found to be specific to each rat. Some rats defected to the goal dish in anticipation of reward while others defected to the CS lever. DAMGO injections increased cue-controlled approach in both types of rats. This shows that MOR agonism within the DLS plays a role in appetitive processes.<sup>35</sup> Additionally, MOR agonism in the central nucleus of the amygdala (CeN) has also been found to enhance the incentive salience of reward-paired cues and increase seeking behavior in rats.<sup>22</sup>

In humans, only systemic manipulations have been made. Cambridge et al gave GSK1521498 to patients with moderate binge-eating behavior.<sup>48</sup> Compared with controls, patients receiving the drug showed reduced effort to maintain images of palatable food on their screens using a grip force transducer. This shows that the drug reduced willingness to work for the rewarding stimuli and indicates that the drug and therefore opiates play a role in incentive mechanisms. However, the role opiates play appears to be complex, as Ziauddeen et al reported that GSK1521498 did not differ from the placebo in its effects on weight, fat mass and binge-eating scores of binge eaters.<sup>39</sup> Thus, MOR antagonists have mixed efficacy on motivated behavior in practice.

In summary, evidence suggests that both opiates and dopamine mediate wanting as well as liking in certain situations. Evidence also suggests that liking is our cognitive appraisal of both incentive and hedonic processes. Hence, there is an overlap between incentive and hedonic processes. This overlap in adult reward-circuitry could have important implications for analyzing theories about adolescent reward-circuitry.

## Reward processing in adolescence: dual-systems theory

During adolescence, sensation-seeking and impulsivity traits follow distinct developmental trajectories.<sup>5</sup> During mid-adolescence, sensation-seeking and impulsivity are both high. Sensation-seeking has a curvilinear relationship with age across adolescence. This is thought to reflect

hyperactivity of reward-circuitry brought about by the rapid maturation of the striatum in comparison to the PFC. Impulsivity has a negative linear association with age across adolescence. This is thought to reflect increased cognitive control as the PFC develops. This forms the basis of dual-systems theory, which states that sensation-seeking and impulsivity increase, at first, during adolescence due to the imbalance between an already mature reward system and an immature cognitive control system in the PFC.<sup>5</sup> The subsequent sections take a closer look at the reward mechanisms during adolescence along with brief descriptions of the cognitive changes that also occur during adolescence, with reference to adolescent studies throughout.

## **Development of neurocircuitry governing sensation-seeking in adolescence**

### **Increased activation of incentive circuitry during adolescence**

It appears that sensation-seeking increases in adolescence due to hyperactivity of the circuitry that mediates incentive processes. Burton et al compared the acquisition of a conditioned response in adolescent and adult rats.<sup>49</sup> First, adolescent and adult rats learnt to associate the delivery of sucrose with a light-tone-CS. Responding on a lever which delivered the CS was then measured to test whether the CS had become a conditioned reinforcer. After a non-extensive training schedule (420 pairings over 14 days), the adolescent rats acquired responding on the lever whereas adult rats did not, demonstrating that with relatively minimal training adolescent rats can acquire responding for a conditioned reinforcer. This suggests that incentive processes may be enhanced in adolescents compared with adults. The authors also gave the adolescent rats dopamine and opioid receptor antagonists and measured the effects on conditioned responding, both manipulations reduced responding for the CS-predicting lever. This indicates that in adolescents, both opiates and dopamine play a role in mediating incentive processes. Dopamine enhances incentive processes through signaling in the mesolimbic pathway and opiates enhance incentive processes either through action at MORs on GABAergic interneurons in the VTA or action at MORs in the BLA.

Evidence from humans also suggests that incentive processes are enhanced in adolescence. A meta-analysis of fMRI studies conducted in adults and adolescents

reported higher activation of the NaC in adolescents compared with adults during the processing of rewards.<sup>50</sup> Additionally, Urošević et al found that during adolescence self-reported increases in sensitivity to environmental cues were mirrored by increases in NaC volume.<sup>6</sup> Taken together, the evidence from these animal and human studies suggests that, due to increased activity in the NaC, adolescents experience greater salience of rewarding stimuli. This helps to explain why sensation-seeking increases in adolescence.

The explanatory power of increased NaC activity in adolescent behavior is further strengthened by evidence that explains the gender differences seen in sensation-seeking. Adolescent boys typically display more sensation-seeking than adolescent girls.<sup>51</sup> Alarcón et al compared adolescent boys' and girls' brain activity during a Wheel of Fortune task.<sup>52</sup> The boys had higher NaC activity compared with the girls, which was also associated with increased risky decisions during the task and increased motivational salience of task reinforcers. It is important to note that the gender differences were not mediated by differences in levels of sex hormones. This therefore indicates that higher NaC activity plays a crucial role in sensation-seeking during adolescence through increasing the salience of rewarding stimuli. Drawing from evidence in rat studies,<sup>49</sup> this higher NaC activity appears to be mediated by an overlap between the activity of the neurobiological substrates involved in incentive and hedonic processes; both dopaminergic transmission and opiate transmission are important here.

An alternative explanation for the finding that adolescents have higher activation of the NaC compared with adults during the processing of rewards<sup>50</sup> is that their brains have an altered phasic dopamine learning signal as opposed to an increased salience of rewarding stimuli. Cohen et al found that, on fMRI, dopaminergic prediction error signals in the striatum were higher in adolescents when compared with adult participants.<sup>53</sup> This suggests that the learning signal associated with rewarding stimuli is altered in adolescence. The heightened dopaminergic prediction error signal could explain the higher activation seen within the NaC and could also contribute to the increased sensation-seeking behavior seen in adolescence.

This theory is further strengthened by evidence from fMRI studies which show that adolescents show decreased striatal activity during the reward anticipation phase when compared with adults;<sup>54</sup> however, they show increased striatal activity during the notification/outcome

of reward phase.<sup>55</sup> These findings are also characteristic of addiction in adults. Luijten et al found that adults with substance use disorder had decreased fMRI activation during reward anticipation but increased ventral striatum activity during the reward outcome phase.<sup>56</sup> An explanation for the findings seen in both adolescence and adult substance use disorder is a deficit in reward learning.<sup>56</sup> During normal reward learning processes, increased activity in striatal regions occurs in response to unexpected rewards (outcome phase).<sup>57</sup> These signals represent prediction error signals.<sup>57</sup> During the learning process, these signals then become associated with cues which predict the reward (anticipation phase).<sup>57</sup> The reduced striatal activity seen during adolescence and adult substance use disorder could reflect a learning deficit whereby there is a fault in the prediction of rewards.<sup>58</sup> This would lead to persistent prediction errors as future rewards would be unexpected.<sup>58</sup> This explains the high striatal activity in the notification/outcome phase of rewarding as they represent precision errors to “unexpected” rewards. From the evidence above it seems that in both adolescence and adult substance use disorder there is a poorer reward learning process. Adolescents who demonstrate this increased NaC activity in the reward outcome phase/impaired reward learning could be at greater risk of developing addiction later in life if they start using drugs during adolescence as their brains are already behaving in a similar way to an adult with substance use disorder.

## Decreased cognitive control

Decreased cognitive control during adolescence also appears to add to the escalation of sensation-seeking seen during this period. Normally the development of the PFC is protracted, ending in late adolescence.<sup>59</sup> As the PFC matures, executive functions such as inhibition and planning are enhanced.<sup>60</sup> This helps to explain why sensation-seeking decreases on approach to adulthood.

## Development of neurocircuitry governing impulsivity in adolescence

The second type of behavior which can be increased during adolescence is impulsivity. Impulsivity is the tendency to act out on desires without thinking about the long-term consequences<sup>61</sup> and is initially high during adolescence. This is thought to be due to decreased cognitive control, which is brought about by immaturity in the PFC.

Impulsivity later declines from middle adolescence into adulthood as the PFC matures.<sup>5</sup>

## Regulatory mechanisms within the NaC

The role that the PFC plays in the top-down control of impulsivity is widely acknowledged. However, there are indications that the NaC may also contribute in a bottom-up fashion.<sup>62</sup> Firstly, the NaC-core appears to be important for the regulation of impulsivity. In a measure of choice impulsivity, food-restricted adolescent rats were given the choice between a lever that delivered 4 food pellets after a delay and a lever that immediately delivered one small food pellet. Excitotoxic lesions of the NaC-core impaired the rats’ ability to choose the delayed larger reward.<sup>63</sup> These data suggest that the NaC-core plays a role in regulating impulsivity.

Further studies have shown that dopaminergic transmission is involved in these regulatory mechanisms. Besson et al used in-situ hybridization to measure the expression of dopamine D<sub>2</sub>-receptor levels in the brains of high-impulsivity and low-impulsivity rats.<sup>64</sup> High-impulsivity rats had lower levels of dopamine D<sub>2</sub>-receptor mRNA in the mesolimbic pathway than low-impulsivity rats. The authors studied this more closely when they gave high-impulsivity rats infusions of a D<sub>2</sub>/D<sub>3</sub>-receptor antagonist into the NaC-core or shell and measured impulsivity on a 5-choice serial reaction time task.<sup>65</sup> NaC-core infusions significantly reduced impulsivity whilst NaC-shell infusions increased impulsivity. Together, these findings implicate accumbal dopamine in the regulation of impulsivity.

In addition to dopaminergic transmission, opioidergic transmission within the NaC could also play a role in regulating impulsivity. Olmstead et al trained adult MOR and DOR knockout mice in a nose poke task that measures motor impulsivity.<sup>66</sup> MOR knockout mice showed decreased motor impulsivity whereas the DOR knockout mice were more impulsive than controls. These data suggest that MOR signaling serves to enhance impulsivity and DOR signaling serves to decrease it. Since the NaC-core is rich in MORs, it is likely that opioidergic transmission here brings about the effects seen in this study. Studies administering MOR-antagonists within the NaC-core or shell and measuring impulsivity in rats would help to confirm the action of opiates here. However, the existing evidence still suggests an overlap in the functions of the substrates that mediate incentive and hedonic processes.

Overlap in the function of substrates mediating incentive and hedonic substrates therefore contributes to both



the increased sensation seeking and the increased impulsivity seen in adolescence. Additionally, the hyperactivity of mechanisms within the NaC is imbalanced by an immature cognitive control system in the PFC. Therefore, dual-systems theory appears to give a coherent account of the sensation-seeking and impulsivity seen in adolescence. However, it is important to note that there are inter-individual differences in the levels of these traits during adolescence. Some youths experience rapid changes in their levels of sensation-seeking and impulsivity as they pass through adolescence while others maintain constant levels of these traits with age.<sup>5</sup> This is significant as these traits are predictive endophenotypes in adult drug addiction. Links between the reward profile in adult drug addiction and the presence of these traits in adolescence could elucidate why age of onset is a major risk factor for the development of addiction.

## Mechanisms promoting addiction from early-onset (adolescence)

Although most teenagers pass through adolescence without any long-term problems, a significant proportion is at risk of later developing drug addiction. Teenagers who initiate substance use before the age of 14 years are at the greatest risk for substance dependence.<sup>67</sup> Hence, adolescence represents a developmentally sensitive period where initiation of drug use can put one at greater risk of later developing drug addiction.

Adult drug addiction is defined as compulsive drug taking that persists despite negative consequences.<sup>68</sup> Loss of control is a central feature of the disorder as behavior is initially goal-directed but then progresses to being habitual and compulsive in nature. Adult drug addiction can be characterized by three main features; incentive sensitization, increased habit formation and decreased cognitive control. Firstly, repeated exposure to addictive drugs causes sensitization of incentive processes. The NaC increases its response to drugs and drug-paired cues causing aberrant motivation to take drugs. Over time, hedonic allostasis also occurs. Because of this, drug users continue to take drugs to alleviate the negative affective states that arise. There is also a shift from goal-directed behavior to habitual behavior over time and impulsive behavior also increases during this period. Finally, aberrant incentive processes and increased habitual control of behavior give rise to incentive habits. These incentive habits mediate the compulsive drug seeking that is seen in adult drug addiction.<sup>68</sup>

The following section aims to discuss the links between the three main features of adult addiction highlighted above and characteristic behavioral traits seen in adolescence. In doing so, we hope to elucidate a possible mechanism for the increased vulnerability of later developing addiction associated with adolescent onset drug use.

## Increased incentive sensitization

Sensitization describes the process whereby repeated administration of a stimulus enhances the response to that stimulus. Evidence suggests that drugs sensitize the mesolimbic dopamine system in adult drug addiction. For example, in rats, intermittent experimenter-delivered doses of amphetamine increase the firing patterns of neurons in mesolimbic structures.<sup>32</sup> These findings have also been replicated in humans where repeated intermittent doses of amphetamine sensitize dopamine release in the NaC. One year later, drug challenge with amphetamine still produced enhanced dopamine release.<sup>69</sup> This shows that the effects of sensitization are long-lasting. The NaC, which is part of the mesolimbic dopamine system, is needed for pavlovian stimuli to control instrumental responding. Under second-order schedules of reinforcement, sensitization of dopamine release is thought to mediate cue-controlled drug seeking. In rats, dopamine receptor antagonists attenuate cue-controlled cocaine seeking.<sup>70</sup> Thus, hypersensitivity of dopaminergic neurons in the NaC appears to be responsible for the aberrant attribution of salience to drugs and drug-paired cues that leads to the pathological wanting for drugs. This is the incentive sensitization theory of adult drug addiction.<sup>32</sup>

The intense wanting for drugs in adult drug addiction resembles the intense wanting for rewards seen in some adolescents. Drug sensitization will not yet have occurred in adolescence but, as previously reviewed, the same system is hyperactive. In adolescence, hyperactivity of this system mediates sensation-seeking, which is a predictor of the initiation of drug use.<sup>11</sup> Adolescents who show high levels of this trait are therefore at increased risk of initiating drug use. It is possible that high sensation-seeking adolescents are more likely to initiate drug use because the hyperactive salience circuitry enhances incentive processes and makes positive rewards extremely attractive.<sup>49</sup>

It is important to note that although sensation-seeking predicts initiation of drug use, it does not confer risk for later developing drug addiction on its own. Evidence suggests that under certain conditions sensation-seeking may even be a protective factor.<sup>9</sup> But what mediates this?

Sensation-seeking is measured in humans using the sensation-seeking scale form (SSS-V). The experience-seeking and boredom-susceptibility subscales of sensation-seeking are a cross-species translation of novelty-preference in rats, a trait that predicts the development of compulsive drug-taking in rats allowed to self-administer cocaine.<sup>71</sup> The thrill-seeking and disinhibition subscales of sensation-seeking are related only to the overall sensation-seeking trait, an overarching trait predicting the initiation of drug use.<sup>71</sup> A dissociation can thus be seen within the sensation-seeking construct where the risk of developing compulsive drug taking is dependent on which subscales adolescents score highly on.

## Increased habit formation

Another characteristic feature of adult drug addiction is increased habit formation.<sup>68</sup> In adult substance use disorder, drug-seeking behavior gradually shifts from being goal-directed to being habitual. This is evidenced by the fact that cocaine and alcohol-seeking behavior is initially sensitive to outcome devaluation in rats; however over-time, behavior becomes stimulus bound and resistant to devaluation.<sup>72,73</sup> Dopamine transmission within the DLS is responsible for this stimulus bound habitual responding for drugs. Everitt et al reported that after prolonged exposure to cocaine, dopamine release increased only in the dorsal striatum during cue-controlled cocaine seeking.<sup>74</sup>

The DLS gains control over drug-seeking behavior via functional striato-nigro-striatal loops that exists between the ventral striatum, midbrain and dorsal striatum, confirmed by evidence from Belin & Everitt in 2008.<sup>75</sup> Rats were given unilateral lesions of the NaC core and infusions of a dopamine antagonist into the contralateral DLS to disrupt the striato-nigro-striatal connections bilaterally. The manipulation decreased cue-controlled drug-seeking behavior in the rats. This shows that the striato-nigro-striatal loops sustain cue-controlled behavior and that this is behavior is mediated by dopaminergic transmission in the DLS.

In adult drug addiction, habitual drug-seeking behavior eventually becomes compulsive.<sup>68</sup> Impulsivity is a predictive endophenotype for the development of compulsive cocaine-seeking and dependence.<sup>10</sup> This puts adolescents that are high on this trait at increased risk for developing compulsive drug-seeking behavior.

Interestingly, the increased risk of developing compulsive drug-taking that is associated with the experience-seeking and boredom-susceptibility subscales of sensation-seeking

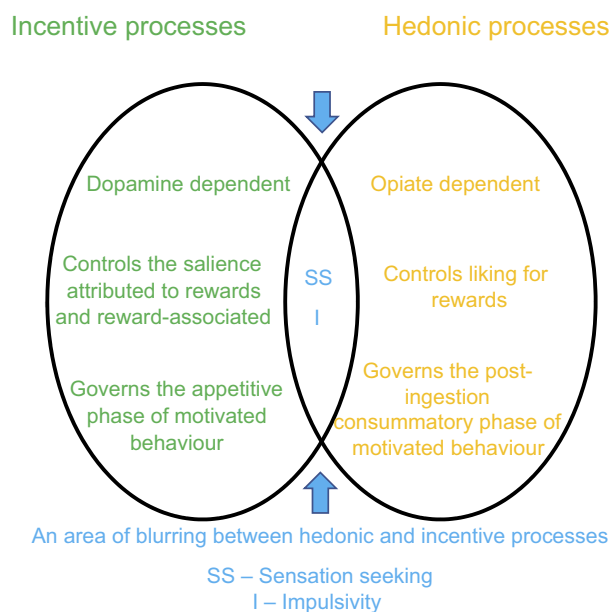
could be brought about by an association of these subscales with impulsivity. Molander et al tested high-impulsivity rats on novelty reactivity and preference.<sup>76</sup> High-impulsivity rats showed a preference for novel environments and were faster to initiate exploratory behavior in novel settings, whereas low-impulsivity rats tended to spend more time in the familiar part of the apparatus. This suggests that the high-impulsivity rats are also high on experience-seeking and boredom susceptibility. Therefore, high measures on the sensation-seeking subscales which correlate to impulsivity could explain why sensation-seeking is not always a protective factor.

In summary, the subscales of sensation seeking; boredom susceptibility and experience seeking are correlated to the later development of compulsive drug taking.<sup>71</sup> Impulsivity is also independently correlated to the later development of compulsive drug taking.<sup>10</sup> However, interestingly the aforementioned subscales of sensation-seeking and impulsivity are also inter-related.<sup>76</sup> This means that these behavioral traits are not so discrete. The blurring between incentive and hedonic processes that is seen neurobiologically<sup>49,66</sup> in adolescence is also seen behaviorally as there is a blurring of the boundaries between the behavioral trait's sensation-seeking and impulsivity.<sup>71</sup> It can be hypothesized that adolescents who score highly on this constellation of blurred traits may be at greater risk of developing addiction later in life (Figure 2).

## Decreased cognitive control

The final characteristic feature of adult drug addiction is decreased cognitive control.<sup>68</sup> The PFC subserves executive functioning. Abnormalities in PFC function play a role in the development of compulsive drug taking. Goldstein et al reported that reduced PFC grey matter density and thickness in drug addicts was associated with increased severity and longer periods of alcohol use disorder and worse executive functions.<sup>77</sup> The effects were seen up to six years after abstinence. These data suggest that the damage that drugs do to the PFC contributes to facilitating and maintaining addiction later in life. However, the long-lasting nature of the effects also suggests that structural abnormalities in PFC grey matter density could be a pre-disposing vulnerability present before drug-taking.

In adolescence, PFC functioning is also sub-optimal. The development of the PFC is protracted until early adulthood; thus, cognitive control is decreased during adolescence. This decreased cognitive control can facilitate



**Figure 2** The blurred dissociation between incentive and hedonic processes. The blurring between incentive and hedonic processes that is seen neurobiologically in adolescence is also seen behaviorally as there is a blurring of the boundaries between the behavioral trait's sensation-seeking (SS) and impulsivity (I). It can be hypothesized that adolescents who score highly on this constellation of blurred traits may be at greater risk of developing addiction later in life.

increases in impulsivity and sensation-seeking in mid-adolescence. Adolescents with high levels of both traits could be at the greatest risk of developing drug addiction later in life.

Perhaps promoting cognitive control in at-risk adolescents on approach to adulthood could reduce risk of developing addiction in adulthood? Promising evidence comes from the trial of the HOPE program for offenders on probation, many of whom are adults with substance use disorders. Individuals in the program must call into a center daily to see if they are required to come in for a random drugs test. This promotes executive functioning and cognitive control as individuals must monitor their own behavior and proactively call into the center daily. The HOPE program was trailed for a year via random assignment. 13% of HOPE members failed their drugs tests compared with 46% of controls. These data are promising as they show the power that increased cognitive control can have on outcomes.<sup>48</sup>

Further evidence supporting this comes from a randomized control trial of 732 secondary school children in London.<sup>78</sup> Participants who scored highly on impulsivity, sensation-seeking and other personality risk factors for substance misuse were assigned to a control group or a coping skills intervention group.

The coping skills intervention aimed to teach goal-setting, awareness of behavior and simplified CBT. The control group had higher rates of drug use and more drugs used than the intervention group over the two-year follow-up period when compared with the intervention group. This further supports the notion that improving cognitive control in at-risk adolescents could prevent the onset of substance use disorder later down the line. Longer studies should also be conducted to assess the long-term drug use rates of adolescents on this type of program.

## Conclusions and future research

A detailed investigation of the mechanisms governing reward in adolescence has enabled the overlap between the functions of the neurobiological substrates which mediate incentive and hedonic processes to be seen. The increased activation of incentive circuitry, which has been found to rely on both dopaminergic and opioidergic processes, contributes to the increased sensation-seeking and impulsivity seen during adolescence. These traits are also predictive endophenotypes for the development of drug addiction later in life; adolescents who are high on both these traits are therefore at the greatest risk of later developing drug addiction. Analyzing links between these predictive traits and the profile of adult drug addiction has highlighted some key areas that future research should focus on.

Firstly, since sensation-seeking and impulsivity are both governed by the activation of salience circuitry, treatments could be targeted here in both adults and adolescents. The overlap between the role of opiates and dopamine means that perhaps drug therapy should focus on dual treatments which work on both pathways.

Secondly, the finding of behavioral traits in adolescence that predict the development of drug addiction later in life opens the possibility of targeted prevention programs aimed at high-risk youths. As evidenced by the HOPE and coping skills program, interventions which strengthen cognitive control could be used as treatment tools in adolescence to reduce levels of sensation-seeking and impulsivity in those at risk. Current treatment outcomes for drug addicts are poor. The external monitoring that occurs in rehabilitation centers does not prevent the relapse of drug taking when the individual returns to the community. In addition, drugs such as GSK1521498, which reduce seeking behavior, do not work well in practice to reduce binge-eating or alcohol consumption. Giving

control and agency back to addicts is clearly key. Ways of managing adult drug addiction need to be proactive; they need to enable individuals to interact with drugs but exercise control.

Future research into these areas may not end up yielding fruitful treatment options for adult drug addiction, but this research will nevertheless expand the knowledge base and get us closer to practical solutions.

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## Author contributions

FK, OO and RM were involved in the conception, design, drafting, writing and final approval of the article. All authors agree to be accountable for all aspects of the accuracy and integrity of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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