

Title: Reappraising the role of dopamine in adolescent risk-taking behavior

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Keywords: adolescence, dopamine, self-regulation, impulsivity, risk-taking

Introduction

Dopamine is one of the main neuromodulators in the brain and has been implicated in a variety of behavioral and cognitive processes (Glimcher, 2011; Salamone and Correa, 2012; Costa and Shoemaker, 2022). In particular, dopamine has received considerable attention due its role in motivation control and reward processing (Glimcher, 2011; Salamone and Correa, 2012; Costa and Shoemaker, 2022). These functions are mostly associated with circuits (see **Figure 1**) organized around two midbrain regions rich in dopaminergic neurons, the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) (Costa and Shoemaker, 2022).

The VTA has dense projections to the nucleus accumbens (NAcc) in the ventral striatum, as well projections to various cortical areas, including prefrontal regions. In fact, the VTA acts as a hub that sends and receives projections to and from a wide variety of brain regions in addition to those mentioned above, including the amygdala, hippocampus, thalamus, and hypothalamus (Pessoa et al., 2021; Costa and Shoemaker, 2022). The pathway between the VTA and subcortical/limbic structures (especially the ventral striatum) is known as the mesolimbic pathway, while the pathway between VTA and prefrontal and other cortical areas is known as the mesocortical pathway (Costa and Shoemaker, 2022). The dopaminergic neurons in the SNc receive inputs from and project to (but not only to) many of the same brain regions as the VTA, including different portions of the striatum and frontal cortices (Menegas et al., 2015; Watabe-Uchida and Uchida, 2018). In particular, the projections of SNc neurons to the striatum form the well-known nigrostriatal pathway (Costa and Shoemaker, 2022). Because the VTA and SNc are implicated in overlapping (though distinct) sets of functions, many studies on dopamine function lump these two dopamine centers together (e.g., Glimcher, 2011; Roesch et al., 2012; Gardner et al. 2018; Watabe-Uchida and Uchida, 2018; Alexander and Gershman, 2022; Costa and Shoemaker, 2022).

During adolescence, the dopaminergic pathways go through extensive changes in their structure and function. These changes include increases in dopamine levels, the development of dopaminergic projections, and changes in the density of dopamine receptors in different brain regions, such as the NAcc and prefrontal cortex, as well as increases in the activities of the VTA and NAcc during reward processing (Galván, 2010; Whalstrom et al., 2010a, 2010b; Walker et al., 2017). Because of the links between dopamine and processes related to reward and motivation, these changes in the dopaminergic pathways have been associated with some of the behavioral changes observed during adolescence, including increases in sensation-seeking, risk-behaviors, and elevated choice impulsivity compared to adults (e.g., Steinberg et al., 2008; Icenogle and Cauffman, 2021). In fact, alterations in the dopaminergic system are commonly regarded as a likely explanation for these behavioral patterns in adolescents (e.g., Steinberg, 2008; Galván, 2010; Whalstrom et al., 2010a, 2010b; Galván, 2021).

The role of dopamine in adolescent behavior is usually discussed within the framework of the dual-systems model and other related theoretical models (Galván, 2010; Whalstrom et al., 2010a, 2010b; Heatherton and Wagner, 2011; Casey, 2014; Casey et al., 2016; Shulman et al., 2016; Galván, 2021; Icenogle and Cauffman, 2021). These models commonly treat adolescent behavior as the result of the competitive interaction between a “hot” system, implicated in affect and reward processing, and a “cool”, higher-order cognitive system, implicated in self-control and responsible for regulating the effects of the hot system (Galván, 2010; Heatherton and Wagner, 2011; Casey, 2014; Casey et al., 2016; Shulman et al., 2016; Galván, 2021). The hot system is commonly associated with subcortical regions, including the ventral striatum/NAcc, while the cool system mainly involves prefrontal regions (Heatherton and Wagner, 2011; Casey, 2014; Casey et al., 2016; Shulman et al., 2016).

The general tenet of the dual systems and related models regarding adolescent behavior is that during adolescence there is an imbalance between the hot and cool systems which results from the earlier maturation of subcortical regions relative to prefrontal regions (Galván, 2010; Heatherton and Wagner, 2011; Casey, 2014; Casey et al., 2016; Shulman et al., 2016). Crucially, this earlier maturation of the hot subcortical system involves a significant role of dopamine. The idea is that the increasing dopamine function in these brain areas, combined with the delayed maturation of the frontal regions, leads to a greater influence of reward sensitivity over behavioral control. This increases sensation-seeking and choice impulsivity, causing failures in self-regulation of behavior when potential rewards are involved and, consequently, leads to risk-taking behavior (Steinberg, 2008; Galván, 2010; Whalstrom et al., 2010a, 2010b; Heatherton and Wagner, 2011; Casey, 2014; Casey et al., 2016).

These models remain extremely popular in explaining adolescent risk taking (Shulman et al., 2016; Icenogle and Cauffman, 2021), possibly because they provide an intuitive, neuroscience-based account of the way adolescents are generally portrayed; however, they have received a significant amount criticism (e.g., Pfifer and Allen, 2012, 2016; Do et al., 2020; Defoe and Romer, 2021). These criticisms highlight the need to re-conceptualize what constitutes risk-taking (e.g., Duell et al., 2016, 2018; Romer et al., 2017), as well as the role of cognitive control in these behaviors (e.g., Do et al., 2020). Critics also point to the lack of unambiguous parallels between behavior and functional imaging data (e.g., Pfeifer and Allen, 2016), including the fact that although connectivity between the hot and cool systems does seem to increase with age, there is still a lack of evidence about how this interaction impacts behavioral development (Duell et al., 2016).

Beyond these critiques of the dual system models, it has also become increasingly clear that this view of the part played by dopamine in adolescent behavior is oversimplified and, in some aspects, misleading. Recent (and not-so-recent) theories about the role of the dopaminergic system

in reward processing, learning, and motivation based on human and animal data (e.g., Friston et al., 2012; Roesch et al., 2012; Salamone and Correa, 2012; Westbrook and Braver, 2016; Romer et al., 2017; Berke, 2018; Gardner et al. 2018; Watabe-Uchida and Uchida, 2018; Gershman and Uchida, 2019; Kim et al., 2020; Langdon and Daw, 2020; Alexander and Gershman, 2022) call for a more nuanced view of the implications of dopamine changes in adolescence, as well as a more refined view of the neural underpinnings of typical adolescent behaviors. In what follows, we provide a brief discussion on some of these recent perspectives on dopamine function, and their implications for adolescent behavior. Our goal here is not to give an exhaustive review of the current evidence and thinking about dopamine function. Instead, we will take a stroll through the gallery of models and theories currently discussed in the literature, stopping here and there to reflect on some of these proposals and their potential to change our understanding about the role of dopaminergic changes in adolescent decision-making.

To this end, we start by discussing theories about the role of dopamine in adolescent cognitive development in light of well-established models of dopaminergic activity as a reward prediction error signal for reinforcement learning, as well as extensions of this view that consider the role of dopamine on signaling uncertainty. We will then discuss more recent models of dopamine and their implications for understanding adolescent behavior that go beyond the classical view of *reward* prediction errors, such as proposals of dopamine as a signal for: 1) threats; 2) general prediction errors including, but not only restricted to those involving rewards; and 3) precision of sensorimotor representations under the active inference framework. Next, we turn to a different side of dopamine function – its role in motivation in adolescent behavior, where we discuss the implications of more nuanced views of dopamine in respect of different aspects of motivation. **Table 1** provides a simplified summary of the main functions of dopamine discussed in this review. We then briefly consider other neuromodulators that interact with dopamine in ways that may be essential to understand before we are able to make sense of behavioral and cognitive changes in

adolescence. Finally, we discuss some of the commonly held assumptions about adolescent behavior that do not have empirical support, and raise questions about how they impact the view of dopamine function in this phase of life.

As we will see, the emerging picture is messier than the dual-systems models suggest, and discourages simple narratives about the part dopamine plays in adolescent behavior. This should come as no surprise, as behavior in situations with potential gains and losses involves many cognitive elements beyond sensitivity to rewards and the ability to control impulsive choices. Actions (or inaction) also depend on motivation, and engage the evaluation of options (including risk appraisal), the formation of preferences, the anticipation of outcomes (which depend on prior experience in similar conditions), the execution of actions, the detection of errors, and the processing of response feedback to enable learning from experience (Ernst et al., 2006), all of which, to some extent, also involve dopaminergic activity, as we discuss next.

Dopamine: craving for rewards or learning from (uncertain) rewards?

The role of dopamine in the dual systems theories centers around this neuromodulator's involvement in reward processing. The increased dopaminergic activity in the mesolimbic pathway during adolescence is believed to elicit hyper-responsivity to rewards, leading to greater reward-sensitivity, sensation-seeking, and increased incentive motivation, which are key factors in decision-making involving potential positive outcomes (Galván, 2010; Luciana et al., 2012; Icenogle and Cauffman, 2021). Moreover, it has been reported that dopamine receptor expression peaks in the striatum earlier than it peaks in the prefrontal cortex; this maturational difference is believed to cause both the hyper-responsiveness of the striatum to rewards described above and an over-reliance on the striatum for decision-making, giving rise to increased affective risk-taking behaviors (Steinberg, 2008; Galván, 2010; Casey, 2015; but see Galván, 2021, for a more nuanced view). The key

question here is whether this view of the cognitive and behavioral implications of dopamine changes in adolescence is consistent with the current evidence and theories about the functions of the dopamine pathways.

Dopamine is, indeed, involved in reward processing, and there is substantial evidence linking increased dopaminergic activity, especially (but not only) in the mesolimbic pathway, to appetitive, positive affectively-charged stimuli (Glimcher, 2011; Costa and Shoemaker, 2022). However, there is also evidence suggesting that the activity of the VTA and NAcc are not directly related to the subjective feeling of reward and pleasure (Salamone and Correa, 2012; Costa and Shoemaker, 2022). Instead, this pathway is involved in learning how to better predict rewards in different contexts (Glimcher, 2011; Costa and Shoemaker, 2022). And here, “learning” and “predict” are the keywords. The activity of many dopamine neurons in the VTA and SNc is well captured by classical reinforcement learning models, in which they are believed to provide a reward prediction error (RPE) signal (Glimcher, 2011). RPEs signal discrepancies between received and predicted rewards, and allow using the experienced value of outcomes to update future predictions associated with similar contexts and behaviors (Glimcher, 2011; Westbrook and Braver, 2016; Kim et al., 2020). In other words, RPEs enable the learning of associations between behaviors, contexts, and rewards.

Crucially, recent studies show that dopamine activity in the striatum varies as a function of the uncertainty about cues, contexts, and the consequences of possible behaviors (Starkweather et al., 2017, 2018; Mascia et al., 2018; Mikhael et al., 2022). This variability seems to code for the uncertainty around states/cues and their value, and some of these studies have shown increased levels of dopamine under conditions of uncertainty. This is consistent with the expected effect of uncertainty based on recent theories about probabilistic representations in the VTA and NAcc (Gershman and Uchida, 2019; Dabney et al., 2020; Langdon and Daw, 2020), which imply greater variance in populational dopamine responses under uncertainty. These effects of uncertainty, which

are not specific to adolescents, should be considered together with observations of adolescents' higher tolerance to ambiguity (Tymula et al., 2012), which may stem from an overly optimistic evaluation of the reward value of novel behavior during this age (Romer et al., 2017). If dopamine neurons do in fact represent probabilistic distributions of expected outcomes, then uncertainty coupled with biased optimistic evaluations should lead to greater overall dopamine activity compared to that of adults. This fits with results from Cohen et al. (2010) showing greater RPE signals in adolescents, compared to children and adults, in a probabilistic learning task. Importantly, this would lead to more exploratory behaviors when choosing between behavior options involving either certain or uncertain outcomes, as there would be an "uncertainty bonus" in the estimated value of the uncertain option (Gershman and Uchida, 2019). This suggests a different view about the significance of reported increases in dopamine secretion in the VTA and NAcc during adolescence. Instead of being viewed as a main marker of sensation or pleasure seeking, increases in dopamine activity in these areas during adolescence may additionally and/or alternatively reflect higher uncertainty about the value of different contexts and possible behaviors.

Uncertainty may play an even larger role considering theories linking dopamine not only to the learning of simple associations between stimulus/behaviors and rewards (as in model-free reinforcement learning), but also to forming mental models to guide future actions (as in model-based reinforcement learning; Daw et al., 2011; Sharpe et al., 2017; Daw, 2018; Collins and Cockburn, 2020). This makes ecological sense, as highlighted in recent developmental models (Murty et al., 2016; Romer et al., 2017; Hartley et al., 2021): adolescents lack life-experience but are rapidly expected to assume a myriad of new social roles and responsibilities, so that this is an age that requires intense capacity to learn how to behave based on each new decision-making experience.

The view of dopamine as a learning signal and a marker of probabilistic representations can help to explain behavioral evidence which suggests that adolescents make more choices associated with possible negative outcomes compared with adults, but only in situations that involve *uncertainty* about what might happen (Tymula et al., 2012; Romer et al., 2017). Thus, it is critical to distinguish between different types of choice-behavior across development (Tymula et al., 2012; Romer et al., 2017). Behavioral evidence shows that sub-optimal decision-making that involves a choice between known outcomes does not peak in adolescents, who avoid disadvantageous choices more often than do children (Tymula et al., 2012; Romer et al., 2017). Differently, choices under ambiguity (i.e., in which outcome probabilities are unclear and therefore constitute actual risks) do peak during adolescence, but not because of self-control failures as implied in dual systems models; rather, adolescents seem to be more tolerant to ambiguity than adults, probably because they do not have enough experience to develop insights about how to function best, so their tolerance to ambiguity is adaptive at this age when the exploration of new situations is essential for learning (Tymula et al., 2012; Romer et al., 2017).

The evidence and ideas presented by Tymula et al. (2012) and Romer et al. (2017) are consistent with the expected consequences of the combination of probabilistic representations and an optimistic bias in the evaluation of rewards discussed above, which would lead to more exploratory behaviors under uncertainty. Data and modeling from Jepma et al. (2020) also support this conclusion, showing increased exploratory behavior by adolescents, compared to adults, in laboratory tasks with different levels of uncertainty. Exploration is in fact a recurrent theme in studies about the role of dopamine in decision-making, and it fits well with the role of dopamine in learning from experience. Tolerating ambiguity and increasing exploratory behaviors is an adaptive strategy for adolescents, as it effectively samples their environment and the possible outcomes of different actions, providing a greater chance of gaining experiences to learn from. Of note, this strategy could help explain adolescent behavior in the real world, as exploratory (and possibly risky) behaviors

would be expected to increase in the short-term while being reduced in the longer term as learning ensues and the knowledge needed to make better (and more informed) decisions is acquired (Cironka and van den Bos, 2021). However, the interpretation of any risk-taking behaviors under this view would be markedly different from that offered by dual systems models, as we discuss below.

The view that emerges from our discussion so far paints the role of dopamine as one of making adolescents well adapted to learning from their experiences, something that is in line with behavioral evidence suggesting adolescents are better at learning from feedback compared to adults (Icenogle and Cauffman, 2021). It should be noted that this emerging view of changes in dopamine during adolescence does not square as well with the dual systems framework as it does with alternative theories such as the Experience-Driven Adaptive Cognitive Model (Murty et al., 2016), the Spiral of Motivated Actions (Ernst et al., 2006), as well as other related perspectives (Romer et al., 2017). We are not going to enter in details about the relative strengths and shortcomings of these later models here, but all of them focus on the interaction between experiences and neurobiological changes during adolescence, and its influence on shaping behavioral development. They put significant weight on the role of dopamine in enhancing learning and memory and in allowing experience to gradually improve adolescent decision-making. As such, while we do not agree with all the details of these proposals (for one thing, they do not incorporate much of current conceptions about dopamine function), we believe they represent steps in the right direction compared to dual-systems models.

Error detection beyond reward

While increased midbrain dopamine activity is usually associated with rewards, and particularly with RPEs, there is considerable evidence for “noncanonical” dopamine activity – activity that does not resemble RPEs. An example of this type of noncanonical activity are the reports of

dopamine responses associated with threatening and aversive stimuli (see Watabe-Uchida and Uchida, 2018, and references therein). These responses are proposed to constitute a threat prediction error that helps guide and adjust avoidance behaviors (Watabe-Uchida and Uchida, 2018). This involvement of dopamine with threat detection and avoidance behaviors raises interesting possibilities in light of some models of adolescent cognitive development, particularly the triadic model (Ernst et al., 2006; Ernst, 2014). The triadic model considers the interplay of both the socioemotional incentive and cognitive control systems proposed in the dual-systems models plus that of a third, amygdala-centered avoidance system module which interacts with the former systems by mediating emotional avoidance of aversive stimuli, fear response, threat avoidance, and negative affect. This module functions to protect individuals from potential harm. Although Ernst and collaborators did not originally consider dopamine as a player in the avoidance module, they do propose that this module responds differently to situations with and without the presence of rewards: during adolescence the avoidance system is supposed to be hyper-responsive to treats in negatively valenced contexts, but is hyporesponsive in positively valenced contexts, when (potential) rewards are present (Ernst et al., 2006; Ernst, 2014). For reasons unclear to us, this model has received much less attention in the literature compared with dual-systems models, even though it is more comprehensive, has recent functional imaging support (Xu et al., 2021) and, importantly, describes many different ways in which dopamine changes modulate various aspects of learning, as in the above-mentioned Spiral of Motivated Actions. Exploring this additional aversive-avoidance aspect of behavioral change in adolescence in light of updated theories of dopamine function may be an interesting direction for future research.

Beyond signaling threat-prediction errors, dopamine activity has also been associated with sensory prediction errors (see Gardner et al., 2018, and references therein). This has motivated proposals of dopamine activity as a general prediction error signal. In this view, dopamine activity signals errors – violations of expectations – for features of the animals' current state that include, but

are not limited to, rewards (Gardner et al., 2018). An alternative proposal that also takes dopamine beyond RPEs has been developed within the Active Inference Framework of brain function (Friston et al., 2012). Here, dopamine activity signals the precision of sensorimotor representations, playing a broader role in the processes of perception and action that includes, but goes beyond, the canonical RPE view (Friston et al., 2012). The perspective of Friston et al. integrates both the reported relationship between dopamine and uncertainty discussed earlier and the above-mentioned evidence for dopamine apparently signaling sensory prediction errors and not just RPEs. Importantly, both interpretations of the meaning of dopamine signals – as a general prediction error and as a precision signal in the active inference framework – can expand the proposed role of dopamine in the development of mental models (Collins and Cockburn, 2020; Daw, 2018; Sharpe et al., 2017; Daw et al., 2011). Moreover, they also fit the emerging views that emphasize the interplay between learning and memory in improving decision-making during adolescence and that propose a role for dopamine in this process beyond a simple relationship with rewards (Murty et al., 2016; Romer et al., 2017; Hartley et al., 2021).

Dopamine and motivation

Besides being commonly associated with pleasure and reward, dopamine is also implicated in motivation (Salamone and Correa, 2012; Westbrook and Braver, 2016). However, the associations commonly made between dopamine and motivation in adolescence tend to ignore more nuanced, and more substantiated, theories about dopamine's relationship to motivation. These theories link dopamine to instrumental behavior, but not to consummatory behaviors (i.e., behaviors that lead to the consummation of the goal; Salamone and Correa, 2012). Thus, for example, a certain concentration of dopamine seems to be necessary for animals to exert effort to obtain food, but does *not* enhance the hedonic value of food or appetite, meaning they are not really related to

pleasure in obtaining rewards but, rather, to willingness to work for rewards. Crucially, the role of dopamine in instrumental behaviors is not restricted to reward-motivated behaviors, but also applies to aversively motivated behaviors (Salamone and Correa, 2012). How this association of dopamine with aversive motivation relates to adolescent is uncertain and remains to be explored.

A biological peculiarity of the relationship between motivation and dopamine is that motivation is not associated with dopamine activity in the sense we have been discussing so far in this paper – namely phasic activity, marked by rapid, high-amplitude fluctuations in dopamine levels. Instead, motivation is associated with dopamine's tonic, slowly varying background concentrations in the extracellular medium in the mesolimbic and mesocortical pathways (Salamone and Correa, 2012; Westbrook and Braver, 2016). Importantly, tonic dopamine levels have been linked to other roles that are relevant to cognitive control, such as stabilizing working memory representations (Westbrook and Braver, 2016) and modulating the integration of expected reward and the effort required to obtain them (Salamone and Correa, 2012; Westbrook and Braver, 2016). These roles are carried out, at least in part, through dopaminergic projections from the midbrain to different regions in the frontal cortex, projections that become denser during adolescence (Hoops and Flores, 2017).

Notably, the view just presented about the involvement of dopamine in motivation is much more complicated than the dual-systems perspective implies. For one thing, this view does not necessarily imply a greater propensity for self-regulation failures and risk-taking *as a consequence* of higher sensitivity to rewards *per se*. In fact, the emerging picture is that of dopamine contributing to (and not hindering) cognitive control by promoting goal-directed effort. This view fits the results of Scheres et al. (2014) in which mid-adolescents had higher willingness than adults and younger individuals to wait to obtain higher monetary rewards, and also to a recent pilot study by Sullivan-Toole et al. (2019), in which adolescents were more willing than adults to expend effort to obtain

rewards, despite not being more responsive to these rewards. These results are consistent with the view of tonic dopamine being involved in motivation to work for rewards, and not necessarily to elevated reckless responsivity to such rewards.

Curiously, recent theories suggest that the distinction between tonic and phasic dopamine – that is, between low, background, slowly varying levels of dopamine and fast, high amplitude variations in dopamine levels related to activity bursts of dopaminergic neurons – is actually an artificial one (Kim et al., 2020). The differential association of motivation and reinforcement learning/prediction error signals with tonic and phasic dopamine levels, respectively, has kept theories about these cognitive processes mostly separate in the literature. However, recent theories propose that these two aspects of dopamine signaling may be facets of the same process involved in signaling the value of exerting effort (Kim et al., 2020; Westbrook e Braver, 2016; Hamid et al., 2015). This highlights something that seems to be a general theme when we consider dopamine changes during adolescence in light of current theories of dopamine function: the competing nature between reward pursuit and cognitive control, the basis of the two systems in dual systems models, is completely blurred in the neurobiology of dopamine function. Instead, it seems dopamine contributes directly to both reward/valuation systems and to cognitive control systems. This makes perfect sense – after all, how can one regulate one’s behavior – or even establish goals for this regulation – without judging the value of ones’ possible actions and their consequences? This point has been repeatedly stressed by researchers studying the role of emotion in decision making (e.g., Lerner et al., 2014; Phelps et al., 2014), but has been largely overlooked in the field of development.

No neuromodulator is an island: why we must consider the interactions between dopamine and other neuromodulators

So far we have discussed a number of cognitive/behavioral processes in which dopamine is implicated. We discussed the involvement of dopamine in reward and threat processing, motivation, decision under uncertainty, cognitive control, error detection, and learning and memory. However, amid all the complexities of dopamine dynamics and function it can be easy to forget that the dopaminergic system is not the only neuromodulator system involved in these functions. Dopamine exerts its influence over neuronal processes in a social milieu of other neuromodulators, both influencing and being influenced by them (Cools and Robbins, 2004; Dayan, 2012; Cools, 2019). While the developmental changes in other neuromodulators during adolescence have not attracted as much attention as dopamine's, there is evidence (though mostly from animal models) that at least some of these systems change during adolescence (e.g., Gross-Isseroff et al., 1990; Yuan et al., 2015, and references therein). It is, therefore, necessary to interpret the effects of the changes in dopamine signaling considering its interactions with other neuromodulators.

To have an idea of how close the interaction between dopamine and other neuromodulators is, let us look at the case of serotonin. The serotonergic system has its hub in the Raphe nuclei (RN) in the brainstem (Hu, 2016; Peters et al., 2021). Crucially, the RN have reciprocal connections with the VTA, and both have reciprocal connections with the NAcc (Hu, 2016). This anatomical association comes with functional associations, and like dopamine neurons in the VTA, serotonergic neurons in the RN respond to rewards and punishments, though not necessarily in a way that represents RPEs (Hu, 2016). The projections from the RN to the VTA have been shown to modulate dopamine release in the NAccs during reinforcement learning, and both dopamine and serotonin seem to act together to regulate synaptic plasticity in the striatum (Peters et al., 2021).

The potential interactions between serotonin and dopamine run deep, as serotonin is proposed to be a functional opponent of dopamine (Cools et al., 2011; Boureau and Dayan, 2011). While dopamine is implicated in reward processing and motivation, serotonin is implicated in

aversive processing and the modulation of behavioral inhibition (Cools et al., 2011; Boureau and Dyan, 2011; Dayan, 2012; Avery and Krichmar, 2017). Therefore, just like dopamine, serotonin participates in value processing and signals the value (or cost) of exerting effort, but while dopamine promotes behavioral activation to work towards rewards, serotonin promotes behavioral inhibition to avoid possible adverse outcomes (Cools et al., 2011; Boureau and Dyan, 2011). While this is an oversimplification of the complex functional implication of the interaction between the dopaminergic and serotonergic systems, which is still a topic of open debate (Hu, 2016; Peters et al., 2021), given serotonin's relations with dopamine, its involvement in impulsive behavior, and the evidence suggesting its goes through changes during adolescence (Gross-Isseroff et al., 1990), it is likely that serotonin is an important player in adolescent behavior, both through and beyond its effects on dopamine function, which merits a review of its own.

To complicate matters further, both dopaminergic and serotonergic neurons are affected by other neuromodulators, such as the endocannabinoids – and not only that, both dopaminergic and serotonergic neurons can also release endocannabinoids, which act on their inputs through retrograde signaling (Peters et al., 2021). There is also evidence that the endocannabinoid system affects dopamine responses during reinforcement learning (Peters et al., 2021). It is of note that the issue of corelease is actually a general problem, as neurons commonly release multiple neurotransmitters and modulators. For example, both dopaminergic and serotonergic neurons can also release glutamate and gamma-aminobutyric acid (GABA), so it can be difficult to know which chemical is doing what when assessing their functions (Hu, 2016).

Other neuromodulators are also implicated in some of the functions which change during adolescent development and that are associated with dopamine. For instance, acetylcholine has been implicated in attention modulation and memory (Dayan, 2012; Avery and Krichmar, 2017), and both acetylcholine and norepinephrine are thought to play a role in decision under uncertainty,

coding for expected and unexpected uncertainty about cues during decision-making, respectively (Yu and Dayan, 2005; Dayan, 2012; Avery and Krichmar, 2017). Additionally, norepinephrine from the locus coeruleus has been implicated in participating in the computations underlying the trade-off between exploration and exploitation (Avery and Krichmar, 2017).

This was just a very brief overview of some of the interactions between dopamine and other neuromodulator systems that are likely to be involved in adolescent maturation and behavior. We barely scratched the surface of this subject, and there is still a lot of work to be done to understand how different neuromodulator systems interact, and how this changes during the course of development. Still, the message is clear: if we want to understand the cognitive and behavioral implications of developmental changes in the dopaminergic system during adolescence, we have to consider these other neuromodulator systems as well.

What are we trying to explain? A note on “typical” adolescent behavior

We would like to conclude with a few words about what is considered “typical” adolescent (impulsive) behavior. As noted at the beginning of this paper, changes in dopamine pathways are frequently invoked to explain some particular aspects of how adolescents act, including in respect of elevated impulsivity/recklessness due to higher sensation-seeking, combined with an immature capacity to self-regulate behavior, reflecting the developmental imbalance between the hot (reward-related) and cool (control-related) systems. However, there are some significant issues that make this premise somewhat inaccurate.

While it is common to interpret adolescent behaviors that put them at risk and that involve heightened sensitivity to rewards/sensation-seeking (e.g., alcohol and drug use or having sex) as stemming from self-regulation failures, this view ignores important psychosocial aspects of

adolescence. What is missing in this view is a better understanding of the different factors that explain and contextualize risk behaviors, such as the extent to which adolescents are aware of the severity of the risks inherent to their behavior, and to what extent they engage in certain activities in spite of the risks or because of the risks (Do et al., 2020; Jessor, 2018). Adolescents may be unaware the real risks of a given behavior, or they may underestimate those risks, either because they do not take warnings seriously or because they have a distorted perception of themselves as being immune to such risks. They may even regard the risks as ambiguous, which could lead to risk behaviors even in the absence of sensation-seeking or reward sensitivity, simply due to exploratory tendencies under uncertainty at this age (Blankenstein et al., 2021). Of course, the risk associated with a given activity may itself be seen as a reward – it may be exciting and pleasurable – and thus adolescents may engage in such behaviors consciously and deliberately. Note that in most of these cases risk-taking does not necessarily follow from failures of self-regulation, which would imply that adolescents knew the risks involved in their behavior, wanted to avoid those risks, but were unable to restrain themselves or acted without thinking. Thus, to actually determine if a risk behavior was the product of a self-regulation failure, we would have to inquire about the adolescents' own views about their behavior, not just the occurrence/frequency a certain behaviors labeled as risky, something that is not usually done (Defoe et al., 2022).

Additionally, the literature often assumes that risk taking is more common in adolescents than in adults. However, research shows that, in fact, real-life health risks, such as drinking, smoking, drug use and unsafe sex, which are often assumed to occur more often during adolescence, actually peak in the third decade of life (Peeters et al., 2019; Duell et al., 2018 Willoughby et al., 2021). This can be explained to some extent by the lower opportunities adolescents have of taking these types of risk due to higher adult supervision; however, it is also likely that our perceptions about these risk behaviors are distorted by the frequent use of double-standards when judging what constitutes “risk” for adolescents and adults. For instance, it is

undeniable that drinking involves risks, but so does driving, at any age, considering the high probability of being involved in traffic accidents (Jessor, 2018). Nonetheless, adults who drive or who drink are not regarded as risk-takers (unless, of course, they do both at the same time). Granted, drinking is indeed riskier for adolescents than for adults given that their brain is still under development, with significant levels of plasticity associated with neurogenesis and synaptogenesis, pruning, and myelination (Fuhrmann et al. 2015; Whitaker et al., 2016; Foulkes and Blakemore, 2018). However, brain development has not yet ended in individuals regarded as young adults, when they are just over the legal age limits, especially regarding frontal regions that continue to mature well into at least the middle of the third decade of life (Foulkes and Blakemore, 2018). Moreover, other risks associated with drinking such as car accidents are also present at any age and it is unclear what defines the level of risk, or what kind of risk/benefit balance, is necessary to classify a behavior as risky. So the main issue stands. The same individual with the same drinking habits can be classified as a risk taker when s(he) is just below the legal age cutoff and a non-risk taker when just above this cutoff even though very little has changed in his(er) brain development and the cognitive processes underlying that behavior.

The available evidence using laboratory choice-making tasks also fails to unambiguously support a peak in general impulsive actions during adolescence (Defoe et al., 2015; Duell et al., 2018). Although some (but not all) laboratory tasks show a higher propensity for impulsive choices at the end of adolescence in many cultures, this seems to be modulated by context as there are significant differences across countries (Duell et al., 2018; Steinberg et al., 2017). However, it is difficult to reconcile these finding with the dual-system models, which propose that lower self-control should be expected in younger adolescents and not in late adolescence and early adulthood, given the protracted development of frontal brain areas. The mixed results reported in these studies may be caused, at least in part, by the behavioral measures used. Most of these laboratory-based studies on the development of “risk-taking” often lack a clear distinction between – or even create composite

scores of – measures of distinct, heterogeneous behaviors, such as deciding between alternatives with known outcomes, or making decisions about probabilistic outcomes, either when the probabilities of outcomes are known, or when such probabilities are uncertain. These different behaviors rely on different cognitive process underpinned by different brain region (Blakenstein et al., 2021), and a lack a clear distinctions between them makes the interpretation of study results unclear, making comparison between studies very problematic.

Another important issue is that sensation-seeking does not necessary reflect a lack of higher order cognitive control, and the two may even be negatively correlated (Romer et al., 2011; Romer et al., 2017; Maslowsky et al., 2019). For example, the motivation for choosing to engage in inherently risky but pleasurable activities, such as parachuting or experimenting with a new drug, can entail recruiting higher (and not lower) self-control abilities to override the natural tendency to avoid the possible negative consequences of our actions (see Do et al., 2020). Indeed, although deliberate, planned, reasoned risk-taking in adolescence seems to be positively correlated with sensation-seeking, it is also associated with higher levels of behavioral self-regulation in the form of better future orientation and the perception of possible benefits or advantages of taking certain risks (Maslowsky et al., 2019). Moreover, as noted above, the uncertainty inherent in the context of adolescence can lead to risk-taking as a consequence of exploratory behaviors even in the absence of sensation-seeking propensities or elevated reward sensitivity (Ciranka and van den Bos, 2021). In this context, it is no surprising to realize that not all risks taken by adolescents are bad (Duell and Steinberg, 2021), and that the strategy of taking deliberate risks may pay off in the longer term, allowing learning and future minimization of risks (Blankestien et al., 2021).

This is not to say that adolescents are not vulnerable to acting without thinking. It seems that they often do make non-deliberate decisions (Maslowsky et al., 2019). The point is that sensation-seeking is not always inversely related with lack of self-control, nor are sensation-seeking effects on

risk-taking restricted to adolescence. To illustrate this point further, although greater reward-seeking has been shown to be positively related with higher risk-taking, it was found that this association did not change with age or differ across different levels of self-regulation abilities in 10 to 30-year-olds from many cultures (Duell et al., 2016). Moreover, there is significant individual variability in the association between sensation-seeking and acting without thinking, contrary to expectations from the dual systems models. In fact, sensation-seeking may lead to risk-taking behaviors only when combined with poor impulse control (Icenogle and Cauffman, 2021). Taken together, the findings described in this section indicate an urgent need for a better characterization of what constitutes “typical rash adolescent behavior” and in which circumstances it is expressed. Only then will it be possible to determine whether, and to what extent, changes in dopamine at this age are related to behavioral maturation.

As a final note, this whole discussion on adolescent behavior highlights the need to reconsider the relationship between risk-taking and self-regulation. Discussions on risk-taking hinge, either tacitly or explicitly, on the notion of (failures of) self-regulation, but often it is not clear when it is appropriate to say that an individual did what s/he wanted and chose to do, and when s/he failed to self-regulate. This is particularly problematic when using questionnaires that focus on the mere occurrence/frequency of behaviors considered risky. But while metacognitive approaches, inquiring about adolescents reasons to make certain choices, can help us distinguish between motivations for different behaviors (Defoe et al., 2022), there are still cases in which it is unclear whether a risky behavior was due to a failure of self-regulation, especially because failing to self-regulate is an imprecise concept. For example, if an adolescent knows the risks involved in a certain behavior, has an appropriate perception of their severity – to the point of even regretting the action later on – and with all this in mind still performs the behavior, is this a failure of self-regulation or simply a bad, but deliberate, decision? After all, there were certainly reasons for doing whatever the adolescent did. People do not really do what they don’t want to do at all. What usually happens is that there are

reasons for doing something (say, to consume alcohol, use a drug, or have unprotected sex) while at same time there are reasons for not doing so. People may well have all these reasons in mind and still make an objectively bad decision. This is, in fact, a deep philosophical issue, recognized not only in the literature on self-regulation (e.g., Baumeister and Heatherton, 1996) but also in the very old debate about the nature and meaning of free will. There are no definite answer for this issue, and we will not further discuss these elusive questions here. We refer the reader to the excellent discussions of free will and self-regulation failures in Frankfurt (1971) and Baumeister and Heatherton (1996). The main point that we wish to stress is that the stance one adopts on these issues may have significant implications in respect of how adolescent behavior is considered and, consequently, on how the significance of the changes in the dopaminergic system during this age is understood.

Conclusion

Structural and functional changes in dopamine pathways during adolescence are commonly assumed to underlie typical adolescent reckless behavior. However, the link between dopamine and these behaviors is often based on oversimplified notions about the function of dopamine in increasing reward sensitivity and sensation-seeking, combined with misconceptions about how risk-prone adolescents actually are, and what is the best way of measuring this in real-life and laboratory settings. Recent (and not so recent) theories suggest a more nuanced view of the role of dopamine as a neuromodulator mostly involved in prediction error detection, learning, and signaling the value of exerting effort. This perspective suggests that observed increases in dopamine signaling are, in part, explained as a response to elevated uncertainty during adolescence, a time of life marked by less experience about the best courses of action compared to adulthood. In this view, there is no

clear separation of valuation systems and control systems necessary for behavioral self-regulation, as dopamine signals dynamically contribute to both these types of abilities.

Although we discussed a variety of different theories and models pertaining to dopamine and behavior in adolescence in this short review, it is unknown how they relate to one another, that is, whether they explain different aspects of dopaminergic influences on behavior or are mutually exclusive. To deepen our understanding, a great deal of work is required to untangle, organize, and compare these different theoretical perspectives and to reexamine the adequacy of the tools that have been used in the literature to measure behavior in adolescence. Future studies must also strive to relate dopamine changes to that of other neurotransmitter systems during this phase of life. The role of maturational changes in different dopamine receptors and the possible effect of sex have also received scant attention and must be further explored. The potential results of future work, both in terms of new experiments and in terms of analysis and synthesis of existing information on these issues, hold great promise to deepen our understanding of how the dopamine system relates to behavior during development. At this point, only one thing is clear: there are more things in the role of dopamine in adolescent behavior than are dreamt of in our current models.

Acknowledgments

This work was supported by the São Paulo Research Foundation (FAPESP: # 2016/14750-0, and 2019/11706-8), the Coordination for the Improvement of Higher Education Personnel (CAPES: finance code 001), the Research Incentive Fund Association (AFIP), and the Brazilian National Council for Scientific and Technological Development (CNPq: #301899/2019-3).

Declarations of interest: none.

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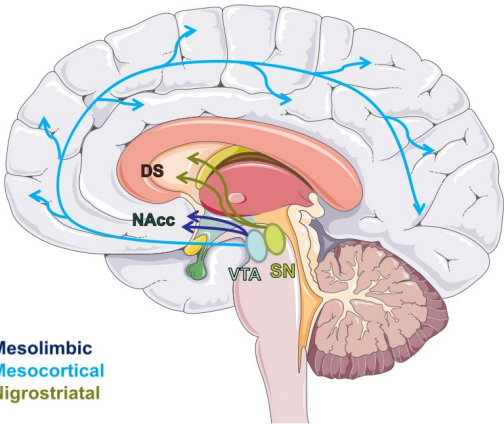
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Figure 1. A) Illustration of the mesolimbic, mesocortical, and nigrostriatal pathways. **B)** Schematic illustration of some of the brain regions connected with the midbrain dopamine regions. Abbreviations: VTA, ventral tegmental area; SN, substantia nigra; DS, dorsal striatum; NAcc, nucleus accumbens; PAG, pariaqueductal grey. Parts of the figure were drawn using pictures from Servier Medical Art, licensed under a Creative Commons Attribution 3.0 Unported License (<https://creativecommons.org/licenses/by/3.0/>). Aspects of the figure design were adapted from Costa and Schoenbaum (2022).

A

Pathways: **Mesolimbic**
Mesocortical
Nigrostriatal

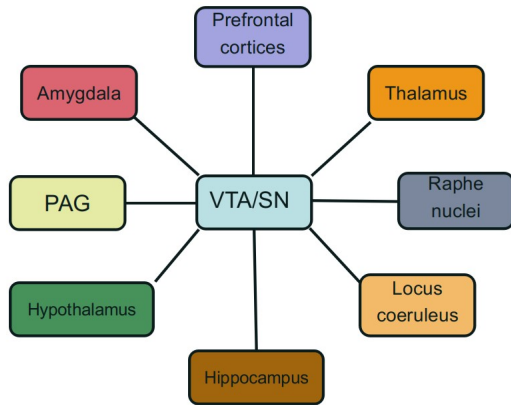
B

Table 1

A (simplified) summary of dopamine functions discussed in the review

Processes affected by dopamine	Role of dopamine
Reward processing	Phasic dopamine signals reward prediction errors that can be used to learn the value associated with different contexts, behaviors, and their possible combinations.
Learning	Related to the process above, dopamine is implicated in both model-free and model-based reinforcement learning.
Motivation	Tonic dopamine influences behavioral activation, possibly by signaling the value of working for a given reward.
Decision under risk/uncertainty and exploration	Dopamine affects decision-making through a combination of all its effects above; moreover, it affects exploratory behaviors in situations with ambiguous outcomes as a consequence of its representation of uncertainty.
Other processes briefly discussed – Working memory, general prediction errors, and precision coding	Dopamine stabilizes PFC representations believed to be neural substrates for working memory; dopamine may represent general prediction errors and/or code for precision of sensorimotor representation, possibly playing a role in various computations in the brain involved in different cognitive/behavioral processes.
