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Dopamine ups and downs in vulnerability to addictions: a neurodevelopmental model

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Addictions are commonly presaged by problems in childhood and adolescence. For many individuals this starts with the early expression of impulsive risk-taking, social gregariousness, and oppositional behaviors. Here we propose that these early diverse manifestations reflect a heightened ability of emotionally salient stimuli to activate dopamine pathways that foster behavioral approach. If substance use is initiated, these at-risk youth can also develop heightened responses to drug-paired cues. Through conditioning and drug-induced sensitization, these effects strengthen and accumulate, leading to responses that exceed those elicited by other rewards. At the same time, cues not paired with drug become associated with comparatively lower dopamine release, accentuating further the difference between drug and non-drug rewards. Together, these enhancing and inhibiting processes steer a pre-existing vulnerability toward a disproportionate concern for drugs and drug-related stimuli. Implications for prevention and treatment are discussed.

An integrative neurodevelopmental model of substance use disorders

Drug addiction is the most prevalent neuropsychiatric disorder affecting society today. The social, medical, and economic costs are enormous, with drug use contributing to 12% of deaths worldwide [1] and costing the US government alone an estimated $400 billion per year [2–4].

Because only a minority of people who try drugs of abuse develop a substance use disorder (SUD), attempts have been made to identify predisposing neurobiological features. One long considered hypothesis is that increased susceptibility reflects pre-existing perturbations in the mesolimbic dopamine system [5]. Still debated, however, is whether this perturbation ultimately expresses itself as a decrease in dopamine activity, as in opponent process and reward deficiency models [6,7], or heightened dopamine activity, as in incentive sensitization models [8,9]. The present neurodevelopmental model integrates each of these features. It recognizes a role for both hypoactivity and hyperactivity in mesolimbic dopamine systems, and outlines how each might become particularly pronounced in individuals at risk.

As summarized below, converging evidence from studies in human adolescents, young adults, and laboratory animals suggests that youth exhibiting heightened dopamine responses to emotionally intense stimuli are at increased susceptibility to engage in a wide range of impulsive, reward-seeking behaviors. Although these behaviors may initially target diverse non-drug stimuli, the initiation of drug use steers the heightened dopamine reactivity toward drug-related cues, leading to drug conditioning and sensitization. These effects further enhance brain dopamine responses to the drugs and drug-paired cues, thereby augmenting the attentional focus of at-risk individuals on these stimuli and obtaining the drug. Because non-drug paired cues simultaneously become associated with comparatively lower dopamine responses, the overall result is a narrowed behavioral repertoire, setting the stage for progressively more frequent drug taking and a SUD.

This model represents a departure from single factor theories of drug abuse (Table 1). By incorporating both hypo-dopamine and hyper-dopamine activations, and combining this with identifiable predisposing factors, the present neurodevelopmental model provides a more comprehensive accounting of the addiction process. It is also, we propose, better positioned to inform the development of more effective therapeutic strategies.

Increased impulsive reward-seeking and dopamine responsivity prior to drug use

A recent series of adoption, twin, and longitudinal follow-up studies have supported a strikingly consistent conclusion: many SUDs reflect the outcome of an 'externalizing' trajectory characterized by risky thrill-seeking, social

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Table 1. Comparison of reward deficiency and incentive sensitization models of vulnerability to the integrative model proposed in this paper[a]

Feature	Opponent process/reward-deficiency	Incentive sensitization	Integrative neurodevelopmental model
Positive reinforcement	No	Yes	Yes
Negative reinforcement	Yes	No	No
Hyperactive incentive salience	No	Yes	Yes
Hypoactive incentive salience	Yes	No	Yes
Pre-existing susceptibility	Yes	Yes	Yes
Intervention strategies			
—Prevention	?	?	Yes
—Treat high dopamine responses	No	Yes	Yes
—Treat low dopamine responses	Yes	No	Yes
—Redirect attentional biases	No	Yes	Yes

[a]Two competing models of predisposing traits to addictions hypothesize increased versus decreased reward system responsiveness. Here we propose an integrative neurodevelopmental model that incorporates both features. In brief, high-risk individuals with externalizing traits initially express elevated incentive motivational and striatal dopamine responses to diverse emotionally salient events. Once substance use begins, these responses become increasingly focused on the drugs and drug-related cues. At the same time, cues paired with the absence of drug can come to inhibit dopamine release and associated motivational states. In this way, a pre-existing vulnerability is steered toward a disproportionate preference for drugs and drug-related stimuli, setting the stage for addictions. Positive reinforcement: increased probability that a behavior will be repeated due to presentation of a positive event. Negative reinforcement: increased probability that a behavior will be repeated due to the removal of an aversive event. Incentive salience: the property of a cue that renders it able to elicit approach and desire. Pre-existing susceptibility: vulnerability traits that pre-exist substance use. Prevention: interventions that can decrease the probability that vulnerable individuals will develop substance use problems.

gregariousness, and oppositional tendencies in childhood and adolescence [10–20]. The core processes underlying these predispositions are thought to include oversensitivity and undersensitivity to reward- and punishment-related cues, respectively [21–23]. For example, adolescents with high externalizing traits make risky choices, preferring high frequency rewards even when the losses are higher [24–26].

Marked individual differences in substance use are also seen in laboratory animals, and not all readily develop drug self-administration behaviors [27]. One of the best-described predictors of susceptibility to acquire drug self-administration is a greater tendency to explore novel environments [27–30]. Among those animals that acquire drug self-administration, only a subset will transition to compulsive use, as defined by willingness to work more for the drug, endure aversive events to obtain it, and persist in drug-seeking behavior for much longer than average [31,32]. These 'compulsive' drug-using rats are distinguished by high novelty preference and forms of impulsivity, such as premature responding to cues [33].

The behavioral traits that predict drug use behaviors co-vary with the tendency to engage with other rewarding stimuli and individual differences in dopamine cell responsiveness. In rats, high dopamine cell firing at baseline and release in response to diverse challenges predict greater novelty exploration [30,34], greater sugar feeding [30,35], more incentive learning [36], and the more rapid acquisition of drug self-administration [5,30,37–39]. The evidence is more than just correlational. Dopamine agonists increase premature responses during tests of impulsivity and a wide range of situation-dependent reward-seeking behaviors including drug seeking (Box 1 [8,9,40–49]).

In humans also, individual differences in externalizing behaviors may be related to differences in dopamine responsiveness. In young healthy adults, greater striatal dopamine responsiveness co-varies with novelty seeking [50,51] and other impulsivity-related traits [51–53]. In functional magnetic resonance imaging (fMRI) studies, similar associations are seen. The greater the striatal responses to monetary reward, the greater the tendency to risky behavior [54–56]. The greater the striatal response to monetary reward anticipation, the higher the positive affective response scores [57]. The greater the striatal response to cues paired with erotic images, the more likely these cues will be chosen 2 months later [58]. And the greater the striatal responses to images of food and sex, the greater the weight gain and sexual activity at follow-up 6 months later [59].

The above associations in humans are thought to reflect causal effects because manipulating dopamine transmission alters many of the same processes [60–62]. Lowered dopamine transmission disrupts corticostriatal functional connectivity [63], top-down regulation by the cortex, and the ability of reward-related cues to activate the striatum [64,65]. These neurophysiological effects are associated with a decreased behavioral tendency to preferentially respond to rewards [66,67], and a decreased willingness to sustain effort to obtain rewards, including alcohol [68], tobacco [69], and money [70]. Elevated dopamine function, in comparison, increases the ability of reward-related cues to guide behavioral choices [66], diminishes the ability to differentiate between high and low value rewards [71], and induces steeper temporal discounting, a form of impulsivity defined by preference for immediately available small rewards over larger, more distal ones [72]. In clinical populations, patients with schizophrenia – considered a

Box 1. Dopamine and reward

Animal studies indicate that risky, reward-seeking behaviors are potently influenced by dopamine. Different components of these behaviors can be anatomically dissected. The best studied is the willingness to approach and sustain effort to obtain a reward, behaviors that are closely influenced by dopamine transmission in the ventral striatum, amygdala, and anterior cingulate [8,9,40–45]. Dopamine also affects the tendency to prematurely respond to reward cues [46], reflecting effects in the striatum [47], the willingness to tolerate delay for a larger reward, reflecting effects in the amygdala and orbitofrontal cortex [43,44,48], and executive control engagement with the task, reflecting effects in the orbitofrontal cortex [48]. The weight of evidence suggests that dopamine is not closely related to pleasure [8,49].

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