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Journal Club

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Differential Dopamine Dynamics in Adolescents and Adults

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Review of McCane et al.

Why do adolescents have a high propensity to engage in maladaptive behaviors? One explanation is that the adolescent nervous system is still undergoing maturation, and incomplete development of key brain regions results in poor behavioral regulation. Notably, the prefrontal cortex (PFC), a region involved in motivated behavior and decision-making (Sturman and Moghaddam, 2011), exhibits delayed maturation in adolescents (Sowell et al., 2001). The dopamine system, which innervates the PFC and has an established role in reward learning and motivation (Flagel et al., 2011), is also incompletely developed in adolescents: evidence indicates that projections from midbrain dopamine neurons, as well as dopamine receptor expression, are in a high state of flux during adolescence (Rosenberg and Lewis, 1995; Naneix et al., 2012). Recent studies have also argued that alterations to PFC structure arise because of improper development of dopamine networks (Illiano et al., 2021), indicating a role for dopamine in cortical development. In contrast, limbic regions that mediate reward processing, such as the nucleus accumbens (NAc), develop earlier than cortical regions (Galvan et al., 2006). The NAc is also densely innervated by dopaminergic projections and has been implicated in adolescent vulnerability to impulse control disorders, including addiction (Chambers et al., 2003). These studies suggest that differing levels of maturation of dopamine networks in executive control and limbic regions may underlie adolescent impulsivity and demonstrate a need for further characterization of developmental changes in the dopamine system.

Dopamine is synthesized in two midbrain regions: the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc). VTA dopamine neurons densely innervate the NAc and comprise the mesolimbic system, while SNc dopamine neurons send projections to the dorsal striatum and comprise the nigrostriatal system (Farassat et al., 2019). Though the role of dopamine in reward processing is primarily associated with the mesolimbic system (Ikemoto and Panksepp, 1999), there is emerging evidence for nigrostriatal contributions. For example, recent evidence showed that nigrostriatal dopamine responds to rewarding cues (Coddington and Dudman, 2018). Furthermore, a role for the dorsal striatum has been implicated in the performance of an instrumental learning task in adolescents (Sturman and Moghaddam, 2012). Therefore, developmental changes in midbrain dopamine projections to the striatum may explain differences in the regulation of behavior and attribution of value to rewarding stimuli in adolescents and adults.

In a recent issue of *The Journal of Neuroscience*, McCane et al. (2021) used single-unit electrode recordings to examine how midbrain dopamine neurons respond to the presentation of reward in both adult and adolescent rats. To assess reward processing and learning, the authors made use of two distinct forms of associative learning: pavlovian and operant conditioning. The decision to use two separate paradigms is important. In pavlovian conditioning, the presentation of a sensory cue predicts the delivery of subsequent reward without any further action required of the animal, while in operant conditioning, correct execution of a specific behavior in response to the presentation of the cue is required for reward delivery. The critical distinction for this study is that operant conditioning requires direct behavioral engagement. Importantly, in both forms of learning, the same reward was delivered; therefore, any differences in the response of midbrain dopamine neurons could be attributed to the added volitional aspect in the instrumental task, rather than to the reward itself.

The most notable finding by McCane et al. (2021) was that dopamine neurons responded differently to reward delivery in adults versus adolescents. In adult rats, the VTA and SNc had comparable reward-dependent increases in dopamine neuron firing rates within the respective conditioning paradigms. In adolescents, increases in VTA and SNc dopamine neuron firing in response to pavlovian reward were even greater than in adults, whereas there was little change in firing rate in either region in response to the operant reward (McCane et al., 2021, their Figs. 3, 4). These results suggest that adolescents attribute higher value to rewards administered in the absence of action. Critically,

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these results were not because of differences in learning rates (McCane et al., 2021, their Fig. 1), or in intrinsic characteristics of the dopamine system, such as baseline firing rate, number of dopamine cells, and cell volume (McCane et al., 2021, their Fig. 2). This suggests that any differences in dopamine neuron activity in response to reward are likely because of age-dependent differences in the network properties of these neurons. However, while there were no age-specific differences in overall learning rate, adolescents did show an increased latency to nose poke in the operant task (McCane et al., 2021, their Fig. 1*B*). This is consistent with the decreased firing rates seen in operant responding: adolescents may experience decreased motivation to work for effort-based reward, and this is reflected in decreased dopamine activity. Furthermore, in adolescents, there was a significantly larger response observed in the SNc relative to the VTA following pavlovian reward (McCane et al., 2021, their Fig. 5). Increased activity in the SNc of adolescents supports the existence of a previously proposed nigrostriatal bias (Sturman and Moghaddam, 2012), in which adolescents preferentially signal through SNc dopamine neurons as opposed to engaging the mesolimbic dopamine system.

Because age-dependent response patterns were incumbent on the manner in which rewards were obtained and there were no discernable differences in the intrinsic properties of adult and adolescent dopamine neurons, McCane et al. (2021) next investigated whether there were changes to dopamine network dynamics that could underlie these findings. To test this, spike correlation ratios were calculated in VTA and SNc dopamine neurons, respectively, during pavlovian and operant conditioning. In both behavioral paradigms, adolescents exhibited greater degrees of correlation, indicating more homogeneous population dynamics (McCane et al., 2021, their Fig. 6). While this finding does not necessarily implicate correlated neural activity in the differences in dopamine response to reward, it does more broadly characterize the state of adolescent dopamine networks. As the dopamine network matures, inhibitory feedback loops form (Rahman and McBride, 2001) and may contribute to decreased spike correlations and more tightly regulated behaviors in adults. Consistent with previous studies demonstrating that dopamine circuitry undergoes rapid changes during adolescence, McCane et al. (2021) find that dopamine release in the NAc was markedly decreased following VTA stimulation [McCane et al., 2021, their Fig. 7; see also lower VTA firing rates in adolescents (McCane et al., 2021, their Fig. 5)]. These findings suggest that while reward centers in adolescents are active and can drive motivated behaviors, delayed maturation of dopamine circuits may result in poor behavioral regulation and increased impulsivity in adolescents.

Observations made by McCane et al. (2021) may also help to reconcile discrepancies in how adolescents ascribe motivational value to reward-predicting cues. Some animals view the cue as a predictor and interact with the region where the reward is delivered, known as “goal tracking.” Others ascribe higher motivational value to and interact more with the cues themselves, termed “sign tracking.” Sign trackers have been shown to exhibit increased impulsivity and susceptibility to addiction (Lovic et al., 2011), and recent studies have argued for a role of the dorsal striatum in impulsivity (Kim and Im, 2019). Given that adolescents exhibit a nigrostriatal bias (McCane et al., 2021, their Fig. 5), high degrees of impulsivity (Romer, 2010), and vulnerability to addiction, it begs the question: do adolescents engage in more sign-tracking behavior than adults? Surprisingly, this is not the case, with recent studies showing that adolescent rats actually engage more in goal-tracking behaviors relative to young adults (Rode et al., 2020). McCane et al. (2021) provide some evidence as to why this may be the case. First, the lack of dopamine neuron activity in response to reward delivered in an operant paradigm supports the finding that adolescents tend toward goal-tracking behaviors; if adolescents tended toward sign tracking, we might expect increases in dopamine neuron firing rates around operant responses (Sokolowski et al., 1998), which was not seen. Second, as dopamine release in the NAc has been shown to be necessary in sign-tracking behavior (Flagel et al., 2011), the current finding that dopamine release in the NAc following VTA stimulation is decreased in adolescents may further explain the adolescent propensity to goal tracking. However, determining the functional implications of the adolescent nigrostriatal bias and the role of dorsal striatum in reward and motivational value more broadly remain relevant areas of investigation.

In conclusion, the results of McCane et al. (2021) help to build a more coherent framework for how differences in neural activity in adults and adolescents lead to differences in behavior. This study also raises a number of important questions about changes in the dopamine system across maturation, such as the following. What are the precise dopamine release dynamics around rewarding stimuli in adolescents? Does the dopamine system play an age-dependent role in mediating responses to aversive stimuli? Future studies can leverage state-of-the-art tools such as transgenic rodent models and *in vivo* fluorescence-based dopamine sensors (Patriarchi et al., 2018) to further build toward an understanding of how the developmental trajectory of dopamine neural networks regulates animal behavior.

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