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Is it worth the effort?:

Individual variation in dopamine affects the weighting of benefits relative to costs

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Before undertaking any task, humans implicitly determine whether reaching the goal is worth the effort. Weighing costs and benefits is a fundamental brain function that often occurs unconsciously, allowing for the adaptive use of resources to attain goals. The neurotransmitter dopamine is a key player in this process (1). On page 1362 of this issue, Westbrook *et al.* (2) clarify the role of dopamine by showing that increasing an otherwise weak dopamine signal shifts attention toward the rewarding outcome, resulting in greater readiness to perform cognitive effort to reach the goal. As such, increasing dopamine appears to be beneficial specifically for those individuals with relatively lower dopamine function. This finding may explain the efficacy of dopamine-enhancing medications such as Ritalin (methylphenidate), which is prescribed to treat attention deficit hyperactivity disorder (ADHD) and has been used without a prescription by students as a “study enhancing drug.”

Dopamine is found throughout the brain in several neurobiological pathways that mediate processes including movement, reward, and cognitive functions such as learning and working memory (3). Given the range of functions influenced by dopamine, there is a need to better understand how dopamine within distinct brain regions affects nuanced elements of cognition and behavior. For example, Westbrook *et al.* expand on the finding that a blunted dopamine signal can result in cognitive dysfunction (4). Specifically, they show that the willingness to expend cognitive effort is diminished in those with lower dopamine function in the caudate nucleus, a portion of the brain involved in goal-motivated behavior (5). This finding blends two known roles of dopamine—motivation and cognition—by indicating that goal-related attention drives the motivation to engage cognitive resources.

Westbrook *et al.* also show that a blunted willingness to expend cognitive effort can be increased by pharmacologically enhancing the dopamine signal using the dopamine agonist methylphenidate. This is consistent with prior findings that dopamine enhancement leads to increased willingness to expend effort in patient populations who have disorders with an underlying dopamine deficit, such as ADHD and Parkinson’s disease (6, 7). Thus, dopamine-enhancing medications may not improve cognitive ability per se, but drive the willingness to expend cognitive effort (8).

More precisely, this greater willingness to expend effort occurs because dopamine-enhancing medications raise the salience of, and attention to, goal-related stimuli that would

otherwise evoke a response too weak to warrant the expenditure of cognitive effort (8). Methylphenidate and similar drugs therefore enhance this aspect of cognition specifically for individuals with relatively lower dopamine function in the caudate nucleus. This indicates that individual variation in dopamine function matters, both for explaining differences in cognitive function across healthy individuals, and also for treatment efficacy. Such reduced dopamine function may render healthy individuals more prone to illicitly use methylphenidate as a study drug. Similarly, those with ADHD who have lower caudate dopamine function are likely to have enhanced efficacy from this treatment (see the figure).

Unfortunately, the effects of dopamine on cost-benefit weighting do not discriminate on the basis of the longer-term repercussions of reaching the goal. For example, methylphenidate also increases the dopamine signal in response to drug-related stimuli in those with a substance use disorder (9), which in the context of the findings of Westbrook *et al.* will enhance the willingness to expend effort to attain the drug-related goal. Even without methylphenidate's facilitatory effects, dopamine plays a key role in substance use disorders, as all abused substances enhance dopamine release (10). After repeated drug use, environmental stimuli associated with drug abuse also evoke dopamine release in regions that include the caudate nucleus (11), the same brain region shown by Westbrook *et al.* to be linked with the motivation to expend cognitive effort. These drug-associated stimuli can then drive the strong desire to acquire the drug of abuse, contributing to relapse even when individuals are trying to abstain (12). Variation in dopamine function plays a role in this example as well. Specifically, drug-associated stimuli evoke more activation in reward-related brain regions such as the striatum and prefrontal cortex, in individuals with a genetic variation in the gene encoding the dopamine transporter (DAT) that results in slower clearance of dopamine and an amplification of the dopamine signal (13).

Determining whether a goal is "worth the effort" is just one aspect of goal-related decision-making. Such decisions are made through the integration of information processed by the striatum, including the caudate nucleus, and other brain regions like the frontal cortex, which allows for learned experiences and potential future consequences to also shape goal-related behavior (3). The influence of dopamine within these frontal brain regions is not straightforward but depends on the relative balance of D1- and D2-like dopamine receptors (14). These receptors act like a lock into which dopamine fits, and their activation results in the propagation of the dopamine signal. This points out that the "dopamine signal" is not only driven by dopamine synthesis, as was measured by Westbrook *et al.*, but also involves the activation of specific receptor subtypes. Next steps should integrate these findings to explain how dopamine synthesis and receptor function across brain regions work together to affect cognition and behavior. Such findings will create a clearer understanding of cognitive function and psychiatric diseases such as ADHD and substance use disorders.

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Caudate dopamine affects the weight of benefits

Individual differences in dopamine function in the caudate nucleus relate to one's willingness to expend cognitive effort, which can be influenced both by medications and drugs of abuse that enhance the dopamine signal.

Drugs of abuse increase caudate dopamine and reduce the perception of effort to acquire them.