COMMENTARY

Between Abstinence and Dependency: Understanding the Brain and Behavioral Correlates of Reward Learning in Occasional Stimulant Users

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When young adults leave home to pursue a career or higher education, they face a variety of new challenges. New ways of thinking and working, along with obligatory time constraints, make focus and a good work ethic essential to thrive. In today's culture, some young adults resort to using prescription stimulants at moments when particular attentiveness is required. For instance, a majority of university students that illegally use prescription stimulants report doing so to stay awake and focus while studying (1). The perceived effectiveness of these stimulants along with their commonplace nature may lead some individuals to become occasional stimulant users (OSUs). However, this infrequent usage may also lead to more regular consumption and risk of developing stimulant dependency in the future. An important issue, then, becomes whether specific characteristics of OSUs serve as precursors to stimulant dependency.

Stimulant-dependent individuals have well-characterized decision-making deficits that are related to difficulties in learning and adapting to reinforcement-based contingencies (2). For instance, there is a tendency of stimulant-dependent individuals to favor decisions resulting in immediate as opposed to delayed rewards, even if these outcomes are maladaptive in the long run (3); and to exhibit difficulty in flexibly adapting to reversal of contingencies wherein responses toward a particular stimulus are required for reward receipt (4). These decision-making patterns can be maladaptive because the consideration of long-term outcomes and the knowledge of one's current environmental state are important for maximizing rewards. Co-occurring with these behavioral irregularities are abnormalities in the neural signature of reward processing and decision making. In healthy control populations, regions of the brain that are involved in reward learning, such as the inferior frontal gyrus (IFG) and dorsal striatum, are active early on during learning, when the consequences of various options in a response set are being learned. However as learning takes place over time, and better discrimination among potential options occurs, activation in these regions during outcome processing is attenuated (5). In contrast, stimulant-dependent individuals show aberrant, increased activation in the dorsal striatum and IFG, along with the insula, which also aids in the decision making process (6), during experimental decision-making tasks (7–9). Although these deficits are well characterized in stimulant dependency, it is unclear when exactly they manifest in particular individuals. That is, when do OSUs begin to show changes in the neural signature of reward learning and decision making that mirror deficits in stimulant-dependent individuals, and how does this reflect the transition from occasional use to dependency? These are the fundamental questions addressed in new research by Stewart *et al.* (10), who examined the behavioral and neural manifestation of decision making in OSUs during a reward learning task.

Stewart *et al.* (10) recruited a group of young adult OSUs (that is, nondependent individuals who had used either cocaine or prescription stimulants more than twice within the previous 6 months) from local universities and the surrounding community. After abstaining from substance use for at least 72 hours, these participants played against the computer in a game of rock-paper-scissors while undergoing functional magnetic resonance imaging. The rules from the classic childhood game prevailed (i.e., paper beats rock, scissors beats paper, rock beats scissors), and participants won or lost points, depending on the outcome of each round. A monetary incentive was added, as a net positive amount of points translated into extra payment for participants. In each block, there was a preferred response that would lead to a win 90% of the time, whereas the other responses were associated with 50% and 10% chances of winning, respectively. Thus, it was beneficial to participants to learn the preferred response in each block. The authors speculated that during the decision-making phase of late experimental trials, when response-outcome contingencies would be fully learned in controls, OSUs would show poor behavioral performance along with sustained activation in brain regions that generally show decreased activation over time with successful learning.

Replicating previous findings, the authors identified several regions associated with reward learning and decision making, including the dorsal striatum, inferior frontal gyrus, and insula (5,6), that showed decreased activation over time in control subjects. In contrast, these same regions showed sustained activation during learning, from early to late trials, in OSUs. The pattern of activation in these brain regions did not differ between the two groups during early trials, but all three regions showed greater activation in OSUs as compared with controls during late trials. Interestingly, behavioral learning rates did not differ between OSUs and controls overall. That is, the probability of choosing the preferred response in each block increased over time, following a nearly identical pattern in both groups. One interpretation put forth by the authors was that compared with controls, OSUs require additional neural resources (in the form of sustained activation in the identified neural circuitry) to maintain learned response-outcome contingencies.

The work of Stewart *et al.* (10) taps into a crucial transitional period between abstinence and substance abuse and raises thought-provoking questions for future investigations. For instance, one particular issue that remains is discerning if potential indicators exist that make certain individuals more vulnerable to developing drug dependencies than others. Research aimed at characterizing such individual differences would benefit from probing how decision-making deficits present in OSUs combine with other environmental and genetic factors to facilitate stimulus dependency. Additionally, longitudinal research tracking OSUs over time would be beneficial for understanding whether individual differences in the decision making of OSUs can predict future stimulant dependence. More specifically, do differences in the level of activation in brain regions identified by Stewart *et al.* (10) during

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reward learning correlate with later dependency for some individuals but not others? And if so, what other characteristics distinguish such individuals?

Exciting potential approaches for investigating the aforementioned questions in future research include application of reinforcement learning models and complex decision-making tasks that more closely model real-world choices (6). Although the work of Stewart *et al.* (10) shows striking deficits in the ability of OSUs to conserve neural resources during decision-making processes, these results were based on decisions that simply involved choosing among reinforced response-outcome contingencies. Using more complex contingencies (e.g., varying the uncertainty or temporal delay to reward) as well as using refined reinforcement learning models that capture expectations and predictions of individuals would provide fine-tuned measures of behavior that better characterize decision-making deficits in OSUs. Additionally, these measures may reveal potential behavioral differences between OSUs and controls that are currently not observed (10).

Another interesting finding from Stewart *et al.* (10) involved a breakdown of differences in the type of stimulant being used. More specifically, OSUs who preferred cocaine over prescription stimulants showed even greater activation in the insula and IFG during late experimental trials than did OSUs who preferred prescription stimulants. Additionally, a subset of OSUs who also frequently used marijuana in addition to other stimulants showed greater activation in insula, IFG, and dorsal striatum during late trials compared with OSUs who reported low levels of marijuana use (the latter group did not differ from controls). Given these differences, it will be important for future research to try and understand whether the effects of certain stimulants as compared with others lead to greater decision-making dysfunction and whether the occasional use of multiple drugs compounds the negative consequences of single drug use.

Understanding the time course of and mechanisms by which drug dependency develops is a chief concern of addiction research. Stewart *et al.* (10) make an important contribution to this domain by examining the brain and behavioral correlates of reward-based decision making during the relatively overlooked intermediary step of occasional drug use. Specifically, their findings suggest that some of the negative consequences of stimulant use on neural circuits of reward learning and decision making manifest prior to dependence. This research nicely sets up future investigations aimed at further characterization of behavioral and neural indicators that mark the transition from OSU to stimulant dependency.

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