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On Cue: Striatal Ups and Downs in Addictions

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To the Editor:

Two recent papers report that problem gamblers exhibit altered striatal responses to cues that predict monetary reward, as compared with healthy controls. Significantly, however, in one study the activation was increased (1), whereas in the other it was decreased (2). We propose that this discrepancy could result from the fact that different types of cues were used. In the study by van Holst *et al.* (1), the cues were images of familiar playing cards. In comparison, Balodis *et al.* (2) used cues that consisted of text. One interpretation of these divergent results could be that in individuals with reward-seeking disturbances incentive processes become pathologically tied to a narrow set of stimuli. When the relevant cues are present, striatal activation is greater; when the cues are absent, it is blunted. Both changes are likely to be important.

In support of this interpretation, a review of the literature indicates that augmented striatal activation is observed consistently when familiar addiction-related cues are present. For example, in positron emission tomography (PET) [^{11}C]raclopride studies, increased striatal dopamine responses have been observed to the following: 1) alcohol ingested by subjects at risk for alcoholism (3); 2) food stimuli in binge eaters (4); 3) a realistic gambling task in patients with severe pathological gambling (5); 4) familiar gambling cues plus L-3,4-dihydroxyphenylalanine (L-DOPA) in patients with comorbid Parkinson's disease and pathological gambling (6); 5) L-DOPA medication in Parkinson's patients exhibiting various impulse control problems (7,8); and 6) the undisguised administration of *d*-amphetamine pills to gamblers (9).

Functional magnetic resonance imaging studies also indicate that, compared with healthy controls, augmented striatal activation occurs in response to the following: 1) alcohol cues in heavy social drinkers (10)[1] and abstinent alcoholics (11–14); 2) playing cards associated with monetary reward in problem gamblers (1); 3) the prospect of reward in high sensation-seeking adolescents (15) and subjects at a familial risk for alcoholism (16,17,18); 4) the Iowa Gambling Task in subjects at familial risk for alcoholism (19); and 5) the receipt of monetary reward in subjects with varying substance use disorders (20). Of note, these augmented responses might aggravate the clinical picture. For example, pathological gamblers who show a greater striatal dopamine release have higher clinical severity scores

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[1]In a large study of heavy drinkers (n = 326), the greater the severity of alcohol use problems, the greater the alcohol cue-induced striatal activation (43).

(5), greater difficulty restraining from gambling (9), and poorer performance scores on the Iowa Gambling Task (21,22).

In striking contrast to the above-mentioned findings, studies that tested subjects in the absence of addiction-related cues have found the opposite effects. Blunted striatal dopamine responses have been observed to stimulant drug challenges administered without drug cues in subjects at ultrahigh risk for substance use disorders (23), in patients with bulimia nervosa (24), and in those with current drug (25–28) and alcohol addictions (29,30).[2] Again, these findings are paralleled by functional magnetic resonance imaging data. Blunted striatal activation occurred in response to the following: 1) pictures of food (31) and intravenous ethanol in heavy drinkers (32); 2) unfamiliar or otherwise neutral monetary reward cues in adolescent smokers (33), detoxified alcoholics (13,34) (cf [20]), subjects at risk for substance use disorders (16,35,36), and pathological gamblers (2,37) (cf [38,39]); and 3) the Balloon Analog Risk Task in patients with Parkinson's disease and comorbid impulse control problems (40).[3]

Together these findings raise the possibility that the striatal translation of motivation to action is dependent on the cues presented. When familiar addiction-related cues are present, striatal activation is augmented; in their absence, it is not (41,42). Individuals who are especially sensitive to these cue-mediated effects might be particularly prone to addictions.

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[2]The lower responses seen in subjects with a long history of severe substance abuse have been proposed to reflect multiple factors, including toxic drug effects and preexisting vulnerability traits. Whether the presence vs. absence of drug-related cues contributes to the blunted responses in these individuals will require further investigation.

[3]In healthy subjects (individuals whose appetitive urges are not pathologically tied to a particular set of stimuli), tasks such as the Balloon Analog Risk Task and the Monetary Incentive Delay are thought to be good tests of representative responses to rewards. In gamblers or others with addictions or impulse control disorders, though, the cues in these tasks might become less salient and less able to activate the striatum. This progressive narrowing of stimuli that can potently activate the striatum might account for a wide range of motivational perturbations (41,42).

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