Elevated Reward Region Responsivity Predicts Future Substance Use Onset But Not Overweight/Obesity Onset

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Background: We tested the hypotheses that adolescents who show elevated reward region responsivity are at increased risk for initial onset of overweight/obesity and substance use, which is important because there have been no such prospective tests of the reward surfeit model of these motivated behaviors.

Methods: One hundred sixty-two adolescents (mean age = 15.3 ± 1.06 years) with healthy weights (mean body mass index = 20.8 ± 1.90) completed functional magnetic resonance imaging paradigms that assessed neural activation in response to receipt and anticipated receipt of palatable food and monetary reward; body fat and substance use were assessed at baseline and 1-year follow-up.

Results: Elevated caudate ($r = .31$, $p < .001$) and putamen ($r = .28$, $p < .001$) response to monetary reward predicted substance use onset over 1-year follow-up, but reward circuitry responsivity did not predict future overweight/obesity onset. Adolescents who reported substance use versus abstinence at baseline also showed less caudate ($r = -.31$, $p < .001$) response to monetary reward.

Discussion: Results show that hyper-responsivity of reward circuitry increases risk for future substance use onset, providing novel support for the reward surfeit model. Results also imply that even a limited substance use history was associated with reduced reward region responsivity, extending results from studies that compared substance-dependent individuals with healthy control subjects and suggesting that substance use downregulates reward circuitry. However, aberrant reward region responsivity did not predict initial unhealthy weight gain.

Key Words: fMRI, prospective, reward sensitivity, substance use, weight gain

Theorists posit that individuals with less responsive reward circuitry are more likely to overeat and use psychoactive substances, because they are compensating for a reward deficit (1). Both of these behaviors cause dopamine (DA) signaling and activation in the striatum and other mesolimbic regions (2,3). In apparent support of the reward deficit theory, obese versus lean rats have lower basal DA levels, ex vivo striatal DA release, and D2 receptor availability (4–6); and obese versus lean humans show less striatal D2 receptor availability (7–9) and weaker striatal activation in response to palatable food intake (10–13). Echoing these findings, substance-using versus non-using rats show less striatal D2 receptor availability and sensitivity (14–17), and humans with versus without various substance use disorders show lower striatal D2 receptor availability and sensitivity (18–20), less DA release from stimulant drug use (21), and less ventral striatal response to anticipated monetary reward (22,23).

However, overeating and substance use seem to downregulate reward circuitry signaling. Women who gained weight over 6 months showed less striatal response to milkshake receipt relative to baseline and women who did not gain weight (24), converging with evidence that pigs randomized to a weight gain intervention versus a stable weight control condition showed less resting striatal activation (25). Other experiments indicate that both overeating (26) and intake of high-fat/sugar food versus isocaloric intake of a low-fat/sugar diet results in downregulation of striatal D1 and D2 receptors in rats (27). Likewise, animal experiments show that substance use reduces striatal D2 receptors (16,17), sensitivity of reward circuitry (14,15), D2 receptor sensitivity, and basal DA transmission (28,29).

Other theorists posit that individuals with more responsive reward circuitry are at greater risk for overeating and substance use (30). In apparent support of the reward surfeit model, obese versus lean humans show greater activation of striatal and other mesolimbic regions and report greater cravings in response to palatable food pictures (31–34) and cues that signal impending palatable food receipt (13,35). Similarly, individuals with versus without various substance use disorders show greater activation of reward processing regions and report greater craving in response to substance use images (36–39).

Yet this hyper-responsivity of reward regions to food and substance use cues might be a consequence of conditioned associations between food/drug reward and cues that predict these rewards rather than an initial vulnerability factor. Rodent studies indicate that firing of DA neurons initially occurs in response to intake of high-fat/high-sugar food and substance use but that firing shifts to cues that predict impending receipt of that food and substances after repeated pairing of food and substance use reward with the predictive cues (40,41), implying that this conditioning process leads to increased reward region responsivity to food and substance use cues.

Because it is unclear whether hypo- or hyper-responsivity of reward regions is an initial vulnerability factor or a consequence of overeating and substance use, it is vital to conduct prospective studies on neural vulnerability factors that predict future weight gain and substance use onset. Low striatal response to intake (12) and images of high-fat/sugar foods (33) predicted future weight gain for young women with a *TaqIA* A1 allele, a genotype associated with lower D2 striatal receptor availability and striatal resting metabolism (42,43), implying that individuals who show less reward region responsivity gain weight if they are at genetic

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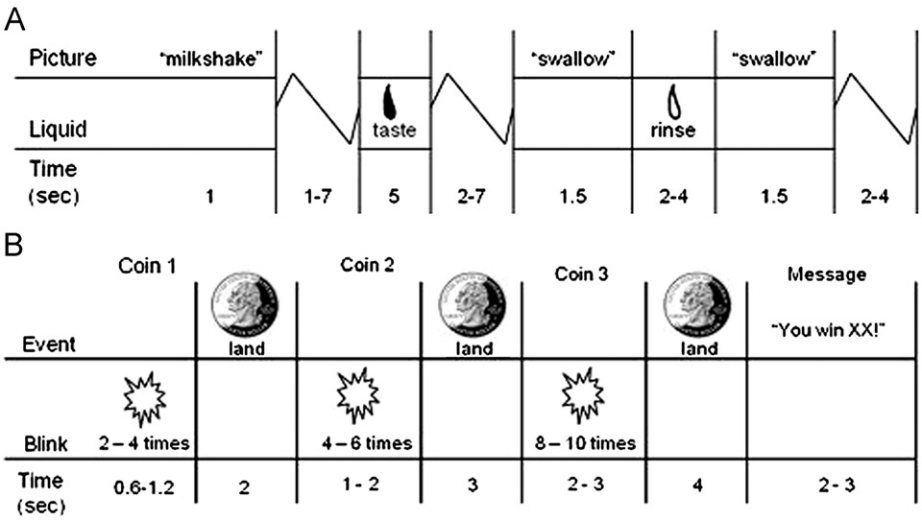

Figure 1. Example of timing and ordering of presentation of **(A)** pictures and beverages during the food reward paradigm and of **(B)** presentation of images and notification of monetary reward during the monetary reward paradigm.

risk for reduced DA signaling in reward circuitry. In contrast, elevated amygdala response to high-fat/sugar food olfactory cues (44), nucleus accumbens response to high-fat/sugar food images (45), and orbitofrontal cortex response to cues signaling impending high-fat/sugar food image presentation (46) predicted future weight gain. Furthermore, greater dorsal striatum and orbitofrontal cortex response to unhealthy food images predicted future weight gain for individuals with a *TaqIA* A2/A2 allele (33), which is associated with higher striatal D2 receptor availability and striatal resting metabolism (42,43).

Collectively, prospective data suggest that both elevated responsivity of reward regions to food images/cues and blunted responsivity to food cues and food receipt for humans at genetic risk for reduced DA signaling capacity increases risk for future weight gain. Yet, because some participants in these studies were overweight, a history of overeating in a subset of participants might have driven these prospective effects. Another gap in the literature is that no research has tested whether hyper- or hypo-responsive reward circuitry predicts future substance use onset or escalation. Thus, we initiated a large prospective study to test whether individual differences in reward region responsivity predicted overweight/obesity onset among initially healthy-weight adolescents and substance use onset among initially abstinent adolescents. We investigated reward region response to a natural unconditioned reward (high-fat/sugar food) and a conditioned reward (money) and investigated reward region response to both receipt and anticipated receipt of food and monetary reward, to provide a comprehensive assessment of reward region responsivity. We also compared neural responsivity of reward regions for adolescents who were in a healthy weight range or overweight/obese at baseline and for those who reported substance use versus abstinence at baseline, to determine whether even a limited history of overeating and substance use was associated with reduced reward region responsivity.

Methods and Materials

Participants

Participants were 82 female and 80 male adolescents (mean age = 15.3 ± 1.1 years; mean body mass index [BMI] = 20.8 ± 1.9; 4% Hispanic, 1% Native-American, 1% Asian/Pacific Islander, 76% European-American, and 18% mixed racial heritage) recruited in a medium-sized town in the Western US via advertisements and flyers. Exclusion criteria were a BMI <18 or >25, current use of psychoactive medications or drugs more than once weekly, pregnancy, head injury with a loss of consciousness, significant cognitive impairment, major medical problems, or current Axis I psychiatric disorder (Supplement 1).

Measures

Body Fat Percentage. Air displacement plethysmography was used to assess percent body fat of participants at baseline and 1-year follow-up with the Bod Pod S/T (COSMED, Pavona di Albano, Italy) with recommended procedures and age/sex-appropriate equations (47). Body density was calculated as body mass (assessed by direct weighing) divided by body volume. Body fat percentage estimates show test-retest reliability (r = .92–.99) and correlate with dual energy x-ray absorptiometry and hydrostatic weighing estimates (r = .98–.99) (48). To determine healthy weight, overweight, and obesity at each assessment, age- and sex-adjusted body fat percentiles were used, where >85th percentile was considered overweight and >95th percentile was considered obese, which are cutoffs associated with elevated weight-related morbidity and mortality (49).

Substance Use. Substance use was assessed with items measuring the frequency of use during the past year of beer/wine/wine coolers, hard liquor, cigarettes, marijuana, stimulants, downers, inhalants, and hallucinogens. This scale has shown internal consistency (mean α = .86), test-retest reliability (mean r = .86), and predictive validity for future increases in substance abuse symptoms (50). In the current study, Cronbach's α = .81, verifying it was appropriate to aggregate across various substances. Furthermore, by 1-year follow-up, 64% of adolescents reporting substance use reported using more than one drug category.

Functional Magnetic Resonance Imaging Paradigms. On the scan day, participants were asked to consume their regular meals but to refrain from eating or drinking caffeinated beverages for 5 hours preceding their scan. The food reward paradigm (Figure 1A) (12) assessed response to receipt and