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Review

Fuel not fun: Reinterpreting attenuated brain responses to reward in obesity

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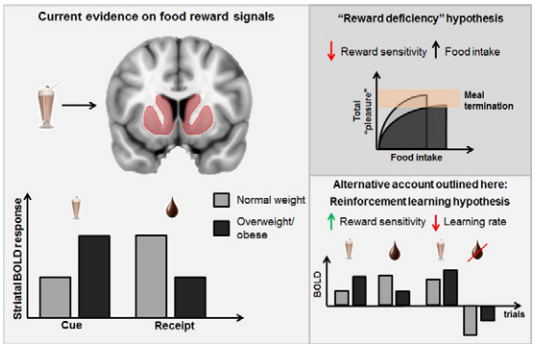
HIGHLIGHTS

- Attenuated response to food reward in dorsal striatum in obesity
- Response to reward does reflect more than "pleasure".
- Reinforcement learning indicates importance of error signals.
- Obesity may be characterized by impairment in reward learning.

GRAPHICAL ABSTRACT



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ABSTRACT

There is a well-established literature linking obesity to altered dopamine signaling and brain response to food-related stimuli. Neuroimaging studies frequently report enhanced responses in dopaminergic regions during food anticipation and decreased responses during reward receipt. This has been interpreted as reflecting anticipatory "reward surfeit", and consummatory "reward deficiency". In particular, attenuated response in the dorsal striatum to primary food rewards is proposed to reflect anhedonia, which leads to overeating in an attempt to compensate for the reward deficit. In this paper, we propose an alternative view. We consider brain response to food-related stimuli in a reinforcement-learning framework, which can be employed to separate the contributions of reward sensitivity and reward-related learning that are typically entangled in the brain response to reward. Consequently, we posit that decreased striatal responses to milkshake receipt reflect reduced reward-related learning rather than reward deficiency or anhedonia because reduced reward sensitivity would translate uniformly into reduced anticipatory and consummatory responses to reward. By re-conceptualizing reward deficiency as a shift in learning about subjective value of rewards, we attempt to reconcile neuroimaging findings with the putative role of dopamine in effort, energy expenditure and exploration and suggest that attenuated brain responses to energy dense foods reflect the "fuel", not the fun entailed by the reward.

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Contents

1. A reinterpretation of the attenuated dorsal striatal response . . . 38
1.1. Positive and negative outcome learning . . . 39
1.2. Striatal circuits and positive and negative outcome learning . . . 39
2. A reinforcement learning perspective on anhedonia . . . 40
3. Differences in brain response to reward illustrated by simulated reinforcement learning . . . 41
4. Endocrine modulation of dopamine signaling . . . 42
5. Where is the "fun"? Opioid receptor signaling and hedonics . . . 43
6. Future directions . . . 43
7. Conclusions . . . 43
Acknowledgement . . . 43
References . . . 44

Obesity results when energy intake chronically exceeds energy expenditure [1]. The neurotransmitter dopamine plays a role in both sides of this energy balance equation by the regulation of food intake [e.g., 2], the invigoration of behavior [3,4], and the integration of metabolic signals into brain reward circuits [5–9]. There is evidence in humans [10–21] and in animals [22–29] that obesity is associated with alterations in dopaminergic neurotransmission. For example, attenuated blood oxygen level dependent (BOLD) response to palatable food receipt is consistently observed in the dorsal striatum in overweight and obese individuals [19,20,30–32]. Although BOLD is only an indirect marker of neural activation, this response is linked to dopamine signaling because it is associated with polymorphisms that affect dopamine D2 receptors [18,19] and positron emission tomography (PET) derived measures of dopamine signaling [33]. Specifically, carriers of the A1 allele of the TaqIA A1 polymorphism show reduced D2 receptor density compared to non-carriers [34,35] and largely drive the inverse association between response in the dorsal striatum to caloric liquids such as milkshake and body mass index (BMI) or weight gain [18–20], while D2 receptor binding potential in the striatum is also associated with BMI [10–17].

Anhedonia commonly refers to a reduced ability to experience pleasure or a diminished response to rewarding stimuli [36–38]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM), anhedonia is one of the core symptoms of major depression [39]. Although anhedonia has received considerable interest in basic neurobiological research, the understanding of the concept has been hampered by ambiguities in the definition and operationalization of anhedonia [38]. In past decades, converging evidence has established that mesolimbic dopamine is related mainly to "wanting", but not "liking" of rewards [40–42]. However, clinical diagnosis and most anhedonia self-report questionnaires do not distinguish between reduced motivation to obtain a reward (wanting) and reduced experience of pleasure when the reward is being obtained (liking; anhedonia [38]).

Similarly, the interpretation of the blunted dorsal striatal response as evidence of anhedonia fails to consider the other functions of dopamine signaling, as well as the considerable evidence that dopamine contributes to regulating motivated behavior rather than "pleasure" per se [43]. We therefore offer a reinterpretation of dorsal striatal attenuations associated with obesity and weight gain susceptibility. Specifically, we apply a reinforcement learning framework [44] and argue that the data are better represented as differences in reward-related learning, which has been consistently linked to dopamine D2 receptor function in animals [e.g., 45] and humans [46–48] but not to anhedonia.

1. A reinterpretation of the attenuated dorsal striatal response

The reduction of D2 receptors in the dorsal striatum has been considered a hallmark finding in drug addiction [49]. Whereas initial evidence suggested similar effects in obese individuals [17], flanked by animal studies indicating that this deficit could be diet-induced [28], this finding has not been consistently replicated to date [10]. Consequently, Horstmann et al. [10] have proposed an alternative interpretation of the conflicting data by arguing in favor of a non-linear relationship between BMI and dopaminergic tone. This notion echoes the non-linear relationship that has been observed between BMI and reward sensitivity [50]. It posits that dopaminergic tone is lowest for overweight and mildly obese individuals, which amplifies phasic dopamine signals (relative to the overall dopaminergic tone), thereby increasing sensitivity to reward [10].

Neuroadaptive changes have been commonly observed with the progression of addictive behavior. Whereas drug-seeking is initially guided by the prospect of positive reinforcement, the "dark side" of reinforcement, which is represented by negative reinforcement due to the reduction of withdrawal, becomes increasingly important with continued substance use [51,52]. This is also reflected in a shift from impulsive to compulsive behavior. The addiction cycle is characterized by three stages: 1) binge/intoxication, 2) withdrawal/negative affect, and 3) preoccupation/anticipation [51]. These stages have been associated with distinct brain networks. Binge/intoxication is supported by the mesolimbic network of ventral tegmental area and ventral striatum, withdrawal/negative affect by the extended amygdala, and the preoccupation/anticipation stage by a more distributed "craving" network involving the orbitofrontal cortex, dorsal striatum, prefrontal cortex, basolateral amygdala, hippocampus, and insula as well as a "cognitive control/inhibition" network involving the cingulum, the dorsolateral prefrontal, and the inferior frontal cortex [51]. Notably, food addiction appears to resemble many aspects of other substance-related addictions, which points to a perhaps more generalized mechanism [53]. Critically, during protracted withdrawal (i.e., after acute withdrawal symptoms have declined), hypofunction in dopamine pathways has been observed as indicated by decreases in D2 receptor expression and decreases in dopamine release [51]. As a result, it has been hypothesized that these neuroadaptations may contribute to anhedonia and amotivation, which are commonly reported by individuals suffering from addiction, while sensitivity to conditioned drug cues might be enhanced at the same time [51]. To summarize, escalation of substance intake driven by positive reinforcement may contribute to neuroadaptations within the striatum that, in turn, lead to changes in reward-seeking behavior, effectively reinstating addictive behavior via negative reinforcement.

In order to improve our understanding of the neurobiological substrates of anhedonia, "reward deficits" can be grouped into different facets. At least four broad categories can be distinguished that have been linked to anhedonia in the past, depending on the experimental operationalization, namely consummatory (e.g., sucrose intake), anticipatory (e.g., food cue), motivational (e.g., effort), and learning (e.g., speed of reward-related learning) deficits [54]. While consummatory deficits map most intuitively onto the definition of anhedonia as reduced experience of pleasure, it is important to note that patients with major depression do not show an attenuated preference for sweet