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Effects of the modern food environment on striatal function, cognition and regulation of ingestive behavior

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Abstract

Emerging evidence from human and animal studies suggest that consumption of palatable foods rich in fat and/or carbohydrates may produce deleterious influences on brain function independently of body weight or metabolic disease. Here we consider two mechanisms by which diet can impact striatal circuits to amplify food cue reactivity and impair inhibitory control. First, we review findings demonstrating that the energetic properties of foods regulate nucleus accumbens food cue reactivity, a demonstrated predictor of weight gain susceptibility, which is then sensitized by chronic consumption of an energy dense diet. Second, we consider evidence for diet-induced adaptations in dorsal striatal dopamine signaling that is associated with impaired inhibitory control and negative outcome learning.

Keywords

nucleus accumbens; dorsal striatum; dopamine; high fat diet; food reward; obesity; neural adaptation; cognition; cue reactivity; inhibitory control; ANKK1

Introduction

There has been considerable effort over the past two decades to identify and characterize behaviors and their underlying neural circuits that confer vulnerability for overeating in the modern “obesogenic” food environment. A general thesis to emerge is that enhanced reactivity to food-associated cues coupled with diminished inhibitory control produces susceptibility for overeating [1,2], particularly in an environment where salient food cues are

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pervasive and palatable, energy dense foods are cheap and easily obtainable. In this review we argue that the relationship between the brain and the food environment is bi-directional. In particular, there is mounting evidence that consumption of palatable foods high in fat and refined carbohydrates produces deleterious effects on neural circuits, thereby contributing to cognitive alterations permissive of overeating. Here we outline two ways in which dietary factors might negatively impact striatal circuits to produce hyper-reactivity to food cues and diminished inhibitory control.

Metabolic control of food cue reactivity in the nucleus accumbens

"Food cue reactivity", defined as the extent to which an individual is prone to eat in the presence of food cues, has long been associated with susceptibility for weight gain [3–6]. Food cues acquire reinforcing properties via Pavlovian conditioning [7], in which a once neutral cue is associated with nutrient ingestion. Once this association is formed, food cues gain access to reward [8] and homeostatic circuits [9], thereby acquiring the ability to elicit reflexive responses such as cephalic phase responses [10], food seeking [11], and craving [6].

The nucleus accumbens (NAc) is critically involved in the formation of learned Pavlovian associations between the unconditioned rewarding properties of nutrient ingestion and conditioned cues such as the sight or flavor of the foods containing nutrients [12]. Accordingly, human neuroimaging studies have shown that NAc response to calorie-predictive food cues is associated with genetic risk for obesity [13], eating in the absence of hunger [14], poor outcomes on weight loss trials [15], unhealthy food choice [16] and weight gain susceptibility [17–19], among other factors. This raises the possibility that individual variations in NAc learning circuits mediating food cue reactivity may increase susceptibility to obesity in a food cue-laden environment.

Conditioning food cue reactivity

Work in rodents suggests that post-ingestive effects following nutrient consumption provide critical signals driving reinforcement and hence food cue reactivity. Infusing glucose directly into the gut, concomitantly to exposure to a non-caloric flavored liquid, results in lasting preferences for that flavor [20–22]. In contrast, sweetness perception in the absence of calories (or caffeine) is neither necessary nor sufficient for animals to form flavor preferences [23,24]. This flavor-nutrient conditioning occurs rapidly, even within the course of a single meal [25], demonstrating the potency with which post-oral signals transform flavors into conditioned cues.

Although it is well established that flavor-nutrient conditioning depends upon brain dopamine signaling [8], the identity of the post-oral signal supporting this learning remains a subject for debate. Direct infusion of nutrients into the gut stimulates dopamine release in the NAc and dorsal striatum (DS) [23] in a calorie-dependent manner [26]. Moreover, this effect is sensitive to glucose utilization rate, and inhibition of glucose oxidation suppresses striatal dopamine levels and reduces glucose intake [23,27]. This suggests that the post-oral "reward" signal is linked to the utilization of the nutrient as fuel.

In humans, response in the NAc to a calorie-predictive flavor is directly proportional to the magnitude of change in blood glucose that occurs when the flavor is consumed with the calorie source [28]. Since glucose availability is a requirement for its utilization this finding provides indirect support for metabolic response contributing to the reinforcing effects of nutrients in humans. Intriguingly, although pairing the flavor with calories increases the rated liking of that flavor, this change in liking does not correlate with NAc response or the change in blood glucose. This suggests that the energetic properties of foods might influence behaviors independently of perceptions of liking. Consistent with this possibility, willingness to pay for food items in an auction task correlates with NAc response and is driven by energy density independently of explicit knowledge of caloric content or rated food liking [29]. Bidding behavior was also associated with the generation of value signals in the ventromedial prefrontal cortex that were associated with actual, but not estimated energy density. Thus, NAc involvement in Pavlovian conditioning and in food choice appears to reflect the energetic characteristics of food independently of explicit awareness or liking, a notion consistent with separate substrates for explicit and implicit components of liking and incentive motivation [30–32]. If so, energy dense foods that produce large glucose excursions may well condition NAc hyper-reactivity, especially in individuals with compromised glucose metabolism. Moreover, this hyper-reactivity, which is associated with weight gain susceptibility [15,17], likely influences intake via implicit processes that may be less amenable to goal-directed behaviors such as dieting.

Effects of energy-dense diets on conditioning food cue reactivity

Emerging evidence suggests that chronic consumption of an unhealthy diet contributes to alterations in NAc-dependent learning. In humans, objectively measured energy intake was associated with greater BOLD response to anticipated food intake in the striatum independent of basal energy needs and adiposity, raising the possibility that excess caloric intake may enhance NAc food cue reactivity [33]. Accordingly, Wald and Meyers assessed flavor-glucose learning in rats that had been exposed to a high-fat, high-carbohydrate (HFHC) choice diet [34]. Learning rapidity and strength (measured by intake) was greater in HFHC-fed rats that became obese compared to chow-fed rats and HFHC-fed rats that were relatively obesity-resistant [34]. This finding points to an association between diet-induced obesity (DIO) and enhanced sensitivity to flavor-nutrient learning, though the directionality of this relationship remains unclear.

To dissociate diet-induced from pre-existing differences associated with obesity, Robinson and colleagues examined cue reactivity in rats before and after chronic exposure to a palatable “junk-food” diet [35]. Rats subsequently identified as susceptible to diet-induced obesity (DIO-prone) displayed enhanced conditioned approach to sucrose-predicting food cues prior to diet exposure and independent of initial body weight. Following diet exposure, both DIO-prone and DIO-resistant rats displayed cross-sensitization to amphetamine and down-regulation of striatal dopamine D2 receptors (D2Rs). Thus, while enhanced food cue reactivity precedes obesity and may confer vulnerability to overeating and diet-induced weight gain, other adaptations in dopamine function may occur as a direct consequence of palatable diet consumption, regardless of weight gain [36].

Further support comes from a recent study showing that NAc insulin modulates flavor-nutrient learning and enhances dopamine release, an effect that is abolished by HFHC diet [37]. Given that insulin also acts in the hypothalamus to promote satiety [38], this suggests a potential mechanism by which diet may influence circuits important for reward learning and homeostasis. Indeed, a number of nutritionally-regulated hormones involved in hypothalamic control of feeding and glucose homeostasis—including glucagon-like peptide 1 [39], amylin [40], leptin [41], and ghrelin [42]—also modulate mesocorticolimbic dopamine signaling. Accordingly, recent data suggest that hypothalamic feeding circuits are regulated by sensory input [9], and may integrate information from reward circuits about nutritional and hedonic properties of food to direct metabolic learning and memory [43]. This metabolic learning regulates food choice and is susceptible to genetic and environmental factors, such as overnutrition [43].

In the modern environment, humans are presented with a daily barrage of food-associated cues in the form of advertisements, most of which promote energy-dense foods high in fat and sugar [44]. Emerging evidence supports the possibility that energy-dense foods and beverages, which produce larger glucose and insulin excursions, will be more effective at driving NAc food cue reactivity and cue-potentiated feeding. Chronic consumption of foods high in fat and carbohydrates may in turn alter this learning by disrupting glucose metabolism and insulin sensitivity, or by directly altering dopamine signaling. Thus, an environment in which palatable foods are readily available and food cues are pervasive may propel a vicious cycle whereby energy-dense foods, via their effect on the NAc, turn neutral cues into powerful conditioned stimuli that drive excessive intake. Excessive intake may in turn alter NAc-mediated learning and behavior, culminating in even greater susceptibility to overeating (FIGURE 1).

Neural adaptations in the dorsal striatum

The nigrostriatal pathway is critically involved in reward-seeking behaviors, including feeding [45,46]. Dopamine release is observed in the DS during food consumption in rodents and humans [47–49], and intact DS dopamine signaling is required for the expression of normal ingestive behavior [50]. Evidence from preclinical studies in rodents consistently report alterations in DS dopamine function in diet-induced obese rodents, including diminished dopamine D2 receptor expression [51,52] and dopamine release [53]. Interestingly, administration of the gastrointestinal messenger oleoylethanolamide restores nutrient-stimulated dopamine release in high-fat fed mice, while simultaneously eliminating motivational deficits during flavorless intragastric feeding and increasing oral intake of low-fat emulsions [53]. These findings suggest that DS dopamine acts as a critical sensor of the nutritional value of ingested calories, and provide support for the notion that excess intake of high-calorie foods may represent a compensatory response to diminished nutrient sensitivity.

The relationship between human obesity and DS circuitry is less clear. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies assessing baseline binding potential (BP) for dopamine ligands report decreased receptor availability [54,55] and evoked dopamine release [56] in morbid obesity, and increased receptor availability [57–59] and evoked dopamine release [60] in overweight and mild

obesity. One interpretation of these findings is that there is a non-linear relationship between obesity and dopaminergic tone: decreased dopamine tone (increased receptor availability) is associated with enhanced phasic responses in overweight/mild obesity, while in severe obesity, increased tone (decreased receptor availability) is associated with blunted phasic responses [61]. This is consistent with evidence of a non-linear relationship between dopamine-dependent functions, such as reward sensitivity, and BMI [62]. However, this interpretation is complicated by conflicting reports of increased [60] and decreased [63] striatal dopamine release in mildly obese subjects with similar BMI range, which suggests that other factors likely contribute to inter-study discrepancies, such as differences in radiotracer characteristics, heterogeneity between studies with respect to nutritional status, genetic variation, metabolic disturbances, and diet.

FMRI studies have also demonstrated alterations in DS function in association with obesity. Cross-sectional studies consistently report enhanced blood oxygen level-dependent (BOLD) response in the DS in response to calorie-predictive cues in overweight/mild obesity [64–67]. In contrast, DS BOLD response to the receipt of a predicted food is decreased in association with overweight/obesity [57,67–71], and is predictive of future weight gain [72,73].

Although the BOLD signal is not a direct measure of neurotransmitter release, there is evidence that these differences in DS responsivity are related to alterations in dopaminergic function. First, the relationship between BMI and BOLD DS response is stronger in individuals who are at genetic risk for reduced D2R signaling capacity by virtue of possessing the A1 allele of the Taq1A polymorphism [72–74]. Furthermore, while studies consistently report a negative association between BMI/weight gain DS response to the receipt of a predicted palatable food [57,67,68,71], when receipt is unpredicted, this association is positive [75]. According to animal literature, dopamine neurons produce bursts of action potentials in response to unexpected food rewards [76]. After repeated pairings with a neutral cue, dopamine neurons begin to fire in response to the reward-predictive cue and cease responding to the receipt of food [77]. Thus, DS BOLD responses to expected and unexpected reward receipt may reflect distinct temporal aspects of dopamine dynamics.

Consistent with this possibility, a recent study by Burger and Stice [78] found that during exposure to repeated pairings of palatable food receipt and cues that predict palatable food receipt, striatal BOLD responses to cues increased, while responses to food receipt decreased. Additionally, the slopes of increases and decreases in striatal response to cues and food receipt observed across learning trials predicted future weight gain, and heightened responsivity to initial receipt accounted for a substantial proportion of variance in future weight gain.

Collectively then, extant data from neuroimaging studies is consistent with the model that overweight and mild obesity is characterized by DS hyper-reactivity to food cues and hypo-reactivity to food receipt, which may reflect greater propensity for cue-reward learning and food reward habituation, respectively.

Considerable evidence suggests that dietary factors contribute to dopamine dysregulation by producing neuroadaptations in DS, which may potentiate overeating by impairing dopamine-dependent learning and cognition; a proposal that very much parallels models of vicious cycles observed in drug addiction [79]. First, decreased DS response to food receipt appears to be consequential rather than causal as it is associated with weight gain over time [71], but not risk for obesity by virtue of parental obesity [80]. Second, the effect is driven primarily by individuals who are at genetic risk for decreased D2R density [72,73]. The single-nucleotide polymorphism that gives rise to this risk (SNP; rs1800497; Accession Number: NP_848605.1) is located 9.5 kb downstream from D2R in exon 9 of the ANKK1 gene (ankyrin repeats and kinase domain containing 1 gene) and causes an amino acid substitution within the C-terminal [81]. The encoded protein, ANKK1, belongs to a family of receptor-interacting protein (RIP) serine/threonine kinases. RIP kinases are of interest because they have emerged as essential sensors of cellular stress, initiating responses to various environmental factors, including nutrient ingestion, by activating transcription factors such as NF-κB and AP-1 [82]. NF-κB response elements exist in the D2R promoter region and NF-κB is a necessary and sufficient signal to induce DRD2 expression [83,84]. Though much remains to be understood about the relationship between the Taq1A polymorphism, ANKK1, and dopaminergic function, these findings suggest a potential mechanism whereby diet-induced interactions between ANKK1 and NF-κB could enhance risk for adaptations in the dopamine system, particularly in individuals with the A1 allele.

DS adaptations have important functional implications. The DS plays a key role in instrumental learning [12,85,86], as well a number of other cognitive functions including habit formation [45,87–89], working memory [90,91], inhibitory control [92,93] and negative outcome learning [94,95], raising the possibility that diet-induced alterations in dopamine function lead to cognitive and behavioral deficits. Accordingly, DS response to milkshake receipt is inversely associated with self-reported impulsivity in overweight/obese but not healthy-weight individuals [68]. In contrast, patients with anorexia nervosa, who exert excessive inhibitory control over feeding, engage the DS more than healthy controls when making food choices, and fronto-striatal connectivity in these patients correlates with food intake [96]. Obese individuals also show impaired working memory [97], as well as negative, but not positive outcome learning [97,98]. This latter finding is of particular interest because negative outcome learning has been specifically associated with striatal D2 signaling [99]. Accordingly, rats with extended access to a palatable high-fat diet display down-regulated DS D2Rs accompanied by reward deficits and compulsive-like food-seeking characterized by insensitivity to negative outcomes [52]. Moreover, lentivirus-mediated knockdown of DS D2Rs rapidly accelerated the development of these behavioral deficits, suggesting a direct link between diet, DS dopamine adaptations, and impulsive, inflexible behavioral patterns.

Revealingly, many of these dopamine-dependent cognitive functions have been identified as risk factors for overeating [100–102], and even targets for behavioral interventions for obesity [103,104]. As such, pre-existing and/or diet-induced alterations in dopamine signaling may produce impairments in executive function, which may increase susceptibility for overeating and weight gain. Consistently, A1 carriers display greater behavioral inflexibility, working memory deficits, and impaired negative outcome learning [98,105–

107], and are at greater risk for developing a variety of psychiatric disorders related to impaired striatal dopamine function including smoking [108], alcoholism [109], and obesity [110,111].

Collectively then, accumulating data suggests that A1 carriers, who constitute 30–40% of the population, possess an increased genetic vulnerability to diet-induced dopamine adaptions, and these adaptations are associated with cognitive impairments that may increase predisposition to obesity (FIGURE 2). Unfortunately, verification of this hypothesis is complicated by the fact that all rodents are A1 homozygotes. Therefore, development of a transgenic “non-carrier” mouse would be of interest to rigorously test this hypothesis and determine the mechanisms by which ANKK1 variants influence D2R expression.

Conclusions

The power of energy dense foods, via their effects on mesoaccumbens and nigrostriatal circuits, to condition cue-reward associations and motivate appetitive behavior is adaptive when food is scarce or its availability unpredictable. In modern societies where energy dense foods and food cues are abundant, these mechanisms can become a liability, promoting energy intake that far exceeds metabolic needs. Indeed, evidence from preclinical and clinical studies suggest that obesity is associated with distinct alterations in ventral (NAc) and DS dopamine signaling, and in behaviors and cognitive functions governed by these circuits. In particular, heightened food cue reactivity and cue-induced dopamine signaling in the NAc have been reported in relation to obesity. In addition, obesity is associated with diminished DS dopamine signaling in response to food receipt and greater DS response to anticipated food reward, in parallel with reward hyposensitivity and impulsive, inflexible behavior. Revealingly, while NAc reactivity to food cues was found to predict subsequent snacking, NAc response was associated with increased BMI only in individuals reporting low self-control [14]. Taken together, the findings presented here are consistent with a model of obesity that is characterized by hypersensitivity to conditioned food cues in combination with hyposensitivity to reward receipt and weakened inhibitory control over appetitive behaviors. Moreover, there is now clear evidence that at least some of the differential brain effects observed in obesity occur as a consequence of high-fat/high-carbohydrate diet consumption, and that some of these adaptations exacerbate behaviors that confer initial vulnerability for overeating and weight gain. It is therefore critical to determine the precise mechanisms underlying these diet-induced adaptations and to evaluate methods for their reversal.

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Highlights

- Striatal circuits involved in associative learning are altered in obesity
- Differences in neural reactivity to food cues and reward confer risk for overeating
- Excess intake of dietary fat and sugar alters striatal dopamine function
- Diet-induced adaptations lead to cognitive impairments that may potentiate risk

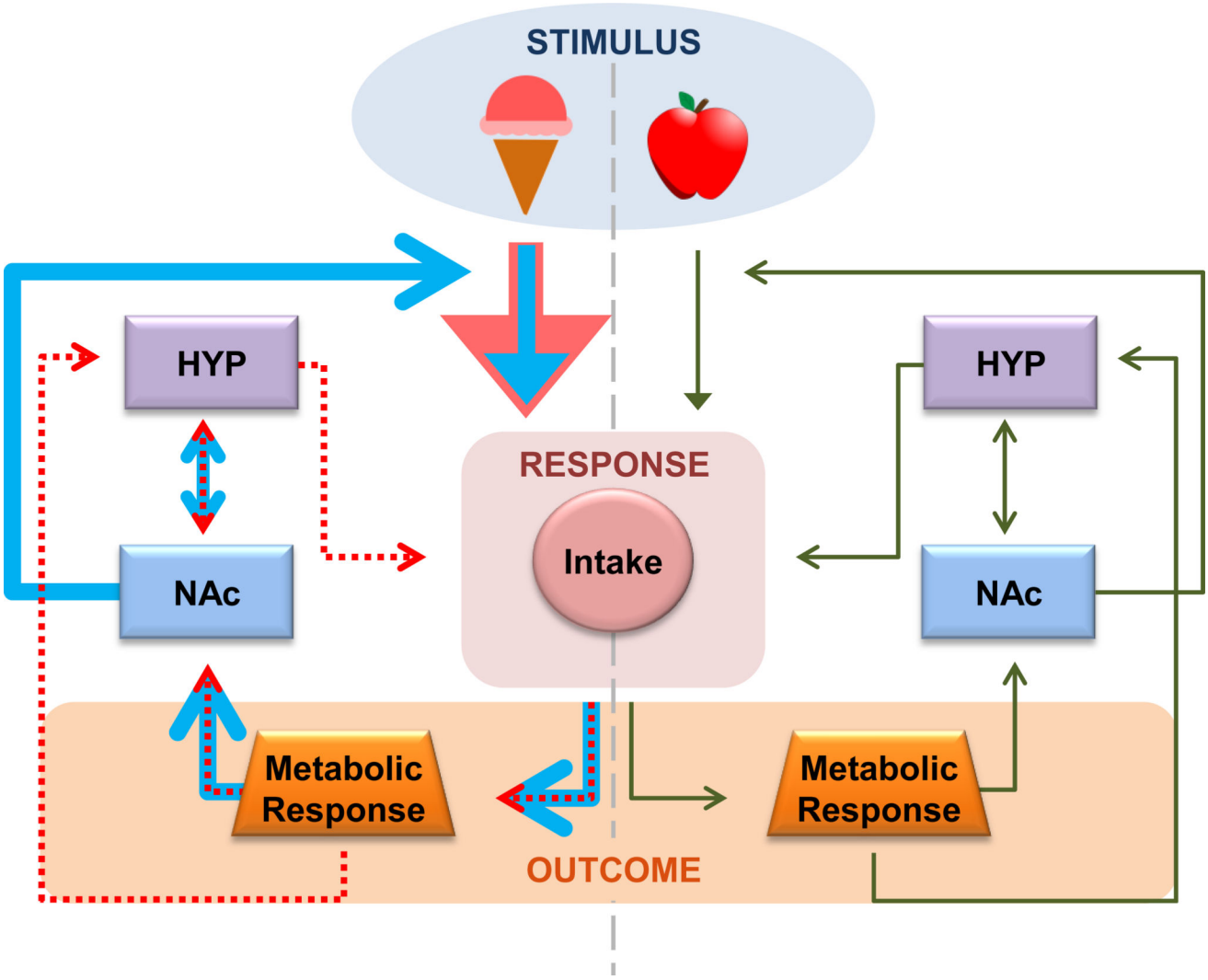

Figure 1. Diet-induced alterations in NAc-mediated learning drive a vicious cycle of overeating

In healthy individuals (green arrows), feeding is regulated by homeostatic and hedonic processes. The NAc facilitates associative learning and promotes adaptive behavioral responses to procure nutrient-rich foods during energy deficit. Energy-dense foods (blue arrows) promote supranormal metabolic responses and DA release in the NAc, thereby strengthening the incentive salience of these foods. Chronic consumption (red arrows) leads to metabolic disturbances (e.g. insulin insensitivity) and neural adaptations (e.g. down-regulated D2Rs), which reduce sensitivity to homeostatic signals and impair NAc-mediated associative learning. Thus, consumption of energy-dense foods promotes the formation of strong cue associations which drive reflexive food seeking irrespective of metabolic outcomes and homeostatic need.

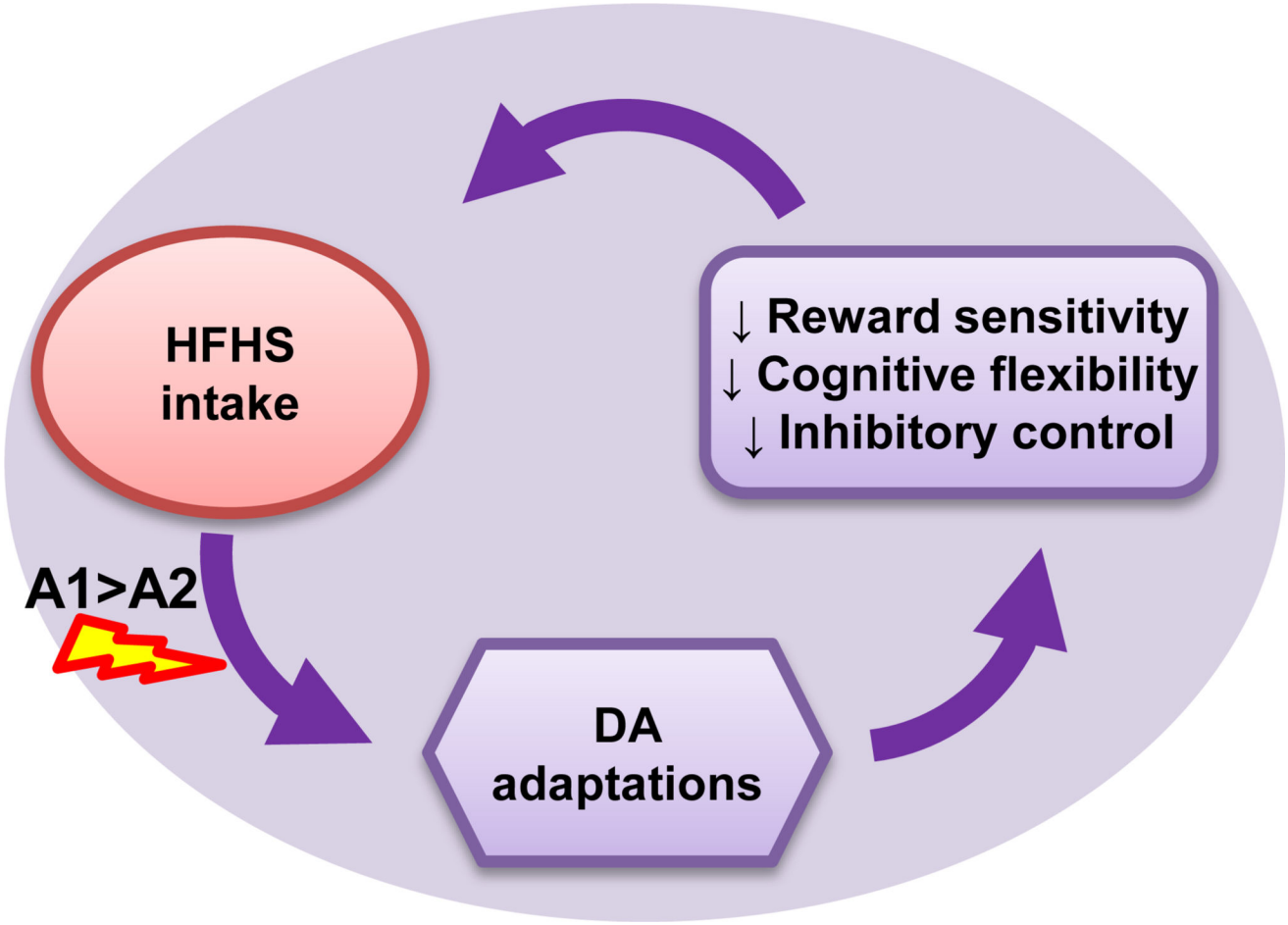

Figure 2. Genetic and dietary factors influence DS function to increase risk for overeating and obesity

Chronic intake of a diet high in fat and sugar leads to neuroadaptations that disrupt striatal DA signaling. These adaptations are associated with cognitive impairments that perpetuate impulsive and inflexible feeding habits (purple). Genetic variants affecting DA signaling capacity (e.g. TaqIA polymorphism) enhance risk for diet-induced DA adaptations associated with overeating and the development of dopamine-dependent cognitive impairments.