

REVIEW

Etiology and Pathophysiology

Withdrawal: A key consideration in evaluating whether highly processed foods are addictive

Lindsey Parnarouskis¹  | Adam M. Leventhal² | Stuart G. Ferguson³ | Ashley N. Gearhardt¹

¹Department of Psychology, The University of Michigan, Ann Arbor, Michigan, USA

²Institute for Addiction Science, University of Southern California, Los Angeles, California, USA

³Tasmanian School of Medicine, University of Tasmania, Hobart, Tasmania, Australia

Correspondence

Lindsey Parnarouskis, Department of Psychology, University of Michigan, 2261 East Hall, 530 Church Street, Ann Arbor, MI 48105, USA.

Email: lparnar@umich.edu

Summary

Researchers are currently debating whether theories of addiction explain compulsive overeating of highly processed (HP) foods (i.e., industrially created foods high in refined carbohydrates and/or fat), which contributes to obesity and diet-related disease. A subset of individuals consumes HP foods with behavioral phenotypes that mirror substance use disorders. Withdrawal, the emergence of aversive physical and psychological symptoms upon reduction or cessation of substance use, is a core component of addiction that was central to historical debates about other substances' addictive potential (e.g., nicotine and cocaine). However, no one has systematically considered evidence for whether HP foods cause withdrawal, which represents a key knowledge gap regarding the utility of addiction models for understanding compulsive overeating. Thus, we reviewed evidence for whether animals and humans exhibit withdrawal when reducing or eliminating HP food intake. Controlled experimental evidence indicates animals experience HP food withdrawal marked by neural reward changes and behaviors consistent with withdrawal from other addictive substances. In humans, preliminary evidence supports subjective withdrawal-like experiences. However, most current human research is limited to retrospective recall. Further experimental research is needed to evaluate this construct. We outline future research directions to investigate HP food withdrawal in humans and consider potential clinical implications.

KEYWORDS

addiction, food addiction, substance use disorders, withdrawal

1 | INTRODUCTION

Addictive substances have long played a role in the human experience. However, what it takes to label a substance or behavior as “addictive” has been a source of heated debate over the last century. Through industrial advances, humans have mastered the ability to

inexpensively and effectively produce large quantities of highly rewarding food ingredients that are then combined with scores of other additives to create thousands of novel and palatable food combinations that do not naturally occur.¹ Highly processed (HP) foods refer to industrially created foods that contain unnaturally high levels of refined carbohydrates (e.g., sugar and white

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flour) and/or fat.² HP foods are now the dominant source of calories for the average US resident.³ HP foods typically contain high levels of saturated fats and refined carbohydrates (i.e., added sugars) and are often high on the glycemic index (GI) (i.e., they cause rapid spikes in blood glucose).²⁻⁴ HP foods are more effective than minimally processed foods (e.g., whole fruits and vegetables) at activating reward-related neural systems that are also activated during substance use.^{5,6} A subset of individuals experiences HP food addiction, which refers to the experience of core behavioral indicators of substance use disorders (SUD; e.g., loss of control and continued use despite negative consequences) in response to HP foods.⁷ HP food addiction is associated with increased rates of obesity⁸ and is elevated in populations with obesity.⁹ Further, a recent study identified HP food addiction as the strongest psychosocial predictor of obesity treatment attrition and poor weight loss outcomes following treatment.¹⁰

The withdrawal syndrome, which refers to aversive physical, cognitive, and affective symptoms that emerge following the reduction or discontinuation of an addictive substance, is another key indicator of addiction, but its role in HP food addiction has received less attention. Withdrawal has major clinical relevance as a predictor of relapse and is an intervention target in SUD.^{11,12} If withdrawal occurs when HP food intake is reduced, it may contribute to high rates of dietary change failure and be a novel intervention target to improve obesity treatment outcomes.¹³

A review of the HP food withdrawal literature could provide definitive evidence that withdrawal exists in this context. If further research is needed, a review could provide guidance regarding future research directions to clarify the existence of HP food withdrawal and understand its role in obesity and obesity treatment. This is the first review to examine these questions. To advance the study of HP food withdrawal, this review (1) outlines the current evidence for HP food

TABLE 1 DSM-5 withdrawal symptoms across different addictive agents

Addictive agent	Alcohol	Caffeine	Cannabis	Opioids	Sedatives, hypnotics, anxiolytics	Stimulants	Tobacco	Gambling
Insomnia	X		X	X	X	X	X	
Anxiety	X		X		X		X	
Depressed or dysphoric mood		X	X	X			X	
Irritability		X	X				X	X
Nausea or vomiting	X	X		X	X			
Autonomic hyperactivity (sweating or elevated heart rate)	X		X	X	X			
Tremor	X		X		X			
Psychomotor agitation	X				X	X		
Restlessness			X				X	X
Headache		X	X					
Fatigue or drowsiness		X				X		
Increased appetite						X	X	
Fever			X	X				
Difficulty concentrating		X					X	
Muscle pain/stiffness		X		X				
Seizures	X				X			
Transient hallucinations/illusions	X				X			
Hypersomnia						X		
Vivid, unpleasant dreams						X		
Psychomotor retardation						X		
Abdominal pain			X					
Decreased appetite or weight loss			X					
Chills			X					
Diarrhea				X				
Yawning, lacrimation, rhinorrhea, piloerection, pupillary dilation				X				

Note: Rows are shaded according to the number of substances for which a given symptom is listed as a withdrawal symptom; darker rows indicate more crosscutting symptoms.

withdrawal from basic science and human research, (2) highlights key research questions for the next steps in evaluating HP food withdrawal, (3) discusses important alternative explanations for current human evidence and recommends methodological best practices for future study of HP food withdrawal, and (4) concludes with a discussion of the clinical implications of HP food withdrawal.

2 | WITHDRAWAL AND ADDICTION

The withdrawal syndrome is a core element of the current conceptualization of SUD.¹⁴ The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) includes a withdrawal section for substances that have an associated withdrawal syndrome (alcohol, caffeine, cannabis, opioids, sedatives, hypnotics, anxiolytics, stimulants, and tobacco) and gambling disorder.¹⁴ Table 1 shows withdrawal symptoms listed in the DSM-5, organized by most crosscutting symptoms (symptoms seen across the most addictive disorders) to least crosscutting symptoms. Physical withdrawal symptoms from some substances (e.g., alcohol and cocaine) can be particularly salient because they can be life threatening and debilitating (e.g., seizures, vomiting). However, withdrawal from most substances is indicated more by psychological symptoms, such as anxiety, depressed or dysphoric mood, and irritability, with minimal physical symptoms. For example, nicotine withdrawal may include irritability, anxiety, difficulty concentrating, increased appetite, restlessness, depressed mood, and/or insomnia.

3 | CONTROVERSY ABOUT THE ADDICTIVENESS OF HP FOODS

As with historical debates about the addictive potential of cocaine and cigarettes, the ability of HP foods to trigger a withdrawal syndrome contributes to the ongoing debate about the addictive potential of HP foods.^{15,16} Chronic overconsumption of HP food is associated with a wide range of public health consequences, including rising rates of obesity, diet-related disease (e.g., diabetes), and binge eating (i.e., episodes of eating marked by loss of control).^{17–19} As with addictive substances (e.g., alcohol), many people consume HP foods to experience pleasure and are able to do so in moderation.²⁰ However, approximately 10%–15% of adults in the United States consume HP foods in a manner that is indicative of a SUD (i.e., an escalating, compulsive pattern of intake that continues despite negative consequences).²¹

Despite significant evidence that HP foods can trigger addictive processes (e.g., loss of control over consumption, continued use despite negative consequences, and intense cravings), the existence of a withdrawal syndrome when HP food intake is reduced is not yet well understood. Comprehensive examination of withdrawal in the context of HP food consumption will be a major step toward resolving the debate about whether these foods are addictive. As with nicotine, understanding which components of HP foods (e.g., refined

carbohydrates and fats) are most strongly implicated in withdrawal may aid in the identification of the addictive agent in these complex products. Further, withdrawal has major clinical relevance as a predictor of relapse and is an intervention target in SUD.^{11,12} If withdrawal occurs when HP food intake is reduced, it may contribute to high rates of dietary change failure.¹³ Research on this topic has been conducted but has never been scientifically reviewed.

4 | CURRENT EVIDENCE FOR HP FOOD WITHDRAWAL

Current evidence for HP food withdrawal from animal models and human research is described below. Key findings from animal research are outlined in Table 2. Key information from human research, including methodology, sample size, key findings, and effect sizes, are outlined in Table 3.

5 | ANIMAL MODELS OF HP FOOD WITHDRAWAL

Animals demonstrate affective and physical symptoms during withdrawal from several addictive substances, including nicotine, alcohol, and cannabis.^{43–45} Most animal models of substance withdrawal have been investigated in rodents.⁴⁶ Common physical indicators of withdrawal in rodents include teeth chattering, paw and body tremors, and wet dog shakes.^{47,48} Common affective indicators of withdrawal in rodents include increased anxiety (often measured by decreased time spent in the open area of an elevated plus maze and more marbles buried during a marble burying test) and depression (often measured by decreased spontaneous locomotor activity and more immobile time in a tail suspension test).^{48–50}

Like other addictive substances, animal models provide evidence that HP foods or ingredients in these foods (i.e., sugar or fat) can change the reward system in a manner that makes removal of these foods from the diet aversive due to the physical and affective symptoms that emerge.⁵¹ Neural reward changes in response to HP food withdrawal are particularly salient for adolescent rodents due to

TABLE 2 Current animal model evidence for HP food withdrawal

Animals express physical indicators of withdrawal during HP food withdrawal^{22,23}

Animals display affective indicators of withdrawal during HP food withdrawal^{24,25}

Animals show neural reward dysfunction during HP food withdrawal^{22–28}

Animals show increased CRF expression during HP food withdrawal²⁹

Animals show enhanced motivational drive/craving to consume HP food during HP food withdrawal^{26,30,31}

Animals show increased binge eating behavior during HP food withdrawal²⁸

TABLE 3 Current human evidence for HP food withdrawal

Sample size	Methods	Relevant finding	Cohen's d^a
231	Self-report Retrospective recall	The Highly Processed Food Withdrawal Scale (ProWS) shows good psychometric properties ³²	-
		The ProWS is associated with more failed lifetime weight loss attempts ³²	0.35
		The ProWS is associated with less self-reported success at cutting down on HP foods ³²	0.74
		Self-reported HP food withdrawal symptoms appear to follow the time course of withdrawal from addictive substances ³²	-
304	Parent report Retrospective recall	The Highly Processed Food Withdrawal Scale for Children (ProWS-C) shows good psychometric properties ³³	-
		The ProWS-C is associated with less parent-reported success at changing their child's diet ³³	0.55
		Parent-reported HP food withdrawal symptoms appear to follow the time course of withdrawal from addictive substances ³³	-
536	Self-report	29.7% of adults in a US community sample endorse withdrawal symptoms on the Yale Food Addiction Scale (YFAS) ³⁴	-
		20.3% of adults in a US community sample report strong craving for HP foods when trying to limit them ³⁴	-
1034	Self-report	18.5% of adults in a representative German sample endorse withdrawal symptoms on the YFAS ³⁵	-
51	Self-report	26% of adolescents with overweight or obesity seeking weight loss treatment endorse withdrawal symptoms on the YFAS ³⁶	-
82	Self-report	54.9% of adults with obesity and binge eating disorder endorse withdrawal symptoms on the YFAS ³⁷	-
25	Self-report Experimental	Adolescents report increased craving following abstinence from sugar-sweetened beverages ³⁸	0.91
		Adolescents report decreased motivation to do work following abstinence from sugar-sweetened beverages ³⁸	1.58
149	Self-report Experimental	Adolescents report improvement on total ProWS-C scores following abstinence from sugar-sweetened beverages ^{39b}	0.53
47 (online sources)	Qualitative coding Pragmatic content analysis	Consumers refer to withdrawal symptoms when sharing personal stories or advising others on how to reduce their sugar intake ⁴⁰	-
16	Qualitative interviews Reflexive thematic analysis	Individuals with food addiction report experiences of withdrawal ⁴¹	-
21	Qualitative interviews Thematic analysis	Parents report withdrawal-like symptoms in their children when they attempt to restrict their sugar-sweetened beverage intake ⁴²	-

^aCohen's d is a measure of effect size. Cohen's d values indicate small effects at $|d| > 0.2$, medium effects at $|d| > 0.5$, and large effects at $|d| > 0.8$.

^bThis finding is inconsistent with the withdrawal hypothesis.

higher cortical and subcortical concentrations of dopamine during this stage.⁵² Importantly, animals only demonstrate withdrawal-like symptoms after exposure to HP food and not following consumption of less rewarding, more nutritious foods like standard chow.^{53,54} Sugar is particularly effective in activating the mesolimbic dopamine system

and the removal of added sugar from the diet triggers higher intensity and more aversive symptoms of withdrawal relative to other macronutrients found in HP foods, like fat.^{26,55-57} However, patterns of withdrawal have also been observed in animals exposed to high-fat diets and cafeteria diets that include a range of HP foods with

elevated sugar and fat content (e.g., bread with cheese, muffins, and sausages).^{58,59}

Animals that are exposed to high levels of HP food and then returned to a standard diet demonstrate aversive physical and affective symptoms that mirror core withdrawal symptoms in animal models of substance withdrawal. Rats who have consumed high levels of sucrose exhibit physical signs of opioid-like withdrawal, such as teeth chattering and paw tremors when returned to standard chow.^{22,26} Young rats that have consumed a cafeteria diet show increased indicators of anxiety in an open field test (measured by time spent in the central area) following a shift to standard chow for 1 week.⁵⁸ Mice that received ad libitum access to a 10% sucrose solution and water for 4 weeks, followed by access to water only for 1 week, showed increased depressive-like symptoms (more immobile time in a tail suspension test) and anxiety-like symptoms (less time in the open arms of the elevated plus maze) compared with mice that only ever received water.²⁷ Withdrawal from sucrose in these mice was associated with decreased dopamine concentration in the nucleus accumbens, a key neural reward region.²⁷ Importantly, reinstatement of a 2% sucrose solution reversed both depressive- and anxiety-like symptoms.²⁷ Notably, the timeframe of emergence of withdrawal symptoms observed in these studies (within 24–36 h after last consumption of HP foods) mirrors the timeframe observed in animal studies of withdrawal from other addictive substances.^{43,44}

Another core component of withdrawal demonstrated by animal models is enhanced motivational drive to consume the substance, which can also be conceptualized as craving.²⁴ Animals exhibit craving for a substance by engaging in behavioral indicators that have previously been paired with administration of the substance (e.g., nose pokes and lever presses).^{24,28} This behavior is also seen when animals are withdrawn from HP foods. When HP foods are removed from the diet, rats exhibit general signs of anhedonia and low overall motivational drive.^{23,27,53} However, motivational drive to consume HP food increases. Animals given ad libitum access to a high-fat, high-sugar diet for 4 weeks and then switched to standard chow demonstrated increased craving for sucrose (measured by motivation to respond in an operant lever-press response task) at 2 weeks post diet change.²⁵ Interestingly, animals that are obesity prone (i.e., those that gain significant weight in response to HP foods in the diet, in contrast to those that do not gain weight when exposed to the same diet) appear to experience more craving than those that are not obesity prone, which suggests weight gain may have a moderating effect on experiences of HP food withdrawal.²⁵

Animal models of addictive substances have found increased motivation to seek out and consume the substance despite negative consequences in withdrawal states.⁶⁰ Similarly, rats who are withdrawn from high levels of HP food exhibit an increased desire for highly rewarding HP food at the expense of more nutritious (but less rewarding) options.^{23,53} For example, when rats are withdrawn from a cafeteria diet, they exhibit little motivation to consume chow and will risk receiving electric shocks to seek out HP food.⁵³

The corticotropin-releasing factor (CRF) system, a neural system that plays a key role in the biological stress response, is a key factor in

animal models of substance withdrawal.⁶¹ Frequent consumption of HP foods leads to withdrawal symptoms that are driven by the CRF system.^{30,31} After frequent HP food exposure, removal of HP food from the diet leads to increased biological (i.e., increased CRF expression) and behavioral (i.e., reduced exploratory behavior and increased aggression) indicators of stress.^{26,62,63} As with craving, obesity-prone animals appear to experience increased stress during HP food withdrawal, which further suggests weight gain may moderate experiences of HP food withdrawal.³¹ The reintroduction of HP food appears to have a calming effect that reduces stress responses, indicating suppression of withdrawal symptoms by reinstatement of the addictive agent, which is a critical process observed in withdrawal syndromes across substances in animals and humans.⁶²

Increased food intake is another known indicator of withdrawal in animal models of nicotine and stimulant withdrawal.^{29,64} Although binge eating behavior is not specifically recognized as a withdrawal symptom for established SUDs, increased appetite is a withdrawal symptom for tobacco and stimulants¹⁴ and may represent animals' attempts to reverse withdrawal symptoms through intake of a rewarding HP food. When animals that were previously exposed to a high-fat diet, then switched to standard chow, were presented with an HP food at 1 week post-diet change, female rats showed binge behavior that persisted at 4 weeks after the diet change.⁵⁹ Interestingly, rats that were exposed to a high-fat diet beginning in adolescence showed more binge behavior during withdrawal than for those that were exposed beginning in adulthood, which suggests that earlier consumption of HP food contributes to more adverse outcomes. For both age groups, binge behavior was accompanied by decreased expression of dopamine receptors in the nucleus accumbens, which did not normalize after 4 weeks on chow. This pattern is consistent with withdrawal in humans, as individuals who begin using substances earlier in life are at greater risk for experiencing SUD symptoms in adulthood, including withdrawal.^{65,66}

A recent review summarized the literature regarding animal models of withdrawal from obesogenic diets (most of which were high in HP foods).⁵¹ The authors identified several animal models consistent with early withdrawal, including behavioral and stress responses, and elaborated upon effects of these diets during long-term withdrawal. The review concluded that although many negative outcomes of obesogenic diets (e.g., metabolic syndrome) normalize with long-term withdrawal, reward dysfunction appears not to normalize over time. The authors also highlight important sex differences in withdrawal effects (e.g., dopaminergic downregulation in certain neural reward regions recover following withdrawal for males, but not females).

Although beneficial for building a preliminary understanding of biological and behavioral effects of HP food withdrawal, it is important to acknowledge that animal models are not directly analogous to the human experience. Although animal models often have strong internal validity, their external validity, or the degree to which they can be generalized to human experiences, is limited.⁶⁷ Aside from the obvious physiological differences between animals and humans, humans are subject to several psychosocial factors that are absent in

animal models (e.g., dieting histories and shape and weight concerns). Thus, human research is necessary to examine whether animal findings translate to humans.

6 | HUMAN MODELS OF HP FOOD WITHDRAWAL

In humans, some behavioral indicators of HP food withdrawal have been investigated. However, these studies have been subject to significant methodological limitations (most notably, a lack of experimental research). Biological indicators of withdrawal have not yet been investigated in humans. Here, we review the state of the literature, which is based mainly on qualitative and retrospective recall (see Table 3) and highlight the need for additional research in this area.

Anecdotal and self-report evidence for HP food withdrawal is common. Popular diets (i.e., Atkins and Whole30) instruct dieters to prepare for a “withdrawal” syndrome marked by headaches, fatigue, irritability, and cravings that follows the timeline of drug withdrawal (i.e., emerges in the first days after dietary change and peaks on Days 2–5).^{68,69} In recent years, scientists have conducted more research examining individuals' experiences of withdrawal when attempting to change their diets.

The recently developed Highly Processed Food Withdrawal Scale (ProWS)³² assesses a range of physical (e.g., headaches and fatigue), cognitive (e.g., difficulty concentrating), and affective (e.g., irritability, anxiety, anhedonia, and cravings) indicators of withdrawal in response to HP food reduction. Participants, particularly those with a higher body mass index (BMI) and a more addictive-like pattern of eating on the Yale Food Addiction Scale (YFAS), reported that withdrawal symptoms across all domains were common when they attempted to reduce their HP food intake. The intensity of HP food withdrawal on the ProWS also appears to follow the time course of substance withdrawal with the peak intensity of symptoms occurring 2–5 days after cutting down on HP foods. Greater endorsement of HP food withdrawal on the ProWS is associated with more failed lifetime weight loss attempts and less self-reported success in cutting down on HP foods.

The ProWS has also been adapted for parent-report of HP food withdrawal symptoms in children aged 3–11.³³ The Highly Processed Food Withdrawal Scale for Children (ProWS-C) measures the same range of physical, cognitive, and affective indicators of withdrawal in a developmentally appropriate way that is observable by parents. Parents who reported attempting to cut down on “junk food” in the past year were asked to report on their children's response to this dietary change. Parents endorsed a wide range of withdrawal indicators and those who reported more ProWS-C withdrawal symptoms following a diet change attempt perceived themselves as less successful at changing their child's diet. The ProWS-C accounted for unique variance in diet change success over and above children's BMI and other symptoms of addictive-like eating. The peak intensity of ProWS-C symptoms appeared to mirror the timeline of substance withdrawal and the ProWS, occurring 2–5 days after cutting down on HP foods. This is

consistent with the possibility that withdrawal-like symptoms may be contributing to the high rates of failure in the earlier stages of dietary change across the lifespan.

Self-report measures also provide preliminary evidence for HP food withdrawal. The YFAS is a commonly used measure that uses the diagnostic criteria for SUD (including withdrawal) to assess features associated with excessive or uncontrolled HP food consumption.³⁴ Endorsement of withdrawal is common on the YFAS. Specifically, 18.5%–29.7% of participants in community samples^{34,35} and 26%–54.9% in samples with overweight, obesity, and binge eating disorder^{36,37} report that when they cut down on HP foods, they “feel irritable, nervous, or sad” or “have physical symptoms like headache or fatigue” and these aversive experiences drive a return to prior levels of HP food consumption. 20.3% of adults also report experiencing strong cravings for HP foods when they try to limit them.³⁴

A recent experimental study of adolescents who drank three or more sugar-sweetened beverages per day showed increased craving and decreased motivation to do work following 3 days of abstaining from sugar-sweetened beverages, with similar results for low- and high-caffeine consumers.³⁸ In contrast, another experimental study with similar methods found that adolescents' symptoms (as measured by the ProWS-C, Caffeine Withdrawal Symptom Questionnaire, and qualitative interviews) improved overall following 3 days of abstinence from sugar-sweetened beverages.³⁹ These conflicting results call into question whether HP food withdrawal occurs in adolescents. However, both studies were limited by a lack of a randomized control group and lack of blinding.

Several qualitative studies suggest individuals report withdrawal-like symptoms when attempting to reduce their consumption of HP foods. A recent study showed that consumers regularly referred to withdrawal symptoms when sharing personal stories or advising others on how to reduce their sugar intake.⁴⁰ Some consumers directly compared cutting down on sugar intake to quitting an addictive drug: “I went cold turkey and went through physical withdrawal symptoms—it was like I was giving up a drug.” Some qualitative research studies have not found that people spontaneously identify withdrawal as a factor.⁷⁰ However, in a recent qualitative study where people with food addiction were directly asked about the experience of withdrawal, individuals did report experiencing it.⁴¹ For example, a female participant (age 45, severe food addiction) described the experience of negative physical and emotional consequences when eliminating sugar and carbohydrates from her diet: “It's usually when we cut carbs. So, the first couple of days, you kinda feel sluggish. And I was irritable, cutting away those sugar items ... I have zero patience or tolerance for things that normally wouldn't bother me. And then stopping carbohydrates, you get the headaches, being lethargic about it. So the first four to six days of stopping eating anything, I think that's the bulk of when that happens.” Most participants who endorsed withdrawal symptoms reported experiencing negative emotions and physical reactions as a result of removing HP foods. Another recent qualitative study examining parents' perceived barriers to reducing their children and adolescents' sugar-sweetened beverage consumption found that parents described withdrawal-like symptoms

in their children, including headaches, becoming more “moody,” and socially isolating, when they attempted to restrict their use.²²

7 | SUMMARY OF EXISTING EVIDENCE OF HP FOOD WITHDRAWAL

In summary, evidence suggests that HP food withdrawal occurs in animals. Well-controlled experimental animal studies have demonstrated behavioral and biological indicators of HP food withdrawal, which follow a similar time course to other addictive substances. Anecdotal and self-report evidence also suggests that humans experience withdrawal-like symptoms when they attempt to reduce their intake of HP foods. The reported symptoms and time course mirror withdrawal from other addictive substances. However, most current research on HP food withdrawal in humans is limited by a reliance on retrospective, self-report data. The two experimental studies conducted on the topic of withdrawal from sugar-sweetened beverages in adolescents have yielded mixed findings and both lacked a randomized control group.^{38,39} Thus, the current human evidence is not sufficient to establish the validity of HP food withdrawal. What remains unknown but important is whether indicators of HP food withdrawal can be observed in humans in real time and distinguished from other factors that may mimic withdrawal effects. Below, we outline future directions to address current gaps in research examining HP food withdrawal in humans, with consideration for alternative explanations and confounding factors.

8 | FUTURE RESEARCH DIRECTIONS ON HP FOOD WITHDRAWAL

Key future directions into the construct of HP food withdrawal are summarized in Table 4.

8.1 | Phenomenology and assessment of withdrawal symptoms

In SUD, although many withdrawal symptoms are observed across several substances, some withdrawal symptoms are unique to one specific substance (e.g., hypersomnia in stimulants).¹⁴ Scales that have

been developed to measure HP food withdrawal are based on existing measures of tobacco and cannabis withdrawal and have met basic thresholds for content, convergent, and discriminant validity in preliminary validation studies.^{32,33} However, if HP food withdrawal exists, there may be symptoms that are specific to this type of withdrawal that these scales currently miss (e.g., hypoglycemia). Qualitative studies may allow for identification of specific withdrawal presentations that may be unique to HP foods that could improve the validity of assessments.

8.2 | Time course of HP food withdrawal

Prospectively evaluating if and when withdrawal symptoms emerge in response to reduced HP food intake is another important step toward evaluating the validity of this construct. To establish the time course of HP food withdrawal, experimental studies may prospectively administer the ProWS or other assessments of withdrawal repeatedly during a controlled dietary change intervention. Ecological momentary assessment (EMA), where participants report their symptoms in real time, in their natural environment, may also illuminate fine-grained temporal changes in withdrawal symptoms.^{71–73} In other addictive substances, physical symptoms tend to peak earlier, whereas psychological symptoms can last for months after a quit attempt.⁷⁴ If HP food withdrawal does not follow a similar time course to other addictive substances, it may call into question whether symptoms experienced during diet change are indicative of withdrawal or some other phenomenon.

8.3 | Identify specific foods or ingredients that produce withdrawal upon cessation/reduction of consumption

Addictive substances are typically processed to alter their potency and speed of absorption into the bloodstream (i.e., processed from the coca leaf into powder cocaine). A substance's addictive potential (including potential for withdrawal) is increased by increasing the dose of the addictive ingredient and increasing the speed of absorption into the bloodstream.^{75,76} HP foods are similar to other addictive substances in that foods that are more processed and contain high concentrations of rapidly absorbed carbohydrates and fat are more commonly implicated in addictive-like eating than minimally processed foods.² Further research is needed to determine what specific component of HP food (e.g., degree of processing, macronutrient combinations, and rapidly absorbed refined carbohydrates) may be most strongly associated with withdrawal symptoms in humans. As with nicotine and cigarettes,⁷⁷ this may be beneficial in identifying what is the most addictive component in a substance as complex as HP foods. This may also point to novel interventions. Just as slow-release nicotine patch or gum was helpful in reducing withdrawal for smokers trying to quit,⁷⁷ there may be dietary parallels for individuals trying to cut down on HP food intake. For example, foods associated with rapid

TABLE 4 Future directions for HP food withdrawal research

1	Examine the phenomenology and assessment of withdrawal symptoms
2	Prospectively examine the time course of HP food withdrawal
3	Identify specific foods or ingredients that produce withdrawal upon cessation/reduction of consumption
4	Examine biological correlates of HP food withdrawal
5	Examine the role of withdrawal in maintaining HP food consumption

spikes and crashes in blood glucose (i.e., high-GI foods) have been associated with greater indicators of addictive eating.² It is plausible that consuming a diet that is composed of regular intake low GI carbohydrates (e.g., steel-cut oats and apples) that stabilize blood sugar and provide a lower dose and slower absorption of carbohydrates may be beneficial in reducing HP food withdrawal. Future research is needed to investigate these possibilities. If HP food withdrawal does not emerge in the context of removal of specific ingredients or combinations of ingredients, it may indicate that withdrawal-like symptoms experienced by people attempting to change their diets emerge in response to a process other than withdrawal.

8.4 | Biological correlates of HP food withdrawal

Withdrawal in SUD is associated with biological correlates in humans, including neurobiological differences. For example, SUD withdrawal is associated with elevated activation in reward-related brain regions (e.g., ACC and amygdala) in response to drug cues.^{78,79} Similarly, individuals show greater reactivity to food cues when fasting or calorically restricted.^{80,81} To expand upon this work, researchers may specifically examine whether withdrawal from HP foods, without caloric restriction, produces patterns of reward-related neural activation and cue reactivity similar to withdrawal from other addictive substances. This research would provide important information regarding the convergent validity of the HP food withdrawal construct.

It will also be important to examine hormonal changes during reduction of HP food consumption. Cortisol is significant due to its key role in the HPA axis and regulation of stress and blood glucose utilization,⁸² and cortisol dysfunction during drug withdrawal is associated with greater likelihood of relapse.^{83,84} There is evidence that cortisol increases in response to caloric restriction,⁸⁵ but there has been less examination of cortisol changes in response to changing the type of food consumed. Investigating whether reducing HP food intake also leads to dysfunction in cortisol response is an important future direction to test the validity of the HP food withdrawal construct.

8.5 | HP food withdrawal in the maintenance of HP food consumption

Withdrawal may also contribute to the motivation to maintain frequent intake of HP foods. Individuals with SUD that are not trying to quit often experience withdrawal symptoms between uses of a substance that emerge within hours of the last use.^{86,87} For example, a consistent pattern of smoking throughout the day (i.e., chain smoking) is thought to be driven in part by a desire to avoid aversive withdrawal symptoms that occur when nicotine levels drop between cigarettes.⁸⁸ Although these symptoms may not reach the same level of intensity that they would following multiple days of abstinence, they play an important role in facilitating the next use of the substance.⁷⁴ Thus, HP food withdrawal, if it exists, may motivate frequent HP food

intake among individuals not attempting to change their diet. Many HP foods are high GI and can cause spikes in blood glucose that are then followed by rapid decline in blood glucose.⁸⁹ This postprandial blood glucose dip has been associated with increases in negative affect (e.g., irritability and agitation).^{90,91} Thus, like chain smoking, blood glucose spikes and crashes associated with high-GI HP foods may drive a consistent and regular pattern of “chain snacking” to avoid aversive withdrawal symptoms. This idea is supported by recent research that found that dips in blood glucose driven by intake of high-carbohydrate HP foods predict sooner period to next eating and higher subsequent caloric intake.⁹² Future research may examine whether a relationship exists between glucose fluctuations, experiences of withdrawal, and continued consumption of HP foods. If this relationship does not exist, it may call into question the validity of the HP food withdrawal construct.

9 | ALTERNATIVE EXPLANATIONS AND METHODOLOGICAL CONSIDERATIONS FOR HP FOOD WITHDRAWAL RESEARCH

Experimentally controlled animal research allows for increased confidence in evidence for HP food withdrawal in animals. However, there are some important alternative explanations for current evidence of HP food withdrawal in humans. Future studies of HP food withdrawal should be designed to consider and account for these alternatives.

First, studies must be designed to distinguish between the effects of caloric deprivation and effects of specifically reducing HP foods, as participants may express withdrawal-like symptoms in response to caloric deprivation (e.g., irritability).⁹³ Further, given that increased appetite and subjective experiences of hunger are documented withdrawal symptoms for various substances,¹⁴ it will be important to understand whether these experiences are due to caloric deprivation or HP food withdrawal. Researchers can address this by providing intervention diets that are isocaloric (i.e., stable in calories) to the baseline diet and differ only in the proportion of HP foods. A recent study that found that reducing the proportion of added sugars in an isocaloric diet increased the reward value of high-sugar foods is an example of a study design that could be adapted to probe these questions.⁹⁴

Expectancy effects may also partially explain self-reported HP food withdrawal. Participants who have more negative expectancies about quitting a substance (i.e., expect to feel more discomfort) are more likely to experience withdrawal symptoms.⁹⁵ Double-blind placebo-controlled studies have been used to mitigate expectancy effects on withdrawal. For example, participants who were aware that they were switched from caffeinated to decaffeinated coffee experienced more withdrawal symptoms than those that were not aware of the change.⁹⁶ The ability to create a double-blind placebo-controlled diet is very challenging, as participants can see and taste what food they are consuming. Replacing sugar with artificial sweeteners may also be problematic, as artificial sweeteners also impact reward functioning.⁹⁷ Although the development of a completely double-blind

placebo-controlled methodology may be challenging to study changes in dietary intake, it will be important for experimenters interacting with participants to be blind to study hypotheses and for all study materials to be carefully reviewed to make sure they do not unintentionally increase negative expectancies about the experience of dietary change.

Several other alternative explanations for self-reported withdrawal symptoms should be considered in future research. Reported symptoms may be related to differences in cost and convenience between HP foods and minimally processed foods, which are more expensive and require more time and energy to plan and prepare. The effects of cost and convenience can be mitigated by ensuring experimental groups do not differ in these ways by directly providing food to participants. Withdrawal-like symptoms may also be driven by the experience of deprivation itself. Perhaps removing desirable foods initiates withdrawal-like symptoms, regardless of the processing level or content of the food. Research might account for this by comparing withdrawal symptoms when HP foods versus calorically equivalent, equally desirable minimally processed foods are removed from the diet. Withdrawal-like symptoms may also be related to social effects of abstaining from socially sanctioned HP foods (e.g., not being able to eat a piece of cake at a birthday party or missing social events to avoid HP foods). This effect may be more difficult to control for in non-laboratory-based settings. However, if studies are not able to fully control for these factors, they can be measured and analyzed to determine their impact on HP food withdrawal outcomes in more ecologically valid settings.

Unique alternative explanations may explain current evidence for HP food withdrawal in children, which currently relies on parent report. Parents are responsible for restricting their children's access to HP foods and often attempt to reduce HP food intake as a family. Thus, they may experience discomfort, fatigue, or their own symptoms of withdrawal that bias their perceptions of their children's behavior. Data collection from multiple informants (e.g., child self-report, teacher observation, and laboratory observation) will help mitigate the impact of parental bias. Additionally, if children do experience withdrawal-like symptoms when their access to HP food is restricted, these symptoms may be caused by experiences other than HP food withdrawal. For example, social isolation may result from children's perceptions that their new eating patterns make them different from their peers. Similarly, changes in children's mood could be due to difficulty with change in general, rather than the specific reduction of HP food. Controlled studies comparing the effects of reduction of HP food intake and other changes to children's daily lives will help distinguish HP food withdrawal from these alternative explanations.

10 | CONCLUSION

In conclusion, this review found compelling animal evidence for a withdrawal syndrome when HP foods are removed from the diet. These studies were well controlled and demonstrated behavioral and neural indicators of withdrawal in response to HP foods but not

nutritionally balanced chow. Thus, we confidently conclude that HP food withdrawal occurs in animals. To date, every substance that elicits signs of addiction in animals also elicits an addictive response in humans.⁷⁷ However, current research in humans is not yet adequate to establish a withdrawal syndrome for HP foods. Compelling preliminary evidence shows that humans subjectively experience withdrawal-like symptoms when reducing their consumption of HP foods, which is associated with perceived decreased success at maintaining a healthier diet. However, human research thus far has been mostly limited to retrospective self-report and experimental studies are mixed, allowing for several potential alternative explanations for results. This highlights the need for further prospective and experimental research. Expanding our understanding of whether HP food withdrawal exists in humans represents a crucial step toward determining the addictive potential of HP foods and may aid in the development of novel approaches to address the widespread overconsumption of HP foods to prevent and treat obesity. Future prospective and experimental research examining HP food withdrawal in humans is an important future direction to investigate the validity and clinical utility of considering HP food withdrawal and addiction.

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CONFLICT OF INTEREST

The authors have no known conflicts of interest to disclose.

ORCID

Lindsey Parnarouskis  <https://orcid.org/0000-0002-9208-0516>

REFERENCES

1. Monteiro CA, Cannon G, Moubarac J-C, Levy RB, Louzada MLC, Jaime PC. The UN decade of nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr.* 2018;21(1): 5-17. doi:10.1017/S1368980017000234
2. Schulte EM, Avena NM, Gearhardt AN. Which foods may be addictive? The roles of processing, fat content, and glycemic load. *PLoS ONE.* 2015;10(2):e0117959. doi:10.1371/journal.pone.0117959
3. Steele EM, Baraldi LG, da Costa Louzada ML, Moubarac J-C, Mozaffarian D, Monteiro CA. Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. *BMJ Open.* 2016;6(3):e009892. doi:10.1136/bmjopen-2015-009892
4. Lennerz B, Lennerz JK. Food addiction, high-glycemic-index carbohydrates, and obesity. *Clin Chem.* 2018;64(1):64-71. doi:10.1373/clinchem.2017.273532
5. Small DM, DiFeliceantonio AG. Processed foods and food reward. *Science.* 2019;363(6425):346-347. doi:10.1126/science.aav0556
6. Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. *Arch Gen Psychiatry.* 2011;68(8): 808-816. doi:10.1001/archgenpsychiatry.2011.32
7. Gearhardt AN, Schulte EM. Is food addictive? A review of the science. *Annu Rev Nutr.* 2021;41(1):387-410. doi:10.1146/annurev-nutr-110420-111710
8. Schulte EM, Gearhardt AN. Associations of food addiction in a sample recruited to be nationally representative of the United States. *Eur Eat Disord Rev.* 2018;26(2):112-119. doi:10.1002/erv.2575

9. Oliveira J, Colombaroli MS, Cordás TA. Prevalence and correlates of food addiction: systematic review of studies with the YFAS 2.0. *Obes Res Clin Pract.* 2021;15(3):191-204. doi:10.1016/j.orcp.2021.03.014
10. Fielding-Singh P, Patel ML, King AC, Gardner CD. Baseline psychosocial and demographic factors associated with study attrition and 12-month weight gain in the DIETFITS trial. *Obesity.* 2019;27(12):1997-2004. doi:10.1002/oby.22650
11. Becker HC. Alcohol dependence, withdrawal, and relapse. *Alcohol Res Health.* 2008;31(4):348-361.
12. Piasecki TM, Jorenby DE, Smith SS, Fiore MC, Baker TB. Smoking withdrawal dynamics: II. Improved tests of withdrawal-relapse relations. *J Abnorm Psychol.* 2003;112(1):14-27. doi:10.1037/0021-843X.112.1.14
13. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Med Clin North Am.* 2018;102(1):183-197. doi:10.1016/j.mcna.2017.08.012
14. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub; 2013.
15. Fletcher PC, Kenny PJ. Food addiction: a valid concept? *Neuropsychopharmacology.* 2018;43(13):2506-2513. doi:10.1038/s41386-018-0203-9
16. Gearhardt AN, Hebebrand J. The concept of "food addiction" helps inform the understanding of overeating and obesity: debate consensus. *Am J Clin Nutr.* 2021;113(2):274-276. doi:10.1093/ajcn/nqaa345
17. Fiolet T, Srour B, Sellem L, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *Bmj.* 2018;360:k322.
18. Schnabel L, Kesse-Guyot E, Allès B, et al. Association between ultra-processed food consumption and risk of mortality among middle-aged adults in France. *JAMA Intern Med.* 2019;179(4):490-498. doi:10.1001/jamainternmed.2018.7289
19. Willett W, Rockström J, Loken B, et al. Food in the Anthropocene: the EAT–Lancet commission on healthy diets from sustainable food systems. *The Lancet.* 2019;393(10170):447-492. doi:10.1016/S0140-6736(18)31788-4
20. Schulte EM, Smeal JK, Gearhardt AN. Foods are differentially associated with subjective effect report questions of abuse liability. *PLoS ONE.* 2017;12(8):e0184220. doi:10.1371/journal.pone.0184220
21. Meule A, Gearhardt AN. Ten years of the Yale food addiction scale: a review of version 2.0. *Curr Addict Rep.* 2019;1-11.
22. Colantuoni C, Rada P, McCarthy J, et al. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes Res.* 2012;10(6):478-488. doi:10.1038/oby.2002.66
23. Teegarden SL, Bale TL. Decreases in dietary preference produce increased emotionality and risk for dietary relapse. *Biol Psychiatry.* 2007;61(9):1021-1029. doi:10.1016/j.biopsych.2006.09.032
24. Koskela M, Piepponen TP, Andressoo J-O, Vöikar V, Airavaara M. Towards developing a model to study alcohol drinking and craving in female mice housed in automated cages. *Behav Brain Res.* 2018;352:116-124. doi:10.1016/j.bbr.2018.03.027
25. Pickering C, Alsjö J, Hulting A-L, Schiöth HB. Withdrawal from free-choice high-fat high-sugar diet induces craving only in obesity-prone animals. *Psychopharmacology (Berl).* 2009;204(3):431-443. doi:10.1007/s00213-009-1474-y
26. Avena NM, Bocarsly ME, Rada P, Kim A, Hoebel BG. After daily bingeing on a sucrose solution, food deprivation induces anxiety and accumbens dopamine/acetylcholine imbalance. *Physiol Behav.* 2008;94(3):309-315. doi:10.1016/j.physbeh.2008.01.008
27. Kim S, Shou J, Abera S, Ziff EB. Sucrose withdrawal induces depression and anxiety-like behavior by Kir2.1 upregulation in the nucleus accumbens. *Neuropharmacology.* 2018;130:10-17. doi:10.1016/j.neuropharm.2017.11.041
28. Xu W, Hong Q, Lin Z, et al. Role of nucleus accumbens microRNA-181a and MeCP2 in incubation of heroin craving in male rats. *Psychopharmacology (Berl).* 2021;1-12:2313-2324. doi:10.1007/s00213-021-05854-3
29. Bunney PE, Burroughs D, Hernandez C, LeSage MG. The effects of nicotine self-administration and withdrawal on concurrently available chow and sucrose intake in adult male rats. *Physiol Behav.* 2016;154:49-59. doi:10.1016/j.physbeh.2015.11.002
30. Cottone P, Sabino V, Roberto M, et al. CRF system recruitment mediates dark side of compulsive eating. *Proc Natl Acad Sci.* 2009;106(47):20016-20020. doi:10.1073/pnas.0908789106
31. Parylak SL, Koob GF, Zorrilla EP. The dark side of food addiction. *Physiol Behav.* 2011;104(1):149-156. doi:10.1016/j.physbeh.2011.04.063
32. Schulte EM, Smeal JK, Lewis J, Gearhardt AN. Development of the highly processed food withdrawal scale. *Appetite.* 2018;131:148-154. doi:10.1016/j.appet.2018.09.013
33. Parnarouskis L, Schulte EM, Lumeng JC, Gearhardt AN. Development of the highly processed food withdrawal scale for children. *Appetite.* 2020;104553.
34. Gearhardt AN, Corbin WR, Brownell KD. Development of the Yale food addiction scale version 2.0. *Psychol Addict Behav.* 2016;30(1):113-121. doi:10.1037/adb0000136
35. Hauck C, Weiss A, Schulte EM, Meule A, Ellrott T. Prevalence of 'food addiction' as measured with the Yale food addiction scale 2.0 in a representative German sample and its association with sex, age and weight categories. *Obes Facts.* 2017;10(1):12-24. doi:10.1159/000456013
36. Gearhardt AN, White MA, Masheb RM, Morgan PT, Crosby RD, Grilo CM. An examination of the food addiction construct in obese patients with binge eating disorder. *Int J Eat Disord.* 2012;45(5):657-663. doi:10.1002/eat.20957
37. Meule A, Hermann T, Kübler A. Food addiction in overweight and obese adolescents seeking weight-loss treatment. *Eur Eat Disord Rev.* 2015;23(3):193-198. doi:10.1002/erv.2355
38. Falbe J, Thompson HR, Patel A, Madsen KA. Potentially addictive properties of sugar-sweetened beverages among adolescents. *Appetite.* 2019;133:130-137. doi:10.1016/j.appet.2018.10.032
39. Kaidbey JH, Ferguson K, Halberg SE, et al. Stop the pop: a mixed-methods study examining children's physical and emotional responses during three days of sugary drink cessation. *Nutrients.* 2022;14(7):1328. doi:10.3390/nu14071328
40. Rodda SN, Booth N, Brittain M, McKean J, Thornley S. I was truly addicted to sugar: a consumer-focused classification system of behaviour change strategies for sugar reduction. *Appetite.* 2020;144:104456. doi:10.1016/j.appet.2019.104456
41. Schiestl ET, Wolfson JA, Gearhardt AN. The qualitative evaluation of the Yale food addiction scale 2.0. *Appetite.* 2022;175:106077. doi:10.1016/j.appet.2022.106077
42. Sylvetsky AC, Visek AJ, Turvey C, et al. Parental concerns about child and adolescent caffeinated sugar-sweetened beverage intake and perceived barriers to reducing consumption. *Nutrients.* 2020;12(4):885. doi:10.3390/nu12040885
43. Chellian R, Behnood-Rod A, Bruijnzeel DM, Wilson R, Pandey V, Bruijnzeel AW. Rodent models for nicotine withdrawal. *J Psychopharmacol.* 2021;02698811211005629.
44. de Guglielmo G, Kallupi M, Cole MD, George O. Voluntary induction and maintenance of alcohol dependence in rats using alcohol vapor self-administration. *Psychopharmacology (Berl).* 2017;234(13):2009-2018. doi:10.1007/s00213-017-4608-7
45. Justinova Z. Animal models of cannabis use disorder. In: *Cannabis Use Disorders*. Springer; 2019:63-74.
46. Kuhn BN, Kalivas PW, Bobadilla A-C. Understanding addiction using animal models. *Front Behav Neurosci.* 2019;13:262. doi:10.3389/fnbeh.2019.00262

47. Rodgers HM, Lim S-A, Yow J, et al. Dopamine D1 or D3 receptor modulators prevent morphine tolerance and reduce opioid withdrawal symptoms. *Pharmacol Biochem Behav.* 2020;194:172935. doi:10.1016/j.pbb.2020.172935
48. Ponzoni L, Moretti M, Sala M, et al. Different physiological and behavioural effects of e-cigarette vapour and cigarette smoke in mice. *Eur Neuropsychopharmacol.* 2015;25(10):1775-1786. doi:10.1016/j.euroneuro.2015.06.010
49. Li W, Zuo W, Wu W, et al. Activation of glycine receptors in the lateral habenula rescues anxiety- and depression-like behaviors associated with alcohol withdrawal and reduces alcohol intake in rats. *Neuropharmacology.* 2019;157:107688. doi:10.1016/j.neuropharm.2019.107688
50. Shabani S, Schmidt B, Ghimire B, et al. Depression-like symptoms of withdrawal in a genetic mouse model of binge methamphetamine intake. *Genes Brain Behav.* 2019;18(3):e12533. doi:10.1111/gbb.12533
51. Casagrande BP, Estadella D. Withdrawing from obesogenic diets: benefits and barriers in the short-and long-term in rodent models. *Am J Physiol Endocrinol Metab.* 2020;319(3):E485-E493. doi:10.1152/ajpendo.00174.2020
52. Reichelt AC, Rank MM. The impact of junk foods on the adolescent brain. *Birth Defects Res.* 2017;109(20):1649-1658. doi:10.1002/bdr2.1173
53. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci.* 2010;13(5):635-641. doi:10.1038/nn.2519
54. Iemolo A, Valenza M, Tozier L, et al. Withdrawal from chronic, intermittent access to a highly palatable food induces depressive-like behavior in compulsive eating rats. *Behav Pharmacol.* 2012;23(5 and 6):593-602. doi:10.1097/FBP.0b013e328357697f
55. DiFeliceantonio AG, Coppin G, Rigoux L, et al. Supra-additive effects of combining fat and carbohydrate on food reward. *Cell Metab.* 2018;28(1):33-44.e3. doi:10.1016/j.cmet.2018.05.018
56. Avena NM, Rada P, Hoebel BG. Sugar and fat bingeing have notable differences in addictive-like behavior. *J Nutr.* 2009;139(3):623-628. doi:10.3945/jn.108.097584
57. Rada P, Avena NM, Hoebel BG. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. *Neuroscience.* 2005;134(3):737-744. doi:10.1016/j.neuroscience.2005.04.043
58. Lalanza JF, Caimari A, Del Bas JM, et al. Effects of a post-weaning cafeteria diet in young rats: metabolic syndrome, reduced activity and low anxiety-like behaviour. *PLoS ONE.* 2014;9(1):e85049. doi:10.1371/journal.pone.0085049
59. Carlin JL, McKee SE, Hill-Smith T, et al. Removal of high-fat diet after chronic exposure drives binge behavior and dopaminergic dysregulation in female mice. *Neuroscience.* 2016;326:170-179. doi:10.1016/j.neuroscience.2016.04.002
60. Deroche-Gamonet V, Piazza PV. Psychobiology of cocaine addiction: contribution of a multi-symptomatic animal model of loss of control. *Neuropharmacology.* 2014;76:437-449. doi:10.1016/j.neuropharm.2013.07.014
61. Roberto M, Spierling S, Kirson D, Zorrilla E. Corticotropin releasing factor (CRF) and addictive behaviors. *Int Rev Neurobiol.* 2017;136:5. doi:10.1016/bs.irn.2017.06.004
62. Cottone P, Sabino V, Steardo L, Zorrilla EP. Consummatory, anxiety-related and metabolic adaptations in female rats with alternating access to preferred food. *Psychoneuroendocrinology.* 2009;34(1):38-49. doi:10.1016/j.psyneuen.2008.08.010
63. Colantuoni C, Rada P, McCarthy J, et al. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes Res.* 2002;10(6):478-488. doi:10.1038/oby.2002.66
64. Orsini CA, Ginton G, Shimp KG, Avena NM, Gold MS, Setlow B. Food consumption and weight gain after cessation of chronic amphetamine administration. *Appetite.* 2014;78:76-80. doi:10.1016/j.appet.2014.03.013
65. Spear LP. Effects of adolescent alcohol consumption on the brain and behaviour. *Nat Rev Neurosci.* 2018;19(4):197-214. doi:10.1038/nrn.2018.10
66. Salmanzadeh H, Ahmadi-Soleimani SM, Pachenari N, et al. Adolescent drug exposure: a review of evidence for the development of persistent changes in brain function. *Brain Res Bull.* 2020;156:105-117. doi:10.1016/j.brainresbull.2020.01.007
67. Pound P, Ritskes-Hoitinga M. Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail. *J Transl Med.* 2018;16(1):1-8. doi:10.1186/s12967-018-1678-1
68. Whole30 Goodness. The Whole30 timeline, version 2.0. 2013. <https://whole30.com/2013/08/revise-timeline/>
69. Atkins RC. *Dr. Atkins' Diet Revolution.* Bantam Books New York; 1981.
70. Malika NM, Hayman LW Jr, Miller AL, Lee HJ, Lumeng JC. Low-income women's conceptualizations of food craving and food addiction. *Eat Behav.* 2015;18:25-29. doi:10.1016/j.eatbeh.2015.03.005
71. Bujarski S, Roche DJ, Sheets ES, Krull JL, Guzman I, Ray LA. Modeling naturalistic craving, withdrawal, and affect during early nicotine abstinence: a pilot ecological momentary assessment study. *Exp Clin Psychopharmacol.* 2015;23(2):81-89. doi:10.1037/a0038861
72. Epstein DH, Preston KL. Daily life hour by hour, with and without cocaine: an ecological momentary assessment study. *Psychopharmacology (Berl).* 2010;211(2):223-232. doi:10.1007/s00213-010-1884-x
73. Ferguson SG, Shiffman S, Gwaltney CJ. Does reducing withdrawal severity mediate nicotine patch efficacy? A randomized clinical trial. *J Consult Clin Psychol.* 2006;74(6):1153-1161. doi:10.1037/0022-006X.74.6.1153
74. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology.* 2001;24(2):97-129. doi:10.1016/S0893-133X(00)00195-0
75. Verebey K, Gold MS. From coca leaves to crack: the effects of dose and routes of administration in abuse liability. *Psychiatric Annals.* 1988;18(9):513-520. doi:10.3928/0048-5713-19880901-06
76. Henningfield JE, Keenan RM. Nicotine delivery kinetics and abuse liability. *J Consult Clin Psychol.* 1993;61(5):743-750. doi:10.1037/0022-006X.61.5.743
77. US Department of Health and Human Services. The health and consequences of smoking. Nicotine addiction: a report of the surgeon general. *US Department of Health and Human Services.* 1988.
78. Gloria R, Angelos L, Schaefer HS, et al. An fMRI investigation of the impact of withdrawal on regional brain activity during nicotine anticipation. *Psychophysiology.* 2009;46(4):681-693. doi:10.1111/j.1469-8986.2009.00823.x
79. Murphy A, Lubman DI, McKie S, et al. Time-dependent neuronal changes associated with craving in opioid dependence: an fMRI study. *Addict Biol.* 2018;23(5):1168-1178. doi:10.1111/adb.12554
80. Pursey KM, Stanwell P, Callister RJ, Brain K, Collins CE, Burrows TL. Neural responses to visual food cues according to weight status: a systematic review of functional magnetic resonance imaging studies. *Front Nutr.* 2014;1(7):1-11. doi:10.3389/fnut.2014.00007
81. Stice E, Burger KS, Yokum S. Caloric deprivation increases responsibility of attention and reward brain regions to intake, anticipated intake, and images of palatable foods. *Neuroimage.* 2013;67:322-330. doi:10.1016/j.neuroimage.2012.11.028
82. Thau L, Sharma S. Physiology, cortisol. In: StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC; 2020.

83. George O, Le Moal M, Koob GF. Allostasis and addiction: role of the dopamine and corticotropin-releasing factor systems. *Physiol Behav.* 2012;106(1):58-64. doi:10.1016/j.physbeh.2011.11.004
84. Sinha R. New findings on biological factors predicting addiction relapse vulnerability. *Curr Psychiatry Rep.* 2011;13(5):398-405. doi:10.1007/s11920-011-0224-0
85. Tomiyama AJ, Mann T, Vinas D, Hunger JM, DeJager J, Taylor SE. Low calorie dieting increases cortisol. *Psychosom Med.* 2010;72(4):357-364. doi:10.1097/PSY.0b013e3181d9523c
86. Hendricks PS, Ditre JW, Drobles DJ, Brandon TH. The early time course of smoking withdrawal effects. *Psychopharmacology (Berl).* 2006;187(3):385-396. doi:10.1007/s00213-006-0429-9
87. Farrell M. Opiate withdrawal. *Addiction.* 1994;89(11):1471-1475.
88. Chandra S, Scharf D, Shiffman S. Within-day temporal patterns of smoking, withdrawal symptoms, and craving. *Drug Alcohol Depend.* 2011;117(2-3):118-125. doi:10.1016/j.drugalcdep.2010.12.027
89. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *Jama.* 2002;287(18):2414-2423. doi:10.1001/jama.287.18.2414
90. Deary IJ, Zammit NN. Symptoms of hypoglycaemia and effects on mental performance and emotions. In: Frier BM, Heller SR, McCrimmon RJ, eds. *Hypoglycaemia in Clinical Diabetes.* United Kingdom: John Wiley & Sons, Ltd.; 2014:23-45.
91. Strachan M, Deary IJ, Ewing F, Frier BM. Recovery of cognitive function and mood after severe hypoglycemia in adults with insulin-treated diabetes. *Diabetes Care.* 2000;23(3):305-312.
92. Wyatt P, Berry SE, Finlayson G, et al. Postprandial glycaemic dips predict appetite and energy intake in healthy individuals. *Nat Metab.* 2021;3(4):523-529. doi:10.1038/s42255-021-00383-x
93. Watkins E, Serpell L. The psychological effects of short-term fasting in healthy women. *Front Nutr.* 2016;3:27. doi:10.3389/fnut.2016.00027
94. Flack KD, Uffholz K, Casperson S, Jahns L, Johnson L, Roemmich JN. Decreasing the consumption of foods with sugar increases their reinforcing value: a potential barrier for dietary behavior change. *J Acad Nutr Diet.* 2019;119(7):1099-1108. doi:10.1016/j.jand.2018.12.016
95. Hendricks PS, Leventhal AM. Abstinence-related expectancies predict smoking withdrawal effects: implications for possible causal mechanisms. *Psychopharmacology (Berl).* 2013;230(3):363-373. doi:10.1007/s00213-013-3169-7
96. Rubin G, Smith AP. Caffeine withdrawal and headaches. *Nutr Neurosci.* 1999;2(2):123-126. doi:10.1080/1028415X.1999.11747270
97. Yunker AG, Alves JM, Luo S, et al. Obesity and sex-related associations with differential effects of sucralose vs sucrose on appetite and reward processing: a randomized crossover trial. *JAMA Netw Open.* 2021;4(9):e2126313. doi:10.1001/jamanetworkopen.2021.26313
98. Dolman JM, Hawkes ND. Combining the audit questionnaire and biochemical markers to assess alcohol use and risk of alcohol withdrawal in medical inpatients. *Alcohol Alcohol.* 2005;40(6):515-519. doi:10.1093/alcac/agh189
99. Duka T, Townshend JM, Collier K, Stephens DN. Kindling of withdrawal: a study of craving and anxiety after multiple detoxifications in alcoholic inpatients. *Alcohol Clin Exp Res.* 2002;26(6):785-795. doi:10.1111/j.1530-0277.2002.tb02606.x
100. Liakoni E, Edwards KC, St. Helen G, et al. Effects of nicotine metabolic rate on withdrawal symptoms and response to cigarette smoking after abstinence. *Clin Pharmacol Ther.* 2019;105(3):641-651. doi:10.1002/cpt.1238
101. Rubinstein ML, Benowitz NL, Auerback GM, Moscicki A-B. Rate of nicotine metabolism and withdrawal symptoms in adolescent light smokers. *Pediatrics.* 2008;122(3):e643-e647. doi:10.1542/peds.2007-3679
102. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther.* 2016;18(S2):S2-3-S2-13. doi:10.1089/dia.2015.0417
103. Herrmann ES, Weerts EM, Vandrey R. Sex differences in cannabis withdrawal symptoms among treatment-seeking cannabis users. *Exp Clin Psychopharmacol.* 2015;23(6):415-421. doi:10.1037/pha0000053
104. Xu J, Azizian A, Monterosso J, et al. Gender effects on mood and cigarette craving during early abstinence and resumption of smoking. *Nicotine Tob.* 2008;10(11):1653-1661. doi:10.1080/14622200802412929
105. Johnston LD, Miech RA, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. Monitoring the future national survey results on drug use, 1975-2018: overview, key findings on adolescent drug use. Institute for Social Research. 2019.
106. Miles G, Siega-Riz AM. Trends in food and beverage consumption among infants and toddlers: 2005-2012. *Pediatrics.* 2017;139(6):e20163290. doi:10.1542/peds.2016-3290
107. Reedy J, Krebs-Smith SM. Dietary sources of energy, solid fats, and added sugars among children and adolescents in the United States. *J Am Diet Assoc.* 2010;110(10):1477-1484. doi:10.1016/j.jada.2010.07.010
108. Ohannessian CM, Finan LJ, Schulz J, Hesselbrock V. A long-term longitudinal examination of the effect of early onset of alcohol and drug use on later alcohol abuse. *Subst Abuse.* 2015;36(4):440-444. doi:10.1080/08897077.2014.989353
109. Aldwin CM, Skinner EA, Zimmer-Gembeck MJ, Taylor AL. Coping and self-regulation across the life span. In: Fingerman K, Berg C, Smith J, Antonucci T, eds. *Handbook of Life-Span Development.* Springer Publishing Company; 2011.
110. De Luca CR, Leventer RJ. Developmental trajectories of executive functions across the lifespan. In: Anderson V, Jacobs R, Anderson P, eds. *Executive Functions and the Frontal Lobes.* New York: Psychology Press; 2010:57-90.
111. Burrows T, Skinner J, Joyner M, Palmieri J, Vaughan K, Gearhardt AN. Food addiction in children: associations with obesity, parental food addiction and feeding practices. *Eat Behav.* 2017;26:114-120. doi:10.1016/j.eatbeh.2017.02.004
112. Epstein LH, Paluch RA, Roemmich JN, Beecher MD. Family-based obesity treatment, then and now: twenty-five years of pediatric obesity treatment. *Health Psychol.* 2007;26(4):381-391. doi:10.1037/0278-6133.26.4.381
113. Connors GJ, Maisto SA, Donovan DM. Conceptualizations of relapse: a summary of psychological and psychobiological models. *Addiction.* 1996;91(12s1):5-14. doi:10.1111/j.1360-0443.1996.tb02323.x
114. Kenford SL, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Predicting relapse back to smoking: contrasting affective and physical models of dependence. *J Consult Clin Psychol.* 2002;70(1):216-227. doi:10.1037/0022-006X.70.1.216
115. Hall SM, Muñoz RF, Reus VI, et al. Mood management and nicotine gum in smoking treatment: a therapeutic contact and placebo-controlled study. *J Consult Clin Psychol.* 1996;64(5):1003-1008. doi:10.1037/0022-006X.64.5.1003
116. Ferguson SG, Shiffman S. The relevance and treatment of cue-induced cravings in tobacco dependence. *J Subst Abuse Treat.* 2009;36(3):235-243. doi:10.1016/j.jsat.2008.06.005
117. Witkiewitz KA, Marlatt GA. *Therapist's Guide to Evidence-Based Relapse Prevention.* Elsevier; 2011.
118. Skelton J, Beech B. Attrition in paediatric weight management: a review of the literature and new directions. *Obes Rev.* 2011;12(5):e273-e281. doi:10.1111/j.1467-789X.2010.00803.x

119. Jiandani D, Wharton S, Rotondi MA, Ardern CI, Kuk JL. Predictors of early attrition and successful weight loss in patients attending an obesity management program. *BMC Obesity*. 2016;3(1):14. doi:[10.1186/s40608-016-0098-0](https://doi.org/10.1186/s40608-016-0098-0)
120. Molendijk M, Molero P, Sánchez-Pedreño FO, Van der Does W, Martínez-González MA. Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. *J Affect Disord*. 2018;226:346-354. doi:[10.1016/j.jad.2017.09.022](https://doi.org/10.1016/j.jad.2017.09.022)
121. Martin CK, O'neil PM, Pawlow L. Changes in food cravings during low-calorie and very-low-calorie diets. *Obesity*. 2006;14(1):115-121. doi:[10.1038/oby.2006.14](https://doi.org/10.1038/oby.2006.14)
122. Schlam TR, Baker TB. Interventions for tobacco smoking. *Annu Rev Clin Psychol*. 2013;9(1):675-702. doi:[10.1146/annurev-clinpsy-050212-185602](https://doi.org/10.1146/annurev-clinpsy-050212-185602)
123. Witkiewitz K, Bowen S, Donovan DM. Moderating effects of a craving intervention on the relation between negative mood and heavy drinking following treatment for alcohol dependence. *J Consult Clin Psychol*. 2011;79(1):54-63. doi:[10.1037/a0022282](https://doi.org/10.1037/a0022282)
124. Dimeff LA, Linehan MM. Dialectical behavior therapy for substance abusers. *Addict Sci Clin Pract*. 2008;4(2):39-47. doi:[10.1151/ascp084239](https://doi.org/10.1151/ascp084239)
125. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009;3:CD002209.
126. West R, Baker CL, Cappelleri JC, Bushmakin AGJP. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology (Berl)*. 2008;197(3):371-377. doi:[10.1007/s00213-007-1041-3](https://doi.org/10.1007/s00213-007-1041-3)

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