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ADDICTIONS (M POTENZA AND E DEVITO, SECTION EDITORS)

Advances in the Neurobiology of Food Addiction

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Abstract

Purpose of Review To summarize recent neurobiological evidence for (1) the addictive potential of ultra-processed foods and (2) the utility of food addiction, defined by behavioral criteria, as a clinically meaningful type of disordered eating.

Recent Findings Ultra-processed foods appear to be capable of triggering biobehavioral mechanisms associated with addiction (e.g., dopaminergic sensitization, enhanced motivation), whereas naturally occurring foods do not appear to produce addictive-like responses. Neuroimaging studies have elucidated parallel mechanisms in food addiction and substance-use disorders, including dopaminergic dysfunction, emotion dysregulation, and impulsivity. Emerging data has also suggested biological distinctions for individuals with food addiction evident by the brain-gut-microbiome connection, hormones, and genetics.

Summary Existing evidence has yielded convincing findings for overlapping features of ultra-processed foods and drugs of abuse. Preliminary findings from neurobiological studies of individuals with food addiction have revealed similar neural pathways triggered by food and related stimuli as observed in prior studies of persons with substance-use disorders.

Keywords Food addiction · Obesity · Ultra-processed foods

Introduction

In the past decade, empirical attention and public interest for the construct of food addiction has grown. Food addiction is a framework positing that some individuals may exhibit addictive-like behavioral responses to certain foods, akin to a substance-use disorder (SUD). While food addiction is not presently a diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1], the construct has been commonly operationalized using the Yale Food Addiction Scale (YFAS) [2, 3]. The current version of the YFAS, the YFAS 2.0 [3], is a self-report measure that directly adapts the eleven DSM-5 diagnostic criteria for SUDs to assess indicators of addictive-like consumption towards certain foods. These eleven criteria are consumed more than planned, unable to cut down or stop, great deal of time spent consuming/recovering, important activities given up, use despite physical/emotional consequences, tolerance, withdrawal, craving, failure to fulfill role obligations, use despite interpersonal/social consequences, and use in physically hazardous situations. This measure can be scored to reflect the number of the eleven diagnostic symptoms met or a dichotomous "diagnostic" cut-off for individuals who endorsed at least two symptoms plus clinically significant impairment or distress [3], which parallels the diagnostic threshold for SUDs in the DSM-5. Demonstrating its wide scope of use to assess food addiction globally and across the lifespan, the YFAS and YFAS 2.0 have been translated into numerous languages (e.g., Spanish, French, German, Italian, and Arabic) [4–8] and adapted for use with children and adolescents [9, 10].

The prevalence of food addiction, as defined by the YFAS, among the general population in the USA has been

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estimated around 13–15% [11, 12••], which is comparable with rates of SUDs for legal substances (14% for alcohol-use disorder [13]; 20% for nicotine-use disorder [14]). Notably, the prevalence of food addiction is higher among individuals with obesity (25%) [12••] and most elevated among those with binge-type eating disorders (e.g., 42–92% of individuals with binge eating disorder (BED) [15–17]). Individuals who meet criteria for food addiction and an eating disorder, such as BED, appear to exhibit more severe binge eating and psychopathology compared to those with only BED [15, 18, 19]. In addition, persons who meet criteria for food addiction in the absence of other eating disorders present with significant impairment, distress, and depressive symptoms [20], suggesting unique psychological features of food addiction. Thus, food addiction appears to reflect a clinically meaningful presentation that has overlap with, but is distinct from, obesity and eating disorders.

The conceptualization of food addiction from a SUD perspective also posits theoretical mechanisms that are not considered to be causal contributors to obesity and eating disorders. Most centrally, the SUD framework necessitates the role of an addictive substance that directly influences and produces the behavioral diagnostic criteria in vulnerable individuals. As such, the food addiction framework asserts that certain foods exhibit an addictive potential that triggers compulsive consumption in susceptible persons [21, 22]. If a specific group of foods, or ingredient(s) within certain foods, cannot be identified as having a direct addictive potential, then a SUD framework would not be appropriate for understanding this presentation of problematic eating behavior. Thus, a core focus of behavioral and neurobiological research has been differentiating which foods are most associated with the indicators of food addiction operationalized by the YFAS/YFAS 2.0 and may be capable of producing addictive-like neurobiological changes following prolonged consumption. Furthermore, preliminary evidence demonstrating neurobiological parallels between overeating and addiction has used individuals with obesity as a proxy for addictive-like eating, a secondary focus of recent work in this area has been examining neural and biological overlaps between addictive disorders and individuals who specifically meet criteria for food addiction.

This review will begin with a brief overview of the parallels observed in prior studies comparing individuals with obesity or persons with a SUD, which provided a foundation for investigating food addiction as a distinct presentation of disordered eating. The goals of this review will then be to highlight recent findings using behavioral neuroscience approaches that speak to (1) which foods may exhibit an addictive potential akin to drugs of abuse and (2) parallels between the food addiction conceptualization and individuals with a SUD. Gaps in the existing literature and immediate next steps in this line of research will also be discussed.

Parallels Between Individuals with Obesity or a SUD

The prevalence of obesity, defined as a body mass index (BMI) ≥30 kg/m^2, is 42.4% in adults in the United States [23] and 13% in adults globally [24]. This chronic disease has a complex and multidimensional etiology, with the brain being an important contributor to the regulation of food intake, metabolism, and weight status. Several studies have demonstrated differences in people with and without obesity in brain structure (e.g., reduced gray matter volume in the frontal and limbic regions) and function (e.g., ventral anterior insula activation in response to smelling chocolate) [25–27]. Notably, similarities have been observed between individuals with obesity or an addictive disorder in several neurobiological-regulated pathways related to reward, motivation, conditioning, and inhibitory control.

One of the most commonly cited neurobiological mechanisms linking food and drug intake is alterations of reward [28, 29], particularly the mesocorticolimbic dopamine system [30]. Theories of both hyperfunctioning (surfeit) and hypofunctioning (deficit) have guided much of the research on reward, weight gain, and obesity [31]. The reward surfeit model suggests that overeating is due to a neurobiological hypersensitivity to food rewards. In cross-sectional studies, adults who have obesity, relative to those who have normal weight, show greater responsivity in reward regions of the brain (e.g., striatum, amygdala) to pictures of high-calorie food versus low-calorie food and control images [32]. Some, but not all, prospective and experimental studies have provided support for elevated reward region response to high-calorie food images as a predictor of weight gain [33–36]. Paralleling these findings, people with substance-use disorders, compared to those without, show greater activation in reward regions of the brain to substance use cues [37, 38]. In an activation likelihood estimation meta-analysis of 87 studies, participants with obesity and those with substance addictions exhibited similar blood-oxygen-level-dependent fMRI hyperactivity in the amygdala and striatum when processing general rewarding stimuli as well as problematic stimuli (i.e., food- or drug-related stimuli) [39].

While reward hyperresponsiveness appears to present as an initial vulnerability to weight gain and obesity, hypofunctioning of dopamine may occur as a result of overeating [40]. Overeating, particularly high-fat, high-sugar foods, results in downregulation of dopamine D_2 receptors and reduced dopamine D_2 and less sensitivity in animals [41, 42], suggesting that these palatable foods affect the plasticity of dopamine receptors. Wang and colleagues [43] found an inverse relationship between

striatal dopamine D_2 receptors and BMI, which has been supported by other studies [44, 45]. Similarly, low dopamine D_2 receptors have been found in individuals with substance-use disorders [46–48]. With repeated drug ingestion, there is reduction in D_2 striatal dopamine receptors. This downregulation produces an anhedonic state and results in increased drug use needed to derive the same reward as at the initial use. Taken together, these findings suggest that individuals may be driven to overeat or seek drugs of abuse to increase brain dopamine [49, 50].

In summary, research reports on alterations in neurobiological networks have found strong similarities in the mechanisms underlying obesity and SUDs. However, there are limitations to using obesity as a proxy for addictive-like eating. As obesity is defined by a BMI $\geq$30 kg/m^2, it does not account for individual differences in body composition (e.g., higher BMI due to a greater amount of fat mass vs muscle mass), the types of foods a person consumes or patterns of eating behavior that may have contributed to having a higher body weight, or contributing factors related to food intake (e.g., medication side effects). Thus, in line with the unique tenets of a food addiction perspective, recent evidence will be reviewed related to which foods may be addictive and biobehavioral mechanisms that have demonstrated specific relevance to persons who meet the YFAS food addiction criteria.

Identifying Which Foods May Be Addictive

Ultra-processed foods are categorized as class 4 foods by the widely used NOVA classification system [51] and defined as foods containing added fat, refined carbohydrates (e.g., white flour, sugar), and/or sodium [52]. Ultra-processed foods do not occur in nature and are typically created industrially [51]. Examples of ultra-processed foods and beverages include packaged snack foods (e.g., potato chips), fast food items (e.g., cheeseburgers, pizza, French fries), sweets and pastries (e.g., donuts, chocolate, ice cream), and sugar-sweetened beverages (e.g., soda, sweet tea) [51]. Ultra-processed foods have consistently been widely associated with elevated responses in regions related to wanting, liking, and reward appraisal (e.g., dorsal striatum, nucleus accumbens (NAc) orbitofrontal cortex) in neuroimaging studies, particularly for individuals with obesity or BED [53–56]. These neural responses have also been related to elevated craving for and overconsumption of ultra-processed foods [57–59]. Notably, these patterns of neural activation and correlations with usage have also been observed for drugs of abuse [60], which contributed to hypotheses about the addictive potential of ultra-processed foods [22, 61].

Thus, it appears that ultra-processed foods are more likely to engage reward regions in a similar manner as drugs of abuse and be consumed in a problematic way, relative to foods in a natural state (e.g., lean meats, nuts, fruits, vegetables), especially for vulnerable individuals (e.g., those with obesity). However, in order for ultra-processed foods to be recognized as addictive, research must demonstrate that these foods trigger reward-based neurobiological and behavioral changes, in a similar manner as has been observed with addictive drugs. This distinction is key for differentiating whether ultra-processed foods may be more appropriately categorized with natural rewards like sexual behavior or exercise, highly addictive substances like nicotine and alcohol, or behavioral addictions such as gambling.

Preclinical Findings

Initial behavioral and neurobiological findings suggesting that ultra-processed foods may be capable of producing addictive-like responses were conducted in preclinical models. Binge-prone rats given intermittent access to ultra-processed foods or sugar (an ingredient added to many ultra-processed foods) have exhibited downregulated dopamine responses indicative of sensitization and tolerance [62] and developed behavioral indicators of addiction (e.g., binge consumption, enhanced motivation to seek out the ultra-processed food, consumption despite negative consequences like foot shock) [63–66]. Interestingly, withdrawal appears to be triggered only when pure sugar (but not pure fat) is removed from the diet, alluding to the differential contributions of the ingredients in ultra-processed foods in producing addictive-like responses [63, 67]. Importantly, these biobehavioral responses align with core processes of SUDs (e.g., reward sensitization, use despite negative consequences, withdrawal) which suggest that ultra-processed foods may be more reinforcing than natural rewards (e.g., minimally processed foods).

Recent findings have further elucidated the direct neurobiological adaptations that appear to be triggered by prolonged ultra-processed food consumption. Oginsky and colleagues [68] observed that ultra-processed foods upregulated NAc calcium-permeable AMPA receptor transmission rapidly in obesity-prone rats, which has been found to mediate cue-induced motivational responses in drug addiction. Importantly, the upregulation of NAc AMPA receptor transmission preceded the onset of obesity in susceptible rats, suggesting the causal and direct contribution of the ultra-processed foods [68]. Brown and colleagues [69••] corroborated that exposure to ultra-processed foods was *required* in order to observe these synaptic impairments in the NAc, which again preceded the development of obesity and was also correlated with addictive behaviors (enhanced motivation for the ultra-processed foods, binge eating). As such, these recent studies appear to provide compelling evidence for a contributing role of ultra-processed foods in driving

neurobiological and behavioral changes that have been seen in SUDs, which suggests that the reinforcing nature of ultra-processed foods exceeds natural rewards including minimally processed foods.

Human Studies

In humans, ultra-processed foods have been highly associated with YFAS/YFAS 2.0 symptoms of food addiction or perceived experiences of addictive-like eating in self-report studies [52, 70–72]. Furthermore, these foods have been linked to elevated endorsement of subjective reward experiences that have signaled the abuse liability of addictive substances, such as increased craving, enjoyment, and future intentions to consume/use [73, 74]. Prior neuroimaging studies have found that refined carbohydrates in ultra-processed foods may be most linked to classic regions associated with craving and reward motivation in SUDs (e.g., NAc, insula) whereas fat is associated with oral somatosensory reward regions (e.g., Rolandic operculum) that may signal its role in enhancing the enjoyable taste of ultra-processed foods [75, 76]. However, self-report and behavioral research specifically examining the correlates of ultra-processed foods with indicators of food addiction underscore that the most problematic foods contain a combination of fat and refined carbohydrates [52, 70–74]. Proponents of the food addiction framework hypothesize that this combination of fat and refined carbohydrates produces an artificially elevated reward response uniquely for ultra-processed foods, as this combination does not exist in any naturally occurring foods [52, 77•]. Thus, recent behavioral and neurobiological research has focused on understanding how fat and refined carbohydrates may interact to elevate the rewarding properties of ultra-processed foods.

DiFeliceantonio and colleagues [78••] found that individuals exhibited a supra-additive reward response in the dorsal striatum and mediodorsal thalamus, regions implicated in motivation and reward valuation, for cues of ultra-processed foods high in both fat and refined carbohydrates that was greater than the sum of the responses to cues of ultra-processed foods high in only fat and only refined carbohydrates. Though this study did not demonstrate causal contributions of ultra-processed foods in producing addictive-like reward responses, it suggests that ultra-processed foods with added fats and refined carbohydrates may have an artificially high reward value and provides context to prior self-report and behavioral research demonstrating that these foods are most implicated in food addiction [52, 70–74].

Speaking more to the direct role of ultra-processed foods in driving overeating behavior, Hall and colleagues conducted a methodologically rigorous inpatient feeding trial using a within-subjects design, where 20 weight-stable adults ate a 14-day diet of ultra-processed foods and a 14-day diet of naturally occurring foods (order of diet condition randomized and counter-balanced) [79•]. This study yielded notable behavioral findings, including individuals consuming approximately 500 calories more per day on the ultra-processed food diet and gaining about two pounds during the 2-week period [79•]. Furthermore, 14-day consumption of ultra-processed foods led to elevated glucose and insulin levels, which may have contributed to overeating [79•]. The increases in glucose and insulin caused by prolonged ultra-processed food intake have also been proposed as biological mechanisms that may motivate cravings and maintain addictive-like consumption of these foods [77•, 80]. This recent work by Hall and colleagues [79•] was the first to demonstrate that ultra-processed food consumption produced biological and hormonal changes that may perpetuate overeating of these foods, whereas a diet of minimally processed foods did not promote appetitive dysregulation and overeating. Thus, while unprocessed and minimally processed foods may be natural rewards, this study supports ultra-processed foods as highly reinforcing in a manner that perpetuates overeating.

Comment on the Addictive Potentials of Food

Broadly, recent research in this area has demonstrated that ultra-processed foods with both added fats and refined carbohydrates exhibit an artificially high reward potential, likely because this ingredient combination does not exist in any naturally occurring foods. Furthermore, prolonged ultra-processed food intake has been related to biological and behavioral changes that may provide insight into the development and maintenance of food addiction. However, future research is needed to disentangle the roles of fat versus refined carbohydrates in order to pinpoint which attribute may be the central addictive agent in ultra-processed foods (similar to nicotine in cigarettes) versus which ingredients may enhance the rewarding nature of the addictive agent (similar to flavor additives in cigarettes making the nicotine more palatable). In addition, research is needed to directly compare the reinforcing potential of drugs of abuse versus ultra-processed foods versus natural rewards, in order to systematically compare the rewarding nature of ultra-processed foods.

Neurobiological Evidence for Food Addiction

Operationalizing food addiction using the YFAS/YFAS 2.0, rather than using obesity as a proxy, has provided more specific evidence for the neurobiological overlaps between addictive-like eating and SUDs. The first functional magnetic resonance imaging (fMRI) study of food addiction was

conducted by Gearhardt and colleagues in 2011 [81], who observed that individuals with higher versus lower YFAS symptoms demonstrated elevated activation in the dorsal striatum (implicated in wanting and craving) when anticipating an ultra-processed food reward but less activation in the orbitofrontal cortex (related to reward appraisal) when consuming the food. This pattern of exhibiting greater reward responses when anticipating ultra-processed foods but blunted responses upon consumption has also been observed for individuals with a SUD for their drug of choice [81].

Recent Neuroimaging Findings

Several recent studies have taken the approach of Gearhardt and colleagues [81] by comparing individuals with higher versus lower YFAS/YFAS 2.0 symptom scores. De Ridder and colleagues [82] used resting-state electroencephalogram (EEG) analyses to directly compare persons with at least three YFAS symptoms and individuals with alcohol-use disorder. These two groups exhibited a common neural substrate indicative of a shared vulnerability for reward dysfunction, evidenced by similarities in the anterior cingulate cortex, medial orbitofrontal cortex, and precuneus [82]. Relatedly, an fMRI study revealed a small association between YFAS symptoms and structural differences in the lateral orbitofrontal cortex, which may reflect impairments in reward appraisal and impulsivity and has been observed for individuals with SUDs [83•]. In a sample of Chinese university students, individuals with higher versus lower symptoms of YFAS food addiction exhibited lower connectivity between brain regions implicated in interoceptive awareness (e.g., insula), reward (e.g., caudate), and decision-making (e.g., ventromedial prefrontal cortex), suggesting greater potential for impulsive, reward-driven decision-making [84]. Neural correlates of impulsivity have also been found for children and adolescents with at least one YFAS symptom of food addiction, marked by less activation in inhibitory control regions (e.g., middle temporal gyrus, precuneus) during a go/no-go task [85•].

Only three neuroimaging studies have examined individuals who meet the criteria for the "diagnostic" score on the YFAS/YFAS 2.0, which reflects the clinically significant manifestation of food addiction among individuals with multiple symptoms plus functional impairment or distress. First, Schulte and colleagues [86••] compared fMRI cue reactivity patterns in a sample of women with overweight or obesity and no history of other eating disorders (e.g., BED), half of whom met the "diagnostic" threshold on the YFAS 2.0. Participants with food addiction exhibited a pattern of activation in the superior frontal gyrus, a region implicated in cue-induced craving, that has been observed in prior studies of individuals with a SUD [86••], providing further support for shared neural substrates of reward dysfunction in food addiction and SUDs.

The second fMRI study of individuals who met the YFAS "diagnostic" threshold for food addiction examined functional connectivity and found higher connectivity between the brainstem and orbitofrontal cortex, suggestive of dysregulation of dopaminergic reward responses [87••]. Notably, women, compared to men, exhibited higher connectivity in the emotion regulation network and reduced connectivity in executive functioning regions, which may indicate a greater propensity towards emotional eating and impulsivity [87••], though future research examining neurobiological gender differences in food addiction is needed. The third study similarly found differences in functional connectivity between the brainstem and dorsal striatum (putamen) for women with obesity who met the YFAS "diagnostic" threshold for food addiction [88••], which complements findings underscoring the role of dopaminergic reward pathway dysfunction as a mechanism contributing to food addiction.

Gut Microbiome, Hormones, and Genetics

While the majority of the existing neurobiological research on food addiction has used neuroimaging techniques, preliminary studies have begun to assess other biological influences that may be shared among food addiction and SUDs. The brain-gut-microbiome (BGM) has long been recognized for its contribution to homeostatic and hedonic hunger and has more recently been suggested to have specific implications for food addiction [89]. The first study to assess BGM alterations in food addiction found a cross-sectional association between greater connectivity in dopaminergic reward regions and fecal indolepropionate in women with obesity who met the YFAS "diagnostic" threshold for food addiction [88••], suggesting that the microbiome may play an important role in the more widely observed neural correlates of reward dysfunction in food addiction.

Given the role of appetitive hormones (e.g., insulin, leptin, ghrelin) in driving food reward [29, 90], assessing these associations among individuals with food addiction has also received recent empirical attention. In a sample of individuals with lower socioeconomic status, YFAS symptoms were associated with higher insulin and leptin levels, providing evidence for hormonal underpinnings related to increased reward and motivational drive for calorie-dense ultra-processed foods [91•].

Lastly, preliminary studies have demonstrated shared genetic predispositions between individuals with food addiction and those with SUDs. Davis and colleagues [92] found that, similar to previous studies of persons with SUDs, individuals who met the YFAS "diagnostic" threshold for food addiction exhibited elevations on a multilocus genetic profile score reflecting a composite index

of increased dopamine signaling. Furthermore, the first genome-wide association study of food addiction identified two loci (*PRKCA* and *NTM*) correlated with YFAS symptoms [93], including one addiction-related pathway (MAPK signaling pathway). However, no significant associations were observed with the specific a priori single-nucleotide polymorphisms (SNPs) identified by prior research in samples with SUDs, which the researchers attributed to potential issues with statistical power and low prevalence of food addiction in the sample [93].

Comment on the Neurobiological Evidence

The majority of studies examining the neurobiological underpinnings of food addiction have used neuroimaging techniques, and only three have investigated differences among individuals who meet the clinically significant YFAS "diagnostic" threshold for food addiction [86••, 87••, 88••]. Existing findings highlight the contributions of reward dysfunction, particularly in the dopaminergic pathway, emotion dysregulation, and impulsivity as potential mechanisms shared between food addiction and SUDs. Preliminary data has also elucidated the roles of the BGM connection, appetitive hormones, and genetics, though substantial future research is warranted in these areas.

Future Directions

There are numerous next steps in this line of research. With respect to identifying which foods may be addictive, behavioral neuroscience approaches can be used to elucidate which food attributes (e.g., fat versus sugar) may be the central addictive agent in ultra-processed foods. Furthermore, subsequent studies are needed to identify commonalities in neural responses, hormonal influences, and genetics between individuals with SUDs and food addiction, particularly assessing persons who meet the YFAS/YFAS 2.0 "diagnostic" threshold indicating a clinically significant food addiction presentation. Finally, findings from the bariatric surgery literature showing changes in the BOLD response in the ventral tegmental area to highly palatable foods 6 months after surgery suggest potential for Roux-en-Y gastric bypass in reducing addictive-like eating for those with extreme obesity [94]. These future directions have potentially meaningful applications for intervention. For example, if shared neurobiological underpinnings are identified between SUDs and food addiction, then evidence-based pharmacological treatments for SUDs may warrant consideration for the treatment of food addiction.

Conclusions

Overlapping behavioral and neurobiological features of obesity and SUDs have been identified through empirical studies for several decades. However, the origins of obesity are multifactorial and not theoretically or clinically synonymous to addictive-like eating. Operationalizing food addiction using the YFAS/YFAS 2.0, which parallels the DSM diagnostic criteria for SUDs, has resulted in a body of literature examining the validity and utility of this specific type of disordered eating. Recent studies using behavioral neuroscience approaches have provided support for the unique role of ultra-processed foods in directly triggering biobehavioral indicators of addiction among individuals with food addiction, whereas naturally occurring, minimally processed foods do not appear to produce an addictive response. Furthermore, neuroimaging studies have elucidated shared mechanisms between food addiction and SUDs, including dopaminergic reward signaling dysfunction, emotion dysregulation, and impulsivity. Very early evidence has also suggested the relevance of the BGM connection, hormones, and genetics as areas for future study.

In summary, compared to the extensive research that has been conducted to investigate the neurobiology of SUDs, research providing insight into the biobehavioral mechanisms implicated in food addiction is in its nascent stages. Nevertheless, existing evidence has yielded promising results distinguishing the addictive potential of ultra-processed foods and distinct correlates of food addiction as a unique presentation of problematic eating behavior. There are ample opportunities for future research in this budding empirical domain that have potentially impactful implications for informing novel intervention approaches.

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Compliance of Ethical Standards

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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