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The impact of caloric availability on eating behavior and ultra-processed food reward

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1. Introduction

The food environment has changed dramatically and rapidly in the last 50 years. Industrial food processing has increased the safety and stability of the food supply, however, a rapid expansion in the scope of food processing in the 1980's has resulted in a market dominated by ultra-processed foods (Monteiro & Cannon, 2019). Given the novelty, levels, and variety of food processing available in our food supply, it is perhaps unsurprising that a definition for these food products is still hotly debated. Some definitions focus on the food's hedonic or sensory properties (Fazzino et al., 2019), while others focus more on the level of industrial processing and additives (Monteiro, 2009; Monteiro et al., 2018; Poti et al., 2015). Here, we use the NOVA definition of category 4 ultra-processed foods (UPFs) as they make up around 58% of total calories consumed in the US and 66% of calories in US children (Monteiro et al., 2018; Neri et al., 2022; Steele et al., 2016). By definition, these foods contain substances with no or infrequent culinary use and often contain additives (emulsifiers, colorants, sweeteners) that themselves have effects on metabolic health (Bhattacharyya et al., 2012; Dalenberg et al., 2020; Monteiro et al., 2018). UPFs are formulated to have a long shelf-life and therefore spend long periods in contact with packaging materials, allowing for the absorption of compounds from those materials that have also been associated with increased type 2 diabetes risk (Hwang et al., 2018). The full implications of this shift to UPFs on human health and disease outcomes are difficult, if not impossible, to quantify. However, UPF consumption is linked with various forms of cancer, increased cardiovascular disease, and increased all-cause mortality (Juul et al., 2021; Micha et al., 2017; Romaguera et al., 2021; Schnabel et al., 2019).

Understanding food choice is, therefore, a critical problem in health research. Although many factors influence food choice(Drewnowski, 1997), here we focus on the properties of the foods themselves. UPFs are generally treated as *food*, not as the highly refined, industrialized *substances* that they are, whose properties and components must be studied. Here, we examine one property of UPFs, that they deliver usable calories rapidly as a potential factor driving UPF overconsumption. First, we explore evidence that UPFs deliver calories more rapidly. Next, we examine the role of the gut-brain axis and its interplay with canonical reward systems, and finally, we describe how speed affects both basic learning processes and drugs of abuse.

2. Food processing alters caloric availability

For the calories in foods to be accessible for use by the body, several physiological processes must occur. First, they must be broken down and removed from the natural matrices present in food (H. Edwards et al., 2015). Next, the macronutrient must pass through the gastrointestinal tract into the bloodstream (Livesey, 1995). From the bloodstream, carbon containing substrates are routed to organs, including the brain, for use. The speed of this process is dependent on the bioaccessibility of nutrients–described here as nutrient uptake, interactions between nutrients in the food, and interaction with the gastrointestinal tract. Interestingly, foods with similar macronutrient content can yield different caloric payoffs after ingestion based on the ease with which calories are extracted from these foods, resulting in altered energetic payoff (Carmody et al., 2011; Mandalari et al., 2008; Traoret et al., 2008).

The Atwater system, a common system used to estimate this energetic payoff, assigns set values for calories derived from each macronutrient category (Atwater & Benedict, 1902). Although there have been adjustments proposed to the system since its creation (Watt & Merrill, 1975), this system of determining caloric content tends to overestimate macronutrient digestibility and caloric availability, especially in foods high in dietary fiber or protein (Baer & Novotny, 2019; Capuano et al., 2018; Carmody et al., 2011; Novotny et al., 2012). Diets high in UPFs tend to lack adequate dietary fiber and protein (Martini et al., 2021). Food processing itself can also alter bioaccessibility. Extensive milling produces flours that are easier to digest (H. Edwards et al., 2015) and processed peanut items like peanut butter or peanut oil release more calories than whole peanuts (Traoret et al., 2008). For almonds, the release of fat is dependent on the amount of slicing and crushing performed prior to consumption by subjects (Mandalari et al., 2008). Simply cooking increases caloric availability, in both low- and high-fiber foods (meat and sweet potato), likely by decreasing the amount of digestion resistant fiber (Carmody et al., 2011). But, a meal consisting of multi-grain bread and cheddar cheese increases energy expenditure (thermic effect of food) more than one of white bread and “cheese product” (Barr & Wright, 2010). While the effects of basic forms of food preparation such as crushing, boiling, baking, and fermentation on food matrices have been well studied individually, the impacts of their combination or the industrial processes involved in formulating UPFs are less well understood (Sensoy, 2014). More detailed studies in humans are needed to understand their effects on both nutrient availability, food choice, and food reward.

3. Post-ingestive signals rapidly reach the brain and drive food reward.

3.1 Modulation of the hypothalamus and mesocorticolimbic structures

To examine how altered nutrient availability might bias food choice, we must consider how this information is relayed to and interpreted by regions of the brain that govern food intake. One of the most important and well-studied central regulators of food intake is the hypothalamus (Watts et al., 2022). Structurally, the hypothalamus is organized such that axonal projections are both received and sent to higher-order brain regions, allowing for integration of sensory information (Azevedo et al., 2021). Thus, the hypothalamus serves as a gatekeeper or control center for sensory information integration (Gouveia et al., 2021).

Two types of neurons within the arcuate nucleus of the hypothalamus form the primary feeding behavior-related centers, integrating signals of both acute hunger and satiety as well as chronic regulation of whole-body energy balance and nutrient availability (Gouveia et al., 2021). Hunger and fasting activate agouti-related protein (AgRP) neurons to promote food-seeking and consummatory behaviors, and proopiomelanocortin (POMC) neurons are activated in positive energy balance to promote fasting and subsequent regulation of body weight (Chen & Knight, 2016).

The role of homeostatic control over these neurons via hormonal activity (i.e., leptin and ghrelin), neurotransmitters (e.g., serotonin; (Donovan & Tecott, 2013), and incretins (e.g., GLP-1; (Holst, 2013)) has been recognized for at least the last two decades, but only within the last decade has advancement in technological approaches allowed for investigation of *in vivo* acute regulation of activity (Chen & Knight, 2016). These *in vivo* studies, with the technological ability to monitor neuronal activation on a time scale of seconds rather than minutes or hours, revealed that anticipatory food cues inhibit AgRP and activate POMC neurons on the order of seconds (Betley et al., 2015; Chen et al., 2015; Chen & Knight, 2016; Gouveia et al., 2021; Mandelblat-Cerf et al., 2015; Su et al., 2017). These findings highlight the importance of signaling speed and demonstrate the dynamics of acute signals integrated with slower homeostatic mechanisms that influence hypothalamic involvement in consummatory behaviors.

Infusions of nutrients directly into the gut result in AgRP neuron inhibition (Beutler et al., 2017; Su et al., 2017), and interestingly, repeated exposure potentiates the response in a manner that is proportional to caloric content but indiscriminate of macronutrient source (Beutler et al., 2017; Su et al., 2017). However, the signaling pathways by which caloric intake influences hypothalamic response differ by macronutrient source. Inhibition of AgRP neurons by lipid infusion requires vagal signaling from the duodenum; this vagal signaling is correlated with a reduction in later feeding and is needed for changes in fat consumption(Goldstein et al., 2021; Ritter & Taylor, 1990). Conversely, vagotomy does not affect the ability of intra-gastric glucose to decrease AgRP neuron activity (Goldstein et al., 2021). Rather, the splanchnic nerve and its connections to the hepatic portal vein are necessary for hypothalamic and AgRP neuron response to intragastric glucose (Goldstein et al., 2021; Schmitt, 1973). Whether UPFs made up of combinations of fat and simple carbohydrates, that therefore use separate but complementary signaling pathways to reach the hypothalamus, result in greater inhibition of AgRP neurons has not been investigated. However, these studies do demonstrate peripheral signals of caloric availability rapidly change neural activity.

3.2 Influence on brain reward, learning, and motivation circuitry

The hypothalamus does not exist in isolation as a central regulator of food intake. Rather it is densely reciprocally connected with many other nuclei. Here, we focus on its connection with nuclei making up the canonical brain “reward system.” The “reward system” is a dopaminergic pathway composed of several mesocorticolimbic structures, including the ventral tegmental area (VTA), striatum, amygdala, and prefrontal cortex (Cox & Witten, 2019). AgRP neuron activity may act through negative valence signaling to influence reward

learning and motivated behaviors (Betley et al., 2015), and interconnectivity between the hypothalamus and dopaminergic targets has been hypothesized to integrate homeostatic and reward information to guide eating behavior (Hsu et al., 2018; Kelley et al., 2005). These same dopaminergic mesocorticolimbic circuits are a critical mediator of motivation, reward, reinforcement, and associative learning (Schultz, 2007). Central to this circuit is the striatum (Cox & Witten, 2019; Mogenson et al., 1980). VTA neurons primarily project to the nucleus accumbens (NAc; ventral striatum), and substantia nigra (SNc) projections primarily innervate the dorsal striatum, though there are exceptions (Cox & Witten, 2019). The striatum projects back to a broad area of midbrain dopamine neurons, regulating dopamine release across both ventral and dorsal striatum (Cox & Witten, 2019; Haber, 2014; Haber & Knutson, 2010). These reward areas are interconnected with hind-, mid-, and forebrain projections that regulate homeostatic functions and goal-directed behaviors, including food-seeking (Hsu et al., 2018). Thus, regulation of dopamine release across the mesocorticolimbic circuit is complex and highly integrated.

Central to reinforcement learning hypotheses of dopamine function is the encoding of a reward prediction error, which is supported by dopamine-dependent neuroplasticity where a repeat of actions or associations with stimuli that unexpectedly produced a reward are encouraged (Glimcher, 2011). Shultz and colleagues' (Schultz et al., 1997) seminal work mapped reward prediction onto dopaminergic neuron activity. After primates were conditioned to receive a juice reward following a stimulus, these neurons spiked in activity following the stimulus, but not the reward (Montague et al., 1996; Schultz et al., 1997). Similarly, when the reward was omitted, the authors observed a pause in firing, lending further support to the prediction error hypothesis(Montague et al., 1996; Schultz et al., 1997). However, learning can occur without increases in dopamine (Flagel et al., 2011). In this study, only a stimulus that acted as an incentive rather than a predictive stimulus is able to elicit changes in striatal dopamine. This example lends support to an alternative hypothesis of dopamine function, that it instead underlies incentive motivation. We do not propose to provide an exhaustive review of the role of dopamine function in motivated behavior, but rather seek to highlight the importance of dopamine signaling in reinforcement learning and motivation as these pathways relate to encoding ingestive and post-ingestive signals.

Most experiments probing the function of dopamine in reward learning have used sweet taste as the primary reward. Taste has been called the gatekeeper to our internal environment, providing essential information on qualities of soon to be ingested foods (Breslin, 2013). Briefly, to reach the brain, taste is carried on the 7th (facial), 9th (glossopharyngeal), and 10th (vagus) cranial nerves and converges on the nucleus of the solitary tract (NTS) of the hindbrain (Breslin, 2013). In primates, afferents of NTS projection neurons go on to innervate the ventral posterior medial nucleus (VPM) of the thalamus (Scott & Small, 2009). However, in rodents, this pathway bifurcates at the NTS with one pathway going to the pontine parabrachial nucleus (PBN), which in turn innervates the VPM and another targeting the amygdala and hypothalamus (Scott & Small, 2009). From the thalamus, taste information is relayed to primary gustatory cortex (insula), orbitofrontal cortex (OFC; often named secondary gustatory cortex), and subcortical areas like the amygdala complex. These terminal fields then project back to the

thalamus, striatum, PBN, and midbrain (Breslin, 2013; Carleton et al., 2010). Through these projections, taste is able to rapidly (~1–2 seconds) alter striatal dopamine efflux (Canchy et al., 2021), Table S2 for review of timescale).

Although orosensation can act as a primary reward and increase striatal dopamine efflux, post-oral signaling can support behavior changes in the absence of taste. For example, mice that lack sweet taste receptors (Trmp5−/− or Tas1r2 −/− and Tas1R3 −/−) still show a robust preference for glucose-paired flavors (Ackroff et al., 2010; Araujo et al., 2008; Sclafani et al., 2014) infusion of lipid emulsions evoke a striatal dopamine efflux and condition licking behavior of an empty drinking spout in mice (Ferreira et al., 2012; Tellez, Medina, et al., 2013). Numerous rodent studies have shown that flavor-nutrient conditioning results from intragastric, intraduodenal, or intrajejunal infusion of nutrients (Ackroff et al., 2010; Drucker & Sclafani, 1997; Sclafani & Ackroff, 2012). Even caloric availability can guide preference. In the studies manipulating cooking described above, naive rodents would consume equal amounts of raw and baked sweet potatoes; however, after exposure to the caloric consequence of the foods, the rodents developed preferences for the cooked sweet potatoes (Carmody et al., 2011). Human studies have shown that preferences are developed for flavors paired with maltodextrin, a long-chain glucose polymer less detectable by sweet taste receptors in humans, but not flavors paired with non-nutritive sweeteners (Yeomans, 2012; Yeomans et al., 2008).

The above studies demonstrate caloric sensing in the gut can change behavior and preference, however, the circuitry and mechanisms involved are not fully understood. Many studies (outlined below) have observed rapid changes in neuronal activity following intragastric infusion of calories, indicating involvement of neural, rather than hormonal, signaling in nutrient reward (Small & DiFeliceantonio, 2019). Fat and carbohydrate seem to have separable peripheral pathways that lead to increases in striatal dopamine efflux (Small & DiFeliceantonio, 2019). The ability of intra-gastric lipids to evoke increases in striatal dopamine is dependent on vagal signaling through a proliferator-activated receptor α specific-mechanism, and activation of a right nodose ganglion-hindbrain-substantia nigra-dorsal striatum pathway (Tellez, Medina, et al., 2013).

The role of the vagus in glucose sensing is more complex. Some studies have shown vagal contributions are not essential to drive dopamine efflux in the striatum following intra-gastric infusion of glucose (Tellez, Ren, et al., 2013), which agrees with studies demonstrating the vagus is not needed for flavor nutrient conditioning to glucose (Qu et al., 2019; Sclafani & Lucas, 1996). However, others report an effect of vagotomy on sucrose dependent changes in VTA activity (Fernandes et al., 2020). Striatal efflux of dopamine following intragastric infusion of glucose is dependent on glucose metabolism, as infusion of 2-deoxy-D-glucose (2-DG), which disrupts glucose utilization, abolishes the rise in dopamine (Zhang et al., 2018). Accordingly, alpha-methyl-D-glucopyranoside (MDG), which is transported by the sodium glucose transporter (SGLT1), but is not metabolizable, does not condition a flavor preference over glucose (Zhang et al., 2018). However, SGLT1 activation by MDG is sufficient to condition a preference over non-nutritive sweeteners, such as saccharin (Zukerman et al., 2013) and acesulfame potassium (Tan et al., 2020). Intragastric MDG also leads to increased activity in the caudal NTS, a target nucleus of

the vagus (Tan et al., 2020). So, while SGLT1 activation seems to play a role in preference and in modulating NTS firing, there is perhaps another sensing mechanism downstream of glucose metabolism. This in combination with redundant signaling from the splanchnic nerve could perhaps reconcile the above conflicting findings on the role of the vagus in glucose sensing.

Just as with hypothalamic responses, there is little data on how macronutrient combinations common in ultra-processed foods may alter dopaminergic responses. There is evidence that participants over-value foods containing fat and carbohydrates, potentially due to the convergence of signals from the periphery onto a common dopaminergic target (DiFeliceantonio et al., 2018; Perszyk et al., 2021; Small & DiFeliceantonio, 2019). While, there is evidence an ultra-processed milkshake containing fat and sugar increases striatal dopamine on post-oral timescales, we do not have data from single macronutrients or from minimally processed foods for comparison (Thanarajah et al., 2019). Most intra-gastric infusion studies in rodents use glucose as a carbohydrate stimulus, Intralipid as a fat stimulus, and protein liquids such as Proteinex (Goldstein et al., 2021; Han et al., 2018; Qu et al., 2019; Tellez, Medina, et al., 2013), but there are no studies on macronutrient combinations or foods (either ultra- or minimally- processed).

4. The Role of Speed in Learning

Whether through vagal or other mechanisms, nutrient information is relayed from the gut to the brain and influences both homeostatic brain systems and those that govern reward, learning, and motivation, leading to changes in behavior. This integration of nutritive signals with the canonical reward network likely serves the essential function of providing information tying the sensory experience of food intake to its later nutritive consequences. From a teleological perspective, linking caloric value with the hedonic response of liking could reinforce preference for a particular food and lead an organism to seek out that food. This concept is often referred to as flavor nutrient conditioning or flavor nutrient learning ((Myers, 2018), for recent review). Supporting its essential survival function, flavor nutrient learning can be acquired rapidly and only requires a single trial (Ackroff et al., 2009). It can be reasoned that if flavor nutrient learning is essentially a Pavlovian conditioning process by which a conditioned stimulus (CS), in this case the smell and taste of food, is paired with an unconditioned stimulus (US) of nutrients in the gut, it must follow similar principles of Pavlovian conditioning. The one most pertinent to the discussion here is that conditioning is more effective the more closely coupled in time a US is to the CS.

Temporal congruency, or that for learning to occur events must occur closely in time, was held as a central principle in learning theory until Rescorla (1967) demonstrated that although congruency did support some forms of conditioning, instead *contingency,* the US reliably followed the CS was the most important factor governing learning acquisition. Contingency has since been the dominant theoretical framework; however, there are many instances where the influence of temporal contiguity can be observed (Balsam et al., 2010). Most pertinent to this discussion are studies of trace-conditioning, where the spacing between CS and US is explicitly manipulated. In these studies, when the delay of US is plotted against trials to acquisition, a near linear relationship is observed, whereby

increased CS-US spacing impairs learning and decreased CS-US spacing enhances learning speed (Balsam & Gallistel, 2009; Gallistel & Gibbon, 2000). In another trace conditioning paradigm, short CS-US intervals lead to more vigorous anticipatory responding, though both short and long intervals lead to learning (Balsam et al., 2010). Similarly, when there are multiple CSs, the CS closest in time to the US gains more motivational value (Tindell et al., 2005). This effect can also be observed in early conditioned taste aversion studies, where rats that experienced a longer passage of time from saccharin consumption to irradiation (to produce malaise) displayed a blunted taste aversion to saccharin compared to those who experienced the events more closely in time (Barker & Smith, 1974). Broadly, these findings demonstrate the importance of time between the CS and US to support both learning and potentially the motivational value of the cue. Applied to flavor nutrient learning, this could mean faster acquisition for flavors that deliver their associated US rapidly as well as higher motivation for these flavors. We see some hints that these processes may be affecting human food choice behavior from studies demonstrating that foods with a higher glycemic index, and thus a high rate of glucose absorption, show a greater potential for addictive-like eating behavior (Schulte et al., 2015, 2017) and elicit greater NAc and striatal responses (Lennerz et al., 2013) compared with foods providing lower glycemic loads.

The importance of speed of reward receipt has also been extensively studied within the framework of delay discounting (Ainslie, 1975; Mazur, 1997). Humans and animals value immediate rewards over those that are delivered at a later date with rewards becoming less and less valuable (“discounted”) the further in time they are delivered in a hyperbolic function (Vanderveldt et al., 2016). This discounting of delayed rewards has been proposed as a reason food reinforcers are often chosen over what should be a more valuable drug reinforcer (Lenoir et al., 2007; Tunstall et al., 2014; Tunstall & Kearns, 2014). In a powerful example of this effect, delaying both saccharin and cocaine rewards led rats who once preferred saccharin to prefer the cocaine reward (Canchy et al., 2021).

5. The Importance of Speed in Reward: Parallels in Studies of Drug Use

The most convincing evidence that the kinetics of reward delivery changes behavior comes from drugs of abuse literature. Drugs of abuse are powerful reinforces because they activate the same reward pathways evolved for natural rewards described above (Avena et al., 2008; Criscitelli & Avena, 2016; Di Chiara et al., 1993). Therefore, we can hypothesize the mechanisms and pathways that underlie vulnerabilities exploited by drugs with fast pharmacokinetic profiles may also be exploited by foods with fast “nutrikinetic” profiles(van Duynhoven et al., 2012). Route of administration is a major early pharmacokinetic determinant of abuse potential; drugs taken in ways that reach the brain faster have a higher abuse and addiction potential, known as the “rate hypothesis” (Greenblatt et al., 1981; Hatsukami & Fischman, 1996; Jones, 1990). Similarly, for people using substances with faster routes of administration (inhalation, intravenous injection, snorting) addiction is not only more likely but also more severe (Barrio et al., 2001; Budney et al., 1993; Carpenter et al., 1998; Ferri & Gossop, 1999; Gossop et al., 1992; Hatsukami & Fischman, 1996; Rawson et al., 2007). The importance of the speed of administration can also be shown through sobriety aids like nicotine patches. Nicotine patches do not support addictive use as

cigarettes do because they slowly deliver nicotine, rather than delivering it rapidly (Fiore et al., 1994).

Given that route of administration plays a key role in behavioral changes and subjective experiences relevant to the progress of addiction, researchers have sought to understand the key neurobiological mechanisms affected by speed. These studies often rely on altering the rate of drug infusion. For example, Samaha and colleagues (Samaha et al., 2004), varied the rate of cocaine infusion from 5 to 100 seconds and found faster infusions led to greater psychomotor sensitization. Similar findings hold for nicotine (Samaha et al., 2005). Later studies demonstrated that although faster infusion rates resulted in psychomotor sensitization, they produced increases in drug-seeking or taking behavior inconsistently (Crombag et al., 2008; Schindler et al., 2009). However, experiencing these faster rates does lead to vulnerability to relapse (Wakabayashi et al., 2010).

These same studies report both behavioral and brain effects of rapid or slow drug infusion. The medial prefrontal cortex, orbitofrontal cortex, and nucleus accumbens core and shell were all more active, as measured by cFos expression, after a fast (5s) cocaine infusion (Samaha et al., 2004). Fast infusions of nicotine, as compared to slower ones, elicited altered cFos expression across the striatum (Samaha et al., 2005). These changes persist even 45 days after the last cocaine experience, with rats that had experienced the fast infusion rate showing a blunted striatal response to acute cocaine challenge as well as a vulnerability to reinstatement (Wakabayashi et al., 2010). These findings can inform our hypotheses of expected behavioral and brain changes to be observed when studying foods that deliver calories more rapidly, especially long-term changes and changes after diet modification or periods of abstinence from certain foods.

In humans, parallel behavioral findings have been observed. Abreu and colleagues (2001) intravenously injected habitual cocaine using participants with cocaine at varying speeds and found that ratings of “high” and “liking” were greater when cocaine was injected more rapidly. It should be noted the same was not found for users of opioids when hydromorphone was infused rapidly. These cocaine findings were later replicated (Nelson et al., 2006). Other studies that varied opioid infusion rate report subjective ratings of “high” and “liking” increasing with increased rate of infusion, this time using morphine (Marsch et al., 2001). Parallels between rise in drug plasma levels and subjective high have been observed in participants given a single pentobarbital bolus over the same dose given more slowly (de Wit et al., 1992).

Parallel neurobiological findings are more difficult to interpret. Volkow and colleagues (Volkow et al., 2000) found that while varying the route of administration of cocaine (smoked, snorted, or intravenous) did alter the subject effects of the drug, there was no correlation with positron emission tomography (PET) measures of dopamine transporter (DAT) blockade. Another similar study, however, reports the time course of DAT blockade in the striatum as measured by PET to be correlated with subjective “high” (Volkow et al., 1997). Blockade of the dopamine transporter is a major way by which cocaine increases dopamine in the synapse. Brain levels of radiolabeled methylphenidate as measured by PET have been reported to be both related to and unrelated to subjective high (Volkow et al.,

1995, 1996). The lack of consistency in these human studies is likely due to a host of factors, from low participant numbers given the cost and radiation load associated with PET imaging, as well as the varied genetic background and drug history of human participants in comparison with experimentally bred and housed rodents. However, these studies do point to a lack of understanding of the neurobiological underpinnings of the rate hypothesis in humans, despite its behavioral effects being well-characterized. Studies that address this gap, for both food and drugs, will provide important insight into how these systems integrate signals that occur over different delays and time-scales.

6. Conclusions and Future Directions

Ultra-processed foods make up an ever increasing proportion of daily caloric intake of both US adults and children (Neri et al., 2022; Steele et al., 2016). Compared to their ubiquity in our modern food environment, there is a dearth of information on how individual components of UPFs affect eating behavior and reward processes. Here, we propose one potential driver of UPF preference is their ability to deliver usable calories rapidly. Gut-derived signals do not act in isolation, however. As stated above, orosensory components are extremely important for supporting food intake. Sweetness, for example, can support intake without caloric consequence in rodents(Holman, 1969; Sclafani, 1995; Sclafani & Lucas, 1996) and as evidenced by the popularity of “diet” sodas and beverages. It should be noted that while diet drinks are popular, they represent just 32% of adult sweetened beverage consumption, with the rest coming from caloric sweeteners (Piernas et al., 2013). Furthermore, the appetitive effects of nonnutritive sweeteners are short-lived in rodent models (Sclafani & Ackroff, 2004). A theoretical framework that incorporates the interactions between oral sensation and post-oral signals would provide a fuller explanation of the current data and consumer trends. While some laboratories have begun these studies (Dalenberg et al., 2020), further careful experiments testing the synergistic effects of oral sensation and post-oral consequences, particularly in humans, are needed.

More broadly, experiments designed to parse individual macro and micronutrient components and food processing steps common in UPFs are necessary to determine their effects on metabolism, brain, and behavior. Foods that contain macronutrient combinations of fat and carbohydrate are valued higher calorie-for-calorie than foods that contain either macronutrient source alone (DiFeliceantonio et al., 2018; Perszyk et al., 2021). It is hypothesized that this overvaluation arises from peripherally separate, but centrally converging post-oral signaling, resulting in greater dopamine efflux relative to either macronutrient alone (Small & DiFeliceantonio, 2019). While we have evidence that fat and carbohydrate combinations increase dopamine in the human striatum at post-oral timescales (Thanarajah et al., 2019), we do not have data on single macronutrients for comparison. Oppositely, work in rodents has tended to isolate each macronutrient and we have little or no data on macronutrient combinations(Beutler et al., 2017; Goldstein et al., 2021; Su et al., 2017). Experiments that test how macronutrients, including protein, individually and in combination contribute to reinforcement would provide a fuller understanding of the effect of UPFs on reward systems.

Ultra-processed foods are extremely complex. They consist of refined ingredients, additives, and flavors in combinations and doses not previously encountered in our evolutionary history. Here, we examine the impact of one aspect of ultra-processed foods, that they deliver calories rapidly, and summarize the pathways UPFs might exploit to lead to their preference. However, this feature is likely part of a larger interplay between speed of delivery, macronutrient content, and taste that leads to an overall preference for these foods. Experiments designed to test each of these components; their impact on physiology, brain, and behavior; and theoretical frameworks that allow for these interactions are necessary steps to improving our understanding of food reward and how it applies to our modern food environment.

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References.

Abreu ME, Bigelow GE, Fleisher L, & Walsh SL (2001). Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. Psychopharmacology, 154(1), 76–84. 10.1007/s002130000624 [PubMed: 11292009]

Ackroff K, Dym C, Yiin Y-M, & Sclafani A (2009). Rapid acquisition of conditioned flavor preferences in rats. Physiology & Behavior, 97(3), 406–413. 10.1016/j.physbeh.2009.03.014 [PubMed: 19303888]

Ackroff K, Yiin Y-M, & Sclafani A (2010). Post-oral infusion sites that support glucose-conditioned flavor preferences in rats. Physiology & Behavior, 99(3), 402–411. 10.1016/j.physbeh.2009.12.012 [PubMed: 20026145]

Ainslie G (1975). Specious reward: A behavioral theory of impulsiveness and impulse control. Psychological Bulletin, 82(4), 463–496. 10.1037/h0076860 [PubMed: 1099599]

Araujo I. E. de, Oliveira-Maia AJ, Sotnikova TD, Gainetdinov RR, Caron MG, Nicolelis MAL, & Simon SA (2008). Food Reward in the Absence of Taste Receptor Signaling. Neuron, 57(6), 930–941. 10.1016/j.neuron.2008.01.032 [PubMed: 18367093]

Atwater W, & Benedict F (1902). Experiments on the metabolism of matter and energy in the human body, 1898–1900. Washington, D. C.: Government Printing Office.

Avena NM, Rada P, & Hoebel BG (2008). Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake. Neuroscience and Biobehavioral Reviews, 32(1), 20–39. 10.1016/j.neubiorev.2007.04.019 [PubMed: 17617461]

Azevedo EP, Ivan VJ, Friedman JM, & Stern SA (2021). Higher-Order Inputs Involved in Appetite Control. Biological Psychiatry, S0006-3223(21)01468-2. 10.1016/j.biopsych.2021.07.015

Baer DJ, & Novotny JA (2019). Metabolizable Energy from Cashew Nuts is Less than that Predicted by Atwater Factors. Nutrients, 11(1), 33. 10.3390/nu11010033

Balsam PD, Drew MR, & Gallistel CR (2010). Time and Associative Learning. Comparative Cognition & Behavior Reviews, 5, 1–22. [PubMed: 21359131]

Balsam PD, & Gallistel CR (2009). Temporal maps and informativeness in associative learning. Trends in Neurosciences, 32(2), 73–78. 10.1016/j.tins.2008.10.004 [PubMed: 19136158]

Barker LM, & Smith JC (1974). A comparison of taste aversions induced by radiation and lithium chloride in CS-US and US-CS paradigms. Journal of Comparative and Physiological Psychology, 87(4), 644–654. 10.1037/h0036962 [PubMed: 4426987]

Barr SB, & Wright JC (2010). Postprandial energy expenditure in whole-food and processed-food meals: Implications for daily energy expenditure. Food & Nutrition Research, 54, 10.3402/fnr.v54i0.5144. 10.3402/fnr.v54i0.5144

Barrio G, De La Fuente L, Lew C, Royuela L, Bravo MJ, & Torrens M (2001). Differences in severity of heroin dependence by route of administration: The importance of length of heroin use. Drug and Alcohol Dependence, 63(2), 169–177. 10.1016/S0376-8716(00)00204-0 [PubMed: 11376921]

Betley JN, Xu S, Cao ZFH, Gong R, Magnus CJ, Yu Y, & Sternson SM (2015). Neurons for hunger and thirst transmit a negative-valence teaching signal. Nature, 521(7551), 180–185. 10.1038/nature14416 [PubMed: 25915020]

Beutler LR, Chen Y, Ahn JS, Lin Y-C, Essner RA, & Knight ZA (2017). Dynamics of Gut-Brain Communication Underlying Hunger. Neuron, 96(2), 461–475.e5. 10.1016/j.neuron.2017.09.043 [PubMed: 29024666]

Bhattacharyya S, O-Sullivan I, Katyal S, Unterman T, & Tobacman JK (2012). Exposure to the common food additive carrageenan leads to glucose intolerance, insulin resistance and inhibition of insulin signalling in HepG2 cells and C57BL/6J mice. Diabetologia, 55(1), 194–203. 10.1007/s00125-011-2333-z [PubMed: 22011715]

Breslin PAS (2013). An evolutionary perspective on food and human taste. Current Biology: CB, 23(9), R409–418. 10.1016/j.cub.2013.04.010 [PubMed: 23660364]

Budney AJ, Higgins ST, Bickel W, & Kent L (1993). Relationship between intravenous use and achieving initial cocaine abstinence. Drug and Alcohol Dependence, 32(2), 133–142. 10.1016/0376-8716(93)80006-Z [PubMed: 8508724]

Canchy L, Girardeau P, Durand A, Vouillac-Mendoza C, & Ahmed SH (2021). Pharmacokinetics trumps pharmacodynamics during cocaine choice: A reconciliation with the dopamine hypothesis of addiction. Neuropsychopharmacology, 46(2), 288–296. 10.1038/s41386-020-0786-9 [PubMed: 32731253]

Capuano E, Oliviero T, Fogliano V, & Pellegrini N (2018). Role of the food matrix and digestion on calculation of the actual energy content of food. Nutrition Reviews, 76(4), 274–289. 10.1093/nutrit/nux072 [PubMed: 29529265]

Carleton A, Accolla R, & Simon SA (2010). Coding in the mammalian gustatory system. Trends in Neurosciences, 33(7), 326–334. 10.1016/j.tins.2010.04.002 [PubMed: 20493563]

Carmody RN, Weintraub GS, & Wrangham RW (2011). Energetic consequences of thermal and nonthermal food processing. Proceedings of the National Academy of Sciences, 108(48), 19199–19203. 10.1073/pnas.1112128108

Carpenter MJ, Chutuape MA, & Stitzer ML (1998). Heroin snorters versus injectors: Comparison on drug use and treatment outcome in age-matched samples. Drug and Alcohol Dependence, 53(1), 11–15. 10.1016/S0376-8716(98)00103-3 [PubMed: 10933336]

Chen Y, & Knight ZA (2016). Making sense of the sensory regulation of hunger neurons. BioEssays: News and Reviews in Molecular, Cellular and Developmental Biology, 38(4), 316–324. 10.1002/bies.201500167 [PubMed: 26898524]

Chen Y, Lin Y-C, Kuo T-W, & Knight ZA (2015). Sensory Detection of Food Rapidly Modulates Arcuate Feeding Circuits. Cell, 160(5), 829–841. 10.1016/j.cell.2015.01.033 [PubMed: 25703096]

Cox J, & Witten IB (2019). Striatal circuits for reward learning and decision-making. Nature Reviews. Neuroscience, 20(8), 482–494. 10.1038/s41583-019-0189-2 [PubMed: 31171839]

Criscitelli K, & Avena NM (2016). The neurobiological and behavioral overlaps of nicotine and food addiction. Preventive Medicine, 92, 82–89. 10.1016/j.ypmed.2016.08.009 [PubMed: 27509870]

Crombag HS, Ferrario CR, & Robinson TE (2008). The rate of intravenous cocaine or amphetamine delivery: Influence on drug-taking and drug-seeking behavior in rats. Pharmacology, Biochemistry, and Behavior, 90(4), 797–804. 10.1016/j.pbb.2008.06.003 [PubMed: 18586051]

Dalenberg JR, Patel BP, Denis R, Veldhuizen MG, Nakamura Y, Vinke PC, Luquet S, & Small DM (2020). Short-Term Consumption of Sucralose with, but Not without, Carbohydrate Impairs Neural and Metabolic Sensitivity to Sugar in Humans. Cell Metabolism, 31(3), 493–502.e7. 10.1016/j.cmet.2020.01.014 [PubMed: 32130881]

de Wit H, Bodker B, & Ambre J (1992). Rate of increase of plasma drug level influences subjective response in humans. Psychopharmacology, 107(2–3), 352–358. 10.1007/BF02245161 [PubMed: 1615136]

Di Chiara G, Acquas E, Tanda G, & Cadoni C (1993). Drugs of abuse: Biochemical surrogates of specific aspects of natural reward. Biochemical Society Symposium, 59, 65–81. [PubMed: 7910742]

DiFeliceantonio AG, Coppin G, Rigoux L, Edwin Thanarajah S, Dagher A, Tittgemeyer M, & Small DM (2018). Supra-Additive Effects of Combining Fat and Carbohydrate on Food Reward. Cell Metabolism, 28(1), 33–44.e3. 10.1016/j.cmet.2018.05.018 [PubMed: 29909968]

Donovan MH, & Tecott LH (2013). Serotonin and the regulation of mammalian energy balance. Frontiers in Neuroscience, 7, 36. 10.3389/fnins.2013.00036 [PubMed: 23543912]

Drewnowski A (1997). Taste preferences and food intake. Annual Review of Nutrition, 17, 237–253.

Drucker DB, & Sclafani A (1997). The role of gastric and postgastric sites in glucose-conditioned flavor preferences in rats. Physiology & Behavior, 61(2), 351–358. 10.1016/s0031-9384(96)00414-3 [PubMed: 9035269]

Fazzino TL, Rohde K, & Sullivan DK (2019). Hyper-Palatable Foods: Development of a Quantitative Definition and Application to the US Food System Database. Obesity, 27(11), 1761–1768. 10.1002/oby.22639 [PubMed: 31689013]

Fernandes AB, Silva J. A. da, Almeida J, Cui G, Gerfen CR, Costa RM, & Oliveira-Maia AJ (2020). Postingestive Modulation of Food Seeking Depends on Vagus-Mediated Dopamine Neuron Activity. Neuron, 106(5), 778–788.e6. 10.1016/j.neuron.2020.03.009 [PubMed: 32259476]

Ferreira JG, Tellez LA, Ren X, Yeckel CW, & de Araujo IE (2012). Regulation of fat intake in the absence of flavour signalling. The Journal of Physiology, 590(4), 953–972. 10.1113/jphysiol.2011.218289 [PubMed: 22219333]

Ferri CP, & Gossop M (1999). Route of cocaine administration: Patterns of use and problems among a brazilian sample. Addictive Behaviors, 24(6), 815–821. 10.1016/S0306-4603(99)00036-2 [PubMed: 10628515]

Fiore MC, Smith SS, Jorenby DE, & Baker TB (1994). The Effectiveness of the Nicotine Patch for Smoking Cessation: A Meta-analysis. JAMA, 271(24), 1940–1947. 10.1001/jama.1994.03510480064036 [PubMed: 8201739]

Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, Akers CA, Clinton SM, Phillips PEM, & Akil H (2011). A selective role for dopamine in stimulus-reward learning. Nature, 469(7328), 53–57. 10.1038/nature09588 [PubMed: 21150898]

Gallistel CR, & Gibbon J (2000). Time, rate, and conditioning. Psychological Review, 107(2), 289–344. 10.1037/0033-295X.107.2.289 [PubMed: 10789198]

Glimcher PW (2011). Understanding dopamine and reinforcement learning: The dopamine reward prediction error hypothesis. Proceedings of the National Academy of Sciences of the United States of America, 108 Suppl 3, 15647–15654. 10.1073/pnas.1014269108 [PubMed: 21389268]

Goldstein N, McKnight AD, Carty JRE, Arnold M, Betley JN, & Alhadeff AL (2021). Hypothalamic detection of macronutrients via multiple gut-brain pathways. Cell Metabolism, 33(3), 676–687.e5. 10.1016/j.cmet.2020.12.018 [PubMed: 33450178]

Gossop M, Griffiths P, Powis B, & Strang J (1992). Severity of dependence and route of administration of heroin, cocaine and amphetamines. British Journal of Addiction, 87(11), 1527–1536. 10.1111/j.1360-0443.1992.tb02660.x [PubMed: 1458032]

Gouveia A, de Oliveira Beleza R, & Steculorum SM (2021). AgRP neuronal activity across feeding-related behaviours. European Journal of Neuroscience, n/a(n/a). 10.1111/ejn.15498

Greenblatt D, Shader R, Divoll M, & Harmatz J (1981). Benzodiazepines: A summary of pharmacokinetic properties. British Journal of Clinical Pharmacology, 11(S1), 11S–16S. 10.1111/j.1365-2125.1981.tb01833.x [PubMed: 6133528]

Haber SN (2014). The place of dopamine in the cortico-basal ganglia circuit. Neuroscience, 282, 248–257. 10.1016/j.neuroscience.2014.10.008 [PubMed: 25445194]

Haber SN, & Knutson B (2010). The reward circuit: Linking primate anatomy and human imaging. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 35(1), 4–26. 10.1038/npp.2009.129 [PubMed: 19812543]

Han W, Tellez LA, Perkins MH, Perez IO, Qu T, Ferreira J, Ferreira TL, Quinn D, Liu Z-W, Gao X-B, Kaelberer MM, Bohórquez DV, Shammah-Lagnado SJ, de Lartigue G, & de Araujo IE (2018). A Neural Circuit for Gut-Induced Reward. Cell, 175(3), 665–678.e23. 10.1016/j.cell.2018.08.049 [PubMed: 30245012]

Hatsukami DK, & Fischman MW (1996). Crack cocaine and cocaine hydrochloride. Are the differences myth or reality? JAMA: The Journal of the American Medical Association, 276(19), 1580–1588. 10.1001/jama.276.19.1580 [PubMed: 8918856]

H. Edwards C, J. Warren F, M. Campbell G, Gaisford S, G. Royall P, J. Butterworth P, & R. Ellis P (2015). A study of starch gelatinisation behaviour in hydrothermally-processed plant food tissues and implications for in vitro digestibility. Food & Function, 6(12), 3634–3641. 10.1039/C5FO00754B [PubMed: 26353047]

Holman GL (1969). Intragastric reinforcement effect. Journal of Comparative and Physiological Psychology, 69(3), 432–441. 10.1037/h0028233 [PubMed: 5349026]

Holst JJ (2013). Incretin hormones and the satiation signal. International Journal of Obesity (2005), 37(9), 1161–1168. 10.1038/ijo.2012.208 [PubMed: 23295502]

Hsu TM, McCutcheon JE, & Roitman MF (2018). Parallels and Overlap: The Integration of Homeostatic Signals by Mesolimbic Dopamine Neurons. Frontiers in Psychiatry, 9, 410. 10.3389/fpsyt.2018.00410 [PubMed: 30233430]

Hwang S, Lim J, Choi Y, & Jee SH (2018). Bisphenol A exposure and type 2 diabetes mellitus risk: A meta-analysis. BMC Endocrine Disorders, 18(1), 81. 10.1186/s12902-018-0310-y [PubMed: 30400886]

Jones RT (1990). The Pharmacology of Cocaine Smoking in Humans. In Research Findings on Smoking of Abused Substances (pp. 30–41). U.S. Department of Health and Human Services, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse.

Juul F, Vaidean G, Lin Y, Deierlein AL, & Parekh N (2021). Ultra-Processed Foods and Incident Cardiovascular Disease in the Framingham Offspring Study. Journal of the American College of Cardiology, 77(12), 1520–1531. 10.1016/j.jacc.2021.01.047 [PubMed: 33766258]

Kelley AE, Baldo BA, & Pratt WE (2005). A proposed hypothalamic–thalamic–striatal axis for the integration of energy balance, arousal, and food reward. Journal of Comparative Neurology, 493(1), 72–85. 10.1002/cne.20769 [PubMed: 16255002]

Lennerz BS, Alsop DC, Holsen LM, Stern E, Rojas R, Ebbeling CB, Goldstein JM, & Ludwig DS (2013). Effects of dietary glycemic index on brain regions related to reward and craving in men. The American Journal of Clinical Nutrition, 98(3), 641–647. 10.3945/ajcn.113.064113 [PubMed: 23803881]

Lenoir M, Serre F, Cantin L, & Ahmed SH (2007). Intense Sweetness Surpasses Cocaine Reward. PLOS ONE, 2(8), e698. 10.1371/journal.pone.0000698 [PubMed: 17668074]

Livesey G (1995). Metabolizable energy of macronutrients. The American Journal of Clinical Nutrition, 62(5), 1135S–1142S. 10.1093/ajcn/62.5.1135S [PubMed: 7484932]

Mandalari G, Faulks RM, Rich GT, Lo Turco V, Picout DR, Lo Curto RB, Bisignano G, Dugo P, Dugo G, Waldron KW, Ellis PR, & Wickham MSJ (2008). Release of Protein, Lipid, and Vitamin E from Almond Seeds during Digestion. Journal of Agricultural and Food Chemistry, 56(9), 3409–3416. 10.1021/jf073393v [PubMed: 18416553]

Mandelblat-Cerf Y, Ramesh RN, Burgess CR, Patella P, Yang Z, Lowell BB, & Andermann ML (2015). Arcuate hypothalamic AgRP and putative POMC neurons show opposite changes in spiking across multiple timescales. ELife, 4, e07122. 10.7554/eLife.07122 [PubMed: 26159614]

Marsch LA, Bickel WK, Badger GJ, Rathmell JP, Swedberg MDB, Jonzon B, & Norsten-Höög C (2001). Effects of Infusion Rate of Intravenously Administered Morphine on Physiological, Psychomotor, and Self-Reported Measures in Humans. Journal of Pharmacology and Experimental Therapeutics, 299(3), 1056–1065. [PubMed: 11714895]

Martini D, Godos J, Bonaccio M, Vitaglione P, & Grosso G (2021). Ultra-Processed Foods and Nutritional Dietary Profile: A Meta-Analysis of Nationally Representative Samples. Nutrients, 13(10), 3390. 10.3390/nu13103390 [PubMed: 34684391]

Mazur JE (1997). Choice, delay, probability, and conditioned reinforcement. Animal Learning & Behavior, 25(2), 131–147. 10.3758/BF03199051

Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, & Mozaffarian D (2017). Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. JAMA, 317(9), 912–924. 10.1001/jama.2017.0947 [PubMed: 28267855]

Mogenson GJ, Jones DL, & Yim CY (1980). From motivation to action: Functional interface between the limbic system and the motor system. Progress in Neurobiology, 14(2), 69–97. 10.1016/0301-0082(80)90018-0 [PubMed: 6999537]

Montague PR, Dayan P, & Sejnowski TJ (1996). A framework for mesencephalic dopamine systems based on predictive Hebbian learning. Journal of Neuroscience, 16(5), 1936–1947. 10.1523/JNEUROSCI.16-05-01936.1996 [PubMed: 8774460]

Monteiro CA (2009). Nutrition and health. The issue is not food, nor nutrients, so much as processing. Public Health Nutrition, 12(5), 729–731. 10.1017/S1368980009005291 [PubMed: 19366466]

Monteiro CA, & Cannon GJ (2019). The role of the transnational ultra-processed food industry in the pandemic of obesity and its associated diseases: Problems and solutions. World Nutrition, 10(1), 89–99. 10.26596/wn.201910189-99

Monteiro CA, Cannon G, Moubarac J-C, Levy RB, Louzada MLC, & Jaime PC (2018). The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutrition, 21(1), 5–17. 10.1017/S1368980017000234 [PubMed: 28322183]

Myers KP (2018). The convergence of psychology and neurobiology in flavor-nutrient learning. Appetite, 122, 36–43. 10.1016/j.appet.2017.03.048 [PubMed: 28377046]

Nelson RA, Boyd SJ, Ziegelstein RC, Herning R, Cadet JL, Henningfield JE, Schuster CR, Contoreggi C, & Gorelick DA (2006). Effect of rate of administration on subjective and physiological effects of intravenous cocaine in humans. Drug and Alcohol Dependence, 82(1), 19–24. 10.1016/j.drugalcdep.2005.08.004 [PubMed: 16144747]

Neri D, Steele EM, Khandpur N, Cediel G, Zapata ME, Rauber F, Marrón-Ponce JA, Machado P, da Costa Louzada ML, Andrade GC, Batis C, Babio N, Salas-Salvadó J, Millett C, Monteiro CA, Levy RB, & for the NOVA Multi-Country Study Group on Ultra-Processed Foods, Diet Quality and Human Health. (2022). Ultraprocessed food consumption and dietary nutrient profiles associated with obesity: A multicountry study of children and adolescents. Obesity Reviews, 23(S1), e13387. 10.1111/obr.13387 [PubMed: 34889015]

Novotny JA, Gebauer SK, & Baer DJ (2012). Discrepancy between the Atwater factor predicted and empirically measured energy values of almonds in human diets. The American Journal of Clinical Nutrition, 96(2), 296–301. 10.3945/ajcn.112.035782 [PubMed: 22760558]

Perszyk EE, Hutelin Z, Trinh J, Kanyamibwa A, Fromm S, Davis XS, Wall KM, Flack KD, DiFeliceantonio AG, & Small DM (2021). Fat and Carbohydrate Interact to Potentiate Food Reward in Healthy Weight but Not in Overweight or Obesity. Nutrients, 13(4), 1203. 10.3390/nu13041203 [PubMed: 33917347]

Piernas C, Ng SW, & Popkin B (2013). Trends in purchases and intake of foods and beverages containing caloric and low-calorie sweeteners over the last decade in the United States. Pediatric Obesity, 8(4), 294–306. 10.1111/j.2047-6310.2013.00153.x [PubMed: 23529974]

Poti JM, Mendez MA, Ng SW, & Popkin BM (2015). Is the degree of food processing and convenience linked with the nutritional quality of foods purchased by US households? The American Journal of Clinical Nutrition, 101(6), 1251–1262. 10.3945/ajcn.114.100925 [PubMed: 25948666]

Qu T, Han W, Niu J, Tong J, & de Araujo IE (2019). On the roles of the Duodenum and the Vagus nerve in learned nutrient preferences. Appetite, 139, 145–151. 10.1016/j.appet.2019.04.014 [PubMed: 31029689]

Rawson RA, Gonzales R, Marinelli-Casey P, & Ang A (2007). Methamphetamine Dependence: A Closer Look at Treatment Response and Clinical Characteristics Associated with Route of Administration in Outpatient Treatment. The American Journal on Addictions, 16(4), 291–299. 10.1080/10550490701389864 [PubMed: 17661197]

Rescorla RA (1967). Pavlovian conditioning and its proper control procedures. Psychological Review, 74(1), 71–80. 10.1037/h0024109 [PubMed: 5341445]

Ritter S, & Taylor JS (1990). Vagal sensory neurons are required for lipoprivic but not glucoprivic feeding in rats. The American Journal of Physiology, 258(6 Pt 2), R1395–1401. 10.1152/ajpregu.1990.258.6.R1395 [PubMed: 2360688]

Romaguera D, Fernández-Barrés S, Gracia-Lavedán E, Vendrell E, Azpiri M, Ruiz-Moreno E, Martín V, Gómez-Acebo I, Obón M, Molinuevo A, Fresán U, Molina-Barceló A, Olmedo-Requena R, Tardón A, Alguacil J, Solans M, Huerta JM, Ruiz-Dominguez JM, Aragonés N, … Amiano P (2021). Consumption of ultra-processed foods and drinks and colorectal, breast, and prostate cancer. Clinical Nutrition, 40(4), 1537–1545. 10.1016/j.clnu.2021.02.033 [PubMed: 33743289]

Samaha A-N, Mallet N, Ferguson SM, Gonon F, & Robinson TE (2004). The Rate of Cocaine Administration Alters Gene Regulation and Behavioral Plasticity: Implications for Addiction. Journal of Neuroscience, 24(28), 6362–6370. 10.1523/JNEUROSCI.1205-04.2004 [PubMed: 15254092]

Samaha A-N, Yau W-YW, Yang P, & Robinson TE (2005). Rapid delivery of nicotine promotes behavioral sensitization and alters its neurobiological impact. Biological Psychiatry, 57(4), 351–360. 10.1016/j.biopsych.2004.11.040 [PubMed: 15705350]

Schindler CW, Panlilio LV, & Thorndike EB (2009). Effect of rate of delivery of intravenous cocaine on self-administration in rats. Pharmacology, Biochemistry, and Behavior, 93(4), 375–381. 10.1016/j.pbb.2009.05.008 [PubMed: 19464316]

Schmitt M (1973). Influences of hepatic portal receptors on hypothalamic feeding and satiety centers | American Journal of Physiology-Legacy Content. https://journals.physiology.org/doi/pdf/10.1152/ajplegacy.1973.225.5.1089

Schnabel L, Kesse-Guyot E, Allès B, Touvier M, Srour B, Hercberg S, Buscail C, & Julia C (2019). Association between Ultraprocessed Food Consumption and Risk of Mortality among Middle-aged Adults in France. JAMA Internal Medicine, 179(4), 490–498. 10.1001/jamainternmed.2018.7289 [PubMed: 30742202]

Schulte EM, Avena NM, & Gearhardt AN (2015). Which Foods May Be Addictive? The Roles of Processing, Fat Content, and Glycemic Load. PLOS ONE, 10(2), e0117959. 10.1371/journal.pone.0117959 [PubMed: 25692302]

Schulte EM, Smeal JK, & Gearhardt AN (2017). Foods are differentially associated with subjective effect report questions of abuse liability. PLOS ONE, 12(8), e0184220. 10.1371/journal.pone.0184220 [PubMed: 28859162]

Schultz W (2007). Multiple dopamine functions at different time courses. Annual Review of Neuroscience, 30, 259–288. 10.1146/annurev.neuro.28.061604.135722

Schultz W, Dayan P, & Montague PR (1997). A Neural Substrate of Prediction and Reward. Science, 275(5306), 1593–1599. 10.1126/science.275.5306.1593 [PubMed: 9054347]

Sclafani A (1995). How food preferences are learned: Laboratory animal models. The Proceedings of the Nutrition Society, 54(2), 419–427. 10.1079/pns19950011 [PubMed: 8524889]

Sclafani A, & Ackroff K (2004). The relationship between food reward and satiation revisited. Physiology & Behavior, 82(1), 89–95. 10.1016/j.physbeh.2004.04.045 [PubMed: 15234596]

Sclafani A, & Ackroff K (2012). Role of gut nutrient sensing in stimulating appetite and conditioning food preferences. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 302(10), R1119–1133. 10.1152/ajpregu.00038.2012 [PubMed: 22442194]

Sclafani A, & Lucas F (1996). Abdominal vagotomy does not block carbohydrate-conditioned flavor preferences in rats. Physiology & Behavior, 60(2), 447–453. 10.1016/S0031-9384(96)80018-7 [PubMed: 8840905]

Sclafani A, Marambaud P, & Ackroff K (2014). Sucrose-conditioned flavor preferences in sweet ageusic T1r3 and Calhm1 knockout mice. Physiology & Behavior, 126, 25–29. 10.1016/j.physbeh.2013.12.003 [PubMed: 24384370]

Scott TR, & Small DM (2009). The role of the parabrachial nucleus in taste processing and feeding. Annals of the New York Academy of Sciences, 1170, 372–377. 10.1111/j.1749-6632.2009.03906.x [PubMed: 19686161]

Sensoy I (2014). A Review on the Relationship Between Food Structure, Processing, and Bioavailability. Critical Reviews in Food Science and Nutrition, 54(7), 902–909. 10.1080/10408398.2011.619016 [PubMed: 24499069]

Small DM, & DiFeliceantonio AG (2019). Processed foods and food reward. Science (New York, N.Y.), 363(6425), 346–347. 10.1126/science.aav0556 [PubMed: 30679360]

Steele EM, Baraldi LG, Louzada M. L. da C., Moubarac J-C, Mozaffarian D, & Monteiro CA (2016). Ultra-processed foods and added sugars in the US diet: Evidence from a nationally representative cross-sectional study. BMJ Open, 6(3), e009892. 10.1136/bmjopen-2015-009892

Su Z, Alhadeff AL, & Betley JN (2017). Nutritive, Post-ingestive Signals Are the Primary Regulators of AgRP Neuron Activity. Cell Reports, 21(10), 2724–2736. 10.1016/j.celrep.2017.11.036 [PubMed: 29212021]

Tan H-E, Sisti AC, Jin H, Vignovich M, Villavicencio M, Tsang KS, Goffer Y, & Zuker CS (2020). The gut–brain axis mediates sugar preference. Nature, 580(7804), 511–516. 10.1038/s41586-020-2199-7 [PubMed: 32322067]

Tellez LA, Medina S, Han W, Ferreira JG, Licona-Limón P, Ren X, Lam TT, Schwartz GJ, & de Araujo IE (2013). A Gut Lipid Messenger Links Excess Dietary Fat to Dopamine Deficiency. Science, 341(6147), 800–802. 10.1126/science.1239275 [PubMed: 23950538]

Tellez LA, Ren X, Han W, Medina S, Ferreira JG, Yeckel CW, & De Araujo IE (2013). Glucose utilization rates regulate intake levels of artificial sweeteners. Journal of Physiology, 591(22), 5727–5744. 10.1113/jphysiol.2013.263103 [PubMed: 24060992]

Thanarajah SE, Backes H, DiFeliceantonio AG, Albus K, Cremer AL, Hanssen R, Lippert RN, Cornely OA, Small DM, Brüning JC, & Tittgemeyer M (2019). Food Intake Recruits Orosensory and Post-ingestive Dopaminergic Circuits to Affect Eating Desire in Humans. Cell Metabolism, 29(3), 695–706.e4. 10.1016/j.cmet.2018.12.006 [PubMed: 30595479]

Tindell AJ, Berridge KC, Zhang J, Peciña S, & Aldridge JW (2005). Ventral pallidal neurons code incentive motivation: Amplification by mesolimbic sensitization and amphetamine. European Journal of Neuroscience, 22(10), 2617–2634. 10.1111/j.1460-9568.2005.04411.x [PubMed: 16307604]

Traoret CJ, Lokko P, Cruz ACRF, Oliveira CG, Costa NMB, Bressan J, Alfenas RCG, & Mattes RD (2008). Peanut digestion and energy balance. International Journal of Obesity, 32(2), 322–328. 10.1038/sj.ijo.0803735 [PubMed: 17912269]

Tunstall BJ, & Kearns DN (2014). Reinstatement in a cocaine versus food choice situation: Reversal of preference between drug and non-drug rewards. Addiction Biology, 19(5), 838–848. 10.1111/adb.12054 [PubMed: 23551949]

Tunstall BJ, Riley AL, & Kearns DN (2014). Drug specificity in drug versus food choice in male rats. Experimental and Clinical Psychopharmacology, 22(4), 364–372. 10.1037/a0037019 [PubMed: 24886157]

van Duynhoven JPM, van Velzen EJJ, Westerhuis JA, Foltz M, Jacobs DM, & Smilde AK (2012). Nutrikinetics: Concept, technologies, applications, perspectives. Trends in Food Science & Technology, 26(1), 4–13. 10.1016/j.tifs.2012.01.004

Vanderveldt A, Oliveira L, & Green L (2016). Delay discounting: Pigeon, rat, human—does it matter? Journal of Experimental Psychology: Animal Learning and Cognition, 42(2), 141–162. 10.1037/xan0000097 [PubMed: 26881899]

Volkow ND, Ding Y-S, Fowler JS, Wang G-J, Logan J, Gatley JS, Dewey S, Ashby C, Liebermann J, Hitzemann R, & Wolf AP (1995). Is Methylphenidate Like Cocaine?: Studies on Their Pharmacokinetics and Distribution in the Human Brain. Archives of General Psychiatry, 52(6), 456–463. 10.1001/archpsyc.1995.03950180042006 [PubMed: 7771915]

Volkow ND, Wang Gene.-J., Fischman MW, Foltin R, Fowler JS, Franceschi D, Franceschi M, Logan J, Gatley SJ, Wong C, Ding Y-S, Hitzemann R, & Pappas N (2000). Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. Life Sciences, 67(12), 1507–1515. 10.1016/S0024-3205(00)00731-1 [PubMed: 10983846]

Volkow ND, Wang G-J, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas N, Hitzemann R, & Shea CE (1997). Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature, 386(6627), 827–830. 10.1038/386827a0 [PubMed: 9126740]

Volkow ND, Wang G-J, Gatley SJ, Fowler JS, Ding Y-S, Logan J, Volkow ND, Hitzemann R, Angrist B, & Lieberman J (1996). Temporal relationships between the pharmacokinetics

of methylphenidate in the human brain and its behavioral and cardiovascular effects. Psychopharmacology, 123(1), 26–33. 10.1007/BF02246277 [PubMed: 8741951]

Wakabayashi KT, Weiss MJ, Pickup KN, & Robinson TE (2010). Rats Markedly Escalate Their Intake and Show a Persistent Susceptibility to Reinstatement Only When Cocaine Is Injected Rapidly. Journal of Neuroscience, 30(34), 11346–11355. 10.1523/JNEUROSCI.2524-10.2010 [PubMed: 20739555]

Watt BK, & Merrill AL (1975). Handbook of the Nutritional Contents of Foods. Courier Corporation.

Watts AG, Kanoski SE, Sanchez-Watts G, & Langhans W (2022). The physiological control of eating: Signals, neurons, and networks. Physiological Reviews, 102(2), 689–813. 10.1152/physrev.00028.2020 [PubMed: 34486393]

Yeomans MR (2012). Flavour–nutrient learning in humans: An elusive phenomenon? Physiology & Behavior, 106(3), 345–355. 10.1016/j.physbeh.2012.03.013 [PubMed: 22465846]

Yeomans MR, Leitch M, Gould NJ, & Mobini S (2008). Differential hedonic, sensory and behavioral changes associated with flavor–nutrient and flavor–flavor learning. Physiology & Behavior, 93(4), 798–806. 10.1016/j.physbeh.2007.11.041 [PubMed: 18201736]

Zhang L, Han W, Lin C, Li F, & de Araujo IE (2018). Sugar Metabolism Regulates Flavor Preferences and Portal Glucose Sensing. Frontiers in Integrative Neuroscience, 12, 57. 10.3389/fnint.2018.00057 [PubMed: 30519164]

Zukerman S, Ackroff K, & Sclafani A (2013). Post-oral appetite stimulation by sugars and nonmetabolizable sugar analogs. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 305(7), R840–853. 10.1152/ajpregu.00297.2013 [PubMed: 23926132]