The Complex Interplay of neural systems underlying addiction and food, and the implications of these findings

Introduction:

According to the World Health Organization, approximately 39% of adults aged 18 or older are considered overweight, and 13% of these are considered obese [1]. The prevalence of obesity has more than doubled since 1980 and with a concurrent rise in associated health issues such as type 2 diabetes, cardiovascular disease, arthritis and some cancers [1, 3]. In the US the medical costs of obesity was estimated to be around 20% of the total health care costs in 2012 [4]. The substantial increase in obesity is likely to have many contributing factors: increase in abundance and ease of access to highly-processed and palatable (high food/sugar) food, an increase in sedentary life styles, and the possible emergence of a food-addiction [5-7].

In 2013, binge eating disorder was officially recognized in DSMV as a distinct eating disorder [8] Under the diagnostic criteria, individuals experience a sense of lack of control over eating with recurrent episodes of binging [9, 10]. It has been suggested that binge eating disorder in particular has several aspects of substance use dependence (SUD) and the hypothesis of food addiction has been developed to model the growing obesity epidemic [6, 10, 11]

Addiction, no matter the substance, has several behavioral attributes: bingeing, sensitization and tolerance, withdrawal, and craving [9, 12]. Binging behavior is defined by a marked increase of administration of a substance at one time, generally after voluntary or forced abstinence. In both human and animal studies of addiction substance use occurs in episodes or binges, even when given unlimited access. Drug cross-sensitization is a characteristic of drug abuse where prior exposure to repeated drug administration induces a hyperactive locomotor response to a different drug with potential for abuse [10, 12]. Tolerance is evident is a gradual

decrease in responsiveness to the substance, where higher doses are needed to produce the same effect [10, 12]. Withdrawal occurs when the substance is removed or its actions blocked, and can result in severe systemic changes including tremor, anxiety and depression, hallucinations, and impaired function. Presentation of stimuli associated with the drug, (place of drug purchase, or administration tools) can trigger feelings of intense drug craving and lead to increased risk of relapse [13]. Craving is characterized by enhanced motivation for the drug either through positive-affect of the drug itself, or negative affect of withdrawal symptoms[10, 12]. Craving behavior in animals is associated to an enhanced motivation to administer an abused substance this is directly measured through operant response to drug associated cues [10, 12].

The Table presented below, modified from DG Smith and TW. Robbins (2013), summarizes the behavioral similarities of Binge Eating Disorder with Substance Dependence. These similarities will be discussed in further sections, with direct regards to behavioral evidence, reward pathways and metabolic homeostasis systems involvement and implications of these studies on the prevalence of obesity as a global epidemic.

Table 1. DSM-IV-TR Definitions of Substance Dependence and Binge Eating Disorder

Comorbid Symptom	Substance Dependence	Binge Eating Disorder
Escalation of Use	The substance is taken in larger amounts or over a longer period than intended.	Eating large amounts of food when not feeling physically hungry.
Loss of Control	There is a persistent desire or unsuccessful effort to cut down or control substance use.	A sense of lack of control during the episodes, e.g., a feeling that one can't stop eating or control what or how much one is eating.
Social Consequences	Important social, occupational, or recreational activities are given up or reduced because of use.	Eating alone because of being embarrassed by how much one is eating.
Personal Distress	The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance.	Feeling disgusted with oneself, depressed, or feeling very guilty after overeating; marked distress regarding binge eating; eating until feeling uncomfortably full.

A categorical comparison of the DSM-IV-TR definitions of substance dependence and binge eating criteria for both bulimia nervosa and binge eating disorder (3).

Part I: The Food Addiction Hypothesis

In this section, several aspects, and evidence for, a food addiction hypothesis will be discussed. First the behavioral attributes of food addiction in animal models will be explored, followed by evidence for their influence on the mesolimbic reward systems. Hormone regulation of appetite will also be addressed in regards to the systems involved. And lastly the contributions of Dopamine and Opioid systems on the promotion and regulation of food addictive behaviors.

1.1 Behavioral Evidence

In traditional animal models one of the first signs of substance abuse is binging behavior, measured as an increase in self-administration during a limited time of access [9, 10, 12]. Rodents on an intermittent feeding schedule with high sugar chow display binge-like behavior, where they consume as much sugar in a shortened 12h period as ad libitum-fed animals do over 24h [10, 14, 15], and steadily increase their intake over time [16, 17]. This behavior is also seen in other models of food addiction, where high fat diet or sweet-fat diets were restricted to either 2hr or 12hr periods [18]. Historically, prior food restriction has been shown and used to enhance drug intake and it is reasonable to predict there is a correlation between food deprivation and reward salience [19, 20]. Taken together there is significant evidence that compulsive binging behavior is evident in these animal models of food addiction.

After a period of forced abstinence, addicted animals often increase their response to cues previously associated with the drug despite lack of drug reinforcement, and this behavior is equated as a measurement of craving and motivation for the drug [10, 12]. A deprivation effect is also charactorized by increased intake after abstinence when the drug is reinstated [10, 12]. This deprivation effect is also seen in intermittent sugar food addiction model, where animals

increase their consumption and motivation for sugar after abstinence [21]. Surprisingly, rodents are more likely to work for sweet rewards, even when not food deprived compared to cocaine [22, 23]. In addition to this, animals will also endure adverse stimuli to obtain both drug [23, 24] and even palatable food [25]. These behaviors are equated to palatable food craving in human studies [26, 27] and highlight the power of the craving to motivate behavior. Alternatively, this behavior may also be indicative of a strong habitual learned response to cues rather than a drug craving per se [23]. Studies of Pavlovian-conditioning in animals, has demonstrated that rodents will still work food rewards that caused adverse effects but decreased in its actual consumption [28].

A third hallmark of substance abuse is cross sensitization to effects of other drugs and is hypothesized to occur due to the similar molecular actions of both drugs on the reward pathway [9, 10, 12]. This phenomenon, can also give light to consummatory cross-sensitization where one drug can lead to increased intake of another drug or substance. Firstly, this is seen with several other common drugs of abuse including amphetamine sensitizing rats to cocaine, cocaine sensitizing to alcohol and stress, and heroin with cannabis [10]. Similarly, intermittent sugar cross sensitizes rats to both amphetamine and cocaine locomotor response, as well as enhanced intake of alcohol in separate studies [15, 29, 30]. In addition to this evidence, prior amphetamine administration sensitized to rats a week later to locomotor hyperactivity in response to 10% sucrose, illustrating similar sensitization behavior to other drugs of abuse [10].

A fourth criterion for substance addiction is the presence of withdrawal symptoms upon forced or sudden abstinence. Severe behavioral and systemic symptoms can occur upon sudden drug withdrawal, such as decreased body temperature, tremors, anxiety, dysphoria and sleep disturbances [10]. Rodents in the intermittent sugar model of food addiction undergo opioid-like withdrawal symptoms when administered an opioid antagonist naloxone [14]. Spontaneous withdrawal symptoms, both systemic and behavioral, have been reported upon

removal of food for an extended period of time [14, 17]. Given this evidence, it is possible that intermittent sugar access can form states of substance dependence.

1.2 Drug Addiction Pathway and Metabolic Homeostasis Convergence

With considerable behavioral evidence in which the intermittent sugar model replicates several aspects of addiction, it is important to review the neurochemical and molecular pathway similarities of this model to more traditional drugs of abuse. Common abused substances and addiction are mediated primarily through the mesolimbic dopamine system, summarized in Figure 1 to the right (modified from J.A. Kauer 2007). The mesolimbic dopamine system involves several key brain structures: the Ventral Tegmental Area (VTA), Nucleus Accumbens (NAc), Amygdala (Amg), Prefrontal Cortex (PFC) and lateral hypothalamus (LH) and several neurotransmitters, Dopamine, Glutamate, GABA and Orexin. This mesolimbic pathway is frequently referred to as the "reward pathway" for its pivotal role in reward prediction, hedonic reinforcement, motivation and incentive salience [31, 32]. According to the food addiction hypothesis (summarized in Avena et al 2008 and DG Smith and TW Robbins, 2012) the effect of palatable food on the reward system may be two-fold: 1.) the convergence of neuro-pathways from sensory taste on

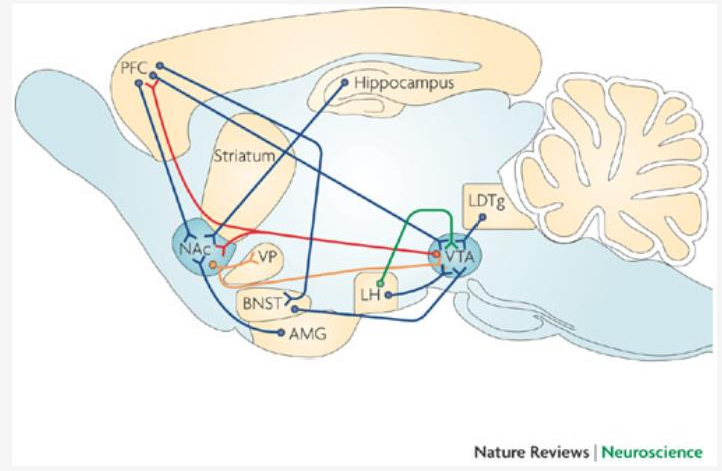

Figure 1. Mesolimbic dopamine system circuitry.

Glutamatergic projection – blue, Dopaminergic projections – red, GABAergic – orange; Orexigenic projections – green. (Figure 1 and caption modified from J.A. Kauer 2007)

the VTA and NAc dopaminergic reward system and 2.) regulatory effects from hormones released from the gut during digestion, as well as input from sensory systems of taste, sight and

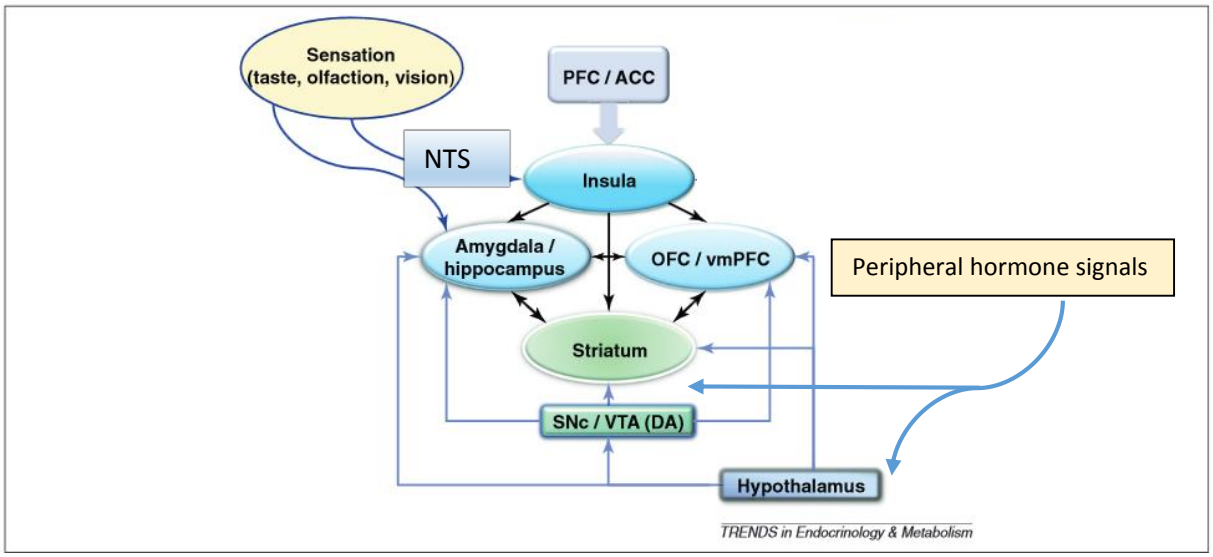

Figure 2. Appetitive Network modified from [2]

Abbreviations used: ACC, anterior cingulate cortex; DA, dopamine; OFC orbitofrontal cortex; PFC, prefrontal cortex; vmPFC, ventromedial prefrontal cortex; SNc, substantia nigra pars compacta; VTA ventral tegmental area; NTS, Nucleus Tractus Solitarious

smell. This interaction is summarized in Figure 2 below, modified from [2]

The direct interaction of sensory taste and the mesolimbic pathway is a key contributor to the rewarding effects of palatable food. This pathway begins at the nucleus tractus solitarious (NTS) in the brain stem, which receives input from taste receptors on the tongue as well as vagal nerve input from gastrointestinal tract. The NTS projects to the Ventroposteromedial (VPM) thalamic nucleus which innervates the primary gustatory cortex (PGC) in the Insula. The PGC also sends projections to secondary gustatory cortex (SGC) in the orbitofrontal cortex (OFC) and interacts with the mesolimbic reward centers (see review:[32], and Figure 2 above). The NTS In addition to its primary function in regulation of eating behaviors, also has a significant role in the regulation of opiate reward and addiction, as well as opiate stimulation of food intake [32, 33]. The Insular cortex is responsible for the encoding of the hedonic properties of palatable food, and regulates the experience of conscious urges and cravings [13].

Interestingly, damage to the insula can cause spontaneous cessation of drug craving in both rodent models and human patients with stroke damage [34]. The OFC region is involved in the experience of the relative motivational value of obtaining palatable food or drug, while not necessarily affecting the hedonic properties of the substance [32] Both Insula and OFC regions (among several others) innervate key dopaminergic structures in reward circuitry and directly modulate drug addiction and compulsive eating behaviors [32]

1.3 Hormone regulation of appetite

Several hormones released from the periphery also directly affect the dopaminergic system. Leptin is a hormone produced by white adipose tissue which normally inhibits feeding through hypothalamic actions to maintain healthy levels of fat stores in the body. It has been shown that animal models of obesity develop resistance to Leptin feeding regulation [35]. Insulin, another hormone adversely affected by obesity, is normally produced and released by beta cells in the pancreas in response to elevated levels of glucose particularly after a meal to promote glucose uptake and utilization. Obesity often results in resistance to insulin signaling and leads to Type 2 Diabetes, where both glucose and insulin remain chronically high. Intracerebroventricular (icv) administration of Leptin or Insulin have direct behavioral effects on normal weight rodents causing reduced sucrose self-administration, and suppressed CPP for sucrose pellets [36, 37]. Early studies showed that VTA dopamine neurons also express both leptin and insulin receptors [38-40] and this evidence provides a direct link to hormone regulation of DA release from the VTA [41, 42].

A third systemic hormone important in feeding behavior is Ghrelin, which is produced primarily by the stomach in a cyclic fashion, where concentration rises during fasting to promote feeding and falls in response to a meal. Ghrelin modifies activity in the hypothalamus where it promotes feeding and metabolic homeostasis [43, 44]. In addition to this, Grehlin also has a direct effect on dopamine neurons in the VTA and induces rapid synaptic plasticity of axonal

inputs onto the VTA to promote excitation [44]. Ghrelin delivery to the VTA directly stimulates food intake in animal models [45] and this action is blocked by ghrelin receptor antagonist delivery in the VTA [46]. With consideration of the above evidence for both neuropathway convergence on the mesolimbic dopamine system and direct hormone modulation of its components, it is reasonable to predict a direct dopaminergic effect on food addiction.

1.4 The Dopamine Hypothesis:

It has been previously established that stimulation of Dopamine cell bodies in the VTA reinforce self-administration in drug abuse studies (highlighted in green in Figure 2), and that any substance that repeatedly causes dopamine release or reduces DA reuptake may be a candidate for abuse [10, 12]. Intermittent sugar model has similar effects on the Dopamine system as other drugs of abuse. Namely, an increase in extracellular DA in the NAc during palatable food consumption when the animal is food deprived, as well as increased D1 receptors in the NAc and decreased D2 receptor binding in the striatum relative to chow fed rats [14, 47]. Therefore this is evidence of fulfilling the first requirement of palatable food as a substance capable of abuse, with direct actions on the dopaminergic reward system.

1.5 Opiate Regulation of Appetite

In addition to dopamine action, endogenous opioids have been shown to mediate feeding behavior in a variety of animal and human studies [48]. The use of opioid antagonists decreased subjective ratings of taste valence without affecting the taste perception in a human study [49]. In animal models, mu opioid agonist DAMGO stimulated food intake when microinjected in several brain regions involved in food reward: NTS, hypothalamus, amygdala, NAc and VTA [29, 50-52]. Ingestion of highly palatable food is associated with increased mu opioid receptor (MOR) gene expression and changes in MOR agonist binding in the NAc shell,

cingulate, hippocampus and locus coeruleus, similar to changes seen in response to cocaine and morphine.

Taken together, the evidence of food addiction in animal models from dopaminergic and opioid processes appears convincing. Although critics of the food addiction hypothesis may argue for greater translational power of these models to the obesity epidemic. These views will be discussed in the following section.

Part II: Distinctions and differences in circuitry underlying drugs of abuse and obesity

Animal models of intermittent sugar and high-fat diets add understanding and evidence for binge-eating disorders and food addiction. Although, some contradictory evidence is seen regarding the dopamine hypothesis of food addiction. While dopamine has been repeatedly shown as a primary component of drugs of abuse, its involvement in food addiction may be more nuanced. In contrast to drug addiction, dopamine depletion in the NAc does not substantially change food consumption [23, 53]. While dopamine deficient mice show severe signs of decreased food consumption [23, 54], it has been shown that they maintain normal sucrose preference but have the inability to actively seek it [23, 40, 55]. In addition to this, when low doses of dopamine receptor antagonists are systemically or directly injected in the NAc, rodents show prolonged and escalated food consumption [56-58]. Conversly, high doses of DA anatgonists can inhibit feeding behavior [58]. This suggests that there may be an optimal dopamine response range which contributes to feeding behavior.

In a recent human imaging study using positron emission tomography (PET) scans, it was found that D_2 receptor availability was equivalent between morbidly obese women and control subjects; while mu-oioid receptor (MOR) was significantly elevated in obese patients [59]. The results of this study suggest that food addiction may follow opiate addiction pathways more closely than traditionally dopamine driven addictions [59]. Contradictory evidence is also

seen, where Cerebral MOR availability was lowered in morbidly obese patients in brain regions implicated in reward processing including ventral striatum, orbitofrontal cortex, amygdala, putamen, insula and anterior cingulate [59]. There is increasing evidence that the changes in the cortical regulation of feeding behavior may be dependent on opioid actions, and may be differentially effected by obesity across brain regions [23, 60, 61].

Through research on the hormonal regulation of food intake and metabolic processes, it has become increasingly evident of the power of these hormones to motivate behavior, with distinctions in food addiction and traditional drugs of abuse. Hypothalamic nuclei receive and integrate hormone signals from digestion, such as Leptin and Ghrelin, and directly inhibit or stimulate feeding behaviors [23]. In Addition to this, direct stimulation of AgRP neurons in the hypothalamus is sufficient to drive food intake in the absence of Dopamine [62]. This idea of the emerging importance of hypothalamic regulation of feeding was summarized effectively in a review from DiLeone R.J. et al 2012, “This leads to the idea that the mesolimbic circuit mediates drug reinforcement, which is modulated by some hypothalamic systems, where the hypothalamus mediates food seeking and consumption, which is modulated by the dopaminergic system” [23].

The food addiction hypothesis is also criticized for the validity of animal binging behavior as an addictive response or whether it is a compulsive pavlovian-learned response to a cue. Results from a study by Galarce EM et al 2007, suggest that increased operant response for food rewards may indicate a strong correlation to habit learning rather than hedonic craving. Important cortical brain regions such as the OFC, PFC are involved in habitual learning and decision making and control of impulsive or compulsive behaviors. In a human study involving patients with binge eating disorder (BED), overweight, and normal weight subjects, all showed significant activation of the OFC and insula in fMRI task presenting visual stimuli of high caloric

foods. In particular, BED patients displayed over-activated OFC and greater self-reported value to the food stimuli [63].

While, dopamine and opioid systems may be involved in regulating feeding behavior, Orexin neuropeptide signaling has increasingly been explored as a key contributor to compulsive and addictive behaviors. Orexin is a neuropeptide produced in the CNS in the neurons located primarily in lateral hypothalamus [40] which project to the VTA and many other brain regions. There are two primary types of orexin receptors (OXr) distributed throughout the brain, OXr1 and OXr2. It is now believed that OXr2 is primarily involved in the regulation of sleep-wake cycle and arousal [64] while OXr1 is involved in modulating motivation and reward [65]. OXr1 appears to be important regulator of the late stages of drug addiction involving compulsive consumption of and craving for the drug or food [66, 67]. Peripheral administration of OXr1 antagonist regulated impulsive behavior under baseline and cocaine stimulated conditions as measured by premature responses in a 5-choice serial reaction time task [68]. Also recent studies have focused on the Orexin system regulation of binge-like consumption of a rewarding stimulus (sucrose, saccharin and ethanol) in non-dependent animals [69-71]. It has been proposed that orexin systems may drive food and other substance addiction via impulsive binge consumption through a positive feedback system to promote transition to a compulsive binging behavior [72].

Part III: Conclusion

With the variety of evidence explored, it appears that palatable food is rewarding, and can lead to compulsive consumption in susceptible animals. But there is a lack of human studies to support the translational power of these studies to directly affect obesity prevalence. One caveat in the sugar binging model as for food addiction and the obesity epidemic is the lack of weight gain seen in the test animals. While these animals develop compulsive eating habits comparable to other drugs of abuse, they are able to maintain proper weight through increased

activity and compensatory decrease in regular chow consumption [10]. Evidence for a circadian impact on the efficiency of metabolism of these calorie dense meals has been proposed to explain why several of these binge-eating models in rodents did not also induce obesity or weight changes [73].

In addition to this, the physiological relevance of the withdrawal symptoms induced from chronic intermittent sugar access and opioid antagonist naloxone, may be questioned. As stated earlier, Naloxone treatment in these animals induced significant withdrawal-like symptoms of anxiety, teeth chatter, fore-paw tremor and head shakes [14]. Although that it should be noted these symptoms were induced using very high doses of drug from 10-20mg/kg intraperitoneal or 3mg/kg subcutaneous administration. This is in stark contrast to very low doses (0.004-0.013 mg/kg) Naloxone treatment in morphine addicted rats to induce the same opioid withdrawal symptoms [74]. This discrepancy leads to a discussion of the physiological relevance of naloxone induced sugar withdrawal to mimic opiate addiction. Despite this confound, there do appear to be similarities in uncontrolled high calorie diets to induce binging, sensitization, tolerance, and craving: all behavioral hallmarks of addiction.

With the results of several neurochemical and neuro-systems studies summarized earlier, there is little question on the possibility of food addiction or the hedonic properties of palatable food. The drive and rewarding properties of seeking palatable food is imprinted over evolution to promote survival, while abundant calorie-dense food in industrial societies can be attributed to the adverse health effects on this drive. The question I propose now is whether this phenomenon of food addiction is seen in human populations. Or rather a point of discussion would be the translational power of these studies to mimic the obesity epidemic seen today.

Obesity is largely attributed to a chronic caloric imbalance, where individuals consume more calories from food than they use and results in weight gain. There may be many factors which contribute to this phenomenon from increased sedentary life-styles to the expansion and

ease of access to calorie-dense foods [75]. With the plethora of animal models on the addictive properties of food, there is need for human studies on the translational power of the food addiction models. Binge Eating Disorder may contribute in part to obesity where it is diagnosed in approximately 30% of obese patients seeking weight control treatment [76]. Although a review of epidemiology studies comparing body mass index (BMI) to substance use disorders, do not indicate a clear connection [75].

An important area of research is lacking on the psychological aspects of food addiction to palatable food involving mood and the possibility of emotional eating as a major contributing factor [11]. Studies using the Temperament and Character Inventory tests to analyze behavioral similarities between overweight patients and those with substance use disorders, have higher novelty-seeking scores and lower self-directedness scores [75]. Anxiety and Depression disorders involve much of the same mesolimbic pathways as food or other substance addiction [77]. It is important to acknowledge the complexity of the issues addressed in regards to obesity, where there is likely no one right answer. Several aspects are involved, from metabolic homeostasis and regulation, the addictive and hedonic properties of food, compulsive and impulsive actions and a variety of psychiatric conditions may contribute to obesity. Further human studies using pharmacological interventions, and fMRI or PET imaging, along with longitudinal studies are needed to fully address the food addiction hypothesis and its efficacy.

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Student B – Pass

Overall the committee thought the student did an excellent job introducing the essay, and provided an accurate and thorough discussion of the behavioral similarities between drug and food intake, including: binging, craving, cross-sensitization, withdrawal for sugar and drugs. However, several concerns were discussed.

Part 2:

- As presented, the orexin discussion seems less appropriate as a response to Part 2 and would be better placed in response to Part 1. That is, it is not clear how it is different for drug and food intake.
- Reference 64 is supposed to be about Orexin receptors in arousal and sleep-wake, but it is not.
- Although the student discusses numerous pathways/circuits there is no mention of peripheral input (e.g. leptin and ghrelin) to the hypothalamus.

Part 3:

- Limited discussion on the implications of food addiction for prevention, diagnosis, and treatment strategies.
- Concludes that there are overlapping circuits modulating drug and palatable natural reward (food) intake. The student, however, also suggests that the concepts of food addiction as studied in animal models does not perfectly translate to the human disease. I think the student is trying to indicate that there is biological relevance for food addiction, but the current data does not fully support it, or at least that food addiction does not fully mimic drug addiction. Nevertheless, their opinion is not clearly stated.