9

Food Addiction, Obesity and Neuroimaging

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1. Introduction

This chapter will be dedicated to addressing various aspects of food addiction (where food is portrayed as being an addictive substance). It will encompass our group's and colleagues' newest neuroimaging research results and methods with respect to the findings of other researchers in the field. The chapter will attempt to elucidate the mechanisms of food addiction (FA) leading to obesity. It will begin with a brief introduction on the major points relating to obesity and FA. The first section will address the neurobiology and neurophysiology of addiction as well as the causes of obesity and its global impacts, concluding with therapeutic measures and future research.

2. Food addiction and obesity: Health problems

Obesity-related deaths rank second in the world (Mokdad et al., 2004). Obesity is linked with stroke, heart disease, diabetes mellitus, osteoarthritis, and certain cancers (Raman, 2002). Developing countries have also been affected by this global epidemic (Zemmet, 2000). The number of adults over the age of 20 with a BMI over 30 has increased rapidly over the past 20 years (Pi-Sunyer, 2002). Although the etiology of obesity has been predominantly correlated with eating behavior, other factors such as individual preferences, mental disorders, genetic makeup, or addictive tendencies have been suggested to play contributing roles (von Deneen and Liu, 2011). Among some known etiological factors, the intrauterine environment plays a role in placing children at risk for becoming obese and having diabetes and high cholesterol levels (Blumenthal & Gold, 2010). McMillen et al. (2009) suggested that specific periods during pregnancy predisposed individuals to obesity, therefore maternal nutrition and perinatal lifestyle played a major role in fetal programming. Over-nutrition during pregnancy led to larger offspring or gestational diabetes associated with obesity, while breastfeeding could counter the effects of obesity (Martorell et al., 2001).

New insights into the obesity issue involved developing an FA model that states food is eaten for pleasure and hedonistic intake of food can be linked with drug addiction and eating disorders.

This section will assess childhood obesity etiology, metabolic syndrome, dietary and behavioral causes with a specific impetus on the Han Chinese population (von Deneen et al.,

2011). Obesity particularly in China has led to worldwide attention and is becoming a pandemic disease resulting from a shift in energy balance caused by altered genes, a sedentary lifestyle, and neurohormonal imbalances as a result of Western influence. Obesity is spreading to low income and middle-income countries, such as China, as a result of novel dietary habits, promoting chronic diseases and premature mortality (Cecchini et al., 2010). Work-related activities declined, whereas leisure time is dominated by television/computer programs and other physically inactive pursuits (Popkin, 2001). The vicious obesity cycle begins with excess adipose leading to chronic low grade inflammation that results in insulin resistance (IR) along with hypertension, atherosclerosis, dyslipidemia and type 2 diabetes mellitus (T2DM), which are consistent findings of metabolic syndrome (MetS) (Achike et al., 2011). Studies have shown that obesity can be linked to lower ghrelin concentrations in obese individuals (Groschl et al., 2005). As a result, ghrelin levels have been found to be negatively correlated with body fat and waist circumference (WC) (Fagerberg, Hulten & Hulthe, 2003).

Metabolic syndrome (MetS) is defined as "a combination of clinical disorders that increase the risk for diabetes and cardiovascular disease, including atherosclerosis, stroke and hypertension" (Achike et al., 2011). The components of MetS include abdominal fat, atherogenic dyslipidemia, hypertension, pro-inflammatory state, pro-thrombic state and IR with or without glucose intolerance (Grundy et al., 2004). Obesity, dyslipidemia and hyperglycemia are all risk factors for colorectal cancer (Giovannucci, 2002). Increased plasma free fatty acids (FFA) in obese Chinese people acted as an important link between obesity and IR, and plasma FFA levels were negatively correlated with insulin sensitivity (Li et al., 2005). The Chinese were five times more likely to have a family history of T2DM than non-Chinese subjects (Xu et al., 2010). Finally, in middle-aged and elderly Chinese living in northeast China, there was a higher incidence of MetS and cardiovascular disease, especially atherosclerosis (Liu et al., 2010), which is increasing as influenced by a Westernized lifestyle (Mi et al., 2008).

2.1 Social and cultural influence on obesity

Parents and extended family members play a crucial role in shaping their children's eating and exercise habits (Rhee, 2008). This is a global phenomenon, but the best example to describe the state the world is in with regards to obesity is China. Even though the Western world (first world countries) has had the greatest problems with obesity and FA, China is following in its footsteps. Approximately 22% of Chinese parents regarded their children as being underweight even if their children weren't. Meanwhile, 23% of overweight children were perceived by their parents as being normal (Shi et al., 2007). Parental assessment of the weights of their children was associated with the physical appearance of the parents themselves (Huang, Becerra & Oda, 2007). Overweight daughters were more likely to be criticized by their mothers (Maynard et al., 2003). Chinese parents tended to misperceive their sons' weights more than their daughters'. Mothers had a better ability to discriminate their children's size. This gender difference could be related to social values and status (Campbell et al., 2006), hence exacerbating the obesity problem. For example, girls with slim and graceful bodies were deemed acceptable by Chinese society, while overweight boys were regarded as "strong and healthy" (Maynard et al., 2003). Parents' and other family members' 'pressure to eat' strategy was correlated with children's caloric consumption (Drucker et al., 1999). Another important factor leading to childhood obesity is that a high

portion of Hong-Kong school children spend too many hours watching television (TV) and playing computer or video games (Kong & Chow, 2010). Overweight or obese adolescents had a tendency to view TV programs and become less physically active. In China, access to Westernized TV programming and food advertising has increased (Hong, 1998). Advertisements for food products, such as soft drinks and salty snacks, constituted more than 80% of commercials in China (Ji & McNeal, 2001). According to mothers surveyed in urban areas in China, many children have their own spending money, and they often use this money to buy snacks and beverages (Zhang & Harwood, 2004). Chinese parents stated that their children influenced most of their purchases, especially of snacks (McNeal & Yeh, 1997). This can be witnessed in most Chinese cities with large supermarkets today. Food products and restaurant chains seen in TV programs and commercials provide food cues to children, thus enhancing the need to snack while watching TV (Coon et al., 2001). TV is present in almost every Chinese household, and TV advertising in China increasingly promotes high-calorie foods (Parvanta et al., 2010). Low-income families spend more hours watching TV than their counterparts (Livingstone, 2002). However, snacks seen on TV tended to be purchased more by those with higher incomes (Wang et al., 2008b). All in all, this evidence portrays that non-physical entertainment does play a major role in weight management in young people all over the world.

China can be portrayed as a "double burden of malnutrition" where under-nutrition coexists with obesity (Popkin et al., 1995). The food selection and consumption in China has resulted in a diet that is more energy-dense and laden with saturated animal fat and processed sugars, and is low in complex carbohydrates, fiber, fresh fruits and vegetables (Zhai et al., 2009). Underprivileged individuals tend to stock up on non-nutritious, high-calorie foods as low-budget staples, whereas nutrient-rich foods and high-quality diets are consumed by more affluent customers (Jones et al., 2007). In China, sugar-sweetened beverages (SSB) are a major food source with a high glycemic index (Murakami et al., 2006), thus are easily exploitable as a form of addictive substance. Another study found associations between frequent SSB intake and obesity predominantly in Chinese women, while lack of exercise, smoking, and high meat consumption increased the risk for greater weight gain in both genders (Ko et al., 2010). One study found that overweight children and adolescents consumed more energy, protein, and fat and ate fewer carbohydrates than did the controls (Guldan, 2010). They consumed less grain, fewer vegetables, more fruits, meats and cooking oil, eggs, fish, milk, and legumes. Those who ate at least 25g of cooking oil, 200g of meat, and 100g of dairy products had a higher chance of being overweight (Li et al., 2007).

From a recent cross-sectional survey done in Jiangsu Province, researchers found that a higher socio-economic status and urban residency were associated with energy-dense foods such as animal and dairy products, soft drinks, Western food, and increased snacking/breakfast skipping behaviors (Shi et al., 2005). Rural and lower income students normally consumed rice porridge, a traditional, thin breakfast gruel. However, they also preferred hamburgers, ice cream, milk, fruits, chocolate, and SSB (Shi et al., 2005). The traditional Chinese high-glycemic diet consists of a variety of high-glycemic staple rice products such as boiled rice, rice congee, and glutinous rice which pose adverse cardiovascular and MetS risks (Ding & Malik, 2008). When the Chinese population was lean and active, this diet did not pose as much risk. However, China today has an obesity epidemic and a dietary transition shifting toward more processed foods such as SSB (Ding & Malik, 2008).

The reason is that these foods are "appetizing, convenient and ready to eat, portable, affordable in single portions," and widely marketed for the younger generation, allowing them to be addicted to these foods. These addictive substances include soft drinks, biscuits, snacks, and fast-food sandwiches (Guldan, 2010). Higher incomes in China allow families to purchase SSB, snacks, and fast food. Supermarkets are packed with highly-processed, energy-dense, nutrient-poor, and lower-priced foods. Preferences include polished grains/white rice products, because Chinese consumers are unaware of the benefits from whole grains (Guldan, 2010). Another major dietary component is glutamate, which is a major taste ingredient of dietary protein described as 'Umami' (Kurihara & Kashiwayangani, 2000). Increasing concern with the rise of obesity in Westernized nations with the addition of monosodium glutamate (MSG) to commercially prepared foods is evident (Shi et al., 2010). There was a positive association between MSG consumption and the socio-economic status in rural China (Shi et al., 2010). Along those lines, Kazaks, Uyghurs and Mongolians are the major minorities in Xinjiang. The Kazaks have been reported to have hypertension (Jumabay et al., 2001), while obesity is common in the Uyghurs and Mongolians (Wang et al., 2006). Significant differences in mean blood pressure between Han, Kazaks, Uyghurs and Tibetan ethnic groups were deemed to be caused by different diet-related habits. It is well-known that alcohol, high-sodium foods and meat are traditionally popular among these groups, which are associated with surviving the cold weather in Xinjiang. Traditionally among Kazaks, Uyghurs and Mongolians in Xinjiang, alcohol consumption is paired with eating large amounts of animal fat or salty dishes, which could lead to an increase in fibrinogen levels. Males in particular traditionally drink spirits to deal with the cold. Additionally, salted milk tea is consumed in large amounts; vegetables are also rare in this region, hence they are not commonly consumed (Xi & Mi, 2009).

Eating disorders ranged from 1.3% to 5.21% among young Chinese females (Fu et al., 2005). However, these data do not represent the entire population. Currently, there is little knowledge about weight control concerns and behaviors in China. Body mass index (BMI), dieting, and eating disorder symptoms are not clearly defined (Fan et al., 2010). Another important study of adolescents in China found a strong association between smoking and the belief that smoking was important in weight control (Ge et al., 1994).

Overall, there are numerous problems arising from this epidemic such as psychosocial, emotional, neurological, cardiovascular, endocrine, musculoskeletal, gastrointestinal and pulmonary issues (Ebbeling, Pawlak & Ludwig, 2002). The costs of healthcare "associated with being overweight or obese projected exceed 850 billion dollars annually by 2030 in United States alone (Wang et al., 2008a)." As a result, this leads to a significant financial burden.

3. Biology and neurobiology of food intake

Food consumption is regulated via peripheral signals and central neuronal circuits (Wang et al., 2009) including the hypothalamus (HYP), amygdala (AMY), hippocampus (HIPP), insula, orbitofrontal cortex (OFC), and striatal brain regions (Dagher, 2009). These pathways regulate mechanisms of food reward, environmental stimuli perception, and integration of homeostasis of energy and gastrointestinal tract contents with food availability (Dagher, 2009). Most importantly, midbrain dopamine (DA) reward circuits motivate food ingestion and hedonistic

sensations resulting from eating (Dagher, 2009) as well as brain opioid peptides (Barbano et al., 2005), which in turn work in tandem with other circuits responsible for enforcing feeding behaviors and weight regulation (Wang et al., 2009), as seen in Figure 1.

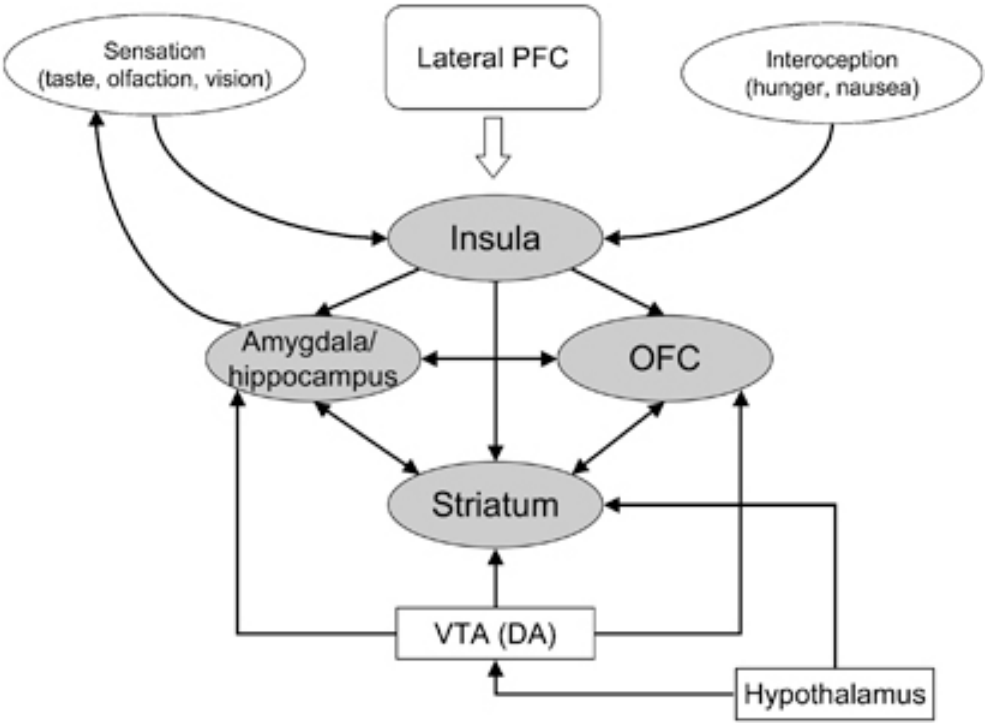

Fig. 1. A generalized brain network for regulation of hunger as depicted from Dagher (2009). PFC, prefrontal cortex; OFC, orbitofrontal cortex; VTA, ventral tegmental area; DA, dopamine.

The HYP and its circuits include orexin (ORX) and melanin concentrating hormone producing neurons in the lateral HYP as well as neuropeptide Y (NPY)/agouti related protein and alpha-melanocyte stimulating hormone producing neurons in the arcuate nucleus (ARC) known as the principal homeostatic brain regions responsible for regulating body weight (Wang et al., 2009). At the cellular level, important factors involved in communicating with the ARC in hunger regulation include ORX, melanin, NPY, and alpha-melanocyte-stimulating hormone (Wang et al., 2009). Ghrelin, leptin, insulin, and peptide YY all regulate hunger, satiety, and metabolism by stimulating neurons in the HYP (Wang et al., 2009). Ghrelin interacts with HYP depending on food intake, while leptin relays information to the HYP as well with regards to adipose storage (Wang et al., 2009). Insulin and peptide YY regulate metabolic changes (Wang et al., 2009). A useful summary of the neuropeptides that have the most dramatic influence on weight and eating regulation is listed in Table 1 and is also described in more detail by Wang et al. (2009).

Stimulate feeding	Inhibit feeding
Decrease energy expenditure	Increase energy expenditure
Anandamide	Calcitonin, Amylin, Bombesin, Somatostatin, Cytokines
β-endorphin	Cholecystokinin
Dynorphin	CRF
GABA	Dopamine
Galanin	Insulin
Ghrelin	Leptin
GHRH	Neurotensin
Neuropeptide Y	Serotonin
Norepinephrine	TRH, MSH, Glucagon, Enterostatin

Table 1. Neuropeptides That Regulate Food Intake (Sahu & Kalra, 1993)

4. Food addiction: Failure in self-regulation

Overeating and obesity are related to other substance addictions, not only in terms of overlapping neural substrates, but also in terms of genetic and environmental influences on eating behaviors and the implications that these influences have on treatment (Joranby, Pineda & Gold, 2005). The interaction between central satiety signals and reward responses to food stimuli with regards to failure in self-regulation will be discussed.

There are two primary circuits depicting reward behavior. The first one is the connected regions of the prefrontal cortex and the AMY. The second one is the limbic system involving the AMY, HYP, septal nuclei, ventral striatum, and dopaminergic innervations (Augustine, 1996). In most addictions, long-term is associated with drastic physiological alterations in the reward circuitry (Goldstein & Volkow, 2002) such as down-regulation of motivation, higher cognition and self-monitoring. Most importantly, emotions are correlated with the strength of the addiction (Shapira et al., 2003). One study found that hunger signals in the right OFC caused cravings and memories of food in fasting patients (Morris & Dolan, 2001). In more detail, those that fasted recognized previously viewed food faster. This is interesting because it implies dissociable roles of the OFC and left AMY in recognition of previously viewed food, while the nucleus accumbens (NA_c) responds to internal reward (Morris & Dolan, 2001).

4.1 Homeostatic substrates of over-eating

Hyperphagia is primarily due to continuous stimulation of NPY receptors (Kalra & Kalra, 1996). An imbalance of NPY signaling at a local level in the hypothalamus (ARC and paraventricular nucleus (PVN)) results in unregulated eating (Kalra & Kalra, 2004a). The neurotransmitter γ-aminobutyric acid (GABA) has also been known to enhance feeding behavior via its receptors, causing decreased melanocortin signaling to the PVN, which in turn results in hyperphagia (Cowley et al., 2001). Furthermore, it is possible that mutations or disturbances of α-melanocyte stimulating hormone (α-MSH) and other peptides involved in satiety can lead to hyperphagia and obesity (Kalra et al., 1999). Finally, in the case of abnormal hypothalamic function that accounts for a variety of eating disorders, it may lead

to hyperglycemia, which in turn causes other endocrine problems (Liu & Gold, 2003). This may be explained by one dietary example where fructose was consumed. Fructose promotes insulin production but blocks its release (Sato et al., 1996). Insulin is known to inhibit feeding by increasing leptin which in turn leads to weight gain (Saad et al., 1998).

Hence, this would be a good model to explain why individuals with FA are obese and are more vulnerable to develop addiction-like behavior towards high carbohydrate foods containing high fructose corn syrup.

From a neurohormonal perspective, glutamate is believed to be the neurotransmitter responsible for transmitting information between the areas depicted above, although the exact mechanism is still not understood (Swanson & Petrovich, 1998). It may be plausible that potential feeding mechanisms involve direct glutamatergic connections from the basolateral amygdala (BLA) to the lateral hypothalamic area (LHA), although the exact LHA neurons involved in this process remain unidentified. Nevertheless, it may be safe to assume that BLA outputs could influence LHA subsystems required for feeding initiation. For example, groups of LHA neurons express two recently discovered neuropeptides, melanin-concentrating hormone (MCH) and ORX, which are regulated by the hunger–satiety state and are linked to initiation of feeding (Elmquist, Elias & Saper, 1999). There is still more information with regards to the interaction between ORX and FA that is outside the realm of this chapter, so refer to Kalra & Kalra (2004b). However, hunger caused by food cues is an adaptive mechanism for survival, but at the same time, learned cues can serve as a harmful force to promote overindulgence in food despite satiety. These particular learned cues can overcome specific satiety signals in order to promote continued eating (De Castro, 1997).

4.2 Metabolic substrates

The gene-environment interaction, as part of the metabolic substrates contributing to obesity, is defined as "the response or the adaptation to an environmental agent, a behavior, or a change in behavior is conditional on the genotype of the individual" (Bouchard, 2009). For example, in Fujian province, the rate of obesity has increased due to poor nutrition before and during pregnancy, economic development, urbanization and improved living standards (McAuley et al., 2001). The genetic loci associated with obesity are: *NEGR1*, *SEC16B-RASAL2*, *TMEM18*, *SFRS10-ETV5-DGKG*, *GNPDA2*, *NCR3-AIF1-BAT2*, *LGR4-LIN7CBDNF*, *MTCH2*, *BCDIN3DFAIM2*, *SH2B1-ATP2A1*, *KCTD15*, and *FTO* (fat mass and obesity associated) (Scuteri et al., 2007). The *FTO* gene is present in all tissues and encodes a non-heme (FeII)-dioxygenase that adapts to hypoxia, lipolysis, or DNA methylation (Gerken et al., 2007). This key protein may serve as a link between the central nervous system and energy homeostasis. *FTO* variants (rs8050136 and rs9939609) were associated with obesity and body mass index (BMI) in Hong Kong, Taiwan, and Singapore populations (Frayling et al., 2007). Further research needs to be done on obesity susceptibility genes for clinical applications. One study found a relationship between *FTO* SNP rs8050136 and BMI. It showed that the combined genetic risk of single-nucleotide polymorphisms (SNPs) may be useful in predicting obesity (Cheung et al., 2010). The A allele was indeed linked to obesity in Chinese adults (Li et al., 2010). Future studies need to be done if there is a link between FA and these obesity genes as well as with other addictions. For further discussion on this topic, please refer to these specific studies (Chen et al., 2009; Ruiz et al., 2010).

Prader-Willi syndrome (PWS) is the primary model for failure in self-regulation and the most important metabolic substrate with regards to hedonic food addiction (von Deneen, Gold & Liu, 2009). Our group has worked in both of these areas and believes that there are many shared neurohormonal pathways as well as distinct differences that may clue researchers in on why certain individuals overeat and become obese. Neuroimaging studies have shown that highly palatable food has characteristics similar to that of drugs of abuse. Many of the brain changes reported for hedonic eating and obesity are also seen in various forms of addictions (von Deneen et al., 2011). Most importantly, overeating and obesity may have an acquired drive such as for alcohol or drugs, and motivation and incentive craving, wanting, and liking occur after early and repeated exposures to stimuli. The acquired drive for great food and relative weakness of the satiety signal would cause an imbalance in drive and hunger centers of the HYP and their regulation. Prader-Willi may be a genetic model of the disease we are seeing on a daily basis. New hypotheses can yield new screening tests for new treatments.

4.3 Increased drive

Volkow & Fowler (2000) believe that reward circuits (NAc, AMY) have been central to drug addiction mechanisms, where the addictive state also involves disruption of circuits involved with compulsive behaviors and with increased drive. Intermittent activation of reward circuitry involving DA leads to dysfunction of the OFC via the striato-thalamo-orbitofrontal circuit. The OFC is hypermetabolic in proportion to the intensity of the craving seen after last cocaine use or during drug-induced craving (Volkow & Fowler, 2000). Since the OFC is directly involved with drive and compulsive repetitive behaviors, abnormal activation in addicted individuals could explain compulsive drug use despite adverse reactions. This indicates that pleasure by itself cannot maintain compulsive substance abuse and drugs that could interfere with the activation of the striato-thalamo-orbitofrontal circuit could be beneficial in the treatment of drug addiction (Volkow & Fowler, 2000).

Carbohydrates, as one of the most commonly abused food substances in FA, have been found to have an interesting psychological effect. For instance, women who craved and sought high-carbohydrate foods did so to alleviate negative feelings and emotions, showing that this food group depicts compulsive behavior (Corsica & Pelchat, 2010). More so, being chronically or acutely stressed led to consumption of high-fat or sugary foods, predisposing these individuals to bingeing and a failure in dieting (Dagher & Robbins, 2009; Dagher, 2009). An interesting concept is the "refined food hypothesis" in which processed foods such as sugars, fat, salt, flour, and caffeine are the source of addiction (Ifland et al., 2009) as well as salty foods which mimic opiate agonists (Cocores & Gold, 2009). Finally, interesting findings have shown that motivation circuits relating to drinking alcohol and eating fat lead to the release of hypothalamic orexigenic peptides, such as ghrelin, which increase the consumption of these foods and raise triglyceride levels (Barson et al., 2009). In a study utilizing rats, the level of triglycerides predicted increased caloric consumption and orexigenic peptide expression following a high-fat meal (Karatayev et al., 2009).

Drugs and food exert their reinforcing effects in part by increasing DA in limbic regions, which may explain how drug abuse/addiction relates to obesity (Volkow et al., 2008). Eating craved food and drug addiction result in reward circuitry activation involving DA pathways. However, these actions activate these pathways in different ways. FA affects

reward circuitry through endogenous opioids and cannabinoids, while drugs share the same circuitry through direct effects on DA neurons or via indirect effects through neurotransmitters (Volkow & Wise, 2005). Overstimulation of DA leads to more compulsive behavior and loss of control of food and drug intake due to increased availability of DAD2 receptors in the striatum (Volkow & Li, 2004). However, FA can be considered more complex than drug abuse due to involvement of peripheral, endocrine and central pathways outside of the reward circuitry (Levine, Kotz & Gosnell, 2003).

The fundamental idea of the reward system hypothesis is that there must be an explicit emotional state connected with the addiction, such as seen in PWS. The stronger the emotional link, the stronger the addiction. There exist a couple of primary circuits for the reward system. The first one involves a reciprocal connection between the prefrontal areas of the brain and the AMY. The second is the limbic system that links the AMY with the HYP and septal nuclei. The Papez limbic system also joins the HYP with the hippocampus and thalamus (Joranby, Pineda & Gold, 2005). Therefore, the reward system hypothesis states that appetizing food and addictive behaviors compete for reward regions such as the NA_C . The act of overeating and obesity can lead to decreasing food reward and addiction (Kleiner et al., 2004). On the other hand, obesity is a "reward deficiency syndrome" (Blum et al., 1996). Most importantly, increased activation in the somatic parietal areas in food addicted individuals suggests that enhanced activity in these regions involves sensory processing of food, making food even more rewarding (Wang et al., 2001), which is not typical in PWS cases. The reward hypothesis was best explained through sugar-dependent rat studies (Avena, Long & Hoebel, 2005; Rada, Avena & Hoebel, 2005; Avena, Rada & Hoebel, 2008). These rats had a disrupted Acetylcholine (ACh) response to hunger, ingested greater amounts of sugar, and produced more DA than control rats (Avena, Long & Hoebel, 2005). This may explain why PWS and obese individuals may be addicted to certain palatable foods that cause a delayed, prolonged increase in ACh levels. In drug addiction, the ventral striatum and midbrain were associated with immediate rewards and the hippocampus responded to reward consequences. The globus pallidus, thalamus, and subgenual cingulate were associated with immediate rewards, while the caudate, insula, and ventral prefrontal cortex (vPFC) responded to reward consequences (Elliott, Friston & Dolan, 2000). The mesolimbic reward system is a common pathway that food and drugs follow in order to reinforce craving behavior (Tartar, Ammerman & Ott, 1998). This pathway is also affected by PWS causing aberrant reward circuitry (James et al., 2007). We are still unable to differentiate the reward system mechanisms in PWS and other addictions.

There are specific circuits and networks in the brain that regulate cravings, appetite, and cue-induced ingestion of addictive foods. The NA_C and DA are specifically responsible for food reward and motivated eating (Cardinal et al., 2002). There are a variety of pathways that depict appetite and food craving regulation (Kalra & Kalra, 2004b). The ability of food-related cues and a food-associated environment to induce eating in healthy humans can shed light on why PWS individuals overeat and become obese. In animal models, brain regions consisting of the BLA, medial prefrontal cortex (mPFC), and LHA act as a network to regulate eating by learned, motivational cues (Elmquist, Elias & Saper, 1999). The AMY has been shown to be crucial in cue-enhanced eating (Arana et al., 2003). The OFC is also involved in food-related cues (Arana et al., 2003). The mPFC regulates eating due to environmental cue pressure (O'Doherty, 2004). Activations of the AMY and medial OFC occur when food-deprived individuals are shown food items, and greater activations are

seen when food items are viewed (Arana et al., 2003). Our group has seen similar activations in PWS (James et al., 2007). The ventral mPFC has a significant role in appetite influenced by motivational cues, as reported by our group in PWS patients who had increased blood oxygen level-dependent (BOLD) responses in the ventral mPFC while viewing pictures of food (James et al., 2007). This would explain the excessive hunger due to increased reward values when viewing food, as well as the importance of the frontal cortex in its role in food responses. This data is also supported by findings of our group (James et al., 2002). Similarly, regions of the PFC may also participate in brain networks involved in cue-induced drug cravings. Other regions overlapping the ventral mPFC are also activated by chocolate- and nicotine-associated contextual cues in rats (Schroeder, Binzak & Kelley, 2001). The ventral mPFC was correlated with decreased consumption of high caloric, sweet and fatty foods, as in the case of PWS. A dysfunctional ventral mPFC could mechanistically depict feeding behavior in PWS or obese humans relevant to overeating, appetite, cues and cravings (O'Doherty et al., 2000). This may be a key point as to why food addicted obese individuals continue to overeat despite satiety. In PWS patients, obsession and preoccupation with food, lack of satiation, and incessant food seeking are typical behaviors as compared to normal obese humans (Ogura et al., 2008). PWS adults show preference for sweet or high carbohydrate foods over any other type of food. This is sometimes the case in normal obese individuals (Ogura et al., 2008). PWS patients will often eat the most desirable foods first, such as sweet, high caloric foods, and the least preferred foods last. Oftentimes, this is a ritualistic procedure in which the PWS-afflicted individual will gather the food and line it up in order of preference and ingest it sequentially (Singh et al., 2008). PWS cases are most susceptible to visual cues, thus passing by a bakery or restaurant, or even seeing sweet or highly palatable foods on television, will cause an enormous increase in craving and appetite despite satiety as compared to normal obese people. PWS patients will often have tantrums and aberrant behavior after seeing or smelling delicious, inviting food (Singh et al., 2008), which is highly uncommon in non-PWS individuals. In PWS, food cues (visual) have a very high emotional attachment and significance leading to bingeing episodes (Simmons, Martin & Barsalou, 2005). PWS is a biological model for hyperphagia and the reward system utilized to explain human obesity using functional magnetic resonance imaging (fMRI). Neuroimaging would be the most logical tool in precisely locating the brain regions responsible for controlling appetite and for being the reward centers specifically for FA (Tataranni & DelParigi, 2003). Using food-related pictures or other visual means to elicit brain responses has been a standard method of determining valid mechanisms that delineate the path to obesity (Jansen, 1998). Hence, the fMRI-supported hypothesis that PWS is a naturally occurring human model for FA or loss of control of eating or absence of satiety would be crucial for further studies. In the end, what remains is how logical and effective past, present, and future research can aid and treat abnormal eating behavior and brain responses to internal and external food cues in individuals afflicted with obesity.

4.4 Increased incentive

Compulsive drug-seeking and drug-taking behaviors are not always motivated by pleasure or by the desire to relieve withdrawal. The question remains, why do addicts compulsively seek drugs? Several groups have attempted to address this question by proposing the concept of "incentive–sensitization" (Robinson & Berridge, 1993; Berridge & Robinson, 1995). The essential concepts of the incentive–sensitization theory are: (1) potentially

addictive drugs produce long-term adaptations in neural systems, hence altering the brain; (2) the brain systems that are altered are involved in the process of incentive motivation and reward; (3) the critical neuroadaptations for addiction hypersensitize these brain reward systems to drugs and drug-associated stimuli; and (4) the brain systems that become sensitized do not mediate the pleasurable effects of addictive substances, but instead they mediate a subcomponent of the reward system known as incentive salience or "wanting" (Robinson & Berridge, 1993; Berridge & Robinson, 1995; Berridge & Robinson, 1998).

A study has shown that low D2 receptor availability places people at risk for FA and obesity (Allison et al., 1999). In morbidly obese individuals, prefrontal regions were responsible for the correlation between D2 receptor availability and glucose metabolism (Volkow et al., 2008). Food cues increased striatal DA production which in turn caused increased hunger and craving for that particular food; this indicated regulation by the NA_C (Volkow et al., 2002). The four major circuits involved in drug and food addictions are reward/saliency, motivation/drive, learning/conditioning and inhibitory control/emotional regulation/executive function (Volkow et al., 2008). Disruption of these circuits leads to decreased motivation for good behavior and potentiates bad behavior that ends with negative results (weight gain in FA and drug overdose in substance abuse). This results in linking new memories of expected pleasurable responses when consuming the addictive substance or viewing similar stimuli (Volkow et al., 2008).

4.5 Food addiction as an addiction

Food addiction results from craving certain food or food-substances so as "to obtain a state of heightened pleasure, energy or excitement (Tartar, Ammerman & Ott, 1998)." It is important to understand the general pathophysiology of obesity in that metabolic alterations are not necessarily a cause of this disease, as seen in other eating disorders. Investigations into non-drug related addictions such as gambling, sex and food have provided insightful findings in understanding the neural mechanisms behind the addiction process (Comings et al., 2001; Bancroft & Vukadinovic, 2004; Petry, 2006; Warren & Gold, 2007; Avena et al., 2008; Cocores & Gold, 2009; Blumenthal & Gold, 2010; Liu et al., 2010; Potenza et al., 2012) .

FA is a chronic relapsing disorder associated with food cravings or food-related substances that lead to euphoria (Gold & Stembach, 1984) or amend negative emotions (Ifland et al., 2009). As a result, the new DSM-V (http: //www.dsm5.org) will revise the category 'Eating Disorders' to 'Eating and Feeding Disorders.' Most food addicts crave carbohydrates or specific foods (Spring et al., 2008). FA is predominantly influenced by compulsive behavior instigated by emotional and environmental factors such as stress, pressure from family to be thinner, religious traditions, etc. (Gold, 1999). Most importantly, FA is related to drug addiction in that DA levels regulate this type of psychological dependence by activating DA pathways responsible for addictive behavior (Warren & Gold, 2007; Wang et al., 2009; Blumenthal & Gold, 2010). In one study, Wang et al. (2009) stated that drug addiction hijacks neurobiological pathways that regulate reward, motivation, decision-making, learning, and memory. Withdrawal results in anti-reward effects due to a loss of brain reward system function and stress when the addictive substance is not available (Dackis & O'Brien, 2005; Koob, 2009).

High-fat and high-sugar foods are being exploited by developed and developing countries (Davis & Carter, 2009) resulting in increased numbers of food addicts. These foods are linked to increasing neurochemicals such as DA (Liu et al., 2010), as demonstrated in animal studies (Rada & Hoebel, 2005), which can be applied to fMRI studies that have shown delayed satiety in obese people, meaning they consume more food despite being full than do normal individuals (Liu et al., 2000). Sugar craving caused a decrease in serotonin levels as well (Wurtman & Wurtman, 1995). As a result, FA is associated with the formation of pathological brain pathways that are reinforced by abnormal eating patterns and behaviors.

Current research in FA and other disorders has shown that there were similar neurobiological pathways as those found in drug addiction (Berry & Mechoulam, 2002; Gearhardt et al., 2009a; Wang et al., 2009; Blumenthal & Gold, 2010). Animal studies attributed addiction to specific foods (Avena et al., 2004; Avena et al., 2005; Avena et al., 2008), although humans have a tendency to respond to external food cues (Benarroch et al., 2007; James et al., 2007; von Deneen et al., 2009). Food and drugs cause DA to be released from dopaminergic neurons, originating from the mesencephalon and projecting to forebrain structures in the ventral striatum depending on the amount of reward obtained (Volkow et al., 2002; Volkow et al., 2008). Brain regions known to be associated with reward circuitry include the OFC, AMY, insula, striatum, anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) (McBride et al., 2006; Franklin et al., 2007). FA can be diagnosed using the Yale Food Addiction Scale (YFAS) based on the Diagnostic Statistical Manual (DSM)-IV-TR substance dependence criteria. This would then allow direct comparison between FA and drug abuse (Gearhardt et al., 2009b). There are numerous current reviews that would be helpful references in explaining the neurobiology and neurophysiology of addiction (please see Detar, 2011; Avena et al., 2102; Urban & Martinez, 2012).

4.6 Neuroimaging of addiction: Main findings

Most imaging projects studied DA involvement in the process of drug addiction because the ability of drugs of abuse to increase limbic DA is considered crucial for their reinforcing effects (Koob et al., 1994; Di Chiara, 1999). However, increased DA does not account for the process of addiction, since drugs of abuse increase DA in non-addicted as well as addicted subjects (Goldstein & Volkow, 2002). In the case of cocaine addiction, drug-induced DA increases and the intensity of self-reports of the drug's reinforcing properties is smaller in addicted subjects (Volkow et al., 1997). This means DA involvement in drug addiction is likely to be mediated by changes in neurocircuitry modulated by DA, including the frontal cortex. Current structural/volumetric MRI studies depicted morphological changes in the frontal lobe in various forms of drug addiction (Goldstein & Volkow, 2002). In one study, frontal lobe volume losses were shown in cocaine-dependent subjects (Liu et al., 1998; Franklin et al., 2002), alcoholic subjects (Jernigan et al., 1991; Pfefferbaum et al., 1997), and heroin-dependent subjects (Liu et al., 1998). The latter study indicated there were negative correlations between normalized prefrontal volumes and prolonged cocaine or heroin use, meaning there was a cumulative effect of substance abuse on frontal volumes. DA activation, as seen during amphetamine administration, also prevented inhibition of the AMY by the medial prefrontal cortex (Rosenkranz & Grace, 2001). A similar process may be occurring in human drug addiction, in which prefrontal top-down processes are diminished

(see Miller & Cohen, 2001). Therefore, if the frontal cortex and its functions become down-regulated in human drug addiction, the motivational, higher cognitive, and self-monitoring processes become affected (Goldstein & Volkow, 2002).

5. Neuroimaging of food addiction: Main findings

This section will briefly examine the neural correlates of addictive-like eating behavior using fMRI as compared to those with substance dependence (Gearhardt et al., 2011c). Other studies of interest relating to FA deal with the addiction potential of hyperpalatable foods (Gearhardt et al., 2011a), the public health and policy implications of FA (Gearhardt et al., 2011b), the diagnostic criteria for FA (Gearhardt et al., 2009a), and the psychological correlates of obesity (Friedman & Brownell, 1995).

Researchers may benefit from functional neuroimaging results depicting shared neural and hormonal pathways to determine similarities between substance abuse and hedonistic overeating, such as in FA and drug abuse individuals who continue to have cravings despite a dysfunctional satiety signal (Zhang et al., 2011). Functional neuroimaging studies have further revealed that good or great smelling, looking, tasting, and reinforcing food has characteristics similar to that of drugs of abuse (James et al., 2002; James et al., 2007). Many of the brain changes in fMRI studies showed that both food and drugs activated the AMY, insula, OFC, and striatum (Jonas & Gold, 1986; Matsuda et al., 1999). Food and drug cravings also showed signal activation in the HIPP, insula, and caudate (Matsuda et al., 1999).

In Brownell's group study (Gearhardt et al., 2011c), the relationship between high food addiction scores and blood oxygen level–dependent (BOLD) functional magnetic resonance imaging activation in response to receiving palatable food was evaluated. FA scores were positively correlated with activation in the ACC, medial OFC, and AMY when anticipating eating highly palatable food such as a chocolate milkshake. There was greater activation in the DLPFC and caudate when anticipating highly palatable food and decreased activation in the lateral OFC when eating palatable foods (Gearhardt et al., 2011c). These regions are associated with positive rewards from food cues (Rolls, 2000) and satiety (Small et al., 2001). Similar patterns of neural activation were seen in substance dependence (Gearhardt et al., 2011c) in response to visual cues. Another interesting finding showed that the urge to cease consumption of a palatable food or drug is suppressed in the lateral OFC (Berridge & Kringelbach, 2008; Schoenbaum & Shaham, 2008). There has been some thought that food addicts eat compulsively but have compensatory behaviors to reduce weight (Fuhrer et al., 2008). Recent functional neuroimaging studies have found abnormal brain activations in obese people. We found that before food intake, obese men had significantly increased baseline activity in the left putamen, left posterior insula, left medial temporal cortex and bilateral parietal cortex relative to lean men using a regional homogeneity (ReHo) analysis method. In this method, we measured temporal homogeneity of the regional BOLD signals. Decreased activity was also found in the medial orbitofrontal lobe, left DPFC, right inferior temporal lobe and right cerebellum in the obese subjects. After food intake, the obese men had remarkably elevated brain activity in the left putamen and bilateral parietal lobe, and reduced activity in the left superior frontal lobe and bilateral middle temporal lobe. These results indicated that, either before or after food intake, obese men might have a stronger desire to eat. This study provided strong evidence supporting the hypothesis that there is

hypo-functioning reward circuitry in obese individuals, in which the prefrontal cortex may fail to inhibit the striatum and insula, and consequently lead to overeating and obesity.

This study (Zhang et al., unpublished results) found a difference in BOLD activation between obese individuals versus controls especially in the left hemisphere as shown in Figure 2. It has been shown that a higher BMI was correlated with decreased gray matter in the left OFC and right cerebellum (Walther et al., 2010), indicating that obese individuals have limited inhibitions than controls (Baylis & Moore, 1994). In this study (Zhang et al., unpublished results), obese men had decreased neural activity in the left DLPFC prior to liquid ingestion, meaning they could not inhibit their hunger and found eating to be more desirable. The obese men also had higher activation in the left insula indicating that the insula could have affected satiety and eating (Zhang et al., unpublished results). Furthermore, greater ReHo activation in the bilateral parietal cortex in obese individuals showed that food was more palatable and enjoyable (Volkow, Fowler & Wang, 2004). Overall, it was found that the obese have hypo-functioning reward circuitry where the medial prefrontal cortex (MPFC) and left DLPFC fail to inhibit the left putamen and insula causing overeating (Zhang et al., unpublished results). fMRI was thus useful in determining the mechanisms of obesity with regards to neural activity.

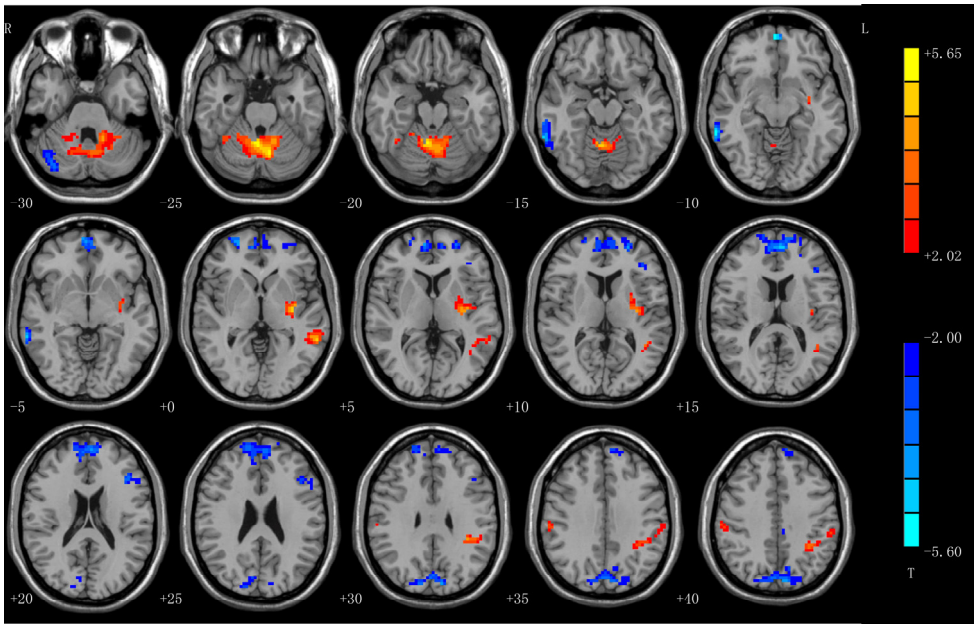

Fig. 2. A T-statistical difference map between obese subjects and controls before liquid ingestion (p<0.05, corrected). Warm and cold colors indicate obese subject-related ReHo increases and decreases, respectively (Zhang et al., unpublished).

6. Food addiction versus drug addiction

This section will introduce similarities and differences between food and drugs of abuse (Blumenthal & Gold, 2010). The DSM fifth edition has been prepared to address addiction with

new terminologies and approaches. For example, the term substance dependence was replaced with substance-use disorder. This is defined as 'A maladaptive pattern of substance-use leading to clinically significant impairment or distress, as manifested by two (or more) of the listed criteria occurring within a 12-month period (http://www.dsm5.org/ProposedRevisions/Pages/Substance-RelatedDisorders.aspx).' Substance-abuse disorder progresses from bingeing to withdrawal, and finally leading to craving the substance (Koob & Volkow, 2010). This cyclic behavior can be sustained and entertained by stress. Substance-use disorder stems from taking over neurobiological pathways regulating reward, motivation, decision-making, learning and memory in order to become responsive to the drug of choice (Everitt & Robbins, 2005; Wise, 2006; Belin et al., 2009; Hyman et al., 2009; Wang et al., 2009). Various neural networks, such as in the dorsolateral striatum, AMY, OFC and midbrain, regulate drug-seeking behavior which depends on feelings associated with using and craving that particular drug (Zapata et al., 2003; Belin & Everitt, 2008; Everitt et al., 2008; Koob, 2009). For a thorough review of this process and the neural structures involved, please see Robbins & Everitt (1999). Furthermore, DA seems to be the essential regulator of dependence, particularly in stimulants, while alcohol, opioids, and nicotine act upon opioid receptors (Koob & Volkow, 2010). This can be seen in individuals with Parkinson's disease who become addicted to dopamine-containing medications (Dagher & Robbins, 2009).

A general figure (Figure 3) of the neurobiology of addiction is provided below.

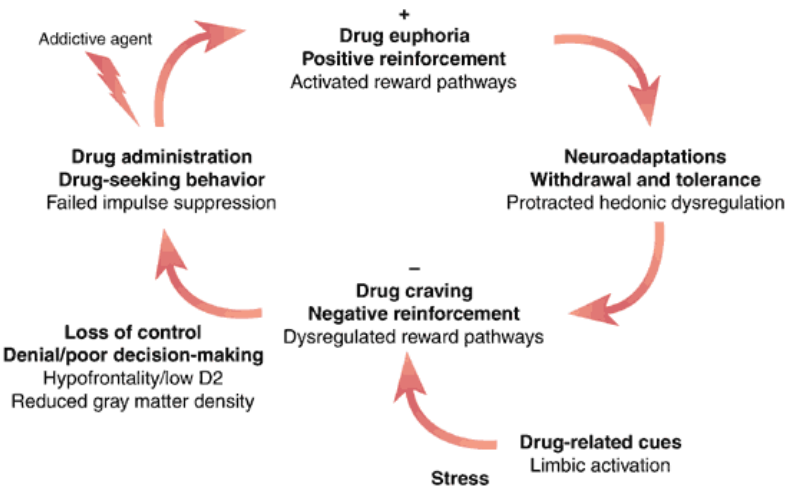

Fig. 3. Neurobiology of addiction that can be applied to food addiction as depicted by Dackis & O'Brien (2005).

The figure clearly depicts how the cycle of drug addiction is positively reinforced by euphoria from drug intake and negatively reinforced during withdrawal, craving for the drug and hedonic dysregulation. This cycle becomes more uncontrollable as the brain becomes more addicted. Drug-related cues and stress increase this craving leading to a loss of control stemming from dysfunction of the prefrontal cortex. Neuronal mechanisms for these components of addiction have been delineated in animal models and human neuroimaging studies (Dackis & O'Brien, 2005).

Accumulating evidence has shown that there are many shared neural and hormonal pathways as well as distinct differences that may help researchers find why certain individuals overeat and become addicted. The FA criteria that provide this evidence are listed in Table 2 below.

Tolerance	Starting out with a single cookie, gradually increasing to several or a whole box
Withdrawal symptoms	Habitually eating to relieve depression, anxiety, and other emotional states; unpleasant physical sensations when cutting back on carbohydrates
Taking in larger amounts or for a longer duration	Intending to eat a single serving but instead eating a whole package; binges extending several hours
Attempts to cut back	Frequent attempts to eat 'correctly'(e.g. avoid overeating or eating certain foods)
Excessive time spent pursuing, using, or recovering from use	Frequent thinking about food, planning intake, preparing, and/or resting or sleeping after excessive intake
Reduction/discontinuation of important activities because of use	Eating instead of spending time with friends; feeling too sick after overeating to do anything
Continued use despite consequences	Overeating in spite of overweight, physical illness, and/or distress about overeating

Table 2. Food addiction characteristics compared with substance abuse criteria based on Ifland et al. (2009).

Most importantly, overeating and obesity may have an acquired drive such as drug addiction with respect to motivation and incentive craving, wanting, and liking which occur after early and repeated exposures to stimuli. The acquired drive for great food and relative weakness of the satiety signal would cause an imbalance between the drive and hunger/reward centers in the brain described earlier and their regulation when conditioned via visual cues (Liu et al., 2010). As mentioned before, FA can be defined as a chronic relapsing problem caused by various fundamental factors that encourage craving for food or food-related substances so as "to obtain a state of heightened pleasure, energy, or excitement (Tartar, Ammerman & Ott, 1998)." An example of this would be carbohydrate cravers that have learned to consume high carbohydrate foods to improve their mood caused by a drop in serotonin levels (Spring et al., 2008). Most FA and eating disorders are the result of loss of control, impulsive and/or compulsive behavior stemming from emotional and environmental conditions and a psychological dependence on food. Abnormal eating behaviors along with other addictions affect the levels of DA in the mesolimbic dopaminergic system (Mogenson, 1982; Blum et al., 1996; Goldstein & Volkow, 2002; Everitt & Robbins, 2005). FA is defined by a system as follows: bingeing consists of "unusually large bouts of intake" (Colantuoni et al., 2001); withdrawal is "indicated by signs of anxiety and behavioral depression" (Colantuoni et al., 2002); craving is "measured during sugar abstinence as enhanced by responding to sugar" (Avena, Long & Hoebel, 2005); and

cross-sensitization results "from sugar to drugs of abuse" (Avena et al., 2004). Furthermore, bingeing is also defined as "escalation of intake with a high proportion of intake at one time, usually after a period of voluntary abstinence or forced deprivation" (Avena, Rada & Hoebel, 2008). FA consists of sensitization and tolerance phases, which initiate addiction (Koob & Le Moal, 2005). Withdrawal resulting from the addictive food or foods has been known to be caused by alterations in the opioid system (Colantuoni et al., 2002). This phase consists of two parts, in which DA decreases and ACh is released from the NA_C.

When sugar was analyzed with regards to withdrawal symptoms, it was stated that it was capable of producing DA, ACh, and opioids similar to most narcotic substances (Avena, Rada & Hoebel, 2008). Withdrawal is marked by anxiety (File et al., 2004) and depression (Avena, Rada & Hoebel, 2008). For more information on using sugar as an addictive substance please refer to the following references (Colantuoni et al., 2001; Colantuoni et al., 2002; Avena et al., 2004; Avena et al., 2005; Avena, Rada & Hoebel, 2008). Food craving can happen after a prolonged period of abstinence since "craving" is better defined by "increased efforts to obtain a substance of abuse or its associated cues as a result of dependence and abstinence" (Avena, Rada & Hoebel, 2008). Cross-sensitization is the last phase of FA and is predominantly defined as "an increased locomotor response to a different drug or substance" (Avena, Rada & Hoebel, 2008). All of these definitions play a major role in helping define and classify food (especially sugar) as a true addictive substance in comparison to the criteria for drug dependence as shown at least in rats (Haddock et al., 2000). People becoming addicted to food may be overweight and may possibly have leptin resistance as well that leads to overeating (Liu & Gold, 2003).

Finally, the most problematic group for an increase in addictive behavior and obesity has been young adults and adolescents in the past 30 years (Dietz, 2001). One study showed that binge eating and drug abuse were linked (Ross & Ivis, 1999). Interestingly, those that smoked had an increased body mass index (BMI) than non-smokers, and they were also at a risk for gaining weight when not using drugs (Hodgkins et al., 2004). Therefore, it is reasonable to conclude that teenagers used food to replace the reinforcement behavior of drug addiction to compensate for the reward systems of the brain. Eating disorders are a form of addiction in a way that individuals are obsessed with body image and compulsively crave certain foods such as in binge eating.

6.1 Intervention and prevention

Besides altering the endocrine makeup of individuals affected by FA via drug therapies, alternative and complementary approaches could play a major role in the intervention and possible prevention of obesity. Decreasing access to highly palatable and addicting foods is necessary (and restriction to all foods and small inanimate objects for patients with PWS) (von Deneen, Gold & Liu, 2009). Management includes 24 hour or constant supervision, planned physical activities, a strict diet (≤ 1200 cal/day) divided into structured, portioned meals at set times, and a static, predictable way of life (Benarroch et al., 2007). Encouraging afflicted groups to exercise or do other enjoyable activities will discourage them from their usual eating behaviors, as well as maintaining a highly controlled eating environment and food regimen with strict, consistent and reinforced rules. There are two common types of non-medicinal methods to decreasing body weight and/or improving the health condition of the individual. The first one is the undieting approach which discourages the use of food

restriction or dieting due to its ineffectiveness and possible health risks (Foster, 2001). The second type is isolated dieting in which one consumes less of a particular type of food or food group such as seen in the Adkins diet where carbohydrates are almost completely eliminated from the diet. Experimental treatments in animals may have practical application in treatment and prevention of obesity. There is a possibility such drugs can be marketed for use in human medicine. Another suggested experimental treatment is the aid of central leptin gene therapy (Kalra & Kalra, 2002), where an injection of recombinant adeno-associated virus vector encoding leptin into the HYP of prepubertal and adult rats resulted in weight gain and suppressed diet-induced obesity. The explanation was that it promoted loss of fatty deposits caused by a decrease in NPY and an increase in MCH and thermogenesis. This is a novel approach that may not be suitable for humans at this point. Indeed, disrupting NPYergic signaling at multiple loci without affecting normal hypothalamic function would be ideal, but more research needs to be done in this area (Kalra & Kalra, 2004a). Another experimental method is based on the theory that ACh inhibits feeding through the M1 receptors if a muscarinic agonist, arecholine, is injected into the NA_C. This can be reversed by using an M1 antagonist pirenzapine (Rada & Hoebel, unpublished). Thus, it would be interesting to determine if arecholine would be a safe and effective method to prevent hyperphagia in individuals with FA and PWS patients. Some studies showed that taste aversion was a very useful therapy in which ACh levels were increased while decreasing DA levels (Mark et al., 1995). Others have found that baclofen, a GABA-B agonist, is useful for those that over-indulge on fatty foods (Buda-Levin, Wojnicki & Corwin, 2005). Other treatments utilized naloxone (an opioid antagonist) to block the opioid system, and rimonabant (a CB1 receptor antagonist) to block the cannabinoid system (Kenny, 2011); these systems have been shown to reinforce feeding behavior, and when used together, they act synergistically to treat obesity (Berry & Mechoulam, 2002). The still-investigational drug is Lorcaserin, a combination of benzazepine and hydrochloride, two neurological agents. Lorcaserin is a selective 5-HT2C receptor agonist, working through the serotonin system, which regulates appetite, mood, and motor behavior. Two other investigational obesity drugs target the DA reward system-Contrave, which is a combination of bupropion and naltrexone, and Qnexa, which combines phentermine and topiramate (Solinas & Goldberg, 2005).

7. Conclusion

Obesity continues to place a tremendous burden on healthcare systems. Our current and future research on the neurobiological systems that motivate appetitive behavior strongly suggests that an acquired drive for highly energy-dense, reinforcing foods is contributing to weight gain. The limitations of current treatments compel healthcare professionals to develop more effective ways based on neurobiological addiction models to curb the obesity epidemic.

Future studies should examine the relation between FA, hunger, and reward circuitry response with food intake and anticipated intake. The use of fMRI technology directly measures DA release or its receptors. It will be important to examine induced DA release and D2 receptor availability in those with FA. Other neurotransmitters are also likely to play an important role. Thus, future studies connecting FA and neural activation associated with these neurotransmitters will also be important. Understanding the mechanisms of hedonic

eating is essential for developing and implementing treatment and management strategies that address the root causes of obesity. In addition, cognitive factors such as social environment, emotional state, or intentional efforts to control consumption can also influence food intake. Most of what we know about these regulatory systems is derived from animal models, but our understanding of the control of eating behavior in humans is very limited. Consistent with the biological imperative to identify and consume food, neuroimaging studies have begun to document the responsiveness of the human brain to food cues such as odors and/or taste samples of food (Wang et al., 2004; Rosenbaum et al., 2008). Future positron emission tomography (PET) and fMRI studies will provide neurobiological insights in brain alterations during addiction. fMRI is ideal for investigating activation in regions involved in a specific function, because scans can detect these simultaneously. It also provides temporal-spatial resolution and anatomical accuracy to be able to describe the interaction between major CNS components. This allows the monitoring of dynamic activities in the brain while processing visual cues (Zhang et al., 2011). Our group has future studies planned to determine brain responses when viewing photographs of food and non-food objects, where we will specifically examine brain regions important to the regulation of appetite and food intake in overweight and normal individuals. For example, one such fMRI study is to scan young healthy subjects of normal weight to measure different brain activation by visual images of highly rewarding-foods (high caloric foods such as hamburgers and chips) compared with images of non-rewarding objects during various physiological states; in particular, we are interested in effects of fast food-branding on the brain and the effects in Chinese children with and without exposure to the Golden Arches (McDonald's®) or the Kentucky Colonel (KFC®). The study tests the hypothesis of 'food addiction' that the fast food brands such as McDonald's® may have reinforcing effects in the brain and such effects may be related to children's drive to eat (Zhang et al., 2011). Using the Chinese population who has never been exposed to such food brands as controls (this CANNOT be done in the USA), this study would have a strong impact in the areas of addiction and obesity. Another research paradigm proposed is mostly based on a bottom-up approach to test the relationship between chronic subcutaneous recombinant leptin injections and weight loss (Benoit et al., 2004). fMRI techniques are powerful tools to probe leptin neurological function in modulation of human ingestive behavior and are ideal for investigating the concerted activity among the ensemble of regions involved in a specific function, because scans can detect all regions of brain activation simultaneously. Many recent studies have employed fMRI techniques to gain neuroanatomical insights into the effects of leptin in brain processing hunger, satiety and food reward in obese human subjects (Farooqi et al., 2007; Baicy et al., 2007). As a result, we propose to assess brain activation in response to acute subcutaneous leptin injection by examining the resting-state and exposure to stimuli consisting of food cues using an fMRI experiment (Zhang et al., 2011). We will also attempt to correlate the fMRI leptin brain response with weight gain based on a cafeteria diet. Positive results from this study will provide an invaluable diagnostic guideline for initiating early adulthood nutritional and behavioral intervention on an individualized basis to temper obesity development. This would constitute a realistic and meaningful cost-effective approach. An obesity-prevention strategy will help curb rising obesity treatment-related health expenditures. Positive study outcomes will also highlight a technological breakthrough for fMRI investigation of region-

specific neural activity in an acutely stimulated brain reactive state rather than in a chronically adapted state following long-term drug treatment or other types of intervention. Thus, we hope to illuminate promising methods that use visual food cues to investigate mechanisms of human eating behavior, and to facilitate a more unified and reproducible approach to neuroimaging studies of FA and obesity. Results from this study can go far beyond obesity studies and could extend to the field of pharmacological research (Zhang et al., 2011). Furthermore, more research needs to be conducted world-wide especially in the Chinese population. Obesity in China is a multifactorial disease where intervention is not always clear-cut or applicable. For instance, specific gene therapy may be available in the future to prevent childhood and adulthood weight gain and endocrine disorders. Lifestyle and behavioral changes need to be addressed and applied to prevent unhealthy physiques. Alternative medicine intervention, such as acupuncture and Traditional Chinese Medicine remedies, may be most appropriate for this part of the world. Overall, obesity is preventable and now is the ideal time in implementing current scientific methods and techniques to battle this epidemic (von Deneen & Liu, 2011).

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