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Comparing the effects of food restriction and overeating on brain reward systems

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ABSTRACT

Both caloric restriction and overeating have been shown to affect neural processes associated with reinforcement. Both preclinical and some clinical studies have provided evidence that food restriction may increase reward sensitivity, and while there are mixed findings regarding the effects of overeating on reward sensitivity, there is strong evidence linking this behavior with changes in reward-related brain regions. Evidence of these changes comes in part from findings that show that such eating patterns are associated with increased drug use. The data discussed here regarding the differential effects of various eating patterns on reward systems may be particularly relevant to the aging population, as this population has been shown to exhibit altered reward sensitivity and decreased caloric consumption. Moreover, members of this population appear to be increasingly affected by the current obesity epidemic. Food, like alcohol or drugs, can stimulate its own consumption and produce similar neurochemical changes in the brain. Age-related loss of appetite, decreased eating, and caloric restriction are hypothesized to be associated with changes in the prevalence of substance misuse, abuse, and dependence seen in this cohort.

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1. Introduction

A unique situation is emerging among the aging population. Although caloric consumption has been shown to significantly decrease with age (Briefel et al., 1995), obesity is on the rise among members of this cohort (Salihu et al., 2009). Patterns of over- and under eating may have deleterious consequences on both the neurochemistry and behaviors associated with reward and reinforcement of behavior. Of particular relevance is the prediction that by the year 2020 the number of individuals over the age of 50 with substance abuse disorder will be two times higher than estimates from each year between 2002 and 2006 (Han et al., 2009). This prediction highlights the importance of better understanding behaviors, such as under- and overeating, which are known to cause alterations in brain reward functioning and therefore may contribute to the pathology of substance abuse.

Both preclinical and some clinical studies suggest that prolonged food restriction leads to heightened reward sensitivity (Carr, 2002; Frank et al., 2005; Frank et al., 2012). Studies examining the effects of overeating on reward sensitivity are mixed, and several theories have been developed to explain what appear to be conflicting findings (Verbeken et al., 2012). Before discussing the effects of food deprivation or overeating on reward sensitivity, however, it is important

to review the neural components associated with responses to reinforcing and rewarding stimuli. Although the brain reward system is complex and consists of a number of different components (i.e., opioids, GABA), this paper will primarily review clinical and preclinical studies investigating the effects of differential feeding behavior on dopamine (DA). Mesolimbic DA neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), and dopamine is considered to play an important role in influencing motivation for and the reinforcing and rewarding experiences of food consumption, drug use, and other stimuli (Everitt and Robbins, 2005; Schultz, 2010).

By studying the effects of food deprivation and overeating, it may be possible to gain a clearer understanding of the mechanisms that underlie changes in reward response or functioning due to non-homeostatic eating behaviors. In addition, by reviewing findings of studies using laboratory animal models, we may be able to gain insight into the associated biological factors without the psychological variables that may accompany aberrant eating behaviors.

2. Effects of food deprivation on reward sensitivity

2.1. Laboratory animal studies

When laboratory animals are food restricted, they show alterations in behavior that suggest increased reward sensitivity. Rats that have been even acutely food deprived exhibit higher rates of intravenous self-administration of drugs of abuse, such as cocaine and phencyclidine (Carroll et al., 1981). Further, chronic food restriction,

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accompanied by weight loss, has been shown to decrease the amount of drug necessary to experience its rewarding effects. For example, lateral hypothalamic intracranial self-stimulation (LHSS) threshold reduction has been reported in chronically food-restricted rats, suggesting lower levels of tolerance to the effects of drugs (Cabeza de Vaca and Carr, 1998). In addition to drugs of abuse, chronically food deprived and underweight animals show increased sensitivity to other, non-drug reinforcers, such as running (Pierce et al., 1986).

Additionally, there is evidence of alterations in the mesolimbic DA system that are concomitant with the behaviors noted above. Rats with a brief history of food restriction show an increase in dialysate DA in the NAc when given food that persists even after repeated exposure to a food, an effect that is not seen among non-food deprived animals (Bassareo and Di Chiara, 1999). Further, rats with restricted food access, decreased body weight, and increased exercise show higher DA release in the NAc when eating (Verhagen et al., 2009). Rats that have been chronically food deprived and are thus underweight also show approximately three times greater extracellular DA levels compared to controls when administered amphetamine in the Nac (Pothos, 2001). Increased D2 receptor availability has been found in both obese and lean rats following a prolonged period of food restriction, suggesting that the effects of food deprivation may be independent of body weight, however, less D2 receptor availability was reported in rats following an acute (24 h) period of food restriction compared to rats without food restriction, suggesting an important distinction between chronic versus acute food deprivation (Thanos et al., 2008). Compared to normal weight rats with a history of brief food deprivation, food deprived rats at 75% of their normal body weight demonstrated increased responding for oral administration of the opiate etonitazene (Carroll and Meisch, 1980). While it can be difficult to discriminate between the effects of the length of food deprivation and body weight status, as these two often coincide, it appears that these variables significantly influence alterations in reward sensitivity.

2.2. Human studies

The study of food restriction in humans may be less straightforward due to certain confounds. For example, populations who are chronically food restricted may have comorbid mental health (e.g., eating disorders) or medical issues (e.g., osteoporosis) (Dirks and Leeuwenburgh, 2006), so findings must be interpreted with caution. While these results have not been universally supported, several studies suggest that sensitivity to reward may be increased following food deprivation in humans (see review (Holsen et al., 2012)). For example, when a food reward (sucrose) was administered unexpectedly, individuals diagnosed with anorexia nervosa showed significantly greater activation in the orbitofrontal cortex (OFC), an area of the brain associated with reward or value (Peters and Buchel, 2010), compared to controls, whereas obese participants showed significantly less activation in this region compared to controls (Frank et al., 2012). This finding supports the idea that food may be especially reinforcing in food-restricted individuals.

Interestingly, when comparing reward-related brain areas of participants when hungry and when sated, Siep et al. (2009) found that when hungry, participants showed a more pronounced activation of the insula, lateral and medial OFC, caudate putamen, cingulate cortex and fusiform gyrus when presented with images of high-calorie versus low-calorie foods. This finding suggests that even a brief period of food restriction may predispose individuals to desire more calorically dense foods. Conversely, subjects showed a more pronounced response to lower calorie foods when sated (Siep et al., 2009). Similar findings have been reported within a sample of participants with obesity, suggesting that this effect may occur independent of body weight (Goldstone et al., 2009).

Similar to the results of the animal studies mentioned above, it appears that DA may play a role in this process. D2 and D3 receptor availability is shown to be higher in the antero-ventral striatum, a brain area involved in reward, of individuals who have recovered from anorexia nervosa (Frank et al., 2005). This was found in a study in which there was no significant difference between the mean body mass index (BMI) of the participants who had recovered from anorexia nervosa and normal controls, suggesting the potentially enduring effects of food deprivation even following weight restoration.

3. Effects of overeating on reward sensitivity

3.1. Laboratory animal studies

There appears to be a strong causal relationship between food restriction and drug use, as food deprivation has been shown to increase self-administration of a number of different drugs in animals (Carr, 2002). Interestingly, overeating (with or without food restriction) may also precipitate addictive behavior, and there have been several studies that suggest neurochemical and behavioral similarities between drug addiction and the more recently researched topic of “food addiction” (Allen et al., 2012; Avena et al., 2008a; Gold et al., 2009), although there is some controversy regarding how this construct should be applied to obesity (Ziauddeen et al., 2012).

Nonetheless, there are several reports that support the idea that overeating affects brain reward systems. Behavioral evidence of decreased reward sensitivity due to overeating comes in part from findings reported by Shin et al. (2011) that show that both diet-induced obese and obesity-prone rats without access to a high-fat diet appear to prefer higher concentrations of sucrose and corn oil, while they do not show much interest in lower concentrations, indicating a higher level of tolerance toward the rewarding effects of these foods. Interestingly, this effect disappeared after a period of chronic food restriction and concomitant weight loss, supporting the idea that chronic food deprivation increases reward sensitivity. These authors have also reported that obesity-prone rats exhibit slower responding for a food reward (measured by completion speed in an incentive runway) compared to obesity resistant rats both before and after access to a high-fat diet. Notably, the obesity-prone rats exhibited significantly slower responding in the incentive runway after the period of access to a high-fat diet than before (Shin et al., 2011). Body weight gain in rats given prolonged access to a cafeteria-style diet coincided with an increase in brain stimulation reward thresholds, further indicating a heightened tolerance to the effects of reward (Johnson and Kenny, 2010).

Rats that become overweight due to access to a cafeteria-style diet show markedly greater levels of extracellular DA when administered systemic amphetamine compared to controls (Pothos, 2001), which might suggest increased, rather than decreased, reward sensitivity. However, these findings of increased DA release must be considered within the context of the effects of overeating on DA receptors. A recent study by Marco et al. (2012) revealed that OLETF rats (which have the satiety-associated cholecystokinin receptor type 1 naturally knocked out) prefer higher concentrations of a sucrose solution, whereas controls showed a decreased interest in a high (1 M) concentration of sucrose over time. Interestingly, D2 receptors in the NAc of the obese OLETF rats decreased over time compared to controls. Like the findings above, subsequent deprivation of food and concomitant weight loss resulted in an increase in D2 receptors in these rats (Marco et al., 2012). Similarly, decreased striatal D2 receptor expression has been found among dietary-induced obese rats compared to controls. Further, it appears that both overconsumption of palatable food and the knockdown of D2 receptors are associated with increased reward thresholds (Johnson and Kenny, 2010), suggesting a higher level of tolerance for reward. Additional evidence linking D2 receptor reduction to food reward comes from the finding

that rats administered the D2 antagonist, remoxipride, tend to eat more (Clifton et al., 1991).

It is important to note that overeating and obesity can be dissociated. Studies using animal models reveal that binge eating (overeating) without concomitant obesity has also been shown to produce increased DA levels in the NAC, and this is also associated with decreased D2 receptor binding (Avena et al., 2008a). Thus, in the studies cited above, it may be that overeating is producing the effects on the DA system, and the results are not necessarily due to increased body weight.

Preclinical studies have also provided evidence for the idea that genetic and environmental variables affect reward functioning. Research investigating obesity-prone rats has found reduced DA function in these animals at birth (Geiger et al., 2008). Recent findings have also revealed that female offspring of rats that consumed high-fructose corn syrup or sucrose during gestation are more likely to consume alcohol and male offspring were found to exhibit increased locomotor activity in response to amphetamine. This study also showed that rats exposed to a high fat diet in utero consumed more of a high fat diet in adulthood compared to controls (Bocarsly et al., 2012). Collectively, these findings indicate that diet during gestation may have profound effects on the reward sensitivity of offspring. Rats that have undergone neonatal handling, which is considered an analog for stressful experiences in early life, have also been shown to consume increased sweet food compared to controls. In a runway test, these rats demonstrated decreased latency to reach the sweet food compared to controls, however, during a place preference test, they spent less time in the space containing sweet food. Together, these findings suggest that exposure to an early life stressor may elicit changes in reward functioning that lead to increased motivation to obtain sweet food but perhaps less reward during consumption. Interestingly, these rats also show more DA in the NAC, which has previously been associated with increased sucrose intake (Hajnal and Norgren, 2001), and evidence of reduced DA metabolism (Silveira et al., 2010).

3.2. Human studies

Overeating can have multifaceted effects on both the brains and behaviors of humans as well. For instance, increased activation of several brain regions associated with food reward has been shown in obese adolescent girls both when anticipating and consuming a highly palatable food compared to lean adolescent girls (Stice et al., 2008). Additionally, activation of the middle insula after tasting food has been positively associated with body weight, with obese individuals and individuals who have previously been obese exhibiting a greater response in this brain region compared to controls (DelParigi et al., 2004). It is important to note that while overeating is usually used synonymously with obesity, as described above with regards to animal models, one can see periodic overeating in normal or underweight individuals, such as in cases of bulimia nervosa (Kaye et al., 2000).

Studies investigating the effects of binge eating disorder (BED), which is characterized by periods of overconsumption of food, offer insight into the effects of overeating on reward functioning apart from the possible influence of weight. For example, obese participants with BED show greater activation of the medial OFC in response to images of palatable food than non-binging obese controls (Schienle et al., 2009). Compared to baseline levels, a greater rise in extracellular DA in the caudate nucleus was also found among obese individuals with BED when exposed to “food stimulation,” which included seeing, smelling, and tasting some of their favorite foods in addition to methylphenidate, which inhibits DA transporters, than obese participants without BED (Wang et al., 2011). Research suggests that the caudate nucleus is involved in “action-contingent” reward processing (Tricomi et al.,

2004). Together, these findings suggest that a heightened response to food may be directly related to patterns of overeating.

Research has also shown reduced activation of the caudate nucleus during palatable food consumption among obese adolescents, which has been proposed to result from a deficit in DA receptor availability (Stice et al., 2008). A prospective study investigating the effects of weight gain on food-related reward also found decreased activation of the right caudate in response to palatable food consumption in women who had gained weight in the previous 6 months compared to baseline (Stice et al., 2010). Adding to the complexity of this issue, research has shown both that obese individuals have less D2 receptor binding compared to normal and overweight controls (Wang et al., 2001), as well as that higher BMI is related to increased D2 availability (Dunn et al., 2012). Dunn et al. (2012) attribute this discrepancy to differences in the time subjects were studied as well as whether or not subjects were fasted prior to scanning and hypothesize that the increased D2 receptor availability found in obese individuals may suggest decreased extracellular DA levels as the radioligand employed during testing is sensitive to competition with endogenous DA.

Thus, the current body of literature on this topic presents two opposing sets of findings: reward sensitivity is reduced, or heightened, in overweight or obese individuals. To explain these findings, two theories have emerged. The first suggests that overweight or obese individuals are less sensitive to the positive effects of reward, and thus, may consume more in an effort to obtain them, while the second theory posits that overweight or obese individuals overeat as a result of increased sensitivity to the effects of food reward (Verbeken et al., 2012). In order to better understand the processes involved in reward functioning within overweight or obese populations, some researchers have proposed a third theory which may serve to reconcile the former two arguments. This theory, referred to as the “dynamic vulnerability model,” suggests that individuals may become overweight as a result of an increased sensitivity to the rewarding effects of food, however, with excessive intake, these individuals may begin to develop a tolerance to these rewarding effects and thus, may require more stimulation (i.e., more food) in order to experience the same degree of satisfaction, similar to the process of tolerance more commonly associated with addiction to drugs of abuse (Burger and Stice, 2011). This theory has received support from studies of reward sensitivity in both adult and child samples that reveal increased levels of reward sensitivity, based on self-report measures, in overweight individuals but decreased reward sensitivity in obese individuals (Davis and Fox, 2008; Verbeken et al., 2012), suggesting that a change in reward sensitivity may occur with increased weight gain, perhaps due to increased consumption.

There may also be genetic influences on reward-related feeding behaviors, as seen in laboratory animals (Geiger et al., 2008). Significant differences have been found between the presence of the Taq1A allele, which suggests fewer D2 receptors, and the A118G allele, which has been linked to an increase in opioid sensitivity, in obese individuals and obese individuals characterized as having BED (Davis et al., 2009). 80% of obese participants with BED were found to have a genotype with the A118G allele but not the Taq1A. In contrast, this genotype was found in 20% of obese controls. This finding suggests that obese individuals with BED may have increased opioid sensitivity, and like DA, opioids are known to play an important role in reward. The genotype most common among obese controls included the Taq1A allele but not the A118G allele, suggesting that obesity may be related to lower levels of D2 receptors. These findings suggest a genetic basis for overeating and obesity. While it may seem that the literature presents contrasting theories of etiology, it may be that both paths of direction are possible; some individuals may be genetically predisposed to overeat and may become obese due to reduced reward function, while others may develop reduced reward response due to food overconsumption.

It should be noted that several variables in addition to eating disorder diagnoses and BMI must be considered when interpreting the results from fMRI studies investigating food reward. Berridge (2009) has proposed, for example, that there is a difference between “wanting” and “liking,” a distinction that may be valuable when measuring and understanding responses associated with reward (Berridge, 2009). Additionally, as noted earlier in the study by Siep et al. (2009), satiation appears to influence neural responses to food. A recent study has also found that problems with experiencing satiation may affect an individual's response to food cues. Overweight or obese participants with higher scores of satiety impairment were shown to have increased activity in the putamen and amygdala, brain regions associated with different aspects of food reward, when viewing images of low calorie food compared to neutral objects following meal consumption (Ho et al., 2012). This finding may help to explain why curtailing food consumption may be particularly difficult for certain individuals, and points to the importance of considering an array of variables when trying to isolate the effect of food cues or consumption on reward.

3.3. Overeating following food deprivation

Evidence from studies that combine both food restriction and overeating lend further support to the theory that feeding behavior affects neural mechanisms involved in reward. For instance, even rats that are classified as binge-eating resistant have been shown to consume significantly more following a brief period of food deprivation (Boggiano et al., 2007). On the neurochemical level, rats also show increased DA release in the NAc shell when bingeing on sugar following a brief period of food restriction compared to rats given unlimited access to sugar and chow (Avena et al., 2008a). This DA release is sustained in the NAc, an effect that is noteworthy as DA release typically habituates following repeated exposure to food (Bassareo and Di Chiara, 1999) and because this pattern of repeated DA release reflects what is seen with drugs of abuse (Di Chiara et al., 2004). Rats maintained on this schedule have also been shown to have significantly increased D1 and decreased D2 receptor binding in both the NAc shell and core compared to controls (Colantuoni et al., 2001), which may contribute to the increased sensitivity to reward and signs of “addiction” to palatable food that have been shown in these animals (see review (Avena et al., 2008a)). Interestingly, following an extended period of food restriction that reduced body weight to 85% of normal, rats that had previous access to a binge-like schedule of sugar consumption (induced by acute food deprivation) showed an even greater increase in DA release in the NAc when given access to sugar, compared to measurements of DA release while binge-eating sugar at a normal weight (Avena et al., 2008b). Together, these results show how a pattern of overeating coupled with periods of food restriction may alter neural mechanisms that underlie reward, potentially increasing the pleasure derived from food consumption and perhaps making it more difficult to resist.

4. Relationship between these findings and the aging population

The information reviewed in this paper may be particularly relevant to the aging population. First, caloric intake has been shown to decrease considerably as age increases. In fact, in the 60 years following 20 years of age, both men and women have been found to substantially decrease their caloric intake per day, with men exhibiting an even greater decrease than their female counterparts (Briefel et al., 1995). If malnutrition is not present, caloric restriction has been reported to delay certain effects of aging in animals, such as reduced muscle loss in rhesus monkeys (Anderson et al., 2009). Alternatively, obesity rates have been increasing. According to the Centers for Disease Control and Prevention, in 2008, the percentage of obesity had increased the most among men ages 60–74 over the prior 20 years compared to any other age group of adult men (Shields et al., 2011). Additionally, in 2009–2010,

women age 60 and over were shown to have a higher percentage of obesity than any other age group of adult women (Ogden et al., 2012). Recent research suggests the detrimental effects of obesity on aging (Tzanetakou et al., 2012). Obesity has been associated with decreased telomere length, which is proposed to be an indicator of the aging process, among women (Valdes et al., 2005), and being overweight or obese has also been shown to be a risk factor for the development of Alzheimer's and dementia among older women (Gustafson et al., 2003). Collectively, these findings highlight the importance of studying the effects of both food restriction and overeating in this population in particular.

Similar to patterns seen in populations who overeat, a reduction in DA functioning is associated with aging (Rollo, 2009). For example, striatal D2 receptors have been shown to decrease approximately 7.9% per decade in humans (Volkow et al., 1996), and D2 transporters have been shown to decrease as people age (Volkow et al., 1994). Based on such patterns, it seems appropriate to consider the ways in which changes in reward sensitivity following food deprivation and overeating may differentially affect the elderly population. This decrease in reward functioning, may for example, pose risks similar to those discussed above for individuals who overeat; older individuals may be more likely to develop patterns of overeating or other addictive behaviors in an effort to achieve previously experienced levels of reward. It has also been hypothesized that if alcohol or substance abuse is increasing among the elderly population, as has been predicted, this may contribute to the decline in caloric intake seen among this population, perhaps a point for further study. Additionally, because pharmacological treatments for Parkinson's Disease that increase DA have been linked to addiction-like patterns of behavior, such as compulsive gambling and “hypersexuality,” it is important to understand how various feeding patterns may alter DA activity in a similar way (Avanzi et al., 2006).

5. Conclusion

Reward sensitivity may be heightened when feeding behavior is reduced as an incentive to eat, thus promoting survival. Such an increase in reward sensitivity may prove maladaptive, however, especially in the absence of need, as is the case in many societies today. Instead, increased sensitivity to reward may result in increased consumption of food and drugs of abuse. Overeating on the other hand, may reduce reward sensitivity over time, potentially perpetuating a cycle of overeating that may resemble, both behaviorally and neurochemically, patterns of addiction more commonly observed with drugs of abuse (Edge and Gold, 2011). It is possible that the contrasting theories regarding overeating and reward sensitivity discussed earlier lie on a continuum, with one set of interactions laying the foundation for the other to develop in some individuals, while genetic makeup may predispose others to have reduced reward sensitivity from birth. Inconsistencies within the literature point to the need for further study.

The current understanding of changes in reward functioning associated with both food restriction and overeating would benefit from both preclinical and clinical longitudinal studies that assess reward functioning prior to food restriction or the overconsumption of food, as well as any lasting effects following recovery from these conditions. Longitudinal studies assessing such changes across the lifespan, including both younger and elderly subjects, would be particularly helpful in understanding the ways in which under- and overeating may affect reward sensitivity in the aging population.

Conflict of Interest

Author has confirmed that there is no conflict of interest.

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