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Dopamine for "Wanting" and Opioids for "Liking": A Comparison of Obese Adults With and Without Binge Eating

Caroline A. Davis[1–3], Robert D. Levitan[2], Caroline Reid[1,2], Jacqueline C. Carter[3], Allan S. Kaplan[2,3], Karen A. Patte[1,2], Nicole King[4], Claire Curtis[1,2] and James L. Kennedy[4]

Obesity research suffers from an overinclusion paradigm whereby all participants with a BMI beyond a certain cutoff value (e.g., 30) are typically combined in a single group and compared to those of normal weight. There has been little attempt to identify meaningful subgroups defined by their salient biobehavioral differences. In order to address this limitation, we examined genetic and psychological indicators of hedonic eating in obese adults with (n = 66) and without (n = 70) binge eating disorder (BED). Our analyses focused on dopamine (DA) and opioid genetic markers because of their conjoint association with the functioning of brain reward mechanisms. We targeted three functional polymorphisms related to the D2 receptor (*DRD2*) gene, as well as the functional A118G polymorphism of the mu-opioid receptor (*OPRM1*) gene. We found that significantly more obese controls had the "loss-of-function" A1 allele of *Taq*1A compared to their BED counterparts, whereas the "gain-of-function" G allele of A118G occurred with greater frequency in the BED group. A significant gene–gene combination χ^2 analysis also indicated that of those participants with the gain-gain genotype (G^+ and A1), 80% were in the BED group whereas only 35% with the loss-loss genotype (G^- and $A1^+$) were in this group. Finally, BED subjects had significantly higher scores on a self-report measure of hedonic eating. Our findings suggest that BED is a biologically based subtype of obesity and that the proneness to binge eating may be influenced by a hyper-reactivity to the hedonic properties of food—a predisposition that is easily exploited in our current environment with its highly visible and easily accessible surfeit of sweet and fatty foods.

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INTRODUCTION

The unprecedented number of temptations in our consumer society has created new challenges for obesity research. Constrained food availability no longer exists in most countries of the world, replaced instead by a superfluity of easily accessible and cheap sources of energy. This dramatic alteration in the food environment has substantially affected our normal food intake and exaggerated the physiologic distinction between *homeostatic* hunger—that which follows a period of relatively prolonged food deprivation—and *hedonic* hunger, which occurs in the absence of privation (1). The latter is largely regulated by the palatability and rewarding properties of food, and is believed to play a critical role in the escalating prevalence of obesity.

Another issue relates to the criterion commonly used to define obesity—viz. a BMI >30. Although the prevalence of obesity has doubled over the past few decades, its "morbid" form (BMI >40) has seen an alarming fourfold increase (2). Consequently, it is not unusual for current research samples to include obese participants with BMIs as high as 60 or 70. By contrast, so-called "normal weight" adults, who are typically used for comparison, comprise the relatively narrow BMI range of 18.5–25. As a result, skewness and heteroscedasticity are highly probable in such case–control studies, and compromise their statistical power (3).

The widening BMI range for obesity also suggests this is probably a condition with causally relevant subtypes. It has even been suggested that some cases of obesity be included as a mental disorder in Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (4). It behooves us, therefore, to focus our research efforts on finding biologically based moderator variables that distinguish one form of obesity from another. An important place to begin this search is by considering qualitative differences in the kind of ingestive behaviors that contribute to weight gain. For some individuals, overeating is a relatively *passive* event that occurs almost without awareness, in the form of liberal snacking, daily meals high in fat and sugar, and large portion sizes (5). For others, however,

[1]Department of Kinesiology and Health Sciences, Faculty of Health, York University, Toronto, Ontario, Canada; [2]Mood and Anxiety Disorders Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; [3]Department of Psychiatry, University Health Network, Toronto, Ontario, Canada; [4]Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. Correspondence: Caroline Davis (cdavis@yorku.ca)

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it can be *compulsive* and excessively driven as seen in those who regularly binge eat.

Brain reward mechanisms and obesity

Dopamine. The mesocorticolimbic brain pathway is a complex neural network "designed" to regulate the many emotional, motivational, and cognitive processes involved in reward. Our engagement in such behaviors increases our sense of pleasure and well-being, and galvanizes our attention in preference to more neutral, and less essential, activities. They also nurture a strong positive memory, which increases their salience and enhances our appetitive motivation in their direction.

The exact role of dopamine (DA) in the process of reward has been vigorously debated in recent years. Berridge (6) has argued convincingly that mesocorticolimbic DA fosters the motivation to engage in rewarding behaviors—what he calls the "wanting" of reward—more than the "liking" of reward. In other words, DA may not be *central* to the normal pleasure or hedonic reactions to food or drugs. However, this position is still open to debate and not easily resolved because reward involves a myriad of emotions including anticipation, expectation, pleasure, and memory that are difficult to separate experimentally. There is also important evidence that DA signaling is modulated by other neurotransmitter and neuropeptide systems including endogenous opioids, and that certain responses to opioids require a functional DA D2 receptor (7).

Human variability in DA availability has been a key focus of research in addiction disorders where a dominant viewpoint is that *hypo*-dopaminergic functioning in brain reward pathways is a key risk factor in their development (8,9). The premise is that addictive substances, which increase brain DA levels, are used as a form of "self-medication" to boost a sluggish DA system and increase hedonic capacity. Recently, these same arguments have been extended to the risk for obesity, with much of the supporting evidence focussed on DA D2 receptors—heavily expressed in the brain's mesolimbic reward pathway—and the D2 receptor (*DRD2*) gene, which regulates their expression (10,11). The most frequently studied polymorphism of the D2 receptor is the *Taq1A*. (For many years, Taq1A was thought to be located in the 3′-untranslated region of *DRD2* (12). However, recently it was shown that this single-nucleotide polymorphism (SNP) does not reside in *DRD2*, but in a neighbouring gene called *Ankyrin Containing Kinase 1* (13). It is not known how this marker influences *DRD2* expression or whether the *Ankyrin Containing Kinase 1* gene is biologically connected to *DRD2* function.) There is reasonable evidence (14) that individuals with the *Taq1*A$^+$ allele (i.e., A1/A1 and A1/A2 genotypes) have reduced brain DA function compared to those with the A1-allele (i.e., the A2/A2 genotype) due to a 30–40% reduction in D2 receptor density in the striatal region (15). The counter argument, which has also garnered support, is that a *hyper*-sensitivity to reward contributes to increased risk for obesity because of an enhanced motivation to approach potentially pleasurable activities such eating (16,17). Although some studies (18) have found significantly higher frequency of the A1 allele in obese subjects, others have found no relationship (19).

Opiates. There is much greater agreement about the role of the endogenous opioid system in reward processes, including food intake. The dominant view is that opioids, especially the mu-opioid system, regulate the "hedonics of feeding"—what Berridge calls the "liking"—by their modulation of the palatability of food. These conclusions are largely based on evidence that opioids increase feeding in sated animals more effectively than in those who are food-deprived and that this effect is selective for highly palatable foods (7). More recent work has identified a major role for mu-opioid receptors, especially in the ventral striatum and amygdala where their activation enhances positive hedonic reactions to sweet and fatty foods (20).

The mu-opioid receptor (*OPRM1*) gene has been extensively studied for its role in drug abuse, especially for substances like alcohol and heroin (21). A functional marker—the A118G SNP—has received particular attention. The rarer G118 allele has shown greater affinity for β-endorphin and morphine, but reduced mRNA and protein expression *in vitro* (22). Although the exact mechanisms remain unclear, *in vivo* evidence supports a "gain-of-function" for those possessing the G allele as seen, for instance, by increased reward from maternal attachment in rhesus macaques infants (23), increased alcohol stimulation in human subjects (24), and a greater tendency to drug use and abuse in general (25). To date, however, we are not aware of any research that has examined *OPRM1* gene in relationship to overeating or weight gain.

Rationale and purpose

Similar to the general body of obesity research, genetic risk-factor studies also suffer from category over-inclusion (10,26). Indeed, in some studies, all participants with a BMI over 25 are combined in a single group and compared to those of normal weight. As yet, there has been little attempt to homogenize obesity subgroups by identifying their salient psycho-behavioral differences.

In the present study—and in order to address these limitations—we examined putative genetic and psychological indicators of hedonic eating in obese adults with and without a diagnosis of binge eating disorder (BED). To focus our analyses on the *wanting* and *liking* distinction described earlier, we restricted our genetic comparisons to three functional polymorphisms of the *DRD2* and the functional A118G (rs1799971) polymorphism of the *OPRM1* gene. In addition to *Taq1*A (described earlier), the T allele of the C957T SNP has also been associated with reduced D2 receptor density in the human striatum, whereas the Del allele of the −141 Ins/Del SNP relates to increased D2 receptor density levels (15,27).

We also included a newly developed self-report questionnaire that assesses the strength of *hedonically based motivations to eat* (28). Although there are several existing measures of overeating, this is the first to differentiate the drive/appetite for food from the person's tendency to (over)consume in response to emotional or environmental cues.

METHODS AND PROCEDURES

Participants and procedure

Adults between the ages of 25 and 50 years who met criteria for BED (n = 66: female = 53; male = 13) were recruited from posters placed at universities, local hospitals, and other public institutions. Advertisements were also placed in local newspapers and online sites like CraigsList. An obese control group (n = 70: female = 53; male = 17) was recruited in the same manner.

Control participants were first screened during a structured telephone interview and excluded if they had any serious medical condition, were not fluent in English, were pregnant (or had given birth within the last 12 months), and were currently being treated for (or had a history of) an eating or substance abuse disorder, or any psychotic disorder. All female participants were also required to be pre-menopausal as identified by the self-reporting of regular menstrual cycles. BED participants were required to meet an operational definition of the disorder based on that provided in the main body of the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (29) where BED is defined as: "recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviors characteristic of bulimia nervosa" (p. 550). This definition was operationalised in the following way: participants had to report at least weekly objective binge episodes over the previous 3 months, but over this period they must not have vomited, fasted, or taken laxatives or diuretics as a means of controlling their shape or weight. Nor must they have met current Diagnostic and Statistical Manual of Mental Disorder (Fourth Edition) diagnostic criteria for bulimia nervosa or anorexia nervosa. BED diagnosis was initially established during a telephone interview carried out by trained personnel. The same exclusion criteria were applied to BED adults as to the control subjects. In both groups, we included subjects who were being treated for unipolar depression without psychotic symptoms (confirmed by a clinical interview prior to the beginning of the study) because of the high comorbidity between obesity and depression.

The procedures employed in this study were approved by the three Research Ethics Boards relevant to the institutional affiliations of the authors, and were carried out in accordance with the Declaration of Helsinki. On the day of testing, informed consent was obtained, and all relevant demographic information was obtained in a face-to-face interview. Subjects then completed the questionnaire measure after which height and weight were measured and the blood sample was taken. For all subjects, a structured clinical interview was carried out to confirm eligibility and reconfirm BED status. At the end of the study, all subjects were paid a stipend for their participation.

Measures

The Power of Food Scale. The Power of Food Scale (28) is a 21-item, 5-point Likert scale that assesses individual differences in the appetitive responsiveness to food in environments replete with highly palatable food—independent of their actual consumption of them. In other words, it differentiates the motivation and appetitive drive to obtain food from the tendency to (over)eat food. As such, there are no items in the questionnaire that describe food consumption. For example, sample items are: "I find myself thinking about food even when I'm not physically hungry" and "Just before I taste a favorite food, I feel intense anticipation." Based on a factor analysis of the items, Lowe *et al.* concluded that a one-factor solution was most appropriate. Accordingly, the Cronbach's α-coefficient in our study was very high (0.95). Lowe *et al.* also report temporal stability of the scale over a 4-month period.

Genotyping. A venous blood sample (20–30 ml) was collected from each participant, and the nonenzymatic, high salt method was used to extract genomic DNA from the whole blood (30). The polymorphisms were genotyped using the commercially available TaqMan 5′ nuclease assay (TaqMan SNP Genotyping Assay; Applied Biosystems, Foster City, CA) (C___8950074_1_ for rs1799971; C___7486676_10 for rs1800497/Taq1A; C__11339240_10 for rs6277). The *DRD2* −141C ins/del was genotyped using a Custom TaqMan SNP Genotyping Assay with primer and probe sequences as follows: Forward 5′-CAAAACAAGGGATGGCGGAATC-3′ and reverse 5′-CCACCAAAGGAGCTGTACCT-3′; probes VIC-TACCCGTTC-CAGGCCG and FAM-CTACCCGTTCAGGCCG. The total volume of the PCR reaction was 10 µl which consisted of 20 ng of DNA, 5 µl of 2× TaqMan Genotyping Master Mix, 0.25 µl of 40× TaqMan Assay. Six negative controls (no DNA) were included on each plate. The PCR cycling conditions included initial denature for 10 min at 95 °C followed by 60 cycles of the following: 92 °C for 15 s and 60 °C for 1 min. The ABI 7500 Sequence Detection System was used to analyze the presence of variation of alleles by comparing to negative controls. Allele discrimination was performed on the ABI 7500 Sequence Detection System using the allelic discrimination end-point analysis mode of the Sequence Detection System software package version 2.0 (Applied Biosystems).

Analysis. Genotype frequency distribution sample groups (BED and obese controls) were tested for fitness to Hardy–Weinberg equilibrium using DeFinetti program (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl). Neither group deviated from Hardy–Weinberg equilibrium ($P > 0.05$). Linkage disequilibrium analyses were conducted separately for whites and nonwhites in the sample. In both groups, there is strong evidence of linkage disequilibrium ($D' > 0.8$) between the −141 Ins/Del and C957T. However, there is a low degree of linkage disequilibrium between the other SNP comparisons in the two groups. Finally, power calculations for a two (Genotype) × two (Group) χ^2 analyses indicate that our sample has 80% power (0.8039) to detect an odds ratio of 2.6 assuming a dominant model, minor allele frequency of 20% and α set at 0.05.

RESULTS

Descriptive statistics

Table 1 presents the means, standard deviations, and minima and maxima for age and BMI as well the P-values for independent t-test differences between the groups on these two variables. Although the BED group was significantly younger than the obese control group, there is no evidence to suggest that the small mean difference was likely to affect any of the study variables. Since the obese group also had a significantly higher BMI than the BED group, this variable was added as a covariate in further statistical analyses.

The percentage of males and females did not differ significantly between the groups (χ^2 = 0.416, df 1, P = 0.519). In the BED group, 79% of the participants were white whereas 73% of the obese controls were in this ethnic category. With very

Table 1 Means, standard deviations, and minima and maxima for age and BMI, and *t*-test *P* values for differences between BED and obese control participants

	BED adults				Obese controls				
	Mean	s.d.	Min.	Max.	Mean	s.d.	Min.	Max.	*P*
BMI	35.6	8.6	25.0	75.2	39.2	8.0	29.3	67.6	0.02
Age	34.7	6.5	25	50	37.0	6.7	25	50	0.04

Table 2 Allele and genotype frequencies for the dopamine D2 receptor (Taq1A, –141C Ins/Del, C957T), and the opioid mu receptor (A118G), polymorphisms for BED participants and non-bingeing obese controls

	Allele		Genotype		
	A1	**A2**	**A1/A1**	**A1/A2**	**A2/A2**
Taq1A[a]					
BED	23 (17.7%)	107 (82.3%)	2 (3.1%)	19 (29.2%)	44 (67.7%)
Obese	39 (29.5%)	93 (70.5%)	5 (7.6%)	29 (43.9%)	32 (48.5%)
	Del	**Ins**	**Del/Del**	**Del/Ins**	**Ins/Ins**
–141C Ins/Del[b]					
BED	20 (15.6%)	108 (84.4%)	3 (4.7%)	14 (21.9%)	47 (73.4%)
Obese	21 (16.4%)	107 (83.6%)	4 (6.3%)	13 (20.3%)	47 (73.4%)
	C	**T**	**C/C**	**C/T**	**T/T**
C957T[c]					
BED	66 (50.8%)	64 (49.2%)	19 (29.2%)	28 (43.1%)	18 (27.7%)
Obese	86 (65.2%)	46 (34.8%)	31 (47.0%)	24 (36.4%)	11 (16.7%)
	A	**G**	**A/A**	**A/G**	**G/G**
A118G[d]					
BED	106 (81.5%)	24 (18.5%)	43 (66.1%)	20 (30.8%)	2 (3.1%)
Obese	123 (90.4%)	13 (9.6%)	57 (83.8%)	9 (13.3%)	2 (2.9%)

[a]Genetic data were not available for five participants. When the A1/A1 and A1/A2 groups were combined—because of the rare occurrence of the homozygous A1 group—the two (Group) by two (Genotype) χ^2 was statistically significant ($\chi^2 = 4.96$; df = 1; $P = 0.026$). [b]Genetic data were not available for eight participants. A two (Group) by three (Genotype) χ^2 was not statistically significant ($\chi^2 = 0.180$; df = 2; $P = 0.914$). [c]Genetic data were not available for five participants. A two (Group) by three (Genotype) χ^2 was not statistically significant ($\chi^2 = 4.87$; df = 2; $P = 0.09$). [d]Genetic data were not available for three participants. A two (Group) by three (Genotype) χ^2 was statistically significant ($\chi^2 = 6.07$; df = 2; $P = 0.05$). When the A/G and G/G groups were combined because of the rare occurrence of the homozygous G group, the two (Group) by two (Genotype) was also statistically significant ($\chi^2 = 5.56$; df = 1; $P = 0.02$).

few exceptions, the nonwhites in both groups were of African descent. The χ^2 test of independence for these data was also nonsignificant ($\chi^2 = 0.650$, df 1, $P = 0.450$).

Questionnaire data

A one-way ANOVA indicated that scores on the Power of Food Scale were significantly higher ($F_{1,129} = 33.96$; $P < 0.0001$) in the BED group (80.0 ± 14.1) than in the obese controls (63.1 ± 18.4) suggesting that the former are considerably more responsive to the hedonic properties of food. Including BMI as a covariate in this analysis did not alter the findings reported above. Indeed, it was a nonsignificant predictor of Power of Food Scale scores, similar to the findings of Lowe *et al.* (28).

Genotype analyses

Allele and genotype frequencies for the SNPs are shown in Table 2. Because of the rare occurrence of the A1/A1 genotype for *Taq*1A, this group is typically combined with the A1/A2 (collectively, $A1^+$) (14) and compared to the A2/A2 genotype ($A1^-$). For the same reason, subjects were defined as –141C Del allele present (+) or Del allele absent (–), and A118G G allele present (+) or G allele absent (–). Initially, the genotype data were analyzed by a Group × Genotype χ^2 analysis for each polymorphism. Results were only statistically significant for *Taq*1A and A118G. In the former case, a larger proportion of the obese control group carried the rare A1 allele whereas for the latter comparison, a greater proportion of the BED group carried the rare G allele.

Table 3 Summary statistics for the logistic regression analysis with Group (BED vs. Obese) as the dependent variable and binary Genotypes (viz. Taq1A and A118G) as the independent variables. BMI is a covariate in the model

Variable	β	s.e.	Wald	df	*P*	Odds ratio
Constant	2.11	1.28	2.71	1	0.1	0.122
Taq1A	0.85	0.38	4.98	1	0.026	0.428
A118G	0.87	0.44	3.97	1	0.046	2.394
BMI	0.05	0.03	4.22	1	0.04	1.054

Negelkerke $R^2 = 0.14$.

In the second stage, binary logistic regression was used to test the combined influence of the two significant SNPs (*Taq*1A and A118G)—and their interaction—as predictors of membership in the two-study groups, with BMI added as a covariate in the model. As the interaction term was not statistically significant it was removed from the model. Table 3 lists the summary statistics for the final model, and Figure 1 provides a graphical representation of these findings. It can be seen that in the genotype combination characterized by $A1^-$ and G^+, 80% are BED participants whereas only 20% are obese controls. The opposite pattern pertains for the genotype group carrying $A1^+$ and G^-, where about 65% were obese controls and about 35% were obese binge eaters. These frequencies were statistically significant as seen from the results of a 4 (Combination) × 2 (Group) χ^2 analysis ($\chi^2 = 10.70$, df = 3, $P = 0.013$).

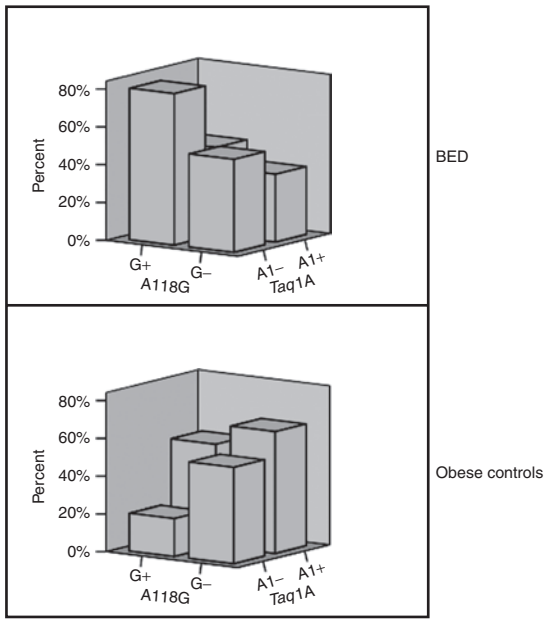

Figure 1 Percentage of Obese Participants with and without binge eating in each of the four gene–gene combination groups formed by the *Taq*1A ($A1^+$ vs. $A1^-$) and A118G (G^+ vs. G^-) SNPs.

DISCUSSION

The results of this study provide good evidence for biologically mediated, and clinically significant, subtypes of obesity based on individual differences in reward responsiveness. As a group, BED individuals appear to have enhanced reactivity to the hedonic properties of food.

To the best of our knowledge, the present study is the first to have examined mu-receptor genotypes in obese individuals, and in relation to different patterns of overeating. The BED group had a greater than expected frequency of the "gain of function" G allele of the *OPRM1* (mu receptor) A118G SNP, whereas this allele was somewhat under-represented in the obese controls. Among whites, about 25% have at least one copy of the G allele, whereas the percentage of carriers is very low in those of African descent (31). Of relevance to this finding is animal research showing that administration of an opioid agonist in the nucleus accumbens induces binge eating of fat, probably by increasing the hedonic properties of this food substrate (32). Extrapolating to the human condition, one might assume that the tendency to binge eat on rich foods would be magnified in G allele carriers given their increased responsiveness to opiates and alcohol, and their higher risk for addiction to these substances (24,33).

By contrast, the obese who do not binge eat may have a diminished physiological capacity for pleasure as seen by the data for the D2 receptor *Taq1*A marker. Due to its association with fewer D2 receptors, the A1 allele has been associated with reduced mesolimbic brain DA signaling, and a deficient ability to experience natural reward. The A1 allele has also been linked to increased risk for various addiction disorders such as alcoholism and pathological gambling (14,34). Approximately 35% of whites carry at least one copy of the A1 allele (35). Among the obese controls in our sample, 51% were carriers of A1 compared to 32% in the BED group. These findings are in accord with reports that an insensitive reward system *increases* the risk for obesity because it fosters the compensatory overeating of calorie-dense food (11). Importantly, however, much of the "reward deficiency" work in obesity was carried out on adults with extremely high BMIs, suggesting that this putative syndrome may be relevant only to a sub-set of obese individuals.

"Wanting" and "liking"

As the A2 allele is associated with a 30–40% increase in DA D2 receptors in the striatum compared to A1, and the G allele is related to an exaggerated response to opioid activation, it could be argued that the $A1^-/G^+$ group reflects an *hedonic-enhanced* genotype combination, whereas its opposite counterpart ($A1^+/G^-$) describes an *hedonic-diminished* combination. Of particular interest in this regard was our finding that a large majority (80%) of the former genotype comprised BED participants, while most of the participants in the latter genotype (65%) were obese controls (see **Figure 1**). These results mesh well with our psychometric data on the *Power of Food Scale* showing substantially elevated scores among the BED adults. Other research has also shown that BED individuals tend to engage in more hedonically driven eating such as a heightened response to external/environmental cues, and more snacking more on sweet foods (36). To use Berridge's (6) terminology, it could be said that individuals with BED tend to be elevated on the reward continua both of "wanting" and of "liking".

Although a clear strength of our research is its novel focus on the opioid system in obese individuals, these results must be viewed cautiously as we only examined a single functional marker of a single opioid gene. Opioid receptors are largely distributed in the brain structures known to modulate food intake and reward and come in various subtypes, which differ from each other regarding their contribution to specific opioid actions (37). Therefore, replication with larger samples and a greater number of genetic markers would strengthen our preliminary conclusions. In addition, it is important to acknowledge the limitations of this study. For example, the majority of our sample was female, which precluded our ability to investigate differences between men and women. In addition, most of the sample was white. Future research with larger samples would allow for an examination of gender and ethnicity main effects, and would also provide greater power to tests of gene–gene and gene–gender/ethnicity interactions.

In summary, our findings suggest that individuals with BED are a specific subtype of obesity. We have obtained evidence—albeit preliminary in nature—that the proneness to binge eating may be influenced by a biologically based hyper-reactivity to the hedonic properties of food, coupled with the motivation to engage in appetitive behaviors. This predisposition can be easily exploited in our current environment with its highly visible and easily accessible surfeit of sweet and fatty things to eat. In our view, these findings are congruent with an addiction model of excessive overeating (38). From this perspective, the shift from normal to compulsive use of highly rewarding

behaviors involves alterations in various aspects of brain reward circuitry including both downregulation and increased sensitization (39). As with other abused substances, chronic exposure to a highly palatable diet can turn normal eating into binge eating, especially in those with a diathesis for addiction.

In conclusion, it is hoped that the results of this study will foster further research in the area of binge eating and obesity. As others have said, a better understanding of how food interacts with brain-reward mechanisms is crucial in differentiating normal food reward from that which is excessive and disordered (40). Our ability to delineate biologically and clinically significant subtypes of overeating and obesity will also greatly aid in the effectiveness of weight loss therapies, whether the approach is educational, behavioral, or pharmacologic.

DISCLOSURE

The authors declared no conflict of interest.

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