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Reward sensitivity and the D2 dopamine receptor gene: A case-control study of binge eating disorder ☆

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Abstract

Objective: The sensitivity of dopamine reward pathways has been implicated in the risk for various psychiatric disorders including compulsive overeating. The evidence is divided, however, about the direction of causal association. One argument is that a *Reward Deficiency Syndrome* is the risk factor, while others contend that hyper-sensitivity to reward enhances the motivation for pleasurable activities like eating. Unfortunately, little human research has bridged the gap between psychological and neurobiological approaches to brain reward functioning and disorder. The present study addressed this issue by implementing psychological and biological markers of reward sensitivity in the assessment protocol.
Methods: Adults with binge eating disorder (BED) were compared to samples of normal-weight and obese controls on two personality measures of reward sensitivity and were genotyped for six markers of the DRD2 dopamine receptor gene.
Results: Genotype × Group ANOVAs revealed significant main effects and an interaction on the personality measures for *Taq1*A. BED and obese subjects reported greater reward sensitivity than normal-weight controls, but only among those carrying the A1 allele. We also found that normal-weight controls with at least one copy of the T allele of the C957T marker had significantly lower reward sensitivity scores than any of the other groups who did not differ from each other.
Conclusions: Given evidence linking the A1 allele with reduced receptor density, an inverse relationship was expected between psychological measures of reward sensitivity and presence of the A1 allele. One explanation for our findings could be that the BED and obese participants possess another genetic variant that interacts with the A1 allele to produce higher dopamine activity. These findings have implications for future studies of the molecular genetics of BED and obesity, and for behavioural and pharmacologic therapies targeting these conditions.
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Keywords: Binge eating disorder; Dopamine; Genetics; Obesity; Reward sensitivity

1. Introduction

Several lines of evidence show that dopamine (DA) pathways in the brain, connecting structures such as the nucleus accumbens, the amygdala, and the orbitofrontal cortex, regulate the anticipation of forthcoming reward and the subsequent pleasure we experience from these behaviours (Kelley et al., 2005; Wise, 2002). Increased activity has been associated with greater appetitive motivation and a stronger reinforcement response to both natural (e.g. food) and pharmacologic (e.g. addictive drugs) rewards (Cota et al., 2006; Kelley, 2004; O'Doherty et al., 2003).

Abbreviations: DA, dopamine; RDS, Reward Deficiency Syndrome; BAS, behavioural activation system; SNP, single nucleotide polymorphism; ANKK1, Ankyrin Containing Kinase 1; BED, binge eating disorder; BMI, body mass index; LD, linkage disequilibrium.

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The sensitivity or reactivity of this neural network is affected by several biological factors such as the density of DA receptors, the amount of DA released into the synapse, and the rapidity of its transport back into the cell by the re-uptake protein.

To completely understand the mechanisms of reward, however, one must also consider how individual differences in psychological traits may reflect these processes (Cohen et al., 2005). The *Behavioural Activation System* was conceived by Gray and colleagues (Gray, 1987; Gray and McNaughton, 2000) as a theoretical construct to describe the physiological mechanisms underlying individual responsiveness to cues of reward and the positive affect derived from engaging in reinforcing behaviours. Subsequently, various self-report questionnaires were developed to assess reward sensitivity as a stable personality trait with a naturally distributed variation in the population (Carver and White, 1994; Torrubia et al., 2002).

1.1. Reward sensitivity and psychiatric disorder

Individual differences in reward sensitivity have been strongly implicated in the risk for addictions such as cocaine abuse (Kreek et al., 2005; Nader and Czoty, 2005) and alcoholism (Bowirrat and Oscar-Berman, 2005; Loxton and Dawe, 2001, 2006; Thanos et al., 2005), as well as in the aetiology of depressive disorders (Nestler and Carlezon, 2006). There have also been recent claims for its role in compulsive overeating (Davis et al., 2007; Davis and Woodside, 2002) and the development of obesity (Epstein et al., 2004; Kelley et al., 2005; Wang et al., 2002). The evidence is divided, however, about the direction of causal association between reward sensitivity and vulnerability for these disorders.

One argument favours the view that hypo-dopaminergic functioning – what has been called a *Reward Deficiency Syndrome* (RDS) – is a key factor in the development of addiction disorders (Blum et al., 2000; Jimenez-Arriero et al., 2006). The premise is that substances (like addictive drugs and palatable food), which increase brain DA levels, are used as a form of 'self-medication' to boost a sluggish DA system and increase hedonic capacity.

The DA receptor subtype 2 (D2) has frequently been linked to the RDS (e.g. Blum et al., 1996; Comings and Blum, 2000; Bowirrat and Oscar-Berman, 2005). Of the commonly studied variants of the D2 gene (DRD2), the *Taq1*A polymorphism has been the focus of most research in the field of addictive disorders (Noble et al, 1991; and Noble, 2003 for a review). Its two alleles are denoted A1 (T allele) and A2 (C allele). *Taq1*A was thought to be located in the 3′-untranslated region of DRD2 (Noble, 2000). 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 (ANKK1) (Dubertret et al., 2004; Neville et al., 2004). It is not known whether this marker influences DRD2 expression or whether the ANKK1 gene is biologically connected to DRD2 function. There is, however, reasonable evidence (Noble, 2003) 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 DA receptor density in the striatal region (Jonsson et al., 1999). Therefore, it is generally assumed that those who carry the A1 allele experience a reduced sensitivity to reward. Various experimental studies support this contention. For example, Tran et al. (2002) observed reduced pre-reward brain activity in the nucleus accumbens of D2 knock-out mice, and Kirsch et al. (2006) found that A1+ subjects were less effective in gaining money, in a monetary-reward anticipation paradigm, compared to A1− subjects.

The counter argument is that hyper-sensitivity to reward contributes to increased risk for addictive behaviours because of enhanced motivation to approach potentially pleasurable activities such as drug taking and eating. In several studies, heightened reward sensitivity was associated with emotional overeating, preference for high fat food, binge eating, and food cravings, as well as with hazardous alcohol consumption (Davis et al., 2004, 2007; Davis and Woodside, 2002; Franken and Muris, 2005; Loxton and Dawe, 2001, 2006). One explanation for the apparent disaccord between the two bodies of research may be a *dual vulnerability* to behavioural disorders whereby both causal paths can confer risk, albeit in different individuals and perhaps with different levels of severity.

The most striking feature of the reward sensitivity research, however, is the different methodologies used to operationally define the construct. Neuroimaging and genetic data comprise much of the evidence linking addictive behaviours to a reward deficit, while psychological measures support the role of high reward sensitivity. Particularly problematic is the paucity of human research bridging the gap between neurobiological and psychological approaches to the study of brain reward functioning. In other words, evidence that personality measures of reward sensitivity correlate with biological markers of DA activation is minimal. Exceptions are two recent studies. One found that a self-report measure of reward sensitivity [BAS-Drive] was positively correlated with degree of activation in brain reward regions in response to visual images of appetizing food (Beaver et al., 2006). A second study, also using the BAS questionnaire, found a DA gene–gene interaction, which prompted the conclusion that high DA activity was associated with high BAS scores (Reuter et al., 2006).

1.2. The present study

Individuals with binge eating disorder (BED) are a phenotype characterized by compulsive overeating and a high risk for obesity — a condition that has been likened to conventional drug addictions (Wang et al., 2004). Here too there are opposing views about whether excessive overeating and obesity reflect a reward deficit (Wang et al., 2001) or a heightened sensitivity to reward (Davis et al., 2007). The purpose of the present study was to re-address this issue by using a case-control design and implementing both biological and psychological markers of reward sensitivity in the assessment protocol. Participants were assessed on the two most commonly used personality measures of reward sensitivity and were genotyped for several DRD2 SNPs. In addition to *Taq1*A, we included two other DRD2 SNPs with the strongest evidence of being functional (−141 Ins/Del and C957T). The Del allele of the −141 Ins/Del SNP has

been associated with increased receptor density levels while the T allele of the C957T SNP has been associated with reduced receptor density in the human striatum (Jonsson et al., 1999; Ritchie and Noble, 2003). Because the DRD2 is a large gene (~70 kilobases), we decided to include in our analyses 3 additional SNPs with unclear functional significance (−241 A/G; *Taq1*D C/T; and rs4648317 C/T) in order to explore other regions of the gene (Hwang et al., 2005).

We predicted that compared to the normal-weight group, the BED and the obese groups, would report higher reward sensitivity, and would have a greater prevalence of alleles associated with enhanced receptor density — for example, the A2 allele of the *Taq1*A SNP, the Del allele of the −141 Ins/Del, and the C allele of the C957T. We also predicted that reward sensitivity scores would be higher in participants possessing these alleles relative to those possessing the counterpart alleles for each SNP.

2. Methods

2.1. Subjects and procedure

Adults between the ages of 25 and 45 years who met criteria for BED (N=56: female=44; male=12) were recruited from posters placed at universities, local hospitals, and other public institutions. Advertisements were also placed in local newspapers. A normal-weight (N=59: female=52; male=7) and an obese (n=51: female=39; male=12) control group were recruited in the same manner. The percentage of males and females did not differ significantly among the groups (χ^2=2.873, *df* 2, p=0.238). In the BED group, 83.9% of the participants were Caucasian, 8.9% were African Canadian, 1.8% were Asian, and 5.4% were Hispanic. In the normal-weight and obese groups the ethnicity proportions were 86.4%, 6.8%, 5.1%, 1.7% and 72.5%, 19.6%, 2.0%, 5.9%, respectively. The chi-square test of independence for these data was also non-significant (χ^2=7.827, *df* 6, p=0.251).

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 recently given birth), and were currently being treated for (or had a history of) any psychiatric disorder including eating disorders and substance abuse.

BED participants were required to meet an operational definition of the disorder using ratings on the *Eating Disorder Examination* (Fairburn and Cooper, 1993). This definition was based on that provided in the main body of the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition [DSM-IV] (American Psychiatric Association, 2004) where BED is defined as: "recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviours 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 three 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 DSM-IV diagnostic criteria for bulimia nervosa or anorexia nervosa. BED diagnosis was established during a telephone interview carried out by trained personnel. The same exclusion criteria were applied to BED adults as to the control subjects, except that we included BED 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 co-morbidity between BED 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 measures after which height and weight were measured and the blood sample was taken. For BED subjects, a structured clinical interview was carried out to confirm eligibility, and for control subjects a briefer non-patient psychiatric screening took place, which included questions about substance use and disordered eating. At the end of the study, all subjects were paid a stipend for their participation.

2.2. Measures

Reward sensitivity is most commonly assessed by two well-validated, self-report questionnaires:

1. The *Sensitivity to Reward* scale of the *SPSR Questionnaire* (Torrubia et al., 2002) reflects both the anticipation of reward (e.g. "Does the good prospect of obtaining money motivate you strongly to do some things?) and pleasure experienced from rewarding activities (e.g. Does you attention easily stray from your work in the presence of an attractive stranger?). This scale has shown good internal consistency, temporal stability, and concurrent validity (e.g. Caseras et al., 2003). However, psychometric evaluation of the factor structure of this scale in two recent studies has identified the same 7 items as problematic (Cogswell et al., 2006; O'Connor et al., 2004). Their authors noted some improvement in the factor structure of the questionnaire – without sacrificing the validity of the scales – when these items were trimmed from the item pool. For this reason, the trimmed 17-item scale will be employed in the data analysis. The alpha coefficient in the present study was 0.80.
2. The 13 items of the *Behavioural Activation (BAS)* scale of the *BIS/BAS* questionnaire (Carver and White, 1994) comprise 3 sub-scales which assess one's persistent pursuit of desired goals (*Drive*), the desire for new and pleasing stimuli (*Fun Seeking*), and the positive anticipation of rewarding events (*Reward Responsiveness*). Since their development, these scales have been widely used and well-validated. The alphas for the current study were 0.80, 0.72, and 0.70 respectively.

Binge eating was assessed by *The Binge Eating Questionnaire* [BEQ] (Halmi et al., 1981), which measures the frequency and severity of symptoms associated with binge eating (such as

loss of control over eating, and negative affect following a binge) and with purging (e.g. self-induced vomiting). Binge eating was quantified by summing the responses to 5 (yes–no) questions tapping relevant aspects of this behaviour (e.g. "Are there times when you feel you cannot voluntarily stop eating?"). The alpha coefficient for this study was 0.89.

Body mass index [BMI] (weight[kg]/height[m^2]) was calculated from height and weight measured with the participant wearing indoor clothing and standing in stocking feet.

2.3. Genotyping

A venous blood sample (20–30 ml) was collected from each subject, and the non-enzymatic, high salt procedure was used to extract DNA from the whole blood (Lihari and Nurnberger, 1991). The DRD2 markers (*Taq1*A, −141C Ins/Del, C957T, *Taq1*D, A-241G, and rs4648317) were genotyped on ABI 7000/7500. The total volume of the PCR reaction was 10ul which consisted of 1 μl (20 ng/μl) of DNA, 5 μl of 2× TaqMan Buffer, 0.25 μl of 40× Assay and 3.75 μl of dH2O. 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 7000/7500 Prism was used to analyze the presence of variation of alleles by comparing to No Template Controls (Grandy et al., 1993).

In order to assure quality control at the genotyping step, 5% of the samples were regenotyped. The duplicate samples were chosen randomly and the genotype results from both runs coincided, giving the error rate of 0%. None of the three sample groups (BED, normal-weight, and obese controls) deviated from Hardy–Weinburg equilibrium, tested using the program called PEDSTATS.

3. Results

3.1. Subject characteristics

Table 1 presents the means and standard deviations for the quantitative variables used in the present study, listed separately for the three comparison groups. One-way ANOVA procedures revealed significant group differences only for BMI, binge eating, and Sensitivity to Reward. *Post hoc* analyses, using the Least Significant Difference (LSD) test, indicated that all three groups differed from each other on BMI and Binge Eating ($p<0.05$). Obese controls had the highest BMI and the normal-weight controls had the lowest. Not surprisingly, the BED subjects also had the highest Binge Eating scores while the normal-weight controls had the lowest. On the Sensitivity to Reward scale, the normal-weight group had significantly lower scores than the BED or obese groups, who did not differ from each other.

Table 1
Means, standard deviations, and one-way ANOVA for the quantitative variables reported in the study

	Normal control		BED		Obese control			
Variable	Mean	SD	Mean	SD	Mean	SD	*F*	*p*
BMI	22.38	2.78	34.71	9.01	39.06	8.33	80.4	<0.0001
Age	33.49	7.53	34.84	6.41	36.29	6.34	2.32	0.102
BE	0.49	0.92	4.32	1.05	2.52	1.79	128.88	<0.0001
SR	5.78	3.69	7.27	3.18	7.35	3.27	3.86	0.023
BAS-RR	15.83	1.92	16.52	1.87	16.41	2.05	2.07	0.129
BAS-D	10.64	2.22	11	2.54	10.92	1.97	0.39	0.677
BAS-FS	10.95	1.76	11.07	2.32	11.59	1.78	1.58	0.209

BMI = Body mass index.
BE = Binge eating scale.
SR = Sensitivity to reward scale.
BAS-RR = Reward to responsiveness scale of the BIS/BAS.
BAS-D = Drive scale of the BIS/BAS.

Fourteen percentage of the total sample were regular smokers (i.e. at least 1 cigarette a day) and there were no differences in frequency among the groups.[1]

Allele and genotype frequencies for the six SNPs are shown in Table 2. Because of the putative effect of the A1 allele as well as the rare occurrence of the A1/A1 genotype, this group is typically combined with the A1/A2 [collectively, A1+] (see Noble, 2003) 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 C957T T allele present (+) or absent (−). For rs4648317, the T allele is rare so the T/T and the C/T genotypes were combined for the purposes of the statistical analyses. For the same reason, A/G and G/G were combined for the −241 A/G SNP. None of the chi-square analyses to test genotype frequency differences among the three case-control groups was statistically significant.

However, because of the ethnic heterogeneity of our sample, and because genotype distributions are typically different between Caucasian and non-Caucasian samples (see, for example, Hwang et al., 2005), we used chi-square analyses to test the genotype frequencies between Caucasians and non-Caucasians for the 3 functional SNPs. As expected, the non-Caucasians ($n=31$) had a significantly higher frequency than the Caucasian sample (61% vs 33%) of the A1+ genotype for *Taq1*A ($p=0.004$). Non-Caucasians also had a significantly greater frequency of the Del+ genotype than Caucasians (55% vs 18%) for the −141 Ins/Del SNP ($p<0.0001$) and a significantly higher frequency (64% vs 32%) of T− for the C957T SNP ($p=0.001$).

3.2. Analyses of variance (ANOVA)

Separate Genotype × Group ANOVAs were conducted for each SNP with the Sensitivity to Reward scale, and the three BAS scales as consecutive dependent variables.

1. *Taq1*A: Results indicated significant main effects and a significant interaction term for Sensitivity to Reward, and for the Reward Responsiveness scale of the BAS. The summary statistics for these two analyses are shown in Tables 3 and 4 and plotted in Figs. 1 and 2, respectively.

[1] These data are in line with 2007 Canadian population statistics reporting that 23% of men and 20% of women in the age range we sampled (25–45years) smoked "on either a daily or occasional basis" — a more liberal criterion than we used to designate our subjects as "smoker".

Table 2
Allele and genotype frequencies for the *Taq1*A, −141C Ins/Del, −241 A/G, *Taq1*D, C957T, and rs4648317 polymorphism for 59 normal-weight controls, 56 BED subjects, and 51 obese controls

	*Taq1*A				
	Allele			Genotype	
	A1	A2	A1/A1	A1/A2	A2/A2
Normal	21 (17.8%)	97 (82.2%)	1 (1.7%)	19 (32.2%)	39 (66.1%)
BED	21 (18.8%)	91 (81.2%)	2 (3.6%)	17 (30.4%)	37 (66.1%)
Obese	28 (27.4%)	74 (72.6%)	3 (5.9%)	22 (43.1%)	26 (51.0%)

When the A1/A1 and the A1/A2 groups were combined, because of the rare occurrence of the homozygous A1 group, the 3 [Group]×2 [Genotype] chi-square was non-significant (χ^2=3.404, *df*=2, *p*=0.182).

	−141C Ins/Del				
	Allele			Genotype	
	Del	Ins	Del/Del	Del/Ins	Ins/Ins
Normal	21 (17.8%)	97 (82.2%)	4 (6.8%)	13 (22.0%)	42 (71.2%)
BED	15 (13.4%)	97 (86.6%)	3 (5.4%)	9 (16.1%)	44 (78.5%)
Obese	16 (16.3%)	82 (83.7%)	4 (8.2%)	8 (16.3%)	37 (75.5%)

Data were not available for 2 obese controls for this polymorphism. When the Del/Del and the Del/Ins groups were combined, because of the rare occurrence of the homozygous Del group, the 3 [Group]×2 [Genotype] chi-square was non-significant (χ^2=0.845, *df*=2, *p*=0.655).

	C957T				
	Allele			Genotype	
	C	T	C/C	C/T	T/T
Normal	72 (61.0%)	56 (39.0%)	24 (40.7%)	24 (40.7%)	11 (18.6%)
BED	56 (50.0%)	56 (50.0%)	16 (28.6%)	24 (42.9%)	16 (28.6%)
Obese	65 (63.7%)	37 (36.3%)	23 (45.1%)	19 (37.3%)	9 (17.6%)

A 3 [Group]×3 [Genotype] chi-square analysis indicated no significant differences in the genotype frequencies (χ^2=4.170, *df*=4, *p*=0.384). When C/T and T/T groups were combined, the chi-square analysis was also non-significant (χ^2=3.385, *df*=2, *p*=0.184).

	−241 A/G				
	Allele			Genotype	
	A	G	A/A	A/G	G/G
Normal	111 (94.1%)	7 (5.9%)	53 (89.8%)	5 (8.5%)	1 (1.7%)
BED	103 (92.0%)	9 (8.0%)	48 (85.7%)	7 (12.5%)	1 (1.8%)
Obese	90 (90.0%)	10 (10.0%)	41 (82.0%)	8 (16.0%)	1 (2.0%)

Data were not available for 1 obese control for this polymorphism. When the G/G and the A/G groups were combined, because of the rare occurrence of the homozygous G group, the chi-square was non-significant (χ^2=1.392, *df*=2, *p*=0.499).

	*Taq1*D C/T				
	Allele			Genotype	
	C	T	C/C	C/T	T/T
Normal	62 (52.5%)	56 (47.5%)	20 (33.9%)	22 (37.3%)	17 (28.8%)
BED	46 (41.1%)	66 (58.9%)	10 (17.9%)	26 (46.4%)	20 (35.7%)
Obese	58 (58.0%)	42 (42.0%)	19 (38.0%)	20 (40.0%)	11 (22.0%)

Data were not available for 1 obese control for this polymorphism. A 3 [Group]×3 [Genotype] chi-square analysis indicated no significant differences in the genotype frequencies (χ^2=6.473, *df*=4, *p*=0.166).

	rs4648317				
	Allele			Genotype	
	C	T	C/C	C/T	T/T
Normal	92 (78.0%)	26 (22.0%)	41 (69.5%)	10 (16.9%)	8 (13.6%)
BED	91 (81.2%)	21 (18.8%)	38 (67.9%)	15 (26.8%)	3 (5.4%)
Obese	83 (81.4%)	19 (18.6%)	33 (64.7%)	17 (33.3%)	1 (2.0%)

When C/T and T/T groups were combined, the chi-square analysis was non-significant (χ^2=0.291, *df*=2, *p*=0.864).

Table 3
Allele frequencies for the *Taq1*A, −141C Ins/Del, and C957T polymorphisms for 135 Caucasian participants and 31 non-Caucasians

	*Taq*1A		C957T		−141 Ins/Del	
	A1+	A1−	T+	T−	Del+	Del−
Caucasian	33.3%	66.7%	31.9%	68.1%	18.5%	81.5%
Non-Caucasian	61.3%	38.7%	64.5%	35.5%	55.2%	44.8%
	χ^2=8.318	p=.004	χ^2=11.423	p=.001	χ^2=8.318	p<.001

Table 4
ANOVA summary with Group (normal vs BED vs obese) and combined *Taq1*A genotype (A1/A1 & A1/A2 vs A2/A2) as independent variables and *sensitivity to reward* as the dependent variable

Variable	*df*	Mean square	*F*	*p*
Group	2	62.98	5.75	0.004
*Taq1*A	1	49.59	4.53	0.035
Group × *Taq1*A	2	41.03	3.75	0.026

ANOVA summary with Group (normal vs BED vs obese) and combined *Taq1*A genotype (A1/A1 and A1/A2 vs A2/A2) as independent variables and *reward responsiveness* as the dependent variable

Variable	*df*	Mean square	*F*	*p*
Group	2	10.24	2.84	0.062
*Taq1*A	1	15.87	4.39	0.038
Group × *Taq1*A	2	12.64	3.5	0.033

Post hoc analyses

i) Within-genotype comparisons
Least Significant Difference (LSD) tests indicated that among A1+ subjects, the BED and the obese subjects had significantly higher Sensitivity to Reward (p<0.001 and p=0.003, respectively) and Reward Responsiveness (p=0.021, and p=0.003, respectively) scores than the normal-weight subjects. They did not, however, differ significantly from each other. However, among the A1− subjects, there were no significant group differences on either of the reward scales.

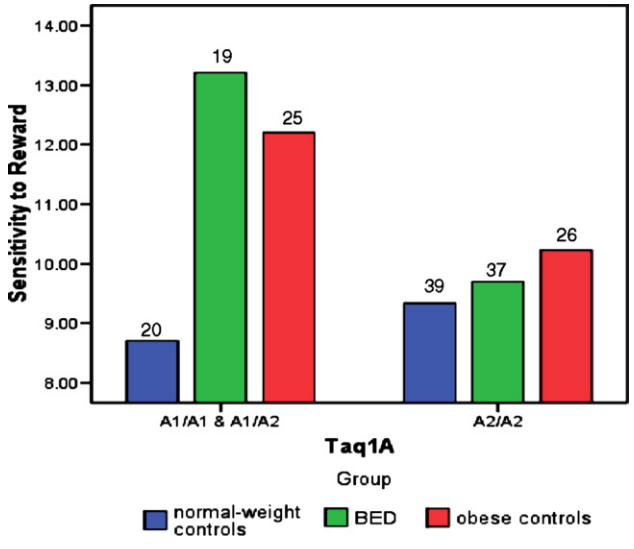

Fig. 1. *Sensitivity to reward* as a function of diagnostic group and *Taq1*A Genotypes.

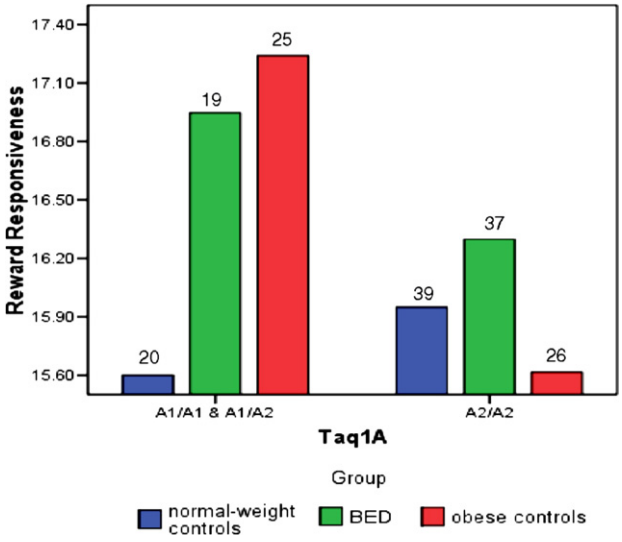

Fig. 2. *Reward responsiveness* as a function of diagnostic group and *Taq1*A Genotypes.

ii) Within-group comparisons
In the normal-weight group there were no differences between A1+ and A1− subjects on either reward scale. In the BED group, however, A1+ subjects had significantly higher sensitivity to reward scores (p=0.002) than A1− subjects, but the two groups did not differ significantly on reward responsiveness. In the obese groups the opposite pattern emerged. Those in the A1+ group had significantly higher scores on the reward responsiveness scale than those in A1− (p=0.004), but the genotype difference only approached significance (0.10) on the Sensitivity to Reward scale.

Additional genotype comparisons

In light of the significant Group × Genotype interactions observed in the ANOVAs, and because the three groups differed in BMI, and binge eating status, A1+ vs A1− differences were examined on these variables. Results of the independent t-tests did not indicate any significant differences.

2. −141 Ins/Del: The 2 (Genotype: Del+ vs Del−) × 3 (Group) ANOVA revealed no significant genotype main effect or interaction for any of the personality variables.
3. C957T: The 2 (Genotype: T+ vs T−) × 3 (Group) ANOVA indicated a significant genotype main effect for the Fun Seeking subscale of the BAS ($F_{1,160}$=7.059, p=0.009). T+

Table 5
ANOVA summary with Group (normal vs BED vs obese) and combined C957T genotype (T− vs T+) as independent variables and *sensitivity to reward* as the dependent variable

Variable	*df*	Mean square	*F*	*p*
Group	2	46.84	2.55	0.081
T− vs T+	1	9.78	0.53	0.467
Group × T	2	57.29	3.12	0.047

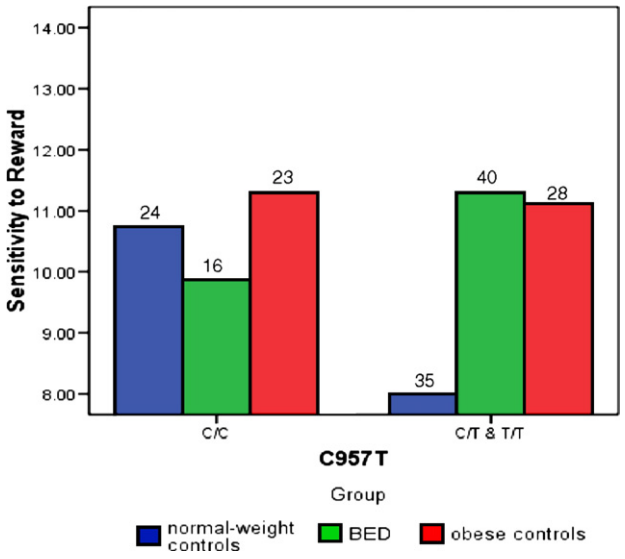

Fig. 3. *Sensitivity to reward* as a function of diagnostic group and C957T genotypes.

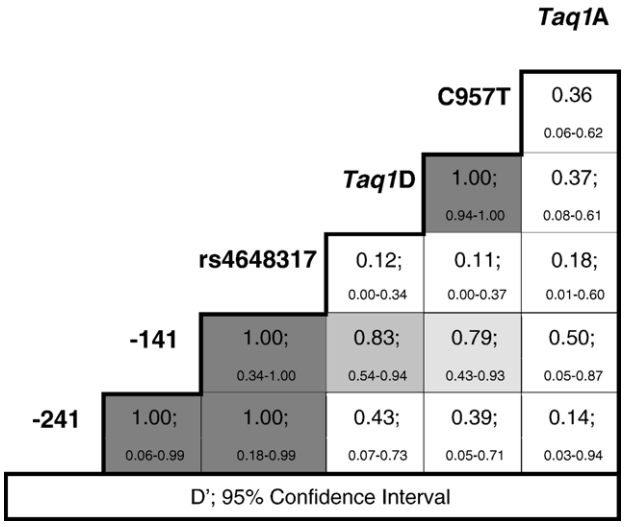

Fig. 4. Pairwise SNP LD analyses (Caucasian).

was associated with lower Fun Seeking scores. There was also a significant Genotype × Group interaction for the Sensitivity to Reward scale. The summary statistics for this analysis are shown in Table 5 and plotted in Fig. 3.

Post hoc analyses

i) Within-genotype comparisons
LSD tests indicated that among T− subjects, there were no differences among the three groups on sensitivity to reward. However, among the T+ subjects, the control group has significantly lower scores than the BED and obese controls ($p=0.002$, and $p=0.006$, respectively) who did not differ from each other.

ii) Within-group comparisons
In the normal-weight group, T+ subjects had significantly lower scores than T− subjects ($p=0.023$) while in the BED and obese groups there were no genotype group differences.

4. *Taq1*D, −241 A/G, and rs4648317: There was no significant main effect for genotype nor a group × genotype interaction on any of the personality variables for these three non-functional SNPs.[2]

[2] Because of the possible confound in our results due to the ethnic heterogeneity of the sample, and the demonstrated genotype frequency differences between Caucasian and non-Caucasian samples for the 3 functional SNPs, we repeated all the analyses described reported above, excluding the non-Caucasian subjects. This reduced the sample size to 135. None of the results changed with respect to their statistical significance except that the Group × Genotype interaction for the C957 SNP (with Sensitivity to Reward as the dependent variable) was no longer statistically significant.

The size of the non-Caucasian sample was too small ($N = 31$) to carry out the full analyses since some of the cells in the 2 × 3 ANOVAs contained no data. We did, however, test A1+ vs A1− personality differences for the *Taq1*A SNP and found – in general accord with our other findings – that the A1+ genotype had higher scores on Sensitivity to Reward and Fun Seeking ($p = 0.016$ and 0.033, respectively). There was also a trend in the same direct for the Reward Responsiveness scale ($p = 0.074$).

3.3. Linkage disequilibrium (LD) analysis

Pairwise LD coefficients between the 6 SNPs are presented separately for Caucasians and non-Caucasians in Figs. 4 and 5, respectively. In this study, we defined a haplotype block as a region over which less than 5% of pairwise comparisons among informative SNPs showed strong evidence of historical recombination (upper confidence bound on D' less than 0.9; Gabriel et al., 2002). Based on this definition, the haplotype block *Taq1*D-C957T is in high LD with a good confidence interval, and this is observed in both the Caucasian and the non-Caucasian sample.

4. Discussion

Among the six SNPs related to DRD2, the findings for the *Taq1*A are perhaps of greatest interest given its considerable

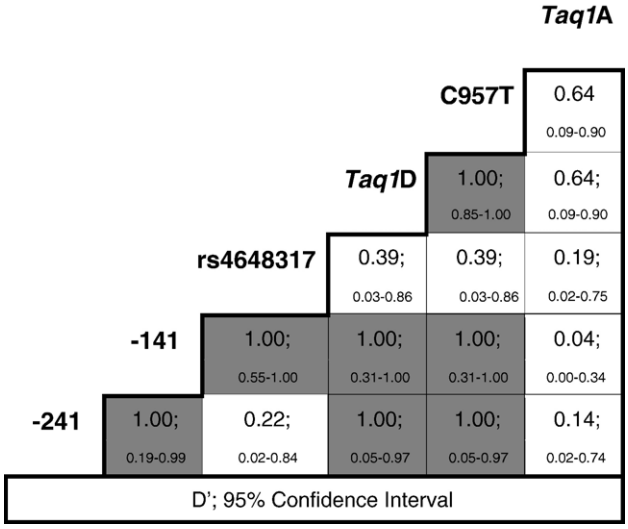

Fig. 5. Pairwise SNP LD analyses (non-Causcasian).

links to addictions in general, and obesity more specifically. As we anticipated, BED and obese participants reported greater reward sensitivity – defined by scores on the Sensitivity to Reward and BAS Reward Responsiveness scales[3] – compared to those with normal-weight. However, the significant interaction term in both analyses demonstrated that *Taq1*A genotype had a moderating influence on this relationship. Higher reward sensitivity was only observed in BED and obese subjects who carried the A1 allele. All other groups reported lower sensitivity to reward on these measures, and did not differ from each other. One exception was the non-significant genotype comparison in the BED group on Reward Responsiveness.

At first glance, these findings are difficult to explain. For example, based on evidence linking the A1 allele with reduced D2 receptor density (Noble et al., 1991; Jonsson et al., 1999), an inverse association between the psychological measures of reward sensitivity and the presence of A1 allele would be expected. Not only was this relationship absent, but in the BED and obese participants, significantly *higher* reward sensitivity was found in the A1+ groups. One reason could be that the BED and obese (but not the normal-weight) participants possess another genetic variant that interacts with the A1 allele to produce higher DA activity. The findings of a recent study are cognate to this possibility.

Reuter et al. (2006) have provided evidence for a gene-interaction model between the catabolic enzyme activity of catechol-*O*-methyl transferase (COMT) and DRD2 receptor density, whereby *disequilibrium* is associated with higher DA levels and higher BAS scores. In other words, high enzyme activity (associated with the Val allele of COMT) and low D2 receptor density (associated with the A1 allele) contribute to relatively high DA levels and correspondingly elevated reward sensitivity scores on the BAS scale. Applying this paradigm to our data provides a compelling, albeit speculative, explanation for our seemingly counterintuitive findings. We would expect BED and obese, but not normal-weight subjects, to possess high enzyme activity (i.e. the Val allele). Reuter et al's model is even more appealing because it could also explain the relatively low BAS scores in the A1− BED and obese participants. Specifically, it predicts that when enzyme activity and D2 density are in *equilibrium* (e.g. Val+ and A1−), low DA levels and low reward sensitivity ensue. In the future, those studying the genetics of overeating and obesity would do well to examine the COMT polymorphism in association with DRD2 markers as potential interactive risk factors for these conditions.

The only other marker that showed significant genotype differences was the C957T SNP. Carriers of the 957T allele have shown markedly lower striatal D2 receptor availability (Hirvonen et al., 2004). Such findings led us to expect genotypic differences in the human capacity for pleasure and reward. Some preliminary evidence for this prediction was found as the T+ subjects reported lower Fun-seeking scores. These results must, however, be taken as tentative until replicated in other samples. We also found lower sensitivity to reward scores in those possessing the T allele, but only in the normal-weight controls. Since both the C957T and the *Taq1*A polymorphisms have been associated with D2 binding potential in the human brain, it is possible that these genetic factors might even operate interactively in this capacity. However, given the large natural variation in reward sensitivity, larger samples are needed for sufficient power to demonstrate a statistically significant gene–gene interaction.

In summary, our results have demonstrated that individuals with BED and/or obesity, who carry the A1 allele, report a relatively high degree of reward sensitivity — a factor that might contribute to their over-consumption. It has been argued that non-homeostatic eating is a prime risk for obesity, and may be fostered by a greater motivation for (or 'wanting' of) food without necessarily any greater pleasure derived from the physical experience of eating (Mela, 2006). Although the obese controls did not have binge eating disorder, there are likely to be many reasons why these individuals have a high BMI. One may be their choice of macro-nutrients or the number of calories they consume each day. Finally, we also found some evidence that the T allele of C957T is related to relatively low values on some measures of reward sensitivity. It is important to emphasize, however, that since approximately 18% our sample was non-Caucasian – and we know that ethnicity correlates with genotypic frequency – our findings may have greater error variance than would be found in more homogeneous samples. On the other hand, the data-analytic results of this study were scarcely changed in their direction, their magnitude, or their statistical significance when we carried out the procedures on the trimmed (Caucasian only) sample. Therefore, we are confident in reporting the findings for the full sample.

One clear limitation of our study is that we have no objective indicator of DA activity in the brain; nor can we make valid inferences about such activity on the basis of genetic markers and measures of personality. A next important step in this area of research is to use neuroimaging techniques in conjunction with genetic analyses to better understand the role of DA activation and reward sensitivity in the risk for obesity. Larger samples will also be needed to test the possibility of interaction effects on measures of reward sensitivity since it is highly plausible that other genes for centrally mediated weight gain, such as DRD3, leptin, the CB1 cannabinoid receptor gene and the mu receptor gene combine with DRD2 to increase DA in BED and obese individuals.

[3] The latter scale has items that focus on positive responses to the occurrence or anticipation of reward, and, of the 3 BAS scales, appears to have the closest content overlap with the Sensitivity to Reward measure.

References

American Psychiatric Association. Diagnostic and Statistical Manual-Version IV. Washington, DC: American Psychiatric Association Press; 2004.

Beaver JD, Lawrence AD, van Ditzhuijzen J, Davis MH, Woods A, Calder AJ. Individual differences in reward drive predict neural responses to images of food. J Neurosci 2006;26:5160–6.

Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJH, Cull JG, et al. The D-2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 1996;89:396–400.

Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoact Drugs 2000;32 Supplement S.

Bowirrat A, Oscar-Berman M. Relationship between dopaminergic neurotransmission, alcoholism, and reward deficiency syndrome. Am J Med Genet Part B-Neuropsychiatric Genetics 2005:29–37 132B.
Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective response to impending reward and punishment: the BIS/BAS scales. J Pers Soc Psychol 1994;67:319–33.
Caseras X, Avila C, Torrubia R. The measurement of individual differences in behavioural inhibition and behavioural activation systems: a comparison of personality scales. Pers Individ Differ 2003;34:999–1013.
Cogswell A, Alloy LB, van Dulmen MHM, Fresco DM. A psychometric evaluation of behavioral inhibition and approach self-report measure. Pers Individ Diff 2006;40:1649–58.
Cohen MX, Young J, Baek JM, Kessler C, Ranganath C. Individual differences in extraversion and dopamine genetics predict neural reward responses. Cogn Brain Res 2005;25:851–61.
Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. Prog Brain Res 2000;126:325–41.
Cota D, Tschop MH, Horvath TL, Levine AS. Cannabinoids, opioids and eating behavior: the molecular face of hedonism? Brain Res Brain Res Rev 2006;51: 85–107.
Davis C, Woodside DB. Sensitivity to the rewarding effects of food and exercise in the eating disorders. Compr Psychiatry 2002;43:189–94.
Davis C, Strachan S, Berkson M. Sensitivity to reward and emotional eating: implications for overweight and obesity. Appetite 2004;42:131–8.
Davis C, Patte K, Levitan RD, Reid C, Tweed S, Curtis C. From motivation to behaviour: a model of reward sensitivity, overeating, and food preferences in the risk profile for obesity. Appetite 2007;48:12–9.
Dubertret C, Gouya L, Hanoun N, Deybach JC, Ades J, Hamon M, Gorwood P. The 3′ region of the DRD2 gene is involved in genetic susceptibility to schizophrenia. Schizophrenia Research 2004;67:75–85.
Epstein LH, Wright SM, Paluch RA, Leddy JJ, Hawk LW, Jaroni JL, et al. Relation between food reinforcement and dopamine genotypes and its effect on food intake in smokers. Am J Clin Nutr 2004;80:82–8.
Fairburn CG, Cooper Z. The eating disorder examination. In: Fairburn CG, Wilson GT, editors. Binge eating: nature, assessment, and treatment. New York: Guilford Press; 1993. p. 317–60.
Franken IHA, Muris P. Individual differences in reward sensitivity are related to food craving and relative body weight in healthy women. Appetite 2005;45: 198–201.
Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B. The structure of haplotype blocks in the human genome. Science 2002;296: 2225–9.
Grandy DK, Zhang Y, Civelli O. PCR detection of the TaqA RFLP at the DRD2 locus. Hum Mol Genet 1993;2:2197.
Gray JA. The neuropsychology of emotion and personality. In: Stahl SM, Iverson SD, Goodman EC, editors. Cognitive neurochemistry. Oxford, UK: Oxford University Press; 1987. p. 171–90.
Gray JA, McNaughton N. The neuropsychology of anxiety: an enquiry into the functions of the septo-hippocampal system. 3rd ed. Oxford: Oxford University Press; 2000.
Halmi KA, Falk JR, Schwartz E. Binge-eating and vomiting — a survey of a college population. Psychol Med 1981;11:697–706.
Hirvonen M, Laakso A, Nagren K, Rinne JO, Pohjalainen T, Hietala J. C957T polymorphism of the dopamine D2 receptor (DRD2) gene affects striatal DRD2 availability in vivo. Mol Psychiatry 2004;9:1060–1.
Hwang R, Shinkai T, De Luca V, Muller DJ, Ni X, Macciardi F, et al. Association study of 12 polymorphisms spanning the dopamine D_2 receptor gene and clozapine treatment response in two treatment refractory/intolerant populations. Psychopharmacology 2005;181:179–87.
Jimenez-Arriero MA, Ponce G, Rodriguez-Jimenez R, Aragues M, Galvan A, Rubio G, et al. Taq1-A polymorphism linked to the DRD2 gene and P300 in alcoholic patients. Eur J Psychiatry 2006;20:45–53.
Jonsson EG, Nothen NM, Grunhage F, Farde L, Nakashima Y, Propping P, et al. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol Psychiatry 1999;4:290–6.
Kelley AE. Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. Neurosci Biobehav Rev 2004;27:765–76.
Kelley AE, Schiltz CA, Landry CF. Neural systems recruited by drug- and food-related cues: studies of gene activation in corticolimbic regions. Physiol Behav 2005;86:11–4.
Kirsch P, Reuter M, Mier D, Lonsdorf T, Stark R, Gallhofer B, et al. Imaging gene–substance interactions: the effect of the DRD2 Taq1A polymorphism and the dopamine agonist bromocriptine on the brain activation during the anticipation of reward. Neurosci Lett 2006;405:196–201.
Kreek MJ, Nielson DA, Butelman ER, LaForge KS. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nat Neurosci 2005;8:1450–7.
Lihari DK, Nurnberger JI. A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. Neucleic Acids Res 1991;19:5444.
Loxton NJ, Dawe S. Alcohol abuse and dysfunctional eating in adolescent girls: the influence of individual differences in sensitivity to reward and punishment. Int J Eat Disord 2001;29:455–62.
Loxton NJ, Dawe S. Reward and punishment sensitivity in dysfunctional eating and hazardous drinking women: associations with family risk. Appetite 2006;47:361–71.
Mela DJ. Eating for pleasure or just wanting to eat? Reconsidering sensory hedonic responses as a driver for obesity. Appetite 2006;47:10–7.
Nader MA, Czoty PW. PET imaging of dopamine D2 receptors in monkey models of cocaine abuse: genetic predisposition versus environmental modulation. Am J Psychiatry 2005;162:1473–82.
Nestler EJ, Carlezon WA. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 2006;59:1151–9.
Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Human Mutat 2004;23:540–5.
Noble EP. Addiction and its reward process through polymorphisms of the D_2 dopamine receptor gene: a review. Eur Psychiatry 2000;15:79–89.
Noble EP. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotype. Am J Med Genet Part B Neuropsychiatric Genetics 2003:103–25 116B.
Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. Arch Gen Psychiatry 1991;48:648–54.
O'Connor RM, Colder CR, Hawk LW. Confirmatory factor analysis of the Sensitivity to Punishment and Sensitivity to Reward Questionnaire. Pers Individ Differ 2004;37:985–1002.
O'Doherty J, Winston J, Critchley H, Perrett D, Burt DM, Dolan RJ. Beauty in a smile: the role of medial orbitofrontal cortex in facial attractiveness. Neuropsychologia 2003;41:147–55.
Reuter M, Schmitz A, Corr P, Hennig J. Molecular genetics support Gray's personality theory: the interaction of COMT and DRD2 polymorphisms predicts the behavioural approach system. Int J Neuropsychopharmacol 2006;9:155–6.
Thanos PK, Rivera SN, Weaver K, Grandy DK, Rubinstein M, Umegaki H, et al. Dopamine D2R DNA transfer in dopamine D2 receptor-deficient mice: effects on ethanol drinking. Life Sci 2005;77:130–9.
Torrubia R, Avila C, Molto J, Caseras X. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Pers Individ Differ 2002;31:837–62.
Tran AH, Tamura T, Uwano T, Kobayashi M, Katsuki G, Matsumoto T, et al. Altered accumbens neural response to prediction of reward associated with place in dopamine D2 receptor knockout mice. Proc Natl Acad Sci U S A 2002;99:8986–91.
Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. Lancet 2001;357:354–7.
Wang GJ, Volkow ND, Fowler JS. The role of dopamine in motivation for food in humans: implications for obesity. Expert Opin Biol Ther 2002;6:601–9.
Wang GJ, Volkow ND, Thanos PK, Fowler JS. Similarity between obesity and drug addiction as assessed by neurofunctional imaging: a concept review. J Addict Dis 2004;23:39–53.
Wise RA. Brain reward circuitry: insights from unsensed incentives. Neuron 2002;36:229–40.