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The Possible Influence of Impulsivity and Dietary Restraint on Associations between Serotonin Genes and Binge Eating

Sarah E. Racine[1], **Kristen M. Culbert**[1], **Christine L. Larson**[2], and **Kelly L. Klump**[1]

[1] Department of Psychology, Michigan State University, East Lansing, Michigan, USA

[2] Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, USA

Abstract

Although serotonin (5-HT) genes are thought to be involved in the etiology of bulimia nervosa and binge eating, findings from molecular genetic studies are inconclusive. This may be due to limitations of past research, such as a failure to consider the influence of quantitative traits and gene-environment interactions. The current study investigated these issues by examining whether quantitative traits (i.e., impulsivity) and environmental exposure factors (i.e., dietary restraint) moderate 5-HT gene/binge eating associations in a sample of young women (N = 344). Binge eating was assessed using the Minnesota Eating Behaviors Survey and the Dutch Eating Behavior Questionnaire (DEBQ). Impulsivity was assessed with the Barratt Impulsiveness Scale-Version 11. Dietary restraint was measured with a factor score derived from common restraint scales. Saliva samples were genotyped for the 5-HT2a receptor T102C polymorphism and 5-HT transporter promoter polymorphism. As expected, impulsivity and dietary restraint were associated with binge eating. Although the T allele of the 5-HT2a receptor gene and the s allele of the 5-HTT gene were associated with higher levels of impulsivity, there were no main effects of 5-HT genotypes on any binge eating measure, and interactions between genotypes, impulsivity, and dietary restraint were non-significant. In conclusion, we found no evidence to suggest that dietary restraint or impulsivity moderate associations between binge eating and these 5-HT genes. Future research should continue to explore interaction effects by examining larger samples, assessing dietary intake directly, and investigating other genes, traits, and environmental factors that may be related to binge eating and bulimia nervosa.

Keywords

binge eating; serotonin; impulsivity; dietary restraint; gene-environment interactions

Twin and adoption studies estimate the heritability of binge eating and bulimia nervosa (BN) to be between 50 and 85% (Bulik et al., 1998; Keski-Rahkonen et al., 2005; Reichborn-Kjennerud et al., 2004; Klump et al., 2000; Klump et al., submitted). Nonetheless, efforts to identify susceptibility genes have largely been unsuccessful. The serotonin (5-HT) system has

Corresponding Author: Kelly L. Klump, Department of Psychology, Michigan State University, 107B Psychology Building, East Lansing, MI 48824-1116, PH: 517-432-9861, FAX: 517-432-2476, E-mail: klump@msu.edu.

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been a primary target in these studies because 5-HT is known to influence food intake, body weight regulation, and mood (Blundell, 1992; Leibowitz & Alexander, 1998), and 5-HT functioning is disrupted in patients with BN (Kaye et al., 2005; Steiger, 2004). In addition, an association between frequency of binge eating and 5-HT dysregulation has been observed in individuals with BN (Jimerson et al., 1992; Monteleone et al., 1998).

Two potentially important 5-HT candidate genes are the serotonin-2a (5-HT2a) receptor gene and the serotonin transporter (5-HTT) gene. Pharmacological studies demonstrate decreased activity of the 5-HT2a receptor and 5-HTT in individuals with BN (Levitan et al., 1997; Steiger et al., 2000), and these 5-HT alterations may be heritable risk factors for BN (Steiger et al., 2006). However, studies examining associations between these genes, BN, and/or binge eating have been inconsistent. Most studies of the 5-HT2a receptor gene have examined a single nucleotide polymorphism (SNP) in the promoter region (-1438G/A). Six studies report no association with BN and/or binge eating (Bruce et al., 2005; Enoch et al., 1998; Fuentes et al., 2004; Nacmias et al., 1999; Ricca et al., 2002; Ziegler et al., 1999), while two studies found a higher frequency of the A allele in individuals with BN compared to controls (Ricca et al., 2002; 2004). By contrast, a significant association between BN and the G allele of the -1438G/A SNP has also been reported (Nishiguchi et al., 2001). Importantly, there is some evidence to suggest that the A allele of this polymorphism may be involved in lower caloric intake and body weight (Aubert et al., 2000; Prado-Lima et al., 2006). Thus, associations between this gene and binge eating behaviors in normal weight and overweight individuals are theoretically possible.

Findings are similarly inconsistent for the 5-HTT gene. The 5-HTT removes 5-HT from the synaptic cleft (Heils et al., 1996), and the transcriptional activity of the 5-HTT gene is modulated by a functional length variation polymorphism (i.e., 5-HTTLPR) located upstream from the transcription region. The short form “s” of the 5-HTTLPR results in an excess of 5-HT in the synaptic cleft as a result of the production of lower concentrations of 5HTT mRNA, less 5-HT binding, and less 5-HT reuptake (Lesch et al., 1996). Thus, unlike the -1438G/A SNP of the 5HT2a receptor gene (Parsons et al., 2004), this polymorphism has well known functional implications. One study found a strong association with the “s” allele of the 5-HTTLPR and BN, where one or two copies of this allele conferred a 7-fold increased risk for BN (Di Bella et al., 2000). Two subsequent studies reported no 5-HTTLPR/BN association (Lauzurica et al., 2003; Matsushita et al., 2004), and recent studies reported an increased frequency of the “l” rather than the “s” allele in women with BN and binge eating disorder (BED; a disorder characterized by regular binge eating in the absence of compensatory behaviors) (Monteleone et al., 2006a; Monteleone et al., 2006b) In addition, the “s” allele of the 5-HTTLPR has been implicated in lowered dietary intake and decreased body mass index (BMI; Fumeron et al., 2001; Moneteleone et al., 2006a). These findings fit nicely with the one study that examined this polymorphism in BED, as these patients are most often overweight (Pike et al., 2001), but they are less clear with regards to BN. Thus, further research is needed to clarify the role of the 5-HTTLPR genotype in binge eating and BN.

Clearly, identifying candidate genes for BN and binge eating has been difficult, and studies of other genes have been similarly inconclusive (see Klump & Culbert, 2007). The lack of replicated associations could be due to several limitations of past studies. For example, studies frequently have not accounted for the substantial phenotypic heterogeneity within BN phenotypes (Culbert et al., 2008; Steiger & Bruce, 2007). Although most women with BN have high levels of neuroticism (Diaz-Marsa et al., 2000), there is a distinct subgroup who are also impulsive and undercontrolled (Westen & Hardnen-Fischer, 2001; Wonderlich et al., 2005). These individuals exhibit a large number of co-morbid impulsive behaviors (e.g., substance use, sexual disinhibition) and are frequently categorized as “multi-impulsive BN” (Bell & Newns, 2002). Research suggests that this BN sub-phenotype may have different etiological

underpinnings than other BN-sub-phenotypes (e.g., high-functioning and constricted/overcontrolled sub-types; Westen & Harnden-Fischer, 2001). One set of differentiating etiologic factors may be genetic risk factors. This is particularly likely given that personality traits are roughly 50% heritable (Loehlin, 1992; Plomin, 1990; Tellegen et al., 1988). Incorporating impulsive traits into association studies of BN and other binge eating phenotypes may help reduce phenotypic and genetic heterogeneity and increase the probability of detecting significant associations.

Association studies of BN have begun to take this approach, and findings have been more consistent for both the 5-HT2a receptor and the 5-HTT gene. These studies have reported both a higher frequency of the 5-HT2a -1438G/A G allele in BN patients with borderline personality disorder (BPD; a disorder characterized by impulsivity; Nishiguchi et al., 2001) and an association between the G/G genotype and increased impulsiveness in BN patients but not controls (Bruce et al., 2005). Similarly, the s allele of the 5-HTTLPR has been linked to higher levels of impulsivity and comorbid BPD in women with BN (Steiger et al., 2005). These studies indicate that 5-HT gene variants may not be relevant for all individuals with BN, but may be specific to those with high levels of impulsivity.

In addition to not accounting for phenotypic/genetic heterogeneity, genetic studies of eating disorders have also largely not considered the influence of gene-environment interactions (Klump & Culbert, 2007). Gene-environment interactions occur when: 1) an environmental stressor is more likely to lead to negative outcomes in the presence of a “risk” genotype or allele; or 2) genetic susceptibility is activated in the presence of an environmental pathogen (Moffitt et al., 2005). Environmental “exposures” in gene-environment interactions are broadly defined and, in addition to chemical or biological exposures, can include behavioral patterns (e.g., cannabis use; Caspi et al., 2005) or life events (Ottman, 1996). As argued by Moffitt et al., (2005), the failure of association studies to identify risk genes may be due to the lack of consideration of gene-environment interaction effects.

One exposure factor that is critically important in the development of BN and binge eating is dietary restraint (i.e., the intent and/or attempt to restrict caloric intake; Jacobi et al., 2004; Polivy & Herman, 1985). Dieting and dietary restraint are strong precursors to binge eating (Polivy & Herman, 1985) and have been shown to predict the onset of binge eating in humans (Stice, 2001; Stice & Agras, 1998) and animals (Placidi et al., 2004). There is debate as to whether self-reported dietary restraint corresponds with actual reductions in food intake (Stice et al., 2004). However, regardless of whether it represents reduced intake or intent to diet, dietary restraint is a strong prospective risk factor (Jacobi et al., 2004) that can be broadly conceptualized as a behavioral “exposure” factor (Ottman, 1996) for the development of binge eating and associated disorders. Thus, dietary restraint may moderate relationships between candidate genes and BN, such that genes only increase risk for BN in the presence of high levels of dietary restraint, and high levels of restraint only increase risk for BN in the presence of genetic risk.[1]

The objective of the present study was to improve upon past research by examining both of the issues detailed above, namely the moderating influence of impulsivity and dietary restraint on relationships between 5-HT candidate genes (i.e., 5-HT2a receptor and 5-HTT genes) and binge eating Binge eating, rather than BN, was investigated in a non-clinical sample of undergraduate women for several reasons. First, we wanted to increase our sample size and

[1]Notably, relationships between 5-HT genes and dietary restraint may also be due to gene-environment correlations (i.e., the tendency for individuals to experience environments that are correlated with their genetic predisposition; Plomin et al., 1990). Nonetheless, examining gene-environment interactions is a logical first step in unraveling gene-environment effects, particularly since with few exceptions (see Burt, 2008), methods for detecting gene-environment correlations in association studies are less advanced than those for gene-environment interactions.

thus statistical power for genetic analyses. Second, we wanted to ensure that variability in dietary restraint was sufficient to examine its moderating effects. Indeed, since nearly all women with BN have high levels of dietary restraint, it would be very difficult to examine interactions between dietary restraint and candidate genes in a clinical sample. Third, binge eating is a core diagnostic criterion for BN, and it shows similar heritability as BN (Bulik et al., 1998). Given past research (Bruce et al., 2005; Steiger et al., 2005), we hypothesized that gene/binge eating associations would be stronger in women who are impulsive. Furthermore, these associations would also be stronger in women who report high levels of dietary restraint, as engaging in dietary restraint may enhance genetic susceptibility towards binge eating.

Methods

Participants

Participants included 344 young adult women (Age: 18-30, M = 19.04, SD = 1.44). Participants were recruited from a volunteer research pool at a large Midwestern university in the U.S.A. Participants received course credit for their participation. Research was approved by the institutional review board and carried out in accordance with the declaration of Helsinki. Only females were included in the current study, as binge eating is more common in women than men (APA, 2000). Also, only Caucasian females were included as preliminary analyses revealed differences in allele frequencies of the 5-HTTLPR genotype according to ethnicity ($\chi^2 = 24.78$, $p < .02$). Participants initially came to the laboratory in group sessions to provide informed consent and saliva samples for genotyping. Within 72 hours of the lab session, participants completed all other measures on-line.

Measures

Binge Eating—Given past concerns about assessing binge eating using self-report measures (Fairburn & Beglin, 1994; von Ranson et al., 2005), we used a multi-method approach to assess the construct. Specifically, we measured binge eating using both the Binge Eating subscale from the Minnesota Eating Behavior Survey (MEBS; Klump et al., 2000; von Ranson et al., 2005)[2] as well as the Emotional Eating subscale from the Dutch Eating Behavior Questionnaire (DEBQ: van Strien et al., 1986). The MEBS is a 30-item true/false self-report measure and the Binge Eating subscale is comprised of 7 items. Support for the reliability and validity of this subscale has been previously reported for young adults (Klump et al., 2000; von Ranson et al., 2005). Internal consistency for this subscale is adequate in the current sample (see Table 1) and previous samples (von Ranson et al., 2005). Finally, discriminant validity of the MEBS Binge Eating subscale is well established, as women with BN score higher on this scale than unaffected control women (von Ranson et al., 2005).

The 13-item DEBQ Emotional Eating subscale assesses the frequency of eating in response to clearly labeled (e.g., irritated, angry) and diffuse emotions (e.g., bored, let down) over the past week using a 5-point scale (never to very often). Eating in response to negative emotions is thought to be a core feature of overeating and binge eating (McManus & Waller, 1995), and women who binge eat and/or have BN score significantly higher on this subscale than obese and non-obese individuals who do not binge eat (Deaver et al., 2003; Wardle, 1987). The subscale has excellent internal consistency in our sample (see Table 1) and others (van Strien et al., 1986), as well as good factorial validity (van Strien et al., 1986).

[2]The Minnesota Eating Behavior Survey (MEBS; previously known as the Minnesota Eating Disorder Inventory (M-EDI)) was adapted and reproduced by special permission of Psychological Assessment Resources, Inc., 16204 North Florida Avenue, Lutz, Florida 33549, from the Eating Disorder Inventory (collectively, EDI and EDI-2) by Garner, Olmstead, Polivy, Copyright 1983 by Psychological Assessment Resources, Inc. Further reproduction of the MEBS is prohibited without prior permission from Psychological Assessment Resources, Inc.

Dietary Restraint—The Restraint Scales from both the Eating Disorder Examination-Questionnaire (EDE-Q) and the DEBQ were used to broadly assess the construct of dietary restraint. The EDE-Q is a 36-item self-report measure. It has been adapted from the Eating Disorder Examination (EDE; Fairburn & Cooper, 1993) which is a semi-structured interview that assesses the presence and severity of eating disorder symptoms. The Restraint subscale of the EDE-Q is comprised of 5 items, rated on a 7-point scale, and inquires about dietary restraint (i.e., tendency to restrict food intake and avoid meals/high calorie foods as well as attempts to obey rigid rules for dieting) over the past 28 days. The Restraint subscale has demonstrated good reliability and validity, including excellent internal consistency in our sample (α = .83) and others (α = .85). In addition, there is high 2-week test-retest reliability (r = .81; Luce & Crowther, 1999). Finally, good concurrent validity between the EDEQ and the EDE Restraint measures has been demonstrated within a sample of eating disorder patients (r = .81; Fairburn & Beglin, 1994).

The 10-item DEBQ Restrained Eating Scale (DRES; van Strien et al., 1986) inquires about restraint (i.e., eating and intending to eat less than he/she would like to eat) during the past week using the same 5-point rating scale described above for the DEBQ Emotional Eating scale. The DRES has demonstrated excellent internal consistency in this (α = .95) and other samples (α = .95; van Strien et al., 1986), as well as high test-retest reliability over a 10-month period (r = .71; Stice et al., 2001).

Impulsivity—The Barratt Impulsiveness Scale, Version 11 (BIS-11; Patton et al., 1995) was used to assess levels of impulsivity. The BIS-11 is a self-report measure that consists of 30 items rated on a 4-point scale from rarely/never to almost always/always. The scale is comprised of three higher-order factor-based dimensions: Attentional Impulsivity (i.e., tendency to have rapid shifts in attention and become impatient with complexity), Motor Impulsivity (i.e., tendency to act in an immediate, unplanned way), and Non-Planning Impulsivity (i.e., absence of considering long-term consequences). The BIS-11 Total Score was used in the current study as it is also the most frequently used measure of impulsivity in eating disorder studies (e.g., Bruce et al., 2005; Steiger et al., 2005).

The BIS-11 has demonstrated excellent reliability and validity (Patton et al., 1995). Support for its internal consistency in individuals with eating disorders, undergraduate students, substance abuse patients, general psychiatric patients, and prison inmates is evidenced by alphas >79 (Patton et al., 1995; Steiger et al., 2000). In our sample, BIS-11 internal consistency was slightly lower (see Table 1). In addition, discriminant validity is well established, as general psychiatric and substance-abuse patients score significantly higher on the BIS-11 as compared to undergraduate students, and prison inmates score the highest of all of these groups (Patton et al., 1995).

DNA—Participants were asked to provide 2 ml of saliva for genotyping using the Oragene DNA Self-Collection kit (disc format; see www.dnagenotek.com). Participants rinsed their mouths with water 10 minutes prior to spitting directly into the container until it was full. Samples were then stored at room temperature until analysis, following manufacturer guidelines.

DNA was extracted from saliva samples and amplified by polymerase chain reaction (PCR) using a Perkin Elmer 9700 PCR machine (Applied Biosystems (ABI), Foster City, CA). Primers for the 5-HT2a T102C SNP were 5′-TCTGCTACAAGTTCTGGCTT-3′ (forward) and 5′-CTGCAGCTTTTTCTCTAGGG-3′ (reverse). Primers for the 5-HTTLPR were 5′ GGCGTTGCCGCTCTGAATGC-3′ (forward) and 5′-GAGGGACTGAGCTGGACAACCAC-3′ (reverse). The final solution contained 10 mM of deoxyribonucleotide triphosphates (dNTPs), 6 pmol/ul of each primer, 25 mM MgCl2, 1 ×

mTaqmaster PCR enhancer, and 0.5 μ1 DNA Taq Polymerase (Eppendorf MasterTaq, Brinkman, Westbury, New York). PCR regime included pre-heating at 95 C for 10 minutes, followed by 50 cycles of denaturation at 92 C (15 seconds), annealing at 60 C (60 seconds), and concluding with a final hold at 4 C until stopped by user. For the 5-HT2a T102C polymorphism, T and C alleles were identified by a SNP analysis run on an ABI 7900HT sequence detection system (ABI, Foster City, CA). For the 5-HTTLPR, a fragment analysis assay was run on an ABI 3130 Genetic Analyzer (ABI, Foster City, CA) and a mm1000 marker from Bioventures was used to size the fragments (484-528 base pairs).

Notably, we investigated the T102C polymorphism rather than the -1438G/A polymorphism of the 5-HT2a receptor gene; however, these polymorphisms are in complete linkage disequilibrium (i.e., the two SNP's have not been separated by recombination; Spurlock et al., 1998). Thus, the C allele of the T102C SNP almost always occurs together on the chromosome with the G allele of the -1438G/A SNP, and the same is true for the T102C T allele and the -1438G/A A allele.

Statistical Analyses

Factor Analysis—Both of our self-report measures of dietary restraint include questions that inquire about intent to diet (e.g., “I try to eat less”) and engagement in behaviors aimed at reducing caloric intake (e.g., “I refuse food offered”). Because of the debate surrounding self-report measures of dieting (Stice et al., 2004), we sought to determine whether intent to diet and the actual behaviors of dietary restriction existed as different restraint constructs in our data and whether type of dietary restraint differentially moderates gene/binge eating associations. Therefore, items from the EDE-Q and DEBQ restraint scales were subjected to a principal-axis exploratory factor analysis. Item scores were standardized prior to this analysis, as DEBQ and EDE-Q items were rated on slightly different scales (5- vs. 7-point scales). Kaiser's criterion (Eigenvalues > 1) in combination with Scree plot analysis was used for factor retention (Osborne & Costello, 2005).

Genetic Analyses—Pearson correlations were used to examine initial relationships between genotype/allele variables, dietary restraint, impulsivity, and binge eating. Hierarchical regression models using a moderated regression framework (Aiken & West, 1991) were then used to examine whether impulsivity and dietary restraint moderate relationships between candidate genes and binge eating Notably, our use of the term “moderator” does not map on to the use by Kraemer et al. (2001), but is more closely related to moderation as discussed in the gene-environment interaction literature (Moffit et al., 2005). The gene-environment literature emphasizes the diathesis-stress model, in which the “diathesis” (baseline characteristic) is the gene, and the “stress” is the environmental exposure/moderator that triggers the diathesis and leads to the outcome. Previous gene-environment interaction studies have used both moderated linear and logistic regression to examine environmental moderation of the relationship between genes and psychiatric symptoms/disorders (e.g., Laucht et al., 2007).

In the regression models, we examined the influence of the following variables on binge eating levels: 1) 5-HT2a T102C genotype/allele variables and 5-HTTLPR genotype/allele variables; 2) dietary restraint and impulsivity; 3) the two-way interactions among genotype and dietary restraint or genotype and impulsivity, and 4) the three-way interaction among genotype, impulsivity, and dietary restraint. The equation for these analyses is as follows:

$$\text{Binge Eating} = b0 + b1\,(5\text{-HT2a/5-HTT genotype}) + b2(\text{dietary restraint/impulsivity/}) + b3(5\text{-HT2a} \times \text{dietary restraint/5-HTT} \times \text{dietary restraint/5-HT2a} \times \text{impulsivity/5-HTT} \times \text{impulsivity}) + b4(5\text{-HT2a} \times \text{impulsivity} \times \text{dietary restraint/5-HTT} \times \text{impulsivity} \times \text{dietary restraint})$$

In this equation, b0 represents the intercept, b1 represents the coefficient for the candidate gene variables, b2 represents the coefficient for the moderator variables, b3 is the coefficient for the 2-way interaction effects, and b4 is the coefficient for the three-way interaction effects. Notably, the candidate gene variables (i.e., 5-HT2a receptor and 5-HTT alleles and genotypes) were effect coded prior to analysis for genotype and the presence vs. absence of the "risk" allele (see Table 2 for a listing of the effect codes). Impulsivity, MEBS Binge Eating, and DEBQ Emotional Eating were standardized through z score transformations prior to analysis. (Note: dietary restraint factor scores were standardized prior to factor analysis). Two-way and 3-way interactions terms were computed by multiplying the independent variables to form interaction terms.

In the two-way interaction models, the main effects of genotype (or allele), and impulsivity or dietary restraint were entered in the first step. The second step tested the interaction between genotype and impulsivity or genotype and dietary restraint, while controlling for the main effects of these variables. In the three-way interaction model, the main effects of genotype, impulsivity, and dietary restraint were entered concurrently in the first step. The second step examined the two-way interactions between both genotype and impulsivity and genotype and dietary restraint. Finally, the third step examined the three-way interaction between genotype, impulsivity, and dietary restraint, while partialing out the main effects and 2-way interactions.

Results

Factor Analysis

Principal axis exploratory factor analysis was used to derive a composite dietary restraint factor from the 10 standardized DEBQ restraint scale items and the 5 standardized EDE-Q restraint scale items. Two Eigenvalues were greater than one (8.76, 1.01), thus a two-factor solution was initially extracted. However, analysis of the scree plot suggested a clear break after the first factor solution. Therefore, we retained a one-factor solution that accounted for 55.7% of the variance in the 15 restraint items. All items had loadings greater than .40 on the first factor and, with one exception, loaded lower than .40 on the second factor. The EDEQ item 4 had a loading of .46 on factor 2, but it was retained due to its content similarity to factor 1 and its high loading on the primary factor (see Table 3 for factor loadings). Items were summed to derive a composite dietary restraint factor that would be used in subsequent analyses.

Descriptive Statistics

Means, standard deviations, and ranges are presented in Table 1. Based on ranges and standard deviations, there appeared to be adequate variability in binge eating, impulsivity, and dietary restraint factor scores to assess moderating effects. Means and standard deviations were comparable to those of previous studies that used these measures with community samples (Klump et al., 2000;Bruce et al., 2005,van Strien et al., 1986)

Table 2 presents genotype and allele frequencies for both the 5-HT2a receptor T102C genotype and the 5-HTTLPR genotype. Tests for Hardy-Weinberg Equilibrium revealed that the 5-HT2a receptor genotype conformed to Hardy-Weinberg Equilibrium in our sample (χ^2 (1) =1.08, p = .30), while the 5-HTTLPR genotype did not (χ^2 (1) = 5.52, p = .02). Nonetheless, the effect size for comparisons of observed and expected 5-HTTLPR genotype frequencies was very

small (φ = .13), suggesting that deviations from Hardy-Weinberg Equilibrium were modest at best.

Genetic Analyses

Table 4 displays the Pearson correlations for genotype/allele variables, impulsivity, dietary restraint, and binge eating. Our two measures of binge eating were significantly correlated (r = .69), although they only shared 48% of their variance. Thus, examining both the MEBS Binge Eating and DEBQ Emotional Eating scales allowed us to ensure that findings were robust and consistent across binge eating measures and constructs.

In terms of correlations between binge eating and its predictors, both dietary restraint and impulsivity were significantly associated with our measures of binge eating. Notably, however, these correlations were moderate in magnitude (r = .31-.38), indicating that binge eating, impulsivity, and dietary restraint are independent constructs that may show differential interactive associations. However, neither the 5-HT2a receptor nor the 5-HTT genotypes/alleles were associated with MEBS Binge Eating or DEBQ Emotional Eating, suggesting that there are not strong main effects of these genotypes on binge eating. By contrast, both the 5-HT2a genotype/alleles and the 5-HTT genotype/alleles were significantly correlated with impulsivity. Specifically, the presence of the T allele of the 5-HT2a receptor T102C polymorphism and the s allele of the 5-HTTLPR was associated with greater levels of impulsivity. These findings corroborate previous research associating these genes with impulsivity in community samples (e.g., Nomura et al., 2006; Paaver et al., 2007; Sakado et al., 2003).

Table 5 presents results from hierarchical linear regression models examining dietary restraint, impulsivity, genotypes, and interactions among these variables as predictors of MEBS Binge Eating and DEBQ Emotional Eating. Notably, findings did not differ when examining genotypes versus alleles and thus, only analyses of alleles are presented.

When considering the MEBS Binge Eating subscale, there were significant main effects for both dietary restraint (p's < .001) and impulsivity (p's < .03) in most all models. Notably, however, regression coefficients were not significant for the main effects of 5-HT2a or 5-HTTLPR risk alleles. In addition, the 2-way interactions between genotype and dietary restraint, genotype and impulsivity, as well as the 3-way interactions of genotype by dietary restraint by impulsivity interactions, were not significant for MEBS Binge Eating. Importantly, we examined whether controlling for BMI in analyses would result in any significant interactive associations. This was done given associations between BMI, dietary restraint, and binge eating (Fitzgibbon et al., 1998; Stewart, 2002) as well as previous research linking both 5-HT risk genes to body weight regulation (Aubert et al., 2000; Fumeron et al., 2001). However, results remained unchanged when BMI was entered in the first step of the regression models (data not shown), suggesting BMI does not play a role in interactive associations.

Similar results were obtained for the DEBQ Emotional Eating subscale. Regression coefficients for dietary restraint (p's < .001) and impulsivity (p's < .01) were uniformly significant. However, the main effects of risk alleles, as well as 2-way and 3-way interaction effects were not significant. Again, accounting for the effects of BMI did not change the pattern of results (data now shown). Thus, for both MEBS Binge Eating and DEBQ Emotional Eating, interaction effects did not predict a significant proportion of variance over and above the main effects of these variables.

Discussion

The current study examined whether impulsivity and dietary restraint are significant moderators in the relationship between 5-HT genes and binge eating. We hypothesized that the failure to identify replicable candidate genes for BN (Culbert et al., 2008; Klump & Culbert, 2007) may be partially due to the lack of consideration of quantitative traits (i.e., impulsivity) and exposure factors (i.e., dietary restraint) in molecular genetics studies. Findings suggest that, although the 5-HT2a receptor and 5-HTT genes may increase risk for impulsivity, neither of the 5-HT genes examined are significantly associated with binge eating. Furthermore, these genes do not appear to interact with impulsivity or dietary restraint to increase risk for binge eating. There are a number of possible explanations for our results.

It may be that different types of impulsivity and/or BN symptoms show interactive relationships. For example, different types of impulsivity (e.g., the BIS-11 subscales of Attentional, Motor, and Non-planning Impulsiveness) may more strongly moderate gene/binge eating relationships than the BIS-11 Total Score, as these subscales have been found to be differentially associated with eating disorder syndromes and symptoms (Rosval et al., 2006). In addition, other symptoms of BN (e.g., weight preoccupation, body dissatisfaction) may be more likely to show significant interactive associations. Post-hoc analyses were conducted to examine these possibilities. However, we found that the BIS-11 subscales (see above) did not significantly moderate gene/binge eating relationships, and interaction effects were not significant for the MEBS Total Score, Weight Preoccupation, and Body Dissatisfaction subscales (data not shown). Nevertheless, we cannot rule out the possibility that other aspects of impulsivity (e.g., borderline traits; (Nishiguchi et al., 2001); urgency (Fischer et al., 2003)) and other BN symptoms are involved in moderating relationships.

In addition, other types of dieting/dietary restraint may be involved in gene-environment interactions. Although our measures appeared to ask about both intent to diet and dieting behavior, our factor analysis extracted one homogeneous dietary restraint factor. Given previous research (Stice et al., 2004; 2007), this factor is hypothesized to be akin to an intent to diet rather than objective dietary restraint. However, it may be *actual caloric restriction*, rather than this intent to diet, that interacts with genotype to increase risk for binge eating. Genetically vulnerable individuals (e.g., those with the “s” allele of the 5-HTTLPR) may be more susceptible to the 5-HT dysregulation that results from dieting (Steiger, 2004), and this may not be captured when using self-report measures of dietary restraint. Thus, future work should attempt to assess caloric intake directly to examine gene-diet interactions.

Another possible explanation is that other candidate genes, quantitative traits, and/or environmental factors that we did not examine are stronger moderators of genetic risk for binge eating. For example, BDNF is an important regulator of food intake (Lebrun et al., 2006), and some studies implicate BDNF genes in the genetic diathesis of BN and the severity of bulimic behaviors (Ribases et al., 2005; Monteleone et al., 2006b). Given BDNF's role in appetite and weight regulation (Hashimoto et al., 2005), individuals with risk variants of this gene may be more susceptible to the effects of dietary restraint. Thus, BDNF genes may be promising candidates for gene-dietary restraint interactions. Dopaminergic genes may also be involved in interactive relationships that increase risk for binge eating and/or BN. There is some evidence to implicate dopamine genes in risk for BN (Shinohara et al., 2004), and these genes have also been associated with novelty seeking/impulsive personality traits (e.g., Benjamin et al., 1996; Schinka et al., 2002). Thus, dopaminergic genes may interact with impulsivity levels to increase risk for binge eating and other BN behaviors

There may also be other quantitative traits that may moderate gene/binge eating relationships. For instance, some women with BN are high on harm avoidance and obsessive-compulsive

traits (Wonderlich et al., 2005), and these traits have been associated with 5-HT candidate genes in individuals with BN (e.g., 5-HTT, 5-HT2C; Monteleone et al., 2006, Ribases et al., 2008). Finally, other environmental risk factors for binge eating and BN may be important to examine for their interactions with candidate genes. These include (but are not limited to) environmental risk factors such as weight-based teasing (Neumark-Sztainer et al., 2002), parental criticism (Fairburn et al., 1999), and participation in weight-focused sports (e.g., ballet dancing; Sundgot-Borgen & Torstveit, 2004). These environmental risk factors may activate/enhance genetic predisposition towards binge eating.

A final possible explanation for our results is that there may be interactive relationships among the variables, but limitations of our study prohibited their detection. Although our sample is the largest to examine associations between these 5-HT genes and bulimic phenotypes to date, it is still relatively small by molecular genetics standards (Hattersley & McCarthy, 2005). Power calculations indicate that we had adequate power (> 80%) to detect interactions of moderate effect (f^2 = .15); however, our sample may not have been large enough to detect interactions of small effect (f^2 = .05-.1). Similar to the main effects of single genes on complex psychiatric disorders (Cardon & Bell, 2001), interactions between genes and quantitative traits/environmental risk factors may represent effects of small magnitude. Therefore, an inability to detect significant interactions may have been due, in part, to a lack of power.

In addition, our use of self-report measures of binge eating may have affected results. We chose to examine continuous measures of binge eating to enhance statistical power, and we included two separate binge eating measures (i.e., MEBS Binge Eating subscale and the DEBQ Emotional Eating subscale) to increase confidence in our pattern of results. However, self-report measures, as opposed to interviews, are thought to overestimate the prevalence of eating disorder symptoms and syndromes, particularly binge eating (Fairburn & Beglin, 1994). Thus, future studies would benefit from looking at binge eating using interview methods in addition to self-report questionnaires Finally, BN is associated with a host of cognitive and behavioral symptoms in addition to binge eating. For this reason, we cannot be sure that our results generalize to patients with BN. Future research is needed to examine moderation of genetic influences in clinical samples.

In conclusion, we did not find evidence to support the hypothesis that impulsivity and dietary restraint moderate relationships between 5-HT candidate genes and binge eating. We did, however, replicate previous findings (see Nomura et al., 2006; Sakado et al., 2003) associating the 5-HT2a receptor and 5-HTT genes with impulsivity in non-clinical populations. Our study used a novel design to examine the moderating effects of impulsivity on 5-HT gene/BN phenotype relationships, and it was the first to investigate the presence of gene-dietary restraint interactions. Future work should further examine these hypotheses in larger samples that include direct assessments of caloric restriction and several different measures of impulsivity. In addition, we hope that our methodology and approach can be used by others to continue examining gene x environment interactions in the development of eating disorders.

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Table 1
Descriptive Statistics for Binge Eating Scales and Moderator Variables

Variables	Number of Items	Mean (SD)	Range	Alpha
MEBS Binge Eating	7	2.30 (1.92)	0-7	.73
DEBQ Emotional Eating	13	2.39 (.84)	1-5	.92
Dietary Restraint Factor	15	0.17 (11.2)	-19.37-30.33	.95
Impulsivity	30	62.90 (10.39)	39-97	.75

Note. MEBS = Minnesota Eating Behaviors Survey. DEBQ = Dutch Eating Behavior Questionnaire. Descriptive statistics for the dietary restraint factor score reflect the fact that individual dietary restraint items were standardized prior to summation.

Table 2

Effect Codes and Allele and Genotype Distributions for the 5-HT2a Receptor T102C and 5-HTTLPR Genes

Gene	Effect Code	Frequency, n (%)
5-HT2a Gene:		
Alleles		
T	-1	290 (42.3)
C	1	398 (58.0)
Genotypes		
T/T	-1, -1	66 (19.2)
T/C	-1, 1	158 (46.1)
C/C	1, 1	119 (34.7)
5-HTTLPR Gene:		
Alleles		
s	1	289 (45.3)
l	-1	349 (54.7)
Genotypes		
s/s	1, 1	55 (17.2)
s/l	1, -1	179 (56.1)
l/l	-1, -1	85 (26.6)

Note. 5-HT2a = serotonin-2A receptor gene; 5-HTTLPR= serotonin transporter length promoter polymorphism. 1 = presence of the risk allele; -1 = absence of the risk allele. Effect codes were used to create interaction terms for moderated regression analyses

Table 3
Dietary Restraint Item Factor Loadings

Dietary Restraint Items	Factor Loadings
EDEQ-Restraint Items	
1. Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight?	.80
2. Have you gone for long periods of time (8 hours of more) without eating anything in order to influence your shape or weight?	.42
3. Have you tried to avoid eating any foods which you like in order to influence your shape or weight?	.70
4. Have you tried to follow definite rules regarding your eating in order to influence your shape or weight, ex. a calorie limit, a set amount of food, or rules about what or when you should eat?	.73
5. Have you wanted your stomach to be empty?	.55
DEBQ-Restraint Items	
4. Eat less after putting on weight	.75
7. Refuse food offered	.80
11. Try to eat less than you would like	.79
14. Watch what you eat	.69
17. Eat slimming foods	.79
19. Eat less after eating too much	.78
22. Eat deliberately less	.89
26. Try not to eat between meals	.81
29. Try not to eat in the evenings	.77
31. Eat while allowing for weight	.80

Note. EDEQ = Eating Disorder Examination-Questionnaire; DEBQ = Dutch Eating Behavior Questionnaire. Item numbers correspond to those of the original scales.

Table 4

Pearson Correlations among Independent and Dependent Variables

Variables	MEBS Binge Eating	DEBQ Emotional Eating	Dietary Restraint	Impulsivity	5-HT2a C vs. no C	5-HT2a genotype	5-HTTLPR s vs. no s	5-HTTLPR genotype
Dependent Variables:								
MEBS Binge Eating	1.00	--	-	-	-	-	-	-
DEBQ Emotional Eating	**.69*****	1.00						
Moderator Variables:								
Dietary Restraint Factor	**.38*****	**.31*****	1.00	-	-	-	-	-
Impulsivity	**.18*****	**.17*****	**.15***	1.00	-	-	-	-
Genotype/Allele Variables:								
5-HT2a C vs. no C	-.06	-.08	-.04	**-.12***	1.00	-	-	-
5-HT2a genotype	-.09	-.10	-.07	**-.12***	**.79*****	1.00	-	-
5-HTTLPR s vs. no s	.10	.03	.02	**.12***	-.05	-.07	1.00	-
5-HTTLPR genotype	.08	.04	.01	**.13***	-.01	-.05	**.83*****	1.00

Note. MEBS= Minnesota Eating Behaviors Survey; DEBQ= Dutch Eating Behavior Questionnaire; 5-HT= serotonin; 5-HT2a T102C= serotonin-2A receptor gene T102C polymorphism; 5-HTTLPR= serotonin transporter length promoter polymorphism.

* $p < .05$,

*** $p < .001$

Table 5

Hierarchical Regression Models Examining Main Effects and Interactions by Allele Status

	MEBS Binge Eating			DEBQ Emotional Eating		
Models	***b***	***SE***	***p***	***b***	***SE***	***p***
Dietary Restraint:						
5-HT2a C allele vs. no C allele						
Dietary Restraint	.35	.01	**<.001**	.25	.07	**<.001**
5-HT2a C vs. no C	-.06	.07	.37	-.09	.07	.20
Dietary Restraint × 5-HT2a	.01	.01	.39	.01	.01	.19
5-HTT s vs. no s allele						
Dietary Restraint	.38	.01	**<.001**	.32	.06	**<.001**
5-HTT s vs. no s	.09	.06	.10	.03	.06	.68
Dietary Restraint × 5-HTT	0	.01	.47	0	.01	.87
Impulsivity:						
5-HT2a C vs. no C allele						
Impulsivity	.21	.07	**.001**	.20	.07	**.003**
5-HT2a C vs. no C	-.03	.07	.60	-.07	.07	.32
Impulsivity × 5-HT2a	-.05	.07	.44	-.05	.07	.43
5-HTT s vs. no s allele						
Impulsivity	.14	.06	**.03**	.16	.07	**.01**
5-HTT s vs. no s	.08	.06	.17	0	.07	.99
Impulsivity × 5-HTT	.07	.06	.26	.02	.07	.75
Dietary Restraint and Impulsivity:						
5-HT2a C vs. no C allele						
Dietary Restraint	.33	.01	**<.001**	.23	.07	**.001**
Impulsivity	.19	.06	**.004**	.21	.07	**.001**
5-HT2a C vs. no C	-.02	.07	.74	-.04	.07	.53
Dietary Restraint × 5-HT2a	0	.01	.30	.01	.01	.13
Impulsivity × 5-HT2a	-.08	.07	.21	-.09	.07	.17
Dietary Restraint × Impulsivity × 5-HT2a	0	0	.64	0	0	.49
5-HTT s vs. no s allele						

	MEBS Binge Eating			DEBQ Emotional Eating		
Models	***b***	***SE***	***p***	***b***	***SE***	***p***
Dietary Restraint	.35	.06	<**.001**	.30	.06	<**.001**
Impulsivity	.10	.06	.10	.17	.07	**.01**
5-HTT s vs. no s	.08	.06	.17	0	.06	.95
Dietary Restraint × 5-HTT	0	.01	.54	0	0	.81
Impulsivity × 5-HTT	.05	.06	.38	0	.07	.89
Dietary Restraint × Impulsivity × 5-HTT	0	.01	.99	0	0	.49

Note. MEBS= Minnesota Eating Behaviors Survey; DEBQ= Dutch Eating Behavior Questionnaire; 5-HT= serotonin; 5-HT2a T102C= serotonin-2A receptor gene T102C polymorphism; 5-HTTLPR= serotonin transporter length promoter polymorphism