Relevance of the 5-HTTLPR Polymorphism and Childhood Abuse to Increased Psychiatric Comorbidity in Women With Bulimia-Spectrum Disorders

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Objective: Individuals with bulimia nervosa have been shown to display heterogeneous profiles of comorbid psychiatric disturbance, possibly due to varying degrees of genetic and environmental vulnerability. Using information about comorbid psychiatric disturbances, we developed an empirically based classification of individuals with bulimia-spectrum disorders, and then explored whether or not the resulting phenotypes corresponded to variations in the serotonin transporter promoter polymorphism (5-HTTLPR) and exposure to childhood abuse.

Method: Eighty-nine women aged 17 to 49 years with DSM-IV bulimia-spectrum disorders completed questionnaires assessing eating and general psychopathologic symptoms, participated in interviews assessing Axis I disorders and childhood abuse, and provided blood samples for genotyping. Data on lifetime Axis I disorders were analyzed using latent class analysis, and resulting classes were compared on eating and psychopathologic symptoms, 5-HTTLPR genotype, and childhood abuse. The study was conducted from June 2002 to October 2006.

Results: The analysis yielded a model with 2 classes: a first class labeled *low comorbidity* (N = 59, 66%), characterized by a high likelihood of major depressive disorder, and another class labeled *high comorbidity* (N = 30, 34%), characterized by a high likelihood of major depressive disorder, anxiety disorder, and substance-use disorders. The high-comorbidity class displayed significantly higher dieting preoccupations and conduct problems, and showed a greater likelihood of carrying the 5-HTTLPR S allele and of childhood abuse than did the low-comorbidity class.

Conclusion: The present results are consistent with previous findings identifying a subgroup of individuals with bulimia characterized by high psychiatric comorbidity and suggest that the 5-HTTLPR polymorphism and childhood trauma may both be pertinent to explaining the presence of greater psychiatric comorbidity in bulimia-spectrum disorders.

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Bulimia nervosa has been linked to heterogeneous profiles of comorbid psychiatric disturbance. For instance, cluster-analytic studies of personality traits converge on the idea that the bulimic population includes at least 2 empirically distinguishable subgroups—one with relatively low comorbid personality pathology and another more "disturbed" group, displaying traits such as affective instability, sensation seeking, self-destructiveness, and conduct problems.[1–3] In a similar vein, using a latent class analysis based on comorbid Axis I disorders in a sample of individuals with bulimia nervosa, Duncan et al.[4] found a best-fitting 2-class solution implying a *low-comorbidity* class (characterized by major depressive disorder only) and a *high-comorbidity* class (characterized by a high likelihood of major depressive disorder, anxiety disorder, alcohol and drug dependence, antisocial personality disorder, and concomitant impulsive behaviors).

Such findings suggest that there exist at least 2 distinct bulimic phenotypes—one relatively intact, and another more disturbed subgroup. In the present study, we sought to replicate such explorations in a sample of individuals with bulimia-spectrum disorders and to examine potential associations with environmental and constitutional factors that are thought to be linked to the etiology of bulimia nervosa, with the expectation that a more disturbed variant might implicate stronger doses of both environmental and constitutional vulnerabilities.

Childhood Abuse in Bulimia-Spectrum Disorders

One factor that has been thought to be causally linked to bulimic syndromes is childhood abuse. Data show that about 30% of adults with bulimia-spectrum disorders report a history of childhood sexual abuse, and 30% or more report a history of childhood physical abuse.[5–7] It is noteworthy that although such rates are elevated compared to control individuals (without a psychiatric disorder), they are comparable to those found in other psychiatric patient groups,[8,9] suggesting that childhood abuse may not be a specific risk factor for bulimia nervosa, but rather, a factor that is generally linked to risk of psychopathology. Moreover, within various samples of individuals with psychiatric disorders, studies show that a history of childhood abuse coincides systematically with more complex comorbidity patterns.[10,11] Consistent with this notion, in individuals with bulimia-spectrum disorders, childhood abuse has been associated with increased self-destructiveness,[12] submissiveness,[5] and borderline personality disorder—a syndrome characterized by marked disturbances of self-regulation, mood-regulation, and impulse-regulation.[13] Taken together, research suggests that childhood abuse is associated with vulnerability to psychiatric disorders in adulthood and that within any given disorder, including bulimia nervosa, abuse may contribute to a pattern of increased comorbid psychopathology.

Serotonin Function in Bulimia-Spectrum Disorders

Just as childhood abuse has been implicated as an environmental factor that may be etiologic for bulimia nervosa, the serotonin (5-hydroxytryptamine; 5-HT) system has been implicated as a neurobiological factor. Studies have consistently documented altered 5-HT system functioning in bulimia nervosa. For example, individuals with active bulimia nervosa have been shown to display reduced platelet binding of 5-HT uptake inhibitors,[12,14,15] reduced hypothalamic and thalamic 5-HT transporter availability,[16] and diminished neuroendocrine responses to 5-HT precursors and agonists.[12,17] Moreover, individuals recovered from bulimia nervosa and unaffected first-degree relatives of individuals with bulimia nervosa have been found to display similar serotonergic abnormalities.[18–21] In line with the preceding, one study links the low function (S) allele of the serotonin transporter promoter polymorphism (5-HTTLPR)—thought to be associated with reduced transcription of 5-HT transporter protein[22]—to bulimia nervosa.[23] However, other studies have found incongruent findings, with 1 reporting an increased prevalence of the high function (L) allele[24] and 2 others reporting absence of association between 5-HTTLPR and bulimia nervosa.[25,26]

One possible explanation for such inconsistencies might be that 5-HTTLPR variations are associated, not with risk of bulimia nervosa per se, but with increased risk of comorbid psychiatric disturbance. In line with this hypothesis, within individuals with bulimia-spectrum disorders, the 5-HTTLPR S allele has been observed to be a stronger predictor of severity of general psychopathologic symptoms (e.g., affective instability, insecure attachment, and borderline personality disorder) than it is of bulimia-specific symptoms (e.g., binge eating or purging).[27] Similar findings have shown associations of 5-HTTLPR S allele with impulsivity[28] and dissocial behavior[29] in individuals with bulimic syndromes. Together, findings suggest that 5-HTTLPR may modulate risk, in bulimia nervosa, of more pronounced comorbid psychopathology.

The Present Study

The current study had 2 main aims: (1) to explore the extent to which we could corroborate the existence of distinct patterns of comorbid psychiatric disturbance in bulimia-spectrum disorders, and (2) to examine possible associations between psychiatric-comorbidity patterns and putative vulnerability factors, including exposure to childhood abuse and genetic (i.e., 5-HTTLPR) variations. To accomplish these aims, we applied latent class analysis (LCA) to lifetime DSM-IV Axis I disorders. LCA is a statistical clustering technique that offers several advantages over traditional cluster-analytic techniques, including probability-based classification estimated directly from the model. On the basis of previous findings, we expected the LCA to produce at least 2 classes; one characterized by relatively low psychiatric comorbidity and another characterized by a higher incidence of psychiatric comorbidity. Relevant research suggesting that comorbidity in bulimia nervosa may be more pertinent to explaining general psychopathologic symptoms than eating-specific ones[30] led us to hypothesize that a class with more Axis I comorbidity would display increased general psychopathology but no elevations on eating-specific symptoms. In addition, in light of previous literature showing that both a history of childhood abuse and 5-HTTLPR variations may be linked to more pronounced comorbidity in bulimia nervosa, we expected to find that a class with a higher likelihood of comorbid psychiatric disorders would also display a higher incidence of childhood abuse and greater genetic vulnerability.

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METHOD

Participants

Written informed consent was obtained from all participants in this institutional ethics board–approved study, which was conducted from June 2002 to October 2006. Participants included 89 women aged 17 to 49 years and with a body mass index (BMI) between 17.5 and 34.0 kg/m^2. These individuals were recruited from the active case register of a specialized Eating Disorders Program. Among the participants, 69 (77.5%) met DSM-IV criteria for bulimia nervosa–purging subtype, 4 (4.5%) met criteria for bulimia nervosa–nonpurging subtype, and 16 (18.0%) met criteria for a bulimia-spectrum eating disorder not otherwise specified (binge eating or purging at less than the requisite twice weekly). Minimum binge frequency was 1 episode per month, over the past 3 months. We felt that these diagnostic variations represented treatment-seeking women with bulimia nervosa, and note reports suggesting that threshold and sub-threshold variants of bulimia nervosa are equivalent on many clinical dimensions.[31] Forty-one participants (46.1%) were on psychoactive medications at the time of testing. Limiting recruitment to unmedicated patients was impractical (and undesirable on grounds of representativeness). Statistical procedures were applied to examine whether LCA-based classes differed in frequency of psychiatric medication use.

Measures

Eating pathology. The Eating Disorders Examination (EDE),[32] a 62-item semi-structured clinical interview, was utilized to assess the presence or absence of a DSM-IV bulimia-spectrum eating disorder diagnosis and eating disorder symptoms such as binge eating, vomiting, and purging frequencies. The EDE has good interrater reliability[32] and good discriminant validity in distinguishing between women with and without eating disorders.[33] To complement our assessment, we computed BMI (kg/m^2) and added the Eating Attitudes Test-26 (EAT-26),[34] a 26-item self-report questionnaire utilized to assess symptoms and concerns characteristic of eating disorders. The EAT-26 yields a global score and 3 subscales (dieting, bulimia and food preoccupation, and oral control). The EAT-26 has been shown to have high internal consistency (0.90), and a cut-off score of 20 reliably identifies clinical-range eating disturbances.[34]

General psychopathology. Diagnosis of lifetime comorbid DSM-IV Axis I disorders was accomplished using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[35] The SCID-I is an "industry standard" interview for assessing current and lifetime history of Axis I disorders. Interrater reliability estimates calculated for a pseudo–randomly selected sample of SCID-I interviews (N = 23) revealed the following interrater reliability estimates: major depressive disorder ($\kappa = 0.80$), anxiety disorder (excluding posttraumatic stress disorder [PTSD]) ($\kappa = 1.00$), alcohol use disorder (including abuse and dependence) ($\kappa = 0.83$), and drug use disorder (including abuse and dependence) ($\kappa = 0.86$). In the majority of cases in the current study (N = 81), PTSD was assessed using the Clinician-Administered PTSD Scale (CAPS).[36] (The other 8 subjects were assessed using the SCID-I.) The CAPS is a standard criterion measure of PTSD diagnostic status and symptom severity, exhibiting excellent convergent and discriminant validity and excellent reliability.[37] The Dimensional Assessment of Personality Pathology-Basic Questionnaire (DAPP-BQ),[38,39] a 290-item self-report measure consisting of 18 scales, was utilized to assess general psychopathologic symptoms. We selected specific subscales that are frequently ascribed to eating disordered populations. The resulting battery measured affective instability, stimulus seeking, conduct problems, compulsivity, anxiousness, social avoidance, insecure attachment, and restricted expression. Estimates of coefficient α for the DAPP-BQ range from .83 to .94, in both the general population and clinical samples.[40]

Childhood abuse. Childhood abuse was assessed using the Childhood Trauma Interview (CTI),[41] a roughly 30-minute structured interview on experiences of abuse prior to age 18 years. We used CTI severity indices (severity ≥ 3) to isolate experiences of unambiguous physical and sexual maltreatment occurring at or before age 18 (in conformity with the standard CTI protocol). Interrater reliability estimates were calculated for our index of abuse in a pseudo–randomly selected sample of CTI interviews (N = 24), revealing $\kappa = 0.81$ for physical abuse and $\kappa = 0.91$ for sexual abuse. CTI indices have been shown to converge with other measures of abuse, and construct validity is supported by logical associations with syndromes having theoretical links to trauma exposure.[41]

5-HTTLPR variations. The 5-HTTLPR polymorphism has traditionally been thought to be biallelic, with long (L) and short (S) variants respectively coding for high or low 5-HT transporter activity.[22] However, recent findings suggest the existence of a low-frequency L-allele variant, L_G (an L allele with A→G single-nucleotide polymorphism in its sequence), whose functioning may be comparable to that of the low-function, S allele.[42,43] Such data imply that 5-HTTLPR may be triallelic, with S and L_G alleles regarded as "low-function" variants and L_A regarded as a "high-function" allele. In other words, a traditional biallelic classification may potentially underestimate the presence of low-function variants and overestimate the presence of high-function variants by classifying L_G as an L (or high-function) allele. Therefore, in the present study we opted to examine 5-HTTLPR using both the traditional biallelic and novel triallelic models.

Genotyping. DNA samples, obtained from whole blood, were amplified by polymerase chain reaction (PCR) in a total volume of 20 μL, which contained 100 ng of genomic DNA, 200 μmol/L of deoxyribonucleoside triphosphates, 10 pmol each of the forward and reverse primer, 1 U of Taq DNA polymerase (Qiagen, Alameda, Calif.), 1 × PCR buffer, and 1 × Q solution (Qiagen). The forward primer (5′-ATG CCA GCA CCT AAC CCC TAA TGT-3′) and reverse primer (5′-GG ACC GCA AGG TGG GCG GGA-3′) were used to amplify a region encompassing 5-HTTLPR; long and short alleles were then resolved on a 2% agarose gel. The PCR protocol involved preheating the samples at 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C (30 s), annealing at 64°C (30 s), and extension at 72°C (45 s), as well as a final hold of 5 minutes at 72°C. The L_G and L_A alleles were subsequently studied by enzymatic digestion of 7 μL of the above mentioned PCR product using 5 U of MspI and incubating at 37°C for a minimum of 3 hours. L_G and L_A alleles were then resolved on a 2% agarose gel.

Statistical Analyses

Latent class analysis. The latent structure of psychiatric comorbidity in individuals with bulimia-spectrum disorders was examined by applying LCA to lifetime comorbid DSM-IV Axis I diagnoses (dichotomized as present or absent), using Latent Gold software.[44] Disorders included in the LCA were major depressive disorder, anxiety disorder (including social phobia, agoraphobia, panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, and PTSD), alcohol abuse/dependence, and substance abuse/dependence (including dependence or abuse of marijuana, stimulants, sedatives, cocaine, opiates, and hallucinogens). Latent class analysis assumes that a set of latent classes exists that accounts for the pattern of observed covariation among a set of indicators measured at the categorical level. Information about the underlying class structure is conveyed through (a) latent class probabilities, which may be thought of as class prevalence estimates, and (b) conditional probabilities, which reflect the probability that an item is endorsed by an individual, given membership in a specific class. Initial estimation began with a 1-class model. Latent classes were then added progressively, and resultant models compared using percentage classification error and information criteria—i.e., Bayesian information criterion (BIC) and Akaike's information criterion (AIC)—that take into account both statistical goodness of fit and the number of parameters estimated to achieve a particular degree of fit.

Comparison of LCA-based classes. Respondents were assigned to classes, using the modal probability, on the basis of posterior probabilities derived from the latent class analysis. Resulting classes were compared on age, BMI, and prevalence of psychoactive medication use. Additionally, classes were compared on eating disorder–related variables, such as eating disorder diagnosis (threshold versus subthreshold bulimia nervosa) and eating symptoms as measured by the EDE (binge eating days, binge eating episodes, vomiting episodes, and purging episodes per month in the past 3 months) and the EAT-26 (dieting, bulimia and food preoccupation, oral control, and total score). Further comparisons were made to contrast classes on selected psychological variables from the DAPP-BQ (affective instability, stimulus seeking, compulsivity, anxiousness, conduct problems, social avoidance, insecure attachment, and restricted expression), presence or absence of childhood abuse (including sexual, physical, and combined sexual or physical abuse before age 18 years), and 5-HTTLPR genotype and allele frequencies. In light of recent findings suggesting that 5-HTTLPR may be triallelic, 5-HTTLPR was examined using both the biallelic (S/S, S/L, L/L) and triallelic (S/S, S/L_G, L_G/L_G, L_G/L_A, S/L_A, L_A/L_A) models. Since the L_G allele has been shown to function in a way that is comparable to the low-function S allele, L_G and S alleles were grouped together under the label *Low* (to indicate that they are low-function variants) and L_A was labeled *High* (to indicate that it is a high-function variant), resulting in the triallelic classification: Low/Low (S/S, S/L_G and L_G/L_G), Low/High (L_G/L_A and S/L_A), and High/High (L_A/L_A).

RESULTS

Latent Class Analysis

We examined 1-class through 5-class LCA solutions reflecting loading of Axis I disorders in potential subgroups of bulimia nervosa. One-class through 3-class solutions displayed similar AIC and BIC statistics (1-class model, AIC = 451.63 and BIC = 461.59; 2-class model, AIC = 446.64 and BIC = 469.03; 3-class model, AIC = 450.46 and BIC = 485.30) and provided a relatively good fit to the data. On the basis of previously published results favoring a 2-class solution[4] and the information criteria for the 2-class model (AIC = 446.64, BIC = 469.03, and classification error = 0.14), we selected a 2-class solution as having the best fit to the data and likely to be most informative. Table 1 displays the conditional probabilities for each class as well as the overall latent class prevalence estimates. The majority of subjects fell into class 1 (N = 59, 66.3%), which featured a high conditional probability for major depressive disorder, a moderate conditional probability for anxiety disorder, and low conditional probabilities for drug and alcohol abuse/dependence. We labeled class 1 the low-comorbidity class. A smaller proportion of subjects fell into class 2 (N = 30, 33.7%), which displayed substantially more psychiatric comorbidity, with high conditional probabilities for all disorders. We labeled this class the high-comorbidity class.

Table 1. Latent Class Analysis: Conditional Probabilities[a] and Class Prevalence Estimates for Lifetime Axis I Comorbidity in Women With Bulimia-Spectrum Disorders

Variable	Class 1 Conditional Probability (SE)	Class 2 Conditional Probability (SE)
Major depressive disorder	0.65 (0.09)	0.67 (0.10)
Anxiety disorder	0.29 (0.10)	0.66 (0.11)
Alcohol abuse/dependence	0.09 (0.10)	0.52 (0.11)
Drug abuse/dependence	0.01 (0.03)	0.57 (0.18)
Class prevalence	0.56 (0.14)	0.44 (0.14)

[a]Conditional probability = probability that an item is endorsed by an individual, given membership in a specific class.

Comparison of LCA-Based Classes

Analyses using t tests revealed no significant differences between classes on age or BMI. Similarly, χ^2 analyses revealed no significant differences as to proportion of cases in the 2 classes using psychiatric medication or proportion of cases in the 2 classes with subthreshold (as opposed to threshold) bulimia nervosa variants. Box-and-whisker plots revealed univariate outliers on EDE variables that code for binge eating, vomiting, and purging episodes. Outliers were transformed to the sample mean plus 2 standard deviations. The EAT-26 oral control subscale and binge eating, vomiting, and purging episodes from the EDE were (as is common) found to be nonnormally distributed and were logarithmically transformed. Analyses using t tests revealed no significant differences between classes in binge eating days or binge eating, vomiting, or purging episodes; however, a significant difference was observed on EAT-26 total score with the high-comorbidity class scoring higher than the low-comorbidity class (Table 2). When EAT-26 subscales were analyzed, it was the dieting subscale that significantly differentiated the 2 classes. No significant group differences were found on the bulimia and food preoccupation and oral control subscales (Table 2). On the DAPP-BQ, t tests revealed a significant difference between classes on conduct problems with the high-comorbidity class, once again, scoring significantly higher than the low-comorbidity class. Significant differences were not obtained between classes on other selected personality trait subscales from the DAPP-BQ (Table 2).

Treating 5-HTTLPR in a biallelic fashion, frequencies of S/S, S/L, and L/L genotypes, respectively occurring in 22 (24.7%), 39 (43.8%), and 28 (31.5%) of our participants, were in conformity with Hardy-Weinberg equilibrium ($\chi^2 = 1.27$, df = 1, p = .260). With a triallelic model, we observed S/S, S/L_G, S/L_A, L_G/L_A, L_G/L_G, and L_A/L_A genotypes to occur, respectively, in 22 (24.7%), 5 (5.6%), 34 (38.2%), 6 (6.7%), 2 (2.2%), and 20 (22.5%) of our participants. Frequencies of Low/Low, Low/High, and High/High genotypes occurred, respectively, in 29 (32.6%), 40 (44.9%), and 20 (22.5%) of our participants. Using the biallelic classification, a χ^2 test revealed a trend-level difference in prevalence of genotypes between the high-comorbidity and low-comorbidity classes, with the high-comorbidity class displaying a higher frequency of S/S and S/L genotypes and a lower frequency of the L/L genotype (Table 3). When S/S and S/L genotypes were grouped together to form a dichotomous S-allele versus no S-allele classification, a significant difference between the 2 classes was revealed, with the high-comorbidity class displaying a significantly greater frequency of S allele than the low-comorbidity class (Table 3). Although results pointed in the same direction, no significant genetic or allele effects were obtained in parallel analyses based on a triallelic model (Table 3).

To ascertain whether or not the rate of S-allele carriers in our sample differed from that observed in the general population, we performed nonparametric χ^2 tests comparing frequency of S allele in both high-comorbidity and low-comorbidity classes to the frequency of S allele in primarily Caucasian, nonpsychiatric samples from previous studies (66% S allele vs. 34% no S allele).[22,45,46] We found that the low-comorbidity group was comparable to population norms ($\chi^2 = 0.65$, df = 1, p = .419) but that the high-comorbidity group was significantly different from the general population, displaying an increased frequency of S allele ($\chi^2 = 4.02$, df = 1, p = .045).

When examining history of childhood abuse in the 2 classes, χ^2 tests revealed no significant difference in the prevalence of sexual abuse; however, a trend-level difference was found in the prevalence of physical abuse, with the high-comorbidity class having experienced a higher prevalence of physical abuse in childhood than the low-comorbidity class (Table 4). When childhood sexual and physical abuse were grouped together to form 1 variable (presence of physical or sexual abuse before age 18 years), a significant difference between the 2 classes was revealed, with the high-comorbidity class displaying a significantly greater incidence of childhood abuse than the low-comorbidity class (Table 4).

Since 5-HTTLPR S allele and childhood abuse were both more prevalent in the high-comorbidity class, we performed a hierarchical logistic regression analysis aimed at isolating independent and interaction effects of these variables. In this analysis, we entered genetic information at step 1 (G = presence or absence of biallelic 5-HTTLPR S allele), childhood abuse information at step 2 (A = presence or absence of physical or sexual abuse before age 18 years), and the interaction between the 2 at step 3 (G × A). No significant G × A interaction effect was found; therefore, a subsequent analysis tested for main effects alone. Results showed the S allele to be a significant predictor of class membership (OR = 3.19, 95% CI = 1.07 to 9.53, p = .037) at step 1. When abuse was added at step 2, the predictive power of the S allele was reduced (OR = 2.98, 95% CI = 0.97 to 9.16, p = .057) and

Table 2. Eating and General Psychopathologic Symptoms Among Women With Bulimia-Spectrum Disorders (N = 89) by LCA-Based Classes

Measure	Class 1, Low-Comorbidity (N = 59), Mean (SD)	Class 2, High-Comorbidity (N = 30), Mean (SD)	Statistic		
			t Test	df	p Value
EDE					
Binge days/month	16.43 (7.94)	14.86 (7.79)	0.89	87	.376
Binge episodes/month[a]	28.37 (23.93)	21.64 (18.68)	1.35	87	.182
Vomit episodes/month[a]	30.20 (37.19)	27.85 (33.40)	0.30	87	.764
Purge episodes/month[a]	34.56 (37.84)	32.56 (33.91)	0.25	87	.802
EAT-26[b]					
Total score	32.96 (12.87)	40.87 (11.41)	–2.81	86	.006
Dieting	1.48 (0.63)	1.89 (0.54)	–2.99	86	.004
Bulimia and food preoccupation	1.80 (0.72)	1.98 (0.61)	–1.15	86	.254
Oral control[a]	0.42 (0.49)	0.63 (0.62)	–1.74	86	.086
DAPP-BQ[b]					
Affective instability	3.36 (0.80)	3.66 (0.85)	–1.57	86	.121
Stimulus seeking	2.79 (0.94)	2.98 (0.98)	–0.87	86	.390
Conduct problems	1.69 (0.59)	2.11 (0.66)	–3.02	86	.003
Compulsivity	3.32 (0.67)	3.41 (0.73)	–0.59	86	.557
Anxiousness	3.59 (0.88)	3.79 (0.98)	–0.92	86	.364
Social avoidance	3.25 (0.80)	3.13 (0.97)	0.58	86	.562
Insecure attachment	2.72 (0.91)	2.91 (1.12)	–0.87	86	.389
Restricted expression	3.16 (0.80)	2.91 (0.76)	1.37	86	.173

[a]Values reported for EDE binge, vomit, and purge episodes and the EAT-26 oral control subscale are actual values. Due to deviations from normality, logarithmic transformations were performed, and resulting analyses (not reported here) revealed similar results.
[b]For EAT-26 and DAPP-BQ, N = 29 for class 2 (total N = 88).
Abbreviations: DAPP-BQ = Dimensional Assessment of Personality Pathology-Basic Questionnaire, EAT-26 = 26-item Eating Attitudes Test, EDE = Eating Disorders Examination, LCA = latent class analysis.

Table 3. 5-HTTLPR (biallelic and triallelic) Genotype and Allele Frequencies Among Women With Bulimia-Spectrum Disorders (N = 89) by LCA-Based Classes

Variable	Class 1, Low-Comorbidity (N = 59), N (%)	Class 2, High-Comorbidity (N = 30), N (%)	Statistic		
			χ^2	df	p Value
5-HTTLPR Biallelic genotype			4.59	2	.101
L/L genotype	23 (39.0)	5 (16.7)			
S/L genotype	23 (39.0)	16 (53.3)			
S/S genotype	13 (22.0)	9 (30.0)			
5-HTTLPR Biallelic S allele			4.59	1	.032
No S allele (L/L)	23 (39.0)	5 (16.7)			
S allele (S/S or S/L)	36 (61.0)	25 (83.3)			
5-HTTLPR Triallelic genotype[a]			3.31	2	.191
High/high genotype (L_A/L_A)	16 (27.1)	4 (13.3)			
High/low genotype (S/L_A or L_G/L_A)	27 (45.8)	13 (43.3)			
Low/low genotype (S/S, S/L_G, or L_G/L_G)	16 (27.1)	13 (43.3)			
5-HTTLPR Triallelic low-function allele			2.17	1	.141
No low-function allele (L_A/L_A)	16 (27.1)	4 (13.3)			
Low-function allele (S/L_A, L_G/L_A, S/S, S/L_G or L_G/L_G)	43 (72.9)	26 (86.7)			

[a]For the 5-HTTLPR triallelic classification, L_G and S alleles were grouped together under the label *Low* (to indicate that they are low-function variants) and L_A was labeled *High* (to indicate that it is a high-function variant), resulting in the following classification: Low/Low (S/S, S/L_G and L_G/L_G), High/Low (S/L_A and L_G/L_A), and High/High (L_A/L_A).
Abbreviations: 5-HTTLPR = serotonin transporter promoter polymorphism, LCA = latent class analysis.

Table 4. History of Childhood Physical or Sexual Abuse Among Women With Bulimia-Spectrum Disorders (N = 89) by LCA-Based Classes

Variable	Class 1, Low-Comorbidity (N = 59), N (%)	Class 2, High-Comorbidity (N = 30), N (%)	Statistic		
			χ^2	df	p Value
History of sexual abuse before age 18 y	16 (27.1)	13 (43.3)	2.38	1	.123
History of physical abuse before age 18 y	25 (42.4)	19 (63.3)	3.50	1	.062
History of sexual or physical abuse before age 18 y	31 (52.5)	24 (80.0)	6.35	1	.012

Abbreviation: LCA = latent class analysis.

abuse emerged as a significant predictor of class membership (OR = 3.42, 95% CI = 1.20 to 9.77, p = .022). The risk of membership in the high-comorbidity class thus appeared to be associated with independent effects of genetic (S-allele) susceptibility and prior childhood abuse, with childhood abuse being a stronger predictor of class membership.

DISCUSSION

To examine the latent structure of psychiatric comorbidity in a sample of individuals with bulimic syndromes, we applied LCA to findings on comorbid DSM-IV Axis I disorders. Using statistical information criteria and evidence from previous studies,[4] a good-fitting solution revealed 2 classes; 1 larger class displayed a high probability of comorbid major depressive disorder only (and was hence labeled low-comorbidity), and a second smaller class had high probabilities for various disorders, including major depressive disorder, anxiety disorder, alcohol abuse/dependence, and drug abuse/dependence (labeled high-comorbidity). The 2-class structure of psychiatric comorbidity found in the present study is strikingly similar to that found by Duncan et al.[4] in a latent class analysis of comorbid psychiatric disorders in individuals with bulimia nervosa. Like ours, results revealed a 2-class solution with 1 class characterized by major depressive disorder only and a second class characterized by a high prevalence not only of major depressive disorder, but also of comorbid anxiety disorder, alcohol and drug dependence, and antisocial personality disorder. Taken together, such findings support the existence of at least 2 empirically distinguishable subgroups within the bulimic population—one relatively intact and another more psychiatrically disturbed.

Comparisons on eating symptoms revealed no differences between the high-comorbidity and low-comorbidity groups with respect to binge eating and purging behaviors. However, the high-comorbidity class was found to have a significantly higher EAT-26 total score than the low-comorbidity class, with a specific elevation on the dieting subscale. Although previous research suggests that comorbidity in bulimia nervosa may be more strongly associated with variations in psychopathologic symptoms than with variations in eating-specific symptoms, some findings suggest that individuals with bulimia who display increased psychiatric comorbidity (e.g., personality disorders and/or major depression) also tend to display more maladaptive attitudes around dieting and drive for thinness, without displaying increased binge eating and purging behaviors.[47–49] A similar tendency appears to be indicated by our findings. A possible implication is that drive to diet may be elevated in individuals with more severe associated psychopathology, whereas other eating symptoms (such as binge and purge frequencies) may be more generally associated with having bulimia nervosa and less associated with comorbid psychopathologic symptoms.

The high-comorbidity class in the current study was also found to have significantly more conduct problems than the low-comorbidity class. Such findings are in line with those of Duncan et al.,[4] who found a high-comorbidity class to display higher likelihood of antisocial personality disorder—a disorder in which conduct problems are pathognomonic. In addition, in both our study and that of Duncan et al.,[4] the high-comorbidity class contained nearly every case of substance use disorder. Fittingly, previous research shows that individuals with bulimia and comorbid substance-use disorder display elevated rates of comorbid Axis I psychiatric disorders and conduct problems.[50–52] Together, available findings support the existence of a relatively small subgroup (about one third) of individuals with bulimia, marked by a high likelihood of psychiatric comorbidity (especially substance use disorder) and increased conduct problems.

Aside from replicating previous observations, the present study introduces the novel element that individuals with bulimia-spectrum disorders and high comorbidity, when compared with individuals belonging to a more intact group, display more-marked susceptibilities, both environmental and genetic:

(1) With respect to environmental risks, the high-comorbidity class was found to display a greater prevalence of childhood abuse than the low-comorbidity class, a finding that is compatible with previous results showing formerly abused individuals with bulimia to display increased psychopathology in adulthood.[5,12,13] Such findings also corroborate results obtained in nonbulimic psychiatric populations (e.g., individuals with depression, anxiety, alcohol abuse) linking a history of childhood abuse to more complex patterns of comorbid psychopathology.[10,11] Such results converge upon the notion that within any given disorder—including bulimia nervosa—the presence of abuse in childhood contributes to a pattern of increased psychiatric comorbidity in adulthood.

(2) The high-comorbidity class was also found to display greater genetic vulnerability, in the form of greater likelihood of carrying the 5-HTTLPR S allele, relative to the low-comorbidity class. This finding is in line with previous research associating the 5-HTTLPR S allele with increased comorbid psychopathology and, in particular, psychopathology of a dissocial nature (e.g., impulsivity, dissocial behavior) in individuals with bulimia nervosa.[27–29] In addition, such findings are in line with literature in the field of substance abuse showing that type 2 or *dissocial* alcoholics (characterized by impulsivity, conduct problems, and deceitfulness) are more likely to have the S allele of 5-HTTLPR than type 1 alcoholics (a more intact subgroup).[53] Together, such findings imply that the S allele of the 5-HTTLPR may be pertinent to

explaining increased psychiatric comorbidity, in particular dissocial phenomena, in psychiatric disorders—such as bulimia—in which such a component is present.

To the preceding, we add the following caveat: Since our sample is of modest size, any genotype-related effects we obtain must be regarded as preliminary and in need of replication. In addition, 5-HTTLPR S allele effects obtained are small, suggesting that if they are indeed repeatable, they must be understood to act within a much larger set of genetic and/or constitutional vulnerability factors that shape phenotypes. Finally, absence of a control group in the present study renders it impossible to ascertain whether or not our high-comorbidity group has a greater likelihood of carrying the S allele than would a group of subjects without an eating disorder from the same population. We do note, however, that our tests comparing S-allele rates in high-comorbidity and low-comorbidity samples to those expected in a normal reference population suggest that the high-comorbidity group might be characterized by a higher-than-expected rate of S allele carriers. Although significant 5-HTTLPR genetic effects were not obtained in parallel analyses based on a triallelic model, we assume that the disparate results may be an artifact of limited statistical power related to our sample size.

Why might women with bulimic symptoms and high psychiatric comorbidity show the combination of increased rates of childhood abuse and 5-HTTLPR S allele? We and other investigators have previously linked psychopathologic manifestations in the bulimic population to underlying 5-HT disturbances.[54] Furthermore, we have documented tendencies for previously abused bulimic women to display more pronounced serotonergic anomalies than do those without a history of abuse.[12] Similarly, previous research has shown associations of 5-HTTLPR S allele with altered 5-HT functioning.[22] On the basis of the preceding, we specifically postulate that variants of bulimia nervosa characterized by marked psychiatric comorbidity may often implicate additive, 5-HT–mediated effects of developmental stressors and latent genetic propensities toward psychopathology. Alternatively, it remains possible that we observe a convergence among 5-HTTLPR S allele, childhood abuse, and elevated psychopathology because the S allele actually increases risk of abuse—through such possible correlates as heightened psychopathology in potentially abusive, genetically disposed parents, or heightened conduct problems or risk-taking in genetically disposed children.

CONCLUSIONS

The results of the current study support the existence of heterogeneous comorbid symptom profiles in bulimia nervosa, revealing one class of individuals with relatively low psychiatric comorbidity and a second class with greater psychiatric comorbidity and concomitant dissocial phenomena. Such findings corroborate those of previous studies suggesting that about one third of individuals with bulimia nervosa fall into a subgroup that is marked by increased lifetime psychiatric comorbidity (in particular, comorbid substance use disorder) and heightened dissocial behavior.[1–4] In addition, the current study shows that within such a subgroup there is an increased prevalence of 5-HTTLPR S allele and a higher incidence of childhood sexual or physical abuse, suggesting that genes and early environment may both be pertinent to explaining increased psychopathology in individuals with bulimia nervosa.

In identifying a more disturbed subgroup of individuals with bulimia, the present study may isolate factors of clinical importance. For this subgroup, interventions focused on eating symptoms may not be sufficient. For example, it has been shown that increased psychiatric comorbidity is associated with longer treatments and poorer outcomes in individuals with bulimia.[55] In addition, a history of abuse—found to be more prevalent in the high-comorbidity subgroup in the present study—has been shown to be related to poorer treatment response and greater dropout rates in the treatment of eating disorders.[56] Furthermore, the 5-HTTLPR S allele—also found to be more prevalent in the high-comorbidity class—has been linked to poor response to pharmacologic treatment in eating disorder patients.[57] Such research findings present the question, Is the high-comorbidity subgroup identified in the present study the same group that does not get better with treatment? And, if so, are there ways of improving therapy (e.g., therapeutic adjuncts aimed at specific comorbid symptoms, posttraumatic therapy techniques, pharmacologic support) so that individuals that fall into such a subgroup have more successful outcomes? Longitudinal outcome studies designed to test such questions could lead to more successful treatments for bulimia nervosa.

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