



Interaction of the BcII glucocorticoid receptor polymorphism and childhood abuse in bulimia nervosa (BN): Relationship to BN and to associated trait manifestations

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ABSTRACT

We recently documented a gene–environment interaction suggesting that individuals with Bulimia Nervosa (BN) differed from normal eaters as to the combined presence of the low-function allele of the glucocorticoid receptor polymorphism, BcII, and childhood abuse. The present study examined the extent to which any such interaction effect may have been attributable to behavioral impulsivity, sensation seeking, affective instability or depression. We had 174 bulimic and 130 nonbulimic women provide blood for genetic assays, and measured psychopathological traits and childhood abuse using structured interviews and self-report questionnaires. As expected, we observed a significant BcII \times abuse interaction indicating genetic and environmental susceptibilities to co-occur significantly more often in bulimic than in nonbulimic individuals. The BcII \times abuse interaction was attenuated when levels of depression were accounted for, but was surprisingly unaffected by controls for motoric impulsivity, sensation seeking or affective instability. Our findings suggest that stress-induced alterations in glucocorticoid sensitivity contribute to BN and depressive disturbances—without being associated with the behavioral/affective dysregulation seen in many BN sufferers. We discuss theoretical and clinical implications of these observations.

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Bulimia Nervosa (BN), a severe eating disorder characterized by recurrent binge-eating and compensations (through such means as vomiting, fasting or laxative abuse), affects from 1% to 3% of adolescent to young-adult females (American Psychiatric Association, 2000). Most contemporary etiological theories attribute BN to the activation, by environmental pressures, of hereditary susceptibilities (e.g., Bulik, 2005; Steiger and Bruce, 2007; Treasure et al., 2010). One such causal path appears to implicate appetitive dysregulation, following the effects of prolonged dieting, in genetically susceptible individuals. Consistent with this notion, several studies report that individuals with certain genetic liabilities (e.g., hereditary risk of ED development, or propensity toward reduced serotonin reuptake), when they also report high levels of antecedent dieting, evince increased bulimic behavior (Akermann

et al., 2011; Racine et al., 2011). Explorations into a second causal path of interest have been guided by the assumption that BN depends upon the amplification, by environmental pressures, of hereditary psychopathological traits (e.g., poor response inhibition, sensation seeking, negative emotionality) that convey risk: In non-eating-disordered contexts, the expression of such traits as depression (Caspi et al., 2003, 2010; Kaufman et al., 2004), behavioral disinhibition (Paaver et al., 2008) and impulsivity (Wagner et al., 2009) has been shown to sometimes involve stress-induced activation of genetic susceptibilities. In parallel, our group has shown that bulimic women carrying low-function alleles of the serotonin transporter promoter polymorphism, 5HTTLPR, when they report exposure to childhood sexual or physical abuse, also evince more pronounced manifestations of such traits as sensation seeking, affective instability (Steiger et al., 2007) and dissocial behavior (Steiger et al., 2008). A related gene–environment interaction effect has been shown to increase risk for AN, in carriers of low-function 5HTTLPR alleles reporting a history of problematic family interactions (Karwautz et al., 2011). Importantly, the studies

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cited report gene \times stress interactions associated with elevations on a targeted symptom (e.g., sensation seeking) or syndrome (e.g., Anorexia Nervosa), but not main genetic effects. In other words, observed expressions of genetic effects appear to occur when there has been an environmental trigger.

Following upon the preceding line of thinking, we recently turned our attention to effects associated with a polymorphism that, in theory, might be quite a direct mediator of stress-induced effects—the *BclI* restriction fragment length polymorphism. Interest in this polymorphism is motivated, in part, by a body of evidence associating BN with altered hypothalamic-pituitary-adrenal (HPA) axis (stress-system) function (Brambilla and Monteleone, 2003; Fichter et al., 1990; Neudek et al., 2001; Steiger et al., 2001). The most widely studied of polymorphisms associated with glucocorticoid receptor (GR) expression, the *BclI* restriction fragment length polymorphism is a C/G single nucleotide polymorphism in intron B, 646 nucleotides downstream of exon 2. *BclI* is believed to mediate inhibitory feedback within the HPA axis and, in this fashion, to contribute to variability in stress reactivity (Wüst et al., 2004; Kumsta et al., 2007; van Rossum et al., 2003). Consistent with an established role of HPA axis function in depression (Belmaker and Agam, 2008), *BclI* has been observed to influence risk of major depression (Spijker and van Rossum, 2009; Zobel et al., 2008). More importantly, in interaction with adverse childhood experiences, *BclI* has been reported to predict increased expressions of biomarkers for, and actual vulnerability to, adult depression (Bet et al., 2009). Such findings led us to predict a BN-linked influence of traumatic experiences in individuals whose genetic propensities (linked to *BclI*) code for lesser modulatory feedback within the HPA axis. Consistent with our hypothesis, compared to 98 comparison women, we found a sample of 129 bulimic women to be significantly more likely to be carriers of *BclI* low-function (C) alleles, to report a history of childhood abuse and, more importantly, to be positive for both factors (Steiger et al., 2011a).

The effect just-described suggests that traumatic stress can be etiological for BN in individuals disposed to lower GR modulation. However, it does not establish the extent to which a *BclI* \times abuse interaction might have a BN-specific effect, or a nonspecific effect associated with increased expressions of such bulimia-related traits as behavioral disinhibition, sensation seeking, affective instability, or depression. To address this question, we aimed to evaluate, in an expanded pool of bulimic and normal eaters, the extent to which any *BclI* \times Abuse interaction effect obtained might be attributable to such psychopathological trait expressions as behavioral impulsivity, affective instability, novelty seeking or depression—that could indirectly, but nonspecifically, contribute to risk of BN. To achieve these ends, we had bulimic and non-eating-disordered comparison women provide blood samples for assays of the *BclI* polymorphism, and complete structured interviews and self-report questionnaires assessing eating symptoms, psychiatric symptoms, and childhood abuse. Should the gene by environment interaction effect of interest here be BN-specific, the effect should reliably predict membership in bulimic or normal-eater groups despite controls for potentially mediating effects of the psychopathological traits. In contrast, if the gene \times environment effect were generalized, or enacted through increased expressions of the psychopathological traits in question, prediction of the bulimic/nonbulimic distinction should be attenuated by inclusion of trait variables in predictive models.

1. Methods

1.1. Participants

This institutional ethics-board approved study was conducted with informed consent. Eating-disordered women were recruited

through a specialized Eating Disorder (ED) program for adults, and were 174 consenting women with a DSM-IV-TR (American Psychiatric Association, 2000) diagnosis of BN. Mean chronicity of illness was 9.15 (± 6.60) years. We also tested 130 normal-eater women, drawn from an age group comparable to that of our ED sample, and recruited using public and university/college-based announcements to attract comparable proportions of student and non-student participants to those found in our ED sample. To be eligible for the normal-eater group, participants had to be free of clinical ED symptoms according to the EDE, of an ED history according to semistructured interview, and to have BMI above 17.5. Normal-eater participants were between the ages of 17 and 49 years (mean = 25.95 \pm 6.36 for bulimic subjects and 24.79 \pm 6.34 for controls). Body Mass Index (BMI: kg/m²) fell between 17.61 and 35.94 for bulimic participants (mean = 22.56 \pm 3.79) and 18.02 and 33.02 for control subjects (mean = 22.10 \pm 2.69). Clinical and control groups did not differ on either dimension. We note that 74.1% of the bulimic cases and 75.4% of the nonbulimic ones reported here figured in the sample described in an earlier report (Steiger et al., 2011b).

Within the eating-disordered group (information available on 150 of 174), 2 (1.3%) had a primary-level education, 41 (27.3%) secondary-level education, 58 (38.7%) college-level, and 49 (32.6%) university level. Within the control group (information available on 128 of 130), 29 (22.7%) had a secondary-level education, 44 (34.4%) college, and 55 (42.9%) university level. Data on household income were available for 138 of the bulimic participants and for 121 of the normal-eater controls. Among the bulimic women, 23 (16.7%) reported a household income under \$10,000, 17 (12.3%) an income between \$10,000 and \$19,999, 13 (9.4%) between \$20,000 and \$29,999, 11 (8.0%) between \$30,000 and \$39,999, 19 (13.8%) between \$40,000 and \$49,999, and 27 (19.6%) income above \$50,000. Among the control women, 28 (23.1%) reported a household income less than \$10,000, 15 (12.4%) an income between \$10,000 and \$19,999, 12 (9.9%) an income between \$20,000 and \$29,999, 9 (7.4%) between \$30,000 and \$39,999, 11 (9.1%) between \$40,000 and \$49,999, and 24 (19.8%) an income above \$50,000. Confirming the impression that clinical and control cases were very similar on these social-standing indices, chi-squared tests detected no significant differences on either variable. Limiting recruitment to unmedicated individuals was impractical (and undesirable on grounds of representativeness), and we therefore included 81 bulimic women (46.6% of the sample) and 2 (1.5%) normal-eater controls who were using a psychoactive medication when tested.

The Quebec population from which this sample was drawn is skewed toward individuals of Caucasian, Western-European descent. Consequently, our bulimic sample included mainly Caucasians ($n = 168$, or 97.1% of the sample), with rare Blacks ($n = 3$, or 1.7% of the sample) and Asians ($n = 1$, or .6% of the sample). Data on race were available for only 67 (51.5%) of the normal-eater participants. However, these data indicated racial composition of our control group— 54 (80.6%) Caucasians, 6 (9.0%) Blacks and 7 (10.4%) Asians—to be similar to that of our bulimic group. Ancillary data-analytic steps (described in the Results section, to follow) provided reassurances that ethnicity-based variations did not confound results.

1.2. Measures

1.2.1. Interviews

ED diagnoses and symptoms were assessed using the Eating Disorders Examination (EDE: Fairburn and Cooper, 1993), a semi-structured interview assessing the presence and severity of core ED symptoms. The current “Gold Standard” for ED diagnosis, the EDE has established reliability and validity (Fairburn and Cooper, 1993).

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