

# Association of Serotonin and Cortisol Indices With Childhood Abuse in Bulimia Nervosa

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**Background:** Bulimia nervosa (BN) is reported to co-occur with childhood abuse and alterations in central serotonin (5-hydroxytryptamine [5-HT]) and cortisol mechanisms. However, findings also link childhood abuse to anomalous 5-HT and cortisol function, and this motivated us to explore relationships between childhood abuse and neurobiological variations in BN.

**Methods:** Thirty-five bulimic and 25 nonbulimic women were assessed for childhood physical and sexual abuse, eating symptoms, and comorbid psychopathological tendencies. These women provided blood samples for measurement of platelet hydrogen-3–paroxetine binding and serial prolactin and cortisol responses following oral administration of the partial 5-HT agonist *meta*-chlorophenylpiperazine (*m*-CPP).

**Results:** Bulimic women showed markedly lower mean  $\pm$ SD density ( $B_{max}$ ) of paroxetine-binding sites ( $631.12 \pm 341.58$ ) than did normal eaters ( $1213.00 \pm$

$628.74$ ) ( $t_{54} = -4.47$ ;  $P = .001$ ). Paroxetine binding did not vary with childhood abuse. In contrast, measures of peak change on prolactin levels after *m*-CPP administration ( $\Delta$ -peak prolactin) indicated blunted response in abused bulimic women ( $7.26 \pm 7.06$ ), nonabused bulimic women ( $5.62 \pm 3.95$ ), and abused women who were normal eaters ( $5.73 \pm 5.19$ ) compared with nonabused women who were normal eaters ( $13.57 \pm 9.94$ ) ( $F_{3,51} = 3.04$ ,  $P = .04$ ). Furthermore, individuals reporting childhood abuse showed decreased plasma cortisol levels relative to nonabused women who were normal eaters.

**Conclusion:** Findings imply that BN and childhood abuse are both generally associated with reduced 5-HT tone but that childhood abuse may be somewhat more specifically linked to reduced cortisol levels (ie, hypothalamic-pituitary-adrenal axis) activity.

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**F**INDINGS LINK traumatic experiences to alterations in central serotonin (5-hydroxytryptamine [5-HT]) and cortisol systems. For example, data have linked posttraumatic stress disorder (PTSD) to reduced platelet binding of the selective 5-HT reuptake inhibitor hydrogen-3–paroxetine ( $[^3H]$ -paroxetine)<sup>1</sup> and childhood abuse (in women with personality disorders) to “blunting” of prolactin and cortisol following the partial 5-HT agonist *meta*-chlorophenylpiperazine (*m*-CPP).<sup>2</sup> Various traumas have similarly been associated with decreased resting cortisol and altered cortisol stress responses, suggesting posttraumatic alterations of the hypothalamic-pituitary-adrenal (HPA) axis.<sup>3,4</sup>

Findings in bulimia nervosa (BN) indicate comparable anomalies. Consistent with reduced 5-HT activity, studies document decreased 5-HT metabolites in ce-

rebrospinal fluid,<sup>5</sup> reduced platelet binding of  $[^3H]$ -paroxetine,<sup>6</sup> and blunted prolactin responses to *m*-CPP.<sup>7</sup> Suggesting altered cortisol function, one study<sup>8</sup> links atypical depression (ie, with hyperphagia and hypersomnolence) in BN to reduced plasma cortisol; another<sup>9</sup> links BN, in general, to decreased nocturnal and postglucose cortisol responses.

Since many bulimic women report childhood sexual and physical abuse,<sup>10,11</sup> one obvious conjecture is that neurobiological and psychopathological variations in BN may sometimes be attributable to abuse history. We compared bulimic women reporting childhood abuse, bulimic women without childhood abuse, normal eaters with a history of abuse, and normal eaters with no abuse history on symptom, 5-HT, and cortisol indices. We expected abuse to coincide with increased eating and psychopathological symptoms and decreased 5-HT and cortisol activity.

## SUBJECTS AND METHODS

### SUBJECTS

Forty-five potential bulimic women were recruited through a specialized eating disorders (ED) clinic, using the following criteria: female, aged 18 to 40 years, actively bingeing, and not pregnant, anorexic, obese (body mass index [BMI], a measure of weight in kilograms divided by the square of height in meters, of  $\leq 28$ ), or taking psychoactive medications. The ED symptoms were confirmed using the Eating Disorders Examination.<sup>12</sup> We excluded 5 individuals because of electrocardiographic (ECG) abnormalities or conditions affecting neuroendocrine function and 1 more case with an enzyme-multiplied immunoassay technique urine screen that revealed amphetamine abuse. In 4 more cases, a vein could not be obtained for blood draws. We thus completed full assays in 35 women, 28 (80%) of whom met *DSM-IV*<sup>13</sup> criteria for BN purging subtype, 5 (14%) for BN nonpurging subtype, and 2 (6%) for a "subclinical" BN purging type (bingeing once vs twice weekly). Subthreshold cases were fully "BN spectrum" and deemed not to render the sample heterogeneous. Mean  $\pm$  SD age and BMI were  $23.95 \pm 4.25$  years and  $21.73 \pm 2.89$ , respectively.

Healthy women, recruited through university classes or newspaper advertisements (to approximate student and nonstudent proportions among bulimic women), were aged 18 to 40 years, had relatively normal BMIs of 19 to 27, and had normal results on physical examination, blood work, and ECG. They denied (past or present) ED; intense weight concerns; periods of marked intentional weight loss, binge eating, or purging; medical problems; mental health problems (eg, depression, anxiety, substance abuse); pregnancy; or use of psychoactive medications. Eleven potential candidates showed abnormal eating or weight, 1 reported regular substance abuse, and 6 reported depression or panic attacks. Two showed ECG abnormalities, and in 5 more, a vein could not be obtained for blood draws. After exclusions, we completed assessments in 25 women, who had a mean  $\pm$  SD age and BMI of  $24.60 \pm 7.28$  years and  $22.02 \pm 1.97$ , respectively. *t* Tests showed no bulimic and nonbulimic differences on age or BMI.

### ASSESSMENTS

To assess ED symptoms, we used the Eating Disorders Examination<sup>12</sup> interview, which quantifies severity of criterion ED symptoms, and the Eating Attitudes Test,<sup>14</sup> which measures global ED attitudes and behaviors. We also

computed BMI from self-reported height and weight. To assess psychiatric comorbidity, we used a self-administered, computerized Diagnostic Interview Schedule, Version IV (DIS4),<sup>15,16</sup> a *DSM-IV* version of the National Institute of Mental Health Diagnostic Interview Schedule,<sup>17</sup> and the well-validated<sup>18</sup> Structured Clinical Interview for *DSM-IV* Axis II.<sup>19</sup> We present findings for current and past major depression and PTSD and for borderline personality disorder (BPD), all entities associated with antecedent trauma. Interrater checks on 12 pseudorandomly selected interview pairs yielded a  $\kappa$  of 0.80 (and 91.7% agreement) for a BPD and non-BPD distinction. A self-injuriousness score was created by adding Structured Clinical Interview for *DSM-IV* Axis II ratings (on a 0-3 scale) for self-mutilation and suicidality. These components yielded respective  $\kappa$  values of 0.73 and 0.59.

Additional psychopathological constructs were measured using the Center for Epidemiological Studies Depression (CES-D) scale,<sup>20</sup> the affective instability subscale from the Dimensional Assessment of Personality Pathology,<sup>21</sup> the Barratt Impulsiveness Scale,<sup>22</sup> and the Dissociative Experiences Scale (DES).<sup>23</sup> In bulimic and nonbulimic women,  $\alpha$  values for CES-D, affective instability, Barratt Impulsiveness Scale, and DES scales were .91 and .91, .85 and .89, .78 and .80, and .92 and .93, respectively.

We assessed childhood abuse with the Childhood Trauma Interview,<sup>24</sup> a structured interview quantifying the nature, frequency, and duration of childhood physical and sexual abuse, establishing perpetrators' and subjects' ages when events occurred, and estimating severity of events (using well-anchored ratings). Subjects were classified as having experienced childhood abuse when they received a score of 2 or greater on severity of sexual abuse occurring at or before the age of 14 years (implying serious "noncontact" experiences, such as being made to observe an adult masturbate, or lesser "contact" experiences, such as being held in a sexualized way) or 3 or greater on severity of physical abuse at or before the age of 14 years (implying serious physical maltreatment, such as being hit and bruised with an object or pushed so hard as to be knocked down). We thought that lower ratings (reflecting concepts such as "being looked at in a sexualized way" or "pushed, but not pushed down") indicated abuse too ambiguously.

Given a bilingual sample, we used official French versions of scales (DIS4,<sup>16</sup> DES, and CES-D) or otherwise developed translations using forward-and-back translation techniques. Comparisons of global scores and  $\alpha$  values support psychometric adequacy of translations.

## RESULTS

### CHILDHOOD ABUSE

Abuse was reported by 26 (76%) of 34 bulimic women and 12 (52%) of 23 nonbulimic women. Significant bulimic and nonbulimic differences were indicated for physical abuse (21 [62%] of 34 vs 7 [30%] of 23, respectively;  $\chi^2_1 = 5.39$ ;  $P = .02$ ), but not for sexual abuse (14 [41%] of

34 vs 8 [33%] of 24, respectively). Among sexually abused bulimic and sexually abused nonbulimic participants, mean  $\pm$  SD severities ( $3.21 \pm 0.89$  vs  $2.75 \pm 1.04$ , respectively) and ages of abuse onset ( $9.50 \pm 3.46$  vs  $9.63 \pm 3.11$  years, respectively) did not differ ( $t_{20} = 1.11$ ,  $P > .25$  and  $t_{20} = -0.08$ ,  $P > .50$ , respectively). Corresponding mean  $\pm$  SD physical abuse severities ( $3.62 \pm 0.92$  vs  $3.71 \pm 0.76$ ) and ages of onset ( $7.43 \pm 3.68$  vs  $5.86 \pm 2.19$  years) did not differ ( $t_{26} = -0.25$ ,  $P > .50$  and  $t_{26} = 1.06$ ,  $P > .25$ , respectively).

## PROCEDURES

Since 5-HT promotes prolactin secretion from the pituitary and (indirectly) of cortisol via the HPA axis, it is conventional to draw inferences about central 5-HT functioning from 5-HT-induced alterations in plasma prolactin and cortisol levels.<sup>25</sup> We measured prolactin and cortisol levels before and after oral administration of the partial 5-HT agonist *m*-CPP, which (since it binds with highest affinity to 5-HT<sub>2c</sub> receptors) is thought to be a fairly specific 5-HT probe.<sup>25</sup> Cortisol was assumed to also reflect HPA axis function. In addition, we measured binding in blood platelets of the selective 5-HT reuptake inhibitor [<sup>3</sup>H]-paroxetine. Platelets possess high-affinity sites for 5-HT, comparable to 5-HT reuptake sites in brain, and platelet binding is selectively associated with binding in brain tissue. Platelet paroxetine binding, usually measured in terms of density of binding sites ( $B_{max}$ ) and binding affinity ( $K_d$ ), is believed to model aspects of central (presynaptic) 5-HT transporter function.<sup>26</sup>

Subjects, tested as outpatients, were required to have been free of psychoactive medications for at least 6 weeks and were tested in follicular phase of menses (ie, 5 to 14 days following start of last menses). Before testing, participants were asked to refrain from alcohol, exercise, or street drugs for 48 hours and from binge eating for 24 hours. On the test morning, participants underwent a urine screen for drug use (enzyme-multiplied immunoassay technique kit). Samples were drawn after an overnight fast. Detailed procedures for biochemical assays are described elsewhere.<sup>6,27</sup> Baseline measures on hormones constitute the mean of 2 values obtained from samples drawn at 8:30 and 9 AM before *m*-CPP administration. Prolactin and cortisol levels were determined by radioimmunoassay, using the corresponding, validated Amersham radioimmunoassay kits from Johnson and Johnson, Markham, Ontario. Our laboratory could not obtain paroxetine-binding indices on 1 bulimic woman and cortisol measurements on 1 woman who was a normal eater.

## STATISTICAL ANALYSES

Using ED diagnosis (BN/non-BN) and abuse criteria (described earlier), we organized participants into 4 subgroups: BN with childhood abuse (BN/CA:  $n=26$ ), BN without abuse (BN:  $n=8$ ), normal eater with CA (NE/CA:  $n=12$ ), and normal eater without abuse (NE:  $n=11$ ). (One bulimic and 2 nonbulimic women who indicated abuse after the age of 14 years only were excluded.) Analyses of variance (ANOVAs) showed no mean  $\pm$  SD group differences in age ( $24.42 \pm 4.32$ ,  $22.00 \pm 3.74$ ,  $24.42 \pm 6.78$ , and  $23.45 \pm 5.52$  years, respectively) or BMI

( $21.75 \pm 2.86$ ,  $21.75 \pm 3.37$ ,  $21.92 \pm 1.93$ , and  $22.05 \pm 2.26$ , respectively).

Groups were compared on eating and psychopathological symptoms using ANOVAs, with Newman-Keuls tests (to control family-wise error). Where measures (eg, binge frequencies) yielded zero values in normal eaters, we applied *t* tests to examine pairwise differences across abused and non-abused bulimic women only. Depending on frequencies obtained, childhood abuse and psychiatric comorbidity indices were analyzed using  $\chi^2$  or Fisher exact tests. We used 1-way ANOVA to explore group effects on indices of paroxetine binding ( $B_{max}$  and  $K_d$ ) and repeated-measures ANOVAs (RANOVAs;  $4 \times 9$ ) to test for group effects on serial prolactin and cortisol indices. RANOVAs treated group (NE, NE/CA, BN, BN/CA) and time (baseline and 30-, 60-, 90-, 120-, 150-, 180-, 210-, and 240-minute) factors. Where the Mauchly test of sphericity indicated heterogeneity of covariance, we verified repeated-measures results with Greenhouse-Geisser corrections. We introduced covariates to control known seasonal variations on prolactin responses after *m*-CPP administration,<sup>28</sup>  $B_{max}$  in paroxetine binding<sup>29</sup> and basal cortisol levels,<sup>30</sup> and effects of oral contraceptive use on cortisol (and possibly prolactin) levels.<sup>31</sup> Because our sample size was not sufficiently large to allow for stable estimation of seasonal effects (once "diagnosis" was crossed with "abuse" and then "contraceptive use"), we turned to published findings for guidance: prolactin response after *m*-CPP administration is reportedly larger in winter than in summer and at intermediate levels in spring and fall.<sup>28</sup> In contrast,  $B_{max}$  for paroxetine binding is reportedly elevated in summer, low in winter, and at intermediate levels in spring and fall.<sup>29</sup> For cortisol, data indicate consistent differences between winter and summer samplings (but inconsistencies as to direction of effects, possibly attributable to geographic, meteorologic, or other differences).<sup>30</sup> Our own data showed trends or effects consistent with high peak prolactin levels in winter, high  $B_{max}$  and cortisol levels in summer, and intermediate values on these indices in spring and fall. To control for this range of effects, we entered 2 dummy variables as covariates, which compared samplings obtained in summer (and then fall and spring) to those obtained in winter. Consistent with published findings,<sup>31</sup> our data showed contraceptive users to show strongly higher range of cortisol values and weakly higher peak prolactin levels. Even though proportions of contraceptive users did not differ significantly across groups, we introduced a covariate to code for being "on" or "off" oral contraceptives. Statistical tests were 2-tailed and conducted at the .05 level of significance. To balance type I and type II errors, we report pairwise group comparisons with and without Bonferroni corrections.

## EATING SYMPTOMS AND PSYCHOPATHOLOGICAL INDICES

**Table 1** shows mean  $\pm$  SD values on measures of eating and psychopathological symptoms for each of the groups. On most indices bulimic women showed expected elevations relative to nonbulimic women. Abused bulimic women reported significantly more self-injuriousness than did non-abused bulimic women or women who were normal eaters.

Prevalences of major depression, PTSD, and BPD obtained in different groups are shown in **Table 2**. (DIS4 values were nonsystematically missing for 4 bulimic women and 1 nonbulimic woman.) Results (tested with Fisher exact tests) indicate lifetime major depression to coaggregate, regardless of abuse, with BN. In contrast, PTSD (lifetime or current) occurred especially often in abused bulimic women. Statistically significant differences were not obtained on BPD.

**Table 1. Mean (SD) Findings in Bulimic (BN), Abused Bulimic (BN/CA), Normal Eater (NE), and Abused Normal Eater (NE/CA) Groups on Eating Symptoms and Psychopathological Indices\***

Variable	BN (n = 8)	BN/CA (n = 26)	NE (n = 11)	NE/CA (n = 12)	Statistics
Monthly binge episodes	43.63 (34.73)	30.32 (27.86)	0.00 (0.00)	0.00 (0.00)	$t_{32} = -1.12$
Monthly binge days	21.92 (9.72)	16.28 (7.04)	0.00 (0.00)	0.00 (0.00)	$t_{32} = -1.81$
Monthly vomit episodes†	56.58 (27.66)	36.77 (35.76)	0.00 (0.00)	0.00 (0.00)	$t_{26} = -1.40$
Monthly vomit days†	19.25 (7.32)	16.20 (9.79)	0.00 (0.00)	0.00 (0.00)	$t_{26} = -0.79$
Eating Attitudes Test	43.00 <sup>b</sup> (7.60)	40.59 <sup>b</sup> (9.43)	3.62 <sup>a</sup> (3.62)	2.92 <sup>a</sup> (3.26)	$F_{3,53} = 121.39$ ( $P < .001$ )
Center for Epidemiological Studies Depression Scale	23.75 <sup>b</sup> (15.17)	30.79 <sup>b</sup> (11.52)	9.55 <sup>a</sup> (7.12)	10.58 <sup>a</sup> (10.01)	$F_{3,53} = 14.28$ ( $P < .001$ )
Affective instability	3.71 <sup>b</sup> (0.79)	3.61 <sup>b</sup> (0.69)	2.65 <sup>a</sup> (0.82)	2.38 <sup>a</sup> (0.67)	$F_{3,53} = 11.36$ ( $P < .001$ )
Impulsivity	2.19 <sup>ab</sup> (0.30)	2.38 <sup>b</sup> (0.33)	2.09 <sup>ab</sup> (0.30)	1.98 <sup>a</sup> (0.29)	$F_{3,53} = 5.28$ ( $P < .01$ )
Dissociative experiences	9.11 (10.26)	13.66 (11.89)	7.50 (5.65)	10.24 (10.94)	$F_{3,53} = 1.06$
Self-injuriousness	2.13 <sup>b</sup> (2.17)	3.88 <sup>c</sup> (2.25)	0.00 <sup>a</sup> (0.00)	0.50 <sup>a</sup> (1.24)	$F_{3,53} = 16.18$ ( $P < .01$ )

\*Results of statistical tests for group differences are shown on the right. In each row, means with different letters in their superscripts differ at the .05 level (or better) on Newman-Keuls tests.

†Measured in vomiters only: n = 8 for BN, n = 20 for BN/CA, n = 11 for NE, and n = 12 for NE/CA.

**Table 2. Count of Comorbid Psychiatric Syndromes in Bulimic (BN), Abused Bulimic (BN/CA), Normal Eater (NE), and Abused Normal Eater (NE/CA) Groups**

Syndrome	Count (%)			
	BN (n = 8)	BN/CA (n = 22)	NE (n = 11)	NE/CA (n = 11)
Major depression	4 (50.0)*	5 (22.7)	0 (0.0)	1 (9.1)
History of major depression	6 (75.0)*	17 (77.3)*	1 (9.1)	2 (18.2)
Posttraumatic stress disorder	0 (0.0)	6 (27.3)*	0 (0.0)	1 (9.1)
History of posttraumatic stress disorder	0 (0.0)	10 (45.5)*	0 (0.0)	2 (18.2)
Borderline personality disorder†	1 (12.5)	7 (26.9)	0 (0.0)	0 (0.0)

\*Cell frequency differs from that in the reference NE group at  $P < .05$  (or better) on Fisher exact test.

†n = 8 for BN, n = 26 for BN/CA, n = 11 for NE, and n = 12 for NE/CA.

## SEROTONERGIC AND NEUROENDOCRINE MEASURES

Results on paroxetine-binding tests were evaluated using analyses of covariance (ANCOVAs) to compare transporter density ( $B_{max}$ ) and binding affinity ( $K_d$ ) indices across groups, with dummy variables for seasonal effects (Table 3 presents unadjusted means and SDs). The analysis on  $B_{max}$  indicated expected winter vs summer ( $F_{1,50} = 7.26, P < .02$ ) and spring or fall vs summer ( $F_{1,50} = 5.93, P < .03$ ) effects, with higher  $B_{max}$  in the summer. Once removed, a significant group effect remained ( $F_{3,50} = 4.61, P < .01$ ). Covariate-adjusted group contrasts (with or without Bonferroni corrections) generally indicate lower  $B_{max}$  in bulimic women, but no differences attributable to childhood abuse (Table 3). No effects were obtained on  $K_d$ .

We analyzed serial prolactin findings (Figure 1, plotting unadjusted means and SEs) using a 2-way repeated-

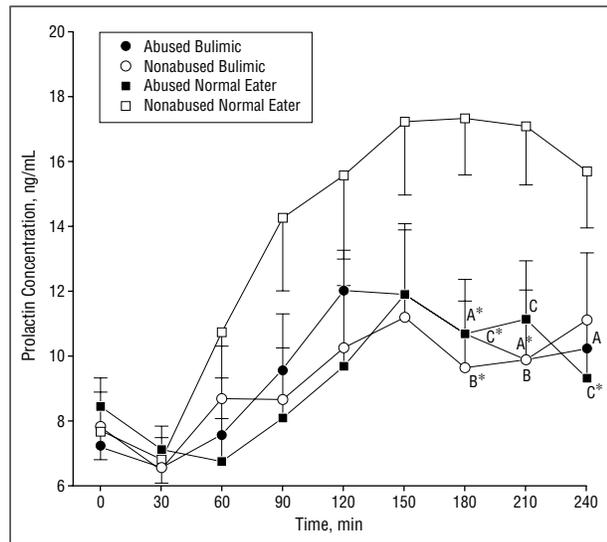
measures analysis of covariance (RANCOVA), with covariates for contraceptive and seasonal effects. The RANCOVA yielded a significant time  $\times$  contraceptive interaction ( $F_{8,400} = 2.83, P < .01$ ), indicative of earlier "peaking" in contraceptive users, which remained significant after Greenhouse-Geisser correction ( $F_{2,77} = 2.83, P < .05$ ). Examination of resulting curves and proportions of contraceptive users across groups indicated that the interaction could not have confounded group and time effects of main interest. There was no main effect of contraceptives or main or interaction effects implicating season of testing. A main effect of time of sampling ( $F_{8,400} = 5.17, P < .005$ ), showing expected stimulation of prolactin after *m*-CPP administration, remained significant after Greenhouse-Geisser correction ( $F_{2,77,138.63} = 5.17, P < .005$ ). More important, after removal of covariates, a significant group  $\times$  time interaction effect was obtained ( $F_{24,400} = 2.10, P < .005$ ), which remained after Greenhouse-Geisser correction ( $F_{8,32,138.63} = 2.10, P < .04$ ). Simple effects of group were indicated at 180 ( $F_{3,50} = 4.50, P < .01$ ) and 210 ( $F_{3,50} = 3.52, P < .025$ ), and, as a trend, at 240 minutes ( $F_{3,50} = 2.74, P < .055$ ). The pattern of results on covariate-adjusted pairwise comparisons, conducted with and without Bonferroni corrections (Figure 1), indicates "blunted" prolactin response in both bulimic and abused participants. An adjunctive analysis, conducted using 1-way ANCOVA (with covariates controlling for seasonal effects) testing group differences on an index of change ( $\Delta$ -peak) on prolactin (ie, peak minus baseline at each time point for each subject), indicated no seasonal effects, but a significant overall group effect ( $F_{3,55} = 3.15, P < .04$ ). Covariate-adjusted contrasts showed mean  $\Delta$ -peak prolactin for bulimic women ( $5.62 \pm 3.95$ ), abused bulimic women ( $7.26 \pm 7.06$ ), and abused women who were normal eaters ( $5.73 \pm 5.19$ ) to always be lower than the score obtained in the group of nonabused women who were normal eaters ( $13.57 \pm 9.94$ ).

The combination of downward diurnal cortisol variations with upward shifts (presumably) due to *m*-CPP administration complicated determination of  $\Delta$ -peak val-

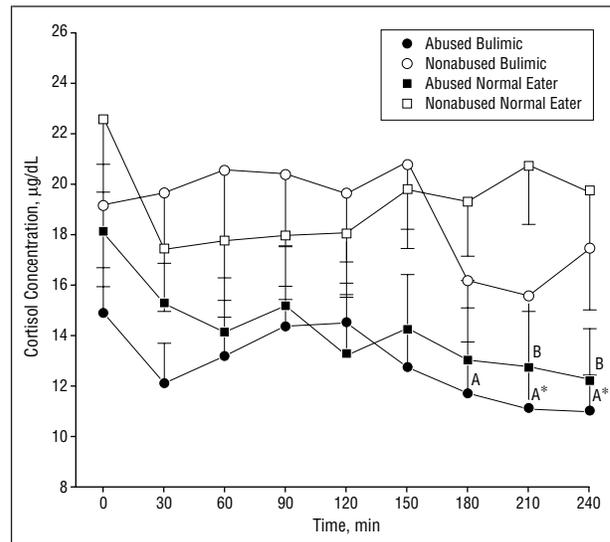
**Table 3. Mean (SD) Platelet Paroxetine-Binding Density ( $B_{max}$ ) and Affinity in Bulimic (BN), Abused Bulimic (BN/CA), Normal Eater (NE), and Abused Normal Eater (NE/CA) Groups\***

Variable	BN (n = 8)	BN/CA (n = 25)	NE (n = 11)	NE/CA (n = 12)
Transporter density $B_{max}$ , fmol/mg of protein	627.63 <sup>a1</sup> (292.44)	632.24 <sup>a1</sup> (361.42)	1049.27 <sup>ab12</sup> (456.11)	1363.08 <sup>b2</sup> (741.71)
Binding affinity $K_d$ , nM	0.20 (0.27)	0.16 (0.15)	0.22 (0.17)	0.33 (0.47)

\*In each row, means with noncorresponding letters in their superscripts differ at the .05 level (or better) according to covariate-adjusted pairwise contrasts. Means with noncorresponding numbers in their superscripts differ on parallel contrasts after Bonferroni corrections.



**Figure 1.** Means (and SEs) obtained at each moment of the serial sampling for prolactin in nonabused bulimic, abused bulimic, nonabused normal eater, and abused normal eater groups. Significant pairwise differences between nonabused women who were normal eaters and (A) abused bulimic women, (B) nonabused bulimic women, and (C) abused women who were normal eaters at  $P < .05$  on covariate-adjusted pairwise contrast; asterisk indicates corresponding contrast differs at  $P < .05$  after Bonferroni correction for family-wise error.



**Figure 2.** Means (and SEs) obtained at each moment of the serial sampling for cortisol in nonabused bulimic, abused bulimic, nonabused normal eater, and abused normal eater groups. Significant pairwise differences between nonabused normal eaters and (A) abused bulimic women and (B) abused women who were normal eaters at  $P < .05$  on covariate-adjusted pairwise contrast; asterisk indicates corresponding contrast differs at  $P < .05$  after Bonferroni correction for family-wise error. To convert cortisol levels from micrograms per deciliter to nanomoles per liter, multiply by 27.59.

ues on cortisol. We therefore analyzed serial cortisol findings using 2-way RANCOVA, with covariates for contraceptive and seasonal effects (**Figure 2**, which plots unadjusted means and SEs). The RANCOVA indicated a significant time  $\times$  contraceptive effect ( $F_{8,392} = 2.58$ ,  $P < .01$ ), even after Greenhouse-Geisser correction ( $F_{4,16,203.71} = 2.58$ ,  $P < .04$ ), and an even stronger main effect of contraceptive use ( $F_{1,49} = 27.43$ ,  $P < .001$ ). Average  $\pm$  SE cortisol level was higher in contraceptive users ( $21.08 \pm 1.18$ ) than in nonusers ( $11.25 \pm 0.99$ ) (and downward diurnal shifts in these individuals were, correspondingly, somewhat larger). Examination of curves suggested that the interaction of time and contraceptive variables could not have confounded effects of main interest. Moreover, after removal of covariate effects, a significant group  $\times$  time interaction was obtained ( $F_{24,392} = 2.03$ ,  $P < .005$ ), even after Greenhouse-Geisser correction ( $F_{12,47,203.71} = 2.03$ ,  $P < .03$ ). There was no main time or group effect. Simple effects of group were indicated at 210 minutes ( $F_{3,49} = 2.89$ ,  $P < .05$ ) and 240 minutes ( $F_{3,49} = 3.15$ ,  $P < .04$ ). Covariate-adjusted pairwise group comparisons indicated significantly lower means at these time points in samples of abused bulimic women and abused women who were normal eaters (Figure 2). How-

ever, after Bonferroni corrections, pairwise differences remained significant in abused bulimic women only.

#### COMMENT

This study shows intriguing patterns of association, in bulimic and nonbulimic women, between childhood abuse, on the one hand, and eating pathology, general psychopathology, and 5-HT and cortisol functioning, on the other. Although we found no systematic association between childhood abuse and expression of eating or affective or impulsive symptoms, we did note symptoms of PTSD and self-destructiveness to be elevated in abused bulimic women compared with levels obtained in other groups. This pattern links abuse (in at least the presumably more vulnerable bulimic individuals in our sample) with symptoms that are believed to sometimes represent posttraumatic sequelae.

On neurobiological indices, different findings were obtained on different measures. We observed reduced platelet paroxetine binding ( $B_{max}$ ) in bulimic women relative to that in nonbulimic women (with no apparent effects due to childhood abuse). These findings replicate our previous finding in 40 bulimic women (16 of whom

were in the present sample) of reduced platelet [<sup>3</sup>H]-paroxetine binding.<sup>6</sup> If paroxetine binding models the central 5-HT transporter, then such findings would indicate reduced 5-HT reuptake at central presynaptic sites. Regardless, our findings link reduced paroxetine binding more strongly to BN than to developmental abuse.

On prolactin, we obtained further evidence of abnormal 5-HT function in BN (Figure 1), replicating well-known tendencies for bulimic women to display smaller prolactin responses after *m*-CPP administration than nonbulimic women.<sup>7</sup> Blunting of prolactin response after *m*-CPP administration has been interpreted as indicating down-regulation of postsynaptic 5-HT receptors on which *m*-CPP acts. Whether such findings reflect “state” effects attributable to active BN (eg, due to sequelae of binge eating on 5-HT mechanisms), “trait” effects related to some stable aspect of those who develop BN, or some combination of the 2 remains unknown, however. Blunting effects obtained in abused women who were normal eaters at some prolactin sampling intervals are consistent with previous findings on prolactin after *m*-CPP administration in abused nonbulimic populations.<sup>2</sup> Such findings would suggest that there may also be an association between childhood abuse and reduced postsynaptic 5-HT activity. However, further work is needed to clarify causal questions, since such effects could constitute a simple correlate (vs consequence) of abuse. For example, connection between 5-HT function and abuse could reflect association with a trait (eg, impulsivity) that might be present in the abusive parent and the vulnerable child, without implying a causal role of abuse.

Results on cortisol levels contrast with our other findings. Compared with levels in nonabused women who were normal eaters, we obtained unequivocal evidence of reduced plasma cortisol levels in abused bulimic women, weak evidence of such reduction in abused women who were normal eaters, but no evidence of such reduction in nonabused bulimic women (Figure 2). In other words, our data did not so much link decreased cortisol levels with BN (as was the case for 5-HT indices such as prolactin and paroxetine binding) as with abuse. Reduced cortisol activity has been thought to represent an adaptation of the HPA axis to prolonged or particularly intense stress.<sup>3,4</sup> From this perspective, abnormally low cortisol values, especially evident in our abused bulimic patients, could reflect a posttraumatic alteration of HPA axis function. Particularly strong effects in the bulimic participants might be attributed to 1 (or both) of the following. First, abused bulimic women more often reported a history of PTSD (Table 2), perhaps indicating that these participants underwent more intensely traumatic experiences than did abused women who were normal eaters. Second, it may be that the same vulnerability that rendered abused bulimic women susceptible to BN also rendered them vulnerable to detrimental effects of abuse—manifested (at a neurobiological level) as cortisol alteration and (at a behavioral level) as PTSD symptoms. Although we are unable to ascertain which of these explanations is correct, rated severities of abuse did not differ significantly across abused bulimic and nonbulimic women, and this argues in favor of an explanation couched in terms of susceptibility to, rather than sever-

ity of, abuse. Regardless, it is striking to note effects, in individuals who are on average in their mid-20s, of events that occurred in childhood.

We note various limitations of our study. Our design did not include measurement of serum estradiol levels and *m*-CPP concentrations to ascertain hormonal and drug effects. It also lacked a placebo condition by which to evaluate neuroendocrine responses under neutral circumstances. Finally, without prospective measurements, we cannot interpret effects observed as either consequences of active BN or stable “trait” antecedents. Regardless, results obtained point to potentially important 5-HT and cortisol effects. Direct and indirect effects of 5-HT and cortisol anomalies observed might have various implications for affected individuals’ stress tolerances, impulse controls, capacities for mood regulation, and abilities to control eating behavior (ie, to satiate). We therefore speculate that, here, we may be observing neurobiological mediators of the link between developmental trauma and heightened susceptibility to BN.

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