Ovarian Hormones and Borderline Personality Disorder Features: Preliminary Evidence for Interactive Effects of Estradiol and Progesterone

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Abstract

Cyclical fluctuations in the ovarian hormones 17β-estradiol (E2; estrogen) and progesterone (P4) predict emotions, cognitive processes, and behaviors relevant to Borderline Personality Disorder (BPD); however, there are individual differences in sensitivity to normal hormone shifts. This study examined associations of naturally occurring hormonal changes with concurrent BPD feature expression. Forty women sampled for a flat distribution of the PAI-BOR (n=10 where T<50, n=10 where 50<T<60, n=10 where 60<T<70, and n=10 where T>70) provided 4 weekly saliva samples and psychological assessments. Across most outcomes (e.g., BPD features, felt rejection, anger rumination, negative urgency) P4 deviation (from one's person mean) moderated the effect of current E2 deviation (from one's person mean) among women high (+1 SD) in trait BPD features such that E2 deviation was negatively associated with symptoms only when P4 was higher-than-usual. Cyclical hormone changes (e.g., higher P4 in the luteal phase; E2 fluctuations at ovulation and in the luteal phase) may impact BPD feature expression among at-risk women.

Keywords

17β-estradiol; estrogen; progesterone; menstrual cycle; borderline personality disorder; rejection sensitivity; anger rumination; negative urgency

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Individuals with Borderline Personality Disorder (BPD) suffer from a distinctive combination of particularly disabling psychological and behavioral symptoms, most of which are characterized by inconsistency and variability (Skodol et al., 2002). Common BPD features include extreme emotional instability and reactivity, an unstable sense of self, frantic reactions to perceived abandonment, chaotic interpersonal relationships characterized by fluctuations between idealizing and devaluing others, dissociative or paranoid reactions to stress, and harmful impulsive behavior, including aggression, substance abuse, self-injury, or suicide attempts. Approximately 10% of outpatients and 20% of inpatients meet criteria for BPD, and epidemiological studies suggest that approximately 6% of the U.S. population will meet criteria for BPD at some point in their lives (DSM-5, 2013; Swartz et al., 1990; Widiger & Weissman, 1991; Grant et al., 2008). Further, a greater number of individuals will show clinically significant BPD "features" without meeting DSM-5 criteria for the disorder (Trull, Useda, Conforti, & Doan, 1997). Although recent epidemiological evidence indicates that BPD is equally prevalent in men and women, BPD is associated with greater functional impairment in women (Grant et al., 2008).

A large and growing body of literature describes environmental, emotional, and cognitive triggers predicting the expression of BPD symptoms at any given time; however, less is known about the physiological factors that contribute to these ups and downs. Identification of underlying physiological triggers relevant to BPD could aid in the development of more efficient, synergistic treatments that target reactivity on both biological and psychosocial levels. Based on evidence that several types of BPD-related psychological constructs (reviewed below) can be influenced by the menstrual cycle, the present study represents a preliminary examination of one set of potential physiological triggers in women— fluctuating levels of the ovarian hormones 17β-estradiol (E2; estrogen) and progesterone (P4).

Ovarian Hormones Across the Menstrual Cycle: A Natural Experiment

Both E2 and P4 fluctuate naturally across the monthly female reproductive cycle. During the week or so following the onset of menstrual bleeding (early follicular phase), E2 and P4 are both low. While P4 remains low throughout the follicular phase, about 8 days after the onset of menses, E2 increases steadily, reaching its peak around ovulation (occurring, on average, around 14 days prior to the onset of the next menses), which marks the beginning of the luteal phase. While E2 initially drops after ovulation, it demonstrates a second rise along with increasing P4 concentrations. Thus, in the second half of the menstrual cycle, both E2 and P4 are relatively elevated until the late luteal phase, when both E2 and P4 decline rapidly a few days before the onset of the next menses. Although true causality of hormonal effects cannot be established without a more rigorous experimental design, the menstrual cycle provides an ecologically valid natural experiment in which to study the associations of naturally-occurring increases and decreases in hormones (i.e., relative to an individual's average hormonal levels) with expression of traits and processes characteristic of BPD.

Ovarian Hormones and Emotional, Cognitive, and Behavioral Constructs Associated with BPD Features

BPD is an extremely heterogeneous disorder; there are 256 different combinations of symptoms that can lead to a diagnosis of BPD using the DSM-5 diagnostic criteria (Ellis, Abrams, & Abrams, 2008). Given this heterogeneity, a great deal of work has focused on disaggregation of BPD into core homogeneous underlying traits and processes (Smith, McCarthy, & Zapolski, 2009). Among other key constructs in BPD, empirical work has identified (1) high negative emotionality, especially sensitivity to feelings of social rejection (Rosenthal et al., 2008; Staebler, Helbing, Rosenbach, & Renneberg, 2011), (2) poor cognitive control over rumination, especially on anger-provoking situations (Baer, Peters, Eisenlohr-Moul, Geiger, & Sauer, 2012; Peters, Geiger, Smart, & Baer, 2013), and (3) various manifestations of behavioral impulsivity, especially under conditions of negative affect (Peters, Upton, & Baer, 2013; Tragesser, Lippman, Trull, & Barrett, 2008; Ball, Tennen, Poling, Kranzler, & Rounsaville, 1997; Brodsky et al., 1997; Trull, Sher, Minks-Brown, Durbin, & Burr, 2000). Although no published work addresses the concurrent within-person associations of ovarian hormones with BPD feature expression per se, a growing body of work indicates that ovarian hormones are relevant to these emotional, cognitive, and behavioral correlates of BPD.

Emotionally, BPD is characterized by intense negative emotionality—and particularly feelings of social rejection. Although exceptions exist (Schwartz, Romans, Meiyappan, De Souza, & Einstein, 2012; Brooks-Gunn and Warren, 1989), many studies have documented greater concurrent negative emotionality at times in the menstrual cycle when E2 is low or P4 is high (e.g., Meaden et al., 2005, Gonda et al., 2008) or during reproductive developmental transitions characterized by greater variability in E2 (as a between-person variable; Freeman et al., 2006; Brooks-Gunn and Warren, 1989, Buchanan, Eccles, & Becker, 1992; Paikoff, Brooks-Gunn, and Warren, 1991; Poromaa, Smith, and Guilinello, 2003). Further, individual differences appear to modulate the impact of changing hormones on emotion. Experimental studies of women with premenstrual dysphoric disorder (PMDD), who show luteal phase increases in various psychiatric symptoms, clearly demonstrate that only certain women show sensitivity to the effects of changing E2 and P4 on mood (e.g., Schmidt, Nieman, Danaceau, Adams, & Rubinow, 1998; Rubinow & Schmidt, 1992). Further, interpersonal emotions such as rejection and anger are the most commonly reported symptom during the premenstrual phase in women with PMDD (Bloch et al., 1997; Pearlstein, Yonkers, Gayyad, & Gillespie, 2005), suggesting that women with a tendency toward interpersonal dysfunction (e.g., women with BPD) may be at greater risk for hormonal reactivity.

Cognitively, BPD is characterized by a negative content bias that is exacerbated by a tendency toward rumination—especially on angry themes (Baer, Peters, Eisenlohr-Moul, Geiger, & Sauer, 2012). Higher levels of both E2 and P4 have been individually linked to enhanced executive functions, a set of cognitive processes that serve, among other things, to downregulate unhelpful thought processes such as rumination (e.g., Davis & Nolen-Hoeksema, 2000; Segerstrom et al., 2010). Several aspects of executive functioning appear to be improved under higher levels of E2 (Lord and Taylor, 1991; Howard, Gifford,

Lumsden, 1988; Gogos, 2013; Rosenberg & Park, 2002, Vranic & Hromatko, 2008, Jacobs & D'Esposito, 2011; Segal, 2012) and higher levels of P4 (Solis-Ortiz & Corsi-Cabrera, 2008; Solis-Ortiz, Guevara, & Corsi-Cabrera, 2004). Experimentally, administration of either E2 *or* P4 following pharmacological hormone suppression normalizes neural activity associated with executive functioning (Berman et al., 1997). As with mood, there appear to be individual differences in the link between hormones and executive cognitive functioning. In one study, cycle-related elevations in E2 were associated with improved working memory (Jacobs & D'Esposito, 2011) only among women who are COMT[Val] carriers, a genotype associated with lower frontal dopamine, greater impulsivity, and poorer executive functioning (Wishart et al., 2011), particularly in women (Qian et al., 2003; Lang, Bajbouj, Sander, & Gallinat, 2007).

Behaviorally, BPD is characterized by impulsivity, and particularly urgency—the tendency to engage in regrettable behavior under conditions of strong emotion (Whiteside & Lynam, 2001). Cyclical changes in ovarian hormones have been linked to several urgency-related behaviors, including substance use, disordered eating, and suicidality. Cyclical reductions in both E2 and P4 predict increased risk for alcohol and tobacco abuse (Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006; Franklin et al., 2004; Evans & Levin, 2011; Epstein et al., 2006; Franklin et al., 2008; Pastor & Evans, 2003; Schiller et al., 2014). Similarly, among women who report binge eating episodes, E2 and P4 may interact to predict binges; in a large study, binges were most likely when E2 and P4 were both relatively low, and were least likely when E2 was high and P4 was low (Klump et al., 2014). Finally, reductions in both E2 and P4 appear to predict more self-harm and suicide attempts, and women who attempt suicide during menses (when E2 and P4 are both low) report the strongest suicidal intentions (Baca-Garcia, Diaz-Sastre, de Leon, & Saiz-Ruiz, 2000; Baca-Garcia et al., 2010; Saunders & Hawton, 2006). Therefore, the preponderance of behavioral evidence suggests that cyclical reductions in both E2 and P4 predict several impulsive behaviors associated with BPD.

Ovarian Hormones and BPD Features

Although no longitudinal studies have explicitly addressed the concurrent or lagged within-person associations of E2 or P4 with BPD features or symptoms per se, some evidence does suggest a link between ovarian hormone changes and BPD feature expression. Across the female lifespan, BPD features are greatest during adolescence and perimenopause, developmental transitions characterized by greater within-person variability in hormones (Bardenstein & McGlashen, 1988; Stone, 1992). These same developmental transitions are characterized by differential prevalence of BPD in men and women, suggesting that changing hormonal environments may be associated with risk for BPD feature expression (Bardenstein & McGlashen, 1988). In the one study specifically examining natural fluctuations in E2 and BPD features, 52 nonclinical women provided four weekly saliva samples for E2 along with a weekly measure of BPD features. The concurrent associations of weekly deviation from an individual's average E2 was not reported; however, a between-person index of *greater overall variability* in E2 across the cycle relative to other participants (as estimated using simple variance scores for each individual) was associated with higher average scores on a measure of BPD features (DeSoto, Geary, Hoard, Sheldon,

& Cooper, 2003). The goal of the present study is to extend this work by examining both (1) correlations between BPD features and between-person differences in hormonal variability and (2) the impact of within-person changes in ovarian hormones on concurrent BPD feature expression.

The Present Study: Aims and Hypotheses

To date, no published work has examined the within-person associations of E2 and P4 with concurrent expression of BPD features; the present study represents a preliminary investigation of these effects. In the present study, 40 women were followed for 4 weeks in order to examine the within-person associations of E2 and P4 with concurrent self-reported BPD features and symptoms as well as BPD-related constructs such as negative emotion, rumination, and impulsivity.

Previous evidence regarding the impact of ovarian hormones in generally healthy women was reviewed above. The review suggests that E2 may have protective within-person effects on executive cognitive functioning and impulsive behavior, whereas P4 may have protective effects on executive cognitive functioning and impulsive behavior but may have deleterious effects on mood. Given the centrality of negative affect and mood lability in BPD, we hypothesize that;

1. Higher E2 and lower P4 relative to one's average levels of E2 or P4 (deviations from one's person mean; see visual definition of deviations in Figure 1) will be associated with lower concurrent reports of BPD features and correlates. We predict that these associations will be replicated across multiple measures of BPD features, symptoms, and correlates. Interactions between changes in E2 and changes in P4 were also tested as exploratory predictors.

2. Trait levels of BPD features (as measured by the average of weekly scores on a measure of BPD features) would moderate the within-person associations of E2 and P4 on expression of BPD features, symptoms, and correlates such that the links in hypothesis 1 will only be present in women with above-average levels of BPD traits.

3. Consistent with previous findings (DeSoto, Geary, Hoard, & Cooper, 2003), greater overall within-person variability in E2 and P4 across four weeks would be associated with more severe average BPD features, whereas a person's average levels of either E2 or P4 across four weeks would not be associated with average BPD features.

Method

Overview and Study Design

The present study consisted of a repeated measures approach to understanding relations between current deviations from one's mean levels of ovarian hormones (E2 and P4) and current ratings of BPD features, symptoms and correlates over four weeks. Forty women, sampled to achieve a flat distribution of trait BPD scores, attended 4 weekly laboratory sessions at which they completed comprehensive repeated assessments of several different

measures of BPD features or symptoms as well as weekly measures of emotion, rumination, and impulsivity. During a fifth and final visit, participants underwent a structured clinical interview for diagnosis of BPD.

Participants

Participants were 40 naturally cycling undergraduate women between the ages of 18 and 30 fulfilling research participation requirements for an introductory undergraduate psychology course. They participated in an initial screening study; using their scores on a trait version of the PAI-BOR (weekly version described in measures section below) administered during this previous study, 10 participants were recruited from each of four symptom ranges on the PAI-BOR: low average ($T<50$), high average ($50<T<60$), above average ($60<T<70$), and high ($T>70$). This recruitment strategy was utilized in order to increase the range of trait BPD features in the sample, thereby increasing the ability to detect interactive effects of trait BPD features and hormones. Descriptive analyses presented below indicate that this strategy was successful in "flattening" the distribution. The following exclusion criteria applied: (1) current use of hormonal birth control, (2) current use of any "as needed" psychiatric medication (e.g., benzodiazepines), (3) inability to speak English fluently, (4) self-reported reproductive cycles typically lasting fewer than 25 days or greater than 35 days, or (5) a history of being diagnosed with a psychotic disorder other than brief periods of dissociation.

Procedure

Screening and Recruitment—Participants completed a trait version of the PAI-BOR as well as a measure of the inclusion and exclusion criteria listed above, then consented to being contacted about future research opportunities. Eligible women were contacted via telephone. Interested participants were asked to schedule five repeating weekly timeslots at the same day and time each week (four weekly assessments and one follow-up appointment).

Weekly Laboratory Protocol—Participants came to the lab once per week for five weeks at the same day and time (four assessments and one diagnostic interview and debriefing session). Reminder emails were sent two days in advance of each session, reminding the participant of the location, date, and time of their next session as well as requesting that participants refrain from chewing gum, drinking alcohol, drinking more than one caffeinated beverage, or taking nonprescription medications for 12 hours prior to sessions on visit days to facilitate accurate salivary hormone measurement. Nearly all missed sessions were rescheduled and completed within three days of the missed appointments; in the few cases where this was not possible (n = 6 sessions), the participant returned to the lab for the next scheduled session and added an additional week to their participation to compensate for the missed session.

Weekly sessions took place individually in a private room. At the first session, participants provided written informed consent. Participants were then given eight minutes to provide the saliva sample and completed all weekly measures, presented in randomized order, on a computer. During the fifth session, the first author administered the SCID-II for BPD diagnosis and debriefed the participant.

Weekly Measures

Ovarian Hormones—Participants were instructed to salivate by passive drool into a polypropylene vial (Salimetrics; State College, PA). During each session, participants recorded use of the following in the past 12 hours: nicotine, caffeine, over-the-counter drugs, prescription drugs, and illicit drugs. No participants reported prescription or illicit drug use. At some assessment points, participants reported that in the past 12 hours they had smoked cigarettes (13 assessment points), had more than 1 caffeinated beverage (2 assessment points), or had used over-the-counter drugs (7 assessment points) in the past 12 hours.[1] Participants passively drooled into a prolyprolyene vial through a straw until 1.8 mL of saliva had been collected. Samples were immediately placed in a chest freezer at −20° C. Later, they were transferred to the University of Kentucky General Clinical Research Center for 17β;-estradiol and progesterone assay using ELISA kits (Salimetrics). Intra-assay coefficient of variation was 1.6% for E2 and 2.7% for P4; inter-assay coefficient of variation was 2.2% for E2 and 5.4% for P4. The standard curves were of expected shape and slope for both E2 and P4.

BPD Features and DSM-5 BPD Symptoms—Weekly BPD features and symptoms were measured using several different instruments, described below, in order to test the consistency of hormonal effects across methods of assessing BPD. Weekly measure instructions were altered from their original trait orientation (i.e., rate yourself in general) to a shorter, more recent time frame (i.e., rate your experiences in the past week); however, research on retrospective self-reports indicates that ratings of symptoms in the past week are disproportionately influenced by one's more recent experiences (i.e., over the past day; Robinson & Clore, 2002; Gray & Watson, 2007).

Personality Assessment Inventory - Borderline Subscale (PAI-BOR; Morey, 1991): The PAI-BOR is a 24-item measure of BPD features, including 4 subscales measuring *affective instability* (e.g., "my mood could shift quite suddenly"), *identity problems* (e.g., "my attitude about myself changed a lot"), *negative relationships* (e.g., "my relationships have been stormy"), and *self-harm* (e.g., "I was a reckless person). Notably, the *self-harm* subscale actually measures tendency toward impulsive behaviors rather than physical self-harm. The PAI-BOR is the best-studied measure of borderline personality disorder features, and has been used widely in both research and clinical settings to predict BPD diagnosis (Morey, 1991; Stein, Pinsker-Aspen, & Hilsenroth, 2007). Participants were asked to rate the extent to which each statement described them in the past week on a scale from 0 (False, Not True at All) to 4 (Very True).

Borderline Feature List - 23 (BSL-23; Bohus et al., 2007): The BSL-23 is a 23-item shortened version of a 95-item measure of BPD features based on the SCID-II DSM-5 diagnosis of BPD (e.g., "I felt helpless", "my mood rapidly cycled in terms of anxiety, anger, and depression", "I was afraid of losing control", "I didn't believe in my right to live"). In the initial validation sample, scores on the full and shortened versions of the BSL

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[1]All hypotheses concerning E2 and P4 were originally tested controlling for the use of these substances; however, use of these substances did not significantly impact E2, P4, or any outcome, and inclusion of these controls in models did not change model outcomes in any substantive way. Therefore, they were not included in final models presented in the results section.

were significantly greater among individuals with a SCID-II diagnosis of BPD than among those with Axis I diagnosis (e.g., mood or anxiety disorders) and among healthy controls. In another validation sample of individuals with a diagnosis of BPD, scores the BSL reduced significantly in response to Dialectical Behavior Therapy, indicating sensitivity to change. Participants were asked to rate the extent to which each statement described them in the past week on a scale from 0 (Not at all) to 3 (Very much).

McLean Screening Instrument for BPD (MSI-BPD; Zanarini et al., 2003): The MSI-BPD uses 10 dichotomous (yes or no) items to measure the nine DSM-5 BPD criteria. Example items include, "Have you been distrustful of other people?", "Have you been extremely moody?", and "Have you deliberately hurt yourself physically (e.g., punched yourself, cut yourself, burned yourself)? How about made a suicide attempt?" Participants were asked to answer with regard to the past week. In several studies, scores on the MSI-BPD were positively associated with other measures of BPD features (Gardner & Qualter, 2009), and predicted actual SCID-II diagnosis of BPD (Zanarini et al., 2003).

DSM-5 Diagnosis of BPD—The BPD module of the Structured Clinical Interview for Diagnosis—II (SCID-II; First et al., 1995) was administered to determine diagnostic status and the number of DSM-5 BPD criteria met. During the final session, the principal investigator (n = 30) and another master's level clinician with experience completing the SCID-II (n = 10) led each participant through the BPD module of the SCID-II. After completion of the study, transcripts of participant responses to interview prompts were reviewed by the clinician who did not complete the interview. According to the DSM-5 diagnostic system, an individual must meet 5/9 of the criteria in order to officially be diagnosed with BPD. In the present study, 22 participants (55%) did not meet any BPD criteria, 8 participants (20%) met one of the criteria, 1 participant (2.55%) met 2 of the criteria, 4 participants (10%) met 4 of the criteria, 3 participants (7.5%) met 5 of the criteria, and 1 participant each met 7 (2.5%) or 8 (2.5%) of the criteria. Therefore, five individuals (12.5% of the sample) met official DSM-5 criteria for BPD. All of the women meeting full criteria for BPD had been recruited from the group of potential participants with T>70 on the PAI-BOR total scale.

Emotional, Cognitive, and Behavioral Correlates of BPD

Positive and Negative Affect—*Positive affect and negative affect* were measured using the Positive and Negative Affect Schedule (PANAS; Watson & Clark, 1994). Participants rated, on a scale from 1 ("very slightly or not at all") to 5 ("extremely"), the extent to which they had felt each type of affect (e.g., scared, excited) in the past week.

Feelings of Social Rejection—Feelings of social rejection were measured using the *social evaluation* scale of the State Self-Esteem Scale (SSES; Heatherton & Polivy, 1991). The *social evaluation* subscale uses 7 items to measure the degree to which individuals feel that they are valued by the members of their social group. The scale has been validated as a measure of felt rejection; social rejection inductions reliably produce temporary reductions in scores on this subscale of the SSES (Gruenewald, Kemeny, Aziz, & Fahey, 2004). Example items include, "I feel inferior to others at this moment" and "I feel that others

respect and admire me" (reverse scored). Participants rated the extent to which they felt each item described their thoughts in the past week on a scale from 1 (Not at all) to 5 (Extremely). Although scores are generally coded such that higher scores indicate greater feelings of social acceptance, for the purposes of the present study the scale was scored such that higher scores indicate greater feelings of *social rejection*.

General Rumination—*General rumination* was measured using the 6 highest-loading items from the 12-item rumination subscale of the Rumination-Reflection Questionnaire (p. 293, Trapnell & Campbell, 1999). Participants rated the extent to which each item characterized them in the past week from 1 ("strongly disagree") to 5 ("strongly agree"). Example items include, "I tended to ruminate or dwell on things that happened to me for a really long time afterward", and "Often I'm playing back over in my mind how I acted in a past situation".

Anger Rumination—*Anger rumination* was measured using the 6 highest-loading items from the Anger Rumination Scale (Sukhodolsky, Golub, & Cromwell, 2001). Participants rated the extent to which each item characterized them in the past week on a scale from 0 ("almost never") to 3 ("almost always"). Example items: "In the past week, I've pondered the injustices that have been done to me", and "In the past week, whenever I experienced anger, I kept thinking about it for a while."

Impulsive Behavior—Impulsive behavior was measured using the UPPS-P Impulsivity scale (Whiteside & Lynam, 2001). Participants were asked to rate the extent to which each item had been true for them in the past week on a scale from 1 ("Not at All") to 4 ("Very much"). Example items include, "It was hard for me to resist acting on my feelings" (*negative urgency*), "When I was happy, I tended to do things that could cause problems in my life" (*positive urgency*), "My thinking was careful and purposeful" (*lack of premeditation*), "I finished what I started" (*lack of perseverance*, and "I sought out new experiences and sensations" (*sensation seeking*).

Analytic Plan

All variables were screened for distributional normality using procedures defined by Tabachnick and Fidell (2000). Each outcome variable was screened for distributional normality. A majority of the outcomes were significantly positively skewed (as defined by Tabachnick and Fidell, 2000), and a square-root transformation was applied. In each case, square root transformation reduced distributional skew to nonsignificance. Transformed variables included all of the PAI-BOR scales, the BSL-23, the MSI-BPD, Negative Affect, Anger Rumination, and Negative Urgency. Preliminary analyses using non-transformed outcome variables produced residuals that were not normally distributed, confirming the need to use the transformed outcome variables in final models. Following these screening procedures, both between- and within-person (i.e., change) reliabilities were computed for each weekly scale using SAS PROC VARCOMP and equations provided by Cranford et al. (2006). Substantive analyses were conducted using multilevel models in SAS PROC MIXED with weekly assessments at Level 1 and people at Level 2.

Weekly E2 and P4 were person-centered to isolate the within-person component of the variable (i.e., [This Week's E2] – [Person's Average E2 Across All Weeks]). Therefore, weekly E2 and P4 variables reflect current deviations in E2 or P4 from one's own person mean for each hormone, with positive values reflecting higher-than-usual levels for that individual and negative values reflecting lower-than-usual levels for that individual (Enders & Tofighi, 2007). See Figure 1 for a visual depiction of this centering method[2]. Note that this weekly index of E2 levels relative to one's person mean is not the same as the between-person measure indexing individual differences in the degree of within-person variance across a given number of assessments, as used in DeSoto et al., 2003. The following method was used to compute DeSoto and colleagues' individual difference measure of within-person variance in hormones for a given participant: each of the four weekly deviation scores were squared, summed, then divided by 4 (the number of samples).

Between-person predictors were standardized to M=0 and SD=1. Initial null multilevel models (i.e., models with no predictors) for each variable allowed for the calculation of intraclass correlation coefficients (ICCs). In addition, these models were used to estimate null model intercepts as a proxy for sample means; given dependencies in the data, the null model intercept is a more valid estimate of sample mean (see Singer & Willett, 2003).

Two sets of substantive multilevel models were used to test the first two study hypotheses. First, models were run predicting each outcome from (1) weekly deviation from one's mean E2, (2) weekly deviation from one's mean P4, and 3) their interaction. Second, models were run predicting each outcome from (1) weekly deviation from one's mean E2, (2) weekly deviation from one's mean P4, (3) their interaction, (4) trait BPD features, measured as one's average scores on the weekly PAI-BOR total scale across all 4 weeks, (5) the interaction between trait BPD features and weekly deviation in E2, (6) the interaction between trait BPD features and weekly deviation in P4, and (7) the three-way interaction between trait BPD features, deviation in E2, and deviation in P4. Where significant interactions emerged, they were probed at 1 standard deviation both above and below the mean of the relevant moderator(s). Using these estimates, standardized coefficients (indicated as β, analogous to r) for the significant simple effects of within-person hormonal changes on the outcome were calculated; this was accomplished by dividing the standard deviation of the predictor by the standard deviation of the outcome, then multiplying the dividend by the unstandardized gamma coefficient for the simple effect of hormonal change (Katz, 2006; Herr, Keenan-Miller, Rosenthal, & Feldblum, 2013). To test the final hypothesis, person-level averages and variances for E2 and P4 were computed for each individual and correlated with the individual's average score on the total scale of the PAI-BOR.

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[2]To account for the possibility that inclusion of current hormone level in the calculation of person hormone means led to skewed estimation of current hormone deviation (relative hormonal status), an alternative deviation variable was created using an alternative person mean that was calculated without the current week's hormone level (i.e., the average of the other three measurements within a given woman). All analyses were run using both deviation scores. None of the outcomes presented in the results section differed substantially when this alternative deviation score was utilized; therefore, we opted to report results using the traditional method of within-person centering described in the main text (Enders & Tofighi, 2007).

For multilevel models, the significance of changes in −2 log likelihood were evaluated in a stepwise manner, comparing: (1) a null model with no predictors and a random intercept, (2) a model adding all relevant predictors for testing hypotheses as fixed effects, and (3) several model adding random effects for either or both within-person predictors (e.g., deviation in E2 and deviation in P4). Random effects were only retained in models where the improvement in model fit was significant with their inclusion.

The present study examined the following 17 outcome variables: PAI-BOR total, as well as each PAI-BOR subscale (Affective Instability, Identity Disturbance, Negative Relationships, Self-Harm), MSI-BPD total, BSL-23 total, Negative and Positive Affect (PANAS), Feelings of Social Rejection (SSES), General Rumination (RRQ), Anger Rumination (ARS), Negative and Positive Urgency (UPPS-P), Lack of Premeditation (UPPS-P), Lack of Perseverance (UPPS-P), and Sensation Seeking (UPPS-P). This large number of analyses meant that there was an inflated chance of type 1 error. However, the relatively small sample size and preliminary nature of this study made a strict correction for multiple tests (e.g., Bonferroni) impractical. Therefore, the significance level was set at <.01 for all analyses in an attempt to mitigate the possibility of type 1 error.

Results

Descriptive Analyses

No participant withdrew from the study, and all missed laboratory sessions were rescheduled; therefore, 160 data points were collected for each measure. Table 1 lists null model intercepts (analogous to sample means) and standard deviations for each weekly variable in the study. Table 1 also lists ICCs for each weekly measure. Although ICCs in Table 1 suggest that all weekly measures showed significant between-person clustering, the measures varied widely in the degree to which they varied within participants across weeks. In addition, Table 1 lists two reliabilities for each measure estimated using PROC VARCOMP in SAS 9.3 and equations given by Cranford and colleagues (Cranford et al., 2006). The first measure (R_{1F}) estimates reliability of a measure between participants at a given week, and the second measure (R_C) estimates reliability of measure change within a given participant. All reliabilities were adequate to excellent in the present study.

Trait BPD features was operationalized as a participant's average score on the total 24-item PAI-BOR scale (ranging from 0 to 3) across four weeks. Examination of the properties of this variable (n = 40) are as follows: Mean = 1.02, SD = .67, Range = .15 to 1.79, Skew = .91, SE Skew = .19. When compared with normative distributions of PAI-BOR total score in undergraduates (e.g., Jackson & Trull, 2001; n = 4,682, Mean = 1.03, SD = 44), the present sample showed a similar average level of PAI-BOR symptoms but a greater standard deviation, indicating greater variability across levels of the PAI-BOR in this sample. Further, one's average score on the total PAI-BOR scale was strongly correlated with number of BPD symptoms on the SCID-II ($r = .72$, $p < .0001$).

Descriptive menstrual cycle statistics indicated that our screening procedures had succeeded in recruiting women with normal (i.e., 25–35 days) menstrual cycle lengths (average menstrual cycle length in the present study = 29.67 days, SD = 4.30). Inspection of

histograms and descriptive information indicated that menstrual cycle day was not related to day of session 1 (mean menstrual cycle day for session 1 = 14.79, SD = 9.59, Range = 1–34). In addition, there were no significant linear or quadratic effects of cycle day (i.e., days since beginning of last menstrual period) on session frequency in the full sample (p's > .53), and inspection of histograms confirmed roughly equal distribution of sessions across menstrual cycle phases. Therefore, the timing of sessions did not appear to be associated with the cycle—women were not more or less likely to have a session at any particular point in their cycle.

Testing Hypothesis 1: Do Weekly Deviations in E2 and P4 Predict Concurrent Levels of BPD Features, Symptoms, and Correlates?

The first set of models predicted weekly BPD features, symptoms, and correlates from weekly fluctuations around one's mean levels of both E2 and P4, as well as the interaction between those two deviations. In each case, model fit was improved with the inclusion of random effects for E2 deviation and P4 deviation, indicating the presence of individual differences in the within-person effects of E2 and P4 on weekly reports of BPD features, symptoms, and correlates. Effects of hormone deviations are interpreted as follows: a positive relationship indicates that higher-than-usual levels of hormone for a given woman are associated with greater current reported levels of that outcome, whereas a negative relationship indicates that higher-than-usual levels of a hormone for a given woman are associated with lesser current reported levels of that outcome.

For the majority of outcomes, neither weekly deviation in E2, weekly deviation in P4, nor their interaction significantly predicted concurrent outcomes (all p's > .20); however, there were a few exceptions. Weekly deviation in E2 predicted concurrent levels of *negative urgency* (negative emotion-related impulsivity), *positive urgency* (positive-emotion related impulsivity), and *lack of perseverance* on the UPPS-P such that higher-than-usual E2 was associated with lower current reports of negative urgency ($\gamma = -.12$, $SE = .04$, $t(117) = -3.08$, $p = .003$; $\beta = -.12$), *positive urgency* ($\gamma = -.11$, $SE = .03$, $t(117) = -3.02$, $p = .003$; $\beta = -.11$), and *lack of perseverance* ($\gamma = -.16$, $SE = .05$, $t(117) = -3.01$, $p = .003$; $\beta = -.17$). In addition, the two-way interaction between deviation in E2 and deviation in P4 was a significant predictor of the Negative Relationships subscale of the PAI-BOR (Interaction $\gamma = -.10$, $SE = .03$, $t(117) = -3.24$, $p < .001$) such that E2 deviations showed a negative association with concurrent relationship problems only at higher-than-usual P4.

In summary, although simple effects of hormones were generally not significant, higher-than-usual E2 was associated with less emotion-related impulsivity and a greater ability to persist on difficult tasks in the full sample. Further, higher-than-usual E2 was associated with fewer difficulties with relationships as measured on the PAI-BOR, but only when P4 was higher than usual. However, because all of the hormonal links just described are qualified by three-way interactions described in the next section, they are not depicted as figures or discussed further.

Testing Hypothesis 2: Do Higher Trait BPD Features Strengthen the Links Between Weekly Deviations in E2 and P4 and Expression of BPD Features and Correlates?

A second set of models tested the hypothesis that deviations in E2, P4, and their interaction would be more predictive of weekly BPD features, symptoms, and correlates among women at risk for BPD—that is, women high in trait levels of BPD features, which was operationalized as each individual's mean score across 4 weeks on the total PAI-BOR scale. The results of each of these multilevel models are reported in detail in Tables 2 (BPD features and symptoms) and 3 (BPD correlates), and significant two-and three-way interaction effects are depicted in Figure 2 (BPD features and symptoms) and Figure 3 (emotional, cognitive, and behavioral BPD correlates). Figures 2 and 3 depict significant two-way interactions; where three-way interactions were significant, only significant two-way interactions are depicted (i.e., the interaction of E2 and P4 at high (+1 SD) levels of trait BPD features).

For most outcomes, there was a significant three-way interaction between trait BPD features, weekly E2 deviation, and weekly P4 deviation predicting outcomes, such that the two-way interaction between E2 deviation and P4 deviation was significant only among women who were high (+1 SD) in trait BPD features. To further decompose this three-way interaction, we tested the simple effects of E2 deviation on each outcome at both lower-than-usual (−1 SD) and higher-than-usual (+1 SD) levels of P4 among women high (+1 SD) in trait BPD. The standardized simple effects of E2 deviation at lower- and higher-than usual P4 are presented in Table 4. To summarize the general pattern of effects depicted in Figures 2 and 3: among women at higher risk for BPD (+1 SD on the average PAI-BOR total[3]), P4 moderated the association of E2 deviation with current BPD features, symptoms, and correlates. This interaction between ovarian hormones among women high in trait BPD features took an identical form across outcomes: Only when P4 was higher than usual, there was a significant negative association between E2 deviation and outcomes such that lower-than-usual levels of E2 appeared deleterious and higher-than-usual levels of E2 appeared protective.

Although the three-way trait BPD X E2 X P4 interaction described above was significant for most outcomes, there were several weekly outcomes that were predicted only by the interaction of trait BPD features with weekly E2 deviation. Specifically, trait BPD features interacted with E2 deviation to predict weekly scores on negative affect, general rumination, lack of perseverance, and identity disturbance. As with the three-way interactions above, probing these two-way interactions at high (+1 SD) and low (−1 SD) levels of trait BPD revealed that higher-than-usual levels of E2 were associated with positive outcomes only among women high (+1 SD) in trait BPD features. Specifically, among women high in trait BPD features, higher-than-usual E2 predicted lower *negative affect* (E2 $\gamma = -.23$, $SE = .08$, $t(117) = -2.86$, $p = .004$; $\beta = -.12$), lower *general rumination* (E2 $\gamma = -.28$, $SE = .09$, $t(117) = -3.12$, $p = .002$; $\beta = -.27$), lower *lack of perseverance* (E2 $\gamma = -.24$, $SE = .05$, $t(117) = -4.98$, $p < .001$; $\beta = -.15$), and lower *identity disturbance* (E2 $\gamma = -.20$, $SE = .06$, $t(117) =$

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[3]Roughly 32.5% (13/40) women in this sample fell at or above +1 standard deviation on the average PAI-BOR total score.

−3.45, $p < .001$; $\beta = -.14$). Finally, there were no significant moderated associations of hormone deviations with sensation seeking.

Testing Hypothesis 3: Are Individual Differences in the Degree of Within-Person Variance in E2 or P4 Associated with Average BPD Features?

DeSoto, Geary, Hoard, Sheldon, & Cooper (2003) found that a *between-person* index of within-person variance in E2 (as measured using simple variance score at the between-person level; see Analytic Plan) was positively correlated with average scores on the weekly PAI-BOR total score. Given the nearly identical study design to that of DeSoto and colleagues (2003), we aimed to replicate and extend their finding by examining correlations between a woman's within-person variance in E2 and P4 across four weeks and average BPD features. Variance scores for both E2 and P4 were calculated for each woman. Contrary to De Soto and colleagues' findings, there were no significant correlations of within-person variance in E2 with either the average total PAI-BOR score ($r(40) = -.07$, $p = .63$) or any PAI-BOR subscale (all ps > than .40). Furthermore, post-hoc power analyses revealed that, with 40 women sampled across 4 weeks and no missing data (n = 160 assessments), we had adequate statistical power to detect the effect size ($r = .45$) described by DeSoto and colleagues. Therefore, the present study did not replicate previous findings that a between-person measure of within-person variance in E2 across 4 weeks is associated with BPD features. In addition, no significant correlations of an individual's variance in P4 with average BPD features were found (all ps > .60). However, consistent with DeSoto and colleagues' findings, there were no significant relationships between average scores on the PAI-BOR total score and either average levels of E2 ($r = -.06$, $p = .42$) or P4 ($r = .09$, $p = .21$), further supporting the notion that absolute levels of ovarian hormones are not predictive of psychopathology (Schmidt et al., 1998).

Discussion

BPD is a disabling psychological condition characterized by fluctuations in emotional experiences, cognitive control, and harmful impulsive behaviors. Given the higher rates of diagnosis and impairment in women (Grant et al., 2008), it has been suggested that naturally occurring changes in E2 and P4 across the female reproductive cycle may modulate the expression of BPD features, thus contributing to the inconsistency characteristic of BPD. Furthermore, cyclical changes in ovarian hormones have been linked to greater expression of negative affect, poorer cognitive control, and impulsive behaviors such as substance abuse, binge eating, and suicidality. The purpose of the present study was to provide an initial investigation of the prospective, within-person associations of E2 and P4 with concurrent BPD features and other closely related, homogeneous constructs.

Hypothesis 1 stated that all women would report higher features and correlates of BPD when E2 was lower than usual or P4 was higher than usual (i.e., relative to one's person mean levels of these hormones). In general, this hypothesis was not supported. Further, the few significant effects that emerged were qualified by significant two- or three-way interaction effects found while testing Hypothesis 2.

Hypothesis 2 stated that the effects of E2 and P4 would be more pronounced among women with higher trait levels of BPD features, evidenced by significant interactions between trait BPD features and within-person changes in hormones. This hypothesis was strongly supported in the present sample, with results generally indicating interactive effects of E2 and P4 deviations only among women high in trait BPD features. Only among women with higher (+1 SD) trait levels of BPD features, there were interactions between weekly deviations in E2 and P4 predicting concurrent reports of many BPD features and symptoms (PAI-BOR total score, as well as affective instability, negative relationships, and self-harm subscales, BSL-23, and MSI-BPD) and BPD correlates (felt social rejection, anger rumination, negative urgency, positive urgency, and lack of premeditation). The form of this interaction among these at-risk women appeared identical for each of these outcomes: only when P4 was higher than usual, the current deviation from one's average E2 was negatively related to symptoms such that lower-than-usual E2 appeared detrimental and higher-than-usual E2 appeared protective (see Figures 2 and 3). In addition, several outcomes were predicted only by the interaction of trait BPD features and E2 deviation, with high trait BPD women showing protective effects of higher-than-usual E2 on negative affect, general rumination, lack of perseverance, and the identity disturbance subscale of the PAI-BOR.

Although these effects are preliminary and should be interpreted cautiously, they suggest promising new hypotheses regarding the role of ovarian hormone fluctuation in BPD symptom expression. Notably, effect sizes were generally medium to large (see Table 4); furthermore, upon examination of the figures, which depict the associations in terms of the full response scale for each outcome, it appears that most of these effects could represent clinically meaningful change. For example, at higher-than-usual P4, predicted current anger rumination moves from "often" at lower-than-usual levels of E2 to "almost never" at higher-than-usual levels of E2.

Although the present study did not time hormone samples to cycle events (e.g., ovulation, menses), it is possible to generate hypotheses regarding the implications of the current findings for cyclical changes in symptom expression among at-risk women. The simpler two-way interactions between trait BPD and E2 deviation may suggest that ovulation is a time of relatively lower negative affect, rumination, and identity disturbance, as well as a relatively enhanced ability to persist on difficult tasks among women high in trait BPD features. The more complicated three-way interaction may suggest that the luteal phase, which is characterized in all women by higher-than-usual P4, may be a time of alternating low and high risk for symptom expression among at-risk women. Compared with the follicular phase, in which P4 is at extremely low, often undetectable levels, the luteal phase is characterized broadly by the appearance of P4 following ovulation (i.e., higher-than-usual P4), which appeared to unmask effects of E2 deviations among vulnerable women in our study. The present findings lead to the hypothesis that, under these conditions of higher-than-usual P4 during the luteal phase: (1) periods of relatively lower luteal E2 that occur following ovulation (i.e., post-ovulatory drop in E2) and during the few days preceding the onset of menses (i.e., late luteal phase drop in E2) are associated with increased risk for BPD symptom expression, whereas (2) periods of relatively higher luteal E2 (e.g., during the secondary E2 peak in the mid luteal phase) are associated with very low levels of BPD symptoms. These hypotheses are merely suggested—and not explicitly supported—by the

present study. Additional work will be needed to replicate the hormonal effects seen here and to determine whether they are actually linked to menstrual cycle events.

Hypothesis 3 represented an attempt to duplicate the results of a study with a nearly identical study design that found that between-person differences in within-person variability in E2 across 4 weekly sessions predicted greater average BPD features (DeSoto, Geary, Hoard, Sheldon, & Cooper, 2003). Despite adequate statistical power for replication—in fact, the present study had a larger number of observations than the original study—neither variance in E2 nor variance in P4 was significantly associated with average BPD symptoms. Further work is needed to determine whether some moderating variable can account for these disparate findings. However, the results of the present study illustrate the power of using ovarian hormone fluctuations to predict *concurrent* (rather than person average) levels of BPD features and symptoms.

Potential Physiological Mechanisms

Although the present study provides useful information about how ovarian hormones and BPD features may covary over time in at-risk women, more rigorous experimental studies will be necessary to make causal inferences regarding the pathophysiological role of hormone deviations in BPD feature expression. Nonetheless, there are many plausible biological pathways through which E2 and P4 might exert direct or indirect effects on symptoms of BPD. Examples include effects of ovarian hormones on cholinergic, serotonergic, dopaminergic, and adrenergic circuits (McEwen, 2002), effects of hormones on both the structure and reactivity of limbic structures (Ossewaarde et al., 2010; Ossewaarde et al., 2013), as well as more general neuroprotective and antiinflammatory effects of ovarian hormones (McEwen & Alves, 1999). Although a discussion of the specific physiological mechanisms of the interactive effects presented here would be premature given the correlational nature of this study, previous work does indicate that E2 and P4 interact physiologically to predict female mood and behavior in both directions, including P4 facilitation or reversal of E2 effects (Pazol, Wilson, & Wallen, 2004; Zweifel & O'Brien, 1997) and E2 facilitation of P4 effects (Romano, Krust, & Pfaff, 1989; Laconi, Casteller, Garguilo, Bregonzio, & Cabrera, 2001; Wihlback, Nyberg, Backstrom, Bixo, & Sundstrom-Poromaa, 2005). Experimental work will be necessary to replicate the interactions found here and to characterize the nature of physiological interactions of E2 and P4.

Potential Psychopathological Mechanisms

The results of this preliminary investigation also provide some clues as to the psychological mechanisms through which relative changes in ovarian hormones may increase BPD feature expression. Among women with high BPD features, within-person changes in ovarian hormones exerted medium-to-large effects on several key mechanisms of BPD dysfunction in the present study—especially feelings of social rejection, anger rumination, negative and positive urgency (i.e., emotion-related impulsivity), and lack of premeditation (i.e., classic impulsivity). Therefore, interpersonally-related dysregulation in emotional and cognitive processes (perceived social rejection, anger rumination, emotional urges) may be particularly sensitive to within-person changes in ovarian hormones. These findings are especially significant given that stressful interpersonal events and social rejection often

trigger impulsive behaviors in BPD (Berman et al., 2006; Brown et al., 2002). Indeed, perceptions of social rejection lead to the expression of BPD features even in nonclinical samples, including impulsivity and risk-taking (Twenge, Catanese, & Baumeister, 2002), anger and aggression (Sampson & Laub, 1990; Twenge et al., 2007), chronic feelings of emptiness (Twenge, Catanese, & Baumeister, 2003), and even identity confusion or malleability (Richman et al., 2014). If within-person changes in ovarian hormones indeed predict perceived social rejection among women at risk for BPD, this disturbance may mediate the link between within-person changes in hormones and other negative outcomes —especially anger and interpersonal aggression, general emotion-related impulsivity, and difficulty pursuing goals (Hughes, Crowell, Uyeji, & Coan, 2012).

Additional work with more fine-grained, frequent sampling methods (e.g., ecological momentary assessment) are required to clarify which associations of within-person changes in hormones with outcomes are the result of direct physiological pathways and which are downstream psychological sequelae of primary effects. Such studies would also allow one to examine the effects of hormones on both concurrent self-impressions (i.e., today's E2 predicting today's ratings; as in the present study) *and* lagged effects of hormones (e.g., today's E2 predicting ratings on the days that follow). Finally, given that the majority of within-person variance in BPD features and symptoms occurs on a more frequent time scale (i.e., across minutes rather than weeks; Ebner-Priemer & Sawitzki, 2007), studies using high-frequency ecological momentary assessment will be useful for determining how daily or weekly changes in hormones interact with specific daily stressors to influence momentary expression of symptoms.

Limitations and Future Directions

As a preliminary attempt to characterize the association between within-person changes in ovarian hormones and BPD feature expression, the present study has several limitations that will inform future work. Perhaps most importantly, the use of a non-clinical sample limits the generalizability of these findings. Although the sample was selected to create a flat distribution of BPD features, the distributions for BPD-related outcomes were still relatively positively skewed, and only 5 participants met criteria for BPD. Future studies should include larger samples and include more women meeting diagnostic criteria for BPD. On the other hand, the present study's emphasis on dimensional risk and the oversampling of those both low and high in trait BPD serves to increase generalizability to the general population.

The present study utilized average PAI-BOR total score—a measure of BPD features and broad risk for BPD diagnosis—as a moderator of within-person hormonal effects. As previously mentioned, BPD is an extremely heterogeneous construct, and this is reflected in the items and scales of the PAI-BOR. Therefore, one's average score on this measure of BPD features is not a particularly useful moderator for developing a broader theory of risk for sensitivity to within-person hormonal changes. Therefore, some core features of BPD, including negative affectivity (PANAS Negative Affect) and impulsivity (UPPS-P Negative Urgency and Lack of Premeditation), were considered in alternative post-hoc moderation analyses. However, these alternative moderators (as measured using the woman's average

score across four weekly measurements) did not significantly interact with hormone deviations to predict weekly outcomes (all interaction p's > .15).

In order to develop more fruitful theoretical models of risk for hormone sensitivity, future work will need to determine which specific aspects of BPD or risk factors for BPD confer risk for psychological and behavioral sensitivity to within-person ovarian hormone changes. The underlying moderators of hormone sensitivity may be environmental (e.g., early life adversity or history of abuse), interpersonal (e.g., rejection sensitivity, attachment disturbances), physiological (e.g., genetic predisposition to low prefrontal dopamine, HPA-axis dysregulation), or some combination of risk factors at multiple levels. Future studies should utilize more comprehensive assessments of developmental, personality, and psychophysiological risk factors and model risk for hormone sensitivity at several levels.

Another limitation of the present study is the hormonal sampling schedule, which was infrequent (4 samples across one month) and not timed to capture reproductive cycle events (e.g., ovulation, menstruation). Individual differences in the extent to which these important cyclical events and their associated hormonal profiles (e.g., peak E2 at ovulation) were captured by assessments due to random differences in assessment schedules or cycle lengths may have significantly reduced the reliability of person mean estimations and, by extension, weekly deviations from those means. Because assessments were not timed to the cycle, the present study focused broadly on within-person deviations from E2 and P4 person means rather than speaking directly to the effect of the cycle; in the future, more reliable measures of person averages (i.e., a greater number of hormonal assessments timed to the cycle) will be necessary to replicate the effects of hormone deviations and to determine whether they map reliably onto reproductive cycle events. Where additional hormone measurements are not possible, urinary ovulation testing or measurements of basal body temperature may be used to improve the timing of samples to menstrual cycle events.

It is also possible that the hormonal associations found here are due to some other variable(s) that fluctuate similarly to E2 and P4 across the cycle. As a preliminary test of the robustness of these links, we re-ran the models found in Tables 2 and 3 controlling for linear and quadratic effects of menstrual cycle day as well as their interactions with trait BPD features. Effect sizes and significance levels of hormonal predictors in these new models did not differ meaningfully from those presented in Tables 2 and 3, indicating that hormonal deviations from one's mean predicted BPD feature expression over and above a simple quadratic menstrual cycle pattern. Although these results are promising, further work will need to rule out the possibility that some third variable that is biologically regulated by (e.g., oxytocin) or derived from (e.g., allopregnanolone) ovarian hormones are mediating hormone effects.

The present study did not examine the impact of physical symptoms on psychological functioning. This is a key weakness, given that recent work revealed that nearly 30% of premenstrual psychological symptoms could be explained by increased physical symptoms (Kiesner, 2009; Kiesner & Pastore, 2010). Future work should track physical symptoms to determine whether greater cyclical physical symptoms are responsible for cyclical changes in psychological distress among women with high trait levels of BPD features.

Two final limitations should be noted. First, despite setting alpha at .01, the large number of statistical tests (multilevel models predicting 17 outcomes) introduces a very real possibility of type 1 error. Second, the present study had inadequate statistical power to detect small interactive effects, and therefore cannot definitively rule out the presence of small undetected effects. Larger sample sizes may be necessary to detect small interactive effects of trait variables with within-person changes in hormones to predict BPD feature expression.

Clinical Implications

Although additional work is needed to replicate and extend these hormone-behavior links to clinical populations, the consistency and size of the associations found here indicate that within-person ovarian hormone changes may have a substantial impact on the emotional, cognitive, and behavioral functioning of women at high risk for BPD. If replicated in larger studies with clinical populations, the model that fluctuating ovarian hormones increase vulnerability to BPD symptom expression in a potentially predictable manner has several important clinical implications. First, female patients with high trait BPD features may benefit from an understanding of their greater sensitivity to cyclical changes in hormones. In dialectical behavior therapy (DBT), a skills-based empirically-supported treatment for BPD, the inclusion of cycle day or phase on daily symptom tracking systems (e.g., on DBT diary cards or smartphone applications) may reveal reliable patterns of symptom expression across the menstrual cycle. These insights might improve predictability of and perceived control over daily symptoms.

Second, awareness of which key processes fluctuate for a given woman may lead to targeted reminders for skill use during days or weeks of increased vulnerability. The results of the present study suggest that reminders to practice skills for noticing and responding effectively to anger rumination or feelings of rejection during periods of vulnerability may be especially helpful. Depending on an individual woman's symptom profile, different types of skills may be relevant to compensating for vulnerability at key times of the month, including the ability to exercise nonjudgmental present-centered awareness of physical symptoms, rumination, or emotional lability (e.g., DBT mindfulness skills), the ability to label, understand, and respond effectively to emotions and thoughts as they arise (e.g., DBT emotion regulation skills), the ability to tolerate distress without acting on potentially harmful impulses (e.g., DBT distress tolerance skills), and the ability to interact with others in useful ways even in the presence of strong emotion (e.g., DBT interpersonal effectiveness skills).

Additionally, these results may have implications for the study of PMDD. Two of the most commonly reported symptoms of PMDD are rejection sensitivity and anger or irritability (Pearlstein et al., 2005). Although BPD and PMDD are distinct clinical entities, the fact that risk for BPD predicted strong links of ovarian hormone change to felt social rejection and anger rumination suggests that there may be some overlap in the phenotypes of these disorders. Future work is needed to determine the degree of symptom overlap in these disorders both at baseline and in response to normal within-person changes in hormones. Additional work should also examine the degree to which overlapping risk factors such as early life abuse account for similarities in these two disorders. If core psychological

processes in PMDD are similar to those of BPD, empirically-supported psychosocial treatments for BPD (e.g., DBT skills training) may also be effective for PMDD.

Conclusions

The present study provides preliminary evidence for a link between changing ovarian hormones and BPD feature expression. Additional work is needed to clarify whether there exists a true causal relationship between ovarian hormones and BPD feature expression, to determine whether these effects are specific to BPD features, to clarify the key BPD-related traits responsible for moderated hormone effects, and to characterize the specific physiological and psychological mechanisms underlying these associations. Continued research on both the psychological and physiological underpinnings of BPD symptom fluctuations will lead to treatments that are more focused, efficient, and effective.

Acknowledgements

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Highlights

We test associations of estradiol and progesterone with weekly borderline features.

Estradiol and progesterone interact to predict features for women high in trait BPD.

Estradiol deviations predict lower features and symptoms when progesterone is high.

Illustration of Between-Person and Within-Person Variability in One Woman's E2 Levels Across 4 Weeks

E2 Person Mean
(Between-Person Differences in E2 Levels)
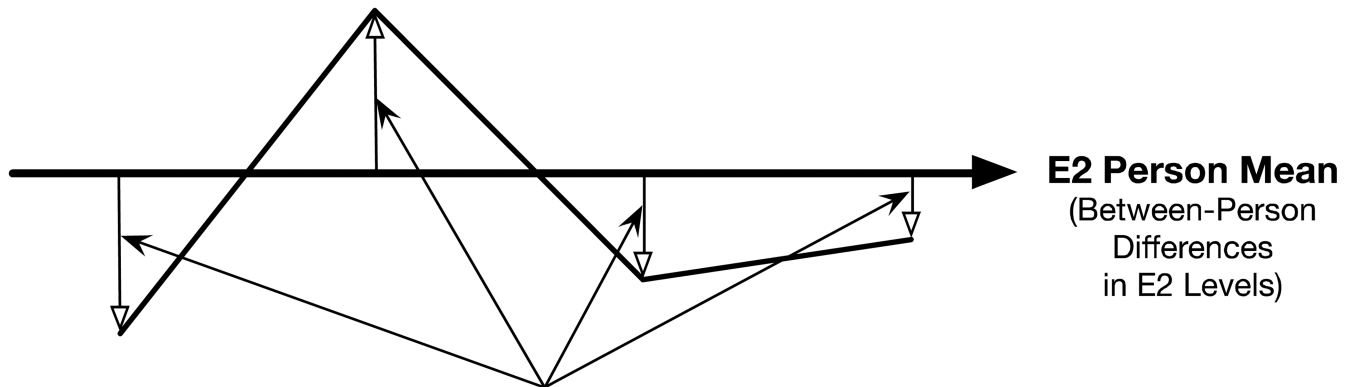
Weekly E2 Deviations from Person Mean
(Within-Person Changes in E2 Levels*)

Figure 1.
An illustration of one woman's hypothetical E2 levels across four weekly samples, labeling within-person and between-person variability. E2 = 17β-estradiol. *Represents a repeated measures, within-person variable.
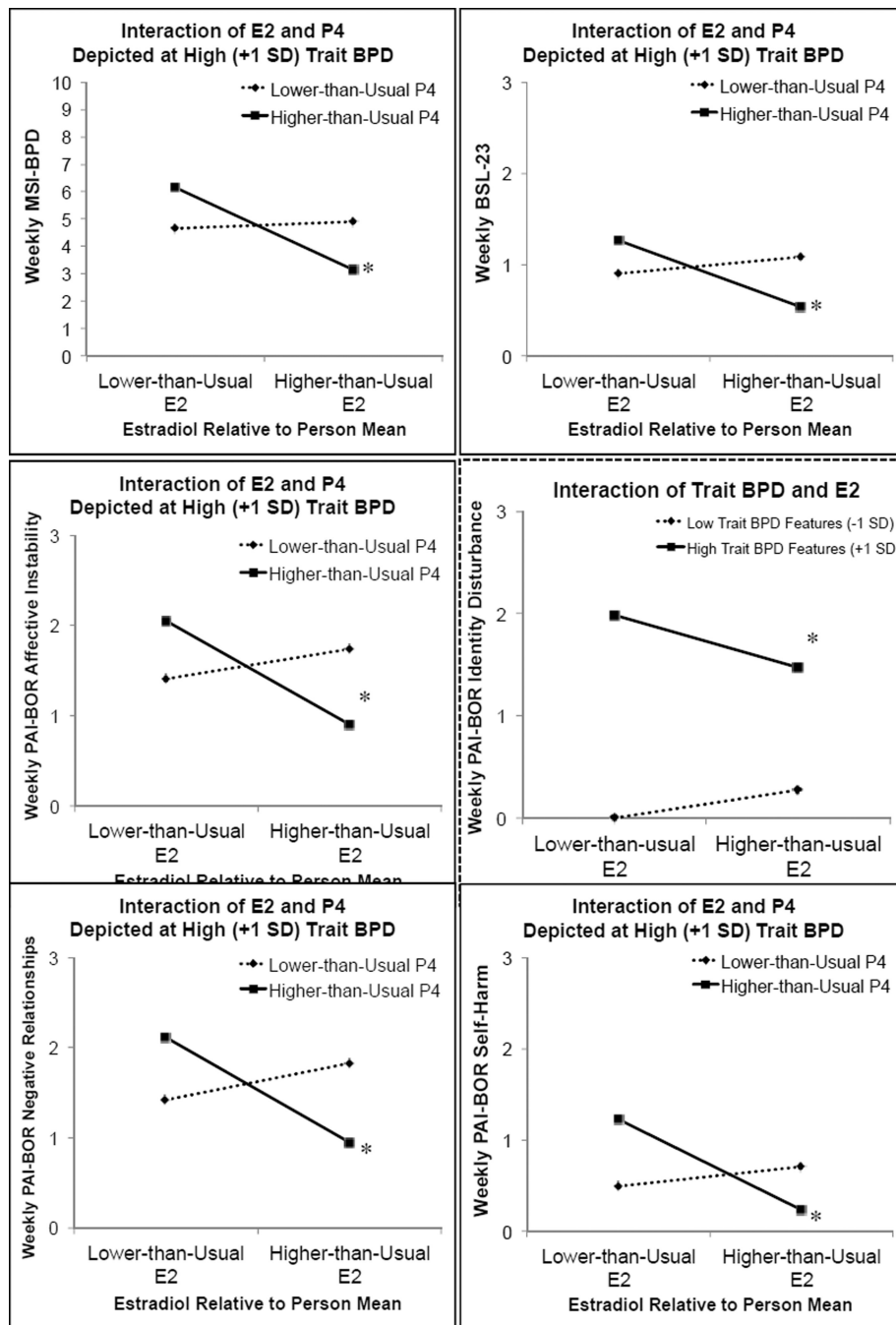
Figure 2.

Graphs depicting two-way interactions predicting weekly BPD features and symptoms from either (1) trait BPD X E2 deviation in all participants (dashed box; identity disturbance) or (2) E2 deviation X P4 deviation among women high in trait BPD (all other outcomes). *Note*. Y Axes depict the full response scale for each outcome. Low/lower-than-usual = 1 SD below mean. High/higher-than-usual = 1 SD above mean. PAI-BOR = Personality Assessment Inventory Borderline Subscale. MSI-BPD = McLean Screening Inventory for BPD. BSL-23 = Borderline Symptom
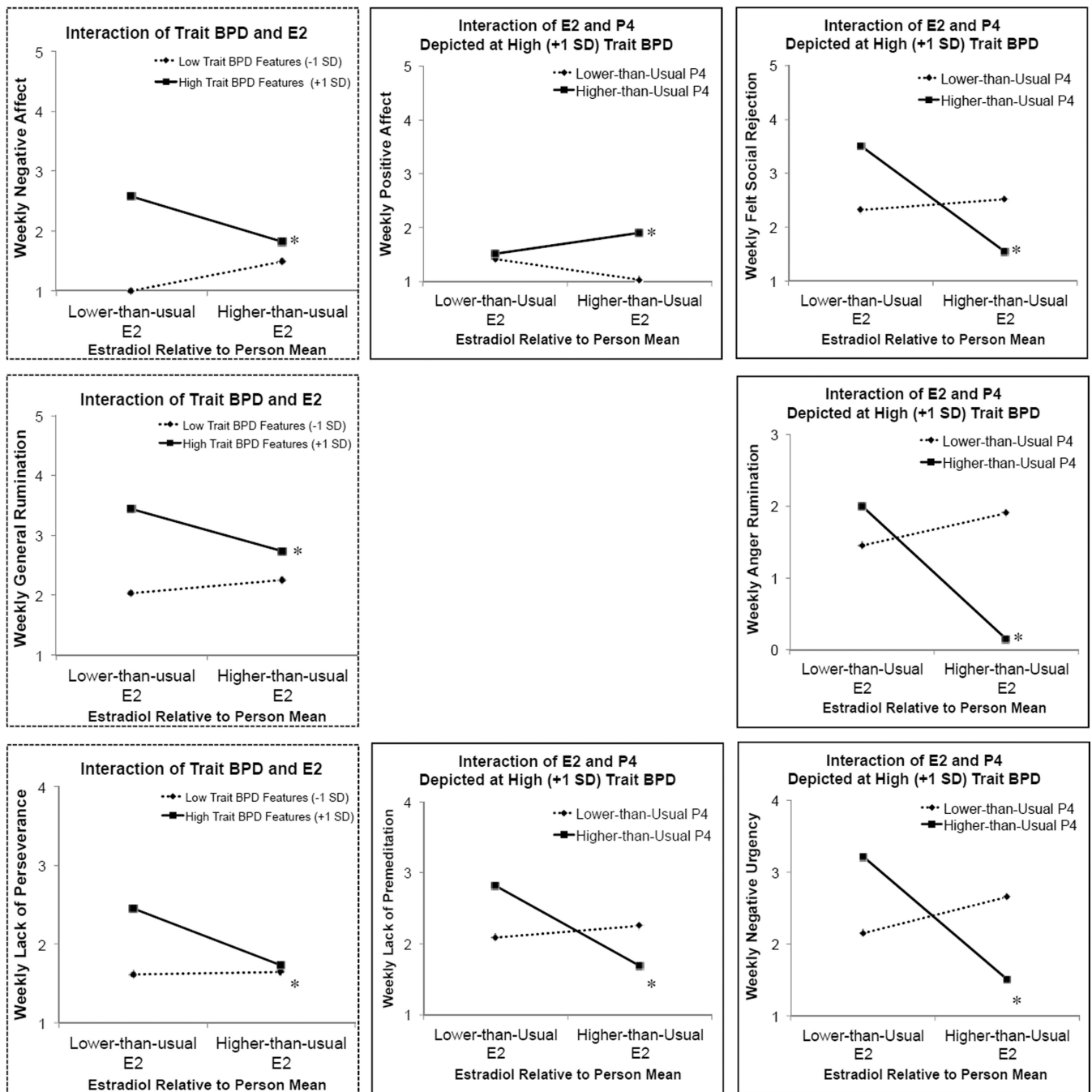
Figure 3.

Graphs depicting two-way interactions predicting BPD correlates from (1) the trait BPD X E2 deviation interaction in all participants (dashed boxes; negative affect, rumination, lack of perseverance) or (2) the E2 deviation X P4 deviation interaction among women high in trait BPD (all other outcomes).

Note. Y Axes depict the full response scale for each outcome. Low/lower-than-usual = 1 SD below mean. High/higher-than-usual = 1 SD above mean. Utilized for following scales:

PANAS for affect, RRQ for rumination, ARS for anger rumination, and UPPS-P for behavioral impulsivity.

Table 1

Null Model Intercepts, Intraclass Correlation Coefficients, and Indices of Between- and Within-Person Reliability for Weekly Measures

Variable	Null Model Intercept (SD)	ICC (Person-Level)	Reliability of Change Within Person (R_C)	Reliability Between People (R_{1F})
E2	3.41 (1.01)	.52	N/A	N/A
P4	92.91 (55.01)	.21	N/A	N/A
PAI-BOR Total Score[†]	.79 (.49)	.72	.74	.90
PAI-BOR - Affective Instability[†]	.74 (.66)	.70	.87	.79
PAI-BOR - Identity Disturbance[†]	.87 (.70)	.74	.75	.75
PAI-BOR - Negative Relations[†]	.80 (.62)	.70	.74	.83
PAI-BOR - Self-Harm[†]	.53 (.53)	.30	.80	.81
McLean Screening Inventory for BPD[†]	1.10 (1.26)	.62	.89	.80
Borderline Feature Checklist-23[†]	.61 (.47)	.81	.87	.67
PANAS – Negative Affect[†]	.81 (.54)	.63	.91	.69
PANAS – Positive Affect	1.72 (.57)	.71	.89	.71
SSES – Social Evaluation (Felt Social Rejection)	1.38 (.89)	.70	.87	.91
RRQ - Rumination Subscale – Short Form	2.61 (1.02)	.53	.83	.85
Anger Rumination Scale – Short Form[†]	.81 (.91)	.60	.99	.78
UPPS-P – Negative Urgency[†]	1.70 (.71)	.68	.68	.82
UPPS-P – Positive Urgency	1.84 (.58)	.60	.85	.76
UPPS-P – Lack of Premeditation	1.85 (.57)	.65	.64	.68
UPPS-P – Lack of Perseverance	1.84 (.64)	.57	.72	.63
UPPS-P – Sensation Seeking	2.24 (.73)	.67	.99	.78

Note.

Scores are presented as mean item responses.

ICC = Intraclass Correlation Coefficient. SD = Standard Deviation. PAI – BOR = Personality Assessment Inventory – Borderline subscale. PANAS = Positive and Negative Affect Scale. SSES = State Self-Esteem Scale – Social Evaluation Subscale; coded such that higher scores indicate greater felt rejection. MSI-BPD = McLean Screening Instrument for Borderline Personality Disorder. BSL-23 = Borderline Feature Checklist- 23-item Version.

[†] Analyses for these outcomes were performed using square root transformations of the outcome variable. However, null model intercepts have been squared so that they can be interpreted with respect to the original response scale.

Table 2

Multilevel Regression Models Predicting Weekly BPD Features and Symptoms from Weekly Deviation from Ovarian Hormone Person Means and their Interactions with Trait BPD Features

Parameter	PAI-BOR Total Score (0–3)	PAI-BOR Affective Instability (0–3)	PAI-BOR Identity Instability (0–3)	PAI-BOR Negative Relationships (0–3)	PAI-BOR Self-Harm (0–3)	MSI-BPD (# Endorsed out of 10)	BSL-23 (0–3)
				Fixed Effects			
Intercept	**.70** **(.01)**	**.74** **(.03)**	**.87** **(.09)**	**.81** **(.03)**	**.41** **(.03)**	**2.12** **(.15)**	**.60** **(.02)**
Trait BPD	**.45** **(.01)**	**.52** **(.03)**	**.58** **(.02)**	**.51** **(.03)**	**.16** **(.03)**	**1.72** **(.38)**	**.36** **(.09)**
Current E2$_{DEV}$	−.01 (.03)	−.05 (.03)	.002 (.03)	−.04 (.03)	−.01 (.02)	−.17 (.11)	−.04 (.03)
Current P4$_{DEV}$	−.007 (.02)	.02 (.03)	.001 (.03)	−.01 (.02)	.02 (.02)	.02 (.10)	−.02 (.02)
E2$_{DEV}$ × P4$_{DEV}$	−.03 (.02)	−.08 (.04)	.03 (.04)	−.09 (.05)	−.05 (.03)	−.16 (.14)	−.06 (.02)
Trait BPD × E2$_{DEV}$	−.10 (.04)	−.15 (.06)	**−.17** **(.04)**	−.10 (.05)	−.18 (.10)	−.26 (.12)	−.10 (.04)
Trait BPD × P4$_{DEV}$	−.04 (.03)	−.02 (.02)	−.02 (.03)	−.03 (.03)	.06 (.03)	−.09 (.10)	−.02 (.02)
Trait BPD × E2$_{DEV}$ × P4$_{DEV}$	**−.23** **(.02)**	**−.24** **(.07)**	.03 (.04)	**−.19** **(.04)**	**−.29** **(.06)**	**−.43** **(.12)**	**−.19** **(.04)**
				Random Parameters			
Intercept	.001 (.0001)	.02 (.01)	.004 (.004)	.01 (.01)	.02 (.01)	.65* (.25)	.65* (.23)
E2$_{DEV}$	.001 (.008)	.002 (.01)	.006 (.004)	.002 (.001)	.003 (.002)	.004 (.01)	.002 (.001)
P4$_{DEV}$	.002 (.007)	.004 (.01)	.007 (.003)	.01 (.009)	.004 (.003)	.002 (.001)	.008 (.01)
Residual	.06** (.002)	.12** (.03)	.13** (.01)	.12** (.02)	.08** (.01)	1.54** (.19)	1.58** (.38)
−2 Log Likelihood	42.3†	19.0†	18.4†	16.6†	33.6†	517.5†	70.4†

Note. Standard errors are in parentheses.

*
  $p < .01$.

**
  $p < .001$.

Trait PAI-BOR Total is z-scored.

Significant fixed effects are shown in bold.

† Change in −2 Log likelihood over a null model (a model with no predictors) is significant at $p < .001$.

E2DEV and P4DEV represent current deviations from one's mean hormone levels (i.e., person's hormone level this week – person's average hormone level across 4 weeks).

PAI-BOR = Personality Assessment Inventory – Borderline subscale. MSI-BPD = McLean Screening Instrument for Borderline Personality Disorder. BSL-23 = Borderline Feature Checklist- 23-item Version.

Trait PAI-BOR total refers to a participant's average score on the PAI-BOR total across all four weeks of measurement. All analyses here were performed on a square root transformation of the outcome variable. All coefficients and standard errors shown in this table have been squared so that they can be interpreted with respect to the original response scale. All outcomes (except the MSI-BPD) were scored as means; therefore, coefficients represent change in average item response per one unit change in the predictor.

Table 3

Multilevel Regression Models Predicting Weekly Expression of Emotional, Cognitive, and Behavioral Correlates of BPD from Ovarian Hormone Person Means and their Interactions with Trait BPD Features

Parameter	PANAS Negative Affect (0–3)	PANAS Positive Affect (0–3)	SSES Social Rejection (1–5)	RRQ General Rumination (1–5)	ARS Anger Rumination‡ (0–3)	UPPS-P Negative Urgency‡ (1–4)	UPPS-P Positive Urgency (1–4)	UPPS-P Lack of Premeditation (1–4)	UPPS-P Lack of Perseverance (1–4)	UPPS-P Sensation Seeking (1–4)
Fixed Effects										
Intercept	**.76** (.03)**	**1.71** (.08)**	**1.38** (.10)**	**2.61** (.11)**	**.79** (.07)**	**1.71** (.05)**	**1.85** (.06)**	**1.85** (.07)**	**1.86** (.07)**	**2.23** (.09)**
Trait BPD	**.38** (.03)**	**−.16** (.03)**	**.38** (.09)**	**.47** (.11)**	**.58** (.07)**	**.51** (.05)**	**.22** (.05)**	**.24* (.07)**	**.23* (.07)**	.12 (.07)
Current E2$_{DEV}$	−.10 (.06)	−.01 (.03)	−.04 (.04)	−.12 (.06)	−.20 (.16)	−.08 (.04)	−.08 (.05)	−.04 (.03)	−.17 (.09)	−.02 (.04)
Current P4$_{DEV}$	−.01 (.02)	−.004 (.002)	.04 (.04)	.03 (.06)	.04 (.04)	.0004 (.03)	−.02 (.03)	−.006 (.03)	.01 (.03)	−.05 (.03)
E2$_{DEV}$ × P4$_{DEV}$	.01 (.02)	.07 (.04)	−.03 (.05)	−.05 (.08)	−.10 (.06)	−.03 (.06)	−.07 (.04)	−.09 (.04)	−.05 (.05)	.01 (.05)
Trait BPD × E2$_{DEV}$	**−.19** (.05)**	.02 (.03)	−.13 (.06)	**−.23** (.07)**	−.10 (.07)	−.29 (.17)	−.17 (.09)	−.15 (.09)	**−.19** (.04)**	.03 (.04)
Trait BPD × P4$_{DEV}$	−.02 (.02)	.02 (.02)	.002 (.03)	−.11 (.06)	−.23 (.15)	−.03 (.03)	−.01 (.03)	.03 (.03)	−.02 (.03)	−.007 (.04)
Trait BPD × E2$_{DEV}$ × P4$_{DEV}$	−.01 (.04)	**.14** (.04)**	**−.23** (.05)**	−.06 (.09)	**−.49** (.09)**	**−.53** (.05)**	**−.23** (.07)**	**−.17** (.05)**	−.03 (.06)	.10 (.06)
Random Parameters										
Intercept	.03** (.007)	.25** (.06)	.47** (.12)	.35** (.10)	.18** (.05)	.07** (.02)	.15* (.05)	.21** (.05)	.18** (.04)	.38** (.09)
E2$_{DEV}$	.003 (.002)	.001 (.002)	.08 (.07)	.002 (.001)	.03 (.03)	.005 (.003)	.003 (.002)	.008 (.01)	.005 (.003)	.03 (.03)
P4$_{DEV}$	.002 (.001)	.002 (.001)	.03 (.04)	.004 (.01)	.01 (.008)	.004 (.002)	.01 (.009)	.02 (.01)	.03 (.002)	.02 (.02)
Residual	.11** (.01)	.10** (.01)	.18** (.02)	.47** (.06)	.25** (.03)	.14** (.01)	.12** (.01)	.13** (.02)	.16** (.02)	.15** (.02)
−2 Log Likelihood	160.9†	148.6†	271.3†	398.0†	261.2†	144.5†	189.6†	201.9†	215.4†	209.2†

Note. Standard errors are in parentheses.

*
$p < .01$.

**
$p < .001$.

Trait PAI-BOR Total is z-scored.

Significant fixed effects are shown in bold.

†Change in −2 Log likelihood over a null model (a model with no predictors) is significant at *p* < .001.

E2DEV and P4DEV represent current deviations from one's mean hormone levels (i.e., person's hormone level this week – person's average hormone level across 4 weeks).

PANAS = Positive and Negative Affect Scale. SSES = State Self-Esteem Scale – Social Evaluation scale; scored such that higher scores indicate greater felt rejection. RRQ = Rumination Reflection Questionnaire. ARS = Anger Rumination Scale. UPPS-P = UPPS-P Impulsive Behavior Scale.

Trait PAI-BOR total refers to a participant's average score on the PAI-BOR total across all four weeks of measurement. All analyses here were performed on a square root transformation of the outcome variable. All coefficients and standard errors shown in this table have been squared so that they can be interpreted with respect to the original response scale. All outcomes were scored as means; therefore, coefficients represent change in average item response per one unit change in the predictor.

Table 4

Standardized Simple Slope Effects of Weekly Deviation from E2 Person Mean on BPD Features, Symptoms, and Correlates at Lower-than-Usual P4 and Higher-than-Usual P4 among Women High in Trait BPD (+1 SD)

Outcome	Standardized Simple Effect of Weekly Deviation from E2 Person Mean (β)	
	At *Lower*-than-usual P4	At *Higher*-than-usual P4
PAI-BOR Total Score[†]	.02	**−.23**[**]
PAI-BOR Affective Instability[†]	.08	**−.62**[**]
PAI-BOR Identity Disturbance[†]	3-way Interaction N.S.	3-way Interaction N.S.
PAI-BOR Negative Relations[†]	.18	**−.33**[**]
PAI-BOR Self-Harm[†]	.06	**−.17**[*]
McLean Screening Inventory for BPD[†]	.12	**−.66**[**]
Borderline Feature Checklist-23[†]	.17	**−.42**[**]
PANAS Negative Affect[†]	3-way Interaction N.S.	3-way Interaction N.S.
PANAS Positive Affect	−.15	**.40**[*]
SSES Social Evaluation (Felt Rejection)	.05	**−.81**[**]
RRQ Rumination (SF)	3-way Interaction N.S.	3-way Interaction N.S.
ARS Anger Rumination (SF)[†]	.02	**−.91**[**]
UPPS-P Negative Urgency[†]	.15	**−.94**[**]
UPPS-P Positive Urgency	−.09	**−.42**[**]
UPPS-P Lack of Premeditation	.18	**−.73**[**]
UPPS-P Lack of Perseverance	3-way Interaction N.S.	3-way Interaction N.S.
UPPS-P Sensation	Seeking Interaction N.S.	3-way Interaction N.S.

Note.

[*]
p < .01.

[**]
p < .001.

For each significant three-way interaction between trait BPD features, E2 deviation, and P4 deviation, the two-way E2 × P4 interaction was significant only among women high (+1 SD) in trait BPD features (measured using one's average score on the PAI-BOR total across all four weeks). Therefore, this table presents the simple slopes of E2 deviation at lower- and higher-than-usual P4 among women high in trait BPD only.

Lower-than-usual = 1 SD below the mean. Higher-than-usual = 1 SD above the mean. P4 Person Mean = Average P4 across 4 weekly samples. PAI – BOR = Personality Assessment Inventory – Borderline subscale. PANAS = Positive and Negative Affect Scale. SSES = State Self-Esteem Scale – Social Evaluation Subscale, which was coded such that higher scores indicate greater felt rejection. RRQ = Rumination-Reflection Questionnaire. MSI-BPD = McLean Screening Instrument for Borderline Personality Disorder. BSL-23 = Borderline Feature Checklist- 23-item Version.

[†]Analyses for these variables were performed on a square root transformation of the variable. However, the coefficients for these outcomes have been squared prior to standardization.