Perimenstrual Symptom Exacerbation in Borderline Personality Disorder: Evidence from Multilevel Models and the Carolina Premenstrual Assessment Scoring System

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Abstract

Background. Individuals with BPD suffer from a constellation of rapidly shifting emotional, interpersonal, and behavioral symptoms. Fluctuations in ovarian hormones across the menstrual cycle may contribute to symptom expression and instability among females with this disorder.

Method. 15 healthy, unmedicated females without dysmenorrhea meeting criteria for BPD reported daily emotional and behavioral symptoms across 35 days. Urine LH surge and salivary progesterone were used to confirm ovulation and verify cycle phase. Cyclical worsening of symptoms was evaluated using (1) phase contrasts in multilevel models and (2) the Carolina Premenstrual Assessment Scoring System (C-PASS), a standardized tool for evaluating clinically significant cycle effects on symptoms.

Results. Despite low retrospective perceptions of perimenstrual symptom change, all symptoms showed marked perimenstrual worsening in prospective ratings, with secondary worsening of certain symptoms in the midluteal and follicular phases. The ovulatory phase was associated with the lowest symptoms. 11 of 15 females met C-PASS criteria for significant premenstrual symptom worsening.

Conclusions. Females with BPD may be at elevated risk for perimenstrual worsening of emotional symptoms. Experimental work is needed to determine the pathophysiology of perimenstrual exacerbation in BPD.

Perimenstrual Symptom Exacerbation in Borderline Personality Disorder: Evidence from Multilevel Models and the Carolina Premenstrual Assessment Scoring System

People with borderline personality disorder (BPD) suffer extreme difficulty in regulating emotions, interpersonal relationships, and behaviors. Diagnostic criteria for BPD highlight instability and flux in a variety of areas, including unstable moods, reactive anger, changing identities, turbulence in interpersonal relationships, and damaging impulsive behaviors. Recurrent self-injurious thoughts and behaviors are also common, with suicide often the tragic outcome of BPD; longitudinal studies indicate that up to 10% of individuals with BPD die by suicide (Paris & Zweig-Frank 2001). Population-based epidemiological studies do not find sex differences in risk for BPD, but do find that the DSM-5 BPD diagnosis can be reliably and validly detected beginning at puberty (Glenn & Klonsky 2013), and that females with BPD suffer from greater functional impairment than males with BPD (Grant *et al.* 2008). Research on the biology of BPD has generally focused on trait-level factors, whereas relatively little research examines biological influences on the *instability* characteristic of BPD. Given that the ovarian steroid hormones estradiol (E2) and progesterone (P4) regulate nearly every brain system implicated in psychiatric disorders (Schiller *et al.* 2016), the rapid changes in ovarian hormones that occur across the monthly female menstrual cycle could represent one source of fluctuating biological vulnerability to BPD symptoms. The present study uses a longitudinal design and standardized diagnostic approach to describe the impact of the menstrual cycle on symptoms in a sample of unmedicated females with BPD.

The prototypical human menstrual cycle is about 28 days and can be divided roughly into two halves, bisected by ovulation. The first half - from menses to ovulation - is the follicular phase, characterized by low progesterone and increasing estradiol that peaks just prior to ovulation. The second half - from ovulation to the next menses - is the luteal phase, characterized by high levels of progesterone and a secondary slower and generally lower peak in estradiol. E2 and P4 fall precipitously just prior to and during the first few days of menses,

and the cycle begins again. Among individuals with the severe cyclical mood diagnosis of DSM-5 premenstrual dysphoric disorder (PMDD), symptoms reach their peak on the day before or the day of menstrual onset, and remit during menses (Epperson *et al.* 2012). Furthermore, in two large samples, the most severe PMDD symptoms were found in the "perimenstrual" window between days –4 and +3 (where day 1 is menstrual onset and there is no day 0) (Hartlage *et al.* 2012). This suggests that the most pronounced period of symptom change occurs during the precipitous withdrawal from E2 and P4 that occurs prior to and during menses, a finding that dovetails with preclinical work showing that ovarian steroid withdrawal can precipitate anxious and depressive behavioral phenotypes (Stoffel & Craft 2004; Smith *et al.* 2006).

Although most females do not suffer from clinically significant changes in emotional (Schwartz *et al.* 2012; Ben Dor *et al.* 2013; Hengartner *et al.* 2017) or cognitive (Schmidt *et al.* 2013; Leeners *et al.* 2017) symptoms across the menstrual cycle, experimental work clearly demonstrates that a subset of females do suffer from an *abnormal sensitivity to normal ovarian steroid changes* (i.e., ***hormone sensitivity)***. This apparent intolerance to hormone change can manifest as emotional, cognitive, and behavioral changes that appear only or primarily in the context of normative reproductive steroid changes, such as the midluteal and perimenstrual (i.e., around menses) cycle phases, as in PMDD (Schmidt *et al.* 1998); during pregnancy and postpartum (Bloch *et al.* 2000); and during the menopause transition (Schmidt *et al.* 2015; Gordon *et al.* 2016). Predictors and causes of abnormal hormone change sensitivity across the menstrual cycle are still under investigation; however, some studies have shown that having a diagnosis of depression or panic disorder as a female does not in itself equate to greater risk of perimenstrual symptom exacerbation, suggesting that risk for cyclical hormone sensitivity may be at least somewhat separate from underlying risk for mood and anxiety disorders (Stein *et al.* 1989; Hartlage *et al.* 2004).

The content of emotional symptoms most commonly observed in these *reproductive mood disorders* overlaps to a greater degree with BPD than with major depressive disorder.

Reproductive mood disorders in general are often characterized by *high arousal negative affect* and *interpersonal* symptoms (Freeman et al. 2011; Eisenlohr-Moul et al. 2017a; Putnam et al. 2017), a profile that is highly consistent with BPD diagnostic content. The most common cyclical symptoms of PMDD are anger and irritability, anxiety, mood swings, and interpersonal sensitivity (Freeman *et al.* 2011; Eisenlohr-Moul *et al.* 2017a, 2017b), with depressive symptoms being less common. While having a mood or anxiety disorder as a female does not in itself equate to greater risk of perimenstrual symptom exacerbation (Stein *et al.* 1989; Hartlage *et al.* 2004), it seems plausible that perimenstrual symptom exacerbation may be more prevalent in a disorder such as BPD that is already characterized by instability in this particular set of symptoms.

Some evidence also ties key correlates of BPD to greater risk of cyclical symptom exacerbation, especially experiences of abuse (Eisenlohr-Moul *et al.* 2016), symptoms of PTSD (Nillni *et al.* 2015), emotion-related impulsivity (Martel et al. in press; Dawson et al., in press), and high trait stress vulnerability (Gollenberg *et al.* 2010). However, disentangling potential menstrually-related variability from other components of instability in BPD symptoms presents methodological challenges. Menstrually-related changes in psychiatric symptoms must be documented using prospective daily ratings because agreement between retrospective and prospective measures is very low (Roy-Byrne *et al.* 1986). Very little prospective evidence is available to evaluate the hypothesis that females with BPD are at high risk for cyclical symptom exacerbation. Only one study has examined the impact of the menstrual cycle in patients with BPD (Ziv, 1995), using a sample of 14 females in outpatient and inpatient treatment blinded to the purpose of the study, most of whom were taking psychotropic medications. This study reported no evidence of reliable changes in symptoms from the premenstrual to postmenstrual phases of the cycle; however, the study had several notable limitations. Most participants were medicated, and drugs such as SSRIs (the gold standard treatment for premenstrual dysphoria; Steiner et al., 2006) may have interfered with cyclicity of symptoms. Hormonal markers (e.g, LH

surge detection and salivary P4) were not used to confirm ovulation or make precise cycle phase delineations, which is critical given that anovulatory cycles are less likely to show cyclical changes in symptoms (Hammarbäck *et al.* 1991).

In a more recent study, undergraduates were recruited to achieve a flat distribution of BPD features (N=40) and were followed across four weeks while blinded to the purpose of the study. Among only individuals with elevated trait BPD features, daily BPD symptoms were highest at visits when P4 was higher-than-usual and E2 was lower-than-usual, a hormonal profile often found in the midluteal and perimenstrual phases (Eisenlohr-Moul *et al.* 2015). These findings suggest the possibility of more pronounced cycle effects in BPD; however, generalizability is limited given the analog, nonclinical sample.

The present study aims to move this line of research forward by examining the prospective impact of ovulatory, hormonally normal menstrual cycles on daily self-reported psychiatric symptoms (e.g., anxiety, anger, depression) and key mediators of BPD symptoms (e.g., felt invalidation (Sturrock & Mellor 2014), anger rumination (Peters *et al.* 2017), and shame (Rüsch *et al.* 2007; Peters & Geiger 2016)) in a sample of community-recruited, unmedicated females meeting DSM-5 criteria for BPD (n = 15) who were NOT recruited for perceived premenstrual symptoms. In addition to examining the significance and size of contrasts between cycle phases, we utilize a standardized diagnostic system, the Carolina Premenstrual Assessment Scoring System (C-PASS; Eisenlohr-Moul *et al.* 2017b), to describe the degree to which clinically significant, PMDD-like symptom differences were observed between the premenstrual to postmenstrual weeks in this sample of females with BPD.

Hypotheses

Given the evidence above, it was hypothesized that females with BPD would show a similar *pattern* of symptom change as is observed in PMDD, where symptoms begin to increase in the midluteal phase, peak around menstrual onset (“perimenstrually”), and are greatly reduced following menses, leading to lower symptoms in the follicular and ovulatory phases.

However, since BPD by definition never remits entirely, we hypothesized cyclical *exacerbation* (midluteal and perimenstrual symptom exacerbation, follicular phase return to moderate symptoms) following this pattern rather than the typical luteal phase confinement of symptoms (luteal phase symptom appearance – follicular phase symptom remission) that is indicative of the diagnosis of PMDD. We examined the following predictions related to our hypotheses:

(1) Given that perimenstrual window (here defined as the four days before menses and first three days of menses) correspond to the greatest hormone withdrawal and the maximum symptoms in those with PMDD, we predicted that symptoms would be at their worst during the perimenstrual phase relative to all other phases,

(2) Given that symptoms in PMDD generally *begin* during the midluteal phase, when P4 rises and begins to fluctuate, we predicted that symptoms would be worse during the midluteal phase than in the follicular and ovulatory phases,

(3) Given that the follicular phase is generally asymptomatic in PMDD, we predicted that participants with BPD would show their normal baseline levels of symptoms during the follicular and ovulatory phases, and that these two phases would not differ from one another (i.e., follicular reduction in symptoms but not full follicular symptom clearance).

(4) Given overlapping risk factors and similar core symptom content in PMDD and BPD, we predicted that a majority (>50%) of the sample would meet the C-PASS diagnostic criterion of *premenstrual elevation* (worsening of at least 30% premenstrually vs. postmenstrually) on at least one emotional symptom.

Methods

Procedure

Participants were recruited from the community using email listservs, flyers, and social media (Facebook) advertisements. Advertisements specifically referred to persistent problems with out-of-control emotions, behaviors, and relationships, and *did not refer to the menstrual cycle*. Advertisements directed people to an online screening survey, which included the

Personality Diagnostic Questionnaire—Borderline Personality Disorder Subscale (PDQ; (Hyler *et al.* 1992) and eligibility questions. Exclusionary criteria included a history of any chronic medical condition, including gynecologic disorders and dysmenorrhea, self-reported histories of severe and persistent menstrual pain regardless of diagnosis, neurological diseases, metabolic diseases, endocrine disorders, immune-mediated diseases, and high blood pressure. People were also excluded if they reported any illicit drug use (including marijuana). Self-reported histories of schizophrenia and manic episode were exclusionary. All psychotropic and hormonal medications were exclusionary, and we required that people be off these medications for 1 month prior to study participation. Pregnancy and breastfeeding were exclusionary, and menstrual cycles between 25-35 days were required.

Individuals were contacted for follow-up phone screening if they met exclusion criteria and had a PDQ score endorsing 5 out of 9 BPD criteria. The phone screen included a verification of exclusion criteria and an additional interview version of the PDQ in which participants were asked to provide one example of each BPD symptom. Participants providing examples meeting SCID-PD (First *et al.* 1997) criteria on at least 5 symptoms were invited to the laboratory for a SCID-PD BPD section interview with a clinical psychologist. Each SCID question was augmented with questions about whether the participant experiences this symptom only during periods of circumscribed depression or anxiety, or whether the symptom is persistently present. As is required by the SCID-PD, only responses consistent with persistent, pervasive, pathological expression of the symptom were coded as meeting the symptom criterion. Participants were paid $15 for their initial visit regardless of the outcome. If they met SCID-PD criteria for BPD during the initial interview, they completed several self-report demographic and clinical characterization questionnaires. They were also instructed in the use of daily online surveys, ovulation tests, and salivary hormone measurements. Participants then completed online daily surveys for 35 days starting on their next menstrual period start day. They also completed daily urine ovulation testing to determine the day of ovulation, and

completed passive drool saliva samples on 8 days across the cycle to verify ovulation and confirm cycle phase. Participants received $100 for participation of the longitudinal sampling study. All procedures were approved by the university institutional review board. The data were collected 2015-2016.

Participants

310 female participants were screened online; of those screened, 104 were eligible for phone screening (n=143 eliminated for insufficient PDQ severity, n=42 eliminated for oral contraceptive use, n=6 eliminated due to irregular cycles, and n=7 eliminated due to medical conditions). 69 participants were lost to follow-up and could not be reached for a phone screen. 43 participants completed the PDQ interview over the phone; of those screened, 31 were invited for an initial visit (n=8 eliminated for subthreshold PDQ examples, n=2 eliminated for oral contraceptive use, n=2 eliminated for pregnancy or nursing). Of the 31 who were invited for an initial visit, 18 participants came to the laboratory for an in-person interview and possible enrollment visit (n=13 declined due to time constraints or lack of interest, or were lost to follow-up). Of the 18 participants who completed the initial visit, 17 met SCID-BPD criteria during the interview and were enrolled. Of the 17 participants enrolled, 15 completed daily diaries and had ovulatory cycles (n=1 did not complete daily diaries, n=1 did not have an ovulatory cycle). Therefore, the final sample included 15 medically healthy, unmedicated females with normal menstrual cycles who met SCID criteria for BPD. Demographics and clinical characteristics are provided in Table 1. One of the 15 participants was currently in psychotherapy. All participants reported having received treatment by a mental health care provider at some point in their lifetime. No participants reported having received any treatment with Dialectical Behavior Therapy (DBT). In general, the sample represents a group of individuals currently meeting criteria for BPD but not currently receiving psychiatric treatment.

Baseline Measures

In addition to undergoing the SCID-II for BPD, participants completed several additional

questionnaires during a baseline study visit in order to characterize their demographics, perceptions of menstrually-related symptom change, dimensional degree of BPD symptomatology, childhood adversity histories, and symptoms of comorbid disorders. Perceptions of menstrually-related symptom change were measured using items from the Premenstrual Assessment Form (Halbreich *et al.* 1982); participants were asked to rate their typical degree of premenstrual symptom exacerbation on a scale where 1=no change, 2=mild change, 3=moderate change, and 4=severe change. Participants rated their perceptions of premenstrual symptom change for the following symptoms: depressed mood, hopelessness, worthlessness or guilt, anxiety, anger, irritability, and interpersonal conflicts. The borderline subscale of the Personality Assessment Inventory (Morey 2014) was utilized to describe the dimensional severity of BPD symptoms in the sample. The Childhood Trauma Questionnaire (Bernstein & Fink 1998) measured childhood experiences of adversity that are common in BPD, and was used in conjunction with validated cut scores to describe such adversity in our sample. The Beck Depression Inventory and the state form of the State-Trait Anxiety Inventory (Spielberger 1983) were utilized to describe the degree of clinically significant depressive and anxious symptoms in the sample.

Daily Measures

The present study utilized standardized methods, developed for the study of PMDD, for evaluating the impact of the menstrual cycle on daily psychiatric symptoms. Participants completed the daily record of severity of problems (Endicott *et al.* 2006) as part of their online daily surveys. Rather than being a psychometric measurement tool with empirically-designed subscales, the DRSP is a list of hormone-sensitive psychiatric symptoms (i.e., DSM-5 PMDD symptoms) which are rated daily by the participant. The DRSP has been developed to reliably detect menstrually-related changes in individual psychiatric symptoms, and can be utilized for determining the presence of clinically-significant premenstrual exacerbation using the C-PASS, a standardized scoring system for evaluating the degree of cyclical symptom change using the

daily DRSP ratings (Eisenlohr-Moul *et al.* 2017b). In the present study, we chose to focus on the core emotional symptoms typically studied in relation to the menstrual cycle, including the following items: depressed, down, or blue (“Depression”); anxious, tense, keyed up, or on edge (“Anxiety”); less interest in usual activities (“Anhedonia”), hopeless (“Hopelessness”); overwhelmed, can’t cope (“Emotional Overwhelm”); more sensitive to rejection or feelings easily hurt (“Rejection Sensitivity”); angry or irritable (“Anger/Irritability”); conflicts or problems with other people (“Interpersonal Conflict”); less interest in daily activities (“Anhedonia”); and the average of the items measuring breast tenderness, breast swelling, bloating, and joint or muscle pain (“Physical Symptoms”). Response ratings range from 1 (Not at All) to 6 (Extreme). Therefore, 9 outcomes from the DRSP were used.

In addition to capturing the core psychiatric outcomes described above, the present study also examined several processes known to play a key role in BPD symptom expression. Participants were asked to rate six additional daily items representing three processes: Shame, Felt Invalidation, and Anger Rumination. Daily shame was measured using two items from the shame subscale of the State Shame and Guilt Scale (Marschall *et al.* 1994); “I wanted to sink into the floor and disappear”, and “I felt humiliated, disgraced”). Daily felt invalidation was measured with two items created for the purposes of this study (“I felt that someone wanted to me to stop feeling the way I was feeling”, “I felt that someone didn’t take my feelings seriously”). Daily anger rumination was measured with two items from the Anger Rumination Scale (Sukhodolsky *et al.* 2001); “I kept thinking about events that have angered me”, and “I turned anger-provoking situations over and over again in my mind”). Each of these items were rated from 1 (Not at All) to 5 (Extremely).

Ovulation Testing and Salivary Hormones

Participants completed home urine testing for the luteinizing hormone (LH) surge each morning using the Clearblue ovulation testing kit. This test has a sensitivity of 40 MIU and is 97% concordant with ovulation as confirmed by an ultrasound(Guermandi *et al.* 2001). The day

after the positive LH surge test was considered the day of ovulation.

Participants also provided saliva samples for hormone assay on 8 days across the cycle in order to confirm ovulation and provide anchors for confirming cycle day: days 2, 3, 8, and 9 following menstrual onset and days 2, 3, 8, and 9 following a positive LH surge test (corresponding to days 15, 16, 21, and 22 of a 28-day cycle, or the early and mid-luteal phases, respectively). Participants collected 5 mL of saliva in polypropylene vials (passive drool) each afternoon between 4pm and 6pm to confirm expected changes in P4. They were instructed to avoid dental work for 48 hours prior to sampling; avoid alcohol for 12 hours prior to sampling; and avoid eating, drinking, or brushing their teeth for 1 hour prior to sample collection. Participants were instructed to rinse their mouths with water 10 minutes prior to sampling. People froze saliva samples in their home freezer in a temperature stability pouch and returned them to the lab after they had completed the study. P4 was assayed in saliva using previously-described methods (Shirtcliff *et al.* 2000). Intra- and inter-assay coefficients of variation were within normal limits. Sensitivity was 5 pg/ml. Salivary P4 demonstrated expected cyclical trajectories (follicular nadir and luteal peak across the cycle). P4 values were used to confirm cycle phases and as descriptive information in graphs.

Menstrual Cycle Phase Coding

Menstrual cycle phase was determined using several sources of information: (1) forward count to day +10 and backward count to day -15 from menses onset (day +1) as described elsewhere (Edler *et al.* 2007), (2) day of positive LH surge, and (3) exponential progesterone rise following ovulation. Four cycle phases were determined: Ovulatory, Midluteal, Perimenstrual, and Follicular. First, the ovulatory phase was determined using backward count (days -15 to -12), and was validated using the LH surge ovulation test and the presence of a substantial postovulatory rise in P4 following the ovulatory phase. Next, the perimenstrual phase was determined using backward and forward count (days -4 to +3, where day 1 is menses onset and there is no day 0), and was further validated by time since positive LH surge (14 +/- 2

days). The midluteal phase was defined as the days falling between the ovulatory and perimenstrual phases, and was validated by the presence of elevated P4. The follicular phase was defined as the days falling between the perimenstrual and ovulatory phases, and was validated by the presence of low P4.

Data Analysis and Power

As reviewed above, there were 12 daily outcomes in this descriptive study: Physical Symptoms, Depression, Hopelessness, Anhedonia, Rejection Sensitivity, Anxiety, Anger/Irritability, Interpersonal Conflict, Emotional Overwhelm, Shame, Anger Rumination, and Felt Invalidation. In order to improve interpretability and isolate the within-person component of the outcome, each outcome was person-standardized (by subtracting the person's mean response on that variable, then dividing by the person's standard deviation of that variable). This method has been used previously to improve the interpretability of changes in symptoms across the menstrual cycle (Edler *et al.* 2007; Klump *et al.* 2013).

In order to test the first three predictions, a series of multilevel models evaluated the impact of cycle phase (coded as a categorical variable with alternating reference categories to evaluate each contrast) on each outcome. SAS PROC MIXED was utilized to account for the nested structure of observations (i.e., random intercept) as well as the autocorrelation of today's rating with yesterday's rating. Random effects of cycle phase contrasts did not improve model fit in any instance and were therefore not included. This likely indicates that impact of the menstrual cycle (and more specifically, the size of the contrasts between different phases) on symptoms evaluated were relatively homogeneous in this sample, with only minimal individual differences in change across the cycle. Because dependent variables were person-standardized prior to use in models, phase contrast estimates represent the average number of person-standard deviations by which the two phases differed on that outcome in our sample. 5-day rolling averages of each person-standardized variable were also calculated and utilized for smoother graphical depictions in Figures.

To determine statistical power for phase contrasts, we calculated the design effect to determine the smallest detectible effect size(Snijders 2005). Each participant provided up to 35 daily surveys (lower-level N was 490), and symptoms generally showed low intraclass correlations (i.e., a high degree of flux within a given person, average ICC for DRSP items = .18). Calculations indicated that power for these models was adequate to detect conventionally small-to-medium sized, clinically significant contrasts between cycle phases (smallest detectible effect size, was, on average, f^2 of .10). That is, the present study was powered to detect significant phase contrasts that accounted for at least 10% of the variance in the daily outcome.

In order to describe, in absolute terms, the degree to which individuals in this sample experienced *clinically significant* cyclical changes in psychiatric symptoms, we also evaluated whether each participant met the C-PASS diagnostic criterion of *premenstrual elevation* on at least one emotional symptom (Eisenlohr-Moul et al., 2017). In contrast to PMDD, which requires luteal phase confinement of symptoms (i.e., symptom remission during the follicular phase), cycle-related symptom *exacerbation* can be identified when at least one core emotional symptom from the DRSP demonstrates a 30% *premenstrual* week (days -7 to -1) elevation of symptoms relative to the postmenstrual week (days 4-10, where menses onset is day 1). This premenstrual and postmenstrual week windowing method was developed to compare more symptomatic (premenstrual) and less symptomatic (postmenstrual) windows while omitting the first few days of menses, which can be complicated by physical symptoms (Eisenlohr-Moul *et al.* 2017b). We used the validated C-PASS percent change calculation method [(premenstrual week average – postmenstrual week average/range of scale ever used by a given woman)*100] to determine the presence of clinically significant premenstrual symptom exacerbation using the 30% increase in symptoms as the cutoff(Eisenlohr-Moul *et al.* 2017b).

Results

Descriptives

Sample demographic and clinical characteristics are described in Table 1. The sample was reasonably diverse with regard to age and race. Participants reported high BPD symptoms on the PAI-BOR, generally moderate depression on the BDI, moderate anxiety on the STAI, and many participants reported significant experiences of childhood trauma; these clinical characteristics are consistent with typical profiles of comorbidity and adverse childhood experiences among individuals with BPD. Proportions of the sample meeting each SCID BPD criterion are also listed in Table 1. On the MAF, participants retrospectively reported an average perception of *mild* premenstrual exacerbation of emotional symptoms (*Mean* = 2.18, *SD* = .73) that was similar across symptom domains (Range of Means = 1.97 to 2.50).

Menstrual Cycle Phase Contrasts

Next, menstrual cycle phase contrasts were performed in order to describe the general pattern of cyclical symptom change in this sample. We also sought to test the prediction that people with BPD demonstrate perimenstrual and, to a lesser extent, midluteal worsening of psychiatric symptoms. Results of multilevel models contrasting symptom levels across different phases are presented in Table 2. All symptoms demonstrated strong cyclical changes; therefore, Figures 1-3 depict patterns of symptom change across cycle day and cycle phase observed in several exemplar symptoms, including interpersonal conflict (Figure 1), felt invalidation (Figure 2), and hopelessness (Figure 3). Graphs by day and by cycle phase are provided for each individual outcome in Supplement 1. All graphs include smoothed person-standardized P4 values to improve interpretability relative to the normative luteal P4 rise and fall.

As predicted, the perimenstrual phase was generally associated with significantly higher symptoms relative to the other three phases, with the largest contrasts generally emerging between the perimenstrual and ovulatory phases. This was true for all symptoms except depression, shame, anhedonia, and hopelessness, which were higher in the perimenstrual phase than in the ovulatory and midluteal phases but, contrary to our expectations, showed no

difference between the perimenstrual and follicular phases; thus, it appears that perimenstrual worsening of depressive symptoms persisted into the follicular phase. As predicted, the midluteal phase was also associated with worsening of some symptoms relative to the follicular and ovulatory phases, specifically in the higher-arousal negative affect symptoms of anxiety, anger/irritability, and interpersonal conflict. Additional models controlled for person-standardized physical symptoms; no substantive changes were found, suggesting that the results presented above are not an artifact resulting from perimenstrual physical pain (e.g., dysmenorrhea) in females with BPD.

C-PASS Diagnostic Calculations: How many participants showed cyclical worsening of at least one DRSP emotional symptom?

In contrast to the previous set of analyses, which focused on describing the typical patterns of symptom exacerbation across the entire menstrual cycle, the next set of analyses used standardized diagnostic procedures to define, in more absolute terms, the percentage of individuals in this sample showing *clinically significant* cyclical symptom exacerbation. 11 of 15 participants (73%) showed at least 30% premenstrual elevation in symptoms relative to the post-menstrual week on at least one DRSP emotional symptom (depression, hopelessness, anhedonia, anxiety, rejection sensitivity, emotional overwhelm, anger or irritability, or interpersonal conflict).

Because it is possible that exclusion of the first three days of menses omitted some of the most symptomatic days, we also conducted similar descriptive analyses replacing the C-PASS pre- and post-menstrual window means with means from the perimenstrual and follicular phases (as described in the contrast analyses above), respectively; these changes did not alter the 73% outcome. Finally, given that participants in the present study appeared to demonstrate greater follicular exacerbation of symptoms than expected (with perimenstrual depressive symptom exacerbation often persisting through the follicular phase), we also conducted similar descriptive analyses replacing the C-PASS pre-menstrual and postmenstrual windows with

means from the perimenstrual and *ovulatory* phases (as defined in the contrast analyses), respectively. The number of participants showing significant cyclical exacerbation of symptoms from the ovulatory to the perimenstrual phase rose to 14 out of 15 (93%), with all but one participant showing at least 30% exacerbation on at least one emotional symptom.

Discussion

Summary

The purpose of the present study was to describe menstrual cycle-related patterns of symptom exacerbation in unmedicated individuals with borderline personality disorder. Despite retrospectively reporting only mild premenstrual changes in symptoms, prospective evaluation of daily ratings unequivocally demonstrates perimenstrual worsening of all symptoms, including depression, anxiety, anhedonia, rejection sensitivity, feelings of overwhelm, anger, conflict, anger rumination, feelings of invalidation, and shame. Additionally, some symptoms showed secondary exacerbations in the midluteal phase (anxiety, anger, conflict) or the follicular phase (depression, anhedonia, hopelessness, shame). Critically, although people with BPD also demonstrated perimenstrual worsening of physical symptoms, physical symptom changes did not account for perimenstrual exacerbation of emotional symptoms. C-PASS calculations indicated that the phase contrasts observed were not only significant, but would be categorized as clinically significant perimenstrual exacerbation in 11 of 15 cases.

The prospective symptom ratings studied here suggest that unmedicated females with BPD have a high risk of perimenstrual exacerbation, whereas retrospective reports of cyclical symptom change indicate a relative lack of awareness of these cyclical changes. Inspection of contrast patterns and daily symptom change across the cycle (see Figures and Supplement 1) leads to the following insights, described as they would chronologically unfold across the cycle. First, all symptoms generally show their lowest levels in the ovulatory phase. Second, in the midluteal phase, high-arousal symptoms of anxiety, anger, and interpersonal conflict worsen but are not yet accompanied by exacerbation of other symptoms. Third, in the perimenstrual phase,

all symptoms become exacerbated, with continued heightening of anxiety, anger, and interpersonal conflict, but also increased experiences of physical discomfort, felt invalidation, shame, rejection sensitivity, anger rumination, emotional overwhelm, depression, anhedonia, and hopelessness. Finally, although high-arousal symptoms return to baseline by the follicular phase, low-arousal, depressive emotions such as depression, hopelessness, shame, and anhedonia continue to be exacerbated in the follicular phase before returning to their lower baseline at ovulation and the midluteal phase.

Although it may be premature to comment on the specific biological mechanisms of perimenstrual symptom exacerbation in BPD, the present study does allow us to compare and contrast the patterns observed in this sample to the patterns of symptom change observed in PMDD, a hormone-sensitive disorder for which the pathophysiology of cyclic symptom change is relatively understood. Midluteal and perimenstrual exacerbation of high-arousal symptoms such as anxiety, anger/irritability, and interpersonal conflict appeared to follow a similar pattern to that typically observed in PMDD, where symptoms are elevated or worsen following the postovulatory P4 surge in the luteal phase and remit or return to baseline once P4 falls at the onset of the follicular phase. One could speculate that the pathophysiology of perimenstrual worsening of these high-arousal symptoms in BPD has a shared pathophysiology with PMDD—that is, an abnormal dysphoric response to luteal fluctuations in the GABAergic neurosteroid metabolites of P4 (Martinez *et al.* 2013; Schiller *et al.* 2014). However, in the case of depressive symptom worsening, the cyclical pattern observed here does not suggest a shared pathophysiology with PMDD. Exacerbations of depressive symptoms did not appear in the midluteal phase, but only premenstrually, and then persisted into the follicular phase. This profile of symptom exacerbation may suggest that females with BPD also show an *additional* sensitivity to withdrawal from—or low levels of—ovarian steroids in the follicular phase. In sum, while the luteal phase worsening of high-arousal symptoms in BPD suggests some shared pathophysiology with PMDD, acute perimenstrual and continued follicular worsening of

depressive symptoms in BPD may indicate the presence of additional hormone sensitivities in BPD that are different from those in PMDD. It is also possible that the emergence of PMDD during puberty interacts with environmental BPD risk factors to precipitate the development of chronic emotion dysregulation and BPD in many females, especially when emotion regulation skills are insufficient to prevent PMDD symptoms from persisting into the follicular phase (Dawson *et al.* n.d.).

Several lines of research indicate that the predictors and characteristics of BPD overlap with those of hormone sensitivity. First, traumatic stress exposure and extreme stress vulnerability have been identified as being both particularly relevant to the etiology of BP0 D(Lynam & Widiger 2001; Ball & Links 2009) and relevant to the pathophysiology of psychiatric hormone sensitivity across the lifespan (Gollenberg *et al.* 2010; Gordon *et al.* 2015; Nillni *et al.* 2015; Eisenlohr-Moul *et al.* 2016). Second, indices of impulsivity, a core feature of BPD (Peters *et al.* 2013), have been found to predict sensitivity to perimenstrual hormone withdrawal in rodents (Löfgren *et al.* 2009) and in humans (Martel et al., in press). Finally, several extreme *behavioral* manifestations of emotion-related impulsivity have been found to show perimenstrual exacerbation across menstrual cycle, including binge eating in bulimia (Edler *et al.* 2007; Klump *et al.* 2013), substance use and abuse (Terner & de Wit 2006), and suicide attempts (Saunders & Hawton 2006). The finding that elevated hopelessness persists into the follicular phase in BPD is particularly consistent with evidence for risk of suicide attempt and more lethal attempts in the perimenstrual and follicular phases (Saunders & Hawton 2006). Although it is not clear exactly which factors contributing to a diagnosis of BPD might increase risk for hormone sensitivity, previous dimensional work (Eisenlohr-Moul *et al.* 2015) combines with the present findings to strengthen the working hypothesis that females with strong BPD features are at elevated risk of abnormal behavioral reactions to changing hormones across the cycle.

Clinical Implications

Despite the development of useful psychotherapies for BPD, such as dialectical behavior

therapy (DBT;(Linehan 2014) and mentalization-based therapy (Bateman & Fonagy 2004), quality of life often remains low following treatment (Linehan *et al.* 2006). Studies like the present one point to the potential benefits of identifying and stabilizing biological sources of instability in BPD and dangerous associated phenomena such as recurrent suicidal behavior (Glenn *et al.* 2017). Future studies are needed to determine whether experimental stabilization of ovarian steroids might benefit females with BPD. Of note, most of the people in this study reported only mild premenstrual symptom change retrospectively, suggesting that some females with BPD may underestimate the role of the cycle in their symptoms. Greater menstrual cycle awareness in the context of psychosocial treatment may also support targeted skills use to improve stability, and the standard DBT diary card could be a natural method of tracking the impact of the cycle. Finally, the dramatic perimenstrual exacerbation of hopelessness observed here combines with previous work(Saunders & Hawton 2006) to highlight the potential role of the perimenstrual phase in elevated acute risk for suicide among this chronically-at-risk population.

Limitations and Strengths

The present study had key limitations, including the small clinical sample and the lack of a healthy or clinical control group. Although the sample size was small, the repeated measures of symptoms within each woman ensured sufficient power to detect the large observed effects of the menstrual cycle. The lack of a control group simply means that we cannot estimate the extent to which people with BPD differ from people without BPD in the size of their phase contrasts. On the other hand, this concern is mitigated by the use of a standardized prospective diagnostic protocol (the C-PASS; Eisenlohr-Moul et al. 2017) to document clinically significant symptom exacerbation that is not seen in controls using this validated assessment tool(Roy-Byrne *et al.* 1986). Nevertheless, the lack of a clinical control group means that we cannot conclude that the symptom exacerbations demonstrated here are due to factors specific to BPD rather than transdiagnostic factors such as trauma exposure(Eisenlohr-Moul *et al.* 2016). More

work is needed to determine the extent to which this risk for cyclicity in BPD differs from other clinical disorders.

Despite the limitations of this study, it also had notable strengths that address methodological limitations of previous work in this area. First, recruitment was conducted so as to blind potential participants to the purpose of the study, reducing the possibility of self-selection due to premenstrual mood concerns. Second, unlike previous work examining the impact of the cycle within BPD, participants were not taking medications that might interfere with cyclicity of symptoms. Third, the use of a community-recruited, demographically diverse, clinical sample improves generalizability of findings. Fourth, previous work has often used pencil-and-paper symptom diaries, which are prone to biased and incomplete reporting; the present study utilizes electronic daily diaries to ensure more accurate and time-verified reporting of both menstrual bleeding and symptoms. Fifth, the present study used both urine LH surge detection and salivary P4 to ensure ovulatory cycles and characterize cycle phases. Finally, the present study examined all pairwise comparisons between phases in order to more precisely describe the nature of cyclical symptom change in BPD, demonstrating both similarities and differences to PMDD with regard to cyclical changes.

Conclusions

People with BPD suffer intense fluctuations in painful emotional and behavioral symptoms. The present work supports the hypothesis that females with BPD may be at high risk of perimenstrual symptom worsening, and secondary worsening during the midluteal (high arousal symptoms) and follicular (low arousal symptoms) phases. Patterns of symptom change suggest shared pathophysiology with PMDD with regard to midluteal and perimenstrual high-arousal symptoms (e.g., possible abnormal sensitivity to changes in P4-derived GABAergic neurosteroids), but also suggest potentially divergent pathophysiology with regard to depression symptoms (e.g., additional deleterious effects of ovarian steroid withdrawal or deprivation in the follicular phase). Experimental studies in clinical samples are needed for the dual purposes of

investigating the therapeutic potential of hormone stabilization while probing the pathophysiologic relevance of ovarian steroid changes to cyclical symptom worsening in BPD. Finally, additional work is needed to evaluate whether PMDD serves as a developmental risk factor for the emergence of BPD in females.

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Table 1. Sample Descriptive Information (N = 15)

Variable	Mean (SD); n (%)	Range
General Characteristics		
Age	32.16 (8.64)	19-44
African American Race	5 (33%)	-
Hispanic Ethnicity	1 (6%)	-
Education Level		
Trade School	1 (6%)	-
Some College	7 (47%)	-
College Grad	7 (47%)	-
Marital Status		-
Married	2 (15%)	-
Living with Partner	5 (33%)	-
Divorced	3 (20%)	-
Never Married	5 (33%)	-
Average Cycle Length in Days	28.97 (1.32)	26-35
Age at Menarche in Years	11.24 (1.08)	10-14
% with Biological Children	4 (26%)	-
Clinical Characteristics		
Trauma Exposure		
Childhood Trauma Questionnaire (CTQ)	43.00 (12.08)	28-64
% Significant Childhood Physical Abuse (>=8)	7 (47%)	-
% Significant Childhood Sexual Abuse (>=8)	4 (27%)	-
% Significant Childhood Physical Neglect (>=8)	7 (47%)	-
% Significant Childhood Emotional Abuse (>=10)	7 (47%)	-
% Significant Childhood Emotional Neglect (>=15)	5 (33%)	-
Borderline Symptom Assessments		
PAI-BOR Score	44.23 (9.84)	29-53
Number of SCID-BPD Criteria Met	6.89 (1.26)	5-8
% Meeting Fear of Abandonment Criterion	10 (67%)	-
% Meeting Affective Lability Criterion	15 (100%)	-
% Meeting Identity Disturbance Criterion	8 (53%)	-
% Meeting Interpersonal Disturbances Criterion	14 (93%)	-
% Meeting Emptiness Criterion	11 (73%)	-
% Meeting Anger Criterion	10 (67%)	-
% Meeting Paranoia/Dissociation Criterion	8 (53%)	-
% Meeting Self-Harm Criterion	6 (40%)	-
% Meeting Impulsivity Criterion	11 (73%)	-
Comorbidity Assessments		
Depression (BDI)	13.66 (4.37)	2-29
% Minimal (0-13)	5 (33%)	-
% Mild (14-19)	5 (33%)	-
% Moderate (20-28)	3 (30%)	-
% Severe (29-63)	2 (13%)	-
Anxiety (STAI-T)	45.36 (8.86)	29-56

Note. CTQ = Childhood Trauma Questionnaire. STAI=State-Trait Anxiety Inventory (Trait Form). BDI = Beck Depression Inventory. PAI-BOR = Personality Assessment Inventory – Borderline Subscale. SCID-BPD = Structured Clinical Interview for Personality Disorders – Borderline Personality Disorder Module.

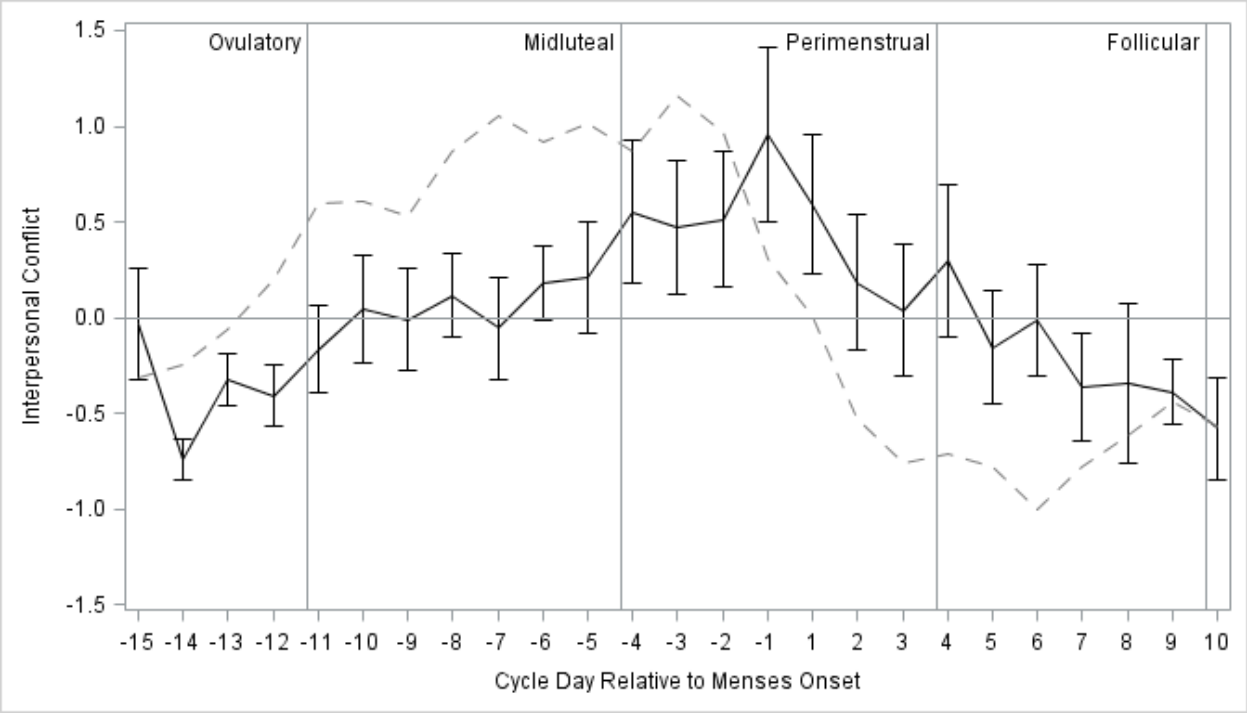
Table 2

Multilevel Model Results: Within-Person Menstrual Cycle Phase Contrasts for Intrapersonal and Interpersonal Symptoms

	Within-Person Phase Contrasts (Standardized Fixed Effects)					
	Perimenstrual Phase (Falling E/P)			Midluteal Phase (High Stable E/P)		Follicular Phase (Low Stable E/P)
	v. Follicular (Low Stable E/P)	v. Midluteal (High Stable E/P)	v. Ovulatory (Rising E/Low P)	v. Ovulatory (Rising E/Low P)	v. Follicular (Low E/P)	v. Ovulatory (Rising E/Low P)
Core Cyclical Emotional Symptoms (DRSP)						
Depression	-.12 (.35)	**-.51*** (.14)**	**-.51** (.17)**	-.01 (.17)	**.39** (.14)**	**-.39** (.15)**
Hopelessness	-.12 (.12)	**-.44** (.14)**	**-.71*** (.16)**	-.26 (.17)	**.32* (.13)**	**.59*** (.16)**
Anxiety	**-.61*** (.13)**	**-.34* (.15)**	**-.70*** (.17)**	**-.37* (.18)**	-.28 (.14)	-.09 (.17)
Rejection Sens	**-.26* (.12)**	**-.33* (.14)**	**-.40* (.16)**	-.07 (.17)	.07 (.13)	-.13 (.15)
Anger/Irritability	**-.51*** (.13)**	**-.24* (.11)**	**-.76*** (.17)**	**-.52** (.18)**	**-.27* (.13)**	-.24 (.17)
Interpersonal Conflict	**-.71*** (.13)**	**-.33* (.14)**	**-.77*** (.17)**	**-.44* (.18)**	**-.37* (.14)**	-.07 (.16)
Additional Symptoms						
Anhedonia	-.12 (.13)	**-.35* (.15)**	**-.34* (.17)**	.004 (.19)	.22 (.14)	-.22 (.17)
Overwhelmed, Can't Cope	**-.50*** (.12)**	**-.36* (.14)**	**-.70*** (.17)**	-.35 (.16)	.14 (.13)	.21 (.16)
Shame	-.22 (.12)	**-.28* (.12)**	**-.54** (.16)**	-.26 (.17)	**.49*** (.13)**	**-.76*** (.16)**
Felt Invalidation	**-.60*** (.13)**	**-.45** (.15)**	**-.53** (.17)**	-.07 (.18	-.15 (.14)	-.08 (.18)
Anger Rumination	**-.54*** (.13)**	**-.42** (.15)**	**-.50** (.17)**	-.07 (.18)	-.12 (.14)	.04 (.17)
Physical Symptoms	**-.36** (.13)**	**-.39* (.15)**	**-.79*** (.17)**	**-.41* (.18)**	-.01 (.14)	**-.43* (.17)**

Note. *$p < .05$; **$p < .01$ *** $p < .001$. Outcomes have been person-standardized to represent the number of standard deviations away from one's mean (0); therefore, estimates reflect the average number of personal standard deviations by which the two phases differ. DRSP=Daily Record of Severity of Problems.

PANEL A



PANEL B

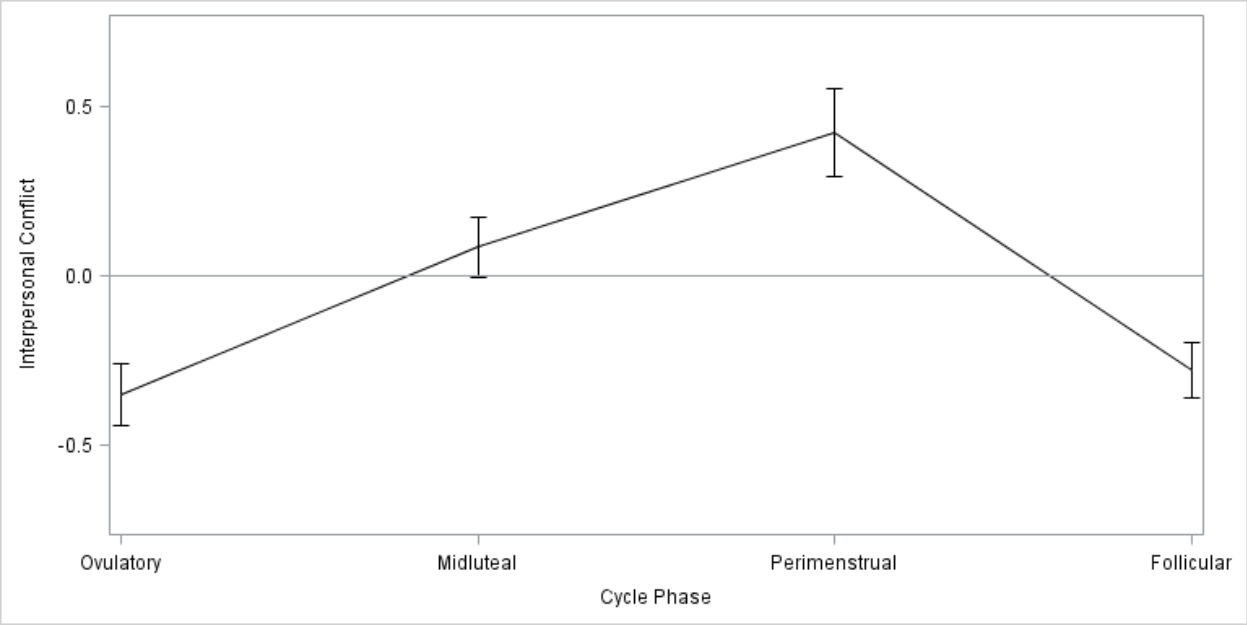
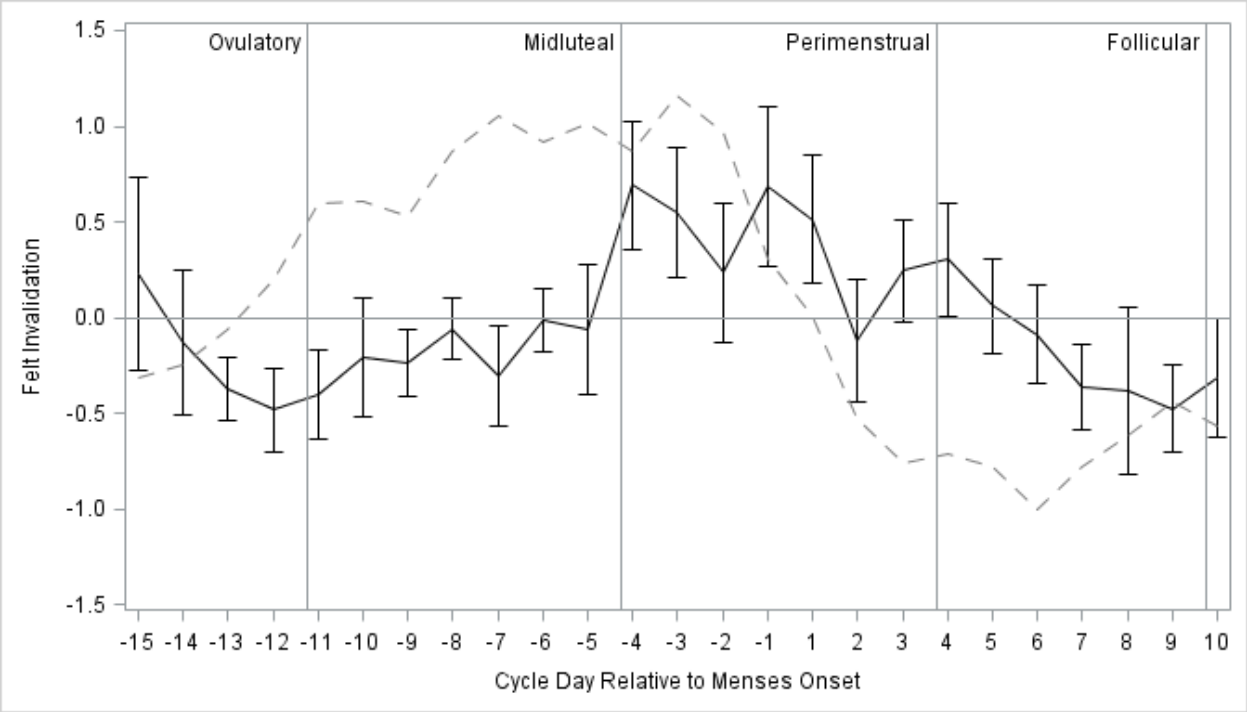


Figure 1. Person-Standardized Progesterone (dashed line) and Interpersonal Conflict Across Menstrual Cycle Day (Panel A) and Person-Standardized Interpersonal Conflict Across Cycle Phase (Panel B) in 15 People with BPD.

PANEL A



PANEL B

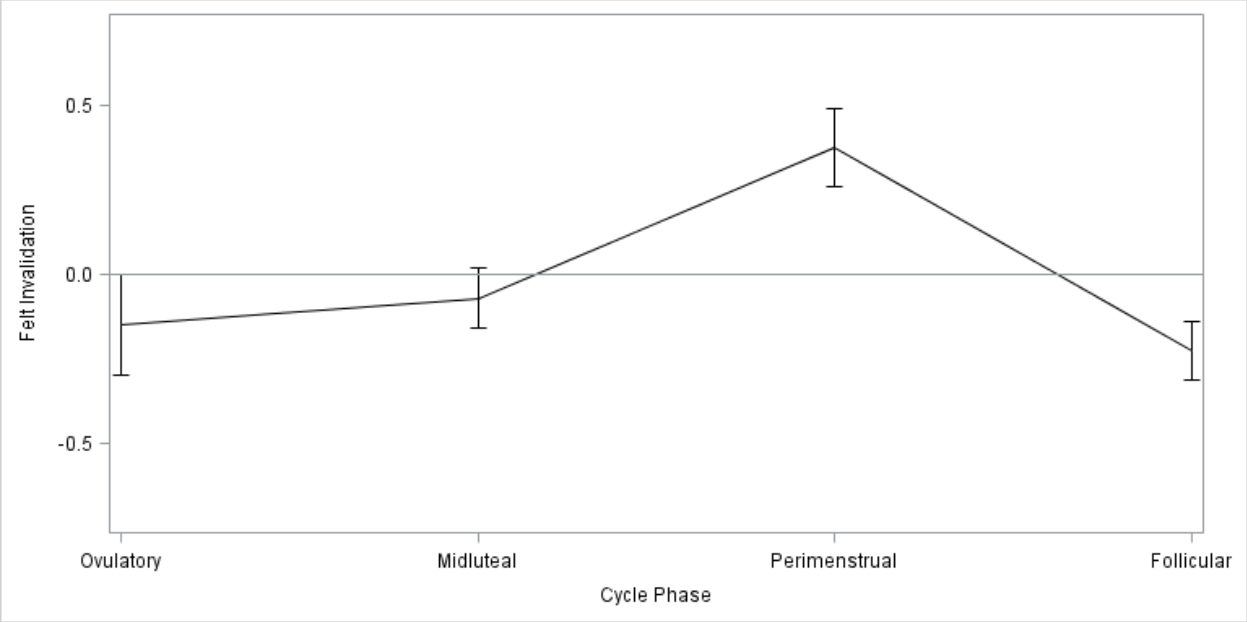
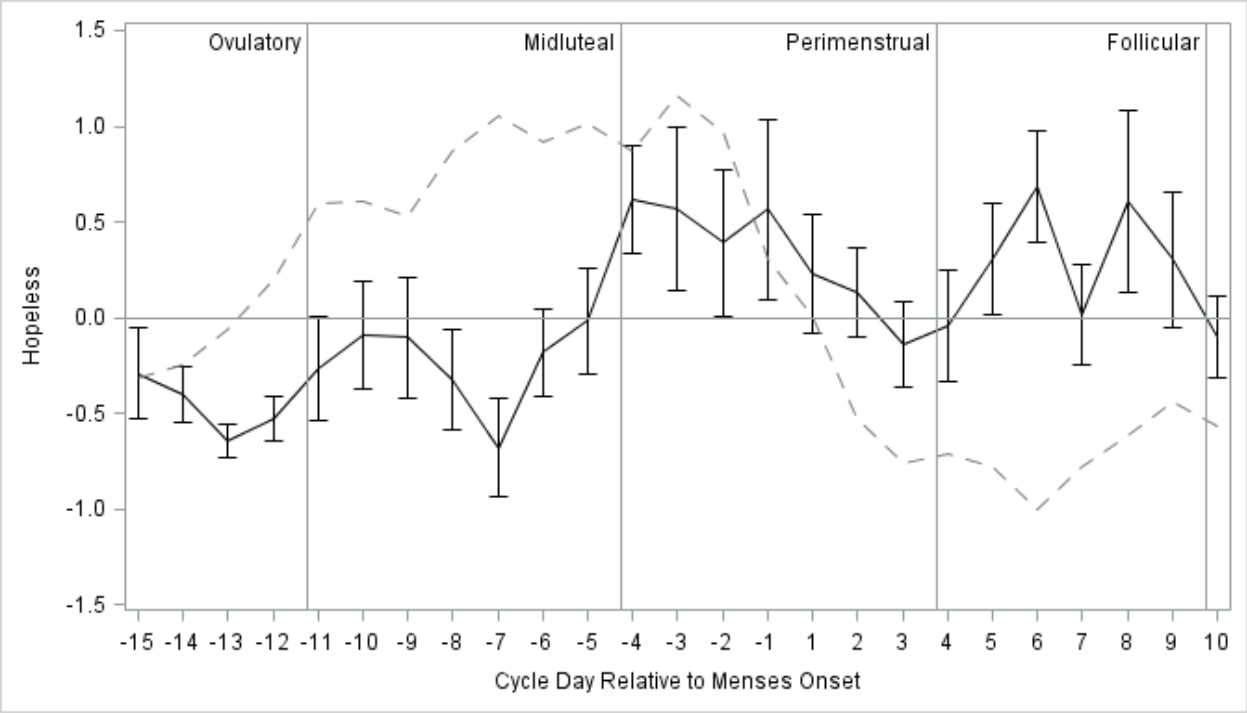


Figure 2. Person-Standardized Progesterone (dashed line) and Felt Invalidation Across Menstrual Cycle Day (Panel A) and Person-Standardized Felt Invalidation Across Cycle Phase (Panel B) in 15 People with BPD.

PANEL A



PANEL B

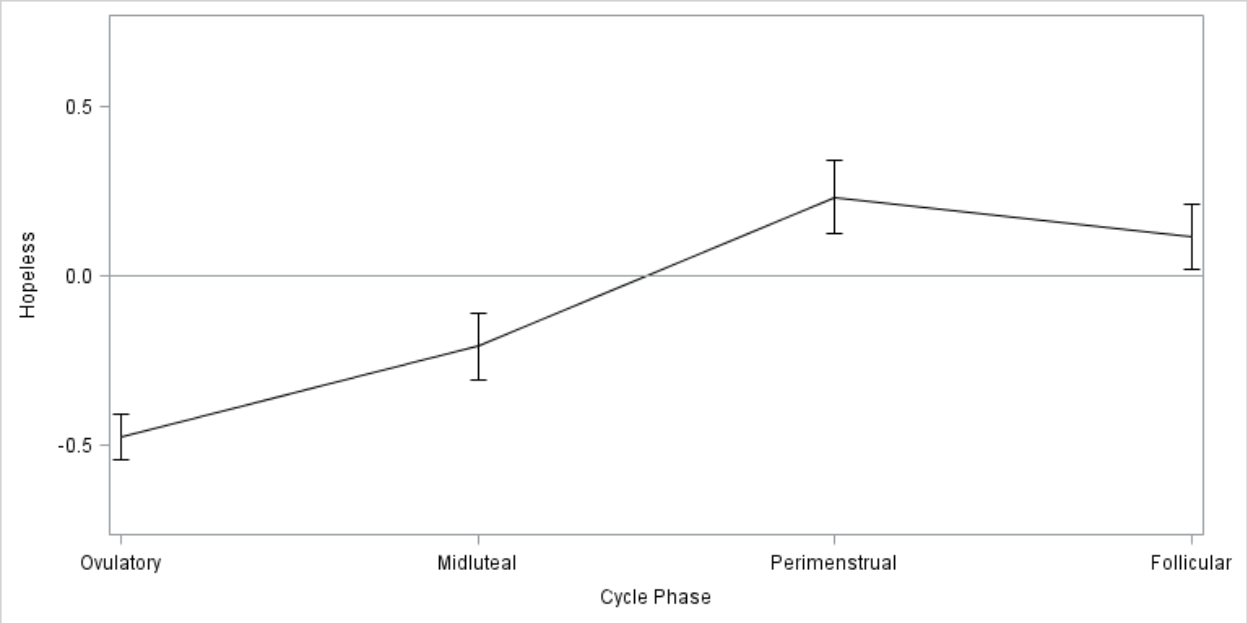
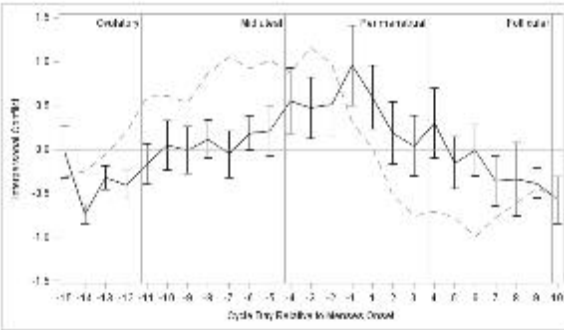


Figure 3. Person-Standardized Progesterone (dashed line) and Hopelessness Across Menstrual Cycle Day (Panel A) and Person-Standardized Hopelessness Across Cycle Phase (Panel B) in 15 People with BPD.

PANEL A



PANEL B

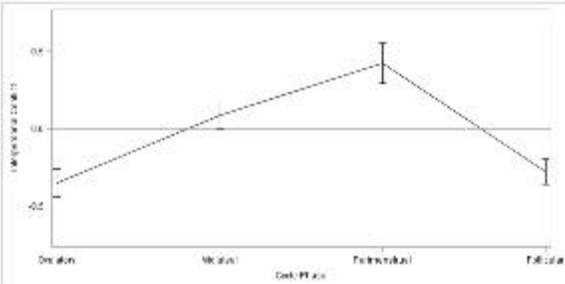
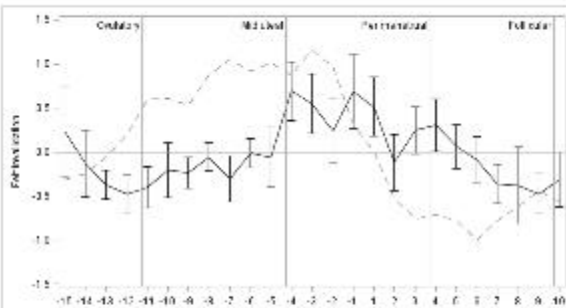


Figure 1. Person-Standardized Progesterone (dashed line) and Interpersonal Conflict Across Menstrual Cycle Day (Panel A) and Person-Standardized Interpersonal Conflict Across Cycle Phase (Panel B) in 15 People with BPD.

PANEL A



PANEL B

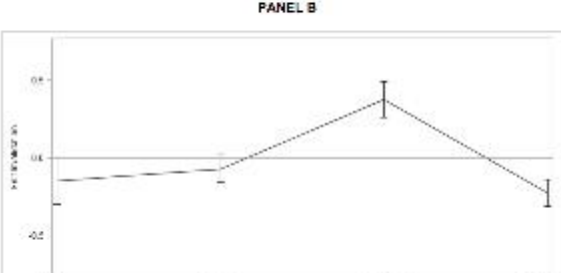


Figure 2. Person-Standardized Progesterone (dashed line) and Felt Invalidation Across Menstrual Cycle Day (Panel A) and Person Standardized Felt Invalidation Across Cycle Phase (Panel B) in 16 People with BPD.

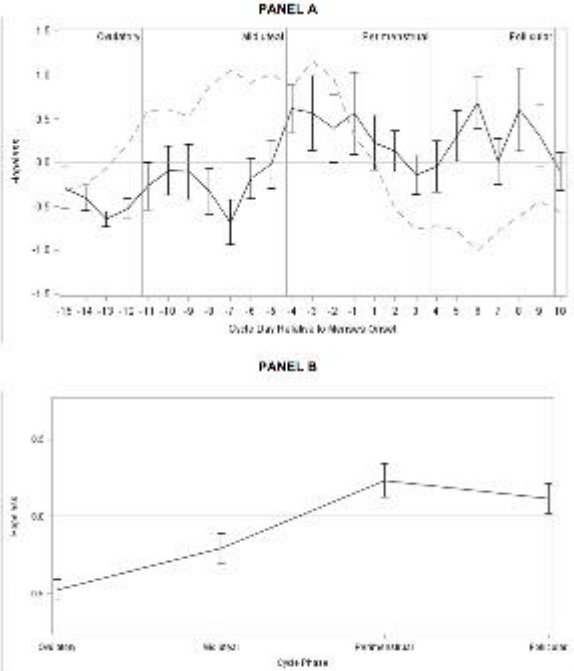


Figure 3. Person-Standardized Progesterone (dashed line) and Hopelessness Across Menstrual Cycle Day (Panel A) and Person-Standardized Hopelessness Across Cycle Phase (Panel B) in 10 People with BPD.