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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 four 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.

1. Introduction

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; Grant et al., 2008; Swartz, Blazer, George, & Winfield, 1990; Widiger & Weissman, 1991). 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).

2. 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

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menstrual bleeding (early follicular phase), E2 and P4 are both low. While P4 remains low throughout the follicular phase, about eight 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.

3. 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, Upton, & Baer, 2013), and (3) various manifestations of behavioral impulsivity, especially under conditions of negative affect (Ball, Tennen, Poling, Kranzler, & Rounsaville, 1997; Brodsky, Malone, Ellis, Dulit, & Mann, 1997; Peters et al., 2013; Tragesser, Lippman, Trull, & Barrett, 2008; 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 (Brooks-Gunn and Warren, 1989; Schwartz, Romans, Meiyappan, De Souza, & Einstein, 2012), many studies have documented greater concurrent negative emotionality at times in the menstrual cycle when E2 is low or P4 is high (e.g., Gonda et al., 2008; Meaden, Hartlage, & Cook-Karr, 2005) or during reproductive developmental transitions characterized by greater variability in E2 (as a between-person variable; Brooks-Gunn & Warren, 1989; Buchanan, Eccles, & Becker, 1992; Freeman, Sammel, Lin, & Nelson, 2006; Paikoff, Brooks-Gunn, & Warren, 1991; Poromaa, Smith, & Gulinello, 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., Rubinow & Schmidt, 1992; Schmidt, Nieman, Danaceau, Adams, & Rubinow, 1998). Further, interpersonal emotions such as rejection and anger are the most commonly reported symptom during the premenstrual phase in women with PMDD (Bloch, Schmidt, & Rubinow, 1997; Pearlstein, Yonkers, Fayyad, & 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 et al., 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, Roach, Evans, Schipper, & Darville, 2010). Several aspects of executive functioning appear to be improved under higher levels of E2 (Gogos, 2013; Howard, Gifford, & Lumsden, 1988; Jacobs & D'Esposito, 2011; Lord & Taylor, 1991; Rosenberg & Park, 2002; Segal, 2012; Vranić & Hromatko, 2008) and higher levels of P4 (Solís-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 (Lang, Bajbouj, Sander, & Gallinat, 2007; Qian et al., 2003).

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; Evans & Levin, 2011; Epstein et al., 2006; Franklin et al., 2004, 2008; Pastor & Evans, 2003; Schiller, Saladin, Gray, Hartwell, & Carpenter, 2012). 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., 2013). 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-García, Díaz-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.

4. 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