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Histories of abuse predict stronger within-person covariation of ovarian steroids and mood symptoms in women with menstrually related mood disorder

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ABSTRACT

Objective: Individual differences in sensitivity to cyclical changes in ovarian steroids estradiol (E2) and progesterone (P4) have been implicated in the pathophysiology of menstrually related mood disorder (MRMD). However, no prospective studies have investigated psychosocial risk factors for sensitivity to hormone effects on mood in MRMD. Using a repeated measures approach and multilevel models, we tested the hypothesis that a history of abuse provides a context in which within-person elevations of E2 and P4 prospectively predict daily symptoms.
Method: 66 women with prospectively-confirmed MRMD recruited for a trial of oral contraceptives provided 1 month of baseline hormone and mood data prior to randomization. Lifetime physical and sexual abuse experiences were assessed. Across one cycle, women completed daily measures of symptoms and provided blood samples on 5 days across the menstrual cycle. Current E2 and P4 were centered within person (CWP) such that higher values represented cyclical elevations in hormones.
Results: Rates of physical (27%) and sexual (29%) abuse were high, consistent with previous work documenting a link between trauma and MRMD. In women with a history of physical abuse, cyclical increases in P4 predicted greater mood and interpersonal symptoms on the three days following that sample. In women with a history of sexual abuse, cyclical increases in E2 predicted greater anxiety symptoms on the three days following that sample.
Conclusions: Results inform further inquiry into the role of severe life stressors and stress response systems in MRMD. We discuss areas for future research on the psychosocial and physiological pathways through which abuse may influence the link between hormones and symptoms.
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1. Introduction

Premenstrual dysphoric disorder (PMDD) affects about 1–6% of women in their reproductive years (Cohen et al., 2002) and can result in luteal phase functional impairment equivalent to that of major depression, panic disorder, and PTSD (Halbreich et al., 2003). However, the restrictive nature of the DSM-5 PMDD diagnostic criteria, particularly the requirement of an arbitrary 5 symptoms, is controversial (Freeman, 2003). The prevalence of clinically significant premenstrual symptoms that are characterized by cyclical distress, impairment, and treatment seeking, but do not meet the five symptom criterion, is estimated at 13–19% (Epperson et al., 2012). The burden of these menstrually related mood disorders (MRMDs) is high, with 4.5 million disability adjusted life years lost/year in the U.S. (Halbreich et al., 2003).

Both observational and experimental studies implicate changes in the ovarian steroids estradiol (E2) and progesterone (P4) in the pathophysiology of MRMDs. However, the effects of E2/P4 on MRMD symptoms do not appear to be due to abnormal lev-

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els of E2/P4 or abnormal cyclical patterns of E2/P4 in women with MRMDs; rather, the best available evidence indicates that MRMD symptoms emerge due to an abnormal sensitivity to cyclical changes in E2 and P4 (Schmidt et al., 1998; Halbreich et al., 1986; Redei and Freeman, 1995; Epperson et al., 2012; Wang et al., 2013). In further support of the idea that MRMDs are caused by individual differences in sensitivity to cyclical hormonal changes, experimental suppression of ovarian steroids using GnRH agonists effectively eliminates symptoms among most women with MRMD (Muse et al., 1984; Brown et al., 1994; Schmidt et al., 1998; Hammarbäck and Bäckström, 2009). Further, addback of luteal phase levels of either E2 or P4 (vs. placebo) causes a re-emergence of symptoms not found in non-MRMD women (Schmidt et al., 1998). In sum, while there is no consistent evidence that women with MRMD show altered levels of, or altered cyclical changes in, ovarian steroids, there is strong evidence that MRMD symptoms are generally linked to abnormal sensitivity to normal cyclical changes in ovarian steroids (Schmidt et al., 1998).

Within the population of women with MRMDs, there exists significant between-person variability in the strength of the within-person links between cyclical steroid changes and daily symptoms (Redei and Freeman, 1995). At present, little is known about the psychosocial correlates of hormonal sensitivity in MRMD. The present study addresses this gap by examining histories of abuse as a psychosocial predictor of the strength of the within-person link between cyclical changes in E2 and P4 and symptom expression in MRMD. There were several reasons for choosing abuse history as a candidate predictor of hormone sensitivity. Because ovarian steroids modulate the hypothalamic-pituitary-adrenal (HPA) axis response to stress (Roca et al., 2003), dysregulation of which has been consistently implicated in affective psychopathology (Heim et al., 2008), including MRMDs (Girdler et al., 2007), we hypothesized that a history of severe stress exposure may modulate affective sensitivity to normal cyclical elevations in ovarian steroids. In support of this hypothesis, a number of studies have linked traumatic experiences to greater odds of MRMD (Perkonigg et al., 2004; Pilver et al., 2011; Bertone-Johnson et al., 2014). Moreover, those with MRMD and histories of abuse show unique alterations in various stress-responsive physiological systems that are not seen in women without a MRMD who have similar abuse histories, including the hypothalamic-pituitary-thyroid axis (Girdler et al., 2004; Bunevicius et al., 2012) and the sympathetic nervous system (Girdler, 2003; Girdler et al., 2007). Finally, we recently found that cyclical increases in P4 were associated with greater susceptibility to mood symptoms and interpersonal problems only among women high in borderline personality features (Eisenlohr-Moul et al., 2015), traits which often develop as adaptations to abuse (Bandelow et al., 2005).

Based on the evidence that traumatic experiences sensitize stress response systems (Ehlert, 2013; McLaughlin et al., 2015), and that these systems (e.g., the HPA axis and sympathetic nervous system) are regulated by ovarian steroids (Patchev et al., 1994; Patchev and Almeida, 1996; Weiser and Handa, 2009; Liu et al., 2012), we hypothesize that sensitization in stress response systems represents a pathway through which women with MRMD develop abnormal mood reactions to normal cyclical changes in ovarian steroids. If this is the case, then histories of traumatic stress should play a role in predicting the links between hormone change and mood symptoms in MRMD (Schmidt et al., 1998).

In a sample of 66 women with prospectively-confirmed MRMD, we sought to test the following predictions:

1) Consistent with evidence that relative elevations in E2 and P4 precipitate symptoms in women with MRMD (Schmidt et al., 1998), we predict that within-person elevations in E2 or P4 (i.e., higher-than-usual relative to one's mean) will be associated with greater symptom severity over three subsequent days among all women with MRMD.
2) Consistent with evidence that stressful life events are correlated with MRMD, we predict that, within a sample of women with prospectively-confirmed MRMD, lifetime presence of either physical or sexual abuse will predict higher negative mood following normal cyclical elevations of ovarian steroids.

2. Method

2.1. Participants

66 participants enrolled in a randomized controlled trial of oral contraceptives (the results of which have not yet been reported; NCT00927095) for the treatment of MRMD were assessed daily (for symptoms) and across five time points (for ovarian steroids) in one baseline menstrual cycle prior to randomization. Descriptive information can be found in Table 1. All women were in good health, reporting no current chronic medical conditions (including any disorder of the reproductive system, such as polycystic ovarian syndrome) and no current Axis I psychiatric disorders. None of the participants self-reported any use of prescription medication for the past 3 months. Participants were paid $150 for their participation in the baseline portion of the study. All procedures were approved by the local IRB and all participants provided informed consent.

2.2. Procedure

First, MRMD diagnosis was prospectively confirmed using daily ratings across 2–4 menstrual cycles. Second, participants meeting criteria for MRMD were assessed for Axis I psychiatric disorders using the MINI (Sheehan et al., 1998) and for abuse history using a validated interview (Leserman et al., 1997). Participants then began data collection for the present study, which began with daily completion of the daily record of severity of problems (DRSP) each evening for an entire menstrual cycle. During the same baseline cycle, a phlebotomist visited participants on five occasions to collect blood samples twice in the follicular phase (days 2 and 5 following the menstrual onset), and three times in the luteal phase (days 17, 21, and 25 following menstrual onset); time of day was constant within a given woman.

2.2.1. Confirmation of MRMD diagnosis

The diagnosis of MRMD was confirmed prospectively using a standardized system for scoring daily ratings on the daily record of severity of problems (DRSP; described below; (Endicott et al., 2006). DRSP forms were completed daily and mailed into the laboratory weekly to discourage retrospective reporting. Each woman completed the DRSP for 2–4 cycles. A diagnosis of MRMD was made based on the following criteria: (1) >=30% decrease in emotional symptom severity from the seven luteal phase days preceding menses (mean of days −7 to −1, where day −1 is the day prior to menstrual onset) to the follicular phase baseline mean during days 4 to 10 following menstrual onset on day 1 (Premenstrual Mean—Postmenstrual Mean/the Scale Range of 5), (2) a rating of emotional symptoms as at least moderate (i.e., rating >=4) on at least two premenstrual week days; (3) remission of symptoms shortly after menstrual onset followed by a symptom free period (>=6 consecutive follicular days where rating <4), and (4) criteria 1–3 met in at least two menstrual cycles.

2.2.2. Interview assessment of axis I psychopathology and abuse history

Next, psychiatric and trauma histories were assessed at a laboratory session. Participants were assessed for Axis I disorders using

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