

# Health Psychology

## **Menstrually Related Mood Disorders and a History of Abuse: Moderators of Pain Sensitivity**

Diana S. Fleischman, Adomas Bunevicius, Jane Leserman, and Susan S. Girdler

Online First Publication, March 25, 2013. doi: 10.1037/a0031900

### CITATION

Fleischman, D. S., Bunevicius, A., Leserman, J., & Girdler, S. S. (2013, March 25). Menstrually Related Mood Disorders and a History of Abuse: Moderators of Pain Sensitivity. *Health Psychology*. Advance online publication. doi: 10.1037/a0031900

# Menstrually Related Mood Disorders and a History of Abuse: Moderators of Pain Sensitivity

Diana S. Fleischman  
University of Portsmouth

Adomas Bunevicius, Jane Leserman, and  
Susan S. Girdler  
University of North Carolina at Chapel Hill

**Objective:** Women with a menstrually related mood disorder (MRMD) have substantially higher rates of physical and sexual abuse and are more sensitive to experimental pain stimuli than women without a MRMD. For the first time, this study examined pain sensitivity and hormonal correlates in women with a MRMD and in non-MRMD controls as a function of abuse history. **Methods:** A total of 126 women (63 with MRMD, 34 with an abuse history; and 63 non-MRMD, 31 with an abuse history) were evaluated for: (1) sensitivity to cold pressor and forearm ischemic pain and (2) basal plasma cortisol and norepinephrine (NE) concentrations. Exploratory analyses examined relationships between plasma cortisol and NE concentrations and pain sensitivity. **Results:** Women with a MRMD and an abuse history showed increased sensitivity to both cold pressor and ischemic pain and lower basal cortisol concentrations, an effect not seen in the women without a MRMD. In all women, the expected relationship between greater plasma cortisol concentration and reduced sensitivity to pain was observed, whereas NE predicted pain sensitivity only in women with a MRMD. **Conclusions:** Menstrually related mood disorder status moderates the effect of a history of abuse on pain sensitivity. The results also suggest that the hypocortisolemia documented in the women with a MRMD and an abuse history may contribute to their greater sensitivity to noxious pain stimuli. This study adds to a growing body of evidence suggesting that a history of abuse may identify a clinically distinct subgroup of women with a MRMD.

**Keywords:** abuse, menstrually related mood disorders, pain sensitivity

Abuse prevalence rates for women in the United States are staggering, with one recent survey of over 3,000 women indicating that 18% had been sexually assaulted and nearly 7% badly beaten before age 18 (Dunn, Gilman, Willett, Slopen, & Molnar, 2012). The public health significance of such experiences in women is underscored by the well-established links between histories of abuse and psychiatric (Kendler et al., 2000), and medical illness (Felitti, 1998; Leserman et al., 1996), especially pain-related disorders (e.g., Finestone et al., 2000; Irish, Kobayashi, & Delahanty, 2010). However, the mechanisms underlying the association of abuse with clinical pain syndromes are unclear.

Because experimental pain sensitivity is predictive of clinical pain (Edwards, Doleys, Fillingim, & Lowery, 2001; Fillingim, Maixner, Kincaid, Sigurdsson, & Harris, 1996), a handful of studies have investigated the association of abuse histories with experimental pain responses in clinical pain patients (Fillingim et al., 1997; Scarinci, McDonald-Haile, Bradley, & Richter, 1994;

Whitehead, Crowell, Davidoff, Palsson, & Schuster, 1997). However, these studies have yielded mixed results that could result from differences in the nature of the noxious stimuli used or in the clinical population studied. Moreover, there is substantial evidence that chronic pain induces remodeling of central nervous system pathways involved in processing painful stimuli (Eide, 2000; Staud, Vierck, Cannon, Mauderli, & Price, 2001). Thus, studies in patients with established clinical pain may obscure the ability to examine biobehavioral and historical factors contributing to the development of clinical pain.

Studies examining abuse history and sensitivity to noxious stimuli in pain-free samples are relatively rare. Fillingim and Edwards (2005) found in a university sample that a history of childhood sexual or physical abuse was associated with decreased sensitivity to suprathreshold thermal heat stimulation in women, but not in men. Similarly, Granot et al. (2011) found that a history of sexual abuse in women was associated with elevated heat pain thresholds (decreased pain sensitivity), but also elevated pain intensity ratings.

Studies examining stress-responsive endogenous pain regulatory mechanisms, including plasma cortisol and norepinephrine (NE) may be particularly relevant to understanding alterations in pain sensitivity in populations with an abuse history for two reasons: 1) alterations in cortisol and NE have been consistently documented in women with abuse histories, although the results are mixed regarding the directional differences in the abuse-related effects (e.g., Girdler et al., 2003, 2007; Heim et al., 2000; Heim & Nemeroff, 2001; Heim, Shugart, Craighead, & Nemeroff, 2010; Young & Breslau, 2004); and 2) cortisol and NE are among several stress-responsive endogenous pain regulatory mechanisms. The relationship of higher cortisol and NE

---

Diana S. Fleischman, Department of Psychology, University of Portsmouth, Portsmouth, UK; Adomas Bunevicius, Jane Leserman, and Susan S. Girdler, Department of Psychiatry, University of North Carolina at Chapel Hill.

This research was supported by NIH-RO1-MH051246 and CTCRC: UL1RR025747.

Correspondence concerning this article should be addressed to Susan S. Girdler, UNC Department of Psychiatry CB#7175, School of Medicine, Psychiatry Wing C, Chapel Hill, NC 27599-7175. E-mail: Susan\_Girdler@med.unc.edu

concentrations to decreased pain sensitivity has been observed in humans (al'Absi, Petersen, & Wittmers, 2000, 2002; Girdler et al., 2005; Straneva et al., 2002; Mechlin et al., 2005) and is thought to reflect an integrated physiological response as part of the defense reaction. No studies we found have examined the relationship of stress-responsive endogenous pain regulatory mechanisms and pain sensitivity in women with abuse histories.

Of additional relevance to understanding pathophysiological mechanisms that link abuse to alterations in pain processing may be studies in women with a menstrually related mood disorder (MRMD). Menstrually related mood disorders are characterized by emotional and physical symptoms that appear during the premenstrual (luteal) phase of the menstrual cycle and remit with the onset of menses (Cunningham, Yonkers, O'Brien, & Eriksson, 2009). During the luteal phase, women with a MRMD show equivalent impairment in quality of life as patients with major depression, posttraumatic stress disorder (PTSD), or panic disorder (Freeman & Sondheimer, 2003). Although emotional symptoms are the diagnostic hallmark of MRMDs, somatic symptoms are prevalent and contribute to functional impairment (Steiner et al., 2001). Women with a MRMD are more likely to have a history of both physical and sexual abuse (Girdler et al., 2003, 2007; Golding, Taylor, Menard, & King, 2000), and women with a MRMD are more sensitive to experimental pain stimuli than controls (Fillingim et al., 1997; Straneva et al., 2002). However, no studies to date have examined the association of abuse histories with pain sensitivity in women with a MRMD.

The aims of the current study were twofold: 1) to examine the independent and interactive effects of a MRMD diagnosis and a history abuse on pain sensitivity and endogenous pain regulatory mechanisms; and 2) to examine the relationship of endogenous pain regulatory mechanisms and pain sensitivity. We hypothesized that an abuse history would predict a unique pain and neuroendocrine phenotype in women with a MRMD, as compared with those without a MRMD (i.e., MRMD  $\times$  Abuse history interactions would emerge) based on the following evidence: 1) women with a MRMD are more sensitive to laboratory-based pain stimuli (hyperalgesia) than women without a MRMD (Fillingim et al., 1995; Straneva et al., 2002); 2) in women without a MRMD, an abuse history is associated with hypoalgesia to painful stimuli; 3) women with a MRMD exhibit blunted hypothalamic-pituitary-adrenal (HPA) axis function, as compared with women without a MRMD (Girdler, Straneva, Light, Pedersen, & Morrow, 2001; Redei & Freeman, 1993; Straneva et al., 2002); and 4) our prior work showing a history of abuse predicted lower plasma NE only in women with a MRMD—an effect not seen in controls with a history of abuse (Girdler et al., 2003). Based on the paucity of studies to date that have examined the relationship between neuroendocrine markers and pain sensitivity in women with prior abuse, no a priori hypotheses were generated regarding these relationships. Thus, analyses involving neuroendocrine markers and pain sensitivity are exploratory.

## Methods

### Participants

Women were recruited from Chapel Hill, North Carolina, and the surrounding area, primarily via advertisements. These adver-

tisements either targeted women with severe premenstrual symptoms (for the MRMD group) or women with no premenstrual symptoms (non-MRMD group). Approximately 15% of the women with a MRMD were recruited via the University of North Carolina Center for Women's Mood Disorders website. In order to obtain equal proportions of women with prior abuse in both the MRMD and non-MRMD categories, it was necessary to also selectively advertise for women without MRMD with a history of abuse. Initial power analyses indicated that 60 women per MRMD group would yield 92% power to detect a difference of 250 seconds (standard deviation [*SD*] = 342 seconds) in ischemic pain tolerance. A total of 126 women (63 MRMD, 34 with abuse and 63 non-MRMD, 31 with abuse) were studied. All women were in good health, without current chronic medical conditions, including pain-related disorders or *DSM-IV* (American Psychiatric Association, 2000) Axis I psychiatric disorders. None of the subjects were taking prescription medication or used over-the-counter analgesics excessively (>10/ month).

### Procedures

After confirming MRMD status, participants were assessed for Axis I psychiatric disorders using the MINI international neuropsychiatric interview (Sheehan et al., 1998), and abuse history using a validated interview (Leserman et al., 1997).

### Confirming MRMD Diagnosis

During an initial enrollment session, participants were screened for medical history and instructed on how to complete the daily record of severity of problems (DRSP) form (Endicott, Nee, & Harrison, 2006). All women completed the DRSP on a daily basis for two to three menstrual cycles. This measure quantifies physical, emotional and behavioral symptoms, using a 6-point scale (1 = absent; 2 = minimal; 3 = mild; 4 = moderate; 5 = severe; 6 = extreme). Participants were classified as having a MRMD if they met all of the following: (1) at least a 30% change in emotional symptom severity between the seven luteal phase days preceding menses compared with follicular phase Days 4–10; (2) a rating of emotional symptoms as moderate, severe, or extreme on at least two of the seven premenstrual days; (3) remission of symptoms within three days of the onset of menses followed by a symptom free period ( $\geq$ six consecutive days) during the early to-mid follicular phase; and (4) criteria 1–3 met in at least two menstrual cycles (Endicott et al., 2006; Rubinow, Roy-Byrne, Hoban, Gold, & Post, 1984). Non-MRMD controls had: (1) only minimal emotional symptoms occurring on two or fewer days during the premenstrual week; and (2) less than a 30% change in symptom severity from the luteal to the follicular phase confirmed in two menstrual cycles.

### Psychiatric and Abuse History Assessment

After meeting our criteria for MRMD or non-MRMD status, women came for a second session during which all women were evaluated for past depressive disorders (e.g., major depressive disorder; MDD), anxiety disorders (e.g., panic disorder, generalized anxiety disorder) and PTSD using the MINI Psychiatric interview (Sheehan et al., 1998). Women with current psychiatric

disorders were excluded from participation. Full remission from depressive disorders for 1 year and from other Axis I disorders for 3 years was required. For analytical purposes, all histories of depressive disorders were considered together as “any depressive disorder” and all histories of anxiety disorders were considered together as “any anxiety disorder,” except for PTSD history.

Following the MINI, women were assessed for abuse histories. Sexual abuse included the following experiences that included force or threat of harm: 1) touching the subject’s breasts, pubic area, vagina, or anus with hands, mouth, or objects; 2) making the subject touch the perpetrator’s pubic area or anus with hands, mouth, or objects; or 3) vaginal or anal intercourse. Force or threat was not required for coding sexual abuse in children (<13 years of age), as it was implied by the age differential between victim and perpetrator. Physical abuse was defined as incidents separate from sexual abuse that included: 1) life threat (physically attacked with the intent to kill or seriously injure), and 2) other physical abuse (beaten up, hit, burned). Because of the relatively small cell sizes associated with specific forms of abuse, women with any sexual or physical abuse history were combined into one group (any abuse) for analyses.

### Pain Testing Protocol

All participants were scheduled during the luteal phase of the menstrual cycle, 5–12 days after home urine ovulation testing (ClearPlan Easy) detected the luteinizing hormone surge that indicates ovulation. To ensure that subjects were hydrated, each was required to consume eight, 8-ounce glasses of water on the day prior to testing and one 8-ounce glass and a low fat breakfast the morning of testing (confirmed with diaries). Subjects were asked to refrain from over-the-counter medications 24 hours prior to testing; from caffeine, exercise, and alcohol the day of testing; and from nicotine 1 hr prior to testing (confirmed via interview). Subjects who had been ill within 7 days of testing or who had fewer than 6 hours of sleep the previous night were rescheduled. All laboratory testing began between 7:00 a.m. and 9:30 a.m. Groups did not differ in laboratory start time (median time for each group was 9:00 a.m.). An intravenous (IV) line was established in an arm vein and once in place, a curtain was drawn that prevented the subject from viewing the IV. A minimum of 15 minutes elapsed between establishing the IV and beginning baseline rest. Subjects were then exposed to the following conditions:

**Baseline rest.** Subjects rested alone for 10 min. Blood was sampled at Min. 10 for basal cortisol and NE concentrations. Plasma levels of NE were determined using the high-pressure liquid chromatography with electrochemical detection technique. The lower limit of quantification is 2.5 pg/ml, and the intra- and interday coefficients of variation are less than 10%. Plasma cortisol was determined using radioimmunoassay techniques commercially available from MP Biomedical. The sensitivity of the assay is .07 µg/dL and the specificity is high, showing .05–2.2% cross-reactivity with similar compounds, except for prednisolone, where 94% cross-reactivity is obtained. The intra- and interassay coefficients of variation from the cortisol assay were approximately 7.7% and 7.4%, respectively.

**Pain tests.** Following baseline, subjects were exposed to the following pain tests, administered in random order with 5 min of rest between tests. Neuroendocrine measures were not taken dur-

ing the pain tests although the IV remained in place because a mental stress battery followed the pain testing protocol (results to be reported elsewhere).

**Hand cold pressor.** Participants submerged their hand to a marked line on their wrist in ice water maintained at 4°C. A water circulator prevented water from warming near the hand. Subjects indicated when sensations in their hand first became painful (pain threshold) and when they were no longer willing or able to tolerate the pain (pain tolerance). A maximum time limit of 5 min was imposed (Girdler et al., 2005), although subjects were not informed of this limit.

**The Submaximal Effort Tourniquet Procedure.** As described previously (Maixner, Gracely, Zuniga, Humphrey, & Bloodworth, 1990) a tourniquet cuff was positioned on the subject’s arm and the arm placed to the side. Before inflating the tourniquet cuff to 200 mm Hg (Hokanson E20 Rapid Cuff Inflator), the subject’s arm was raised for 30s to promote venous drainage, and then the cuff was inflated, the experimenter’s stopwatch started, and the arm returned to the side. To promote ischemia, subjects engaged in 20 handgrip exercises at 30% of their maximum force. Pain threshold and tolerance were determined as described above. A maximum time limit of 20 min was enforced (Maixner et al., 1990) although subjects were not informed of this limit.

**Pain intensity and unpleasantness ratings.** Pain intensity and unpleasantness are considered separate dimensions of pain (McGuire, 1992). To measure these dimensions, immediately before deflating the tourniquet cuff and before removal of the hand from the ice bath, subjects rated the intensity and unpleasantness of the test using a 0–100 cm visual analogue scale.

### Data Reduction and Analysis

Due to the inability to obtain some blood samples for specific hormone markers, cortisol was available for 123 subjects and NE was available for 119 subjects. First, demographic and historical variables were examined using a 2 (abuse) × 2 (MRMD status) analysis of variance (ANOVA) for continuous variables and Pearson’s chi-square test or Fisher’s exact test for dichotomous variables, as appropriate. Next, for each dependent measure of pain sensitivity, as well as for endocrine measures, a 2 (abuse) × 2 (MRMD status) analysis of covariance (ANCOVA) was employed, with age as the covariate. Significant interactions ( $p < .05$ ) were followed by post hoc ANCOVA analyses. Exploratory analyses among neuroendocrine data and pain data were examined using Pearson’s correlations ( $r$ ). Correlational analyses were conducted separately in MRMD ( $n = 63$ ) and non-MRMD women ( $n = 63$ ), collapsed across abuse groups. Data were analyzed with PASW Statistics 18 (IBM, Chicago, Illinois).

## Results

### Screening Outcomes

From July 2007 through September 2011, 321 women presenting with MRMD were prospectively evaluated as described above. Of these, 96 (30%) met MRMD criteria, 109 (34%) did not meet MRMD criteria (primarily due to not meeting symptom severity threshold criteria), 111 (34%) withdrew or were lost to follow-up,

and 6 (2%) were excluded due to a current Axis I disorder (four with MDD, two with anxiety disorders). Of the 96 women with MRMD, four declined to participate in the research study, five did not meet eligibility criteria (one with polycystic ovarian syndrome, three with recent depression, and one with recent anorexia nervosa), and nine were lost to follow-up, yielding 78 women with MRMD who enrolled into the laboratory study. Sixty-three (81%) of these women with MRMD completed all aspects of testing and are included in the present report.

During the same time frame, 127 women were prospectively evaluated as non-MRMD controls. Of these, 84 (66%) met non-MRMD control criteria, 9 (7%) did not meet control criteria (primarily due to chronic affective symptoms), 32 (25%) withdrew or were lost to follow-up, and 2 (2%) were excluded due to a current Axis I disorder (one with PTSD and one with MDD).

### Demographic and Historical Variables

Demographic characteristics, type of abuse and psychiatric histories of all subjects, stratified by MRMD and abuse status are presented in Table 1. There was a significant MRMD  $\times$  Abuse interaction for age,  $F(3, 125) = 4.23, p = .04$ , because women with a MRMD plus an abuse history were younger than women with a MRMD without an abuse history,  $t(61) = -2.45, p = .02$ . There was a higher proportion of current smokers in women with MRMD as compared with women without MRMD,  $\chi^2(1, 125) = 6.95, p = .008$ . The prevalence of sexual abuse only, physical abuse only, or any abuse history (sexual and/or physical abuse) was not different in MRMD women as compared with non-MRMD women. Chi-square analyses indicated proportional differences as a function of MRMD status and abuse histories for prevalence of depression histories,  $\chi^2(3, 125) = 15.27, p = .002$  and PTSD histories,  $\chi^2(3, 125) = 15.96, p = .001$ . Post hoc tests indicated that histories of depression,  $\chi^2(1, 62) = 15.02, p < .001$  and PTSD (Fisher's exact test,  $p < .001$ ) were more prevalent in women without a MRMD but with an abuse history, as compared with other women without a MRMD but had never been abused.

### Pain Sensitivity in Relation to MRMD Status and Abuse History

Controlling for age, cold pressor pain tolerance was predicted by the interaction of MRMD and history of abuse,  $F(3, 125) = 5.77, p = .02$ ; Figure 1. Within the group of women with a MRMD, those with an abuse history had lower cold pressor tolerance levels than those without such a history,  $F(63) = 7.15, p = .01$ , whereas a history of abuse was not associated with a significant difference in tolerance in women without a MRMD. There were no significant effects involving cold pressor pain threshold and unpleasantness (see Table 2). However, disregarding abuse history, women with a MRMD had significantly higher cold pressor pain intensity ratings than women without a MRMD,  $F(1, 125) = 6.18, p = .01$ ; Table 2).

There was a marginally significant interaction of MRMD status and abuse history for ischemic pain tolerance,  $F(3, 123) = 3.67, p = .058$  (Table 2) because women with MRMD and an abuse history tended to have lower ischemic pain tolerance than women with MRMD without such a history,  $F(60) = 3.54, p = .065$  (Table 2). Abuse history was not associated with a significant difference in ischemic pain tolerance in women without MRMD. Women with MRMD had lower ischemic pain threshold values,  $F(1, 123) = 6.23, p = .01$ , and higher ischemic pain intensity ratings,  $F(1, 124) = 9.33, p = .003$ , as compared with controls, regardless of abuse history (see Table 2). There were no significant effects involving ischemic pain unpleasantness.

### Plasma Neuroendocrine Measures in Relation to MRMD and Abuse

The interaction of abuse history and MRMD status predicted cortisol concentrations,  $F(3, 122) = 6.03, p = .02$ . Comparing only women with a MRMD, those with an abuse history had lower cortisol concentrations than those without,  $F(59) = 7.11, p = .01$ ; Figure 2, whereas there were no differences in cortisol as a function of abuse history in non-MRMD women. For NE, there was a marginally significant MRMD  $\times$  Abuse History interaction,

Table 1

Age, Education (Mean [SD]), Abuse Histories, and Psychiatric Histories (N [%]) of All Participants and Stratified by MRMD Status and Abuse Status

Characteristics	All women, $n = 126$	MRMD		Non-MRMD	
		Any abuse, $n = 34$	No abuse, $n = 29$	Any abuse, $n = 31$	No abuse, $n = 32$
Age (years)*	34.2 (8.0)	31.9 (7.1)	36.5 (7.8)	34.9 (8.5)	33.7 (8.1)
Non-Hispanic white	82 (65)	24 (71)	19 (66)	21 (68)	18 (56)
Education	2.6 (.8)	2.3 (.8)	2.8 (1.0)	2.7 (.7)	2.7 (.8)
Current smokers**	10 (8)	6 (18)	3 (10)	1 (3)	0
Sexual abuse only	22 (34)	13 (38)	—	9 (29)	—
Physical abuse only	18 (28)	10 (29)	—	8 (26)	—
Sexual or physical abuse	25 (39)	11 (32)	—	14 (45)	—
Depression history***	46 (37)	14 (41)	12 (41)	17 (55)	3 (9)
Anxiety history	21 (17)	6 (18)	7 (24)	7 (23)	1 (3)
PTSD history***	16 (13)	3 (9)	3 (10)	10 (32)	0 (0)

MRMD = menstrually related mood disorder; PTSD = posttraumatic stress disorder.

Education: 1 = less than a high school education; 2 = high school degree; 3 = college degree; and 4 = post-graduate degree.

\* MRMD women: any abuse < no abuse,  $p < .05$ . \*\* MRMD women > non-MRMD women,  $p < .01$ . \*\*\* Non-MRMD women: any abuse > no abuse,  $p < .05$ .

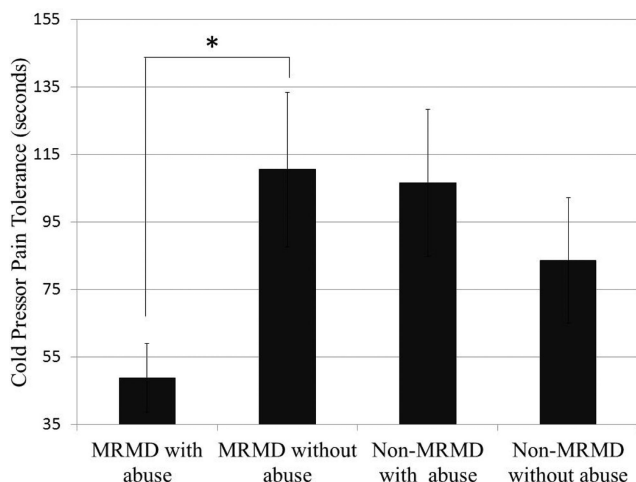


Figure 1. Cold pressor pain tolerance (in seconds) stratified by MRMD status and any abuse status; mean (± SEM). \* MRMD women only: with abuse < without abuse,  $p = .01$ .

$F(3, 118) = 3.40, p = .068$ , as women with MRMD with an abuse history had elevated NE concentrations relative to other women with MRMD with no such history,  $F(60) = 3.82, p = .055$ .

### Correlations Involving Neuroendocrine and Pain Sensitivity Measures

Because we observed main effects of MRMD status on pain sensitivity (described above), but not main effects of abuse status, correlational analyses were conducted separately in MRMD and non-MRMD groups, collapsing across abuse history groups. As summarized in Table 3, for both groups of women, higher plasma cortisol concentrations predicted lower cold pain unpleasantness ratings ( $r = -.30, p = .02$  and  $r = -.26, p = .04$ , respectively), and for the women with a MRMD, higher plasma cortisol also predicted higher cold pain tolerance levels ( $r = .32, p = .01$ ). In

those women with a MRMD, greater plasma NE concentrations were correlated with greater cold pain unpleasantness ratings ( $r = .26, p = .04$ ).

### Discussion

The primary findings of this study are that in women with a MRMD, an abuse history is associated with enhanced pain sensitivity (hyperalgesia), as evidenced by reduced pain tolerance to both cold pressor and ischemic pain, relative to other women with a MRMD but no abuse history. However, our results are also consistent with other reports (Fillingim et al., 1995; Straneva et al., 2002) that women with a MRMD are hyperalgesic relative to women without a MRMD irrespective of abuse history, as all women with a MRMD had lower ischemic pain threshold levels and higher ischemic and cold pressor pain intensity ratings compared to all women without a MRMD. Evidence suggests that the sensory/discriminatory aspects of pain (e.g., pain threshold and intensity) and the affective/motivational dimensions of pain (e.g., pain tolerance and unpleasantness) involve different endogenous pain regulatory systems (Gracely, Dubner, & McGrath, 1979; Gracely, McGrath, & Dubner, 1978). Thus, the possibility exists that in women with a MRMD, there is a trait vulnerability to alterations in sensory processing of noxious stimuli, while an abuse history moderates the affective/motivational experience of pain. This could contribute to both the premenstrual somatic symptoms experienced by 80% of all women with MRMD (McHichi, Tahiri, Moussaoui, & Kadri, 2002), and to the greater somatic premenstrual symptom severity experienced by women with a MRMD who also have an abuse history relative to other women with MRMD with no such history (Girdler et al., 2007).

It is unclear why we did not find that an abuse history influenced pain sensitivity in the women without a MRMD, as two previous studies using thermal pain stimuli reported (Fillingim & Edwards, 2005; Granot et al., 2011). One explanation might be that thermal heat is associated with a sharp, pricking heat sensation, whereas both the cold pressor and ischemic pain tests induce a deep, tonic, aching sensation similar to that seen in clinical pain syndromes

Table 2

Pain Sensitivity and Neuroendocrine Measures Stratified by MRMD Status and Any Abuse Status; Mean (SD)

	MRMD		Non-MRMD	
	Any abuse, $n = 34$	No abuse, $n = 29$	Any abuse, $n = 31$	No abuse, $n = 32$
<b>Cold pain task</b>				
Threshold (seconds)	22.3 (39.4)	25.0 (53.9)	26.2 (39.3)	25.1 (47.9)
Tolerance (seconds)*	48.8 (59.3)	110.6 (123.4)	106.6 (120.9)	83.6 (103.4)
Intensity (score)**	57.1 (22.8)	53.3 (18.1)	48.3 (20.4)	44.6 (17.2)
Unpleasantness (score)	57.8 (20.3)	53.97 (23.3)	53.4 (23.2)	48.4 (23.6)
<b>Ischemic pain task</b>				
Threshold (seconds)‡	180.8 (187.7)	275.9 (279.6)	399.1 (387.1)	336.7 (357.7)
Tolerance (seconds)**	427.1 (318.7)	581.5 (354.4)	641.9 (431.7)	513.3 (413.6)
Intensity (score)**	41.9 (21.9)	40.3 (17.5)	30.9 (18.8)	30.6 (17.5)
Unpleasantness (score)	39.5 (21.2)	42.2 (18.5)	42.9 (17.0)	37.3 (17.4)
<b>Neuroendocrine measures</b>				
Cortisol ( $\mu\text{g/dL}$ )*	6.8 (2.7)	9.4 (4.8)	8.0 (2.2)	7.9 (3.1)
Norepinephrine ( $\text{pg/mL}$ )§	337.4 (202.2)	297.3 (92.4)	306.4 (77.8)	317.2 (107.2)

MRMD = menstrually related mood disorder.

\* MRMD women only: any-abuse < no abuse,  $p < .05$ . \*\* MRMD > non-MRMD,  $p < .05$ . ‡ MRMD < non-MRMD,  $p < .05$ . \*\* MRMD women only: any-abuse < no abuse,  $p = .065$ . § MRMD women only: any-abuse > no abuse,  $p = .055$ .

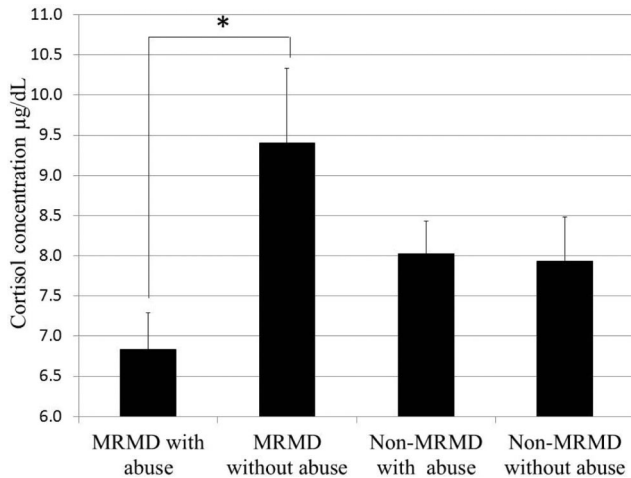


Figure 2. Cortisol concentrations ( $\mu\text{g/dL}$ ) stratified by MRMD status and any abuse status; mean ( $\pm$  SEM). \* MRMD women only: with abuse < without abuse,  $p = .01$ .

(Fillingim et al., 1996). Moreover, sensitivity to tourniquet-induced ischemic pain involves endogenous opioid mechanisms (Frid et al., 1979, 1981), whereas sensitivity to cold pressor pain may be mediated by systemic vascular resistance and noradrenergic mechanisms (Girdler et al., 2005). Thus, different endogenous pain regulatory mechanisms may be differentially modulated by histories of abuse.

Our study is among the first to assess endogenous neuroendocrine pain regulatory mechanisms in those with a MRMD. All women in our sample regardless of MRMD status showed the expected relationship between elevated plasma cortisol and reduced sensitivity to cold pressor pain, a relationship that has been previously replicated (al' Absi et al., 2002; Girdler et al., 2005). This is thought to reflect an integrated, adaptive mechanism involving nociceptive modulation by the HPA axis. Corticotrophin-releasing hormone acts on a large number of brain structures involved in pain processing, including the locus coeruleus (LC), and HPA-axis factors can act both centrally and peripherally to produce analgesia (see Lariviere & Melzack, 2000 for review). In women with a MRMD, those with an abuse history showed significantly lower cortisol concentrations than those without such a history, suggesting that hypocortisolimia may contribute to hyperalgesia in this group. Blunted HPA-axis function has been fairly consistently documented in MRMD samples (Girdler et al., 2003; Girdler, Straneva, Light, Pedersen, & Morrow, 2001; Redei & Freeman, 1993; Straneva et al., 2002), though not assessed by abuse status in these prior studies. Hypocortisolimia has been observed in a number of disorders associated with pain, including fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome (Fries, Hesse, Hellhammer, & Hellhammer, 2005), conditions that are also associated with greater rates of abuse (Pratchett et al., 2010; Leserman & Drossman, 2007). Regardless of mechanism(s), to the extent that sensitivity to experimental pain predicts clinical pain, our results for abuse-related hyperalgesia in MRMD women add to evidence suggesting that histories of abuse predict a clinically distinct subgroup of women with a MRMD (Girdler et al., 2007; Girdler & Klatzkin, 2006).

In contrast to the correlations involving higher cortisol concentrations and reduced sensitivity to pain, in women with a MRMD higher plasma NE concentrations were associated with increased cold pressor unpleasantness. This seemingly contradicts both animal and human studies showing that higher concentrations of NE are associated with increased pain tolerance (Girdler et al., 2005; Mechlin et al., 2005; Sagen, Kemmler, & Wang, 1991). This is consistent with the findings in chronic pain patients who show a (reverse) sensitivity to NE, such that administration of NE increases pain, whereas it has no effect in controls (Torebjörk, Wahren, Wallin, Hallin, & Koltzenburg, 1995; Ali et al., 2000). Higher circulating NE may reflect activation of LC neurons in brain, the major site of central nervous system adrenergic neurons. The LC plays a critical role in modulating sensory input via descending pain inhibitory noradrenergic pathways (Maixner, 1989) and, like the HPA-axis, is involved in an integrated response to modulate nociception. Thus, the finding that higher NE is associated with greater cold pressor pain unpleasantness in women with a MRMD may provide further support for alterations in endogenous pain regulation in MRMD, and may contribute to our findings that all women with a MRMD, regardless of abuse histories, exhibited hyperalgesia relative to women without a MRMD. Alternatively, it is possible that the association between elevated plasma NE concentrations and pain unpleasantness ratings may relate to NE-induced vasoconstriction that could independently evoke unpleasant sensations.

Our study has several limitations, including the relatively small MRMD  $\times$  Abuse cell sizes, the potential limited generalization of findings to women without a MRMD with abuse histories based on our selection strategies and requirement for the absence of current psychopathology, and lack of control for time of awakening which could affect cortisol concentrations (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). Additionally, this is a cross sectional study that cannot demonstrate causality between MRMD status, a history of abuse and pain sensitivity. Moreover, although we controlled for group differences in age in the analyses, abuse history groups also differed in rates of prior depression and PTSD which, although expected, could potentially confound the neuroendocrine and pain results. Like other populations with mood disorders (Grant, Hasin, Chou, Stinson, & Dawson, 2004), women in

Table 3  
Pearson's Correlation Coefficients (R) Relating Pain Sensitivity and Neuroendocrine Measures in Women Stratified by MRMD Status

	MRMD women		Non-MRMD women	
	Cortisol	NE	Cortisol	NE
Cold pressor pain task				
Tolerance	.32*	.01	-.07	.19
Intensity	-.24	.08	-.10	.04
Unpleasantness	-.30*	.26*	-.26*	.03
Ischemic pain task				
Tolerance	.02	-.15	-.08	.05
Intensity	-.15	.18	-.03	-.03
Unpleasantness	-.09	.09	.01	.06

Note. MRMD = menstrually related mood disorder; NE = norepinephrine.  
\*  $p \leq .05$ .

our sample with MRMD were more likely to smoke but this is unlikely to bias our findings since smokers are less sensitive to experimental pain tests than nonsmokers (Girdler et al., 2005).

In conclusion, the results of our study suggest that the presence of a MRMD moderates the relationship between an abuse history and sensitivity to pain stimuli, and provides further evidence that a history of abuse may identify a clinically distinct subgroup of women with a MRMD.

## References

- al' Absi, M., Petersen, K. L., & Wittmers, L. E. (2000). Blood pressure but not parental history for hypertension predicts pain perception in women. *Pain, 88*, 61–68.
- al' Absi, M., Petersen, K. L., & Wittmers, L. E. (2002). Adrenocortical and hemodynamic predictors of pain perception in men and women. *Pain, 96*, 197–204.
- Ali, Z., Raja, S. N., Wesselmann, U., Fuchs, P. N., Meyer, R. A., & Campbell, J. N. (2000). Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. *Pain, 88*, 161–168.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: American Psychiatric Association.
- Cunningham, J., Yonkers, K. A., O'Brien, S., & Eriksson, E. (2009). Update on research and treatment of premenstrual dysphoric disorder. *Harvard Review Psychiatry, 17*, 120–137.
- Dunn, E. C., Gilman, S. E., Willett, J. B., Slopen, N. B., & Molnar, B. E. (2012). The impact of exposure to interpersonal violence on gender differences in adolescent-onset major depression: Results from the national comorbidity survey replication (ncs-R). *Depression and Anxiety, 29*, 392–399.
- Edwards, R. R., Doleys, D. M., Fillingim, R. B., & Lowery, D. (2001). Ethnic differences in pain tolerance: Clinical implications in a chronic pain population. *Psychosomatic Medicine, 63*, 316–323.
- Eide, P. K. (2000). Wind-up and the NMDA receptor complex from a clinical perspective. *European Journal of Pain, 4*, 5–15. doi:53/eujp.1999.0154
- Endicott, J., Nee, J., & Harrison, W. (2006). Daily Record of Severity of Problems (DRSP): reliability and validity. *Archives of Women's Mental Health, 9*, 41–49.
- Felitti, V. (1998). Childhood trauma tied to adult illness. *American Journal of Preventative Medicine, 14*, 245–258.
- Fillingim, R. B., & Edwards, R. R. (2005). Is self-reported childhood abuse history associated with pain perception among healthy young women and men? *The Clinical Journal of Pain, 21*, 387–397.
- Fillingim, R. B., Girdler, S. S., Booker, D. K., Light, K. C., Harris, M. B., & Maixner, W. (1995). Pain sensitivity in women with premenstrual dysphoric disorder: A preliminary report. *Journal of Women's Health, 4*, 367–374.
- Fillingim, R. B., Maixner, W., Girdler, S. S., Light, K. C., Harris, M. B., Sheps, D. S., & Mason, G. A. (1997). Ischemic but not thermal pain sensitivity varies across the menstrual cycle. *Psychosomatic Medicine, 59*, 512–20.
- Fillingim, R. B., Maixner, W., Kincaid, S., Sigurdsson, A., & Harris, M. B. (1996). Pain sensitivity in patients with temporomandibular disorders: Relationship to clinical and psychosocial factors. *The Clinical Journal of Pain, 12*, 260–269.
- Finestone, H. M., Stenn, P., Davies, F., Stalker, C., Fry, R., & Koumanis, J. (2000). Chronic pain and health care utilization in women with a history of childhood sexual abuse. *Child Abuse & Neglect, 24*, 547–556.
- Freeman, E. W., & Sondheimer, S. J. (2003). Premenstrual dysphoric disorder: Recognition and treatment. *Primary Care Companion Journal Clinical Psychiatry, 5*, 30–39.
- Frid, M., Singer, G., & Rana, C. (1979). Interactions between personal expectations and naloxone: Effects on tolerance to ischemic pain. *Psychopharmacology (Berl), 65*, 225–231.
- Frid, M., Singer, G., Oci, T., & Rana, C. (1981). Reactions to ischemic pain: Interactions between individual, situational and naloxone effects. *Psychopharmacology (Berl), 73*, 116–119.
- Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology, 30*, 1010–1016.
- Girdler, S. S., & Klatzkin, R. R. (2006). Biological responses to stress in premenstrual dysphoric disorder: Influence of histories of abuse and depression. *Gynaecology Forum, 11*, 27–32.
- Girdler, S. S., Leserman, J., Bunevicius, R., Klatzkin, R., Pedersen, C. A., & Light, K. C. (2007). Persistent alterations in biological profiles in women with abuse histories: Influence of premenstrual dysphoric disorder. *Health Psychology, 26*, 201–213.
- Girdler, S. S., Maixner, W., Naftel, H. A., Stewart, P. W., Moretz, R. L., & Light, K. C. (2005). Cigarette smoking, stress-induced analgesia and pain perception in men and women. *Pain, 114*, 372–385.
- Girdler, S. S., Sherwood, A., Hinderliter, A. L., Leserman, J., Costello, N. L., Straneva, P. A., . . . Light, K. C. (2003). Biological correlates of abuse in women with premenstrual dysphoric disorder and healthy controls. *Psychosomatic Medicine, 65*, 849–856.
- Girdler, S. S., Straneva, P. A., Light, K. C., Pedersen, C. A., & Morrow, A. L. (2001). Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. *Biological Psychiatry, 49*, 788–797.
- Golding, J. M., Taylor, D. L., Menard, L., & King, M. J. (2000). Prevalence of sexual abuse history in a sample of women seeking treatment for premenstrual syndrome. *Journal of Psychosomatic Obstetrics & Gynecology, 21*, 69–80.
- Gracely, R. H., Dubner, R., & McGrath, P. A. (1979). Narcotic analgesia: Fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations. *Science, 203*, 1261–1263.
- Gracely, R. H., McGrath, P., & Dubner, R. (1978). Ratio scales of sensory and affective verbal pain descriptors. *Pain, 5*, 5–18.
- Granot, M., Somer, E., Zisman-Ilani, Y., Beny, A., Sadger, R., Mirkin, R., . . . Yovell, Y. (2011). Characteristics of response to experimental pain in sexually abused women. *The Clinical Journal of Pain, 27*, 616–622.
- Grant, B. F., Hasin, D. S., Chou, S. P., Stinson, F. S., & Dawson, D. A. (2004). Nicotine dependence and psychiatric disorders in the United States: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry, 61*, 1107.
- Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry, 49*, 1023–1039.
- Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., . . . Nemeroff, C. B. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA: The Journal of the American Medical Association, 284*, 592–597.
- Heim, C., Shugart, M., Craighead, W. E., & Nemeroff, C. B. (2010). Neurobiological and psychiatric consequences of child abuse and neglect. *Developmental Psychobiology, 52*, 671–690.
- Irish, L., Kobayashi, I., & Delahanty, D. L. (2010). Long-term physical health consequences of childhood sexual abuse: A meta-analytic review. *Journal of Pediatric Psychology, 35*, 450–461.
- Kendler, K. S., Bulik, C. M., Silberg, J., Hettema, J. M., Myers, J., & Prescott, C. A. (2000). Childhood sexual abuse and adult psychiatric and substance use disorders in women: An epidemiological and cotwin control analysis. *Archives of General Psychiatry, 57*, 953.
- Kirschbaum, C., Kudielka, B. M., Gaab, J., Schommer, N. C., & Hellhammer, D. H. (1999). Impact of gender, menstrual cycle phase, and oral



- contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosomatic Medicine*, *61*, 154–162.
- Lariviere, W. R., & Metzack, R. (2000). The role of corticotropin-releasing factor in pain and analgesia. *Pain*, *84*, 1–12.
- Leserman, J., & Drossman, D. A. (2007). Relationship of abuse history to functional gastrointestinal disorders and symptoms: Some possible mediating mechanisms. *Trauma, Violence, & Abuse*, *8*, 331–343.
- Leserman, J., Drossman, D. A., Li, Z., Toomey, T. C., Nachman, G., & Glogau, L. (1996). Sexual and physical abuse history in gastroenterology practice: How types of abuse impact health status. *Psychosomatic Medicine*, *58*, 4–15.
- Leserman, J., Li, Z., Drossman, D. A., Toomey, T. C., Nachman, G., & Glogau, L. (1997). Impact of sexual and physical abuse dimensions on health status: Development of an abuse severity measure. *Psychosomatic Medicine*, *59*, 152–160.
- Maixner, W. (1989). Autonomic and somatosensory interactions: Physiological and pathophysiological implications. *Proceedings of the Finnish Dental Society*, *85*, 395–407.
- Maixner, W., Gracely, R. H., Zuniga, J. R., Humphrey, C. B., & Bloodworth, G. R. (1990). Cardiovascular and sensory responses to forearm ischemia and dynamic hand exercise. *American Journal of Physiology*, *259*, R1156–R1163.
- McGuire, D. B. (1992). Comprehensive and multidimensional assessment and measurement of pain. *Journal of Pain and Symptom Management*, *7*, 312–319.
- McHichi, A. K., Tahiri, S. M., Moussaoui, D., & Kadri, N. (2002). Assessment of premenstrual dysphoric disorder symptoms: Population of women in Casablanca. *Encephale*, *28*, 525–530.
- Mechlin, M. B., Maixner, W., Light, K. C., Fisher, J. M., & Girdler, S. S. (2005). African Americans show alterations in endogenous pain regulatory mechanisms and reduced pain tolerance to experimental pain procedures. *Psychosomatic Medicine*, *67*, 948–956.
- Pratchett, L. C., Pelcovitz, M. R., & Yehuda, R. (2010). Trauma and violence: Are women the weaker sex? *Psychiatric Clinics of North America*, *33*, 465–474.
- Redei, E., & Freeman, E. W. (1993). Preliminary evidence for plasma adrenocorticotropin levels as biological correlates of premenstrual symptoms. *Acta Endocrinologica*, *128*, 536–542.
- Rubinow, D. R., Roy-Byrne, P., Hoban, M. C., Gold, P. W., & Post, R. M. (1984). Prospective assessment of menstrually related mood disorders. *American Journal of Psychiatry*, *141*, 684–686.
- Sagen, J., Kemmler, J. E., & Wang, H. (1991). Adrenal medullary transplants increase spinal cord cerebrospinal fluid catecholamine levels and reduce pain sensitivity. *Journal of Neurochemistry*, *56*, 623–627.
- Scarinci, I. C., McDonald-Haile, J., Bradley, L. A., & Richter, J. E. (1994). Altered pain perception and psychosocial features among women with gastrointestinal disorders and history of abuse: A preliminary model. *The American Journal of Medicine*, *97*, 108–118.
- Sheehan, D., Janavs, J., Baker, R., Harnett-Sheehan, K., Knapp, E., Sheehan, M., & Dunbar, G. (1998). MINI-Mini International Neuropsychiatric Interview-English Version 5.0.0-DSM-IV. *Journal of Clinical Psychiatry*, *59*, 34–57.
- Staud, R., Vierck, C. J., Cannon, R. L., Mauderli, A. P., & Price, D. D. (2001). Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain*, *91*, 165–175.
- Steiner, M., Romano, S. J., Babcock, S., Dillon, J., Shuler, C., Berger, C., . . . Judge, R. (2001). The efficacy of fluoxetine in improving physical symptoms associated with premenstrual dysphoric disorder. *BJOG: An International Journal of Obstetrics & Gynaecology*, *108*, 462–468.
- Straneva, P. A., Maixner, W., Light, K. C., Pedersen, C. A., Costello, N. L., & Girdler, S. S. (2002). Menstrual cycle, beta-endorphins, and pain sensitivity in premenstrual dysphoric disorder. *Health Psychology*, *21*, 358–367.
- Torebjörk, E., Wahren, L. K., Wallin, G., Hallin, R., & Koltzenburg, M. (1995). Noradrenaline-evoked pain in neuralgia. *Pain*, *63*, 11–20.
- Whitehead, W. E., Crowell, M. D., Davidoff, A. L., Palsson, O. S., & Schuster, M. M. (1997). Pain from rectal distension in women with irritable bowel syndrome (relationship to sexual abuse). *Digestive Diseases and Sciences*, *42*, 796–804.
- Young, E. A., & Breslau, N. (2004). Saliva cortisol in posttraumatic stress disorder: A community epidemiologic study. *Biological Psychiatry*, *56*, 205–209.

Received February 24, 2012

Revision received June 6, 2012

Accepted August 23, 2012 ■