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Menstrually Related Mood Disorders and a History of Abuse: Moderators of

Physical and Emotional Pain Sensitivity

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Abstract

Objective. Women with menstrually related mood disorders (MRMD) have substantial rates of physical and sexual abuse, are more sensitive to experimental pain stimuli than women withoutnon-MRMD women, and endorse increased sensitivity to interpersonal rejection (emotional pain) in the premenstrual phase. For the first time, this study examined physical and emotional pain sensitivity in women with MRMD and in non-MRMD controls as a function of abuse history. **Methods.** A total of 126 women (63 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; (2) emotional pain sensitivity based on daily prospective ratings of sensitivity to interpersonal rejection; and (3) basal plasma cortisol and norepinephrine (NE) concentrations. Exploratory analyses examined relationships between plasma cortisol and NE concentrations and physical pain sensitivity.

Results. Abused MRMD Wwomen with 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 non-MRMD women. However, abused non-MRMD women with an abuse history showed increased sensitivity to emotional pain relative to non-MRMD women with no such history. In all subjects, the expected relationship between greater plasma cortisol concentration and reduced sensitivity to physical pain was observed. While only in women with MRMD women only, plasma NE predicted pain sensitivity.

Conclusions. MRMD status moderates the effect of a history of abuse on both physical and emotional pain sensitivity. The results also suggest that the hypocortisolemia documented in the MRMD women with MRMD and an abuse history may contribute to their greater sensitivity to noxious experimental stimuli. This study adds to a growing body of evidence suggesting that a history of abuse may identify a clinically distinct subgroup of MRMD women with MRMD.

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Physical and Emotional Pain Sensitivity

Abuse rates for women in the United States are staggering, with more than one third of women from the general population having experienced sexual or physical abuse (Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993). 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) as well as medical illness (Felitti, 1998; Leserman et al., 1996), especially pain-related disorders (e.g., Sachs-Ericsson, Cromer, Hernandez, & Kendall-Tackett, 2009; Finestone et al., 2000; Irish, Kobayashi, & Delahanty, 2010). However, the mechanisms underlying the association of abuse with clinical pain syndromes are unclear.

Since experimental pain sensitivity is predictive of clinical pain (R. R. 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; Fillingim, Maixner, Kincaid, & Silva, 1998). 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 comparatively rare. Fillingim & 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, though the results are mixed regarding the directional differences of the effects in women with a history of abuse (e.g. Girdler, et al. 2003, 2007; Heim, et al. 2000 (in JAMA), 2001, 2010; Young et al., Biol Psychiatry 2004), potentially due to differences across studies in lifetime psychiatric illness or psychotropic medication use (e.g. Girdler, et al. 2003, 2007; Heim, et al. 2001, 2010); and 2) cortisol and NE are among several stress-responsive endogenous pain regulatory mechanisms. The relationship of higher cortisol and NE 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 of which we are aware 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

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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, PTSD or panic disorder (Freeman et al., 2003). While 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 much 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 arehave been shown to be 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 MRMD women with a MRMD.

The aims of the current study were two-fold: 1) to examine the independent as well as interactive effects of a MRMD diagnosis and a history abuse on physical pain sensitivity, emotional 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 compared women without a MRMD (i.e., that MRMD x Abuse history interactions would emerge) for the following reasons: 1)Based on our prior research showing that women with a MRMD women are more sensitive to laboratory-based physical pain stimuli (hyperalgesia) than non-MRMD women without a MRMD (Straneva et al., 2002 Fillingim et al., 1995), while; 2)the literature summarized above indicating that in non-MRMD women without a MRMD, an abuse history is associated with hypoalgesia to painful stimuli; 3) the evidence that

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women with women with a MRMD exhibit blunted HPA-axis function women without a MRMD (Girdler, Straneva, Light, Pedersen, & Morrow, 2001; Redei & Freeman, 1993; Straneva et al., 2002); and 4) our prior work showing that only in women with a MRMD does women only, a history of abuse predicts lower plasma NE – an effect not seen in non-MRMD women with a history of prior 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, U.S.A. and the surrounding area primarily via advertisements placed in local periodicals. These advertisements 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 sample 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 abused women in both the MRMD and non-MRMD groups, it was necessary to also selectively advertise for non-MRMD with a history of abuse survivors. Initial power analyses indicated that 60 women per MRMD group would yield 92% power to detect a difference of 250 seconds (sd = 342 seconds) in ischemic pain tolerance. AA 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 Axis I psychiatric disorders,

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including post-traumatic stress disorder (PTSD). None of the subjects were taking prescription medication or used over-the-counter analgesics ~~excessively~~ (> 10/month).

Procedures

~~Participants were screened for medical history and instructed on the daily record of severity of problems (DRSP) form (Endicott, Nee, & Harrison, 2006) that was used to confirm MRMD or non-MRMD status~~ (see below).). ~~For education, women were assigned a score (1-4) based on degree: (1) less than a high school education, (2) high school degree, (3) college degree, or (4) post-graduate degree.~~ 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 the daily record of severity of problems (DRSP) form (Endicott, Nee, & Harrison, 2006) that was used to confirm MRMD or non-MRMD status. All women completed the ~~Daily Record of Severity of Problems~~ (DRSP~~)~~ on a daily basis for two to three menstrual cycles. This measure allows quantification of the severity of 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 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 clear symptom free period ($\geq$ six consecutive days) during the early-to-mid follicular phase and (4) criteria 1-3 met in at least two

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menstrual cycles (Endicott et al., 2006; Rubinow, Roy-Byrne, Hoban, Gold, & Post, 1984). Non-MRMD women 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.

Quantifying emotional pain sensitivity

Sensitivity to interpersonal rejection (or emotional pain sensitivity) was measured with the following item from the DRSP: "Was more sensitive to rejection or my feelings were easily hurt". This item is similar to emotional rejection items used in other research evaluating the connection between emotional and physical pain (DeWall et al., 2010). Emotional pain sensitivity ratings from the first menstrual cycle only were analyzed in order to avoid the possible therapeutic effect of continuous daily ratings on emotional symptoms (Blake, Salkovskis, Gath, Day, & Garrod, 1998). Follicular phase emotional pain sensitivity was based on the average ratings for days 1-14 of menstrual cycle and luteal phase emotional pain sensitivity was based on average ratings for days 15 through the end of the first menstrual cycle.

Psychiatric history assessment

After meeting 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, chronic depression), anxiety disorders (e.g. panic disorder, generalized anxiety disorder) and post-traumatic stress disorder (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 histories of PTSD which was considered separately.

Following the MINI, women were assessed for abuse histories. Sexual abuse included the following experiences where force or threat of harm is used: 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 and 3) vaginal or anal intercourse. Force or threat was not required for coding sexual abuse in children (< 13 years of age), if it was implied by the age differential between victim and perpetrator. Physical abuse is 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). This instrument also allows for a quantitative measure of abuse severity (range 0 – 6), calculated as follows: if sexual abuse involving only touch (+1) versus rape (+2); if 1 – 3 physical abuse experiences (+1) versus more than 3 physical abuse experiences (+2); if serious injury during sexual abuse (+2). Because of the relatively small cell sizes associated with physical versus sexual abuse, women with any sexual or physical abuse history were combined into one group (Any Abuse) for analyses.

Psychiatric history assessment

All participants were scheduledtested during the luteal phase of the menstrual cycle, 5-12 days after home urine ovulation testing (ClearPlan Easy®) indicated the luteinizing hormone surge that indicatesprecedes ovulation. Cycle phase was subsequently confirmed based on serum progesterone concentrations. To ensure that subjects were hydrated, each was required to

consume eight, eight-ounce glasses of water on the day prior to testing and one eight-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 one hour 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 (I.V.) line was established in an arm vein and once in place, a curtain was drawn which prevented the subject from viewing the I.V.. A minimum of 15 minutes elapsed between establishing the I.V. and beginning baseline rest. Subjects were then exposed to the following conditions:

Baseline Rest: Subjects rested alone for 10 minutes. Blood -was sampled at minute 10 for basal cortisol and NE concentrations. Plasma levels of NE were determined using the high-pressure liquid chromatography with electrochemical detection (HPLC-ECD) technique. The lower limit of quantification is 2.5 pg/ml, and the intra- and inter-day 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 prednisolone, where 94% cross-reactivity is obtained. The intra- and inter-assay 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 minutes of rest between tests. Neuroendocrine measures were not taken during the pain tests although the I.V. remained in place since a mental stress

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battery followed the pain testing protocol (results to be reported elsewhere). The arm used for pain induction was opposite to the one with the I.V. (chosen based on vein characteristics), and therefore was not selected based on dominance. since the presence of an I.V. needle on the contralateral arm may have acted as a counter-irritant stimulus eliciting diffuse noxious inhibitory control mechanisms (R. R. Edwards, Ness, & Fillingim, 2004) and thereby altering pain sensitivity to the tests.

Hand cold pressor

For the cold pressor task, participants submerged their hands to a marked line on their wrist in ice water maintained at 4°C. A water circulator prevented water from warming near the subject's 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 minutes was imposed (Girdler Pain paper), though 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 30 seconds 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 minutes was enforced (Maixner and Gracely 1990 ref), though subjects were not informed of this limit.

Pain intensity and unpleasantness

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 - 100cm visual analogue scale. Thus, ratings were provided before the tests was terminated.

Data Reduction and Analysis

Due to the inability to obtain some blood samples, cortisol was available for 123 subjects and NE was available for 119 subjects. First, demographic and historical variables were examined using a 2 (Abuse) X 2 (MRMD status) analysis of variance (ANOVA) for continuous variables and Pearson's Chi-squared test or Fisher's exact test for dichotomous variables as appropriate. Next, Ffor each dependent measure of pain sensitivity, as well as for endocrine measures, a 2 (Abuse) X 2 (MRMD status) analysis of covariance (ANCOVA) was employed, with age as the covariate while controlling for age (see Results). Significant interactions (p<.05) were followed by t tests post-hoc ANCOVA analyses adjusting for age. Exploratory analyses among neuroendocrine data and pain data were examined using Pearson's correlations (r). In order to minimize the likelihood of spurious correlations resulting from small cell sizes, (n = 63), collapsed across abuse groups. Emotional pain data were collected distally from neuroendocrine data and thus their relationships are not explored here. Data were analyzed with PASW Statistics 18 (IBM, Chicago, Illinois, USA).

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), 110 (34%) withdrew or were lost to follow-up, and 7 (2%) were excluded due to a current Axis I

disorder (Need to fill this in). 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 76 women with MRMD who enrolled into the laboratory study. Sixty three (83%) 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 control women. Of these, 84 (66%) met non-MRMD control status, 9 (7%) did not meet control criteria (primarily due to chronic affective symptoms), 26 (20%) withdrew or were lost to follow-up, and 8 (6%) were excluded due to a current Axis I disorder (need to fill this in stills).

*Demographic and Historical Variables*Age, abuse histories and psychiatric histories

Demographic characteristicsAge, 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 x Abuse interaction for age ($F(3,125) = 4.23$, $p =.04$) since MRMD women with abuse histories were younger when compared to MRMD women without abuse histories (t(61)=-2.45, p=.02). There was a significantly higher proportion of current smokers in women with MRMD women when compared to no women without MRMD women ($X^2(1,125)=6.95$, 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 when compared to non-MRMD women due to targeted recruitment. Moreover, the two abused groups did not differ in severity of their abuse. Chi-squared analyses indicated proportional differences as a function of MRMD status and abuse histories for prevalence of depression histories ($X^2(3,125)=15.27$, p=.002) and PTSD histories ($X^2(3,125)=15.96$, p=.001). Post-hoc tests indicated that histories of depression (X^2

$(1,62)=15.02$, p<.001) and PTSD (Fisher's exact test, p<.001) were significantly more prevalent in non-MRMD women with abuse histories when compared to non-MRMD women without abuse histories, while the prevalence of these psychiatric histories in MRMD women was not influenced by abuse status.

Physical pain sensitivity in relation to MRMD status and Abuse history

After adjusting for age, we found that Ccold pressor pain tolerance was predicted by the interaction of MRMD and history of abuse ($F(3,125) = 5.2077$, *p* =.02; Figure 1). MRMD women with abuse had lower tolerance levels than MRMD women without abuse ($F(63)=7.15$, p=.01)(t(61)=2.47, p=.02), while a history of abuse was not associated with a significant difference in pain tolerance in non-MRMD women. There were no significant effects involving cold pressor pain threshold and unpleasantness (Table 2). However, MRMD women had significantly higher cold pressor pain intensity ratings when compared to non-MRMD women regardless of abuse history ($F(1,125)=6.18$, p=.01)(F(1,125) = 6.19, p =.01). (Table 2).

There was a marginal significancetrend for Tthe interaction of MRMD status and abuse history for predictinged tolerance to the ischemic pain task ($F(3,123)=3.67$, p=.058; Figure 2)(F(3,123) = 4.25, p=.04; Figure 2). MRMD women with abuse histories had a trend for lower ischemic pain tolerance than MRMD women without abuse ($F(60)=3.54$, p=.065; Figure 2)(t(60)= 1.81, p=.08; Figure 2), while abuse history was not associated with a significant difference in pain tolerance in non-MRMD women. MRMD women had lower ischemic pain threshold values ($F(1,123)$-6.23, p=.01)(F(1,123) = 6.21, p=.01) and higher ischemic pain intensity ratings ($F(1,124)=9.33$, p=.003)(F(1,124) = 9.18, p=.003) when compared to non-MRMD women, regardless of abuse history (see Table 2). There were no significant effects involving ischemic pain unpleasantness.

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Emotional pain sensitivity in relation to MRMD status and Abuse history

The interaction of history of abuse and MRMD status significantly predicted follicular phase emotional pain sensitivity $(F(3,125)=6.98, p=.009)$ ~~$(F(3,125) = 5.90, p =.02)$~~ (Figure 3). Non-MRMD women with abuse had *greater* emotional pain sensitivity compared with non-MRMD women without abuse $(F(61)=5.38, p=.02)$ ~~$(t(61)=2.23, p=.03)$~~, while a history of abuse did not predict emotional pain sensitivity in MRMD women in the follicular phase. As expected, in the luteal phase MRMD women had greater emotional pain sensitivity than non-MRMD women $(F(1,125) = 123.56, p <.001)$~~$(F(1,125) = 124.11, p <.001)$~~, but a history of abuse did not predict emotional pain sensitivity in either group in the luteal phase (Table 2).

Plasma neuroendocrine measures in relation to MRMD and abuse

The interaction of abuse history and MRMD status predicted cortisol concentrations $(F(3,122)=6.03, p=.02)$~~$(F(3,122) = 5.10, p=.03)$~~. MRMD women with abuse histories had lower cortisol concentrations than MRMD women without abuse histories $(F(59)=7.11, p=.01;$ Figure 4$)$~~$(t(59)= 2.65, p=.01;$ Figure 4$)$~~, while there were no differences in cortisol as a function of abuse history in non-MRMD women. There was also marginal significance ~~a trend~~ for the MRMD status and abuse history~~ies~~ interaction $(F(3,118)=3.40, p=.068)$, since in MRMD women abuse histories were associated with ~~a trend for~~ elevated norepinephrine concentrations $(F(60)=3.82, p=.055)$. ~~There were no significant group main or interactive effects involving plasma norepinephrine concentrations.~~

Since 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 MRMD and non-MRMD women, higher plasma cortisol concentrations predicted lower

cold pain unpleasantness ratings ($r = -.30$, $p = .02$ and $r = -0.26$, $p = .04$, respectively), and for the MRMD women, higher plasma cortisol also predicted higher cold pain tolerance levels ($r = .32$, $p = .01$). In MRMD women, 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 sensitivity to physical pain stimuli (hyperalgesia), as evidenced by reduced pain tolerance to both cold pressor and ischemic pain, relative to other women with a MRMD but who had women with no abusesuch history. In contrast, women withoutin non- a MRMD women, an abuse history was associated with enhanced emotional pain, measured here as sensitivity to interpersonal rejection, relative to other women without anon-MRMD who had women with no such abuse history. These results suggest that MRMD status moderates the association of an abuse history with both physical and emotional pain sensitivity. However, our results are also consistent with other reports (Fillingim et al., 1995; Straneva et al., 2002) that women with a MRMD women are hyperalgesic relative to non-MRMD women without a MRMD irrespective of abuse history since all women with a MRMD women had lower ischemic pain threshold levels and higher ischemic and cold pressor pain intensity ratings compared to all non-MRMD women. Evidence suggests that Since pain threshold and intensity reflect 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, while pain tolerance reflects the affective properties of pain (Gracely RH, Dubner R, McGrath PA.Science. 1979 Mar 23;203(4386):1261-3; . Gracely RH, McGrath P, Dubner R. Pain. 1978 Jun;5(1):19-29). Thus, the possibility exists

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(Price, Harkins, & Baker, 1987), these results suggest that women with a MRMD may have a noxious stimuli, while an abuse history moderates the affective/motivational experience of pain in women with a MRMD. This could then contribute to both the premenstrual somatic symptoms experienced by 80% of all women with MRMD (McHichi et al., 2002), and to the greater emotional and somatic premenstrual symptom severity experienced by MRMD women aMRMD who also have with an abuse history relative to other women with MRMD women with abuse 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 non-MRMD women, 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 while both the cold pressor and ischemic pain tests induce a deep, tonic, aching sensation similar to that seen in clinical pain syndromes (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 more or less modulated by histories of abuse.

Our study is among the first to assess endogenous neuroendocrine pain regulatory mechanisms in MRMD. For both the MRMD and the non-MRMD women, we found the expected relationship between elevated plasma cortisol and reduced sensitivity to cold pressor pain. The relationship between elevated cortisol and decreased pain sensitivity has been documented in other studies (al'Absi et al., 2002; Girdler et al., 2005; Mechlin et al.,2005), and is thought to reflect an integrated, adaptive mechanism as part of the defense reaction, 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 and Melzack, 2000 for review). Since MRMD women with an abuse history showed significantly lower cortisol concentrations than MRMD women with no abuse history, hypocortisolima in MRMD women with prior abuse may contribute to their hyperalgesia. Blunted HPA-axis function has been fairly consistently documented in MRMD samples compared with non-MRMD controls (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 a body of work suggesting that histories of abuse predict a clinically distinct subgroup of MRMD women (Girdler et al., 2007; Girdler & Klatzkin, 2006).

In contrast to the correlations involving higher cortisol concentrations and reduced sensitivity to pain, in MRMD women higher plasma NE concentrations were associated with increased cold pressor unpleasantness, a specific dimension of the pain experience (McGuire, DB, 1992, J Pain Symptom Manage.) ratings in MRMD women. This seemingly contradicts both animal and human studies showing that higher concentrations of circulating NE are associated with increased pain tolerance (Girdler et al., 2005; Mechlin, Maixner, Light, Fisher, & Girdler, 2005; Sagen, Kemmler, & Wang, 1991). However, in contrast to healthy, pain-free

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control groups, studies in groups at risk for clinical pain have shown that higher, and not lower, plasma NE is associated with greater experimental pain sensitivity (Mechlin et al 2005; 2011). This is consistent with the findings in chronic pain patients who show a (reverse) hypersensitivity to NE, such that administration of NE increases pain, whereas it has no effect in healthy controls (Ali et al., 2000; Torebjork, Wahren, Wallin, Hallin, & Koltzenburg,1995). Higher circulating NE may reflect activation of LC neurons in brain, the major site of CNS adrenergic neurons. The LC plays a critical role in modulating sensory input via descending pain inhibitory noradrenergic pain pathways (Maixner et al., 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 unpleasantnesssensitivity in MRMD women may provide further support for alterations in endogenous pain regulatory mechanisms in MRMD, and may contribute to our findings that all MRMD women, regardless of abuse histories, exhibited hyperalgesia relative to non-MRMD women. An alternative explanation, however, for the association between elevated plasma NE concentrations and cold pain unpleasantness ratings may relate to NE-induced vasoconstrictive actions that could independently evoke unpleasant painful sensations.

In contrast to MRMD women, non-MRMD women with abuse histories were more sensitive to emotional pain relative to their non-abused counterparts, at least in the follicular phase, but were slightly (though not significantly) less sensitive to physical pain. Others have also found a paradoxical relationship between rejection sensitivity and physical pain sensitivity in subjects where rejection was experimentally induced (MacDonald, Kingsbury, & Shaw, 2005). It has been proposed that rejection and physical pain both prime the fight or flight system but that flight is usually the best option up until the threat system is intensely activated at which

point the "fight" mechanisms engage, thereby decreasing physical pain sensitivity (MacDonald & Leary, 2005). Consistent with this idea, and our findings, women who are very sensitive to rejection show decreased pain sensitivity in an experimental paradigm when exposed to a strong experimental rejection scenario (MacDonald, Kingsbury, & Shaw, 2005). Thus, non-MRMD with abuse history may have also shown a non-significant decrease in sensitivity to experimental pain in our paradigm due to their greater rejection sensitivity.

While we must acknowledge limitations of our study, including the relatively small MRMD x Abuse cell sizes, ~~and~~ the potential limited generalization of findings to non-MRMD women 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 (REF). ~~the study also has notable strengths~~. 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, while expected, could potentially confound the neuroendocrine and pain results. MRMD groups also differed in smoking status, with more women with MRMD being smokers relative to women without MRMD. This is consistent with the robust findings that patients with mood disorders are more likely to smoke (REF), but is unlikely to contribute to our findings for greater pain sensitivity in women with MRMD since, if anything, smokers are less sensitive to experimental pain tests than non-smokers (Girdler 2005, Pain). These limitations are balanced, in part, by the notable strengths of the study which include t~~T~~he use of daily prospective symptom ratings and a validated interview to determine MRMD and Abuse status, the use of two different physical pain tests that vary in underlying endogenous pain regulatory mechanisms, the prospective measure of

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emotional pain sensitivity, and the inclusion of biomarkers of risk that are endogenous pain regulators., are among the strengths of the design.

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

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Table 1: Age 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) [A]	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 [B]	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)	-
			-	2.14 (1.36)	-
Depression history [BC]	46 (37)	14 (41)	12 (41)	17 (55)	3 (9)
Anxiety history	21 (17)	6 (18)	7 (24)	7 (23)	1 (3)
PTSD history [BC]	16 (13)	3 (9)	3 (10)	10 (32)	0 (0)

MRMD = menstrually related mood disorder; PTSD = post-traumatic stress disorder.
Education: 1 = less than a high school education; 2 = high school degree; 3 = college degree, and 4 = post-graduate degree.

[A] MRMD women: abuse < no abuse, p <=.052 p<.05
[B] MRMD women > non-MRMD women, p < .01 =.008
[BC] Non-MRMD women: any abuse > no abuse, (p <.05)

Table 2. Physical pain sensitivity, emotional 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
Cold pain task				
Threshold (seconds)	22.3 (39.4)	25.0 (53.9)	26.2 (39.3)	25.1 (47.9)
Tolerance (seconds) [A]	48.8 (59.3)	110.6 (123.4)	106.6 (120.9)	83.6 (103.4)
Intensity (score) [B]	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)
Ischemic pain task				
Threshold (seconds) [C]	180.8 (187.7)	275.9 (279.6)	399.1 (387.1)	336.7 (357.7)
Tolerance (seconds) [AD]	427.1 (318.7)	581.5 (354.4)	641.9 (431.7)	513.3 (413.6)
Intensity (score) [B]	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)
Emotional pain sensitivity				
Luteal phase (score) [B]	2.8 (.97)	2.9 (1.4)	1.3 (.4)	1.1 (.3)
Follicular phase (score) [DE]	1.3 (.4)	1.5 (.8)	1.4 (.8)	1.1 (.2)
Neuroendocrine measures				
Cortisol (-µg/dL) [A]	6.8 (2.7)	9.4 (4.8)	8.0 (2.2)	7.9 (3.1)
Norepinephrine (pg/mL) [F]	337.4 (202.2)	297.3 (92.4)	306.4 (77.8)	317.2 (107.2)

MRMD = menstrually related mood disorder.
[A] MRMD women only: any-abuse < no abuse, p<.05
[B] MRMD > non-MRMD
[C] MRMD < non-MRMD
[D] MRMD women only: any-abuse < no abuse, p=.065
[DE] Non-MRMD women only: any abuse > no abuse, p<.05;
[F] MRMD women only: any-abuse > no abuse, p=.055

Table 3. Pearson's correlation coefficients (r) relating physical 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

In **bold** p≤.05
MRMD = menstrually related mood disorder; NE = norepinephrine.

Figure legends.

Figure 1:   Cold pressor pain tolerance (in seconds) stratified by MRMD status and any abuse

status; mean (±SEM).

Figure 2:   Ischemic pain tolerance (in seconds) stratified by MRMD status and any abuse

status; mean (±SEM).

Figure 3:   Ratings of emotional sensitivity in the follicular phase of menstrual cycle

stratified by MRMD status and any abuse status; mean (±SEM).

Figure 4:   Cortisol concentrations (µg/dL) stratified by MRMD status and any abuse status;

mean (±SEM).
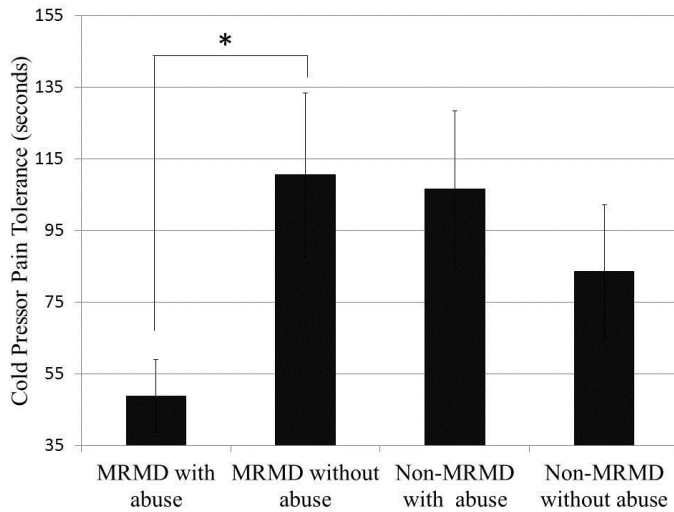
Figure 1.

*MRMD women only: with abuse < without abuse, p=.01~~2~~.
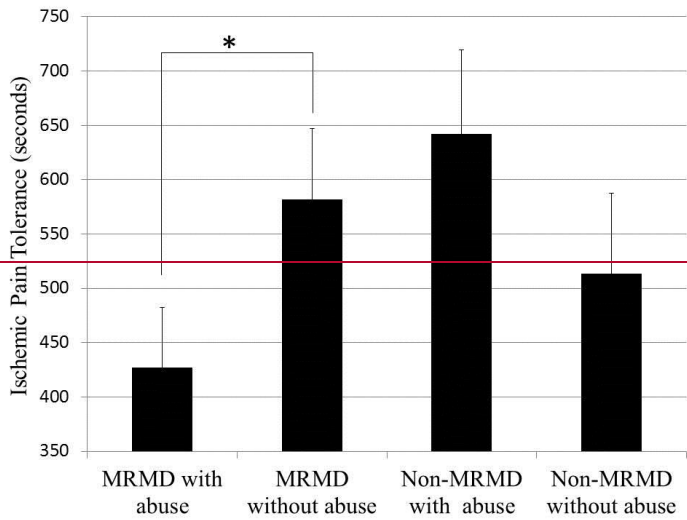
Figure 2.

* ~~MRMD women only: with abuse < without abuse, p=.065~~08.
Figure 3.
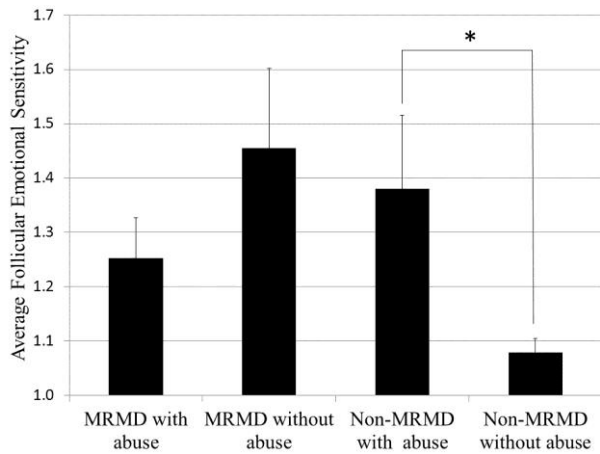
*non-MRMD women only: without abuse < with abuse, p=.0402.

Figure 4.

*MRMD women only: with abuse < without abuse, p=.01.