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The Influence of Early Life Sexual Abuse on Oxytocin Concentrations and Premenstrual Symptomatology in Women with a Menstrually Related Mood Disorder

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Abstract

Oxytocin (OT), associated with affiliation and social bonding, social salience, and stress/pain regulation, may play a role in the pathophysiology of stress-related disorders, including menstrually-related mood disorders (MRMD's). Adverse impacts of early life sexual abuse (ESA) on adult attachment, affective regulation, and pain sensitivity suggest ESA-related OT dysregulation in MRMD pathophysiology. We investigated the influence of ESA on plasma OT, and the relationship of OT to the clinical phenomenology of MRMD's. Compared to MRMD women without ESA (n=40), those with ESA (n=20) displayed significantly greater OT [5.39 pg/mL (SD, 2.4) vs. 4.36 pg/mL (SD, 1.1); t (58) = −2.26, p =.03]. In women with ESA, OT was significantly, inversely correlated with premenstrual psychological and somatic symptoms (r's = −.45 to −.64, p's < .05). The relationship between OT and premenstrual symptomatology was uniformly low and non-significant in women without ESA. In women with ESA, OT may positively modulate MRMD symptomatology.

Keywords

Oxytocin; Menstrually Related Mood Disorder (MRMD); Early Life Abuse; Sexual Abuse; Stress

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Introduction

The prevalence rates of childhood abuse in U.S. women are sobering. One recent survey of over 3,000 women indicated that 18% had been sexually assaulted and nearly 7% badly beaten before the age of 18 years (Dunn, Gilman, Willett, Slopen, & Molnar, 2012). The public health significance of early life abuse (ELA) in women is underscored by the well-established links between histories of abuse and psychiatric (Kendler et al., 2000) and medical illnesses (Felitti et al., 1998; Leserman et al., 1996).

There is ample evidence which suggests that ELA during critical developmental periods is associated with long-term dysregulation in stress responsive physiologic systems (Heim & Nemeroff, 2002; Heim, Newport, Bonsall, Miller, & Nemeroff, 2003; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 2003; Taylor, 2010). To date, the vast majority of studies in this area have examined sympathetic nervous system (SNS) and hypothalamic pituitary adrenal (HPA) axis stress mediators (e.g., cardiovascular reactivity, cortisol) (De Bellis et al., 1994; Heim et al., 2000; Murray-Close & Rellini, 2012). In the context of ELA, particularly for those women exposed to early life sexual abuse (ESA), which is associated with negative long-term psychosocial affiliative consequences (Pierrehumbert et al., 2009; Stalker & Davies, 1995), disruption in neurobiological pathways related to both social attachment and stress regulation may be especially relevant for the processing of emotionally and physically aversive stimuli.

Considering the negative impact of ESA on adult attachment and affective regulation (Kim & Cicchetti, 2010; Stalker & Davies, 1995), oxytocin (OT), which has received considerable attention in both animal and human research for its role in mediating social affiliation, mother–child attachment, social support, love, and trust (Campbell, 2010; Olff et al., 2013), may represent a candidate mechanism for the study of the neurophysiological underpinnings of ESA-related adverse mental health sequelae. In addition, OT has been implicated in the salience of social cues, suggesting that it may influence the processing of positive and negative social stimuli (Bartz, Zaki, Bolger, & Ochsner, 2011). Results from animal studies also suggest that increases in OT activity are capable of activating an integrated stress response that also exerts analgesic actions (Carter, 2014; Olff, et al., 2013; Rash, Aguirre-Camacho, & Campbell, 2013). Dysregulation in OT systems might therefore provide a unifying physiologic mechanism which may, in part, explain psychological and somatic symptoms in women presenting with menstrually related mood disorders (MRMD's), who have been exposed to ESA.

Women with MRMDs have a substantially higher rate of ELA than women without the disorders (Bertone-Johnson et al., 2014; Girdler et al., 2007). Premenstrual dysphoric disorder (PMDD), the most severe form of a MRMD, afflicting 5-8% of reproductive age women, is characterized by the cyclic recurrence of affective and somatic symptoms in the luteal phase of the menstrual cycle, and results in luteal phase impairment equivalent to that of major depression, panic disorder, and PTSD (Freeman & Sondheimer, 2003; Halbreich, Borenstein, Pearlstein, & Kahn, 2003). However, the restrictive nature of the DSM-IV PMDD criteria, particularly the requirement of an arbitrary 5 symptoms, is controversial (Freeman & Sondheimer, 2003; Halbreich, et al., 2003). The prevalence of clinically

significant premenstrual symptoms that are characterized by impairment, treatment seeking, and suicide risk, but do not meet the five symptom criterion, is 13-19% (Angst, Sellaro, Merikangas, & Endicott, 2001; Halbreich, 2003; Halbreich, et al., 2003; Spitzer, Williams, Kroenke, Hornyak, & McMurray, 2000; Wittchen, Becker, Lieb, & Krause, 2002).

While impairment in MRMDs correlates more strongly with affective symptoms than with somatic symptoms (Bloch, Schmidt, & Rubinow, 1997; Ekholm & Backstrom, 1994), somatic symptoms affect 80% of MRMD women (McHichi alami, Tahiri, Moussaoui, & Kadri, 2002) and contribute to impairment (Bloch, et al., 1997; Ekholm & Backstrom, 1994; Steiner et al., 2001). The causes of MRMDs are currently unknown and the burden is high, with 4.5 million disability adjusted life years lost/year in the U.S. (Bloch, et al., 1997; Ekholm & Backstrom, 1994; Halbreich, et al., 2003). Thus, there is a substantial proportion of women in the general population with a MRMD who have impairment and distress, warranting continued investigations into the pathophysiology of MRMDs.

The extent to which dysregulation in OT may play a role in the often co-morbid negative affect and somatic complaints in patients with a history of abuse, has yet to be fully investigated. To our knowledge, no studies have examined the relationships among OT and MRMD symptomology in women with an MRMD and ESA. This report represents an exploratory secondary analysis of previously completed work (Fleischman, Bunevicius, Leserman, & Girdler, 2013) in order to investigate the moderating influence of ESA on associations among OT and premenstrual psychological and somatic symptoms in women with a MRMD.

Methods

Participants

Women were recruited from Chapel Hill, North Carolina, U.S.A. and the surrounding area, primarily through advertisements in the community and via the University of North Carolina Center for Women's Mood Disorders website. Those women who chose to participate in the study were invited to sign a written informed consent approved by the institutional review board (IRB) of the University of North Carolina. A total of 60 women (20 with ESA, 40 with no history of ESA) with a MRMD, confirmed via prospective symptom ratings, were included in the current study analysis. All women were in good health, without chronic medical conditions (including pain-related disorders or current DSM-IV Axis I psychiatric disorders). Participants were not taking prescription medications, and none of the participants in the study used over-the-counter analgesics excessively (> 10/month).

Screening and Enrollment

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 (77%) women with confirmed MRMD's had complete abuse history and OT assay data and are included in the present report.

Confirming MRMD diagnosis

Study participants completed the daily record of severity of problems (DRSP) form for two to three menstrual cycles. The DRSP consists of 24 likert scale items, which assess eleven psychological and physical symptoms, and three items which describe specific types of impairment in functioning caused by the symptoms (Endicott, Nee, & Harrison, 2006). The DRSP 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 criteria: (1) exhibited 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) rated emotional symptoms as moderate, severe or extreme on at least two of the seven premenstrual days; (3) displayed remission of symptoms within three days of the onset of menses, followed by a symptom free period (≥ six consecutive days) during the early-to-mid follicular phase; and (4) criteria 1-3 were met in at least two menstrual cycles (Endicott, et al., 2006; Rubinow, Roy-Byrne, Hoban, Gold, & Post, 1984).

Psychiatric and Abuse History Assessment

Participants were evaluated for past depressive disorders (e.g., major depressive disorder; MDD), 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 DSM–IV (American Psychiatric Association, 2013) Axis I psychiatric disorders at study enrollment were excluded from participation. Full remission from depressive disorders for one year and from other Axis I disorders for three years was required. To create clinically and conceptually meaningful categories, all histories of depressive disorders were categorized as ‘any depressive disorder’ and all histories of anxiety disorders were categorized as ‘any anxiety disorder’, with the exception of PTSD history.

Abuse histories were assessed via standard interview (Leserman, et al., 1996). ESA was defined as first sexual abuse experienced prior to the age of 17 years of age. Definitions of sexual abuse included: 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. A history of physical abuse was also assessed. 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 (hit, kicked, burned). Based on the evidence to date which suggests that early life sexual abuse is more likely than early life physical abuse to impact the development of key behavioral systems associated with OT regulation (affiliation, trust, bonding, etc.) (Pierrehumbert, Torrisi, Ansermet, Borghini, & Halfon, 2012; Pierrehumbert

et al., 2009), and the evidence that ESA experiences are associated with more severe and chronic medical and psychological sequelae (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Heim, Shugart, Craighead, & Nemeroff, 2010; Talbot et al., 2009); we grouped our sample according to ESA versus no ESA. Consequently, both groups included women who had a history of early life physical abuse, but the groups did not significantly differ in the number of women (n=4 in the ESA group vs. n=5 in the group without ESA) with prior early life physical abuse.

Laboratory Session

Blood samples for the current study were collected from an indwelling catheter following an extended baseline rest period that preceded (25 minutes) a laboratory stress testing paradigm that has been described elsewhere (Fleischman, et al., 2013). During the baseline rest period, the subject rested alone quietly in a comfortable chair. A curtain shielded the catheter and the blood sampling from the subject's view. Blood was sampled at the end of the 25 minute rest period for basal OT. Each participant participated in a single laboratory session, which was scheduled between 7:00 a.m. and 9:30 a.m. In addition, 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 Participants began testing five days prior to their estimated time of ovulation based on previously determined cycle lengths. To ensure that participants were hydrated prior to the laboratory session, each participant was asked to consume eight, eight-ounce glasses of water on the day prior to sampling, and one eight-ounce glass and a low fat breakfast the morning of testing (confirmed via self-report diary). Participants 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 at study visit). Participants who had been ill within seven days of testing or who had fewer than six hours of sleep the previous night were rescheduled.

OT Assays

Blood for OT was collected into EDTA-treated tubes, immediately placed on ice, and cold centrifuged to separate plasma within a few minutes after collection. Plasma was aliquoted into tubes, rapidly frozen, and maintained at −80°C until assayed. The level of OT in EDTA-treated plasma (pg/mL) was determined by extraction and radioimmunoassay (RIA) using commercially available kits (Peninsula Laboratories, San Carlos, CA). The intra-assay coefficient of variance (CV) was 4.05% and inter-assay CV was 8.95%, sensitivity was approximately 0.5 pg, and cross-reactivity of the antibody with Arg8-vasopressin was < 0.01%.

Data Reduction and Analysis

Descriptive statistics (means, SD's, proportions) were used to describe demographic and behavioral characteristics of the study population separately for women with or without histories of ESA. T-tests and chi-square tests (or fisher's exact tests as necessary) were used to compare the means of continuous variables and the prevalence of categorical variables, respectively.

For each of the 24 DRSP scale items, mean luteal phase (using the seven days just prior to menses) values were calculated for each cycle, then averaged to create an overall luteal phase value for: (1) total summary score (sum total of all 24 items); (2) core emotional symptoms summary score (sum total of the 4 core symptoms domains: depression, anxiety, irritability/anger, labile mood) and, the somatic symptom summary score. These categories were selected using established diagnostic criteria (Endicott, et al., 2006).

Two sample t-tests were conducted to examine group differences in basal OT concentrations between women with or without histories of ESA. The relationships among plasma OT and DRSP measures were then examined using Pearson's correlational analyses (r). Where significant correlations were obtained involving the symptom domains, we then examined the relationship between OT and the individual symptoms comprising the domain to obtain: (1) a depression domain mean summary score (feeling depressed/sad/down, hopeless, worthless or guilty); (2) an anxiety domain mean summary score (single item); (3) an anger/irritability domain mean summary score (felt angry or irritable, had interpersonal conflicts); (4) a labile mood domain mean summary score (had mood swings, sensitivity to rejection/hurt feelings); and (5) a somatic symptoms mean summary score (breast swelling/felt bloated/had weight gain, breast tenderness, headache, joint or muscle pain). The three impairment items were examined separately since they represented separate domains of impairment: work/school/home/daily routine, hobbies or social activities, and interference with relationships. Correlational analyses were conducted separately in women with histories of ESA (n = 20) and women without histories of ESA (n = 40). All *p* values reported are 2-sided with an alpha level of .05. Due to the exploratory nature of the study, primary analyses did not correct for multiple comparisons. However, secondary analyses applied Bonferroni adjustments for comparison sake (0.05/21comparisons), yielding a Bonferroni-adjusted alpha level of 0.002. All statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

Table 1 presents demographic and baseline characteristics of study participants. No significant differences were observed between women with or without histories of ESA. As shown in Figure 1, MRMD women with ESA displayed higher basal plasma OT concentrations, compared to MRMD women without ESA [means = 5.39 pg/mL (SD, 2.4) vs. 4.36 pg/mL (SD, 1.1); t (58) = −2.26, p =.03]. We did not observe any significant differences in global premenstrual symptomatology (based on the total DRSP summary score of 24 items) between women with ESA [mean = 2.9 (SD, 0.9)] and women without ESA histories [mean = 2.8 (SD, 0.8); t (53) = −0.42, p =.68]. Similarly, no group differences were noted in the composite score for all four core emotional symptom summary scores, which included the summary scores for depression, anxiety, anger/irritability, and labile mood [means = 2.7 (SD, 0.7) in women with ESA histories vs. 2.9 (SD, 0.9) in women without ESA; t (58) = 1.05, p =.30].

As shown in table 2, only for women with a MRMD and a history of ESA did plasma OT concentrations predict premenstrual symptomatology. Specifically, in those women, greater plasma OT were associated with lower global premenstrual symptomatology based on the

total DRSP summary score of 24 items (r = −.56, p =.01). Subsequent analyses indicated that the relationship between higher plasma OT concentrations and lower premenstrual symptomatology was evident in the composite score for all four core emotional symptom summary scores (summary of depression, anxiety, anger/irritability, and labile mood; r = −.45, p =.05). In order to determine the source of this effect, we examined the individual core emotional domains separately and found that higher OT predicted reduced premenstrual symptomatology only in the anger/irritability (r = −.50, p =.02) and labile mood (r = −.58, p =.01) domains. Further examination of individual symptoms which comprised the anger/irritability domain mean summary score revealed that, in MRMD women with ESA only, OT was significantly and inversely correlated with feelings of anger or irritability (r = −.55, p = .01), but not with the interpersonal conflicts item. In the labile mood domain, greater OT concentrations predicted lower symptom severity scores for both mood swings (r = −.48, p = .03) and rejection sensitivity (Figure 2: r = −.64, p = .002). There was no relationship between plasma OT and any emotional symptoms in MRMD women who had not experienced ESA.

In addition to the core emotional symptoms, we explored relationships among OT concentrations and the somatic symptoms domain of the DRSP scale. Again, only for women with a MRMD and a history of ELA was OT predictive of somatic symptomatology. Specifically, higher plasma OT concentrations predicted lower severity ratings for the somatic symptom domain (r = −.55, p = .02), an effect that was driven by inverse correlations between OT and breast swelling/felt bloated/had weight gain (r = −.45, p = .05); headache (r = −.52, p = .02); and joint or muscle pain (r = −.54, p = .01), but not breast tenderness (r = −.27, p = .25). There were no significant relationships involving OT and any somatic symptom in MRMD women who did not have a history of ESA.

Consistent with the effects of ESA on the relationship between OT and symptom severity, only women with a MRMD and a history of ESA showed a significant relationship between plasma OT concentrations and impairment, though this was evident only in the domain of interference with relationships (r = −.50, p = .02), and not in the domains of work or social activities. Again, no relationships were observed between plasma OT concentrations and any impairment score in women without ESA histories.

Discussion

Compared to MRMD women without ESA histories, OT concentrations were significantly higher in those with ESA histories. Studies report that maltreated girls often develop poor social relationships (Christine Heim, Shugart, Craighead, & Nemeroff, 2010; Ullman & Filipas, 2005), so it may seem counterintuitive that these women would show higher levels of OT, a hormone implicated in the maintenance of affiliative behaviors and intimate relationships. While some reports indicate that adverse early experience is associated with reduced OT levels in aduthood (C. Heim et al., 2009; Meinlschmidt & Heim, 2007), a number of studies indicate a contrasting and seemingly paradoxical finding - comparatively high OT in individuals who have experienced early life abuse, in particular, early life sexual abuse (Parker et al., 2010; Pierrehumbert et al., 2010). Higher OT has also been found in individuals who report unsatisfying relationships (Taylor et al., 2006; Taylor, Saphire-

Bernstein, & Seeman, 2010). These findings appear to parallel findings from animal studies where higher OT levels have been observed in socially isolated animals (Ebner, Wotjak, Landgraf, & Engelmann, 2000; Grippo et al., 2007).

There is strong literature which suggests that OT's actions are context dependent. For example, it has been shown that OT functions, in part, to facilitate attachment. However, this may be the case only for certain individuals, in certain contexts. Moreover, it is becoming apparent that the early social environment has the potential to substantially shape OT systems, which, in turn, can alter the expression of OT and the regulation of social behavior throughout life (Veenema, 2012). For example, in rejection-sensitive individuals with bipolar disorder, OT administration decreases the levels of trust exhibited when playing a cooperation game (Bartz et al., 2011). Conversely, in a similar game paradigm, administration of OT reduces betrayal aversion, but only in individuals who have a tendency to fear intimacy and dependence on others (De Dreu, Shalvi, Greer, Van Kleef, & Handgraaf, 2012). Consequently, context may influence the direction of association between ELA and later life OT concentrations, thus contributing to the discrepancies in the literature.

An alternative, though not mutually exclusive explanation for our finding of higher OT concentrations in those with ESA, is that peripheral OT measures, such as basal plasma OT, may be a marker of ongoing physical or social distress (Parker et al., 2010; Taylor, Saphire-Bernstein, & Seeman, 2010), signaling the need to seek social affiliation. Indeed, many women with ESA histories display socially avoidant attachment behaviors (Pierrehumbert, et al., 2009; Ullman & Filipas, 2005), therefore higher OT concentrations in MRMD women with ESA might serve as a biomarker of ongoing self-regulatory processes needed for coping with social isolation, and other stressful experiences, including emotional distress and physical pain. Thus, higher basal OT concentrations in MRMD women with ESA may be indicative of a persistent hyper-activation of OT (critical for affiliation, bonding, and trust) as part of a compensatory, adaptive response initially induced by early life stress (Pierrehumbert, et al., 2012; Riggs, 2010), and further perpetuated by chronic stressful experiences in adulthood. Indeed, women with MRMD's report more stressful life events than women without the disorders (Girdler, Pedersen, Stern, & Light, 1993; Woods, Lentz, Mitchell, Heitkemper, & Shaver, 1997).

Higher OT concentrations in MRMD women with ESA may therefore reflect the emotional distress and somatic pain they experience only premenstrually, but which have been reported chronically in many women with affective disorders and histories of early life abuse (Irish, Kobayashi, & Delahanty, 2010; Landa, Peterson, & Fallon, 2012; Meyer-Lindenberg & Tost, 2012; Nelson, Baldwin, & Taylor, 2012). However, the absence of follicular phase assessments in the present study limits this interpretation. Another possibility is that childhood maltreatment, such as ESA, may interfere with the oxytonergic system at the level of the OXTR receptor gene, perhaps via epigenetic mechanisms (Bakermans-Kranenburg & van, 2013) modulating the effectiveness of OT (Chen et al., 2011; Marsh et al., 2012). Studies investigating these phenomena in humans are just emerging. For example, a recent study by Bradley and colleagues observed that individuals with the GG genotype on rs53576 (the most commonly studied marker on the OXTR receptor gene) who experienced severe childhood maltreatment were more likely to have disorganized attachment styles and higher

levels of emotional dysregulation (Bradley et al., 2011), suggesting that ESA may indeed interact with the oxytonergic system at the level of the OXTR receptor gene to influence behavior.

Moreover, oxytocin has been associated with dampening of the stress response in humans (Heinrichs, von Dawans, & Domes, 2009; Vargas-Martinez, Uvnas-Moberg, Petersson, Olausson, & Jimenez-Estrada, 2014). Studies of intranasal administration of OT have shown that OT attenuates neuroendocrine stress reactivity (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003) and decreases amygdala activation in response to threatening stimuli (Domes et al., 2007; Kirsch et al., 2005). Furthermore, studies in rodents have shown that peripheral administration of OT can both elevate nociceptive thresholds (Petersson, Alster, Lundeberg, & Uvnas-Moberg, 1996; Uvnas-Moberg, Bruzelius, Alster, Bileviciute, & Lundeberg, 1992) and lessen the anxiety behavior of rats placed in a potentially stressful environment (Uvnas-Moberg, Ahlenius, Hillegaart, & Alster, 1994). Considering the strong association between chronic stress and MRMD's, these observations suggest a role for OT in decreasing premenstrual psychological and somatic symptoms prevalent in women with MRMD's.

To our knowledge, this is the first study to investigate the role of OT in the phenomenological presentation of women with MRMD's, and the influence of early life sexual abuse in these associations. It was unexpected that we did not observe group differences in emotional and somatic symptoms between MRMD women with or without ESA histories in the present study. However, we speculate that the heightened luteal phase emotional and physical distress seen in MRMDs may mask the effects of ESA on premenstrual symptom severity. Previous work from our lab lends support to this concept, since we found greater evidence for an association between histories of abuse and elevated symptom severity in women with a MRMD during their follicular, low symptom phase of the menstrual cycle, than during their luteal phase (Girdler, et al., 2007).

Despite the lack of an association of ESA with greater premenstrual symptom severity in the current study, we did find robust correlations among OT concentrations and premenstrual symptoms in MRMD women with ESA histories, but no associations whatsoever in those without ESA histories. It is perhaps important to underscore the specificity of these effects. Although OT concentrations were negatively related to total symptom severity scores and to an average measure across all of the core emotional symptoms, more fine grained analyses demonstrated that greater OT concentrations predicted lower severity ratings primarily in premenstrual symptom domains which have been consistently associated with impairment in relationships and social function (i.e., anger/irritability, mood swings and rejection sensitivity). These symptoms are not only the most frequently reported MRMD symptom domains in women with MRMD's (Hartlage & Arduino, 2002; Qiao et al., 2012), but are also more often associated with impairment in interpersonal relationships (Bloch, et al., 1997; Pearlstein & Steiner, 2008; Soyda Akyol, Karakaya Arısoy, & Çayköylü, 2013). This is consistent with our results showing that higher OT predicted less impairment in interpersonal relationships in those with ELA, though not in work function or social activities. OT did not predict any premenstrual depression or anxiety symptoms in those with ESA. Specificity was also observed for somatic symptoms, since OT was negatively associated with severity in premenstrual somatic symptoms including breast swelling/felt

bloated/had weight gain headache, and joint or muscle pain, but not for breast tenderness. It should be noted, however, that when the significance level was adjusted for number of comparisons, only the relationship between OT and rejection sensitivity withstood the correction (see Table 2).

What mechanism might account for the inverse association between OT concentrations and premenstrual interpersonal and somatic symptoms only in MRMD women with ESA history? In women with MRMD's, who have been exposed to ESA, a downregulation of social salience by OT might serve to buffer the threatening features of social information, which would otherwise increase the luteal phase severity of socially-contextual symptoms, including mood lability, anger/irritability, and emotional/rejection sensitivity. Similar inverse associations among OT concentrations and social stress have been observed in individuals with borderline personality (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011) and social anxiety disorders (Hoge, Pollack, Kaufman, Zak, & Simon, 2008). In addition, peripherally measured OT has been inversely correlated with symptom severity in women with schizophrenia (Rubin et al., 2010). Limited research has shown that women with severe PMS have significantly more personality disorder traits, particularly those involving affective lability, (e.g., borderline/histrionic/dramatic and anxious/fearful traits), and have a greater prevalence of personality disorders than healthy control women (Sassoon, Colrain, & Baker, 2011). Thus, the possibility exists that the MRMD women in the present study with ELA included a larger proportion of women with personality disorders, accounting for the inverse association of OT with premenstrual symptom severity. However, the absence of personality assessment in this study precludes that interpretation.

While our study has many strengths, including the daily prospective measurement of premenstrual symptom severity, the use of a structured interview to assess abuse history, and the collection of plasma OT under a highly standardized procedure, the results must be interpreted in light of its limitations. First, the results reported herein should be considered preliminary as they represent secondary analyses from a study designed for other purposes. Hence there is no measure of attachment style or relationship satisfaction which would have aided interpretation of the findings. Additionally, due to the cross-sectional nature of this study, we cannot demonstrate causality between ESA history, OT, and premenstrual symptom severity ratings. Moreover, generalization of findings is limited to women with MRMD's who are free of other current psychiatric diagnoses. Additionally, though literature suggests that hydration status (hypernatremia and hyponatremia) may influence OT levels (Ivanyi, Dohanics, & Verbalis, 1995; Krause et al., 2011), our requirement for 8, 8 ounce glasses of fluid over the 24 hours that preceded laboratory testing is entirely within the realm of normal fluid consumption and thus should not negatively impact on the generalizability of the findings.

Second, our associations are based on peripheral OT measurement, and the literature remains mixed regarding whether peripherally measured OT is indicative of central release patterns and OT activity within the brain, and whether peripherally measured OT is therefore associated with social and emotional behaviors. However, several mechanisms by which peripheral levels of OT may reflect central effects of OT have been postulated. It has been hypothesized that the small quantity of OT which can return to the central nervous

system once it leaves the posterior pituitary, may cross the blood–brain barrier in sufficient enough amounts to activate OT receptors (Burbach et al., 1983; Mens, Witter, & van Wimersma Greidanus, 1983). It has been shown that peripheral administration of OT increases central levels in animals (Neumann, Maloumby, Beiderbeck, Lukas, & Landgraf, 2013). Another mechanism that has been hypothesized to explain the relationship between peripheral and central OT measurement involves the release of OT into the periphery by the posterior pituitary, which receives inputs from both the paraventricular (Kozorovitskiy, Hughes, Lee, & Gould, 2006; Seltzer, Ziegler, Connolly, Prososki, & Pollak, 2013) and supraotic nuclei of the hypothalamus (Landgraf & Neumann, 2004). This may, in part, account for the successful use of peripheral OT measurement in social and behavioral research (Feldman, Gordon, & Zagoory-Sharon, 2011; Modahl et al., 1998; Parker et al., 2014; Rubin, et al., 2010; Wismer Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005). Additional studies, however, are needed to clarify the precise relationship between behavioral processes and peripheral OT measures.

Third, the limited evidence in humans, to date, suggests that our sampling may have occurred on the descending curve of the diurnal rhythm (Forsling, Montgomery, Halpin, Windle, & Treacher, 1998). However, each participant in our study was tested within this time frame in order to control for time of day effects and thus is should not have affected the group differences observed.

Fourth, individuals with low trust have been shown to show lack of habituation across repeated testing sessions (Tops et al., 2013), and the possibility could exist that increased OT levels in ESA women in our study may have been reflective of this lack of habituation. However, informed consent and screening was obtained in a different environment than the lab environment, therefore, while it was possible that women may have encountered the person from which they obtained consent during the second appointment, the lab environment and tasks for the second appointment were novel, decreasing the chance for habituation. Moreover, studies which have investigated OT levels in individuals with histories of early life abuse and/or impaired social relationships (Parker, et al., 2010; Pierrehumbert, et al., 2010) suggests higher basal OT levels in these individuals vs. control subjects. The weight of the evidence thus suggests that habituation to the lab setting is an unlikely explanator of our results.

Fifth, without a non-MRMD group, our interpretation for increased OT levels in MRMD women with ESA is limited. Future research comparing MRMD women with non-MRMD women would clarify whether our findings are unique to MRMD women, or whether a similar relationship between OT levels and premenstrual symptoms may exist in women without a MRMD. Alternatively, for treatment implications, it may also be important to know whether OT levels in MRMD women with or without ESA are decreased or increased relative to normal, thus future research including a non-MRMD group might help to clarify these relationships.

Conclusions

Results from this exploratory study implicate a role for OT mechanisms in modulating premenstrual symptom severity in women with a MRMD and a history of ESA and also

highlight the importance of a more fine-grained approach to the analysis of symptom severity in women with MRMD's, particularly in the investigation of pathophysiology. This approach (the identification of endophenotypes for MRMD's) has the potential to inform personalized treatment for women with MRMD's, with a future goal towards individualized medicine for women's mental health.

Our finding of higher OT in MRMD women with ESA (vs. MRMD women with no ESA), and inverse associations among premenstrual symptomatology and OT in MRMD women with ESA may also be indicative of context-specific effects of OT, particularly with regards to approach avoidance. Approach avoidance motivation behaviors include behaviors conducted in response to personally relevant emotionally evocative cues (including social rejection and physical pain)(Harari-Dahan & Bernstein). Accordingly, MRMD women with ESA may experience premenstrual physical and emotional symptoms as more emotionally evocative, leading to social withdrawal. Our observed findings that OT levels were higher in MRMD and ESA, yet inversely correlated with premenstrual symptoms primarily in symptom domains which have been consistently associated with impairment in relationships and social function (i.e., anger/irritability, mood swings and rejection sensitivity) suggest that in MRMD women with ESA, long-term dysregulation in OT systems, may be an adaptive mechanism in response to early childhood trauma, which is further maintained by behavioral responses to physically and emotionally salient MRMD symptoms.

While the precise mechanisms underlying the associations between early life stress, affective disorders, and clinical pain syndromes are still under investigation; our study suggests that OT may provide another stress adaptive mechanism, which, in MRMD women with ESA histories, may be functioning to positively modulate affective and somatic symptoms of the disorder. This study adds to the accumulating body of evidence which suggests that a history of abuse may identify a distinct subgroup of women with MRMD's (A. Bunevicius, Leserman, & Girdler, 2012; Girdler et al., 2003).

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Highlights

- Early life sexual abuse (ESA) moderates basal oxytocin (OT) levels in MRMD's.
- Basal OT levels are associated with premenstrual symptoms in MRMD women with ESA.
- OT may help to modulate premenstrual symptom severity in women with a MRMD and ESA.

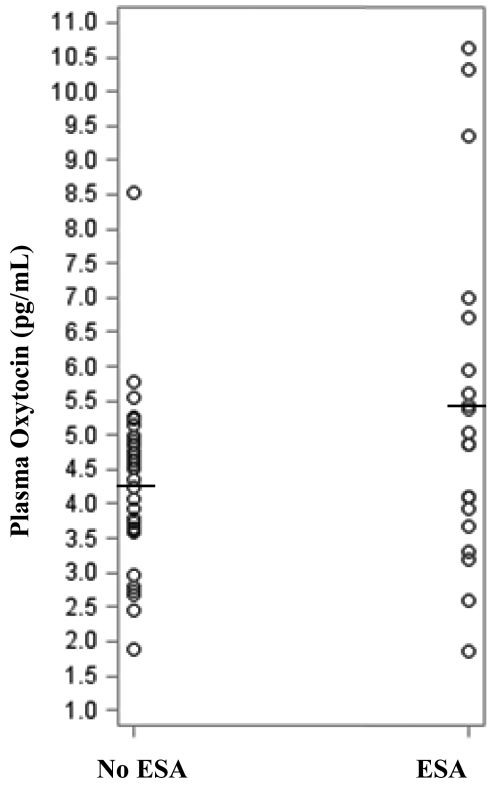

Fig 1.

Scatterplot of basal levels of plasma oxytocin, stratified by abuse groups. Horizontal bars represent mean values. ESA: Early Sexual Abuse, defined as sexual abuse occurring prior to the age of 17.

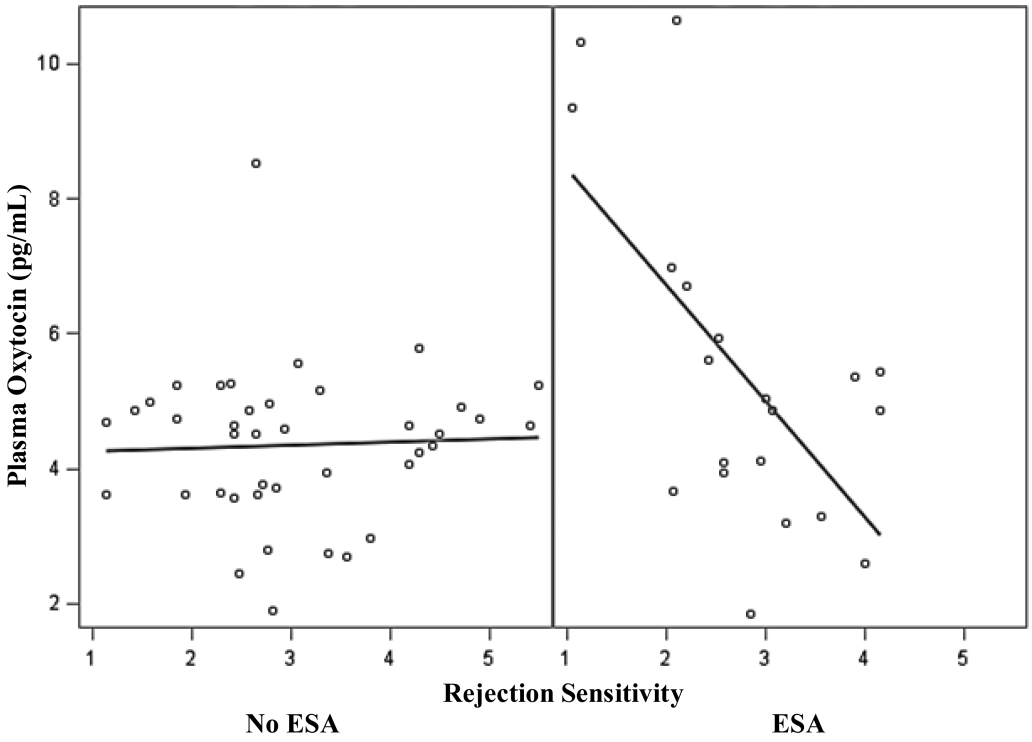

Fig 2.

Relationship between oxytocin levels and rejection sensitivity in MRMD women without a history of early life sexual abuse (ESA) and with a history of ESA.

Table 1

Characteristics of MRMD Women, Stratified by Abuse Categories.

Characteristics	ESA	No ESA	*P* value
Participants, *n* (%)	20 (33.3)	40 (66.7)	-
Age, years (mean ± SD)	32.9 ± 6.8	34.7 ± 8.0	0.385
Race			0.458
African American, *n* (%)	5 (25.0)	7 (17.5)	
Non-Hispanic White, *n* (%)	12 (60.0)	30 (75.0)	
Other, *n* (%)	3 (15.0)	3 (7.5)	
Education			0.493
High school degree or less, *n* (%)	3 (15.0)	3 (7.5)	
Associates degree/some college, *n (%)*	4 (20.0)	9 (22.5)	
College degree, *n* (%)	8 (40.0)	14 (35.0)	
Graduate degree or higher, *n* (%)	3 (15.0)	13 (32.5)	
No answer, *n* (%)	2 (10.0)	1 (2.5)	
Marital status			0.279
Married/living with partner, *n* (%)	7 (35.0)	21 (52.5)	
Not married, *n* (%)	9 (45.0)	14 (35.0)	
No answer, *n* (%)	4 (20.0)	5 (12.5)	
Depression history, *n* (%)	9 (45.0)	14 (35.0)	0.453
Anxiety history, *n (%)*	3 (15.0)	7 (17.5)	1.000
PTSD history, *n* (%)	1 (5.0)	5 (12.5)	0.653
Early life physical abuse			0.464
Yes, *n* (%)	4 (20.0)	5 (12.5)	
No, *n* (%)	16 (80.0)	35 (87.5)	
DRSP summary score (all 24 items; mean ± SD)	2.9 ± 0.9	2.8 ± 0.8	0.680
DRSP summary score for core symptoms (4 domains; mean ± SD)	2.7 ± 0.7	2.9 ± 0.9	0.300

MRMD: Menstrually-Related Mood Disorder; ESA: Early Sexual Abuse, defined as sexual abuse occurring prior to the age of 17; Early life physical abuse: physical abuse occurring prior to the age of 17; DRSP: Daily Rating of Severity of Problems (mean score from 7 days just prior to menses, averaged over two cycles).

Table 2

Pearson's Correlation Coefficients (r) of OT and Premenstrual Symptoms in MRMD Women, Stratified by Abuse Categories.

	ESA (n=20)	No ESA (n=40)
	OT	OT
DRSP summary score (all 24 items)	−0.56*†	−0.05#
DRSP summary score for core symptoms (4 domains)	−0.45*	0.07
DRSP depression domain summary score average	−0.30	0.12
Felt depressed, sad, down, or blue	−0.40	0.17
Felt hopeless	−0.21	0.05
Felt worthless or guilty	−0.29	0.12
DRSP anxiety domain (single item) score	−0.27	0.06
DRSP anger/irritability domain summary score average	−0.50*	0.05
Felt angry/irritable	−0.55*	0.06
Had interpersonal conflicts	−0.38	0.04
DRSP labile mood domain summary score average	−0.58*	0.01
Had mood swings	−0.48*	−0.03
Had increased rejection sensitivity	−0.64*‡	0.05
DRSP somatic symptoms summary score average	−0.55*†	−0.12#
Had breast swelling, felt bloated, or had weight gain	−0.45*†	−0.28
Had headache	−0.52*†	−0.09
Had joint or muscle pain	−0.54*	0.16
DRSP impairment summary score average	−0.31	−0.14
At least one symptom decreased productivity/inefficiency	−0.27	−0.16
At least one symptom interfered with hobbies or social activities	−0.06	−0.12
At least one symptom interfered with relationships	−0.50*	−0.12

MRMD: Menstrually-Related Mood Disorder; DRSP: Daily Rating of Severity of Problems (mean score from 7 days just prior to menses, averaged over two cycles); ESA: Early Sexual Abuse, defined as sexual abuse occurring prior to the age of 17

* $p \leq .05$

‡ p≤ bonferroni adjusted p value criterion

† n=19

n=38.