

Prior Depression, PMDD, and Pain: Biological Mechanisms

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ABSTRACT

Rebecca R. Klatzkin: Prior Depression, PMDD, and Pain: Biological Mechanisms
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The purpose of this study was to examine the extent to which premenstrual dysphoric disorder (PMDD) and major depressive disorder (MDD), two depressive disorders unique or more common to women, exhibit distinct alterations in stress-responsive measures and experimental pain sensitivity. A total of 38 women completed all aspects of testing. Of these women, 17 met strict Diagnostic and Statistical Manual of Mental Disorders criteria for PMDD and were compared with 21 non-PMDD women for PMDD-related differences. For analyses regarding the influence of MDD on dependent measures, a history of MDD was used to model clinical MDD. In our sample, 13 women had a history of MDD and 25 women were classified as never depressed. All women were tested for pain sensitivity to cold pressor and tourniquet ischemic tasks, sympathetic nervous system (SNS) (blood pressure, heart rate, norepinephrine) and hypothalamic pituitary adrenal (HPA)-axis (cortisol and β -endorphin) functioning at baseline, and SNS responses to mental stress tasks.

PMDD women displayed decreased threshold and tolerance to the cold pressor task (i.e. greater pain sensitivity), and blunted SNS reactivity to speech stress when compared to non-PMDD women. In addition, while Non-PMDD women showed a more consistent relationship between higher BP levels and decreased pain sensitivity, PMDD women showed a more robust relationship between greater β -endorphin levels and decreased pain sensitivity. Women with prior MDD showed persistent biological disturbances beyond the remission of

the depressive episode, reflected in increased cold pressor tolerance (i.e. decreased pain sensitivity), increased premenstrual mood symptoms, greater diastolic blood pressure (BP) responsivity to stress, and an enhanced relationship between BP and pain than never depressed women. Finally, no diagnosis-related differences were found for any baseline HPA-axis factor.

These results indicate that dysregulation in pain mechanisms and SNS stress reactivity, as well as in the relationship between pain and stress-related factors in PMDD and prior MDD, may be underlying physiological mechanisms contributing to the etiology of both disorders.

DEDICATION

This dissertation is dedicated with deepest love and gratitude to my family. Thank you for always believing in me.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic Hormone
ALLO	Allopregnanalone
ANOVA	Analysis of Variance
APA	American Psychiatric Association
BDI	Beck Depression Inventory
BN	Bulimia Nervosa
BP	Blood Pressure
CAD	Coronary Artery Disease
CRH	Corticotropin Releasing Hormone
CSF	Cerebrospinal Fluid
DEP	Depression
DBP	Diastolic Blood Pressure
DEX	Dexamethasone
DRSP	Daily Record of Severity of Problems
DST	Dexamethasone Suppression Test
DSM-III-R	Diagnostic and Statistical Manual III Revised Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
EPI	Epinephrine
fMRI	Functional Magnetic Resonance Imaging
FSH	Follicle Stimulating Hormone

GAS	General Adaptation Syndrome
GnRH	Gonadotropin Releasing Hormone
HPA	Hypothalamic-Pituitary-Adrenal
HR	Heart Rate
HRV	Heart Rate Variability
LC	Locus Coeruleus
LH	Luteinizing Hormone
LLPD	Late Luteal Phase Dysphoric Disorder
MAP	Mean Arterial Pressure
MDD	Major Depressive Disorder
NE	Norepinephrine
PASAT	Paced Auditory Serial Addition Task
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
RBD	Recurrent Brief Depression
SBP	Systolic Blood Pressure
SES	Socioeconomic Status
SIA	Stress Induced Analgesia
SNS	Sympathetic Nervous System
STAI-Y1	Spielberger State Anxiety Questionnaire
STAI-Y2	Spielberger Trait Anxiety Questionnaire
TSST	Trier Social Stress Test

CHAPTER 1

INTRODUCTION

Mood Disorders in Women

Mood and anxiety disorders are highly prevalent in women throughout their lifetime. Female gender is substantially related to increased risk for affective disorders [1], since lifetime prevalence rates for affective disorders in the United States are 24% for women compared to 15% for men [2]. Specifically, mood disorders such as major depression, dysthymia, seasonal affective disorder, and generalized anxiety disorder are more prevalent in women than men [1, 3, 4], making the diagnosis and treatment of these disorders a strong focus in women's health research [5].

The importance of gender in mood disorders is further emphasized by the fact that although the prevalence of affective disorders does not discriminate between prepubescent boys and girls, the risk for mood disorders increases in females upon puberty [6]. Additionally, increased rates of affective disorders in females during the reproductive years, as well as menstrually-related mood disturbances such as premenstrual dysphoric disorder (PMDD) and perimenopausal and postpartum depression provide fuel for the notion that women are distinct in their susceptibility to psychiatric illness [1].

Not only do women suffer from affective disorders at a greater rate than men, they may experience a more severe form of these disorders. Korstein et al. [7] studied both males and females with chronic MDD and found that women experienced more psychomotor

retardation, reported increased psychosocial impairment, and were therefore more severely depressed than men. Furthermore, the World Health Organization named major depressive disorder (MDD) the number one cause of disease burden for women aged 18 to 44 [4]. Thus, the present study seeks to explore the potential biological and psychosocial mechanisms underlying women's mood disorders in order to inform the development of future treatments.

Major Depressive Disorder

In 1990, Major Depressive Disorder (MDD) was ranked as the 4th leading cause of disability worldwide by the World Health Organization, and is projected to rise in the rankings by 2020 [8]. Since the disorder places such a great burden on societies around the world [8], it is important to fully understand MDD by recognizing the diagnostic criteria and the heterogeneous nature of the mood disorder. The major criterion for MDD, as stated by the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) [9], is the presence of at least one major depressive episode. This is characterized by at least a two week period during which an individual experiences no less than 5 key components of major depressive symptomatology. Specifically, one symptom must be either: 1) depressed mood and 2) loss of pleasure in normal activities, while the others may include insomnia or hypersomnia, psychomotor agitation or retardation, significant weight fluctuation, considerable fatigue, indecisiveness, feelings of worthlessness or excessive guilt, and recurrent thoughts of death or suicide [9].

It is important that MDD is distinguished from other depressive disorders such as minor depressive disorder, dysthymia, and adjustment disorder with depressed mood, due to the similarities between the disorders and the need for accurate diagnoses to guide treatment.

Minor depressive disorder is differentiated from MDD by the lifestyle impact and number of symptoms, although both disorders are identical in duration [9]. For minor depression, two, but no more than five of the same symptoms listed for MDD must be present over a two week period. A more chronic depressive disorder is dysthymia, which is characterized by dysphoric mood present during the majority of days in at least a two year period, with no incidence of a major depressive episode during that time. Finally, adjustment disorder with depressed mood occurs in response to a significant psychosocial stressor, causing emotional and behavioral symptoms that develop within three months of the stressor onset. The symptoms of adjustment disorder must either be above and beyond what would normally be expected in response to the stressor, or must significantly interfere with day to day functioning. Symptoms must not persist for more than 6 months after an acute stressor has terminated, but may last longer if the stressor was chronic or had enduring consequences. Specifically, the subtype of adjustment disorder with depressed mood is diagnosed when the symptoms are predominantly depressed mood, feelings of hopelessness, and tearfulness [9]. In order to achieve greater homogeneity regarding histories of DEP, the current study excluded women with prior minor depressive disorder, dysthymia, and adjustment disorder with depressed mood if no history of MDD had ever been present.

Within the category of MDD, two distinct subtypes of the disorder are distinguished from one another, melancholic and atypical DEP [10]. Melancholic DEP is characterized by a general state of hyperarousal, commonly displayed in self-loathing that invades all thoughts and emotions, severe anxiety, insomnia, and loss of appetite, as well as a hyperactive hypothalamic-pituitary-adrenal (HPA) axis. Atypical DEP is distinguished not only by a reversal of most melancholic symptoms, but also by a reversal of HPA-axis functioning.

Patients with atypical DEP are generally hypoaroused, reflected in low anxiety, increased food intake and sleep, feelings of emptiness, disconnectedness from their emotions, and a downregulated HPA-axis and sympathetic nervous system (SNS) [10]. Despite the opposing nature of atypical and melancholic DEP, many patients with MDD present with a variety of symptoms that do not clearly fit into either category. Both subgroups of DEP are characterized by anhedonia and dysphoria, and only 25-30% of patients with MDD have purely melancholic features, while 15-30% present with purely atypical feature [10], making it difficult to distinguish between the two. However, due to the opposing neuroendocrine and sympathetic profiles, all subsequent literary references to the diagnosis of MDD will include only the melancholic subtype of the disorder.

The current study also focuses exclusively on women, since data show a great divide between the genders in terms of the prevalence, etiology, and burden of MDD [11, 12]. MDD is the leading cause of disease-related disability in women, affecting a greater percentage of females (21.3%) versus males (12.7%) [12], and this gender gap can be partially accounted for by endocrine control of the female reproductive system and hormonal fluctuations throughout the menstrual cycle. Hormone changes during a woman's life cycle, such as during the menstrual cycle, during the postpartum period, and during the menopausal transition, are associated with increased vulnerability to mood disturbances [1, 3, 4]. Moreover, depressive disorders such as PMDD, postpartum depression, and menopausal depression are all associated with these hormonal fluctuations.

Further understanding of the biological determinants underlying the greater prevalence of MDD in women comes from studies on genetics [13], a major contributor to the onset of this highly heritable disorder [6-8]. Kendler et al. [13] found that the heritability

of liability to lifetime MDD was 30% greater in women than in men. The study also determined that the genetic risk factors for MDD in males and females are positively correlated, but do not overlap completely, and thus contribute to the gender gap in MDD. Replication of this study in a Swedish sample yielded similar results, showing that the proportion of population risk in MDD ascribed to genetics is greater in women than in men [14]. This study [14], as well as a recent meta-analysis [15], found that genetic risk factors in men and women were positively correlated, but not identical. Thus, the correlational data suggests that men and women share some, but not all, of the genetic determinants for MDD. In contrast, this sizeable meta-analysis [15] as well as a recent review [16] report no consistent sex difference in heritability of MDD, indicating that the gender differences in the prevalence of this disorder may not be explained by genetic factors. Despite the inconsistencies in the literature on the genetics of MDD, the greater prevalence of this disorder in women and the various mechanisms underlying this difference provide cause to examine this disorder separately in women, as we do in the present study.

Irrespective of the biological, psychosocial, and personality factors underlying the gender difference in prevalence rate of MDD, the disorder is an encumbrance that both men and women are likely to carry for the duration of their lives. The chronic nature of the disorder does not discriminate on the basis of gender, since the risk of a recurrent episode is similar for both men and women [17]. Over 75% of individuals who have had an episode of MDD will battle with remissions and recurrences of the disorder over their lifetime, with some estimates showing that after an individual experiences a second major depressive episode, the risk of a third becomes 70% within three years [18]. Furthermore, the degree of stress or disturbance necessary to trigger an episode of major depression decreases as the

number of recurrent episodes increases [19]. One possibility suggested by the statistics is that the high recurrence rate in MDD may be due to persistent disturbance in endogenous stress [20-26] and pain [27, 28] -related factors, indicating underlying neurobiological mechanisms involved with the disorder. The current study focuses on women with a history of MDD who do not currently suffer from the disorder in order to avoid the inclusion of PMDD women with co-morbid MDD, a group that is biologically and clinically distinct from PMDD [29-34]. The goals of the current study include confirming our earlier work and that of others suggesting persistent biological and psychosocial disturbances beyond the remission of the depressive mood disturbance, and determining the special relevance prior MDD may have to PMDD.

Premenstrual Dysphoric Disorder

Premenstrual symptoms in women have been described for centuries, with one of the earliest accounts written by the Greek writer, Semonides, 2600 years ago stating, “One day she is all smiles and gladness. A stranger in the house seeing her will sing her praise.... But the next day she is dangerous to look at or approach: she is in a wild frenzy... savage to all alike, friend or foe.” Although it is not for certain, Semonides may have been describing the debilitating mood swings that coincide with the menstrual cycle in women with severe premenstrual symptoms. In the same vein, Hippocrates believed that many psychological and behavioral problems were due to “retained menstrual blood”, and the ancient Greeks used the word “hysteria” to describe the belief that the uterus could “wander around” inside the body looking for a baby, causing mental illness that would remit upon menstruation [35]. In 1847, Dr. Ernst von Feuchtersleben wrote “Menstruation is always attended, in sensitive

individuals, with mental uneasiness, which manifests itself according to the temperament, as irritability or sadness [36],” and taking the description of premenstrual symptoms further was the 11th century Italian gynecologist, Trotula of Salerno, who not only described the distress felt by these “sensitive” women but also the cyclic nature that characterizes the disorder: “There are young women who suffer in the same manner and are relieved when the menses are called forth [37].”

It was not until the Great Depression in 1931 that New York physician Robert Frank coined the term “premenstrual tension” and gave the first modern biological description of cyclic variations in mood associated with the menstrual cycle [38]. Frank [38] described premenstrual tension as a syndrome comprising edema, weight gain, feelings of restlessness, irritability, and indescribable tension, in which women engaged in “foolish and ill-considered actions” (p. 1054) before menses, and also documented the remission of symptoms shortly after menstruation. Although this description was a breakthrough in the medical literature, the symptoms listed were wide ranging emotional and physical ones, and thus did not clearly state the criteria for the disorder of premenstrual tension.

In 1953, Dr. Katharina Dalton coined the term “premenstrual syndrome” [39] but it was not until 1986 that the British endocrinologist defined specific diagnostic criteria for the disorder that included premenstrual psychological and physical symptoms as well as the remittance of these symptoms with the onset of menstruation [40]. It was at this time that the American Psychiatric Association (APA) added Late Luteal Phase Dysphoric Disorder (LLPD) to the Diagnostic and Statistical Manual III Revised Edition (DSM III-R) under the heading “Proposed Diagnostic Categories Needing Further Study” [41]. After the addition to the DSM III-R was made, Spitzer and colleagues [42] described the rationale behind the

decision to give a precise and universally accepted definition to this syndrome. They reasoned that mental health professionals were not properly informed about LLPD and therefore could not accurately diagnose and treat the disorder in their clients. Furthermore, researchers studying the syndrome had difficulty differentiating women with the strict set of cyclic symptoms that would qualify as LLPD with women who only reported physical or mild emotional premenstrual symptoms or presented with chronic psychiatric disturbance that worsened premenstrually. After the standardized diagnostic criteria for LLPD was published, clinicians were then able to accurately diagnose and treat women with the disorder, and researchers studying premenstrual symptoms were then able to follow the same diagnostic criteria to promote the generalizability of their findings [42].

In 1994, the APA revised the operational definition of LLPD by reordering the symptoms and adding a new symptom (a subjective sense of being overwhelmed or out of control) and renamed it Premenstrual Dysphoric Disorder, the title which is currently used today. PMDD, categorized by the DSM-IV [9] as a depressive disorder not otherwise specified, is described as the cyclic recurrence of a variety of emotional and physical symptoms of sufficient severity to interfere with function during the luteal phase of the menstrual cycle. Such symptoms include irritability, anxiety, fatigue, mood swings, headache, and dysphoric mood, causing significant impairments to marital, parental, social, and work relationships [43].

Strictly defining PMDD in the DSM-IV was also important in distinguishing the disorder from the commonly used generic term Premenstrual Syndrome (PMS) [43]. The distinction between PMS and PMDD lies in the severity of the premenstrual symptoms and in the diagnostic criteria, with the criteria for PMDD being more well-defined and stringent

(e.g. excluding symptom profiles consisting only of physical symptoms) [44]. However, Johnson et al. [29] points out that a common misconception is that PMS is characterized by strictly physical symptoms, whereas PMDD is strictly emotional. She asserts the clinical reality to be that emotional, behavioral, and somatic premenstrual symptoms are experienced by women with PMDD and PMS, but the distinguishing factor is symptom severity, classified as mild, moderate, or severe. Simply stated, PMDD is severe, functionally impairing PMS [29], with every PMDD woman experiencing PMS, but only a small percentage of PMS women meeting diagnostic criteria for PMDD [35].

Similarly, only approximately 35% of all women presenting as PMDD will meet DSM prospective criteria [45, 46], while the percentage of potential PMDD women meeting retrospective criteria is much larger [47] due to the unreliability of the method [45]. Women completing daily ratings in a retrospective fashion have been shown to report more significant symptoms and greater functional impairment than women prospectively reporting their PMDD symptoms [45]. Thus, obtaining prospective daily ratings in order to confirm strict, accurate PMDD diagnoses is an important methodological component in PMDD research, and is the practice employed by the current study.

In order to meet PMDD criteria as outlined in the DSM-IV [9], there must be clear evidence of at least 5 of 11 specified symptoms during most of the last week of the luteal phase, accompanied by complete symptom remission shortly after the onset of menstruation during most menstrual cycles in a given year. One of these 5 symptoms must be either 1) feeling sad, hopeless, or self-deprecating; 2) feeling tense, anxious, or on edge; 3) marked lability of mood interspersed with frequent tearfulness; or 4) persistent irritability, anger, and increased interpersonal conflicts. Finally, these symptoms must markedly interfere with

work, school, social activities, and relationships with others, must be confirmed by prospective daily symptoms records over a minimum of two menstrual cycles, and because symptoms must be absent the week following menses, must be differentiated from the premenstrual exacerbation of a chronic depression, dysthymia or other mood disturbance [9]. Although the DSM-IV [9] does outline strict diagnostic criteria, there is still the need for each research study to operationally define PMDD, since the DSM-IV [9] does not specify the use of any particular instrument for the completion of daily symptom ratings, nor does it provide threshold levels for symptom severity.

In the general population, community-based studies that have prospectively assessed symptoms have shown that PMDD afflicts 4.6 – 6.7% of women in their reproductive years [48], and although the symptoms of PMDD are of shorter duration than those of other depressive disorders, the impact of PMDD symptoms on quality of life during the premenstrual luteal phase is equivalent to that seen with MDD, post-traumatic stress disorder, and panic disorder [31]. PMDD may begin at puberty and continues until menopause, lasting on average 37 years [30], with the disorder being most severe in the twenties to mid-thirties [43]. Thus, the burden of illness of PMDD is great due to the chronic nature of the disorder, as well as the functional impairment of work productivity, social and family relationships, and health related quality of life [48, 49]. For instance, during their reproductive years, women with the disorder have been estimated to suffer approximately 3.8 years of disability [30], and experience an economic burden of \$4333 of indirect costs per year in the form of loss of productivity at work and missed work days [50].

Histories of Depression and Premenstrual Dysphoric Disorder

A strong association between histories of depression (DEP) and PMDD has been documented, indicating a high comorbidity of PMDD and a history of mood disorders, with lifetime estimates of mood disorders in PMDD women ranging from 30-70% [45, 51, 52]. Harrison et al. [53] used the DSM-III-R [41] criteria to diagnose women with LLPD, and found that 70% of the 86 women with the disorder had a prior episode of MDD lasting at least four weeks. Subsequent studies have found much lower prevalence rates, although the association between PMDD and prior DEP remains strong [54]. Pearlstein et al. [51] assessed the prevalence of prior MDD in prospectively diagnosed PMDD women and found 36 of the 78 women (46%) to have experienced MDD in their lifetime. Furthermore, Cohen et al. [45] assessed the prevalence and predictors of PMDD in a large community-based sample of women and, using prospective daily ratings as a diagnostic tool, and found that 19 of the 33 women (57.6%) with PMDD had a prior history of DEP, and that PMDD women were significantly more likely to have had prior DEP than non-PMDD women (58% vs. 28%) [45].

Due to the high prevalence rate of a history of DEP in PMDD, it has been suggested that histories of DEP may play a role in the etiology of the disorder [55]. Kendler et al. [55] performed a longitudinal population-based twin study and found that premenstrual symptomatology and MDD share environmental and genetic risk factors, but the biological processes influencing the risk for premenstrual symptoms are only modestly related those affecting the risk for MDD.

Women with PMS [56] and PMDD [57, 58] are also more likely to develop a future episode of MDD than are non-PMS or non-PMDD women. Graze et al. [59] showed that

PMDD women with the highest depression scores on the Premenstrual Assessment Form were the most likely to develop an episode of MDD in the two to four year follow-up period, while Hartlage et al. [58] found that a small sample of women with PMDD were 14 times more likely to develop MDD in a two year follow up period than women without PMDD. It is important to note that PMDD may also co-occur with other axis I disorders such as MDD, although the symptoms must be clinically distinct from the 11 symptoms associated with PMDD [60].

Distinguishing between PMDD with a coexisting mood disorder and premenstrual exacerbation of a current mood disorder is a difficult but significant task, since treatment outcomes differ based on diagnosis [61]. Such differences in pharmacological treatment outcomes between PMDD and premenstrual exacerbation of MDD serve to support the biological distinction between the two disorders. For instance, SSRIs are efficacious in relieving emotional, behavioral, and physical symptoms much more quickly [32-34] and at a lower dosage [31, 48] in PMDD than other psychiatric disorders, including MDD. Additionally, there is evidence that in women diagnosed with both atypical MDD and PMDD, the symptoms specific to PMDD may remain after successful pharmacological treatment of the major depressive symptoms [62]. Thus, these data suggest that while PMDD and MDD have higher than expected rates of comorbidity, they are clinically and pathologically distinct disorders.

Moreover, a recent study by Pincus et al. [63] confirmed that the temporal pattern of symptoms in PMDD is distinct from that of a similar disorder, recurrent brief depression (RBD). Specifically, the study used pulse detection algorithms, augmented by the statistical technique Approximate Entropy [64], to diagnose women with either PMDD, RBD, or

healthy controls based on defining characteristics of both disorders without reference to the menstrual cycle, by identifying the presence and degree of regularity in random prospective daily mood ratings. Findings revealed that the symptom pattern of PMDD has more regularity, less brief or staccato spikes, and a greater standard deviation than that of RBD and control subjects, distinctions that can assist in more accurate diagnosis, and enhance the prediction and evaluation of treatment outcomes [63].

Although a distinct disorder, a prior history of DEP may have special relevance in PMDD symptomatology and biological responses to mental stress. Examination of daily ratings made by women prospectively diagnosed with PMDD from an existing study performed in our laboratory led to the finding that for PMDD women, prior DEP was associated with greater luteal phase somatic severity ratings compared with never depressed PMDD women. Furthermore, in that study, we reported that only in PMDD women with prior DEP did alterations in the progesterone-derived neurosteroid response to stress predict worse premenstrual symptoms, while neurosteroid reactivity failed to predict symptoms in PMDD women with no prior DEP [65].

Etiology of PMDD

The characterizing component to PMDD is its cyclic nature, since the ebb and flow of symptoms coincide with the menstrual cycle. An idealized menstrual cycle is 28-days in length and is composed of three phases: follicular, ovulatory, and luteal. The follicular phase, starting on day one of menstruation and ending at approximately day 12, is characterized by low progesterone levels and a lack of symptoms. At the end of the follicular phase, gonadotropin releasing hormone (GnRH) released from the hypothalamus causes the

pituitary gland to release greater concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH), signaling the ovulatory phase. Ovulation occurs mid-cycle and lasts up to 48 hours, followed by the luteal phase of the menstrual cycle, in which high levels of both reproductive hormones estradiol and progesterone are present. Thus, the distinguishing feature of the luteal phase is the presence of elevated progesterone. The symptomatic luteal phase begins at approximately day 15 and continues until day 28, with the onset of menses marking the beginning of the next cycle. Although women with PMDD only experience severe symptoms during the luteal phase of the menstrual cycle, this symptomatic phase causes a lasting detriment on their social and parental relationships during the remaining weeks of the menstrual cycle as well [43].

Due to the cyclical nature of the mood disturbance in PMDD, much early attention was paid to the pathophysiological role of the gonadal steroid hormones, particularly progesterone [66]. These studies determined, however, that women with or without premenstrual symptoms do not differ in their absolute levels of gonadal hormones [67], finding little evidence to support the view that either an excess or deficiency in progesterone or estradiol concentrations are etiologically relevant to the disorder [68]. Moreover, the majority of controlled trials have failed to find that progesterone administration is efficacious in PMDD [69, 70].

Consequently, researchers suggested that premenstrual symptoms are most likely caused by aberrant reactions to normal fluctuations in hormone levels throughout the menstrual cycle [66, 71] and that PMDD women may be more sensitive to the mood modulatory effects of gonadal hormones [72]. Studies have shown evidence against a causal role for the fluctuating levels of estradiol and progesterone specifically during the late luteal

phase, however [48]. Specifically, findings have shown that a number of PMDD women are symptomatic with ovulation and during the early luteal phase prior to any significant change in progesterone concentration, that administration of progesterone during the luteal phase is ineffective in treating the disorder [66, 73], and that characteristic symptoms of PMDD are still present in the follicular phase of the next menstrual cycle after elimination of the mid- and late luteal phase via a progesterone receptor antagonist [46]. The latter study supports the notion that changes occurring prior to the mid- to late luteal phase, such as ovulation, influence PMDD symptomatology [46].

Many studies have supported the importance of ovulation in PMDD, finding an absence of symptoms during non-ovulatory cycles, after ovariectomy, and following treatment with ovulation inhibitors [66]. Thus, GnRH agonists are highly effective at alleviating mood symptoms and somatic symptoms in PMDD women [74], since they induce a menopausal-like state of anovulation and amenorrhoea via decreased LH and FSH and consequently estrogen and progesterone concentrations [48, 73]. Long term use of GnRH agonists, however, has been shown to cause negative medical effects such as osteoporosis, increased risk of cardiovascular problems, menopausal symptoms, and hypoestrogenism, the last of which can be reversed with “add-back” estrogen-progesterone supplementation [29, 73]. Unfortunately, some, but not all studies have shown that exogenous hormone replacement causes reinstatement of mood and anxiety symptoms in PMS and PMDD women, but not in controls [71, 75, 76]. In contrast, one study found that the reinstatement of symptoms in PMDD women remitted within four weeks of add-back treatment [71], suggesting that exogenous hormone replacement may only cause a short-term reinstatement of negative mood symptoms. The fact that exogenous hormone treatment is eventually

needed to counteract the negative health effects of GnRH agonists, yet may reverse the positive effect on symptoms, supports the etiological theory that PMDD women display an abnormal response to normal hormone levels [71, 77], and also points to the idea that GnRH agonists may only be a short-term solution to the lifelong problem of PMDD [48].

Despite the strict diagnostic criteria and more than 60 years of research into this disorder, the underlying pathophysiologic mechanisms underlying PMDD are only beginning to be determined. The lack of a consensus on the biological determinants of PMDD and the subsequent failure to find a treatment that is efficacious in all women suffering with disorder speaks to the heterogeneity of PMDD and suggests that there may be certain subgroups of PMDD women, based on genetic predisposition or environmental factors, as well as a history of psychiatric conditions such as MDD, who do not respond to available treatments and for whom underlying biological mechanisms need to be identified. Thus, one goal of the present study is to explore stress-responsive measures in PMDD women as well as in women with and without a history of MDD, since PMDD women have a high likelihood of having experienced a prior depressive episode [45, 51, 53, 54]. Our study intends to yield findings that will be important in clarifying the nature of PMDD as well as identifying subgroups of the disorder that may have a specific neurobiology and thus respond differently to treatments.

Hypothalamic Pituitary Adrenal Axis and Sympathetic Nervous System Function in Response to Stress

There is consistent evidence that women with histories of DEP and PMS experience increased daily stress [78-82]. Based on the findings for a major role of life stress in the pathophysiology of psychiatric illness [83], the assessment of neurobiological responses to

stress in patients versus controls has been used as an approach to elucidate the stress-illness relationship [84]. Furthermore, since both MDD and PMDD are either triggered or exacerbated by stressful life events [83], it is possible that long-term dysregulation in stress responsive systems contributes to both mood disorders as well as to the high comorbidity rates [45, 51-55].

The concept of stress dates back to the beginning of medical history itself, with Hippocrates referring to both the suffering associated with disease (pathos) and to the toil (ponos) that the body had to endure to restore homeostasis [85]. In more recent history, both Walter Cannon [86] and Claude Bernard [87] described the ability of all organisms to maintain a constancy of their internal milieu or homeostasis. Seventy years ago, an individual's response when faced with a significant physical or emotional stressor was referred to by Hans Selye [88] as the general adaptation syndrome (GAS). The GAS is characterized by an integrated response involving multiple systems contributing to enhanced focus on the perceived threat, accelerated cardiac output (CO) and respiration, as well as blood flow to brain, heart and muscles to provide the fuel necessary to react to the potential threat [89]. Selye described the GAS as consisting of three distinct stages: 1) an initial brief alarm reaction, 2) a prolonged period of resistance, and 3) the final stage of exhaustion and death. The first stage is now referred to as the "fight or flight" response, during which the sympathetic nervous system (SNS) acts to combat the stressor through mechanisms such as increased BP, HR, and respiration. If the stressor persists, the second stage of resistance begins, increasing the potential for overuse of the body's defense mechanisms. In this stage, the SNS as well as the HPA-axis work even harder to maintain the heightened state of

arousal and sustained energy. Exhaustion or death finally ensues if the body runs out of its reserve of energy and immunity [88].

The SNS and the HPA-axis constitute the two major stress axes that work in concert to render the body capable of reacting to stressful stimuli and to bring the body back to homeostatic levels once the stress is terminated [90]. When a stressor arises, many counter-regulatory systems are activated, but one of the primary stress response systems is the HPA-axis, beginning with the activation of the hypothalamus. The paraventricular nucleus of the hypothalamus releases corticotrophin releasing hormone (CRH), which travels in the hypophyseal portal circulation to the anterior pituitary gland, signaling the pituitary to release adrenocorticotrophic hormone (ACTH) into the peripheral circulation. ACTH then binds to receptors on the adrenal cortex to release glucocorticoids such as cortisol [91]. Cortisol then binds to postsynaptic glucocorticoid receptors (GRs), inducing a G-protein second messenger cascade and influencing gene protein expression.

As an integral part of the stress response, cortisol acts throughout the body to inhibit the gonadal axis as well as inflammatory and immune responses, maintain muscle function and CO, and most importantly, elevate blood glucose to provide the body with the necessary fuel for the increased metabolic demands of stress [90, 92]. Under resting conditions, approximately two to three pulsatile bursts of CRH are secreted into the blood stream per hour, and these pulses follow a circadian pattern with greater amplitude in the morning. Under stressful conditions, however, the amplitude of CRH secretory bursts increases, which therefore also causes increases in ACTH and cortisol secretions [89].

The initial “fight or flight” reaction of the body to a stressor is only half the battle, since it is also necessary to shut off the body’s stress response when the threat is no longer

present. Cortisol, as well as other stress hormones, acts as part of the negative feedback system of the HPA-axis that serves to regulate hormone levels produced in response to stress. Receptors on brain regions such as the hypothalamus and pituitary sense the excess, and less often deficiency, of stress hormones, and respond by either decreasing or increasing production of those hormones, respectively [90]. The endogenous opioid β -endorphin, released from both the hypothalamus and the pituitary gland, also plays a key role in the negative feedback loop by acting on the hypothalamus to inhibit the release of CRH, while additionally suppressing pain sensations in response to a stressor [92]. The negative feedback system is essential, since it allows the body to return to baseline levels of hormone secretion and helps to maintain homeostasis.

The SNS, the other major player in the stress response, is comprised of preganglionic neurons that originate in the spinal cord and synapse with postganglionic neurons that innervate many muscles, organs, and glands throughout the body. When a stressor arises, the SNS directly and indirectly causes the release of the catecholamines norepinephrine (NE) and epinephrine (EPI). The locus coeruleus, the primary noradrenergic network in the central nervous system located in the mid-pons region of the brain stem, is activated and directly causes the secretion of the neurotransmitter NE from nerve endings innervating the heart, vasculature, and muscles among others [10]. The nerve endings of the SNS also innervate the adrenal medulla, thereby indirectly causing the release of NE and EPI from this region into the blood stream. NE acts as a neurotransmitter in the SNS, and as a hormone when released from the adrenal medulla as part of the HPA-axis. However, since EPI is the primary catecholamine released from the adrenal medulla in response to stress, plasma concentrations of NE mostly reflect SNS rather than HPA-axis functioning [93]. NE acts

primarily at α_1 -adrenergic receptors to increase smooth muscle contraction and vasoconstriction, and β_1 -adrenergic receptors in the heart to increase contractility, together causing increased HR, CO, and BP [94]. Thus, the SNS is the primary mediator of cardiovascular responses to stress.

Although both systems are distinctly important entities, the SNS and HPA-axis work together in responding to a challenge. Neural connections exist between the HPA-axis and the locus coeruleus, enabling both CRH and NE to stimulate the release of the other. For example, the HPA-axis production of CRH not only stimulates the release of ACTH from the pituitary, but also activates the locus coeruleus to release NE in response to a stressor. The SNS is also capable of activating the HPA-axis at the level of the hypothalamus, causing CRH release and consequently ACTH secretion, while it is also capable of suppressing the HPA-axis by inhibiting glucocorticoid activity through negative feedback [89, 94]. Integration of the stress systems allows behavioral and peripheral changes that improve the ability of the organism to maintain homeostasis and increases the likelihood of survival [89].

Hypothalamic Pituitary Adrenal and Sympathetic Nervous System Function in Depression

Dysregulation of the HPA-axis is well established in DEP, reflected in elevated baseline cortisol [95-102], CRH [97, 100], ACTH [96, 103], β -endorphin [101, 104], as well as diurnal cortisol [105, 106], NE [106] and ACTH [107, 108] compared to healthy controls. In response to stress, DEP is associated with decreased ACTH responses to CRH challenge [98, 99, 109, 110], and decreased ACTH [96] and cortisol [20, 96, 111] responses to mental stress, each reflecting CRH hypersecretion and thus an overactive HPA-axis at rest.

Furthermore, the majority of patients with DEP show cortisol non-suppression in response to dexamethasone (DEX) [102] and to a combined DEX/CRH test [103, 112-115], reflecting HPA-axis negative feedback dysfunction. The SNS is also hyperactive in DEP, with patients showing elevated baseline NE [116-118], systolic BP (SBP) [119], and HR [106, 118, 120], stress-induced HR [117, 120, 121] and NE [117], as well as diurnal NE [105, 106], BP [105, 122], and HR [105, 122, 123], indicative of heightened sympathetic activation.

HPA-axis Dysfunction in Depression

Basic biological mechanisms

Despite the fact that the upregulation of the HPA-axis in DEP is one of the most common findings in the field of biological psychiatry [124-126], some variation in the literature regarding neuroendocrine as well as SNS functioning in DEP still exists in part due to the heterogeneity of the disorder. Specifically, variations in biological mechanisms (e.g. hypercortisolism and DEX non-suppression) and timing (acute vs. chronic), as well as differences between the two main subtypes (i.e. melancholic vs. atypical) of the disorder [10, 97, 127-130] contribute to the difficulty in characterizing HPA-axis and SNS dysregulation. A recent review reported that at any given time, only 40-60% of medication-free patients with MDD display hypercortisolism, or an upregulation in cortisol secretion, which was once thought to be a fundamental attribute of the disorder [130]. Similarly, another biological marker once thought to signify a depressive disorder was the non-suppression of cortisol in response to DEX [131].

The DEX suppression test (DST), in which a synthetic glucocorticoid is administered to provide negative feedback to the pituitary and consequently suppresses the release of

ACTH and cortisol in normal controls, was classically used as the major assessment of HPA-axis functioning in DEP. However, since DEX non-suppression of cortisol is now known to be present in only approximately 20-50% of depressed patients [113, 132], this once universal test is no longer a diagnostic tool for DEP nor widely used in the assessment of HPA-axis functioning [131]. DEX non-suppression, indicative of dysfunction in negative feedback control of the pituitary gland, does however have predictive power in that the response is associated with a more severe course of DEP and enhanced risk for relapse [133-135] (see below).

In 1981, CRH was discovered [136], and the production of a synthetic version of this hormone allowed further exploration into HPA-axis functioning in DEP, since administration of CRH causes the release of ACTH and cortisol [131]. Using this CRH challenge paradigm, many studies have found diminished ACTH but normal to elevated cortisol responses in DEP compared to healthy controls [10, 130, 137, 138]. A plausible explanation for this finding is the downregulation of pituitary CRH receptors in response to CRH overproduction, coupled with adrenal hypertrophy due to chronic stimulation. This in turn leads to enhanced adrenal responsiveness to the diminished ACTH, explaining the increased cortisol response to CRH [10, 130, 137, 138]. Support for this explanation comes from a recent study by Newport and colleagues who found reduced ACTH secretion in response to CRH in women with MDD, and estimated that almost 60% of the variance in the blunted CRH/ACTH response in women with MDD was accounted for by CRH hypersecretion [109]. Enhanced cerebrospinal fluid (CSF) CRH levels in DEP is a common finding in the literature, and is considered a state marker of the disorder, as is adrenal hypertrophy and adrenal hyperresponsiveness to ACTH, since normalization occurs with successful treatment [97, 133, 137, 139-141].

Changes in pituitary and adrenal responsiveness to heightened CRH over time and in accordance with DEX suppression status may provide an explanation for the multiple theories regarding the underlying mechanisms of HPA-axis upregulation in DEP. For example, Parker et al [130] explains that acute DEP is characterized by an upregulated HPA-axis at baseline coupled with normal pituitary and adrenal responsiveness to CRH and ACTH. However, over time, chronic DEP is associated with elevated glucocorticoid negative feedback as well as blunted ACTH and normal cortisol responses to CRH due to adrenal hypertrophy [130]. Additionally, blunted ACTH responses to CRH infusion have been shown to occur in DEX non-suppressors, but not in those depressed subjects with normal DEX suppression [142]. Thus, variations in the length of the depressive state as well as the presence of DEX suppression may explain some of the discrepancies in the literature [130], and further studies controlling for these factors while assessing HPA-axis dysfunction in DEP are indicated.

Regardless of the inconclusive nature regarding the long-term, downstream consequences of enhanced CRH production, there is consistent evidence for heightened CRH concentrations in DEP [122, 166, 168, 170-172], for which animal studies have discovered important behavioral implications relating to the disorder. Keen-Rhinehart et al. [143] discovered that female rats who show continuous production of CRH display increased depression-like behavior in response to the forced swim test compared to control females, and Holsboer and colleagues [144] found that CRH causes depression-like symptoms such as impaired sleep and motor behavior, decreased food consumption and sexual activity, and increased anxiety in animals. The results of animal studies have further clinical implications, since CRH₁ receptor antagonists have been shown to cause anxiolytic and anti-depressive

behaviors in pre-clinical animal models, and are currently being tested as potential treatments for melancholic DEP [132, 138, 145]. Thus, enhanced CRH production in DEP, reflecting heightened HPA-axis activity, has meaningful clinical implications.

Impairment of HPA-axis negative feedback in depression

Chronic CRH hypersecretion, and overall hyperactivity of the HPA-axis in MDD are thought to be strongly related to impairment or downregulation of GRs affecting negative feedback to the hypothalamus [131, 132, 137, 139]. Negative feedback is crucial for the proper regulation of the HPA-axis, since endogenous glucocorticoids must be able to bind to GRs at the level of the hypothalamus and the pituitary gland in order to slow the release of CRH and ACTH, otherwise causing a major disruption of the natural homeostatic mechanisms of the stress axis [131, 146, 147].

A study by Wong et al. [106] supports the hypothesis that downregulated GR functioning, leading to impaired negative feedback, may cause of HPA-axis upregulation in DEP. The study reported an absence of a negative correlation between CSF levels of CRH and plasma cortisol in depressed subjects, a correlation seen in controls, indicating an abnormal HPA-axis negative feedback system in DEP. More recently, support for this hypothesis comes from studies using the combined DEX/CRH challenge, in which the once common CRH challenge paradigm is enhanced to include pretreatment with oral DEX one day in advance of CRH administration [148, 149]. The addition of DEX pretreatment allows the test to be more sensitive (greater than 80%) in detecting HPA-axis dysfunction, particularly in negative feedback control to the pituitary gland [112]. Studies using the combined DEX/CRH test support HPA-axis overdrive in MDD, since in controls,

pretreatment with DEX results in the expected suppression of ACTH and cortisol responses to CRH, but depressed patients respond to DEX pretreatment with an increased hormonal response to CRH [103, 112-115, 125, 138, 150].

Studies using this DEX/CRH paradigm have given clinical relevance to the disruption of the HPA-axis negative feedback system in DEP. Kunzel et al. [125] found a positive correlation between cortisol reactivity to the DEX/CRH test, reflecting non-suppression, and number of previous episodes of a depressive disorder, as well as with overall score on the Hamilton Depression Scale. The combined DEX/CRH test has also been found to predict the clinical response to treatment. Ising et al. [128] found that DEX suppression on admission and persistent non-suppression of cortisol to DEX/CRH at follow-up predicted unfavorable responses to antidepressant treatment. Thus, the literature points to dysfunction in negative feedback mechanisms in DEP that are associated with HPA-axis upregulation and contribute to the depressive symptoms associated with the disorder.

HPA-axis responses to psychological stress in depression

In contrast to DEX/CRH challenges and GR manipulations, mental stressors have yielded less conclusive observations of HPA-axis hypo-responsivity in DEP, reflecting heightened basal output, which may be due to variability in the type of psychological stressor used [151]. However, a recent meta-analysis by Burke and colleagues [127], assessed eight methodologically sound studies for cortisol responses to psychological stress in MDD and found that in patients with MDD compared to controls, higher baseline cortisol levels were associated with blunted cortisol stress responses [127]. The relationship between increased baseline and decreased stress-induced cortisol is consistent with physiological research

showing that heightened baseline cortisol has an inhibitory effect on stress levels [95]. Thus, the meta-analysis supports the findings of the CRH and DEX/CRH challenge literature for HPA-axis upregulation in DEP, since blunted cortisol in response to psychological stress reflects HPA-hyperactivity at baseline.

One study assessed in the meta-analysis [127] was a one by Gotthardt and colleagues [96], who found increased levels of ACTH, cortisol, BP, and HR prior to a signal-detection task stressor in MDD patients compared to controls. In response to the stressor, depressed subjects showed no significant increase in ACTH and cortisol, while control subjects showed a normal stress-induced increase [96]. The meta-analysis [127] not only included studies using laboratory stressors, but daily life stressors as well. For example, Peeters et al. [111] assessed cortisol responses in subjects with MDD and found that although cortisol was significantly elevated in response to negative life events in controls, those with MDD experienced no cortisol response. Furthermore, manipulation of participants' feelings of control via induction of success and failure in a number addition test was used as the stressor in a study by Croes and colleagues [152]. Although there were no differences at baseline, the study found that while controls showed the expected decrease in cortisol to controllable success and an increase in cortisol in response to the uncontrollable failure stressor, individuals with MDD showed an average decrease in saliva cortisol in response to both conditions, reflecting HPA-axis dysregulation [152].

Additionally, Young et al. [95] found partial support for HPA-axis hyperactivity in MDD in a study assessing cortisol and β -endorphin levels in subjects with MDD both before and after a mental stress battery. The study replicated previous findings for heightened baseline levels of both cortisol and β -endorphin in DEP [101, 104] which would be expected

to inhibit the HPA-axis stress response. The heightened baseline cortisol and β -endorphin in MDD did inhibit the β -endorphin response to mental stress, since MDD patients showed a blunted β -endorphin response compared to controls, but did not inhibit the cortisol stress response in MDD patients, since both MDD patients and controls exhibited normal cortisol responses to mental stress. Thus, baseline and post-stress cortisol levels were inversely correlated in controls, but not in patients with MDD. These results are clinically relevant, since repeated heightened cortisol responses to continuous life stressors may be involved with the etiology of DEP and the mood changes that exacerbate the disorder [95].

Patients with Cushing's disease, a condition characterized by cortisol overproduction, also give evidence for the negative mood consequences of chronic cortisol exposure, since the condition is associated with a high rate of mood disorders that resolve following successful treatment with metyrapone, adrenalectomy, and pituitary irradiation [124]. Moreover, chronically enhanced cortisol levels due to long term stress can have detrimental consequences such as loss of bone mineral density, hippocampal suppression resulting in deficient short-term memory, as well as neuronal death in the hippocampus [153].

In summary, the majority of studies in current DEP point to a hyperactive HPA-axis, reflected in heightened levels of β -endorphin, cortisol, and ACTH at baseline, levels hypothesized to inhibit the stress response and contribute to the blunted HPA-axis responsiveness to stress seen in DEP. HPA-axis overdrive manifested in a reduced stress response in women with MDD may at first seem counterintuitive, but is consistent with the allostatic load model of chronic stress [153-155]. In humans, the price of repeated biological adaptations to stress has been termed allostatic load and refers to the long-term effect of physiologic responses to stress. Allostatic load may be expressed as repeated elevations of

neurohormonal stress mediators (e.g. cortisol, NE) over long periods, as a failure to adapt to the same stressor, as a failure to shut off the normal stress response, or as an inadequate hormonal response to stress that may allow other systems that are normally counter-regulated to become overactive (e.g. inadequate secretion of glucocorticoids resulting in increased levels of inflammatory factors that are normally regulated by the glucocorticoids). It has been suggested that such hypoactivation of stress responses may result from a wearing out or exhaustion of the stress-responsive system due to long-term allostatic load [153-155].

SNS Dysregulation in Depression

Upregulation of the SNS in addition to the HPA-axis has been found in current DEP. A strength of the present study is our assessment of both SNS and HPA-axis factors in MDD, since there is a comparative lack of SNS versus the HPA-axis assessments in DEP. Existing studies that have in fact measured SNS factors report that patients with DEP show heightened baseline [116-118], diurnal [105, 106], and stress-induced NE [117], elevated baseline [119] and diurnal BP [105, 122], along with heightened baseline [106, 118, 120], diurnal [105, 122, 123], and stress-induced [117, 120, 121] HR.

Even elevated depressive symptoms in the absence of clinical DEP are associated with increased 24 hour urinary NE and HR in daily life [156], as well as increased BP, HR, CO, and NE in response to a speech stressor [157], and heightened systolic BP in response to an exercise challenge [104]. A meta-analysis of 11 studies on the relationship between cardiovascular reactivity and depressive symptoms found reasonable support for a positive relationship between SBP, DBP, HR reactivity and severity of depressive symptoms, with moderate to small effect sizes reported in the literature [158]. A recent study [159] assessed

caregivers of spouses with Alzheimer's disease for plasma NE concentrations at baseline and in response to a speech stressor, and found that depressive symptoms was a positive predictor of post-stress NE levels.

Despite the literature showing increased SNS measures in current DEP, opposing results have been reported. Two recent studies [160, 161] found a negative correlation between depressive symptoms and SNS factors, specifically systolic BP and HR during psychological stress in medically healthy controls [160], and both systolic and diastolic BP at psychological stress, and change in HR and diastolic BP from baseline to stress in coronary artery disease (CAD) patients [161]. However, in the latter study, in addition to having CAD, many participants had multiple co-morbid health conditions and were taking antidepressant medication [161], while the former study reported only small effect sizes [160]. Despite these contradictory findings, the majority of the available evidence suggests that current DEP, or elevated depressive symptoms in the absence of clinical DEP, are associated with heightened sympathetic as well as HPA-axis functioning, though it must be acknowledged that this pattern may reflect melancholic DEP only [129, 162].

HPA-axis and SNS Dysregulation in Individuals with a History of Depression

HPA-axis and SNS functioning in prior depression compared to current and no prior depression

One aim of the current study is to examine whether altered sympathetic and HPA-axis activation persists in women who are currently free of depressive illness but who have a history of MDD. Possible SNS and HPA-axis dysregulation in healthy subjects with a history of DEP may contribute to the risk for development of subsequent mood disorders,

due to the high rate of recurrence of the depressive disorders and the negative correlation between episodes of DEP and amount of stress needed to trigger an episode of major depression [18]. Although many intervention studies have been performed assessing SNS and HPA-axis functioning both before and after successful antidepressant treatment (see below) [128], only a handful of studies have made these assessments in euthymic individuals with a history of MDD without using a pre- versus post-treatment design.

One such study was performed by Young et al. [21] using a cohort of monozygotic twins, finding higher diurnal salivary cortisol in currently euthymic participants with a history of MDD, compared to individuals without a history of MDD. Additionally, Kathol and colleagues [22] found that individuals recently in remission from MDD had greater diurnal mean urinary cortisol levels than those who had no history of MDD. Similarly, Broadley et al. [24] found greater resting diastolic BP and HR in euthymic participants with prior recurrent MDD compared to controls with no history of psychiatric illness. Recently, Davydov et al. [23] conducted a study in which resting SNS factors in patients in partial remission from MDD (as defined by scores between 7 and 18 on the Hamilton Depression Scale) and taking various antidepressant medication were examined and compared to healthy controls. The study found heightened systolic BP and low-frequency HR variability in the patients compared to controls, indicative of increased SNS activity, after partial remission of the depressive illness [23], though the current use of psychotropic medications limits the conclusions that can be drawn.

Stress-responsive SNS and HPA-axis measures have also been assessed in individuals with prior DEP, with results supporting the notion of sustained dysfunction of the HPA-axis and SNS following remission. For example, in a study comparing patients with current and

prior MDD and controls for HPA-axis responses to a mental arithmetic stressor, findings showed a blunted cortisol response in current and former MDD patients compared to controls, reflecting an inhibition of the stress-response due to heightened baseline HPA-axis factors [20]. Additionally, Pintor et al. [163] found no differences between outpatients in recovery from MDD and those who were currently depressed in their cortisol and ACTH responses to CRH challenge, with depression groups showing lower ACTH coupled with greater cortisol responses compared to healthy controls. Since 72% of those patients with current MDD had at least one previous depressive episode, and those in recovery from MDD had, on average, 2.75 previous episodes, it follows that these results are consistent with the literature in chronic DEP for heightened cortisol but reduced ACTH versus acute DEP [130]. It is important to note, however, that the majority of subjects in both groups were taking tricyclic antidepressants, which have been shown to directly regulate the HPA-axis by increasing GR concentrations [25], and thereby enhancing GR-mediated negative feedback capabilities.

In contrast, a recent study compared women with remitted MDD to those with no history of affective disorders for SNS and HPA-axis factors at baseline and in response to mental stressors, finding overall hypoactivity in the remitted subjects [26]. Specifically, Ahrens et al. [26], found decreased mean arterial pressure (MAP), serum cortisol and NE at baseline as well as a blunted serum cortisol and ACTH response to the stressors in remitted subjects compared to controls. However, the results are far from consistent, since no differences between groups were seen in ACTH at baseline, HR and heart rate variability (HRV) at any time point, as well as in the NE and MAP response to stress. Furthermore, the results may be skewed by the presence of other current or past mood disorders such as

anxiety and post-traumatic stress disorders, which were not assessed via formal interview. The present study controls for these factors, and thus holds the opposing hypothesis that women with prior MDD will show upregulation of the HPA-axis and SNS, the former reflected by heightened baseline levels serving to inhibit the HPA-axis stress response, as supported by the vast majority of the literature [124, 126]. Thus, the present investigation extends previous literature by being the first, to our knowledge, to assess SNS measures of BP and HR in response to mental stress in euthymic women with a history of MDD.

Strengthening the notion of persistent HPA-axis hyperactivity in individuals with prior DEP are studies assessing euthymic first degree relatives of depressed patients [114, 164]. In these reports, this high risk group showed cortisol release in response to the DEX/CRH test that was between healthy controls and currently depressed patients [164], which was maintained over a four year follow up period [114] and suggests a stable genetic component contributing to HPA-axis dysregulation, possibly affecting the vulnerability for development of a depressive disorder [114, 131]. The genetic link between HPA-axis hyperactivity and DEP is enlightened by the fact that DEP is highly heritable [6-8] and family and twin studies show that a genetic predisposition is a major contributor to the development of an affective disorder [114]. Thus, it is possible that women who show persistent, non state-dependent HPA-axis upregulation beyond the remission of the depressive disorder may be more likely to have a genetic predisposition for the disorder.

Post-treatment HPA-axis and SNS dysregulation

Studies examining HPA-axis and SNS dysregulation in patients in remission from DEP after successful antidepressant treatment have yielded mixed results. A minority of

studies have found evidence for an elevated HPA-axis that endures beyond antidepressant treatment and remission of the depressive episode. For example, Banki et al. [165] showed persistently heightened CSF-CRH levels both before and after antidepressant treatment despite symptom improvement, while Deuschle et al. [166] found that saliva cortisol concentrations remained high compared to pretreatment levels after treatment of MDD with the SSRI paroxetine, despite a decrease in depressive symptoms. However, this study [166], along with two others [103, 148] also treated MDD patients with another type of antidepressant, tricyclics, and found mixed results. Although cortisol concentrations and responses to the DEX/CRH challenge normalized as DEP symptoms improved, ACTH levels and responses to DEX/CRH remained higher than controls.

Further support for dysregulation beyond the remission of the depressive disorder comes from a study by Veith et al. [116] who found heightened NE concentrations at baseline in MDD patients being treated with tricyclic antidepressants compared to controls. Although the antidepressant reduced NE levels initially in all subjects, this effect was reversed after 28 days of treatment. These results should be interpreted with caution, as should any findings from antidepressant treatment studies assessing SNS functioning by measurement of NE, since upregulated NE activity may be indicative of a reduction of NE synaptic clearance and not SNS activity per se [116, 167]. Overall, these studies show persistently heightened HPA-axis and sympathetic functioning even after successful treatment of the depressive disorder.

In contrast, the majority of studies have reported normalization of HPA-axis and SNS parameters following antidepressant treatments [103, 146, 149, 166, 168-171], vagus nerve stimulation [110], and cognitive behavioral therapy [172]. These studies show a reduction of

high pretreatment levels of HR [172], CSF-CRH [168, 170], β -endorphin [170], arginine vasopressin [168], and saliva cortisol [166], as well as a decreased ACTH [110, 169] and cortisol [103, 148, 169, 171] responses to DEX/CRH challenge. Ising and colleagues [128] argued that HPA-axis normalization, specifically GR functioning, is a key factor in the success of antidepressant drugs, and that the degree of normalization of the HPA system correlates with and predicts clinical efficacy of antidepressants [173]. These results support the theory that GR dysregulation is crucial for HPA axis hyperactivity in DEP, as do further reports that antidepressants increase GR expression and function, as well as GR-mediated HPA axis feedback inhibition, thus downregulating baseline and stress-induced HPA axis functioning [146, 147].

A limitation of many of the abovementioned studies finding normalization of SNS and HPA-axis hyperactivity after successful treatment is the relatively short length of time between baseline and post-treatment testing. The majority of studies scheduled the follow-up testing 6 weeks or less after baseline [103, 112, 166, 168, 169], while others scheduled their post-treatment assessment 3-4 months after the initial visit [110, 172]. Therefore, normalization of HPA-axis as well as SNS factors after treatment may be a short-term phenomenon that initially overrides the “trait” characteristic of heightened HPA-axis and SNS activity, but returns over time and becomes uncoupled from symptom improvement. The current study addresses this issue by assessing baseline and stress-induced SNS activity in women with prior MDD who have been free of the disorder for at least one year, irrespective of the type of treatment or cause of remission, and therefore is an important addition to the existing literature.

Relationship between risk of depression relapse and persistent HPA-axis upregulation

The inconsistencies in the literature regarding HPA-axis dysregulation after antidepressant treatment may be due to individual variation in the risk for relapse and poor outcomes [134, 146]. Aubry and colleagues [174] assessed cortisol suppression in response to the combined DEX/CRH test in controls and in subjects with prior MDD taking various antidepressants, and proceeded to follow those with prior MDD for one year to determine relapse rates. Cortisol concentrations in response to the DEX/CRH challenge were significantly greater in the subjects who relapsed than in controls, although there was no difference in cortisol suppression between controls and those in prolonged remission [174]. This study showed the ability of heightened cortisol responses to the DEX/CRH test to predict MDD relapse. This predictive outcome of non-suppression after successful treatment was verified by Ribeiro et al. [134], who performed a meta-analysis of seven methodologically sound studies assessing patients with DEP for non-suppression of cortisol after DST, and found that overall, the persistent non-suppressors had worse outcomes, such as hospitalization, suicide, and symptom recurrence, than did suppressors.

More recently, Zobel et al. [175, 176] discovered that inpatients in remission from MDD whose plasma cortisol responses to the combined DEX/CRH test remained high or increased after various antidepressant medications, were more likely to have relapsed within six months of discharge than those remitted patients with low cortisol reactivity. Similarly, Appelhof and colleagues [177] showed that regardless of treatment strategy for patients with MDD (antidepressant, thyroid hormone, or placebo), cortisol non-suppressors to DEX/CRH challenge after successful remission were at higher risk for relapse than suppressors. These studies showing patient variation in risk for relapse may explain the discrepancies in the

literature regarding baseline HPA-axis dysregulation as well as sustained HPA-axis overdrive after symptom remission, since studies failing to find upregulated HPA-axis factors at either time point may only be assessing those patients who will never develop a future depressive episode. Systematic studies are needed to specifically address this notion by assessing cortisol non-suppression in response to DEX/CRH challenge in controls and MDD patients at baseline, after successful antidepressant treatment, and at long-term follow-up.

Many explanations for the predictive abilities of HPA-axis non-suppression at post-treatment have been proposed. It may be that the phenomenon is indicative of an active but resolving depressive state that changes with severity of the disorder, or that persistent non-suppression only occurs in a specific population of patients with certain demographics or characteristics of the disorder, or finally that persistent non-suppressors and suppressors differ on the pathophysiological mechanisms underlying the disorder [134]. Future studies are needed to address these theories in order to determine the potential for HPA-axis non-suppression to be a predictive tool for the development of future MDD episodes as well as the effectiveness of treatment.

In conclusion, despite some discrepancies in the literature and various plausible explanations regarding HPA-axis dysfunction in DEP, the clinical relevance of this phenomenon cannot be discounted. Due to the predictive abilities of the combined DEX/CRH test to determine antidepressant treatment outcome, the test may become a surrogate marker providing information at the pre-treatment stage regarding the potential for antidepressants to be clinically efficacious by normalizing GR signaling. Studies assessing this exciting possibility are underway, and will no doubt have a profound effect on improving treatment for this debilitating disorder [128, 145].

Hypothalamic Pituitary Adrenal and Sympathetic Nervous System Function in Premenstrual Dysphoric Disorder

Despite the longstanding interest in menstrually related mood disorders and their prevalence, experimental studies examining sympathetic and HPA-axis function in PMS and PMDD women have been scant. A review of the literature on physiological stress responses in PMDD and PMS [178] reported that existing studies have yielded inconsistent results but, when considered together, the majority of available evidence points toward downregulated HPA and SNS axes. For instance, PMS women have been shown to display reduced peripheral β -endorphin levels during the luteal, symptomatic phase of the menstrual cycle compared to their own follicular phase [179], and also compared to non-PMS women during the luteal [179-181] and follicular [182] phases. Low β -endorphin levels have been found to significantly increase with the alleviation of premenstrual symptoms with hormone replacement therapy in PMS women [183], results that signify a putative role for the neurotransmitter in the etiology of the disorder.

In addition to any pathophysiological role of estradiol or progesterone in PMDD, dysregulation in GABAergic progesterone-derived neurosteroids, or a differential sensitivity to these metabolites, has also been implicated in the disorder [65, 184, 185]. Of particular relevance to PMDD may be the neuroactive steroid allopregnanolone (ALLO), a metabolite of progesterone produced by the ovaries, adrenals, and de novo in brain [186], since plasma levels of ALLO follow closely those of progesterone during the symptomatic luteal phase [187]. ALLO is a potent modulator of GABA_A receptors, enhancing inhibitory neurotransmission by increasing the time during which Cl⁻ ion channels are open [188, 189], and it is through this mechanism that it exerts profound anxiolytic effects [190-192]. While

the literature on baseline ALLO concentrations in PMDD is quite mixed [187], it has been hypothesized that an increase in ALLO after successful SSRI treatment is an important source of symptom improvement [48], supporting studies showing associations between symptom improvement after SSRI treatment and ALLO increases in MDD [193-195]. Additionally, ALLO attenuates stress-induced HPA-axis activity [196, 197] and can be used as a measure of HPA-axis activity since it is released by the adrenal gland. Lombardi et al. [198] found that PMDD women had a significantly blunted adrenal ALLO response to an ACTH stimulation test following DEX suppression compared to controls during the luteal, but not the follicular phase. Since ACTH normally elicits an increase in ALLO production by the adrenals [199], blunted ALLO in this study may reflect adrenal hyporesponsivity to stress in PMDD women during their symptomatic phase of the menstrual cycle [198].

Exercise stress paradigms have also been used to assess HPA-axis downregulation in PMS. Roca et al. [200] physically challenged both PMS and control women with a treadmill exercise and found that PMS women did not show the luteal phase enhancement of HPA-axis factors compared to follicular phase levels, a menstrual cycle effect normally seen in controls [201]. Specifically, Roca et al. [200] found that controls showed a luteal phase increase in arginine vasopressin, ACTH, and cortisol compared with the follicular phase, while PMS women failed to show this difference. Also observed was a trend towards a lower exercise-induced cortisol/ACTH ratio in PMS women across the menstrual cycle, indicating a diminished adrenal responsivity to exercise stress.

Blunted HPA-axis responses to serotonergic agents have also been documented in PMS [34, 202]. Su et al. [34] found reduced ACTH responses to *m*-Chlorophenylpiperazine, a serotonin receptor agonist, in PMS women compared to controls in both the follicular and

luteal phases of the menstrual cycle, as well as blunted cortisol responses to *m*-Chlorophenylpiperazine in PMS versus controls in the luteal phase only. Additionally, Bancroft et al. [202] found reduced cortisol responses to L-tryptophan, a serotonin precursor, in women with PMS versus controls in both menstrual cycle phases. In another challenge paradigm, Facchinetti et al. [181] compared women with severe PMS and asymptomatic controls for plasma cortisol responses to naloxone, an opioid receptor antagonist, and CRH during the symptomatic luteal phase of the menstrual cycle and found conflicting results. The expected increase in cortisol in response to naloxone occurred in the controls, but was significantly blunted in the PMS women, supporting HPA-axis downregulation in PMS. In contrast, the expected release of cortisol in response to the CRH challenge was heightened in PMS women compared to controls, which the authors suggest may be a compensatory mechanism for the reduced HPA-axis negative feedback from endogenous opioids [181].

Further discrepancies in the literature regarding stress responses in PMS come from studies showing no PMS related differences in the biological stress response. For example, Van den Akker and Steptoe [203] found no differences in HR at baseline and in response to mental stress between women with PMS and healthy controls. Methodological factors potentially contributing to these inconsistencies concerning SNS and HPA-axis functioning in PMS include small samples, differences in the timing of cycle phase, and lack of hormonal verification of phase. Another important factor involves the lack of prospective symptom assessment to classify PMS women in many of these studies [204-208], increasing the likelihood of false positive diagnoses [209]. Thus, the PMS cohorts were likely to have been heterogeneous with respect to symptom severity, ranging from mildly symptomatic, to PMDD.

Earlier work from our laboratory using prospective ratings to confirm DSM criteria for PMDD and which excluded women with current Axis I disorders, did find evidence for reduced sympathetic activation in response to stress in PMDD women in both cycle phases [78]. Although no differences were found at baseline, PMDD women showed blunted HR and diastolic BP reactivity, as well as a trend toward reduced CO and systolic BP reactivity to a variety of laboratory psychological stressors relative to non-PMDD women [78]. Additionally, in a separate cohort of women, our laboratory found lower stroke volume, CO, and cortisol both at baseline and in response to mental stress in PMDD women versus controls [79]. More recently, in a 3rd cohort of PMDD women with or without prior abuse, evidence showed that never abused PMDD women have lower stress-induced systolic and diastolic BP and HR than never abused non-PMDD controls [210]. The present study builds on these findings by introducing prior MDD status, a disorder that is prevalent in PMDD [45, 51-54], as a potential moderator of the relationship between SNS and HPA-axis dysregulation and PMDD.

Stress Response Dysregulation In PMDD May Be Due To Higher Prevalence Of Depression History

A factor that was not accounted for in the vast majority of these earlier studies on SNS and HPA-axis functioning in PMDD, and which research from our laboratory suggests would impact biological responses to stress [65], concerns the impact of histories of psychiatric disorders. Our research in women with PMDD indicates that histories of affective illness can result in persistent dysregulation in stress-responsive biological measures, including measures reflecting HPA-axis and SNS dysfunction, even in the absence

of current psychiatric illness [65]. As described above, studies from our laboratory as well as others assessing stress responses in women with PMDD have shown distinct SNS and HPA-axis profiles in PMDD versus non-PMDD women. However, more recent studies from our laboratory have revealed that these differences may have reflected, at least in part, the higher prevalence rates of prior DEP in PMDD [39, 40]. Thus, this earlier work was limited by its failure to recognize the special relevance that prior DEP may have for PMDD women.

Consequently, our laboratory went on to examine whether histories of DEP in PMDD were associated with alterations in the ALLO response to stress in 26 PMDD women (14 with prior DEP) and 39 non-PMDD controls (17 with prior DEP) tested in the luteal phase of the menstrual cycle [65]. In this study, all women with prior DEP, regardless of PMDD status, showed a decrease in ALLO in response to stress compared with a moderate ALLO increase in never depressed women, and also failed to show the expected decrease from venipuncture to baseline rest compared to never depressed women [65]. Results suggested that in women with histories of DEP, even in the absence of current DEP, there is a failure of ALLO mechanisms to respond appropriately to challenge as evidenced by lack of an increase in response to mental stressors found in never depressed women. Furthermore, regression analyses revealed that only in PMDD women with prior DEP did greater ALLO concentrations at extended baseline rest, reflecting failure to recover from venipuncture stress, and more blunted ALLO reactivity to mental stress predict worse premenstrual symptoms of depression, irritability and labile mood. ALLO failed to predict symptoms in PMDD women with no prior DEP, indicating special relevance of prior DEP to PMDD symptomatology [65]. The association of ALLO concentrations with a history of DEP, but not with PMDD status per se, provides additional support for the evidence that PMDD is

biologically and clinically distinct from other forms of DEP, a distinction that has been repeatedly debated in the literature [56, 61].

In our prior research in the same cohort of PMDD and prior DEP women described above [65], using a placebo-controlled design, we measured plasma ALLO concentrations following progesterone administration. We reported that, over a 255 minute period consisting of periods of resting and mental stress tasks, women with prior DEP had consistently lower ALLO levels compared to never depressed women, and that this was especially evident in the non-PMDD women [184]. These results are consistent with the hypotheses that there may be persistent dysregulation in stress-responsive measures in women with prior DEP, even after complete remission (>1 year). Since ALLO readily crosses the blood brain barrier and is produced by the adrenals [186], the finding of a decrease in plasma ALLO in response to stress in women with prior DEP is consistent with prior research finding a reduced HPA-axis response to mental stress in women with current [127] and prior MDD [20].

In the present study, strict criteria to define and confirm cycle phase was used in assessing PMDD women for SNS and HPA-axis functioning at baseline and SNS responsivity to mental stress during the luteal phase, and thus addresses the methodological concerns from the existing literature as well as those regarding the impact of psychiatric histories in PMDD.

Depression: Influence on Clinical and Experimental Pain

Investigations into the physical, or somatic, components of both MDD and PMDD allow for a broader understanding of these disorders by incorporating the less publicly

emphasized, yet clinically significant, symptoms contributing to functional impairment. Somatic symptoms such as headache, fatigue, and back pain are core components of depressive illness, since over 75% of depressed patients report chronic or recurring pain to their primary care physician [211]. Furthermore, a study of 685 patients from a family medicine clinic found that 75%–80% of depressed patients reported somatic symptoms such as headache, stomach, neck, back, and generalized pain [212]. Additionally, a positive correlation between clinical pain intensity and the severity of MDD has been reported, as well as a trend towards a positive correlation between clinical pain intensity and number of depressive episodes in premenopausal women [213].

Despite the fact that laboratory-based methods of assessing pain sensitivity, specifically ischemic and cold pressor threshold and tolerance used in the present study, are positively related to clinical pain in both healthy adults [214, 215] and chronic pain patients [216-218], few studies have explored the relationship between experimental pain sensitivity and clinical DEP. A systematic review and meta-analysis examined the effect of current DEP on experimental pain perception, concluding that pain threshold was higher in depressed individuals than healthy controls [219]. However, only 2 of the 6 studies in the meta-analysis assessed pain tolerance, which may be especially relevant for mood disorders since pain tolerance reflects the affective experience of pain, while pain threshold reflects the sensory experience [220]. More recent studies have assessed both threshold and tolerance to multiple pain stimuli in depressed patients, and although findings have been mixed, they indicate a reduced sensitivity to experimental pain in depressed subjects compared to controls [221-225].

For instance, a recent study found increased threshold and tolerance to thermal and electrical pain stimuli in patients with adjustment disorder, a mild form of DEP associated with a life stressor [223]. A different approach was taken by Lautenbacher and colleagues [221], who were not only interested in determining the differences in pain thresholds between depressed patients and controls, but whether these differences were in fact due to dysregulated perceptual processing speed or reaction time. Results showed that subjects with current DEP had increased heat pain thresholds compared to controls, regardless of whether or not subjects were required to rely on perceptual processing speed. Depressed subjects and controls also did not differ significantly on their skin sensitivity for non-noxious warmth, cold, and vibration stimuli, indicating that the decreased sensitivity in DEP is specific to pain perception [221]. Giesecke et al. [226] also provides evidence against overall perceptual processing as a mechanism underlying pain perception in DEP in their study assessing neural activation to pressure pain sensitivity using functional magnetic resonance imaging (fMRI) in fibromyalgia patients with or without MDD. Self-reported depressive symptoms and diagnosis of MDD were not correlated with pain-evoked neuronal activation in brain areas associated with the sensory-discriminative aspects of pain (e.g. somatosensory cortices), but were associated with neuronal activations in brain regions associated with the motivational-affective dimension of pain (e.g. amygdala).

What has yet to be thoroughly examined is whether there is persistent dysregulation in experimental pain perception and underlying pathophysiological mechanisms in women with prior MDD, since this may have implications for risk for subsequent MDD. Bar et al. [27] assessed thermal pain sensitivity in women who were in full clinical recovery from MDD and found significantly increased pain threshold and tolerance in women with prior

MDD compared to controls. However, most of the women in recovery from MDD were taking antidepressant medication, which could be a confounding factor due to its analgesic effects [72, 73]. Moreover, for the purposes of the present study, examination of existing symptom calendar data collected in a prior study in our laboratory led to the finding that women with prior DEP, irrespective of PMDD status, experienced elevated daily somatic symptoms. Specifically, women with a history of DEP reported more severe headache, fatigue, bloating, cramping, swelling, and breast tenderness than women with no prior DEP [unpublished data]. These pilot data are consistent with the hypotheses of the current study regarding persistent effects of prior MDD on somatic complaints for all women, and support the aims to confirm this finding and also investigate biological mechanisms that may contribute to somatic symptoms.

Another more recent study from our laboratory was among the first to compare women with or without prior mood disorders (diagnosis of prior minor DEP, major DEP, or bipolar mixed episode) for experimental pain threshold and tolerance to heat, ischemic, and cold pressor pain [28], in women who were not taking any medications. The study showed that women with prior mood disorders were less sensitive to ischemic pain than women with no prior mood disorders, although no significant differences were seen for heat or cold pressor pain. These results support persistent disturbance in pain modulatory mechanisms in women with a history of mood disorders, which may have implications for the development of future mood disturbances. The present study seeks to aid in clarifying the underlying mechanisms contributing to alterations in pain sensitivity in women with a history of MDD.

Premenstrual Dysphoric Disorder: Influence on Clinical and Experimental Pain

While the literature on pain sensitivity in current and past MDD is lacking, there are even fewer studies assessing pain sensitivity in PMDD [182, 204, 205, 227], despite the fact that somatic symptoms such as breast tenderness, bloating, and joint or muscle pain are important features of PMDD and contribute to overall dysfunction [228]. Examining the percentage of PMDD women reporting luteal phase somatic complaints based on daily prospective ratings from a previous study in our laboratory determined that a full 100% of the confirmed PMDD women endorsed at least one somatic symptom in the luteal phase (e.g. headache, cramping) severe enough to interfere with function, while 63% of the PMDD women had at least one somatic symptom severe enough to be temporarily disabling [unpublished data].

Despite the evidence for the role of physical symptoms in PMDD, studies assessing pain sensitivity in women with this disorder are scant. Prior studies from our laboratory show that women with PMDD exhibit shorter ischemic pain threshold and tolerance times compared with controls in both the follicular [227] and luteal phases [182, 227], and other studies have shown that PMDD women endorse higher pain intensity ratings in response to pressure pain irrespective of menstrual cycle phase [204, 205]. Additionally, using a non-traditional means of assessing experimental pain threshold, Chae and colleagues [229] recently compared middle school girls with high and low PMS scores on the Menstrual Distress Questionnaire for pressure pain threshold at a targeted acupuncture point known to be associated with gynecological and obstetric dysfunctions, and also at various other acupuncture and non-acupuncture points on the body. The study found significantly lower pressure pain threshold in girls with severe PMS compared to girls with mild to moderate

PMS at the targeted acupuncture point, as well as a trend in the same direction at the majority of other body points, thus supporting the hypothesis that PMS is associated with heightened pain sensitivity [229]. What has yet to be established, however, is whether prior MDD, which is more prevalent in PMDD [45, 51-54], distinguishes subgroups of PMDD women in terms of their sensitivity to pain. Studies comparing PMDD and non-PMDD women, as well as women with and without prior MDD, for sensitivity to experimental pain stimuli may clarify the nature of the clinical pain experience in these disorders.

Stress-Responsive Endogenous Pain Regulatory Mechanisms

The relevance of altered SNS and HPA-axis responses to stress may not only have implications for mood disorders, but for clinical pain syndromes as well. Clinical pain is an associated feature of both MDD [211, 212, 230] and PMDD [228, 231], and cardiovascular and neuroendocrine responses to stress exert profound antinociceptive effects in both animals and humans [232]. The phenomenon is known as stress-induced analgesia (SIA). For example, higher resting and stress-induced NE levels are associated with reduced pain sensitivity to ischemic, cold pressor, and heat pain, at least in Caucasian non-smokers [233, 234]. In rats, adrenal medullary transplants have been shown to increase CSF catecholamine levels, thereby reducing pain sensitivity [235].

The most well-documented relationship in SIA, however, is between high BP and reduced pain sensitivity [233, 235-246], which has been shown in individuals with hypertension, a familial risk for hypertension, as well as in healthy normotensives [247]. For instance, Sheps and colleagues [238] showed support for the BP-pain association by finding a positive association between MAP and thermal pain threshold (pain onset) and tolerance

levels in both normotensive and hypertensive male subjects. Zamir and Shuber [237] also examined pain threshold in normotensive and hypertensive males, and found that normotensive subjects showed a reduced threshold to tooth pulp stimulation compared to hypertensives, indicating a relationship between high BP and reduced pain sensitivity. Similarly, Bruehl et al. [244] administered a pressure pain task to the fingers of normotensive males and found an inverse relationship between resting systolic BP and pain ratings throughout the 60 second pressure stimulus. Further support for the BP/pain relationship can be found in a study by Bragdon et al. [242] that assessed thermal pain sensitivity both at baseline and after a mental stress battery. The study observed that both pre- and post-stress thermal pain tolerance was positively related to both pre- and post-stress systolic BP.

Breuhl and Chung [247] outlined three potential mechanisms that may underlie the relationship between blood pressure and pain. The first is the arterial baroreceptors, which is a negative feedback system that acts like pressure sensors to regulate BP through reflex changes in autonomic activity [248]. When BP rises in response to the experience of pain, baroreceptors are activated, causing descending pain inhibitory activity intended to bring the body back to homeostatic cardiovascular levels. Noradrenergic activity, specifically α_2 -adrenergic mechanisms, may also play a role in the BP/pain relationship, since central noradrenergic pathways are an essential part of the descending pain inhibitory system, and are crucial to maintaining stable cardiovascular functioning [247].

In addition to baroreceptors and adrenergic factors, the HPA-axis is also involved with SIA. Many studies have reported increased concentrations of β -endorphin to be associated with reduced pain sensitivity in humans [182, 233, 245, 249-252]. Specifically, Guasti et al. [245] found a negative correlation between baseline β -endorphin levels and pain

sensitivity to the pulpar test, which involves the administration of intermittent bursts of electrical stimuli to the tooth. McCubbin and Bruehl [240] examined the relationship between BP, pain, and β -endorphin from a different view, using a within-subjects design to administer either saline or naloxone to normotensive males prior to a cold pressor pain task and measured BP. After saline pretreatment, resting systolic BP was negatively associated with cold pressor pain ratings, and although this association became non-significant following naloxone administration, the drug did not completely eliminate the inverse relationship between systolic BP and pain ratings, indicating potential for non-opioid as well as opioid mediators. This study [240], as well as others [245, 250-252], suggests that the relationship between BP and pain sensitivity is at least partially mediated by endogenous opioids such as β -endorphin.

Although many studies report correlations between high BP with high β -endorphin and low pain sensitivity, β -endorphin levels are often not associated with the degree of pain responsiveness [247]. Breuhl and Chung [247] also cite endogenous opioids, such as the HPA-axis factor β -endorphin, as potential mediators of the relationship between BP and pain, although they acknowledged that results are mixed and point to an important but not sufficient role. Finally, while animal studies find strong substantiation for opioid involvement in the BP/pain association, human studies fail to provide consistent support.

Similarly, studies have implicated another HPA-axis factor, cortisol, as a partial yet insufficient mediator of SIA [233, 234, 243, 249]. For example, Al'absi et al. [243] found that salivary cortisol concentrations at baseline predicted lower self-reported pain during and after the cold pressor task, however only in men. CRH, which is released from the hypothalamus in response to a stressor, has also been shown to be a mediating factor of SIA,

since intravenous, intradermal, intracranial, and subcutaneous administration of CRH produces analgesia in animal models, although the effect is primarily due to the release of β -endorphin as well as the anti-inflammatory effects of cortisol [253]. Additionally, previous studies from our laboratory reported that greater cortisol in response to mental stress was associated with greater pain tolerance in nonsmokers [233] and in Caucasians [234]. In summary, these relationships between the SNS and HPA-axis and pain are thought to reflect an integrated response during the defense reaction, which is characterized by increases in SNS activity such as BP, HR and the release of catecholamines, and increases in HPA-axis activity such as the release of ACTH, endogenous opioids (β -endorphin), and cortisol [254].

While the perception of pain is adaptive, the suppression of pain might prove adaptive in the short term as part of the fight or flight response. Recent studies from our laboratory found that higher systolic BP, NE, and cortisol were associated with higher pain tolerance to ischemic, cold pressor, and thermal heat pain in healthy men and women [234], and that β -endorphin levels were positively associated with higher pain tolerance to cold pressor pain [249]. To date, only one group of researchers has recently assessed whether alterations in sympathetic and HPA-axis mechanisms are related to increased pain sensitivity in women with current depressive disorders. Frew and Drummond [255] determined the BP/pain relationship to be initially absent in patients with MDD, but when the opioid antagonist naltrexone was administered, the inverse relationship between BP and cold pressor pain sensitivity emerged. Thus, endogenous opioids, such as β -endorphin, seem to mask the BP/pain relationship in MDD, but mediate the relationship in non-depressed controls. The present study seeks to further examine stress-responsive endogenous pain regulatory

mechanisms in euthymic women with prior MDD, as well as be the first to investigate these mechanisms in PMDD women.

Primary Hypotheses:

1. Women with prior MDD will be less sensitive to experimental pain stimuli compared to women with no prior MDD, and PMDD women will be more sensitive to experimental pain stimuli than non-PMDD women. Thus, it is hypothesized that there will be a main effect of both PMDD status and prior MDD for experimental pain sensitivity.
2. All women with prior MDD will experience greater severity of daily somatic symptoms than women with no prior MDD (Main effect of MDD). It is fully expected that all PMDD women will have greater daily somatic symptoms, especially in the luteal phase relative to all non-PMDD women (Main effect of PMDD).
3. All women with prior MDD will show increased HPA-axis factors at rest, and thus a main effect of prior MDD for HPA-axis factors is hypothesized. Also, all women with MDD will show increased sympathetic activity both at baseline and in response to stress relative to never depressed women. Therefore, it is hypothesized that there will be a main effect of prior MDD for SNS factors, irrespective of condition (baseline or stress), since prior MDD will have increased SNS factors compared to never depressed subjects.
4. All women with PMDD will have decreased SNS factors both at baseline and in response to stress. Thus, it is hypothesized that there will be a main effect of PMDD status for SNS factors, irrespective of condition, since PMDD will show decreased SNS factors compared to non-PMDD controls. Additionally, all women with PMDD will have decreased HPA-axis factors at baseline, and thus a main effect of PMDD status for HPA-axis factors is hypothesized.

Secondary Hypotheses:

1. Since it is well established that increased SNS factors are associated with reduced sensitivity to experimental pain, it is hypothesized that group differences in SNS activation will predict group differences in pain sensitivity.
2. Although the literature associating HPA-axis factors and pain sensitivity in humans is limited, it is hypothesized that group differences in HPA-axis activation will predict group differences in pain sensitivity.

CHAPTER 2

RESEARCH METHODS

Participants:

A total of 38 women (19-50 years of age) completed all aspects of testing. Of these women, 17 met strict DSM-IV [9] criteria for PMDD and were compared with 21 non-PMDD women for PMDD-related differences. For analyses regarding the influence of MDD on dependent measures, a history of MDD was used to model clinical MDD. In our sample, 13 women had a history of MDD and 25 women were classified as never depressed. The current study enrolled and prospectively screened 74 potential PMDD women to yield the 17 confirmed PMDD women (23%) (See Appendix A: Enrollment Statistics), reflecting the employment of strict diagnostic criteria, since the literature shows that approximately 35% of potential PMDD women actually meet DSM prospective criteria [45, 46]. As seen in Appendix A (Enrollment Statistics), the current study enrolled and prospectively screened 46 potential non-PMDD women to yield 21 non-PMDD women who met study criteria. Approximately 35% of the PMDD sample had prior MDD, a percentage that falls slightly lower than the expected rates for PMDD women [45, 51]. As for the non-PMDD sample, since only approximately 24% of women have a history of MDD [256], targeted advertisements enabled the recruitment of 33% of this group to have prior MDD (see Appendix A).

Excluded was any subject with a current Axis I psychiatric disorder, however subjects who met this criteria were referred for treatment. Also excluded was any woman who was

pregnant or breastfeeding, had irregular menstrual cycles, was taking prescription medication (including oral contraceptives and psychotropics), had a cardiovascular disorder, a history of or a current chronic or acute pain condition, an endocrine disorder including diabetes or thyroid disorder, or other chronic medical illness. A history of MDD was based on interview (see below) with one year in full remission required. Because of the relatively small sample, in order to achieve greater homogeneity regarding DEP histories, excluded from the MDD groups were women with a history of minor DEP, dysthymia, or adjustment disorder with depressed mood, if they did not also have at least one episode of MDD. The never depressed groups were free of any lifetime depressive illness, including minor DEP or adjustment disorder. Although not a focus of this study, the four groups were closely matched for abuse histories due to the aims of the overarching parent project focused on histories of sexual and physical abuse in women.

Procedures:

Screening and Enrollment: After an initial phone-screening interview, each subject was scheduled for their enrollment session. During this session, informed consent was obtained, a medical history questionnaire, Beck Depression Inventory, and Spielberger Trait Anxiety Inventory were administered and reviewed, a series of stethoscopic blood pressures was taken, and subjects underwent a diagnostic interview using the MINI International Neuropsychiatric Interview for Axis I disorders as well as a validated structured interview to assess previous abuse experiences [257]. Once determined to be eligible, subjects were introduced to the Daily Record of Severity of Problems (DRSP) [258], which they were asked to fill out daily for 2-3 consecutive menstrual cycles. Once the subjects had completed

the DRSP ratings and they were reviewed to determine eligibility, subjects were called to schedule a second screening visit. During the second screening visit, subjects were instructed on how to use the ovulation testing kits, which enabled the approximation of the late luteal phase and the proper scheduling of the laboratory testing protocol.

Confirming PMDD Diagnosis: The Daily Record of Severity of Problems (DRSP) [258] was used to confirm PMDD and non-PMDD status for all subjects. This form allows for quantification of the severity of physical, emotional, and behavioral symptoms. The DRSP incorporates measures of life-style impact together with information on life events that may modify symptomatology. In order to discourage retrospective reporting, calendars were mailed back weekly. To classify subjects with PMDD, each met the DSM-IV criteria for ‘Premenstrual Dysphoric Disorder’: **1)** at least a 30% increase in symptom severity during the seven days preceding menses (premenstrual days) compared with follicular days 4-10; **2)** rating of symptoms as moderate and/or severe (as opposed to mild) on at least three of the seven premenstrual days; **3)** a total of five or more symptoms premenstrually; **4)** at least one severe emotional symptom on three of seven premenstrual days; **5)** symptoms severe enough to impact/disrupt normal activities or interpersonal relationships; **6)** complete remission of symptoms within three days of menses onset followed by a clear symptom free period (\geq six consecutive days) during the early-to-mid follicular phase and **7)** criteria 1-6 met on two menstrual cycles.

Non-PMDD women met the following criteria: **1)** no more than mild emotional symptoms occurring during the premenstrual days; **2)** no evidence for functional impairment associated with emotional symptoms; **3)** these criteria will be met on two menstrual cycles.

Since up to 50% of women with MDD report a premenstrual exacerbation of symptoms [43, 259], and premenstrual depressive changes independently predict the development of MDD [59], the following strategies were in place to insure accuracy of the PMDD differential diagnosis: **1)** we also interviewed subjects for medical conditions that may present with a pattern of premenstrual exacerbation (e.g. thyroid); **2)** Dr. Susan Girdler's nearly 20 years of experience in reviewing daily ratings for determining PMDD criteria, including the criteria for a symptom free period in the follicular phase, further ensured the exclusion of dysthymia or premenstrual exacerbation of chronic dysphoria or functional impairment; **3)** we excluded women with both a premenstrual and menstrual pattern (i.e., symptomatic throughout menses) even if a symptom free period follows in the follicular phase since this pattern may reflect refractory underlying DEP [260]; and **4)** we required three years in full remission for any Axis I disorder (other than MDD, for which 1 year was required) as to reduce further the likelihood that premenstrual symptoms reflect underlying current Axis I psychopathology.

Diagnostic Interview: During the enrollment session, subjects underwent the MINI International Neuropsychiatric Interview for Axis I disorders. Any woman meeting criteria for a current Axis I disorder was excluded and referred for treatment. As mentioned above, a minimum of one year in full remission from MDD, and three years in full remission from other Axis I disorders were required. Number of MDD episodes and time since last MDD episode were carefully evaluated. Any individual exhibiting significant psychological distress, currently in crisis, or currently suicidal were not enrolled into protocol but instead, immediately referred for treatment. Following the MINI Plus, using a validated structured interview [257], subjects were asked about previous abuse experiences.

Test Session: Each of the subjects were tested once during the luteal phase of the menstrual cycle, 5-12 days after home urine testing reveals the LH surge that precedes ovulation. Cycle phase were be confirmed to be ovulatory based upon serum progesterone. We tested in the luteal phase only since this is the phase in the menstrual cycle when PMDD women suffer from clinical levels of distress. Thus, this is a good comparison phase to determine diagnosis-related differences between PMDD and prior MDD. Furthermore, there is little consistent evidence that the menstrual cycle influences blood pressure and heart rate in healthy controls [261, 262] as well as blood pressure, heart rate, and neuroendocrine differences between PMDD and non-PMDD groups at rest or during stress [34, 78, 79, 182]. Lastly, a recent report from our laboratory determined that the menstrual cycle does not influence experimental pain perception in all women [263]. Hence, this would be the best phase to investigate relationships involving endogenous pain regulatory factors and hyperalgesia without jeopardizing our ability to detect group differences.

All laboratory testing began between the hours of 7:00am and 9:30am. The laboratory visit lasted approximately three hours and thirty minutes and followed a fixed sequence. The order of testing was as follows: 1) Instrumentation for blood pressure monitoring (Suntech 4240 Exercise blood pressure monitor) and stethoscopic blood pressure assessments to ensure reliable cuff placement and microphone position; 2) I.V. setup; 3) Baseline 1 Rest (10 min); 4) Administration of the Beck Depression Inventory and The Spielberger State Anxiety Inventory; 5) Pain Testing (approximately 30 min); 6) Recovery and Baseline 2 Rest (10 min); 7) Trier Social Stress Test (20 min)

I.V. Setup: A research nurse inserted a butterfly needle into a forearm vein. A non-heparinized, multi-stop-cock system was employed, which allowed the nurse to draw blood samples without the added stress involved in multiple venipunctures.

Baseline 1 Rest: Quiet rest ensued for 10 minutes and served as recovery from any stress effects associated with I.V. setup. BP and HR measures were taken at minutes 1, 3, 6, and 9, and averaged. Blood was sampled at min 10 for NE, β -endorphin, cortisol, and for progesterone.

Pain Testing Procedures: Subjects were exposed to two pain tests. The tests were chosen to differ along several dimensions, including quality of pain sensation (i.e., sharp vs. dull) and underlying endogenous pain modulatory systems (i.e., opioid vs. non-opioid). One of two task orders were used, insuring that each pain task is in the 1st and 2nd position, and that order was matched across groups.

The Submaximal Effort Tourniquet Procedure: This procedure produces graded increases in BP, forearm vascular resistance, and HR [264] and activates intrinsic opioid systems [265-267]. The tonic nature of this stimulus produces a deep, aching pain, similar to many clinical pain syndromes [268]. In this procedure, a tourniquet cuff was positioned on the subject's arm. Subjects verbally indicated when the sensations in their arm first become painful (threshold) and when they were no longer willing or able to tolerate the task (tolerance), though there was a maximum time (unspecified) at which they will not be allowed to continue (20 mins). Using a Visual Analog Scale (0-100), subjects rated both the intensity and unpleasantness of the pain at tolerance (see Appendix A). Before the tourniquet cuff was rapidly inflated to 200 mmHg, each subject's arm was raised for 30 seconds to promote venous drainage, the tourniquet cuff was inflated, the experimenter's stopwatch

started, and subjects engaged in 20 handgrip exercises at 30% of maximum force. Time (sec) to pain threshold and time to pain tolerance constituted the primary dependent measures.

The Hand Cold Pressor: This task is also characterized by a deep, tonic aching sensation but, unlike the tourniquet test, the cold pressor elicits much larger increases in BP, which are mediated solely via increases in total systemic vascular resistance [269]. A container was filled with ice and water maintained at 4° C. At the onset of the test, subjects submerged their hand to a marked line on their wrist and kept their hand still. The use of a water circulator prevented the water from warming near the subject's hand. Subjects indicated when the sensations in their hand first became painful (threshold) and when they were no longer willing or able to tolerate the pain (tolerance). Immediately before removing their hand, subjects rated the pain for intensity and unpleasantness using the Likert scale. A maximum time limit of 5 min was imposed.

Recovery and Baseline 2 Rest: Quiet rest ensued for 10 minutes, serving as a baseline from which to calculate reactivity. BP and HR measures were taken at minutes 1, 3, 6, and 9 and averaged. Blood was sampled at min 10 for NE, β -endorphin, and cortisol.

The Trier Social Stress Test (TSST): The TSST reliably induces large and consistent HPA-axis, cardiovascular, and NE responses [270-273] and involves four parts:

Pre-Task Instructions (5 min): Subjects were introduced to 3 people (the 'selection committee') after which the experimenter asked the subject to take over the role of a job applicant who is invited for a personnel interview with the company's staff managers (the selection committee). Subjects were instructed that after a preparation period, they should introduce themselves to the committee in a free speech of 5 minutes duration and convince the committee that they would be the perfect applicant for the position. Subjects were

instructed that they would be tape-recorded and that the committee members were specially trained to monitor nonverbal behavior and that tape-recorded speech will be analyzed for performance.

Speech Preparation (5 min): Subjects were provided with paper and pencil for outlining their talk but were not allowed to use these notes during the talk.

Job Speech (5 min): The selection committee returned and asked the subject to deliver her talk describing to the committee why she would be the perfect applicant for the position. If the subject finished before five minutes, the committee responded with prepared questions to ensure that the subject spoke for the entire period.

Paced Auditory Serial Addition Task (PASAT; [274]) (8.5 min): Immediately following the end of the speech, the same committee of individuals asked the subject to listen to a tape-recorded presentation of numbers from 1 to 9. Participants added each number presented on the tape to the immediately preceding number and stated the answer aloud. There were four series of numbers, with progressively shorter interdigit intervals. The experimenter remained in the room to monitor performance.

Task Assessments (see Appendix A): Task assessment questionnaires were administered after the cessation of each pain task, as well as at the end of the TSST (i.e. a separate assessment for the speech task and the PASAT given at the end of stress testing). The questionnaire asks the individual to draw a vertical line on a continuum from 0-10 indicating 1) how difficult they found the task; 2) how tense they were during the task; 3) how well they were able to concentrate during the task; and 4) how much effort they put into the task.

Cardiovascular and Neuroendocrine Sampling During TSST: BP and HR measures were taken at minutes 1, 3, and 5 of the Speech Preparation Period, minutes 1, 3, and 5 of the Job Speech, and minutes 2, 4, 6, and 8 of Serial Addition and averaged to constitute task levels. NE was sampled at the end of minute 2 of Speech and minute 2 of Serial Addition since catecholamines peak within the first minutes of stress and have a short half-life (3 min).

Measurements:

MINI International Neuropsychiatric Interview: We used the MINI International Neuropsychiatric Interview to screen all subjects for current and lifetime psychiatric symptomatology for DSM-IV psychotic, mood, substance use, anxiety, and eating disorders. Validation and reliability studies have been done comparing the M.I.N.I. to the Structured Clinical Interview for DSM-III-R (patient edition) and the Composite International Diagnostic Interview. The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time than the above referenced instruments [275].

All interviews were performed by Rebecca Klatzkin. The results of the interview were reviewed with clinical psychologist, Dr. Catherine Forneris, at a diagnostic conference. At the end of this interview, subjects were asked about sexual and physical abuse experiences using a structured interview developed by Dr. Leserman and colleagues [257]. As stated earlier, for present purposes, these data were only used to ensure equivalency of abuse across the four groups.

Beck Depression Inventory (BDI [276]): This 21-item scale comprehensively assesses dysphoric symptoms, including affective, cognitive, somatic, overt behavior and

interpersonal symptoms of depression. The BDI possesses a high degree of internal consistency with a mean alpha coefficient of .81 for nonpsychiatric populations [277], and a reasonable amount of validity with mean correlations of the BDI with clinical ratings and other questionnaires being 0.60 and 0.74 respectively in nonpsychiatric populations [277].

Spielberger Trait Anxiety Questionnaire (STAI-Y2 [278]): The STAI-Y2 is a questionnaire that measures symptoms of anxiety, and was used to measure how anxious the subject felt “in general”. The questionnaire has 20 statements, and the participant chose if they felt a certain way almost never, sometimes, often, or almost always.

Spielberger State Anxiety Questionnaire (STAI-Y1 [278]): The STAI-Y1 is a questionnaire that measures symptoms of anxiety, and was used to measure how anxious the subject felt at the very moment the questionnaire was administered. The questionnaire has 20 statements, and the participant chose if they felt a certain way almost never, sometimes, often, or almost always.

Blood Pressure and Heart Rate: The Suntech Exercise BP monitor, Model 4240 (SunTech Medical Instruments, Inc., Raleigh, NC) provided automated measurement of BP and HR during the sessions. The Suntech Exercise BP monitor uses the auscultatory technique, with R-wave Gating. This BP monitor is accurate within +/- 2 mmHg between 0 mmHg and 300 mmHg. Prior to initiating the baseline rest period, five standard stethoscopic blood pressures were taken simultaneously with the automated pressures in order to ensure correct microphone placement and cuff positioning.

Plasma Norepinephrine: Norepinephrine concentrations were determined using the high performance liquid chromatography technique. All high performance liquid chromatography procedures were conducted at the Core Laboratory of the UNC Hospitals

General Clinical Research Center. The lower limit of quantification with this system is 25 pg/ml, and the intra- and interday coefficients of variation are less than 10%.

Plasma cortisol and serum progesterone: Plasma cortisol and serum progesterone were determined using radioimmunoassay techniques commercially available from ICN Biomedical, Inc. The specificity of the antiserum for P is very high, showing only 0.01-2.5% cross-reactivity with other steroid compounds. Luteal phase P levels <3 mg/ml were considered reflective of an anovulatory cycle. The specificity of the antiserum for estradiol is high, showing only 0.01-1.45% cross-reactivity with steroid hormones with the exception of estrone, for which there is up to 6% cross-reactivity. For cortisol, the sensitivity of the assay is excellent at 0.07 µg/dL and the specificity high, showing 0.05-2.2% cross-reactivity with similar compounds, except prednisolone, where 94% cross-reactivity is obtained.

Plasma β-endorphin: Plasma β-endorphin levels in EDTA plasma were determined following extraction by radioimmunoassay using a kit from INCSTAR Corporation (Stillwater, Minnesota). The intra- and inter-assay coefficients of variation from the assay are approximately 10% and 15%, respectively, and the assay sensitivity is 3 pmol/L.

Data Analysis:

Total Recruitment and Screening:

In the present study, 479 women (PMDD = 325; Non-PMDD = 154) completed a phone screening interview (see Appendix A: Enrollment Statistics) that served as a preliminary screening tool for the study. Three hundred and fifty nine of these respondents did not meet phone screen criteria (due to medical, psychiatric, or other exclusion criteria) and thus did not participate in the study (PMDD = 108; Non-PMDD = 251). The remaining

122 women (PMDD = 76; Non-PMDD = 46) met phone screen criteria and subsequently signed a consent form in order to begin the protocol. For data analysis purposes, these 122 women were placed into various groups (outlined below and depicted visually in the Appendix A: Enrollment Statistics) in order to address the multiple aims of the present study. The full sample of 122 women who signed a consent form were used to assess predictors of study retention (see Appendix A: Enrollment Statistics [highlighted in green]), yet only 38 of these women completed the laboratory study protocol (PMDD = 17; Non-PMDD = 21), and therefore comprise the main data set used for analyses in the present study.

The other 84 out of these 122 women (PMDD = 59; non-PMDD = 25) failed to complete the laboratory study protocol, 15 of whom completed the 2-3 months of daily ratings required for a PMDD (N = 8) or non-PMDD (N = 7) diagnosis, but did not complete the laboratory study protocol due to voluntarily dropping out of the study prior to completion (PMDD = 3; non-PMDD = 5) or due to various reasons outside of their control (i.e. had not yet completed the laboratory study protocol at the time of data analysis or were unable to complete the laboratory study protocol due to medical issues: PMDD = 5; non-PMDD = 2). Although they did not complete the laboratory study protocol, these 15 women did receive a PMDD or non-PMDD diagnosis and were thus included in the daily ratings analyses based on both PMDD and prior MDD status along with the abovementioned 38 women who comprise the main data set (Total N = 53; see Appendix A: Enrollment Statistics [highlighted in red]).

Furthermore, 69 of the 84 women who failed to complete the laboratory study protocol also failed to complete the 2-3 months of daily ratings required for a PMDD (N = 51) or non-PMDD (N = 18) diagnosis. These 69 women either chose to drop out of the study

(presenting as PMDD = 20; non-PMDD = 9), or were excluded from the study based on daily ratings criteria (PMDD = 25; non-PMDD = 7) or enrollment criteria (presenting as PMDD = 6; non-PMDD = 2). Thirty six (13 plus 23; see Appendix A: Enrollment Statistics) of these 69 women completed both the psychiatric interview and at least one month of daily ratings, while 26 (16 plus 9; see Appendix A: Enrollment Statistics) failed to do so. These 36 women (13 plus 23; see Appendix A: Enrollment Statistics) were thus included in the analyses of daily ratings examined as a function of prior MDD status along with the 53 women who received a PMDD or non-PMDD diagnosis (N = 89; see Appendix A: Enrollment Statistics [highlighted in blue text]).

Demographics:

Group differences in demographic factors, trait anxiety scores assessed during enrollment, state anxiety and depression scores assessed during the laboratory protocol, and baseline SNS and HPA-axis factors were examined using a one-way analysis of variance (ANOVA) or chi square analysis separately for PMDD (yes vs. no) and for Prior MDD (yes vs. no). In order to assess whether the proportion of PMDD women as well as the proportion of women with a history of MDD differed by race, a 2 (PMDD) x 2 (Race: Non-Hispanic Whites vs. Minorities: African American, Hispanic, Asian, or Multi-racial) chi square analysis, and a 2 (Prior MDD) x 2 (Race) chi square analysis were utilized. Similarly, a 2 (PMDD) x 2 (Abuse: yes vs. no) chi square analysis as well as a 2 (Prior MDD) x 2 (Abuse) chi square analysis were performed to determine whether the proportion of women with an abuse history differed by PMDD and by Prior MDD status. For women with prior MDD,

PMDD and non-PMDD groups were compared on months since last depressive episode and number of prior MDD episodes with a one way ANOVA.

Pain Sensitivity and Task Assessments for Cold Pressor and Tourniquet Ischemic Tasks:

In order to determine whether pain sensitivity to the tourniquet ischemic and cold pressor task differed by PMDD and by Prior MDD status, a 2 (PMDD) x 2 (Period: Threshold vs. Tolerance) repeated measures ANOVA with Period as the repeated factor was performed, followed by a 2 (Prior MDD) x 2 (Period) repeated measures ANOVA with Period as the repeated factor. The subjective experiences of each pain task (difficulty, tension, inability to concentrate, effort) as measured by the task assessment questionnaire (see Appendix A) was analyzed separately by PMDD and by Prior MDD status using a one way ANOVA. The analyses were performed separately for each pain task and for each of the 4 items on the task assessment. For the first 3 questions assessing difficulty, tension, and inability to concentrate, higher scores indicated a more negative subjective experience, while for the fourth question assessing effort put into the pain task, higher scores indicated greater effort. Lastly, pain intensity and unpleasantness ratings from 0-100 (see Appendix A) given immediately following voluntary tolerance for each pain task were analyzed separately by PMDD and by Prior MDD status using a one way ANOVA.

Daily Symptom Ratings:

Daily Symptom Ratings as a Function of Prior MDD Status (N = 89):

The goal of the next analyses were to explore group differences in Daily Record of Severity of Problems (DRSP) symptoms in women (N = 89) who were assessed for prior

MDD via structured psychiatric interview (Prior MDD = 42; No Prior MDD = 47), and completed at least one month of daily mood ratings (see Appendix A: Daily Record of Severity of Problems). This group of 89 women was comprised of participants who completed the laboratory study protocol (N = 38), those who received a PMDD or non-PMDD diagnosis but were unable to complete the laboratory study protocol (N = 15), and those who did not complete the 2-3 months of daily ratings necessary to receive a PMDD or non-PMDD diagnosis (N = 36).

For each of the 24 symptoms on the DRSP (depressed, hopeless, worthless or guilty, anxious, mood swings, more sensitive, angry or irritable, conflict, less interest, difficulty concentrating, fatigue, increased appetite or overate, food cravings, slept more, trouble sleeping, overwhelmed, out of control, breast tenderness, breast swelling or bloating, headache, joint or muscle pain, less productivity or efficiency due to above problems, interference with hobbies or social activities due to above problems, and interference with relationships due to the above problems), a follicular (days 1 through 10) and luteal (days -7 through -1) phase average was calculated for cycle one and cycle two. For each of the 24 symptoms, cycle one and cycle two were averaged to create an overall follicular and an overall luteal phase average. Next, each symptom was placed into one of five core symptom categories [258]: 1. Somatic (fatigue, breast tenderness, breast swelling or bloating, headache, joint or muscle pain); 2. Depression: (depressed, hopeless, worthless or guilty, slept more, trouble sleeping, overwhelmed); 3. Anger/Irritability: (anger or irritability, conflict); 4. Anxiety: (anxiety); and 5. Impairment: (less productivity or efficiency, interference with hobbies or social activities, interference with relationships), and averaged to yield one total follicular and luteal score for each of the five categories.

All 89 women were assessed for differences in the five core symptom categories based on prior MDD diagnosis using a 2 (Prior MDD) x 2 (Menstrual Cycle Phase) repeated measures ANOVA with Menstrual Cycle Phase as the repeated factor. Where significant interactions emerged, simple effects analyses and/or least square means comparisons were conducted to explore the source of the interaction.

Daily Symptom Ratings as a Function of PMDD (N = 53):

Similar analyses to determine group differences in symptom severity based on PMDD status were next performed in a smaller group of women (N = 53) comprised of those who completed the laboratory study protocol (n = 38), and women who did not complete the laboratory study protocol, but who completed the 2-3 months of daily ratings necessary to be given a PMDD or non-PMDD diagnosis (N = 15) (see Appendix A: Enrollment Statistics). The entire group (N = 53) underwent a formal assessment of prior MDD via structured psychiatric interview (Yes = 18; No = 35) and PMDD via the daily mood ratings (Yes = 25; No = 28). Although many participants filled out daily ratings for three consecutive menstrual cycles in order to determine PMDD or non-PMDD diagnosis, daily ratings from only two menstrual cycles in which PMDD or non-PMDD criteria were met were used in the analyses.

Group differences in the five somatic symptom categories means were explored using a 2 (PMDD) x 2 (Menstrual Cycle Phase) repeated measures ANOVA with Menstrual Cycle Phase as the repeated factor. Where significant interactions emerged, simple effects analyses and/or least square means comparisons were conducted to explore the source of the interaction.

Hypothalamic Pituitary Adrenal (HPA)-Axis and Sympathetic Nervous System (SNS):

For the 38 women who completed the laboratory study, group differences in baseline HPA-axis factors of cortisol and β -endorphin were analyzed separately by PMDD and by Prior MDD status using a one way ANOVA. Next, stress responsivity of the SNS factors of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and norepinephrine (NE) based on PMDD and Prior MDD status were explored by calculating delta scores (Speech task – Baseline), and using separate one way ANOVAs for PMDD and for Prior MDD. SNS factors from the speech task were used to calculate the delta score since this task has been shown to elicit a greater SNS stress response than the math task [234, 279].

Relationship Between SNS and HPA-axis Factors and Pain Sensitivity and Pain Intensity and Unpleasantness Ratings:

To examine the relationship between SNS and HPA-axis factors and pain sensitivity, consistent with other published reports [280], a median split for baseline and speech stress SBP was conducted separately, first by PMDD status (PMDD vs. non-PMDD), and then by prior MDD status (prior MDD vs. no prior MDD). In order to reduce the number of separate analyses, only SBP at baseline and speech stress, as well as baseline cortisol and β -endorphin, were examined for their relationship to pain sensitivity. For each physiological measure, a 2 (Group: High vs. Low) x 2 (Time: Threshold vs. Tolerance) repeated measures ANOVA was conducted first as a function of PMDD status and then as a function of prior MDD status for each pain task.

Next, the relationship between SNS and HPA-axis factors and pain intensity and unpleasantness was examined using the median splits analytic approach mentioned above.

Speech and Math Task Assessments:

The subjective experiences of each stress task as measured by task assessment questionnaires (see Appendix A) regarding difficulty, tension, inability to concentrate, and effort were analyzed separately by PMDD and by Prior MDD status using one way ANOVAs. Analyses were performed separately for the speech and math task and for each of the 4 items on the task assessment. For the first 3 questions assessing difficulty, tension, and inability to concentrate, higher scores indicated a more negative subjective experience, while for the fourth question assessing effort put into the pain task, higher scores indicated greater effort.

Study Retention:

Demographic Variables as a Function of Dropout Status ('Completion' vs. 'Dropouts') (N = 75):

In the following analyses assessing study retention, 'completers' refer to women who completed the laboratory study protocol (N = 38), while 'dropouts' refer to women who voluntarily dropped out of the study at any time prior to completion (N = 37; see Appendix A: Enrollment Statistics [highlighted in dotted pattern]). Multiple stepwise regression analyses were performed in order to examine the degree to which certain demographic variables (BDI, trait anxiety, age, race [Non-Hispanic Whites = 1 vs. Minorities = 0], self-reported psychological history [Yes = 1 vs. No = 0], self-reported psychological treatment history [Yes = 1 vs. No = 0], self-reported alcohol consumption [number of drinks per month], and self-reported PMDD or non-PMDD diagnosis [Yes = 1 vs. No = 0]) served as independent predictors of voluntary dropout status (Completion = 1 vs. Dropout = 0).

In stepwise regression each independent variable specified is entered into the regression one at a time until all variables have been added with the provision that each meets a specified criterion. The criterion employed by SAS, the statistical software used for these analyses, was one of significance level $p < .15$. Furthermore, the stepwise approach involves an additional procedure in which all variables are reexamined after the addition of other variables to verify that each remains a significant and independent predictor. Thus, this approach helps to circumvent the problem of multicollinearity of independent variables.

Demographic Variables as a Function of Completion Status ('Completion' vs. 'Non-Completion') (N = 122):

In the following analyses assessing study retention, 'completers' refer to women who completed the laboratory study protocol (N = 38), while 'non-completers' refer to women who signed a consent form but did not complete the laboratory study protocol (N = 84). These 84 women consist of 'dropouts' as described above (N = 37; see Appendix A: Enrollment Statistics [highlighted in dotted pattern]), in addition to women who did not complete the laboratory study protocol due to various forces outside of their control (i.e. presence of medical issues (N = 2), had not completed the laboratory study protocol at the time of data analysis (N = 5), ineligibility based on inclusion criteria (N = 7) or daily ratings (N = 32); see Appendix A: Enrollment Statistics). Multiple stepwise regression analyses were performed in this sample (N=122) in order to examine the degree to which the demographic variables (BDI, trait anxiety, age, race [Non-Hispanic Whites = 1 vs. Minorities = 0], self-reported psychological history [Yes = 1 vs. No = 0], self-reported psychological treatment history [Yes = 1 vs. No = 0], self-reported alcohol consumption [number of drinks

per month], and self-reported PMDD or non-PMDD diagnosis [Yes = 1 vs. No = 0]) served as independent predictors of completion status (Completion = 1 vs. Non-Completion = 0).

CHAPTER 3

RESULTS

Demographics:

As seen in Table 1, analyses revealed no group differences based on PMDD status in age, BMI, race, or abuse history (p s > .05). PMDD women had slightly higher state anxiety scores ($F(1, 37) = 2.4, p = .13$) and significantly greater trait anxiety scores ($F(1, 37) = 16.4, p < .001$) than non-PMDD women. PMDD women also showed higher BDI scores than non-PMDD women ($F(1, 37) = 14.1, p < .001$), results that would be expected during the symptomatic luteal phase of the menstrual cycle when the inventory was administered.

Table 1. Mean (+SEM) Demographic Factors as a Function of PMDD Status

	Non-PMDD (N = 21)	PMDD (N = 17)
Age	32.6 (1.8)	34.4 (2.0)
Body Mass Index (BMI)	25.5 (1.3)	25.1 (1.4)
^A Beck Depression Inventory (BDI)	2.0 (0.9)	7.1 (1.0)
^B State Anxiety	27.9 (2.0)	32.5 (2.2)
^A Trait Anxiety	28.9 (1.5)	38.2 (1.7)
Race (Non-Hispanic Whites : Minorities)	15 : 6	12 : 5
Abuse History (Yes : No)	9 : 12	9 : 8
Prior Episodes of MDD	1.86 (.33)	1.67 (.35)
Months in Remission from MDD	72.3 (30.5)	106 (32.9)

^A PMDD > non-PMDD , $p < .001$

^B PMDD > non-PMDD , $p = .13$

As seen in Table 2, analyses revealed no group differences based on Prior MDD status in age, BMI, BDI, state anxiety, or abuse history (p s > .05). However, women with a history of MDD had greater trait anxiety ($F(1, 37) = 5.0, p < .05$) compared to women with no history of MDD. In addition, a greater proportion of non-Hispanic Whites ($N=27$) had a history of MDD than participants categorized as Minorities ($N=11$; African American, Hispanic, Asian, or Multi-racial) ($\chi^2 = 4.3, p < .05$), while the proportion of women with abuse histories did not significantly differ based on Prior MDD status ($p > .05$). Lastly, in analyses performed in women with prior MDD only, PMDD and non-PMDD women did not differ in number of prior episodes of MDD or months in remission from MDD (all p s > .05).

Table 2. Mean (+SEM) Demographic Factors as a Function of Prior MDD Status

	No Prior MDD (N = 25)	Prior MDD (N = 13)
Age	33.4 (1.7)	33.2 (2.3)
Body Mass Index (BMI)	25.5 (1.2)	24.9 (1.6)
Beck Depression Inventory (BDI)	3.8 (1.0)	5.2 (1.3)
State Anxiety	30.7 (1.9)	28.5 (2.6)
^A Trait Anxiety	31.0 (1.6)	37.1 (2.2)
^B Race (Non-Hispanic Whites : Minorities)	15 : 10	12 : 1
Abuse History (Yes : No)	11 : 14	7 : 6

^A Prior MDD > No Prior MDD, $p < .05$

^B Percentage with Prior MDD Diagnosis: Non-Hispanic Whites > Other, $p < .05$

Pain Sensitivity to Cold Pressor and Tourniquet ischemic Tasks¹:

Cold Pressor Task:

As anticipated, PMDD women displayed lower threshold and tolerance to the cold pressor task than non-PMDD women ($F(1, 35) = 7.1, p < .05$) (see Figure 1). However, a PMDD x Period interaction ($F(1, 35) = 5.8, p < .05$) was also present, with simple effects

¹ Figure legend: $\pm p < .0001$; $\dagger p < .001$; $\ddagger p < .01$; $* = p < .05$; $\# = p < .10$; $+ = p < .15$

analyses conducted separately by Period revealing that this PMDD diagnosis-related difference in pain sensitivity was more evident at tolerance ($F(1, 37) = 5.8, p < .05$) than at threshold ($F(1, 36) = 2.4, p = .13$). Also as expected, women with a history of MDD displayed greater cold pressor threshold and tolerance than women with no history of MDD ($F(1, 35) = 8.2, p < .01$) (see Figure 2). However, a Prior MDD x Period interaction ($F(1, 35) = 7.3, p < .05$) was also present, with simple effects analyses conducted separately by Period indicating that this prior MDD diagnosis-related difference in cold pressor pain sensitivity was only present at tolerance ($F(1, 37) = 8.6, p < .01$).

Figure 1: Cold Pressor Threshold and Tolerance as a Function of PMDD Status

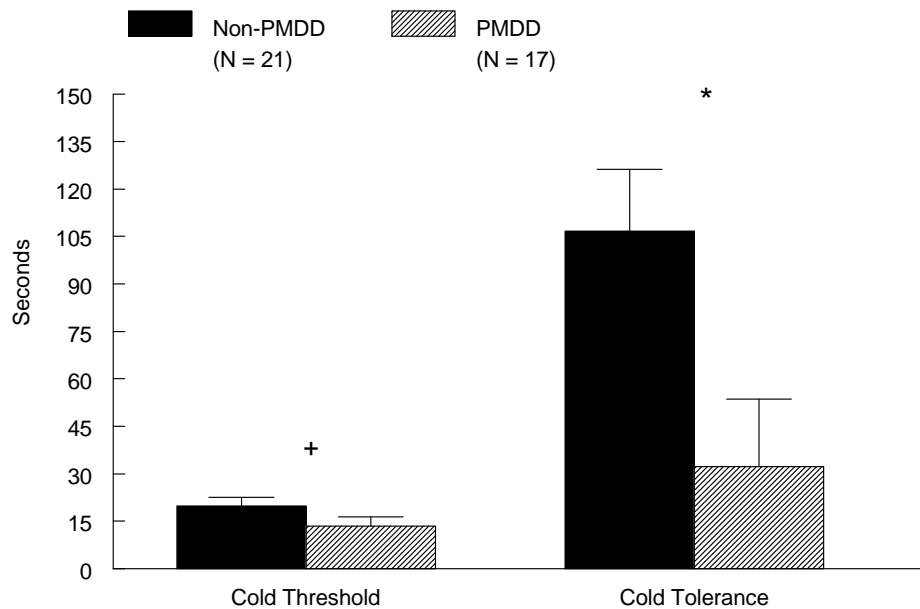
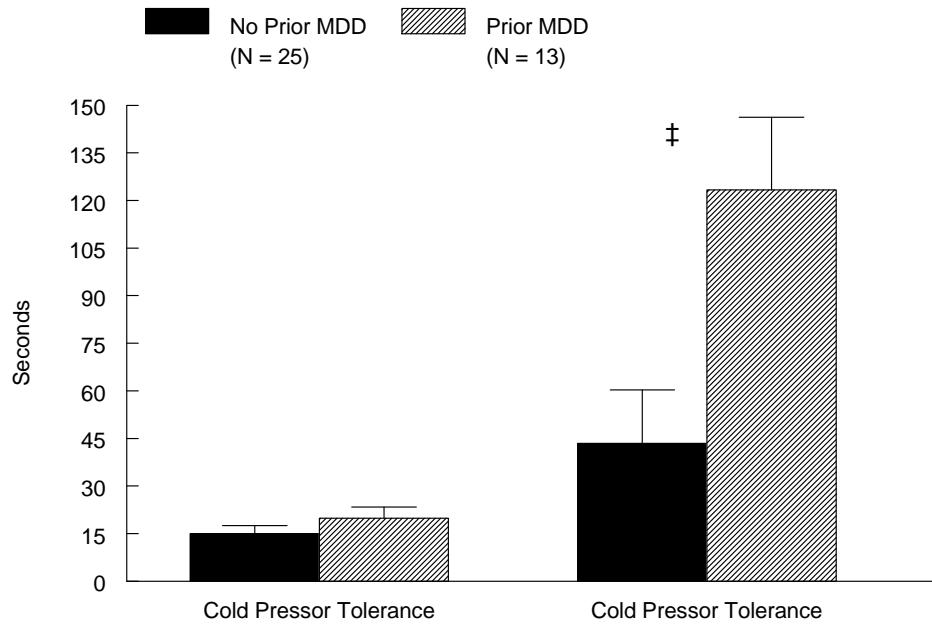


Figure 2: Cold Pressor Pain Threshold and Tolerance as a Function of Prior MDD Status



Tourniquet Ischemic Task:

As depicted in Figures 3 and 4, no significant main effects or interactions were present for the tourniquet ischemic task in either diagnostic group.

Figure 3: Tourniquet Ischemic Threshold and Tolerance as a Function of PMDD Status

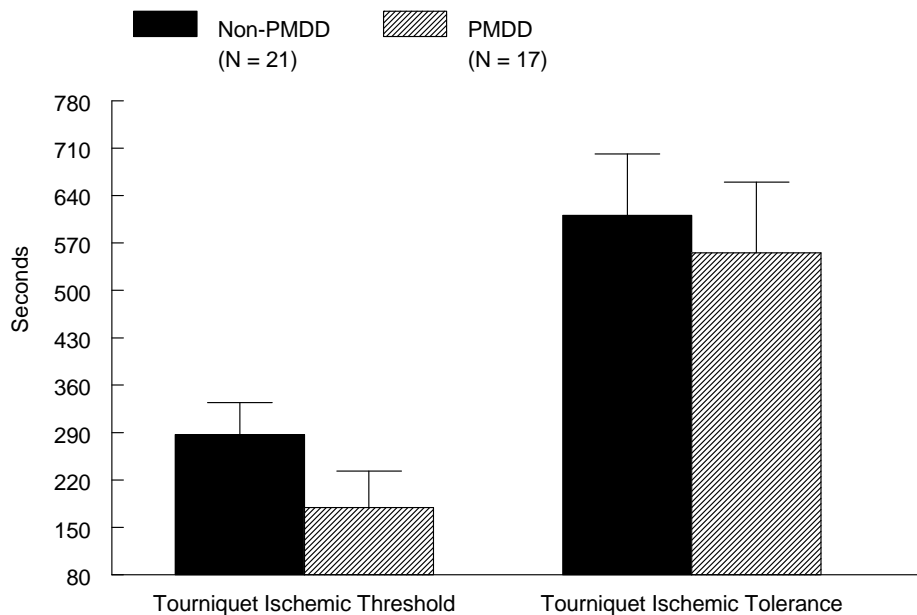
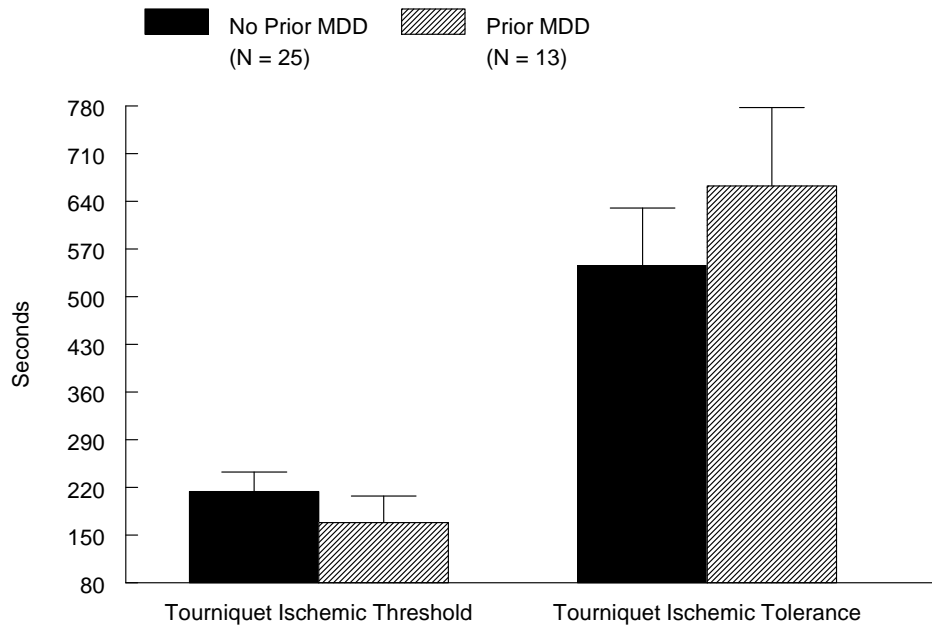


Figure 4: Tourniquet Ischemic Pain Threshold and Tolerance as a Function of Prior MDD Status



Pain Task Assessments and Intensity and Unpleasantness Ratings:

Cold Pressor Task:

As seen in Figure 5, PMDD women reported somewhat greater difficulty during the cold pressor task than did non-PMDD women ($F(1, 37) = 2.9, p = .10$). No other significant main effects or interactions were present for cold pressor pain task assessments (see Figures 5 and 6) or pain intensity and unpleasantness ratings in either diagnostic category (see Table 3) ($ps > .15$).

Figure 5: Cold Pressor Task Assessments as a Function of PMDD Status

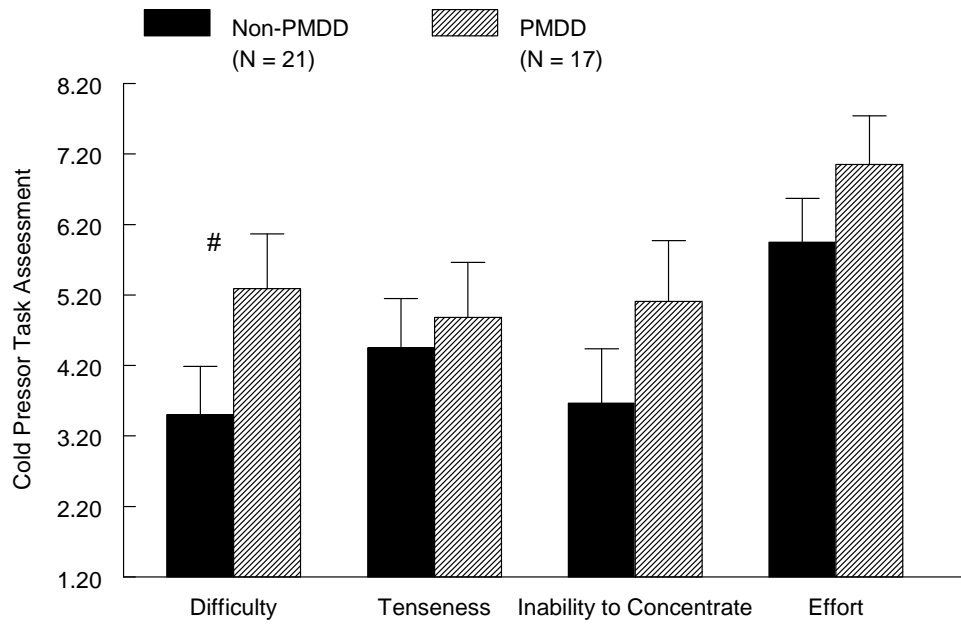


Figure 6: Cold Pressor Task Assessments as a Function of Prior MDD Status

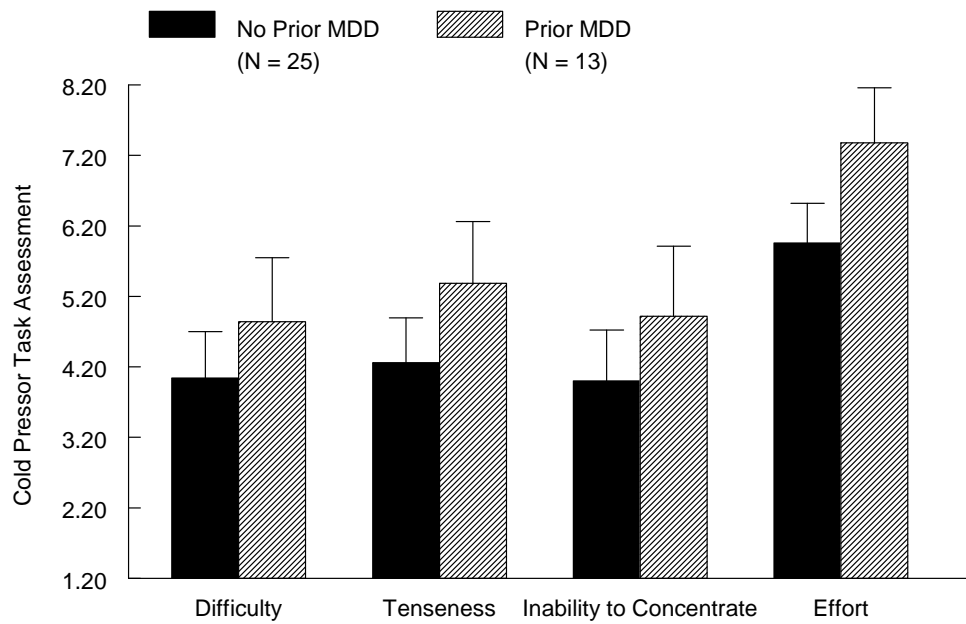


Table 3. Mean (+SEM) Cold Pressor and Tourniquet Ischemic Pain Intensity and Unpleasantness Ratings as a Function of PMDD and Prior MDD Status

	Non-PMDD	PMDD	No Prior MDD	Prior MDD
Cold Pressor Intensity	44.5 (4.4)	48.7 (4.9)	48.2 (4.0)	42.9 (5.6)
Cold Pressor Unpleasantness	44.9 (5.0)	53.6 (5.6)	48.2 (4.7)	50 (6.5)
Tourniquet Intensity	34.0 (3.7)	34.3 (4.1)	36.0 (3.3)	30.5 (4.6)
Tourniquet Unpleasantness	41.1 (3.7)	42.4 (4.2)	42.1 (3.4)	40.8 (4.8)

Tourniquet Ischemic Task:

No significant main effects or interactions were present for the tourniquet ischemic pain task assessments (see Figures 7 and 8) or pain intensity and unpleasantness ratings in any diagnostic category (see Table 3) (p s > .15).

Figure 7: Tourniquet Ischemic Task Assessments as a Function of PMDD Status

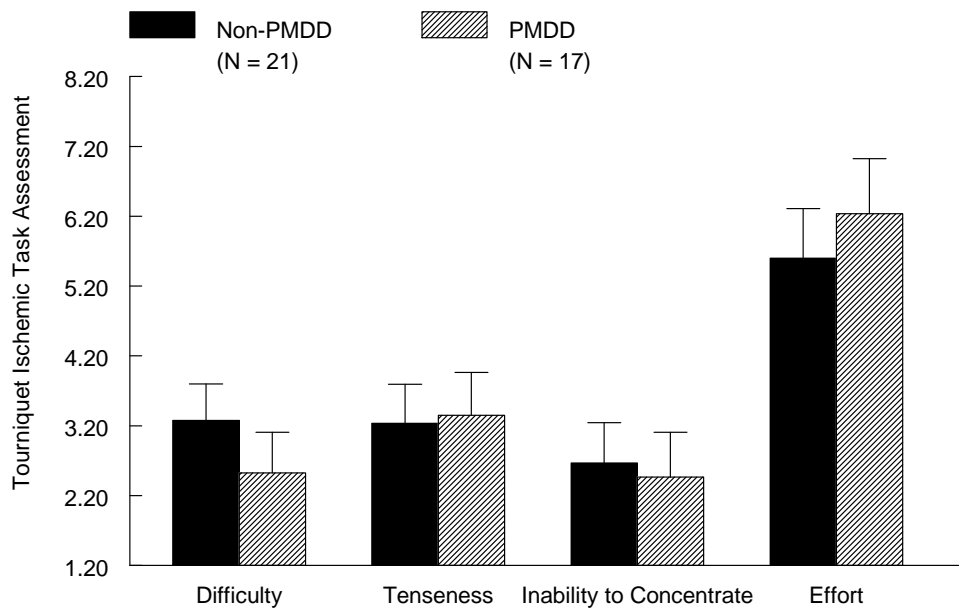
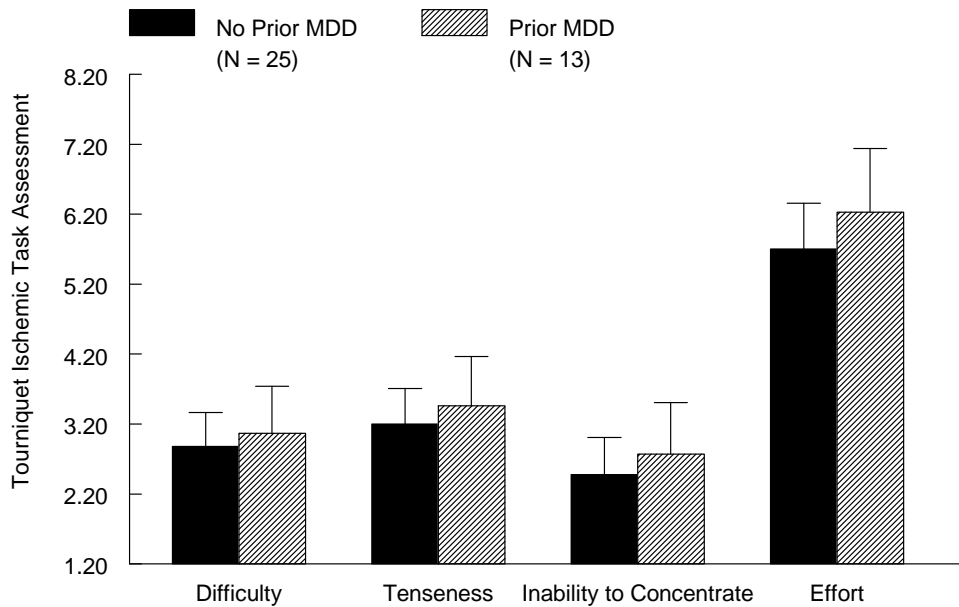


Figure 8: Tourniquet Ischemic Task Assessments as a Function of Prior MDD Status

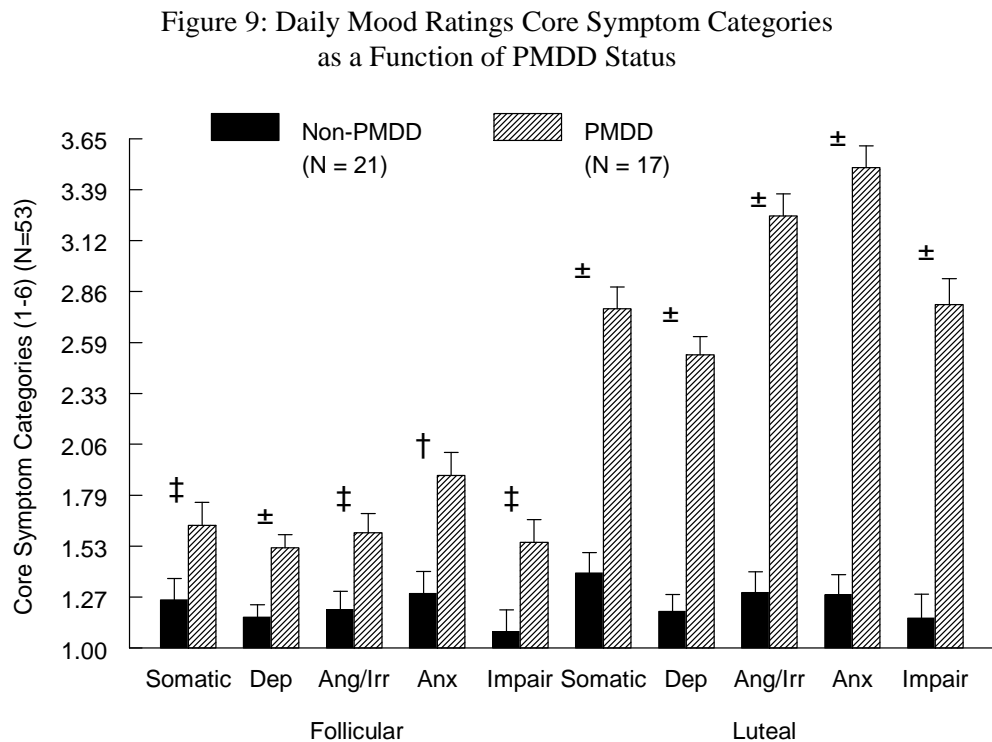


Daily Symptom Ratings:

Daily Symptom Ratings as a Function of PMDD Status (N=53):

A total of 53 women successfully completed their daily mood ratings and met either PMDD or non-PMDD criteria. Thus, analyses were conducted for symptom severity as a function of PMDD status in this group, as depicted in Figure 9. As anticipated, PMDD x Menstrual Cycle Phase interactions were present for somatic symptom severity ($F(1, 51) = 42.7, p < .0001$), depression ($F(1, 51) = 49.0, p < .0001$), anger/irritability ($F(1, 51) = 93.0, p < .0001$), anxiety ($F(1, 51) = 93.4, p < .0001$), and impairment ($F(1, 51) = 45.1, p < .0001$). Simple effect analyses conducted separately by Phase revealed that although PMDD women reported greater symptom severity than non-PMDD women in both menstrual cycle phases, these PMDD-related differences were greater in the luteal phase [somatic ($F(1, 52) = 104.9, p < .0001$), depression ($F(1, 52) = 106.7, p < .0001$), anger/irritability ($F(1, 51) = 154.5, p < .0001$), anxiety ($F(1, 52) = 213.4, p < .0001$), and impairment ($F(1, 51) = 89.4, p < .0001$)]

than in the follicular phase [somatic ($F(1, 52) = 9.4, p < .01$), depression ($F(1, 52) = 17.5, p < .0001$), anger/irritability ($F(1, 51) = 9.3, p < .01$), anxiety ($F(1, 52) = 13.6, p < .001$), and impairment ($F(1, 51) = 8.1, p < .01$)] (see Figure 9).

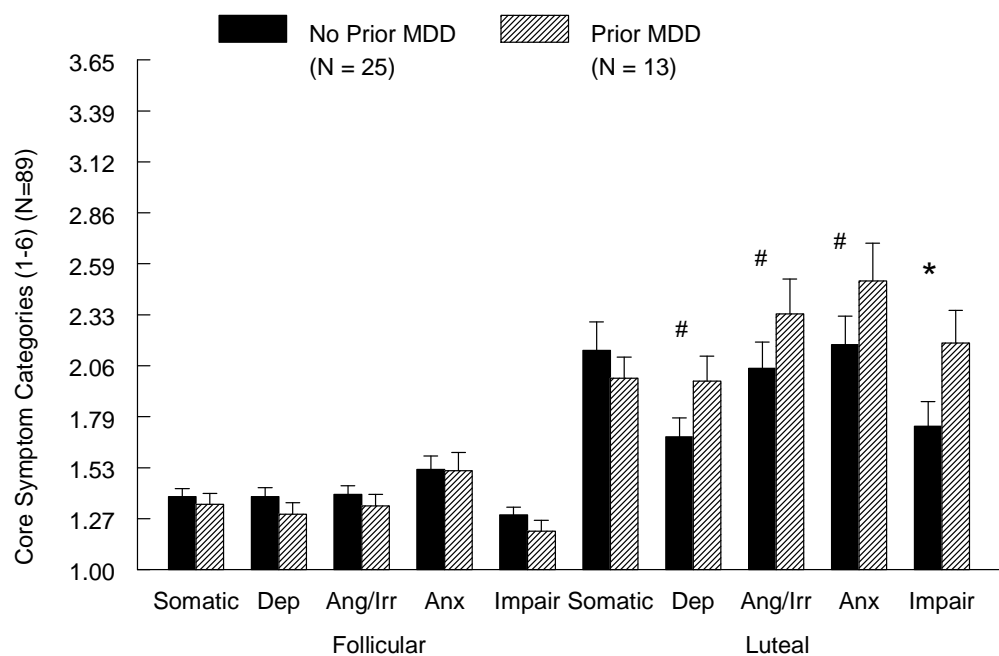


Daily Symptom Ratings as a Function of Prior MDD Status (N=89):

Although there were no main effects present based on prior MDD status for any core symptom category, Prior MDD x Menstrual Cycle Phase interactions were found for depression ($F(1, 87) = 8.5, p < .01$) and impairment ($F(1, 87) = 7.2, p < .01$). Simple effects analyses conducted separately by phase revealed that women with a history of MDD reported greater severity of depression ($F(1, 88) = 3.1, p = .08$) and impairment ($F(1, 88) = 4.0, p < .05$) than women with no history of MDD only in the luteal phase (see Figure 10). Trends for Prior MDD x Menstrual Cycle Phase interactions were also found for anger/irritability ($F(1,$

87) = 2.8, $p = .10$) and anxiety symptoms ($F(1, 87) = 2.9$, $p = .09$), since women with prior MDD reported greater severity of these symptoms only in the luteal phase (see Figure 10). No significant main effect or interactions were found for the core somatic symptoms (all $ps > .05$).

Figure 10: Daily Mood Ratings Symptom Categories as a Function of Prior MDD Status



Hypothalamic Pituitary Adrenal Axis:

Our results indicated that there were no differences in baseline cortisol or β -endorphin (see Table 4) between PMDD and non-PMDD women (all $ps > .05$). Similarly, no differences in baseline cortisol or β -endorphin (see Table 5) were observed between women with and without prior MDD (all $ps > .05$).

Table 4. Mean (+SEM) Baseline SNS and HPA-axis Factors as a Function of PMDD Status

	Non-PMDD (N = 21)	PMDD (N = 17)
Baseline cortisol (ng/ml)	8.2 (.80)	7.7 (.90)
Baseline β -endorphin (ng/ml)	0.067 (0.007)	0.081 (0.008)
Baseline systolic blood pressure (SBP)	110.6 (2.1)	112.2 (3.0)
Baseline diastolic blood pressure (DBP)	67.5 (1.6)	68.8 (2.2)
Baseline heart rate (HR)	65.0 (2.3)	65.4 (3.2)
Baseline norepinephrine (NE) (pg/ml)	420.4 (34.6)	328.7 (48.9)

Table 5. Mean (+SEM) Baseline SNS and HPA-axis Factors as a Function of Prior MDD Status

	No Prior MDD (N = 25)	Prior MDD (N = 13)
Baseline cortisol (ng/ml)	7.8 (0.73)	8.3 (1.0)
Baseline β -endorphin (ng/ml)	0.07 (0.008)	0.08 (0.012)
Baseline systolic blood pressure (SBP)	111.4 (2.3)	110.7 (2.5)
Baseline diastolic blood pressure (DBP)	68.3 (1.7)	67.4 (1.9)
Baseline heart rate (HR)	66.1 (2.5)	63.9 (2.8)
Baseline norepinephrine (NE) (pg/ml)	379.2 (39.1)	403.1 (43.7)

Sympathetic Nervous System:

Despite a lack of differences in SBP, DBP, HR, or NE based on PMDD or Prior MDD status at baseline (p s > .15) (see Tables 4 and 5), PMDD women showed a blunted HR ($F(1, 36 = 5.6, p < .05)$), SBP ($F(1, 35 = 4.8, p < .05)$), DBP ($F(1, 35 = 6.4, p < .05)$), and NE ($F(1, 34 = 7.8, p < .01)$) response to stress compared to non-PMDD women (see Figures 11 and 12). In addition, women with a history of MDD tended to show a greater increase in DBP from baseline to speech stress than women with no history of MDD ($F(1, 35 = 2.5, p = .13)$) (see Figure 13), although no other delta SNS factor differed by prior MDD status (see Figures 13 and 14).

Figure 11: Change in SNS factors from Baseline to Speech Stress as a Function of PMDD Status

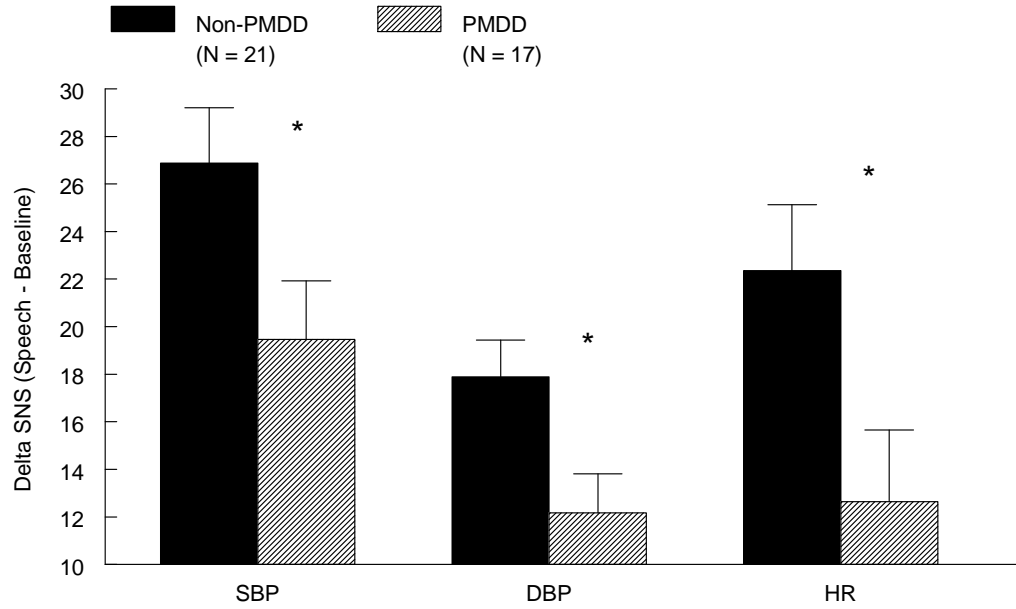


Figure 12: Change in Norepinephrine from Baseline to Speech Stress as a Function of PMDD Status

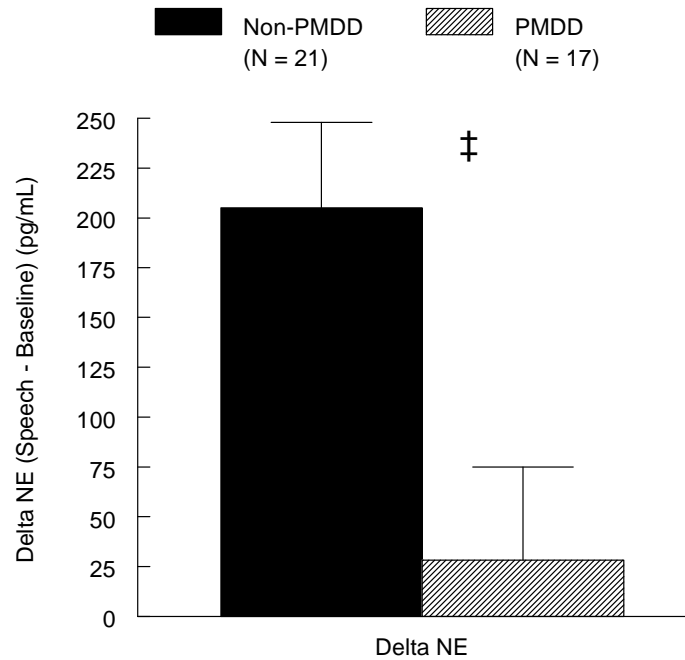


Figure 13: Change in HR and BP from Baseline to Speech Stress as a Function of Prior MDD Status

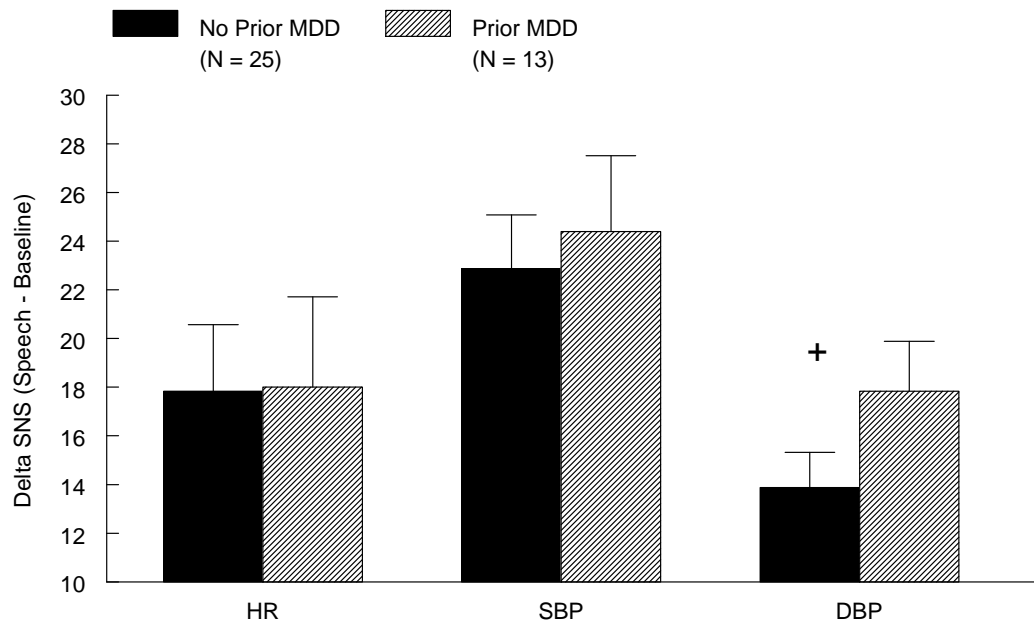
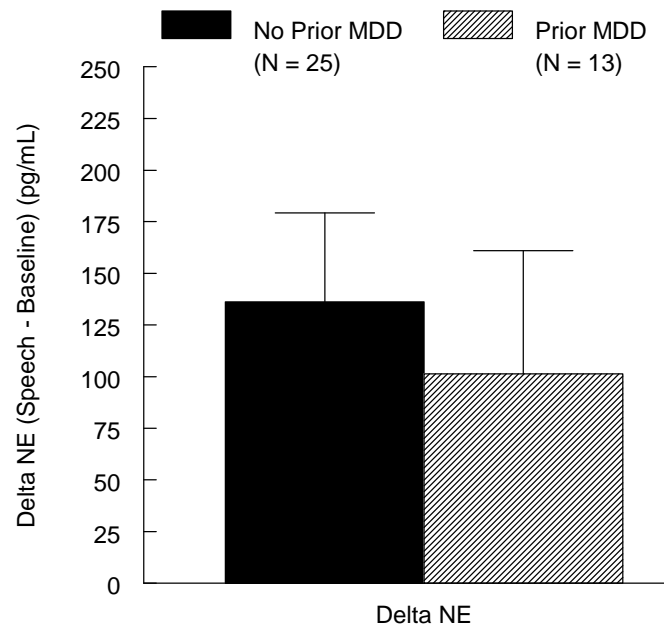


Figure 14: Change in Norepinephrine from Baseline to Speech Stress as a Function of Prior MDD Status



Speech and Math Task Assessments:

Speech Task Assessments:

As depicted in Figure 15, PMDD women reported more difficulty ($F(1, 36) = 2.7, p = .11$), more tension ($F(1, 36) = 5.5, p < .05$), and a greater inability to concentrate ($F(1, 36) = 7.0, p < .05$) during speech stress than non-PMDD women. Women with or without prior MDD did not differ on any measure of the speech task assessment ($ps > .15$) (see Figure 16).

Figure 15: Speech Task Assessments as a Function of PMDD Status

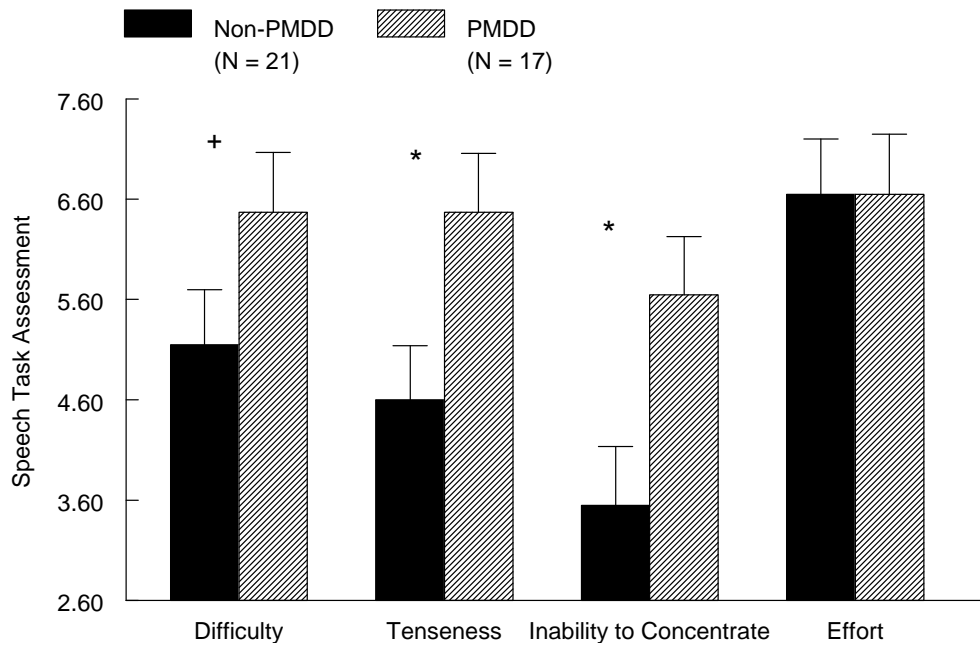
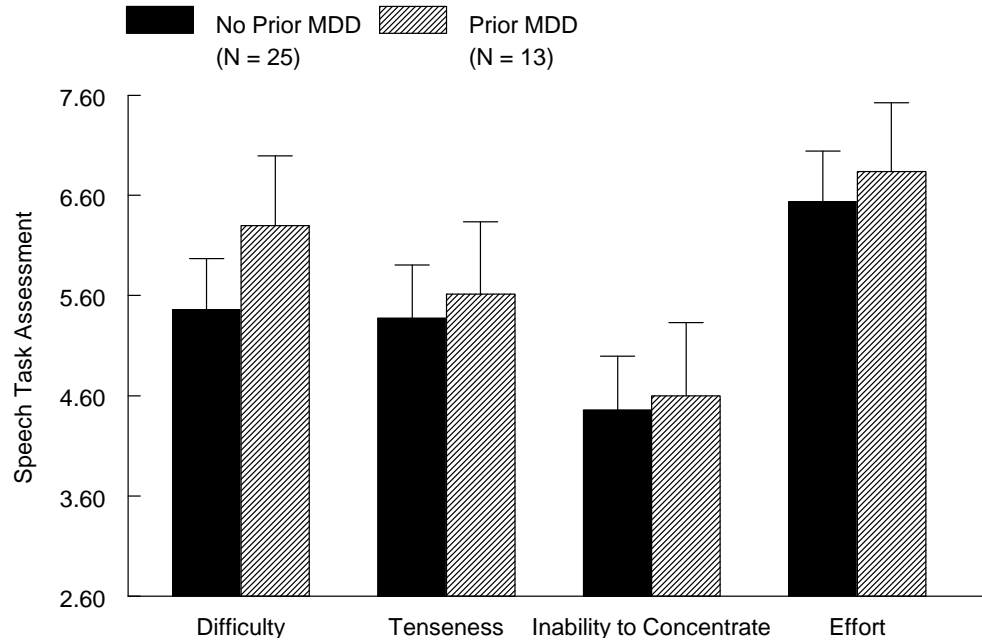


Figure 16: Speech Task Assessments as a Function of Prior MDD Status



Math Task Assessments:

During the math stressor, PMDD women reported a marginally greater impairment in concentration than non-PMDD women ($F(1, 36) = 3.4, p = .07$) (see Figure 17), and there was also a trend for women with prior MDD to have reported greater difficulty than women with no prior MDD ($F(1, 36) = 2.8, p = .10$) (see Figure 18).

Figure 17: Math Task Assessments as a Function of PMDD Status

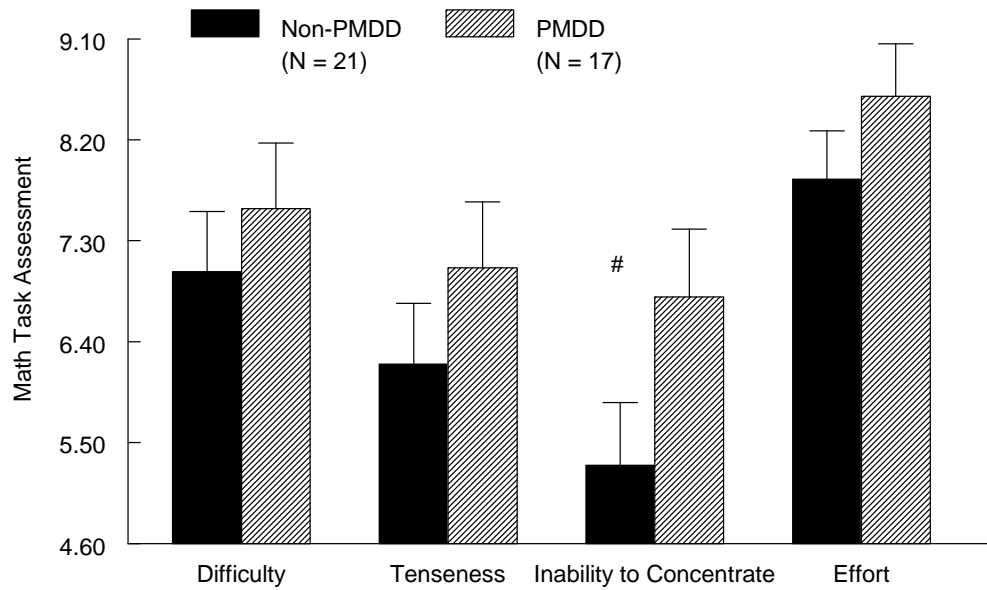
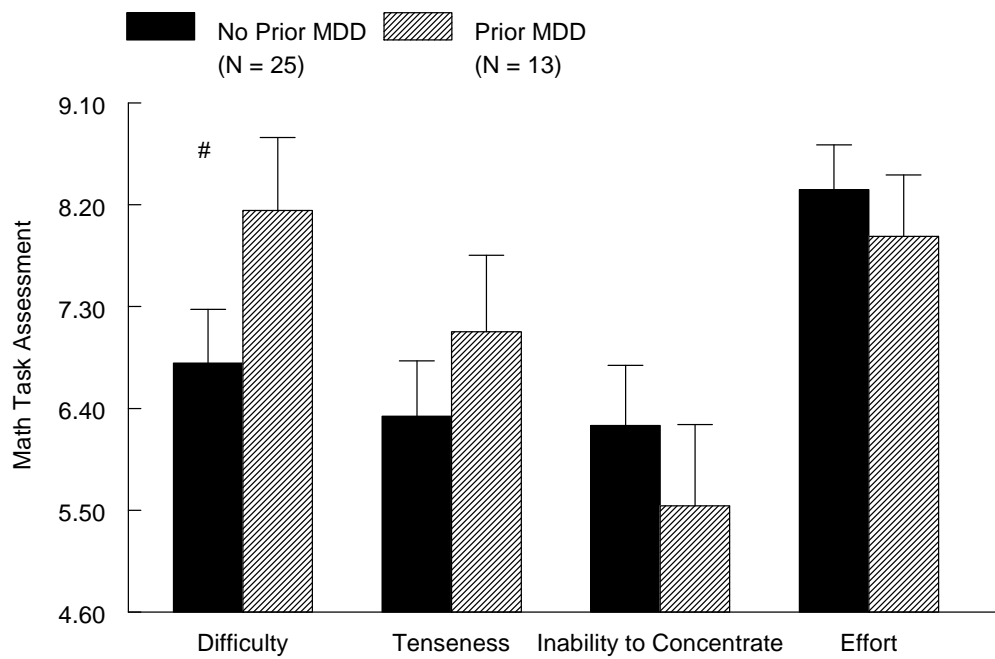


Figure 18: Math Task Assessments as a Function of Prior MDD Status



Relationship Between Hypothalamic Pituitary Adrenal Axis and Sympathetic Nervous System Factors and Pain Factors of Threshold, Tolerance, Intensity, and

Unpleasantness:

As a Function of PMDD Status:

For PMDD women, although no measures of pain sensitivity were associated with baseline cortisol in PMDD women ($p > .15$) (see Table 6), the higher baseline β -endorphin group showed trends for decreased cold pressor ($F(1, 15) = 3.3, p = .09$) pain sensitivity than the lower baseline β -endorphin group. However, a Group x Period interaction was observed ($F(1, 14) = 3.0, p = .10$), and simple effects analyses conducted separately by Period revealed that the difference in the cold pressor pain sensitivity based on baseline β -endorphin group status was only present at pain tolerance ($p = .08$) (see Figure 19). Additionally, the lower baseline β -endorphin group reported somewhat greater cold pressor intensity than the higher baseline β -endorphin group ($F(1, 16) = 2.4, p = .14$) (see Figure 20). Furthermore, the higher baseline β -endorphin group showed trends for decreased tourniquet ischemic pain sensitivity ($F(1, 14) = 2.8, p = .12$), and this difference was an overall effect of threshold and tolerance.

Table 6. Relationship Between HPA-axis and SNS Factors and Mean (+SEM) Cold Pressor and Tourniquet Ischemic Pain Threshold, Tolerance, Intensity, and Unpleasantness in PMDD Women

	Baseline Cortisol		Baseline β -endorphin		Baseline SBP		Speech SBP	
	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher
Cold Pressor Threshold	13.9 (2.6)	13 (2.7)	11.2 (2.5)	16 (2.6)	11.5 (2.7)	15.2 (2.5)	13.9 (2.7)	13.1 (2.6)
Cold Pressor Tolerance	35.1 (6.0)	29.2 (6.4)	# 25.3 (5.5)	40.3 (5.8)	27.1 (6.2)	37 (5.8)	31.5 (6.4)	31.1 (6.1)
Cold Pressor Intensity	50.9 (6.6)	46.3 (7.0)	+ 55.3 (6.2)	41.3 (6.6)	50.6 (7.0)	47.0 (6.6)	48.1 (7.1)	49.2 (6.7)
Cold Pressor Unpleasantness	59.4 (6.3)	47.1 (6.7)	59.1 (6.3)	47.5 (6.7)	60.3 (6.7)	47.8 (6.3)	57.8 (6.9)	50 (6.5)
Tourniquet Threshold	148 (24.2)	218 (27.5)	+ 164 (28.3)	194 (28.3)	169 (28.7)	193 (28.7)	204 (27.3)	154 (27.3)
Tourniquet Tolerance	504 (125)	621 (142)	+ 412 (123)	698 (123)	+ 408 (123)	702 (123)	440 (128)	670 (128)
Tourniquet Intensity	33.7 (5.4)	35.0 (5.7)	33.7 (5.4)	35.0 (5.8)	39.4 (5.5)	29.8 (5.1)	37.5 (5.6)	31.4 (5.3)
Tourniquet Unpleasantness	37.2 (5.1)	48.1 (5.2)	38.3 (5.3)	46.9 (5.3)	47.5 (5.5)	37.8 (5.2)	49.4 (5.3)	36.1 (5.0)

Figure 19: Cold Pressor Pain Threshold and Tolerance as a Function of High vs. Low Baseline Beta-Endorphin in PMDD Women

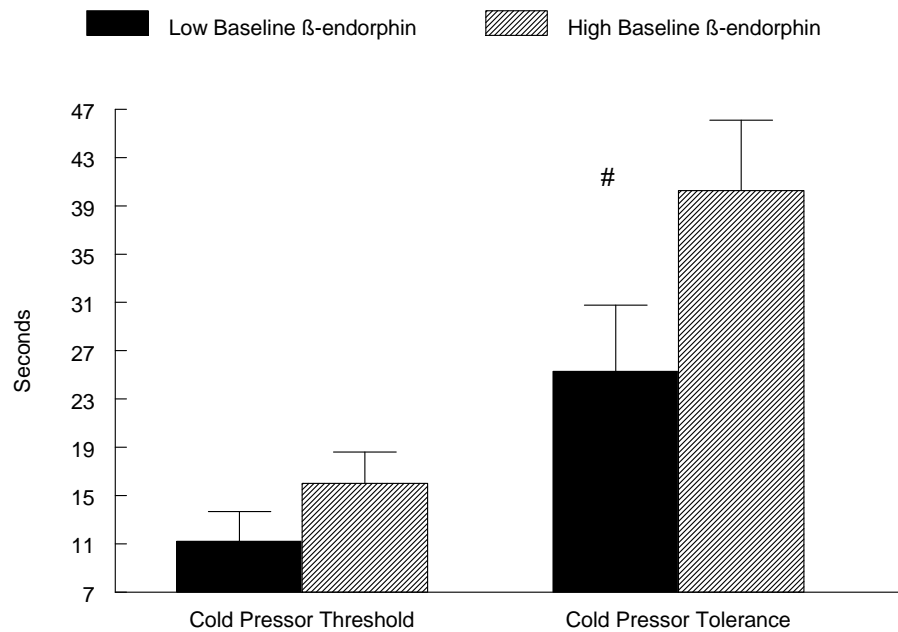
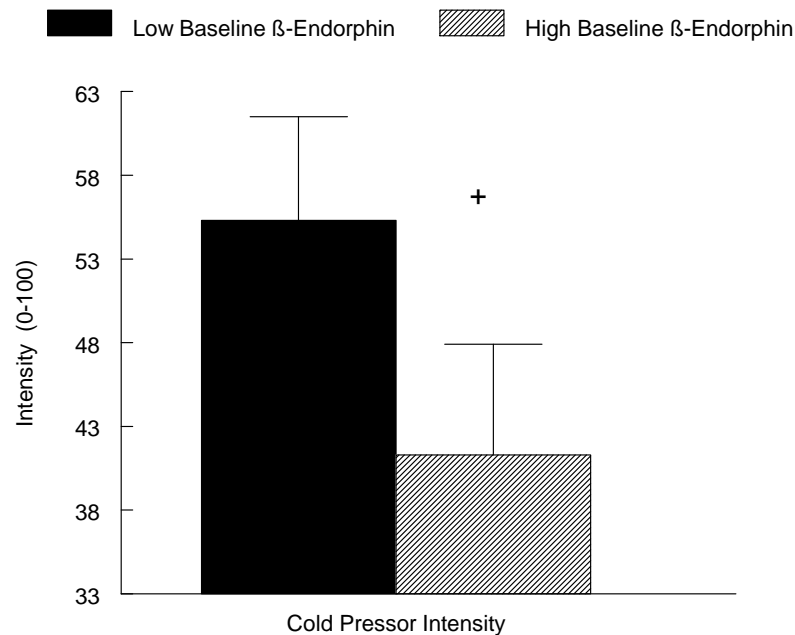


Figure 20: Cold Pressor Pain Intensity as a Function of High vs. Low Baseline Beta-Endorphin in PMDD Women



Also in PMDD women, the higher baseline SBP group was somewhat less sensitive to pain than the lower baseline SBP group ($F(1, 14) = 2.8, p = .12$) during the tourniquet ischemic task, although a weak trend for a Group x Period interaction ($F(1, 14) = 2.7, p = .13$) revealed that this difference was only evident at tourniquet ischemic tolerance ($p = .11$), while no SBP-status related differences were found at threshold. In addition, a trend for a Group x Period interaction was observed for speech stress SBP-status during the tourniquet ischemic task ($F(1, 14) = 2.8, p = .11$), since only at tolerance was there evidence that stress SBP status influenced pain sensitivity. However, neither baseline nor speech stress SBP-status was associated with cold pressor pain sensitivity nor any measure of pain intensity or unpleasantness ($ps > .15$) (see Table 6).

For non-PMDD women, the lower baseline cortisol group had reported somewhat greater cold pressor intensity ($F(1, 20) = 2.4, p = .13$) and marginally greater tourniquet ischemic unpleasantness ($F(1, 20) = 4.1, p = .06$) than the higher cortisol group. Cold pressor

and tourniquet ischemic threshold and tolerance did not differ based on baseline β -endorphin or cortisol group status, and no measure of pain sensitivity differed based on baseline β -endorphin group status (all p s > .05) (see Table 7).

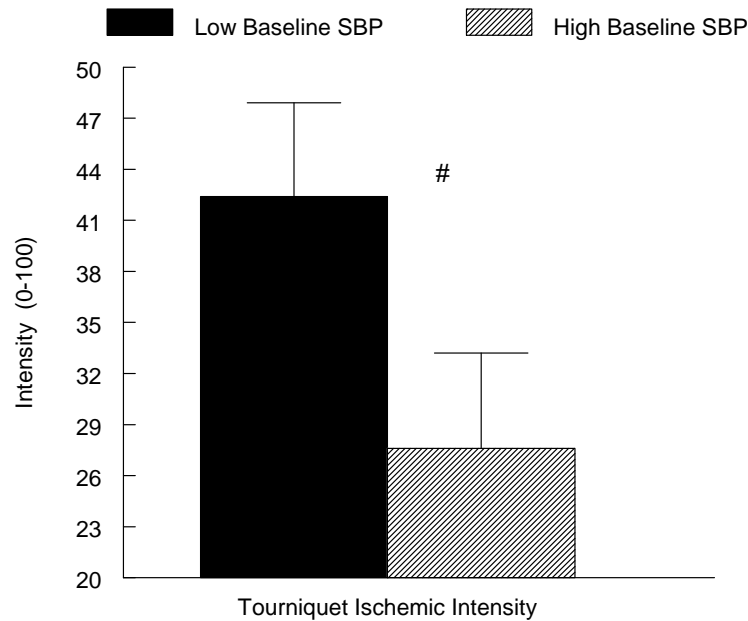
Table 7. Relationship Between HPA-axis and SNS Factors and Mean (+SEM) Cold Pressor and Tourniquet Ischemic Pain Threshold, Tolerance, Intensity, and Unpleasantness in non-PMDD Women

	Baseline Cortisol		Baseline β -endorphin		Baseline SBP		Speech SBP	
	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher
Cold Pressor Threshold	16.6 (4.8)	23.1 (4.8)	18.7 (4.9)	21 (4.9)	16.9 (5.5)	21.8 (4.5)	19.5 (5.0)	20.2 (5.0)
Cold Pressor Tolerance	88.2 (37.8)	125 (37.8)	90.2 (37.9)	123 (37.9)	* 44.5 (38.4)	148 (31.4)	+ 67.4 (36)	145 (36)
Cold Pressor Intensity	+ 52.9 (7.5)	36.0 (7.8)	43.5 (6.7)	43.5 (6.4)	# 53.5 (6.5)	37.8 (5.6)	48.4 (6.3)	40.3 (6.6)
Cold Pressor Unpleasantness	50.0 (6.1)	38.5 (6.4)	41.7 (8.2)	47.7 (7.9)	48.6 (8.7)	42.1 (7.5)	41.5 (7.9)	48.5 (8.2)
Tourniquet Threshold	303 (85.7)	268 (89.9)	279 (90.1)	293 (85.9)	175 (88.7)	370 (76.8)	229 (83.8)	349 (87.9)
Tourniquet Tolerance	541 (137)	686 (144)	497 (141)	713 (135)	510 (151)	686 (130)	‡ 370 (114)	875 (119)
Tourniquet Intensity	38.9 (5.6)	42.5 (5.9)	35.3 (5.6)	46.4 (5.3)	# 42.4 (5.5)	27.6 (4.8)	35.5 (5.5)	32.3 (5.8)
Tourniquet Unpleasantness	# 40.9 (5.0)	26.3 (5.2)	34.2 (5.8)	33.7 (5.5)	37.6 (6.1)	43.8 (5.3)	38.9 (5.5)	43.5 (5.8)

Also in non-PMDD women, the higher baseline SBP group had less cold pressor pain sensitivity than the lower baseline SBP group ($F(1, 18) = 3.5, p < .05$). However, a Group x Period interaction was present for cold pressor pain ($F(1, 14) = 4.1, p = .06$), with simple effect analyses conducted separately by Period indicating that this difference in cold pressor pain sensitivity based on baseline SBP group status was only present at pain tolerance ($p = .05$). The lower baseline SBP group also reported marginally greater cold pressor intensity ($F(1, 20) = 3.4, p = .08$) and greater tourniquet ischemic pain intensity ($F(1, 20) = 4.2, p = .06$) (see Figure 21) than the higher baseline SBP group. Finally, for non-PMDD women

baseline SBP-status was not associated with cold pressor pain threshold or tolerance ($p > .15$) (See Table 7).

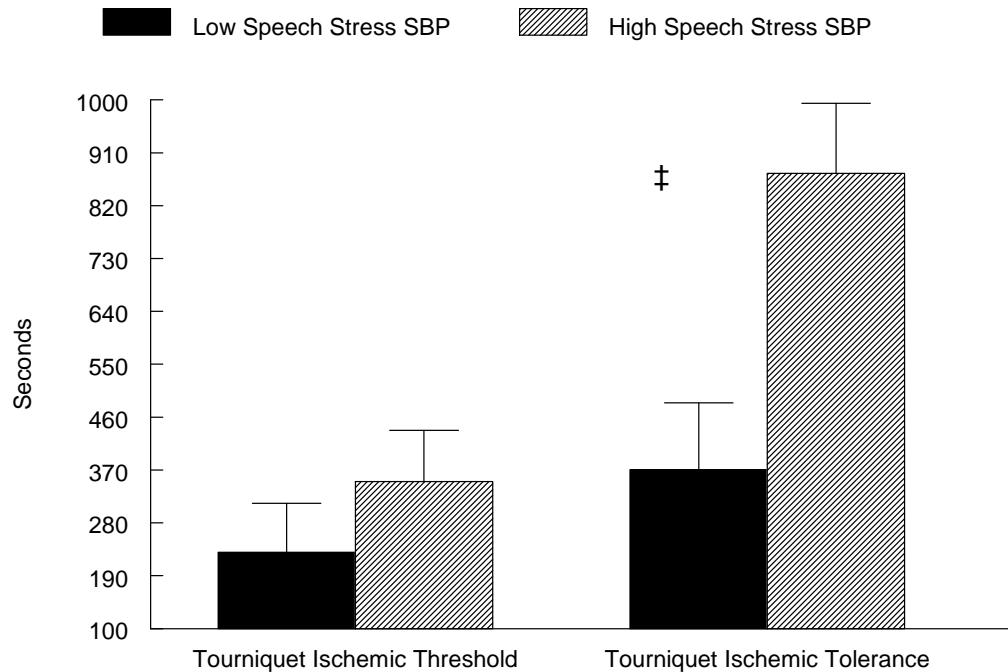
Figure 21: Tourniquet Ischemic Intensity as a Function of High vs. Low Baseline SBP in non-PMDD Women



Finally in non-PMDD women, a weak trend for a Group x Period interaction ($F(1, 18) = 2.5, p = .13$) revealed that the higher speech stress SBP group had somewhat less sensitive to cold pressor pain than the lower speech stress SBP group, although only at cold pressor tolerance ($p = .14$). As seen in Figure 22, the higher speech stress SBP group was less sensitive to tourniquet ischemic pain than the lower speech stress SBP group ($F(1, 19) = 5.9, p < .05$), although a Group x Period interaction ($F(1, 19) = 8.4, p < .01$) revealed that this difference was only present at tolerance ($p < .01$). No measure of pain intensity or unpleasantness was associated with speech SBP-status ($p > .15$) (see Table 7).

In summary, PMDD women showed more robust relationships involving greater β -endorphin levels and decreased pain sensitivity, while for non-PMDD women, greater BP and cortisol were associated with decreased pain sensitivity.

Figure 22: Tourniquet Ischemic Pain Threshold and Tolerance as a Function of High vs. Low Stress SBP in non-PMDD Women



As a Function of Prior MDD Status:

In women with prior MDD, no measures of pain sensitivity differed by baseline cortisol group status (all p s > .05) (see Table 8). However the higher baseline β -endorphin group was somewhat less sensitive to cold pressor pain than the lower baseline β -endorphin group ($F(1, 11) = 2.4$, $p = .14$), although a weak trend for a Group x Period interaction ($F(1, 11) = 2.7$, $p = .13$) indicated that this difference was only present at tolerance ($p = .14$). The higher baseline β -endorphin group also reported greater tourniquet ischemic pain unpleasantness than the lower baseline β -endorphin group ($F(1, 12) = 5.0$, $p < .05$).

Table 8. Relationship Between HPA-axis and SNS Factors and Mean (+SEM) Cold Pressor and Tourniquet Ischemic Pain Threshold, Tolerance, Intensity, and Unpleasantness in Women with Prior MDD

	Baseline Cortisol		Baseline β -endorphin		Baseline SBP		Speech SBP	
	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher
Cold Pressor Threshold	15.2 (4.9)	25.3 (5.3)	20.3 (5.3)	19.4 (5.7)	13.5 (5.1)	25.3 (4.7)	21.7 (5.7)	18.3 (5.3)
Cold Pressor Tolerance	145 (48)	97.5 (51.9)	+ 75.1 (44.1)	179 (47.6)	85.2 (50.6)	156 (46.8)	84.5 (50.5)	156 (46.8)
Cold Pressor Intensity	40.4 (5.8)	45.8 (6.3)	41.9 (5.9)	44.2 (6.3)	+ 50.0 (5.7)	36.9 (5.2)	42.5 (6.4)	43.3 (5.9)
Cold Pressor Unpleasantness	54.3 (7.4)	45.0 (8.0)	53.6 (7.4)	45.8 (8.0)	# 60.0 (7.1)	41.4 (6.6)	# 60.0 (7.1)	41.4 (6.6)
Tourniquet Threshold	137 (31.8)	204 (34.4)	116 (25.8)	229 (27.8)	* 123 (32.6)	206 (30.2)	157 (37.1)	178 (34.4)
Tourniquet Tolerance	591 (131)	746 (142)	577 (130)	763 (140)	* 472 (123)	826 (113)	# 484 (126)	816 (117)
Tourniquet Intensity	29.7 (4.2)	31.3 (4.6)	27.6 (4.0)	33.8 (4.4)	# 35.8 (4.0)	25.9 (3.7)	28.8 (4.5)	31.9 (4.5)
Tourniquet Unpleasantness	37.1 (7.2)	45.0 (7.8)	* 31.4 (6.2)	51.7 (6.7)	44.2 (7.9)	37.9 (7.3)	43.3 (7.9)	38.6 (7.4)

Also in women with a history of MDD, the lower baseline SBP group reported somewhat greater cold pressor intensity ($F(1, 12) = 2.9, p = .12$) and cold pressor unpleasantness ($F(1, 12) = 3.7, p = .08$) (see Figure 23) than the higher baseline SBP group. Also, the higher baseline SBP group had greater tourniquet ischemic threshold and tolerance ($F(1, 11) = 5.6, p < .05$) (see Figure 24), and lower tourniquet ischemic intensity ($F(1, 12) = 3.3, p = .10$), than the lower baseline SBP group. Furthermore, the lower speech stress SBP group reported marginally greater cold pressor unpleasantness than the higher speech stress SBP group ($F(1, 12) = 3.7, p = .08$), and the higher speech stress SBP group had somewhat lower tourniquet ischemic pain sensitivity than the lower speech stress SBP group ($F(1, 11) = 3.1, p = .11$). However, a Group x Period interaction ($F(1, 11) = 4.1, p = .07$) revealed that this latter difference based on speech stress SBP-status occurred only at tolerance ($p = .08$).

Figure 23: Cold Pressor Unpleasantness as a Function of High vs. Low Baseline SBP in Women With Prior MDD

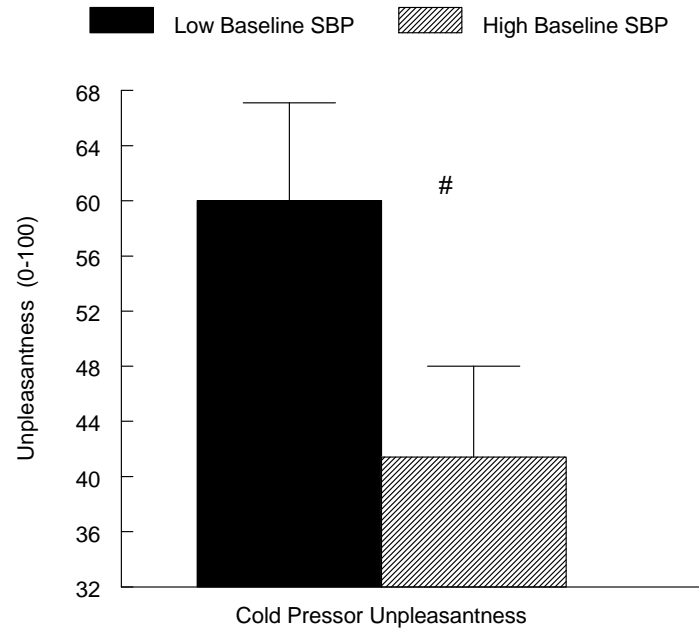
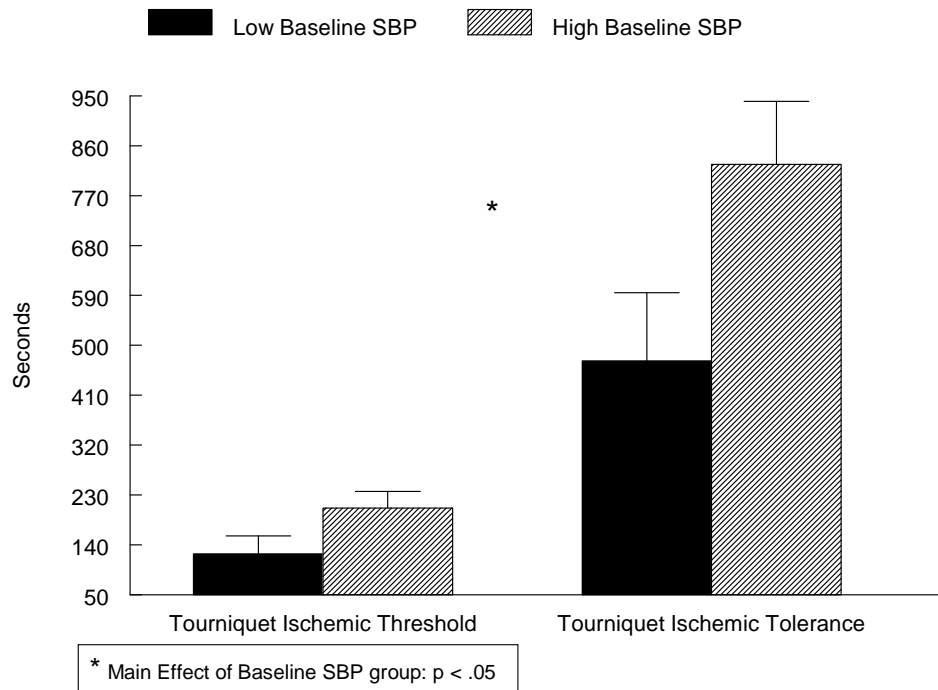


Figure 24: Tourniquet Ischemic Threshold and Tolerance as a Function of High vs. Low Baseline SBP in Women With Prior MDD



In women with no prior MDD, the lower cortisol group reported marginally greater cold pressor intensity ($F(1, 24) = 3.5$ $p = .07$) (see Figure 25), cold pressor unpleasantness ($F(1, 24) = 3.4$, $p = .08$), and tourniquet ischemic intensity ($F(1, 24) = 2.8$, $p = .11$) than the higher cortisol group, although no measure of pain sensitivity differed by β -endorphin or baseline SBP group status (all $ps > .05$) (see Table 9). Finally, the lower speech stress SBP group reported somewhat greater tourniquet ischemic intensity than the higher speech stress SBP group ($F(1, 24) = 2.4$, $p = .13$).

To summarize, women with prior MDD displayed stronger relationships between greater BP and decreased pain sensitivity, while women with no prior MDD showed a more consistent pattern of relationships between increased baseline cortisol and decreased pain intensity and unpleasantness than never depressed women.

Figure 25: Cold Pressor Intensity as a Function of High vs. Low Baseline Cortisol in Women With No Prior MDD

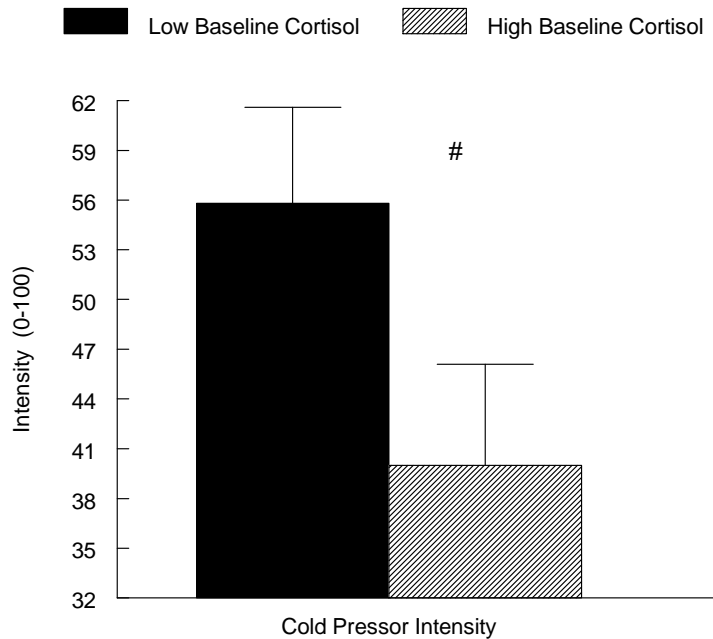


Table 9. Relationship Between HPA-axis and SNS Factors and Mean (+SEM) Cold Pressor and Tourniquet Ischemic Pain Threshold, Tolerance, Intensity, and Unpleasantness in Women with No Prior MDD

	Baseline Cortisol		Baseline β -endorphin		Baseline SBP		Speech SBP	
	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher
Cold Pressor Threshold	15.1 (3.5)	14.8 (3.5)	15.5 (3.4)	14.3 (3.7)	14.7 (3.7)	15.1 (3.4)	15.8 (3.9)	14.3 (3.3)
Cold Pressor Tolerance	54.4 (13.7)	32.6 (15.7)	47.2 (13.5)	39.2 (14.6)	52.5 (14.5)	36.0 (13.3)	40.4 (15.4)	45.8 (13)
Cold Pressor Intensity	# 55.8 (5.8)	40.0 (6.1)	51.2 (6.2)	45.0 (6.5)	52.1 (6.4)	42.6 (6.2)	52.5 (6.7)	44.9 (6.0)
Cold Pressor Unpleasantness	# 56.7 (6.7)	39.8 (7.0)	47.2 (7.2)	49.2 (7.5)	49.9 (7.5)	46.5 (7.2)	48.1 (7.8)	48.2 (6.9)
Tourniquet Threshold	234 (45.7)	189 (49.6)	229 (47.8)	198 (47.8)	197 (47.8)	230.1 (47.8)	209 (50.1)	217 (46.1)
Tourniquet Tolerance	489.3 (125)	612 (136)	445 (128)	645 (128)	415 (126)	675.5 (126)	460 (135)	617 (125)
Tourniquet Intensity	+ 41.9 (5.1)	29.6 (5.3)	36.2 (5.4)	35.9 (5.6)	41.3 (5.4)	31.2 (5.2)	+ 42.5 (5.6)	30.9 (4.9)
Tourniquet Unpleasantness	39.5 (45)	45.0 (4.7)	39.1 (4.5)	45.4 (4.7)	41.1 (4.8)	43.1 (4.6)	41.2 (5.0)	42.9 (4.4)

Study Retention:

Demographic Variables as a Function of Dropout Status ('Completion' vs. 'Dropout') (N = 75):

As depicted in Table 10, multiple stepwise regression analyses revealed that the race classification of Minority ($R^2 = .06$), presence of a self-reported psychological history ($R^2 = .06$), greater self-reported alcohol consumption ($R^2 = .05$), and presenting as PMDD ($R^2 = .04$) were found to be significant predictors of voluntarily dropping out prior to completing the laboratory study protocol (Total Model $R^2 = .19$, $p < .05$) or being a 'dropout'.

Table 10. Predictors of Completion and Voluntary Dropout Status on the Basis of Multiple Regression Analyses

Predictor Variable	Voluntary Dropout Status (N = 75) Completers = 1 (N = 38) Dropouts = 0 (N = 37)	Completion Status (N = 122) Completers = 1 (N = 38) Non-Completers = 0 (N = 84)
BDI	--	$R^2 = .06$ $\beta = -.17$
Trait Anxiety	--	--
Age	--	--
Race Non-Hispanic Whites = 1 Minorities = 0	$R^2 = .06$ $\beta = .37$	$R^2 = .04$ $\beta = .21$
Psychological History Yes = 1; No = 0	$R^2 = .06$ $\beta = -.26$	$R^2 = .04$ $\beta = -.22$
Treatment History	--	--
Alcohol Consumption (Drinks per month)	$R^2 = .03$ $\beta = -.19$	--
PMDD Status PMDD = 1; Non-PMDD = 0	$R^2 = .04$ $\beta = -.21$	$R^2 = .02$ $\beta = -.17$
Total Model R^2	$R^2 = .19$ $F(4, 64) = 3.6$ $p < .05$	$R^2 = .15$ $F(4, 97) = 4.3$ $p < .01$

-- indicates that the predictor variable did not account for significant variance

Demographic Variables as a Function of Completion Status ('Completion' vs. 'Non-Completion') (N = 122):

Women who signed a consent form but did not complete the laboratory study protocol, irrespective of whether they voluntarily dropped out at any time prior to completion or if they were unable to complete the study due to forces outside of their control (i.e. presence of medical issues, had not completed at the time of data analysis, and ineligibility based on inclusion criteria or daily ratings) were given the title 'non-completers'. As seen in Table 10, multiple stepwise regression analyses revealed that a higher BDI score reflecting

greater depression ($R^2 = .06$), race classification of Minority ($R^2 = .04$), presence of a self-reported psychological history ($R^2 = .04$), and presenting as PMDD ($R^2 = .02$) were significant predictors of non-completion of the laboratory study protocol (Total Model $R^2 = .15$, $p < .01$) or being a 'non-completer'. Therefore, even in women who are free of current depressive illness, the factors of self-reported psychological history, as well as race and PMDD presentation, played a role in decreasing the likelihood of completing the 5-6 month study protocol.

CHAPTER 4

DISCUSSION

Summary of Findings in PMDD vs. Non-PMDD Women

The present investigation confirms previous literature on heightened laboratory-based pain sensitivity and reduced SNS stress reactivity in PMDD versus non-PMDD women, and also adds to the field of women's mood disorder research by being the first to examine the relationship between stress-responsive endogenous pain regulators and experimental pain sensitivity and stress responsivity in PMDD. Specifically, we observed decreased threshold and tolerance to the cold pressor task (i.e. greater pain sensitivity), and blunted SNS reactivity to psychosocial stress when compared to non-PMDD women. We also found PMDD-related differences in endogenous pain regulation, since non-PMDD women showed a more consistent relationship involving BP and pain sensitivity, while PMDD women showed a more robust relationship involving β -endorphin and pain sensitivity. In addition to blunted SNS reactivity patterns during mental stress, PMDD women also reported more difficulty, tension, and impairment in their ability to concentrate during the stressors than non-PMDD women. Thus, PMDD women displayed different physiological and cognitive responses to stress, enhanced pain sensitivity, and a different pattern of endogenous pain regulation than non-PMDD women.

Pain Sensitivity in PMDD vs. Non-PMDD Women

Although emotional symptoms are the key feature of the disorder, PMDD women report a variety of physical symptoms during the luteal phase of the menstrual cycle, playing a role in the impairment of social and occupational functioning [228]. For instance, 54% of prospectively confirmed PMDD women report moderate to severe somatic symptoms on at least 3 of 6 premenstrual days [31], while up to 82% of PMDD women experience some degree of physical discomfort premenstrually [231]. Further evidence for the significance of somatic symptoms in PMDD comes from SSRI clinical trials which consistently find that, in addition to improving mood, SSRIs reduce luteal phase pain symptoms relative to placebo in PMDD women [228], and that this reduction in pain symptoms contributes to overall efficacy of SSRIs in women with PMDD [69, 228, 281]. Reduction in somatic symptoms as a result of SSRI treatment may be due to a secondary effect of a reduction in mood disturbance allowing the perception of physical symptoms to seem less severe, to a primary effect of increasing serotonin levels, to a general effect of SSRIs on alleviating PMDD as a whole, a disorder that encompasses both mood and physical symptoms [228], or to changes in hormone-responsive peripheral tissue [66]. The study of experimental pain sensitivity in women with PMDD not only yields greater understanding of the biological underpinnings of the disorder, but also gives insight into the experience of painful somatic symptoms that comprises PMDD.

Such prior studies from our laboratory have shown that PMDD women exhibit shorter ischemic pain threshold and tolerance times in both the follicular [227] and luteal [182, 227] phases of the menstrual cycle than non-PMDD women, while others have shown that PMDD women endorse higher pressure pain intensity ratings regardless of menstrual cycle phase

[204, 205]. The present data support these previous findings for increased pain sensitivity in PMDD women, specifically to the cold pressor task. Since laboratory-based methods of assessing pain sensitivity are positively related to clinical pain in both healthy adults [214, 215] and chronic pain patients [216-218], and predict the onset of clinical pain in initially pain free women [282], and since physical, or somatic, symptoms contribute to overall dysfunction in PMDD women [228], one would anticipate heightened pain sensitivity in PMDD, as we observed in the present study.

As a caveat to our pain sensitivity findings, our task assessment results indicated that the greater pain sensitivity in PMDD women versus non-PMDD women may be related to group differences in the subjective experience, since PMDD women reported greater difficulty during the cold pressor task than non-PMDD women. Since PMDD is a disorder characterized by heightened mood symptoms during the luteal phase of the menstrual cycle when the laboratory study protocol took place, their subjective reports of greater difficulty to the pain task may simply be a reflection of this cyclic mood disorder, or may be secondary to their greater sensitivity to the cold pressor task.

Symptom Severity in PMDD vs. Non-PMDD Women

We observed that PMDD women reported greater symptom severity than non-PMDD women during the luteal phase of the menstrual cycle, which was expected based on our strict diagnostic criteria, and since PMDD is characterized by both somatic and dysphoric symptoms occurring in the luteal phase that relinquish at the start of menses. We did not, however, anticipate finding greater symptom severity in PMDD versus non-PMDD women during the follicular phase, even though this difference was less robust than during the luteal

phase. One potential explanation for this follicular phase difference in symptom severity may be the fact that PMDD women anecdotally report follicular phase guilt regarding their actions, behaviors, and mood during the symptomatic luteal phase [43]. The negative interpersonal interactions experienced during the luteal phase can carry over into the follicular phase when PMDD women must atone for their actions and repair relationships. Thus, these feelings of remorse and guilt may have influenced the follicular phase symptom ratings in our PMDD sample.

Another explanation for the greater follicular phase symptom severity in PMDD versus non-PMDD women may be that our PMDD sample had a greater proportion of women with an abuse history than non-PMDD women (53% vs. 43%). Although this difference was statistically non-significant due to specifically recruiting non-PMDD women with prior abuse, it may be clinically meaningful. Abuse has been robustly associated with women's mood disorders, including MDD [283], and anxiety disorders such as PTSD [284]. Thus, although no subject met criteria for a current Axis I disorder, residual symptoms associated with these disorders may have influenced symptom severity across the menstrual cycle. Consistent with this hypothesis is that PMDD women reported a high level of trait anxiety at enrollment, which took place in the follicular phase of the menstrual cycle, and therefore may have influenced the heightened follicular phase symptom ratings. Lastly, given the small sample size of our study, the greater percentage of PMDD women with abuse, although non-significant, may have carried more weight than in a larger sample.

Hypothalamic Pituitary Adrenal Axis and Sympathetic Nervous System Function in PMDD vs. Non-PMDD Women

In addition to greater symptom severity, PMS women also report higher rates of traumatic life stress and a greater impact of these stressful events relative to non-PMS women [78, 285-288]. Moreover, since stress can trigger or exacerbate PMDD [83], it is possible that long-term dysregulation in stress responsive systems associated with greater life stress contributes to this disorder [45, 51-55]. Therefore, another goal of the present investigation was to examine the major stress axes in PMDD versus non-PMDD women, specifically the HPA-axis and SNS. Although there were no diagnosis-related differences in baseline SNS or HPA-axis measures, we observed differences in SNS stress responsivity between PMDD and non-PMDD women. Specifically, PMDD women showed blunted HR, DBP, SBP, and NE response to speech stress compared to non-PMDD women, results that are in the expected direction based on the literature showing a downregulated SNS in PMDD [178].

Prior studies from our laboratory assessing SNS responses to stress in PMDD found no SNS differences at baseline, but blunted HR and DBP reactivity, as well as a trend toward reduced cardiac output and systolic BP reactivity to mental stress, in PMDD women relative to non-PMDD women [78]. In a separate cohort of women, our laboratory found lower stroke volume (i.e. the amount of blood ejected per cardiac cycle) both at baseline and in response to psychological stress in PMDD women versus non-PMDD women [227], and in a third cohort, never abused PMDD women had lower stress-induced SBP, DBP, and HR than never abused non-PMDD women [210]. Despite the consistent research showing a hypoactive SNS stress response in PMDD, it is still not clear why this dysregulation occurs.

However, the experience of severe and chronic stress in PMDD women may be a pertinent factor, particularly the perception of increased stressful events during the luteal phase of the cycle [79]. Some studies suggest that it is not the number of stressors that are greater in PMDD women, but that it is instead the perception of the impact [80], unpleasantness [289], and stressful nature [290] of the stressors that is greater during the luteal phase. Further studies have shown that the cognitive coping strategies are also impaired during the luteal phase in PMDD versus non-PMDD women [80]. Our own results showing increased perceived difficulty, tension, and impairment in concentration during mental stress in PMDD compared to non-PMDD women are consistent with this interpretation, since our laboratory protocol occurred in the luteal phase of the menstrual cycle. Therefore, further studies addressing perception, cognitive coping, and other psychosocial and stress-related factors are needed to explain the downregulation of the SNS stress response in PMDD women.

In addition to reflecting altered perceptions/appraisals in the luteal phase in PMDD women, our task assessment results may shed light on the blunted SNS response in PMDD women versus non-PMDD. As mentioned above, coping style may not only explain the blunted SNS responses to the speech stress task in PMDD, but also may be indicative of the reported negative subjective experience during the task in PMDD women. Passive emotional coping is usually induced by stressors that are perceived to be inescapable and uncontrollable, such as a speech task in the case of the present study, and cause an individual to detach from the environment by using “conservation-withdrawal” strategies. Such disengagement is associated with decreased SNS reactivity [291, 292]. In contrast, active emotional coping strategies are usually evoked by escapable, controllable stress and cause engagement with the environment, resulting in increased SNS reactivity to the stressor [291,

292]. Both animals and humans consistently display this pattern [293] in which passive coping involves immobility and quiescence, while active coping is behaviorally manifested in confrontation, fight, or escape [292]. The greater reports of task difficulty, tension, and inability to concentrate in PMDD women may reflect a passive coping response to the stressor.

Since PMDD women are consistently faced with the uncontrollable stress of premenstrual mood changes, they may be prone to passive emotional coping strategies that are the most adaptive to this inescapable time of the month. When PMDD women are confronted with a stressor they perceive to be inescapable and uncontrollable, such as the speech task, they may revert to familiar passive coping strategies, causing decreased sympathetic reactivity. Future studies assessing active versus passive coping styles or cognitive appraisals regarding stressors in PMDD versus non-PMDD women are warranted, as they may inform new strategies for cognitive behavioral therapy or other psychological intervention methods.

A further possibility for our findings of hypoactive SNS stress responses in PMDD, as well as for the use of passive coping strategies in this disorder, may involve downregulated β -adrenergic receptor activity. Studies have shown that passive coping leads to less β -adrenergic receptor activity on both the heart and the vasculature, while active coping leads to heightened β -adrenoceptor involvement [294]. Moreover, β -adrenergic receptors influence sympathetic responses to stress by mediating the ability of NE to increase cardiac activity [295]. Specifically, NE acts on β_1 -adrenergic receptors in the heart to increase myocardial contractility, causing increased HR and BP [94]. Therefore, since PMDD women showed blunted sympathetic activity to the speech stressor and may have

utilized passive emotional coping mechanisms during the stressor, and since decreased β -adrenergic activity is associated with both of these phenomena, it is possible that PMDD women may have decreased β -adrenergic receptor density. There have been only a small handful of studies assessing β -adrenergic receptor responsivity involvement in PMDD. In one study, heightened β_2 -adrenergic receptor density on platelets was found in PMDD versus non-PMDD women [296], while another found reduced myocardial and vascular β -adrenergic receptor responsivity in never-abused PMDD women relative to PMDD women with an abuse history. Thus, there may be distinct subgroups of PMDD women based on histories of abuse or other factors who show differential β -adrenergic receptor functioning, and thus contributing to the currently mixed literature in this area. Although our study did include PMDD women with abuse and MDD histories, our sample sizes were too small to test this hypothesis, and thus further study is necessary to truly determine β -adrenergic activity in PMDD women. These studies would have the potential to enlighten the mediating role of β -adrenergic receptor responsivity in the relationship between coping style and SNS reactivity, as well as inform pharmacological treatments specific to subgroups of PMDD women who may differ in β -adrenergic receptor activity.

Relationship Between Hypothalamic Pituitary Adrenal Axis and Sympathetic Nervous System Factors and Pain Factors of Threshold, Tolerance, Intensity, and Unpleasantness in PMDD vs. Non-PMDD Women

Although the relationship between pain sensitivity and SNS [233, 235-247] and HPA-axis factors [182, 233, 234, 243, 245, 249-252] has been robustly reported in the literature, most of this work has been done in men, and our study is the first to explore this association

in PMDD women. A consistent pattern emerged in PMDD women for high β -endorphin levels to be associated with increased cold pressor pain tolerance and decreased pain intensity ratings as well as increased tourniquet ischemic threshold and tolerance. For non-PMDD women, however, β -endorphin group status was not related to any measure of pain sensitivity.

The lack of the expected associations between baseline β -endorphin and decreased pain threshold and tolerance in non-PMDD women was unanticipated, since many prior studies have reported this relationship in healthy subjects [182, 233, 245, 249-252]. Our method of obtaining β -endorphin concentrations from plasma as opposed from the central nervous system can be ruled out as a potential explanation, since the relationship between plasma β -endorphin levels and analgesia has been shown to be mediated by peripheral opioid receptors in addition to centrally located receptors. Plasma β -endorphin binds to peripheral opioid receptors and directly decreases pain sensitivity by inhibiting the firing of peripheral somatosensory fibers that modulate nociception [297]. In patients with angina, Jarmukli et al. [298] administered ketoconazole, which stimulates the release of β -endorphin from the pituitary gland into the periphery, and found increased thresholds to heat pain compared to control conditions. Since β -endorphin cannot cross the blood brain barrier, this study indicates that this endogenous opioid does not need to be centrally active to exert analgesic-like effects [298, 299].

Our lack of findings regarding β -endorphin and pain sensitivity in non-PMDD women may instead have resulted from the absence of a stress sample of β -endorphin and our reliance instead on exclusively baseline samples. For example, previous studies showing relationships between β -endorphin and pain sensitivity in humans either administered

endogenous β -endorphin to participants [300, 301], or measured changes in β -endorphin response to a pain procedure [252, 302, 303], exercise test [304], or pharmacological manipulation [298]. Two studies did, however, administer a mental stress task and subsequently measure β -endorphin levels, but results were inconsistent and possibly reflected incorrect timing of the stress sample [305, 306]. Specifically, Bragdon et al. [305] found the expected positive relationship between ischemic pain tolerance and stress β -endorphin levels, but a negative relationship between ischemic pain tolerance and β -endorphin reactivity from baseline to stress in pain free women. Sheps et al. [306] observed a positive relationship between thermal pain threshold and β -endorphin levels at stress, but not at baseline, in normotensives and hypertensives. Furthermore, although not tested in response to mental stress, Jarmukli et al. [298] reported no effect of basal β -endorphin levels on angina pain in patients with this heart condition. In fact, only two studies of which we are aware found a relationship between baseline levels of β -endorphin and pain sensitivity, one in PMDD and non-PMDD women [182], and the other in non-Hispanic Whites [249].

An additional possibility for the absence of a relationship involving β -endorphin and pain sensitivity is that our sample size may not have been large enough to detect such associations, since in general, results were in the expected direction in non-PMDD women (i.e. higher β -endorphin and lower pain sensitivity), and our sample was smaller than previous studies documenting relationships between β -endorphin and pain sensitivity [233, 234, 243, 249].

Although the expected β -endorphin/pain relationship was absent in non-PMDD women, they did, however, display a more consistent pattern of associations between high SBP and decreased pain sensitivity and reported pain intensity than PMDD women.

Increased BP coupled with decreased pain perception can still exist in the absence of the β -endorphin/pain relationship, since Breuhl et al. [307] reported that endogenous opioids did not mediate the relationship between greater baseline BP and decreased pain sensitivity in normotensives. In fact, in a later review, Breuhl and Chung [247] confirmed the lack of substantial evidence for the mediation of endogenous opioids such as β -endorphin in the BP/pain relationship in humans.

The relationship between high BP and reduced pain sensitivity, which is the most well-documented form of stress-induced analgesia (SIA) [233, 235-246], appears instead to be mediated by the activation of arterial baroreceptors [248]. The relationship between cardiovascular and pain regulatory systems is thought to be mediated by blood pressure-induced stimulation of mechanoreceptive afferents (i.e. baroreceptors), which are involved in maintaining cardiovascular homeostasis. Baroreceptors are located in the carotid sinus, aortic arch, and cardiopulmonary regions of the cardiovascular system, reflexively responding to increases in arterial pressure or blood volume increases and subsequently causing an increase in parasympathetic output (i.e. vasodilation and decreases in HR and cardiac output) via the vagus nerve, and subsequently decreases in BP [239, 254].

Stimulation of baroreceptors in animal models has been shown to diminish somatomotor reflexes indicative of analgesic-like effects [239, 254, 308] and in humans, natural increases in baroreceptor activity are associated with decreased pain sensitivity and clinical pain [239, 309-312]. In humans, studies have examined the relationship of pain sensitivity to natural variations in baroreceptor activation, such as being more active during systole (the active cardiac contraction phase) than during diastole (the passive cardiac filling phase) [313]. Breuhl et al. [247] describes the process by which baroreceptors mediate the

relationship between pain sensitivity and blood pressure, beginning with pain increasing sympathetic arousal through the somatosensory reflex. Next, increases in blood pressure occur, leading to heightened activation of baroreceptors, which stimulates descending pain inhibitory pathways and returns the body to homeostatic levels of arousal [247]. More specifically, Maixner et al. [239] reviewed the literature on the relationship between baroreceptors and pain sensitivity and determined that cardiopulmonary vagal afferent stimulation in response to baroreceptor activation impairs the ability of nociceptive dorsal horn neurons to respond to noxious stimuli, subsequently causing analgesia. In summary, there is robust evidence suggesting that baroreceptor mechanisms play a significant role in the relationship between BP and pain, which may explain the presence of the BP/pain relationship non-PMDD women.

In addition to BP, another biological factor that has been shown to be related to pain sensitivity is cortisol [243]. Individuals with low back pain, rheumatoid arthritis, chronic pelvic pain, fibromyalgia, headaches, persistent sciatic pain and other pain conditions have been shown to display decreased adrenocortical activity [243]. Moreover, previous research from our laboratory reported associations between greater cortisol responses to mental stress and greater pain tolerance in nonsmokers [233] and in Caucasians [234], and Al'absi et al. [243] found that baseline salivary cortisol predicted lower self-reported pain during and after the cold pressor task in men, but not in women. Furthermore, cortisol has been implicated as a partial mediator of SIA [233, 234, 243, 249]. Thus, the relationship between increased cortisol and decreased pain intensity and unpleasantness found only in non-PMDD women in our study supports previous research, and also distinguishes adrenocortical activity on the basis of PMDD status. In summary, PMDD women failed to display the expected

associations between decreased pain sensitivity and increased BP and cortisol that were observed in non-PMDD women. This finding in combination with increased pain sensitivity and blunted SNS responses to stress compared to non-PMDD women suggest stress- and pain-related dysfunction that may contribute to the etiology of PMDD.

Summary of Findings in Prior MDD vs. No Prior MDD

The present investigation also supports the existing literature suggesting decreased laboratory-based pain sensitivity and hyperactive SNS and HPA-axis functioning in euthymic women with a history of MDD. Our study is the first, however, to include women with prior MDD who were currently free of medications, including antidepressants, and who had been in extended remission from their depressive episodes (mean = 88 months). We found that women who had been free of MDD for, on average, over seven years, showed persistent biological disturbances beyond the remission of the depressive episode, reflected in increased cold pressor tolerance (i.e. decreased pain sensitivity), increased premenstrual mood symptoms, and greater DBP responsivity to stress than never depressed women. Moreover, our study was the first to investigate the association between pain sensitivity and stress-responsive pain regulatory mechanisms in women with and without prior MDD. We observed that women with prior MDD displayed more consistent relationships between greater BP and decreased pain sensitivity than women with no prior MDD, a group who showed a more consistent pattern of relationships between increased baseline cortisol and decreased pain intensity and unpleasantness than never depressed women. These results reveal persistent dysfunction in pain mechanisms and stress reactivity, as well as an enhanced relationship between BP and pain, in euthymic women with a history of MDD.

Pain Sensitivity in Prior MDD vs. No Prior MDD

Our pain sensitivity results comparing women with and without prior MDD status were consistent with prior literature finding lower pain sensitivity in women with both current [221-225] and prior MDD [27, 28] compared to controls. Decreased pain sensitivity in both MDD and prior MDD is clinically significant, since a positive correlation between clinical pain intensity and the severity of MDD has been reported [213]. Somatic symptoms such as headache, fatigue, and back pain are core components of MDD, since approximately two-thirds of those with DEP first present to their doctors about physical, not emotional symptoms [230]. Additionally, data from the World Health Organization was used to assess somatic symptoms in 15 countries on 5 continents, and revealed that the overall prevalence of depressed individuals reporting only somatic symptoms as the reason for visiting their physician was 69% [230].

The importance of somatic symptoms and DEP is also supported by the finding that as DEP remits with the use of SSRIs, the severity of physical symptoms also decreases [314]. Data also suggests that somatic painful symptoms that remain after successful treatment predicts future relapse [315]. This phenomenon may occur independently of the positive effects on mood, since the analgesic effects of antidepressants have been shown to present prior to any changes in the depressed mood state, and at lower starting doses than those necessary to bring about a therapeutic effect on DEP [316]. SSRIs may also have positive effects on impaired descending inhibition found in DEP, since they increase serotonin, and in some cases, NE, neurotransmitters that aid in sending descending peripheral messages that inhibit ascending pain signals [317]. Furthermore, and most relevant to the present study, Bromberger et al. [256] found that currently euthymic women with prior DEP were more

susceptible to reporting high body pain (e.g. headaches, backaches) than women without prior DEP, despite being free of DEP for, on average, more than 14 years. These findings reveal that clinical pain in women persists beyond the remission of the depressive episode.

Only a handful of studies have explored experimental pain sensitivity in DEP. Lautenbacher et al. [224] showed support for reduced experimental pain sensitivity in MDD, but only for certain pain modalities. They observed increased pressure pain sensitivity, but no difference in ischemic or heat pain sensitivity, in MDD versus controls. In a similar fashion, Bar et al. [222] also show that decreased pain sensitivity depends on pain modality. That study compared patients with MDD and controls on heat, electrical and ischemic pain sensitivity, finding increased pain threshold and tolerance to electrical and heat pain, but decreased threshold and tolerance to ischemic pain in MDD. These studies provide support for our lack of diagnosis-related differences in tourniquet ischemic pain sensitivity in both prior MDD and PMDD women, and also for our observations of decreased cold pressor pain sensitivity in women with prior MDD.

A systematic review and meta-analysis examined the effect of current DEP on experimental pain perception, concluding that pain threshold was higher (i.e. less sensitive) in depressed individuals than healthy controls [219]. However, only 2 of the 6 studies in the meta-analysis assessed pain tolerance, which may be especially relevant for mood disorders. Pain tolerance reflects the affective experience of pain, while pain threshold reflects the sensory experience [220], and this may explain the diagnosis-related differences in pain sensitivity that we observed only at cold pressor tolerance.

Since PMDD and MDD are both depressive disorders characterized primarily by emotional symptoms, it follows that women with these disorders would differ on the

affective aspects of pain perception (i.e. tolerance). Studies have shown that DEP is not associated with a deficit in perceptual processing of pain, and thus would not differentiate women with or without the disorder on the basis of their sensory pain perception (i.e. threshold). For instance, Lautenbacher et al. [221] showed that subjects with current DEP had increased heat pain thresholds compared to controls, regardless of whether or not subjects were required to rely on perceptual processing speed, and depressed subjects and controls did not differ on skin sensitivity to non-noxious warmth, cold, and vibration stimuli [221]. Furthermore, Giesecke et al. [226] assessed neural activation to pressure pain sensitivity using fMRI in fibromyalgia patients with or without MDD. Self-reported depressive symptoms and diagnosis of MDD were not correlated with pain-evoked neuronal activation in brain areas associated with the sensory-discriminative aspects of pain, but were associated with neuronal activations in brain regions associated with the motivational-affective dimension of pain. Therefore, women with the depressive disorders of PMDD and MDD only differed from their respective control groups in pain tolerance, and not threshold, possibly due to specific deficits in the affective/motivational aspect of pain.

Despite the fact that the majority of existing research on experimental pain sensitivity and mood disorders have been performed in patients with current mood disorders, studies assessing laboratory-based pain in prior MDD are also present. For instance, Bar et al. [27] assessed thermal pain sensitivity in women who were in full clinical recovery from MDD and found significantly increased pain threshold and tolerance in women with prior MDD compared to controls. Additionally, a recent study from our laboratory showed that women with prior mood disorders were less sensitive to ischemic pain than women with no prior mood disorders [28].

Several hypotheses have been proposed to explain the reduced experimental pain sensitivity in MDD, such as the presence of a more stoic behavior or affective indifference in DEP [318], a true sensory deficit in psychiatric affective illness [319, 320], increased somatosensory perception thresholds in DEP [321], impaired descending inhibition [317], and increased prefrontal and lateral thalamic activation [322]. The latter was proposed by Bar et al. [322], who studied cerebral responses to thermal pain perception in women with acute MDD using fMRI. The study showed that women with MDD had higher thermal pain thresholds than healthy controls, which may be related to the additional finding that women with MDD had increased activation in the lateral prefrontal cortices (PFC) and lateral thalamus during pain perception compared to controls. The lateral PFCs control the continuous monitoring of the external environment, processing aspects of working memory, cognitive control, and are important in modulating pain processes, while the lateral thalamus regulates sensory discriminative processing of painful stimuli [322]. Activation in the lateral PFCs and the thalamus during and after painful stimuli has been repeatedly described in the literature, and Bar et al. [322] suggest a strong relationship between hyperactivity in these regions and decreased sensitivity to experimental pain in DEP.

Given the well documented evidence that women have increased clinical pain [323] and also show decreased experimental pain tolerance [324, 325], it may seem paradoxical that women with DEP, who also have increased clinical pain [256], show increased experimental pain tolerance (i.e. reduced pain sensitivity). Lautenbacher and Krieg [326] have addressed this paradox of increased clinical pain complaints and reduced experimental pain sensitivity in DEP, hypothesizing that diminished processing of painful stimuli could be responsible for both phenomena. The authors argue that reduced processing of nociceptive

stimuli at both spinal and subcortical stages may cause hypoalgesia to phasic experimental pain, and at the same time cause hyperalgesia to endogenous clinical pain due to deficient activation of inhibitory systems. This theory is supported by Bar et al. [222] who found increased pain sensitivity to ischemic pain (deep somatic pain), but decreased pain sensitivity to heat and electric pain (phasic surface pain) in patients with MDD compared to controls. Although Lautenbacher et al. [224] failed to find a significant correlation between clinical pain complaints and pain threshold in depressed patients, this does not rule out the possibility that alterations in central and peripheral pain processing contribute to both phenomena. Thus, our results indicating that women with a history of MDD continue to display dysfunctions in pain regulation, specifically during cold pressor tolerance, are consistent with the vast majority of the literature on experimental pain sensitivity in MDD and may, in fact, coincide with the increased clinical pain observed in the disorder.

Symptom Severity in Prior MDD vs. No Prior MDD

Further evidence for continued dysfunction beyond the remission of MDD exists in our findings for heightened reported symptom severity in women with prior MDD. Although these women with prior MDD were not currently suffering from a depressive episode, this symptom perseverance may be indicative of the risk for development of a future MDD episode, since it has been shown that over 75% of MDD sufferers will battle with recurrences of the disorder at some point in their lifetime [10]. Approximately 54% of women in our study had experienced MDD two or more times in the past, and since studies show that after an individual experiences a second major depressive episode, the risk of a third becomes 70% within three years [18], there is a high probability of recurrence of the disorder. Thus,

the current findings, along with previous data from our laboratory [unpublished] showing that women with prior DEP experience elevated daily somatic symptoms than never depressed women, may predict a high rate of recurrence of the disorder.

Not only may enduring symptom severity predict future major depressive episodes, but persistent disturbance in endogenous stress [20-26] and pain [27, 28]-related factors may also be predictive of relapse. Banki and colleagues [165] showed that patients who relapsed within six months of antidepressant treatment had higher CRH levels during remission than those who remained asymptomatic. Additionally, persistent DEX/CRH non-suppression of cortisol, indicative of an upregulated HPA-axis and dysregulation in negative feedback mechanisms, has been shown to be predictive of MDD relapse, as discussed above [134, 174, 176, 177]. Finally, a recent animal study shows that HPA-axis dysregulation may be related not only to the likelihood of DEP relapse, but also to the persistency of the depressed state [327]. Mizoguchi et al. [327] exposed rats to a chronic stressor, which is known to induce behavioral depression, followed by a three month rest period, and found that the behaviorally depressed state assessed via rotarod test persisted even after the extensive rest period, coupled with persistent HPA-axis dysregulation via DEX non-suppression. These studies show that sustained HPA-axis hyperactivity during symptom remission in those with prior DEP may be indicative of a subsequent episode of DEP [165, 173], and that CRH hypersecretion may be a stable or “trait” indicator of vulnerability to DEP [131]. While we did not find evidence for sustained HPA-axis hyperactivity in prior MDD, possibly due to our sample size limitations, we did find evidence for sustained SNS upregulation in prior MDD, specifically increased DBP responses to speech stress when compared to women with no prior MDD. Alterations in underlying pain pathways, whether manifested as increased

clinical pain or decreased experimental pain sensitivity, may be the common denominator resulting from persistent disturbance in stress-responsive pain regulatory mechanisms, such as heightened SNS activation [233, 235-246], that are also known to affect mood states.

Sustained clinical pain has also been shown to predict depression outcomes has also been observed in the literature [328]. For instance, Von Korff et al. [329] assessed the severity of physical disease in patients with MDD at baseline and at 6- and 12-month follow-ups and found that patients who showed mean improvement in their depressive symptoms had decreased physical disease severity at baseline than those patients whose depression symptoms did not improve. Additionally, a review by Von Korff and Simon [330] observed that pain-related functional impairment and number of days in pain predicted greater severity of depressive disorders. Our findings of persistent dysregulation in pain sensitivity to cold pressor pain in women with prior MDD may be predictive of future depressive episodes. A replication of the current study including longitudinal data on relapse rate would allow future studies to determine the predictive nature of persistent symptoms, stress-response dysregulation, and pain, on future episodes of MDD.

Role of Endogenous Steroid Hormones in Current and Prior MDD

Our results indicating that women with prior MDD reported more severe depression, impairment, anger/irritability, and anxiety than women with no history of MDD only in the luteal phase of the menstrual cycle might lead one to speculate that greater luteal phase symptoms in women with prior MDD may be due to a disproportionately high percentage of PMDD women compared to non-PMDD in this group. However, our data shows that the percentage of women diagnosed as PMDD did not differ between women with or without

prior MDD (46% vs. 44%), and suggest an alternative explanation. Therefore, these results may be better explained by previous data showing that an estimated 64% of women with current MDD experience premenstrual exacerbation of their depressive symptoms [331], and studies showing that women demonstrate increased rates of DEP and suicide attempts premenstrually [54, 331, 332]. Furthermore, despite remission due to effective treatment, DEP may recur only during the luteal phase [61]. Thus, our findings may support the notion that premenstrual magnification of mood symptoms may remain beyond the remission of the depressive episode.

The exclusively premenstrual presence of symptoms in women with a history of MDD may also reflect the pathophysiological link between female gonadal hormones and depressive disorders. MDD is the leading cause of disease-related disability in women, affecting approximately 21.3% of females, while only 12.7% of males [12]. However, some estimates of the gap between the genders are even greater, finding prevalence rates in women to be 1.5 - 3 times greater than men [17]. Endocrine control of the reproductive system and hormonal fluctuations throughout the menstrual cycle play key roles in the development of certain mood disturbances in women and therefore contribute to this gender gap. Although the explanatory abilities of sex hormones are not sufficient to explain gender differences in the prevalence of MDD since the pathogenic mechanism of action is not well understood [16], the importance of gonadal hormones in women's mood disorders may provide a partial explanation for the increase in luteal phase mood symptoms in our prior MDD women.

Distinct time periods in the female life cycle when hormonal changes arise, such as during the menstrual cycle, after the birth of a child, and during the menopausal transition, are associated with increased vulnerability to dysphoric states [1, 3, 4]. Mood disturbances

associated with these hormonal changes such as PMS, PMDD, postpartum depression, and perimenopausal depression, all require the female brain to adapt to fluctuating hormones or to a new baseline hormone level. If the brain does not properly respond and adjust its function accordingly, this may lead to the development of mood disorders such as MDD [333]. For example, women are more likely to develop MDD, including new onset MDD, in the menopausal transition period than when premenopausal [334, 335], and this MDD risk is no longer present in the postmenopausal stage [336]. Therefore, it may not be the absolute levels of gonadal hormones, but the premenstrual change in the levels of these hormones that contribute to the increase in mood symptoms observed exclusively during the luteal phase.

Support for this comes from research suggesting that aberrant reactions to normal fluctuations in hormone levels throughout the menstrual cycle may be a cause of PMDD [66, 71] and that PMDD women may be more sensitive to the mood modulatory effects of gonadal hormones [72]. For example, using a GnRH agonist to suppress ovarian function, Schmidt et al. [71] showed that within the context of ovarian suppression [and symptom elimination] in PMDD women, the addition of either progesterone or estradiol precipitates (within 1-2 weeks) the return of symptoms comparable in severity to those seen at baseline. Moreover, that study [71] also showed that the same manipulation was without effect in women without PMDD, demonstrating for the first time a differential sensitivity to gonadal steroid hormones in PMDD. The importance of changes in gonadal steroids in PMDD was suggested by an early observational study of Halbreich et al. [337], who found that the strongest predictor of premenstrual symptom severity in PMDD women was the rate of change in luteal phase progesterone and estradiol following peak levels, and not the absolute hormone levels per se. This observation provides further evidence that the dysphoric mood

states in women with PMDD are consequent to changes in normal ovarian steroid hormone concentrations across the menstrual cycle, similar to pathophysiological mechanisms postulated for the induction of postpartum depression [338, 339].

Further evidence implicating changes in hormone levels in the onset of DEP comes from a study assessing the effect of hormone manipulations in currently euthymic women with and without a history of postpartum depression, Bloch et al. [339] administered GnRH agonist leuprolide acetate in order to produce a hypogonadal state, added back high doses of estradiol and progesterone to mimic pregnancy, and then withdrew both steroids in order to induce a simulated post-partum period. The study observed that only women with a history of postpartum depression reported increased mood symptoms during hormone add-back and withdrawal, indicating that women with a history of postpartum depression have a differential response to changes in gonadal steroids than women with no history of postpartum depression. The results of these studies [71, 337, 339] indicate that not only may women with PMDD be more sensitive to fluctuations in gonadal steroid levels, but a history of DEP may confer a heightened state of vulnerability in certain subgroups of PMDD women.

Further studies that may explain the exclusively premenstrual increase in mood symptoms in our sample of women with prior MDD are those showing a higher likelihood for women to develop depressive symptoms during perimenopause than when premenopausal [334, 340]. Freeman et al. [334] followed premenopausal women with no histories of DEP throughout the transition to menopause, and found that the variability and not the absolute levels of hormones during perimenopause mediated increased depressive symptoms as well as MDD. Thus, it is not surprising that women who are free of current depressive illness, but

who have a history of MDD, continue to experience symptoms associated with their former depressive state in accordance with hormone fluctuations during the menstrual cycle.

Hypothalamic Pituitary Adrenal Axis and Sympathetic Nervous System Function in

Prior MDD vs. No Prior MDD

Although we observed no diagnosis-related differences in HPA-axis factors at baseline, women with prior MDD showed somewhat greater increases in DBP from baseline to speech stress than women with no history of MDD. The latter supports previous research for an upregulated SNS stress-response in current MDD patients [117, 120, 121], and those displaying current depressive symptoms [104, 157]. For example, Lechin et al. [117] found increased NE at baseline, as well as heightened NE and HR in response to orthostatic and exercise stress in patients with MDD compared to control subjects, and Udupa and colleagues [119] reported increased SNS activity in MDD patients, reflected in baseline systolic BP and measures of HRV. Additionally, a recent animal study found SNS upregulation in rats during a chronic stress-induced depressive state, finding heightened resting HR and MAP, and reduced HRV compared to non-depressed rats [248].

Even elevated depressive symptoms in the absence of clinical DEP are associated with increased 24 hour urinary NE and HR in daily life [156], as well as increased BP, HR, CO, and NE in response to a speech stressor [157], and heightened systolic BP in response to an exercise challenge [104]. A study by Hamer and colleagues [121] supports the positive relationship between DEP and SNS factors, finding that subjects with high depression scores displayed greater HR and 3-methoxy-phenylglycol (the major metabolite of NE) reactivity to

anger and depression-inducing speech stressors than those low on the depression scale, although these measures did not differ at baseline.

Although previous studies have observed a hyperactive SNS in patients in remission from MDD at baseline [23, 24], ours is the first study, to our knowledge, to assess stress-induced SNS factors in euthymic women not taking antidepressant medications. Although our results for a hyperactive SNS in women with prior MDD were not as robust as the literature in current MDD [117, 120, 121], we were able to extend and support previous research suggesting that the upregulation in BP stress reactivity persists beyond the remission of the depressive episode [23].

Relationship Between Hypothalamic Pituitary Adrenal Axis and Sympathetic Nervous System Factors and Pain Factors of Threshold, Tolerance, Intensity, and Unpleasantness in Prior MDD vs. No Prior MDD

The BP/pain relationship was also present in women with a history of MDD, since the high SBP groups had consistently decreased pain sensitivity and subjective pain ratings than the low SBP groups, while women with no history of MDD failed to show any consistent relationship involving BP and pain. Although these results in women with no prior MDD were unanticipated due to robust literature reporting the positive association between BP and pain, [233, 235-247], the majority of the work was conducted in men or mixed gender samples without separate analyses in women.

Moreover, a recent study that suggests distinct biological underpinnings of the relationship between BP and pain sensitivity in MDD versus non-depressed individuals that may shed light on the observations of the present investigation [255]. Frew and Drummond

[255] assessed cold pressor pain tolerance, intensity, and unpleasantness ratings both before and after administration of the opioid antagonist naltrexone or placebo in subjects with and without current MDD. They discovered that in non-depressed controls, the BP/pain relationship was present in the placebo group, but not in the naltrexone group, indicating that endogenous opioids are necessary to maintain the association between BP and pain in controls. In contrast, in MDD patients, the BP/pain relationship existed in the naltrexone group, but not in the placebo group, indicating that endogenous opioids may block the association between BP and pain in MDD [255]. This study shows that the biological mechanisms underlying the association between high BP and reduced sensitivity to acute pain may differ between those with and without MDD. Furthermore, since our cohort failed to show greater β -endorphin levels in MDD that have previously been supported [101, 104], levels that have been shown to block the BP/pain relationship, it is possible that in our sample of women with prior MDD, the lack of heightened β -endorphin typically found in other MDD samples resulted in the emergence of this relationship between BP and pain in the present study (i.e. a functional blockade of opioid tone associated with lower levels).

Another potential explanation for stronger and more consistent relationships between heightened SBP and decreased pain sensitivity and perception in women with prior MDD compared to never depressed women may involve upregulated baroreceptor mechanisms. Evidence for enhanced baroreceptor stimulation in prior MDD comes from our findings for hyperactive BP responses to stress coupled with decreased sensitivity to pain in this population. Since individuals with remitted MDD show persistently heightened levels of perceived daily stress [81], as well as persistent SNS reactivity to stress as seen in our study, baroreceptor mechanisms must be consistently stimulated in order to activate homeostatic BP

control mechanisms, subsequently causing an enhancement of the BP/pain sensitivity relationship over time.

Heightened baroreceptor stimulation causing a stronger link between stress responses and pain may be advantageous in the sense of allowing heightened SNS reactivity to stress [21-24] to combat increased acute pain during the defense reaction, but may be, under certain circumstances, a maladaptive adaptation that serves to sustain the disorder that may last beyond the remission of the depressive episode. A clinical example comes from patients with silent myocardial ischemia, where increased baroreceptor activation influences a strong relationship between BP and pain and is thought to be maladaptive. Since individuals with this disorder are asymptomatic, the hypertensive-associated hypoalgesia serves not only to sustain the disorder, but to keep it hidden from the patient who is in need of medical attention [341].

A case in addition to MDD in which a stronger BP/pain relationship in women with a psychiatric disorder might be maladaptive is in bulimia nervosa (BN). Women with BN have been shown to display a strong association between BP and pain sensitivity not seen in controls [342], since a study from our laboratory reported BP-related hypoalgesia in response to the tourniquet ischemic pain task in women with BN that was absent in healthy controls. Given this association, increases in BP as a result of bingeing and purging may reduce the physical discomfort that coincides with these behaviors, serving as a maladaptive mechanism for the individual in the sense of maintaining the disorder [342]. Since both MDD and BN are highly associated with depressive symptomatology [343] and heightened SNS responsivity (i.e. bingeing and purging in BN [342]), it is possible that enhancement of baroreceptor activation occurs during their development as a maladaptive mechanism,

decreasing the pain associated with both disorders, but also acting as a rewarding mechanism contributing to their maintenance.

The results of our study indicate that dysregulation in pain and stress mechanisms found in patients with current MDD persist beyond the remission of the depressive episode, and thus are key underlying components of the disorder that may contribute to the etiology of MDD.

Comparisons and Contrasts Between PMDD and Prior MDD

Although the majority of our findings support divergent physiological profiles involving pain and stress mechanisms between women with prior MDD compared to women with PMDD, certain similarities in our data did in fact exist. For instance, only the cold pressor pain task was able to elicit the greater pain sensitivity found in PMDD and the decreased pain sensitivity present in prior MDD compared to their respective control groups, while the tourniquet ischemic pain task did not uncover any diagnostic differences in pain sensitivity based on either PMDD or prior MDD status. An explanation for the absence of the expected diagnosis-related differences in pain sensitivity during the tourniquet task may come from the fact that experimental pain tests have been shown to activate different endogenous pain mechanisms. Sensitivity to tourniquet ischemic pain involves endogenous opioid mechanisms [265, 266]], whereas sensitivity to cold pressor pain may be mediated by systemic vascular resistance and noradrenergic mechanisms, or in other words, the SNS [233].

A recent study from our laboratory lends support for cold pressor pain sensitivity to be mediated by SNS factors, finding that NE was an independent predictor of cold pressor

pain tolerance, but not tourniquet ischemic tolerance, in non-smokers [233]. Furthermore, studies have shown that the selective opioid receptor antagonist naloxone increases tourniquet ischemic [265, 344], but not thermal [345, 346], pain sensitivity. The current study observed greater SNS reactivity in prior MDD and blunted SNS reactivity in PMDD compared to their respective control groups, but no diagnosis-related differences in baseline β -endorphin. Thus, since the anticipated diagnosis-related differences are only present for SNS factors, one would expect differences in pain sensitivity only for the laboratory-based test that is mediated by sympathetic mechanisms. In summary, our findings for exclusively SNS dysregulation in women with PMDD and a history of MDD correspond to our observation of pain dysregulation in the SNS-mediated cold pressor pain task, but not in the opioid-mediated tourniquet ischemic task.

Another similarity between all women in our study was the lack of diagnostic-related differences in the HPA-axis factors of baseline β -endorphin and cortisol. Due to logistical reasons, our laboratory study protocol was restricted to early morning hours, which may explain the lack of diagnosis related differences in our HPA-axis factors. Our decision to sample β -endorphin only at baseline was due to the lack of an established time course for capturing a β -endorphin response to mental stress, and to the lack of reliability of stress-induced HPA-axis measures during the early morning hours when our study took place. Research has shown that cortisol levels show only small spontaneous fluctuations in the late afternoon as compared to the morning [347], and that cortisol levels rise for approximately the first hour an individual is awake and then decline steadily throughout the rest of the day [348, 349]. Specifically, the lowest concentration of the plasma cortisol circadian rhythm is at midnight, rising to a peak between 6:00 and 8:00am, and falling until day's end [350].

Therefore, many studies that aim to observe a cortisol response to stress have been conducted in the late afternoon to early evening [270, 272, 351], since the ability to detect a stress response is diminished in the morning when cortisol levels are at their most rapid decline and stress perturbation is acting against the strong diurnal decline [350]. Thus, since stress-responsive β -endorphin concentrations mimic that of cortisol [95], measurements of both HPA-axis factors in response to stress are unreliable in the early morning when our study was conducted. Thus, we restricted our HPA-axis measurement to occur strictly at baseline rest, and since prior studies assessing baseline levels of cortisol and β -endorphin in both PMDD and prior MDD do not consistently support diagnostic related differences, our ability to detect diagnosis-related differences may have been stronger if stress-responsive factors were assessed.

The literature on baseline β -endorphin levels in PMDD women has not been well established, and earlier studies reporting decreased β -endorphin levels in PMDD [60, 180, 181] have been questioned in terms of their accuracy by PMDD experts participating in a roundtable discussion of the biological determinants of the disorder [60]. Similarly, evidence regarding decreased baseline cortisol concentrations in PMDD versus non-PMDD women has been described as scant, inconsistent, and mainly focused on cortisol responses to neuroendocrine challenge tests [352]. In contrast, women with PMS, a syndrome that is less strictly defined clinically and less severe than PMDD, have been shown to display reduced peripheral β -endorphin levels during the luteal phase of the menstrual cycle compared to non-PMS women during the luteal [179-181] and follicular [182] phases, and a recent study from our laboratory found decreased peripheral baseline β -endorphin levels in PMDD versus non-PMDD women [182]. Comparable evidence for a hypoactive HPA-axis in PMDD

comes from two separate studies from our laboratory, finding decreased baseline cortisol in PMDD versus non-PMDD women [79, 182]. In light of the latter findings for a hypoactive HPA-axis at baseline in PMDD women, our lack of support for these findings may be spurious and a reflection of our small sample size.

A similar explanation may be given for our lack of prior MDD-related differences in HPA-axis factors. Although prior studies assessing β -endorphin in patients with current DEP have mostly focused on responses to challenge, finding increased β -endorphin levels compared to healthy controls, or on responses to successful treatment, observing a concurrent decrease in depressive symptoms and β -endorphin concentrations [95, 101, 104, 170, 183], the majority of studies in current and prior MDD have shown support for a hyperactive HPA-axis. For instance, increased levels of cortisol at baseline [95-102] and diurnal (i.e. mean daily concentrations assessing fluctuations due to circadian rhythm) [105, 106] cortisol levels in women with current MDD compared to non-depressed subjects have been reported, and in research assessing individuals with histories of MDD, results have shown higher diurnal salivary cortisol [21], and greater diurnal mean urinary cortisol [22] compared to those with no history of MDD. Moreover, Goodwin et al. [101] found greater β -endorphin levels in patients with MDD at rest compared to non-depressed controls, and Krittayaphong et al. [104] reported that coronary artery disease patients with high depression scores had higher resting β -endorphin levels than those patients with low depression scores. Therefore, the lack of differences in baseline HPA-axis factors based on prior MDD status, similar to that found in our PMDD women, may be due to our small sample sizes. Thus, future studies that include larger samples may enlighten our potentially spurious findings in women with PMDD and prior MDD.

The null findings regarding cortisol levels in our study are not likely due to issues regarding the reliability of our plasma measurement. Cortisol exists in two forms, free cortisol, and total cortisol, the latter of which comprises free plus bound cortisol. Plasma concentrations reflect only total cortisol concentrations, and thus has been criticized for its lack of clinical relevance, since only free cortisol is biologically active [350, 353, 354]. However, Wedekind et al. [355] assessed salivary, free plasma, and total plasma (free and bound) at baseline in patients with panic disorder and healthy controls, and found elevated cortisol concentrations in patients compared to controls irrespective of cortisol measurement. Similarly, Carroll and colleagues [356] assessed individuals with and without current mood disorders for cerebrospinal fluid cortisol, total cortisol in plasma, and urinary free cortisol, and found that regardless of the measurement used, mood disorder patients showed higher cortisol concentrations compared to healthy controls. The results of these studies indicate the plasma total cortisol is an accurate biological measure and allows for the differentiation of HPA-axis dysfunction in affective disorders.

An important distinction between PMDD and prior MDD may be differences in baroreceptor regulation of BP and pain sensitivity. In PMDD women, despite showing decreased SNS responsivity to mental stress coupled with increased sensitivity to cold pressor pain, we found no evidence for consistent relationships between BP and pain sensitivity. Thus, the less persistent baroreceptor stimulation resulting from decreased SNS activation in PMDD women may contribute to the absence of the BP/pain relationship. A similar explanation can be utilized to explain the contrasting relationship in prior MDD. Women with prior MDD in our study showed increased BP responses to the speech stressor coupled with decreased sensitivity to cold pressor pain, as well as a strong relationship

between BP and pain. The chronically heightened SNS found in women with prior MDD may result in more persistent baroreceptor activity, thus explaining the robust association between BP and pain in these women. In summary, differential activation of baroreceptor pathways influenced by opposing SNS activation in PMDD versus prior MDD may explain the presence of the BP/pain relationship in prior MDD, but not PMDD.

Study Limitations

There are several limitations to this study that should be acknowledged. First, due to logistical issues surrounding time of day of testing, we were unable to assess the stress-induced HPA-axis factors of cortisol and β -endorphin, factors that would be expected to differ based on both PMDD [178] and prior MDD [127] status. The ability to measure these HPA-axis factors in response to mental stress in our study would have enabled us to not only replicate prior findings for diagnostic related differences in cortisol and β -endorphin, but to be the first to find differences in the relationship between these measures and experimental pain sensitivity in both women with PMDD and women with prior MDD. Future research assessing stress-responsive measures of cortisol and β -endorphin during the late afternoon are warranted in order to determine any diagnosis-related dysregulation in the HPA-axis/pain relationship.

Furthermore, future studies assessing additional HPA-axis measures such as ACTH and CRH would further enlighten the exact mechanisms involved in the downregulation of the HPA-axis in PMDD and the hyperactive HPA-axis in current and prior MDD. Since the majority of the evidence for HPA-axis dysregulation in MDD comes from studies showing increased CRH levels in MDD [122, 166, 168, 170-172], levels that have been shown to

cause decreased ACTH but normal to elevated cortisol in response to CRH [10, 130, 137, 138], the assessment of all components of the HPA-axis in women with a history of MDD is necessary in order to paint a full picture of persistent HPA-axis dysfunction. Since chronic CRH hypersecretion and overall hyperactivity of the HPA-axis in MDD are strongly related to impairment in negative feedback to the hypothalamus [131, 132, 137, 139], the assessment of CRH and ACTH would allow for the measurement of HPA-axis factors that are responsive to negative feedback mechanisms.

Impairment of HPA-axis negative feedback has indeed been assessed in euthymic individuals with a history of MDD, finding normalization after successful treatment [103, 148, 169, 171]. Although Ising and colleagues [128] argued that normalization of HPA-axis negative feedback is a key factor in the success of antidepressant drugs, and studies show that the degree of normalization correlates with and predicts clinical efficacy of antidepressants [173], a limitation of many of the existing studies is the relatively short length of time between baseline and post-treatment testing, with the majority of studies retesting 6 weeks or less after baseline [112, 148, 169]. Normalization of HPA-axis after treatment may be a short-term phenomenon that initially overrides the “trait” characteristic of heightened HPA-axis activity, but may return over time and become uncoupled from symptom improvement. Thus, further studies are needed to determine if impairment in HPA-axis negative feedback shows long-term persistence in euthymic women with prior MDD.

Another limitation that deserved mention is the small sample size for women with prior MDD (N = 13). We were thus unable to explore interactions involving PMDD and prior MDD, which limited our ability to investigate the potential interplay in the underlying mechanisms of PMDD and prior MDD. Further studies including a larger sample of women

with prior MDD may have the analytic capacity to observe interactions between PMDD and prior MDD, and possibly concluding that PMDD does not stand alone in its biological and psychosocial determinants, but instead occurs in the context of MDD. As Rubinow and Schmidt [67] asked when attempting to understand why gonadal steroids play a role in the manifestation of PMDD in some women, but not others, “What is the context of susceptibility?” They determined that the answers to this question lie within a tangled web of individual differences that may cause gonadal steroids to trigger PMDD in some women, but not others. Future research may discover that another “context of susceptibility” for PMDD may in fact involve the presence or absence of a history of MDD.

Another limitation of the small sample size is that we were unable to control for differences in baseline anxiety and depression, differences that may have contributed to our stress responsivity and pain sensitivity results. However, mood disturbances are significant aspects of both PMDD and MDD, especially during the luteal phase of the menstrual cycle when state anxiety and depression were assessed, and thus the more negative mood found in PMDD and prior MDD was likely a manifestation of the disorder, as opposed to an extraneous variable. Thus, controlling for these baseline differences may have resulted in the masking of critical aspects of the disorders, and subsequently hindering our ability to determine diagnosis related differences in stress and pain sensitivity.

Study Retention

Due to the need for strict PMDD diagnostic criteria involving 2-3 months of daily ratings and long-term commitment necessary to complete the laboratory study protocol, many women who were enrolled and signed a consent form did not remain through the

study's completion. Thus, another goal of our study was to determine if certain demographic factors were predictive of voluntarily dropping out of the laboratory study protocol at any time prior to completion, or being classified as a 'dropout'. We found that race classification of Minority, presence of a self-reported psychological history, greater self-reported alcohol consumption, and presenting as PMDD were found to be significant predictors of voluntarily dropping out of the study.

These results are logical, since women who have experienced depression symptoms either currently or in the past, who think they have PMDD, or consume higher amounts of alcohol per month may be more likely to drop out due to lack of dedication, time, motivation, and emotional stability necessary to complete the multiple visits involved in the study protocol. Furthermore, only approximately 8% of women who presented as PMDD and voluntarily dropped out of the study actually met diagnostic criteria for PMDD. Thus, the vast majority of women presenting as PMDD did not in fact suffer from the disorder, consistent with numerous other reports [45, 46, 78]. Most likely, these women were suffering from a sub-threshold psychiatric disorder other than PMDD, and thus may have contributed to PMDD presentation predicting dropout status in our model.

We also assessed the predictive value of the abovementioned demographic variables in a larger group of women called 'non-completers' that included the 'dropouts', or those who voluntarily dropped out of the study, and also included women who signed a consent form but either had not completed the study at the time of data analysis, or were withdrawn from the study due to forces outside of their control, such as medical concerns or failing to meet diagnostic or inclusion criteria. We determined that a higher BDI score, self-identified

Minority race, presence of a self-reported psychological history, and presenting as PMDD were predictors of non-completion of the laboratory study protocol.

The finding for the presentation of PMDD to be a predictor of being a ‘non-completer’ is a reflection of our strict diagnostic criteria for PMDD, since many women who believe they have PMDD do not meet criteria upon daily ratings inspection. Instead, while some have simply overestimated the severity of their symptoms, a sizeable proportion of these women are those with chronic, phase-independent dysphoria. Thus, the presentation of PMDD may likely reflect current mood disturbance and is consistent with the ability of high BDI scores to predict non-completion. Moreover, the ability of depression scores and self-reported psychological history to predict non-completion of the laboratory study protocol is understandable, since women who currently feel depressed or anxious, or have suffered from a psychological disorder in the past, are less likely to meet non-PMDD as well as PMDD criteria due to ongoing symptoms, irrespective of the menstrual cycle.

Although there were no demographic factors distinguishing non-Hispanic Whites from Minorities that could potentially explain the ability of Minority status to predict both non-completion and voluntarily dropping out of the laboratory study protocol, other factors that were not measured in the current study, such as daily life stress and chronic stressors, may have played a role. It is well established that African Americans experience more psychosocial stress such as racism, and experience more chronic stress due to unemployment, low socioeconomic status (SES), and lower social status than Caucasians [357]. Although there were no race-related differences in SES in our study, African Americans generally experience more chronic stress in the form of discrimination compared to Caucasians, regardless of SES [358]. Therefore, since African American women made up the most of our

Minority sample, had we measured these stress-related factors, we may have seen that they negatively impacted our Minority sample in a way that would decrease the likelihood of completing our laboratory protocol.

In order to obtain a true sense of the final sample of women in our study, it is important to compare the factors that distinguish ‘completers’ from ‘non-completers’ to the factors that distinguish ‘completers’ from ‘dropouts’. Greater alcohol consumption predicted dropping out of the study, but did not predict non-completion of the study, indicating that alcohol use contributed to voluntarily dropping out prior to laboratory study protocol completion, but did not contribute to meeting diagnostic or inclusion criteria. This implies that alcohol consumption may be related to non-compliance with the study in terms of missing visits to the laboratory, forgetting to complete the daily ratings, etc., but does not necessarily affect PMDD symptomatology. On the other hand, greater BDI scores predicted non-completion of the study, but did not predict dropping out of the study. This finding suggests that the higher depressive symptoms may be a factor that made women less likely to complete the laboratory study protocol due to failing to meet inclusion or diagnostic criteria (due to the chronic nature of depressive symptoms), instead of due to voluntarily dropping out of the study.

Summary of Primary Findings and Hypotheses Regarding Differential Adaptation to

Stress in PMDD and MDD

In the present investigation, we determined that women with PMDD displayed heightened cold pressor pain sensitivity and reduced SNS stress reactivity in addition to reporting more difficulty, tension, and inability to concentrate during mental stress than non-

PMDD women. Furthermore, non-PMDD women showed a more consistent relationship between BP and pain sensitivity, while PMDD women showed a more robust relationship between β -endorphin and pain sensitivity. In contrast to the profile of PMDD women, euthymic women with prior MDD showed decreased cold pressor pain sensitivity and greater DBP responsivity to stress than never depressed women. Since women with a history of MDD were free of the disorder for, on average, over seven years, our study has documented persistent biological disturbances beyond the remission of the depressive episode. Lastly, we observed that women with prior MDD displayed a more consistent pattern of relationships between greater BP and decreased pain sensitivity, while women with no prior MDD showed more consistent associations between increased baseline cortisol and decreased pain intensity and unpleasantness.

Based on the results of the present investigation, one may argue that downregulation of the stress axes in PMDD women may have developed as an adaptive mechanism to combat the heightened experience of stress, whereas this adaptation failed to occur in individuals with current and prior MDD. However, the MDD literature suggests viewing the dysregulation of the stress axes as a pre-cursor to the development of MDD as opposed to a failure to adapt to a heightened stress experience. For example, as mentioned above, CRH causes symptoms of MDD in animals [144], normalization of HPA-axis and SNS parameters upon remission following antidepressant treatments have been robustly reported [103, 146, 149, 166, 168-171], and persistent HPA-axis upregulation following treatment of MDD predicts relapse [134]. Moreover, since euthymic first degree relatives of depressed patients show persistently intermediate levels of cortisol release in response to the DEX/CRH test that is between healthy controls and currently depressed patients [114, 164], there may also be a

stable genetic component contributing to HPA-axis dysregulation in MDD. Finally, since our study found a heightened DBP stress response in currently euthymic women with prior MDD compared to never depressed women, it may be argued that if the upregulation of the HPA-axis and the SNS found in MDD reflects the failure of the organism to adapt to the disorder, the hyperactivity would not persist beyond remission. Thus, upregulation of the stress axes in current and prior MDD seems to be a contributor to, rather than an effect of, the depressive disorder.

A similar argument for pre-existing biological disturbances contributing to the onset of MDD can be made regarding the decreased experimental pain sensitivity found in current and prior MDD. Painful somatic symptoms that remain after successful treatment of MDD have been shown to predict future relapse [315], and since increased somatic pain and decreased sensitivity to experimental pain share a common biological origin (i.e. downregulation in central pain processing in MDD [326]), it can be inferred that decreased sensitivity to laboratory-based pain found in current and prior MDD may be an underlying mechanism serving as a physiological precursor to the development of the disorder. Moreover, although it may be argued that decreased pain sensitivity would logically be an adaptive mechanism in patients with MDD in order to cope with the heightened painful symptoms associated with the disorder [212], the persistence of pain dysregulation in the absence of current MDD can be viewed as evidence against this argument, since the adaptation would no longer be necessary beyond the remission of the disorder. However, it is also possible that the decreased pain sensitivity found in women with a history of MDD may be viewed as a persistent adaptation to heightened somatic symptoms associated with MDD that has become a permanent remnant of the disorder. Further longitudinal studies,

such as those examining high risk family members of patients with MDD, are necessary to determine the extent to which the decreased pain sensitivity in MDD is an antecedent or consequence of the disorder.

The viewpoint that the dysregulation of the stress axes and pain sensitivity found in current and prior MDD reflects a physiological precursors to the development of MDD parallels the diathesis-stress model of psychology and psychiatry. Diatheses in the psychological realm are considered relatively stable individual differences (i.e. genetic dispositions, cognitive style, biological dysfunction, or deficient social skills) that make people vulnerable to depression when confronted with stressful life events [357]. The pain and stress axes dysregulation in MDD may function as a diathesis, or biological substrate, on which a significant life stressor acts to trigger the onset of the disorder. Research in the diathesis-stress model of depression shows that stressful life events interact with this substrate or vulnerability, triggering distress that affects the individual's resilience and drives the individual toward the depressive condition [358]. Further understanding of the biopsychosocial diathesis-stress model of MDD will inform the development of future integrative treatments focusing on biological vulnerabilities and the life stressors that contribute to the onset of the disorder.

Since differential sensitivity to the fluctuations in female gonadal hormones in PMDD have been designated as the foremost underlying mechanisms associated with the disorder [71], there have been no studies to date examining the ability of the hypoactive stress axes or increased sensitivity to pain to predict or contribute to the development of PMDD. However, these studies implicating menstrual cycle-related hormone changes as a precipitating factor in PMDD may not only play a role in the emotional symptoms associated

with the disorder, but to the physical somatic symptoms as well. Since estrogen has been shown to have both analgesic as well as pain-inducing properties [359], the fluctuation in estrogen and other hormones throughout the menstrual cycle may play a role in the increased somatic symptoms reported by PMDD women. Furthermore, since clinical pain has been associated with laboratory-based pain in healthy controls [214, 215] and chronic pain patients [216-218], these hormone fluctuations may also affect sensitivity to experimental pain in women with PMDD [360]. Thus, as opposed to considering increased sensitivity to pain as a consequence of PMDD, it is more likely that it is a contributing factor of the disorder, although studies addressing the causal nature of pain mechanisms in PMDD are warranted in order to further understand the underlying mechanisms of the disorder.

In contrast to our hypothesis for MDD, it is possible that the downregulated HPA-axis and SNS found in PMDD did in fact develop as a homeostatic adaptation to the disorder, allowing women with PMDD to physiologically cope with their heightened subjective experience of stress. Supporting evidence comes from post-traumatic stress disorder (PTSD), an illness that is also associated with a hypoactive HPA-axis [361]. Since both PMDD and PTSD share a high prevalence of abuse histories [361], the adaptive HPA-axis dysregulation may have arisen via similar mechanisms in both disorders. The hypothesis that the hypoactive stress axes found in PMDD developed as an adaptation to the heightened stress associated with the disorder is accordance with the overall conclusion of the present study that PMDD and MDD each have a distinct pathophysiology. The hypothesis suggests that the dysregulation of the stress axes serves not as an underlying mechanism and biological substrate in MDD, but as a homeostatic adaptation to the disorder in PMDD. Unlike MDD, PMDD is not a recurrent disorder, and thus research investigating the ability of

certain psychophysiological variables to predict PMDD relapse is not applicable. Therefore, longitudinal studies are necessary to determine whether downregulated stress axes precipitate the development of PMDD or arise in response to certain stress-related biological or psychological manifestations of the disorder.

Conclusions

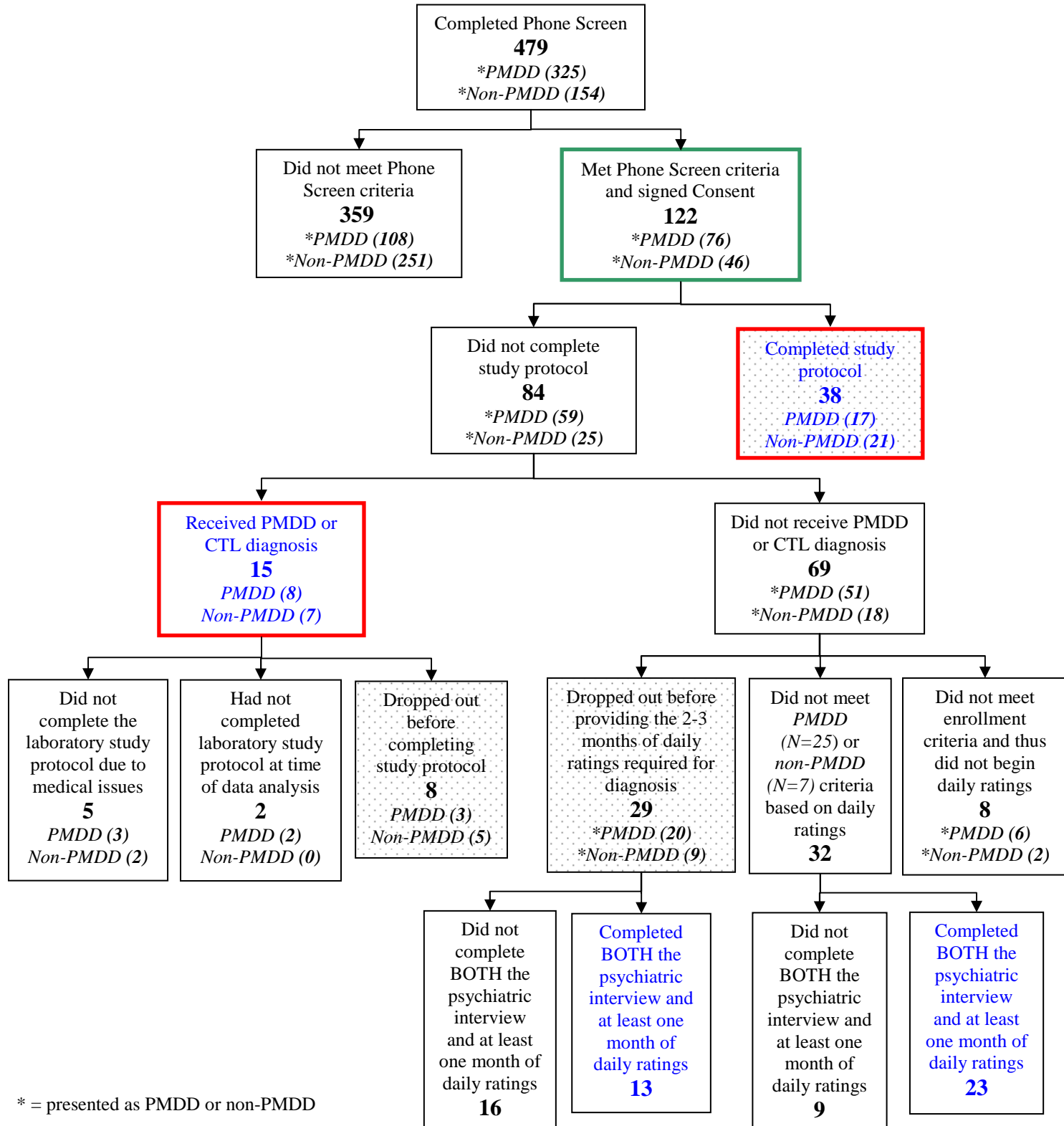
The results of the present study revealed distinct pathophysiology between women with prior MDD and women with PMDD. Despite the fact that our results support the dichotomy of PMDD from MDD, PMDD women are more likely to have a history of DEP [45, 51-54] as well as develop a future depressive episode [56-59]. Thus, since we observed that women with prior MDD displayed decreased pain sensitivity, increased premenstrual symptom severity, increased SNS stress responsivity, and a stronger relationship between pain sensitivity and BP compared to women with no history of MDD, these results may have special relevance to PMDD women. The present investigation underscores the need to assess DEP histories in women who present with PMDD in the clinical setting as well as in future research. Since PMDD women with prior MDD may represent a biologically and clinically distinct subgroup of PMDD women, assessing psychological history may serve to inform treatment options in terms of stress and pain management in addition to refining the inconsistent PMDD literature in these areas.

Furthermore, since histories of DEP are more common in PMDD, and since PMDD and prior MDD show opposing SNS stress reactivity, pain sensitivity, and pattern of endogenous pain regulation factors, histories of MDD may have special relevance for PMDD, and women with prior MDD should be recognized as a distinct subgroup of the

disorder. Although our small sample size did not allow us to reliably determine the distinct physiological profile of co-morbid PMDD and prior MDD, we conducted preliminary analyses to investigate if in fact PMDD women with a history of MDD showed differential patterns of pain sensitivity, baseline HPA-axis factors, stress-responsive SNS factors, subjective ratings of pain and stress tasks, and severity of daily mood ratings (see Appendix B). PMDD women with prior MDD showed biological profiles that more closely resembled that of PMDD (i.e. greater pain sensitivity, decreased cortisol, blunted NE response to stress, heightened effort and increased negative subjective experiences during the pain and stress tasks), indicating that the current pathophysiology predominates over the prior depressive disorder. However, this co-morbid subgroup did differ from PMDD women with no prior MDD, and thus may still represent a distinct subgroup of PMDD women. Although further research is necessary to determine the reliability of our preliminary findings, the entirety of our results implicate MDD and PMDD as two distinctive disorders, and show that a history of MDD may have special physiological and clinical relevance for women with PMDD.

APPENDIX A

Enrollment Statistics



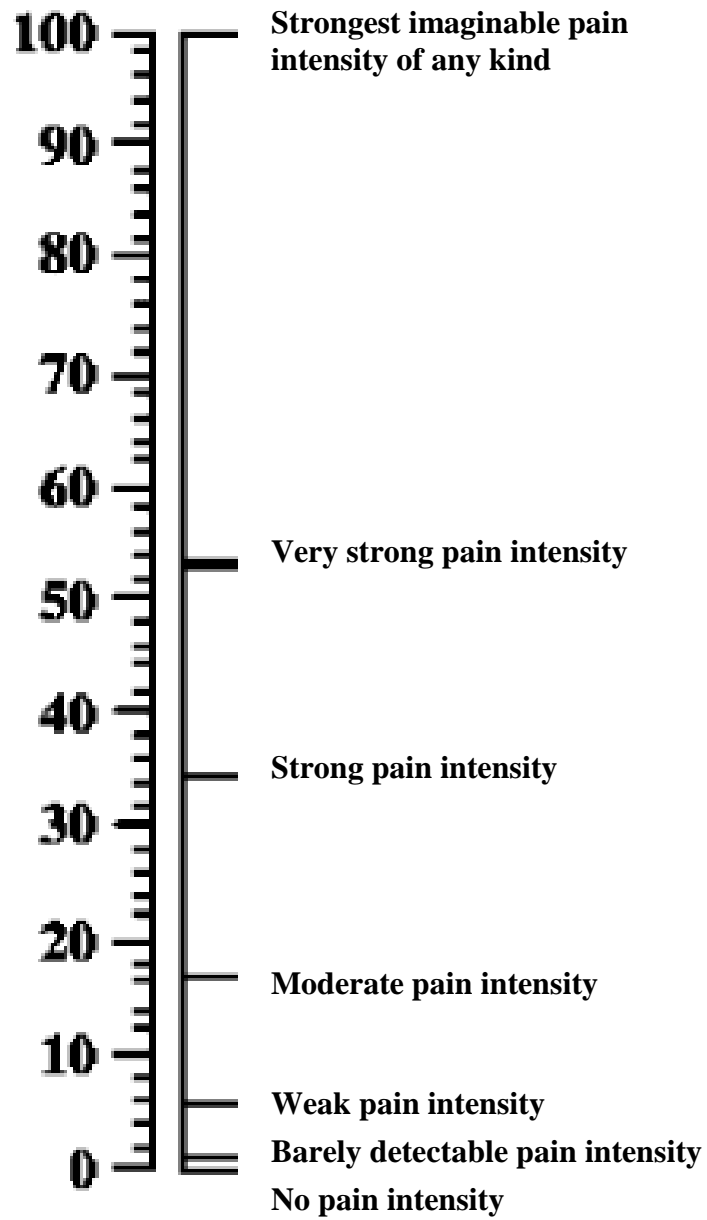
N = 53: women given a PMDD or CTL diagnosis

N = 89: women who completed both the psychiatric interview and at least one month of daily ratings

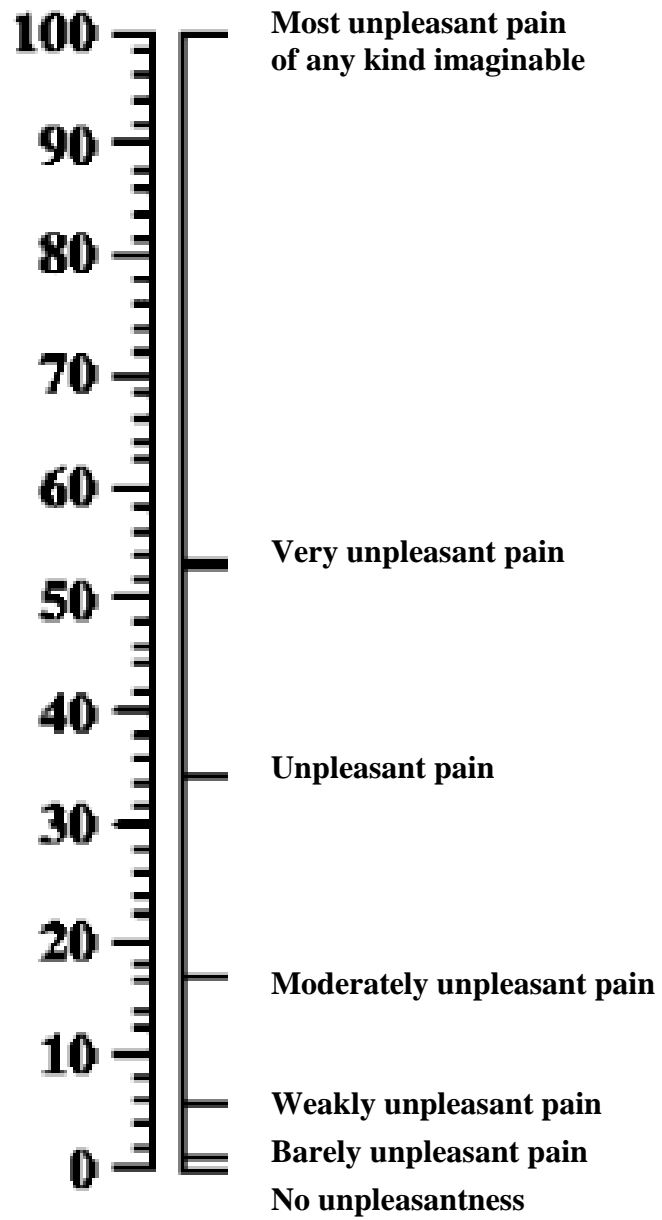
N = 75: women used in the analyses comparing dropouts and completers

N = 122: women used in the analyses to compare dropouts, non-completers, and completers

Visual Analog Intensity Scale



Visual Analog Unpleasantness Scale



Task Assessment Scale

1. Indicate on each of the scales below, by circling a number on the number line, your experience during the preceding task.

Not Difficult _____ Very
Difficult
0 1 2 3 4 5 6 7 8 9 10

Not Tense _____ Very Tense
0 1 2 3 4 5 6 7 8 9 10

Able to _____ Not Able to
Concentrate 0 1 2 3 4 5 6 7 8 9 10 Concentrate

2. Indicate on the scale before, by circling a number on the number line, how much effort you put into the preceding task.

Very Low _____ Very High
Effort 0 1 2 3 4 5 6 7 8 9 10 Effort

ID# _____

DAILY RATING FORM INSTRUCTIONS

There are 24 items listed on the following pages. Additionally, there are four blank columns where you may add items describing other changes that trouble you premenstrually. This is where you can notify us of any symptoms that you wish to add.

1. Rate each item every evening, preferably before bed. It is usually a good idea to "post" the ratings where you will see them each night (e.g., the closet door, the mirror on the medicine cabinet), or to keep them on your nightstand.
2. The levels of severity for rating each item are given at the top of each page. The ratings should indicate the degree to which you experienced the feelings or behaviors described in the item for that particular day. See attached form for descriptions of each rating. The severity ratings you select should reflect the average intensity for that feeling for the whole day.
3. Start with the correct day of the week for the first day's ratings (the same day as your screening visit).
4. Continue to the end of all the pages (page 8) each day.
5. In the column indicated, note only those days on which you are menstruating with an X. Remember that spotting is also considered menstruating and that you make symptom ratings every day, regardless of whether or not you are menstruating.
6. Comment on the last page if there have been unusual events that have affected your feelings or behavior for that day (e.g., illness, very bad news), and **make sure to write down the date.**
7. If you forget to complete the ratings on any evening, try to do it as early as possible on the next day, but do not complete more than one day's ratings from memory. If you miss a day, skip the column, but indicate that it was a missed day.
8. When you have completed each packet (each is good for 7 days) please place it in an envelope and mail it to us EVERY MONDAY. It is very important for our record keeping that the calendars are returned in a timely fashion. We will keep records of when each calendar is due.
9. Call Becky at 919-966-2547 at the start of each period and for any additional questions you may have.

TURN EACH PAGE EACH DAY, RATING A TOTAL OF AT LEAST 24 ITEMS.

All information contained on this form and data summarized from it will be kept confidential. Any written or verbal reports will be done in a way which precludes identification of individuals.

*Developed by Jean Endicott, Ph.D., Sybil Schacht, M.S.W., and Uriel Halbreich, M.D., Research Assessment and Training Unit, 722 West 168th Street, New York, New York 10032.

Severity Ratings: 1 = Not at all, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Severe, 6 = Extreme

Day of Week	Date	Menstruating?	Felt depressed, sad, "down", or "blue"	Felt hopeless	Felt worthless or guilty	Felt anxious, keyed up or "on edge"	Comments on back page?
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No

Severity Ratings: 1 = Not at all, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Severe, 6 = Extreme

Day of Week	Date	Menstruating?	Had mood swings, (e.g. suddenly felt sad or tearful)	Was more sensitive to rejection or my feelings were easily hurt	Felt angry, irritable	Had conflict or problems with people	Comments on back page?
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No

Severity Ratings: 1 = Not at all, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Severe, 6 = Extreme

Day of Week	Date	Menstruating?	Had less interest in usual activities (e.g., work, school, friends, hobbies)	Had difficulty concentrating	Felt lethargic, tired, fatigued, or had a lack of energy	Had increased appetite or overate	Comments on back page?
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	—	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No

Severity Ratings: 1 = Not at all, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Severe, 6 = Extreme

Day of Week	Date	Menstruating?	Had cravings for specific foods	Slept more, took naps, found it hard	Had trouble getting to sleep	Felt overwhelmed, that I couldn't cope	Comments on back page?
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No

Severity Ratings: 1 = Not at all, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Severe, 6 = Extreme

Day of Week	Date	Menstruating?	Felt out of control	Had breast tenderness	Had breast swelling, felt "bloated" or had weight gain	Had headache	Comments on back page?
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No

Severity Ratings: 1 = Not at all, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Severe, 6 = Extreme

Day of Week	Date	Menstruating?	Had joint or muscle pain	At work, school, home or in daily routine, at least on of the above problems caused less productivity	At least one of the above problems interfered with hobbies or social activities	At least one of the problems above interfered with relationships	Comments on back page?
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Mon	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Tue	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Wed	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Thu	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Fri	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sat	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
Sun	/	___	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Yes No

Severity Ratings: 1 = Not at all, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Severe, 6 = Extreme

[illegible]

Comments:

APPENDIX B

SUPPLEMENTARY RESULTS: ANALYSES AS A FUNCTION OF PMDD AND PRIOR MDD STATUS

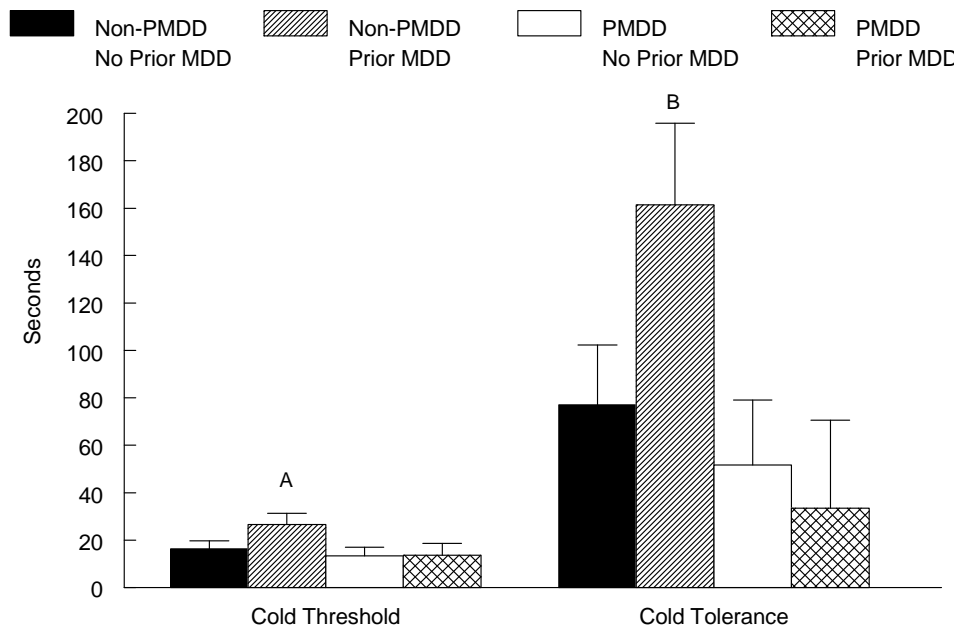
Mean (+SEM) Demographic Factors as a Function of PMDD Status and Prior MDD

	PMDD		Non-PMDD	
	Prior MDD (n = 6)	No Prior MDD (n = 11)	Prior MDD (n = 7)	No Prior MDD (n = 14)
Age	33.8 (3.5)	34.6 (2.6)	32.7 (3.2)	32.5 (2.3)
BMI	22.8 (2.4)	26.4 (1.8)	26.7 (2.2)	24.9 (1.6)
^A BDI	7.5 (1.7)	6.8 (1.3)	3.1 (1.6)	1.4 (1.1)
State Anxiety	27.8 (3.7)	35.1 (2.7)	29.1 (3.4)	27.3 (2.4)
^B Race (Non-Hispanic White : Other)	5 : 1	7 : 4	7 : 0	8 : 6
Abuse History	2	7	5	4
Prior Episodes of MDD	1.67 (0.35)	0	1.86 (0.33)	0
Months in Remission from MDD	106 (33)	NA	72.3 (30)	NA

^A PMDD > Non-PMDD, $p < 0.01$

^B MDD Diagnosis: Non-Hispanic Whites > Other, $p < 0.05$

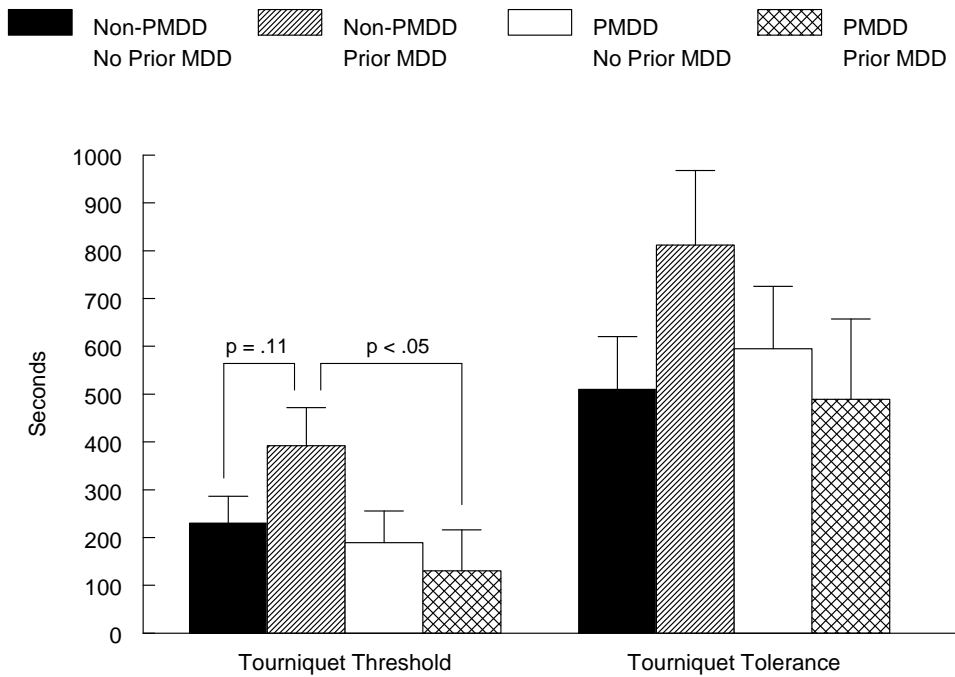
Cold Pressor Threshold and Tolerance as a Function of PMDD and Prior MDD Status



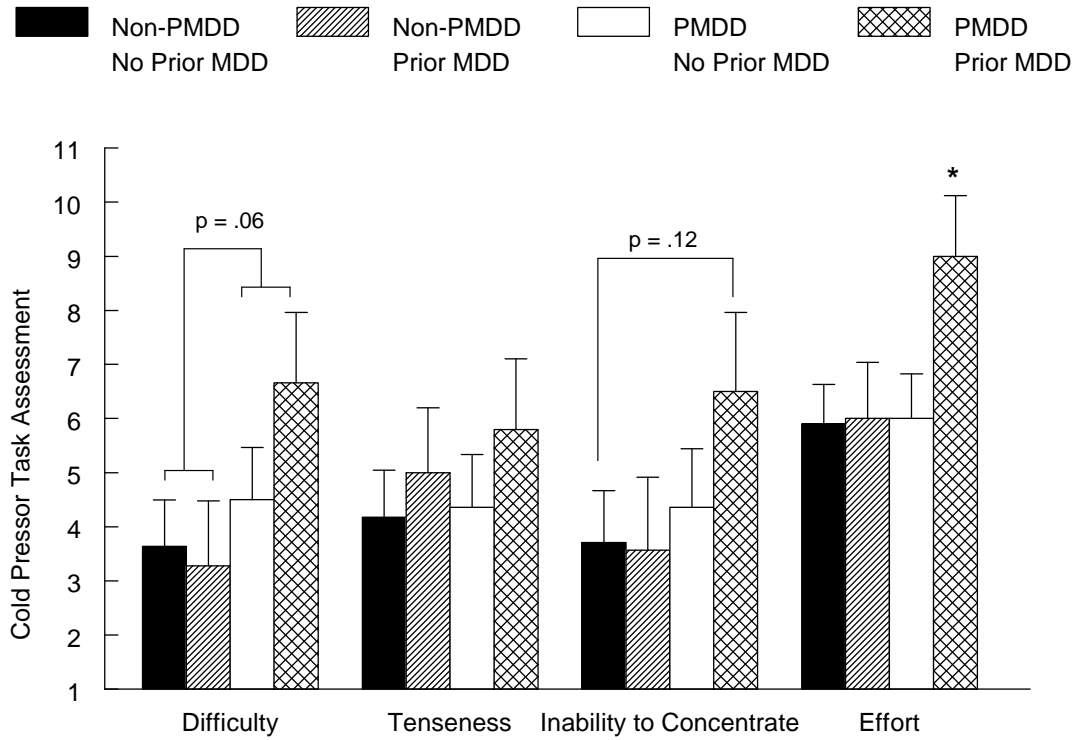
^A Non-PMDD women with prior MDD > all other groups, $p_s < .09$

^B Non-PMDD women with prior MDD > all other groups, $p_s < .06$

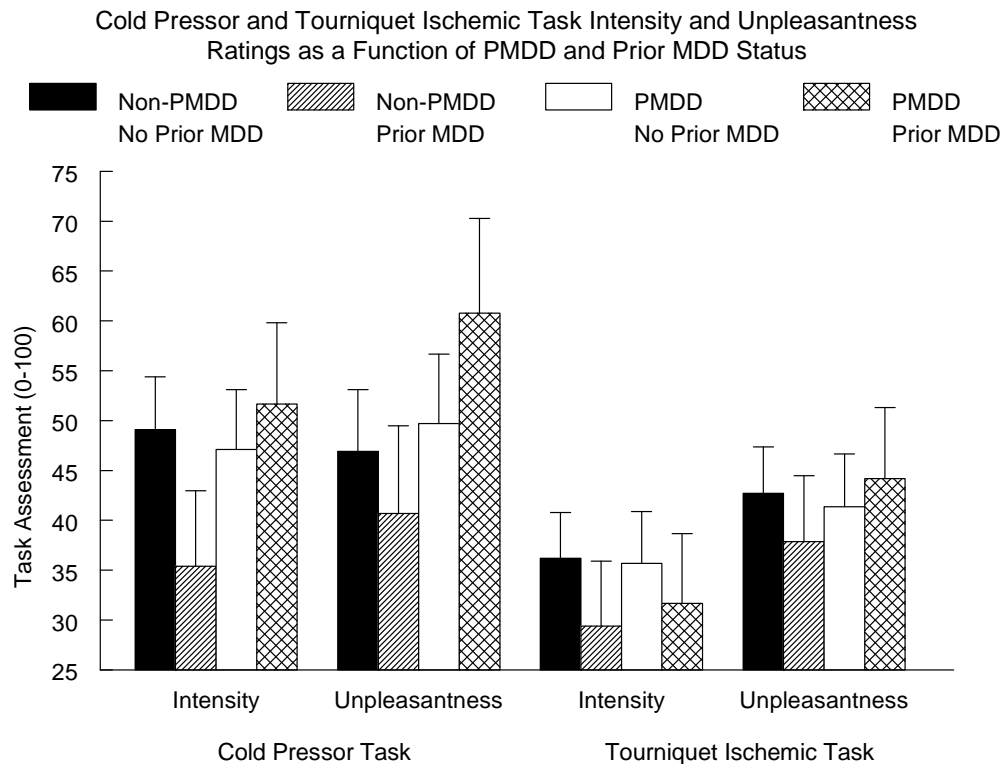
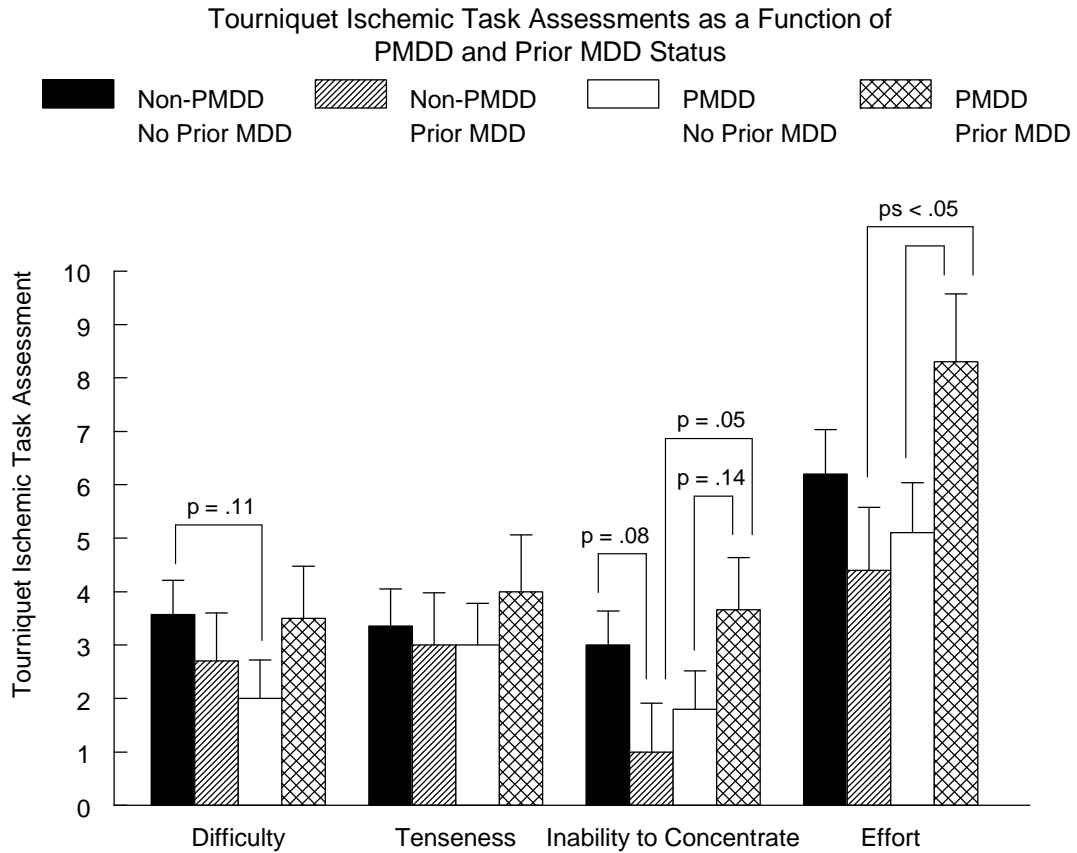
Tourniquet Ischemic Pain Threshold and Tolerance as a Function of PMDD and Prior MDD Status



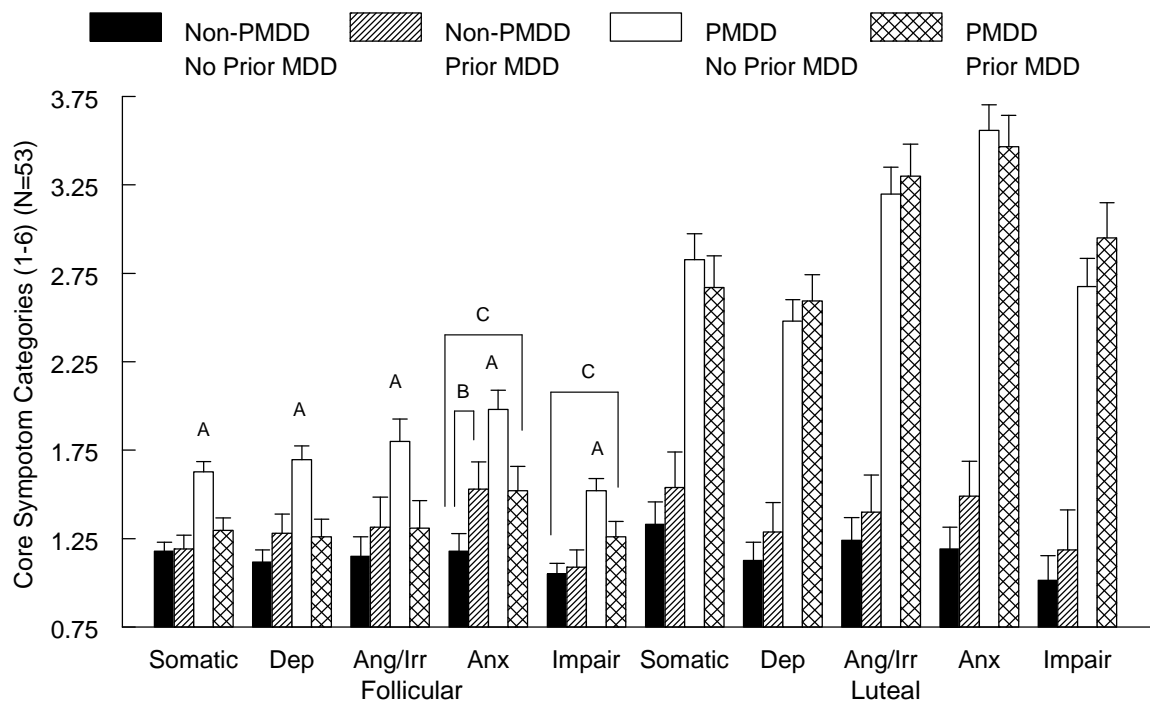
Cold Pressor Task Assessments as a Function of PMDD and Prior MDD Status



* PMDD women with prior MDD > all other groups, $ps < .06$



Daily Mood Ratings Core Symptom Categories as a Function of PMDD and Prior MDD Status

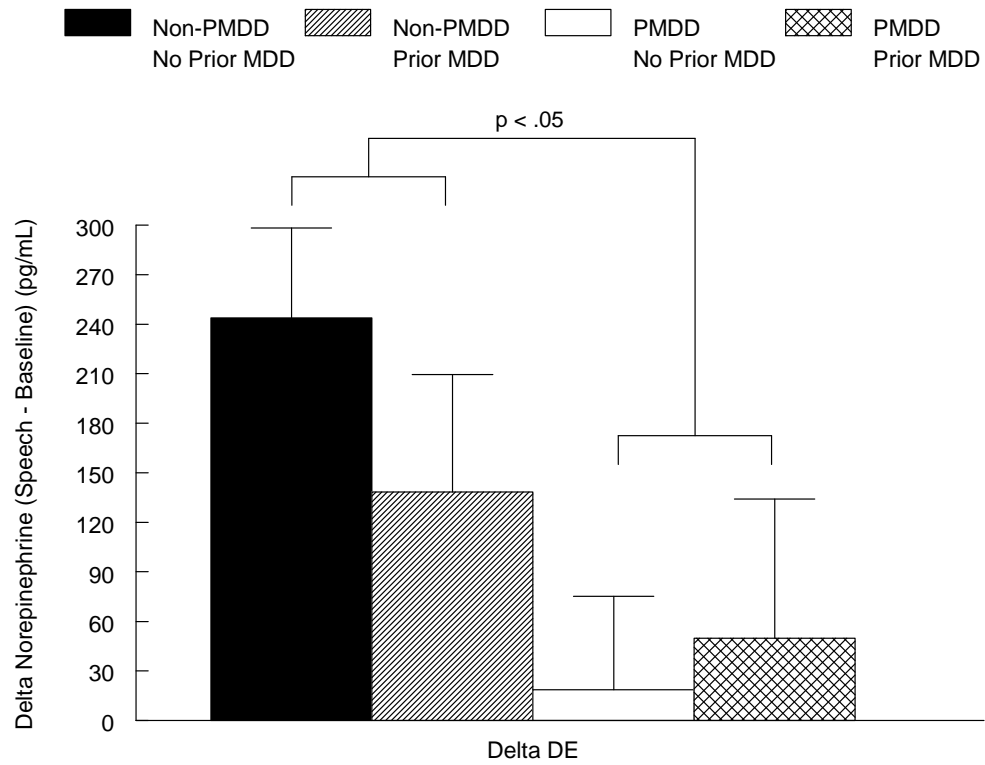


^A PMDD with no prior MDD > all other groups, $p_s < .05$

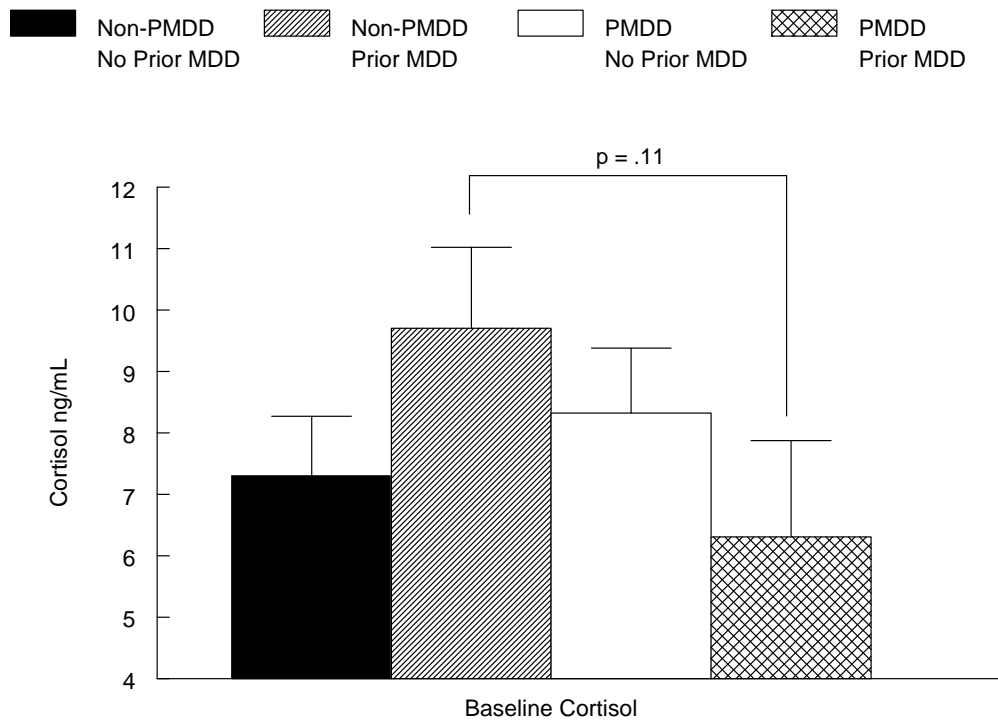
^B non-PMDD with prior MDD > non-PMDD with no prior MDD, $p = .06$

^C PMDD with prior MDD > non-PMDD with no prior MDD, $p < .05$

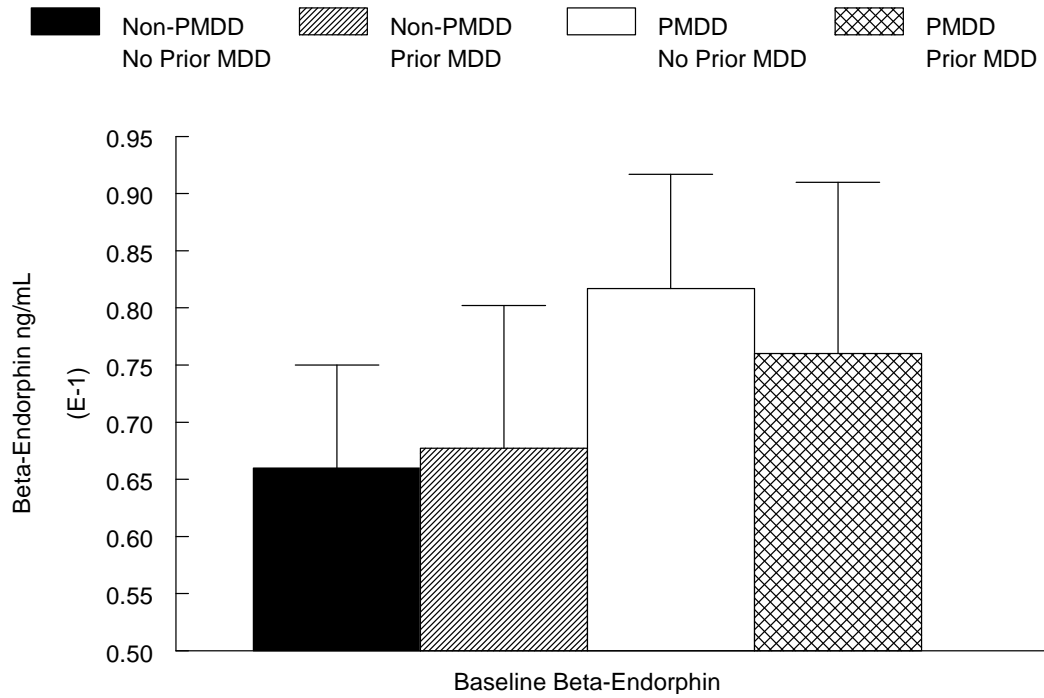
Change in Norepinephrine from Baseline to Speech Stress as a Function of PMDD and Prior MDD Status



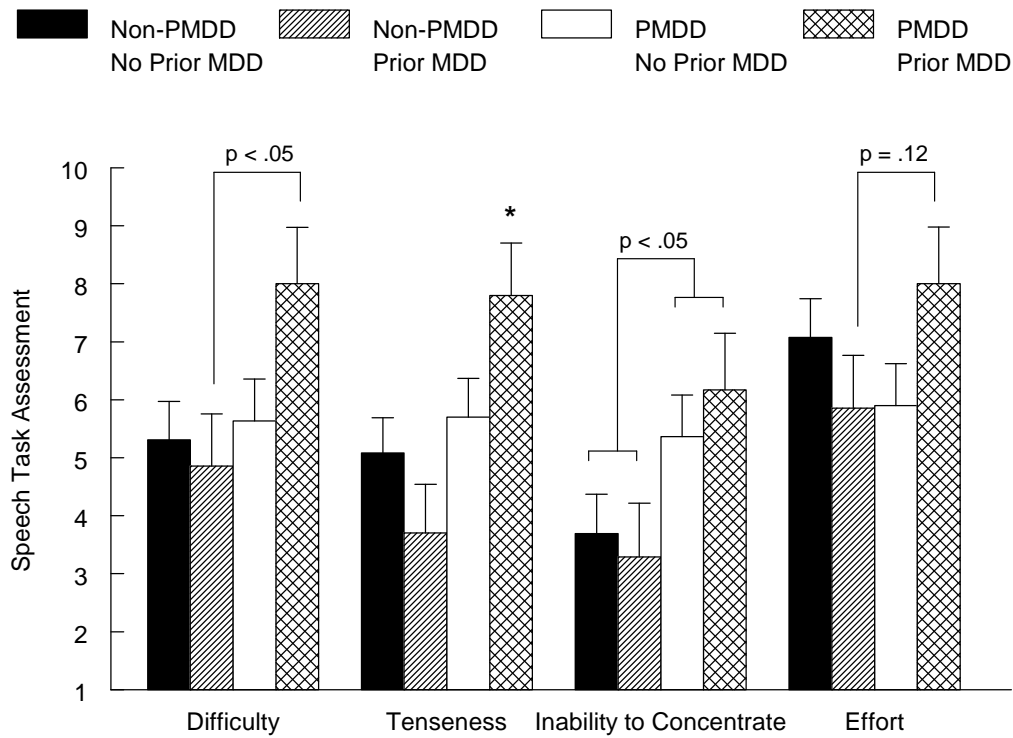
Cortisol as a Function of PMDD and Prior MDD Status



Beta-Endorphin as a Function of PMDD and Prior MDD Status

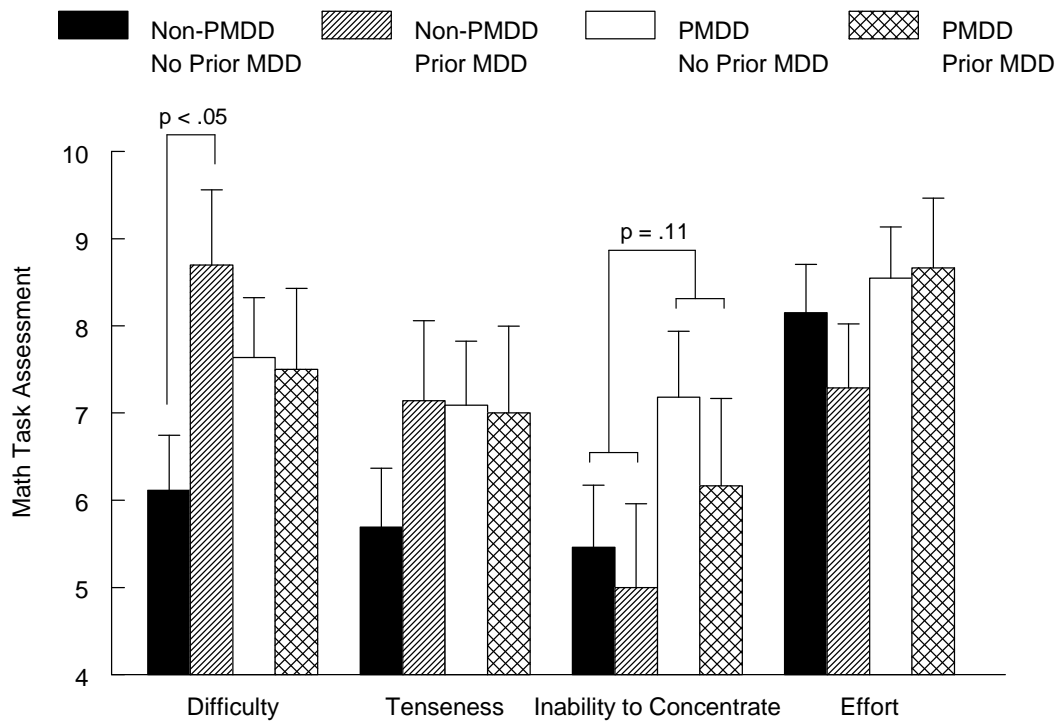


Speech Task Assessments as a Function of PMDD and Prior MDD Status



* PMDD women with prior MDD > all other groups; $p < .05$

Math Task Assessments as a Function of PMDD and Prior MDD Status



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