# FRONTAL ALPHA ELECTROENCEPHALOGRAPHY (EEG) ASYMMETRY AS A RISK FACTOR FOR PRE-MENSTRUAL DYSPHORIC DISORDER (PMDD); A PSYCHOPHYSIOLOGICAL AND FAMILY HISTORY APPROACH.

by

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As members of the Dissertation Committee, we certify that we have read the dissertation prepared by Eynav Elgavish Accortt entitled "Frontal Alpha Electroencephalography (EEG) Asymmetry as a risk factor for Pre-Menstrual Dysphoric Disorder" and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

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## DEDICATION

I dedicate this work to my family. You all exemplify scholarship with your passion for knowledge, meaning and truth. I hope my career as a psychologist will inspire others as you have inspired me.

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## ABSTRACT

Premenstrual dysphoric disorder (PMDD) is a severe dysphoric form of premenstrual syndrome (PMS) that is included as a diagnosis for further study in the DSM-IV (APA, 2000). A primary aim of the present study was to characterize the co-occurrence of PMDD and major depression, in a sample that spans the entire range of depressive severity. The range included non-depressed controls, women meeting criteria for dysthymia, and women meeting criteria for current Major Depressive Disorder (MDD). Co-occurrence of MDD and PMDD were only statistically significant when considering Lifetime MDD. Resting frontal electroencephalographic (EEG) asymmetry has been hypothesized to tap a diathesis toward depression or other emotion-related psychopathology. Another primary aim was to assess Frontal EEG asymmetry in college women who meet criteria for Pre-Menstrual Dysphoric Disorder (n = 25) and 25 matched controls. Participants were assessed four times in a two week period. Women reporting low premenstrual dysphoric symptomatology exhibited greater relative left frontal activity at rest than did women high in premenstrual dysphoric symptomatology. These results are consistent with a diathesis–stress model for premenstrual dysphoric symptomatology. A secondary aim was to assess whether individuals with PMDD or menstrual related mood variability, but no current diagnosis of depression, have an increased family history of depression. Promising evidence of a relationship between family history of MDD and a likelihood of PMDD was discovered. A trend was found for Spectrum PMDD women: a higher rate of Family History of MDD (36%) than non PMDD women (19.6%). Ideally, resting frontal electroencephalographic (EEG)

asymmetry could help us learn more about the etiology of depression and hormonal-related depression specifically, and test whether they may share etiological factors.

# CHAPTER 1

# INTRODUCTION

## 1.1 The Broader Context

Premenstrual dysphoric disorder (PMDD) is classified in the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; American Psychiatric Association, 1994) among the depressive disorders not otherwise specified, and has an estimated prevalence of 3%-8% (Steiner, 2000) and an additional 19% identified as 'near-threshold' cases that failed to meet the strict PMDD criteria (Wittchen, 2002). Although the specific pathophysiologic etiology of PMDD has not yet been elucidated, consensus is growing that it is closely associated with an active hypothalamic-pituitary-adrenal axis (Panay and Studd, 1998). Beyond consideration of PMDD as a distinct clinical entity (Endicott et al., 1999), results from a rather large epidemiological study reveal that premenstrual exacerbation of depression also appears to be relatively common and that such premenstrual exacerbation in depressive disorders predicts greater deterioration in functioning (Hartlage, Brandenburg, & Kravitz, 2004). Relatively little is known about the etiology of PMDD and premenstrual exacerbation of depression (PME-DD), although relatively high response rates to selective serotonin reuptake inhibitors among those with PMDD (Endicott et al., 1999; Steiner, 2000) as well as those with major depressive disorder (Steffens, Krishnan, & Helms, 1997) suggest the possibility of a common underlying diathesis involving serotonergic dysfunction.

Identifying an individual difference measure that may have predictive power to identify people vulnerable to hormone-related mood problems could be very important

for several reasons. In general, psychophysiological measures can provide an important link between social, behavioral, psychological, and cellular levels of analysis (Anderson & Scott, 1999), and can thus serve as endophenotypes (Gottesman & Gould, 2003; Iacono, 1998). Endophenotypes are measurable endogenous characteristics of an individual that are related to underlying mechanisms presenting risk. Such risk may stem from genetic or environmental factors, or their interaction, but in all cases the function of the endophenotype is to provide a relatively easily measured correlate of underlying mechanisms of risk, a correlate that ideally can be identified in at-risk individuals regardless of whether currently symptomatic. It might not be reasonable to expect that all individuals with the symptom-based diagnosis of PMDD would exhibit the marker. Identifying a sizable subset with the endophenotype, however, may prove useful in identifying a subset of those at risk for developing PMDD, and may ultimately assist in identifying the underlying mechanisms that may point to new treatments and preventions. Such a measure could help us learn more about the etiology of depression and hormonal related depression specifically, and test whether it may share etiological factors in common with MDD.

The present study therefore examined whether a putative marker of risk for depression, frontal electroencephalographic (EEG) asymmetry, would also be sensitive to premenstrual dysphoric symptomatology in women with and without major depression or dysthymia. The current study builds on previous work (Accortt & Allen, 2006) that found that women reporting low pre-menstrual distress (n=11) exhibited significantly greater relative left frontal-temporal activity at rest than women high in pre-menstrual distress

(n=12), an effect that was not qualified by phase of cycle (follicular versus luteal). This suggests the possibility of a common diathesis for both major depression and premenstrual dysphoria.

## 1.2 Menstrual Hormonal Fluctuation and Mood

A recent review of the menstrual cycle literature (Clayton, 2008) reports that up to 85% of menstruating women report one or more menstrual cycle-related symptoms, 20-40% report Premenstrual Syndrome (PMS), and 2-9% report PMDD. Clayton adds that when compared to women without menstrual-related problems, the women who did report these problems were 2.5-3 times more likely (adjusted odds ratio) to report frequent anxiety and depression, insomnia, excessive sleepiness, and pain in the previous 12 months.

The influence of hormones on women's depression is suggested by the fact that rates of depression are similar in girls and boys before puberty but that women experience depression approximately twice as often as men in adulthood, and that the sex difference is less pronounced in the elderly (Sprock and Yoder 1997 & Wolk and Weissman 1995). Studies have also shown that women are at increased risk for psychiatric illnesses immediately following childbirth as levels of estrogen and progesterone drop dramatically with the discharge of the placenta following childbirth. (Winstead & Sanchez, 2005). Depression does not, however, only threaten women during a few specific times in their reproductive life span. Some women battle with depressive symptoms monthly, most likely due to the natural cycling of their hormones.

Dramatic changes in mood and behavior in some women in relation to the menstrual cycle have been the focus of recent research (Freeman, 2003). The mechanisms underlying the variability of responses of normal participants to hormonal changes and mood are not clear. Several studies have therefore focused on the symptoms associated with Pre-Menstrual Syndrome and changing hormone levels. Collins, Eneroth and Landgren (1985) studied the psychoneuroendocrine stress response and mood as related to the menstrual cycle. Self-reported mood and somatic symptoms showed distinct phase-related changes, with more negative mood states predominating in the luteal (phase preceding onset of menses) and menstrual phases and increased positive mood states in the follicular and ovulatory phases (Collins, Eneroth, & Landgren, 1985). The follicular phase marks the start of the growth of the endometrium due to increased estradiol. During the luteal phase the endometrium stops growing and during the menstrual phase the endometrium sheds due to a lower level of progesterone. Therefore, the results found by Collins et al. and others support the hypothesis that increased levels of estrogen during a normal menstrual cycle may have a positive effect on mood.

On the other hand, McFarlane and colleagues studied mood fluctuations in women during their menstrual cycles and found that there may be an influence of stereotypes about moods on self-reports of mood. Recollections of menstrual mood changes differed from actual changes. Women retrospectively recalled more pleasant moods in the follicular phase and more unpleasant moods in the premenstrual and menstrual phases than they had reported concurrently. There was also a bias in recollections of weekday mood fluctuations: Weekend highs were exaggerated and Monday blues were reported

even though they were not reported concurrently (McFarlane, 1988). These results point to a need to assess emotion using a variety of measures in addition to self report, and suggest the utility of identifying an individual difference measure that may have predictive power to identify people vulnerable to hormone-related mood problems.

### 1.3 Pre-menstrual Dysphoric Disorder (PMDD) Research

Premenstrual dysphoric disorder (PMDD) is a severe dysphoric form of premenstrual syndrome (PMS) that is included as a diagnosis for further study in the DSM-IV (APA, 2000). PMDD is a complex, chronic, psychoneuroendocrine disorder that affects functioning and well-being and continues throughout the reproductive years. Like all premenstrual syndromes, PMDD is characterized by its symptom pattern being linked to the menstrual cycle, with pronounced symptoms in the late luteal phase, symptom remission during the menstrual flow, and a symptom-free period in the follicular phase of the cycle (Freeman, 2004).

The criteria for a diagnosis of PMDD as described in the DSM-IV include the following: (i) at least five of 11 symptoms, including at least one of the mood symptoms, that are severe pre-menstrually and abate post-menstrually; (ii) the symptoms markedly impair functioning; (iii) the symptoms are not an exacerbation of another physical or mental disorder; and (iv) the symptoms are confirmed by daily ratings for at least two consecutive menstrual cycles. The 11 PMDD symptoms are depressed mood, anxiety/tension, mood swings, irritability/marked anger, decreased interest, difficulty

concentrating, fatigue, appetite changes, sleep difficulties, feeling out of control and physical symptoms (APA, 2000).

Yonkers (2004) reports that premenstrual conditions can be grouped into 3 broad categories: 1) Severe PMDD affects about 2% to 9% of women. 2) Moderate-to-severe PMS affects about 20% to 40% of women. Women with moderate-to-severe PMS have fewer than 5 symptoms but at least 2, and they experience distress associated with the condition and 3) Mild PMS may affect up to 80% of women but does not result in functional impairment (Yonkers, 2004). The baseline 12-month prevalence of PMDD in a population of 1488 reproductive-aged women (ages 14-24) was specifically estimated in a prospective longitudinal survey to be 6%, with an additional 19% identified as 'near-threshold' cases that failed to meet the strict PMDD criteria, mostly because they failed to meet the mandatory impairment criterion. Diagnoses were calculated using DSM-IV algorithms, but daily ratings of symptoms, as required, were not available (Wittchen, 2002).

Addressing treatment of this disorder, Freeman focuses on current information about luteal phase administration (i.e. typically for the last 2 weeks of the menstrual cycle) of pharmacological agents for the treatment of premenstrual dysphoric disorder (PMDD). The symptoms of PMDD, by definition, occur only in the luteal phase of the menstrual cycle and subside following menses, and therefore Freeman explains that treatments that can be limited to the luteal phase are important for limiting exposure to medications and reducing costs. Based on observations of an unexpectedly rapid response to serotonergic medication in PMDD, studies were initiated to determine the efficacy of

luteal phase administration with SSRIs. The efficacy of both fluoxetine (Steiner et. al., 1995 and Wood et. al., 1992) and of sertraline (Yonkers et. al., 1997 and Young et. al., 1998) was convincing. Based on this evidence from randomized clinical trials, SSRIs are the first-line treatment for PMDD at this time. Additionally, when used to treat PMDD, SSRI doses are consistent with those used for major depressive disorder (Freeman, 2004).

Freeman (2004) points out that the involvement of the serotonergic system in PMDD appears to differ from that of other depressive disorders in several ways. First, the response to SSRIs appears to be more rapid than is commonly observed for other depressive disorders, within 1–2 days rather than weeks of the initiation of treatment. Furthermore, the SSRIs are effective when administered only in the luteal phase of the menstrual cycle, indicating both a rapid onset of action and an on/off administration pattern that is clearly effective in the several-month treatment intervals that have been studied. These obvious differences suggest that the underlying mechanisms of PMDD differ from those of other depressive disorders, although these mechanisms have not been identified (Freeman, 2004).

The predominant evidence for the involvement of the serotonergic system in PMDD is this clear response of patients with PMDD to serotonergic antidepressants. The response rates in the studies of these agents ranged from 52% to 69%, with placebo improvement ranging from 15% to 47% (Steiner et. al., 1995, Wood et. al., 1992, Yonkers et. al., 1997 and Young et. al., 1998). These responses are similar to those seen in major depressive disorder and other affective disorders, which have been repeatedly associated with abnormal serotonergic activity. Preliminary reports, however, suggest

that symptoms such as irritability, anger, and affect lability may respond rapidly to SSRIs in patients with conditions such as stroke, dementia, and brain injury [for references, see Eriksson, 1999]. In view of these reports, the rapid onset of action of SSRIs in PMDD may be taken as support for the notion that irritability and affect lability, rather than depressed mood or anxiety, should be regarded as the most prominent target symptoms when these drugs are used for PMDD (Landen & Eriksson, 2003).

Yonkers (2004) adds that although the SSRIs are the gold standard, (approximately 55% to 60% of women will respond to treatment) there are other PMDD treatment options. Gonadotropin-releasing hormone (GnRH)-agonist therapy, for example, suppresses ovulation and reduces ovarian steroid production. Although shown to benefit a broad range of symptoms of PMS and PMDD, GnRH-agonist therapy induces menopause and requires add-back hormone therapy (HT) for bone preservation if it is administered for 6 months or longer. The GnRH agonists are therefore effective in treating PMDD, although the initiation of menopause and potential symptom recurrence with add-back HT diminishes the utility of the treatment (Yonkers, 2004).

To test the hypothesis that estrogen and progesterone are indeed linked to menstrual cycle-related symptoms, Schmidt et al. (1998) studied the effects of leuprolide, an ovulation suppressor, in 20 women with PMS. Women receiving leuprolide showed a significant decrease in most symptoms compared with women who were given placebo ($p<0.05$). As a follow-up study, women with PMS were also given leuprolide followed by supplemental hormone replacement with estradiol and progesterone. Compared with women with PMS who were given leuprolide plus placebo, the women receiving

hormone replacement after ovulation suppression showed a significant recurrence of many PMS symptoms, suggesting that estrogen and progesterone may play a role in the etiology of these symptoms. Because women with PMS or PMDD typically have levels of estrogen and progesterone within normal levels, they may be experiencing a heightened sensitivity to normal changes in sex steroids across the menstrual cycle (Clayton, 2008).

Therefore, Oral contraceptives (OC) agents have been considered a potentially effective treatment for PMDD. OCs are, however, under-researched although Drospirenone (DRSP, a newly available progestin), is being investigated and offers promise with respect to treatment of PMS/PMDD, although data at this point are inconclusive. If new data continue to support the benefit of OC agents, they may represent an appropriate choice for many women, particularly those who seek contraception but also require treatment for PMS and PMDD (Yonkers, 2004).

Wihlback et al. (2004) agree that neuroendocrine factors are likely to contribute to the overall increased risk for developing mood disorders in women, and that the neuroendocrine influence is most obviously seen in women with premenstrual dysphoric disorder (PMDD) as these women experience depressed mood and anxiety premenstrually only during ovulatory cycles. Wihlback adds that dysfunction of serotonergic transmission has been regarded as an important mechanism in several psychiatric disorders and ovarian steroids have been shown to profoundly influence the activity of the serotonergic system. Given these facts, Wihlback and colleagues (2004) examined whether binding of [3 H] paroxetine to the platelet serotonin transporter or

binding of [3 H] lysergic acid diethylamide ([3 H] LSD) to the platelet 5-HT2A receptor were influenced by the cyclical changes in circulating estradiol and progesterone that occur during the menstrual cycle. Twenty-eight healthy (no PMDD diagnosis) women, without oral contraceptives and with regular menstrual cycles were examined. Wihlback found a decrease in binding for both serotonin transporter and serotonin2A receptor during the luteal phase, a period of time during which women with PMDD experience negative mood changes. These findings may provide a link between the ovarian steroids and serotonergic neurotransmission, which in turn could explain part of the specific vulnerability that women have for the development of mood and anxiety disorders and for the deterioration in mood seen so frequently during the luteal phase (Wihlback et al., 2004).

On the other hand, Hsiao (2004) notes that even though a number of studies have demonstrated the correlation of depression and anxiety to estrogen and progesterone in premenstrual dysphoric disorder (PMDD), the findings are still controversial. For example, one study showed no alterations in estrogen and progesterone levels in women with premenstrual syndrome and another study showed that the efficacy of progesterone for PMDD was no better than placebo (Backstrom et al, 1983; Smith, 1976, cited in Hsiao, 2004). Hsiao thus sought to determine the relationships between hormonal changes and mood changes in a larger sample of Taiwanese women with PMDD by directly measuring estrogen and progesterone levels. They found that there were no statistically significant correlations between depression or anxiety ratings and estrogen or progesterone concentrations (Hsiao et al, 2004). Hsiao explains that peripheral blood

hormone values (that these other investigators collected) may not accurately reflect levels within the central nervous system and, moreover, that estrogen and progesterone dynamics in the brain are not well understood. For example, estrogen and progesterone are metabolized to other hormones that influence depression or anxiety in the brain, such as allopregnanolone and pregnanolone (Hsiao et al., 2004).

Some research, however, supports Hsiao's conclusions. A large epidemiological study found that among women with PMDD who were starting hormone-based contraceptives, most women showed no change in mood, with mood improving in some women and worsening in others (Joffe et al., 2003). This finding in a community-based study agrees with that of an earlier report that hormone-based contraceptives have no effect on mood in this population (Oinonen and Mazmanian, 2002). Studies of ''normal women'' given hormone-based contraceptives generally report little change in mood (Masse et al., 1998), or they report an altered pattern of mood changes across the menstrual cycle when women on hormone-based contraceptives were compared to those on non-hormone contraceptives (Abraham et al., 2003). To complicate matters, there is some literature suggesting that progestin-only forms of contraceptive may actually worsen mood in women who are susceptible to depression (Lawrie et al., 1998).

A research group (Young et al., 2007) set out to examine the association of hormone-based contraceptives with mood in a population of premenopausal women with non-psychotic major depressive disorder (MDD) to determine whether those that use combined hormone contraception, progestin-only contraception, or neither differ in terms of depression severity, function and quality of life, and general medical and psychiatric

comorbidity. Young and colleagues found that women on progestin-only had significantly more general medical comorbidities (greater hypersomnia, weight gain and gastrointestinal symptoms) and worse physical functioning than women in either of the other groups. Those on combined hormone contraception were significantly less depressed than those with no hormone treatment (by the 16-item Quick Inventory of Depressive Symptomatology—Self-Rated). The combined hormone group also demonstrated better physical functioning and less obsessive compulsive disorder comorbidity than either of the other groups. Young et al. concluded that synthetic estrogen and progestin may influence depressive and physical symptoms in depressed women (Young et al., 2007).

### 1.4 Co-occurrence of PMDD and Depression

PMDD is classified as a ‘‘Depressive Disorder Not Otherwise Specified (NOS)’’ in the DSM-IV-TR and perhaps the most difficult differential diagnosis for clinicians to make is distinguishing between PMDD and Major Depressive Disorder (MDD). There are several possible explanations for co-occurrence: MDD is a risk factor for PMDD, PMDD is a risk factor for MDD, they are completely separate disorders, they are different manifestations of the same underlying problem, they are a standard comorbid disorder, and/or there is pre-menstrual exacerbation of major depressive symptoms (PME-DD).

Women with PMDD are more likely to have had a history of depression (Endicott & Halbreich, 1988) and are more likely to develop a subsequent episode of MDD

(Yonkers, 1997). The comorbidity between the two disorders is significant, ranging from 30 to 70% (Endicott, 1994). MacQueen (2004) reports that the likelihood of past depression in women with PMDD is 30% to 97% (Yonkers, 1997; Cohen et al, 2002; Pearlstein et al., 1990). Additionally, PMDD is associated with an increased risk of developing MDD, above and beyond a family history of depression and a personal history of depression (Graze et al., 1990).

The similarities in symptoms between PMDD and MDD are evident; in fact, a severe case of PMDD can resemble a full depressive episode. Some of the overlapping symptomatic criteria include: depressed mood, irritability, decreased interest, difficulty concentrating, fatigue, changes in appetite, and changes in sleep (Yonkers, 1997). However, some women with PMDD do not report depressive symptoms at all (Bhatia and Bhatia, 2003). For example, Angst and colleagues (2001) reported that the prevalence of depressed mood in women with PMDD was 30.8%, thus, over two-thirds of women did not report feeling depressed. Yet, the majority of women with MDD (83% current MDD; 57% past MDD) have premenstrual changes, including an increase in the severity of depressive symptoms, the appearance of new symptoms (including physical ones), and less control of suicidal impulses (Endicott & Halbreich, 1988)

According to Di Guilio and Reissing (2006), several differences can be noted between PMDD and MDD which clearly distinguish them from one another. Diagnostically, the criteria of anxiety and tension, affective lability, marked anger/irritability, a sense of being overwhelmed, and physical symptoms (i.e., breast pain, bloating) are not typically found in MDD. The most frequently endorsed symptom was

irritability (46.2%), which suggests that irritability may be the key feature of PMDD rather than depressed mood (Landen & Eriksson, 2003; Angst et al, 2001). The course of PMDD (detailed in section above) is more predictable than that of MDD. MDD has a more unstable and unpredictable course, tends to have an earlier onset, and no decline of symptoms associated with hormonal changes (Endicott et al, 1999).

Further evidence differentiating PMDD from MDD can be found in treatment outcome studies. Symptoms of PMDD tend to persist beyond successful pharmacological treatment of MDD in women diagnosed with both (Glick et al., 1991). The most striking treatment difference is found in the administration and course of effectiveness of SSRIs. SSRIs are almost immediately effective in relieving symptoms of PMDD, detailed above (Freeman, 2004).

Hartlage et. al. (2004) state that premenstrual exacerbation of the symptoms of depressive disorders (PME-DD) must be distinguished from premenstrual dysphoric disorder (PMDD). Symptoms of PMDD are absent or mild post-menstrually, and are marked or severe premenstrually and interfere with functioning. Some people argue that PMDD is mistaken for depression that becomes worse premenstrually (Endicott et al., 1999). Indeed, up to half of women seeking treatment for premenstrual disorders have PME-DD (Plouffe et al., 1993). Moreover, six symptoms of major depressive disorder (MDD) also are symptoms of PMDD (e.g., depressed mood). In such cases, the difference between PME-DD and PMDD is not the nature of symptoms, but their timing (Hartlage et al., 2001). Both groups experience more severe symptoms pre-versus post-menstrually. However, women with PME-DD also experience marked or severe

symptoms during the follicular phase. Other symptoms of PME-DD (e.g., suicidal ideation) may become worse pre-menstrually and differ from those of PMDD. Additionally, repeated episodes of depression may sensitize depressed women to PME-DD. For example, past episodes may act as a "kindling" mechanism in which increasingly severe depression occurs with little provocation (Post and Ballenger, 1981). The provocation may be fluctuations of hormones and neurotransmitters related to the menstrual cycle (Breaux et al., 2000; Kendler et al., 2001).

Hartlage studied premenstrual exacerbation of depressive disorders (PME-DD) in a representative sample. Of the 900 menstruating females from ages 13 to 53 who completed semi-structured psychiatric diagnostic interviews and rated symptoms of depression daily for two menstrual cycles; 58 had major depressive, dysthymia, or subclinical depressive disorders, and the remaining 842 were the non-depressed portion of the representative sample. Depressed females had on average 1.34 symptoms exacerbated pre-menstrually. The best model for predicting exacerbation contained only age with older women having symptoms worsen more often. Symptoms during the follicular phase were most severe for clinically depressed, intermediate for subclinically depressed and least severe for non-depressed participants. Consistent with the hypothesis that exacerbation is related to cyclicity in all females, the number of symptoms that became worse did not differ between groups ($p < 0.46$). Additionally, only 56% of non-depressed females taking antidepressants were asymptomatic all month long; the remaining 44% still had symptoms pre-menstrually. Therefore, women may be

susceptible regardless of severity of depression, number of episodes, or remission status (Hartlage et al, 2004).

Yonkers et al. raise the issue that interventions need to be examined in these ‘‘special’’ but not necessarily ‘‘pure’’ PMDD populations. Many women have symptoms throughout the menstrual cycle and experience premenstrual worsening, as Hartlage et al report above. Reports from ob-gyn primary care practices (Plouffe et al., 1993; West, 1989), and community cohorts (Wittchen et al., 2002) show that many patients with severe premenstrual symptoms also have concurrent conditions such as dysthymic disorder, minor depressive disorder or an anxiety disorder. Clinically, women with comorbid illness may comprise a substantial proportion of the population with unique characteristics that influence treatment response. Yonkers adds that currently, there are no data to guide clinicians in the management of this group of patients and treatment research for women with comorbid illness is essential to lead to a better understanding regarding the generalizability of efficacy findings. To add to this literature Yonkers recruited women from 6 primary care obstetric gynecological practices. 47% of 904 women screened in practice settings (n=426) endorsed current PMS symptoms. 93 women (22% of the 426) had comorbid MDD, 23 (5.4%) had minor depressive disorder and 61 (14%) had panic disorder. Moreover, 24% of women with possible PMDD endorsed suicidal thoughts at any level (several days, more than half the days or every day), and 20% endorsed these thoughts for several days. These preliminary findings show that many women in primary care ob-gyn settings endorse serious premenstrual symptoms and have concurrent psychiatric conditions (Yonkers et al., 2003).

Several studies have reported that women with severe premenstrual complaints are at greater risk for panic disorder, generalized anxiety disorder, and depression [for references, see Angst et al., 2001; Breaux et al., 2000; Wittchen et al., 2002; Yonkers, 1997a,b]. Landen et al (2003) point out that when interpreting these results, one must take into consideration that participants with depression or an anxiety disorder, experiencing premenstrual aggravation of this condition, may tend to confirm PMS or PMDD at interview, without actually meeting the criteria for these diagnoses. The marked comorbidity reported in many studies may hence reflect the difficulty in correctly diagnosing PMDD in the absence of prospective symptom rating, rather than a genuine comorbidity.

### 1.5 Resting Frontal EEG Asymmetry as a Moderator of Emotion

Studies assessing resting electroencephalographic (EEG) activity reveal that relatively less left than right frontal brain activity characterizes depressed individuals both when symptomatic (Allen, Iacono, Depue, & Arbisi, 1993; Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1991; Schaffer, Davidson, & Saron, 1983), as well as when euthymic (Allen et al., 1993; Gotlib et al., 1998; Henriques & Davidson, 1990), although not without exception (Reid, Duke, & Allen, 1998). Such data raise the possibility that resting frontal EEG asymmetry may tap a diathesis towards risk for depression or other emotion-related psychopathology (Allen, Urry, Hitt, & Coan, 2004; Coan & Allen, 2004).

The putative diathesis tapped by frontal EEG asymmetry is frequently interpreted in terms of the approach-withdrawal model (Davidson 1993 &1998) of anterior brain asymmetry. Resting frontal EEG asymmetry has been hypothesized to relate to approach-related and withdrawal-related emotion and motivation, with relatively greater left frontal resting activity (relatively less left frontal alpha) associated with positive emotions and approach-directed motivation to attractive cues and appetitive goals. Greater relative right frontal activity, on the other hand, is hypothesized to be a part of a neural system that facilitates negative emotions and withdrawal-directed responses to aversive or threatening stimuli (Harmon-Jones & Allen, 1997; Miller & Tomarken, 2001).

Greater left resting frontal activity has been found to be related to trait-like dispositions such as behavioral activation sensitivity (Coan and Allen, 2003; Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997), while greater right resting frontal activity has been found to be related to psychopathology such as depression (Henriques & Davidson,1991) and anxiety (Davidson et. al., 2000). Additionally, resting frontal EEG asymmetry has been found to predict subsequent emotional responses such as responses to film clips (Wheeler et al., 1993) or infant responses to separation from mother (Fox & Davidson, 1988). In Wheeler's study, greater left frontal activity at rest was associated with reports of more intense positive affect in response to positive films, whereas greater right frontal activation was associated with more intense reports of negative affect in response to negative films, as predicted by the model. Davidson and Fox studied resting frontal EEG asymmetry in 13 healthy infants and found that infants who cried during maternal separation showed greater right frontal activity during a

baseline period compared with infants who did not cry. Findings such as these suggest that frontal EEG asymmetry may moderate subsequent emotional responses, and suggest that resting frontal EEG asymmetry may similarly identify those individuals likely to show the greatest mood variability as a function of the phase of menstrual cycle.

### 1.6 Sex Steroids: Effects On Frontal EEG: Human Studies

Regardless of precisely how estrogen has its biochemical effect on mood, there have been investigations into how this complicated sequence of events culminates in general EEG changes (not specific to frontal regions) due to varying levels of estrogen. This is not easily studied in humans, and the short literature on the topic is a testament to that difficulty. As early as 1971, psychologists attempted to study the effect of hormones on the EEG of women (Vogel, Broverman, & Klaiber, 1971), specifically photic driving responses. Subsequently, Contreras et al, 1989, investigated the relationship between anxiety, psychophysiological variables and the menstrual cycle in healthy women, finding EEG frequency changes. They did not, however, specifically examine frontal asymmetry. Another study (Saletu et al., 1995) examined the antidepressant and vigilance-promoting properties of transdermal estrogen in post-menopausal depression using hormonal, syndromal and EEG mapping evaluations. There was a significant improvement, after a three-month treatment with transdermal estrogen or placebo, as assessed by the Kupperman Index as well as the Hamilton Depression Rating Scale in both groups, with no intergroup difference. Saletu and colleagues concluded that the

neurophysiological findings suggest improvement of vigilance by estrogen, but added that there were no changes in the frontal alpha asymmetry index (Saletu et al., 1995).

More recently, a group set out to specifically examine frontal asymmetry in women with menstrual-related distress. Baehr, Rosenfeld, Miller, & Baehr (2004) observed two monthly cycles for five women diagnosed as having Premenstrual Dysphoric Disorder (PMDD) and one monthly cycle for five non-PMDD control participants. Asymmetry percent scores for the five PMDD women, and for the five control participants before and after the luteal phase were typically within the normal non-depressed range, however the asymmetry scores for the PMDD group fell into the negative range (more right frontally active) during the luteal period while the control participants remained stable. In contrast to that of Baehr et al. (2004), Accortt and Allen (2006) used a larger sample that was not taking antidepressant medications, with carefully timed late luteal and follicular visits by women either high or low in self-reported premenstrual negative affect. Results showed that women reporting low pre-menstrual distress (n=11) exhibited significantly greater relative left frontal-temporal activity at rest than women high in pre-menstrual distress (n=12), an effect that was not qualified by phase of cycle (follicular versus luteal). This suggested the possibility of a common diathesis for both major depression and premenstrual dysphoria (Accortt & Allen, 2006).

### 1.7 Sex Steroids: Neurobehavioral Effects on the Brain

One functional neuroimaging study of PMDD used single photon emission computed tomography to examine regional cerebral blood flow (rCBF) in 7 women with

severe PMS and 7 control participants. Decreases in rCBF in the temporal lobes (which correlated with changes in Hamilton–Depression scores) were found on the premenstrual scan in PMS patients (Buchpiguel et al., 2000). A more recent fMRI study investigated menstrual cycle-dependent brain activity and focused on menstrual cycle times of greatest expected hormonal divergence. Goldstein et al found higher blood oxygen level-dependent (BOLD) responses in a number of limbic regions associated with negative emotional processing in the early follicular vs. midcycle phase (Goldstein et al., 2005). Based on this research and given the phenomenology of PMDD (Landen and Eriksson, 2003), it is reasonable to hypothesize that PMDD patients (vs. asymptomatic controls) in the pre- vs. postmenstrual phase would display enhanced processing of negative emotion, diminished inhibitory control (particularly in the context of negative emotion), and diminished processing of positive emotion.

Dreher et al (2007) investigated the influence of estrogen and progesterone on the human reward system. They used functional MRI and an event-related monetary reward paradigm to study women in a repeated-measures, counterbalanced design across the menstrual cycle. During the midfollicular phase (days 4–8 after onset of menses) women anticipating uncertain rewards activated the orbitofrontal cortex and amygdala more than during the luteal phase (6–10 days after luteinizing hormone surge). At the time of reward delivery, women in the follicular phase activated the midbrain, striatum, and left fronto-polar cortex more than during the luteal phase. These data demonstrate increased reactivity of the reward system in women during the midfollicular phase when estrogen is unopposed by progesterone. Correlation between brain activity and gonadal steroid levels

also revealed that the amygdalo-hippocampal complex was positively correlated with estradiol level, regardless of menstrual cycle phase (Dreher, 2007).

Goldstein's recent study did not compare sex differences in brain activity and did not assess hormonal levels directly, and therefore could not specify whether the observed changes correlated with estrogen and/or progesterone. They did, however, demonstrate that generally arousing stimuli may modulate similar brain networks across menstrual cycle phases. Dreher's recent results add to the understanding of sex differences in emotion-related behavior and show that the response of the amygdalo-hippocampal complex to different types of arousing stimuli depends on both sex differences and the actions of gonadal steroids. These sex differences in the amygdala's function may be related to structural and developmental sex differences, such as the higher concentration of sex hormone receptors and larger size of the amygdala in men, as well as to circulating estrogen and progesterone levels (Dreher, 2007).

Protopopescu et al (2008) examined PMDD pathophysiology by using a functional magnetic resonance imaging (fMRI) probe of fronto-limbic function. Protopopescu et al examined BOLD response to emotional words in the context of an emotional Go/NoGo inhibitory control task. They examined alterations in this response across the menstrual cycle. In the premenstrual (vs. postmenstrual) phase, PMDD participants (n=8), compared with asymptomatic participants (n=12), showed an increased amygdala response to negative vs. neutral stimuli, and a decreased ventral striatum response to positive vs. neutral stimuli. By contrast, asymptomatic participants showed patterns of increased medial and decreased lateral orbitofrontal cortex (OFC)

response to negative vs. neutral stimuli in the premenstrual vs. postmenstrual phase, whereas the PMDD participants failed to show any such effects.

Overall these results support a neurobiological model of enhanced negative emotional processing, diminished positive emotional processing, and diminished top-down control of limbic activity in PMDD during the premenstrual phase. Protopopescu's findings specifically provide a basis for a neurocircuitry model of PMDD, and have implications for studies of mood/emotional regulation across the human menstrual cycle (Protopopescu et al., 2008).

## 1.8 Familial Risk of Depression and Premenstual Dysphoria

A substantial body of evidence has established that major depression is a familial phenotype (Merikangas et al, 1988; Winokur et al 1982) or at the very least, a risk for major depression appears to be heritable. In case-control family studies, the risk of depression for relatives of depressed probands has been substantially and significantly higher than the risk for relatives of normal controls. Relative risks ranged from approximately 2-fold to 6- fold (Gershon et al., 1982; Weissman et al., 1984, 1993; Kutcher et al., 1991; Bland et al., 1986; Warner et al., 1995).

Twin studies have further suggested that the familial nature of MDD reflects a substantial genetic influence (Bertelsen, 1977; Torgersen, 1986; Englund and Klein, 1990; Kendler et al 1992; McGuffin et al. 1996; Lyons et al. 1998). The diverse methods, sample sizes, and diagnostic criteria used in these studies may account for the variation in reported heritability estimates. Although some twin studies have not indicated a genetic

component in depression (Andrews et al, 1990) two recent large studies using modern diagnostic criteria and blinded assessments provide evidence for at least a moderate genetic contribution (Kendler and Prescott, 1999 & McGuffin et al, 1996). Finally, in the largest sample to date (Kendler et. al., 2006), lifetime major depression was moderately heritable, with estimates similar to those in prior studies. In accord with some but not other previous investigations, Kendler's study suggests both that the heritability of major depression is higher in women than in men and that some genetic risk factors for major depression are sex-specific in their effect.

Genetic factors seem to contribute to the occurrence of menstrual cycle-related symptoms as well. Seventy percent of women whose mothers had PMS also have PMS, compared with 37% of women whose mothers were not affected, although these data are collected from anecdotal accounts reported by mothers and daughters. In addition, more than 90% of monozygotic twins are concordant for PMDD versus only 44% of dizygotic twins (Parry & Rausch, 1995).

# CHAPTER 2

# RELEVANCE OF THE DISSERTATION

## 2.1 The Present Study

The present study sought to investigate whether a putative endophenotype of risk for depression, resting frontal EEG asymmetry, would also identify those with PMDD. The current study builds on previous work (Accortt & Allen, 2006), which found that women reporting low pre-menstrual distress exhibited greater relative left frontal-temporal activity at rest than women high in pre-menstrual distress, an effect that was not qualified by phase of cycle (follicular versus luteal), suggesting the possibility of a common diathesis for both major depression and premenstrual dysphoria. The present study allows for an examination of frontal brain activity in a larger sample, and one that includes individuals with major depression and dysthymia. This provides a stronger test of the role of resting frontal EEG asymmetry as a risk factor for menstrual-related dysphoria. Lastly, the present study sought to add to the family history literature by assessing whether individuals with PMDD or menstrual related mood variability have an increased family history of major depression.

## 2.2 Specific Aims

The primary aims are: 1) to characterize the co-occurrence of PMDD and major depression, in a sample that spans the entire range of depressive severity including non-depressed controls, women meeting criteria for current major depressive disorder (MDD)

and current dysthymia; and 2) to examine whether resting frontal electroencephalography (EEG) asymmetry may serve as a marker of premenstrual dysphoria, and whether such a relationship is independent of any history of major depressive disorder and/or dysthymia;

A secondary aim is to assess whether individuals with PMDD or menstrual related mood variability have an increased family history of depression.

# CHAPTER 3

# METHODS

## 3.1 Participant Selection

This sample was obtained in the context of a larger study on EEG asymmetry and risk for depression that included both males and females. During a large survey as part of the introductory psychology course each semester, 800-1200 women completed the Beck Depression Inventory (BDI). Women selected from all BDI score ranges were invited to participate in the present study, with the aim of having a roughly rectangular distribution of BDI scores. Potential participants were telephoned if they expressed interest in further participation on the screening questionnaire. Potential participants were then queried about inclusion and exclusion criteria (see below). Those not excluded were given a face-to-face intake interview by an advanced graduate student interviewer, consisting of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967) and the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1994) as well as a custom interview covering PMDD symptoms. The purpose of the intake was to confirm inclusion and exclusion criteria and to classify women in terms of whether they meet criteria for MDD (past or current), Dysthymia, or Pre-Menstrual Dysphoric Disorder.

Once women were included in the study, they were asked about their current phase of cycle, by counting backwards from the first day of the next anticipated menses, and about their use of hormone-based contraceptives in order to determine cycle timing. The custom PMDD interview involved asking each woman a series of questions concerning

PMDD symptoms. This structured interview was created from the DSM-IV-TR criteria for PMDD, and modeled after the SCID in terms of format. Women who met criteria for PMDD were asked to complete a daily symptom rating checklist (Endicott et al., 2006) for two consecutive cycles.

Also during this intake, family history of depression was obtained by a proxy interview (cf. Burnam et al., 1985) using a version of the Family History method (Andreasen, Endicott, Spitzer, & Winokur, 1977). Each participant was asked to provide information for both biological parents, and any children or full siblings. For each relative, the interviewer inquired about lifetime presence of depressive symptoms in that relative using question stems adapted from the corresponding SCID question. The interviewer asked additional probe questions until presence or absence of major depression could be determined. Although the proxy interview may tend to underestimate psychopathology in these nonparticipating family members, it rarely misidentifies nonexistent psychopathology (Burnam et al., 1985; Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002). If any of their first degree relatives met criteria for MDD, the participants would be classified as being family history positive. Lastly, one of the 164 participants in the present study was adopted, therefore results for a total of 163 participants are included in the family history analyses.

## 3.2 Exclusion/Inclusion Criteria

Participants were included if they: 1) provided contact information and expressed interest in further study; 2) had normal or corrected-to-normal vision in order to perceive

all stimuli presented on a computer monitor; 3) reported no current prescription and/or use of psychotropic medication and were not under the influence of psychoactive substances; 4) had no current diagnosis of any psychological disorder (other than PMDD, Major Depressive Disorder (MDD), or Dysthymia), and no history of mania or psychosis; 5) had no disorders affecting the Central Nervous System (e.g., previous head injury resulting in the loss of consciousness); and 6) reported strong right-handedness as indicated by a score of 36 or greater on the 39-point inventory of Chapman and Chapman (1987).

### 3.3 Population Details

Recruitment began in the fall semester of 2004 and was completed in the spring of 2007. Across these 6 semesters approximately 177 women were recruited. Seven women dropped out of the study, and six women did not complete the PMDD interview for various reasons, resulting in a total of 164 women included in the study. All participants were university undergraduate students with an age range of 18 to 25 years, and an average age of 18.9 years (± 1.2 s.d.). Of the 164 women participants 121 were White (73.8%), 15 identified themselves as “other” (9.1%), 9 were Asian (5.5%), 6 were Black (3.7%), 6 were American Indian (3.7%), 6 did not respond to the question (3.7%) and 1 was “More than Once Race” (0.6%). The number of women in the present study using hormonal-based contraceptives (HBC) including birth control pills (BCP), the patch, implants etc. was 60 out of 164 (36.6%). Moreover there was no relationship between the use of HBC and PMDD, regardless of whether PMDD was defined as Strict or

Spectrum (defined below; Strict, $X^2$ (1, N=164) = .21, p>.60; Spectrum, $X^2$ (1, N=164) = .15, p>.60). Table 1 presents demographic details for the sample by diagnostic status.

3.4 Participant Grouping

For the purpose of examining the relationship between MDD status and PMDD classification the following groups were defined among the 164 total women included in the analyses. A total of 30 women endorsed sufficient pre menstrual symptoms to be invited to participate in the daily diary monitoring (Daily Record of Severity of Problems, DRSP). Because participants were not compensated for participating in the diary, compliance was generally poor. Therefore the diary data were unable to provide conclusive evidence of 2 consecutive cycles with late luteal phase mood worsening. On the other hand, partial diary data were able to disconfirm at least one cycle of late luteal mood worsening in 5 participants all of whom were excluded from the PMDD classification. Among the remaining 25 interview identified participants,13 participants were classified as Strict PMDD because they met DSM-IV-TR criteria by self report during the interview, endorsing five or more of the DSM-IV-TR items with symptoms that lasted four or more days. The other 12 participants endorsed five or more of the DSM-IV-TR items during interview, but symptoms lasted less than four days, which does not meet the DSM requirement of symptoms lasting more than half of the week. These 12 women, together with the women meeting the strict criteria (totaling 25 participants), were classified as Spectrum PMDD.

Participants were further categorized in terms of Major Depressive Disorder status into the following non-mutually exclusive groupings: 1) Current Major Depressive Disorder (MDD); 2) Currently Euthymic, MDD Hx + referring to participants with past MDD only and no current MDD diagnosis; 3) Lifetime MDD for participants with either past or current MDD diagnosis; and, 4) Dysthymic Disorder.

For group comparisons assessing resting frontal EEG asymmetry, it was necessary to match PMDD participants with controls on the presence or absence of the depressive diagnoses described above. Therefore a group of 25 control subjects were selected for the 25 Spectrum PMDD participants, matching these participants for MDD and Dysthymia status. In terms of matching, although there were 2 women in the Spectrum PMDD classification who met criteria for dysthymia status, there was only 1 individual without a PMDD diagnosis with dysthymia; thus the other Spectrum PMDD participant was matched with a woman meeting criteria for MDD status instead. Lastly, study controls were included in the control category because they either endorsed fewer than 5 items on the PMDD interview (five or more of the DSM-IV-TR items are required for a diagnosis of PMDD) and/or they did not meet the day or functional interference criteria. On average, the 25 PMDD positive cases endorsed 6.72 PMDD symptoms and the 139 controls endorsed 1.35 PMDD symptoms. Demographic information provided by participant grouping in Table 3.1 below.

Table 3.1: Demographic Information

| | Entire Sample | Matched Controls for EEG | Strict PMDD | Spectrum PMDD |
|---|---|---|---|---|
| N subjects | 164 | 25 | 13 | 25 |
| Mean Age | 18.85 +/- 1.2 | 18.8 +/- 0.62 | 19.3 +/- 1.7 | 18.9 +/- 1.4 |
| % HBC | 36.6 % | 32 % | 30.8 % | 40 % |
| N with Dysthymia | 11 | 1 | 0 | 2 |
| N with MDD | 35 | 10 | 5 | 9 |
| Race Percentage | | | | |
| Caucasian | 73.8 % | 76 % | 69.2 % | 84 % |
| Other | 9.1 % | 16 % | | |
| Asian | 5.5 % | 4 % | 7.7 % | 4 % |
| Black | 3.7 % | 4 % | 15.4 % | 8 % |
| Am. Indian | 3.7 % | | 7.7 % | 4 % |
| More than one | 0.6 % | | | |
| No Response | 3.7 % | | | |

### 3.5 Preparation for physiological recording

Participants interested in and eligible for the study then made four visits to the laboratory for EEG sessions, within a two-week period (with the exception of three women that were seen within 18 days). Participants were prepared for psychophysiological recording by placing a stretch-lycra cap with Ag-AgCl electrodes on their heads, and additional electrodes were placed to monitor eye movements and electrocardiographic (EKG) activity, which will not be reported here. Impedances at all sites were required to be less than 20K ohms. Signals were recorded from sixty-four scalp sites (in the 64-channel Quickcap by Neuroscan Inc, El Paso TX) with a SynAmps2 amplifier with a Gigaohm input impedance. All EEG sites were referenced online to a reference lead posterior to Cz, recorded with digital differential amplifiers (bandpass 0.1 to 200 Hz), and digitized continuously at 1000 Hz. At all sites, skin was prepared by gently cleaning with of Omni-Prep and denatured alcohol.

After preparation for psychophysiological recording, participants were seated in a comfortable chair in a room with dim incandescent lighting. Resting EEG was recorded for two different eight minute periods, each in blocks with eyes-open (O) and with eyes-closed (C), in one of two counterbalanced orders (OCCOCOOC or COOCOCCO).

### 3.6 Data Reduction

Each record was visually screened to remove epochs with movement and muscle artifacts. A computer-based blink rejection algorithm then rejected any epoch with activity greater than ± 75 microvolts in amplitude (the prototypic minimum amplitude of

blinks) in the vertical EOG channel. Each participant's data were then re-referenced off-line to Cz, to computer averaged mastoids (LM; "linked" mastoids), and to the average of active EEG sites (AR; average reference).

Each one-minute EEG block was divided into 119 two-second epochs that overlapped by 1.5 seconds. A Fast Fourier Transform (FFT) was applied to all artifact-free epochs, after the data was weighted with a Hamming window that tapered the distal 50% of each epoch. The power spectra of these epochs were then averaged across all eight minutes. Average power in the 8-13 Hz band was taken as an index of alpha power. Finally, an asymmetry score was computed by taking the difference of natural log transformed scores for all sites that had symmetrical left and right locations. The asymmetry score was computed such that the left log transformed score was always subtracted from the right (i.e. ln[right]-ln[left]), with higher values on this index putatively reflecting relatively greater left activity (i.e. relatively greater right alpha; Allen, Nazarian, & Coan, 2004). The natural log transformation is customary in research examining EEG asymmetry as EEG power values tend to be positively skewed (e.g. Allen et al., 2004; Tomarken, Davidson, Wheeler, & Kinney, 1992).

# CHAPTER 4

# RESULTS

## 4.1 Prevalence Rates

PMDD prevalence rates were found to be approximately 8% for the Strict PMDD classification and an additional 7% that met DSM-IV-TR criteria for PMDD (including the impairment criterion) but symptoms did not last "most of the week," totaling 15% who were thus considered among the Spectrum PMDD classification. For reference, the most recent prevalence data in the literature was reported by Wittchen who estimated the baseline 12-month prevalence of PMDD in a population of 1488 reproductive-aged women (ages 14-24) to be 6%. (Wittchen, 2002).

## 4.2 Aim 1: Co-occurrence of Diagnoses

To address specific aim #1, to characterize the co-occurrence of PMDD and major depression in a sample that spans the entire range of depressive severity, a series of Chi Square tests were carried out to test the independence of PMDD status and Major Depressive status. Analyses were run separately for classifications of Strict PMDD (13 PMDD+ and 151 PMDD-) and Spectrum PMDD (25 PMDD+, 139 PMDD-), and also separately for Current MDD status (35 MDD+, 129 MDD-), and participants with any History of depression (current or past MDD status) called Lifetime MDD status (79 MDD+, 85 MDD-). Moreover, to assess whether there was an increased likelihood of a past MDD status among those classified as PMDD, unconfounded by current MDD or dysthymia symptoms that could account for the overlap, the relationship of PMDD to

past history of depression was assessed among currently euthymic women (N=123) who had no current MDD and no Dysthymia symptoms, some of whom had a history of depression (40 Hx +, 83 Hx-). For this last analysis, 15 of the 25 Spectrum PMDD cases remained and 8 of the 13 Strict PMDD cases remained in the analyses. Figure 4.1 (below) shows that in general terms, PMDD diagnoses are associated with a higher likelihood of depression diagnoses.

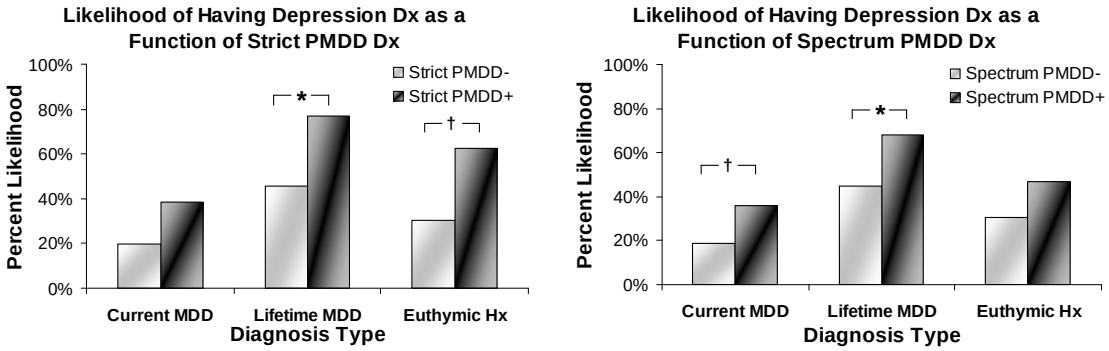



Figure 4.1: Co-occurrence of PMDD and MDD, assessed for strict and spectrum PMDD, and for three MDD classifications. Lifetime MDD=current or past MDD. Euthymic Hx = Currently Euthymic, no current depression or dysthymia, but positive for history of MDD.

Significance * is $p<0.05$ and † is $p<0.065$

For the Strict PMDD classification, chi square showed no significant relationship between the Strict PMDD classification and Current MDD status ($X^2$ (1, N=164) = 2.5, p>0.11). A significant relationship emerged between Strict PMDD classification and a Lifetime MDD status ($X^2$ (1, N=164) = 4.7, p<0.05), with PMDD women having a significantly higher rate of Lifetime MDD than non PMDD women. Among the sample of currently euthymic women, rates of having a history of depression were descriptively higher if these women also had PMDD, but this relationship was not significant for Strict PMDD ($X^2$ (1, N=123) = 3.5, p= 0.061).

For the Spectrum PMDD classification, there was a trend for a relationship between Spectrum PMDD and current MDD diagnosis ($X^2$ (1, N=164) = 3.8, p<0.06) and a significant relationship ($X^2$ (1, N=164) = 4.6, p< 0.05) between Lifetime MDD and this Spectrum PMDD classification. Again, in each case, PMDD women had a higher rate of MDD (current or Lifetime) than non PMDD women. Among the sample of currently euthymic women, rates of having a history of depression were descriptively higher if these women also had PMDD, but this relationship was not significant for Spectrum PMDD ($X^2$ (1, N=123) = 1.6, p< 0.22).

## 4.3 Aim 1: Follow up analyses regarding PMDD and Severity and Lability

In order to answer the question of whether PMDD women have greater depressive symptom severity, and are more labile (unstable) in general, HRSD and BDI scores were examined. HRSD scores at intake, and Beck Depression Inventory (BDI) scores over all 4 sessions were examined (if they had fewer than 4 BDIs they were still included in these

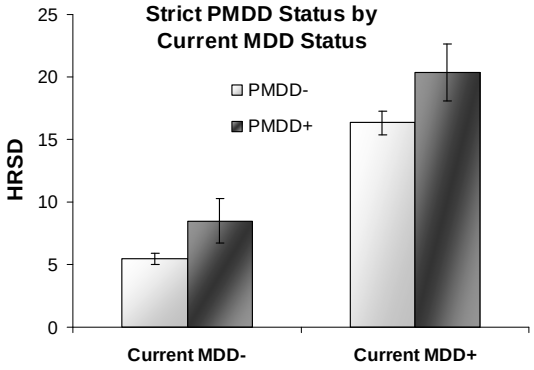
analyses). Severity was indexed by the HRSD score or the mean of all 4 BDI scores. Lability was indexed by the standard deviation of the 4 BDI scores for each participant. Both HRSD and BDI severity scores, as well as BDI lability scores were compared among participants as a function of PMDD diagnosis and MDD diagnosis. Analyses were run separately as a function of Strict or Spectrum PMDD classifications, and separately for Current MDD status or Euthymic History status).

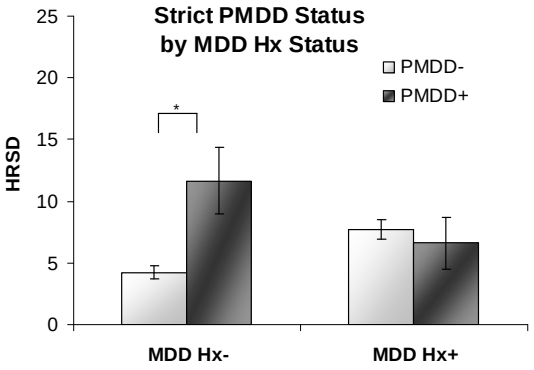
Results of these analyses are displayed below in Figure 4.2. Panels A, C, and E. represent PMDD classification by Current MDD status interactions amongst participants classified in terms of Strict PMDD criteria: Panel 2A shows that MDD+ participants had higher HRSD scores and also that PMDD + participants had higher HRSD scores compared to non-symptomatic individuals, in the absence of a significant interaction. Panel 2C shows that MDD+ participants had higher mean BDI scores compared to non-symptomatic individuals, however, no significant interaction emerged. Panel 2E shows a trend for a main effect of PMDD, specifically that PMDD+ participants tend to be more labile, with higher BDI Variability, compared to non-symptomatic individuals. No significant interaction emerged.

Panels B, D, and F represent PMDD classification by Currently Euthymic, History of MDD status interactions amongst participants classified in terms of Strict PMDD criteria. Panel 2B shows that no main effects were found, however a significant PMDD X MDD interaction was discovered. Breaking down this interaction showed that PMDD+ participants have higher HRSD scores compared to non-symptomatic individuals, but only among those currently euthymic and without a history of MDD.

Panel 2D shows that neither main effects nor interactions were found regarding mean BDI scores. Panel 2F shows that PMDD+ participants are more labile, having higher BDI Variability, compared to non-symptomatic individuals. A significant interaction was also found. Breaking down this interaction showed that PMDD+ participants are more labile, have higher BDI variability, compared to non-symptomatic individuals, but only among those currently euthymic and without a history of MDD status.

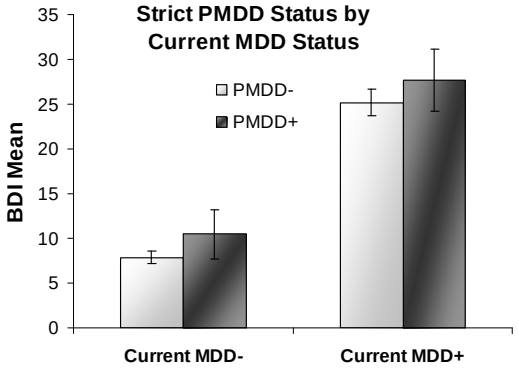
**Current MDD** | **Currently Euthymic**

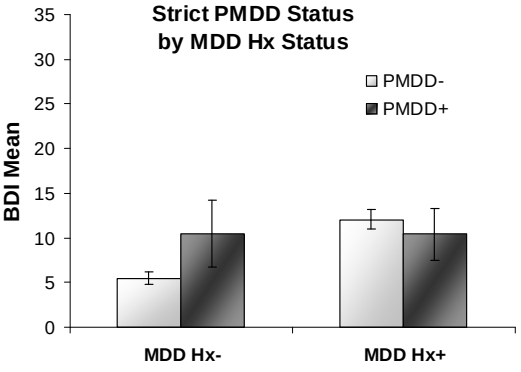



**A** PMDD Main Effect: F(1,160)=5.38, p<.05
MDD Main Effect: F(1,160)=54.87, p<.05
PMDD x MDD Interaction: F(1,160)=0.10, ns

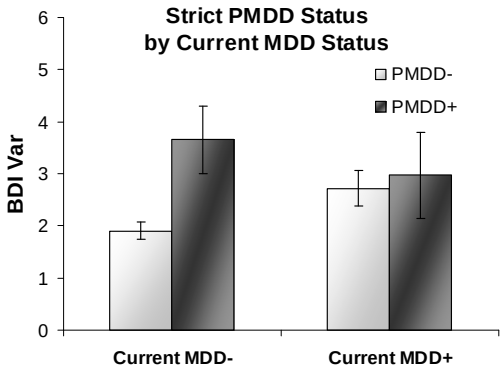
**B** PMDD Main Effect: F(1,119)=3.30, ns
MDD Main Effect: F(1,119)=.22, ns
PMDD x MDD Interact: F(1,119)=5.95, p<.05

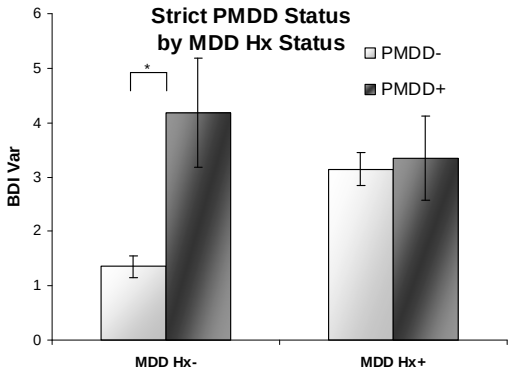



**C** PMDD Main Effect: F(1,158)=1.17, ns
MDD Main Effect: F(1,158)=52.72, p<.01
PMDD x MDD Interaction: F(1,158)=.00, ns

**D** PMDD Main Effect: F(1,118)=.48, ns
MDD Main Effect: F(1,118)=1.76, ns
PMDD x MDD Interaction: F(1,118)=1.81, ns




**E** PMDD Main Effect: F(1,158)=3.23, p=.07
MDD Main Effect: F(1,158)=.01, ns
PMDD x MDD Interaction: F(1,158)=1.8, ns

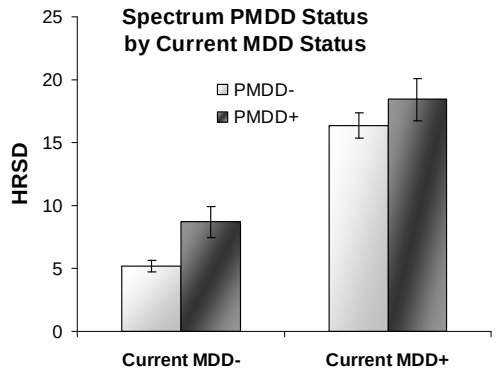
**F** PMDD Main Effect: F(1,118)=5.26, p<.05
MDD Main Effect: F(1,118)=0.53, ns
PMDD x MDD Interact: F(1,118)=3.96,p<.05

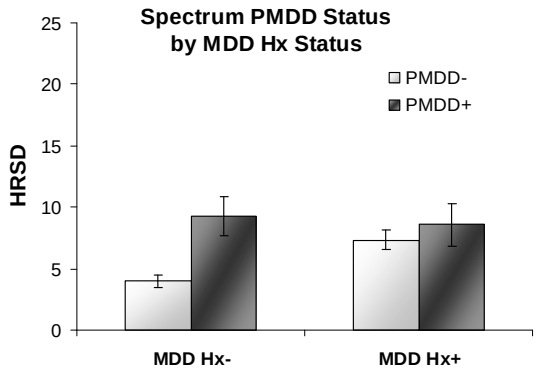
Figure 4.2: Depression Severity and Lability as a function of PMDD classifications and Depression status among subjects classified in terms of Strict PMDD (13 PMDD+, 151 PMDD-).

Results for participants classified in terms of Spectrum PMDD classification are presented in Figure 4.3 below. Panels A, C, and E represent PMDD classification by Current MDD status interactions amongst participants meeting Spectrum PMDD criteria: Panel 3A shows that MDD+ participants had higher HRSD scores and also that PMDD + participants had higher HRSD scores compared to non-symptomatic individuals. No significant interaction emerged. Panel 3C shows that MDD+ participants had higher mean BDI scores and PMDD+ participants had higher mean BDI scores compared to non-symptomatic individuals, however, no significant interaction emerged. Panel 3E shows that PMDD+ participants are more labile, with higher BDI variability, compared to non-symptomatic individuals. No significant interaction emerged.

Panels B, D, and F represent PMDD classification by Currently Euthymic, History of MDD status interactions amongst participants classified in terms of Spectrum PMDD criteria. Panel 3B shows that PMDD+ participants have higher HRSD scores compared to non-symptomatic individuals. No significant interaction emerged. Panel 3D shows that MDD Hx+ participants had higher mean BDI scores compared to non-symptomatic individuals. Additionally a trend was discovered for the interaction. Panel 3F shows that MDD Hx+ participants are more labile, having higher BDI Variability, compared to non-symptomatic individuals.

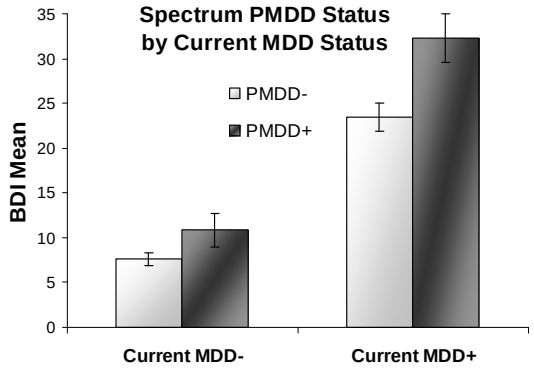
**Current MDD** | **Currently Euthymic**

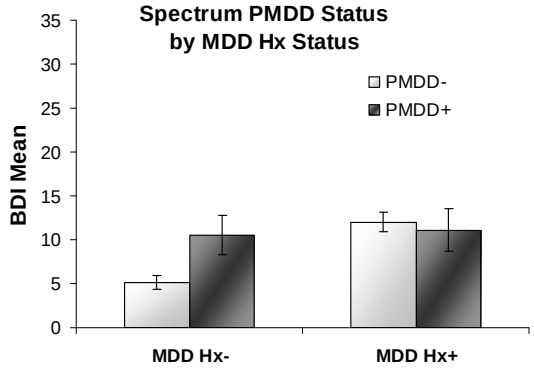



**A** PMDD Main Effect: F(1,160)=5.51, p<.05
MDD Main Effect: F(1,160)=78.01, p<.05
PMDD x MDD Interaction: F(1,160)=.37, ns

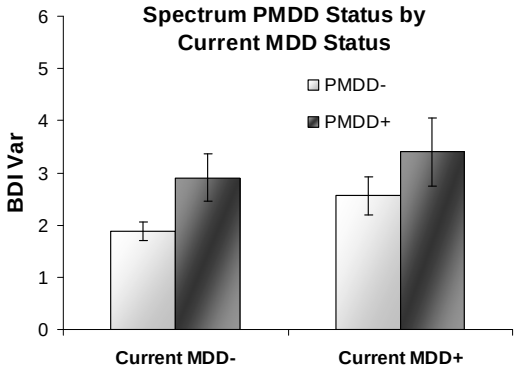
**B** PMDD Main Effect: F(1,119)=6.48, p<.05
MDD Main Effect: F(1,119)=1.09, ns
PMDD x MDD Interaction: F(1,119)=2.48, ns

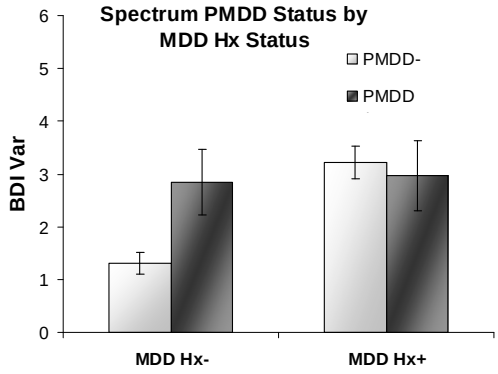



**C** PMDD Main Effect: F(1,158)=10.64, p<.05
MDD Main Effect: F(1,158)=101.90, p<.05
PMDD x MDD Interaction: F(1,158)=2.29, ns

**D** PMDD Main Effect: F(1,118)=1.60, ns
MDD Main Effect: F(1,118)=4.29, p<.05
PMDD x MDD Interaction: F(1,118)=3.13, p=.08




**E** PMDD Main Effect: F(1,158)=4.37, p<.05
MDD Main Effect: F(1,158)=1.70, ns
PMDD x MDD Interaction: F(1,158)=.04, ns

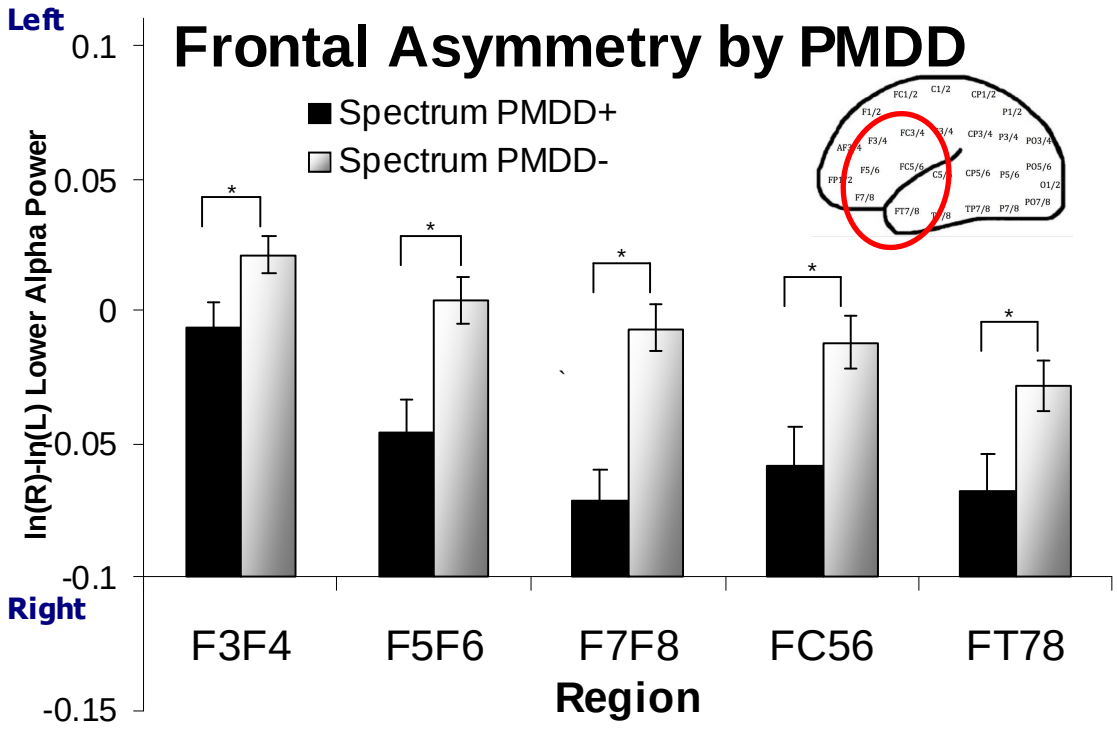
**F** PMDD Main Effect: F(1,118)=1.76, ns
MDD Main Effect: F(1,118)=4.33, p<.05
PMDD x MDD Interaction: F(1,118)=3.26, p=.07

Figure 4.3: Depression Severity and Lability as a function of PMDD classification and Depression status among subjects classified in terms of Spectrum PMDD (25 PMDD+, 139 PMDD-).

## 4.4 Aim 2: Resting EEG

Specific aim #2 was to assess whether resting frontal electroencephalography (EEG) asymmetry may serve as a marker of premenstrual dysphoria, and whether such a relationship is independent of any history of major depressive disorder. For each of five frontal regions, data were examined using a mixed linear model (SPSS 16.0) including data from each of three reference schemes, and all four occasions of measurement, with specific effects of interest being a main effect of PMDD classification, main effect of MDD status, and their interaction. By examining these effects, aggregated across day and reference scheme, is predicated on the rationale that multiple occasions of measurement provide a trait estimate of frontal asymmetry and that effects that persist across reference scheme are robust. This analysis was planned to be carried out only for the 25 subjects classified as Spectrum PMDD and the 25 matched controls, to allow adequate sample size for the model. Additionally, based on findings from the larger parent study that individuals with unstable symptom scores from mass screening to testing were different than those with stable scores in terms of symptoms and EEG asymmetry, analyses were carried for only those Spectrum PMDD and matched control participants who did not exhibit a change of more than five points on the BDI from mass survey to the first EEG assessment, resulting in a final sample of 13 Spectrum PMDD+ and 21 Spectrum PMDD- subjects. Finally, because previous studies have shown that lower alpha (8-10.5 Hz) more closely covaries with other measures of brain metabolism (Oakes et al., 2004) only lower alpha results are reported here.

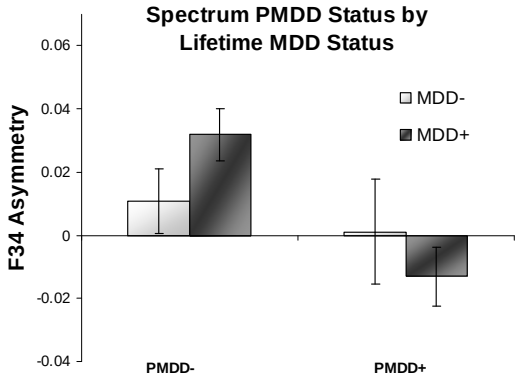
Figure 4.4 displays asymmetry scores by region for each group, and reveals that low distress participants show relative greater left activity at frontal, fronto-temporal, and fronto-central sites. A main effect of group at each of these 5 frontal regions was found, essentially replicating previous work (Accortt and Allen, 2006). Compared to women without a PMDD diagnosis, women classified as Spectrum PMDD have trait levels of higher relative right frontal activity consistent with MDD asymmetry research. To assess the frontal specificity of these effects, analogous mixed linear models were run on asymmetry scores from three parietal regions (P1P2, P3P4, and P5P6). A main effect of PMDD was revealed at two of these three sites: P3P4, $F(1,697.3)=12.2$, $p<.05$ and P5P6, $F(1,641.3)=19.6$, $p<.05$. Both were in the opposite direction than that found in frontal sites, revealing higher relative left parietal activity in women with PMDD. Thus the effects observed in the frontal regions, of lower left frontal activity in PMDD+ women, were indeed specific to the frontal region and not a global hemispheric difference.

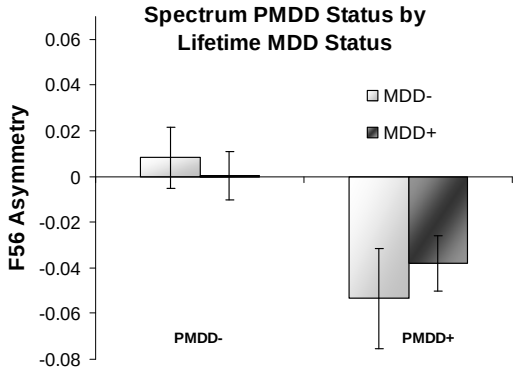



F34, PMDD Main Effect: F (1,709.2)=5.7, p<.05
F56, PMDD Main Effect: F(1,746.56)=10.94, p<.05
F78, PMDD Main Effect: F(1,726.20)=19.97, p<.05
FC56, PMDD Main Effect: F(1,765.90)=7.10, p<.05
FT78, PMDD Main Effect: F(1,731.33)=5.57, p<.05

Figure 4.4: Frontal EEG alpha asymmetry at five frontal regions as a function of PMDD status (13 PMDD+, 21 PMDD-). Results are for lower alpha power (8-10.5 Hz).

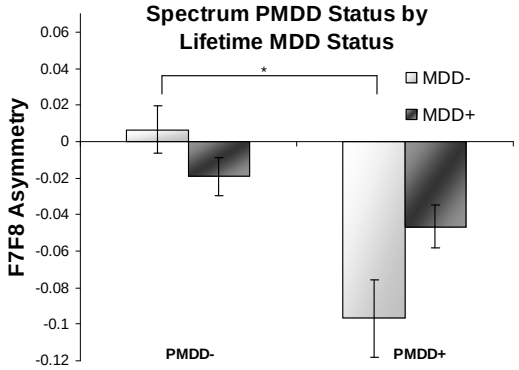
Figure 4.5 Panels A-E present mean asymmetry scores at these same five frontal sites as a function of PMDD classification and Lifetime MDD status, revealing two significant interactions. Main effects of PMDD classification, presented above, will not be reiterated in the description of these results, instead focusing on interactions involving MDD status and PMDD classification. Significant interactions were observed at F7F8 and FT78. Panel C depicts the break down of the interaction at F7F8, showing that PMDD+ participants have higher trait levels of relative right frontal activity compared to non-symptomatic individuals, but only among those without a history of Lifetime MDD. Among women with a lifetime history of MDD, however, PMDD exerts a much smaller influence ($p<0.07$). Similarly, as seen in panel E, breaking down the interaction at region FT78 showed that PMDD+ participants have higher trait levels of relative right frontal activity compared to non-symptomatic individuals, but only among those without a history of Lifetime MDD.

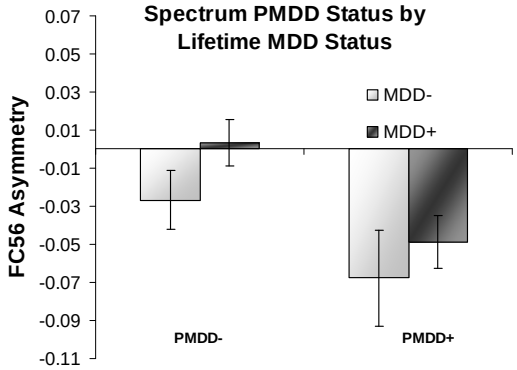



**A** PMDD Main Effect: F(1,709.2)=5.67, p<.05
MDD Main Effect: F(1,709.2)=.09, ns
PMDD x MDD Interaction: F(1,709.2)=2.32, ns

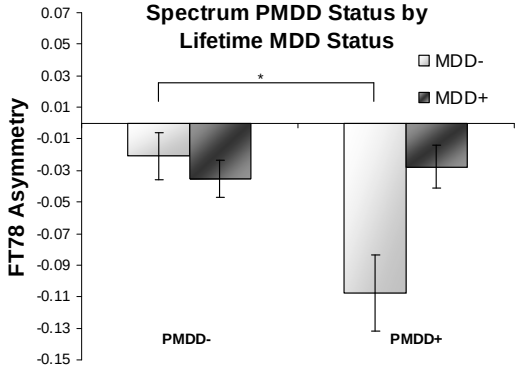
**B** PMDD Main Effect: F(1,746.6)=10.94, p<.05
MDD Main Effect: F(1,746.6)=.06, ns
PMDD x MDD Interaction: F(1,746.6)=.58, ns




**C** PMDD Main Effect: F(1,726.2)=19.97, p<.05
MDD Main Effect: F(1,726.2)=.70, ns
PMDD x MDD Interact: F(1,726.2)=6.71, p<.05

**D** PMDD Main Effect: F(1,765.9)=7.10, p<.05
MDD Main Effect: F(1,765.9)=1.99, ns
PMDD x MDD Interaction: F(1,765.9)=.10, ns




**E** PMDD Main Effect: F(1,731.3)=5.57, p<.05
MDD Main Effect: F(1,731.3)=3.80, p=.052
PMDD x MDD Interact: F(1,731.3)=7.89, p<.05

Figure 4.5: Mean asymmetry scores at the five frontal sites as a function of PMDD classification and Lifetime MDD status.

## 4.5 Secondary Aim: Family History of Depression

To assess whether individuals with PMDD or menstrual related mood variability have an increased family history of depression, Chi Square tests were carried out to test the independence of PMDD classification and family history of depression. Analyses were run separately for as a function of Strict PMDD (13 PMDD+, 150 PMDD-) and Spectrum PMDD (25 PMDD+, 138 PMDD-) classifications. These two Chi Square tests assessed whether premenstrual disorders are independent of a reported family history of depression.

For Strict PMDD, no significant relationship between this PMDD classification and Family History of Depression emerged ($X^2$ (1, N=163) = 0.62, p>0.1). For Spectrum PMDD, there was a trend for a relationship ($X^2$ (1, N=163) = 3.32, p=0.068) between Family History and this PMDD classification. In this case, Spectrum PMDD+ women had a higher rate (36.0 %) of Family History of MDD than Spectrum PMDD- women (19.6 %).

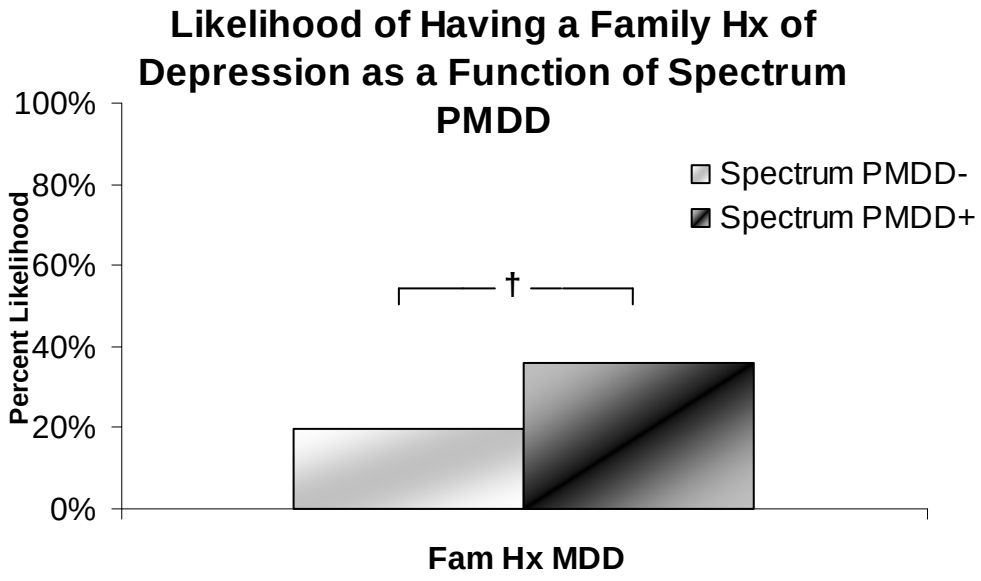

Likelihood of Having a Family Hx of Depression as a Function of Spectrum PMDD
Percent Likelihood
100%
80%
60%
40%
20%
0%
Spectrum PMDD-
Spectrum PMDD+
†
Fam Hx MDD

Figure 4.6

# CHAPTER 5

# DISCUSSION

## 5.1 Overview

In this large sample of women recruited for a study of risk for depression, and not initially recruited based on the presence of PMDD symptoms, it was found that symptoms of depression and PMDD symptoms tend to co-occur. This was true whether symptoms were characterized in terms of dichotomous DSM categories (e.g., current MDD, lifetime MDD) or continuous measures (e.g. HRSD or BDI severity). Moreover, women classified as having PMDD showed greater mood variability across the four assessment sessions, replicating previous work on PMDD course and symptomatology (see Endicott et al., 1999 for review). Moreover, PMDD is characterized by a pattern of resting brain asymmetry that is like that seen in depression and that replicates previous findings with a sample of women with high levels menstrual-related dysphoria (Accortt & Allen, 2006). Finally, results concerning family history of MDD among those with PMDD were suggestive, but not definitive.

## 5.2 Co-occurrence of MDD and PMDD

Despite a generally consistent pattern across different depression diagnoses (Current MDD, Lifetime MDD, Euthymic Hx+), the present study findings of co-occurrence of MDD and PMDD were only statistically significant when considering Lifetime MDD for both Strict and Spectrum PMDD classifications. Importantly, these findings refute the possibility that currently depressed women are simply endorsing pre-

menstrual symptoms due solely to current depressive symptoms (I feel depressed, so 'everything' is wrong with me). In such a scenario, a comorbid current MDD diagnosis would have been most strongly related to PMDD.

The present study results are consistent with the notion that a similar biological predisposition to hormonal related depression exists in women with a lifetime history of depression. As previously reported, repeated episodes of depression may sensitize depressed women to Pre-Menstrual Exacerbation of their symptoms. For example, past depressive episodes may act as a "kindling" mechanism in which increasingly severe depression occurs with little provocation (Post and Ballenger, 1981). The provocation, in this case, may be fluctuations of hormones and neurotransmitters related to the menstrual cycle (Breaux et al., 2000; Kendler et al., 2001).

The age range of our cohort is 18-25, so these women have not had a long period of risk for either MDD or PMDD. The most recent PMDD prevalence, incidence and stability data in the literature were reported by Wittchen and colleagues who studied 1488 reproductive-aged women ages 14-24 (Wittchen et al., 2002). In their cohort with a wider age range, 900 women aged 13-53, Hartlage et al (2004) found that premenstrual symptoms worsened with age. Steiner (2000), also reported symptoms worsening over time and added that the average age of onset is around 26 years of age. Therefore, it is important to be aware that the present study is an early onset sample, both in terms of PMDD and in terms of MDD, the latter with a median age of onset of 30 years of age (Kessler et al., 2005). Kessler adds that later onsets of MDD are mostly of comorbid conditions, and did not report sex differences in age of onset. This is a sample that would

be expected to have more lifetime mood instability and more lifetime episodes than those with later onset. To some extent mood instability may be a feature in common among depressed women and women meeting criteria for PMDD. The mood instability characteristics of PMDD may also place women at greater risk for MDD (Endicott & Halbreich, 1988; Yonkers, 1997; Endicott, 1994). For these reasons it is imperative to begin investigating symptomatology, course and risk for PMDD (and other mood disorders) prospectively, and at a young age.

PMDD is classified as a ‘‘Depressive Disorder Not Otherwise Specified (NOS)’’ in the DSM-IV-TR and as discussed in the background section above, perhaps the most difficult differential diagnosis for clinicians to make is distinguishing between PMDD and Major Depressive Disorder (MDD). The comorbidity between the two disorders is significant, ranging from 30 to 70% (Endicott, 1994). The present study found similar comorbidity rates regardless of whether a strict or spectrum classification was used: rates of depressive diagnoses were 36 to 68%, for Spectrum PMDD (Current & Lifetime MDD, respectively) and 39 to 77%, for Strict PMDD (Current & Lifetime MDD, respectively). Many researchers have been trying to understand these ‘‘special’’ and not necessarily ‘‘pure’’ PMDD populations. Many women have symptoms throughout the menstrual cycle and experience premenstrual worsening (Hartlage et al, 2004;Yonkers et al., 2003). That being said, it is important not to confuse premenstrual exacerbation of the symptoms of depressive disorders (PME-DD) from premenstrual dysphoric disorder (PMDD). Symptoms of PMDD are absent or mild post-menstrually, and are marked or severe premenstrually and interfere with functioning. Some argue that PMDD is mistaken

for depression that becomes worse premenstrually (Endicott et al., 1999). In fact, up to half of women seeking treatment for premenstrual disorders has PME-DD (Plouffe et al., 1993). Moreover, six symptoms of major depressive disorder (MDD) also are symptoms of PMDD (e.g., depressed mood). In these cases, the difference between PME-DD and PMDD is not the nature of symptoms, but their timing (Hartlage et al., 2001). In the present study, women who met criteria for PMDD and current MDD were asked whether they had experienced pre-menstrual symptoms during months when they were not experiencing a major depressive episode. If they had not, they did not receive any PMDD diagnosis; thus the PMDD women in this study did not have PME-DD.

It is important to understand the true differences between an episode of PMDD and one of MDD. As mentioned above, the present study found that when women meet the strict DSM-IV criteria for PMDD (see Strict versus Spectrum PMDD in Figure 1) they have a descriptively but non-significantly higher chance of also meeting criteria for Current MDD. The importance of elucidating key features of Strict PMDD, and properly diagnosing the disorder with 2 months of daily diary reports (as compared to Spectrum PMDD, PME-DD and current MDD) thus become even more apparent.

### 5.3 Follow up analyses regarding PMDD Lability and Symptom Severity

According to several researchers (see Endicott et al., 1999 for review) one of the main differences between an episode of PMDD and one of MDD is the severity of symptoms and affective lability. Additionally, Freeman's treatment research (2004) points out obvious differences suggesting that the underlying mechanisms of PMDD

differ from those of other depressive disorders, although these mechanisms have not been identified. Finally, a PMDD diagnosis, by definition in the DSM-IV criteria, excludes the possibility of pre-menstrual exacerbation (PME) of major depressive symptoms (women with current or past MDD could have PME-DD, however) (Hartlage et al., 2001).

Research has shown that one of the key features of PMDD (one that sets it a part from MDD) is emotional lability. Although the daily diary data were insufficiently completed to examine mood variability, the results examining the variation in BDI scores across the 4 visits to the lab indeed corroborate that PMDD+ subjects showed grater mood variability than PMDD- subjects. These results were found for the Strict PMDD classifications, but only for those without a history of depression who were not currently depressed or dysthymic. In fact, the results were not significant for either classification of PMDD for those who were also currently depressed. This may highlight the possibility that current major depression increases severity and reduces variability, and when a woman is currently depressed her symptomatology, course etc. will present like Major Depression.

## 5.4 Resting EEG

The main finding was that controls exhibited greater relative left fronto-tempo-central activity at rest than women meeting criteria for Spectrum PMDD, ($p<0.05$). The significant results were found at three frontal sites, one fronto-central site and one fronto-temporal site. The finding that relatively less left trait frontal activity characterizes those with a PMDD diagnosis is consistent with a diathesis-stress model for menstrual-related

dysphoria. Thus in addition to evidence suggesting relatively less left frontal activity is a risk factor for depression, it may serve as a diathesis for a broader range of dysphoric mood including that of menstrual related dysphoria. Moreover, analyses examining parietal sites confirmed the specificity of the frontal effects, as two of the three parietal regions showed significant effects of PMDD, but in the opposite direction from those in frontal regions. PMDD+ participants exhibited higher relative left parietal activity.

The present study further investigated whether the PMDD-Asymmetry relationships found were independent of any history of major depressive disorder and/or dysthymia. Overall, for women without MDD, the effect of PMDD was substantial and significant ($p<0.01$); among women with a lifetime history of MDD, however, PMDD exerted a much smaller influence ($p<0.07$). These results expand upon previous work (Accortt & Allen, 2006) by using a structured clinical interview based upon the DSM-IV criteria to confirm PMDD classifications (as opposed to the Menstrual Distress Questionnaire, Moos 1968). Another improvement to the previous findings is the inclusion of women meeting criteria for other mood disorders in addition to PMDD in order to assess that the asymmetry effect in these women is independent of other mood symptoms.

Although all women of child-bearing age experience regular monthly hormonal fluctuation, other factors may result in only some of them experiencing PMDD. The present results suggest that frontal EEG asymmetry may index a diathesis to experience such negative affect when faced with the challenge of cyclical hormonal variation. The results also imply that these women may share a common risk factor with those meeting

criteria for Major Depression. Interestingly, PMDD participants have higher trait levels of relative right frontal activity compared to non-symptomatic individuals, but only among those without a history of Lifetime MDD. Therefore, it would seem unlikely that the greater relative right frontal activity among those with PMDD is an artifact of a higher rate of MDD among these women.

### 5.5 Secondary Aim: Family History of Depression

The present study provided promising but non-definitive evidence of a relationship between family history of MDD and a likelihood of PMDD, as only a trend was discovered. Additionally, this trend was found only for PMDD classified as a spectrum diagnosis, with Spectrum PMDD women having a higher rate of Family History of MDD (36%) than non PMDD women (19.6%). This trend could be due to the high comorbidity with MDD in the PMDD group. Both Strict and Spectrum PMDD groups had similar rates of comorbid MDD: 38% of Strict PMDD women also met criteria for MDD and 36% of Spectrum PMDD women also met criteria for MDD.

Future work might profitably gather family history of premenstrual symptoms to see if there exists a higher rate of familial risk for PMDD as well as MDD among female relatives of participants with PMDD. Kendler et al (1998) found that the liability to premenstrual symptoms was only modestly affected by those genetic factors that influence major depression. They conducted a genetic study examining concordance between monozygotic and dizygotic twins, lifetime and major depression, and three pre-menstrual related symptoms (tiredness, sadness and irritability) that they assessed twice

over six years in 1312 twins. A comparison of the concordance for the two groups showed that liability to premenstrual symptoms was only modestly affected by those genetic factors that influence major depression. Conversely, the environmental factors that influence premenstrual symptoms only modestly affected the liability to major depression (Kendler et al., 1998). Based on Kendler's study, Endicott concluded that premenstrual symptoms appear independent of the risk for MDD (Endicott et al., 1999).

## 5.6 Strengths, Limitations, and Future Directions

A limitation of the present study was that endocrinological measures of each woman's menstrual cycle were not collected. Ideally, blood or saliva samples would have been obtained to precisely measure estrogen levels. The onset of menstrual cycles was assessed accurately from self-report, thus making assessment times as accurate as possible without collecting endocrinological assays. It is, however, the amount of circulating estrogen that is presumably of greatest interest as opposed to simply which phase women report to be in. On the other hand, the present study did not seek to access EEG asymmetry at each phase of the menstrual cycle.

A second limitation was that two months of diary data were not collected in order to properly confirm a PMDD diagnosis. It is very important to properly diagnose women with PMDD according to the DSM-IV-TR, which states that two months of prospective menstrual symptoms must be acquired daily. A daily web diary was set up to assess this information, however, women did not consistently fill out the diary every day for two months. Therefore, it was impossible to confirm the diagnosis made by interview,

although some diary data were sufficient to exclude women from consideration of a diagnosis of PMDD.

For future research, PMDD studies might profitably assess family history of premenstrual symptoms to investigate whether a higher rate of familial risk for PMDD would be found. Additionally, in view of the rapid onset of action of SSRIs in PMDD and the notion that irritability and affect lability, rather than depressed mood or anxiety, should be regarded as the most prominent target symptoms when these drugs are used for PMDD (Landen & Eriksson, 2003), it could be hypothesized that symptoms such as irritability and affect lability would be higher in a sample of women meeting criteria for PMDD. Irritability, anger, and affect lability also respond rapidly to SSRIs in patients with conditions such as stroke, dementia, and brain injury (Eriksson, 1999) which may be taken as support for the hypothesis. Recent preliminary reports (Di Guilio and Reissing, 2006) note several differences between PMDD and MDD which clearly distinguish them from one another. Diagnostically, the criteria of anxiety and tension, affective lability, marked anger/irritability, a sense of being overwhelmed, and physical symptoms (i.e., breast pain, bloating) are not typically found in MDD, and anxiety of clinical severity would specifically have excluded participants from the present study. The most frequently endorsed symptom in a recent PMDD study was irritability (46.2%), which suggests that irritability may be the key feature of PMDD rather than depressed mood (Landen & Eriksson, 2003; Angst et al, 2001). Therefore assessing whether women classified with PMDD have more of these symptoms could further separate them from generally mood disordered women.

Lastly, it could be hypothesized, based upon the literature that highlights the use of oral contraceptives (OC) as a treatment for PMDD, that OC would play a role in studies of PMDD. In the present study the rate of hormonal-based contraceptive (HBC) use did not vary largely between groups; HBC use for the sample as a whole was 37%. HBC use for the matched EEG controls was 32%. HBC use for Strict PMDD was 31% and was 40% for Spectrum PMDD. Yonkers (2004) offers promise of OCs as treatment for PMS/PMDD, although they state that data at this point are inconclusive. Young et al. concluded that combined OC (synthetic estrogen and progestin) as opposed to progestin-only OCs, may influence depressive and physical symptoms in depressed women (Young et al., 2007). More specifically they found that those on combined hormone contraception were significantly less depressed than those with no hormone treatment. An important future direction could be to gather information about the specific composition of the HBCs used in one's samples.

Future studies might benefit from assessing estrogen levels, from confirming the PMDD diagnosis via two months of daily diary data, from assessing familial risk of PMDD, from assessing for rates of specific symptoms, and from assessing HBC type. Nonetheless, the current study provided evidence consistent with previous findings, suggesting that resting frontal EEG asymmetry may tap as a risk factor for menstrual-related dysphoria. By utilizing a clinical diagnostic interview for PMDD, and including a larger sample and expanding recruitment to include women with and without major depressive disorder and dysthymia, the present results provide a remarkably consistent pattern (as compared to Accortt and Allen, 2006).

Currently, it appears that the etiology of depression in women across the reproductive lifespan is multi-faceted. Depression may arise, in part, from a genetically influenced biological vulnerability that can be described as an overactive neurobiological response to stressful life events, which in some cases may manifest as PMDD or MDD. Otherwise normal female hormonal cycling may serve as one of these stressful life events. These events are thought to activate stress hormones, including cortisol, which have wide-ranging effects on neurohormones and neurotransmitter systems (particularly involving serotonin) likely involved in the onset of depression.

The main focus of future research should be aimed at developing ways to assess risk for depression and pre-menstrual dysphoric disorder very early, perhaps in childhood or adolescence. Assessments aimed at these earlier stages would be essential in order to protect vulnerable individuals from developing full-blown clinical depression or PMDD later in life. It is therefore incredibly important to identify a sizable subset of those at risk for developing PMDD and MDD, which may ultimately assist in identifying the underlying mechanisms that may point to new treatments and preventions. This study found that a putative marker of risk for depression, frontal electroencephalographic (EEG) asymmetry, is also sensitive to premenstrual dysphoric symptomatology in women with and without major depression or dysthymia. It remains to be determined whether it can also prospectively identify those women at risk for the future development of PMDD. Ideally, this measure could help us learn more about the etiology of depression and hormonal-related depression specifically, and test whether they may share etiological factors.

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