Aus der Klinik für Psychiatrie und Psychotherapie
des Zentralinstituts für Seelische Gesundheit Mannheim
der Medizinischen Fakultät Mannheim
(Direktor: Prof. Dr. med. Andreas Meyer-Lindenberg)
Arbeitsgruppe Verlaufs- und Interventionsforschung
(Leitung: Prof. (apl.) Dr. Christine Kühner)

Ambulatory Assessment of Psychological and Psychoendocrinological Characteristics across the Menstrual Cycle in Women with Premenstrual Dysphoric Disorder

Inauguraldissertation
zur Erlangung des Doctor scientiarum humanarum (Dr. sc. hum.)
der Medizinischen Fakultät Mannheim
der Ruprecht-Karls-Universität
zu
Heidelberg

vorgelegt von
Theresa Beddig
aus
Wiesbaden
2020

Dekan: Herr Prof. Dr. med. Sergij Goerdt

Referentin: Frau Prof. (apl.) Dr. Christine Kühner

TABLE OF CONTENTS

page

ABBREVIATIONS

AA	Ambulatory Assessment
AIC	Akaike information criterion
BDI	Beck Depression Inventory
BIC	Bayesian information criterion
B-S	Between-subject
CAR	Cortisol awakening response
CBT	Cognitive-behavioral therapy
cf.	Confer, compare
CIMH	Central Institute of Mental Health
DCS	Diurnal cortisol slope
DSM	Diagnostic and Statistical Manual of Mental Disorders
e.g.	example gratia, for example
EMA	Ecological Momentary Assessment
HPAA	Hypothalamic-pituitary-adrenal axis
i.e.	Id est, that is
ICD	International Classification of Diseases and Related Health Problems
M	Mean
NA	Negative affect
PA	Positive affect
PMDD	Premenstrual Dysphoric Disorder
PSST	Premenstrual Symptom Screening Tool
RCT	Randomized control study
RDoC	Research Domain Criteria
SCID	Structured Clinical Interview for DSM
SCID-PMDD	Structured Interview for DSM-IV TR defined PMDD
SD	Standard Deviation
SSRI	Selective serotonin reuptakte inhibitors
W-S	Within-subject

1 INTRODUCTION

1.1 Scope of the present dissertation

While mild premenstrual complaints are reported by the majority of women in fertile ages and are therefore considered part of the normal menstrual cycle (Nevatte et al., 2013; Tschudin, Bertea, & Zemp, 2010), a certain proportion of women suffer from a severe variant of premenstrual symptoms characterized by principal affective symptoms. This condition has been classified as Premenstrual Dysphoric Disorder (PMDD). PMDD is associated with clinically significant distress, and affected women suffer from marked impairment in their normal functioning, which can be as disabling as Major Depressive Disorder (Halbreich, Borenstein, Pearlstein, & Kahn, 2003). The disorder has recently been included as a full diagnostic category in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association (APA), 2013) and the eleventh revision of the International Classification of Diseases and Related Health Problems (ICD-11, World Health Organization (WHO), 2018). Despite its inclusion, many questions remain unanswered including possible mechanisms associated with the disorder such as particularities of the endocrinologic stress axis activity and psychological factors as well as characteristics contributing to a poor clinical course of the disorder. The present thesis aims to focus on these issues by studying affective, cognitive, and endocrinological processes over the menstrual cycle in women with PMDD during their daily life using an Ambulatory Assessment (AA) design with electronic diaries. As such, this may open the way for a more systematic investigation of new therapeutic strategies in the future that help to reduce the burden of PMDD.

The theoretical background comprises an introduction to PMDD, followed by discussed risk and associative factors, existing treatment strategies and new research approaches via AA, leading to our research questions, which were investigated in three substudies. Study 1 examines stress-related facets of mood, cognitions and cortisol over the menstrual cycle in women with and without PMDD, Study 2 investigates possible menstrual cycle-related reciprocal effects of cognitive and affective processes in these women, and Study 3 focuses on the role of daily-life phenotypes for the clinical course of the disorder. In a general discussion section the findings from studies 1 to 3 are discussed in detail, with a focus on the integration

into previous research and future perspectives in treatment research, taking into account the limitations of the findings and concluding with a brief summary.

1.2 Premenstrual Dysphoric Disorder as a new diagnostic category in DSM-5

PMDD is characterized by the cyclical recurrence of severe key affective symptoms, which are accompanied by other psychological and/or physical symptoms in the week before menses (late luteal phase). The recognition of PMDD as a clinical condition requiring treatment in DSM-5 (APA, 2013) is a result of intensive research activity during the last 40 years. Already in the early 1930s, premenstrual symptoms were outlined as a clinical entity by Frank (1931). Much later, in 1987, formal criteria were specified for the first time, and the syndrome was described as “late luteal phase dysphoric disorder” by the American Psychiatric Association (APA, 1987). Subsequently, in 1994 diagnostic criteria were included in the appendix of DSM-IV as a “condition requiring further study” and renamed in PMDD (APA, 1994). Accumulating clinical and epidemiological evidence finally led to the inclusion of PMDD as a distinct clinical entity in the current fifth version of the DSM (Epperson et al., 2012; Reed et al., 2019). Here, PMDD is located in the chapter of depressive disorders due to the prominence of mood symptomatology (APA, 2013).

For a diagnosis of PMDD - according to DSM-5 (APA, 2013) - different diagnostic criteria need to be met: First, at least five out of eleven specific symptoms must occur during the last week (late luteal phase) of the menstrual cycle, which remit during the first week after menstruation onset. This must be valid for the majority of menstrual cycles during the last 12 months (Criterion A). Second, at least one out of four affective key symptoms must be present: affective lability, anger or irritability, depressed mood or anxiety. These core symptoms are accompanied by further affective, cognitive, and/or physical symptoms including decreased interest in usual activities, subjective difficulty in concentration, fatigue or lack of energy, change in appetite, hypersomnia or insomnia, the feeling of being overwhelmed or out of control, or physical symptoms such as breast tenderness or muscle pain (Criterion C). Symptoms must be associated with clinically significant distress or interference in the area of work, school, social activities, or relationships (Criterion D). It is important to note that these symptoms may not merely represent a premenstrual exacerbation of another psychiatric disease. For example, a woman suffering from current Major Depressive Disorder needs to show at least one key affective symptom different from depressed mood (e.g. affect lability or anger) to be diagnosed with coexistent PMDD

(Criterion E). In order to confirm the PMDD diagnosis, daily symptom ratings over at least two symptomatic cycles are required, although a provisional diagnosis of PMDD based on clinical history can be made without (Criterion F). Finally, the symptoms must not be attributable to physiological effects of a substance or a general medical condition (Criterion G).

Compared to the research diagnosis in DSM-IV, the diagnostic criteria in DSM-5 are softened in a few points: 1) The time criterion, which states that the complaints must persistent "most of the time during the last week of the luteal phase," has been deleted. 2) It is no longer required that symptoms disappear completely within a few days after the onset of menstruation, but it is rather if they remit after menses onset. 3) In addition, the previously required impairment criterion in everyday life has been broadened; now women may suffer from clinically significant distress *or* impairment, thereby including those who maintain their functional level under severe suffering. 4) It is indicated that PMDD may co-occur with - rather than be superimposed on - other disorders. It is possible that these minor changes in the diagnostic criteria will affect prevalence rates of PMDD (cf. Beddig & Kuehner, 2017). Besides, the predominance of premenstrual high arousal negative mood and mood lability over depressed mood in PMDD has led to a change in the respective listing of symptoms from DSM-IV to DSM-5 (Hantsoo & Epperson, 2015). The core symptoms “affect lability” and “irritability or anger” are now listed first as they are more common than “depressed mood”, which was originally listed first in DSM-IV (Hartlage et al., 2012, Epperson et al., 2012).

Epidemiological and clinical data suggest that the onset of PMDD typically occurs during late adolescence or young adulthood (for review see Dennerstein, Lehert, & Heinemann, 2012), and that the disorder frequently takes a chronic course (Wittchen, Becker, Lieb, & Krause, 2002). Symptom severity rises with advancing age until the cycle-related symptomatology disappears after menopause (APA, 2013).

Epidemiological studies have identified PMDD prevalence rates according to DSM-IV criteria varying from 3-8% of women of reproductive age (cf. Beddig & Kuehner, 2017; Dennerstein et al., 2012; Lanza di Scalea & Pearlstein, 2019). In Germany, a large epidemiological study with 1,251 women aged between 14 and 24 identified a twelve-month prevalence of 5.8% (Wittchen et al., 2002). Other studies have shown that women who meet the criteria for PMDD experience their quality of life and psychological functioning being reduced to a degree comparable to that seen in other

major affective disorders (Halbreich et al., 2003). Especially affective and cognitive symptoms appear to be linked to functional impairment, whereas physical symptoms seem less relevant (Schmalenberger, Eisenlohr-Moul, Surana, Rubinow, & Girdler, 2017). Impairment has been found to be particular severe regarding partnership relationships and domestic activities (Halbreich et al., 2003; Robinson & Swindle, 2000; Tschudin et al., 2010). Substantial clinical relevance of the disorder is indicated in studies by Pilver, Libby, and Hoff (2013) and Wittchen et al. (2002) who showed that PMDD led to an increased rate of suicidal ideation, plans, and attempts, independent of psychiatric comorbidity.

In contrast to PMDD, the premenstrual syndrome (PMS) is considered a less severe form of premenstrual complaints affecting 18-35% of menstruating women, depending upon applied diagnostic criteria (Yonkers, O'Brien, & Eriksson, 2008). PMS is not an official diagnosis in DSM-5 and hence a consensus on universally-accepted diagnostic criteria is lacking (cf. O'Brien et al., 2011). Consequently, the distinction between PMS and PMDD frequently remains unclear (cf. Kues, Janda, Kleinstauber, & Weise, 2014). The often-used diagnostic criteria based on the American Congress of Obstetricians and Gynecologists (ACOG) is relatively liberal (cf. O'Brien et al., 2011). Here, PMS is defined by the presence of at least one symptom out of a list of affective and somatic symptoms in the five days prior to the onset of menses, which adversely affects social or work related activity (ACOG, 2000). Respectively, in contrast to the definition of PMDD – which requires the presence of affective symptoms while less attention is paid to physical symptoms – a diagnosis of PMS can be made in the absence of affective symptoms.

The inclusion of PMDD as a diagnostic category in DSM-5 has attracted considerable controversy (Browne, 2015; Chrisler & Caplan, 2002; Hartlage, Breaux, & Yonkers, 2014; Ussher & Perz, 2013). While opponents fear that the label could pathologize normal female body processes and stigmatize affected women (Chrisler & Caplan, 2002; Cosgrove & Caplan, 2004; Ussher, Hunter, & Browne, 2000), recent research indicates that these concerns lack scientific evidence and that women with PMDD are likely to benefit from the new diagnosis (Hartlage et al., 2014). This is due to a variety of reasons including greater acceptance of the disorder in the general public, encouragement of research and improved opportunities through appropriate research funding, a more rigorous characterization of patients participating in randomized control studies (RCTs), improvement in the knowledge of adequate treatment

approaches and thus ultimately better evidence-based care (Hartlage et al., 2014; Epperson et al., 2012).

The diagnosis of PMDD is also included as a new diagnostic category in the recently-approved ICD-11 (WHO, 2018). Here, PMDD is primarily listed as a disease of the genitourinary system, although it is cross-listed as a depressive disorder due to the prominence of key affective symptoms (cf. Reed et al., 2019). This inclusion emphasizes the importance of PMDD as a public health issue and it is likely that this will further support appropriate recognition and improved treatment in clinical practice, thereby helping more women to relieve the premenstrual burden.

1.3 Risk and associative factors

The pathophysiology of PMDD is not yet fully understood. Work in this area largely focuses on factors such as genetic vulnerabilities, circulating gonadal hormones, and central neurotransmitters such as serotonin or gamma-aminobutyric acid (GABA) (Beddig & Kuehner, 2017; Epperson et al., 2012). However, biological factors do not seem sufficient to completely illuminate the etiology of premenstrual disorders (cf. Eggert, Witthöft, Hiller, & Kleinstäuber, 2016). This is illustrated by the fact that, although only women of reproductive age are affected and the timing of symptom onset and offset is closely related to the menstrual cycle (i.e. increased symptoms during the week before menses compared with the week after menses), no abnormalities in gonadal steroid function have been identified in women diagnosed with PMDD (e.g. Backstrom et al., 2003; Cunningham, Yonkers, O'Brien, & Eriksson, 2009; Yen et al., 2018). Therefore, recent research suggests that affected women show heightened sensitivity to normal hormonal fluctuation during the premenstrual phase (cf. Cunningham et al., 2009; Hantsoo & Epperson, 2015). In this context, a phase-specific altered sensitivity to the gamma-aminobutyric acid (GABAA) receptor agonist effect of allopregnanolone has been proposed for PMDD (Backstrom et al., 2014; Hantsoo & Epperson, 2015; Timby et al., 2016). The neuroactive steroid progesterone metabolite allopregnanolone enhances GABAergic transmission and confers sedative effects during times of stress (Hantsoo & Epperson, 2015). One study demonstrated alterations in allopregnanolone reactivity towards stress in women with PMDD (Girdler, Straneva, Light, Pedersen, & Morrow, 2001). Given these findings on allopregnanolones and GABAs potential role in PMDD pathophysiology, recent research provides preliminary evidence that targeting

allopregnanolone could potentially improve PMDD treatment (Bixo et al., 2017; Martinez et al., 2016).

Up to date, various experts agree upon a multifactorial genesis, which integrates multiple biological, psychological, environmental and social aspects (cf. Beddig & Kuehner, 2017; Epperson et al., 2012; Kleinstauber, Witthoft, & Hiller, 2012). In this regard, it is suggested that psychological factors interact with hormonal changes during the menstrual cycle to produce clinical distress and functional impairment (Beddig & Kuehner, 2017; Craner, Sigmon, & Martinson, 2015; Eggert et al., 2016; Saglam & Basar, 2019). In order to better understand and identify such interactions, research examining associations between vulnerability factors and premenstrual symptomatology among women with and without PMDD can contribute important knowledge to the psychobiological framework. While existing research points towards an imbalanced stress system as a possible mechanism underlying the pathogenesis of PMDD (Owens & Eisenlohr-Moul, 2018; Parry, Javeed, Laughlin, Hauger, & Clopton, 2000), its contribution to significant premenstrual distress remains unclear and methodologically well-designed investigations of subjective and endocrinologic stress responses are warranted. Furthermore, future research should also shift more towards the role of psychological factors in PMDD. Dysfunctional cognitions such as rumination have been found to trigger negative emotions in various psychiatric disorders (Lyubomirsky, Layous, Chancellor, & Nelson, 2015; Nolen-Hoeksema & Watkins, 2011; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), but there is a paucity of studies assessing their role in PMDD. In the present thesis, we therefore focus on evaluating subjective and endocrinological stress responses as well as on the role of cognitive processes as potential mechanisms involved in PMDD.

1.3.1 Subjective stress perception and stress responses

Numerous studies have documented that higher levels of subjective and objective stress are associated with severe premenstrual symptoms (e.g. Gollenberg et al., 2010; Owens & Eisenlohr-Moul, 2018). This is supported by a large number of cross-sectional studies showing that PMDD deteriorates with stressful life events (Huang, Zhou, Wu, Wang, & Zhao, 2015; Klatzkin, Lindgren, Forneris, & Girdler, 2010) and that work stress is associated with more severe premenstrual symptoms (Namavar Jahromi, Pakmehr, & Hagh-Shenas, 2011). Furthermore, women with severe premenstrual symptoms experience more stress (Kleinstauber et al., 2016; Lustyk,

Widman, Paschane, & Ecker, 2004). In addition, longitudinal studies show that early sexual abuse, exposure to domestic violence, and other traumata lead to an increased risk of developing PMDD (Perkonigg, Yonkers, Pfister, Lieb, & Wittchen, 2004; Wittchen, Perkonigg, & Pfister, 2003). Therefore, PMDD is regarded as a stress-related condition.

With regard to a possible heightened stress perception, it further remains unclear whether women with PMDD show respective alterations throughout the menstrual cycle or if elevated stress appraisal is limited to the symptomatic premenstrual phase. Initial results from two earlier studies point towards a cycle-related negative bias. Fontana and Badawy (1997) showed that affected women perceived events as more severe and unpleasant solely during the premenstrual phase. Brown and Lewis (1993) identified an association of premenstrual symptoms with more hassles and fewer uplifts in the premenstrual compared with the postmenstrual phase. Unfortunately, more recent studies allowing to identify cycle-related variations in stress perception in women with PMDD are lacking. Furthermore, there is a lack of studies assessing reactivity to daily life stressors in PMDD research. Such momentary stress responses might express themselves through momentary affect and cognitions (e.g. rumination, self-focused attention). The first evidence of increased cognitive stress-reactivity comes from an experimental study by Craner et al. (2015) showing that women with PMDD demonstrated increased self-focused attention toward a standardized laboratory stressor. In order to assess affective stress reactivity in PMDD, it seems fruitful to differentiate between specific mood facets. According to the circumplex affect model (Russell, 1980), a subdivision of affect can be made based on the degree of arousal states, which have also been found to be related to different cortisol patterns (Hoyt et al. 2015). Since epidemiological and clinical studies have shown that anger and irritability are the most prominent premenstrual symptoms above depression (Hantsoo & Epperson, 2015; Owens & Eisenlohr-Moul, 2018; Pearlstein, Yonkers, Fayyad, & Gillespie, 2005), women with PMDD might respond to stress situations especially with high arousal negative affect states such as being upset or irritated, which may further contribute to interpersonal conflicts.

Given the currently limited state of research, it is likely that women with PMDD show heightened stress perception and stress reactivity in the premenstrual phase of the menstrual cycle. In light of increased high arousal symptoms in PMDD, premenstrual

stress may lead to high arousal negative affect states in particular. Studies in daily life could contribute important knowledge on the role of potential mechanisms associated with increased stress perception. From a therapeutic standpoint, a clearer understanding of such stress-related characteristics might then allow more targeted interventions aimed at reducing the impact of stress experiences.

1.3.2 Basal and stress-related endocrinologic patterns

Given findings of heightened stress sensitization in PMDD, there has been an interest in possible alterations of the hypothalamic-pituitary-adrenal axis (HPAA) system. In this regard, it is thought that the reported increased stress experience in affected women might be the result of an altered neurobiological system leading to changes in normal HPAA activity (cf. Kleinstauber et al., 2016). Controlled by GABAergig signaling (Maguire, 2019), activation of the HPAA due to stress perception typically leads to increased cortisol release (Nader, Chrousos, & Kino, 2010). Respectively, the response of the HPAA to an acute stressor is considered as an important biomarker indicating individual stress regulation.

The phenomenon of HPAA dysregulation has been described for a variety of stress-related disorders and chronic illness conditions, such as posttraumatic stress disorder, bodily disorders or depression (Adam et al., 2017; Doane et al., 2013; Heim et al., 2000). Thus, altered HPAA function might not be symptom specific, but may rather reflect a generally impaired recovery. Following this reasoning, it is proposed that prolonged stress periods elicit enhanced activation of the HPAA, which may eventually result in a downstream effect in the long run, leading to blunted activity of the HPAA and attenuated responsiveness to stressors (Huang et al., 2015; Adam et al., 2017).

PMDD shows significant comorbidity and considerable symptom overlap (i.e. irritability, mood lability, depression, anxiety) with other stress-related conditions (e.g. Pilver, Levy, Libby, & Desai, 2011), pointing towards a possible spectrum of stress-related disorders with similar endocrinologic characteristics. However, studies investigating basal and reactive cortisol secretion in women with PMDD are scarce and preliminary empirical findings on possible alterations in cortisol patterns are mixed.

A review study by Kiesner and Granger (2016), on 39 studies assessing basal and stress-related cortisol secretion across different study types including correlational

studies, environmental challenge studies and pharmacological challenge studies, revealed no clear picture concerning whether HPAA alterations are indicative for PMDD, with the predominance of studies showing null effects. Unfortunately, the review is limited in its generalizability due to the lack of a clear distinction between women suffering from PMS and those with more severe PMDD with obligatory affective symptoms. This is troubling because other studies indicate that women with PMDD may differ from those with PMS regarding physiological stress patterns, suggesting that only the former show a pronounced and sustained imbalance of the HPAA (Hoyer et al., 2013; Odber, Cawood, & Bancroft, 1998).

A first line of research has focused on basal HPAA activity. Hoyer et al. (2013) found a premenstrual increase in basal cortisol levels in women with mild premenstrual symptoms, proposing that this could represent a physiological and healthy response to subjective stress caused by monthly mood changes. By contrast, in women with PMDD a reverse pattern was identified by Odber et al. (1998), who showed a premenstrual decrease in basal cortisol levels. These studies suggest that a compensation mechanism is still intact in women with less severe premenstrual symptoms, whereas it could be impaired in patients suffering from PMDD, thereby emphasizing the importance of distinguishing between PMS and PMDD.

A second research line has investigated HPAA activity in response to stress. Preliminary data from laboratory settings lend support towards blunted endocrinologic stress reactivity in women with premenstrual disorders. An experimental study by Huang et al. (2015) – again by including women with PMS and PMDD – revealed attenuated cortisol reactivity in affected women irrespective of the menstrual cycle phase. Similarly, Klatzkin and colleagues (2010) found reduced physiological stress reactivity (blood pressure, heart rate) in women suffering from premenstrual symptoms in response to an experimental stressor, regardless of whether these women had a history of depression. Correspondingly, in a subsequent study the authors demonstrated that the extent of dysregulation in HPAA responses to a standardized stressor predicted stronger symptoms in affected women (Klatzkin, Bunevicius, Forneris, & Girdler, 2014).

Following the reported observations, a blunted HPAA activity may characterize a possible mechanism underlying heightened subjective stress reactivity in women with PMDD (cf. Owens & Eisenlohr-Moul, 2018). In line with this theory, results from a non-clinical study by Het et al. (2012) point to a possible mood-buffering effect of

cortisol. In this study, lower cortisol levels in response to acute stressors were linked to higher levels of negative affect, suggesting that cortisol buffers emotional arousal in stressful situations, possibly by inhibiting autonomic stress reactions. Correspondingly, cortisol is regarded as a stress buffer normalizing emotional circuits (Schlotz et al., 2008).

In summary, a detailed investigation of basal and stress-reactive components of HPAA activity during daily life appears crucial to understand its role in PMDD. First experimental studies provide weak support for blunted HPAA activation combined with heightened subjective stress reactivity in women with PMDD (cf. Owens & Eisenlohr-Moul, 2018). However, the findings are scarce and remain mixed. The observed heterogeneity may partly be the result of a lack of differentiation between PMDD and the less severe PMS, the latter lacking clearly defined criteria. This differentiation is considered particular important for determining potential physiological mechanisms (Hoyer et al., 2013). In this regard, studies applying more rigorous PMDD inclusion criteria combined with frequent measures of cortisol parameters throughout the menstrual cycle appear ideally suited to shed more light on a possible HPAA dysfunction in PMDD.

1.3.3 Psychological processes

Considering the high comorbidity and symptom overlap with other unipolar mood disorders (Cohen et al., 2002), anxiety disorders (D. R. Kim et al. 2004; Landen & Eriksson, 2003; Perkonigg et al., 2004) and somatoform disorders (Angst, Sellaro, Merikangas & Eriksson, 2003), but also with bipolar disorders (Fornaro & Perugi, 2010; D. R. Kim et al., 2004), as well as the increased risk of women with PMDD developing postpartum depression (Buttner et al., 2013), research on shared vulnerability factors is warranted. As PMDD is defined by a strong emphasis on affective symptoms, the possible contribution of dysfunctional cognitions and behaviors in response to premenstrual emotional states holds particular interest. In this context, rumination, anxiety sensitivity or dysfunctional coping strategies such as avoidance are being discussed (Craner, Sigmon, Martinson, & McGillicuddy, 2014). In particular, rumination has received attention as a transdiagnostic factor within the last decade. It is conceptualized as a thought process that includes persistent and repetitive thinking about one’s negative mood and other negative aspects of oneself (Lyubomirsky et al., 2015; Nolen-Hoeksema et al., 2008). Aggravating effects of

rumination on negative mood have been identified in several mental disorders including affective, anxiety and eating disorders (Aldao & Nolen-Hoeksema, 2010; McLaughlin & Nolen-Hoeksema, 2011; Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013). In depressed patients, ruminative thinking is associated with the onset of depressive episodes (Nolen-Hoeksema, 2000) and a chronic symptom course (Struijs, Lamers, Spinhoven, van der Does, & Penninx, 2018). There is evidence that especially women tend to use more ruminative coping strategies than men, which partly accounts for the gender gap in depression rates (Kuehner, 2017). Research aimed at assessing such phenomena in PMDD would significantly enhance our understanding of which cognitive processes might serve as triggers for cycle-related mood symptoms. However, only a handful of PMDD studies to date have explored characteristics such as ruminative thinking or self-focused attention. In this regard, it has been suggested that while self-focussing on cycle-related changes represents a dysfunctional strategy to deal with premenstrual symptoms (cf. Craner, Sigmon, & Young, 2016), a mindful state of mind may be a protective factor buffering from aggravating effects on PMDD symptoms (cf. Lustyk, Gerrish, Shaver, & Keys, 2009).

Indeed, this is supported by initial evidence from between-person studies: dispositional brooding rumination was heightened in women with premenstrual disorders (Craner et al., 2014) and associated with steeper increases in premenstrual depressive symptoms (Dawson et al., 2018), whereas high habitual mindfulness appeared to be linked to less cycle-related symptoms (Lustyk, Gerrish, Douglas, Bowen, & Marlatt, 2011). A daily life study across the menstrual cycle in a non-clinical sample of women demonstrated that high trait ruminators showed increased levels of momentary irritability towards the end of the cycle, whereas women low in habitual rumination experienced a more positive mood on these days (Welz et al., 2016). Similarly, Sigmon, Schartel, Hermann, Cassel, and Thorpe (2009) investigated the impact of rumination and anxiety sensitivity on distress from premenstrual symptoms in a non-clinical sample, demonstrating that rumination mediated the relationship between anxiety sensitivity and premenstrual distress.

In contrast to the aforementioned literature on trait aspects of dysfunctional cognitions based on self-report questionnaires, there is a lack of PMDD research examining relationships between cognitive processes and premenstrual distress at the within-person level. Only one study to date has assessed the relationship

between momentary psychological processes and PMDD. In this study, women with PMDD showed increases in self-focused attention during the premenstrual week, which partially explained the degree of premenstrual mood changes (Craner et al., 2016).

To conclude, in light of significant findings from previous studies assessing trait-like aspects of rumination (e.g. Craner et al., 2014, 2015) and transdiagnostic evidence of rumination as a dysfunctional key mechanism in various psychopathologies (Lyubomirsky et al., 2015; Nolen-Hoeksema et al., 2008), the investigation of dysfunctional cognitive states in PMDD women may help to identify menstrual cycle-related or trait-like psychological mechanisms associated with the disorder. In this context, it would be interesting to further explore whether trends from between-person studies are also evident at the level of individual persons. In this regard, within-person changes in daily-life cognitions may serve as drivers for PMDD symptom severity. Consequently, it is likely that negative affect is reinforced during the premenstrual phase by a maladaptive tendency to react with ruminating thoughts (cf. Craner et al., 2014, 2015). Surprisingly, no PMDD study to date has examined whether mood worsening and momentary dysfunctional cognitions reinforce each other in daily life. If so, accounting for such effects in PMDD treatment could be an important step towards improved therapeutic strategies.

1.4 Therapeutic options

Several therapeutic approaches have been discussed for premenstrual symptoms, ranging from modifying serotonin transmission to suppressing ovulation and improving coping skills via psychotherapy.

In this context, SSRIs (selective serotonin reuptakte inhibitors, e.g. fluoxetine, paroxetine, citalopram) are seen as the first line treatment by numerous experts (e.g. Hantsoo & Epperson, 2015; Ismaili et al., 2016; Sepede, Sarchione, Matarazzo, Di Giannantonio, & Salerno, 2016). Emerging evidence of their efficacy is provided by several meta-analyses (Marjoribanks, Brown, O'Brien, & Wyatt, 2013; Shah et al., 2008). For instance, the most recent Cochrane review by Marjoribanks et al. (2013) including 31 RCTs showed that the administration of SSRIs was effective for symptom relief. In addition, the review identified that SSRIs have almost the same effects when administered continuously or intermittently limited to the luteal phase. However, this review again did not differentiate between PMDD and other

premenstrual complaints such as PMS. The positive response to SSRIs does not appear to reflect a general antidepressant effect. Other antidepressants (i.e. tricyclic antidepressants, noradrenergic antidepressants) which are effective in women with Major Depressive Disorder have been found to be no more effective than placebo in women with PMDD (Cunningham et al., 2009; Nevatte et al., 2013).

Of particular note, both the rapid onset of action of SSRIs which is considered as a prerequisite for intermittent treatment (Marjoribanks et al., 2013) as well as the lacking efficacy of augmenting noradrenergic activity alone (Cunningham et al., 2009) may imply that different mechanisms underlie the efficacy of SSRIs for PMDD compared with Major Depression (cf. Yonkers & Simoni, 2018). This lends support to the view that PMDD and Major Depression should be seen as distinct clinical entities, an issue that should certainly be investigated in further detail in future research.

Since symptoms appear cycle-related with occurrence in the premenstrual phase and absence in anovulatory cycles, suppression of ovulation and hence inhibiting the luteal phase is a popular choice to relieve premenstrual symptoms (Rapkin et al., 2005). A meta-analysis on hormonal replacement therapy including five RCTs and involving 1,920 women with PMS and PMDD reported promising effects for ovulation inhibitors, even though studies showed high dropout rates (Lopez, Kaptein, & Helmerhorst, 2012). Furthermore, some evidence suggests that ovulation inhibitors appear to primarily improve physical rather than mood-related symptoms (Joffe, Cohen, & Harlow, 2003; Rapkin, 2005).

Novel therapeutic interventions in pharmacologic treatment regarding options that impact the HPAA via modulation of allopregnanolone and GABAergic function show promising effects. A study by Martinez et al. (2016) demonstrated that stabilization of allopregnanolone levels from the follicular to the luteal phase of the menstrual cycle is useful to treat women with PMDD, and another explorative study by Bixo et al. (2017) indicated positive results for a GABAA modulating antagonist to allopregnanolone (Sepranolone) as a potential treatment in the premenstrual phase.

Despite the reported beneficial effects of drug treatment, it is supposed that more patients prefer non-pharmaceutical options due to large rates of potential adverse side effects (e.g. nausea, decreased energy, sexual dysfunction) (Kleinstauber et al., 2012; Ussher & Perz, 2017). A treatment alternative could be cognitive-behavioral therapy (CBT), which may include self-monitoring, modification of irrational thinking, and increasing coping strategies or relaxation strategies (Busse, Montori, Krasnik,

Patelis-Siotis, & Guyatt, 2009; Nevatte et al., 2013). However, compared to pharmacotherapeutic options, these approaches have not been investigated in comparable detail, and only a small number of RCTs have investigated CBT in women with cyclically recurring symptoms. Evidence of clinical efficacy has been shown in an experimental study by Hunter et al. (2002), who compared CBT, fluoxetine (SSRI), and combined treatment with CBT and fluoxetine. The authors found no differences between groups after six months, although CBT had superior long-term maintenance effects at one-year follow-up. The latter holds particular importance given the chronic course of the disorder. Two review studies conducted meta-analyses of RCTs on cognitive-behavioral interventions using n=22 (Kleinstauber et al., 2012) and n=9 studies (Busse et al., 2009). Both reviews provide evidence of symptom relief via psychotherapy. Unfortunately, findings on women with PMDD and PMS were again pooled together.

In Germany, a research group from Philipps University Marburg focuses on developing and evaluating therapeutic strategies for patients suffering from severe premenstrual symptoms. A study by Janda, Kues, Kleinstaeuber, and Weise (2015) presents a newly-developed modularized treatment approach comprising different modules. It involves psychoeducation, cognitive interventions on dysfunctional cognitions, strategies to change dysfunctional behaviors, and targeting lifestyle issues. Another recent study by this research group evaluated the efficacy of an eight-week internet-based cognitive-behavioral therapy in PMDD treatment (Weise et al., 2019). The authors showed that the manualized internet-based therapy was highly effective in reducing the burden of PMDD, even after six months. Thus, it may offer treatment for a greater number of women due to its internet-based design. The study also highlights the importance of addressing coping strategies in PMDD treatment by showing that the use of active coping resulted in improved outcomes. Nonetheless, the question of which specific components of the numerous included psychotherapy modules in this study hold relevance to reduce premenstrual distress remains unanswered.

Taken together, there is a paucity of studies assessing factors that may be relevant for therapy. Given the limited empirical evidence for PMDD treatments, the German National Disease Management Guideline does not provide evidence-based recommendations regarding the efficacy of pharmacological and psychological treatments (DGPPN et al., 2017). In this context, earlier studies suffer from a lack of

distinction between PMS and PMDD, high placebo response rates as well as missing follow-up assessments (cf. Beddig & Kuehner, 2017). Notwithstanding these caveats, results from initial research on CBT lend support to the notion that interventions addressing active coping strategies in terms of seeking positive-affect-inducing activities might be helpful. Here, more research on the core group of women with PMDD is needed to confirm clinical efficacy, and further research on potential mechanisms (e.g. stress appraisal and the interplay between affective and cognitive processes) that can be translated into optimizing therapy outcomes is clearly warranted. In order to intervene and further reduce the burden of PMDD, it is also worthwhile to determine how these characteristics might predict the clinical symptom course.

1.5 Ambulatory Assessment

1.5.1 Ambulatory Assessment as an innovative approach to study the role of psychological daily-life processes in women with PMDD

Ambulatory Assessment (AA) is seen as an innovative methodology offering insights into daily-life experiences (J. Kim, Marcusson-Clavertz, Yoshiuchi, & Smyth, 2019; Myin-Germeys et al., 2018; Trull & Ebner-Priemer, 2014). This method allows recurrent and systematic recordings of momentary subjective experiences outside the laboratory in daily living environments and has increasingly provided new insights to the understanding of the etiology and expression of mental disorders (Myin-Germeys et al., 2018). Over the last decade, with the release of smartphones and tablets, AA has been increasingly applied in many fields of research (cf. Brietzke et al., 2019; J. Kim et al., 2019). For example, to date there are reviews on AA studies on mood (aan het Rot, Hogenelst, & Schoevers, 2012; Brietzke et al., 2019), anxiety (Walz, Nauta, & Aan Het Rot, 2014), and eating disorders (Haedt-Matt & Keel, 2011). In contrast, no previous study has used an electronic AA design to study PMDD, although this has been repeatedly called for by different experts in the field (e.g. Bosman, Jung, Miloserdov, Schoevers, & aan het Rot, 2016; Craner et al., 2014; Owens & Eisenlohr-Moul, 2018).

An AA study design offers important advantages over retrospective ratings. Benefits include minimizing the recall bias of self-reports (Carpenter, Wycoff, & Trull, 2016; Trull & Ebner-Priemer, 2014), increasing generalizability and ecological validity (Brietzke et al., 2019; Trull & Ebner-Priemer, 2013), verifying the correct timing of

data collection through automatically time-stamped responses (Trull & Ebner-Priemer, 2013) and advanced statistical power through the application of sophisticated analysis methods such as multilevel modeling (Carpenter et al., 2016). A further important advantage of AA studies is their ability to capture both variability between and variability within individuals (cf. Hamaker & Wichers, 2017; Schlotz, 2019). In contrast, within-person variability is difficult to impossible to assess with traditional retrospective measures (Hamaker, 2012). In PMDD research, this is particularly important given that mood swings belong to the core symptoms of the disease. Nonetheless, existing studies typically rely on single assessments using daily diaries or questionnaires (e.g. Cohen et al., 2004; Freeman, Sammel, Lin, Rickels, & Sondheimer, 2011; Schmalenberger et al., 2017). In this regard, AA with multiple real-time assessments per day at unpredictable intervals appears to be superior for a more specific detection of symptoms and symptom variability, which may not be seen via retrospective reports (cf. Brietzke et al., 2019). Moreover, AA data collection enables the coverage of the entire menstrual cycle. Given the cyclic nature of PMDD symptoms, this seems to be particularly helpful for research on menstrual cycle-related changes. Only by doing so is it possible to compare different cycle phases within the same woman. Furthermore, when tracking women over different cycle phases, researchers can identify both characteristics occurring only in the late luteal phase and those observable throughout the whole cycle. The latter might then indicate trait-like characteristics. Finally, while in laboratory conditions it is difficult to study reciprocal relationships across time, AA measures allow for an advanced modeling of temporal relationships within individuals, e.g. from moment to moment (cf. Garland, Geschwind, Peeters, & Wichers, 2015; Walz et al., 2014). For instance, former studies with other clinical samples (e.g., patients with depression and generalized anxiety disorder) investigated prospective effects of cognitive states on subsequent levels of mood and vice versa (Kircanski, Thompson, Sorenson, Sherdell, & Gotlib, 2018; Ruscio et al., 2015).

These aforementioned factors clearly point to the need for well-designed longitudinal AA studies covering the course of the menstrual cycle, thereby being able to explore within-person associations in the context of PMDD.

1.5.2 AA as a research methodology to study cortisol secretion

AA designs yield opportunities for multimodal assessment due to the integration of psychological, physiological and behavioral data (cf. Kubiak & Stone, 2012; Schlotz, 2019; Trull & Ebner-Priemer, 2014; van Os et al., 2017). In the context of stress research, it facilitates the collection of non-invasive saliva cortisol during the flow of daily life, which is considered an important marker of HPAA functioning (Schlotz, 2019; Trull & Ebner-Priemer, 2013). Therefore, it allows tying objective measures of cortisol with subjective momentary daily-life experiences. For instance, an AA study by Huffziger et al. (2013) explored whether the daily life cortisol pattern in remitted depressed persons would differ from healthy controls. The authors found that increased levels of rumination were linked to higher cortisol activity over the day in both groups, whereas lower mood predicted higher cortisol levels only in healthy controls. By using AA as a research tool to assess cortisol levels, former studies have reached good compliance rates, suggesting that the repeated collection of salivary cortisol while undergoing daily routine appears not to be problematic (e.g. Huffziger et al., 2013; Smyth, Zawadzki, Juth, & Sciamanna, 2017).

Different standard cortisol parameters have been widely used and can be assessed by self-collected saliva samples during AA (e.g., see Beddig, Timm, et al., 2019). First, the size of the post-awakening cortisol increase – a phenomenon termed cortisol awakening response (CAR) – is a key parameter for psychoneuroendocrinologic research (Stalder et al., 2016). Cortisol increases immediately after awakening and peaks within the first 30-45 min thereafter (Boggero, Hostinar, Haak, Murphy, & Segerstrom, 2017; Kudielka, Gierens, Hellhammer, Wüst, & Schlotz, 2012). Both increased and blunted CAR have been associated with a wide range of pathologies, so deviations from a typical CAR pattern are assumed to mark maladaptive neuroendocrine processes (Adam & Kumari, 2009; Stalder et al., 2016). Second, frequent sampling over the day allows for the accurate construction of the diurnal cortisol slope. Cortisol output follows a marked circadian pattern with a decline from morning to evening, reaching the lowest point near midnight (Schlotz, 2011). A flatter diurnal cortisol slope – indicated by a slower rate of decline in cortisol across the day – has been linked to poor health outcomes and to stress-related disorders (cf. Adam et al., 2017). Third, in addition to investigations of basal HPAA activity, AA also enables capturing cortisol responses following real-life stressors. In particular, while stress tasks in laboratory settings

represent rather artificial situations, assessing cortisol in response to daily life stressors might have more ecological validity (cf. Vaessen et al., 2018). Cortisol peaks typically follow stressful events or negative emotional states with a lag of approximately 10-20 min (Schlotz et al., 2008), whereby delaying the signal for collection of the saliva probes by approximately 15 min is recommended (Schlotz, 2019). Accordingly, AA allows analyzing individual cortisol responses towards within-person increases of daily-life stress. Interestingly, while there is emerging research on aggregated cortisol measures in various mental disorders, there has been little respective research exploring within-person stress-cortisol associations (Schlotz, 2019). Similarly, the already mentioned recent review on cortisol in premenstrual disorders by Kiesner & Granger (2016) stresses the need for such within-person analyses on multiple parameters of cortisol regulation. In fact, although existing literature suggests that women with PMDD show increased subjective sensitivity to stress (Owens & Eisenlohr-Moul, 2018), no study to date has investigated how subjective experiences during daily life relate to HPAA function in affected women. In order to study such phenomena in detail, a well-designed AA approach is most appropriate.

1.5.3 Investigation of AA phenotypes for the prediction of the clinical course of PMDD

The combination of multiple assessments of daily-life experiences at the micro-level using AA and illness-related factors measured at the macro level over longer term intervals has recently been regarded as a promising approach to explore mental disorders (Barnett et al., 2018; Brietzke et al., 2019; Wichers, 2014).

Clinical studies have investigated the role of respective AA-derived so called “experience sampling phenotypes” as predictors of the clinical course of depression (Timm et al., 2017; Wichers et al., 2010), anxiety disorders (Adam et al., 2014) and schizophrenia (Barnett et al., 2018). In a study by Timm et al. (2017) it was shown that higher instability of daily life mood and rumination predicted recurrence and symptom levels of depression three years after baseline. Similarly, Wichers et al. (2010) found that reward experience and daily-life fluctuations in negative affect significantly improved the prediction of future depressive and anxiety symptoms after more than one year. Adam et al. (2014) provided first evidence of a prospective relation between HPAA functioning, assessed on three consecutive weekdays, and

first onsets of anxiety disorders over the subsequent six years. Furthermore, Barnett et al. (2018) identified higher rates of AA-derived behavioral abnormalities in the days before relapse in patients diagnosed with schizophrenia.

By contrast, AA characteristics have not been investigated so far as potential micro-level predictors for the clinical course of PMDD. This holds particular importance given that previous research has shown that PMDD frequently develops a chronic course. For instance, in a German community sample, Wittchen et al. (2002) demonstrated that the syndrome was stable across 48 months with less than 10% complete remissions among baseline cases. In light of the apparent unfavorable long-term course of PMDD, the assessment of the predictive value of experience sampling phenotypes for the clinical course of PMDD is important and may help to develop target treatments.

1.6 Research questions

At present, there is a surprising lack of research assessing subjective and endocrinologic processes in the natural environment of women with PMDD. We addressed this limitation by implementing an electronic AA study design. The following three substudies of the thesis are based on an overarching AA study "*Menstrual cycle-dependent variations in mood, rumination, and cortisol in women with and without Premenstrual Dysphoric Disorder: An Ambulatory Assessment study*" which was funded by the Deutsche Forschungsgemeinschaft (DFG KU1464/6-1). The AA approach enabled us to study momentary experiences and cortisol secretion in the flow of daily life and to compare respective temporal within-person processes and their interplay across the menstrual cycle in women with and without PMDD, as well as to investigate the predictive value of daily life characteristics (i.e., AA-related phenotypes) for the clinical course of PMDD. The study aims and hypotheses of the present thesis were as follows.

Study 1

Specifically, Study 1 aimed to examine stress-related facets of mood and cognitions together with basal and stress-related HPAA activity over the menstrual cycle in women with PMDD compared to non-affected women. With regard to previous research showing that PMDD exacerbates with stressful life events (cf. Beddig & Kuehner, 2017) and that PMDD women exhibit higher levels of stress perception

(Owens & Eisenlohr-Moul, 2018), it was hypothesized that affected women would be more sensitive towards daily life stressors and would react with increased levels of rumination and negative affect, particularly in the premenstrual phase. We further investigated whether women with PMDD would demonstrate altered cortisol patterns and if these alterations would be cycle-phase specific. There is initial indication that PMDD women show blunted basal and stress-reactive HPAA function (Owens & Eisenlohr-Moul, 2018; Huang et al., 2015; Klatzkin et al., 2014). Hence, consistent with these prior reports, we expected attenuated basal (cortisol awakening response (CAR) and diurnal slope) as well as blunted stress-reactive cortisol activity in affected women compared to asymptomatic controls across the menstrual cycle.

Study 2

In Study 2, we explored menstrual cycle-related variations of cognitive and affective daily-life states as well as time-lagged associations between these states. With regard to the cyclical pattern of clinical symptoms (APA, 2013), we expected that women with PMDD would report highest levels of negative affect and rumination and lowest positive affect and self-acceptance in the premenstrual phase. Furthermore, following findings from studies with other clinical samples (e.g. Kircanski et al., 2018; Ruscio et al., 2015), we hypothesized that PMDD would be linked to stronger prospective effects between within-person changes in rumination and negative affect, and between within-person changes in self-acceptance and positive affect states. Furthermore, in women with PMDD these reciprocal time-lagged relationships were expected to be strongest in the late luteal phase.

Study 3

Study 3 focused on the role of specific AA phenotypes within the framework of longitudinal research on PMDD, which is to date generally lacking. Specifically, it aimed to investigate the possible predictive value of affective, cognitive, and endocrinologic daily-life characteristics for the clinical course of PMDD. For this purpose, we conducted a four-month follow-up to examine whether AA characteristics measured at baseline would add value in predicting the clinical symptom course in PMDD women. Here, we assumed that adverse affective and cognitive states, low cortisol levels, and heightened subjective and endocrinologic

stress reactivity during daily life at baseline would predict a poor clinical symptom course over and above relevant demographic and clinical characteristics.

2 STUDY 1: STRESS, MOOD, AND CORTISOL DURING DAILY LIFE IN WOMEN WITH PREMENSTRUAL DYSPHORIC DISORDER (PMDD)

An adapted version of this chapter has been published as: „Beddig, T., Reinhard, I., & Kuehner, C. (2019). Stress, mood, and cortisol during daily life in women with Premenstrual Dysphoric Disorder (PMDD). *Psychoneuroendocrinology, 109*, Article 104372. DOI: 10.1016/j.psyneuen.2019.104372. Epub 2019 Jul 23."

2.1 Abstract

Premenstrual Dysphoric Disorder (PMDD) is characterized by significant emotional, physical and behavioral distress during the late luteal phase that remits after menses onset. Outlined as a new diagnostic category in DSM-5, the mechanisms underlying PMDD are still insufficiently known. Previous research suggests that PMDD exacerbates with stressful events, indicating a dysregulation of the hypothalamic-pituitary-adrenal axis. However, studies measuring stress-related processes in affected women in real-time and real-life are lacking. We conducted an Ambulatory Assessment (AA) study to compare subjective stress reactivity together with basal and stress-reactive cortisol activity across the menstrual cycle in women with and without PMDD. Women with current PMDD (n=61) and age- and education matched controls (n=61) reported momentary mood, rumination, and daily events via smartphones at semi-random time points 8 times a day over two consecutive days per cycle phase (menstrual, follicular, ovulatory, and late luteal). Twenty minutes after assessments participants collected saliva cortisol samples. Three additional morning samples determined the cortisol awakening response (CAR). Women with PMDD reported particular high daily life stress and high arousal negative affect (NA_{high}) towards stressors during the late luteal phase. High momentary stress levels were linked to lower levels of high arousal positive affect (PA_{high}) and to higher levels of rumination in PMDD women compared to controls irrespective of cycle phase. Across groups, more stress was linked to higher levels of low arousal NA (NA_{low}) and to lower levels of low arousal PA (PA_{low}). Moreover, PMDD was associated with a delayed CAR peak and a flattened diurnal cortisol slope. While neither group showed cortisol reactivity towards daily life stress directly, high momentary NA_{high} and low

momentary PA predicted high levels of cortisol across groups, whereas high momentary rumination predicted high cortisol output only in healthy women. In this AA-study we identified important stress-related psychological and endocrinological within-person variability in women with PMDD during daily life. Further research is warranted targeting identified AA-based mechanisms to study their predictive role for the clinical course of PMDD and to provide evidence-based therapeutic options for affected women.

2.2 Introduction

2.2.1 Premenstrual Dysphoric Disorder (PMDD)

Cyclically recurring premenstrual symptoms to a degree that they interfere with normal functioning are characteristic for women suffering from Premenstrual Dysphoric Disorder (PMDD). Due to particular core symptoms, a specific cycle-dependent course and high symptom-specific stability, PMDD has been outlined as a new diagnostic category in DSM-5 (American Psychiatric Association, APA, 2013). Here, PMDD is defined by the occurrence of at least five symptoms in most menstrual cycles during the past year such as affective lability, irritability, depressed mood, anxiety (at least one of these four), loss of interest, fatigue, feeling emotionally overwhelmed and physical symptoms. These symptoms need to occur during the week before and to improve shortly after menses onset (APA, 2013). Epidemiological research suggests that PMDD affects 3 – 8% of premenopausal women (cf. Beddig & Kuehner, 2017). Lifetime comorbidity with other mental disorders, particularly with depressive and anxiety disorders is high; more than 50% of women with PMDD report a lifetime diagnosis of Major Depressive Disorder (MDD, Cohen et al., 2002).

2.2.2 Subjective stress responses in PMDD

The mechanisms underlying PMDD are still insufficiently known, findings indicate a multifactorial genesis (Beddig & Kuehner, 2017; Epperson et al., 2012). An important factor might be stress. Higher levels of subjective and objective stress were identified as risk factors for the onset of PMDD (Perkonigg et al., 2004), PMDD exacerbates with stressful life events (Huang et al., 2015), and women suffering from severe premenstrual symptoms perceive more chronic stress (Kleinstauber et al., 2016). In an earlier study women with severe premenstrual syndromes perceived stressors as

more severe and unpleasant than controls premenstrually, but not postmenstrually (Fontana & Badawy, 1997). Hoyer et al. (2013) identified higher subjective stress perception in the luteal phase in women with premenstrual symptoms during an emotional stroop task. Accordingly, PMDD women appear to show enhanced stress appraisal especially premenstrually. However, little is known about their stress responsivity during daily life, although this is important to determine generalizability and ecological validity of lab results and to identify potential mechanisms relevant to everyday life that can be targeted by appropriate therapeutic interventions. Subjective stress reactivity is mainly operationalized by negative affect (NA) towards stressors (Wichers et al., 2009). According to the circumplex affect model by Russell (1980), NA and positive affect (PA) can be further subdivided into low and high arousal states. Given that anger and irritability are the most prominent premenstrual symptoms (Hantsoo & Epperson, 2015; Owens & Eisenlohr-Moul, 2018) the distinction of arousal states might especially be important when studying mood states in PMDD. While low arousal NA states (NA_{low}) in response to stress could be more common for MDD, women with PMDD might more frequently react to stress especially with high arousal NA states (NA_{high}) such as being upset or irritated. Similarly, the differentiation between positive affect states high (PA_{high}) and low in arousal (PA_{low}) has not been addressed in PMDD research to date.

Furthermore, retrospective research has shown that women with PMDD use less helpful coping strategies such as rumination and increased self-focused attention in response to stress (Craner et al., 2015; Craner et al., 2014), and deficits in emotion regulation strategies were shown to be linked to higher premenstrual symptom levels in PMDD women (Dawson et al., 2018). In a similar line we could show that habitual rumination moderated menstrual cycle effects on mood in a nonclinical sample, with high ruminating women showing increased irritation towards the end of the cycle (Welz et al., 2016). In contrast, the possible significance of cognitions in everyday life such as state rumination in response to stress has so far been totally neglected in PMDD research.

2.2.3 Basal and stress-reactive cortisol activity in PMDD

Sustained stressors can cause alterations in the activity of the hypothalamic–pituitary–adrenal axis (Adam et al., 2017; Zorn et al., 2017), which is tightly controlled by GABAergic signaling (Maguire, 2019). Very few studies investigated basal and

stress-reactive cortisol activity in women suffering from premenstrual symptoms, and these studies normally did not distinguish PMDD from the milder premenstrual syndrome (PMS). The cortisol awakening response (CAR) and the diurnal cortisol slope (DCS) are the two main indicators measuring basal cortisol activity during the day (cf. Adam et al., 2017; Kudielka et al., 2012), whereas cortisol stress reactivity is mainly being measured in experimental settings using standardized stressors (cf. Zorn et al., 2017). A review by Kiesner and Granger (2016) found no consistent evidence for a basal or stress-reactive cortisol dysregulation in women with PMS/PMDD. A small number of studies indicated blunted activation across the cycle, and there was only modest evidence that affected women would show blunted cortisol reactivity toward environmental stressors (Kiesner and Granger, 2016). However, included studies used heterogeneous methodology regarding types of stressors, cortisol measures and criteria for diagnosis. More recently, Huang et al. (2015) found attenuated cortisol activity in women with premenstrual syndromes when experiencing an experimental stressor. Taken together, previous studies give first but weak support for attenuated basal and reactive HPAA activity during daily life in women with PMDD (cf. Owens and Eisenlohr-Moul, 2018).

2.2.4 Ambulatory Assessment (AA) in PMDD

Introducing AA into the study of PMDD has been repeatedly called for (e.g. Bosman et al., 2016; Owens and Eisenlohr-Moul, 2018) because it has important advantages over retrospective approaches. First, due to the multiple real-time assessments recall bias is reduced (Trull and Ebner-Priemer, 2013). The latter represents a limitation particularly in mere retrospective studies but also in prospective daily rating studies when women are asked to summarize their symptoms over the past day (Bosman et al., 2016). Furthermore, AA enables to capture the variability of affect, cognitions, and physiological states within and across days and cycle phases, thereby allowing to study both between- and within person variability (cf. Bosman et al., 2016; Owens and Eisenlohr-Moul, 2018; Schlotz, 2019). The present study mainly focuses on within-person relations of stress with subjective and cortisol outcomes, thereby reflecting for example the extent to which an individual's negative affect increases when appraising stress and whether PMDD and control women differ with this regard. Using a longitudinal AA-design that includes all menstrual cycle phases does also allow to distinguish between possible state-like alterations in PMDD occurring

only in the late luteal phase of the cycle and trait-like alterations occurring throughout the whole cycle. Moreover, the more detailed consideration of arousal in the assessment of affect states during daily life (cf. Hoyt, Craske, Mineka, & Adam, 2015) allows to identify possible distinct patterns of reactivity towards minor daily stressors within the PMDD context.

2.2.5 Study aims and hypotheses

The present study employed AA to examine subjective stress-reactivity together with basal and stress-reactive cortisol activity over the menstrual cycle in women with PMDD during their everyday life. We expected that women with PMDD would show (1) particularly high stress appraisal and (2) large subjective stress reactivity in the late luteal phase compared to other cycle phases whereas no such cyclicity was expected in healthy women. Particularly, we expected that PMDD women would respond to momentary within-person increases in stress with high levels of NA_{high}, and (3) with high levels of rumination especially in the late luteal phase. We further hypothesized that women with PMDD would display a pattern of basal cortisol secretion characterized by (4) a flatter CAR, (5) a flatter DCS, and (6) a blunted cortisol response to daily life stressors irrespective of cycle phase. As part of the stress response we further investigated cortisol responses to facets of momentary NA, PA and rumination. Here, we expected that PMDD women would show blunted cortisol responses in particular towards high arousal mood states and rumination, especially in the late luteal phase.

2.3 Method

2.3.1 Participants

Women with PMDD were recruited using different sources (newspapers, local family doctors and gynecologists practices, homepage of the Central Institute of Mental Health (CIMH), social networks). After telephone screening, possible eligible women underwent a clinical baseline interview to assess study in- and exclusion criteria (see 2.2). Inclusion criteria were fulfilling the DSM-5 criteria for PMDD A to E using the Structured Interview for DSM-IV TR Defined PMDD (SCID-PMDD, Accortt, Bismark, Schneider, & Allen, 2011 see 2.3.2.) with the diagnostic algorithm adapted for DSM-5. To avoid further participant burden, criterion F (prospective daily ratings during at

least two symptomatic cycles before study inclusion) was not required. In parallel, age- and education-matched controls were recruited. Control participants were excluded if they met criteria for any affective core symptoms of PMDD (criterion B) according to DSM-5 (see 2.3.2.). In contrast, premenstrual physical symptoms were not an exclusion criterion, given the fact that the majority of naturally cycling women are experiencing physical symptoms of varying degree during the late luteal and menstrual phase (Tschudin et al., 2010). Exclusion criteria for both samples included unfamiliarity with the German language, age < 20 and > 42, a reported cycle length of < 22 or > 34 days, a reported variation of cycle length of more than five days, use of hormonal contraceptives, antidepressants or other medication affecting the HPAA during the last three months, heavy exercise (≥1 h per day), late evening or night shifts, body mass index <18 or >35, birth of a child or lactation/breastfeeding during the last 6 months, history of gynecological diseases, bipolar or psychotic disorders, and substance dependence or current substance abuse (see 2.3.2). Consistent with DSM-5, other concurrent and past Axis-I disorders such as MDD and anxiety disorders were allowed, both in the PMDD and in the control sample. However, to differentiate PMDD from premenstrual exacerbation of another mental disorder, we included PMDD women with a current comorbid diagnosis only if their affective core symptoms for PMDD (A-criterion in DSM-5) differed noticeable from the affective core symptoms of the comorbid disorder, as suggested in DSM-5 (see APA, 2013). Of five women with a current comorbid depression diagnosis, we therefore had to exclude n=2 women from the PMDD sample who reported depressed mood as the affective core symptom for PMDD, while we retained n=3 women reporting irritability and mood lability as affective core symptoms for PMDD.

Of 138 women screened for PMDD, n=22 were excluded due to insufficient severity of affective core symptoms or insufficient distress/impairment, n=21 due to other exclusion criteria, and n=25 refused to participate due to anticipated temporal overload linked to study participation.

Of 118 screened controls, n=15 did not meet the inclusion criteria, n=8 were excluded due to the presence of affective core symptoms, n=15 refused to participate due to anticipated temporal overload, and n=10 could not be matched due to non-fitting matching criteria. Participants' data were analyzed if they had AA-assessments during at least three out of four menstrual cycle phases. Women who did not meet this criterion and did not repeat the missing assessment in the subsequent cycle

were considered dropouts. In total, 18 women (9 PMDD, 9 controls) withdrew (12.9%). The reasons for discontinuating were: inconsistencies with menstrual cycle reports (n=14), severe technical problems (n=2), decision to start hormonal contraceptives (n=1) and positive pregnancy test (n=1). The final sample consisted of 61 PMDD women and 61 controls. The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants gave written informed consent and received 100 € for participation.

2.3.2 Study Procedure and Measures

Data were collected in the period from 3/2016 to 10/2018. The procedure included a telephone screening, a baseline session, and AA (see Supplementum, Figure S1). During the baseline session at the CIMH the SCID-PMDD was administered to assess the inclusion criteria for PMDD. The SCID-PMDD is a structured clinical interview for PMDD developed and psychometrically evaluated by Accortt et al., (2011). Derived from the PMDD-DSM criteria, it includes all symptom criteria relevant for DSM-5 together with the required impairment and exclusion criterion for a mere exacerbation of symptoms of another disorder. The interview format is modeled after SCID-I (see below) and has shown high interrater reliability (kappa=0.96) (Accortt et al., 2011). For inclusion into the PMDD group, the criteria for PMDD according to the SCID-PMDD had to be met while control women had to be free of any PMDD affective core symptom. Additionally, the SCID for DSM-IV Axis I disorders (SCID–I, (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) was administered to assess current and lifetime diagnoses of other mental disorders and early trauma (traumatic events that occurred before the age of 18 as reported in the Posttraumatic Stress Disorder section of SCID-I). All interviews were performed by a trained research psychologist. Furthermore, the Premenstrual Symptom Screening Tool (PSST) was assessed at baseline to measure the self-rated severity of premenstrual symptoms and related impairments in different areas of daily life (Steiner, Macdougall, & Brown, 2003). In a subsample of participants (n=38 PMDD women, n=53 controls) the PSST was assessed twice, namely at the baseline interview (to assess the typical severity of premenstrual symptoms and impairments) and after performing the AA-period (to assess the late luteal phase covered by the AA). Participants also rated the degree of depressive symptoms on the BDI-2 (Hautzinger, Keller, & Kuehner, 2006) at the baseline interview.

Individual calendars were then prepared for each woman based on the date of her last menstruation onset and the average length of her menstruation and of her menstrual cycle. The menstrual cycle was divided into the menstrual, follicular, ovulatory, and late luteal phase (see Wolfram, Bellingrath, & Kudielka, 2011). Assessments during the menstrual phase took place on the second and third day of menstruation (mean = 2.95 days, SD = 2.21). The follicular phase was examined on the second and third day after the end of menstruation (mean = 8.61 days, SD = 1.94). The ovulatory phase (mean = 17.15 days, SD = 2.0) was determined by a chromatographic ovulation test (gabControl hlH Ovulationsteststreifen, gabmed, Cologne) indicating a rise in luteinizing hormone levels in urine. Testing began a few days before the predicted ovulation and participants were instructed to continue the tests daily until a positive result occurred and then to perform the AA on the two days immediately following ovulation. If ovulation did not occur, participants were asked to repeat the test in the following menstrual cycle. Assessments of the luteal phase took place on the fourth and third day before the next menstruation was expected (mean = 26.38 days, SD = 3.02). The phases were validated according to the ovulation test and the exact time of the onset of the next menses. The calendar specified the exact days on which the AA were to be carried out and when to begin with the ovulation test. For example, if a woman's cycle had a regular duration of 28 days and bleeding lasted approximately five days, she assessed the menstrual phase at day 2 and 3 after menses onset, and the follicular phase at day 7 and 8. She began testing ovulation on day 11 and assessed the ovulation phase the day immediately after the test turned positive, and the late luteal phase at day 25 and 26 (i.e., days -4 and -3 before new menses onset). Participants were asked to repeat assessments during the next cycle if the assessment days were not accurate (e.g., if the actual time of menses onset was several days earlier or later than expected). To counteract potential sequential effects women started in different phases of their menstrual cycle, depending on the time point of the baseline session. Among women with PMDD 36.1% started in the menstrual, 24.6% in the follicular, 31.1% in the ovulatory and 8.2% in the late luteal phase, among controls 37.7% started in the menstrual, 26.2% in the follicular, 29.5% in the ovulatory and 6.6% in the late luteal phase. After three months of assessment we decided to stop women starting in the luteal phase to verify that the luteal phase was in fact assessed during an ovulatory cycle as confirmed by the ovulation test.

2.3.3 Ambulatory assessment

The AA was carried out using Motorola Moto G 2nd Generation smartphones with the software My Experience movisensXS, Version 0.6.3658 (movisens GmbH, Karlsruhe, Germany). The smartphone app was developed specifically for this study. There were eight subjective assessments per day, with the first at 9 am and the last at 9:30 pm. Inter-assessment intervals were semi-randomized and varied between 45 and 120 min. Each assessment was announced by a beep and took 3-4 min to complete. Participants had 5 min to respond, and assessments could be delayed by 15 min. If participants were unable to respond or rejected the alarm, the assessment was saved as missing. At each assessment participants rated momentary mood and rumination.

1. Momentary NA and PA were assessed with 12 items based on the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) and previous AA studies (e.g. Kuehner, Welz, Reinhard, & Alpers, 2017; Timm et al., 2018) which were collapsed according to the circumplex model of affect (Russell, 1980) and in line with Nezlek (2005) and Hoyt et al., (2015) into NA_{high} (upset, irritated, nervous, Cronbach's alpha = 0.80), NA_{low} (listless, down, bored, α = 0.73), PA_{high} (cheerful, energetic, enthusiastic, α = 0.80), and PA_{low} (content, calm, relaxed, α = 0.88) items. Outcomes were calculated by averaging the respective item scores, ranging from 1 (not at all) to 7 (very much).
2. Momentary rumination was measured with the item „right before the beep I was stuck on negative thoughts and could not disengage from them" (range 1 to 7, cf. Kuehner, 2017; Timm et al., 2018).
3. Recent event-related stress was conceptualized in terms of subjective appraisals of events that continually occur in the natural flow of daily life. Participants were instructed to describe via free-text the most important event they encountered since the last beep or, at the first beep, since waking up. Participants' appreciation of the event was rated on a 7-point bipolar Likert scale, ranging from "very unpleasant" to "very pleasant." This item was subsequently recoded to allow high scores to reflect stress (-3 = very pleasant, 0 = neutral, +3 = very unpleasant; van der Stouwe et al., 2019; Wittchen et al., 2002). The daily stressor types were coded subsequently according to the categorization by Gilbert, Mineka, Zinbarg, Craske, and Adam (2017).

4. Sleep quality and sleep duration were assessed by single items that were presented after awakening; sleep quality: “How did you sleep last night?” (1 = very bad; 7 = very good), sleep duration: “How many hours did you sleep last night approximately?”.

Participants were able to contact a member of the research team by telephone in case of questions at any time.

2.3.4 Salivary measure of cortisol

Twenty minutes after each subjective rating, participants collected saliva cortisol samples with standard salivettes (Sarstedt, Germany). Subjects were instructed to refrain from strenuous exercise during the AA-day and not to eat, drink other than water, smoke, physically exercise or brush their teeth 20 minutes before completing saliva sampling. The smartphone briefly presented a random three-digit code which participants recorded on the label of the salivette tube they were using during each saliva collection (cf. Schlotz, 2019). After collection of the samples, participants indicated on the smartphone whether they had eaten, drunk, smoked or exercised during the last 20 min. By realizing a time-lag of 20 min between subjective assessments and cortisol samples, we could control for these possibly confounding effects and examine the actual influence of subjective variables on cortisol, since cortisol peaks with a time lag of 10—20 minutes (Schlotz, 2019). In addition, the CAR was measured by three saliva samples, directly after awakening before getting up, and 30 and 45 minutes later. Participants were instructed to wake before 8:00 and to refrain from eating, drinking (except water) and teeth brushing during the CAR assessment period. The DCS was assessed with the awakening sample and the eight samples following the subjective assessments, i.e. by excluding CAR samples 2 and 3. All samples were stored in the participant's home freezer until collection and subsequently frozen at −20 °C at the laboratory until biochemical analysis at the laboratory of Prof. Kirschbaum (Dresden, Germany). There, samples were centrifuged at 3,000 rpm for 5 min, resulting in a clear supernatant of low viscosity. Saliva cortisol concentrations were measured using commercially available chemiluminescence-immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were <8%.

2.3.5 Data Analytic Strategy

Data were analyzed with multilevel models using IBM SPSS version 23. Analyses showed that for all dependent variables the three-level model had a better fit than the two-level model according to fit indices (AIC and BIC) (Hox, Moerbeek, & Van de Schoot, 2017). Therefore, a multilevel model assuming three levels was applied with AA (level 1) nested within days (level 2) nested within persons (level 3). Momentary mood scores, rumination and cortisol were entered in separate models as dependent variables. Cycle phase was entered as a categorical variable in all models (0= menstrual phase, 1 = follicular phase, 2 = ovulatory phase, 3 = luteal phase). In the analyses on subjective outcomes we controlled for assessment day and time, which was centered at 9:00 to indicate hours since first assessment. For each dependent variable we checked whether time² was significant and if so retained it in the models, if not, time of assessments was included as a linear effect. All models included random intercepts at level 2 and 3, allowing individual levels of the dependent variables to differ between persons and days. To evaluate stress appraisal , group and menstrual cycle dependent variations for the prediction of mood and cortisol we included all predictor variables as well as the two- and three-way interactions between these predictors (cf. Huffziger et al., 2013; van der Stouwe et al., 2019). Only significant interactions were maintained in the final model. Post hoc tests for within- and between group analyses were conducted with Bonferroni corrections. In contrast, the hypothesis-driven main analyses were not corrected for multiple testing. The level 1 predictors were transformed by centering around the within-person mean, thereby yielding within-subject predictors that vary within, but not between individuals (Curran & Bauer, 2011). In addition, the main effects of level 1 predictors aggregated at the person level were added to the models to adjust for their potential effects. Importantly, however, the present paper focuses on within-subject associations of relevant variables, whereas between-subject effects will not be reported unless otherwise stated.

Cortisol data was log-transformed to adjust for skewness. Log data were examined for outliers, and outliers more than three standard deviations from the group mean were winsorized to 3 standard deviations (Stalder et al., 2016). In order to estimate basal cortisol secretion (CAR and DCS), time was centered at the waking time sample (i.e., higher values correspond to later times in the day). CAR compliance was defined as follows: Sample 1 had to be collected within 15 min of awakening,

sample 2 30 ± 10 min and sample 3 45 ± 10 min after awakening. Samples extending these periods were excluded (25.9%). For reactive cortisol, samples were excluded if collected more than 10 min after the prompt (5.5%). The models estimating CAR and DCS indicated a significant effect of both time and time², and model comparisons (AIC, BIC) indicated a better fit for the quadratic model. Therefore, multilevel models assuming that CAR and DCS data followed a quadratic trend were applied. Possible confounders were analyzed in three separate models for CAR (1), diurnal slope (2), and reactive cortisol (3) in the total sample. Depending on the respective outcome we examined the effects of age, current medication use, early trauma, habitual smoking, time, time of awakening, sleep quality, sleep duration, whether it was a workday or not (models 1,2,3), and if participants had recently ingested drinks, smoked cigarettes, had eaten anything, brushed their teeth, and their level of physical activity (models 2,3) by including these variables as fixed effects. Possible confounders were only retained in the models if significant ($p < 0.05$), which applied to time² (models 1,2,3), time of awakening (2,3), workday (yes/no) (1), physical activity (3) and sleep duration (3).

Models were estimated with Maximum Likelihood (ML) to compare model fit and Restricted Maximum Likelihood (REML) for all other analyses. The significance level was set at $\alpha=0.05$. For visualization purposes, plots of the analyses were made using the raw cortisol values (in nmol/l, retransformed from the valid log-transformed values).

2.4 Results

2.4.1 Compliance

Altogether, 6818 of 7808 possible subjective assessments (4 menstrual cycle phases x 16 assessments per phase x 122 participants) were recorded, corresponding to an overall response rate of 87.3% (PMDD: 86.6%, controls: 88%). Overall compliance for cortisol assessments (collected samples) reached 87.5% (PMDD: 87.6%, controls: 87.3%).

Table 1. Demographic, Clinical, and Daily Life Characteristics for Women with PMDD and Controls.

	PMDD (n=61) % / mean (SD)	Controls (n=61) % / mean (SD)	Test statistic	*p*
Demographic variables				
Age	29.4 (5.8)	29.5 (5.1)	t=-0.03	.977
Education (% with high school degree	72.1%	75.4%	Chi^2=0.17	.681
Work situation (% in regular job or education)	80.3%	90.2%	Chi^2=2.35	.126
Marital status (% married or living together)	60.7%	59.0%	Chi^2=0.03	.853
Children (%)	24.6%	26.2%	Chi^2=0.04	.835
BMI	23.6 (4.1)	23.5(4.3)	t=0.12	.903
Clinical variables				
Lifetime diagnosis of Major Depressive Disorder (MDD, SCID-I)	54.1%	21.3%	Chi^2=13.96	<.001
Early trauma	18.0%	3.2%	Chi^2=5.235	.022
BDI-II[1] at baseline	10.9 (8.9)	4.8 (5.6)	t=4.53	<.001
PSST[2] at baseline	34.6 (9.8)	6.6 (6.9)	t=18.26	<.001
PSST[2] following the AA[3]	32.3 (10.0)	7.1 (8.4)	t=13.04	<.001
Cycle-related variables				
Previous use of hormonal contraceptives	82.0%	90.2%	Chi^2=1.71	.191
Duration (in days) of menstrual cycle during AA	29.0 (3.1)	29.4 (3.7)	t=-0.77	.444
Duration (in days) of period during AA	5.3 (1.1)	5.6 (1.7)	t=-0.85	.399
Momentary variables[4] (AA)				
Stress appraisal	-0.7 (0.5)	-0.9 (0.6)	t=1.89	0.062
NA_{high}	2.8 (0.5)	2.1 (0.7)	t=5.64	<.001
NA_{low}	2.9 (0.6)	2.4 (0.7)	t=4.35	<.001
PA_{high}	3.9 (0.6)	4.4 (0.8)	t=-3.85	<.001
PA_{low}	4.4 (0.7)	5.0 (0.8)	t=-4.26	<.001
Rumination	2.4 (0.8)	1.9 (0.8)	t=3.78	<.001

[1]BDI-II=Beck Depression Inventory-Revised. [2]PSST=Premenstrual Symptom Screening Tool. [3] PMDD (n=38), controls (n=53). [4]Aggregated mean at the person level.

2.4.2 Sample description

As depicted in Table 1, women with PMDD and controls did not significantly differ with respect to age, education, marital status, work situation, percentage with children, mean duration of menstrual cycle, previous use of hormonal contraceptives, and time since stopping contraception. In contrast, women with PMDD displayed significantly higher depression scores (BDI-II) and included a markedly higher percentage of individuals with a lifetime diagnosis of MDD. Women with PMDD scored higher on the PSST both at baseline and with regard to the late luteal phase covered by AA. Paired t-tests between PSST scores at baseline and following the AA indicated comparable premenstrual symptom severity, both in the PMDD sample (M = 34.5 (SD = 10.1) vs. M = 32.3 (SD = 10.0), t(37) = 1.24, p = 0.222) and in the control sample (M = 6.7 (SD = 6.2) vs. M = 7.1 (SD = 8.4), t(52) = -0.50, p = 0.618). Furthermore, a higher percentage of women with PMDD than controls had experienced an early trauma. Moreover, women with PMDD showed higher aggregated mean levels of NA_{high} and NA_{low}, rumination, and lower aggregated mean levels of PA_{high} and PA_{low}, whereas the aggregated mean levels of stress appraisal was only marginally higher in PMDD women. The following daily event types were reported: performance-related (23.1%), interpersonal (15.8%), sleep (5.0%), self (1.2%), other (24.5%) and no stress (2.4%).

2.4.3 Stress appraisal

As hypothesized, the interaction effect of group*cycle phase on stress appraisal was significant (F (3, 829) = 5.12, *p* = 0.002). Separate analyses per group revealed a significant effect of cycle phase on stress appraisal in PMDD women (F (3,416) = 3.58, *p* = 0.014). Post hoc tests using Bonferroni correction showed significantly higher perceived stress during the luteal phase compared to the follicular phase (Mean Difference = 0.26, SE = 0.09, *p* = 0.023). No cyclicity in stress appraisal was identified for healthy women (F (3, 412) = 1.72, *p* = 0.163).

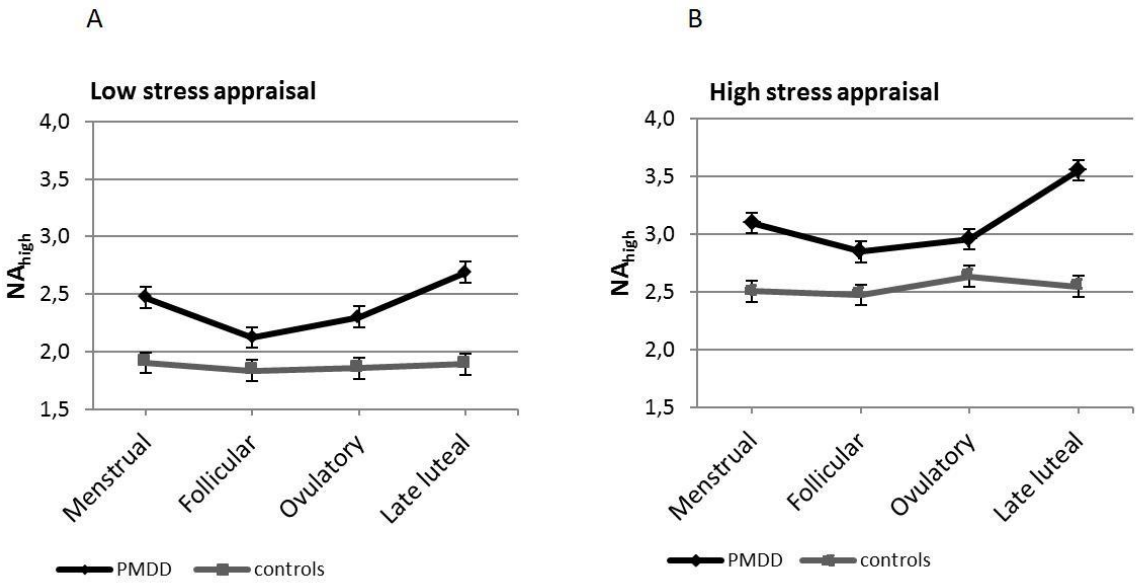

Fig. 1. Estimated mean values for NA_{high} mean and standard errors per menstrual cycle phase toward situations with low (-1 SD, Fig. 1A), and high (+1 SD, Fig. 1B) individual stress appraisal for women with PMDD and controls. Note. Error bars represent standard error of the mean. Model includes time, time², assessment day, and aggregated stress as covariates.

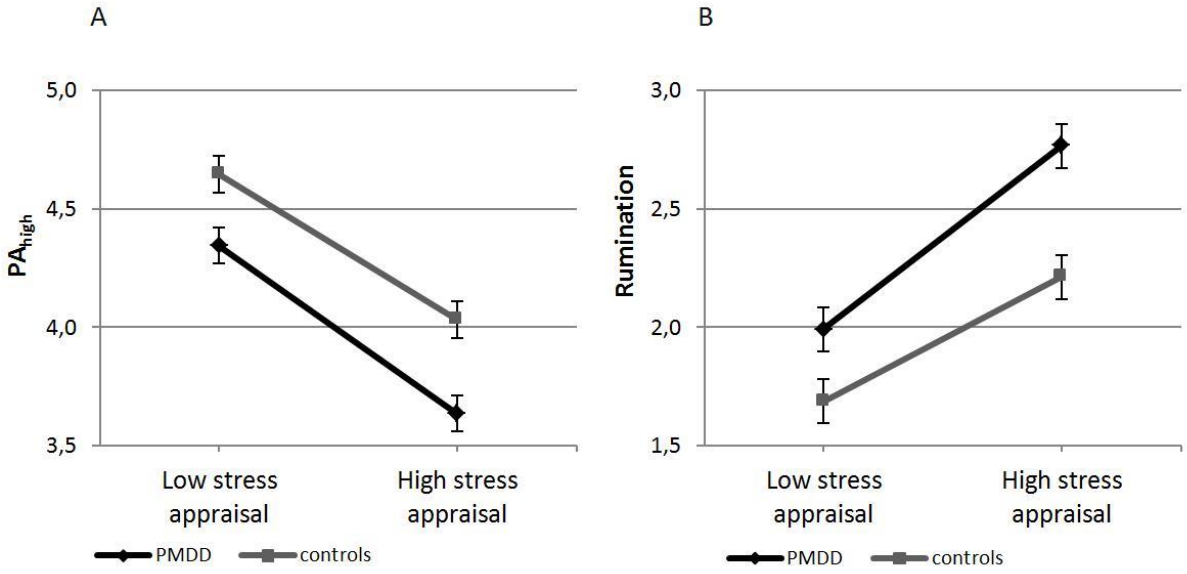

Fig. 2. Estimated mean values towards situations with low (–1 SD) and high (+1 SD) individual stress appraisal for PA_{high} (Fig. 2A) and rumination (Fig. 2B). Note. Error bars represent standard error of the mean. Models include time, assessment day, cycle phase, and aggregated PA_{high} (Fig. 2A), and aggregated rumination (Fig. 2B) as covariates.

2.4.4 Momentary within-person effects of stress on mood and rumination

To examine effects of stress on mood states, NA_{high}, NA_{low}, PA_{high}, PA_{low}, and rumination were entered as dependent variables in five separate models (complete models with stepwise removal of non-significant interaction terms see Supplementum, Table S1). Multilevel analyses revealed a significant three-way interaction group*cycle phase*stress on momentary NA_{high} ($F (3, 6364) = 2.83$, $p = 0.037$, see Table S1). Post hoc tests with separate models per group showed a significant two-way interaction stress*cycle phase in women with PMDD ($F (3, 3161) = 2.89$, $p = 0.034$). As shown in Figure 1A and B, in PMDD women high within-person levels of stress appraisal were associated with high levels of NA_{high} particularly in the late luteal phase, indicating larger subjective NA_{high} stress responses in this phase compared to other cycle phases. This interaction was not significant in controls ($F (3, 3214) = 2.02$, $p = 0.109$), indicating no cycle-dependent variability in stress reactivity in healthy women (see Figure 1A and B). All other models revealed no significant three-way interaction effect of group*cycle phase*stress on outcomes (NA_{low}: $p = 0.325$, PA_{high}: $p = 0.198$, PA_{low}: $p = 0.308$, rumination: $p = 0.211$, see Table S1). After stepwise removal of non-significant interaction terms in order to get a more parsimonious model and to facilitate interpretation, we identified significant two-way interactions (group*stress) for PA_{high} ($F (1, 6403) = 5.32$, $p = 0.021$) and for rumination ($F (1, 6547) = 22.28$, $p < 0.001$). As shown in Figure 2A and B, within-person increases in stress predicted lower levels of PA_{high} and higher levels of rumination in PMDD women compared to controls. In contrast, no group*stress effects were found for NA_{low} ($p = 0.338$) and PA_{low} ($p = 0.208$, see Table S1). Here, we identified main effects of stress on low activation mood in the total sample (NA_{low}: $F (1, 6383) = 662.55$, $p < 0.001$, $B = 0.18$, $SE = 0.01$, $p < 0.001$; PA_{low}: $F (1, 6445) = 1517.39$, $p < 0.001$, $B = -0.29$, $SE = 0.01$, $p < 0.001$, see Table S1).

2.4.5 Cortisol diurnal rhythm

To examine whether women with PMDD would show a flattened profile of basal cortisol activity two separate models were calculated. For the CAR the multilevel model yielded no significant effect of group*cycle phase*time² ($p = 0.379$, see Table S2). After stepwise removal of non-significant interaction terms we identified a significant interaction group*time² ($F (1, 1547) = 5.87$, $p = 0.016$). Figure 3A shows

different CAR peaks in PMDD women and controls with highest values 30 min after awakening among controls and 45 min among PMDD women, indicating that PMDD was associated with a delayed peak. Similarly, no significant threefold interaction (group*cycle phase*time²) was identified for the DCS (p = 0.499, see Table S2). After stepwise removal of non-significant interaction terms, the interaction group*time² demonstrated a significant effect on DCS (F (1, 6277) = 7.53, p = 0.006). As shown in Figure 3B, PMDD was associated with a flatter DCS throughout the day.

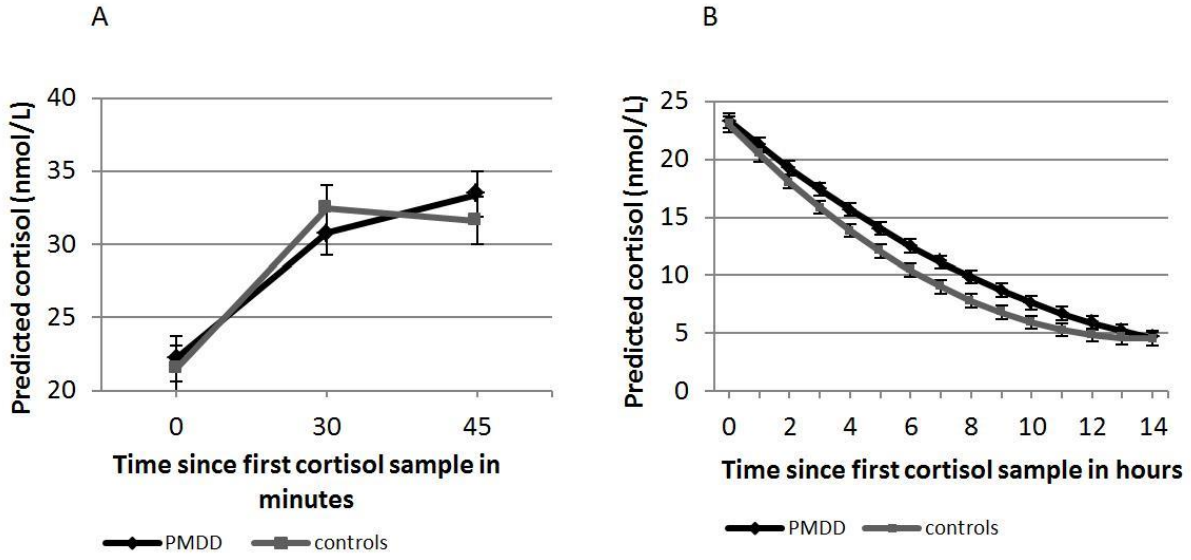

Fig. 3. Estimated CAR in women with PMDD and controls (Fig. 3A), and estimated DCS in women with PMDD and controls (Fig. 3B). Note. Error bars represent standard error of the mean. Models include cycle phase, workday (Fig. 3A), and time of awakening (Fig. 3B) as covariates.

2.4.6 Momentary within-person effects of stress, mood, and rumination on cortisol

To examine effects of stress, high and low affect states, and rumination on cortisol, we performed six separate models, one for each set of person mean-centered momentary daily-life predictors using cortisol secretion 20 min later as the dependent variable. In all models the interaction term predictor*group*cycle phase was non-significant (stress*group*cycle phase: p = 0.787, NA_{high}*group*cycle phase: p = 0.484, NA_{low}*group*cycle phase: p = 0.945, PA_{high}*group*cycle phase: p = 0.922, PA_{low}*group*cycle phase: p = 0.740, rumination*group*cycle phase: p = 0.713, see Table S3). After stepwise removal of non-significant interaction terms we identified a significant group*rumination effect (F (1, 5517) = 4.21, p = 0.040) revealing a

different association of within-person rumination variability with HPAA activity in women with and without PMDD. Figure 4 shows that higher within-person levels of rumination were linked to stronger cortisol activity in controls, while for women with PMDD momentary rumination and cortisol were uncoupled. In contrast no significant group*predictor interaction effect resulted for stress ($p = 0.853$), NA_{high} ($p = 0.797$), NA_{low} ($p = 0.268$), PA_{high} ($p = 0.106$), and PA_{low} ($p = 0.082$, see Table S3). After stepwise removal of non-significant interaction terms we identified main effects for NA_{high} ($F (1, 5236) = 13.94$, $p < 0.001$, $B = 0.04$, $SE = 0.01$, $p < 0.001$), PA_{high} ($F (1, 5201) = 4.58$, $p = 0.032$, $B = -0.02$, $SE = 0.01$, $p = 0.032$), and PA_{low} ($F (1, 4901) = 9.26$, $p = 0.002$, $B = -0.03$, $SE = 0.01$, $p=0.002$, see Table S3). Thus, across groups, higher within-person levels of momentary NA_{high} and lower levels of momentary PA_{low} and PA_{high} were linked to higher cortisol secretion 20 min later. In contrast, no main effects were identified for stress ($p = 0.879$) and NA_{low} ($p = 0.125$, see Table S3).

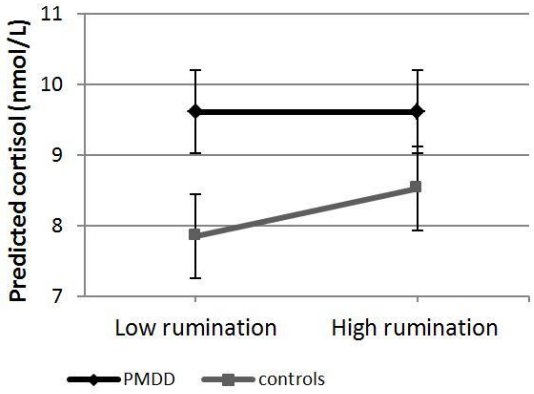

Fig. 4. Estimated mean cortisol levels for women with PMDD and controls for low (-1 SD) and high (+1 SD) individual momentary rumination scores. Note. Error bars represent standard error of the mean. Model includes time, time², cycle phase, time of awakening, physical activity, sleep duration, and aggregated rumination scores as covariates.

2.5 Discussion

To our knowledge, this is the first AA study to examine stress-related facets of mood and cognition together with basal and stress-reactive cortisol activity over the menstrual cycle in women with PMDD.

Consistent with previous reports (for reviews see Epperson et al., 2012; Owens and Eisenlohr-Moul, 2018), women with PMDD rated stressors as more aversive in the late luteal compared to the follicular phase, whereas no respective cyclicity was

found in healthy women. Our results furthermore highlight a specific response pattern toward daily life stressors in PMDD women. Women with PMDD showed a significant increase particularly in high-arousal negative affect states (upset, irritated, nervous) toward daily stressors in the late luteal phase compared to all other cycle phases and compared to healthy controls. Thereby, PMDD women appear to react with high intensity negative feelings of arousal towards stressors particularly during this phase, which may reciprocally contribute to a vicious circle between mood and interpersonal conflicts (the latter is also included in Criterion B2 of DSM-5 as “marked irritability or anger or increased interpersonal conflicts”). Interestingly, the preponderance of premenstrual high arousal negative emotions and mood lability over depressed mood in PMDD has led to a change in the respective listing of symptoms from DSM-IV to DSM-5 (Hantsoo and Epperson, 2015). In this context, some authors (Kuehner, 2017; Payne, Palmer, & Joffe, 2009) propose a female-specific reproductive subtype of depression given that PMDD links to postpartum and perimenopausal depression due to specific symptom presentation, comorbidity, and biological response to hormonal changes. Additionally, there seems to be heterogeneity within the diagnosis of PMDD itself regarding treatment response, symptom content and symptom timing. In a large sample of PMDD women, Eisenlohr-Moul et al. (2019) observed different temporal subtypes and conclude that particularly those with late occurring symptoms might represent a hormone-withdrawal-sensitive subtype of PMDD, which may also indicate increased risk during postpartum and late menopausal transition, which are similarly characterized by neurosteroid withdrawal or deprivation. Here, AA-studies can importantly contribute to systematically examine possible different phenotypes underlying reproductive and nonreproductive subtypes of depression but also to identify possible more homogeneous subgroups of PMDD.

We further identified an enhanced within-subject effect of stress on rumination in PMDD women regardless of cycle phase. Affected women seem to cope with more stressful situations with stronger ruminative thoughts compared to controls. The missing cycle effect suggests that this reflects a trait-like feature. While retrospective studies have shown that women with severe premenstrual symptoms use more dysfunctional coping strategies such as rumination in general (e.g. Craner et al., 2014), the present study adds to previous research by showing specific accentuated within-subject stress-rumination associations in PMDD women in their everyday life.

There is first indication that PMDD women show blunted basal HPAA function throughout the menstrual cycle (Owens and Eisenlohr-Moul, 2018), which is clearly supported by our results. First, their cortisol peak of the CAR was delayed. Although not entirely consistently, a blunted CAR (particularly the dynamic component) has been identified in various stress-related conditions such as posttraumatic stress disorder, chronic fatigue syndrome, atypical depression, in women having experienced early abuse (Kudielka et al., 2012; Powell, Liossi, Moss-Morris, & Schlotz, 2013; Tak et al., 2011), and in individuals with genetic or cognitive vulnerability to depression (Kuehner, Holzhauer, & Huffziger, 2007; Kuehner, Huffziger, Witt, & Rietschel, 2011). Furthermore, hypoactivation of the CAR was most consistently predicted by a "burnout/fatigue/exhaustion" type of psychosocial stressors in a large meta-analysis (Boggero et al., 2017). Similarly, the DCS of PMDD women was flattened in the present study. In their recent review, Adam et al., (2017) identified significant associations between flatter DCS and poorer emotional and physical health across studies and conclude that flatter slopes may reflect or contribute to stress-related circadian mechanisms affecting multiple aspects of health. In the present study, delayed and flattened basal HPAA activation (CAR, DCS) was seen across the menstrual cycle, thereby again indicating a trait-like characteristic.

Our study further extends previous PMDD stress research by assessing cortisol reactivity towards stress, arousal facets of NA and PA, and rumination in everyday life. Contrary to expectation, we did not identify any main or interaction effect of stress on cortisol. Our current results therefore do not support research from laboratory settings showing a blunted cortisol response towards stressors in women with PMDD (Huang et al., 2015). One explanation for the missing effect of stress on cortisol in the present study might be that stressors were minor daily life events and thus may have had less impact on the HPAA compared to standardized laboratory stressors. Further, the interval between two assessments might have been too long in some cases (i.e., > 1 hr, cf. Schlotz, 2019) for optimal peak cortisol detection in response to a stressor occurring during the interval. For power reasons, we also included all types of events that were mentioned during daily life, although specific event types such as interpersonal stressors might be stronger predictors for cortisol responses than others (Gilbert et al., 2017). Here larger studies are clearly needed to be able to subdivide daily life events in a more detailed way.

In contrast, high scores of momentary high arousal NA and of high and low arousal PA were linked to high cortisol 20 min later regardless of group or cycle phase. While facets of PA have been understudied in daily life stress research so far, our results confirm earlier findings on within-subject associations between momentary NA and cortisol in different study populations (summarized in Schlotz, 2019). Here, specifically high arousal NA demonstrated a significant activating effect on HPA axis activity while the effect of low arousal NA was nonsignificant. Furthermore, our study revealed that in controls, but not in women with PMDD, high levels of momentary rumination were linked to high levels of momentary cortisol across the menstrual cycle. Therefore, while our results on healthy women are in line with earlier studies showing rather consistent positive associations between state measures of rumination and cortisol (Zoccola & Dickerson, 2012), momentary rumination and cortisol activity appear to be decoupled in PMDD women.

2.5.1 Clinical Implications

Our study holds significant clinical implications. The observation that women with PMDD rate daily events as more stressful and show increased high arousal NA and rumination in face of stressful situations suggests that affected women could profit both from the use of helpful emotion regulation strategies and from coping with daily life stressors. In addition, since the identified association between stress and rumination in affected women was independent of menstrual cycle phase, therefore ruminative thoughts in PMDD women appear to reflect a trait-like rather than a state-like characteristic. Paralleling our results, questionnaire-based retrospective studies (e.g. Craner et al., 2014; Petersen et al., 2016) showed that women with severe premenstrual symptoms use less helpful strategies to regulate their emotions. Such processes were also identified at an implicit level (Eggert et al., 2016). The role of a ruminative coping style in PMDD has also been stressed in a recent study by Dawson et al., (2018) showing that brooding predicted a more rapid premenstrual increase and a slower postmenstrual symptom remission. Mindfulness-based technics have been suggested as valuable means for emotion regulation (Chambers, Gullone, & Allen, 2009) and single studies have shown that mindfulness may help women suffering from PMS (Bluth, Gaylord, Nguyen, Bunevicius, & Girdler, 2015; Panahi & Faramarzi, 2016). Methodologically sound mindfulness-based RCTs are warranted to evaluate whether these strategies are also useful to treat the more

severe distress in PMDD. Importantly, these studies should include daily life assessments of mood, cognition and stress perception as well as of basal and stress-reactive HPAA activation to study intervention effects on respective AA-based micro-processes during daily life together with clinical symptomatology at the macro-level.

From a pharmacological view, GABAergig and neurosteroid mechanisms influencing the biological stress response system and their possible dysregulation in PMDD are important. For example, recent work by Kanes et al. (2017) has identified lower GABA levels in women with postpartum depression and showed effectiveness of neurosteroid-based treatment in these women. Similarly, a phase-specific sensitivity of the GABAA receptor has been suggested for PMDD (Backstrom et al., 2014; Hantsoo & Epperson, 2015). Therefore, clearly more work is warranted examining treatment options that impact the HPAA via neurosteroid modulation of GABAergic function in affected women.

2.5.2 Strengths and Limitations

Strengths of the current study include the application of electronical AA to compare within-person variability of stress, arousal-related facets of NA and PA, rumination, and cortisol activity repeatedly during daily life in PMDD women and narrowly matched healthy controls, the use of a longitudinal design to cover all phases of the menstrual cycle, and the validation of ovulatory cycles through an ovulation test.

Our study has also some limitations. First, the study sample size was only modest. Although it clearly exceeds the recommended minimum size for estimating cross-level interactions (cf. Hox et al., 2017), statistical power may have been limited particularly for estimating three-way interactions. Therefore, the present results should be regarded as preliminary and validated in future studies with larger samples. Second, although the PMDD diagnosis was assessed with a reliable structured interview (SCID-PMDD, Accortt et al., 2011), this is nevertheless a retrospective measure, and confirmation by prospective daily ratings over at least two cycles was not required for study inclusion to prevent participant burden. Therefore, the PMDD-diagnoses in this study must be regarded as provisional (APA, 2013). However, our approach is in line with a majority of studies using retrospective reports to assess PMDD, and prevalence rates of moderate to severe premenstrual symptoms derived from retrospective epidemiological studies are consistent with

those using prospective ratings (Cunningham et al., 2009). Furthermore, low consistency among daily symptom rating instruments has been observed, with a widely varying magnitude of symptom change between the pre- and postmenstrual week required for a PMDD diagnosis (Bosman et al., 2016). Future studies could profit from applying AA over two cycles (which was not possible for us due to financial restrictions) and combining them with daily symptom ratings. Third, our sample may have not been representative of patients with PMDD seeking for treatment, given the voluntary nature of the study. Even though the sample was heterogeneous regarding age, education, job and family situation, women with higher education levels were somewhat overrepresented. Further, since antidepressant medication and hormonal contraceptives are currently the most frequent treatments for PMDD (Epperson et al., 2012) the exclusion of women taking pharmaceutics and hormonal contraceptives - although necessary for our study purposes - may have led to the exclusion of patients suffering from particularly severe symptomatology. Fourth, to restrict participant burden only two assessment days per cycle phase were scheduled, which could be critical, however, especially with regard to the late luteal phase. Clinical studies have shown that women with PMDD have the peak of distress one to two days before menses onset (Epperson et al., 2012), though symptom timing and severitiy has been observed to be heterogeneous (Eisenlohr-Moul et al., 2019). The decision to schedule the third and fourth day was due to the fact that these days are in the middle of the premenstrual week (as required for DSM-5) and therefore still within the acceptable range if menses had started one or two days earlier or later than expected. However it cannot be ruled out that thereby we missed days with the most severe premenstrual distress in some women. Fifth, although the PSST scores did not differ between a retrospectively assessed “typical” late luteal phase and the late luteal phase assessed by AA, our study design did not control whether an individual PMDD woman became asymptomatic or a control woman became symptomatic during the late luteal phase. Future studies could combine AA with daily ratings of premenstrual symptoms to investigate how the latter directly influence experiences measured by AA. Sixth, given the diurnal pattern of cortisol secretion, further studies should control for the possible influence of different chronotypes (morningness versus eveningness). Seventh, assessing daily life stress in AA studies in general presents some challenges (cf. Schlotz, 2019). In our semi-randomized design, the most important event could have occurred up to 120 min

before the beep. With cortisol probes being sampled with a 20 min lag, we therefore might have missed some relevant cortisol peaks. Moreover, the addition of more objective stress measurements may be useful in future studies (Owens and Eisenlohr-Moul, 2018). Next, while we did not identify an effect of early trauma on cortisol, future PMDD studies should examine childhood trauma with more detailed measures (e.g. Bernstein et al., 2003). Furthermore, negative affect may have biased the recall of negative events and of stress appraisal to some extent. Finally, since all subjective constructs were assessed concurrently, a clear causal link from daily events to mood and rumination cannot be established with the present data.

2.5.3 Conclusions

In conclusion, this is likely the first study to examine stress, mood, cognition, and cortisol activity in women with PMDD during daily life using electronic AA. Our results revealed particularly high stress appraisal and high subjective stress reactivity in terms of NA_{high} in women with PMDD during the late luteal phase as well as blunted basal HPAA function irrespective of cycle phase. While high levels of NA_{high} together with low levels of PA_{high} and PA_{low} were related to high momentary cortisol across groups and cycle phases, a distinct cortisol response to rumination was only seen in healthy women. With the application of electronic AA during daily life and the covering of four cycle phases, our study adds to existing knowledge on cycle-related and general alterations in PMDD. Identified characteristics in daily life experiences might also be predictive for the development and clinical course of PMDD which can easily be studied with respective longitudinal designs (cf. Adam et al., 2014; Timm et al., 2017 for other mental disorders). Premenstrual changes in affective, behavioural and physiological patterns in women with PMDD as assessed by AA do also represent dimensional entities particularly suitable for being studied across domains within the Research Domain Criteria (RDoC) framework (Insel, 2014), which might finally help to gain more insight into the biological and psychological mechanisms and their interplay involved in PMDD (cf. Owens & Eisenlohr-Moul, 2018). Further research is also warranted targeting identified AA-based mechanisms in the context of intervention studies to provide respective evidence-based therapeutic options for affected women.

2.6 Online supplementary material

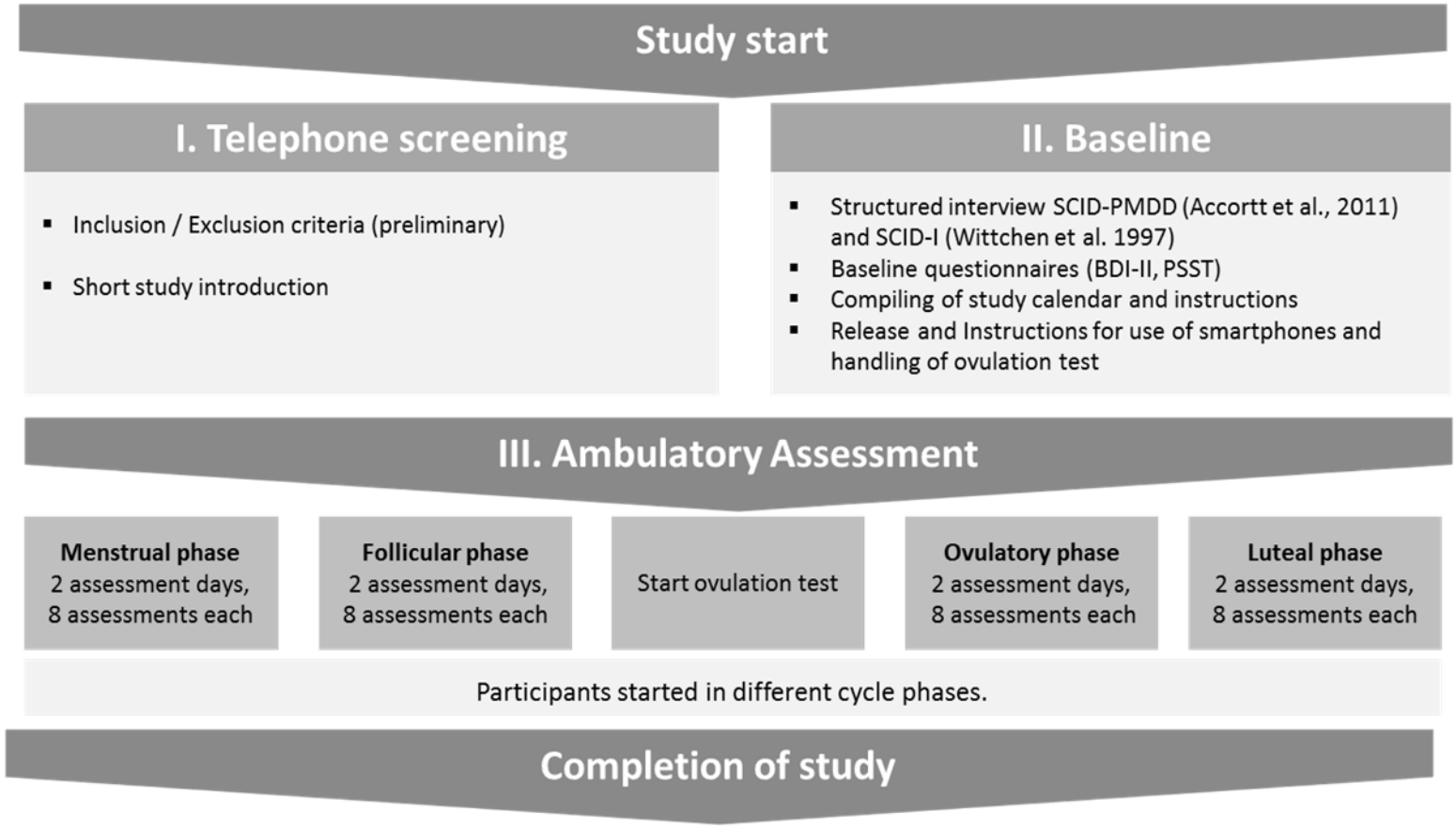

Figure S1. Schematic representation of the study's procedure.

Table S1. Fixed effects of stress, cycle phase, and group on momentary NA_{high}, NA_{low}, PA_{high}, PA_{low}, and rumination.

	Model 1			**Model 2**			**Model 3**		
	df	**F**	***p***	**df**	**F**	***p***	**df**	**F**	***p***
Outcome NA_{high}									
Fixed effects									
Intercept	(1,162)	726.07	<.001						
Group	(1,118)	27.78	<.001						
Cycle phase	(3,829)	17.04	<.001						
Aggregated mean stress	(1,119)	26.54	<.001						
Stress (W-S)	(1,6425)	1157.60	<.001						
Group * cycle phase	(3,829)	14.03	<.001						
Stress (W-S) * cycle phase	(3,6363)	2.27	.079						
Stress (W-S) * group	(1,6425)	1.36	.243						
Stress (W-S) * group * cycle phase	(3,6364)	2.83	.037						
Outcome NA_{low}									
Fixed effects									
Intercept	(1,152)	702.82	<.001	(1,152)	703.12	<0.001	(1,152)	703.02	<.001

Group	(1,118)	15.19	<.001	(1,118)	15.21	<0.001	(1,118)	15.25	<.001
Cycle phase	(3,830)	18.40	<.001	(3.829)	18.42	<0.001	(3,829)	18.54	<.001
Aggregated mean stress	(1,119)	14.88	<.001	(1,119)	14.85	<0.001	(1,119)	14.89	<.001
Stress (W-S)	(1,6370)	652.21	<.001	(1,6372)	651.61	<0.001	(1,6383)	662.55	<.001
Group * cycle phase	(3,830)	14.44	<.001	(3,830)	14.46	<0.001	(3,830)	14.48	<.001
Stress (W-S) * cycle phase	(3,6308)	.13	.940	(3,6318)	.19	.901	-[1)]	-[1)]	-[1)]
Stress (W-S) * group	(1,6370)	.87	.351	(1,6373)	.92	.338	-[1)]	-[1)]	-[1)]
Stress (W-S) * group * cycle phase	(3,6309)	1.16	.325	-[1)]	-[1)]	-[1)]			
Outcome PA_{high}									
Fixed effects									
Intercept	(1,159)	1236.44	<.001	(1,159)	1237.71	<.001	(1,159)	1238.01	<.001
Group	(1,119)	10.63	.001	(1,119)	10.71	.001	(1,119)	10.69	.001
Cycle phase	(3,842)	19.21	<.001	(3,841)	19.22	<.001	(3,841)	19.22	<.001
Aggregated mean stress	(1,119)	53.42	<.001	(1,119)	53.54	<.001	(1,119)	53.50	<.001
Stress (W-S)	(1,6398)	1048.88	<.001	(1,6400)	1045.79	<.001	(1,6398)	1048.88	<.001
Group * cycle phase	(3,842)	10.87	<.001	(3,841)	10.89	<.001	(3,841)	10.89	<.001
Stress (W-S) * cycle phase	(3,6338)	.08	.972	(3,6348)	.04	.991	-[1)]	-[1)]	-[1)]

Stress (W-S) * group	(1,6398)	5.29	.022	(1,6401)	5.28	.022	(1,6403)	5.32	.021
Stress (W-S) * group * cycle phase	(3,6339)	1.56	.198	-[1)]	-[1)]	-[1)]			
Outcome PA_{low}									
Fixed effects									
Intercept	(1,152)	1361.61	<.001	(1,152)	1363.97	<.001	(1,152)	1365.75	<.001
Group	(1,119)	14.49	<.001	(1,119)	14.56	<.001	(1,119)	14.55	<.001
Cycle phase	(3,839)	21.05	<.001	(3,838)	21.18	<.001	(3,838)	21.51	<.001
Aggregated mean stress	(1,119)	58.26	<.001	(1,119)	58.39	<.001	(1,119)	58.40	<.001
Stress (W-S)	(1,6432)	1499.25	<.001	(1,6434)	1497.18	<.001	(1,6445)	1517.39	<.001
Group * cycle phase	(3,839)	13.02	<.001	(3,839)	13.11	<.001	(3,839)	13.29	<.001
Stress (W-S) * cycle phase	(3,6370)	1.86	.134	(3,6380)	1.85	.135	-[1)]	-[1)]	-[1)]
Stress (W-S) * group	(1,6433)	1.56	.212	(1,6435)	1.59	.208	-[1)]	-[1)]	-[1)]
Stress (W-S) * group * cycle phase	(3,6371)	1.20	.308	-[1)]	-[1)]	-[1)]			
Outcome Rumination									
Fixed effects									
Intercept	(1,152)	376.80	<.001	(1,152)	377.26	<.001	(1,152)	376.80	<.001

Group	(1,118)	10.79	.001	(1,118)	10.82	.001	(1,118)	10.89	.001
Cycle phase	(3,825)	10.63	<.001	(3,824)	10.76	<.001	(3,824)	10.72	<.001
Aggregated mean stress	(1,118)	16.10	<.001	(1,118)	16.09	<.001	(1,118)	16.18	<.001
Stress (W-S)	(1,6543)	591.80	<.001	(1,6546)	588.87	<.001	(1,6546)	588.87	<.001
Group * cycle phase	(3,825)	13.06	<.001	(3,825)	13.16	<.001	(3,824)	13.10	<.001
Stress (W-S) * cycle phase	(3,6484)	1.48	.217	(3,6493)	1.35	.258	-[1)]	-[1)]	-[1)]
Stress (W-S) * group	(1,6544)	22.35	<.001	(1,6546)	22.52	<.001	(1,6547)	22.28	<.001
Stress (W-S) * group * cycle phase	(3,6485)	1.51	0.211	-[1)]	-[1)]	-[1)]			

Note. Aggregated mean: Aggregated mean at the person level. W-S: within-subject (person mean-centered). Models include random intercepts at level 2 and 3 as well as fixed effects for time, (time² if significant), and assessment day. [1)] Non-significant interactions were excluded stepwise.

Table S2. Fixed effects of group, cycle phase, and time on basal cortisol activity (CAR and DCS).

	Model 1			**Model 2**			**Model 3**		
	df	**F**	***p***	**df**	**F**	***p***	**df**	**F**	***p***
Outcome CAR									
Fixed effects									
Intercept	(1,156)	3002.81	<.001	(1,155)	3013.69	<.001	(1,155)	3013.69	<.001
Time	(1,1418)	66.04	<.001	(1,1418)	66.04	<.001	(1,1511)	64.25	<.001

Time²	(1,1435)	20.90	<.001	(1,1435)	20.90	<.001	(1,1547)	16.59	<.001
Group	(1,142)	.10	.758	(1,141)	.15	.697	(1,141)	.15	.697
Cycle phase	(3,1468)	2.87	.035	(3,678)	2.49	.059	(3,678)	2.49	.059
Group * cycle phase	(3,1467)	1.44	.230	(3,678)	.88	.451	-[1)]	-[1)]	-[1)]
Cycle phase * time	(3,1401)	1.44	.231	(3,1512)	2.81	.038	-[1)]	-[1)]	-[1)]
Cycle phase * time²	(3,1415)	.93	.426	(3,1558)	2.48	.059	-[1)]	-[1)]	-[1)]
Group * time	(1,1391)	.30	.587	(1,1418)	.83	.361	(1,1511)	4.15	.042
Group * time²	(1,1403)	.54	.463	(1,1434)	1.31	.253	(1,1547)	5.87	.016
Group * cycle phase * time	(3,1401)	1.15	.329	-[1)]	-[1)]	-[1)]			
Group * cycle phase * time²	(3,1415)	1.03	.379	-[1)]	-[1)]	-[1)]			
Outcome DCS									
Fixed effects									
Intercept	(1,930)	523.32	<.001	(1,31)	525.12	<.001	(1,31)	525.12	<.001
Time	(1,6241)	287.88	<.001	(1,6247)	289.01	<.001	(1,6253)	286.93	<.001
Time²	(1,6238)	22.47	<.001	(1,6244)	22.21	<.001	(1,6251)	22.74	<.001
Group	(1,158)	.04	.850	(1,158)	.04	.852	(1,158)	.04	.838
Cycle phase	(3,5035)	4.00	.007	(3,5042)	3.99	.007	(3,791)	2.61	.051
Group * cycle phase	(3,5042)	1.79	.148	(3,788.48)	.71	.549	-[1)]	-[1)]	-[1)]
Cycle phase * time	(3,6275)	1.89	.128	(3,6259)	1.88	.130	-[1)]	-[1)]	-[1)]

Cycle phase * time²	(3,6285)	1.89	.129	(3,6282)	1.87	.132	-[1)]	-[1)]	-[1)]
Group * time	(1,6247)	5.99	.014	(1,6254)	5.94	.015	(1,6260)	5.72	.017
Group * time²	(1,6271)	8.07	.005	(1,6270)	7.79	.005	(1,6277)	7.53	.006
Group * cycle phase * time	(3,6253)	1.27	.283	-[1)]	-[1)]	-[1)]			
Group * cycle phase * time²	(3,6276)	.79	.499	-[1)]	-[1)]	-[1)]			

Note. The dependent variable cortisol was entered log-transformed. CAR: Cortisol awakening response. DCS: Diurnal cortisol slope. Models include random intercepts at level 2 and 3. Confounding variables were only retained in the models when significant ($p < 0.05$), which applies to workday (yes, no) for CAR and time of awakening for DCS. [1)] Non-significant interactions were excluded stepwise.

Table S3. Fixed effects of momentary NA_{high}, NA_{low}, PA_{high}, PA_{low}, rumination, cycle phase, and group on cortisol output.

	Model 1			**Model 2**			**Model 3**		
Outcome cortisol	**df**	**F**	***p***	**df**	**F**	***p***	**df**	**F**	***p***
Fixed effects (predictor stress)									
Intercept	(1,783)	333.62	<.001	(1,783)	333.28	<.001	(1,782)	335.99	<.001
Group	(1,116)	.95	.332	(1,116)	.94	.335	(1,116)	.97	.326
Cycle phase	(3,758)	2.91	.034	(3,756)	2.97	.031	(3,758)	2.88	.035
Aggregated mean stress	(1,116)	5.46	.021	(1,116)	5.47	.021	(1,116)	5.43	.022

Stress (W-S)	(1,5505)	.03	.874	(1,5505)	.02	.895	(1,5527)	.02	.879
Group * cycle phase	(3,756)	.61	.610	(3,757)	.59	.619	-[1)]	-[1)]	-[1)]
Stress (W-S) * cycle phase	(3,5454)	1.17	.319	(3,5464)	1.10	.350	-[1)]	-[1)]	-[1)]
Stress (W-S) * group	(1,5500)	.02	.878	(1,5500)	.03	.853	-[1)]	-[1)]	-[1)]
Stress (W-S) * group * cycle phase	(3,5479)	.35	.787	-[1)]	-[1)]	-[1)]			
Fixed effects (predictor NA_{high})									
Intercept	(1,300)	204.42	<.001	(1,300)	203.67	<.001	(1,298)	204.61	<.001
Group	(1,117)	.69	.409	(1,117)	.63	.429	(1,116)	.66	.419
Cycle phase	(3,783)	3.48	.016	(3,777)	3.69	.012	(3,768)	3.69	.012
Aggregated mean NA_{high}	(1,116)	.39	.535	(1,116)	.37	.544	(1,116)	.37	.542
NA_{high} (W-S)	(1,5373)	13.65	<.001	(1,5380)	13.45	<.001	(1,5236)	13.94	<.001
Group * cycle phase	(3,782)	.59	.619	(3,774)	.54	.653	-[1)]	-[1)]	-[1)]
NA_{high} (W-S) * cycle phase	(3,5550)	.38	.765	(3,5531)	.18	.905	-[1)]	-[1)]	-[1)]
NA_{high} (W-S) * group	(1,6376)	.04	.846	(1,5372)	.07	.797	-[1)]	-[1)]	-[1)]

NA_{high} (W-S) * group * cycle phase	(3,5548)	.82	.484	-[1)]	-[1)]	-[1)]			
Fixed effects (predictor NA_{low})									
Intercept	(1,286)	152.48	<.001	(1,286)	153.91	<.001	(1,284)	153.25	<.001
Group	(1,117)	.03	.854	(1,117)	.03	.856	(1,117)	.03	.867
Cycle phase	(3,782)	3.21	.023	(3,777)	3.16	.024	(3,765)	3.19	.023
Aggregated mean NA_{low}	(1,118)	4.07	.046	(1,118)	4.04	.047	(1,117)	4.01	.048
NA_{low} (W-S)	(1,6314)	2.87	.090	(1,5318)	2.85	.092	(1,6168)	2.35	.125
Group * cycle phase	(3,781)	.63	.598	(3,774)	.65	.587	-[1)]	-[1)]	-[1)]
NA_{low} (W-S) * cycle phase	(3,5523)	.59	.625	(3,5500)	.66	.575	-[1)]	-[1)]	-[1)]
NA_{low} (W-S) * group	(1,5319)	1.18	.277	(1,5311)	1.23	.268	-[1)]	-[1)]	-[1)]
NA_{low} (W-S) * group * cycle phase	(3,5524)	.13	.945	-[1)]	-[1)]	-[1)]			
Fixed effects (predictor PA_{high})									
Intercept	(1,189)	109.93	<.001	(1,189)	110.01	<.001	(1,189)	109.69	<.001
Group	(1,117)	.39	.536	(1,116)	.38	.541	(1,116)	.39	.534

Cycle phase	(3,782)	3.27	.021	(3,777)	3.23	.022	(3,765)	3.36	.018
Aggregated mean PA_{high}	(1,116)	.02	.882	(1,116)	.02	.822	(1,116)	.03	.868
PA_{high} (W-S)	(1,5303)	5.37	.021	(1,5305)	5.34	.021	(1,5201)	4.58	.032
Group * cycle phase	(3,781)	.53	.665	(3,771)	.54	.658	-[1]	-[1)]	-[1)]
PA_{high} (W-S) * cycle phase	(3,5523)	.50	.683	(3,5507)	.58	.631	-[1)]	-[1)]	-[1)]
PA_{high} (W-S) * group	(1,5311)	2.57	.108	(1,5310)	2.61	.106	-[1)]	-[1)]	-[1)]
PA_{high} (W-S) * group * cycle phase	(3,5520)	.16	.922	-[1)]	-[1)]	-[1)]			
Fixed effects (predictor PA_{low})									
Intercept	(1,178)	92.01	<.001	(1,178)	92.06	<.001	(1,181)	90.68	<.001
Group	(1,117)	.58	.449	(1,117)	.55	.461	(1,116)	.63	.429
Cycle phase	(3,784)	3.17	.024	(3,778)	3.32	.019	(3,703)	3.28	.021
Aggregated mean PA_{low}	(1,117)	.34	.560	(1,117)	.33	.565	(1,117)	.32	.572
PA_{low} (W-S)	(1,5381)	12.22	<.001	(1,5384)	12.19	<.001	(1,4901)	9.26	.002
Group * cycle phase	(3,784)	.46	.708	(3,774)	.45	.720	-[1)]	-[1)]	-[1)]
PA_{low} (W-S) * cycle phase	(3,5556)	.41	.743	(3,5540)	.33	.802	-[1)]	-[1)]	-[1)]

PA_{low} (W-S) * group	(1,5384)	3.00	.083	(1,5389)	3.03	.082	-[1)]	-[1)]	-[1)]
PA_{low} (W-S) * group * cycle phase	(3,5556)	.42	.740	-[1)]	-[1)]	-[1)]			
Fixed effects (predictor rumination)									
Intercept	(1,445)	276.55	<.001	(1,445)	276.61	<.001	(1,443)	278.90	<.001
Group	(1,116)	.62	.434	(1,116)	.62	.431	(1,116)	.69	.409
Cycle phase	(3,770)	3.05	.029	(3,765)	2.99	.030	(3,765)	2.83	.038
Aggregated mean rumination	(1,118)	.58	.449	(1,118)	.60	.439	(1,117)	.62	.435
Rumination (W-S)	(1,5530)	5.67	.017	(1,5533)	5.76	.016	(1,5513)	5.89	.015
Group * cycle phase	(3,769)	.70	.555	(3,766)	.67	.571	-[1)]	-[1)]	-[1)]
Rumination (W-S) * cycle phase	(3,5586)	1.37	.250	(3,5590)	1.69	.167	-[1)]	-[1)]	-[1)]
Rumination (W-S) * group	(1,5531)	4.65	.031	(1,5531)	4.71	.030	(1,5517)	4.21	.040
Rumination (W-S) * group * cycle phase	(3,5587)	.46	.713	-[1)]	-[1)]	-[1)]			

Note. Aggregated mean: Aggregated mean at the person level. W-S: within-subject (person mean-centered). The dependent variable cortisol was entered log-transformed. Models include random intercepts at level 2 and 3 as well as fixed effects for time and time². Confounding variables were only retained in the models when significant ($p < 0.05$), which applies to time of awakening, physical activity and sleep duration. [1)] Non-significant interactions were excluded stepwise.

3 STUDY 2: RECIPROCAL EFFECTS BETWEEN COGNITIVE AND AFFECTIVE STATES IN WOMEN WITH PREMENSTRUAL DYSPHORIC DISORDER: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY

An adapted version of this chapter is under 2nd review *as* „Beddig, T., Reinhard, I., Ebner-Priemer, U., and Kuehner, C. Reciprocal effects between cognitive and affective processes in women with Premenstrual Dysphoric Disorder: An Ambulatory Assessment Study.“

3.1 Abstract

Premenstrual Dysphoric Disorder (PMDD) is characterized by cyclical mood changes resulting in clinically significant distress and functional impairment. Studies on momentary cognitive and affective states and their interplay during daily life over the menstrual cycle in affected women are still lacking. Using Ecological Momentary Assessment with electronic diaries, 61 women with current PMDD and 61 healthy control women reported their current mood, rumination, and self-acceptance eight times a day over two consecutive days per cycle phase (menstrual, follicular, ovulatory, and late luteal phase). Results revealed that women with PMDD showed significant increases in negative affect and rumination and decreases in positive affect and self-acceptance toward the end of the cycle. Lagged analyses demonstrated stronger within-person reciprocal effects of cognitions and mood in PMDD women compared to controls with the effect of rumination on subsequent negative affect being limited to the late luteal phase. Identified stronger prospective associations between cognitive processes and mood deteriorations in women with PMDD suggest that affected women are more sensitive to detrimental effects of either dimension. Hence, therapeutic strategies aiming at reducing ruminative thoughts and improving self-acceptance such as mindfulness-based interventions could be promising for reducing the burden of PMDD.

3.2 Introduction

3.2.1 Background

Premenstrual Dysphoric Disorder (PMDD) is the most severe form of premenstrual burden, causing clinically significant distress and marked impairment of psychosocial functioning (Lanza di Scalea & Pearlstein, 2019). Outlined as a new diagnostic category in DSM-5, PMDD is defined by the presence of at least five symptoms during the late luteal phase of the menstrual cycle including at least one out of four marked affective symptoms such as affective lability, irritability, depressed mood or anxiety (APA, 2013). A full diagnosis requires daily symptom ratings over two symptomatic cycles, although a provisional diagnosis of PMDD can be made without (APA, 2013). While the less severe premenstrual syndrome has a prevalence of about 13-20% in community samples depending on the underlying diagnostic criteria (Beddig & Kuehner, 2017; Wittchen et al., 2002), PMDD afflicts 3-8% of women in fertile ages (Dennerstein et al., 2012; Lanza di Scalea & Pearlstein, 2019). PMDD frequently takes a chronic course (Wittchen et al., 2002), and suicidality is increased (Owens & Eisenlohr-Moul, 2018; Pilver et al., 2013).

In light of the high comorbidity and symptom overlap between PMDD with Major Depression and anxiety disorders shared vulnerability factors have been proposed. One such transdiagnostic factor might be rumination, defined as the tendency to passively and repetitively analyze one's distress, problems, and concerns, without taking actions (Nolen-Hoeksema & Watkins, 2011). Previous research showed that rumination in response to negative mood is a stable risk factor for mental disorders, especially for depression (e.g. Huffziger, Reinhard, & Kuehner, 2009; Lyubomirsky et al., 2015; Nolen-Hoeksema et al., 2008) but also for other common mental disorders (Nolen-Hoeksema & Watkins, 2011). Following the transdiagnostic perspective, maladaptive cognitive processes such as rumination could also play a role in the etiology and maintenance of PMDD. In women with PMDD, cognitive processes have been relatively understudied and if so have been dominated by investigations of respective traits or habitual coping styles. It is thought that those women suffering from premenstrual changes who have a ruminative response style may be more vulnerable to developing PMDD (cf. Craner et al., 2014; 2015) pointing toward a multifactorial model in which psychological factors interact with physiological cycle changes. In fact, former studies found that women with premenstrual disorders tend

to use less helpful coping strategies such as rumination (Craner et al., 2014), behavioral impulsivity (Petersen et al., 2016), non-acceptance of emotional responses (Reuveni et al., 2016), catastrophizing (Eggert et al., 2016) or harm-avoidance (Hsu, Liu, & Hsiao, 2007; Miller et al., 2010). There is also some evidence that trait rumination is associated with steeper increases in premenstrual depressive symptoms (Dawson et al., 2018). Furthermore, trait rumination was found to mediate the relationship between anxiety sensitivity and premenstrual distress (Sigmon et al., 2009). A study by Craner et al. (2015) examined momentary maladaptive psychological processes showing that in response to experimentally induced negative affect (NA) women with premenstrual disorders reacted with high levels of self-focused attention. Affected women also reported higher general use of ruminative coping and self-focused attention compared to controls. The authors propose that the tendency of affected women to use a passive, emotion-focused, ruminative coping style is likely to increase emotional symptoms. Correspondingly, in a recent randomized controlled trial the use of active coping strategies was associated with symptom relief in PMDD (Weise et al., 2019).

In contrast to studies investigating trait aspects of rumination, research on moment-to-moment relationships between state cognitions and distress during daily life in women with PMDD is lacking. To study such phenomena, an Ecological Momentary Assessment (EMA) study design is most appropriate. Here, multiple real-time assessments take place during daily life, and the resulting longitudinal data series allow the investigation of variability of momentary affect and cognitions and their temporal relationship within individuals (cf. Trull & Ebner-Priemer, 2013). In the context of PMDD research, EMA also enables to study variability of such phenomena across the menstrual cycle within persons and to compare women with and without PMDD with this regard. In contrast to PMDD research, there is growing EMA-literature examining prospective effects of momentary cognitive processes on affect and vice versa in other populations. For example, momentary rumination predicted subsequent levels of NA in clinical (e.g. Kircanski et al., 2018; Ruscio et al., 2015) and in community samples (e.g. Moberly & Watkins, 2008). Naturally occurring NA was in turn found to be followed by increased levels of rumination, suggesting a reciprocal relation between these two constructs (Moberly & Watkins, 2008). Furthermore, effects of momentary cognitive processes on positive emotions have been documented in the context of mindfulness (Garland et al., 2015; Jimenez, Niles,

& Park, 2010; Timm et al., 2018; Welz, Reinhard, Alpers, & Kuehner, 2018). There is evidence that dispositional mindfulness is associated with higher levels of positive emotions and self-acceptance during daily life (Jimenez et al., 2010), and a recent study by Timm et al. (2018) demonstrated that mindfulness training led to improved positive affect (PA) and self-acceptance in remitted depressed patients, whereas NA and rumination decreased. Following these findings, rumination and NA as well as self-acceptance and PA appear to be tightly linked in daily life. While ruminative thinking and negative mood seem to be driven by a downward spiral especially in clinical samples (e.g. Kircanski et al., 2018; Nolen-Hoeksema et al., 2008), an upward spiral has been proposed for positive thinking and PA (Garland, et al. 2015).
Given the strong affective component in PMDD, the possible role of cognitive processes in influencing affective processes is of particular interest. Since symptoms occur in a cyclical recurring pattern, it is likely that women with PMDD are especially vulnerable to dysfunctional cognitions during the late luteal phase of the menstrual cycle (cf. Read, Perz, & Ussher, 2014). Hence, similar to studies with other clinical samples (e.g. Kircanski et al., 2018), a downward spiral of increased rumination and decreased self-acceptance exerting mood worsening and vice versa might be effective in PMDD women particularly in the late luteal phase. Using EMA in PMDD research has been repeatedly called for (see Bosman et al., 2016; Owens & Eisenlohr-Moul, 2018), and we have implemented a first EMA study in this context (Beddig, Reinhard, & Kuehner, 2019). Here, we could already demonstrate that women with PMDD showed heightened subjective stress reactivity towards daily life stressors particularly during the late luteal phase and a blunted activity of the hypothalamic-pituitary-adrenal axis (HPAA) across the menstrual cycle.

3.2.2 Study aims

Aims of the present paper were as follows. We first sought to examine possible menstrual cycle-related variations in affective and cognitive states in the PMDD sample by Beddig, Reinhard, et al. (2019). It was expected that in PMDD women negative mood and rumination would be highest whereas positive mood and self-acceptance would be lowest during the late luteal phase compared to other cycle phases, while no such cycle-related effects were expected for controls. The second aim was to investigate possible reciprocal time-lagged relationships between rumination and NA as well as between self-acceptance and PA by also checking for

possible cycle-dependent effects. Specifically, it was hypothesized that prospective effects of cognitive on affective states and vice versa would be stronger in PMDD women compared to controls, particularly in the late luteal phase.

3.3 Method

3.3.1 Participants

Women were recruited via local family doctors and gynecologists, flyers, social networks, and the homepage of the Central Institute of Mental Health (CIMH, for detailed information see also Beddig, Reinhard et al., 2019). To take part in the study, women had to fulfill the following inclusion criteria: a) age between 20 and 42, b) consistent length of menstrual cycle between 22 and 34 days, c) fulfillment of diagnostic criteria of a PMDD diagnosis based on DSM-5 criteria (PMDD group) or exempt from any PMDD affective core symptoms (control group). Exclusion criteria were being pregnant or lactating during the last six months, a history of gynecological diseases, use of hormonal contraceptives and pharmaceutical medication, late evening or night shifts, body mass index < 18 or > 35, a lifetime history of psychotic or bipolar disorder, and current alcohol or substance abuse or dependence. Controls were matched regarding age and education. Initially 140 women were enrolled, of whom 18 (12.9%, nine per group) withdrew from the study during the EMA phase. Reasons for discontinuating included inconsistencies with menstrual cycle reports (n = 14), severe technical problems (n = 2), decision to start hormonal contraceptives (n = 1), and positive pregnancy test (n = 1). Hence, the final sample consisted of 61 women diagnosed with PMDD and 61 controls. The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants gave written informed consent and were paid 100€ for completing the study.

3.3.2 Ecological Momentary Assessment (EMA) procedure

EMA was carried out using Motorola Moto G 2nd Generation smartphones with the software movisensXS, version 0.6.3658 (movisens GmbH, Karlsruhe, Germany). EMA took place during four cycle phases of a menstrual cycle with two consecutive EMA-days per cycle phase. Individual calendars were prepared for each woman based on the date of her last menstruation onset and the average length of her

menstruation and of her menstrual cycle. Assessments during the menstrual phase took place on the second and third day of menstruation (M = 2.95 days, SD = 2.21). The follicular phase was examined on the second and third day after the end of menstruation (M = 8.61 days, SD = 1.94). The ovulatory phase (M = 17.15 days, SD = 2.0) was determined by a chromatographic ovulation test (gabControl hlH Ovulationsteststreifen, gabmed, Cologne) indicating a rise in luteinizing hormone levels in urine. Participants were asked to start testing a few days before the predicted ovulation until the result was positive, and then to complete the diary on the next two days. If ovulation did not occur, participants were asked to repeat the test in the following menstrual cycle. Assessments of the late luteal phase took place on the fourth and third day before the next menstruation was expected (M = 26.38 days, SD = 3.02). Phases were validated according to the ovulation test and the exact time of the onset of the next menses. To avoid sequence effects, participants started EMA in different cycle phases.

There were eight assessments per day, with the first assessment taking place at 9.00 a.m. and the remaining seven assessments taking place between 10:00 a.m. and 09:30 p.m. at random time points at averaged 103 min apart (SD = 25.0) with a minimum interval of 45 min. Each assessment was announced by an acoustic signal and took 3-4 min to complete. Participants had 5 min to respond, and assessments could be delayed by 15 min. If participants were unable to respond or rejected the alarm, the assessment was saved as missing. After having completed the EMA days participants returned the device and were compensated for their participation.

3.3.3 Structured assessment of psychopathology

The diagnosis of PMDD was verified using the Structured Interview for DSM-IV TR PMDD (SCID-PMDD; Accortt et al., 2011) during the diagnostic baseline session. The SCID-PMDD includes all symptom criteria together with the required impairment criterion and the exclusion criterion of a mere exacerbation of symptoms of another disorder. The interview format is modeled after SCID-I (see below) and has shown high interrater reliability (α = 0.96) (Accortt et al., 2011). For the PMDD group, the criteria for PMDD according to the SCID-PMDD had to be met with the diagnostic algorithm adapted for DSM-5. To avoid further participant burden, prospective daily ratings during at least two symptomatic cycles before study inclusion were not required. Control women had to be free of any PMDD affective core symptoms.

Premenstrual physical symptoms were not an exclusion criterion for controls, given the fact that the majority of naturally cycling women are experiencing physical symptoms of varying degree during the late luteal and menstrual phase (Tschudin, Bertea, & Zemp, 2010).

Other mental health comorbidities and exclusion criteria were assessed with the SCID-I Interview (Wittchen et al., 1997), a psychometrically sound semi-structured interview for mental disorders. Furthermore, demographics were assessed during the baseline session together with the severity of depressive symptoms, measured with the 21-item Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996) and trait anxiety measured with the 20-item Spielberger Trait Anxiety Inventory (STAI-T; Spielberger, Gorsuch, & Lushene, 1970). Interviews were conducted by a trained research psychologist.

3.3.4 Ecological Momentary Assessment (EMA) variables

NA and PA. At each assessment, participants responded on a 7-point Likert scale to negative and positive mood adjectives. For NA, participants were asked to rate how upset, irritated, nervous, listless, down and bored they felt and for PA how cheerful, energetic, enthusiastic, satisfied, relaxed and calm they felt. These items were derived from the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) and have been used in previous EMA-studies (Kuehner et al., 2017; Timm et al., 2018; Welz et al., 2018).

Rumination. Rumination was assessed on a 7-point Likert scale with the item “At the moment I am stuck on negative thoughts and cannot disengage from them”, capturing the uncontrollability facet of rumination (cf. Kuehner et al., 2017; Raes, Hermans, Williams, Bijttebier, & Eelen, 2008; Timm et al., 2018).

Self-acceptance. Self-acceptance was assessed with the item “At the moment I accept myself how I am” on a Likert scale 1-7 (cf. Timm et al., 2018).

Daily stress events. To assess daily stress events subjects reported on a 7-point bipolar scale (−3 = very unpleasant, 0= neutral, and 3 = very pleasant) the most important event between the current and the previous beep (cf. Wichers et al., 2009).

3.3.5 Data Analysis

Statistical analyses were performed using multilevel models, taking into account that the present data were organized within nested levels. Analyses showed that for all

dependent variables the three-level model including the day-level had a better fit than the two-level model according to fit indices (AIC and BIC) (Hox et al., 2017). Therefore, for each outcome a multilevel model assuming three levels was applied with single assessments (level 1) nested within days (level 2), nested within persons (level 3). All models included random intercepts at level two and three, allowing individual baseline levels of the dependent variables to differ between persons and days. All statistical models included group status (PMDD/controls), cycle phase (menstrual, follicular, ovulatory, and late luteal) as a categorical variable, and the interaction group*menstrual cycle phase. Further we controlled for day (sampling days 1 to 8) to account for assessment reactivity and for time of the day to account for time-dependent variation within days in respective outcomes. For each outcome we checked whether time² was significant, and if so retained it in the models. The quadratic time effect was only significant for NA which was highest in the mid-afternoon.

To examine prospective effects of daily life variables, lagged values were constructed for all observations, except for those representing the first response of a day. In the respective models, all main effects as well as the 2- and 3-way interactions between predictors were included. The models tested the effect of the lagged predictor variable (e.g. rumination) at time t on the respective outcome variable (e.g. NA) at time t + 1, while controlling for the lagged outcome at time t to account for any carryover, and for the lagged predictor aggregated at the person level at time t to adjust for time invariant between-subject effects (B-S). To facilitate interpretation, predictor variables were person-mean centered prior to the analyses. This produced within-subject (W-S) predictors that vary within, but not between individuals. Importantly, these predictors, originally measured on a continuous scale, were entered as dichotomized variables via person mean split due to the application of complex multilevel models. Dichotomization resulted in binary variables. Here, the focus of analysis was to compare worse states than usual with usual or better states (e.g. NA (W-S) > 0 describes NA above the intraindividual average level compared to NA (W-S) ≤ 0, which describes NA equal or below average level). In doing so we were able to estimate and test conditional interactions (in case of significant 3-way interactions) and to evaluate simple effects (in case of significant 2-way interactions), which is essential especially if checking for cycle-dependent changes (i.e., 3-way

interactions group*cycle phase*predictor, in which interactions of each pair of variables are allowed to vary with the level of the third variable).

As an example of such a multilevel model (here: lagged rumination predicting negative affect (NA)), the level 1 model can be described as:

$Y\ (\text{negative affect})_{ijk} = \pi_{0jk} + \pi_{1jk}(\text{cp\_nr}) * \text{cycle phase}(\text{cp\_nr})_{ijk} + \pi_{2jk} * \text{lagged negative effect}_{ijk} + \pi_{3jk} * \text{time of day}_{ijk} + \pi_{4jk} * (\text{time of day})^2_{ijk} + \pi_{5jk} * \text{lagged rumination (dich)}_{ijk} + \pi_{6jk}(\text{cp\_nr}) * \text{cycle phase}(\text{cp\_nr})_{ijk} \times \text{lagged rumination (dich)}_{ijk} + \varepsilon_{ijk}$.

Here, Y_{ijk} represents the level of negative affect at time i at assessment day j for person k. The π coefficients represent the intercept and the fixed main and interaction effects at level 1, the ε_{ijk} denote the residuals at level 1. The level 2 model can be described as:

$\pi_{0jk} = \beta_{00k} + \beta_{01k} * \text{assessment day}_{jk} + u_{0jk}$ (and $\pi_{1jk} = \beta_{10k}$; $\pi_{2jk} = \beta_{20k}$; $\pi_{3jk} = \beta_{30k}$; $\pi_{2jk} = \beta_{20k}$; …; $\pi_{6jk} = \beta_{60k}$) with the u_{0jk} representing random intercepts for the assessment day j within person k. The level 3 model can be described as:

$\beta_{00k} = \gamma_{000} + \gamma_{001} * \text{group}_k + \gamma_{002} * \text{lagged rumination (B-S)}_k + v_{00k}$;

$\beta_{01k} = \gamma_{010}$; $\beta_{10k} = \gamma_{100} + \gamma_{110} * \text{group}_k$; $\beta_{20k} = \gamma_{200}$; $\beta_{30k} = \gamma_{300}$; $\beta_{40k} = \gamma_{400}$;

$\beta_{50k} = \gamma_{500} + \gamma_{510} * \text{group}_k$; $\beta_{60k} = \gamma_{600} + \gamma_{610} * \text{group}_k$.

Here the v_{00k} indicate the random intercept for person k. Note that we included three dummy variables for the categorical variable cycle phase, and the appendix “(cp_nr)” indicates a specific cycle phase.

To control for possible confounding effects of depressive symptom severity, trait anxiety symptoms and daily stress events, analyses were repeated by controlling for these variables.

Our hypotheses-driven main analyses investigating 3-way interactions (cycle phase*lagged predictor*group) were not Bonferroni-adjusted. In case of a nonsignificant effect with cycle phase, we looked at possible significant 2-way interactions (group*lagged predictor) in the model, the latter indicating phase-independent group differences in the association between lagged predictor and outcome. Since these analyses were explanatory, respective significance levels were Bonferroni-corrected for multiple testing. Similarly, all post hoc tests were Bonferroni-adjusted. All statistical analyses were performed using the statistical software IBM SPSS Version 23. The significance level was set at $\alpha = 0.05$.

3.4 Results

3.4.1 Compliance

Statistical analyses were based on 122 participants (PMDD group: N = 61; control group: N = 61). Altogether, 6818 of 7808 possible assessments were recorded, which corresponds to an overall response rate across participants of 87.3%, reflecting a high level of compliance (cf. Courvoisier, Eid, & Lischetzke, 2012).

Table 1

Descriptions of Women with PMDD and Controls

	PMDD (*n* = 61) % / *M* (*SD*)	Controls (*n* = 61) % / *M* (*SD*)	Test statistic	*p*
Demographic Variables				
Age	29.4 (5.8)	29.5 (5.1)	t=-0.03	.977
Education (% with high school degree	72.1%	75.4%	Chi^2=0.17	.681
Work Situation (% in regular job or education)	80.3%	90.2%	Chi^2=2.35	.126
Marital Status (% married or living together)	60.7%	59.0%	Chi^2=0.03	.853
Children (%)	24.6%	26.2%	Chi^2=0.04	.835
BMI	23.6 (4.1)	23.5(4.3)	t=0.12	.903
Clinical Variables				
Lifetime Diagnosis of Depression (SCID-I)	54.1%	21.3%	Chi^2=13.96	<.001
BDI-II[1] score at baseline	10.9 (8.9)	4.8 (5.6)	t=4.53	<.001
STAI-T[2] score at baseline	45.6 (11.3)	37.2 (8.6)	t=4.61	<.001
EMA[3] Variables				
Compliance Rate	86.6%	88.0%	Chi^2=33.62	.071
Duration (in days) of Menstrual Cycle during EMA	29.0 (3.1)	29.4 (3.7)	t=-0.77	.444
Duration (in days) of Period during EMA	5.3 (1.1)	5.6 (1.7)	t=-0.85	.399

[1]BDI-II=Beck Depression Inventory-Revised.[2]STAI-T= Spielberger Trait Anxiety Inventory. [3]EMA=Ecological Momentary Assessment

3.4.2 Descriptives

Descriptive information on demographic, clinical, and EMA variables are listed in Table 1. Groups did not significantly differ with respect to age, education, marital status, work situation, percentage with children, and mean duration of the menstrual cycle. In contrast, PMDD women displayed higher BDI-II mean scores, higher trait anxiety levels, and a larger percentage had a lifetime diagnosis of depression.

3.4.3 Cycle dependent variation of affect and cognitions

To investigate whether women with and without PMDD differed in cognitive and affective states over the menstrual cycle, four separate models were calculated. As shown in Table 2, the group*cycle phase interaction was significant in predicting NA ($p < 0.001$), PA ($p < 0.001$), rumination ($p < 0.001$), and self-acceptance ($p < 0.001$). Post hoc tests using Bonferroni correction revealed higher levels of NA and rumination as well as lower levels of PA during the late luteal phase in women with PMDD compared to all other cycle phases (p's ≤0.01) and decreased levels of self-acceptance compared to the follicular and ovulatory phase ($p_{menstrual} = 0.164$, $p_{follicular} < 0.001$, $p_{ovulatory} < 0.001$). In contrast, no cycle phase effect on momentary states was observed in control women (all p's > 0.55). For graphical demonstration, see Figure 1.

Table 2

Fixed Effects of Menstrual Cycle Phase and Group on Negative Affect, Positive Affect, Rumination, and Self-Acceptance

Outcome		Menstrual Cycle Phase				Group * Cycle Phase		
	Group	Menstrual	Follicular	Ovulatory	Late Luteal	*df*	F	*p*
Negative Affect	PMDD	2.8±1.2	2.4±1.1	2.6±1.1	3.2±1.2	(3,836)	20.07	<.001
	Controls	2.1±1.1	2.1±1.1	2.2±1.2	2.2±1.1			
Positive Affect	PMDD	3.8±1.3	4.2±1.2	4.2±1.2	3.5±1.1	(3,845)	15.87	<.001
	Controls	4.4±1.2	4.5±1.1	4.4±1.2	4.3±1.2			
Rumination	PMDD	2.5±1.5	2.1±1.4	2.2±1.5	2.8±1.7	(3,830)	15.80	<.001
	Controls	1.8±1.1	1.9±1.3	1.9±1.3	1.9±1.3			
Self-Acceptance	PMDD	4.7±1.6	5.2±1.5	5.1±1.4	4.5±1.5	(3,840)	18.92	<.001
	Controls	5.6±1.3	5.5±1.3	5.5±1.4	5.5±1.4			

Note. Models included random intercepts at level 2 and 3 as well as fixed effects for time, time² (if significant), day, group, and cycle phase.

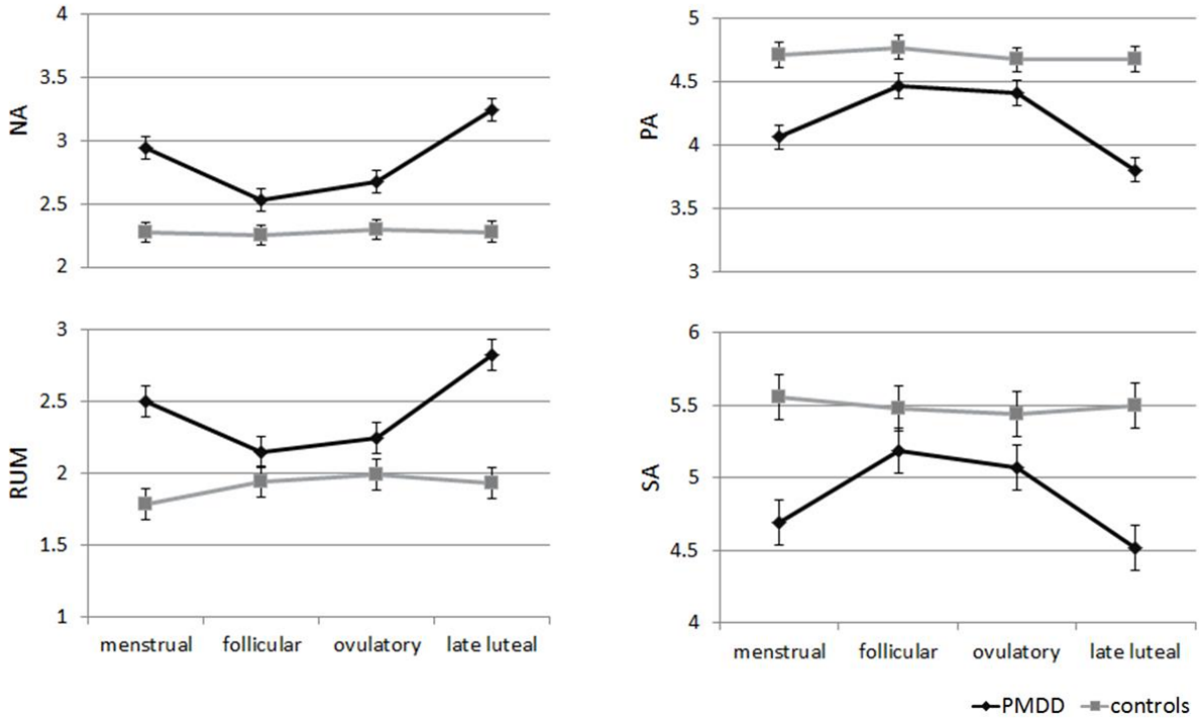

Fig. 1. Estimated mean scores of daily life variables (NA: negative affect; PA: positive affect; RUM: rumination; SA: self-acceptance) over the menstrual cycle for women with PMDD and controls. Note. Error bars represent standard error of the mean. Models include random intercepts at level 2 and 3 as well as fixed effects for time, time² (if significant), assessment day, group, and cycle phase.

3.4.4 Time-lagged models of predictors and outcomes

3.4.4.1 Time-lagged models of NA and rumination

The analysis investigating lagged rumination predicting NA revealed significant time-lagged associations varying across menstrual cycle phases and groups (group* cycle phase* rumination lag (F(3, 4935) = 2.87, p = 0.035, see Table 3). Post hoc tests using Bonferroni correction revealed that in PMDD women, momentary levels of rumination (at time t) above their individual average significantly predicted a premenstrual increase in NA at the subsequent time point (t+1) ($p < 0.01$), whereas for controls no menstrual cycle-related effect was observed (all p's > 0.37) (see Figure 2 A).

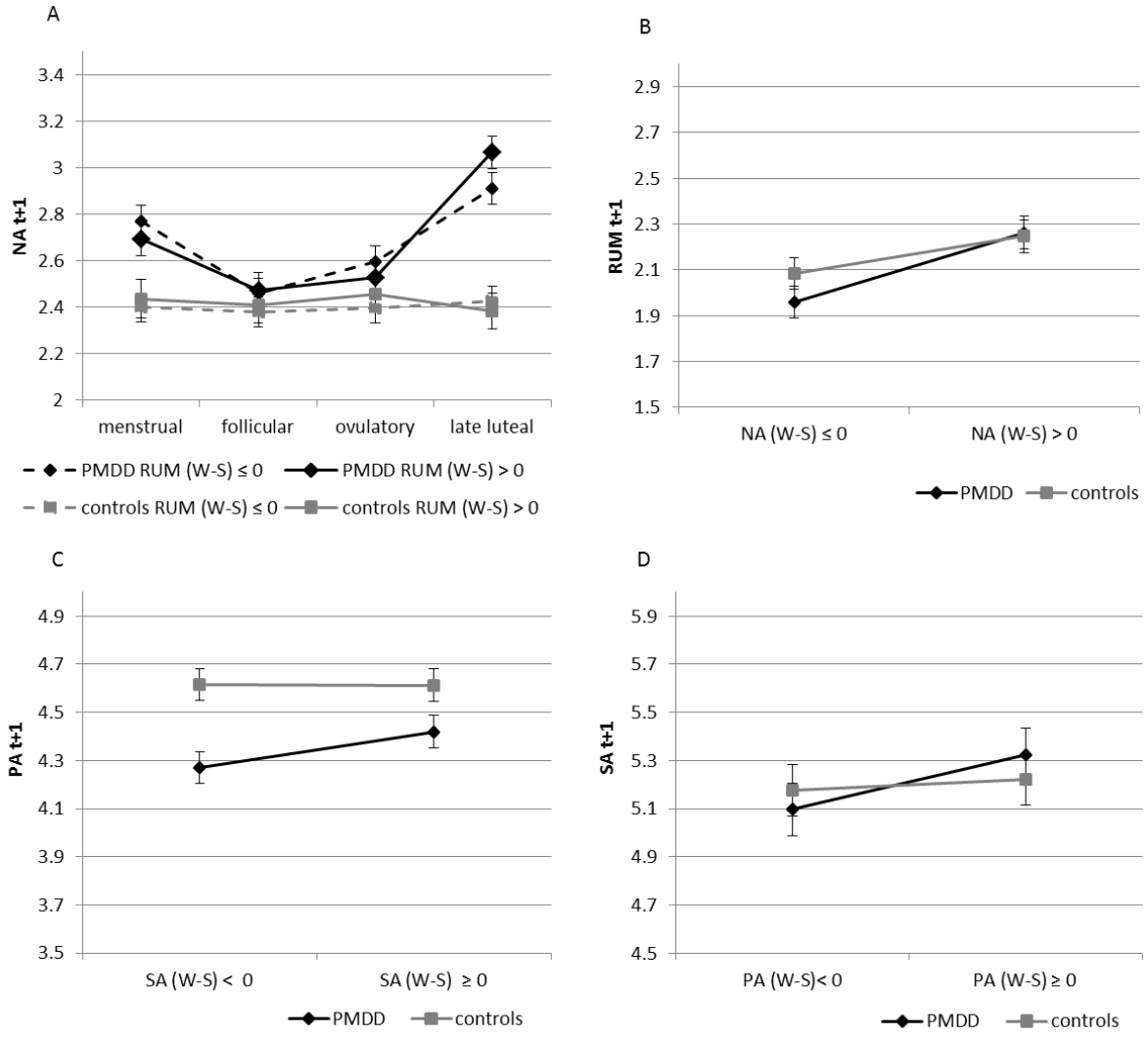

Fig. 2. Estimated mean values of the time-lagged outcomes negative affect (NA, with predictor rumination (RUM), Fig. 2 A) and RUM (with predictor NA, Fig. 2 B) as well as time-lagged outcomes positive affect (PA, with predictor self-acceptance (SA), Fig. 2 C) and SA (with predictor PA, Fig. 2 D) for women with PMDD and controls. Note. Error bars represent

standard error of the mean. W-S: within-subject (person mean-centered). Models include time, time² (if significant), assessment day, group, cycle phase, lagged outcome and lagged predictor aggregated at the person level as covariates.

The analysis investigating lagged NA predicting rumination revealed no significant three-way interaction group* cycle phase* NA lag (F(3, 5270) = .24, p = 0.868). However, we identified a significant group* NA lag effect (F(1, 5242) = 7.42, p = .018 (Bonferroni-corrected), see Table 3). Figure 2 B indicates that in PMDD women momentary NA levels (at time t) above average resulted in a stronger increase in momentary rumination at the subsequent time point (t+1) compared to controls regardless of cycle phase. Post hoc tests revealed that for both groups the prospective effect of NA on rumination was significant (PMDD: p < 0.001, controls: p < 0.001).

Table 3

Time-lagged Models of Negative Affect and Rumination

	3-way Interaction Model		
	df	F	*p*
Outcome Negative Affect t+1			
Fixed effects			
Intercept	(1,160)	90.33	<.001
Group	(1,121)	13.75	<.001
Cycle phase	(3,585)	16.05	<.001
Negative Affect (W-S) (t)	(1,4814)	355.84	<.001
Rumination (B-S)	(1,119)	167.01	<.001
Rumination (W-S) (t)	(1,5257)	.25	.618
Group * Cycle phase	(3,588)	16.86	<.001
Rumination * Group	(1,5306)	.11	.746
Rumination * Cycle phase	(3,4942)	.55	.648

Rumination * Group * Cycle phase	(3,4935)	2.87	.035
Outcome Rumination t+1			
Fixed effects			
Intercept	(1,128)	3.81	.053
Group	(1,118)	.24	.624
Cycle phase	(3,5215)	9.82	<.001
Rumination (W-S) (t)	(1,5207)	168.78	<.001
Negative Affect (B-S)	(1,117)	168.19	<.001
Negative Affect (W-S) (t)	(1,5244)	56.77	<.001
Group * Cycle phase	(3,5216)	12.68	<.001
Negative Affect * Group	(1,5242)	7.42	.006[1]
Negative Affect * Cycle phase	(3,5271)	1.43	.233
Negative Affect * Group * Cycle phase	(3,5270)	.24	.868

[1]before Bonferroni correction

Note. W-S: within-subject (person mean-centered). B-S: between-subject. Models include random intercepts at level 2 and 3 as well as fixed effects for time, and assessment day. Time t+1 denotes the following prompt

3.4.4.2 Time-lagged models of PA and self-acceptance

The analysis investigating lagged self-acceptance predicting PA revealed no significant effect of group*cycle phase*self-acceptance lag (F(3, 2779) = 0.49, p = 0.689). We identified a significant interaction group*self-acceptance lag (F(1, 44400) = 7.86, p = 0. 015 (Bonferroni-corrected), see Table 4). Figure 2 C indicates that in PMDD women momentary levels of self-acceptance below average (at time t) resulted in a stronger decrease in PA at the subsequent time point (t+1) compared to controls regardless of cycle phase. Post hoc tests revealed that the prospective effect of self-acceptance on PA was only significant in women with PMDD (p < 0.001), not in controls (p = 0.936).

While the analysis investigating lagged PA predicting self-acceptance revealed no significant three-way interaction group*cycle phase* PA lag (F(3, 5212) = 0.90, p = 0.438), the interaction group* PA lag demonstrated a significant effect on self-acceptance (F(1, 5201) = 16.70, p < 0.001 (Bonferroni-corrected), see Table 4). Figure 2 D indicates that in PMDD women momentary levels of PA below average (at time t) resulted in a stronger decrease in self-acceptance to the subsequent time point (t+1) compared to controls regardless of cycle phase. Post hoc tests revealed that the prospective effect of PA on self-acceptance was only significant in women with PMDD (p < 0.001), not in controls (p = 0.147).

Table 4

Time-lagged Models of Positive Affect and Self-acceptance

	3-way Interaction Model		
	df	F	*p*
Outcome			
Positive Affect t+1			
Fixed effects			
Intercept	(1,128)	124.89	<.001
Group	(1,120)	8.07	.005
Cycle phase	(3,486)	13.73	<.001
Positive Affect (W-S) (t)	(1,4758)	372.84	<.001
Self-acceptance (B-S)	(1,120)	125.69	<.001
Self-acceptance (W-S) (t)	(1,4886)	5.80	.016
Group * Cycle phase	(3,487)	8.61	<.001
Self-acceptance * Group	(1,4440)	7.86	.005[1]
Self-acceptance * Cycle phase	(3,2797)	2.39	.067
Self-acceptance * Group * Cycle phase	(3,2779)	.49	.689
Outcome			
Self-acceptance t+1			
Fixed effects			

Intercept	(1,120)	.20	.656
Group	(1,119)	.02	.894
Cycle phase	(3,5199)	7.23	<.001
Self-acceptance (W-S) (t)	(1,5197)	789.63	<.001
Positive Affect (B-S)	(1,119)	133.12	<.001
Positive Affect (W-S) (t)	(1,5200)	31.79	<.001
Group * Cycle phase	(3,5199)	11.05	<.001
Positive Affect * Group	(1,5201)	16.70	<.001[1]
Positive Affect * Cycle phase	(3,5212)	2.35	.071
Positive Affect * Group * Cycle phase	(3,5212)	.90	.438

[1] before Bonferroni correction

Note. W-S: within-subject (person mean-centered). B-S: between-subject. Models include random intercepts at level 2 and 3 as well as fixed effects for time, and assessment day. Time t+1 denotes the following prompt.

3.4.4.3 Confounder analysis

Including the severity of depressive symptoms (BDI-II), anxiety symptoms (STAI-T) and daily stress events as covariates did not change any of the reported effects. Therefore, the present results were not affected by possible group differences in depressive and anxiety symptom severity and daily stress events.

3.5 Discussion

3.5.1 Summary of Results

The purpose of the current EMA study was to explore menstrual cycle-related variations of affective and cognitive states during daily life and to examine time-lagged associations between these states in women with PMDD and healthy controls. While affective symptoms of low mood, decreased interest, irritability, and anxiety occur as part of many mental disorders, the prominent feature that distinguishes PMDD from similar entities is its time course, with the late luteal phase confinement of symptoms (APA, 2013). In this regard, our EMA data - prospectively

collected over the menstrual cycle and analyzed with multilevel models – show that women with PMDD exhibited the highest NA and the lowest PA in the late luteal phase, thereby clearly confirming a symptomatic state of mood deterioration during this phase in a naturalistic, real-time context in the present PMDD sample. Moreover, PMDD women also reported highest levels of rumination and lowest levels of self-acceptance during the late luteal phase. In contrast, healthy women did not show any cycle-dependent variation of mood and cognitions.

Lagged models revealed that especially in the late luteal phase PMDD women reacted to high levels of rumination with increased levels of NA. Therefore, intensive rumination seems to have a particular mood-impairing effect toward the end of the cycle in these women. Previous studies have indicated that habitual rumination is associated with experiencing premenstrual distress (Craner et al., 2014; Dawson et al., 2018). By focusing on momentary within-person associations this study adds significantly to existing research by showing that particularly in the late luteal phase intraindividual high levels of rumination predicted deterioration in NA in women with PMDD. Our results further indicate that in PMDD women increased NA levels predicted a stronger subsequent increase in rumination compared to controls regardless of cycle phase. This adds to previous research examining habitual coping styles in the context of premenstrual disorders (e.g. Craner et al., 2014, 2015; Petersen et al., 2016; Reuveni et al., 2016). By focusing on state cognitions the present study shows that women with PMDD tend to ruminate in response to negative affective states more strongly than nonaffected women across the menstrual cycle, thereby pointing toward a trait-like characteristic of ruminative responses to negative affect in PMDD.

Taking both lagged paths together our findings suggest a reciprocal relationship between rumination and NA especially in the late luteal phase. Following the transdiagnostic perspective of rumination as a dysfunctional key mechanism in mental disorders (e.g. Lyubomirsky et al., 2015; Nolen-Hoeksema et al., 2008, Nolen-Hoeksema & Watkins, 2011) our findings align with this concept by demonstrating a characteristic cycle-dependency in the context of PMDD.

Moreover, momentary levels of low self-acceptance resulted in a stronger decrease in PA and vice versa in PMDD women compared to controls. These observations further indicate a stronger sensitivity of affected women for the effects of negative or lack of positive self-referential thoughts. Again, we did not identify cycle-dependency

for these associations, thereby pointing toward a more general underlying vulnerability of negative self-referential thoughts that could make women also more likely to developing PMDD. Importantly, controlling for daily stress events, depressive symptom severity as well as for trait anxiety levels did not affect the study results. Therefore, although comorbidity with lifetime depression was high, our study suggests that PMDD characteristics uniquely contributed to the present findings.

In conclusion, our study points to the relevance of assessing affective and cognitive processes by EMA in real world settings to be able to demonstrate heightened vulnerability in women with PMDD towards worsening of their mood and towards increased negative and decreased positive self-referential thinking during the late luteal phase of their menstrual cycle. Furthermore, EMA enabled us to identify phase-specific and phase-unspecific reciprocal associations between dysfunctional momentary affective and cognitive states in respective within-person associations in these women. In general, our findings also strengthen previous research highlighting the role of psychological factors in premenstrual disorders (e.g. Craner, et al., 2016; Kleinstauber et al., 2016; Reuveni et al., 2016; Weise et al., 2019).

3.5.2 Future perspectives and clinical implications

This is likely the first EMA study assessing menstrual cycle-related variations of cognitive and affective daily life processes and their interplay in women with PMDD. In this context, EMA can clearly improve PMDD research due to higher ecological validity of assessed phenomena compared to retrospectively assessed clinical symptoms. EMA also typically covers more basic affective and cognitive features and may therefore provide greater sensitivity for connecting psychological with biological processes (cf. Conner & Barrett, 2012; Huffziger et al., 2013). Furthermore, EMA appears to be optimally suited to capture between- as well as within-person variability in momentary states and their interplay across the menstrual cycle, which is particularly important for studying premenstrual disorders (cf. Bosman et al., 2016; Owens & Eisenlohr-Moul, 2018).

Study findings might be relevant for therapeutic perspectives in PMDD. Results revealed that women with PMDD seem to be more prone of using rumination as a trait-like emotion regulation strategy to deal with negative affect states across cycle phases, whereas high intraindividual rumination levels seem to trigger affect deterioration particularly in the late luteal phase. Hence, rumination, identified as

transdiagnostic risk factor for a series of mental disorders (cf. Nolen-Hoeksema & Watkins, 2011) may also be a potential therapeutic target for reducing the burden of PMDD. In this context mindfulness based interventions appear to be promising (cf. Petersen et al., 2016). For example a non-clinical study by Lustyk et al. (2011) found that high dispositional mindfulness was linked to less premenstrual symptoms, and studies with other clinical samples (e.g. Garland et al., 2015; Timm et al., 2018) showed that mindfulness training reduced negative and enhanced positive daily life cognitions such as momentary rumination and self-acceptance, and improved affect. However, methodological sound randomized controlled trials examining mindful interventions in women with PMDD are still lacking, which might be an important purpose for future research. In parallel, a first randomized controlled trial examining internet-based cognitive-behavioral therapy for PMDD by Weise et al. (2019) demonstrated that active coping when dealing with premenstrual symptoms predicted better treatment outcome, thereby underlining the importance to address coping styles. Clearly, further research is warranted to assess which interventions are effective in women with PMDD. Moreover, longitudinal research would aid in identifying predictive effects of momentary cognitive and affective processes and their interplay for the clinical course of PMDD, which could, in turn, provide targeting aims for therapy.

3.5.3 Strengths and limitations

Strengths of the current study include the investigation of a relatively large PMDD sample together with a control sample strictly matched regarding age and education level, the intensive longitudinal EMA-design covering all four cycle phases, the validation of the ovulation phase by a chromatographic ovulation test and the focus on temporal within-person processes to understand the momentary relationships between cognitive and affective states.

The study also has some limitations. First, given the exclusion of antidepressant and hormonal treatments, which are currently the most frequent treatments for PMDD (Epperson et al., 2012; Marjoribanks et al., 2013) the results might not be representative of all women with PMDD. Second, even though overall compliance was high and comparable between groups, nine women per group (12.9%) dropped out due to different reasons. This could have led to a sample of more highly motivated women. Third, we did not apply the criterion of confirmation of daily

symptom ratings during two consecutive symptomatic cycles prior to study inclusion. The reason for this was to reduce participant burden in this type of intensive repeated random measurement design. Thus, the diagnosis of PMDD must be considered provisional. However, prevalence rates of moderate to severe premenstrual symptoms derived from retrospective epidemiological studies have been found to be consistent with those using prospective ratings (Cunningham et al., 2009). Fourth, model complexity of multilevel models resulted in dichotomizing the main time-lagged variables of interest, which may have led to reduced explanatory variance. Fifth, to further increase the accuracy of conclusions, it would be beneficial to apply the EMA protocol over two or more consecutive menstrual cycles, which was not possible in the present study due to limited resources and may also provoke participant burden. Sixth, the EMA items were administered in a fixed order, thus a potential inflation of their associations cannot be excluded. Seventh, our study design does not allow to determine causal pathways between PMDD and daily life experiences. So it is unclear whether strong time-lagged associations between cognitive and affective daily life variables represent a vulnerability factor for developing PMDD or are rather the consequence of the disorder. Here, clearly more longitudinal research is warranted. A further limitation refers to the assessment of only two days per cycle phase. Although a regular cycle was a premise to take part in the study, we sometimes might have missed days with the highest impairment. Finally, we did not assess the content of ruminative thoughts. Ruminating about symptoms might be especially crucial for affect deteriorations in women with PMDD (cf. Craner et al., 2014). Further research might address these aspects as well.

3.5.4 Conclusions

This EMA-study examined cycle-related variations of momentary cognitive and affective characteristics and their time-lagged associations in women with PMDD. Findings suggest stronger associations between cognitive (rumination and self-acceptance) and mood variables (NA and PA) in affected women compared to controls. These findings highlight the role of cognitive processes in everyday settings and may have important implications for interventions aimed at preventing and treating PMDD.

4 STUDY 3: AMBULATORY ASSESSMENT CHARACTERISTICS PREDICT THE CLINICAL COURSE OF PREMENSTRUAL DYSPHORIC DISORDER

An adapted version of this chapter has been published as „Beddig, T. & Kuehner, C. (2020). Ambulatory Assessment Characteristics predict the Clinical Course of Premenstrual Dysphoric Disorder. *Psychotherapy and Psychosomatics,* 1-2. DOI: 10.1159/000505999 [Epub ahead of print]."

4.1 Manuscript

Premenstrual dysphoric disorder (PMDD, DSM-5) is characterized by severe key mood symptoms (mood lability, irritability, depression, anxiety) accompanied by cognitive and/or physical symptoms starting during the week before menses (late luteal phase) and becoming minimal or absent within the first week after menses onset. Symptoms must be severe enough to cause significant suffering or psychosocial impairment. The symptom pattern must have been present during a majority of cycles within the past year and may not merely represent a premenstrual exacerbation of another mental disorder. Research has provided satisfactory empirical evidence for the diagnosis which finally led to its inclusion in DSM-5 and ICD-11(Reed et al., 2019).

PMDD affects 2-8% of women of fertile age (Kuehner, 2017). Lifetime comorbidity with depressive and anxiety disorders is high, and an overlap with reproductive subtypes of depression is common (Kuehner, 2017). Potential etiological factors include central nervous system sensitivity to reproductive hormones, genetic factors, and psychosocial factors such as stress (Hantsoo & Epperson, 2015). PMDD frequently develops a chronic course: in a community sample of affected women the syndrome was stable across 48 months with <10% complete remissions (Wittchen et al., 2002). Furthermore, suicide risk was elevated even after controlling for psychiatric comorbidity. Therefore, it appears of primary importance to identify risk factors contributing to the clinical course of PMDD.

There is still a striking lack of course-related PMDD research in general, and most studies do not distinguish between PMDD and the less severe premenstrual syndrome (PMS), which does not require key mood symptoms for diagnosis.

Furthermore, the possible course-related significance of momentary affect, cognitions, and physiological stress responses during daily life in women with PMDD has so far been totally neglected. To study such phenomena, electronic Ambulatory Assessment (AA) is most appropriate. Here, multiple real-time assessments take place during daily life, and the resulting longitudinal data series allow the investigation of momentary processes and their temporal relationship within individuals (Myin-Germeys et al., 2018). In PMDD, AA also enables to study variability of such phenomena across the menstrual cycle (Owens & Eisenlohr-Moul, 2018). We recently conducted a first AA-study where we showed that PMDD women compared to healthy control women demonstrated heightened subjective stress reactivity towards daily life stressors and a blunted activity of the hypothalamic-pituitary-adrenal (HPA) axis across the cycle (Beddig, Reinhard, et al., 2019), thereby paralleling patterns of other stress-related disorders.

Aim of the present paper was to examine whether AA-characteristics measured at baseline in the Beddig, Reinhard, et al. (2019) study would predict the clinical PMDD symptom course during a four-month interval, over and above relevant demographic and clinical predictors. Specifically, we aimed to test the degree to which a) levels of negative affect, positive affect, rumination and cortisol, and b) subjective and psychoendocrinological stress reactivity during daily life might improve the prediction of future PMDD symptomatology.

Non-medicated women with current PMDD at baseline (n=61, cf. Beddig, Reinhard, et al. (2019)) reported negative affect, positive affect, rumination, and daily events via electronic diaries at semi-random time points eight times a day over two consecutive days per cycle phase (menstrual, follicular, ovulatory, and late luteal; ovulation was validated by an ovulation test). Twenty minutes after each assessment they collected saliva cortisol samples. PMDD symptomatology was measured at baseline and four months after AA using a structured clinical interview, the SCID-PMDD (Accortt et al., 2011). The SCID-PMDD includes all PMDD-DSM criteria, is modeled after the SCID-I and has shown good psychometric properties (Accortt et al. 2011). One woman dropped out at follow-up, resulting in a sample of n=60 women.

Predictor analysis followed a two-step procedure. In a first step, random effects parameters (i.e., intercepts and slopes of stress appraisal) of negative affect, positive affect, rumination, and cortisol across the menstrual cycle were estimated with Restricted Maximum Likelihood using the PROC MIXED procedure of SAS. Here,

person-specific intercepts reflect individual differences in the mean levels of momentary cognitive, affective and endocrinological states and slope values reflect individual differences in stress appraisal effects on these states. In a second step, regression analyses were carried out in SPSS. Standardized SCID-PMDD symptom scores at follow-up served as outcome while controlling for age, baseline SCID-PMDD and depressive (BDI-II) symptom scores, and use of psychotropic medication at follow-up. In the following, the standardized random effects of AA-predictors were added a) in separate regression analyses to the control variables to analyze the incremental value of each predictor separately, and b) in a stepwise multiple regression analysis where AA-predictors were entered stepwise. All models were compared to the control model in terms of proportion of explained variance (see online supplement for methodological details of the study).

Compliance with AA was high (86.5% completed prompts; sample description see online Table S1). Multilevel analyses showed significant variation of mood and rumination across the cycle with worse outcomes during the late luteal compared to all other cycle phases (see online supplement). Separate regression analyses showed that high negative affect (beta=0.330, p=.005), rumination (beta=0.265, p=.033), ruminative stress reactivity (beta=0.240, p=.039) and low positive affect (beta=0.298, p=.015) significantly predicted higher levels of PMDD-symptom scores at follow-up, and low cortisol levels showed a trend (beta=0.197, p=.098). These individual AA-derived predictors explained between 3.5% and 9.6% incremental outcome variance (see online Table S2). In the multiple regression model, high negative affect (beta=0.370, p=.001) and low cortisol levels (beta=0.254, p =.023) remained as significant independent AA-predictors. This model explained 15.4% incremental outcome variance compared to the control model (p=.002; see online Table S3).

Summarized, our study revealed that levels of momentary negative and positive affect, rumination, cortisol, and ruminative stress-reactivity improved the prediction of the clinical course of PMDD over and above well-known clinical risk factors such as symptom severity at baseline. While individual AA-predictors were partially overlapped (probably mainly due to their common overlap with negative affect), high negative affect and low cortisol output independently predicted a worse clinical course of PMDD. The identified substantial added value of individual AA-predictors points to the importance to consider such daily life variables more systematically in

future longitudinal PMDD research. In a next step, it could be tested whether addressing such AA characteristics as direct targets in therapy will improve psychological and/or pharmacological interventions for PMDD. Particularly rumination, a transdiagnostic factor in psychopathology, may constitute a promising therapy target, e.g., in the context of mindfulness-based interventions, which have already proven effective in reducing daily life rumination in patients with recurrent depression (Timm et al., 2018). Respective research could also investigate whether changes in momentary mood, rumination, subjective stress reactivity and/or HPA axis activation during daily life will mediate intervention effects on clinical symptomatology in PMDD. Strengths and limitations of the study are discussed in the online supplement.

4.2 Online supplement material

4.2.1 Supplementary Materials and Methods

4.2.1.1 Participants

Women with Premenstrual Dysphoric Disorder (PMDD) were recruited using different sources (e.g., newspapers, gynecologists practices, homepage of the Central Institute of Mental Health (CIMH). They underwent a clinical baseline interview to assess study in- and exclusion criteria and baseline sociodemographic and clinical variables. Inclusion criteria were fulfilling the DSM-5 criteria for PMDD A to E using the Structured Interview for DSM-IV TR Defined PMDD (SCID-PMDD, Accortt et al., 2011) with the diagnostic algorithm adapted for DSM-5. To avoid further participant burden, criterion F (prospective daily ratings during at least two symptomatic cycles before study inclusion) was not required. Exclusion criteria included age < 20 and > 42, a reported cycle length of < 22 or > 34 days, a reported variation of cycle length of more than five days, use of hormonal contraceptives, psychotropic medication or other medication affecting the HPAA during the last three months, heavy exercise (≥1 h per day), late evening or night shifts, body mass index <18 or >35, birth of a child or lactation/breastfeeding during the last 6 months, history of gynecological diseases, bipolar or psychotic disorders, and substance dependence, or current substance abuse.

In total, n=61 women with PMDD completed the baseline interview including the Ambulatory Assessment (AA). One woman dropped out during the four-month

interval between baseline assessment and follow-up, resulting in a sample of n=60 PMDD women for the present paper.

4.2.1.2 Study Procedure

Data were collected from 3/2016 to 12/2018. During the baseline session at the CIMH the Structured Clinical Interview for DSM-IV TR PMDD (SCID-PMDD, Accortt et al., 2011) was administered to assess inclusion and exclusion criteria for PMDD. The SCID-PMDD is a structured clinical interview modeled after SCID-I that includes all symptom criteria relevant for DSM-5 together with the required impairment and exclusion criterions. The interview has shown high interrater reliability (kappa=0.96, Accortt et al., 2011). Interviews were performed by a trained research psychologist.

For each woman individual calendars were prepared based on the date of her last menstruation onset and the average length of her menstruation and of her menstrual cycle. The menstrual cycle was divided into the menstrual, follicular, ovulatory, and late luteal phase (see Wolfram et al., 2012). Assessments during the menstrual phase took place on the second and third day of menstruation, and the follicular phase was examined on the second and third day after the end of menstruation. The ovulatory phase was determined by a chromatographic ovulation test (gabControl hIH Ovulationsteststreifen, gabmed, Cologne). Participants started testing a few days before the predicted ovulation and continued daily testing until the ovulation test was positive. The AA for the ovulatory phase was then performed on the two days following ovulation. Assessments of the luteal phase took place on the fourth and third day before the next menstruation was expected. The calendar specified the exact days on which the respective AA was to be carried out and when to begin with the ovulation test. Participants were asked to repeat assessments during the next cycle if the assessment days were not accurate (e.g., if the actual menses onset was several days earlier or later than expected). To prevent sequential effects, women started the AA in different phases of their menstrual cycle. Four months after completion of the AA procedure, participants underwent a clinical follow-up interview at the CIMH where the SCID-PMDD was reassessed. The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants gave written informed consent.

4.2.1.3 Measures

Interview and questionnaire scores

For the present analysis, the sum score of PMDD symptoms assessed with the SCID-PMDD (see above) was used as a predictor variable at baseline and as the dependent variable at follow-up. Furthermore, depressive symptoms were measured at baseline and at follow-up with the 21-item Beck Depression Inventory (BDI-II, German version (Hautzinger et al., 2006)).

Ambulatory Assessment (AA)

The AA took place following the diagnostic baseline interview. It was carried out using Motorola Moto G 2nd Generation smartphones with the software My Experience movisensXS, Version 0.6.3658 (movisens GmbH, Karlsruhe, Germany). There were eight subjective assessments per day, with the first at 9 am and the last at 9:30 pm. Inter-assessment intervals were semi-randomized and varied between 45 and 120 min. Each assessment was announced by a beep and took 3-4 min to complete. Participants had 5 min to respond, and assessments could be delayed by 15 min. If participants were unable to respond or rejected the alarm, the assessment was saved as missing. At each assessment participants rated momentary mood and rumination on 7-point likert scales (1=not at all, 7=very much).

Momentary negative and positive affect were assessed with six items each which were balanced with respect to arousal (negative affect: upset, irritated, nervous, listless, down, bored; positive affect: cheerful, energetic, enthusiastic, satisfied, relaxed, calm). Outcomes for negative and positive affect were calculated by averaging the respective item scores. Rumination was assessed with the item “at the moment I am stuck on negative thoughts and cannot disengage from them”, thereby capturing the uncontrollability facet of rumination. In accordance with other AA studies on daily life stress (e.g. van Stouwe et al., 2019; Wichers et al. 2010), stress appraisal of recent daily life events was measured as the degree of unpleasantness of the most important event subjects encountered since the last beep (ranging from -3=very pleasant to +3=very unpleasant).

Twenty minutes after the subjective ratings, participants collected saliva cortisol samples with standard salivettes (Sarstedt, Germany). Participants were instructed to refrain from strenuous exercise during the AA day and not to eat, drink other than water, smoke, physically exercise or brush their teeth 20 min before completing saliva sampling (further details see (Beddig, Reinhard, et al., 2019)). Three further samples were collected after awakening (without subjective ratings) to determine the

cortisol awakening response (Beddig, Reinhard et al., 2019). These samples were excluded from the present analyses. Saliva cortisol concentrations were measured using commercially available chemiluminescence-immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were <8%.

4.2.1.4 Data analytic strategy

Data were analyzed using SAS and IBM SPSS version 23. Stress appraisal was transformed by centering around the person mean, thereby varying within but not between individuals (Curran & Bauer, 2011). With this approach, interindividual differences in mean stress appraisal do not affect the parameter estimates but are controlled (see Nezlek, 2014, p. 365), and the predictor indicates higher/lower stress appraisal than usual. Cortisol data were log-transformed to adjust for skewness. Log cortisol data were examined for outliers, and outliers more than three standard deviations from the group mean were winsorized to 3 standard deviations (cf. Schlotz, 2019; Stalder et al., 2016).

Predictor analysis followed a two-step procedure. In a first step, random effects parameters (i.e., intercepts, slopes of stress appraisal) for four AA variables (negative affect (average of six items), positive affect (average of six items), rumination, and salivary cortisol secretion) over the total menstrual cycle for each woman were estimated with Restricted Maximum Likelihood using the PROC MIXED procedure of SAS with time, time-squared (if significant), sampling day and stress appraisal as fixed effects. Hence, the estimated person specific intercept values reflect interindividual differences in the average level of momentary negative affect, positive affect, rumination and cortisol secretion over the menstrual cycle, while the estimated slope values reflect interindividual differences in the effect of stress appraisal levels on these state variables over the menstrual cycle.

All random effects for AA variables were then standardized and these standardized parameters were entered as predictors of the intensity of PMDD symptomatology at follow-up. For this purpose, regression analyses were carried out in SPSS in a second step. The standardized SCID-PMDD symptom score at follow up served as the outcome variable while controlling for baseline SCID-PMDD symptom scores and baseline BDI-II scores (raw means and standard deviations of these variables see Table S1). In addition, we included further possible confounding variables: age, psychotropic medication intake at follow-up (selective serotonin reuptake inhibitors: n

= 2, tricyclic antidepressants: n = 1, methylphenidate: n=1), oral contraceptive use (n = 4), and time lag in days between the last day of AA and follow up (Mean = 134, SD = 20, Min = 104, Max = 206). If any of these variables were significant or showed a trend ($p \leq .10$), they were retained in the regression models. This was true for age and psychotropic medication intake, indicating lower PMDD symptom scores in younger women and in those taking respective medication at follow-up.

Thus, all following regression models were corrected for age, baseline PMDD symptoms, baseline depressive symptoms and psychotropic medication intake, which were entered as standardized covariates in a single step. This model including only baseline predictors without any AA variables served as the control model.

Finally, the standardized random effects for all AA variables were used as predictors 1) in separate regression analyses to analyze the incremental effect of each predictor compared with the control model in terms of proportion of explained variance separately, and 2) in a stepwise multiple regression analysis to identify significant independent predictors of follow-up PMDD symptomatology compared with the control model.

4.2.2 Supplementary results

4.2.2.1 Sample characteristics

Compliance with AA was high (3381 of 3904 = 86.6% completed prompts). Sociodemographic and clinical characteristics of the sample (n=60) together with mean levels of the AA variables are presented in Table S1.

4.2.2.2 Variation of mood, rumination, and cortisol over the menstrual cycle

Multilevel analyses with cycle phase, time, time² (if significant) and day as fixed effects showed significant effects of cycle phase on mood, rumination and cortisol in the PMDD sample. The cycle phase effect was significant in predicting NA ($F(3,412) = 34.0$, $p<.001$), PA ($F(3,418) = 30.2$, $p<.001$), rumination ($F(3,413) = 19.7$, $p\leq.005$) and cortisol ($F(3,395) = 2.6$, $p=.05$). Post hoc tests using Bonferroni correction revealed higher negative affect and rumination as well as lower positive affect during the luteal phase compared to all other cycle phases (ps ≤ .005) but no differences in cortisol levels between the late luteal and other cycle phases ($p \geq .082$).

4.2.2.3 Predictors of PMDD symptomatology at follow-up

Online Table 2 shows the results of separate regression models of random effect parameters of individual AA variables as predictors of PMDD symptoms at follow up. Table S3 shows the results of the stepwise multiple regression model of random

effect parameters of negative affect and cortisol as the remaining independent predictors of PMDD symptoms at follow up after stepwise regression. Further explanations see main text.

4.2.3 Supplementary section: Strengths and limitations of the study

Strengths of the present study include the investigation of a relatively large sample size of women with PMDD, the validation of ovulatory cycles through an ovulation test, and the combination of data assessed on the micro (AA) and macro (clinical symptom) level within the framework of a longitudinal study. Here, we could show that AA-variables at baseline yielded unique predictive information and did not merely reflect clinical symptoms but additionally contributed to these known risk factors in affecting the clinical course of PMDD. AA of daily life experiences have also been proposed to provide greater sensitivity for connecting psychological with biological processes than retrospectively assessed symptoms and traits (cf. Conner & Barrett, 2012), which we could previously show in a study with depressed patients (Huffziger et al. 2013). The AA approach may similarly help to advance knowledge regarding psychological and biological mechanisms and their interplay involved in PMDD (Owens & Eisenlohr-Moul, 2018). Finally, AA may constitute a fruitful tool for identifying possible transdiagnostic risk factors at the micro-level of experience which can eventually be addressed by transdiagnostic therapy approaches.

A limitation of the study is the provisional diagnosis of PMDD, since we did not request prospective daily ratings of PMDD symptoms over at least two symptomatic cycles prior to study entry to prevent participant burden. Therefore, the PMDD diagnosis has to be regarded as provisional. However, this approach is in line with a majority of studies using retrospective reports to assess PMDD, and prevalence rates of moderate to severe premenstrual symptoms derived from retrospective epidemiological studies have been found to be consistent with those using prospective ratings (cf. Cunningham et al., 2009). The use of a single item to assess uncontrollable rumination, although it has already shown good sensitivity as well as construct and predictive validity in previous studies (Kuehner et al., 2017; Lydon-Staley et al., 2019; Timm et al., 2018), may be regarded as a potential further limitation of the study.

Table S1. Sample characteristics of women with PMDD (n=60)

Variables	% / M (SD)
Demographic variables	
Age	29.4 (5.8)
Education level (% with high school degree)	73.3%
Marital status (% married or living with partner)	60.0%
Children (%)	23.3%
Clinical variables	
SCID-PMDD[1] symptom score at baseline	7.7 (1.6)
SCID-PMDD[1] symptom score at follow-up	6.8 (2.2)
BDI-II[2] score at baseline	11.0 (9.0)
BDI-II[2] score at follow-up	11.5 (8.9)
Psychotropic treatment at baseline[3]	0%
Psychotropic treatment at follow-up	6.7%
Ambulatory Assessment variables (baseline)	
Compliance Rate	86.5%
Negative affect[4]	2.8 (0.5)
Positive affect[4]	4.2 (0.6)
Rumination[4]	2.4 (0.7)
Stress appraisal[4]	-0.7 (0.5)
Cortisol levels (nmol/l)[4]	11.0 (4.9)

[1]SCID-PMDD = Structured Interview for DSM-IV TR Defined Premenstrual Dysphoric Disorder. [2]BDI-II = Beck Depression Inventory-Revised. [3]Psychotropic treatment at baseline was an exclusion criterion. [4]For illustrative purposes, AA-variables are presented as aggregated variables at the person level.

Table S2. Results of simple regression models of random effect parameters of AA variables as predictors of PMDD symptoms at follow up

Predictors[1]	*df*	$F_{increase}$	Beta	SE	*p*	Explained variance
Random Intercepts (AA[2])						
Negative Affect	(1,53)	8.489	0.330	0.113	0.005	9.6%
Positive Affect	(1,53)	6.376	-0.298	0.118	0.015	7.5%
Rumination	(1,53)	4.783	0.265	0.121	0.033	5.8%
Cortisol	(1,53)	2.846	-0.197	0.117	0.098	3.5%
Random Slopes for stress reactivity (AA[2])						
Stress on Negative Affect	(1,53)	0.861	0.114	0.123	0.358	1.1%
Stress on Positive Affect	(1,53)	1.100	-0.129	0.123	0.299	1.4%
Stress on Rumination	(1,53)	4.458	0.240	0.114	0.039	5.4%
Stress on Cortisol	(1,53)	0.293	0.064	0.119	0.590	0.4%

[1]All models include baseline PMDD symptom scores (Structured Interview for DSM-IV TR Defined Premenstrual Dysphoric Disorder, SCID-PMDD), baseline depressive symptom scores (Beck Depression Inventory II, BDI-II), age, and psychotropic medication intake (0=no, 1=yes) at follow up. [2]AA = Ambulatory Assessment.

Table S3. Results of the stepwise multiple regression model of random effect parameters of AA variables as predictors of PMDD symptoms at follow up

Predictors[1]	Beta	SE	*p*	*df*	$F_{increase}$	*p*	Explained variance
Random Intercepts (AA[2])				(2,52)	7.36	0.002	15.4%
Negative Affect	0.370	0.110	0.001				
Cortisol	-0.254	0.108	0.023				

[1]Model includes baseline PMDD symptom scores (Structured Interview for DSM-IV TR Defined Premenstrual Dysphoric Disorder, SCID-PMDD), baseline depressive symptom scores (Beck Depression Inventory II, BDI-II), age, and psychotropic medication intake (0=no, 1=yes) at follow up. [2]AA = Ambulatory Assessment.

5 GENERAL DISCUSSION

5.1 Summary of the present findings

Important results of Study 1

Objective of Study 1 was to investigate whether women diagnosed with PMDD and asymptomatic controls differed with regard to within-person influences of daily life stress on mood, cognitions and cortisol activity and with regard to their basal cortisol activity over the menstrual cycle. Findings revealed that PMDD women in contrast to controls demonstrated a premenstrual increase in stress appraisal and high arousal negative affect in response to daily life stressors. Affected women also showed heightened levels of rumination towards daily stressors irrespective of menstrual cycle phase. Furthermore, PMDD was associated with blunted basal cortisol secretion across the menstrual cycle: the CAR peak was delayed and the diurnal cortisol slope was flattened in comparison to controls. In both groups within-person increases in high arousal negative affect and decreases in positive affect predicted higher subsequent cortisol levels, whereas there was no evidence for cortisol changes after experiencing within-person increases in stress appraisal in any group. Another key finding of the study was that the link between rumination and cortisol appeared to be decoupled in women with PMDD: a distinct cortisol response to rumination was only identified in healthy women, which was irrespective of cycle phase. Together, these results point towards heightened subjective stress appraisal and subjective stress reactivity during the late luteal phase and blunted basal HPAA dysfunction in women with PMDD compared to healthy control women.

Important results of Study 2

Study 2 examined menstrual cycle-related variations in emotional and cognitive states and their time-lagged associations in PMDD women and controls. Findings showed that women with PMDD reported highest levels of negative affect and rumination and lowest levels of positive affect and self-acceptance in the late luteal phase, thereby lending empirical support to the cyclic pattern of symptoms. In addition, lagged models revealed that intraindividually increased rumination and decreased self-acceptance predicted subsequent mood worsening more strongly in the PMDD group, with the effect of rumination being limited to the late luteal phase.

Findings point toward a contribution of momentary cognitions to premenstrual mood worsening in PMDD women. In turn, decreased positive affect and increased negative affect were more strongly associated with subsequent deterioration in rumination and self-acceptance in affected women. These results suggest that PMDD women are more sensitive than healthy women to detrimental effects of both dysfunctional thinking and low mood.

Important results of Study 3

Study 3 investigated the role of AA-characteristics for the prediction of the clinical course of PMDD. Findings revealed that a number of daily life characteristics were linked to a more severe clinical PMDD psychopathology four months later. Specifically, high levels of negative affect, rumination, and ruminative stress-reactivity as well as low levels of positive affect and cortisol secretion explained incremental proportions of variance after controlling for relevant conventional demographic and clinical course-related factors. Mean negative affect and low cortisol output independently predicted a worse clinical course of PMDD explaining more than 15% incremental variance of interviewer-rated PMDD symptoms at follow-up. Importantly, these findings were not attributable to levels of depressive and anxiety symptoms at baseline.

5.2 Interpretation of study results in light of previous studies and future directions

As a whole, this thesis adds to the PMDD-literature by performing an electronic AA with smartphones as a method for a repeated collection of a woman's momentary psychological and physiological states across the menstrual cycle, which has been repeatedly called for in the respective up-to-date literature on PMDD (e.g. Bosman et al., 2016; Craner et al., 2014; Owens & Eisenlohr-Moul, 2018). Knowledge of possible disease-related mechanisms in daily life, as identified in the present study, may be beneficial for future research and treatment.

Study 1

In Study 1 we identified significant stress-related psychological and endocrinological within-person variability in women with PMDD during daily life. While sensitivity to daily life stressors has been identified as an important psychological mechanism for many psychiatric disorders (Myin-Germeys et al., 2018), little is known about stress-

related characteristics in PMDD such as momentary stress appraisal, and subjective as well as endocrinologic stress-responsitivity.

In line with evidence from previous crosssectional studies showing that PMDD is linked to higher stress appraisal toward the end of the cycle (for reviews see Epperson et al., 2012; Owens & Eisenlohr-Moul, 2018; Beddig & Kuehner, 2017), our findings revealed that women with PMDD appraised daily life stressors as more aversive in the late luteal phase compared to the follicular phase, pointing toward a relationship between perception of daily life stressors and menstrual cycle phase in PMDD women.

Subjective reactivity to daily life stressors is usually expressed through momentary affect and cognitions. While previous studies with other clinical populations mostly focused on negative affect in response to a stressor (e.g. van der Stouwe et al., 2019; Wichers et al., 2009), our study differentiated between specific mood facets (e.g., negative affect high versus low in arousal), thereby highlighting the importance of arousal in the context of PMDD. In particular, we observed premenstrual within-person elevations in high arousal negative affect states (i.e. being upset, nervous or irritated) in response to increased momentary stress-levels in affected women. These findings are consistent with previous epidemiological research emphasizing the role of premenstrual irritability and anger as the most frequent and impairing symptoms in the context of PMDD (e.g. Epperson et al., 2012; Hantsoo & Epperson, 2015; Hartlage et al., 2012; Owens & Eisenlohr-Moul, 2018). The preponderance of high arousal negative affect and mood lability over depressed mood has led to a change in the respective listing of symptoms from DSM-IV to DSM-5 (Hantsoo & Epperson, 2015). In this context, it has been discussed whether the location of the PMDD diagnosis in the chapter on depressive disorders in DSM-5 is appropriate, considering that women with PMDD experience very diverse symptoms and respond to high stress situations particular with high intensity negative affect. Hence, it has been suggested that PMDD should not be classified as a variant of depression (Landen & Eriksson, 2003). A different point of view is taken by Payne et al. (2009) and Kuehner (2017). They propose the presence of a female-specific reproductive phenotype of depression given that PMDD links to postpartum and perimenopausal depression due to shared clinical characteristics, significant lifetime comorbidity and susceptibility to normal hormone fluctuations. Here, further AA-studies may aim at

identifying possible common or different daily life phenotypes underlying PMDD and Major Depression.

Notably, we identified an enhanced within-subject effect of stress on rumination in PMDD women irrespective of cycle phase. The only study to date investigating cognitive stress responses in women with premenstrual disorders found evidence for increased levels of self-focused attention to an elicited stressor (Craner et al., 2015). Given these findings, affected women seem to respond to more stressful situations with heightened dysfunctional attentional and cognitive features (ruminative thinking, self-focused attention). The lacking cycle effect of rumination in the present study suggests that this reflects a trait-like characteristic.

Some authors propose that the altered perception of stressful events may be linked to an altered biological stress reaction (e.g. Girdler et al., 2007; Kleinstauber et al., 2016), and a few previous studies have found differences in basal cortisol activity (Hoyer et al., 2013; Odber et al., 1998) and in endocrinologic stress reactivity (Huang et al., 2015; Klatzkin et al., 2014; Roca et al., 2003) between women with premenstrual disorders and asymptomatic controls. However, results have been inconclusive by now (cf. Kiesner & Granger, 2016). With regard to endocrinologic stress reactivity, the current results provide no evidence for altered cortisol reactivity to daily stressors in women with PMDD. Explanations for the null finding might be attributable to several factors: First, given the naturalistic everyday life context, stressors were minor daily life events and thus may have had less impact on the HPAA compared to induced strong single-event stressors in standardized laboratory research paradigms. Second, as our stress data refer to self-reports in a time-sampling protocol, a potential recall bias cannot be excluded. Third, some research suggests that cortisol responses are particularly increased following interpersonal stressors (Gilbert et al., 2017; Lustyk, Olson, Gerrish, Holder, & Widman, 2010). However, due to a lack of power, we did not differentiate between specific event types (e.g. social interaction, work stressors). Therefore, future PMDD research with larger samples might consider a possibly heterogeneous activation of the HPAA in response to different stressor types.

Apart from responses to daily life stress events, our results indicate a different relationship between rumination and HPAA activity in women with and without PMDD. While cortisol levels in response to rumination rose in asymptomatic controls, reports of increased rumination in PMDD women did not significantly affect their

cortisol levels, suggesting a decoupling of cognitive and neuroendocrinological processes. This may reflect a general impaired ability to adapt cortisol levels depending on situational demands and might therefore point to an important pathophysiological marker of PMDD. Similar findings of reduced stress-cortisol coupling in daily life have been reported from other clinical populations. For instance, Peeters, Nicholson, and Berkhof (2003) showed that in acutely depressed patients, cortisol levels did not significantly increase following everyday negative events as seen in controls. Therefore, adaptive cortisol responses might represent a protective factor to buffer negative mood (Heim et al., 2000; Het et al., 2012; Schlotz, 2008).

With regard to basal cortisol, the present data suggest that PMDD is linked to blunted basal cortisol activity throughout the menstrual cycle. Blunted HPAA activity has also been identified in other stress-related conditions such as posttraumatic stress disorder, chronic fatigue syndrome or atypical depression (Adam et al., 2017; Heim et al., 2000; Tak et al., 2011), and in individuals with genetic or cognitive vulnerability to depression (Kuehner et al., 2007; 2011). In this context, it has also been proposed that women with PMS, in contrast to women with PMDD, show adaptive cortisol activation (Hoyer et al., 2013), which should be however addressed in more detail in future research. Furthermore, we observed that alterations in cortisol activity were not confined to the luteal phase, suggesting that they represent a more stable or traitlike feature. Finally, it remains to be investigated whether basal cortisol characteristics contribute to or are merely a consequence of PMDD. Accordingly, more research is needed in order to assess the exact mechanisms behind the identified blunted basal cortisol activity in PMDD.

Taking together, this study expanded previous work on PMDD by assessing stress-related psychological and neuroendocrinological characteristics across the menstrual cycle with electronic AA, by distinguishing arousal facets of affect as well as basal and stress-related components of cortisol activity, and by examining within-person associations between stress and respective factors.

Study 2

Study 2 investigated menstrual cycle-related variations in emotional and cognitive states and their possible reciprocal effects in PMDD women compared to controls. Results suggest that women with PMDD are more sensitive to detrimental effects of dysfunctional cognitive states on subsequent mood and vice versa.

Affective symptoms of low mood, decreased interest, irritability, and anxiety occur as part of many mood and anxiety disorders, including PMDD. The feature that most highly distinguishes PMDD from similar entities is its time course with the luteal phase confinement of symptoms (APA, 2013). Not surprisingly, results of the study confirm characteristics of PMDD as delineated in DSM-5, including menstrual cycle related variations in affective and cognitive states in women with PMDD but not in asymptomatic controls, such as state reports of substantial mood worsening and increase in dysfunctional thinking in the late luteal phase.

Furthermore, the findings of our study suggest that cognitions and affect may mutually reinforce each other during everyday life in PMDD women, and may thereby contribute to a vicious circle. Notably, this was true even when adjusting for depressive symptoms, trait anxiety levels and daily life stressors, suggesting that the identified sensitization is not a direct or indirect effect of comorbid depressive or anxiety symptoms or heightened stress experience. Therefore, our study contributes to the existing literature in two important ways. First, while previous studies investigated trait aspects of rumination with various self-report measures (cf. Craner et al., 2014, 2015; Dawson et al., 2018), our AA study focused on moment-to-moment within-person relationships between affective and cognitive states across different menstrual cycle phases. Second, in line with the transdiagnostic perspective of rumination as a dysfunctional key mechanism in mental disorders (e.g. Lyubomirsky et al., 2015; Nolen-Hoeksema et al., 2008; Nolen-Hoeksama & Watkins, 2011), we identified a characteristic rumination-related cycle dependency in the PMDD sample. Therefore, while reciprocal effects between affective and cognitive states have already been identified for patients with Major Depression using daily life studies (e. g. Kircanski et al., 2018; Ruscio et al., 2015), our study showed a specific mutually reinforcing relationship between rumination and negative affect which was particularly pronounced during the late luteal phase in women with PMDD.

In general, our findings provide empirical support that affected women are more sensitive to detrimental effects of dysfunctional thinking and mood deterioration in a kind of vicious circle, particularly toward the end of the menstrual cycle. Findings also support previous findings by highlighting the contribution of psychological factors for premenstrual disorders (e.g. Craner et al., 2016; Kleinstauber et al., 2016; Reuveni et al., 2016; Weise et al., 2019). Future research could examine whether interventions addressing dysfunctional cognitive states such as momentary rumination are able to

interrupt the identified cycle-dependent vicious circle between cognitions and mood worsening in PMDD.

Study 3

AA is seen as a promising approach to examine mental states at the micro-level of experience during daily life that can be connected to macro-levels of mental health (Myin-Germeys et al., 2018; Wichers, 2014). A respective recent review by Brietzke et al. (2019) provides encouraging results thereby emphasizing the potential of AA-phenotypes for clinically relevant outcomes such as symptom course, relapses and recurrences, and functional impairment. In contrast, to date there is a complete gap in research examining the predictive value of possible AA-derived experience sampling phenotypes for the clinical course of PMDD. Given that PMDD shows a high risk for chronification (Wittchen et al., 2002) and increased suicidality (Pilver et al., 2013), it is of primary importance to identify possible course-related risk factors. The results of Study 3 suggests that cognitive, affective and cortisol-related daily life states and processes may represent important AA-phenotypes that are prospectively linked to the clinical course of symptoms in PMDD, even after controlling for relevant demographic and clinical predictors. Here, AA characteristics at baseline provided unique predictive information and yielded substantial incremental explained variance of PMDD symptomatology at the four-months follow-up. The present results also point to AA as a fruitful tool for identifying transdiagnostic risk factors such as negative affect and rumination. In this context, it has also been proposed that AA of daily life experiences may provide greater sensitivity for connecting psychological with biological processes than retrospectively assessed symptoms and traits (cf. Conner & Barrett, 2012), which are therefore particularly suitable for being studied across domains and units of analysis within the Research Domain Criteria (RDoC) framework (Insel et al., 2014) and may also be addressed through transdiagnostic intervention approaches. Future research in this area should also take a look at longer follow-up intervals. In doing so, it would be interesting to see whether the present findings represent reliable phenotypes with prognostic value for the longer-term course of PMDD. In a next step, it could be investigated whether explicitly targeting these AA-characteristics in psychological or pharmacological therapy will improve treatment and outcome for PMDD.

5.3 Strengths and Limitations

5.3.1 Strengths

The current study has several strengths to mention. First, it was based on a relatively large and carefully selected sample of women with PMDD. The final criteria for study inclusion were assessed by a trained research psychologist using structured clinical interviews, namely the SCID-PMDD (Accortt et al., 2011) for PMDD criteria (DSM-5) and the SCID-I (Wittchen et al., 1997) for comorbid mental disorders. We applied strict exclusion criteria (for a detailed overview see Beddig, Reinhard et al., 2019); for instance, women were excluded if they took hormonal contraceptives, antidepressants, or other medication affecting the HPAA. Moreover, in previous studies women with PMDD and PMS were often pooled together. However, it is of particular importance to distinguish PMDD from milder forms of premenstrual disorders when investigating potential disease mechanisms (cf. Hoyer et al., 2013; Odber et al., 1998). In order to address this issue, only women were included who fulfilled DSM-5 core and accompanying criteria for PMDD. In addition, the control sample was narrowly matched with regard to age and education level. A further advantage of the study design was the gathering of all four cycle phases (menstrual, follicular, ovulatory, and late luteal). The ovulatory phase of the cycle was determined by a chromatographic ovulation test indicating a rise in luteinizing hormone levels in urine. If ovulation did not occur, subjects had to repeat the missing phases (ovulatory and late luteal phase) in the following cycle. Thus, in contrast to previous studies which frequently made use of self-report data to determine different menstrual cycle phases, we included an objective measure of ovulation and ensured that only ovulatory cycles were assessed. Besides, possible sequence effects were avoided by having participants start AA in different phases of their menstrual cycle.

Furthermore, the innovative assessment approach using electronic diaries with semi-randomly high-frequency sampling enabled to collect prospective data in the participants' natural environment with high accuracy as well as high generalizability and external validity (cf. Schlotz, 2019; Trull & Ebner-Priemer, 2013). As in all naturalistic studies, missing data were inevitable. However, we reached high compliance rates for our daily life subjective variables and cortisol samples (Courvoisier et al., 2012), which represents a further strength of this study. Regarding item selection, we made use of affective items allowing to differentiate

valence (positive versus negative) and degree of arousal (high versus low), which has been called for recently in the relevant up-to-date literature on PMDD (Bosman et al., 2016).

In the statistical analyses, three-level multilevel models were performed (level 1 = single assessments, level 2 = days, level 3 = individuals) with random intercepts for individuals and days. This approach allows the consideration of the hierarchical data structure and includes an improved handling of missing data (cf. Hox, 2010). Bonferroni correction was used for multiple comparisons. As we could rely on intensive longitudinal data, our analyses are based on higher statistical power compared to traditional group comparisons (cf. Hox, 2010).

A key methodological advantage of the realized electronic AA approach with multilevel analysis was the ability to focus on within-person processes. The multiple measurement occasions allowed the investigation of intraindividual changes by allowing each woman to serve as her own control. By using person-mean centering, the influence of between-person effects was controlled for in respective analyses.

While previous studies have shown an increased subjective sensitivity to stress in women with PMDD (cf. Owens & Eisenlohr-Moul, 2018), there is minimal work tying this to physiological measures of stress responses such as cortisol. By contrast, our cortisol assessment included the repeated measurement of standard cortisol parameters (CAR, daily slope) and the linking of cortisol outcomes to subjective daily life experiences, thereby enhancing reliability and generalizability. Further advantages in this context include: 1) We log-transformed raw cortisol data to account for skewed distribution and windsorized outliers more than three standard deviations from the group mean. 2) For every cortisol pattern we tested a linear and a quadratic model. 3) Our CAR included three time-points. Even though in most studies only two time points were included, at least three assessments (on awakening, 30 min and 45 min) are highly recommended for research in adult populations (Stalder et al., 2016). 4) Our daily slope included nine cortisol samples, thereby clearly exceeding the recommended minimum of three samples for estimating diurnal slopes (Adam et al., 2017; Hoyt, Ehrlich, Cham, & Adam, 2016). 5) By realizing a time-lag of 20 min between subjective assessments and cortisol samples, we took into account the delayed cortisol rise in response to subjective experiences (Schlotz, 2019) and were able to control for a number of possible confounding variables (e.g. eating, drinking, physical exercise). 6) Data from noncompliant participants with saliva

samples of more than 10 min after the prompts were excluded. 7) Salivary measure ratings were time-verified by the demand to note a random three-digit number on the salivettes.

Finally, in recent years experts became increasingly aware of the potential of AA to predict psychiatric symptoms and clinical outcomes in mental disorders (Barnett et al., 2018; Brietzke et al., 2019; van Os et al., 2017; Wenzel, Kubiak, & Ebner-Priemer, 2016). In Study 3, we used this approach to investigate for the first time the role of micro-level psychological and physiological processes at baseline for the prediction of the clinical course of symptomatology in our PMDD sample.

Taken together, with the application of electronic AA, the coverage of four menstrual cycle phases, the focus on within-person-effects and the investigation of the predictive value of AA-derived experience sampling phenotypes, we believe that the study was characterized by an innovative approach and by methodological strengths offering novel opportunities to explore PMDD.

5.3.2 Limitations

Apart from the strengths of the study, a number of limitations have to be considered, which will be discussed in the following. A first limitation relates to the diagnostic procedure for determining the PMDD diagnosis. The study inclusion criteria were based on the Structured Clinical Interview for PMDD (SCID-PMDD, Accortt et al., 2011) following the requirements of DSM-5 (APA, 2013) that symptom criteria of PMDD should be fulfilled in more than half of the cycles during the last 12 months. Therefore, although the PMDD diagnosis was made by clearly defined, replicable DSM-5 criteria, it was nevertheless based on the retrospective recall of premenstrual symptoms within the last year. A prospectively-confirmed diagnosis with daily charting of symptoms for two symptomatic cycles, as defined by DSM-5 (APA, 2013), was not required before study inclusion to avoid participants burden as the study already demanded the participating women to intensively track one menstrual cycle with multiple AA-measurements. Consequently, the diagnosis of PMDD should be considered ‘provisional’ and some women might have experienced a cycle with lower symptom load, during the covered AA period. However, this fact may partly reflect a general problem concerning the lack of precision and consistency in how PMDD is defined in DSM-5, particularly that symptoms must be present in the majority of cycles (i.e. implicating that there might also be nonsymptomatic cycles in PMDD) and

that symptom criteria should be confirmed by prospective ratings during two symptomatic cycles (i.e. again implicating that there might also be nonsymptomatic cycles, which would not exclude a PMDD diagnosis) (APA, 2013). In clinical practice, symptom diaries are not commonly used; instead, a diagnosis is predominantly based on retrospective reports (Craner et al., 2014). Importantly, however, studies showed that prevalence rates of moderate to severe premenstrual symptoms derived from retrospective epidemiological studies are consistent with those using prospective ratings (Cunningham et al., 2009). Another possible limitation concerns the representativity of our sample. Participants were not necessarily treatment-seeking, and their symptom levels may have been less severe and impairing compared to women presenting for treatment of PMDD in medical settings. Additionally, participants were recruited from different sources (i. e. newspapers, local family doctors and gynaecologists practices, homepage of the CIMH, social networks), which may represent a further limitation. Moreover, we explicitly excluded participants with ongoing hormonal or antidepressant treatment, since these medications could blur normal fluctuating cortisol activity. However, given that antidepressant and hormonal treatments are currently the most frequent treatments for PMDD (Epperson et al., 2012; Marjoribanks et al., 2013), the results of our study might not be representative for all women with PMDD. Furthermore, we only examined participants between 20 and 42 years of age as a regular menstrual cycle was obligatory for this study. Thus, the results cannot necessarily be generalized to younger or older women. Besides, even though our sample was heterogeneous with regard to age, education, job and family situation, women with higher education levels were somewhat overrepresented. Regarding potential demand characteristics, women with diagnosed PMDD presumably were aware that affect and stress are expected to vary across the menstrual cycle. Therefore, their subjective responses might have been biased in some way. Nonetheless, results regarding the cycle-specific heightened subjective stress reactivity and the tendency to react with rumination in face of stressful events were unlikely to be biased, decreasing the likelihood that demand characteristics were an important factor.

With regard to the AA procedure, several limitations need to be considered. First, limited resources and the time-consuming procedure with multiple measurements per day did not allow for the daily assessment over the whole menstrual cycle. Instead, to reduce participants' burden while undergoing daily routines, we used shorter

timeframes of two days duration to characterize different phases of the cycle, which may have resulted in a lack of power. Furthermore, due to the small number of days per cycle phase we might have missed the days with the highest impairment. Second, we did not measure sex hormone levels, which would have further increased confidence in an accurate assessment of menstrual cycle phases given that each menstrual cycle phase features specific fluctuations of estrogen and progesterone. Instead, we determined the luteal phase based on participants' reports of their first day of their last menses and the typical duration of the cycle length. Hence, even though a regular cycle was a premise to take part in the study and the ovulation phase was confirmed by a chromatographic ovulation test, future research might benefit from an extension of the AA over the whole menstrual cycle and from measurements of hormonal parameters to verify correct phasing. Third, to further increase the accuracy of conclusions the AA could be performed over two or more consecutive menstrual cycles in future studies (cf. Kiesner, 2011; although this would have to be balanced out against even greater burden for participants). Fourth, the assessment of daily stressful events was still retrospective as it asked for the most important event since the last assessment. On the other hand, a higher sampling frequency might have deluted the effects of stressful events by including more events of relatively minor importance. Fifth, we did not assess additional specific features of stress responses (i.e. recovery and pile-up) which may be of interest to broaden the examination of stress-related features in future research (cf. Smyth et al., 2018). Sixth, constructs of rumination and self-acceptance were assessed using single items. While previous studies have demonstrated high sensitivity as well as construct and predictive validity of these measures (e.g., Kuehner et al., 2017; Lydon-Staley et al., 2019; Timm et al., 2018), they do not allow for robust psychometric testing. Finally, the focus of the present AA-study was on affective, cognitive or endocrinological factors in everyday life. Respectively, our design did not account for specific premenstrual symptoms involved in PMDD including physical (e.g., cramping, swelling, bloating) and vegetative (e.g., changes in sleep or food cravings) symptoms. Therefore, future studies could include additional items to assess specific facets of premenstrual symptoms. This procedure would also allow to investigate how premenstrual symptoms directly influence the assessed subjective and endocrinologic daily life experiences.

5.4 Conclusions and implications for further research and the treatment of PMDD

The present thesis provides several methodological and clinical implications for the assessment and treatment of PMDD. Our study showed that AA is well-suited to assess daily life mood and cognitions in PMDD women across the menstrual cycle. Given the widespread availability of smartphones and tablets, electronic AA applications are increasingly considered a useful tool for diagnostic issues and treatment in clinical practice (cf. Barnett et al., 2018; Brietzke et al., 2019; van Os et al., 2017). AA also offers the possibility to capture the variability of affect in more detail (cf. Brietzke et al., 2019), which is of particular importance given that mood swings represent one of the cardinal symptoms of PMDD. Instead of the required daily symptom ratings in routine monitoring, which are typically assessed with single-point assessments via paper-pencil at the end of the day and thus prone to recall bias, the implementation of electronic AA with multiple repeated real-time sampling might help to more accurately identify affected women. Furthermore, the within-person approach provided by AA may allow for rapid personalized feedback of current symptomatology and impairment, and the temporal relationship between various symptoms, e.g. between rumination and mood deterioration. Such individual profiles might serve as an important tool to improve professional PMDD treatment and clearly deserve more attention in future research. If proven effective, the implementation of electronic AA symptom tracking in the treatment of women with PMDD would be desirable in the long term.

Another important avenue of future research are studies addressing and increasing the understanding of possible different subtypes of PMDD (cf. Pearlstein, 2010; Yonkers & Simoni, 2018). Recent studies revealed heterogeneity within the diagnosis of PMDD with respect to symptom patterns and timing of symptom onset (Eisenlohr-Moul et al., 2019; Schmalenberger et al., 2017; Yonkers & Simoni, 2018). On top of that, women with PMDD are known to suffer from high rates of comorbid disorders (e.g., Cohen et al., 2002; Landen & Eriksson, 2003; Pilver et al., 2011), probably further increasing diagnostic heterogeneity. It is conceivable that different PMDD subtypes are associated with partly distinct underlying disease mechanisms and may also differ with regard to their responsivity to treatments (cf. O'Brien et al., 2011). Therefore, knowledge of diversified subtypes of PMDD might influence treatment recommendations. In this context, AA might be particularly suitable for helping to identify and to examine respective subtypes over the course of the menstrual cycle.

An additional area in need of improvement is the establishment of clear guidelines for psychotherapy. Up to now, the German National Disease Management Guideline for unipolar depression does not provide evidence-based treatment recommendation for PMDD due to a lack of well-designed RCT studies (DGPPN et al., 2017). The present thesis provides important starting points for the development of intervention studies by highlighting the role of cognitions as a driver for mood deteriorations and for long-term severity of symptomatology in PMDD. Specifically, we could show that PMDD women seem to be more prone to using rumination as a trait-like emotion regulation strategy in response to stressful situations (Study 1) and towards negative affect states (Study 2) irrespective of menstrual cycle phase. Beyond that, high intraindividual rumination levels seem to trigger affect deterioration particularly in the late luteal phase, suggesting a vicious circle between rumination and affect (Study 2). Finally, both average levels of momentary rumination as well as stress-reactive rumination during everyday life contribute to a more severe clinical course (Study 3). In this context, future research might benefit from investigating the impact of specific contents of ruminative thoughts. Our study revealed that rumination had particular detrimental effects on mood in the late luteal phase (Study 2). Together with the results by Craner et al. (2014) showing that ruminating about premenstrual symptoms might be particularly toxic, it can be suspected that PMDD women primarily ruminate about their premenstrual complaints. However, this should be examined in deeper detail in future research.

Our findings further suggest that it appears worthwhile to specifically target dysfunctional cognitive processes in women with PMDD and to investigate which interventions aimed at reducing ruminative thoughts and at preventing a vicious circle between dysfunctional thinking and mood worsening might reduce burden. In this regard, particularly mindfulness-based interventions have been suggested that have proven effective to modulate affect, stress, arousal, and emotion regulation in patients with various disorders (e.g. Bluth et al., 2015; Eggert et al., 2016; Petersen et al., 2016). Furthermore, a recent study by our group has shown that a mindfulness-based training reduced momentary rumination and improved momentary mood during daily life in patients with recurrent depression (Timm et al., 2018). Two studies have already demonstrated that such interventions may help women suffering from premenstrual disorders (Bluth et al., 2015; Panahi & Faramarzi, 2016). However, well-controlled mindfulness-based intervention studies for women with

PMDD are still lacking, highlighting the need for further clinical trials. Until then, treatment implications should be drawn with caution.

6 SUMMARY

Premenstrual Dysphoric Disorder (PMDD), outlined as a new diagnostic category in DSM-5, is characterized by key affective and accompanying psychological and physical symptoms during the premenstrual (late luteal) phase of the menstrual cycle, resulting in clinically significant distress and functional impairment. Despite its high prevalence (3%-8% in women of fertile age) and risk of chronic developments, psychological and biological mechanisms underlying PMDD are so far not well understood. Among other factors, a dysregulation of the stress axis is being discussed.

The present thesis integrates three substudies from a project using Ambulatory Assessment (AA) with electronic diaries (smartphones) to compare the course of mood, cognitions, and cortisol release in the daily life of women diagnosed with PMDD and healthy control women over the course of the menstrual cycle. AA took place at semi-random time points eight times a day during two consecutive days per cycle phase (menstrual, follicular, ovulatory, and late luteal). In particular, the thesis focused on identifying possible cycle-related within-person changes in affective, cognitive, and endocrinological states and their interrelations as captured in real time and real life. A clinical follow-up was conducted four months after baseline.

Study 1 examined the stress-related facets of mood, cognition and cortisol together with basal cortisol activity over the menstrual cycle in women suffering from PMDD and asymptomatic controls. Findings revealed that affected women showed increased subjective stress appraisal and enhanced high arousal negative affect towards daily life stressors particularly in the late luteal phase of the menstrual cycle. Furthermore, PMDD was associated with blunted basal activity of the hypothalamic-pituitary adrenal axis (delayed cortisol awakening response peak, flatter daily cortisol slope) and reduced cortisol reactivity toward periods of enhanced rumination irrespective of menstrual cycle phase. This study revealed substantial cycle-related intraindividual variability in stress appraisal and psychological responses to stress together with blunted basal cortisol activity in PMDD, with the latter similarly observed in other stress-related disorders.

Study 2 focused on menstrual cycle-related variations in momentary cognitive and affective daily life states as well as on their time-lagged reciprocal effects in women

with PMDD and controls. PMDD women, in contrast to controls, showed higher levels of momentary negative affect and rumination, and lower levels of positive affect and self-acceptance toward the end of the menstrual cycle. Lagged analyses showed stronger reciprocal within-person effects of cognitions and mood in PMDD women, whereby the effect of rumination on subsequent negative affect was limited to the late luteal phase. Stronger prospective associations of daily life cognitions and affective states in PMDD suggests that affected women seem to be more sensitive to detrimental effects of either dimension in a kind of vicious cycle. The study emphasizes the role of cognitions in the context of PMDD suggesting that ruminative thinking might be an important therapeutic target.

Study 3 investigated whether AA-characteristics of momentary mood, cognitions, and cortisol, measured across the menstrual cycle at baseline, would predict the four-month clinical symptom course in women with PMDD. Levels of momentary negative and positive affect, rumination, cortisol, and ruminative stress-reactivity improved the prediction of clinical PMDD symptomatology at follow-up after controlling for relevant demographic and clinical risk factors. High negative affect and low cortisol output independently predicted higher PMDD symptom scores and explained more than 15% incremental outcome variance. The identified substantial added value of individual AA-predictors points to the importance to consider such AA-derived phenotypes more systematically in future longitudinal PMDD research.

In conclusion, with the application of electronic AA the three studies add to existing knowledge on cycle-related variations in daily life affect, cognitions, and stress hormone release, and their temporal within-person associations in women with PMDD. Moreover, the combination of AA data at the micro-level of daily life experiences with longitudinal data at the macro-level of clinical symptomatology confirmed predictive validity of AA-derived phenotypes for the clinical course of PMDD. Findings may provide a starting point for future intervention research to provide respective evidence-based therapeutic strategies for affected women.

7 REFERENCES

aan het Rot, M., Hogenelst, K., & Schoevers, R. A. (2012). Mood disorders in everyday life: a systematic review of experience sampling and ecological momentary assessment studies. *Clinical psychology review, 32*(6), 510-523. doi:10.1016/j.cpr.2012.05.007

Accortt, E. E., Bismark, A., Schneider, T. R., & Allen, J. J. (2011). Diagnosing premenstrual dysphoric disorder: the reliability of a structured clinical interview. *Archives of women's mental health, 14*(3), 265-267. doi:10.1007/s00737-011-0209-3

American College of Obstetricians and Gynecologists (2000). ACOG practice bulletin: premenstrual syndrome. ACOG Compendium of Selected Publications; 15: 1–9. *Washington, DC.*

Adam, E. K., & Kumari, M. (2009). Assessing salivary cortisol in large-scale, epidemiological research. *Psychoneuroendocrinology, 34*(10), 1423-1436. doi:10.1016/j.psyneuen.2009.06.011

Adam, E. K., Quinn, M. E., Tavernier, R., McQuillan, M. T., Dahlke, K. A., & Gilbert, K. E. (2017). Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. *Psychoneuroendocrinology, 83*, 25-41. doi:10.1016/j.psyneuen.2017.05.018

Adam, E. K., Vrshek-Schallhorn, S., Kendall, A. D., Mineka, S., Zinbarg, R. E., & Craske, M. G. (2014). Prospective associations between the cortisol awakening response and first onsets of anxiety disorders over a six-year follow-up--2013 Curt Richter Award Winner. *Psychoneuroendocrinology, 44*, 47-59. doi:10.1016/j.psyneuen.2014.02.014

Aldao, A., & Nolen-Hoeksema, S. (2010). Specificity of cognitive emotion regulation strategies: a transdiagnostic examination. *Behaviour research and therapy, 48*(10), 974-983. doi:10.1016/j.brat.2010.06.002

American Psychiatric Association (1987). Diagnostic and Statistical Manual of Mental Disorders. Third Edition Revised. *Washington, DC: APA.*

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. *Washington, DC: APA.*

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. Fifth edition. DSM-5. *Washington, DC: APA.*

Angst, J., Sellaro, R., Merikangas, K. R., & Endicott, J. (2001). The epidemiology of perimenstrual psychological symptoms. *Acta Psychiatrica Scandinavica, 104*(2), 110-116. doi:10.1034/j.1600-0447.2001.00412.x

Backstrom, T., Andersson, A., Andree, L., Birzniece, V., Bixo, M., Bjorn, I., . . . Zingmark, E. (2003). Pathogenesis in menstrual cycle-linked CNS disorders. *Annals of the New York Academy of Sciences, 1007*, 42-53. doi:10.1196/annals.1286.005

Backstrom, T., Bixo, M., Johansson, M., Nyberg, S., Ossewaarde, L., Ragagnin, G., . . . van Wingen, G. (2014). Allopregnanolone and mood disorders. *Progress in neurobiology, 113*, 88-94. doi:10.1016/j.pneurobio.2013.07.005

Barnett, I., Torous, J., Staples, P., Sandoval, L., Keshavan, M., & Onnela, J. P. (2018). Relapse prediction in schizophrenia through digital phenotyping: a pilot study. *Neuropsychopharmacology, 43*(8), 1660-1666. doi:10.1038/s41386-018-0030-z

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck depression inventory-II. *San Antonio, 78*(2), 490-498.

Beddig, T., & Kuehner, C. (2017). [Current aspects of premenstrual dysphoric disorder-a review]. *Psychotherapie Psychosomatik Medizinische Psychologie, 67*(12), 504-513.

Beddig, T., Reinhard, I., & Kuehner, C. (2019). Stress, mood, and cortisol during daily life in women with Premenstrual Dysphoric Disorder (PMDD). *Psychoneuroendocrinology, 109*, 104372. doi:10.1016/j.psyneuen.2019.104372

Beddig, T., Timm, C., Ubl-Rachota, B., Zamoscik, V., Ebner-Priemer, U., Reinhard, I., . . . Kuehner, C. (2019). Mindfulness-based focused attention training versus progressive muscle relaxation in remitted depressed patients: Effects on salivary cortisol and associations with subjective improvements in daily life. *Psychoneuroendocrinology, 113*, 104555.

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., . . . Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child abuse & neglect, 27*(2), 169-190.

Bixo, M., Ekberg, K., Poromaa, I. S., Hirschberg, A. L., Jonasson, A. F., Andreen, L., . . . Backstrom, T. (2017). Treatment of premenstrual dysphoric disorder with the GABAA receptor modulating steroid antagonist Sepranolone (UC1010)-A randomized controlled trial. *Psychoneuroendocrinology, 80*, 46-55. doi:10.1016/j.psyneuen.2017.02.031

Bluth, K., Gaylord, S., Nguyen, K., Bunevicius, A., & Girdler, S. (2015). Mindfulness-based stress reduction as a promising intervention for amelioration of premenstrual dysphoric disorder symptoms. *Mindfulness, 6*(6), 1292-1302. doi:10.1007/s12671-015-0397-4

Boggero, I. A., Hostinar, C. E., Haak, E. A., Murphy, M. L., & Segerstrom, S. C. (2017). Psychosocial functioning and the cortisol awakening response: Meta-analysis, P-curve analysis, and evaluation of the evidential value in existing studies. *Biological psychology, 129*, 207-230.

Bosman, R. C., Jung, S. E., Miloserdov, K., Schoevers, R. A., & aan het Rot, M. (2016). Daily symptom ratings for studying premenstrual dysphoric disorder: A review. *Journal of affective disorders, 189*, 43-53. doi:10.1016/j.jad.2015.08.063

Brietzke, E., Hawken, E. R., Idzikowski, M., Pong, J., Kennedy, S. H., & Soares, C. N. (2019). Integrating digital phenotyping in clinical characterization of individuals with mood disorders. *Neuroscience & Biobehavioral Reviews, 104*, 223-230. doi:10.1016/j.neubiorev.2019.07.009

Brown, M. A., & Lewis, L. L. (1993). Cycle-phase changes in perceived stress in women with varying levels of premenstrual symptomatology. *Research in nursing & health, 16*(6), 423-429.

Browne, T. K. (2015). Is premenstrual dysphoric disorder really a disorder? *Journal of Bioethical Inquery, 12*(2), 313-330. doi:10.1007/s11673-014-9567-7

Busse, J. W., Montori, V. M., Krasnik, C., Patelis-Siotis, I., & Guyatt, G. H. (2009). Psychological intervention for premenstrual syndrome: a meta-analysis of randomized controlled trials. *Psychotherapy and psychosomatics, 78*(1), 6-15. doi:10.1159/000162296

Buttner, M. M., Mott, S. L., Pearlstein, T., Stuart, S., Zlotnick, C., & O'Hara, M. W. (2013). Examination of premenstrual symptoms as a risk factor for depression in postpartum women. *Archives of women's mental health, 16*(3), 219-225. doi:10.1007/s00737-012-0323-x

Carpenter, R. W., Wycoff, A. M., & Trull, T. J. (2016). Ambulatory Assessment. *Assessment, 23*(4), 414-424. doi:10.1177/1073191116632341

Chambers, R., Gullone, E., & Allen, N. B. (2009). Mindful emotion regulation: An integrative review. *Clinical psychology review, 29*(6), 560-572.

Chrisler, J. C., & Caplan, P. (2002). The strange case of Dr. Jekyll and Ms. Hyde: how PMS became a cultural phenomenon and a psychiatric disorder. *Annual Review of Sex Research, 13*, 274-306.

Cohen, L. S., Soares, C. N., Lyster, A., Cassano, P., Brandes, M., & Leblanc, G. A. (2004). Efficacy and tolerability of premenstrual use of venlafaxine (flexible dose) in the treatment of premenstrual dysphoric disorder. *Journal of Clinical Psychopharmacology, 24*(5), 540-543.

Cohen, L. S., Soares, C. N., Otto, M. W., Sweeney, B. H., Liberman, R. F., & Harlow, B. L. (2002). Prevalence and predictors of premenstrual dysphoric disorder (PMDD) in older premenopausal women. The Harvard Study of Moods and Cycles. *Journal of affective disorders, 70*(2), 125-132.

Conner, T. S., & Barrett, L. F. (2012). Trends in ambulatory self-report: the role of momentary experience in psychosomatic medicine. *Psychosomatic medicine, 74*(4), 327.

Cosgrove, L., & Caplan, P. J. (2004). Medicalizing menstrual distress. *Bias in psychiatric diagnosis*, 221-230.

Courvoisier, D. S., Eid, M., & Lischetzke, T. (2012). Compliance to a cell phone-based ecological momentary assessment study: The effect of time and personality characteristics. *Psychological assessment, 24*(3), 713.

Craner, J. R., Sigmon, S., & Young, M. (2016). Self-focused attention and symptoms across menstrual cycle phases in women with and without premenstrual disorders. *Cognitive Therapy and Research, 40*(1), 118-127.

Craner, J. R., Sigmon, S. T., & Martinson, A. A. (2015). Self-focused attention in response to laboratory stressors among women with premenstrual disorders. *Archives of women's mental health, 18*(4), 595-606. doi:10.1007/s00737-015-0505-4

Craner, J. R., Sigmon, S. T., Martinson, A. A., & McGillicuddy, M. L. (2014). Premenstrual disorders and rumination. *Journal of clinical psychology, 70*(1), 32-47. doi:10.1002/jclp.22007

Cunningham, J., Yonkers, K. A., O'Brien, S., & Eriksson, E. (2009). Update on research and treatment of premenstrual dysphoric disorder. *Harvard review of psychiatry, 17*(2), 120-137. doi:10.1080/10673220902891836

Curran, P. J., & Bauer, D. J. (2011). The disaggregation of within-person and between-person effects in longitudinal models of change. *Annual review of psychology, 62*, 583-619. doi:10.1146/annurev.psych.093008.100356

Davydov, D. M., Shapiro, D., & Goldstein, I. B. (2004). Moods in everyday situations: effects of menstrual cycle, work, and personality. *Journal of psychosomatic research, 56*(1), 27-33. doi:10.1016/s0022-3999(03)00602-0

Dawson, D. N., Eisenlohr-Moul, T. A., Paulson, J. L., Peters, J. R., Rubinow, D. R., & Girdler, S. S. (2018). Emotion-related impulsivity and rumination predict the perimenstrual severity and trajectory of symptoms in women with a menstrually related mood disorder. *Journal of clinical psychology, 74*(4), 579-593. doi:10.1002/jclp.22522

Dennerstein, L., Lehert, P., & Heinemann, K. (2012). Epidemiology of premenstrual symptoms and disorders. *Menopause international, 18*(2), 48-51. doi:10.1258/mi.2012.012013

DGPPN, BÄK, KBV, AWMF (2017) für die Leitliniengruppe Unipolare Depression. S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression – Kurzfassung, 2nd edition, version 1. 2017. Available at: http://www.depression.versorgungsleitlinien.de. Accessed January 27, 2020.

Doane, L. D., Mineka, S., Zinbarg, R. E., Craske, M., Griffith, J. W., & Adam, E. K. (2013). Are flatter diurnal cortisol rhythms associated with major depression and anxiety disorders in late adolescence? The role of life stress and daily negative emotion. *Development and psychopathology, 25*(3), 629-642. doi:10.1017/s0954579413000060

Eggert, L., Witthöft, M., Hiller, W., & Kleinstäuber, M. (2016). Emotion regulation in women with premenstrual syndrome (PMS): Explicit and implicit assessments. *Cognitive Therapy and Research, 40*(6), 747-763.

Eisenlohr-Moul, T. A., Kaiser, G., Weise, C., Schmalenberger, K. M., Kiesner, J., Ditzen, B., & Kleinstauber, M. (2019). Are there temporal subtypes of premenstrual dysphoric disorder?: using group-based trajectory modeling to identify individual differences in symptom change. *Psychological medicine*, 1-9. doi:10.1017/s0033291719000849

Epperson, C. N., Steiner, M., Hartlage, S. A., Eriksson, E., Schmidt, P. J., Jones, I., & Yonkers, K. A. (2012). Premenstrual dysphoric disorder: Evidence for a new category for DSM-5. *American Journal of Psychiatry, 169*(5), 465-475. doi:10.1176/appi.ajp.2012.11081302

Fontana, A. M., & Badawy, S. (1997). Perceptual and coping processes across the menstrual cycle: an investigation in a premenstrual syndrome clinic and a community sample. *Behavioral medicine, 22*(4), 152-159.

Fornaro, M., & Perugi, G. (2010). The impact of premenstrual dysphoric disorder among 92 bipolar patients. *European Psychiatry, 25*(8), 450-454. doi:10.1016/j.eurpsy.2009.11.010

Frank R.T. (1931). The hormonal causes of premenstrual tension. *Archives of Neurology & Psychiatry* 1931; 26: 1053–1057

Freeman, E. W., Sammel, M. D., Lin, H., Rickels, K., & Sondheimer, S. J. (2011). Clinical subtypes of premenstrual syndrome and responses to sertraline treatment. *Obstetrics & Gynecology, 118*(6), 1293-1300. doi:10.1097/AOG.0b013e318236edf2

Garland, E. L., Geschwind, N., Peeters, F., & Wichers, M. (2015). Mindfulness training promotes upward spirals of positive affect and cognition: multilevel and autoregressive latent trajectory modeling analyses. *Frontiers in psychology, 6*, 15. doi:10.3389/fpsyg.2015.00015

Gilbert, K., Mineka, S., Zinbarg, R. E., Craske, M. G., & Adam, E. K. (2017). Emotion regulation regulates more than emotion: Associations of momentary emotion regulation with diurnal cortisol in current and past depression and anxiety. *Clinical psychological science : a journal of the Association for Psychological Science, 5*(1), 37-51. doi:10.1177/2167702616654437

Girdler, S. S., Leserman, J., Bunevicius, R., Klatzkin, R., Pedersen, C. A., & Light, K. C. (2007). Persistent alterations in biological profiles in women with abuse histories: influence of premenstrual dysphoric disorder. *Health psychology, 26*(2), 201.

Girdler, S. S., Straneva, P. A., Light, K. C., Pedersen, C. A., & Morrow, A. L. (2001). Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. *Biological Psychiatry, 49*(9), 788-797. doi:10.1016/s0006-3223(00)01044-1

Gollenberg, A. L., Hediger, M. L., Mumford, S. L., Whitcomb, B. W., Hovey, K. M., Wactawski-Wende, J., & Schisterman, E. F. (2010). Perceived stress and severity of perimenstrual symptoms: the BioCycle Study. *Journal of Women's Health, 19*(5), 959-967. doi:10.1089/jwh.2009.1717

Haedt-Matt, A. A., & Keel, P. K. (2011). Hunger and binge eating: a meta-analysis of studies using ecological momentary assessment. *International Journal of Eating Disorders, 44*(7), 573-578. doi:10.1002/eat.20868

Halbreich, U., Borenstein, J., Pearlstein, T., & Kahn, L. S. (2003). The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). *Psychoneuroendocrinology, 28 Suppl 3*, 1-23.

Hamaker, E. L., & Wichers, M. (2017). No time like the present: Discovering the hidden dynamics in intensive longitudinal data. *Current Directions in Psychological Science, 26*(1), 10-15.

Hamaker, E. L. (2012). Why researchers should think "within-person": A paradigmatic rationale. In M. R. Mehl & T. S. Conner (Eds.), Handbook of Research Methods for Studying Daily Life, pp. 43–61. Guilford, New York.

Hantsoo, L., & Epperson, C. N. (2015). Premenstrual dysphoric disorder: Epidemiology and treatment. *Current psychiatry reports, 17*(11), 87-87. doi:10.1007/s11920-015-0628-3

Hartlage, S. A., Breaux, C. A., & Yonkers, K. A. (2014). Addressing concerns about the inclusion of premenstrual dysphoric disorder in DSM-5. *The Journal of clinical psychiatry, 75*(1), 70-76. doi:10.4088/JCP.13cs08368

Hautzinger, M., Keller, F., & Kuehner, C. (2006). *[Beck depression inventory (BDI-II)]*. Frankfurt: Harcourt Test Services.

Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., . . . Nemeroff, C. B. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *Jama, 284*(5), 592-597. doi:10.1001/jama.284.5.592

Het, S., Schoofs, D., Rohleder, N., & Wolf, O. T. (2012). Stress-induced cortisol level elevations are associated with reduced negative affect after stress: indications for a mood-buffering cortisol effect. *Psychosomatic medicine, 74*(1), 23-32. doi:10.1097/PSY.0b013e31823a4a25

Hox, J. J. (2010). *Multilevel analysis: Techniques and applications (2nd ed.)*. New York: Routledge.

Hox, J. J., Moerbeek, M., & Van de Schoot, R. (2017). *Multilevel analysis: Techniques and applications*. New York, NY: Routledge.

Hoyer, J., Burmann, I., Kieseler, M. L., Vollrath, F., Hellrung, L., Arelin, K., . . . Sacher, J. (2013). Menstrual cycle phase modulates emotional conflict processing in women with and without premenstrual syndrome (PMS)--a pilot study. *Plos one, 8*(4), e59780. doi:10.1371/journal.pone.0059780

Hoyt, L. T., Craske, M. G., Mineka, S., & Adam, E. K. (2015). Positive and negative affect and arousal: cross-sectional and longitudinal associations with adolescent cortisol diurnal rhythms. *Psychosomatic medicine, 77*(4), 392-401. doi:10.1097/psy.0000000000000178

Hoyt, L. T., Ehrlich, K. B., Cham, H., & Adam, E. K. (2016). Balancing scientific accuracy and participant burden: testing the impact of sampling intensity on diurnal cortisol indices. *Stress (Amsterdam, Netherlands), 19*(5), 476-485.

Hsu, S. C., Liu, C. Y., & Hsiao, M. C. (2007). A comparison of the Tridimensional Personality Questionnaire in premenstrual dysphoric disorder and major depressive disorder. *Comprehensive psychiatry, 48*(4), 366-370. doi:10.1016/j.comppsych.2007.02.006

Huang, Y., Zhou, R., Wu, M., Wang, Q., & Zhao, Y. (2015). Premenstrual syndrome is associated with blunted cortisol reactivity to the TSST. *Stress (Amsterdam, Netherlands), 18*(2), 160-168. doi:10.3109/10253890.2014.999234

Huffziger, S., Ebner-Priemer, U., Zamoscik, V., Reinhard, I., Kirsch, P., & Kuehner, C. (2013). Effects of mood and rumination on cortisol levels in daily life: an ambulatory assessment study in remitted depressed patients and healthy controls. *Psychoneuroendocrinology, 38*(10), 2258-2267.

Huffziger, S., Reinhard, I., & Kuehner, C. (2009). A longitudinal study of rumination and distraction in formerly depressed inpatients and community controls. *Journal of abnormal psychology, 118*(4), 746-756. doi:10.1037/a0016946

Hunter, M. S., Ussher, J. M., Browne, S. J., Cariss, M., Jelley, R., & Katz, M. (2002). A randomized comparison of psychological (cognitive behavior therapy), medical (fluoxetine) and combined treatment for women with premenstrual dysphoric disorder. *Journal of Psychosomatic Obstetrics & Gynecology, 23*(3), 193-199. doi:10.3109/01674820209074672

Insel, T. R. (2014). The NIMH Research Domain Criteria (RDoC) Project: Precision medicine for psychiatry. *The American journal of psychiatry, 171*(4), 395-397. doi:10.1176/appi.ajp.2014.14020138

Ismaili, E., Walsh, S., O'Brien, P. M. S., Backstrom, T., Brown, C., Dennerstein, L., . . . Yonkers, K. (2016). Fourth consensus of the International Society for Premenstrual Disorders (ISPMD): auditable standards for diagnosis and management of premenstrual disorder. *Archives of women's mental health, 19*(6), 953-958. doi:10.1007/s00737-016-0631-7

Janda, C., Kues, J. N., Kleinstaeuber, M., & Weise, C. (2015). A therapeutic approach to premenstrual syndrome (PMS): modularized treatment program. *Verhaltenstherapie, 25*(4), 294-303.

Jimenez, S. S., Niles, B. L., & Park, C. L. (2010). A mindfulness model of affect regulation and depressive symptoms: Positive emotions, mood regulation expectancies, and self-acceptance as regulatory mechanisms. *Personality and individual differences, 49*(6), 645-650.

Joffe, H., Cohen, L. S., & Harlow, B. L. (2003). Impact of oral contraceptive pill use on premenstrual mood: predictors of improvement and deterioration. *American Journal of Obstetrics & Gynecology, 189*(6), 1523-1530. doi:10.1016/s0002-9378(03)00927-x

Kanes, S., Colquhoun, H., Gunduz-Bruce, H., Raines, S., Arnold, R., Schacterle, A., . . . Meltzer-Brody, S. (2017). Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. *Lancet, 390*(10093), 480-489. doi:10.1016/s0140-6736(17)31264-3

Kiesner, J. (2011). One woman's low is another woman's high: Paradoxical effects of the menstrual cycle. *Psychoneuroendocrinology, 36*(1), 68-76. doi:10.1016/j.psyneuen.2010.06.007

Kim, D. R., Gyulai, L., Freeman, E. W., Morrison, M. F., Baldassano, C., & Dube, B. (2004). Premenstrual dysphoric disorder and psychiatric co-morbidity. *Archives of women's mental health, 7*(1), 37-47. doi:10.1007/s00737-003-0027-3

Kim, J., Marcusson-Clavertz, D., Yoshiuchi, K., & Smyth, J. M. (2019). Potential benefits of integrating ecological momentary assessment data into mHealth care systems. *Biopsychosocial Medicine, 13*, 19. doi:10.1186/s13030-019-0160-5

Kircanski, K., Thompson, R. J., Sorenson, J., Sherdell, L., & Gotlib, I. H. (2018). The everyday dynamics of rumination and worry: precipitant events and affective

consequences. *Cognition & emotion, 32*(7), 1424-1436. doi:10.1080/02699931.2017.1278679

Klatzkin, R. R., Bunevicius, A., Forneris, C. A., & Girdler, S. (2014). Menstrual mood disorders are associated with blunted sympathetic reactivity to stress. *Journal of psychosomatic research, 76*(1), 46-55.

Klatzkin, R. R., Lindgren, M. E., Forneris, C. A., & Girdler, S. S. (2010). Histories of major depression and premenstrual dysphoric disorder: Evidence for phenotypic differences. *Biological psychiatry, 84*(2), 235-247. doi:10.1016/j.biopsycho.2010.01.018

Kleinstauber, M., Schmelzer, K., Ditzen, B., Andersson, G., Hiller, W., & Weise, C. (2016). Psychosocial profile of women with premenstrual syndrome and healthy controls: A comparative study. *International journal of behavioral medicine, 23*(6), 752-763. doi:10.1007/s12529-016-9564-9

Kleinstauber, M., Witthoft, M., & Hiller, W. (2012). Cognitive-behavioral and pharmacological interventions for premenstrual syndrome or premenstrual dysphoric disorder: a meta-analysis. *Journal of Clinical Psychology in Medical Settings, 19*(3), 308-319. doi:10.1007/s10880-012-9299-y

Kubiak, T., & Stone, A. A. (2012). Ambulatory monitoring of biobehavioral processes in health and disease. *Psychosomatic medicine, 74*(4), 325-326. doi:10.1097/PSY.0b013e31825878da

Kudielka, B. M., Gierens, A., Hellhammer, D. H., Wüst, S., & Schlotz, W. (2012). Salivary cortisol in ambulatory assessment—some dos, some don'ts, and some open questions. *Psychosomatic medicine, 74*(4), 418-431.

Kuehner, C. (2017). Why is depression more common among women than among men? *The Lancet Psychiatry, 4*(2), 146-158.

Kuehner, C., Holzhauer, S., & Huffziger, S. (2007). Decreased cortisol response to awakening is associated with cognitive vulnerability to depression in a nonclinical sample of young adults. *Psychoneuroendocrinology, 32*(2), 199-209. doi:10.1016/j.psyneuen.2006.12.007

Kuehner, C., Huffziger, S., Witt, S. H., & Rietschel, M. (2011). PCLO rs2522833 impacts HPA system activity in healthy young adults. *Translational psychiatry, 1*, e10. doi:10.1038/tp.2011.11

Kuehner, C., Welz, A., Reinhard, I., & Alpers, G. W. (2017). Lab meets real life: A laboratory assessment of spontaneous thought and its ecological validity. *Plos one, 12*(9), e0184488.

Kues, J. N., Janda, C., Kleinstauber, M., & Weise, C. (2014). Internet-based cognitive behavioural self-help for premenstrual syndrome: study protocol for a randomised controlled trial. *Trials, 15*, 472. doi:10.1186/1745-6215-15-472

Landen, M., & Eriksson, E. (2003). How does premenstrual dysphoric disorder relate to depression and anxiety disorders? *Depression and anxiety, 17*(3), 122-129. doi:10.1002/da.10089

Lane, T., & Francis, A. (2003). Premenstrual symptomatology, locus of control, anxiety and depression in women with normal menstrual cycles. *Archives of women's mental health, 6*(2), 127-138. doi:10.1007/s00737-003-0165-7

Lanza di Scalea, T., & Pearlstein, T. (2019). Premenstrual Dysphoric Disorder. *The Medical clinics of North America, 103*(4), 613-628. doi:10.1016/j.mcna.2019.02.007

Lopez, L. M., Kaptein, A. A., & Helmerhorst, F. M. (2012). Oral contraceptives containing drospirenone for premenstrual syndrome. *The Cochrane database of systematic reviews*(2), Cd006586. doi:10.1002/14651858.CD006586.pub4

Lustyk, M. K., Gerrish, W. G., Douglas, H., Bowen, S., & Marlatt, G. A. (2011). Relationships among premenstrual symptom reports, menstrual attitudes, and mindfulness. *Mindfulness, 2*(1), 37-48. doi:10.1007/s12671-011-0041-x

Lustyk, M. K., Gerrish, W. G., Shaver, S., & Keys, S. L. (2009). Cognitive-behavioral therapy for premenstrual syndrome and premenstrual dysphoric disorder: a systematic review. *Archives of women's mental health, 12*(2), 85-96. doi:10.1007/s00737-009-0052-y

Lustyk, M. K., Olson, K. C., Gerrish, W. G., Holder, A., & Widman, L. (2010). Psychophysiological and neuroendocrine responses to laboratory stressors in women: implications of menstrual cycle phase and stressor type. *Biological psychiatry, 83*(2), 84-92. doi:10.1016/j.biopsycho.2009.11.003

Lustyk, M. K., Widman, L., Paschane, A., & Ecker, E. (2004). Stress, quality of life and physical activity in women with varying degrees of premenstrual symptomatology. *Women & health, 39*(3), 35-44. doi:10.1300/J013v39n03_03

Lydon-Staley, D. M., Kuehner, C., Zamoscik, V., Huffziger, S., Kirsch, P., & Bassett, D. S. (2019). Repetitive negative thinking in daily life and functional connectivity among default mode, fronto-parietal, and salience networks. *Translational psychiatry, 9*(1), 234. doi:10.1038/s41398-019-0560-0

Lyubomirsky, S., Layous, K., Chancellor, J., & Nelson, S. K. (2015). Thinking about rumination: the scholarly contributions and intellectual legacy of Susan Nolen-Hoeksema. *Annual review of clinical psychology, 11*, 1-22. doi:10.1146/annurev-clinpsy-032814-112733

Maguire, J. (2019). Neuroactive Steroids and GABAergic Involvement in the Neuroendocrine Dysfunction Associated With Major Depressive Disorder and Postpartum Depression. *Frontiers in cellular neuroscience, 13*, 83. doi:10.3389/fncel.2019.00083

Marjoribanks, J., Brown, J., O'Brien, P. M., & Wyatt, K. (2013). Selective serotonin reuptake inhibitors for premenstrual syndrome. *The Cochrane database of systematic reviews*(6), Cd001396. doi:10.1002/14651858.CD001396.pub3

Martinez, P. E., Rubinow, D. R., Nieman, L. K., Koziol, D. E., Morrow, A. L., Schiller, C. E., . . . Schmidt, P. J. (2016). 5alpha-Reductase Inhibition Prevents the Luteal Phase Increase in Plasma Allopregnanolone Levels and Mitigates Symptoms in Women with Premenstrual Dysphoric Disorder. *Neuropsychopharmacology, 41*(4), 1093-1102. doi:10.1038/npp.2015.246

McLaughlin, K. A., & Nolen-Hoeksema, S. (2011). Rumination as a transdiagnostic factor in depression and anxiety. *Behaviour research and therapy, 49*(3), 186-193. doi:10.1016/j.brat.2010.12.006

Michl, L. C., McLaughlin, K. A., Shepherd, K., & Nolen-Hoeksema, S. (2013). Rumination as a mechanism linking stressful life events to symptoms of depression and anxiety: longitudinal evidence in early adolescents and adults. *Journal of abnormal psychology, 122*(2), 339-352. doi:10.1037/a0031994

Miller, A., Vo, H., Huo, L., Roca, C., Schmidt, P. J., & Rubinow, D. R. (2010). Estrogen receptor alpha (ESR-1) associations with psychological traits in women with PMDD and controls. *Journal of psychiatric research, 44*(12), 788-794. doi:10.1016/j.jpsychires.2010.01.013

Moberly, N. J., & Watkins, E. R. (2008). Ruminative self-focus and negative affect: an experience sampling study. *Journal of abnormal psychology, 117*(2), 314-323. doi:10.1037/0021-843x.117.2.314

Myin-Germeys, I., Kasanova, Z., Vaessen, T., Vachon, H., Kirtley, O., Viechtbauer, W., & Reininghaus, U. (2018). Experience sampling methodology in mental

health research: new insights and technical developments. *World Psychiatry, 17*(2), 123-132. doi:10.1002/wps.20513

Nader, N., Chrousos, G. P., & Kino, T. (2010). Interactions of the circadian CLOCK system and the HPA axis. *Trends in Endocrinology & Metabolism, 21*(5), 277-286.

Namavar Jahromi, B., Pakmehr, S., & Hagh-Shenas, H. (2011). Work stress, premenstrual syndrome and dysphoric disorder: Are there any associations? *Iranian Red Crescent medical journal, 13*(3), 199-202.

Nevatte, T., O'Brien, P. M., Backstrom, T., Brown, C., Dennerstein, L., Endicott, J., . . . Yonkers, K. (2013). ISPMD consensus on the management of premenstrual disorders. *Archives of women's mental health, 16*(4), 279-291. doi:10.1007/s00737-013-0346-y

Nezlek, J. B. (2005). Distinguishing affective and non-affective reactions to daily events. *Journal of personality, 73*(6), 1539-1568. doi:10.1111/j.1467-6494.2005.00358.x

Nezlek, J. B. (2014). Multilevel modeling analyses of diary-style data. *Handbook of research methods for studying daily life*, 357-383.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of abnormal psychology, 109*(3), 504-511.

Nolen-Hoeksema, S., & Watkins, E. R. (2011). A Heuristic for Developing Transdiagnostic Models of Psychopathology: Explaining Multifinality and Divergent Trajectories. *Perspectives on psychological science : a journal of the Association for Psychological Science, 6*(6), 589-609. doi:10.1177/1745691611419672

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking Rumination. *Perspectives on psychological science: a journal of the Association for Psychological Science, 3*(5), 400-424. doi:10.1111/j.1745-6924.2008.00088.x

O'Brien, P. M. S., Bäckström, T., Brown, C., Dennerstein, L., Endicott, J., Epperson, C. N., . . . Ismail, K. M. (2011). Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: the ISPMD Montreal consensus. *Archives of women's mental health, 14*(1), 13-21.

Odber, J., Cawood, E. H., & Bancroft, J. (1998). Salivary cortisol in women with and without perimenstrual mood changes. *Journal of psychosomatic research, 45*(6), 557-568. doi:10.1016/s0022-3999(98)00061-0

Owens, S. A., & Eisenlohr-Moul, T. (2018). Suicide risk and the menstrual cycle: A review of candidate RDoC mechanisms. *Current psychiatry reports, 20*(11), 106. doi:10.1007/s11920-018-0962-3

Panahi, F., & Faramarzi, M. (2016). The effects of mindfulness-based cognitive therapy on depression and anxiety in women with premenstrual syndrome. *Depression research and treatment, 2016*, 9816481-9816481. doi:10.1155/2016/9816481

Parry, B. L., Javeed, S., Laughlin, G. A., Hauger, R., & Clopton, P. (2000). Cortisol circadian rhythms during the menstrual cycle and with sleep deprivation in premenstrual dysphoric disorder and normal control subjects. *Biological Psychiatry, 48*(9), 920-931. doi:10.1016/s0006-3223(00)00876-3

Payne, J. L., Palmer, J. T., & Joffe, H. (2009). A reproductive subtype of depression: conceptualizing models and moving toward etiology. *Harvard review of psychiatry, 17*(2), 72-86. doi:10.1080/10673220902899706

Pearlstein, T. (2010). Premenstrual dysphoric disorder: out of the appendix. *Archives of women's mental health, 13*(1), 21-23. doi:10.1007/s00737-009-0111-4

Pearlstein, T., Yonkers, K. A., Fayyad, R., & Gillespie, J. A. (2005). Pretreatment pattern of symptom expression in premenstrual dysphoric disorder. *Journal of affective disorders, 85*(3), 275-282.

Peeters, F., Nicholson, N. A., & Berkhof, J. (2003). Cortisol responses to daily events in major depressive disorder. *Psychosomatic medicine, 65*(5), 836-841. doi:10.1097/01.psy.0000088594.17747.2e

Perkonigg, A., Yonkers, K. A., Pfister, H., Lieb, R., & Wittchen, H. U. (2004). Risk factors for premenstrual dysphoric disorder in a community sample of young women: The role of traumatic events and posttraumatic stress disorder. *The Journal of clinical psychiatry, 65*(10), 1314-1322.

Petersen, N., London, E. D., Liang, L., Ghahremani, D. G., Gerards, R., Goldman, L., & Rapkin, A. J. (2016). Emotion regulation in women with premenstrual dysphoric disorder. *Archives of women's mental health, 19*(5), 891-898. doi:10.1007/s00737-016-0634-4

Pilver, C. E., Levy, B. R., Libby, D. J., & Desai, R. A. (2011). Posttraumatic stress disorder and trauma characteristics are correlates of premenstrual dysphoric disorder. *Archives of women's mental health, 14*(5), 383-393. doi:10.1007/s00737-011-0232-4

Pilver, C. E., Libby, D. J., & Hoff, R. A. (2013). Premenstrual dysphoric disorder as a correlate of suicidal ideation, plans, and attempts among a nationally representative sample. *Social psychiatry and psychiatric epidemiology, 48*(3), 437-446. doi:10.1007/s00127-012-0548-z

Powell, D. J., Liossi, C., Moss-Morris, R., & Schlotz, W. (2013). Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: A systematic review and subset meta-analysis. *Psychoneuroendocrinology, 38*(11), 2405-2422.

Raes, F., Hermans, D., Williams, J. M. G., Bijttebier, P., & Eelen, P. (2008). A “Triple W”-model of rumination on sadness: Why am I feeling sad, what’s the meaning of my sadness, and wish I could stop thinking about my sadness (but I can’t!). *Cognitive Therapy and Research, 32*(4), 526-541.

Rapkin, A. J. (2005). New treatment approaches for premenstrual disorders. *American Journal of Managed Care 11*(16 Suppl), S480-491.

Read, J. R., Perz, J., & Ussher, J. M. (2014). Ways of coping with premenstrual change: development and validation of a premenstrual coping measure. *BMC Womens Health, 14*, 1. doi:10.1186/1472-6874-14-1

Reed, G. M., First, M. B., Kogan, C. S., Hyman, S. E., Gureje, O., Gaebel, W., . . . Saxena, S. (2019). Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. *World Psychiatry, 18*(1), 3-19. doi:10.1002/wps.20611

Reuveni, I., Dan, R., Segman, R., Evron, R., Laufer, S., Goelman, G., . . . Canetti, L. (2016). Emotional regulation difficulties and premenstrual symptoms among Israeli students. *Archives of women's mental health, 19*(6), 1063-1070. doi:10.1007/s00737-016-0656-y

Robinson, R. L., & Swindle, R. W. (2000). Premenstrual symptom severity: impact on social functioning and treatment-seeking behaviors. *Journal of Women s Health & Gender-Based Medicine, 9*(7), 757-768.

Ruscio, A. M., Gentes, E. L., Jones, J. D., Hallion, L. S., Coleman, E. S., & Swendsen, J. (2015). Rumination predicts heightened responding to stressful

life events in major depressive disorder and generalized anxiety disorder. *Journal of abnormal psychology, 124*(1), 17-26. doi:10.1037/abn0000025

Russell, J. A. (1980). A circumplex model of affect. *Journal of personality and social psychology, 39*(6), 1161.

Saglam, H. Y., & Basar, F. (2019). The relationship between premenstrual syndrome and anger. *Pak J Med Sci, 35*(2), 515-520. doi:10.12669/pjms.35.2.232

Schlotz, W. (2011). Ambulatory psychoneuroendocrinology: assessing salivary cortisol and other hormones in daily life. In: Mehl, M.R., Conner, T.S. (Eds.), Handbook of Research Methods for Studying Daily Life, pp. 193–209. Guilford, New York.

Schlotz, W. (2019). Investigating associations between momentary stress and cortisol in daily life: What have we learned so far? *Psychoneuroendocrinology, 105*, 105-116. doi:10.1016/j.psyneuen.2018.11.038

Schlotz, W., Kumsta, R., Layes, I., Entringer, S., Jones, A., & Wust, S. (2008). Covariance between psychological and endocrine responses to pharmacological challenge and psychosocial stress: a question of timing. *Psychosomatic medicine, 70*(7), 787-796.

Schmalenberger, K. M., Eisenlohr-Moul, T. A., Surana, P., Rubinow, D. R., & Girdler, S. S. (2017). Predictors of premenstrual impairment among women undergoing prospective assessment for premenstrual dysphoric disorder: a cycle-level analysis. *Psychological medicine, 47*(9), 1585-1596. doi:10.1017/s0033291716003524

Sepede, G., Sarchione, F., Matarazzo, I., Di Giannantonio, M., & Salerno, R. M. (2016). Premenstrual Dysphoric Disorder Without Comorbid Psychiatric Conditions: A Systematic Review of Therapeutic Options. *Clinical Neuropharmacology, 39*(5), 241-261. doi:10.1097/wnf.0000000000000173

Shah, N. R., Jones, J. B., Aperi, J., Shemtov, R., Karne, A., & Borenstein, J. (2008). Selective serotonin reuptake inhibitors for premenstrual syndrome and premenstrual dysphoric disorder: a meta-analysis. *Obstetrics & Gynecology, 111*(5), 1175-1182. doi:10.1097/AOG.0b013e31816fd73b

Sigmon, S. T., Schartel, J. G., Hermann, B. A., Cassel, A. G., & Thorpe, G. L. (2009). The relationship between premenstrual distress and anxiety sensitivity: the mediating role of rumination. *Journal of Rational-Emotive & Cognitive-Behavior Therapy, 27*(3), 188-200.

Smyth, J. M., Sliwinski, M. J., Zawadzki, M. J., Scott, S. B., Conroy, D. E., Lanza, S. T., . . . Stoney, C. M. (2018). Everyday stress response targets in the science of behavior change. *Behaviour research and therapy, 101*, 20-29.

Smyth, J. M., Zawadzki, M. J., Juth, V., & Sciamanna, C. N. (2017). Global life satisfaction predicts ambulatory affect, stress, and cortisol in daily life in working adults. *Journal of Behavioral Medicine, 40*(2), 320-331. doi:10.1007/s10865-016-9790-2

Spielberger, C., Gorsuch, R. L., & Lushene, R. (1970). Manual for the State-Trait Anxiety Inventory. *Palo Alto, CA: Consulting Psychologists Press.*

Stalder, T., Kirschbaum, C., Kudielka, B. M., Adam, E. K., Pruessner, J. C., Wust, S., . . . Clow, A. (2016). Assessment of the cortisol awakening response: Expert consensus guidelines. *Psychoneuroendocrinology, 63*, 414-432. doi:10.1016/j.psyneuen.2015.10.010

Steiner, M., Macdougall, M., & Brown, E. (2003). The premenstrual symptoms screening tool (PSST) for clinicians. *Archives of women's mental health, 6*(3), 203-209. doi:10.1007/s00737-003-0018-4

Struijs, S. Y., Lamers, F., Spinhoven, P., van der Does, W., & Penninx, B. (2018). The predictive specificity of psychological vulnerability markers for the course of affective disorders. *Journal of psychiatric research, 103*, 10-17. doi:10.1016/j.jpsychires.2018.04.017

Tak, L. M., Cleare, A. J., Ormel, J., Manoharan, A., Kok, I. C., Wessely, S., & Rosmalen, J. G. (2011). Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. *Biological psychology, 87*(2), 183-194.

Timby, E., Backstrom, T., Nyberg, S., Stenlund, H., Wihlback, A. N., & Bixo, M. (2016). Women with premenstrual dysphoric disorder have altered sensitivity to allopregnanolone over the menstrual cycle compared to controls-a pilot study. *Psychopharmacology (Berl), 233*(11), 2109-2117. doi:10.1007/s00213-016-4258-1

Timm, C., Rachota-Ubl, B., Beddig, T., Zamoscik, V. E., Ebner-Priemer, U., Reinhard, I., . . . Kuehner, C. (2018). Mindfulness-based attention training improves cognitive and affective processes in daily life in remitted patients with recurrent depression: A randomized controlled trial. *Psychotherapy and psychosomatics, 87*(3), 184-186. doi:10.1159/000488862

Timm, C., Ubl, B., Zamoscik, V., Ebner-Priemer, U., Reinhard, I., Huffziger, S., . . . Kuehner, C. (2017). Cognitive and affective trait and state factors influencing the long-term symptom course in remitted depressed patients. *Plos one, 12*(6), e0178759. doi:10.1371/journal.pone.0178759

Trull, T. J., & Ebner-Priemer, U. (2013). Ambulatory assessment. *Annual review of clinical psychology, 9*, 151-176. doi:10.1146/annurev-clinpsy-050212-185510

Trull, T. J., & Ebner-Priemer, U. (2014). The Role of Ambulatory Assessment in Psychological Science. *Current Directions in Psychological Science, 23*(6), 466-470. doi:10.1177/0963721414550706

Tschudin, S., Bertea, P. C., & Zemp, E. (2010). Prevalence and predictors of premenstrual syndrome and premenstrual dysphoric disorder in a population-based sample. *Archives of women's mental health, 13*(6), 485-494. doi:10.1007/s00737-010-0165-3

Ussher, J. M., Hunter, M. S., & Browne, S. J. (2000). Representations of femininity in narrative accounts of PMS. *Culture in psychology. Philadelphia, PA: Routledge*, 87-99.

Ussher, J. M., & Perz, J. (2013). PMS as a process of negotiation: women's experience and management of premenstrual distress. *Psychology & Health, 28*(8), 909-927. doi:10.1080/08870446.2013.765004

Ussher, J. M., & Perz, J. (2017). Evaluation of the relative efficacy of a couple cognitive-behaviour therapy (CBT) for Premenstrual Disorders (PMDs), in comparison to one-to-one CBT and a wait list control: A randomized controlled trial. *Plos one, 12*(4), e0175068. doi:10.1371/journal.pone.0175068

Vaessen, T., Kasanova, Z., Hernaus, D., Lataster, J., Collip, D., van Nierop, M., & Myin-Germeys, I. (2018). Overall cortisol, diurnal slope, and stress reactivity in psychosis: An experience sampling approach. *Psychoneuroendocrinology, 96*, 61-68. doi:10.1016/j.psyneuen.2018.06.007

van der Stouwe, E. C. D., Groenewold, N. A., Bos, E. H., de Jonge, P., Wichers, M., & Booij, S. H. (2019). How to assess negative affective reactivity to daily life stress in depressed and nondepressed individuals? *Psychiatry research*. doi:10.1016/j.psychres.2019.03.040

van Os, J., Verhagen, S., Marsman, A., Peeters, F., Bak, M., Marcelis, M., . . . Delespaul, P. (2017). The experience sampling method as an mHealth tool to

support self-monitoring, self-insight, and personalized health care in clinical practice. *Depression and anxiety, 34*(6), 481-493. doi:10.1002/da.22647

Walz, L. C., Nauta, M. H., & Aan Het Rot, M. (2014). Experience sampling and ecological momentary assessment for studying the daily lives of patients with anxiety disorders: a systematic review. *Journal of Anxiety Disorders, 28*(8), 925-937. doi:10.1016/j.janxdis.2014.09.022

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology, 54*(6), 1063-1070.

Weise, C., Kaiser, G., Janda, C., Kues, J. N., Andersson, G., Strahler, J., & Kleinstauber, M. (2019). Internet-Based Cognitive-Behavioural Intervention for Women with Premenstrual Dysphoric Disorder: A Randomized Controlled Trial. *Psychotherapy and psychosomatics, 88*(1), 16-29. doi:10.1159/000496237

Welz, A., Huffziger, S., Reinhard, I., Alpers, G. W., Ebner-Priemer, U., & Kuehner, C. (2016). Anxiety and rumination moderate menstrual cycle effects on mood in daily life. *Women & health, 56*(5), 540-560.

Welz, A., Reinhard, I., Alpers, G. W., & Kuehner, C. (2018). Happy thoughts: Mind wandering affects mood in daily life. *Mindfulness, 9*(1), 332-343.

Wenzel, M., Kubiak, T., & Ebner-Priemer, U. W. (2016). Ambulatory assessment as a means of longitudinal phenotypes characterization in psychiatric disorders. *Journal of Neuroscience Research, 102*, 13-21.

Wichers, M. (2014). The dynamic nature of depression: a new micro-level perspective of mental disorder that meets current challenges. *Psychological medicine, 44*(7), 1349-1360.

Wichers, M., Geschwind, N., Jacobs, N., Kenis, G., Peeters, F., Derom, C., . . . van Os, J. (2009). Transition from stress sensitivity to a depressive state: longitudinal twin study. *The British journal of psychiatry: the journal of mental science, 195*(6), 498-503. doi:10.1192/bjp.bp.108.056853

Wichers, M., Peeters, F., Geschwind, N., Jacobs, N., Simons, C. J., Derom, C., . . . van Os, J. (2010). Unveiling patterns of affective responses in daily life may improve outcome prediction in depression: a momentary assessment study. *Journal of affective disorders, 124*(1-2), 191-195.

Wittchen, H. U., Becker, E., Lieb, R., & Krause, P. (2002). Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. *Psychological medicine, 32*(1), 119-132.

Wittchen, H. U., Perkonigg, A., & Pfister, H. (2003). Trauma and PTSD - an overlooked pathogenic pathway for premenstrual dysphoric disorder? *Archives of women's mental health, 6*(4), 293-297. doi:10.1007/s00737-003-0028-2

Wittchen, H. U., Wunderlich, U., Gruschwitz, S., & Zaudig, M. (1997). SCID: Structured Clinical Interview for DSM-IV Axis I Disorders. *Göttingen: Hogrefe*.

Wolfram, M., Bellingrath, S., & Kudielka, B. M. (2011). The cortisol awakening response (CAR) across the female menstrual cycle. *Psychoneuroendocrinology, 36*(6), 905-912.

World Health Organization (2018). ICD-11 for mortality and morbidity statistics (ICD-11 MMS) 2018 version. Available at: http://www.who.int/classifications/icd/en/. Accessed January 27, 2020.

Yen, J. Y., Wang, P. W., Su, C. H., Liu, T. L., Long, C. Y., & Ko, C. H. (2018). Estrogen levels, emotion regulation, and emotional symptoms of women with premenstrual dysphoric disorder: The moderating effect of estrogen receptor

1alpha polymorphism. *Progress in neuro-psychopharmacology & biological psychiatry, 82*, 216-223. doi:10.1016/j.pnpbp.2017.11.013

Yonkers, K. A., O'Brien, P. M., & Eriksson, E. (2008). Premenstrual syndrome. *Lancet, 371*(9619), 1200-1210. doi:10.1016/s0140-6736(08)60527-9

Yonkers, K. A., & Simoni, M. K. (2018). Premenstrual disorders. *American Journal of Obstetrics & Gynecology, 218*(1), 68-74. doi:10.1016/j.ajog.2017.05.045

Zoccola, P. M., & Dickerson, S. S. (2012). Assessing the relationship between rumination and cortisol: A review. *Journal of psychosomatic research, 73*(1), 1-9.

Zorn, J. V., Schur, R. R., Boks, M. P., Kahn, R. S., Joels, M., & Vinkers, C. H. (2017). Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology, 77*, 25-36.

8 CURRICULUM VITAE

PERSONALIEN

Name und Vorname:	Theresa Josefine Beddig
Geburtsdatum:	29.12.1988
Geburtsort:	Wiesbaden
Familienstand:	Ledig

WERDEGANG

2005 – 2008	Martin-Niemöller-Schule, Wiesbaden
13.06.2008	Abitur
10/2008-08/2011	Bachelor of Science Psychologie Westfälische-Wilhelmsuniversität Münster
25.08.2011	Bachelor of Science
10/2011 – 09/2013	Master of Science Psychologie, Schwerpunkt: Klinische Psychologie und experimentelle Psychopathologie Masterarbeit: „Subgruppen der Krankheitsangst“ Westfälische-Wilhelmsuniversität Münster
05.09.2013	Master of Science
01/2014-04/2019	Weiterbildung zur Psychologischen Psychotherapeutin (Schwerpunkt Verhaltenstherapie) am Ausbildungsinstitut IVT-Kurpfalz

01/2016-10/2019	Wissenschaftliche Mitarbeiterin in der Klinik für Psychiatrie und Psychotherapie, AG Verlaufs- und Interventionsforschung, Zentralinstitut für Seelische Gesundheit, Mannheim (Leitung: apl. Prof. Dr. Christine Kühner)
Seit 01/2016	Doktorandin, Medizinische Fakultät Mannheim, Ruprecht-Karls-Universität Heidelberg

9 PUBLICATIONS

Beddig, T., Kuehner, C., 2017. [Current aspects of premenstrual dysphoric disorder-a review]. *Psychotherapie Psychosomatik Medizinische Psychologie* 67, 504-513.

Beddig, T., Reinhard, I., Kuehner, C., 2019. Stress, mood, and cortisol during daily life in women with Premenstrual Dysphoric Disorder (PMDD). *Psychoneuroendocrinology*, 104372. DOI: 10.1016/j.psyneuen.2019.104372. Epub 2019 Jul 23.

Beddig, T. & Kuehner, C. (2020). Ambulatory Assessment of characteristics predict the clinical course of premenstrual dysphoric disorder. *Psychotherapy and Psychosomatics*, 1-2. DOI: 10.1159/000505999 [Epub ahead of print].

Beddig, T., Timm, C., Ubl-Rachota, B., Zamoscik, V., Ebner-Priemer, U., Reinhard, I., Kirsch, P., & Kuehner, C. (2020). Mindfulness-based focused attention training versus progressive muscle relaxation in remitted depressed patients: Effects on salivary cortisol and associations with subjective improvements in daily life. *Psychoneuroendocrinology*, 113, 104555.
DOI: 10.1016/j.psyneuen.2019.104555. [Epub ahead of print].

Beddig, T., Reinhard, I., Ebner-Priemer, U., and Kuehner, C. (under 2nd review). Reciprocal effects between cognitive and affective processes in women with Premenstrual Dysphoric Disorder: An Ambulatory Assessment Study.
DOI: 10.1055/s-0043-113816. Epub 2017 Aug 4

Timm, C., Rachota-Ubl, B., Beddig, T., Zamoscik, V., Ebner-Priemer, U., Reinhard, I., Kirsch, P., & Kühner, C. (2018). Mindfulness-Based Attention Training improves cognitive and affective processes in daily life in remitted patients with recurrent depression: A Randomized Controlled Trail. *Psychotherapy and Psychosomatics*, 87(3), 184–186. DOI: 10.1159/000488862. Epub 2018 May 16.

10 DANKSAGUNG

Mein herzlichster Dank gilt an allererster Stelle meiner Doktormutter Frau Prof. Dr. Christine Kühner, die mir die Möglichkeit gegeben hat, in einem äußerst spannenden und vielseitigen Projekt, mitarbeiten und promovieren zu dürfen. Im Besonderen möchte ich mich für ihr außergewöhnliches Engagement, ihre umfassende Betreuung, kompetente fachliche Unterstützung und lange Begleitung sowie die bereit gestellte Möglichkeit an einer Vielzahl von Kongressen und Fortbildungen teilzunehmen, bedanken. Vielen Dank für die gute, produktive Zusammenarbeit die letzten Jahre!

Ebenso möchte ich mich bei Frau Dipl. Math. Iris Reinhard für die vielen hilfreichen statistischen Anregungen in der Planung und Auswertung der Studie und die stets nette Unterstützung bedanken.

Dann danke ich insbesondere meiner Kollegin Dr. Christina Timm für die schöne gemeinsame Promotionszeit und Isabelle Schricker, die mich in den Monaten begleitete. Bei Frau Sabine Meidner bedanke ich mich für die Hilfe bei den Speichelproben, deren Lagerung und Versand. Weiterhin möchte ich mich bei allen studentischen Hilfskräften des Projektes bedanken: Clara Brossmann, Sibel Nayman, Desiree Gehl und Anna Carle. Ohne ihre Mitarbeit hätten all die Untersuchungen nicht erfolgreich durchgeführt werden können.

Selbstverständlich gilt mein Dank allen Probandinnen, die bei der aufwändigen Studie mitgemacht haben. Ohne Ihre Bereitschaft, ihren Alltag zu tracken und bis zu 88 Cortisolproben abzugeben, wäre unser wissenschaftliches Projekt nicht möglich gewesen.

Mein ganz besonderer Dank gilt auch allen in meinem privaten Umfeld, die mich in der Promotionszeit untersützt haben. Allen voran meiner Freundin Iris, die mich immer motivierte, Tanja die mich in dem Promotionsvorhaben bestärkte, meinen Mitbewohnern Falk und Marcel, die mich durch die vergangen Jahre in Mannheim intensiv begleitet haben, meinen Eltern, die mir in den letzten Jahren immer wieder einen unglaublichen Rückhalt geschenkt haben und zu guter Letzt danke ich Philipp, der besonders in der letzten Phase der Promotion intensiv für mich da gewesen ist und es immer wieder schaffte, mich zu motivieren, mir den Rücken zu stärken und mich aufzufangen.