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Menstrual cycle-dependent psychological and psychoendocrinological processes, and effects of induced attention foci during daily life 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
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Kamp-Lintfort, Deutschland
2024

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PREFACE

This thesis is a compilation of five research articles, four of which have been published and one of which is in press. The publications presented in Chapter II and V are based on data of the first funding phase of a project on menstrual-cycle-related variations of mood, rumination and cortisol in daily life in women with and without Premenstrual Dysphoric Disorder (PMDD), which was funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, KU1464 6-1 Kuehner). The publications presented in Chapter III, IV, and V are based on the second funding phase of the DFG KU1464 6 project (Deutsche Forschungsgemeinschaft, DFG, KU1464 6-3 Kuehner).

An adapted version of Chapter II has been published as:

Nayman, S., Beddig, T., Reinhard, I., & Kuehner, C. (2023). Effects of cognitive emotion regulation strategies on mood and cortisol in daily life in women with premen-strual dysphoric disorder. Psychological Medicine, 53(11), 5342–5352. https://doi.org/10.1017/S0033291722002495

An adapted version of Chapter III has been published as:

Nayman, S., Schricker, I. F., Reinhard, I., Dreer, J. K., Richter, A. S., & Kuehner, C. (2024). State and trait cognitions differentially affect cyclicity of mood and cortisol in individuals with and without Premenstrual Dysphoric Disorder. *Journal of Psychopathology and Clinical Science, 133*(4), 309–320. https://doi.org/10.1037/abn0000894

An adapted version of Chapter IV has been published as:

Nayman, S., Schricker, I. F., Reinhard, I., Grammatikos, I., & Kuehner, C. (in press). Induced Rumination and Mindful Self-focus in Daily Life across the Menstrual Cycle in Women with and without Premenstrual Dysphoric Disorder. *Behaviour Research and Therapy*. https://doi.org/10.1016/j.brat.2024.104630

An adapted version of Chapter V has been published as:

Nayman, S., Konstantinow, D. T., Schricker, I. F., Reinhard, I., & Kuehner, C. (2023). Associations of premenstrual symptoms with daily rumination and perceived stress and the moderating effects of mindfulness facets on symptom cyclicity in Premenstrual Syndrome. *Archives of Women's Mental Health, 26*(2), 167-176. https://doi.org/10.1007/s00737-023-01304-5

An adapted version of Chapter VI has been published as:

Nayman, S., Schricker, I. F., Reinhard, I., & Kuehner, C. (2023). Childhood adversity predicts stronger premenstrual mood worsening, stress appraisal and cortisol decrease in women with Premenstrual Dysphoric Disorder. *Frontiers in Endocrinology*, *14*, Article 1278531, 1-10. https://doi.org/10.3389/fendo.2023.1278531

Table 1

Overview of the doctoral candidate's personal contributions in percentages

	Chapter				
	II	**III**	**IV**	**V**	**VI**
Conception (%)	80	80	80	80	80
Literature research (%)	100	100	100	100	100
Ethics approval (%)	-	-	-	-	-
Animal research proposal (%)	-	-	-	-	-
Data collection (%)	20	90	90	-	90
Data analysis (%)	90	100	100	100	90
Interpretation of results (%)	90	90	90	90	90
Manuscript writing (%)	90	90	90	90	90
Revision (%)	90	90	90	90	90
Figures / Tables	Table 2.1-2.3 Figure 2.1-2.2	Table 3.1-3.3 Table S1 Figure 3.1-3.2	Table 4.1-4.4 Figure 4.1-4.2	Table 5.1-5.3 Figure 5.1-5.3	Table 6.1-6.4 Figure 6.1

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ABBREVIATIONS

AA	Ambulatory Assessment
ACOG	American College of Obstetricians and Gynecologists
ACTH	Adrenocorticotropic Hormone
AFAB	Assigned Female at Birth
ALLO	Allopregnanolone
APA	American Psychiatric Association
BDI-II	Beck Depression Inventory-II
BMI	Body Mass Index
B-S	Between-Subject
CAR	Cortisol Awakening Response
CBI	Cognitive Behavioural Interventions
CBT	Cognitive Behavioural Therapy
CRH	Corticotropin-Releasing Hormone
CTQ	Childhood Trauma Questionnaire
DBT	Dialectical Behaviour Therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
E2	Estradiol
EMI	Ecological Momentary Intervention
ER	Emotion Regulation
ERQ	Emotion Regulation Questionnaire
ERQ.R	Emotion Regulation Questionnaire_Reappraisal Subscale
ESR1	Estrogen Receptor-1
ESR2	Estrogen Receptor-2
GABA	Gamma-Aminobutyric Acid
GnRH	Gonadotropin-Releasing Hormone
HC	Healthy Controls
HFERST	Heidelberg Form of Emotion Regulation Strategies
HFRST_A	Heidelberg Form of Emotion Regulation Strategies_Acceptance Subscale
HPA	Hypothalamic-Pituitary-Adrenal Axis
HPG	Hypothalamic-Pituitary-Gonadal Axis
ICC	Intraclass Correlation Coefficient
ICD-11	International Classification of Diseases 11th Revision
ISPMD	International Society for Premenstrual Disorders
JITAI	Just-in-Time Adaptive Intervention
MAAS	Mindfulness Attention Awareness Scale
MLM	Multilevel Models
NA	Negative Affect
NEO-FFI	NEO Five Factor Inventory
P4	Progesterone
PA	Positive Affect
PANAS	Positive and Negative Affect Schedule

PHQ-9	Patient-Health-Questionnaire-9
PMA	Present-Moment-Awareness
PMD	Premenstrual Disorders
PMDD	Premenstrual Dysphoric Disorder
PME	Premenstrual Exacerbation
PMS	Premenstrual Syndrome
PSST	Premenstrual Symptoms Screening Tool
PTQ	Perseverative Thinking Questionnaire
PTSD	Post-Traumatic Stress Disorder
REML	Restricted Maximum Likelihood Estimation
rMDD	Remitted Major Depressive Disorder
RNT	Repetitive Negative Thinking
rPMDD	Retrospectively Diagnosed Premenstrual Dysphoric Disorder
SCID-I	Structured Clinical Interview for DSM-IV Axis I
SSRI	Selective Serotonin Reuptake Inhibitor
WHO	World Health Organization
W-S	Within-Subject

CHAPTER I: GENERAL INTRODUCTION

1.1 Premenstrual Disorders

Many women[1] of reproductive age report experiencing at least one emotional and/or physical change in the week before the menstruation onset, during the late luteal phase, which subsides after menstruation onset during the follicular phase (American College of Obstetricians and Gynecologists [ACOG], 2023). In the majority of cases, these cyclical psychological and/or somatic changes are mild and do not cause significant impairment (ACOG, 2023; Wittchen et al 2002; Yonkers et al 2008), whereas in some cases, these premenstrual changes can reach a severity causing functional impairment and/or distress. According to the International Society for Premenstrual Disorders (ISPMD; Ismaili et al., 2016), Premenstrual Disorders (PMDs) can be divided into two main categories, including 1) core PMDs with the functionally impairing Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD), and 2) variants of PMDs, such as Premenstrual Exacerbations (PMEs) of ongoing mental or somatic disorders (Handy et al., 2022; Kuehner & Nayman, 2021). Premenstrual symptoms can develop at any time from menarche and persist throughout the female reproductive years until the menopause. They can transiently remit during pregnancy or anovulatory cycles and resolve completely after menopause (Yonkers & Simoni, 2018). PMS affects approximately 20-30% of women of reproductive age and is characterised by mild to moderate psychological and/or physical symptoms (ACOG, 2023; Yonkers and Simoni, 2018). PMS does not have a unique definition that specifies distinct characteristics or a minimum number of required symptoms, which in turn leads to broad definitions comprising a wide array of milder physical, emotional, behavioural, and/or cognitive symptoms during the luteal phase (Yonkers and Simoni, 2018). ACOG (2014) defines PMS as a condition marked by at least one symptom that causes occupational, social, or interpersonal dysfunction during the late luteal phase for at least three consecutive menstrual cycles and resolves shortly after the onset of menstruation in the follicular phase.

PMDD can be considered to be the most severe manifestations of the core premenstrual disorders, affecting approximately 1.8-5.8% of women of reproductive age (12-

[1] In this thesis, the term "woman" is used to refer to individuals who are assigned female at birth (AFAB)

month prevalence; American Psychiatric Association [APA], 2013). PMDD has been recognised as a diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the International Classification of Diseases (ICD-11), and is listed in the chapter "Depressive Disorders" in the DSM-5 (but coded as a gynaecological disorder; APA, 2016) and in the chapter "Diseases of the Female Genital System" in the ICD-11 (with a cross-reference in the chapter of Depressive Disorders; World Health Organization [WHO], 2019). Compared to PMS, PMDD is distinguished by a recurrent predominance of affective symptoms.
This thesis will particularly focus on PMDD and its cognitive and endocrinological risk factors.

1.2 Diagnostic Criteria for Premenstrual Dysphoric Disorder in DSM-5 and ICD-11

For a PMDD diagnosis, DSM-5 requires a cyclical on-off-pattern in at least one of the four affective core symptoms (i.e. marked mood swings, irritability/anger, depressed mood or anxiety/tension) with additional psychological and/or somatic symptoms (i.e. decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite, hypersomnia or insomnia, feeling overwhelmed / out of control, and physical symptoms) to reach a total of at least five cyclical symptoms. These symptoms occur during the luteal phase, particularly during the final week before menstruation onset, in the late luteal phase and subside within a week following menstruation onset during the follicular phase (APA, 2013). This cyclical PMDD symptom pattern must be confirmed by prospective daily ratings over at least two symptomatic cycles (APA, 2013). Although more liberally worded, the ICD-11 also recommends the prospectively confirmed occurrence ("[…] *should ideally be confirmed* […]" (WHO, 2019) of at least one core affective symptom and additional somatic or cognitive symptom(s) over at least two symptomatic cycles, but does not specify a minimum total number of symptoms required for a PMDD diagnosis.
The lack of specification of a minimum number of required symptoms in ICD-11 may contribute to overdiagnoses of PMDD, but it may also open up the possibility of considering subthreshold cases of PMDD with clinical distress. Women who do not meet the required minimum number of five DSM-5 criteria for PMDD may still experience clinical distress or functional impairment in daily life (Yonkers and Simoni 2018). The DSM's five-symptom threshold was chosen to prevent a medicalisation of the menstrual cycle and overdiagnosing healthy women (Epperson et al., 2012). However, this

threshold may fail to identify clinically affected women with premenstrual symptoms (Kadian and O'Brian 2012). In this context, Halbreich et al. (2003) showed that 13-18% of women with PMS appear to have symptoms of sufficient severity to warrant clinical treatment, despite not meeting the number of symptoms required for a PMDD diagnosis. Relatedly, the optimal threshold for predicting cyclical functional impairment has been shown and proposed to be four symptoms (Hartlage et al., 2012; Schmalenberger et al., 2017) rather than the five symptoms stipulated by the DSM-5 (APA, 2013).

In both, DSM-5 and ICD-11, a PMDD diagnosis requires that the cyclical symptoms have been experienced during the majority of menstrual cycles in the previous year, and are not merely an exacerbation of another ongoing disorder (APA, 2013; WHO, 2019). PMDD symptoms have to be severe enough to cause marked clinical distress or functional impairment in educational or occupational activities, social activities or relationships to others (APA, 2013; WHO, 2019), with a burden comparable to other chronic mental disorders such as moderate or severe depression (Halbreich et al., 2003). Relatedly, the condition has been shown to lead to impairments in work productivity, absenteeism and increased use of health services, resulting in heightening societal costs (Tiranini & Nappi, 2022). Moreover, women with PMDD show an increased risk for suicidality, including suicidal ideation, plans and attempts, independent of psychiatric comorbidities (Eisenlohr-Moul et al., 2022; Osborn et al., 2021; Yan et al., 2021). PMDD is highly comorbid with other mental disorders, including mood and anxiety disorders, and appears to be associated with postpartum and perimenopausal depression (Kuehner et al., 2017; Mattina & Steiner, 2020; Pereira et al., 2021).

The representation of PMDD in the chapters of Depressive and Gynaecological Disorders of the DSM-5 (APA, 2013) and ICD-11 (WHO, 2019) may reflect the multifactorial approach involving a complex interaction of biological (e.g. genetic, neuroendocrinological), social and psychological factors that contribute to the development and maintenance of PMDD (Eisenlohr-Moul 2019; Hantsoo & Payne, 2023; Schweizer-Schubert et al. 2021).

1.3 Biological Risk Factors of Premenstrual Dysphoric Disorder

Genetics: Family and twin studies estimate a genetic predisposition of 35.1% to 56% to premenstrual symptoms (Hantsoo & Payne 2023). However, the majority of these studies used retrospective self-reports rather than prospective monitoring of premenstrual symptoms, which may have contributed to diagnostic bias and thus prevents

conclusions about whether there is a genetic aetiology for premenstrual symptoms (Hantsoo & Payne 2023). Candidate gene studies have identified preliminary evidence for genetic variation in the estrogen receptor-1 (ESR1) and the ESR2 genes as well as in the serotonergic 5-hydroxytryptamine transporter 1A gene (Hantsoo & Payne, 2023), with both positive and negative findings (McEvoy et al. 2017). Another association of PMDD was found with altered function of the ESC/Z complex, an ovarian steroid-regulated gene silencing complex (Dubey et al., 2017). Finally, women with PMDD who were carriers of the Met allele of the Val66Met polymorphism in the brain derived neurotrophic factor gene showed reduced activation of the fronto-cingulate cortex in response to an emotional processing task during the luteal phase compared to healthy controls (Comasco et al., 2014). Further studies are needed to improve our understanding of the genetic contribution to the pathophysiology of PMDD.

Ovarian steroids. The close temporal link between the menstrual cycle and PMDD symptomatology points to the involvement of the ovarian steroids *progesterone* and *estradiol* in the development and maintenance of PMDD. Typical fluctuations in these ovarian steroids follow a predictable temporal pattern over the menstrual cycle in women of reproductive age (Schmalenberger et al., 2021). After the onset of menarche, levels of the ovarian steroids progesterone and estradiol fluctuate systematically and consistently over the menstrual cycle, as shown in Figure 1.1. A typical menstrual cycle spans approximately 28 days, with cycle lengths between 21 and 37 days considered healthy (Schmalenberger et al 2021). The onset of menstruation marks the beginning of the cycle and initiates the follicular phase, which lasts until ovulation. Throughout the follicular phase, progesterone levels are constantly low, while estradiol levels gradually increase from the mid-follicular phase, peaking before ovulation and declining rapidly after ovulation. Ovulation occurs approximately 14 days before the next menses and signals the start of the luteal phase, which lasts until the day before the next menses. Both estradiol and progesterone increase during the early luteal phase, peak during the mid-luteal phase and then decline rapidly before the next menses, especially during late luteal phase (Schmalenberger et al 2021).

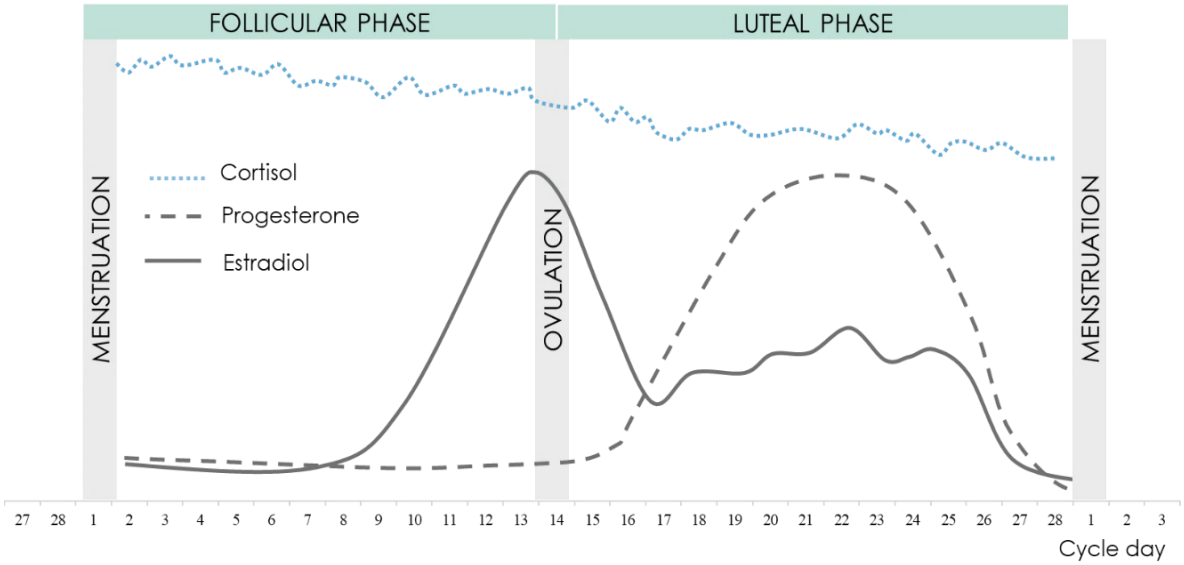

Figure 1.1 Temporal variations of progesterone, estradiol and basal cortisol activity over the menstrual cycle.

Note. This figure is adapted from Hamidovic et al., 2020 and Schmalenberger et al., 2021

Progesterone and estradiol receptors are widespread in cortico-limbic brain regions, including the amygdala, hippocampus, thalamus, hypothalamus and prefrontal cortex, and are implicated in psychiatric disorders (Comasco & Sundström-Poromaa, 2015; Dubol et al., 2021). They further exert an influence on glutamergic, GABA-(Gamma-Aminobutyric Acid) ergic, dopaminergic and serotonergic systems, thereby modulating emotional and cognitive processes as well as mental health in women of reproductive age (Comasco & Sundström-Poromaa, 2015; Dubol et al., 2021). Contrary to initial expectations in PMDD research, affected women with PMDD exhibit normative concentrations of serum progesterone and estradiol across the menstrual cycle (e.g. Schweizer-Schubert et al 2021; Sikes-Keilp and Rubinow 2023). Instead, experimental studies demonstrated that PMDD symptoms result from a hypersensitivity of the central nervous system towards these normative cycle-related fluctuations in progesterone and estradiol and their neuroactive metabolites, in particular the progestorene-derived allopregnanolone (ALLO) (Schmidt et al., 1998). ALLO fluctuates in concert with progesterone over the cycle with an average lag of 2-3 days (Sundström-Poromaa et al., 2020) and is a positive allosteric modulator of the GABA-A receptor, leading to sedative, calming and anxiolytic effects in healthy women (see Hantsoo & Payne, 2023; Sikes-Keilp & Rubinow, 2023). However, in women with PMDD, the GABAergic system appears to respond paradoxically to fluctuating ALLO levels during the luteal phase, possibly due to impaired $GABA_A$-R plasticity in response to ALLO fluctuations, as a mechanism contributing to increased premenstrual irritability and other premenstrual

affective core symptoms (e.g. Bäckström et al., 2014; Hantsoo & Epperson, 2020; Hantsoo & Payne, 2023).

Neurobiological sensitivity to normative ovarian steroid fluctuations may lie on a continuum, with a spectrum of no, mild, moderate and severe premenstrual symptoms (Peters et al., 2024). Neurobiological hypersensitivity may in turn interact with further neuroendocrinological processes that may be implicated in the etiology and/or maintenance of PMDD.

Cortisol activity. The Hypothalamic-Pituitary-Adrenal (HPA) axis involves a cascade of neuroendocrinological pathways to maintain physiological homeostasis in response to stress (DeMorrow, 2018). It starts with the paraventricular nucleus of the hypothalamus, which releases corticotropin-releasing hormone (CRH) in response to stress signals. CRH stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH), which then stimulates the adrenal gland to produce the stress hormone cortisol (DeMorrow, 2018). HPA axis dysfunction can manifest in changes in cortisol activity and represents a biological marker for several mental disorders, with elevated cortisol levels for example in depression with psychotic or melancholic symptoms, bipolar disorder or schizophrenia (e.g. Dziurkowska et al., 2021; Høifødt et al., 2019; Keller et al., 2017; Stetler & Miller, 2011) and reduced levels in stress-related disorders such as post-traumatic stress disorder (PTSD) (Adam et al., 2017; Ehlert et al., 2001). Premenstrual symptoms also appear to be associated with changes in cortisol activity (Hantsoo et al., 2023).

In women of reproductive age, the Hypothalamic-Pituitary-Gonadal (HPG) axis, in particular ovarian steroid fluctuations, appears to interact with the HPA axis, possibly via GABAergic transmission (Hantsoo et al., 2023; Schweizer-Schubert et al., 2021). Relatedly, two recent meta-analyses on healthy women identified menstrual-cycle-related variations in cortisol activity, with lower levels during the luteal phase compared to the follicular phase (Hamidovic et al., 2020; Klusmann et al., 2022). The decrease in cortisol activity during the luteal phase is assumed to be due to premenstrually elevated ALLO levels, which potentiate the effects of the GABAergic system, thereby inhibiting the HPA axis activity and resulting in reduced premenstrual cortisol activity in healthy women (Hamidovic et al., 2020; Klusmann et al., 2022).

In women with PMS and PMDD, the interaction between ovarian neuroactive steroids and the HPA axis may be impaired (Crowley & Girdler, 2014; Hantsoo et al., 2023; Schweizer-Schubert et al., 2021). Possibly due to inconsistent definitions of PMS, the evidence on cortisol activity in PMS is mixed (Hantsoo et al., 2023). Whereas some

studies have found no group differences in cortisol activity between women with PMS and healthy controls (Hantsoo et al., 2023), other studies showed that women with PMS exhibit higher cortisol levels during the luteal phase than during the follicular phase (Odber et al., 1998), as well as higher cortisol levels during the luteal phase when compared to healthy controls (Rasgon et al., 2000). In addition, lower evening plasma cortisol levels (Rabin et al., 1990) and attenuated cortisol awakening response (CAR; Hou et al., 2019) have been found across the cycle in women with PMS compared to healthy controls. Initial evidence from PMDD research suggests that cortisol activity may be dampened across the menstrual cycle compared to healthy controls (Beddig et al., 2019; Hantsoo et al., 2023), consistent with findings of blunted cortisol activity in other stress-related disorders such as PTSD (Adam et al., 2017; Ehlert et al., 2001; Hantsoo et al., 2023). In particular, women with PMDD have been shown to exhibit lower basal and stress-reactive cortisol activity (Girdler et al., 1998, 2001, 2003) as well as a later circadian peak in cortisol over the cycle compared to healthy controls (Parry et al., 2000). Moreover, in a more recent study, women with PMDD exhibited blunted basal cortisol activity in daily life across the menstrual cycle, with a delayed CAR peak and a flattened diurnal cortisol slope compared to healthy controls (Beddig et al., 2019). Dysregulated stress processing, particularly HPA axis hypoactivation is in turn associated with poorer mental and physical health, reflecting an endocrinological marker of stress-related disorders (e.g. Adam et al., 2017).

1.4 Social and Environmental Risk Factors of Premenstrual Dysphoric Disorder

While biological factors, including genetics, hormone sensitivity and HPA axis dysfunction in PMDD provide an explanation, distal and proximal social and psychological factors are also implicated in premenstrual symptoms. Recent research suggests that PMDD may manifest in subtypes, with both biological and psychosocial factors contributing to interpersonal variability between affected women (Hantsoo & Payne, 2023).

Childhood and lifetime adversity. Exposure to childhood adversity may be a potential distal socio-environmental risk factor contributing to premenstrual symptoms in PMS and PMDD. Childhood adversity refers to exposure to physical, sexual and emotional abuse, physical and emotional neglect as well as to growing up in a dysfunctional home environment before the age of 18 (Anda et al., 2010). Childhood adversity increases the risk of a range of deleterious mental health outcomes across the lifespan, such as impaired cognitive, social and emotional functioning with poor anger control,

increased daily negative affect, high perceived stress and increased risk of mental disorders (Anda et al., 2010; Daníelsdóttir et al., 2024; Hughes et al., 2017; Lippard & Nemeroff, 2020; Nayman, Jones et al., 2021). A recent cohort study using twin data showed that childhood adversity, including emotional and/or physical neglect or abuse, sexual abuse, rape, hate crime, and family violence, predicted clinically confirmed psychiatric disorders in adulthood, such as depressive, anxiety, substance use or stress-related disorders (Daníelsdóttir et al., 2024). Childhood adversity may not only increase the risk of developing mental disorders, but also contribute to an earlier disorder onset, a more severe clinical course and poorer treatment response (Lippard & Nemeroff, 2020).

In the context of premenstrual symptoms, cross-sectional non-clinical studies revealed that experiences of childhood adversity are associated with higher premenstrual symptoms in adulthood (Morishita et al., 2022; Younes et al., 2021). In addition, a 14-year prospective cohort study by Bertone-Johnson et al. (2014) found that exposure to emotional and physical abuse in childhood increased the risk of moderate to severe PMS in women who were initially free from PMS symptoms. Relatedly, experiences of childhood adversity or early life trauma before the age of 18 appear to be more prevalent in women with PMDD compared to healthy controls (Beddig et al., 2019) or compared to the general female population (Kulkarni et al., 2022). A cross-sectional study in turn demonstrated that the more childhood traumas reported, the higher the severity and number of premenstrual symptoms were in women with PMS and PMDD (Azoulay et al., 2020).

Women with PMDD were also found to have more lifetime experiences of sexual and physical abuse and a younger age of first abuse than healthy controls (Girdler et al., 2003). Traumatic events at any time in life have been shown to increase the likelihood of developing PMDD at follow-up in a prospective community cohort study over 42 months (Perkonigg et al., 2004). Similarly, a cross-sectional study showed that lifetime trauma and PTSD were independently linked with PMDD or with premenstrual symptoms (Pilver et al., 2011). Another study showed that the association of cyclical fluctuations in estradiol and progesterone with severe PMS and PMDD symptoms was more pronounced in women with a history of abuse (Eisenlohr-Moul et al., 2016). Thus, among affected women with clinically relevant premenstrual symptoms, reported lifetime history of abuse was linked to higher affective reactivity to cyclical fluctuations of ovarian steroids and consequently higher premenstrual symptom severity (Eisenlohr-Moul et al., 2016).

The link between childhood adversity and premenstrual symptoms may involve psychological and neurobiological mechanisms. At the psychological level, childhood adversity may increase the risk of later emotion regulation difficulties (e.g. Miu et al., 2022; Repetti et al., 2002; Zhao et al., 2022) and mediate the association between reported childhood adversity and premenstrual symptoms (Azoulay et al., 2020). In particular rumination, which appears to be elevated in women with PMDD (e.g. Eggert et al., 2016; Kappen et al., 2022) and in individuals with a history of childhood adversity regardless of clinical status (e.g. Mansueto et al., 2021), may act as a psychological mechanism by which childhood adversity contributes to higher premenstrual symptom severity in women with PMDD (as discussed in Nayman & Kuehner, in press).

Another pathway by which exposure to childhood adversity may increase the risk of later mental disorders is through the resulting neuroendocrinological changes, particularly dysfunction in the HPA axis, which may persist into adulthood (e.g. Hantsoo et al., 2023; Maj et al., 2020; Raymond et al., 2018). Childhood adversity has been shown to cause alterations in the HPA axis that manifest as elevated or blunted cortisol activity in the general population (Fogelman & Canli, 2018; Hantsoo et al., 2023). Adversity-related HPA axis dysfunction in women vulnerable to cycle-related fluctuations in ovarian steroids may in turn interact with the HPG axis, potentially contributing to the development, maintenance, and amplification of premenstrual symptoms in PMS and PMDD (cf. Eisenlohr-Moul et al., 2016; Schweizer-Schubert et al., 2021). Exposure to childhood adversity may generally lead to chronic activation of the HPA axis, resulting in increased or decreased cortisol levels and impaired negative feedback in response to elevated cortisol levels (Hantsoo et al., 2023). Previous research suggests that more severe traumatic events are associated with blunted cortisol activity, whereas less severe adverse experiences are associated with increased cortisol activity (Hantsoo et al., 2023; Hosseini-Kamkar et al., 2021).

In women with PMDD, potential adversity-related alterations in the HPA axis function remain understudied. A study with small subsamples of abused (n = 20) and non-abused (n = 8) women with PMDD found no group differences in basal or stress-reactive plasma cortisol (Girdler et al., 2003). In a further study comparing women with and without PMDD, women with a history of abuse exhibited lower plasma cortisol at rest and during stress regardless of PMDD status (Girdler et al., 2007). In these studies, the time window of exposure to abuse was not specified such that it remains unclear if these findings are specific to childhood adversity. To this end, further research with a clear distinction between childhood adversity and recent stressors is needed to explore

the unique role of unique childhood adversity in variations of cortisol activity across the cycle in PMDD. Given that there is evidence suggesting that both childhood adversity (cf. Hakamata et al., 2022) and PMDD (cf. Hantsoo et al., 2023) are associated with blunted cortisol activity, it is plausible to expect that childhood adversity amplifies PMDD-related HPA axis dysregulation and premenstrual mood deterioration.

Furthermore, childhood adversity may contribute to increased vulnerability and risk of developing psychopathology in adulthood by sensitising affective, cognitive and cortisol processes and responses to recent stress (e.g. Lippard & Nemeroff, 2020) and daily life minor-stressors (e.g. Rauschenberg et al., 2017).

Proximal stress: Not only childhood and lifetime adversity and traumas, but also recent life stressors and high daily life stress in adulthood appear to exacerbate premenstrual symptoms (e.g. Gollenberg et al., 2010; Namavar Jahromi et al., 2011). Women with PMDD have been shown to perceive more stress than healthy controls in both the follicular and luteal phase (Kappen et al., 2022; Kleinstäuber et al., 2016). In turn, women with PMDD responded to daily stressors in the luteal phase with stronger increases in momentary high-arousal negative affect compared to the follicular phase and compared to healthy controls (Beddig et al., 2019). In contrast to healthy women, women with PMDD responded to premenstrual laboratory-induced psychological and physiological stress with higher levels of self-focused attention, including rumination, anxiety sensitivity, and body vigilance, even though both groups experienced the experimental tasks as equally stressful (Craner et al., 2015). Thus, the same stressor may trigger more pronounced internal cognitive processes in women with PMDD than in healthy controls.

Not only the intensity of perceived recent stressors, but also the timing of stressors, in particular the temporal proximity, may be important. The majority of previous studies on distal and proximal stressors in PMDD have not clearly differentiated between specific windows of adversity exposure. Women with PMDD may show inter- and intra-individual heterogeneity in premenstrual symptom intensity. Interpersonally, particularly exposure to distal stressors such as childhood adversity may contribute to different subtypes of PMDD.

Lifestyle risk factors. In a prospective cohort study, a Body-Mass-Index of ≥27.5 kg/m2 at baseline was associated with an increased risk of PMS in women of reproductive age (Bertone-Johnson et al., 2010a). Similarly, a recent prospective cohort study showed that higher childhood BMI predicted a higher risk of developing a PMD (PMS, PMDD) and an early onset of PMD (onset before the age of 20 years),

independent of psychiatric comorbidities (Lu et al., 2022). It has been hypothesised that adiposity contributes to an increased risk of PMDs by increasing chronic inflammatory processes, which in turn may be associated with PMDs (Bertone-Johnson et al., 2010a; Granda et al., 2021; Lu et al., 2022). Other life-style-related risk factors for the development of PMS or PMDD include smoking (Choi & Hamidovic, 2020), in particular early onset (during adolescence or young adulthood) and high total consumption (Bertone-Johnson et al., 2008). While a systematic review and meta-analysis including cross-sectional and prospective studies demonstrated a positive moderate association between alcohol consumption and PMS (Fernández et al., 2018), a prospective cohort study showed that in particular early begin (during adolescence) and long-term consumption of alcohol minimally increased the incidence of PMS and PMDD (Bertone-Johnson et al., 2010b). A prospective case-control study found no association between caffeine intake and PMS (Purdue-Smithe et al., 2016).

1.5 Psychological Risk Factors of Premenstrual Dysphoric Disorder

1.5.1 Habitual Emotion Regulation

Emotion regulation involves processes by which individuals attempt to modify the quality, intensity, or duration of their emotional responses (Gross, 2015). Strategy-based models classify emotion regulation strategies in terms of their formal characteristics, as either adaptive (e.g. reappraisal, acceptance) or maladaptive (e.g. rumination, avoidance) (Naragon-Gainey et al., 2017), depending on their associations with mental health outcomes (Aldao et al., 2010; Schäfer et al., 2017). When used habitually, adaptive strategies have been shown to reduce physiological emotional reactivity and to be linked to favourable long-term mental and physical health outcomes and functional social interactions, whereas maladaptive strategies are associated with stronger psychopathology (McRae & Gross, 2020). Thus, transdiagnostic maladaptive emotion regulation strategies are implicated in the development and maintenance of several mental disorders such as affective and anxiety disorders, and represent potential psychotherapy targets (e.g. Aldao et al., 2010; Watkins, 2022).

In the context of PMDD, in particular habitual tendencies towards maladaptive cognitive emotion regulation strategies have been discussed (Owens and Eisenlohr-Moul 2018), with initial evidence suggesting that women with PMDD are more prone to habitual rumination (e.g. Craner et al., 2015; Eggert et al. 2016; Kappen et al. 2022) and avoidant or impulsive emotion-driven behaviours (Craner et al., 2014; Petersen et al.,

2016) compared to healthy controls. Rumination, as a form of repetitive negative thinking, is mainly considered to be a maladaptive emotion regulation strategy that involves a recurring negative thinking pattern that focuses on the causes, meanings, and consequences of negative emotional states and events (Nolen-Hoeksema et al., 2008). It is a transdiagnostic risk factor characterised by an abstract and decontextualised processing style that impairs executive control and problem-solving, and leads to negative biases in attention and interpretation of ambiguous stimuli. Consequently, rumination can contribute to vulnerability to various mental disorders (e.g. mood and anxiety disorders) as well as increased symptom severity and persistence, and higher rates of comorbidity and relapse (Watkins, 2022). Rumination is also associated with poorer treatment response to Cognitive Behavioural Therapy (CBT) in other mental disorders characterised slower remission, increased post-treatment residual symptoms, or therapy resistance (Watkins, 2022).

Dawson et al. (2018) showed that higher habitual rumination contributed to steeper increases in depressive symptoms in the late luteal phase and to slower postmenstrual symptom clearance in the follicular phase in women with at least one affective premenstrual symptom. Thus, habitual rumination may not only exacerbate premenstrual symptoms, but also contribute to difficulties in recovering from premenstrual distress to return to the postmenstrual baseline (Dawson et al., 2018). This in turn can lead to to carry-over effects of premenstrual distress into the postmenstrual follicular phase (Nayman & Kuehner, in press) and possibly prolong the distress throughout the entire cycle, thereby increasing the risk of comorbid cycle-independent disorders, such as a comorbid depressive episode (Dawson et al., 2018).

Mindfulness-based emotion regulation strategies, including present-moment-awareness and acceptance, have been shown to decrease rumination and negative affect by improving self-regulation of attention and facilitating a non-judgmental approach towards present-moment experiences (e.g. Blanke et al., 2018; Shapero et al., 2018). Similarly, as a more elaborate semantic strategy, reappraisal (i.e. reframing a situation or an emotional stimulus to change its emotional impact) appears to be associated with lower negative affect in response to emotional stimuli (e.g. Denny & Ochsner, 2014; Troy et al., 2018) and higher daily positive affect (e.g. Brockman et al., 2017). Related to premenstrual symptoms, higher levels of habitual reappraisal (Wu et al., 2016) and mindfulness (Lustyk et al., 2011) were also associated with lower premenstrual symptom severity in non-clinical samples. In addition, a small pilot study on 21 women with PMDD found beneficial effects of an eight-week mindfulness-based stress reduction

program on reduced premenstrual affective symptoms (Bluth et al., 2015), supporting the potential of mindfulness for managing PMDD symptoms.

Given that emotion regulation occurs and fluctuates in response to affect, goals, and contextual factors, an approach that takes into account that emotion regulation is also dynamic and iterative may be more precise and suitable (Aldao, 2013; Aldao et al., 2015; Bonanno & Burton, 2013; Pruessner et al., 2020). Particularly in women with PMDD, there may be cycle-phase-specific variations in the use of emotion regulation strategies, in line with the so-called strategy-situation fit hypothesis.

1.5.2 Strategy-Situation Fit Hypothesis

The use of specific emotion regulation strategies may vary in frequency and effectiveness depending on contextual demands (Aldoa et al., 2015; Wenzel et al., 2020). Different emotional contexts require different demands, favouring the use of certain emotion regulation strategies. According to the strategy-situation fit hypothesis (Bonanno & Burton, 2013; Haines et al., 2016), the flexible and context-sensitive use of emotion regulation strategies, matching contextual demands, shows the greatest mental health benefits (Blanke et al., 2020; Wenzel et al., 2021). To date, contextual factors that have been investigated include the intensity and controllability of emotions and social factors (e.g. being alone, among close others, or nonclose others; Paul et al., 2023). For example, reappraisal has been shown to be associated with greater mental health outcomes when used in the context of uncontrollable stress (e.g. Haines et al., 2016) or in moments of aloneness and less after moments of higher presence of close others (Paul et al., 2023). Conversely, difficulties in flexibly adapting strategies to specific situations may serve as a psychological marker in mental disorders. For example, patients with PTSD (Fine et al., 2021; Levy-Gigi et al., 2016) and dysfunctional eating behaviours such as purging and excessive exercise (Dougherty et al., 2020) were found to be less able to adapt their use of emotion regulation strategies to context than healthy participants.

When transferring this theory to PMDD, the cycle phase may represent the main context factor due to the cycle-related on-off-pattern of PMDD symptomatology. Thus, it is plausible to suggest that not only symptoms, but also the use of emotion regulation strategies may fluctuate across the cycle, and that effective emotion regulation may need to meet the cycle-phase-specific needs of women with PMDD. In order to study these processes across the cycle, specific methods are needed to capture cyclical

variations of affect and emotion regulation and to examine cycle-phase-specific risk and protective factors.

1.6 Daily Diaries and Ambulatory Assessment in the PMDD research

Psychological and endocrinological processes and their interactions unfold in individuals' real-time ecological contexts. Thus, to capture cycle-phase-specific temporal dynamics in affective, cognitive, and endocrinological processes across the cycle, daily life methods, in particular daily diaries and Ambulatory Assessment (AA) approaches are well suited (Bosman et al., 2016; Eisenlohr-Moul, 2019).

Daily diary approaches involve the assessment of individuals' psychological states (e.g. affective, cognitive, and behavioural) once a day over consecutive days. Participants typically report their experiences and behaviour at the end of each day using structured diaries or electronic forms. AA goes a step further by involving repeated intensive assessments of momentary experiences several times a day (e.g. eight times) over a number of consecutive days using electronic devices such as smartphones, thereby minimising recall bias. In contrast to daily diary methods, AA provides more detailed and fine-grained information about individuals' experiences and behaviours in real time with high ecological validity (Ebner-Priemer & Trull, 2009; Myin-Germeys et al., 2018). In addition to self-report measures, AA also includes passive data collection methods to assess physiological functioning, such as heart rate variability using wearables (e.g. electrocardiography) or cortisol activity using saliva samples, to examine biological markers associated with psychological states (e.g. Beddig, Timm et al., 2020; Myin-Germeys and Kuppens 2022; Reichert et al., 2021; Schick et al. 2023; Schricker et al., 2023a; Seiferth et al., 2023). Further passive data collection methods include, e.g. accelerometry and geolocation tracking (Schick et al., 2023).These approaches allow the investigation of within-person psychological and physiological processes in the real-life and real-world context in which they naturally occur (Trull & Ebner-Priemer, 2013), thereby accounting for their dynamic nature and reducing recall bias. Thus, while commonly used one-time questionnaires aim to assess habitual manifestations of psychological factors that represent individuals' general, persistent and automatic tendencies and are stable across time and situations (trait; between-person level), these daily life approaches assess states that represent momentary, temporally dynamic manifestations of psychological factors in daily life (state; within-person level). Relatedly, AA designs hold the potential to identify moments of risk for intense symptoms within an individual, and consequently, also the

potential for momentary interventions to effectively manage these symptoms. In line with the principles of precision psychiatry, which advocates personalised treatment approaches rather than one-size-fits-all interventions, this information could be helpful not only to define individually tailored treatments, but also in delivering treatments at opportune moments of need or within critical windows for early intervention in the future (cf. Reichert et al., 2021).

While observational AA designs allow to identify causal associations by analysing cross-lagged within-person couplings of, for instance, momentary cognitive states with subsequent affective states, experimental approaches remain the gold standard for addressing causality (Schmiedek & Neubauer, 2020). Respective within-subject experimental approaches in daily life would allow to combine the high internal validity typically found in laboratory studies with the high ecological validity of AA studies. However, only a few studies to date have transferred experimental designs from the laboratory to daily life using AA (e.g. Huffziger et al., 2012, 2013; Kuehner et al., 2023).

In the context of menstrual cycle and PMDD research, there are only a handful of observational studies using daily diary (e.g. Craner et al., 2016; Dawson et al., 2018) or AA methods (Beddig et al., 2019, 2020; Beddig & Kuehner, 2020), to uncover cognitive risk factors for PMDD.

Both, studies using daily diaries and AA designs in the context of PMDD, provided evidence for menstrual-cycle-related variations in self-focused attention or rumination (Beddig et al., 2020; Craner et al., 2016), highlighting that parallel to affective cyclicity, there may also be cyclicity in cognitive processes in PMDD. In particular, women with PMS and PMDD showed increased daily self-focused attention involving rumination in a prospective diary study (Craner et al., 2016), which in turn partially contributed to elevated premenstrual symptom severity (Craner et al 2016). Similarly, previous AA studies revealed increased momentary rumination, negative affect and stress appraisal as well as decreased momentary positive affect and self-acceptance during the late luteal phase compared to the follicular phase in women with PMDD, whereas no such cyclical variations were found in healthy women (Beddig et al., 2019, 2020). Similarly, an earlier AA study on a non-clinical sample found no cycle-phase-specific variations in mood characteristics, including positive valence, energetic arousal and irritability, except for calmness (Welz et al. 2016). Calmness was higher during the luteal and menstrual phases than during the follicular and ovulatory phases, which contradicts the typical temporal PMS/PMDD pattern of mood worsening during the luteal phase (Welz et al 2016). However, individual levels in habitual rumination appeared to be

associated with premenstrual mood worsening in this non-clinical sample. In particular, higher habitual rumination was linked to increased levels of premenstrual irritability, whereas lower habitual rumination was linked to higher calmness and positive mood valence towards the late luteal phase, pointing to protective effects of lower rumination against premenstrual mood worsening (Welz et al 2016). Thus, habitual rumination may also serve as a risk factor of premenstrual symptoms, potentially increasing the likelihood for the transition from non-clinical or milder PMS symptoms to full syndrome PMDD (Nayman & Kuehner, in press).

In addition, in previous AA studies by Beddig et al. (2019, 2020), women with PMDD responded to higher perceived stress or momentary negative affect with increased subsequent momentary rumination compared to healthy controls, regardless of the cycle phase, indicating that ruminative responses to stress and negative mood may be trait-like in women with PMDD (Beddig et al 2019, 2020). In contrast, higher momentary rumination predicted more pronounced increases in subsequent negative affect during the late luteal phase than during the follicular phase in women with PMDD, possibly contributing to premenstrual mood deterioration in affected women (Beddig et al., 2020). Especially in the late luteal phase, women with PMDD appear to be sensitive to dysfunctional thinking, such that momentary rumination unfolds more unfavourable consequences and triggers negative affect (Beddig et al., 2020). This in turn may maintain and exacerbate rumination. Consequently, an upward spiral between rumination and negative affect may develop, thereby contributing to elevated premenstrual symptoms in affected women. Such an upward spiral between rumination and negative affect was originally conceptualised as a transdiagnostic process within Response Styles Theory (Nolen-Hoeksema and Watkins 2011). In PMDD, this model seems to be particularly valid during the late luteal phase (Nayman & Kuehner, in press). Moreover, increased sensitivity to rumination during the luteal phase may exacerbate feelings of hopelessness and loss of control (cf. Nayman & Kuehner, in press). These experiences in turn may contribute to perceived internal entrapment and consequently, to suicidal ideation and intent as modelled in the transdiagnostic Integrated Motivational-Volitional Model of Suicidal Behaviour (O'Connor and Kirtley 2018). Thus, rumination might represent a pathway explaining the increased risk of suicidality in PMDD (Eisenlohr-Moul et al 2022; Wikman et al 2023).

With regard to cortisol activity, AA allows the investigation of the interplay between cortisol activity and psychological states in daily life throughout the cycle. In this con-

text, Beddig et al. (2019) showed that momentary rumination appeared to be decoupled from momentary cortisol activity after 20 minutes in women with PMDD, whereas healthy controls showed higher cortisol activity in response to momentary rumination, regardless of cycle phase.

Cycle-phase-specific characteristics represent potential ambulatory markers predicting the longer-term clinical course of PMDD. Relatedly, momentary negative affect, rumination, and ruminative stress-reactivity as well as low levels of positive affect and cortisol activity contributed to a worse clinical course with higher PMDD symptom intensity at a 4-month follow-up (Beddig & Kuehner, 2020). However, more research is needed on potential AA phenotypes that vary across the cycle in women with PMDD, possibly prolonging and increasing premenstrual symptoms (as discussed in Nayman & Kuehner, in press).

Furthermore, to my knowledge, there are no studies that have applied the Ambulatory Induction approach to experimentally assess causal effects of induced cognitive emotion regulation strategies on affect in daily life in women with PMDD. Two non-clinical studies involving both women and men showed that ambulatory induction of rumination led to immediate mood deterioration and increased rumination in daily life (Huffziger et al., 2012, 2013), thereby supporting the conceptualization of rumination as a transdiagnostic cognitive risk factor for mood deterioration (Watkins, 2022). In a recent ambulatory induction study of individuals with remitted Major Depressive Disorder (rMDD) and healthy controls, the clinical sample showed more pronounced increases in rumination and decreases in self-acceptance in response to rumination inductions compared to mindful self-focus inductions, pointing to heightened cognitive reactivity in rMDD (Kuehner et al., 2023). Another study on a non-clinical sample demonstrated that an induced mindful self-focus predicted increased momentary calmness (Huffziger et al., 2013), supporting the functional role of mindfulness. However, cycle-specific effects of state or induced rumination and mindfulness on affect in women with PMDD have not been investigated to date.

1.7 Treatment of Premenstrual Dysphoric Disorder

For an effective treatment of PMDD, an accurate diagnostic procedure using prospective symptom diaries over at least two symptomatic menstrual cycles is essential (ACOG 2023; APA 2013). Since there is no "universal" strategy for PMDD treatment that is equally effective for all affected women, information on the temporal course, type and severity of patients' premenstrual symptoms should be used to develop an

individualised treatment plan that involves shared decision making and includes evidence-based interventions. There are a variety of approaches with treatment targets ranging from modifying serotonin transmission to inhibiting ovulation and improving coping skills.

As of now, the recommended pharmacological interventions for PMDD are Selective Serotonin Reuptake Inhibitors (SSRIs) or Combined Oral Contraceptives (i.e. Combined Oral Contraceptives containing drospirenone + ethinyl estradiol) (ACOG, 2023; Hantsoo & Riddle, 2022). According to a Cochrane review of 31 randomised placebo-controlled trials, SSRIs showed moderate effects on relieving premenstrual symptoms in affected women (Marjoribanks et al., 2013), with moderate-quality evidence (ACOG, 2023). SSRIs can be administered continuously or intermittently during the luteal phase, either from ovulation or at the onset of symptoms (ACOG, 2023; Hantsoo & Riddle, 2022; Marjoribanks et al., 2013; Reilly et al., 2022). As an alternative, there is low-quality evidence showing that Combined Oral Contraceptives reduce overall premenstrual symptom severity and functional impairment (ACOG, 2023). Monthly injections of Gonadotropin-Releasing Hormone (GnRH) analogues, such as leuprolide acetate, with added estradiol and progesterone, may be considered for patients with severe symptoms who have been resistant to multiple treatment trials. This therapy option should be considered only as ultima ratio due to its induction of a chemical menopause, associated with multiple side-effects and long-term risks including vasomotor symptoms, elevated risk of osteoporosis, cardiovascular diseases and higher rates of memory deteriorations or dementia (ACOG, 2023; Hantsoo and Riddle, 2021; Wagner-Schuman et al., 2023). Surgical bilateral salpingo-oophorectomy with or without hysterectomy for irreversible induction of anovulation may be a final option for patients with severe premenstrual symptoms who are therapy-resistant and responsive to GnRH analogues (ACOG 2023; Hantsoo and Riddle 2021).

New pharmacological approaches under investigation and not yet approved aim to 1) inhibit progesterone receptors in the brain, 2) reduce the conversion of progesterone to its metabolite ALLO, and 3) modulate the action of ALLO on the GABAergic system (Sikes-Keilp & Rubinow 2023; Sundström-Poromaa & Comasco 2023).

CBT has also been recommended for the treatment of PMDD, particularly for premenstrual affective symptoms (ACOG, 2023; Hantsoo & Riddle, 2022). In addition, in cases of severe PMS and PMDD with an inadequate response to pharmacological treatment, a combination with CBT has been suggested as potentially beneficial (Casper and Yonkers 2023; Wagner-Schuman et al, 2023). However, to date, there are no trials to

support the incremental efficacy of combined CBT and pharmacotherapy over monotherapy. In fact, a trial comparing monotherapy using either CBT or Fluoxetine with a combination of both found no additive effects of the combination therapy (Hunter et al 2002). Moreover, no differences were found between these two treatment options in their effects on reducing premenstrual symptoms and PMDD cases, while Fluoxetine showed more rapid effects and greater efficacy on anxiety symptoms. In contrast, CBT was more effective in improving cognitive and behavioural coping, and showed higher maintenance effects than fluoxetine at one-year follow-up. The attrition rate was high with around 50% (Hunter et al 2002).

It is also worth noting that there are no manualised psychotherapeutic programs specifically for PMDD (Hantsoo & Riddle, 2021), which take the cycle phase into account in the delivery of specific interventions. Instead, psychotherapy research to date has mainly examined the effects of conventional CBT interventions, including symptom monitoring, cognitive restructuring, and stress reduction skills. Related reviews have shown that CBT reduces premenstrual affective symptoms, promotes positive behavioural change (Busse et al., 2009), and reduces functional impairment (Busse et al., 2009; Kleinstäuber et al., 2012) in women with PMDD, albeit with small to moderate effect sizes. However, the majority of studies reviewed in these meta-analyses were subject to significant methodological limitations (Busse et al., 2009; Han et al., 2019; Kleinstäuber et al., 2012). These limitations include small sample sizes, high attrition rates, the lack of randomised controlled trials or blinding, or unclear diagnostic procedures without consideration of comorbidities and no clear distinction between PMS and PMDD (Busse et al., 2009; Kleinstäuber et al., 2012). ACOG rates the evidence quality of psychotherapy for PMDD as low-to-moderate (ACOG, 2023).

Two recent randomised controlled trials demonstrated that an eight-week internet-based CBT program, including psychoeducation along with cognitive and behavioural coping strategies, significantly reduced premenstrual functional and psychological impairment as well as symptom intensity in women with PMDD in both Germany (Weise et al., 2019) and Iran (Borji-Navan et al., 2022). However, due to the multimodal design of these intervention programs, specific effects of individual intervention modules cannot be extracted, and it remains uncertain which psychotherapeutic components are most effective for severe premenstrual symptoms. Future dismantling trials are therefore needed. However, cycle-specific risk and protective factors, which may represent potential psychotherapeutic targets specifically for PMDD treatment, have not yet been fully elucidated.

1.8 Research Gaps

Significant research gaps remain, particularly regarding the role of cognitive emotion regulation and its interplay with mood and cortisol cyclicity in women with PMDD. PMDD symptomatology is characterised by affective cyclicity, but less is known about the dynamic nature of cognitive emotion regulation strategies in daily life and their within-person cycle-related effects on affect and cortisol activity. Determining if and when across the cycle specific cognitive emotion regulation strategies are most influential in women with PMDD can hold the potential to inform future PMDD-specific psychotherapeutic interventions. Given that hypersensitivity to ovarian steroid fluctuations probably exists on a continuum resulting in a spectrum of premenstrual symptom intensity (Eisenlohr-Moul, 2019), research on the role of cognitive emotion regulation in subthreshold PMDD may help to identify potential protective factors, representing targets for prevention measures. Furthermore, preliminary research suggests blunted cortisol activity in PMDD, but there is limited understanding of its cyclicity and the role of emotion regulation and early life adversity on cortisol activity across the cycle in women with and without PMDD. Most studies have not differentiated between childhood and adulthood adversity, leaving the independent impact of childhood adversity on premenstrual symptoms unclear. Stress exposure during sensitive developmental sensitive periods can cause lasting dysfunctional neuroendocrinological and affective changes (Li et al., 2022; Pervanidou et al., 2018). Thus, fine-grained research is needed to examine how childhood adversity affects cycle-related variations in affect, stress appraisal, and cortisol activity in women with PMDD, especially when accounting for recent stressful life events.

1.9 Aims and Outline of this Thesis

The present dissertation examines the temporal dynamics of affective, cognitive and endocrinological processes across the menstrual cycle in women with PMDD and explores the role of cognitive emotion regulation strategies and childhood adversity on these processes. Specifically, first, the role of habitual, momentary, and induced cognitive emotion regulation strategies on affect and cortisol across the cycle in women with PMDD are examined using multiple methods, including retrospective self-report scales (trait), ambulatory assessments (state), and ambulatory inductions (induced state) (Chapters 2, 3, 4). Second, a further aim is to examine the associations of cog-

nitive emotion regulation strategies and stress in subthreshold PMDD, which may represent a milder form of PMDD (Chapter 5). Finally, this dissertation aims to examine the association of experiences childhood adversity as an environmental risk factor on momentary affect, stress appraisal and cortisol activity across the menstrual cycle in PMDD (Chapter 6). Overall, these research questions seek to enhance our understanding of the complex interplay between cognitive, affective and endocrinological processes across the cycle and to identify (cycle-phase-specific) cognitive risk and protective as well as endocrinological mechanisms of PMDD, paving the way for more effective psychotherapeutic interventions and prevention measures for PMDD .

Study 1 (Chapter II) aimed to examine group differences in the tendency to use habitual cognitive emotion regulation strategies, including trait mindfulness, reappraisal and rumination, between women with and without PMDD, and the role of these habitual cognitive emotion regulation strategies in the cycle-related course of momentary mood and cortisol activity in women with PMDD. We expected lower levels in habitual mindfulness and reappraisal and higher levels in habitual repetitive negative thinking in women with PMDD than in healthy controls. In addition, it was hypothesised that lower habitual mindfulness and reappraisal as well as higher habitual repetitive negative thinking in women with PMDD would be associated with more pronounced premenstrual mood worsening, in particular (a) higher negative affect, (b) lower positive affect and (c) lower cortisol activity, especially in the late luteal phase, compared to women with more favourable levels cognitive emotion regulation strategies.

Study 2 (Chapter III) built on Study 1, to (1) replicate the findings on habitual cognitive emotion regulation strategies and (2) to extend previous analyses by examining the differential effects of habitual (trait) versus momentary (state) cognitive emotion regulation strategies on momentary mood and cortisol activity across the menstrual cycle in women with and without PMDD. We hypothesised that women with PMDD would exhibit affective cyclicity with higher negative affect and lower positive affect during the late-luteal phase compared to the follicular phase, whereas no such mood cyclicity would be expected for HCs. In addition, HCs were expected to exhibit cortisol cyclicity with lower cortisol levels during the late luteal phase compared to the follicular phase, whereas women with PMDD would exhibit overall lower cortisol levels throughout the cycle compared to HCs and lacking cyclicity. Regarding the cycle-related associations of habitual and momentary repetitive negative thinking and present-moment-awareness with momentary mood and cortisol, we expected to replicate the finding from Study 1 by showing that lower habitual repetitive negative thinking and higher habitual

present-moment-awareness would be associated with better mood only during the follicular phase in women with PMDD. Such cycle-phase-specific associations were not expected in HCs. In contrast, the state components of these traits, lower momentary rumination and higher momentary present-moment-awareness, were hypothesised to predict decreased subsequent negative affect and increased subsequent positive affect, especially during the late luteal phase in women with PMDD, with no cycle-specific effects in HCs. The effects of habitual and momentary repetitive negative thinking and present-moment-awareness on the cortisol activity across the cycle in women with and without were investigated exploratively.

Study 3 (Chapter IV) took this a step further and investigated the causal effects of experimental ambulatory inductions of rumination and mindful self-focus in natural daily life on momentary negative and positive affect, momentary rumination, present-moment-awareness, and self-acceptance in women with and without PMDD during the follicular and the late luteal phases. Based on the findings of Study 1 and Study 2, more pronounced differential effects of ruminative versus mindful self-focus inductions were expected in women with PMDD compared to healthy controls, especially during the late luteal phase.

Study 4 (Chapter V) focused on women with subthreshold PMDD who experienced functional impairment but did not meet the required number of PMDD criteria, and combined retrospective assessments of psychological traits with a prospective symptom diary over two menstrual cycles. The aim was to examine cycle-related variations in PMS symptoms, perceived impairment, daily rumination and perceived stress, as well as the concurrent associations of premenstrual symptoms and impairment with daily rumination and perceived stress during the late luteal phase. Finally, the associations of habitual mindfulness and acceptance with premenstrual symptoms and impairment were assessed. First, cyclical variations with higher premenstrual core, secondary, and somatic symptoms and functional impairment during the late luteal phase were expected. Second, we hypothesised that higher increases in symptom severity during the late luteal phase would be linked to higher daily rumination and perceived stress during this phase. Finally, habitual mindfulness and acceptance were hypothesised to be associated with lower premenstrual increases in symptoms and impairment towards the late luteal phase.

Study 5 (Chapter VI) aimed to examine the independent associations of self-reported experiences of childhood adversity on the cycle-specific course of mood, stress appraisal and cortisol activity in daily life, by adjusting for possible confounding effects of

recent stressful life events in women with PMDD. First, cyclical variations in momentary mood, stress appraisal and cortisol activity as well as the change in these potential variations over an interval of five months were examined. Next, the associations of childhood adversity with these micro-processes across the cycle were investigated. We expected cyclicity in mood and stress appraisal with deteriorations towards the late luteal phase and lack of cortisol activity. Childhood adversity was hypothesised to be linked to more pronounced mood worsening and increased stress appraisal during the late luteal phase. The possible impacts of childhood adversity on cortisol levels and menstrual cycle related cortisol cyclicity were assessed exploratorily.

CHAPTER II: EFFECTS OF COGNITIVE EMOTION REGULATION STRATEGIES ON MOOD AND CORTISOL IN DAILY LIFE IN WOMEN WITH PREMENSTRUAL DYSPHORIC DISORDER (STUDY 1)

An adapted version of this chapter has been published as **'**Nayman, S., Beddig, T., Reinhard, I., & Kuehner, C. (2023). Effects of cognitive emotion regulation strategies on mood and cortisol in daily life in women with premenstrual dysphoric disorder. *Psychological Medicine*, *53*(11), 5342–5352.https://doi.org/10.1017/S0033291722002495**'**

2.1 Abstract

Background. The psychological risk factors of premenstrual dysphoric disorder (PMDD) are not fully understood, but initial evidence points to a potential role of unfavorable cognitive emotion regulation (ER-) strategies. Given the symptom cyclicity of PMDD, ambulatory assessment is ideally suited to capture psychological and physiological processes across the menstrual cycle. Our study examines habitual ER-strategies in women with PMDD and their predictive value for the course of mood and basal cortisol across the cycle in affected women. **Methods**. Women with and without PMDD (*n* = 61 each) were compared regarding habitual mindfulness, reappraisal, and repetitive negative thinking (RNT). Momentary affect and cortisol output were assessed over two consecutive days per cycle phase (menstrual, follicular, ovulatory, late luteal). **Results.** Women with PMDD reported lower mindfulness, less use of reappraisal and stronger RNT than controls (*p*s < .035). In women with PMDD, higher mindfulness and reappraisal and lower RNT predicted decreased negative and increased positive affect across the menstrual cycle (*p*s < .027). However, women using more favorable ER-strategies displayed stronger mood cyclicity, resulting in stronger mood deterioration in the late luteal phase, thereby resembling women with more unfavorable ER-strategies towards the end of the cycle. Lower mindfulness predicted lower cortisol in the menstrual phase. **Conclusions.** Protective ER-strategies seem to be generally linked to better momentary mood in women with PMDD, but do not appear to protect affected women from premenstrual mood deterioration. Habitual mindfulness, in turn, seems to buffer blunted cortisol activity in women with PMDD, especially in the menstrual phase.

2.2 Introduction

Premenstrual Dysphoric Disorder (PMDD) is characterized by key affective and further psychological, behavioral and physiological symptoms, which occur during the late luteal phase of the menstrual cycle and remit within the week following menses (American Psychiatric Association (APA), 2013). PMDD affects around 5% of women of fertile age (Beddig & Kuehner, 2017; Eisenlohr-Moul, 2019) and causes clinically significant distress or functional impairment in daily life (APA, 2013) with increased risk of a chronic symptom course (Wittchen et al., 2002) and suicidality (Osborn et al., 2020). PMDD must be differentiated from the more frequent and less severe premenstrual syndrome (PMS), which is not uniformly defined and does not necessarily require affective symptoms (Hantsoo & Riddle, 2021).

Research on PMDD risk factors has mainly focused on its pathophysiology, suggesting a hypersensitivity to normal fluctuations of reproductive steroid hormones, which interacts with the GABAergic, serotonergic and HPA-axis systems (Beddig & Kuehner, 2017; Eisenlohr-Moul, 2019; Hantsoo & Epperson, 2015). Regarding the latter, research on PMDD suggests that higher levels of perceived stress are linked to exacerbations of premenstrual symptoms (e.g., Gollenberg et al., 2010; Namavar Jahromi et al., 2011; Owens & Eisenlohr-Moul, 2018), pointing to a possible role of HPA-axis dysfunction in PMDD (Kiesner & Granger, 2016; Owens & Eisenlohr-Moul, 2018). However, respective evidence is mixed, ranging from blunted to increased cortisol activity in women with premenstrual disorders (e.g., Huang et al., 2015; Kiesner & Granger, 2016; Owens & Eisenlohr-Moul, 2018). The missing differentiation between PMDD and PMS in previous research may be one reason for these inconsistencies. For example, Odber et al. (1998) identified higher premenstrual basal cortisol levels compared to postmenstrual levels in women with mild PMS symptoms, but demonstrated a reverse cortisol pattern with significantly decreased basal cortisol levels in the premenstrual phase for women with severe premenstrual mood changes. Similarly, experimental studies point to hypoactivation of the HPA-axis in response to stress in women with PMDD (Huang et al., 2015; Klatzkin et al., 2010). Reduced HPA-axis activation, in turn, has been shown to be associated with poorer mental and physical health, reflecting a biological mechanism of a spectrum of stress-related disorders (e.g., Adam et al., 2017).

Multifactorial approaches emphasize the additional role of intrapersonal psychological factors, which interact with possible biological characteristics in PMDD (Blake, 1995;

Kleinstäuber et al., 2016). In this regard, the high lifetime comorbidity of PMDD with depressive and anxiety disorders (Cohen et al., 2002; Yen et al., 2020) point to the potential role of transdiagnostic psychological risk factors in the development and maintenance of PMDD. In particular, the role of possible cognitive emotion regulation (ER) dysfunction has been discussed (Owens & Eisenlohr-Moul, 2018). According to strategy-based models, ER-strategies can be classified in terms of their formal characteristics, such as being adaptive versus maladaptive (Naragon-Gainey, McMahon, & Chacko, 2017). When used habitually, adaptive and maladaptive ER-strategies have been shown to be linked to favorable versus unfavorable long-term psychological and physiological health outcomes (McRae & Gross, 2020).

Initial evidence indicates that women with PMDD tend to use more maladaptive strategies, such as avoidance coping, catastrophizing and ruminative strategies (Craner et al., 2014, 2016; Eggert et al., 2017). In particular, habitual rumination has been shown to contribute to larger increases in premenstrual depressive symptoms in women with premenstrual mood disorders (Dawson et al., 2018). In turn, habitual reappraisal (Wu et al., 2016) and mindfulness (Lustyk et al., 2011) were linked to less premenstrual symptom severity in nonclinical samples.

Since neuroticism was found to be positively associated with PMDD (Aperribai et al., 2016; Miller et al., 2010) and higher neuroticism may foster the use of more maladaptive ER-strategies (Yang et al., 2020), it is essential to take neuroticism scores into account when studying the use of habitual ER-strategies in PMDD. The same applies to clinical symptom levels, such as concurrent depression scores, which may affect the assessment of the habitual use of certain ER-strategies.

Previous PMDD research has mainly studied the role of habitual ER-strategies in cross-sectional study designs (e.g., Craner et al., 2014; Lustyk et al., 2011). However, only few studies have investigated their effects on cycle-related symptom change (e.g., Craner et al., 2016; Dawson et al., 2018). Furthermore, to our knowledge, studies investigating associations of ER-strategies with cortisol activity across the menstrual cycle in women with PMDD are totally lacking.

Given the cyclicity of PMDD symptomatology, Ambulatory Assessment (AA) designs with multiple real-time assessments during daily life are well-suited (Bosman et al., 2016; Owens & Eisenlohr-Moul, 2018). AA allows to capture within-person psychological and physiological processes across the menstrual cycle, reduces recall biases and increases ecological validity (Trull & Ebner-Priemer, 2013). In this context, our previous

research provided clear evidence of menstrual cycle-related variations of daily life experiences in women with PMDD compared to healthy controls (Beddig et al., 2019, 2020). In particular, women with PMDD showed increased negative and decreased positive affect (Beddig et al., 2020) and increased psychological stress-reactivity during the late luteal phase as well as a delayed cortisol awakening response and flattened diurnal cortisol slope across the menstrual cycle compared to healthy controls (Beddig et al., 2019). Moreover, high negative affect and low cortisol output independently predicted a worse clinical course of PMDD symptomatology over a four months interval (Beddig & Kuehner, 2020).

The current study

In the present AA study, we aimed to examine the role of habitual ER-strategies for the cyclical course of momentary mood and cortisol activity in women with PMDD. Consistent with previous research, we expected that women with PMDD would report lower levels of mindfulness and reappraisal and higher levels of repetitive negative thinking (RNT) compared to controls. We further expected that in women with PMDD, lower levels of mindfulness and reappraisal and higher levels of RNT would predict (a) increased negative affect (NA), (b) decreased positive affect (PA) and (c) decreased cortisol activity, especially in the late luteal phase compared to women with more favorable ER-strategies. Finally, we examined whether observed associations would hold when controlling for levels of neuroticism and depressive symptoms.

2.3 Methods

Participants

The present sample and study design have been previously described in detail in Beddig et al. (2019). Women with and without PMDD (n = 61 each) were recruited at the Central Institute of Mental Health (CIMH), Mannheim, Germany between March 2016 and October 2018. Inclusion criteria included: a) age between 20 and 42, b) consistent length of menstrual cycle between 22 and 34 days, and c) fulfillment of diagnostic criteria of a PMDD diagnosis based on DSM-5 criteria (PMDD group) or exemption from any PMDD affective core symptoms (control group). Women were ineligible if they were pregnant or lactating during the last six months, taking hormonal contra-

ceptives and pharmaceutical medication during the last three months, or if they reported a body mass index <18 or >35, late evening or night shifts, a history of gynecological diseases (e.g., hysterectomy or ovariectomy), psychotic or bipolar disorder, and current alcohol or substance abuse or dependence. 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 their participation.

Procedure

The procedure consisted of a preliminary telephone screening, a baseline session, and eight days of subsequent AA. Demographic and clinical characteristics, inclusion and exclusion criteria, as well as psychological traits (i.e., habitual ER-strategies; see below) were assessed during the baseline session at the CIMH in Mannheim (Germany). Eligible participants then received a study smartphone and detailed instructions regarding the AA procedure.

To verify the diagnosis of PMDD, the SCID-PMDD, a reliable Structured Interview for DSM-IV-TR PMDD (κ = 0.96; Accortt et al., 2011) was administered to both samples during the diagnostic baseline session. The SCID-PMDD covers all symptom criteria of PMDD together with the criterion of relational, occupational and recreational impairment or distress and the exclusion criterion of a mere exacerbation of symptoms of another disorder (cf. Kuehner & Nayman, 2021). The interview format for eleven symptoms of PMDD is modeled after the Structured Clinical Interview for DSM-IV for Axis I (SCID-I; Wittchen et al., 1997), with additional questions on the timing of symptom-on- and offset across the menstrual cycle and the number of symptomatic cycles experienced for each of the eleven symptoms. A diagnosis of PMDD required fulfilling respective criteria within the diagnostic algorithm adapted for DSM-5, according to which functional impairment as a criterion is not mandatory if the premenstrual symptoms are associated with clinically significant distress (APA, 2013). Controls had to be free of any PMDD affective core symptom. In order to keep the compliance rate high and to avoid further participant burden within the AA-design, additional prospective daily symptom ratings during at least two symptomatic cycles before study inclusion were not required. Current and lifetime DSM-IV-TR Axis I psychiatric comorbidities and exclusion criteria were assessed with the SCID-I (Wittchen et al., 1997). All interviews were performed by a trained research psychologist (T.B.).

Ambulatory assessment (AA)

AA was carried out using *Motorola Moto G 2nd Generation* smartphones with the software *movisensXS, version 0.6.3658* (movisens GmbH, Karlsruhe, Germany). AA took place over two consecutive days per menstrual cycle phase (menstrual, follicular, ovulatory and late luteal phase).

The typical menstrual cycle lasts about 28 (21 to 35) days and can be divided into four cycle phases with predictable fluctuations of the ovarian hormones *progesterone* (P4) and *estradiol* (E2). It starts with the onset of menstruation, which represents the cycle day 1, endures about five days and is characterized by low P4 and E2 levels. The follicular phase is marked by consistently low P4 and rising E2 levels with a peak prior to ovulation, which is followed by a rapid E2 decrease after ovulation. The luteal phase covers the days from ovulation until menses during which E2 and P4 gradually rise, reaching their highest levels during the mid-luteal phase, and then show a rapid withdrawal during the late luteal (premenstrual) phase, i.e., the week prior to the next menses (Schmalenberger et al., 2021).

Individual cycle calendars were prepared based on the date of the last menstruation onset and the average cycle length in order to specify the start date of ovulation testing and exact days of the AA. The ovulation phase was identified by a chromatographic ovulation test (gabControl hIH Ovulationsteststreifen, gabmed, Cologne). The testing started a few days before the predicted ovulation and had to be continued until a positive result occurred. If ovulation did not occur, women were asked to repeat the testing in the next menstrual cycle. In order to avoid sequence effects, they started AA in different cycle phases.

The *menstrual phase* was assessed on the second and third days of menstruation (*M* = 2.95 days, *SD* = 2.21). The assessments during the *follicular phase* were examined on the second and third days after the end of menstruation (*M* = 8.61 days, *SD* = 1.94). The *ovulatory phase* (*M* = 17.15 days, *SD* = 2.0) was assessed on the two days following a positive ovulation test result. In case of a negative test, participants were asked to repeat the testing during the following menstrual cycle. Assessments of the *late luteal phase* took place on the fourth and third day before the next expected menstruation (*M* = 26.38 days, *SD* = 3.02). If the menstruation occurred at least three days earlier or later than expected, women were asked to repeat the AA during the next cycle in order to ensure a late luteal-phase assessment.

Women performed eight assessments per day starting exactly at 9.00 a.m. The remaining seven assessments took place between 10.00 a.m. and 09.30 p.m. at semi-random time points with a completion time of 3-4 min per assessment. Ignored or rejected alarms were coded as missing (for detailed information see Beddig et al., 2019).

Ambulatory Assessment (AA) variables

Momentary negative (NA) and positive affect (PA) were assessed using 12 items from previous AA studies by our group (e.g., Kuehner et al., 2017; Timm et al., 2018). At each assessment, women reported the extent to which they felt several negative (upset, irritated, nervous, listless, down and bored, α = .832[2]) and positive (cheerful, energetic, enthusiastic, satisfied, relaxed and calm, α = .708) emotions on a 7-point Likert scale ranging from 1 (not at all) to 7 (very much).
At the first assessment (09.00 am) of each AA day, women further reported time of awakening and sleep duration (number of hours) as well as sleep quality ("How did you sleep last night?") measured on a 7-point Likert scale ranging from 1 (very bad) to 7 (very good) by single items.

Salivary measure of cortisol

Twenty minutes after each subjective AA, women collected saliva cortisol samples with standard salivettes (Sarstedt, Germany), resulting in eight saliva samples per day for analysis. Women were instructed not to eat, drink anything other than water, smoke, physically exercise and brush their teeth the next 20 min until saliva collection, and also to refrain from strenuous exercise during AA days (cf. Schlotz, 2019). Immediately after collection of each cortisol sample, they indicated whether they had eaten, drunk anything other than water, smoked or brushed their teeth (0 = no, 1 = yes) and the extent of their physical activity (7-point Likert scale: 1 = not at all to 7 = very much) during the last 20 min. The smartphone further provided a random three-digit code, which had to be recorded on the respective label of the salivette tube used during each saliva collection (Schlotz, 2019). Until being returned, all samples were stored in the participants' home freezer and were frozen at −20 °C at the laboratory prior to biochemical analysis. At the laboratory of Prof. Kirschbaum (Dresden, Germany), salivettes were centrifuged

[2] All reported Cronbach's alpha values (α) in the paper refer to the present sample

at 3000 rpm for 5 min, resulting in a clear supernatant of low viscosity. Salivary concentrations were measured using commercially available chemiluminescence-immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were below 8%.

Trait-level measures

Mindfulness

The German version of the 15-item Mindfulness Attention Awareness scale (MAAS; Brown & Ryan, 2003) was administered to measure participants' habitual tendency to be attentive and aware of present-moment experiences. The items were rated on a 6-point Likert scale, with higher scores indicating greater mindfulness (α = .891).

Reappraisal

The 6-item subscale of the Emotion Regulation Questionnaire (ERQ; Abler & Kessler, 2009) was used to assess habitual usage of reappraisal. All items were rated on a 7-point-Likert scale with higher scores indicating higher usage of reappraisal (α = .842).

Repetitive Negative Thinking (RNT)

Participants completed the German version of the Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011), a well-validated 15-item scale assessing the habitual tendency to engage in RNT. All items were answered on a 5-point Likert scale with higher scores signifying higher levels of RNT (α = .957).

Neuroticism

Neuroticism was measured with the 12-item Neuroticism Subscale derived from the NEO Five Factor Inventory (NEO-FFI; Costa & McCrae, 1992; α = .879).

Depressive Symptoms

The severity of self-rated depressive symptoms during the last two weeks was measured with the 21-item Beck Depression Inventory-II (BDI-II; Beck et al., 1996; α = .915).

Statistical Analyses

Group differences in ER-Strategies

To test group differences in habitual ER-strategies, a one-way multivariate analysis of variance (MANOVA) was conducted with group (PMDD vs. controls) as the independent variable and cognitive ER-strategies (mindfulness, reappraisal and RNT) as dependent variables.

Associations of ER-strategies with daily affect and cortisol in women with PMDD

To examine the predictive value of ER-strategies on the course of momentary affect and cortisol across the menstrual cycle in women with PMDD (N = 61), multilevel models (MLM) were estimated to take into account that assessments (level 1) were nested within participants (level 2) (Nezlek et al., 2006). Prior to the main analyses, intercept-only models were fitted for each outcome to calculate intraclass correlation coefficients (ICC). Furthermore, possible confounders of daily affect (time since awakening, time since first assessment, assessment day) were analyzed in separate intercept-only-models and were retained in the models if significant ($p < 0.05$). This applied to assessment day. All level 2-predictors were grand-mean-centered within the PMDD-group to improve the interpretability of the resulting MLM parameters.

Cortisol data were log-transformed to adjust for skewness. Then, outliers more than three standard deviations from the group mean were winsorized to 3 standard deviations (Stalder et al., 2016). Time was centered at waking time. Possible confounders of basal cortisol secretion (age, current medication use, habitual smoking, time, time^2, time of awakening, sleep quality, sleep duration, weekday versus weekend, and drinking anything other than water, smoking cigarettes, eating, brushing the teeth, and the level of physical activity during the last 20 minutes) were analyzed in separate intercept-only-models, and were retained in the models if significant ($p < 0.05$). This applied to time, time^2, time of awakening, sleep duration as well as recent physical activity and drinking.

Random-intercept models, in which the intercept was allowed to vary between individuals, were estimated using restricted maximum likelihood estimation (REML). MLMs were carried out in two steps. First, we estimated the main effects of each habitual ER-strategy (mindfulness, reappraisal and RNT) on each momentary outcome (NA, PA, cortisol) in separate MLMs and controlled for cycle phase as a categorical level 2 variable. In a second step, these models were expanded by entering the interaction effects of cycle phase with ER-strategies (cycle phase*ER-strategy) on each momentary outcome. In case of a significant interaction effect, we subsequently estimated simple slopes for each ER-strategy on mood and cortisol per cycle phase in post-hoc analyses. Finally, all analyses were repeated by controlling for possible main effects of neuroticism and depressive symptoms.

Statistical analyses were performed using IBM SPSS version 25 (IBM Corp., 2017) with the significance level set at α = .05. This value was not adjusted for multiple testing as the tests were based on preplanned hypotheses (Armstrong, 2014).

2.4 Results

Sample Description

The descriptives on demographics and questionnaire measures are listed in Table 2.1. Groups did not significantly differ with respect to age, education level, work situation, partner status, and percentage of having children. However, as expected, women with PMDD displayed higher levels of depressive symptoms and neuroticism scores.

Table 2.1

Demographic and clinical characteristics 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)	$t(120) = -0.03$	.977
Education (% with high school degree)	72.1%	75.4%	$\chi^2(1) = 0.17$	.681
Work Situation (% in regular job or education)	80.3%	90.2%	$\chi^2(1) = 2.35$	.126
Partner Status (% married or living together)	60.7%	59.0%	$\chi^2(1) = 0.03$	.853
Children (%)	24.6%	26.2%	$\chi^2(1) = 0.04$	.835
BMI	23.6 (4.1)	23.5(4.3)	$t(120) = 0.12$	.903
Clinical Variables				
SCID-I Lifetime Diagnosis of Depression	54.1%	21.3%	$\chi^2(1) = 13.96$	<.001
BDI-II depression score	10.9 (8.9)	4.8 (5.6)	$t(119) = 4.51$	<.001
NEO-FFI neuroticism	2.11 (0.7)	1.5 (0.7)	$t(118) = 4.46$	<.001

Note. BMI = Body Mass Index; SCID-I = Structured Clinical Interview for DSM-IV Axis I; BDI-II=Beck Depression Inventory-II; NEO-FFI = NEO Five Factor Inventory.

Group differences in ER-strategies

The MANOVA yielded a significant effect of group (PMDD vs. controls) on ER-strategies (Wilks' Lambda = 0.852; $F(3,116) = 6.71$, $p < .001$). Univariate ANOVAs revealed significant group differences in habitual mindfulness, $F(1,3) = 4.55$, $p = .035$, reappraisal, $F(1,7) = 5.31$, $p = .023$ and RNT, $F(1,12) = 18.19$ $p < .001$. In particular, women with PMDD reported lower levels of mindfulness ($M_{PMDD} = 4.13$, $SD_{PMDD} = 0.96$; $M_{controls}$

= 4.45, $SD_{controls}$ = 0.69), less use of reappraisal strategies (M_{PMDD} = 4.19, SD_{PMDD} = 1.34; $M_{controls}$ = 4.67, $SD_{controls}$ = 0.88) and higher levels of RNT (M_{PMDD} = 1.92, SD_{PMDD} = 0.91; $M_{controls}$ = 1.29, $SD_{controls}$ = 0.70).

Multilevel Analyses (MLM)

Compliance

MLMs were based on 61 women with PMDD. Altogether, 3381 of 3904 possible subjective assessments (four menstrual cycle phases x 16 assessments per phase x 61 participants) were recorded, which corresponds to a response rate of 86.6%. This reflects a high level of compliance (cf. Courvoisier et al., 2012). The compliance rate for cortisol assessments in the PMDD group amounted to 84.5%.

Intra-Class Correlation (ICC)

ICCs indicated that 22% of variability in NA and 26% of variability in PA of the PMDD sample were attributable to between-person differences. For cortisol assessments, the ICC indicated that 16% of variability in cortisol levels were due to between-person differences.

Associations of ER-strategies with momentary affect across the cycle

The main effect analyses revealed that lower mindfulness (B = -0.15, SE = 0.07, t(59) = -2.30, p = .025) and reappraisal (B = -0.12, SE = 0.05, t(59) = -2.68, p = .010), and higher RNT levels (B = 0.16, SE = 0.07, t(59) = 2.27, p = .027) predicted increased NA across the menstrual cycle (Table 2.2). In turn, higher mindfulness (B = 0.22, SE = 0.08, t(59) = 2.93, p = .005) and reappraisal (B = 0.15, SE = 0.06, t(59) = 2.81, p = .007) and lower RNT levels (B = -0.23, SE = 0.08, t(59) = -2.80, p = .007) predicted increased PA across the menstrual cycle (Table 2.2).

Our second-step analyses identified significant interaction effects of cycle phase by mindfulness (F_{NA}(3,3317) = 6.76, p <.001; F_{PA}(3,3317) = 4.03, p = .007), reappraisal (F_{NA}(3,3317) = 5.37, p <.001; F_{PA}(3,3317) = 3.21, p =.022), and RNT (F_{NA}(3,3318) = 6.97, p <.001; F_{PA}(3,3317) = 6.17, p <.001) in predicting NA and PA (Table 2.2). As depicted in figures 2.1 and 2.2 for illustration purposes, post-hoc tests revealed that favorable ER-strategies, i.e., higher mindfulness and reappraisal and lower RNT levels, predicted decreased NA and increased PA only in the menstrual, follicular and ovulatory phases (all ps < .029, see Table 2.3 for post-hoc test results), while these ER-strategies did not show any effect on momentary affect in the late luteal phase (all

*p*s > .05). Thus, contrary to our hypotheses, women with favorable ER-strategies showed stronger mood deterioration towards the late luteal phase, thereby converging with women with unfavorable ER-strategies (see figures 2.1, 2.2).

Associations of ER-strategies with momentary cortisol activity across the cycle

The main effects of mindfulness (*B* = 0.13, *SE* = 0.07; *t*(59) = 1.78, *p* = .080), reappraisal (*B* = 0.04, *SE* = 0.05; *t*(59) = 0.72, *p* = .478) and RNT (*B* = -0.03, *SE* = 0.08; *t*(59) = -0.37, *p* = .712) on momentary cortisol activity were not significant (Table 2.2). However, there was a significant interaction effect of cycle phase and mindfulness on momentary cortisol activity (*F* (3, 3007) = 3.09; *p* = .026). As shown in figure 2.1C, again for illustration purposes, lower mindfulness was associated with decreased basal cortisol activity only in the menstrual phase, with no associations in the follicular, ovulatory and luteal phase (see Table 2.3).

Confounder analysis

Neuroticism and severity of depressive symptoms (BDI-II) as covariates did not change the size of any reported ER strategy*cycle phase interaction effects.

Table 2.2

Main and interaction effects of ER-strategies with cycle phase on momentary affect and cortisol activity

	Negative affect (NA)[a]			Positive affect (PA)[a]			Cortisol [b]		
Predictor	*df*	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
Mindfulness									
Step 1									
Cycle Phase	3, 3320	105.30	<.001	3, 3320	91.19	<.001	3,3011	0.87	.458
Mindfulness	1, 59	5.30	.025	1, 59	8.60	.005	1,59	3.18	.080
Step 2[c]									
Cycle Phase*Mindfulness	3, 3317	6.76	<.001	3, 3317	4.03	.007	3,3007	3.09	.026
Reappraisal									
Step 1									
Cycle Phase	3, 3320	105.37	<.001	3, 3320	91.27	<.001	3,3011	0.86	.462
Reappraisal	1, 58	7.17	.010	1, 59	7.90	.007	1,59	0.51	.478
Step 2 [c]									
Cycle Phase*Reappraisal	3, 3317	5.37	<.001	3, 3317	3.21	.022	3,3007	2.58	.052
Repetitive Negative Thinking(RNT)									
Step 1									
Cycle Phase	3, 3320	105.37	<.001	3, 3320	91.27	<.001	3,3010	0.86	.461
RNT	1, 59	5.16	.027	1, 59	7.81	.007	1,59	0.14	.712
Step 2 [c]									
Cycle Phase * RNT	3, 3318	6.97	<.001	3,3317	6.17	<.001	3,3008	2.06	.103

Note. ER-strategies = Emotion regulation strategies; RNT = Repetitive negative thinking. All Models include random intercepts at level 2. [a] Models include fixed effects of assessment day. [b] Models include fixed effects of time, time^2, time of awakening, sleep duration as well as physical activity and drinking during the past 20 min. [c] Step-2 models additionally include main effects of cycle phase and mindfulness.

Table 2.3

Estimated simple slopes of mindfulness, reappraisal and repetitive negative thinking (RNT) on negative affect, positive affect and cortisol activity per cycle phase

		Negative affect		***Positive affect***		**Cortisol[1]**	
ER-strategy	**Cycle Phase**	***B (SE)***	***p***	***B (SE)***	***p***	***B (SE)***	***p***
Mindfulness	Menstrual Phase	-0.22 (0.07)	.002	0.29 (0.08)	<.001	0.20 (0.08)	.012
	Follicular Phase	-0.18 (0.07)	.014	0.25 (0.08)	.003	0.10 (0.08)	.201
	Ovulatory Phase	-0.17 (0.07)	.017	0.24 (0.08)	.005	0.09 (0.08)	.243
	Luteal Phase	-0.04 (0.07)	.619	0.13(0.08)	.120	0.13 (0.08)	.096
Reappraisal	Menstrual Phase	-0.17 (0.05)	.001	0.14 (0.06)	.024	---	---
	Follicular Phase	-0.13 (0.05)	.014	0.19 (0.06)	.002	---	---
	Ovulatory Phase	-0.15 (0.05)	.004	0.19 (0.06)	.001	---	---
	Luteal Phase	-0.05 (0.05)	.306	0.10 (0.06)	.085	---	---
Repetitive negative thinking	Menstrual Phase	0.22 (0.08)	.005	-0.28 (0.09)	.002	---	---
	Follicular Phase	0.17 (0.08)	.029	-0.23 (0.09)	.010	---	---
	Ovulatory Phase	0.22 (0.08)	.004	-0.31 (0.09)	<.001	---	---
	Luteal Phase	0.03 (0.07)	.675	-0.10 (0.09)	.248	---	---

Note. ER-strategy = Emotion regulation strategy. [1] Log-transformed cortisol values in nmol/l. Simple slope values are presented only for significant interaction terms of cycle phase by ER-strategy.

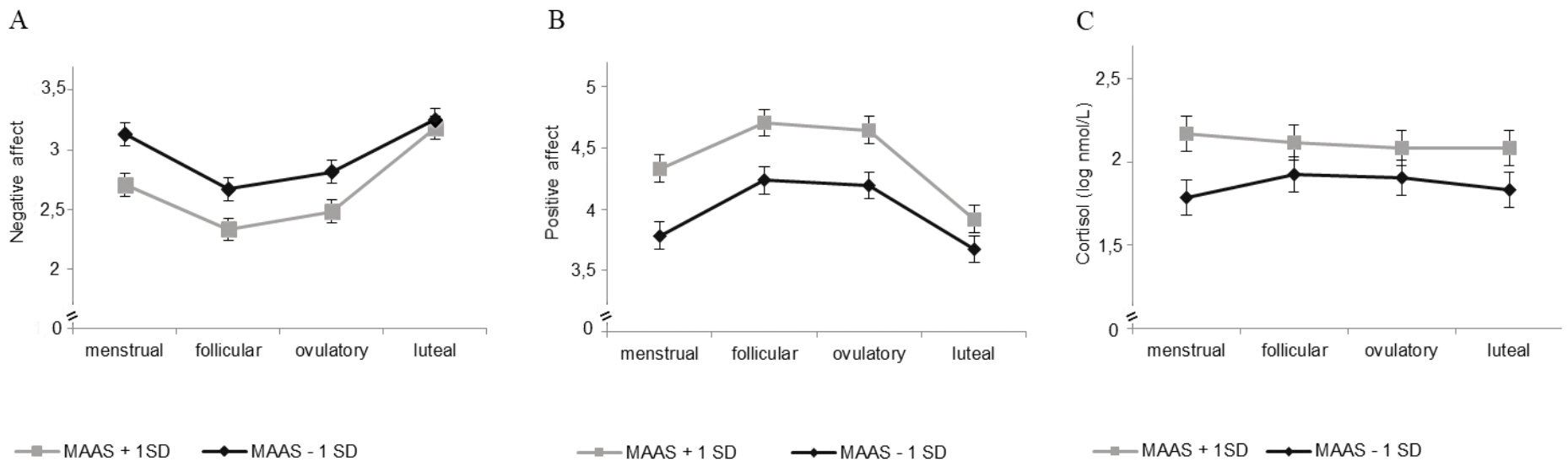

Figure 2.1 Interaction effects of mindfulness and cycle phase on momentary affect and cortisol activity.

Note. MAAS = Mindfulness Attention Awareness scale. Estimated mean values of momentary negative affect (Fig. 1A), positive affect (Fig.1B) and log-transformed basal cortisol activity (Fig. 1C) per menstrual cycle phase for low and high scores on MAAS (M ± 1SD) from multilevel models for illustration purposes. Error bars represent standard error of the estimated mean. All models include random intercepts at level 2. Models in Fig.1A and Fig.1B include fixed effects of assessment day. The model in Fig.1C includes fixed effects of time, time^2, time of awakening, sleep duration as well as physical activity and drinking during the past 20 min.

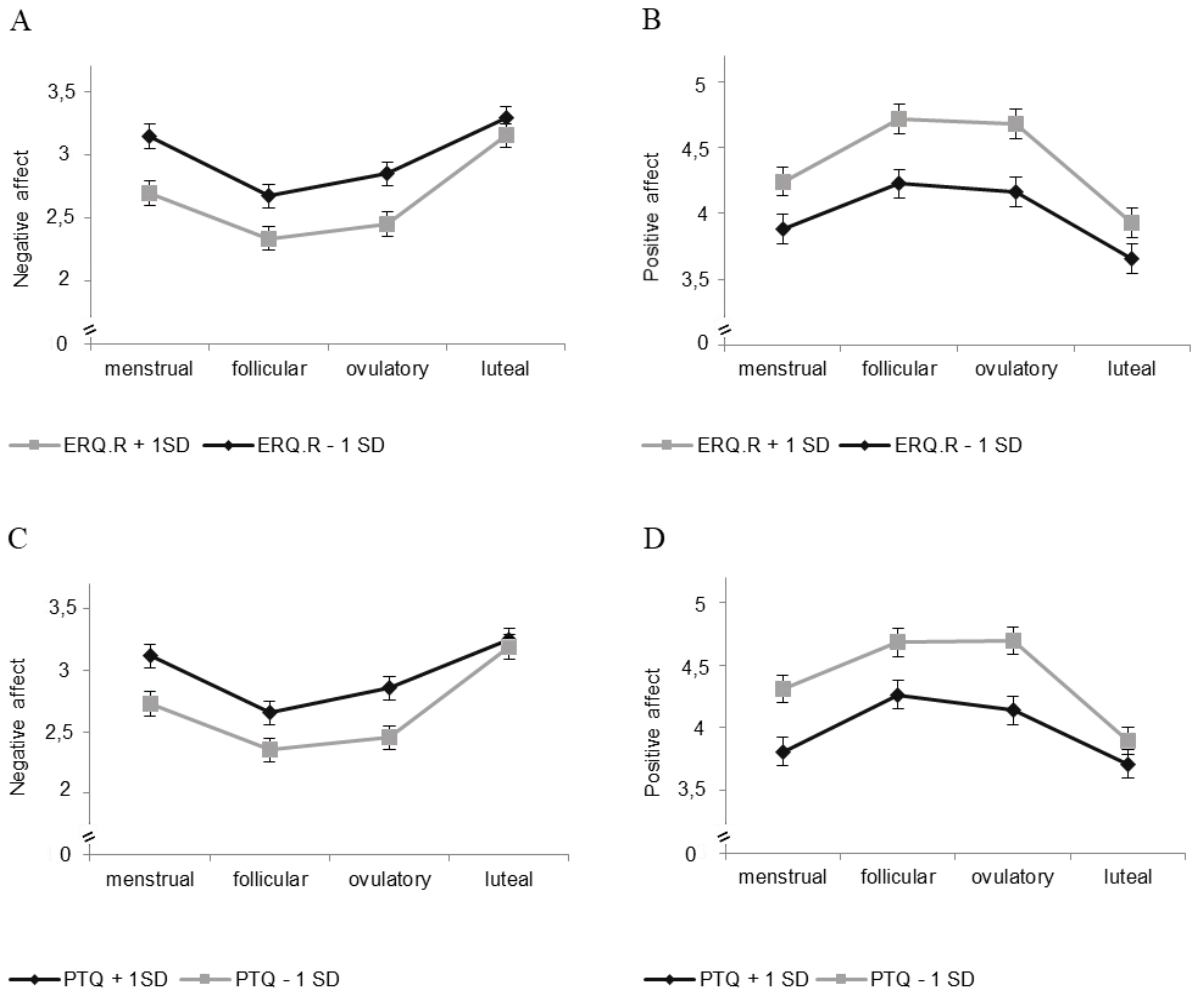

Figure 2.2 Interaction effects of reappraisal and repetitive negative thinking with cycle phase on momentary affect

Note. ERQ.R = Emotion Regulation Questionnaire_reappraisal subscale; PTQ = Perseverative Thinking Questionnaire. Estimated mean values of momentary negative affect and positive affect per menstrual cycle phase for low and high scores ($M \pm 1SD$) on ERQ.R (Fig 2A, Fig 2B) and PTQ (Fig 2C, Fig 2D) for illustration purposes. Error bars represent standard error of the estimated mean. All models include random intercepts at level 2 and fixed effects of assessment day.

2.5 Discussion

Emotion regulation deficits are transdiagnostic risk factors and important treatment targets for a variety of psychological disorders (Aldao et al., 2010). Unfavorable ER-strategies may interact with the menstrual cycle to contribute to cycle-related changes in mood and cortisol activity in women with PMDD. The present study aimed to compare cognitive ER-strategies in women with and without PMDD, and to explore the predictive value of these strategies for momentary affect and basal cortisol activity across

the menstrual cycle in women with PMDD. As expected, women with PMDD reported more maladaptive and less adaptive strategies than healthy controls. Favorable strategies were generally linked to better mood in women with PMDD, whereas they did not appear to protect affected women from cycle-dependent mood worsening during the late luteal phase. Habitual mindfulness was associated with higher cortisol levels during the menstrual phase.

Differences in the use of ER-strategies between women with and without PMDD

In our study, women with PMDD showed lower mindfulness and reappraisal and higher RNT levels than controls. This is consistent with previous research (Craner et al., 2014; Dawson et al., 2018; Lustyk et al., 2011; Wu et al., 2016), indicating heightened vulnerability towards unfavorable ER-strategies in affected women.

ER-Strategies x cycle phase on momentary affect in women with PMDD

In women with PMDD, higher habitual mindfulness and reappraisal and lower RNT predicted lower NA and higher PA during the menstrual, follicular and ovulatory phases, but not during the luteal phase. Women reporting more favorable ER-strategies displayed larger mood cyclicity with stronger mood worsening towards the luteal phase, thereby converging with those using more unfavorable strategies. Thus, contrary to our expectations, favorable habitual cognitive ER-strategies seem not to protect affected women from cycle-related mood worsening.

These results may provide first indications of possible limitations of cognitive behavioral interventions (CBI) addressing cognitive ER-strategies in the treatment of PMDD and underscore the need for more nuanced research on possible differential effects of specific interventions. Previous reviews found mixed evidence for CBIs in the treatment of premenstrual dysphoric symptoms (Kleinstäuber et al., 2012; Lustyk et al., 2009). A recent review (Han et al., 2019) showed that, in particular, the acquisition of active behavioral coping strategies were helpful in premenstrual symptom relief. However, the trials included in these reviews suffer from inadequate study designs and inclusion of women with PMS. A first trial specifically on women with PMDD (Hunter et al., 2002) again showed that the use of active behavioral strategies at the end of a CBI, but not changes in causal attributions, predicted a good clinical outcome after one year. A recent eight-week internet-based CBI trial on women with PMDD, which consisted of

psychoeducation and cognitive and behavioral strategies, revealed high effect sizes for symptom reduction and psychosocial functioning (Weise et al., 2019). While the effects of specific strategies cannot be extracted from this multimodal intervention, the authors showed that habitual active coping with premenstrual symptoms predicted improved treatment outcomes. Altogether, these results point to potential incremental effects of behavioral over cognitive strategies in PMDD treatment, and may also explain the lack of luteal-phase effects of cognitive ER-strategies on mood in the present study. Evidence-based therapies targeting behavioral skills such as Dialectical-Behavioral-Therapy have already been suggested, but not yet evaluated for PMDD treatment (Eisenlohr-Moul, 2019). However, since we investigated trait characteristics of ER-strategies and not respective interventions, we are aware that these conclusions are highly speculative, but can be tested, for example, in studies with dismantling designs (Papa & Follette, 2015). On the other hand, it is quite conceivable that higher levels of favorable ER-strategies do not necessarily imply that women are able to use these strategies effectively in the premenstrual phase in which mainly biologically determined mood changes occur. The lacking predictive value of habitual ER-strategies for mood-related changes during the luteal phase may also indicate that the unilateral classification of ER in adaptive versus maladaptive may be reductive and may ignore the dynamic nature of ER (Aldao, 2013). Instead, the affective impact of ER-strategies may depend on the flexibility to apply them in accordance with contextual demands and individuals' regulatory goals (Aldao et al., 2015; Mikkelsen et al., 2021; Wenzel et al., 2020). In PMDD, contextual, especially cycle-phase-specific, characteristics may predict the choice and the efficacy of ER-strategies (cf. Aldao, 2013; Sheppes et al., 2011; Wenzel et al., 2021). In this context, AA is particularly suited to assess the possible cycle-phase-specific use of certain ER-strategies at the state level. Furthermore, it offers the opportunity to directly induce specific ER-states and to assess their cycle-specific effects in an experimental field design (cf. Huffziger et al., 2013 for a similar approach; Huffziger et al., 2012). In this way, future research can gain a deeper understanding of ER-processing and its impact on affect across the menstrual cycle in women with PMDD.

ER-strategies x cycle phase on momentary cortisol activity in women with PMDD

To our knowledge, our study is the first to investigate the impact of ER-strategies on cycle-related variations of basal cortisol activity in women with PMDD. Mindfulness,

reappraisal and RNT did not predict overall or luteal-phase-specific cortisol output. In contrast, higher trait mindfulness was linked to higher cortisol levels in the menstrual phase.

The high intra-individual variability of cortisol release in the current study (ICC=16%) matches with the observation that substantial variance in diurnal cortisol is due to moment-to moment and day-to-day fluctuations rather than to stable between-person differences (Doane et al., 2015). In experimental studies inducing mental stress, women with affective disorders and women with PMDD show blunted cortisol activity (Hantsoo & Epperson, 2015; Zorn et al., 2017). In contrast, no clear associations have been identified between induced ER-strategies and cortisol responses in general (Mikkelsen et al., 2021). The effects of trait ER-strategies on diurnal cortisol levels outside the lab have also only been rarely examined (Otto et al., 2018).

The lacking effect of trait reappraisal on daily life cortisol is in line with results from nonclinical samples (Otto et al., 2018; Rnic et al., 2021) and has been attributed to the low physiological effort required for reappraisal as a more automatic process in the long term (Otto et al., 2018). There is also some indication that reappraisal is more effective in the context of controllable stressors (cf. Mikkelsen et al., 2021). Given that women with PMDD often describe themselves as feeling out of control during the late luteal phase (cf. APA, 2013), this may explain why this ER-strategy may not be able to affect cycle-related cortisol activity. Similarly, the lacking effect of trait RNT on cortisol is in accordance with findings, which show that state measures of RNT are more closely related to cortisol activity than trait measures, particularly if the latter do not specifically measure stress-related RNT (Zoccola & Dickerson, 2012).

High habitual mindfulness appeared to counteract low cortisol secretion particularly in the menstrual phase, but not in the luteal phase (as expected). Blunted presentation of cortisol secretion seems to be associated with a triad of increased pain, stress sensitivity, and fatigue (Fries et al., 2005), and higher cortisol concentrations are commonly related to lower pain intensity (cf. Ubeda-D'Ocasar et al., 2020). In turn, studies have shown beneficial effects of mindfulness-based interventions on menstrual pain and pain perception (Payne et al., 2020; Purnamasari et al., 2020), and the activation of cortisol release may constitute one possible mechanism through which habitual mindfulness can dampen respective symptoms. However, these considerations are again speculative because we did not measure cycle-related physical symptoms in our study, which is clearly warranted in future AA-studies.

Limitations and Future Directions

Our study has some limitations. First, the sample size was modest although exceeding the recommended minimum size for estimating cross-level interactions (Hox et al., 2017). Second, in order to keep participants' burden low and compliance rates high within this intensive AA-design, the PMDD diagnosis was assessed with a retrospective, although well-validated, structured interview (SCID-PMDD; Accortt et al., 2011). This in turn can bear the risk of recall-bias towards false positive symptom reports (Schmalenberger et al., 2021). DSM-5 requires prospective daily symptom ratings for at least two symptomatic cycles for a definite diagnosis. Thus, the present PMDD-diagnoses must be considered provisional (APA, 2013).

Furthermore, we only examined cognitive ER-strategies. The further inclusion of behavioral ER-strategies (e.g., stress-reduction-skills) would allow to assess possible effects of specific classes of strategies. We also focused on measures of self-assessed habitual ER-strategies, which are characterized by possible recall-bias, restriction to conscious emotion regulation, and by unclear predictive validity regarding their use in daily life (Naragon-Gainey et al., 2017). In this context, implicit assessments of ER (e.g., Eggert et al., 2017) and AA-designs can help to uncover automatic aspects of ER-processes and possible cycle-specific ER-deficits and, consequently, possible treatment targets.

Conclusions

The present findings suggest that protective habitual cognitive ER-strategies are generally linked to improved momentary mood in women with PMDD but do not appear to protect affected women from cycle-dependent mood deteriorations. Conversely, habitual mindfulness seems to exert a beneficial effect on basal cortisol activity only in the menstrual phase. These findings emphasize the importance of a refined research on emotion regulation and its interaction with cycle phases to predict psychological and endocrinological changes in PMDD across the menstrual cycle. This will also help th

CHAPTER III: STATE AND TRAIT COGNITIONS DIFFERENTIALLY AFFECT CYCLICITY OF MOOD AND CORTISOL IN INDIVIDUALS WITH AND WITHOUT PREMENSTRUAL DYSPHORIC DISORDER (STUDY 2)

An adapted version of this chapter has been published as **'**Nayman, S., Schricker, I. F., Reinhard, I., Dreer, J. K., Richter, A. S., & Kuehner, C. (2024). State and trait cognitions differentially affect cyclicity of mood and cortisol in individuals with and without Premenstrual Dysphoric Disorder. *Journal of Psychopathology and Clinical Science, 133*(4), 309–320. https://doi.org/10.1037/abn0000894**'**

3.1 Abstract

Premenstrual Dysphoric Disorder (PMDD) is characterized by a cyclical symptom course. Previous research provides limited findings on possible menstrual-cycle-related psychological and psychoendocrinological processes in PMDD. By using Ambulatory Assessment (AA), we aimed to compare mood and cortisol cyclicity in individuals with PMDD and healthy controls (HC), and to assess effects of habitual and momentary repetitive-negative-thinking (RNT) and present-moment-awareness (PMA) on mood and cortisol across the cycle in both groups. Individuals with PMDD and HCs (*n* = 60 each) completed baseline questionnaires on habitual RNT and PMA. Momentary rumination and PMA, positive and negative affect, and saliva-cortisol were assessed over four consecutive days during both the follicular and the late-luteal phase. Individuals with PMDD showed mood cyclicity indicating mood worsening while HCs showed cortisol cyclicity indicating decreasing cortisol levels toward the late-luteal phase. In individuals with PMDD, lower habitual RNT and higher habitual PMA predicted better mood only during the follicular phase whereas lower momentary rumination and higher momentary PMA predicted better mood during the late-luteal phase. No effects on cortisol activity were found. In HCs, higher habitual PMA predicted lower negative affect during the late-luteal phase whereas lower momentary rumination and higher momentary PMA predicted stronger cortisol reduction toward the late-luteal phase. While favorable habitual cognitions might not protect individuals with PMDD against premen-

strual mood deterioration, respective momentary cognitions may reflect possible protective factors, suggesting an opportunity for micro-interventions to directly target late-luteal-phase-specific state processes in affected individuals. The lack of cortisol cyclicity might represent an endocrinological marker for PMDD.

3.2 Introduction

Ovarian hormone receptors are highly prevalent in cortico-limbic brain regions involved in the processing of cognitions and emotions, such as the amygdala, hippocampus and prefrontal cortex (Le et al., 2020; Sundström-Poroma, 2018). The ovarian hormones estradiol and progesterone specifically interact with neurotransmitter systems including serotonergic, GABA-ergic and dopaminergic pathways. Thus, their menstrual-cycle-related fluctuations can modulate emotional and cognitive processes in naturally-cycling individuals assigned female at birth (AFAB) of reproductive age (Dubol et al., 2021). While for the majority of AFAB individuals, the menstrual cycle has no clinical impact on their mood, cognitions or behavior (Gehlert et al., 2009), some individuals with mental disorders show premenstrual exacerbations of ongoing disorders (e.g., Handy et al., 2022; Kuehner & Nayman, 2021).

The menstrual cycle also plays an important role in Premenstrual Dysphoric Disorder (PMDD), which has to be differentiated from premenstrual exacerbations of other mental disorders (American Psychiatric Association [APA], 2013). PMDD is characterized by distressing or impairing core mood as well as additional psychological, and physical symptoms during the late-luteal phase, which remit within a few days after menses during the follicular phase (APA, 2013). Research has shown that individuals with PMDD do not exhibit abnormal sex hormone levels during the menstrual cycle, but a neural hypersensitivity of affective brain circuits toward the natural cyclical fluctuations of these hormones (Le et al., 2020), in particular of progesterone and its metabolite allopregnanolone (ALLO; Kaltsouni et al., 2021).

Physiological Factors

There is also initial evidence for altered basal cortisol levels in individuals with PMDD compared to healthy controls. Healthy individuals seem to show cortisol cyclicity with significantly lower cortisol levels during the luteal compared to the follicular phase – however with effect sizes not reaching the threshold for a small effect (Hamidovic et

al., 2020; Klusmann et al., 2022). Increasing levels of ALLO during the luteal phase, which has a homoeostatic function in acute distress regulation and inhibitory effects on the hypothalamic-pituitary-adrenal- (HPA) axis activity (Pisu et al., 2022), seem to account for reduced cortisol activity during this phase in healthy individuals (Hamidovic et al., 2020; Klusmann et al., 2022). In contrast, in individuals with PMDD, ALLO appears to show paradoxical effects on the GABAergic system and to induce premenstrual mood symptoms (Bäckström et al., 2014, Hantsoo & Epperson, 2020). Relatedly, in individuals with retrospectively diagnosed PMDD (rPMDD), a delayed cortisol awakening response, a flattened diurnal cortisol slope across cycle phases and no cycle-related variations in cortisol activity were identified (Beddig et al., 2019). Furthermore, low cortisol levels predicted a worse clinical course of PMDD symptoms during a 4-months follow-up (Beddig & Kuehner, 2020). Consequently, alterations in cortisol activity might reflect impaired stress regulation in individuals with PMDD.

Psychological Factors

So far, there are no manualized psychotherapeutic treatments for PMDD (Hantsoo & Riddle, 2021) specifically addressing the cyclicity of symptoms. Studies on the impact of psychological traits and respective interventions on cortisol levels in PMDD are also lacking. Previous psychotherapy research mainly examined cognitive behavioral therapy (CBT) interventions and showed small to medium effect sizes for premenstrual mood symptoms (Busse et al., 2009) or functional impairment (Kleinstäuber et al., 2012). In addition, one small-scale pilot study showed reduced premenstrual symptoms after a mindfulness-based group intervention in individuals with PMDD (Bluth et al., 2015), indicating the potential of mindfulness for managing PMDD symptoms. A recent randomized controlled trial showed an internet-based CBT intervention, including psychoeducation, cognitive and behavioral strategies, to be effective in reducing premenstrual symptoms, impairment and distress in individuals with PMDD (Weise et al., 2019). However, effects of specific intervention elements were not investigated in this study, and psychological factors, which could be addressed as psychotherapeutic targets in PMDD treatment, have not been fully uncovered in PMDD research yet.
Regarding cognitive coping strategies, previous research showed higher habitual (trait) rumination and lower habitual mindfulness in individuals with retrospectively or prospectively diagnosed PMDD compared to healthy controls (Craner et al., 2014; Craner

et al., 2016; Nayman et al., 2023a), but also point to the need for more nuanced research with respect to their cycle-specific role (cf. Nayman et al., 2023a). Relatedly, individuals with rPMDD showed the highest levels of momentary (state) rumination during the late-luteal phase compared to other cycle phases and responded to higher momentary rumination with increased negative affect (NA) especially during the late-luteal phase, indicating a particular mood-worsening effect of momentary rumination during the late-luteal phase (Beddig et al., 2020). In contrast, a recent Ambulatory Assessment (AA) study showed that while lower habitual repetitive negative thinking (RNT) was generally linked to better mood across the cycle, individuals with lower RNT displayed stronger mood cyclicity with stronger mood worsening toward the late-luteal phase, thereby approaching those with higher habitual RNT toward the end of the cycle (Nayman et al., 2023a). The same pattern was shown for habitual mindfulness (Nayman et al., 2023a). These results suggest that adaptive and maladaptive psychological traits are decoupled from mood during the late-luteal phase in individuals with PMDD. Consequently, diverging findings on the associations of trait (Nayman et al., 2023a) and state (Beddig et al., 2020) aspects of psychological factors with mood cyclicity may point to their differential roles in PMDD. This may also suggest the need for interventions temporally adjusted to the late-luteal phase to target cycle-phase-specific momentary psychological processes (as discussed in Nayman et al., 2023a). For this purpose, however, potential cycle-phase specific psychological mechanisms of action need to be uncovered.

Aims

The current study first aimed to compare mood and cortisol cyclicity in AFAB individuals with rPMDD, diagnosed via a structured clinical interview for PMDD, and healthy controls (HCs). The second aim was to examine cycle-related associations of habitual and momentary repetitive negative thinking (RNT) and present-moment-awareness (PMA) with momentary mood and cortisol. Overall, the following hypotheses were formulated:

Hypothesis 1: In individuals with rPMDD, we expected higher negative affect (NA) and lower positive affect (PA) during the late-luteal phase compared to the follicular phase, whereas no mood cyclicity in HCs was expected.

Hypothesis 2: Furthermore, we hypothesized that HCs would show lower cortisol levels during the late-luteal phase compared to the follicular phase. In individuals with rPMDD, we expected lower cortisol levels compared to HCs over the cycle and lacking cyclicity.

Hypothesis 3: (a) Lower habitual RNT and (b) higher habitual PMA were hypothesized to be linked to better mood only during the follicular phase in rPMDD (cf. Nayman et al., 2023a), whereas no cycle-phase-specific associations of these traits with momentary mood were expected in HCs.

Hypothesis 4: In contrast, (a) lower momentary rumination (as a state manifestation of RNT) and (b) higher momentary PMA (as a state manifestation of PMA) were expected to predict lower subsequent NA and higher subsequent PA, especially during the late-luteal phase in individuals with rPMDD, whereas no cycle-specific effects were expected in HCs.

Finally, the effects of habitual and momentary RNT and PMA on the cyclical course of cortisol were exploratively investigated in individuals with rPMDD and HCs.

3.3 Methods

Participants

Individuals with rPMDD (*n* = 60) and healthy controls (HC; *n* = 60) were recruited via online advertisement on the website of the Central Institute of Mental Health (CIMH) in Mannheim, Germany, and via social media and online PMDD support groups. They either had to meet the DSM-5 diagnostic criteria for PMDD (rPMDD group) or had to be free of any core mood symptoms of PMDD (HC group), assessed using the Structured Interview for PMDD (SCID-PMDD, Accortt et al., 2011; see below). Exclusion criteria for both groups comprised a) age < 20 and > 42 years (to ensure regular post-menarche ovulatory cycles, a minimum age of 20 years was selected; Itriyeva, 2022), b) shift working (regular late and night shifts), and c) regular intensive exercising (> one hour/day) due to their potential impact on cortisol activity (Schlotz, 2019), and d) use of oral contraceptives or medication with lasting effects on cortisol activity during the last six months, e) pregnancy or lactating during the last six months, f) irregular menstrual cycle (fluctuations > 5 days), g) average cycle length of < 22 or > 34 days, h) BMI < 18 or > 35, i) current comorbid depressive episode or panic, generalized

anxiety, eating or substance use disorder, j) lifetime history of bipolar disorder or psychosis, and k) hysterectomy, ovariectomy or current endometriosis. In total, 229 individuals were screened for the rPMDD group and 125 for the HC group. Based on the predefined in- and exclusion criteria, 69 participants were recruited per group. In each group, nine participants dropped out of the study due to an anticipated temporal overload during the study. Consequently, the final sample resulted in N = 120 with n = 60 participants in each group, which were concurrently recruited and individually matched with respect to age and highest school degree.

Procedure

The data collection for the present study consisted of a telephone screening, a baseline session and an Ambulatory Assessment (AA) part during daily life. After the telephone screening to preliminarily check for inclusion and exclusion criteria, potentially eligible participants were invited to the baseline session, which was held either in person at the CIMH (n = 19 participants with rPMDD; n = 17 HCs), or, due to Covid-19-related contact restrictions, online via RedConnect (Red Medical Systems GmbH, Munich, Germany; n = 41 rPMDD group; n = 43 HCs). The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants provided written informed consent and were compensated with 120€ for study completion.

Baseline Measures

Psychopathology. The PMDD criteria were assessed with the SCID-PMDD (Accortt et al., 2021; interrater reliability κ = 0.96), which was adapted for DSM-5 criteria (cf. Nayman et al., 2023a). The SCID-PMDD assesses all eleven symptom criteria of PMDD with respect to their presence, onset and offset during the cycle as well as their frequency during the last 12 months, together with the criterion of relational, occupational, and recreational impairment or distress and the exclusion criterion of a mere exacerbation of symptoms of another disorder (cf. Kuehner & Nayman, 2021). In order to keep the participants' burden within the extensive AA-design at a reasonable level and the compliance rate high, the diagnostic criteria were not prospectively verified by daily symptom ratings during two symptomatic cycles. Current and lifetime psychiatric

comorbidities and exclusion criteria were checked using the Structured Clinical Interview for DSM-IV-TR Axis I (SCID-I; Wittchen et al., 1997). All interviews were conducted by trained research psychologists.

Trait repetitive negative thinking (RNT). The German version of the 15-item Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011) was administered to measure the habitual tendency to engage in RNT on a 5-point Likert scale - with higher scores indicating higher levels of RNT (Cronbach's α in the present study = 0.959).

Trait present-moment-awareness (PMA). The German version of the 15-item Mindful Attention Awareness Scale (MAAS; Brown & Ryan, 2003) was used to assess participants' habitual tendency to be attentive and aware of present-moment experiences on a 6-point Likert scale – with higher scores indicating greater PMA (Cronbach's α in the present study = 0.837).

Ambulatory Assessment (AA)

The AA was carried out in two different cycle phases (follicular and late-luteal phase) on four consecutive days each, resulting in eight assessment days in total, by using smartphones (Motorola e^{6s}, Motorola g^{8}, Nokia 4.2) with the software movisensXS, Version 1.5.12 (movisens GmbH, Karlsruhe, Germany, 2020).

In order to identify the relevant assessment days, an individual cycle calendar was created for each participant, based on the reported average cycle length and the onset date of the last menses. The expected date of ovulation was calculated using the backward counting method (Schmalenberger et al., 2021) and was validated during a chromatographic ovulation testing phase using Femometer® LH ovulation rapid test strips (sensitivity: 25 mIU/ml) and a corresponding smart app with an intelligent interpretation function (Femometer® app). The ovulation testing phase was scheduled around the expected date of ovulation. Participants were instructed to conduct an ovulation test every evening at a similar time until receiving a positive result. In case of negative or invalid testing results, participants were asked to repeat the ovulation testing during the next cycle and the AA of the late-luteal phase was postponed to the next cycle. Assessments during the follicular phase were scheduled for days six to nine of the menstrual cycle (cycle-day of AA-start: M_{rPMDD} = 6.18, SD_{rPMDD} = 0.57; M_{HCs} = 6.15, SD_{HCs} = 0.52) and during the late-luteal phase for the last four days before the onset of the next menses (cycle-day of AA-start: M_{rPMDD} = 25.47, SD_{rPMDD} = 2.44; M_{HCs} =

25.17, SD_{HCs} = 2.58). To avoid sequence effects, the AA-start was randomized between the follicular and the late-luteal phase. Among participants with rPMDD, 61.7% started in the follicular phase and 38.3% in the late-luteal phase whereas 55.0% of HCs started in the follicular and 45.0% in the late-luteal phase.

Participants were asked to wake up no later than 8:00 a.m. on each AA day. The AA started at a fixed time-point at 9:00 a.m. followed by seven further assessments at semi-random time points until 9:30 p.m. with inter-assessment intervals varying between 45 and 165 min. Each assessment was announced by an acoustic signal or vibration alert and took 2 to 5 min. Assessments could be rejected or postponed for up to 15 min. Rejected or ignored signals were coded as missing. At each prompt, participants were asked to rate their momentary mood and cognitions. After a time lag of 10 min, they were instructed to collect saliva samples.

State rumination. Momentary rumination was assessed on a 7-point Likert scale ranging from 1 (not at all) to 7 (very much) with the item "*At the moment, I am stuck on negative thoughts and cannot disengage from them*", thereby reflecting the uncontrollability facet of rumination (cf. Beddig et al., 2020; Schricker et al., 2023b).

State PMA. Participants indicated their momentary PMA on a 7-point Likert scale ranging from 1 (not at all) to 7 (very much) using the item "*At the moment, I am attentive to the present moment, without thinking about the past or the future*", which was adapted from the MAAS (Brown & Ryan, 2003).

Momentary mood. NA and PA were assessed using 12 items, which were derived from the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) and previous AA studies (e.g., Beddig et al., 2019; Nayman et al., 2023a; Schricker et al., 2023b). For momentary NA, participants rated how *upset*, *irritated*, *nervous*, *listless*, *down*, and *bored* they felt and for momentary PA how *cheerful*, *energetic*, *enthusiastic*, *satisfied*, *relaxed*, and *calm* they felt at the moment on a 7-point Likert scale ranging from 1 (not at all) to 7 (very much).

Salivary measure of cortisol. Participants were instructed to restrain from general strenuous exercise during AA days and from eating, drinking anything but water, smoking, intense physical exercise and brushing their teeth during the 10 min between subjective AA and saliva collection (cf. Schlotz, 2019). Ten min after each subjective assessment, participants were asked to collect saliva samples with standard salivettes

(Sarstedt, Germany), resulting in eight saliva samples per day. In addition, they were instructed to indicate whether they had eaten, drunk anything but water, smoked, or brushed their teeth (binary items: yes/no each) and to which extent they were physically active (7-point Likert scale: 1 = not at all to 7 = very much) during the last 10 min. At the first assessment, the smartphone provided a random three-digit code, which had to be recorded on the salivette bag of the respective assessment day. Saliva samples were stored in participants' home freezers until being returned and were subsequently frozen at −20 °C at the laboratory of the Department of Biopsychology, Technical University of Dresden, Germany, prior to biochemical analysis. Samples were centrifuged at 3000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary concentrations were measured using commercially available chemiluminescence-immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were below 9%.

Sleep. Time of awakening, sleep duration in hours as well as sleep quality ('*How did you sleep last night?*' 7-point Likert scale: 1 [very bad] - 7 [very good]) were assessed by single items at the first assessment at 09:00 a.m.

Statistical analyses

Group comparisons (rPMDD group vs. HCs) regarding demographic and clinical variables and aggregated person-mean scores of AA-variables were computed using t-tests for continuous and Chi-square tests for dichotomous variables. Due to the hierarchical data structure with daily assessments (level 1) nested within participants (level 2), we fitted multilevel models (MLM) for main analyses.

First, the following pre-processing steps were conducted: Cortisol data were log-transformed to adjust for skewness, and outliers more than three standard deviations from the group mean were winsorized to three standard deviations (Schlotz, 2019; Stalder et al., 2016). Then, intercept-only-models were fitted to estimate intraclass correlation coefficients (ICC) for all AA-variables (i.e., NA, PA, rumination, present-moment-awareness, cortisol). Finally, trait predictors were centered around the group-specific grand-means for between-subject effects, and state predictors around the cycle-phase-specific person-means for within-subject effects (Neubauer & Schmiedeck, 2020). Furthermore, confounder analyses were run. For all outcomes (i.e., NA, PA, cortisol), assessment day and time since first assessment at 09:00 a.m. were checked

as possible confounders with additional confounder analyses for cortisol activity which included medication use, time of awakening, BMI, habitual smoking, sleep quality, sleep duration, age as well as eating, drinking, smoking, brushing the teeth and physical activity during the last 10 min. If significant, the respective possible covariates were retained in the MLMs, which applied for assessment day regarding all outcomes, and additionally time since first assessment, time of awakening as well as smoking and physical activity during the last 10 min for cortisol as outcome.

Study hypotheses were tested with random-intercept-models using restricted maximum likelihood estimation. First, cycle-related variations in NA, PA and cortisol were investigated by separate MLMs including group (rPMDD vs. HCs) and cycle phase (follicular vs. late-luteal phase) as well as their interaction *group*cycle phase* as predictors (Hypotheses 1 and 2). Thereafter, the moderation effects of cognitive traits on cyclical variations of mood and cortisol were estimated by further separate MLMs per group including cycle phase and trait RNT or PMA as well as their interaction *cycle phase * trait* as predictors (Hypotheses 3a, b). Finally, cross-lagged MLMs were estimated, in which (time-lagged; T-1) states of rumination or PMA predicted subsequent states of NA and PA at time T in dependence of the cycle phase (Hypotheses 4a, b). In particular, cross-lagged MLMs included cycle phase and states of rumination or PMA as well as their interaction *cycle-phase * state* as predictors. These models additionally included grand-mean centered aggregated person-means of level-1 predictors to isolate within- from between-subject components (Bolger & Laurenceau, 2013), as well as the lagged outcome (i.e., NA_{T-1} or PA_{T-1}) to control for carryover effects. For an exemplary equation, see Equation S1 in the online supplemental materials. Following a reviewer's suggestion, we run additional cross-lagged MLMs to examine the interaction effects of cycle phase by both NA and PA at T-1 on subsequent rumination and PMA at time T. These models included cycle phase and states of cycle-phase-specific within-person-centered NA or PA as well as their interaction *cycle-phase * state* as predictors, together with grand-mean-centered aggregated person-means of these mood predictors and lagged outcomes. In case of significant interaction effects, we subsequently estimated simple slopes for respective trait or state cognitions on mood and cortisol per cycle phase in post-hoc analyses. As our analyses were based on preformulated hypotheses, our main analyses were not adjusted for multiple testing (Armstrong, 2014).-The summary-statistics-based power analysis for mixed-effects models

(Murayama et al., 2022) revealed that our sample size per group (*n* = 60 each) was sufficient to achieve 80% power to detect small to medium effect sizes with α set at .05. All statistical analyses were conducted via IBM SPSS Statistics Version 28 (IBM Corp., 2021) with the significance level set at α = 0.05.

3.4 Results

Descriptives

Descriptive statistics on demographics, clinical and psychological measures are presented in Table 3.1. Participants with rPMDD reported higher habitual RNT and lower habitual PMA than HCs. Across groups, 6974 subjective ambulatory assessments out of possible 7656 assessment points were completed, which resulted in an overall compliance rate of 92.0%, reflecting a high level of compliance (cf. Wrzus & Neubauer, 2023). There were no group differences identified with respect to compliance (rPMDD: 92.1%, HC: 90.1%), $t(118) = 1.53$, $p = .130$. Regarding cortisol samples, the average compliance rate across groups amounted to 91.7%, again with no significant group differences (rPMDD: 91.9%, HC: 91.6%), $t(118) = 0.20$, $p = .840$. The ICCs, means, standard deviations (within and between persons) and group comparisons regarding all AA-variables are presented in Table 3.2. In comparison to HCs, participants with rPMDD showed significantly higher momentary NA and rumination as well as lower PA, PMA and cortisol (all *p*s < .013; see Table 3.2). The ICCs of subjective AA-variables indicated higher within-subject variabilities in participants with rPMDD compared to HCs. At the between- and within-subject level, traits and subjective AA-variables showed weak to strong bivariate correlations, whereas their correlations with cortisol were consistently weak (see Table S1 in the online supplemental online materials).

Table 3.1

Demographic, clinical and psychological characteristics of individuals with retrospectively diagnosed Premenstrual Dysphoric Disorder (rPMDD) and mentally healthy controls (HC)

	rPMDD (*n* = 60)	HC (*n* = 60)	rPMDD vs. HC
	M (*SD*) / %	*M* (*SD*) / %	Test statistic
Demographic Variables			
Age	30.37 (5.99)	29.85 (5.31)	$t(118) = 0.50$, $p = .618$
Education (% with high school degree)	83.3%	90.0%	$\chi^2(1) = 1.15$, $p = .283$
Work situation (% in regular job or education)	93.3%	90.0%	$\chi^2(1) = .436$, $p = .509$
Children (%)	35%	18.3%	$\chi^2(1) = 4.26$, $p = .039$
BMI	22.40 (3.27)	23.43 (3.77)	$t(118) = -1.60$, $p = .113$
Clinical Variable			
SCID-I History of Diagnosis of Depression	11.7%	1.7%	$\chi^2(1) = 4.82$, $p = .028$
Psychological Variables			
Trait Repetitive Negative Thinking – PTQ	2.02 (0.75)	1.20 (0.73)	$t(118) = 6.06$, $p < .001$
Trait Present Moment Awareness – MAAS	4.20 (0.76)	4.82 (0.72)	$t(118) = -4.59$, $p < .001$

Note. BMI = Body Mass Index; SCID-I = Structured Clinical Interview for DSM-IV Axis I; PTQ = Perseverative Thinking Questionnaire; MAAS = Mindful Attention Awareness Scale. For PTQ and MAAS, mean scores were calculated

Interaction effects of group by cycle phase (Hypotheses 1 and 2)

The interaction effects of *group* by *cycle phase* on NA, $F(1, 6860) = 966.33$, $p < .001$, PA, $F(1, 6864) = 855.55$, $p < .001$, and cortisol activity, $F(1, 6376) = 11.85$, $p < .001$, were significant. In participants with rPMDD, simple effect analyses revealed higher NA (mean difference = 1.06, $SE = 0.03$, $p < .001$) and lower PA (mean difference = -1.17, $SE = 0.03$, $p < .001$) during the late-luteal phase compared to the follicular phase, indicating significant mood cyclicity (see Figure 3.1). In HCs, no associations of cycle phase with NA (mean difference = -0.02, $SE = 0.03$, $p < .380$) and PA (mean difference = -0.01, $SE = 0.03$, $p = .770$) were identified (see Figure 3.1). In contrast, cycle phase was associated with cortisol activity in HCs, indicating significantly lower cortisol levels during the late-luteal phase compared to the follicular phase in HCs (mean difference = -0.06, $SE = 0.02$, $p = .003$). Participants with rPMDD showed no significant cyclicity in cortisol activity (mean difference = 0.04, $SE = 0.02$, $p = .065$; see Figure 3.1).

Table 3.2

Descriptive and Variability Statistics for Ambulatory Assessment Variables

	rPMDD (n = 60)				HC (n = 60)				rPMDD vs. HC
AA-Variables	*M*	SD_{W-S}	SD_{B-S}	ICC	*M*	SD_{W-S}	SD_{B-S}	ICC	Test statistic[b]
Negative Affect	2.86	0.99	0.51	.20	2.03	0.55	0.56	.50	$t(118) = 8.45$, $p < .001$
Positive Affect	4.12	1.10	0.53	.18	4.94	0.68	0.71	.51	$t(118) = -6.69$, $p < .001$
Rumination	2.82	1.43	0.62	.15	1.93	0.89	0.65	.33	$t(118) = 7.62$, $p < .001$
State PMA	4.59	1.39	0.80	.24	5.06	1.16	1.05	.44	$t(118) = -2.76$, $p = .007$
Cortisol[a]	2.03	0.82	0.28	.13	2.17	0.81	0.31	.15	$t(118) = -2.51$, $p = .013$

Note. AA = Ambulatory Assessment; rPMDD = Retrospectively diagnosed Premenstrual Dysphoric Disorder; HC = Mentally Healthy Controls; PMA = Present Moment Awareness; SD_{W-S} = Within-subject standard deviation; SD_{B-S} = Between-subject standard deviation; ICC = Intraclass Correlation Coefficient. Means and between-subject standard deviations were calculated based on aggregated person-mean scores.
[a] log-transformed and winsorized to three standard deviations
[b] test statistic (t test) for mean differences between groups

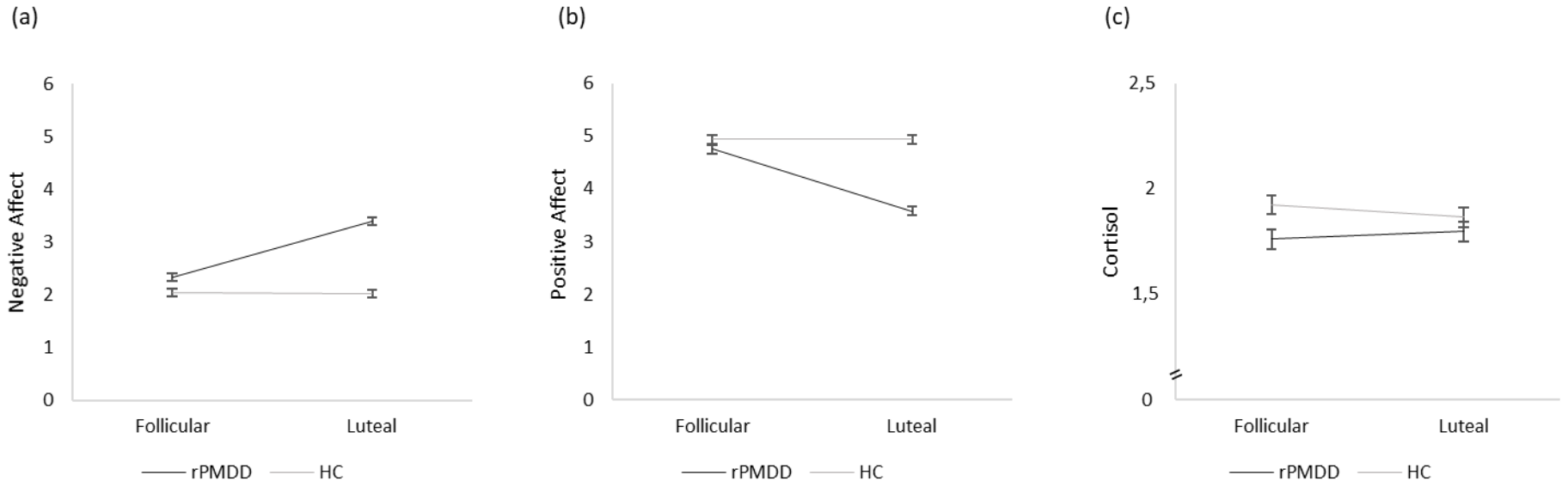

Figure 3.1 Interaction effects of group by cycle phase on momentary mood and cortisol activity

Note. Estimated mean values of momentary (a) negative affect, (b) positive affect and (c) log-transformed cortisol activity during the follicular and late-luteal phase in individuals with rPMDD and HC. rPMDD = Retrospectively diagnosed Premenstrual Dysphoric Disorder; HC = Healthy controls. Error bars represent standard errors of the mean.

Interaction effects of cycle phase by trait cognitions (Hypotheses 3a, b)

In participants with rPMDD, interaction effects of cycle phase by both trait RNT, $F_{NA}(1, 3452) = 71.75$, $p < .001$; $F_{PA}(1, 3454) = 47.76$, $p < .001$, and trait PMA, $F_{NA}(1, 3451) = 22.24$, $p < .001$; $F_{PA}(1, 3452) = 6.54$, $p = .011$, were significant for NA and PA in daily life. Results of respective estimated simple slopes are presented in Table 3.3. As depicted in Figure 3.2 for illustration purposes, in participants with rPMDD, both lower trait RNT and higher trait PMA were associated with lower NA and higher PA during the follicular phase whereas no associations of these traits with momentary mood were identified during the late-luteal phase (see Table 3.3). As expected, interaction effects of cycle phase by trait RNT on NA, $F(1, 3404) = 3.82$, $p = .051$ and PA, $F(1, 3406) = 0.67$, $p = .413$, were not significant in HCs. Contrary to our hypothesis, in HCs, the interaction effect of cycle phase by trait PMA was significant for NA, $F(1, 3404) = 14.75$, $p < 001$, indicating that HCs with higher trait PMA showed lower NA during the follicular and the late-luteal phase with a stronger association during the late-luteal phase (see Table 3.3). No interaction effect of cycle phase by PMA was identified for PA, $F(1, 3406) = 1.60$, $p = .260$. Finally, in both groups, the interaction effects of cycle phase by trait RNT, $F_{rPMDD}(1, 3205) = 0.65$, $p = .420$; $F_{HC}(1, 3167) = 1.90$, $p = .169$ and by trait PMA, $F_{rPMDD}(1, 3200) = 1.56$, $p = .211$; $F_{HC}(1, 3168) = 0.40$, $p = .530$, on cortisol activity were not significant.

Interaction effects of cycle phase by state cognitions (Hypotheses 4a, b)

For participants with rPMDD, interaction effects of cycle phase by both state rumination, $F_{NA}(1, 2797) = 10.12$, $p < .001$; $F_{PA}(1, 2798) = 5.05$, $p = .025$ and PMA, $F_{NA}(1, 2796) = 10.95$, $p < .001$; $F_{PA}(1, 2798) = 5.37$, $p = .021$ at time T-1 significantly predicted subsequent NA and PA at time T. Results of respective estimated simple slopes are presented in Table 3.3. In participants with rPMDD, lower state rumination and higher state PMA during the late-luteal phase predicted decreased subsequent NA and increased subsequent PA, whereas state rumination and PMA during the follicular phase did not show significant effects on subsequent mood (see Table 3.3). This indicates higher mood reactivity toward momentary cognitions during the late-luteal phase in individuals with rPMDD. In HCs, no interaction effects of cycle phase by state rumination, $F_{NA}(1, 2685) = 1.68$, $p = .196$; $F_{PA}(1, 2687) = 0.58$, $p = .445$ and PMA, $F_{NA}(1,$

2685) = 0.29, p = .592; F_{PA}(1, 2688) = 0.29, p = .591, on subsequent NA and PA were identified. Regarding cortisol as outcome, in participants with rPMDD the interaction effects of cycle phase by state rumination, F(1, 3194) = 3.10, p = .078 and PMA, F(1, 3194) = 0.69, p = .793, were not significant. In contrast, in HCs, interaction effects of cycle phase by both state rumination, F(1, 3160) = 4.04, p = .045 and PMA, F(1, 3158) = 5.15, p = .023, on cortisol activity 10 min later were identified. In particular, when HCs ruminated less than usual or showed more PMA than usual during the late-luteal phase, they exhibited stronger decreases in cortisol activity during this phase (see Table 3.3).

Additional interaction analyses (*cycle phase * momentary (state) mood*) revealed significant cycle-phase-specific effects of both NA and PA on subsequent momentary rumination, F_{NA}(1, 2801) = 17.83, p < .001; F_{PA}(1, 2799) = 15.57, p < .001, and PMA, F_{NA}(1, 2796) = 9.00, p = .003; F_{PA}(1, 2797) = 9.84, p = .002 in participants with rPMDD. Higher momentary NA during the late luteal phase predicted higher subsequent rumination, Estimate = 0.33, SE = 0.05, t(2800) = 7.20, p < .001 and lower PMA, Estimate = -0.26, SE = 0.04, t(2796) = -5.79, p < .001, whereas no such effects were found during the follicular phase (rumination: Estimate = 0.07, SE = 0.05, t(2801) = 1.34, p = .181; PMA: Estimate = -0.06, SE = 0.05, t(2797) = -1.03, p = .305). Higher momentary PA, in turn, predicted lower subsequent rumination during both the follicular, Estimate = -0.09, SE = 0.04, t(2800) = -2.09, p = .037, and the late luteal phase, Estimate = -0.30, SE = 0.04, t(2799) = -7.05, p < .001, with higher effects during the late luteal phase, as well as higher PMA during the late luteal phase, Estimate = 0.26, SE = 0.04, t(2797) = 6.38, p < .001, but not during the follicular phase, Estimate = 0.08, SE = 0.04, t(2798) = 1.84, p = .066. In HCs, no interaction effects of cycle phase * momentary (state) mood were found (all ps > .068).

Table 3.3

Estimated simple slopes of cognitive traits and states on negative affect, positive affect and cortisol activity per group and cycle phase

			Negative affect				Positive affect				Cortisol			
	Group	**Cycle Phase**	***B (SE)***	***df***	***t***	***p***	***B (SE)***	***df***	***t***	***p***	***B (SE)***	***df***	***t***	***p***
Traits														
Trait RNT	rPMDD	Follicular	0.32 (0.09)	64	3.64	<.001	-0.30 (0.09)	64	-3.17	.002				
		Luteal	6.14E-5 (0.09)	64	.001	.999	-0.01 (0.09)	65	-0.06	.955				
	HC	Follicular												
		Luteal												
Trait PMA	rPMDD	Follicular	-0.26 (0.09)	64	-2.99	.004	0.20 (0.09)	65	2.17	.034				
		Luteal	-0.08 (0.09)	65	-0.89	.378	0.09 (0.09)	65	0.98	.332				
	HC	Follicular	-0.24 (0.10)	60	-2.52	.015								
		Luteal	-0.35 (0.10)	60	-3.58	<.001								
States														
State Rumination	rPMDD	Follicular	-0.02 (0.02)	2797	-1.01	.315	-0.01 (0.02)	2798	-0.26	.795				
		Luteal	0.06 (0.02)	2797	3.15	.002	-0.07 (0.02)	2799	-3.32	<.001				
	HC	Follicular									0.02 (0.02)	3159	1.06	.290
		Luteal									0.06 (0.02)	3159	3.85	<.001
State PMA	rPMDD	Follicular	0.02 (0.02)	2795	1.09	.276	-0.02 (0.02)	2798	-1.10	.270				
		Luteal	-0.06 (0.02)	2795	-3.38	<.001	0.04 (0.02)	2798	2.01	.045				
	HC	Follicular									8.79E-5 (0.02)	3158	.01	.994
		Luteal									-0.04 (0.01)	3158	-3.20	.001

Note. Simple slope values are presented only for significant interaction terms of *cycle phase* by *trait or state*. RNT = Repetitive Negative Thinking; PMA = Present Moment Awareness; rPMDD = Retrospectively diagnosed Premenstrual Dysphoric Disorder; HC = Mentally Healthy Controls

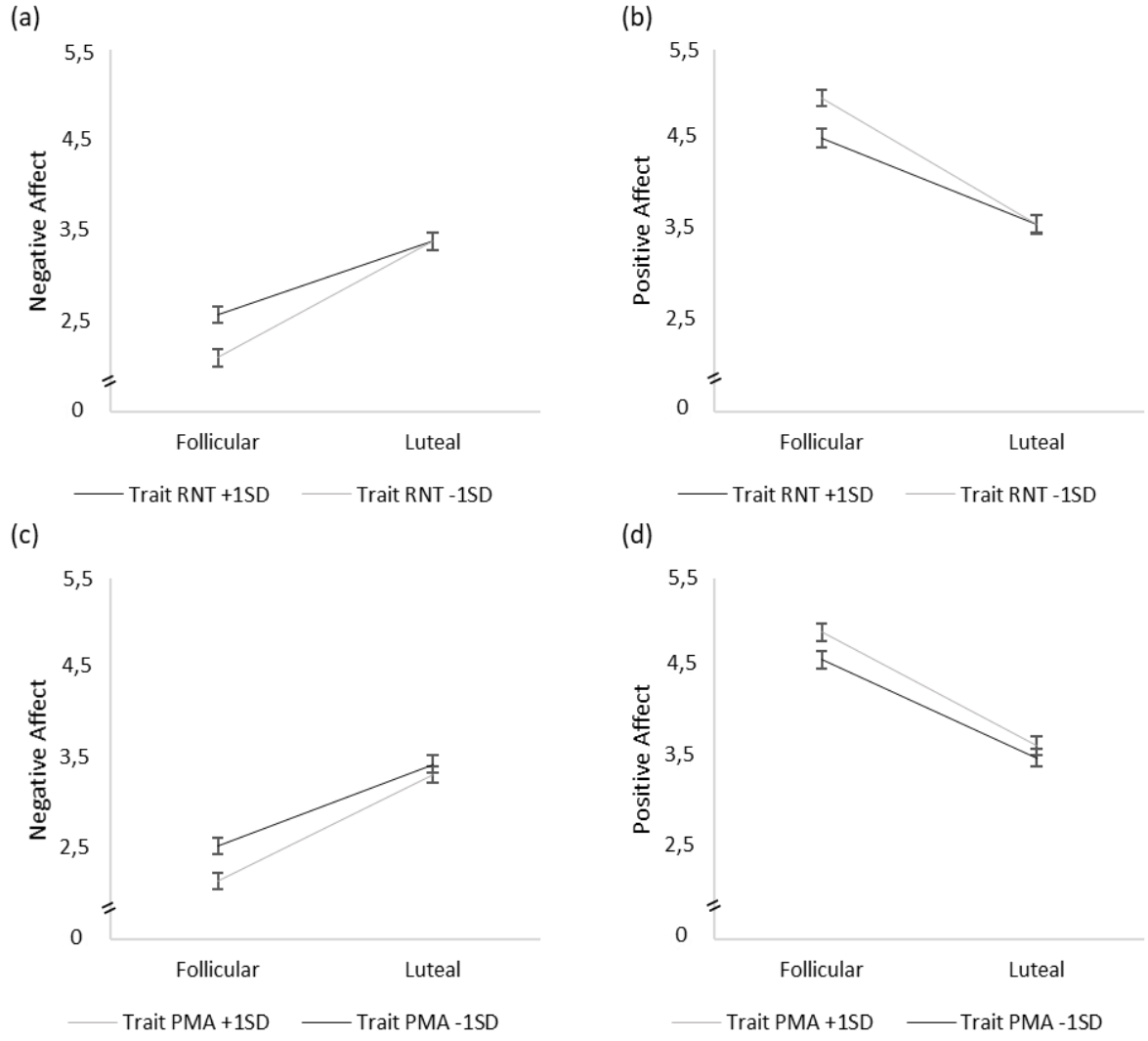

Figure 3.2 Interaction effects of cycle phase by cognitive traits on momentary mood and cortisol activity in individuals with retrospectively diagnosed Premenstrual Dysphoric Disorder (rPMDD)

Note. Estimated mean values of momentary negative affect and positive affect during the follicular and late-luteal phase for low and high scores in (a-b) trait RNT (± 1SD) and (c-d) trait PMA (± 1SD) in individuals with rPMDD. RNT = Repetitive Negative Thinking; PMA = Present Moment Awareness. Error bars represent standard errors of the mean

3.5 Discussion

The current study aimed to uncover possible cognitive psychological determinants of the menstrual-cycle-related course of mood and cortisol in AFAB individuals with PMDD in order to identify potential psychotherapeutic targets for PMDD. Our findings show that individuals with rPMDD exhibited pronounced mood cyclicity characterized by mood worsening toward the late-luteal phase, but not cortisol cyclicity. In contrast,

healthy controls (HC) did not show mood but cortisol cyclicity, characterized by a reduction in cortisol levels toward the late-luteal phase. Our study further showed that in individuals with rPMDD, not cognitive traits but respective cognitive states influenced subsequent mood during the late luteal phase. In particular, lower momentary rumination and higher momentary PMA predicted better subsequent mood during the late-luteal phase, indicating a higher mood reactivity toward momentary cognitions during this phase in PMDD. Neither cognitive traits nor cognitive states were associated with cortisol activity across the menstrual cycle in individuals with rPMDD. Within the HC group, individuals with higher trait PMA showed lower NA in both cycle phases, with a stronger association during the late-luteal phase, whereas state manifestations of rumination and PMA did not predict cyclical mood variations. In contrast, following moments in which HCs showed lower momentary rumination or higher PMA than usual during the late-luteal phase, they exhibited stronger decreases in cortisol levels.

Cyclical variations in mood and cortisol activity

The identified mood cyclicity with premenstrual increases in NA and premenstrual decreases in PA in individuals with rPMDD (but not in HCs) is in line with a previous AA-study (Beddig et al., 2020). In contrast, HCs but not individuals with rPMDD, showed cortisol cyclicity with lower cortisol levels during the late-luteal phase. This finding supports previous meta-analyses pointing to slightly lower cortisol levels during the luteal phase in nonclinical samples (Hamidovic et al., 2020; Klusmann et al., 2022). Such lower cortisol levels during the luteal phase in healthy individuals may be explained by premenstrual increases in ALLO levels, which in turn negatively modulate HPA-axis activity (Li & Graham, 2017), resulting in reduced cortisol levels (Hamidovic et al., 2020; Klusmann et al., 2022). Individuals with rPMDD, in turn, showed lower cortisol concentrations than HCs irrespective of cycle phase, which supports previous findings for blunted cortisol activity in individuals with PMDD (Beddig et al., 2019; Girdler et al., 2003), similar to other stress-related psychological disorders such as posttraumatic stress disorder (Adam et al., 2017; Ehlert et al., 2001). Low cortisol levels across the cycle and lacking cortisol cyclicity may indicate a dysfunctional HPA-axis activity and reflect an endocrinological marker for PMDD, which in turn may impair emotion processing (e.g., Sundström-Poromaa et al., 2020) and predict a more severe clinical symptom course of PMDD (Beddig & Kuehner, 2020).

Interaction of cycle phase with habitual RNT and PMA on mood and cortisol activity

Low habitual RNT and high habitual PMA did not seem to protect against premenstrual mood worsening in individuals with rPMDD. More precisely, favorable levels in these cognitive traits were linked to better mood during the follicular but not during the late-luteal phase. Consequently, individuals with favorable cognitive trait levels showed stronger mood worsening toward the late-luteal phase, thereby converging with those with more unfavorable trait levels. These results replicate findings from a previous AA-study (Nayman et al., 2023a), demonstrating that favorable cognitive traits do not seem to be protective against premenstrual mood worsening in PMDD. Thus, both studies independently show that adaptive cognitive tendencies to regulate emotions may not adequately be accessed or effectively used during the late-luteal phase in individuals with PMDD.

Within the HC group, individuals with higher habitual PMA showed lower NA across both cycle phases. Contrary to our expectations, the association of habitual PMA with NA was stronger during the late-luteal phase, indicating that also in healthy individuals, trait PMA appears to be associated with mood variations across the menstrual cycle. Similarly, Welz et al. (2016) showed premenstrually increased calmness, positive valence and energetic-arousal in daily life in healthy individuals with low (vs. high) trait anxiety. One reason for these findings could be that protective traits such as PMA or lower trait anxiety possibly strengthen the described anxiolytic and sedative effects of ALLO in healthy individuals during the luteal phase (Bäckström et al., 2014; Timby et al., 2016). This conclusion is, however, clearly speculative and should be investigated in more detail in further studies.

Regarding cortisol activity, habitual cognitive factors did not show moderating effects on cycle-related variations in individuals with rPMDD or in HCs, which is in line with previous findings by Nayman et al. (2023a). Given cortisol's dynamic nature, context-specific within-subject fluctuations, in particular cycle-phase-specific cognitive states at the micro-level appear to shed more light on cortisol variations across the menstrual cycle, as described below.

Interaction of cycle phase with momentary rumination and PMA on mood and cortisol activity

While trait manifestations of cognitions reflect between-subject differences, respective state manifestations also entail fine-grained context-specific within- subject variations. The investigation of the dynamic interplay of momentary cognitive processes with mood and cortisol in daily life allows to take their possible cycle-related within- subject variations into account. In fact, in the current study, menstrual cycle and cognitive states interacted to predict mood changes in individuals with rPMDD. Specifically, during the late-luteal phase, stronger mood deterioration (increased NA and decreased PA) was observed following moments in which individuals ruminated more or showed less PMA than usual. Similarly, the previous study by Beddig et al. (2020) showed that individuals with rPMDD reported increased NA following moments in which they ruminated more than usual especially during the late-luteal phase, indicating stronger mood-impairing effects of momentary rumination during the late-luteal phase in PMDD. Conversely, higher NA and lower PA predicted higher subsequent momentary rumination and lower PMA, particularly during the late luteal phase. This highlights that reciprocal effects of cognitive processes and mood deteriorations in individuals with PMDD are particularly evident in the late luteal phase, indicating that these individuals may be premenstrually more sensitive to detrimental effects of either dimension.

Within the HC group, momentary cognitions did not predict cycle-related mood variations. Relatedly, Schricker et al. (2023b) recently showed momentary rumination to predict a stronger decrease in subsequent PA in individuals with remitted recurrent depression but not in HCs. This is consistent with the current results showing that momentary mood was not influenced by momentary rumination or PMA either in the non-symptomatic follicular phase in individuals with rPMDD or in any cycle phase in HCs. Thus, increased mood reactivity toward higher levels of momentary rumination and lower levels of momentary PMA might represent a risk factor particularly deteriorating mood during vulnerable states such as the late-luteal phase in individuals with PMDD or in individuals vulnerable for depressive relapses.

In individuals with rPMDD, state cognitions did not show any significant impact on the menstrual-cycle-related course of cortisol activity. In contrast, when HCs reported lower momentary rumination or higher momentary PMA than usual during the late-

luteal phase, they exhibited a stronger decrease in cortisol activity during this cycle phase. Thus, favorable state cognitions may possibly strengthen the described inhibitory effects of ALLO on the HPA-axis in healthy individuals (cf. Almeida et al., 2021; Pisu et al., 2022) to predict stronger decreases in cortisol levels from the follicular toward the late-luteal phase.

Clinical implications

In sum, our results point to differential effects of trait and state manifestations of cognitive processes in PMDD and imply that favorable cognitive traits do not protect individuals with PMDD from premenstrual mood deterioration whereas respective cognitive states (i.e., lower momentary rumination and higher momentary PMA) predict weaker premenstrual mood worsening in affected individuals. This may indicate possible limitations of general cycle-independent psychotherapeutic interventions addressing habitual cognitions (cf. Nayman et al., 2023a). Thus, when aiming to improve premenstrual mood in individuals with PMDD, interventions targeting momentary protective cognitions directly during the late-luteal phase might be more effective, which should be evaluated in future research. Adjusting psychotherapeutic interventions to cycle-phase-specific targets has already been proposed for other psychological disorders such as anxiety or trauma- and stressor-related disorders (Li & Graham, 2017; Pineles et al., 2016) e.g., by intensifying cognitive restructuring during the luteal phase or targeting exposure-based CBT elements specifically during cycle phases with increased oestradiol levels in patients with anxiety disorders (Li & Graham, 2017). In PMDD, micro-interventions targeting momentary rumination and PMA, but also more specific PMDD symptoms such as irritability or lack of a sense of control immediately during the late-luteal-phase may hold the potential to directly address the cyclical dynamics in the interplay of cognitions and mood. Along these lines, subjective and sensor data assessed via AA may be suitable to deliver tailored brief and specific just-in-time adaptive interventions in moments with high levels of distress or in moments of changing internal (e.g., rumination) and contextual (e.g., cycle phase) states (c.f. Nahum-Shani et al., 2018; Schick et al., 2022).

Furthermore, cortisol cyclicity with lower levels during the late-luteal phase, and stronger cortisol reductions in moments with favorable cognitive states during the late-luteal phase of healthy individuals may reflect adaptive processes of the HPA-axis. In

contrast, generally reduced cortisol activity together with a lack of cortisol cyclicity as well as a reduced cortisol response toward cognitions in PMDD might be reflective of a possible pathophysiological marker and support initial evidence for dysregulated HPA-axis activity in PMDD.

Strengths and limitations

To our knowledge, this study is the first investigating the interplay of RNT and PMA at the trait and state level with mood and cortisol in daily life, thereby taking the menstrual cycle into account in both individuals with rPMDD and healthy individuals. This study is an extension of the previous AA-study by Nayman et al. (2023a) with an independent sample and an augmented study design by also including healthy individuals and investigating state manifestations of cognitive traits. Strengths of the current study include repeated assessments of subjective measures and cortisol activity across the menstrual cycle, thereby replicating cortisol cyclicity in healthy individuals, which has been recently reported in two meta-analyses (Hamidovic et al., 2020; Klusmann et al., 2022). Moreover, the present AA-design helps to minimize possible recall bias, to increase ecological validity (Mestdagh & Dejonckheere, 2021) and to capture cycle-specific variations and interactions of cognitive states with mood states and cortisol in a within-subject design. A further strength is the use of chromatographic ovulation tests for the validation of cycle phases.

Nevertheless, the present findings should be considered in light of some limitations. First, in order not to overburden participants within the extensive AA-study-design, PMDD diagnoses were assessed retrospectively by administering a structured and validated diagnostic interview (SCID-PMDD; Accortt et al., 2011) but were not confirmed by daily ratings over two consecutive cycles as requested in DSM-5 for a definite diagnosis (APA, 2013). Thus, the PMDD-diagnoses in the present study must be considered provisional (APA, 2013). Second, in order to avoid sequence effects, the AA-start was counterbalanced between the follicular and late luteal phase. This approach led to the limitation that for individuals who started during the follicular phase, the assessments of the follicular and late-luteal phase covered different perimenstrual windows. However, assessed symptom cyclicity should ideally center around the emergence of symptoms in the luteal phase and their clearance in the following follicular phase (i.e., in the same perimenstrual window; cf. Schmalenberger et al. 2021). Third,

the generalizability of the current results might be limited by our strict selection criteria during the recruitment phase, excluding individuals with specific psychiatric comorbidities and those taking psychotropic drugs. Fourth, state rumination, by focusing on its process character uncontrollability, as well as state and trait PMA were assessed unidimensionally, and future research could profit from including other facets of state rumination (e.g., content-related aspects; cf. Rosenkranz et al., 2020) and of mindfulness (e.g., nonjudgmental acceptance; cf. Blanke & Brose, 2017) in addition to PMA. Moreover, additional fine-grained assessments of contextual characteristics within cycle phases (i.e., current social or physical activities) by combining active (e.g., momentary self-reports) and passive data acquisition (e.g., mobile sensing) may advance our understanding of risk factors as well as of critical external and internal determinants (Schick et al., 2022) of mood and cortisol variability in PMDD. Lastly, whereas within-subject couplings with time-lagged analyses, as done in the present study, are considered a good starting point to uncover potential causal associations, there is need for additional within-subject experimental approaches in daily life (cf. Huffziger et al., 2013; Kuehner et al., 2023; Schmiedek & Neubauer, 2020).

Conclusions

This study underlines the relevance of the distinction between trait and state cognitions in AFAB individuals with PMDD. Especially late-luteal-phase-specific momentary rumination and PMA seem to represent possible internal contributing factors for premenstrual mood variations and might reflect potential cycle-specific intervention targets for PMDD. Alterations in the HPA-axis characterized by reduced cortisol levels with lacking cyclicity, possibly reflecting a pathophysiological marker in PMDD, warrant further research.

CHAPTER IV: INDUCED RUMINATIVE AND MINDFUL SELF-FOCUS IN DAILY LIFE ACROSS THE MENSTRUAL CYCLE IN WOMEN WITH AND WITHOUT PREMENSTRUAL DYSPHORIC DISORDER (STUDY 3)

An adapted version of this chapter has been published as **‘**Nayman, S., Schricker, I. F., Reinhard, I., Grammatikos, I., & Kuehner, C. (in press). Induced Rumination and Mindful Self-focus in Daily Life across the Menstrual Cycle in Women with and without Premenstrual Dysphoric Disorder. *Behaviour Research and Therapy*. https://doi.org/10.1016/j.brat.2024.104630**’**

4.1 Abstract

Rumination and mindfulness are transdiagnostic risk and protective factors while their role in Premenstrual Dysphoric Disorder (PMDD) is unclear. Thus, we aimed to investigate the cycle-phase-specific effects of rumination and mindful self-focus on momentary mood and cognitions in women with and without PMDD. This study involved brief ambulatory inductions of ruminative and mindful self-focus along with ambulatory assessments of negative (NA) and positive affect (PA), and rumination, present-moment-awareness (PMA) and self-acceptance on two days during both the follicular and late luteal phase in women with and without PMDD (n = 60 each). Compared to healthy controls, women with PMDD showed stronger increases in PA in response to mindful self-focus inductions during the late luteal phase, whereas no such group differences were identified during the follicular phase. Independent of clinical status and cycle phase, induced ruminative self-focus immediately increased momentary NA and rumination and decreased PMA, whereas induced mindful self-focus inductions increased momentary self-acceptance. Overall, higher PA-reactivity toward mindful self-focusing during late-luteal-phase-specific in women with PMDD points to the potential of cycle-phase-specific mindfulness interventions for PMDD. Irrespective of cycle phase, rumination and mindfulness appear to represent targets for brief prevention and intervention measures for both non-clinical and clinical groups.

4.2 Introduction

Premenstrual Dysphoric Disorder (PMDD) is characterized by impairing or distressing menstrual cycle dependent affective core symptoms and additional psychological and somatic symptoms, which occur during the late luteal phase and subside within a few days after menses during the follicular phase (American Psychological Association [APA], 2013). Cross-sectional studies showed that women with PMDD tend to use maladaptive emotion regulation strategies, exhibiting higher levels of habitual rumination and lower levels of habitual mindfulness compared to healthy controls (Eisenlohr-Moul, 2019; Nayman et al., 2023a). At first glance, this suggests that trait rumination and mindfulness could be potential psychotherapy targets in PMDD, as has been demonstrated for other affective disorders such as major depressive disorder (Enkema et al., 2020; Watkins & Roberts, 2020).

Previous research suggests that in non-clinical and transdiagnostic clinical samples, individuals with higher habitual (trait) mindfulness appear to ruminate less in daily life (Enkema et al., 2020) and exhibit lower affective symptoms (Carpenter et al., 2019). Moreover, mindfulness-based interventions reduce symptoms of a wide range of mental disorders, particularly in depression, substance use disorders and chronic pain (Creswell, 2017; Enkema et al., 2020; Goldberg et al., 2018, 2022). One potential pathway through which mindfulness may exert its beneficial effects is by enhancing the self-regulation of attention towards a non-judgmental awareness of the present moment and thereby reducing rumination (e.g., Perestelo-Perez et al., 2017). Relatedly, mindfulness-based interventions have been found to significantly reduce rumination (Li et al., 2022; Mao et al., 2023; Perestelo-Perez et al., 2017; Timm et al., 2018).

However, in the context of PMDD, two recent independent Ambulatory Assessment (AA) studies have shown that in women with PMDD, lower habitual rumination and higher habitual mindfulness were associated with improved mood during the follicular phase but not during the symptomatic late luteal phase (Nayman et al., 2023a, 2024). These findings possibly suggest that adaptive cognitive dispositions may not protect women with PMDD from premenstrual mood worsening. Consequently, there may be limitations of psychotherapy approaches that solely address these traits. In contrast, considering the menstrual cycle related dynamics of time-varying cognitive states in

women with PMDD, Beddig et al. (2019) demonstrated that state rumination was elevated during the late luteal phase in women with PMDD and predicted higher subsequent momentary increases in negative affect in this phase compared to the follicular phase (Beddig et al., 2020). Relatedly, Nayman et al. (2024) showed that lower state rumination and higher state present-moment-awareness during the late luteal phase, but not during the follicular phase, predicted better subsequent momentary mood. This suggests higher affective reactivity toward momentary cognitions during this phase in PMDD. Consequently, it may be more effective to address late-luteal-phase-specific momentary rumination and PMA as potential cycle-specific intervention targets for women with PMDD (Nayman et al., 2024).

While AA-designs with intensive longitudinal assessments in daily life hold the potential to uncover *causal* associations by investigating cross-lagged within-person couplings of momentary cognitive states with subsequent affective states, experimental approaches still represent the gold standard for such research questions (Schmiedek & Neubauer, 2020). Corresponding within-subject experimental approaches in daily life are highly warranted, combining the quality characteristics of high internal validity of laboratory studies with the higher ecological validity of AA studies. As for now, experimental approaches have primarily been limited to laboratory settings, with only a few studies that have transferred experimental designs into daily life using AA (e.g., Kuehner et al., 2023; Huffziger et al., 2012, 2013). In two non-clinical samples (Huffziger et al., 2012, 2013), induced ruminative self-focus predicted immediate mood worsening and increases in momentary rumination, supporting the conceptualization of rumination as a cognitive risk factor for mood deterioration. Conversely, an induced mindful self-focus specifically led to increases in momentary calmness (Huffziger et al., 2013), emphasizing mindfulness as an adaptive state. A recent study using the same experimental ambulatory induction paradigm showed detrimental effects of induced ruminative self-focus compared to mindful self-focus on momentary cognitions in individuals with remitted Major Depressive Disorder (rMDD) compared to healthy controls (Kuehner et al., 2023). Specifically, the clinical sample exhibited more pronounced increases in rumination and decreases in self-acceptance during rumination inductions compared to mindful self-focus inductions, pointing to heightened cognitive reactivity in rMDD (Kuehner et al., 2023).

Until now, there has been a lack of experimental AA-studies that incorporate experimental inductions in daily life to examine causal effects of induced ruminative and mindful states in women with PMDD. In PMDD research, such experimental approaches would allow to consider possible menstrual-cycle-related variations in the effects of ruminative and mindful self-focus on momentary cognitions and mood. Consequently, understanding potential cycle-phase-specific variations in these effects might help develop respective cycle-related cognitive interventions to realize their full potential for women with PMDD.

Aims of the present study

The current study aimed to investigate the effects of experimental ambulatory inductions of ruminative and mindful self-focus in an ecologically valid setting on negative (NA) and positive affect (PA), momentary rumination, present-moment-awareness (PMA), and self-acceptance in women with and without PMDD throughout the menstrual cycle. Building upon recently identified more pronounced positive effects of lower state rumination and higher state mindfulness on mood during the late luteal phase, as opposed to the follicular phase, in women with PMDD, we expected more pronounced differential effects of ruminative vs mindful self-focus inductions in women with PMDD compared to healthy controls, especially during the late luteal phase.

4.3 Methods

Participants

This study is part of a larger project (Nayman et al., 2024) and expands previous analyses on cycle related associations of cognitive states and mood in women with PMDD and healthy controls by including ambulatory inductions of ruminative and mindful-self-focus. The current study included 60 women with PMDD according to the DSM-5 criteria for PMDD and 60 women without PMDD who were free of any affective PMDD symptoms. The two groups were matched for age and level of education. Exclusion criteria included a) age < 20 and > 42, b) BMI < 18 and > 35, c) shift work, including regular late and night shifts, d) irregular menstrual cycle (fluctuations > 5 days), e) average cycle lengths of< 22 or > 35 days, f) use of hormonal contraceptives, g) diag-

nosis of hysterectomy, ovariectomy or current endometriosis, h) pregnancy or breast-feeding during the past 6 months, i) regular pharmaceutical medication with hormonal effects, j) lifetime history of bipolar or psychotic disorder, and k) current major depressive, panic, generalized anxiety, substance use or eating disorder.

Baseline Session

During the baseline interview, the Structured Interview for DSM-IV TR PMDD (SCID-PMDD; Accortt et al., 2011; κ =.96), which was adapted for the DSM-5 criteria for PMDD, was administered to both samples. The SCID-PMDD (Accortt et al., 2011) assesses the 11 PMDD symptoms regarding their on- and offset-time across the menstrual cycle, and the number of symptomatic cycles during the last 12 months, along with functional impairment and distress, as well as the exclusion criterion of a possible premenstrual exacerbation of another psychiatric disorder (cf. Kuehner & Nayman, 2021). In order to keep the participants' burden at a reasonable level within the extensive AA-design, we decided against the additional administration of prospective daily symptom ratings during the current study. Possible current and life-time Axis-I disorders were assessed using the Structured Clinical Interview of DSM-IV for Axis-I (SCID-I; Wittchen et al., 1997). Participants' current mindfulness-related practices, including yoga, meditation, or other mindfulness practices during the past three months (0 = no vs 1 = yes) were assessed as a possible covariate, together with demographic and menstrual cycle related variables (see Table 4.2).

Ambulatory Assessments and Inductions

The AA was carried out using smartphones with the software movisensXS (movisens GmbH, Karlsruhe, Germany) over four consecutive days during both the follicular and late luteal phase, resulting in eight days of data collection. The follicular phase was assessed on days six to nine of the menstrual cycle, with day one representing menstruation onset. The late luteal phase was assessed during the four days preceding the expected onset of menstruation, which was estimated by a chromatographic ovulation testing phase around the expected ovulation date with Femometer® LH ovulation rapid test strips. If there was a deviation in the menstruation onset-time of at least plus or minus 3 days, participants were asked to repeat the AA of the late luteal phase

during the next cycle. In order to prevent sequence effects, women initiated the AA in different cycle phases.

AAs started at 9:00 a.m. and occurred eight times per day at semi-random intervals until 09:30 p.m. (interassessment interval = 45-120 min), with the option to reject or postpone prompts for up to 15 minutes. On the first and third days of each four-day AA-period within each cycle phase, assessments of momentary mood and cognitions (for items, see Table 4.1) were followed by inductions of ruminative or mindful self-focus four times throughout the day. Within a day, the induction mode of ruminative or mindful self-focus was not switched, but was alternated on the following induction day. Participants were randomly assigned to either start with the ruminative (A) or mindful (B) induction day (i.e., AB/AB or BA/BA). Immediately after completing the respective inductions, participants provided ratings of post-induction momentary mood and cognitions.

Table 4.1

Ambulatory Assessment items

Construct	**N_{items}**	**Item**	**Scale**
Negative Affect	6	"*At the moment, I feel… upset / irritated / nervous / listless / bored / down*" (cf. Nayman et al., 2023a)	7-point Likert scale: 1 (not at all) to 7 (very much)
Positive Affect	6	"*At the moment, I feel … satisfied / calm / cheerful / energetic / enthusiastic / relaxed*" (cf. Nayman et al., 2023a)	
Rumination	1	"*At the moment, I am stuck on negative thoughts and cannot disengage from them*" (cf. Schricker et al., 2023b)	
Present-Moment- Awareness	1	"*At the moment, I am attentive to the present moment, without thinking about the past or the future*" (Brown & Ryan, 2003)	
Self-Acceptance	1	"*At the moment, I accept myself as I am*" (cf. Beddig et al., 2020)	

Note. English translations of German item versions.

Experimental induction paradigm. The AA-induction paradigm consisted of brief statements designed to induce either a ruminative or mindful attention focus. It was adapted from a previous experimental AA study (Huffziger et al., 2013) and had been

previously validated in both a non-clinical (Huffziger et al., 2013) and a clinical sample with patients with rMDD (Kuehner et al., 2023). The ruminative self-focus inductions included neutrally valenced thoughts related to emotions and symptoms (e.g., "*Think about the way you feel inside*", "*Think about the possible consequences of the way you feel*"). In contrast, mindful self-focus was induced using statements that directed attention to the present-moment-awareness of the breath and encouraged a non-judgmental acceptance of one's experiences (e.g., "*Consciously attend to your breath for some seconds",* "*Take note of your thoughts and feelings without judging them*"). A total of nine statements per induction mode were divided into three parts. Each part was displayed on the smartphone screen for 1 min, resulting in a duration of 3 min in total. Participants were instructed to concentrate and focus their attention on the statements, advancing to the next screen when an acoustic signal occurred. They also had the flexibility to proceed to the next screen at their discretion, depending on their possibility to concentrate. The duration of screen-time for each induction presentation served as a compliance check (cf. Huffziger et al., 2013), and screen-times below 90 s or above 270s (180s +/- 90s) were coded as missing.

Statistical analyses

Only ambulatory data of the induction days, specifically of day 1 and 3 of each four-day AA-phase during both the follicular and the late luteal phase, were included in the statistical analyses, since we aimed to investigate the immediate effects of momentary inductions on momentary outcomes within the same day. For the corresponding statistical analyses, we calculated difference scores by subtracting pre- from post-induction scores for affective (NA, PA) and cognitive (rumination, PMA, self-acceptance) outcomes.

Given the hierarchical data structure with ambulatory assessments (level 1) being nested within participants (level 2), we conducted multilevel models (MLM) with restricted maximum likelihood estimation in R (Version 4.2.2; R Core Team, 2022), using the lmer functions from the package lme4 (Bates et al., 2015) and lmerTest (Kuznetsova et al., 2017). Prior to the main analyses, we examined possible confounders (i.e., assessment day, time since 9:00 a.m., current mindfulness practice, screen-time during induction presentation) for each outcome variable (pre-post-induction difference

values). We retained these covariates in the models only if they were found to be statistically significant. This applied only for current mindfulness practice regarding pre-post-induction difference values for momentary NA and PA.

Deviance testing for model comparisons with random intercepts versus random slopes did not reveal significant differences in model fits ($p > .941$). Consequently, we opted for the more restrictive random intercept models. First, to investigate possible cycle-phase-specific group differences in the effects of induction mode on pre-post-induction difference scores of momentary mood (NA, PA) and cognitions (rumination, PMA, self-acceptance), we estimated separate random-intercept models. These models included *induction mode* (ruminative = 0 vs mindful self-focus = 1), *group* (PMDD = 0 vs healthy controls = 1) and *cycle phase* (follicular = 0 vs late luteal phase = 1) as predictors, along with their two-way and three-way interaction terms. For significant three-way interactions, we computed simple effects with p value adjustment using the Tukey Method.

We built our statistical analyses in a top-down approach, starting with the inclusion of higher-order interaction terms. When three-way interactions were non-significant, we retained the two-way interaction term of *group* * *induction mode* in our models. This allowed us to explore group differences in induction effects across the two cycle phases. If this two-way interaction did not reach statistical significance either, we proceeded to include only main effects of induction mode, along with respective covariates, in the models.

4.4 Results

Descriptives

Demographic information is presented in Table 4.2, while Table 4.3 displays descriptive statistics, intraclass correlation coefficients (ICCs), and test statistics for cycle phase comparisons within each group for all level 1 variables. Women with PMDD consistently exhibited significant cycle phase differences, indicating higher NA and rumination, as well as lower PA, PMA, and self-acceptance during the late luteal phase compared to the follicular phase. In contrast, no such cycle phase differences were observed for healthy controls.

Overall, 3501 out of possible 3840 daily assessments on the two induction days per cycle phase were recorded, resulting in a high overall compliance rate of 91.2% across all participants (cf. Wrzus & Neubauer, 2023). Based on screen times during the induction presentations (M = 119.85 s, SD = 77.45 s, range = 1 – 660 s) – serving as a compliance check – 40.9% of the possible inductions in the PMDD group (compliance rate = 59.1%) and 38.0% in the control group (compliance rate = 62%) had to be excluded from the analyses due to inadequate screen time values (below 90 s or exceeding 270 s), with significantly more inadequate screen-times in women with PMDD compared to healthy controls (χ^2 = 4.33, p = .037). No cycle-phase-specific differences in these screen-time related exclusions were found in women with PMDD (χ^2 = 0.56, p = .456) or in healthy controls (χ^2 = 0.41, p = .522).

Table 4.2

Demographic and cycle-related characteristics of women with Premenstrual Dysphoric Disorder (PMDD) and mentally healthy controls

	PMDD group (*n* = 60)	**Control group (*n* = 60)**	**Test statistic**	***p***
	***M* (*SD*) / %**	***M* (*SD*) / %**		
Demographic variables				
Age	30.37 (5.99)	29.85 (5.31)	$t(118) = 0.50$	.618
Education (% with high school degree)	83.3%	90.0%	$\chi^2(1) = 1.15$	.283
Relationship status (% in a relationship)	61.7 %	71.7 %	$\chi^2(1) = 1.35$	.245
Mindfulness experiences				
Current practice[a] (%)	40.0 %	58.3 %	$\chi^2(1) = 4.03$	.045
Cycle-related variables				
Menstrual cycle length (in days) during AA	28.46 (3.33)	28.08 (2.51)	$t(118) = 0.70$	.487
Period length (in days) during AA	5.40 (1.23)	5.12 (1.07)	$t(102) = 1.22$	.225

Note. AA = Ambulatory Assessment.
[a] Mindfulness practice during the past three months.

Table 4.3

Descriptive and variability statistics for Ambulatory Assessment variables

State variables (AA)	Group	Follicular		Late Luteal		Test statistic[a]
		M (*SD*)	ICC	*M* (*SD*)	ICC	
NA	PMDD	2.39 (0.54)	*0.45*	3.42 (0.77)	0.34	$F(1, 59)= 85.32$, $p < .001$
	HC	2.07 (0.60)	*0.51*	2.01 (0.57)	0.55	$F(1, 59)= 1.09$, $p = .301$
PA	PMDD	4.70 (0.67)	*0.34*	3.55 (0.69)	0.37	$F(1, 59)= 107.00$, $p < .001$
	HC	4.94 (0.81)	*0.49*	4.96 (0.68)	0.60	$F(1, 59)= 0.15$, $p = .703$
Rumination	PMDD	2.30 (0.74)	*0.30*	3.46 (0.92)	0.25	$F(1, 59)= 68.98$, $p < .001$
	HC	2.00 (0.77)	*0.35*	1.88 (0.66)	0.42	$F(1, 59)= 2.59$, $p = .113$
PMA	PMDD	4.85 (1.04)	*0.33*	4.19 (0.95)	0.36	$F(1, 59)= 19.94$, $p < .001$
	HC	5.00 (1.18)	*0.46*	5.07 (1.09)	0.51	$F(1, 59)= 0.15$, $p = .537$
Self-acceptance	PMDD	5.49 (0.89)	*0.61*	4.36 (1.15)	0.57	$F(1, 59)= 70.92$, $p < .001$
	HC	5.69 (0.96)	0.65	5.75 (0.82)	0.72	$F(1, 59)= 0.66$, $p = .422$

Note. AA = Ambulatory Assessment; PMDD = Premenstrual Dysphoric Disorder; HC = Mentally Healthy Controls; ICC = Intraclass Correlation Coefficient; NA = Negative Affect; PA = Positive Affect; PMA = Present-Moment-Awareness. Means and standard deviations were calculated based on aggregated person-mean scores. State variables represent data of pre-induction assessments during induction days (two days during each cycle phase).

[a] Test statistics on mean differences between cycle phases within each group.

Group- and cycle-phase-specific effects of induction mode

First, we investigated whether there were cycle-phase-specific group differences in the effects of induction mode on momentary outcomes (*induction mode * group * cycle phase)*. The respective three-way interaction analyses revealed significant effects on PA, but not on NA, rumination, PMA or self-accceptance (see Models 1 in Table 4.4). As depicted in Figure 4.1, simple effects indicated that, compared to healthy controls, women with PMDD showed stronger increases in PA toward the mindful self-focus induction during the late luteal phase (Estimate = -0.24, *SE* = 0.08, $t(484) = -3.13$, $p = .039$), whereas no group differences were identified during the follicular phase (Estimate = -0.08, *SE* = 0.08, $t(486) = -1.12$, $p = .953$). Regarding the ruminative self-focus induction, no differential group-specific effects were identified during the follicular (Estimate = -0.03, *SE* = 0.08, $t(497) = -0.40$, $p = .999$) or the late luteal phase (Estimate = 0.09, *SE* = 0.08, $t(512) = 1.12$, $p = .953$). These results indicate that, especially during

the late luteal phase, women with PMDD exhibited higher PA-reactivity toward the mindful self-focus induction compared to healthy controls.

After removing the non-significant three-way interaction term and the two-way interaction terms of *induction mode * cycle phase* and *group * cycle phase*, the interaction effects of *group * induction mode* on immediate momentary NA, rumination, PMA and self-acceptance were not significant (see Models 2 in Table 4.4).

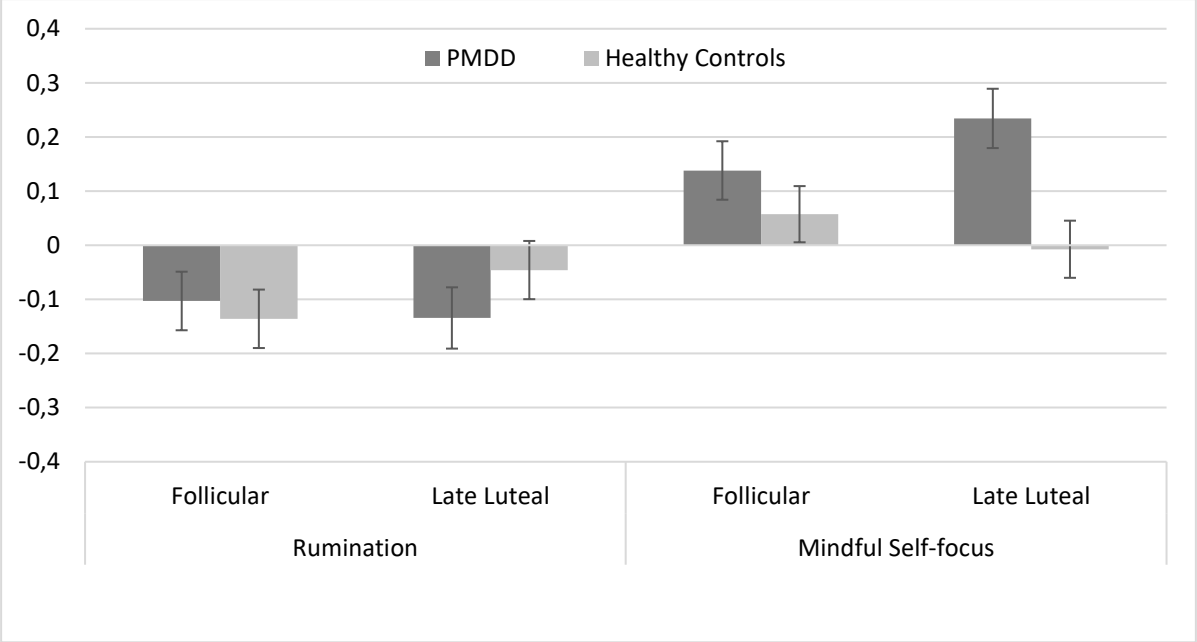

Figure 4.1 Pre-post mean differences in momentary positive affect after rumination and mindful self-focus inductions per cycle phase in women with and without Premenstrual Dysphoric Disorder

Note. PMDD = Premenstrual Dysphoric Disorder. The y-axis represents the estimated marginal means of pre-post-induction change scores. Error bars represent the standard error of the estimated means.

Differential main effects of induction mode in the total sample over the menstrual cycle

Finally, the non-significant interaction terms of *group * induction mode* were removed from models to examine the main effects of induction mode (ruminative vs mindful self-focus) on the pre-post-induction difference scores for momentary NA, rumination, PMA, and self-acceptance. Respective results, presented in Table 4.4, revealed that the ruminative self-focus induction predicted a stronger immediate increase in momentary NA and rumination as well as a stronger decrease in PMA and self-acceptance compared to the mindful self-focus induction across both groups and cycle phases.

As illustrated in Figure 4.2, estimated marginal mean difference scores per induction mode revealed that ruminative self-focus induction predicted immediate increases in momentary NA (*M* = 0.13, *SE* = 0.03, 95% CI [0.08; 0.18]) and rumination (*M* = 0.37, *SE* = 0.06, 95% CI [0.25; 0.49]), as well as immediate decreases in PMA (*M* = -0.34, *SE* = 0.08, 95% CI [-0.49; -0.18]) in the total sample across the cycle phases, with no significant effects on self-acceptance (*M* = -0.05, *SE* = 0.04, 95% CI [-0.12; 0.02]). The mindful self-focus induction only predicted significant increases in self-acceptance (*M* = 0.14, *SE* = 0.03, 95% CI [0.08; 0.21]), but did not predict changes in NA (*M* = -0.02, *SE* = 0.02, 95% CI [-0.06; 0.03]), rumination (*M* = 0.01, *SE* = 0.06, 95% CI [-0.11; 0.13]) or PMA (*M* = 0.06, *SE* = 0.08, 95% CI [-0.09; 0.21]) compared to baseline.

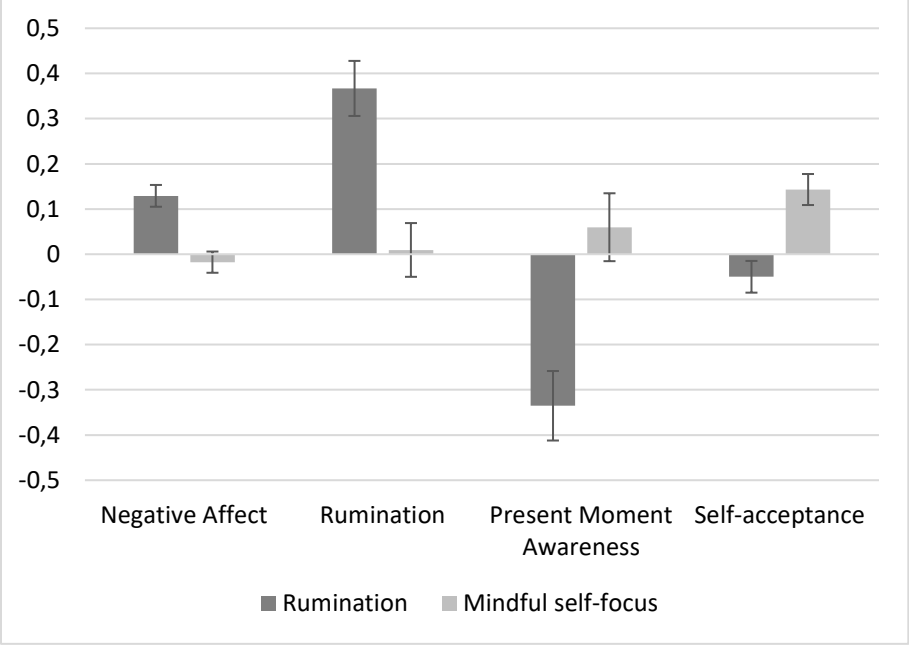

Figure 4.2 Pre-post differences in momentary mood and cognitions after rumination and mindful self-focus inductions across both groups and cycle phases

Note. PMDD = Premenstrual Dysphoric Disorder. The y-axis represents the estimated marginal means of pre-post-induction change scores. Error bars represent the standard error of the estimated means.

Table 4.4

Effects of induction modes (rumination vs mindful self-focus) on momentary mood and cognitions in women with and without Premenstrual Dysphoric Disorder

	Model 1[a]				**Model 2[b]**				**Model 3**			
	Induction[c] * Group[d] * Cycle phase[e]				Induction * Group				Induction			
Outcome	***B (SE)***	***df***	***t***	***p***	***B (SE)***	***df***	***t***	***p***	***B (SE)***	***df***	***t***	***p***
NA	0.07 (0.12)	960	0.61	.539	0.01 (0.06)	970	0.19	.850	-0.15 (0.03)	971	-4.90	< .001
PA	-0.27 (0.14)	959	-2.00	.049	---	---	---	---	---	---	---	---
Rumination	0.37 (0.27)	957	1.39	.165	0.10 (0.14)	967	0.74	.461	-0.36 (0.07)	967	-5.30	< .001
PMA	-0.12 (0.35)	961	-0.34	.738	0.15 (0.18)	970	0.84	.403	0.40 (0.09)	972	4.47	< .001
Self-Acceptance	-0.23 (0.17)	954	-1.35	.179	-0.03 (0.09)	964	-0.36	.720	0.19 (0.04)	965	4.46	< .001

Note. NA = Negative Affect; PA = Positive Affect; PMA = Present-Moment-Awareness. All models on NA and PA include fixed effects of mindfulness experiences. Models 2 and 3 were estimated in case of non-significant interaction effects in the previous model.

[a] Models 1 additionally include main effects of induction mode, group and cycle phase as well as interaction terms of induction mode * group, induction mode * cycle phase, group * cycle phase.
[b] Models 2 additionally include main effects of induction mode and group.
[c] Reference category: Rumination
[d] Reference category: PMDD
[e] Reference category: Follicular phase

4.5 Discussion

To our knowledge, this is the first study using a combined approach of ambulatory assessments and brief ambulatory inductions in daily life within the context of PMDD research. The aim of the present study was to enhance the understanding of differential affective and cognitive responses toward ruminative and mindful self-focusing in women with and without PMDD across the menstrual cycle. We expected more pronounced differential effects of these induction modes on momentary mood and cognitions, indicating higher reactivity to both ruminative and mindful self-focus in women with PMDD compared to healthy controls, especially during the late luteal phase.

The present study revealed a significant interaction effect involving induction mode, group, and cycle phase on PA, but not on NA, rumination, PMA, or self-acceptance. Our analyses showed that the differential effects of ruminative vs mindful self-focusing on PA were more pronounced in women with PMDD than in healthy controls, especially during the late luteal phase. Specifically, compared to healthy controls, women with PMDD showed stronger increases in PA in response to mindful self-focus inductions during the late luteal phase, whereas no such group differences were identified during the follicular phase. The absence of group-specific reactivity during the follicular phase is consistent with the symptom profile of PMDD, as symptom levels during this phase are similarly low to those in women without PMDD. Increased premenstrual PA-reactivity toward induced mindful self-focus, in turn, aligns with a previous examination on this sample (Nayman et al., 2024). In this prior analysis, utilizing data from both the pre-induction assessments of the induction days and those of the non-induction days of the current study, we demonstrated that in women with PMDD, higher momentary spontaneous PMA during the late luteal phase predicted improved subsequent momentary mood in daily life. Conversely, no such effects were found during the follicular phase, and respective effects were absent in both cycle phases in healthy controls (Nayman et al., 2024). The present paper extends these previous cross-lagged analyses by examining the immediate pre-post effects of ambulatory inductions of rumination and PMA, thereby experimentally replicating the increased PA-reactivity toward mindfulness during the symptomatic late luteal phase in women with PMDD. However, it raises the question of why this increased premenstrual reactivity in women with PMDD was not observed for affective and cognitive states other than PA.

Garland et al. (2015) proposed that the efficacy of mindfulness trainings specifically arises from an upward spiral of positive affect and cognitions, which maintain and reinforce each other. They demonstrated that this upward spiral is primarily driven by PA. Therefore, the positive effects of our brief mindful self-focus induction on PA could represent an initial stage of the upward spiral, which, according to the Broaden-and-Build theory (Fredrickson et al., 2004), might increase psychological resources to broaden individual's awareness and activate further positive thoughts and behaviors. Increased PA-reactivity during the late luteal phase identified in the current study, along with previous findings indicating that spontaneous momentary PMA predicts improved subsequent mood during the late luteal phase (Nayman et al., 2024), further points to the potential for late-luteal-phase-specific applications of brief mindfulness interventions in women with PMDD to achieve immediate effects, given that their heightened psychological distress is confined to the luteal phase. In this context, ultra-brief mindfulness of breath meditation practices have already been shown to improve positive affect outcomes in the general population (Strohmeier et al., 2022) and could therefore be evaluated for cycle-phase-specific application, specifically during times of need in the late luteal phase.

Except for PA, we did not identify any cycle-specific or general group differences in the effects of induction mode for the remaining momentary outcomes, which included NA, rumination, PMA and self-acceptance. Instead, ruminative vs mindful self-focus inductions exhibited differential immediate effects on these affective and cognitive state variables across both groups and cycle phases. Simple effect analyses revealed that independent of clinical status and cycle phase, ruminative self-focus inductions led to an immediate increase in momentary NA and rumination and to an immediate decrease in momentary PMA, with no effects on self-acceptance. Mindful self-focus inductions, in contrast, immediately increased momentary self-acceptance with no effects on NA, rumination and PMA. These results are generally consistent with and methodologically expand previous cross-sectional, lab-based experimental as well as observational AA-studies that provide evidence for the detrimental effects of rumination (e.g., Watkins & Roberts, 2020) and the beneficial effects of mindfulness (e.g., Enkema et al., 2020) on affective and cognitive outcomes in clinical and non-clinical samples. Thus, rumination and mindfulness both as enduring traits and as momentary naturally occurring states, as well as when induced, can be seen as transdiagnostic risk and protective factors.

This suggests that they could serve as possible targets for brief cognitive interventions in daily life, regardless of clinical status (cf. Enkema et al., 2020; Watkins & Roberts, 2020). However, especially as the lack of effects of induced mindful self-focus on momentary rumination contradicts previous evidence that suggests beneficial effects of mindfulness-based interventions in reducing rumination and increasing mindfulness levels (Li et al., 2022; Mao et al., 2023; Perestelo-Perez et al., 2017; Timm et al., 2018), specific interventions targeting rumination in daily life remain to be uncovered.

The finding that, across both groups and cycle phases, mindful self-focus specifically predicted increases in self-acceptance, while ruminative self-focus had a broader impact on momentary mood and cognitions, including NA, rumination and PMA, may be attributed to the rather common presence of rumination in the general population (cf. Parmentier et al., 2019) and in clinical samples (e.g., Nayman et al., 2023a; Watkins & Roberts, 2020). Consequently, ruminative self-focus inductions may activate individuals' well-known cognitive processes, leading to stronger affective and cognitive reactions compared to mindful self-focus inductions, which may engage less familiar thinking modes.

Limitations and Future Directions

The present study has some limitations. First, although the PMDD diagnoses in our sample were determined using a structured and well-validated diagnostic interview (SCID-PMDD; Accortt et al., 2011), they were not confirmed through daily ratings over two consecutive cycles. This decision was made to minimalize participant burden within this extensive AA-design. Therefore, the PMDD diagnoses in this study must be considered provisional (APA, 2013).

Second, although the current study had high overall compliance rates for ambulatory assessments (91.2%), the screen-time based compliance rates for ambulatory inductions were lower (59.1 – 62.0%), which might have reduced the statistical power to detect two-way or three-way interactions. Due to the lack of comparable published studies or available pilot data on the menstrual-cycle-specific effects of ambulatory inductions, from which parameters for simulation-based power calculations could have been drawn, we did not conduct an a priori or sensitivity power calculation. Third, momentary rumination, PMA, and self-acceptance were assessed with single items, potentially limiting their reliability (Mestdagh & Dejonckheere, 2021), and emphasizing

the necessity for replicating these analyses using validated, AA-specific multi-item scales. Specifically, the PMA item represents only the present-moment-awareness facet of the mindfulness construct, while the mindful self-focus inductions also included instructions for nonjudgmental acceptance (Kuehner et al., 2023). Thus, the single item assessing pre- and post-induction PMA likely captured only a partial representation of the mindful self-focus induction effects on participants' mindfulness state.

Moreover, ultra-brief mindfulness intervention or induction elements may be efficacious in daily life (e.g., Johnson, Zawadski et al., 2022), particularly when considering the dynamics of internal and external contextual states and tailoring interventions to moments of need, as implemented in just-in-time-interventions (Qian et al., 2022). In contrast, in the present study, the inductions were delivered at semi-random time points during the day, possibly interfering with momentary activities and bearing the risk for disengagement with the induction (cf. Qian et al., 2022).

Conclusions

This study demonstrated increased effects of late-luteal-phase-specific mindful self-focusing on positive affect in women with PMDD, thereby suggesting the potential of cycle-phase-specific mindfulness interventions for PMDD. Moreover, our findings generally point to differential immediate effects of brief ruminative vs mindful self-focus inductions on affective and cognitive processes in daily life, irrespective of clinical status and cycle phase. This supports the evidence that rumination and mindfulness are transdiagnostic factors representing potential targets for brief prevention and intervention measures for both non-clinical and clinical groups.

CHAPTER V: ASSOCIATIONS OF PREMENSTRUAL SYMPTOMS WITH DAILY RUMINATION AND PERCEIVED STRESS AND THE MODERATING EFFECTS OF MINDFULNESS FACETS ON SYMPTOM CYCLICITY IN PREMENSTRUAL SYNDROME (STUDY 4)

An adapted version of this chapter has been published as ‘Nayman, S., Konstantinow, D. T., Schricker, I. F., Reinhard, I., & Kuehner, C. (2023). Associations of premenstrual symptoms with daily rumination and perceived stress and the moderating effects of mindfulness facets on symptom cyclicity in Premenstrual Syndrome. *Archives of Women's Mental Health, 26*(2), 167-176. https://doi.org/10.1007/s00737-023-01304-5’

5.1 Abstract

Purpose. Subthreshold premenstrual symptoms can be impairing even if the diagnostic criteria for Premenstrual Dysphoric Disorder (PMDD) are not reached. Previous research suggests shared psychological risk factors without a clear differentiation of Premenstrual Syndrome (PMS) from PMDD. This study focuses on a sample with a wide range of premenstrual symptoms not reaching PMDD-criteria and aims to investigate within-person associations of premenstrual symptoms with daily rumination and perceived stress during the late luteal phase as well as cycle-phase specific associations of habitual mindfulness including present-moment-awareness and acceptance with premenstrual symptoms and impairment.

Methods. Fifty-six naturally cycling women with self-reported premenstrual symptoms completed an online diary on premenstrual symptoms, rumination and perceived stress over two consecutive menstrual cycles, and baseline questionnaires on habitual present-moment-awareness and acceptance.

Results. Multilevel analyses revealed cycle-related variations in premenstrual symptoms and impairment (all *p*s < .001). Higher within-person levels of core and secondary premenstrual symptoms during the late luteal phase predicted increased daily rumination and perceived stress (all *p*s < .001) and increased somatic symptoms predicted increased rumination ($p \leq .018$). Higher habitual present-moment-awareness was linked to lower premenstrual symptom and impairment levels towards the late luteal

phase whereas higher habitual acceptance was associated with lower premenstrual functional impairment ($p \leq .015$).

Conclusions. Premenstrual symptom increases during the late luteal phase in women with PMS seem to be linked to increased daily rumination and perceived stress. Trait present-moment-awareness and acceptance in turn seem to reflect protective factors against premenstrual distress and may represent useful targets for interventions.

5.2 Introduction

Most women of reproductive age experience premenstrual symptoms in the week before menses (late luteal phase) which remit within a few days after menstruation onset (follicular phase) (Hofmeister & Bodden 2016; Tschudin et al. 2010). About 1.8% - 5.8% of these women report severe distress or impairment, and meet the diagnostic criteria of Premenstrual Dysphoric Disorder (PMDD) with at least five symptoms, including at least one core affective symptom (American Psychiatric Association [APA] 2013). If the minimum of required criteria is not reached, the symptoms are classified as Premenstrual Syndrome (PMS), affecting about 20 - 30% of women (Mattina & Steiner 2020). The International Society for Premenstrual Disorders (ISPMD) considers PMDD and PMS as categories of core premenstrual disorders (Ismaili et al. 2016). In contrast to PMDD, PMS does not have a unique definition with a specified minimum number of symptoms and is not included in DSM-5 as a diagnostic entity. The PMS definition proposed by the American College of Obstetricians and Gynecologists (ACOG) requires at least one affective and one physical premenstrual symptom with functional impairment during the previous three menstrual cycles – confirmed by a prospective symptom diary (ACOG 2014).

Women who fall short of the required number of five DSM-5 criteria for PMDD may nevertheless experience clinical distress and functional impairment in daily life (Yonkers & Simoni, 2018). A dichotomous categorization (PMDD vs. non-PMDD) with a minimum of five symptoms possibly fails to consider these women and can lead to an exclusion from adequate treatments (Kadian & O'Brian 2012). Halbreich et al. (2003) estimate that 13% - 18% of women with PMS seem to display symptoms to a degree that warrants clinical treatment, although failing to reach the required number of symptoms for a PMDD diagnosis. Relatedly, Hartlage et al. (2012) and Schmalenberger et al. (2017) showed that the number of premenstrual symptoms presenting an optimal

threshold to predict functional impairment was four instead of the five symptoms as required by APA (2013).

Dimensional diagnostic approaches represent an alternative to the categorical approach to psychopathology (Michelini et al. 2021). Relatedly, underlying mechanisms of premenstrual disorders have been suggested to exist on a continuum across the spectrum of normal functioning and psychopathology (Eisenlohr-Moul 2019). This perspective results in premenstrual spectrum disorders - with PMDD as the most severe manifestation at the upper end of the continuum, PMS as a milder manifestation, and the absence of symptoms at the lowest end (Yonkers & Simoni 2018). In this regard, samples including PMS as subthreshold-cases of PMDD allow to explore potential common mechanisms involved in the development and maintenance of premenstrual disorders. Identified risk factors or processes in these subthreshold-cases may indicate etiological as well as predictive continuity (cf. van Os 2013) and can be targeted to prevent the transition to a full syndrome disorder (e.g., Shankman et al. 2009).

Psychological risk factors for premenstrual disorders have been insufficiently examined. There is initial evidence for a heightened tendency to ruminate and increased levels of perceived stress in women with premenstrual spectrum disorders (Eisenlohr-Moul 2019; Kappen et al. 2022, preprint; Nayman et al. 2023a), especially during the late luteal phase (Beddig et al. 2019; Craner et al. 2016). Habitual rumination (Dawson et al. 2018), momentary rumination in daily life (Beddig et al. 2020) and perceived stress (Beddig et al. 2019; Schweizer-Schubert et al. 2021), in turn, seem to be associated with higher premenstrual mood and symptom worsening in women with PMS or PMDD. Less is known about favorable traits such as present-moment-awareness and acceptance as facets of mindfulness, which has been shown to be linked to lower levels of psychopathology (A-Tjak et al. 2014; Tomlinson et al. 2018). Mindfulness involves deliberately paying attention to present-moment experiences with an accepting and non-judgemental attitude (Kabat-Zinn, 2003). A nonclinical study showed that habitual mindfulness with the facets of present-moment-awareness, observing, describing and nonreacting was associated with less premenstrual symptoms (Lustyk et al. 2011), and mindfulness-based interventions appear to reduce premenstrual symptom severity in women with premenstrual disorders (Bluth et al. 2015; Mazaheri Asadi et al. 2022; Panahi & Faramarzi 2016). Similarly, habitual acceptance – possibly weakening the dysfunctional link between detrimental experiences and maladaptive forms

of coping (Hayes et al. 2012) – was linked to increased perceived ability to cope with PMS (Read et al. 2014). Kleinstäuber et al. (2016), in contrast, identified no effects of habitual acceptance on premenstrual symptom severity. Nonetheless, higher acceptance has been shown to be associated with lower functional impairment despite existing symptoms in in individuals with chronic pain (Lami et al., 2018).

A recent Ambulatory Assessment study (Nayman et al. 2023a) with repeated intensive longitudinal measurements showed that higher habitual present-moment-awareness and reappraisal and lower habitual rumination in women with PMDD were generally associated with better mood in daily life. However, affected women with favorable traits showed a stronger mood worsening towards the late luteal phase, thereby resembling those with less favorable traits. Nonetheless, these results do not preclude the potential role of protective psychological factors during the late luteal phase in women with less severe premenstrual disorders.

In sum, research on psychological factors in women with PMS is sparse and limited by the fact that previous studies did not always strictly differ between PMS and PMDD, which in turn can result in inconsistent findings.

The current study takes a comprehensive approach by combining retrospective assessments of psychological traits with prospective assessments of premenstrual symptoms and functional impairment as well as rumination and perceived stress in daily life over two menstrual cycles in a sample of women with a wide range of premenstrual symptoms, who did, however, *not* meet the number of criteria required for PMDD. Thus, in the current study, we first aimed to investigate cycle-related variations in prospectively assessed PMS symptomatology and impairment across the menstrual cycle in women reporting premenstrual symptoms during a retrospective baseline interview. We expected increases in all prospectively assessed outcomes (core, secondary and somatic symptoms, functional impairment) from the follicular to the late luteal phase. Second, we expected that higher increases in PMS severity (core, secondary and somatic symptoms) in the late luteal phase would be associated with simultaneously increased rumination and perceived stress during daily life. Third, we expected that habitual present-moment-awareness and acceptance would be associated with weaker premenstrual increases in symptoms and impairments towards the late luteal phase.

Given the high comorbidity of premenstrual disorders with depressive disorders (Yonkers & McCunn 2007), we further investigated, whether the expected moderator effects would hold when controlling for depressive symptom levels.

5.3 Methods

Participants and procedure

Sixty-one female students with premenstrual complaints were recruited from the University of Mannheim, Germany via post prints, mailing lists and the digital study register SONA of the University of Mannheim. Women were eligible for the study if they reported at least one affective and one somatic premenstrual symptom as well as functional impairment to at least a mild degree on the Premenstrual Symptom Screening Tool (Bentz et al. 2012; see *Measures* section). Of these women, only those who did not meet the full PMDD criteria (APA 2013) according to the subsequent two-month symptom diary (see *Online diary* section) were included to focus on subthreshold PMDD cases. In order to ensure that women had a natural and typical menstrual cycle, further inclusion criteria included age between 18 and 40 years, a reported cycle length between 22 and 34 days, and a body mass index between18 and 35. Women were ineligible if they had been pregnant or lactating within the last six months, had taken hormonal contraceptives during the last three months, had a history of ovariectomy, a lifetime diagnosis of bipolar or psychotic disorder or current substance dependence. Of the 61 recruited women, five met the PMDD criteria (APA 2013) according to the subsequent two-month symptom diary and were thus excluded from the analyses. The final sample consisted of $N = 56$ women. All participants gave written informed consent and were compensated with 50€ or study credit points for their participation.

During an initial telephone-screening, participants provided information on demographics, cycle-related aspects, medical history and psychiatric comorbidities (based on a checklist for DSM-IV criteria). Preliminarily eligible participants were then invited to the in-person-session at the Central Institute of Mental Health, Mannheim, for the assessment of baseline measures of clinical and psychological trait variables (see *Measures* section), and the introduction to the daily diaries. Daily diaries started on the evening of the in-person-session. Participants rated their symptoms and daily experiences once per day in the evening using a link to the online server of SoCi Survey (www.socisurvey.de) over two menstrual cycles. For the current analyses, data of

the late luteal and follicular phase were included. The late luteal phase covered the seven days before menstruation onset (cycle days -7 to -1), whereas the follicular phase covered days 4 to 10 of the menstrual cycle, with day 1 presenting menstruation onset (for a similar approach see Schmalenberger et al. 2017).

Baseline measures

Retrospective screening of premenstrual symptoms. The German version of the 19-item *Premenstrual Symptoms Screening Tool* (PSST; Bentz et al. 2012) was used to screen for premenstrual symptoms and functional impairment on a 4-point-scale (0 = "*not at all*", 1 = "*mild*", 2 = "*moderate*", 3 = "*severe*"; Cronbach's α = .903[3]).

Depressive symptoms. The German version of the 9-item subscale *PHQ-9* of the Patient-Health-Questionnaire (PHQ; Löwe et al. 2002) was administered to assess depression symptom severity during the previous two weeks on a 4-point-Likert scale (Cronbach's α = .784[1]).

Present-moment-awareness. Participants' habitual tendency to be attentive and aware of present-moment experiences as one of the facets of the construct of mindfulness was measured using the German version of the 15-item Mindfulness Attention Awareness scale (MAAS; Brown & Ryan 2003). The items were rated on a 6-point Likert scale, with higher scores indicating greater present-moment-awareness (Cronbach's α = .849[1]).

Acceptance. Trait acceptance as a further facet of the construct of mindfulness was assessed with the respective 3-item subscale ("When I cannot change something, I accept the situation as it is", "I am able to tolerate and endure uncomfortable situations", "I am able to accept things as they are") of the German version of the Heidelberg Form of Emotion Regulation Strategies (HFERST; Izadpanah et al. 2019). Items were rated on a 5-point-scale (Cronbach's α = .594[1]).

[3] All reported Cronbach's alpha values (α) in this paper refer to the present sample

Online diary

***Daily premenstrual symptoms*.** In the first part of the online diary, participants provided self-reports on current premenstrual symptoms and potential functional impairments using the validated 30-item Questionnaire for the Screening of Premenstrual Symptoms (Ditzen et al. 2011) on a daily basis over two menstrual cycles. The questionnaire was validated as both a retrospective questionnaire and a prospective symptom diary (Ditzen et al., 2011; Janda et al., 2017). The first 27 items covered premenstrual symptoms, which were categorically summed into core symptoms (items 1-11; affective lability, irritability, depressed mood, anxiety/tension), secondary symptoms (items 12-19 additional psychological/behavioral symptoms) and somatic symptoms (items 20-27). Three additional items assessed functional impairment. All items were rated on a 4-point Likert-scale ranging from 0 ("*not true at all*") to 3 ("*absolutely true*"). Based on the scoring approach by Janda et al. (2017), only items which were rated at least ≥ 2 over two consecutive days in the late luteal and a maximum of ≤ 1 in the follicular phase, were considered as "marked". A DSM-5 PMDD symptom was considered present if one of the corresponding items was rated as "marked" for at least two days. Women were excluded from the study if they showed at least five out of eleven symptoms including one affective symptom and functional impairment during the two menstrual cycles and thus met the DSM-5 criteria for PMDD (APA 2013).

Daily rumination and perceived stress. The second part of the daily diary included three additional items for the assessment of further facets of daily life experiences including rumination (2 items: "*Today, I was stuck on negative thoughts and could not disengage from them*", "*Today, I ruminated*") and perceived stress (1 item: "*Today, I had a stressful day*") on a 7-point Likert scale.

Statistical analysis

Given that daily assessments (level 1) were nested within participants (level 2), we fit multilevel models (MLM) estimating random intercept models with restricted maximum likelihood estimation (REML). All statistical analyses were performed in IBM SPSS Statistics Version 28 with the significance level set at $\alpha = .05$. This value was not adjusted for multiple testing as the tests were based on preplanned hypotheses (Armstrong 2014).

First, cycle-phase-specific variations in daily ratings of premenstrual symptom clusters (core, psychological secondary and somatic symptoms) and functional impairment were estimated in four separate random intercept models. These models included the factor cycle phase (late luteal vs. follicular phase) and the continuous covariate cycle day (1-7) as main effects as well as an interaction term between the two, with premenstrual symptom clusters and functional impairment as outcome variables. Within-person associations of each premenstrual symptom cluster (level 1 predictors) with further facets of daily life experiences (level 1 outcomes: rumination, perceived stress) during the late luteal phase were investigated by separate random intercept models with the data of the late luteal phase. For these analyses, level-1 predictors were decomposed into within- and between-person components by late-luteal-phase-specific person-mean- and grand-mean-centering. Within-person effects reflect how variations of daily experiences within a person are associated with variations in subjective or physiological outcomes (e.g., how intraindividual variations in daily premenstrual symptoms affect daily rumination within a person; Myin-Germeys & Kuppens 2022). Between-person effects reflect differences between individuals (e.g., how women with higher premenstrual symptoms differ from those with lower premenstrual symptoms with regard to daily rumination).

Finally, moderator effects of habitual present-moment-awareness and acceptance (level 2) on the associations of cycle phase with each premenstrual symptom cluster and functional impairment were tested with a set of additional models. These models included interaction terms of psychological traits by cycle phase. In a further set of interaction analyses, depressive symptom severity (PHQ-9) was added to the models as a level 2 covariate. Here, all level-2 variables were grand-mean centered, allowing the estimation of between-person effects.

According to the summary-statistics-based power analysis for mixed-effects models (Murayama et al., 2022), our sample size of N = 56 was sufficient to achieve 80% power to detect small to medium effect sizes with α set at .05.

5.4 Results

Table 5.1 presents demographic, psychological and clinical characteristics of the current sample (N = 56). Overall, 1497 out of a total of 1568 daily assessments (56 participants x 7 assessment days x 2 cycle phases x 2 menstrual cycles) were recorded,

corresponding to a high compliance rate of 95.5% (cf. Wrzus & Neubauer 2023). The Intra-Class Correlations (ICC) of daily records of symptoms (ICC_{core} = .24, $ICC_{secondary}$ = .32, $ICC_{somatic}$ = .32), functional impairment ($ICC_{functional\_impairment}$ = .33), and further daily life experiences ($ICC_{rumination}$ = .35, $ICC_{perceived\_stress}$ = .24) indicated that a considerable amount of variance in state outcomes is attributable to within-person differences.

Table 5.1

Demographics and psychological measures

	M (SD)	*range*
Demographic Variables		
Age	22.1 (3.3)	18 – 33
Menstrual Cycle during the study		
Length of cycle 1	29.0 (4.3)	20 – 42
Length of cycle 2	28.4 (3.2)	19 – 39
Baseline Measures		
MAAS	62.3 (10.4)	35 – 83
HFERST_A	9.4 (2.1)	3 – 13
PHQ-9	7.1 (3.9)	1 – 20
PSST	24.63 (10.38)	7 – 47
Daily Measures		
Daily rumination	6.10 (3.14)	2 – 14
Daily perceived stress	3.41 (1.74)	1 – 7

Note. For all baseline measures, sum scores were calculated. MAAS, Mindfulness Attention Awareness scale; HFERST_A, Heidelberg Form of Emotion Regulation Strategies – Acceptance Subscale; PHQ-9, Patient-Health-Questionnaire-9; PSST, Premenstrual Symptoms Screening Tool.

Cycle-phase-specific variations of premenstrual symptoms

Random intercept models revealed significant interaction effects of cycle phase by cycle day on daily symptom ratings. As illustrated in Fig. 5.1, core ($F(1,1439) = 17.84$, $p < .001$), secondary ($F(1, 1439) = 40.44$, $p < .001$) and somatic symptoms ($F(1,1439) = 103.12$, $p < .001$) as well as perceived functional impairment ($F(1,1439) = 31.61$, $p < .001$) increased in the late luteal phase and decreased in the in the follicular phase.

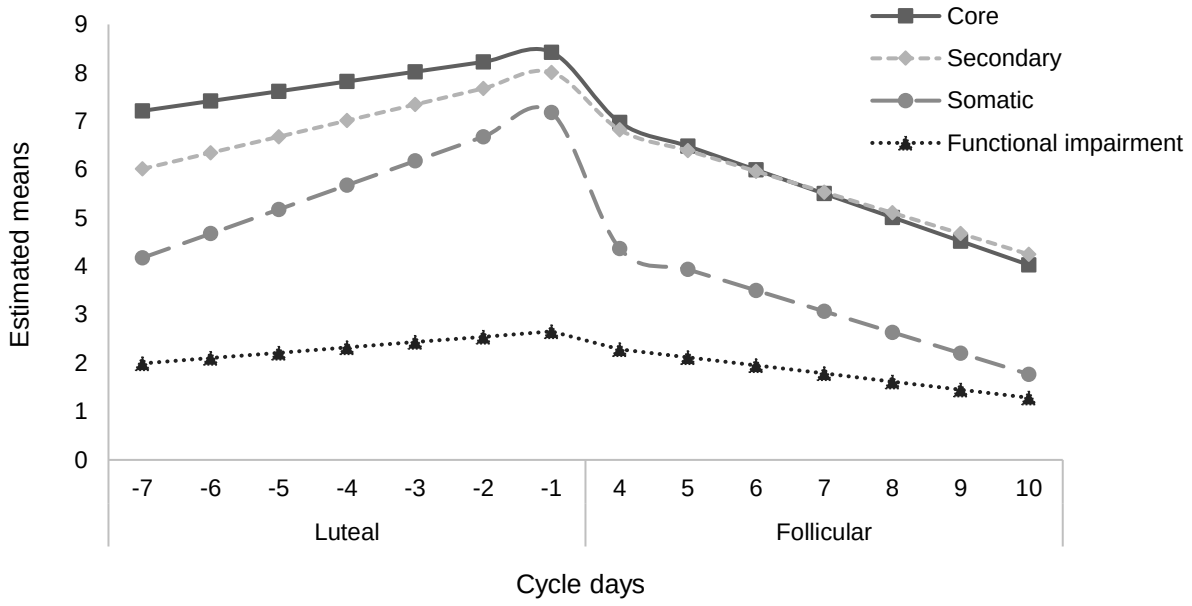

Figure 5.1 Cycle-related variations of core, secondary and somatic symptoms and functional impairment.

Note. Four separate random intercept models of cycle day * cycle phase on each symptom cluster and functional impairment were estimated.

Effects of premenstrual symptoms on daily rumination and perceived stress

Next, we examined the associations of daily premenstrual symptoms with daily rumination and perceived stress in the late luteal phase. Results are presented in Table 5.2. Random intercept models revealed that higher within-person levels of core and secondary symptoms were associated with increased daily rumination (all *p*s < .001) and perceived stress (all *p*s ≤ .018) in the late luteal phase. Higher within-person levels of somatic symptoms predicted increased daily rumination ($p < .001$), with no effects on perceived stress in the late luteal phase ($p = .111$).

Table 5.2

Main effects of premenstrual symptom clusters on daily rumination and perceived stress during the late luteal phase

	Rumination				Perceived stress			
Predictor	*B (SE)*	*df*	*t*	*p*	*B (SE)*	*df*	*t*	*p*
Core symptoms								
Intercept	1.91 (0.18)	55	10.85	<.001	2.84 (0.22)	53	12.69	<.001
Core symptoms (B-S)	0.16 (0.02)	56	8.34	<.001	0.06 (0.02)	55	2.39	.020
Core symptoms (W-S)	0.12 (0.01)	675	19.86	<.001	0.05 (0.01)	674	6.02	<.001
Secondary symptoms								
Intercept	1.88 (0.22)	54	8.77	<.001	2.57 (0.23)	53	11.11	<.001
Secondary symptoms (B-S)	0.18 (0.03)	55	6.72	<.001	0.10 (0.03)	53	3.67	<.001
Secondary symptoms (W-S)	0.10 (0.01)	676	10.46	<.001	0.03 (0.01)	674	2.36	.018
Somatic symptoms								
Intercept	2.42 (0.24)	54	10.02	<.001	3.11 (0.24)	53	13.22	<.001
Somatic symptoms (B-S)	0.13 (0.04)	54	3.55	<.001	0.03 (0.03)	53	0.88	.383
Somatic symptoms (W-S)	0.08 (0.01)	676	6.32	<.001	0.03 (0.02)	675	1.60	.111

Note. All models include random intercepts at level 2. B-S, between-person (grand mean centered); W-S, within-person (person mean centered); *B*, unstandardized coefficient; *SE*, standard error; *df*, degrees of freedom.

Interaction effects of psychological traits and cycle phase

In a next step, we investigated possible moderator effects of habitual present-moment-awareness and acceptance on cycle-phase-specific levels of premenstrual symptoms. Results are presented in Table 5.3. Trait present-moment-awareness significantly moderated the associations of cycle phase with core, secondary and somatic symptoms, and functional impairment (all *p*s ≤. 015). The interaction effect of trait acceptance and cycle phase was significant for functional impairment ($p = .015$), but not for premenstrual symptom clusters ($p > .05$). As depicted in Fig. 5.2 for illustration purposes, higher present-moment-awareness was linked to lower levels in core, secondary and somatic premenstrual symptoms as well as to lower levels in functional impairment towards the late luteal phase. Acceptance, in turn, was only associated with lower increases in functional impairment in the late luteal phase (Fig. 5.3).

The severity of depressive symptoms (PHQ-9) as a covariate did not change the results of any reported trait × cycle phase interaction effects (all interaction *p*s ≤. 016).

Table 5.3

Interaction effects of psychological traits and cycle phase on daily premenstrual symptoms and functional impairment

	Core symptoms			**Secondary symptoms**			**Somatic symptoms**			**Functional impairment**		
Predictor	*df*	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
MAAS x Cycle phase[a]	1, 1440	5.94	.015	1, 1440	12.80	<.001	1, 1440	25.53	<.001	1, 1440	9.63	.002
HFERST_A x Cycle phase[a]	1, 1441	1.25	.264	1, 1440	2.54	.112	1, 1440	0.04	.845	1, 1440	5.92	.015

Note. All models include random intercepts at level 2 and fixed effects of cycle phase and respective psychological traits. MAAS, Mindfulness Attention Awareness scale; HFERST_A, Heidelberg Form of Emotion Regulation Strategies – Acceptance Subscale; *df,* degrees of freedom.[a] Reference category: follicular phase.

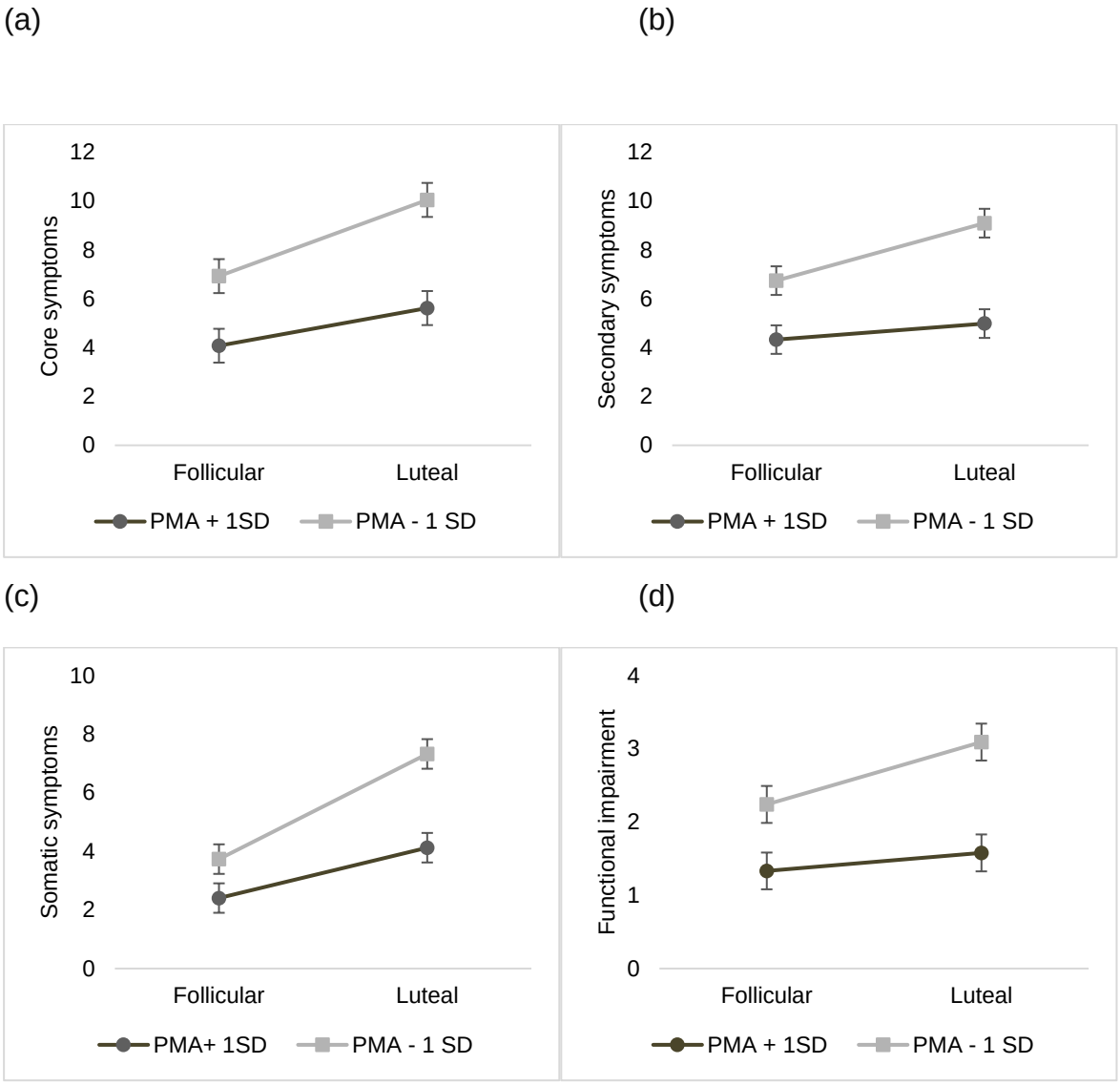

Figure 5.2 Interaction effects of trait present-moment-awareness (PMA) and cycle phase on premenstrual (a) core, (b) secondary and (c) somatic symptoms, and (d) functional impairment

Note. Estimated mean values of premenstrual symptoms and functional impairment per menstrual cycle phase for low and high scores on PMA (Mindfulness Attention Awareness scale; M ± 1SD).

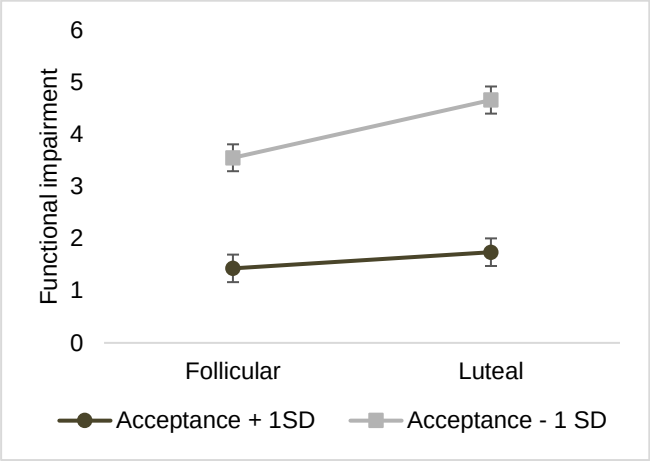

Figure 5.3 Interaction effect of trait acceptance and cycle phase on premenstrual functional impairment

Note. Estimated mean values of premenstrual functional impairment per menstrual cycle phase for low and high scores on acceptance (Heidelberg Form of Emotion Regulation Strategies – Acceptance Subscale; M ± 1SD).

5.5 Discussion

The present study aimed to investigate the cyclical variation of premenstrual symptoms and functional impairment in a sample of women with a wide range of premenstrual symptoms, excluding cases with PMDD. Additional goals were to uncover within-person associations of premenstrual symptoms with further facets of daily life experiences (i.e., rumination and perceived stress) during the late luteal phase, as well as to explore associations of habitual present-moment-awareness and acceptance with premenstrual symptoms and impairment over the cycle. As expected, both premenstrual symptoms and impairment showed a cyclical pattern by increasing towards the late luteal phase and decreasing during the follicular phase after menstruation onset. In particular, the demonstrated premenstrual increase in functional impairment indicates that premenstrual symptoms, which do not reach the DSM-5 criteria for PMDD (APA 2013), may also interfere with daily activities during the late luteal phase and thus should be considered clinically relevant if premenstrual impairment is present (cf. Halbreich et al. 2003; Schmalenberger et al. 2017).

Higher within-person levels of premenstrual symptoms were associated with increased daily rumination and perceived stress during the late luteal phase. These results coincide with previous findings (Beddig et al. 2019; Craner et al. 2016) and point to a broader impact of premenstrual symptoms on daily life experiences, even in women

with subthreshold PMDD symptoms. Premenstrual increases in daily rumination and perceived stress, in turn, have been shown to impede premenstrual mood (Beddig et al. 2019; Beddig et al. 2020). Consequently, premenstrual symptoms, perceived stress, and daily rumination may reciprocally reinforce each other and result in a vicious cycle, possibly maintaining and worsening premenstrual symptomatology in the long-term. Thus, subthreshold conditions of PMDD might represent an important target group for interventions to prevent symptom chronification or transition to PMDD.

Trait present-moment-awareness was associated with weaker increases in core, secondary and somatic premenstrual symptoms and impairment towards the late luteal phase. These results extend limited findings from previous cross-sectional (Lustyk et al. 2011) and treatment studies (e.g. Bluth et al. 2015), indicating protective effects of habitual mindfulness in women with premenstrual disorders. In contrast, a recent Ambulatory Assessment study on women with PMDD showed that whereas trait present-moment-awareness was generally linked to better mood, women with higher levels of present-moment-awareness paradoxically showed a stronger mood worsening towards the late luteal phase, such that their premenstrual mood levels converged with those of women with lower present-moment-awareness (Nayman et al. 2023a). These apparently opposing patterns in the associations of trait present-moment-awareness and premenstrual mood in women with PMDD and those with less severe premenstrual symptoms might reflect a differential role of transdiagnostic psychological factors such as present-moment-awareness for these conditions. This may also imply that addressing present-moment-awareness could represent a psychotherapy target especially for less severe variants of premenstrual disorders such as PMS. However, this conclusion is clearly speculative and requires further research using intervention studies with randomized controlled trials.

In line with Kleinstäuber et al. (2016), habitual acceptance was not linked to premenstrual symptom severity in the present study. However, women with higher acceptance scores showed lower premenstrual functional impairment such that higher acceptance seems to be linked to lower symptom interference with daily activities despite existing symptoms, as already shown for other chronic conditions such as chronic pain (e.g., Lami et al. 2018). Similarly, Read et al. (2014) assume that women with PMS who accept their symptoms may be more likely to perceive a higher ability to cope with premenstrual symptoms. Thus, the attitude of accepting distressing experiences such

as premenstrual symptoms may put individuals into a more active and flexible state to handle daily life activities in spite of symptoms (cf. Hayes et al. 2012).

Strengths and limitations

A major strength of this study is its comprehensive approach combining trait assessments with an online diary to assess different clusters of premenstrual characteristics (i.e., symptoms, impairment, daily rumination, and perceived stress) over two cycles. In the context of research on premenstrual disorders, longitudinal designs with repeated assessments allow to consider cycle-related within-person variations in clinical and psychological characteristics (Bosman et al. 2016; Eisenlohr-Moul 2019). Additionally, the use of an online symptom diary with records of survey dates instead of paper-pencil versions of cycle calendars enabled us to monitor participants' compliance with diary records.

Some limitations of this study are noteworthy. The sample consisted of university students without psychiatric comorbidities and hormonal contraceptive use, thus possibly limiting the generalizability of the results. Another limitation is the lack of ovulation testing to validate ovulatory cycles. Furthermore, to our knowledge, there are no standardized scales for the daily assessments of rumination and perceived stress, and the current findings should be replicated with standardized scales for daily assessments in future research. In this context, the Experience Sampling Method (ESM) Item Repository initiative (Kirtley et al., 2022) may contribute to generating reliable short scales in future. Finally, given that this study did not use an experimental design and assessed habitual present-moment-awareness and acceptance only once during the baseline-session without considering the current cycle phase, no conclusions on cycle-phase-specific characteristics and causality of the associations between the respective trait and state variables can be drawn. Moreover, possible overlapping effects of premenstrual symptoms such as concentration difficulty on the measurement of trait of present-moment-awareness cannot be ruled out.

Conclusions

The present longitudinal study confirms that both premenstrual symptoms and functional impairment increase towards the late luteal phase in women with a broader range of PMS manifestations, and shows that premenstrual symptoms predict increased daily

rumination and perceived stress during the late luteal phase. In addition, both habitual present-moment-awareness and acceptance seem to reflect protective factors with regard to premenstrual distress in these conditions and thus might represent useful targets for interventions in women with PMS.

CHAPTER VI: CHILDHOOD ADVERSITY PREDICTS STRONGER PREMENSTRUAL MOOD WORSENING, STRESS APPRAISAL AND CORTISOL DECREASE IN WOMEN WITH PREMENSTRUAL DYSPHORIC DISORDER (STUDY 5)

An adapted version of this chapter has been published as ‘Nayman, S., Schricker, I. F., Reinhard, I., & Kuehner, C. (2023). Childhood adversity predicts stronger premenstrual mood worsening, stress appraisal and cortisol decrease in women with Premenstrual Dysphoric Disorder. *Frontiers in Endocrinology*, *14*, Article 1278531, 1-10. https://doi.org/10.3389/fendo.2023.1278531’

6.1 Abstract

Background. Lifetime traumatic events are prevalent in women with Premenstrual Dysphoric Disorder (PMDD) and predict stronger premenstrual symptom intensities. Less is known about the unique effects of childhood adversity on PMDD. This study aims to investigate the menstrual cycle related course of mood, stress appraisal and cortisol activity over time and the effects of childhood adversity – by controlling for recent stressful life events – on the cyclicity of these outcomes.

Methods. Fifty-two women with PMDD completed questionnaires on childhood adversity and stressful life events during the past 12 months. Momentary negative and positive affect, stress appraisal, and saliva-cortisol were assessed within an Ambulatory Assessment (AA) design over four consecutive days during both the follicular and the late luteal phase. This AA was repeated after five months, resulting in two measurement bursts.

Results. Women with PMDD showed expected cycle related variations in mood and stress appraisal, whereby these effects weakened over time. No cortisol cyclicity was identified. Higher childhood adversity was linked to stronger increases in negative affect and stress appraisal, and stronger decreases in positive affect from the follicular toward the late luteal phase. Women with higher childhood adversity exhibited lower cortisol levels during the late luteal phase compared to the follicular phase whereas no such cyclicity was found in women with lower childhood adversity.

Conclusions: Childhood adversity appears to show independent deteriorating effects on premenstrual mood worsening and stress appraisal in women with PMDD. The observed cortisol cyclicity in women with higher childhood adversity may point to different neuroendocrine subtypes of PMDD in relation to childhood trauma and requires further systematic research.

6.2 Introduction

Childhood adversity is a potential environmental risk factor for numerous mental and physical diseases in adulthood (Lippard & Nemeroff, 2020). Prolonged exposure to childhood adversity, including experiences of physical, sexual or emotional abuse as well as physical or emotional neglect, can cause chronic stress and result in neuroendocrine system malfunctions such as dysregulations of the Hypothalamic-Pituitary-Adrenal (HPA) axis (Agorastos et al. 2019).

Hantsoo & Epperson (Hantsoo & Epperson, 2020) suggest that childhood adversity makes women also vulnerable to reproductive mood disorders such as to perinatal (Choi et al., 2016) or perimenopausal depression (Eppperson et al., 2017). However, less is known about its role as a risk factor for Premenstrual Dysphoric Disorder (PMDD). PMDD is characterized by cyclical recurrences of impairing or distressing key affective symptoms and additional psychological and somatic symptoms during the late luteal phase of the menstrual cycle, with symptom remission after the onset of menstruation during the follicular phase (American Psychiatric Association [APA], 2013). Cases with milder symptom intensities or lacking key affective symptoms with moderate distress are classified as Premenstrual Syndrome (PMS). In contrast to PMS, PMDD has been acknowledged as a separate diagnostic entity in the chapter of depressive disorders in DSM-5 (APA, 2013) and as a gynecological disorder in ICD-11 (World Health Organization [WHO], 2019). These differential classifications mirror the multifactorial etiology of PMDD, including psychosocial and (neuro-) endocrinological factors (Hantsoo, & Payne, 2023; Schweizer-Schubert et al., 2021). Regarding the latter, previous research consistently suggests that women with PMDD exhibit normal ovarian steroid levels, but show increased central nervous system sensitivity to these normal fluctuations of ovarian steroids and their neuroactive metabolites, especially allopregnanolone (ALLO) (Hantsoo & Payne, 2023). In addition, there is initial evidence for altered HPA axis function in women with premenstrual disorders, such as lower

basal and stress-reactive cortisol activity in women with PMS (Hou et al., 2019) and PMDD (Girdler et al., 1998, 2001, 2003; Nayman et al., 2024) as well as a delayed cortisol awakening response peak and a flattened diurnal cortisol slope across the menstrual cycle in women with PMDD compared to healthy controls (Beddig et al., 2019). Two previous meta-analyses revealed menstrual cycle related variation of cortisol activity in healthy women, with lower cortisol levels during the luteal phase compared to the follicular phase (Hamidovic et al., 2020; Klusmann et al., 2022). In line with these meta-analyses, we identified respective menstrual cycle related cortisol cyclicity in healthy women, but not in women with PMDD (Nayman et al., 2024). Given that cyclical ovarian steroid levels and their metabolites interact with the HPA axis, a history of chronic stress and adversity related HPA axis dysfunction may consequently contribute to the etiology and maintenance of PMDD and increase premenstrual symptom severity (cf. Eisenlohr-Moul et al., 2016; Schweizer-Schubert et al., 2021).

Self-reported childhood adversity has been shown to be associated with higher premenstrual symptoms in adulthood in non-clinical samples (Morishita et al., 2022; Younes et al., 2021). Furthermore, in a prospective cohort study over 14 years, childhood adversity, particularly emotional and physical abuse, increased the risk of moderate-to-severe PMS in a sample of women who were free from PMS at baseline (Bertone-Johnson et al., 2014). Relatedly, in women with PMDD, a high prevalence (83%) of childhood adversity has been observed, with all adversity types (i.e., physical abuse, sexual abuse, emotional abuse, and neglect) being more common in women with PMDD compared to the general female population in Australia (Kulkarni et al., 2022). Similarly, a higher percentage of early life trauma before the age of 18 was found in women with PMDD compared to healthy controls in a German sample (Beddig et al., 2019).

However, previous research on PMDD has mainly investigated effects of traumatic or stressful events at any stage of life on premenstrual symptoms, without differing between childhood (prior to age 18) and adulthood adversity (after age 18). For example, a prospective cohort study over 42 months showed that traumatic events at any time up to baseline increased the odds of developing PMDD at follow-up (Perkonigg et al., 2004). Similarly, in a cross-sectional study, lifetime trauma and post-traumatic stress disorder (PTSD) were independently associated with PMDD or with premenstrual symptoms (Pilver et al., 2011), and in women with prospectively assessed cycle related

mood disorders (PMDD and PMS), a lifetime history of abuse predicted a stronger intensity of premenstrual symptoms (Eisenlohr-Moul et al., 2016). In this context, Girdler et al. (Girdler et al., 2003) showed that women with PMDD report more lifetime sexual and physical abuse as well as a younger age of first abuse compared to healthy controls. Less is known about the effect of childhood adversity on alterations in HPA axis functioning in PMDD. Hitherto, research has included only small subsamples of abused versus non-abused women with PMDD, thereby showing that these subgroups did not differ with regard to basal or stress-reactive plasma cortisol, while alterations in adrenergic physiology were observed in the abused subsample (Girdler et al., 2003). Another study from the same group showed that regardless of PMDD status, abused women showed lower plasma cortisol at rest and during stress, whereas again adrenergic indicators, i.e., vascular resistance and blood pressure during rest and during stress, were increased only in abused women with PMDD (Girdler et al., 2007). However, due to a lack of studies with larger samples, more research on the role of childhood adversity for HPA axis related alterations in women with PMDD is warranted. Since a majority of studies shows that both childhood adversity (cf. Hakamata et al., 2022) and PMDD (cf. Owens & Eisenlohr-Moul, 2018) result in blunted HPA axis activity in women, the possible role of childhood adversity as an aggravating factor for respective HPA axis dysregulation in PMDD remains to be resolved.

To sum up, according to the biological embedding model, especially stress exposure during developmental sensitive periods during childhood (prior to age 18) may lead to dysfunctional structural and functional neuroanatomical as well as neuroendocrine changes (Li et al., 2022; Pervanidou et al., 2018) with long-lasting effects contributing to the development and maintenance of psychopathology. However, most previous studies in women with PMDD did not differ between childhood and adulthood adversities, and therefore the independent role of childhood adversity remains understudied.

Aims

The present study was designed to focus on childhood adversity by controlling for more recent stressful life events, and to investigate independent effects of childhood adversity on the cycle related course of mood, stress appraisal and cortisol activity in daily life in women with PMDD. First, the menstrual cycle related variation of mood, stress appraisal and cortisol activity was investigated together with its possible change over

a five-month interval. Next, we hypothesized that childhood adversity would be associated with stronger increases in negative affect and stress appraisal, and stronger decreases in positive affect from the follicular to the late luteal phase. In addition, we investigated the possible impact of childhood adversity on cortisol levels and menstrual cycle related cortisol cyclicity. Due to the overall lack of research with larger samples in this area, these analyses were exploratory.

6.3 Methods

This study is part of a larger project and an extension of previous analyses on cycle related mood and cortisol in women with PMDD and healthy controls (Nayman et al., 2024). The present study includes a second wave (burst) of Ambulatory Assessment (AA) for the subsample of women with PMDD, and the analyses of menstrual cycle related cyclicity as a function of childhood adversity in these women.

Participants

The present study consisted of two measurement bursts separated by an interval of five months (*M* = 20.61 weeks, *SD* = 2.99). Participants were recruited via online advertisement on the website of the Central Institute of Mental Health (CIMH) in Mannheim, Germany, and via social media and online PMDD support groups. Women were eligible for the study if they fulfilled the DSM-5 diagnostic criteria for PMDD, as assessed using the Structured Interview for PMDD (SCID-PMDD, see below; Accortt et al., 2011). A diagnosis of PMDD requires meeting at least five of eleven PMDD symptoms, including at least one affective symptom, in the majority of menstrual cycles of the preceeding 12 months. These symptoms must be associated with clinically significant distress or functional impairment and may not merely represent an exacerbation of another disorder (APA, 2013).

Further inclusion criteria included ages between 20 and 42 years, regular menstrual cycles (fluctuations < 5 days), an average cycle length of > 22 and < 34 days, and a BMI of > 18 and < 35. Exclusion criteria comprised a) pregnancy or breastfeeding during the last six months, b) intake of hormonal contraceptives, psychotropic drugs (e.g., Selective Serotonin Intake Inhibitors) and other medications with lasting effects on cortisol activity during the last six months, c) gynecological disorders (i.e., endometriosis, hysterectomy, oophorectomy), d) current depressive, generalized anxiety, eating and

substance use disorder, e) lifetime history of bipolar disorder and psychosis. Shift working with regular late or night shifts and regular intensive exercising (> one hour/day) were additional exclusion criteria due to possible effects on cortisol activity. Initially, 60 women with PMDD were recruited at burst 1. Thereof, 52 completed both burst 1 and burst 2 and were included into the current measurement burst analyses. Four individuals provided information for their decision not to complete the AA at burst 2 (i.e., stay abroad, experienced burden at burst 1, lack of interest), whereas four further participants did not respond to our e-mails regarding the appointment proposals at burst 2. The description of the total sample at burst 1, including a comparison sample of healthy controls, can be found in (Nayman et al., 2024).

Procedure

Both bursts consisted of a baseline session and an AA-phase during the follicular and the late luteal phase of the menstrual cycle. If the inclusion criteria were preliminarily met during a telephone screening session, participants were invited to a baseline session. At burst 1, baseline sessions took place either in person at the CIMH (n = 14) or, due to Covid-19 related contact restrictions, online via RedConnect (Red Medical Systems GmbH, Munich, Germany; n = 38). Given the high feasibility of the online format for the baseline sessions, all baseline sessions at burst 2 were also held online via RedConnect (n = 52). The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants provided written informed consent and were compensated with 240€ for the completion of both measurement bursts.

Baseline sessions

During the baseline sessions at burst 1 and burst 2, structured clinical interviews were administered and additional demographic, clinical and cycle related characteristics were assessed.

Psychopathology. For the assessment of PMDD criteria, we administered the Structured Interview for DSM-IV-defined PMDD (SCID-PMDD, interrater reliability κ = 0.96) (Accortt et al., 2011), which was adapted for DSM-5 criteria (cf. Nayman et al., 2023a). The SCID-PMDD covers all eleven symptom criteria of PMDD and assesses their presence, their onset- and offset-time during the cycle, as well as their frequency during

the last 12 months. In addition, the SCID-PMDD checks for the criterion of relational, occupational, and recreational impairment or distress and the exclusion criterion of a mere exacerbation of symptoms of another disorder (cf. Kuehner & Nayman, 2021). For the current study, we decided against the additional administration of prospective symptom ratings as required by DSM-5 (APA, 2013) in order not to overburden participants within the extensive AA-design with two bursts. Diagnostic exclusion criteria regarding current and lifetime psychiatric comorbidities at burst 1 were checked by administering the Structured Clinical Interview for DSM-IV-TR Axis I (SCID-I) (Wittchen et al., 1997). All interviews were performed by trained research psychologists.

Childhood Adversity. Childhood adversity was assessed at burst 1 using the self-report Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) (German version: Klinitzke et al., 2012), which consists of 25 items measuring physical, sexual, and emotional abuse as well as physical and emotional neglect. Each subscale contains five items on a five-point Likert-scale ranging from 1 (never true) to 5 (very often true). For the current analyses, these subscales were summed up, resulting in a CTQ total score range from 29 to 85. Cronbach's α of the total score amounted to α = .919 in the present study.

Recent stressful life events. Stressful life events during the last 12 months before burst 1 were assessed using a list of 12 stressful life events (Berntson et al., 2017), which were adapted from the List of Threatening Experiences (Brugha et al., 1985) and the Schedule of Recent Events (Brugha et al., 1985; Holmes & Rahe, 1967) by Berntson et al. (2017). The assessed events fall into the domains of health (e.g., "Did any of your family members or close friends die?", social (e.g., "Did you have serious problems with a neighbour, friend or relative?", job (e.g., "Were you fired or laid off from a job?", and legal (e.g., "Did you or a family member have trouble with the police, get arrested or get sent to jail?") (Berntson et al., 2017). At burst 1, participants were asked to indicate whether or not they had experienced some of the listed 12 stressful life events (0 = no; 1 = yes). For the statistical analyses, we computed a stressful life events score by summing up the number of indicated events (cf. Berntson et al., 2017).

Premenstrual Symptoms. Participants were asked to complete the German version of the 19-item *Premenstrual Symptom Screening Tool* (PSST) (Steiner et al., 2003)(German version: Bentz et al., 2011) after the last AA-prompt of the 4-day AA-

period during both the follicular and the late luteal phase. The original instruction, in which the items refer to the premenstrual phase, was modified such that participants were asked to rate their symptoms during the last four days (i.e., during the respective AA-period) on a 4-point Likert-scale (0 = not at all, 1 = mild, 2 = moderate, 3 = severe). In the present study, the internal consistency was high in both cycle phases and bursts (follicular phase: Cronbach's $\alpha_{Burst\text{-}1}$ = .931, Cronbach's $\alpha_{Burst\text{-}2}$ = .955; late luteal phase: Cronbach's $\alpha_{Burst\text{-}1}$ = .894, Cronbach's $\alpha_{Burst\text{-}2}$ = .905).

Ambulatory Assessment (AA)

The AA protocol was identical for burst 1 and burst 2. During both bursts, the AA took place on four consecutive days during both the follicular and the late luteal phase, resulting in eight assessment days per burst. The AA was carried out using smartphones (Motorola e^{6s}, Motorola g^{8}, Nokia 4.2) with the software movisensXS, Version 1.5.12 (movisens GmbH, Karlsruhe, Germany, 2020).

Individual cycle calendars presenting scheduled AA days during the follicular and the late luteal phase were prepared based on participants' self-reported average cycle length and the onset date of the last menses. The AA phase during the follicular phase was identified as days six to nine of the menstrual cycle with the day of menses onset representing day 1 of the cycle (cycle-day of AA-start: $M_{Burst\text{-}1}$ = 6.19, $SD_{Burst\text{-}1}$ = 0.53; $M_{Burst\text{-}2}$ = 6.28, $SD_{Burst\text{-}2}$ = 0.78). The late-luteal phase was defined as days −4 to −1 (cycle-day of AA-start: $M_{Burst\text{-}1}$ = 25.56, $SD_{Burst\text{-}1}$ = 2.55; $M_{Burst\text{-}2}$ = 24.51, $SD_{Burst\text{-}2}$ = 1.98), counting backward from the last day before the expected subsequent menses (cf. Schmalenberger et al., 2021). The expected date of the subsequent menses onset was validated by a chromatographic ovulation testing phase around the expected date of ovulation using Femometer® LH ovulation rapid test strips with a corresponding smart app with an intelligent interpretation function (Femometer® app). This ovulation testing phase lasted until receiving a positive result. In case of persistent negative or invalid testing results over 10 days, we asked the participants to repeat the ovulation testing during the next cycle. In these cases, the AA of the late-luteal phase was postponed to the next cycle. We provided constant technical support regarding the study procedure during the entire study via phone, e-mail or online-meetings.

To prevent sequence effects, the AA-start was randomized between the follicular and the late luteal phase. In burst 1, 32 women and in burst 2, 28 started their AA during

the follicular phase. During the AA-phases, participants were instructed to wake up no later than 8:00 a.m. At each assessment point at semi-random times with inter-assessments intervals of 45 to 145 min, starting at a fixed time of 9:00 am and ending approximately at 9:30 pm, they were asked to rate their momentary affect and stress-appraisal since the last prompt (or during the last 1.5 hours at the first assessment). Participants could reject or postpone prompts for up to 15 min. Rejected or ignored signals were coded as missings. With a time lag of 10 min after the completion of subjective assessments, participants were prompted to collect saliva samples.

Subjective AA-measures*.* At each assessment, momentary affect was assessed using 12 items, which were derived from the PANAS (Watson et al., 1988) and previous AA-studies (e.g., Beddig et al., 2020; Nayman et al., 2023a). The participants were asked to indicate the extent to which they experienced negative affect (NA; i.e., felt *upset*, *irritated*, *nervous*, *listless*, *down*, and *bored)* and positive affect (PA; i.e., felt *cheerful*, *energetic*, *enthusiastic*, *satisfied*, *relaxed*, and *calm)* on a 7-point Likert scale ranging from 1 (not at all) to 7 (very much). For NA and PA scores, means of the respective subscales for each assessment time point were calculated.
For the assessment of stress appraisal, the participants were instructed to think about the most important event since the last prompt (or the last 1.5 hours at the first assessment of the day) and to indicate how stressful they perceived the respective event on a 7-point Likert scale ranging from 1 (not at all) to 7 (very much).

Sleep. At the first assessment time at 09:00 a.m., time of awakening, sleep duration in hours and sleep quality (‘*How did you sleep last night?*’ 7-point Likert scale: 1 [very bad] - 7 [very good]) were assessed as possible covariates of cortisol activity.

Saliva Cortisol. Saliva samples were collected 10 min after each subjective assessment resulting in eight saliva samples per day. At the end of subjective assessments, participants were reminded not to eat, drink anything but water, smoke, physically exercise, and brush their teeth during the next 10 min until saliva collection (Schlotz, 2019). Directly after saliva collection, participants indicated whether they had eaten, drunk anything but water, smoked or brushed their teeth (dichotomous items yes/no each) and to what extent they had engaged in physical activity on a 7-point Likert scale (1 = not at all to 7 = very much) during the last 10 min.

Saliva samples were stored in the participants' home freezers until return to the lab. In the lab, the samples were frozen at -20°C until the biochemical analysis at Dresden LabService GmbH, Germany. After thawing, the samples were centrifuged at 3,000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary concentrations were measured using commercially available chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were below 9%.

Statistical Analyses

The data consisted of momentary measurements (Level-1) within bursts (Levels-2), which were nested within individuals (Level-3), such that multilevel models (MLM) were fit.

First, cortisol raw data were log-transformed to adjust for skewness. Per burst, outliers above 3 standard deviations from the group mean were winsorized to 3 standard deviations (Schlotz, 2019; Stalder et al., 2016). Next, we checked for potential confounding effects of study day and weekday vs weekend on all outcomes (NA, PA, stress appraisal, cortisol activity). Additionally, possible confounding effects of time since first assessment were tested for subjective measures. For cortisol activity, we checked for the following additional possible confounders: saliva collection time since awakening, habitual smoking, age, sleep quality, sleep duration, as well as drinking anything but water, smoking cigarettes, eating, brushing teeth, and the level of physical activity during the last 10 min before saliva collection. If significant, these possible covariates were retained in the models ($p < 0.05$). This applied to assessment day for all outcomes. For stress appraisal, weekday was retained as an additional covariate in the respective models. For cortisol activity, additional covariates were saliva collection time since awakening, weekday vs. weekend, sleep duration and smoking during the last 10 min. Furthermore, the Level-3 predictors *childhood adversity* and *stressful life events* were grandmean-centered. For statistical purposes, the burst variable (1 vs 2) was recoded as (0 vs 1).

In general, the statistical analyses were performed through three steps. First, we estimated main effects of cycle phase (0 = follicular phase vs 1 = late luteal phase), childhood adversity and recent stressful life events on each outcome in separate MLMs (models 1). Next, the main effects of *burst* (0 = burst 1 vs 1 = burst 2) and the interaction

term of *cycle phase * burst* were added to these models in order to investigate whether the effects of cycle phase on daily outcomes would be stable over bursts (models 2). Models 2 estimating burst related effects were rerun by including the difference score of premenstrual symptom severity between burst1 and burst 2 (PSST-scores during the late luteal phase) as a covariate in order to control for possible premenstrual symptom alterations over time.

In a third step, these models were expanded by entering the interaction term of childhood adversity with cycle phase to assess the impact of childhood adversity on the cyclicity of daily outcomes (models 3). In case of significant interaction effects, we subsequently estimated simple effects for significant interaction terms. Additionally, we examined possible age-related differences in cycle-specific effects of childhood adversity on mood and cortisol activity by adding age as a main factor and childhood *adversity * age * cycle phase* as an interaction term to respective models.

The main analyses were performed in R (R Core Team, 2022), using the lmer functions from the package lme4 and lmerTest (Bates et al., 2015; Kuznetsova et al., 2017). Due to numeric limitations of the software R, simple effects for models 2 and 3 were estimated via IBM SPSS Statistics Version 28 (IBM Corp., 2021).

A repeated measures ANOVA was performed to compare the PSST-scores between burst 1 and burst 2 during the follicular and the late luteal phase.

6.4 Results

Descriptives

Table 6.1 shows descriptives on demographics and clinical characteristics of the current sample. The repeated-measures ANOVA showed that PSST scores differed significantly across cycle phases and bursts ($F(2, 85) = 140.901$, $p < .001$). Post hoc pairwise comparisons showed that PSST-scores during the follicular phase did not differ between burst 1 and burst 2 (mean difference = -0.667, $SE = 1.209$, $p = .584$). However, the participants showed lower PSST-scores during the luteal phase in burst 2 compared to burst 1 (mean difference = -3.375, $SE = 1.129$, $p = .004$), indicating that premenstrual symptoms weakened over the time interval of five months. Burst-specific descriptives and bivariate correlations of AA-variables, childhood adversity and stressful life events are provided in Table 6.2. At the between- and within-subject level, most variables showed negligible to moderate bivariate correlations, except for the within-

subject correlation of NA and PA being highly negative. Table 6.215 also includes intraclass correlation coefficients (ICC) of AA-variables. Variance decomposition using the ICC showed that 66% to 85% of the total variance in AA-variables could be attributed to within-person variations (for ICC per variable, see Table 6.215). During the AA-phase in burst 1, the compliance rate regarding subjective assessments amounted to 93.0%, and to 88.8% in burst 2, reflecting high levels of compliance (cf. Wrzus & Neubauer, 2023). The AA compliance rate for cortisol sampling amounted to 92.9% in burst 1 and to 87.4% in burst 2.

Participants who were interviewed in person and those interviewed online via RedConnect did not statistically differ in their age ($t(50) = 1.45$, $p = .155$), the number of their PMDD symptoms as assessed with SCID-PMDD (Accortt et al., 2011) ($t(50) = -0.45$, $p = .655$) and in their PSST-sumscores ($t(50) = -0.17$, $p = .870$) at baseline.

Table 6.1

Demographic and clinical characteristics

	M (*SD*)	*n (%)*
Demographic Variables at Burst 1		
Age	30.54 (5.59)	
Education (% with high school degree)		43 (82.7%)
Children (%)		15 (28.8%)
BMI	22.61 (3.36)	
Psychotherapy		9 (17.3%)
SSRI intake		0 (0%)
Hormonal medication intake		0 (0%)
Relationship status (% in a relationship)		25 (48.1%)
Burst 1		
Cycle length during AA	28.60 (3.47)	
PSST during Follicular Phase	10.41 (9.40)	
PSST during Luteal Phase	37.50 (9.79)	
Burst 2		
Psychotherapy start after burst 1		4 (7.7%)
SSRI intake start after burst 1		1 (1.9%)
Hormonal medication intake after burst 1		0 (0%)
Cycle length during AA	28.00 (2.34)	
PSST during Follicular Phase	10.83 (11.21)	
PSST during Luteal Phase	34.66 (11.01)	

Note. BMI, Body Mass Index; AA, Ambulatory Assessment; PSST, Premenstrual Symptoms Screening Tool; SSRI, Selective Serotonin Reuptake Inhibitor. PSST scores represent sum scores.

Table 6.2

Descriptives, correlations, variability statistics of momentary outcomes and level-3 predictors

		Bivariate Correlations						Descriptives		
Burst	Variable	1	2	3	4	5	6	M	SD_{B-S}	SD_{W-S}
1	1. Negative Affect	1	-0.55	0.39	0.10	0.20	0.18	2.90	0.49	1.02
	2. Positive Affect	-0.85	1	-0.46	-0.08	-0.24	-0.27	4.12	0.47	1.12
	3. Stress appraisal	0.38	-0.38	1	-0.18	0.13	0.05	0.73	0.73	1.44
	4. Cortisol [a]	0.05	-0.03	0.06	1	-0.08	0.09	1.78	0.34	0.81
	5. CTQ	-	-	-	-	1	0.22	42.07	12.78	-
	6. SLE	-	-	-	-	-	1	2.64	1.70	-
2	1. Negative Affect	1	-0.67	0.33	0.17	0.06	0.23	2.80	0.60	0.88
	2. Positive Affect	-0.82	1	-0.27	-0.09	-0.06	-0.27	4.13	0.62	1.00
	3. Stress appraisal	0.25	-0.26	1	-0.24	-0.09	0.02	2.17	0.71	1.22
	4. Cortisol	0.04	0.00	0.04	1	0.03	0.08	1.78	0.37	0.77
	5. CTQ	-	-	-	-	-	0.24	-	-	-
	6. SLE	-	-	-	-	-	1	-	-	-
	ICCs across Bursts									
	$ICC_{Personlevel}$	0.18	0.17	0.17	0.09	-	-	-	-	-
	$ICC_{Burstlevel}$	0.06	0.17	0.05	0.06	-	-	-	-	-

Note. CTQ, Childhood Trauma Questionnaire; SLE, Stressful Life Events; ICC, Intraclass Correlation Coefficient; SD_{B-S}, Between-subject standard deviation; SD_{W-S}, Within-subject standard deviation. Between-subject correlations are presented above the diagonal; within-subject correlations among momentary measures are presented below the diagonal. Given that CTQ and SLE represent single time-point scores as cross-sectional data, no within-subject correlations between trait and state measures could be computed. Means and between-subject standard deviations were calculated based on aggregated person-mean scores.

[a] Cortisol data were log-transformed and winsorized to three standard deviations of the sample mean.

Effects of cycle phase and burst

Main results are presented in models 1 of Table 6.3 and Table 6.4. Across bursts, cycle phase was significantly associated with all subjective outcomes (i.e., NA, PA, stress appraisal), but not with cortisol activity (F(1, 5538) = 0.612, p = .805). In particular, women with PMDD showed higher NA (F(1, 5817) = 2005.917, p < .001), lower PA (F(1, 5825) = 1939.921, p < .001) and higher stress appraisal (F(1, 5820) = 53.627, p < .001) during the late luteal phase compared to the follicular phase (see respective models 1 in Table 6.3 & Table 6.4). In contrast, no main effects of childhood adversity were identified on NA (F(1, 101) = 0.890, p = .347), PA (F(1, 102) = 0.819, p = .368), stress appraisal (F(1, 102) = 0.056, p = .813) and cortisol activity (F(1, 103) = 0.053, p = .818). Recent stress life events were associated with lower momentary PA (F(1, 102)

= 5.850, p = .017; see model 1 in Table 6.3), with no main effects on NA (F(1, 101) = 2.754, p = .100), stress appraisal (F(1, 102) = 0.027, p = .869) and cortisol activitiy (F(1, 101) = 0.167, p = .684).

Next, longer-term cycle-phase-specific variations in daily life outcomes were investigated (see respective models 2 in Table 6.3 & 6.4). Burst significantly moderated the effects of cycle phase on NA (F(1, 5812) = 30.250, p < .001), PA (F(1, 5820) = 41.845, p < .001) and stress appraisal (F(1, 5814) = 25.497, p < .001), but not on cortisol activity (F(1, 5532) = 1.739, p = .187). In both bursts, NA (mean difference $_{\text{Burst-1}}$ = 1.099, $SE_{\text{Burst-1}}$ = 0.030, p < .001; mean difference $_{\text{Burst-2}}$ = 0.861, $SE_{\text{Burst-2}}$ = 0.031, p < .001) was higher and PA (mean difference $_{\text{Burst-1}}$ = -1.235, $SE_{\text{Burst-1}}$ = 0.034, p < .001; mean difference $_{\text{Burst-2}}$ = -0.921, $SE_{\text{Burst-2}}$ = 0.035, p < .001) was lower during the late luteal phase compared to the follicular phase, with smaller cycle phase differences in burst 2 compared to burst 1. Stress appraisal in daily life was higher during the late luteal phase compared to the follicular phase only in burst 1 (mean difference $_{\text{Burst-1}}$ = 0.430, $SE_{\text{Burst-1}}$ = 0.049, p < .001) but not in burst 2 (mean difference $_{\text{Burst-2}}$ = 0.079, $SE_{\text{Burst-2}}$ = 0.051, p = .122). In sum, these results indicate that deteriorations in momentary mood from the follicular to the late luteal phase weakened over the 5-months period but were still significant, whereas the premenstrual increase in stress appraisal was no longer apparent in burst 2. Cortisol activity, in turn, showed no variations across cycle phases and bursts.

After including the PSST difference scores of the late luteal phase between burst 1 and burst 2, the interaction effects of cycle phase and burst in models 2 on all outcomes remained unchanged (NA: b = -0.246, SE = 0.044, p <.001; PA: b = 0.324, SE = 0.049, p <.001; stress appraisal: b = -0.312, SE = 0.071, p <.001; cortisol: b = -0.015, SE = 0.031, p = .628).

Cycle-specific associations of childhood adversity and daily variables

Childhood adversity moderated the effects of cycle phase on all momentary outcomes across bursts, with significant interaction effects of *cycle phase * childhood adversity* on NA ($F(1, 5811) = 33.450$, $p < .001$), PA ($F(1, 5818) = 63.428$, $p < .001$), stress appraisal ($F(1, 5813) = 15.477$, $p < .001$) and cortisol activity ($F(1, 5530) = 6.171$, $p = .013$) (see respective models 3 in Table 6.3 & Table 6.4). As can be seen in Figure 6.1 (A-C), women with higher childhood adversity showed higher increases in NA (mean difference = 1.106, $SE = 0.031$, $p < .001$) and stress appraisal (*mean difference* = 0.395, $SE = 0.050$, $p < .001$) as well as higher decreases in PA (mean difference = -1.269, $SE = 0.034$, $p < .001$) from the follicular to the late luteal phase compared to women with lower childhood adversity (NA: mean difference$_{NA}$ = 0.855, SE_{NA} = 0.031, $p_{NA} < .001$; stress appraisal: mean difference$_{stress}$ = 0.115, SE_{stress} = 0.050, p_{stress} = .021; PA: mean difference = -0.887, SE_{PA} = 0.034, $p_{PA} < .001$). Regarding cortisol activity, women with higher childhood adversity showed lower basal cortisol activity during the late luteal phase compared to the follicular phase (*mean difference* = -0.044, $SE = 0.022$, $p = .048$) whereas women with lower childhood adversity did not exhibit cycle-phase-specific variations in cortisol activity (mean difference = -0.033, $SE = 0.022$, $p = .128$; see Figure 6.1D).

In addition, we examined possible age-related differences in cycle-specific effects of childhood adversity on mood and cortisol activity. The respective interaction analyses of *childhood adversity * age * cycle phase* revealed no significant effects on NA ($F(1, 5806) = 0.512$, $p = 0.474$), PA ($F(1, 5811) = 1.691$, $p = 0.193$), stress appraisal ($F(1, 5806) = 2.90$, $p = 0.089$) or cortisol activity ($F(1, 5522) = 0.362$, $p = 0.574$).

Table 6.3

Multilevel Analyses of Cycle Phase, Childhood Adversity and Burst on Negative Affect and Positive Affect

	Negative Affect						Positive Affect					
	Model 1		**Model 2**		**Model 3**		**Model 1**		**Model 2**		**Model 3**	
	B	**SE**	***B***	**SE**	***B***	**SE**	***B***	**SE**	***B***	**SE**	***B***	**SE**
Fixed Effects												
Intercepts	2.351***	0.058	2.342***	0.079	2.338***	0.080	4.660***	0.058	4.711***	0.079	4.717***	0.079
Study day	0.003	0.005	0.003	0.005	0.003	0.005	0.004	0.005	0.004	0.005	0.003	0.005
Cycle[a]	0.986***	0.022	1.100***	0.030	1.099***	0.030	- 1.085***	0.025	- 1.234***	0.034	- 1.234***	0.035
SLE	0.054	0.032	0.054	0.032	0.0530	0.033	-0.077*	0.032	-0.077*	0.032	- 0.076*	0.032
CTQ	0.004	0.004	0.004	0.004	-0.001	0.004	-0.038	0.042	-0.004	0.004	0.004	0.004
Burst[b]			0.028	0.109	0.030	0.110			- 0.114	0.111	- 0.118	0.108
Cycle x Burst			-0.238***	0.043	-0.236***	0.043			0.313***	0.048	0.310***	0.048
Cycle x CTQ					0.010***	0.002					-0.015***	0.002

Note. CTQ, Childhood Trauma Questionnaire; SLE, Stressful Life Events.
***** $p < .05$, ****** $p < .01$, ******* $p < .001$
[a] Reference category = Follicular phase
[b] Reference category = Burst 1

Table 6.4

Multilevel Analyses of Cycle Phase, Childhood Adversity and Burst on Stress Appraisal and Cortisol Activity

	Stress Appraisal						Cortisol[c]					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	B	**SE**	***B***	**SE**	***B***	**SE**	***B***	**SE**	***B***	**SE**	***B***	**SE**
Fixed Effects												
Intercepts	2.486***	0.082	2.538***	0.109	2.533***	0.110	3.086***	0.082	3.075***	0.088	3.083***	0.088
Time	---		---		---		-0.138***	0.002	-0.138***	0.002	-0.138***	0.002
Weekday	-0.136**	0.042	-0.137***	0.042	-0.133**	0.041	-0.037*	0.018	-0.037*	0.018	-0.038*	0.018
Study day	-0.060***	0.008	-0.060***	0.008	-0.060***	0.008	0.010**	0.003	0.010**	0.003	0.010**	0.003
Smoking	---		---		---		0.283	0.154	0.283	0.154	0.292	0.154
Sleep duration	---		---		---		-0.030**	0.011	-0.030**	0.011	-0.031**	0.011
Cycle[a]	0.262***	0.036	0.431***	0.049	0.431***	0.049	-0.004	0.011	0.015	0.021	0.015	0.021
SLE	0.007	0.044	0.008	0.044	0.007	0.044	0.008	0.019	0.007	0.002	0.008	0.019
CTQ	0.001	0.006	0.001	0.005	-0.004	0.006	-0.001	0.003	-0.001	0.002	0.001	0.003
Burst[b]			- 0.090	0.148	-0.087	0.149			0.029	0.066	0.028	0.066
Cycle x Burst			- 0.354***	0.070	-0.353***	0.007			-0.041	0.031	-0.042	0.031
Cycle x CTQ					0.011***	0.003					-0.003*	0.001

Note. CTQ, Childhood Trauma Questionnaire; SLE, Stressful Life Events. The covariate *time* represents time of saliva collection since awakening

***** $p < .05$, ****** $p < .01$, ******* $p < .001$

[a] Reference category = Follicular phase

[b] Reference category = Burst 1

[c] Cortisol data were log-transformed and winsorized to three standard deviations of the sample mean

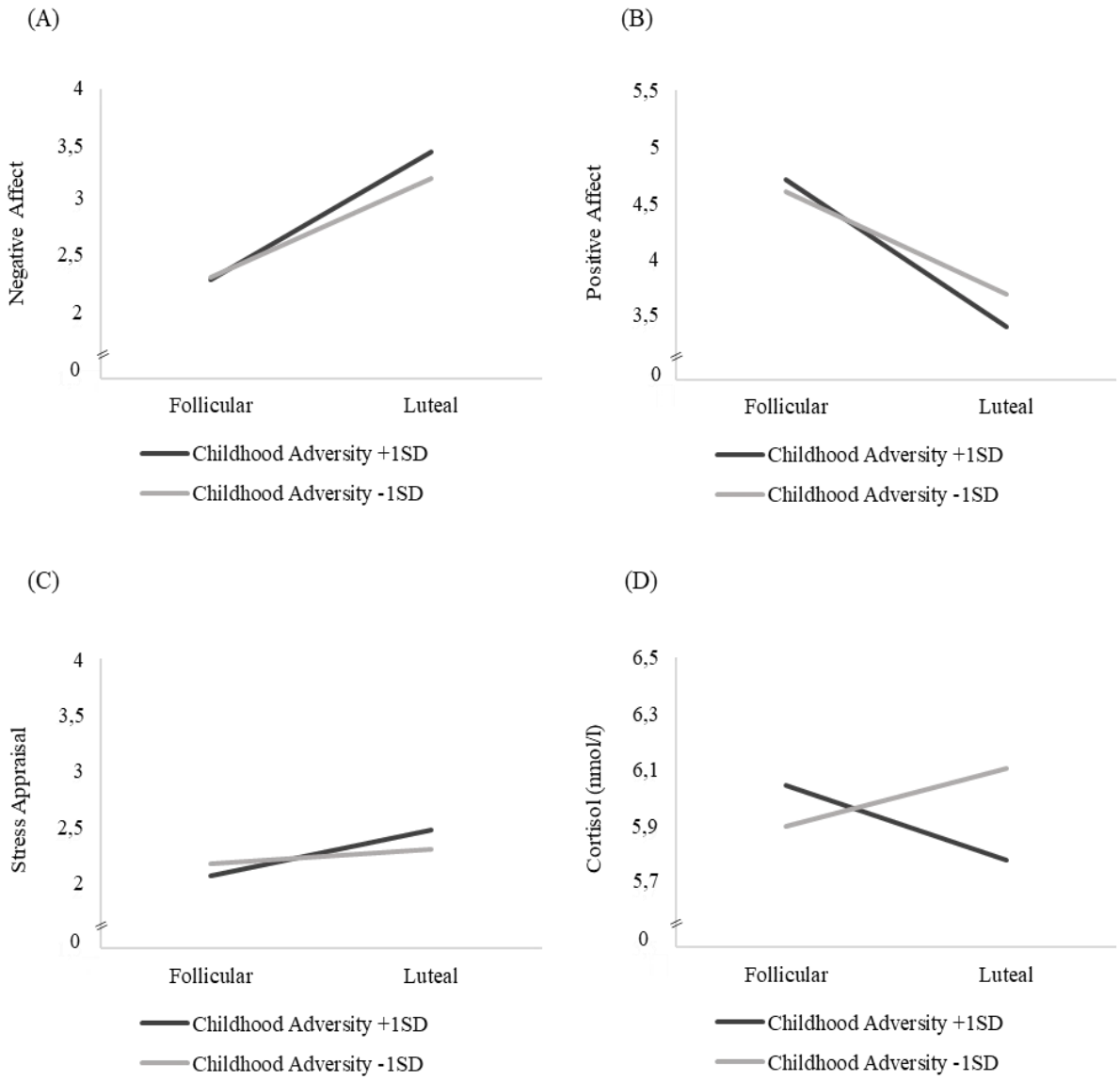

Figure 6.1 Interaction effects of childhood adversity and cycle phase on mood, stress appraisal and cortisol activity in daily life

Note. Estimated mean values of momentary (A) negative affect, (B) positive affect (C) stress appraisal and (D) cortisol activity (nmol/l) during the follicular and late-luteal phase for high (+ 1SD) and low (- 1SD) childhood adversity.

6.5 Discussion

Traumatic events during lifetime are prevalent in women with PMDD and predict higher premenstrual symptom levels (Eisenlohr-Moul et al., 2016; Kulkarni et al., 2022). Given that especially childhood adversity interferes with sensitive developmental periods regarding affective-cognitive and neuroendocrine processes, the present study focused on the role of childhood adversity for menstrual cycle related variations of mood, stress appraisal and cortisol during daily life in women with PMDD. In the current study with two waves (bursts) of intensive AA-periods, which were separated by a 5-month interval, women with PMDD showed premenstrual worsening of positive and negative affect as well as stress appraisal across bursts, with weakening effects of cycle phase from burst 1 to burst 2. In contrast, no cyclicity of cortisol release was identified across bursts in the total sample, and the lack of cortisol cyclicity remained stable over time. By controlling for recent stressful life events, higher childhood adversity was linked to stronger mood worsening and to a stronger increase in stress appraisal from the follicular to the late luteal phase. Childhood adversity also moderated cortisol cyclicity. Women with higher childhood adversity exhibited lower cortisol levels during the late luteal compared to the follicular phase, whereas no such cyclicity was found in women with lower childhood adversity.

Effects of cycle phase and time

Consistent with findings from a previous AA-study (Beddig et al., 2020), negative affect during daily life increased and positive affect decreased from the follicular to the late luteal phase in the current sample, thereby mirroring the clinical presentation of PMDD characterized by key premenstrual affective symptoms (APA, 2013). Furthermore, previous research has shown that women with severe premenstrual symptoms generally report higher perceived chronic stress compared to healthy controls (cf. Kleinstäuber et al., 2016). In line with Beddig et al. (Beddig et al., 2019), the current study further shows that in women with PMDD, perceived stress in daily life appears to be particularly high during the late luteal phase. Regarding cortisol activity, no such cyclicity was identified in the current total sample, which was, however, moderated by childhood adversity (see below).

Over a period of five months, the premenstrual increase in negative affect and the decrease in positive affect weakened, while the effect of cycle phase was still significant. In general, fluctuations of premenstrual symptoms over time have to be considered (cf. Nappi et al., 2022), and a previous population-based cohort study showed that only 46% of women diagnosed with severe PMS at baseline qualified for severe PMS one year later, whereas 19% qualified for moderate PMS and further 35% reported premenstrual symptom and impairment levels no more qualifying for the condition (Potter et al., 2009). Similarly, Hart et al. (1987) demonstrated that prospective scores in premenstrual symptoms from one cycle predicted only 14% of the variance in the next cycle, pointing to inter-cycle variability in premenstrual symptoms.

The premenstrual increase in stress appraisal, in turn, was no longer observed at burst 2 in the present study. One possible reason for the diminished cyclicity in stress appraisal together with reduced premenstrual symptoms (PSST) over time might be that for the majority of participants, the baseline-interview at burst 1 was the first time when they were validated and recognized for their PMDD related distress. This might have led to an increased awareness and accepting attitude toward their premenstrual symptoms or to behavioral life-style changes to cope with them over time. It seems noteworthy that four women started psychotherapy and one woman started pharmacotherapy with a Selective Serotonin Reuptake Inhibitor after burst 1, indicating possible increased awareness and active coping. However, these explanations are highly speculative, and more research systematically investigating protective factors against the chronification of mood and stress cyclicity in PMDD is warranted. Furthermore, it is to note that the observed weakening of premenstrual mood worsening and stress appraisal from burst 1 to burst 2 could not be sufficiently explained by the observed parallel improvement in premenstrual symptoms, as assessed by the PSST. Thus, repeated assessments of mood and stress perception during daily life may yield a more fine-graded picture of the cyclicity of subjective experiences and their fluctuations over time than difference scores in premenstrual symptoms as assessed retrospectively at the end of the luteal phase (cf. Bosman et al., 2016).

Effects of childhood adversity

Research on childhood adversity indicates that childhood adversity is associated with higher negative affect, lower positive affect (Nayman, Jones et al., 2022; Xiang et al.,

2021) and higher perceived stress (Van Dammen et al., 2019) during daily life in adult non-clinical samples, and with the development of various forms of psychopathology (cf. Hakamata et al., 2022; Teicher et al., 2022). In these various contexts, researchers generally investigated and identified main effects of childhood adversity on respective outcomes. However, childhood adversity did not exert any main effects on mood and stress appraisal in daily life, when investigated across the total cycle, in the present sample. In contrast, our results suggest that childhood adversity appears to specifically impact the *cyclicity* of daily life experiences in women with PMDD. As hypothesized, childhood adversity was associated with stronger increases in negative affect and stronger decreases in positive affect from the follicular toward the late luteal phase. These findings align with initial evidence that lifetime trauma and recent stressful life events increase the severity of premenstrual symptoms in women with severe PMS and PMDD (Schweizer-Schubert et al., 2021), thereby indicating that childhood adversity represents a distal risk factor for severe clinical manifestations of PMDD. The current findings additionally refine previous findings by disentangling childhood and adulthood adversity, thereby focusing on the net-effects of childhood adversity. The present study also demonstrates that the premenstrual increase in daily stress appraisal is particularly strong in women with higher childhood adversity. Thus, childhood adversity appears to render women with PMDD even more sensitive to daily life stress, especially during their vulnerable late luteal phase.

In parallel to mood and stress appraisal, childhood adversity did not exert a general main effect on cortisol activity during daily life in the present sample when cumulated across the cycle. This is again different to demonstrated main effects of childhood adversity on cortisol when samples with other psychopathologies are investigated. Here, a majority of studies show that childhood adversity is associated with lower resting cortisol activity and blunted cortisol reactivity in clinical and non-clinical samples (Hakamata et al., 2022; O'Connor et al., 2020; Teicher et al., 2022).

In contrast to these studies, and similar to the current subjective outcomes, childhood adversity specifically affected the *cyclicity* of cortisol, thereby supporting the assumption of an interaction of adversity related HPA axis alterations and the HPG-axis in PMDD (cf. Kulkarni et al., 2022; Morishita et al., 2022). In particular, women with higher childhood adversity displayed cortisol cyclicity with lower levels during the late luteal phase compared to the follicular phase, while no such cyclicity was identified in women

with lower childhood adversity. Placing these results in the context of previous findings, the study by Girdler et al. (2003) found that, regardless of cycle phase and abuse history, women with PMDD showed significantly lower resting baseline plasma cortisol levels compared to controls. Furthermore, prior abuse was not associated with altered cortisol reactivity in response to mental stress (Girdler et al., 2003). In contrast, Girdler et al. (2007) reported a trend for lower cortisol levels in abused compared to non-abused women, regardless of PMDD status, whereas in both studies (Girdler et al., 2003, 2007), abused women with PMDD specifically displayed higher adrenergic activity at rest and during stress. However, our studies are not completely comparable, since we assessed saliva cortisol during daily life and not plasma cortisol before and during stress.

The observed cortisol cyclicity with lower levels during the late luteal phase in women with higher childhood adversity should also be discussed in light of the two recent meta-analyses in healthy women (Hamidovic et al., 2020; Klusmann et al., 2022). Both meta-analyses identified menstrual cycle related cortisol variation with lower levels of cortisol during the luteal compared to the follicular phase, suggesting that this pattern may be an adaptive response to increasing ALLO levels in the luteal phase. ALLO is a neurosteroid metabolit of progesterone and a positive allosteric modulator of the GABAA receptor in the brain, thereby potentiating the anxiolytic and sedative effects of GABA, which plays a critical role in negative modulation of the HPA axis (cf. Hantsoo & Payne, 2023; Sikes-Keilp & Rubinow, 2023). However, a growing body of evidence suggests that women with PMDD show a paradoxical reaction toward the fluctuating ALLO levels during the luteal phase with typically increased premenstrual irritability and other affective core symptoms (e.g., Bäckström et al., 2014; Hantsoo & Epperson, 2020).

In our previous analysis from the present project with data from burst 1 (Nayman et al., 2024), we identified cortisol cyclicity with lower levels during the late luteal phase in a sample of healthy women (cf. Hamidovic et al., 2020; Klusmann et al., 2022). In contrast, no such cyclicity was found in the latter total sample of women with PMDD, together with overall decreased cortisol levels in the PMDD sample compared to healthy controls. The present analysis replicates the lack of cortisol cyclicity for the total PMDD sample, now combined for burst 1 and burst 2 (cortisol data for healthy women were collected only at burst 1). However, when considering the moderator effect of childhood

adversity, we observed a further decrease during the late luteal phase in those women with higher childhood abuse, pointing to a possible specific “ecophenotype” (Teicher et al., 2022) in PMDD. Such childhood adversity related ecophenotypes, stemming from the environmental experience of high childhood adversity and their consequences, have been identified for individuals with a variety of mental disorders, which are clinically and neurobiologically distinct from those with low exposure. These differences include abnormal HPA axis activity and autonomic responses to stressors (Teicher et al., 2022). The particularly low luteal cortisol levels in women with high childhood adversity may therefore indicate a unique ecophenotype of PMDD which, in turn, contributes to the observed aggravating effects of childhood adversity on premenstrual mood and stress appraisal. While these conclusions are still highly speculative, the search for adversity related ecophenotypes in PMDD as a cyclic disorder appear highly promising since they are directly implicated in the interaction of early adversity with the HPA and the HPG axes (Kulkarni et al., 2022). However, more detailed future research is clearly warranted aiming at elucidating possible childhood adversity related PMDD subtypes with respect to their molecular and physiological consequences, not least in order to be able to offer more individualized treatment options to affected women.

Clinical Implications

In sum, our results imply that women with PMDD and higher childhood adversity differ from those with lower childhood adversity with respect to their cyclical course of mood, stress appraisal and cortisol release during daily life. In particular, childhood adversity appears to increase the risk for premenstrual affective and cognitive deteriorations and neuroendocrinological vulnerabilities, which in turn may predict a worse clinical course and a poorer treatment response, as observed in other psychiatric disorders (e.g., Lippard & Nemeroff, 2020; Teicher et al., 2022). Therefore, the potential impact of childhood adversity on the clinical course of PMDD needs to be considered in future research. For example, pharmacological research, which currently mainly focuses on novel agents aiming at stabilizing the ALLO level signaling during the luteal phase (for reviews, see Sikes-Keilp & Rubinow, 2023; Sundström-Poromaa & Comasco, 2023), should investigate whether childhood adversity moderates the efficacy of these drugs. In psychotherapy research, a similar consideration should be given to possible early

adversity related affective-cognitive dysregulations. Notably, childhood adversity is linked to a higher rumination tendency in adulthood, which in turn is associated with worse clinical outcomes (Mansueto et al., 2021). Women with PMDD exhibit higher habitual rumination compared to healthy controls (e.g., Nayman et al., 2023a) and higher momentary rumination during the late luteal phase compared to the follicular phase (Beddig et al., 2019), which in turn predicts higher negative affect specifically during the late luteal phase (Beddig et al., 2020). Thus, rumination might represent a psychological mechanism by which childhood adversity is linked to higher premenstrual mood worsening, and future studies should take clinical adversity into account in interventions addressing rumination. Furthermore, the inclusion of childhood adversity related treatment components could be investigated in clinical trials, for example by targeting adversity related core beliefs or specific stress management skills in affected women with PMDD.

In general, a more systematic consideration of potential childhood adversity in PMDD research and treatment is clearly warranted, and childhood adversity should be regularly assessed in the clinical care of women with PMDD. The identification of possible targeted and individualized treatment options for affected women will hopefully improve the hitherto only modest treatment achievements in PMDD (cf. Hantsoo & Riddle, 2021), and will also prevent premature treatment termination due to weak therapeutic alliance, as already discussed in the context of other mental disorders (cf. Maj et al., 2020).

Strengths and Limitations

This is the first study investigating associations of childhood adversity with momentary mood, stress appraisal and cortisol activity across the menstrual cycle in women with PMDD using an intensive AA design with two measurement bursts. In order to rule out possible effects of psychiatric comorbidities and pharmacology, we used strict exclusion criteria such as the presence of a current depressive episode as well as the intake of psychopharmacology and drugs affecting the HPA axis. We further controlled for recent stressful life events. Thus, the current findings represent unique effects of childhood adversity on cycle related mood, stress appraisal and cortisol in women with PMDD. Another strength is the use of a chromatographic ovulation test for the validation of ovulatory cycles.

The present study also has some limitations. First, we decided not to administer prospective symptom ratings over two cycles, as required by DSM-5 for a definite diagnosis of PMDD (APA, 2013), in order to avoid overburdening participants within the extensive AA-design with two bursts. Instead, provisional PMDD diagnoses were made using a structured and validated diagnostic interview (SCID-PMDD) (Accortt et al., 2011). Moreover, with *N* = 52, our sample size was generally moderate. However, considering the number of Level 3 units (participants) and Level 1 units (observations: 2 bursts * 8 assessments days * 8 assessments per day) in our AA-design, the power was expected to reach the threshold of 80% to detect small to medium effect sizes (Mathieu et al., 2912). Furthermore, although adversity during the entire childhood has been shown to be linked to the development of psychopathology, the duration, timing, and developmental stage during exposure to childhood adversity may lead to differential effects regarding psychological and neuroendocrine outcomes (cf. Agorastos et al., 2019; Li et al., 2022). Future research delineating specific critical developmental windows during which childhood adversity specifically influences the HPA-HPG interaction and has the most clinical impact on premenstrual symptoms is warranted. Similarly, not only recent life events during the past 12 months but also traumas and major stressful life events at different life stages during the entire adulthood period might be relevant for the extent of premenstrual symptoms. Thus, while our analyses controlled for the potential confounding recency effects of experiences during the past year, future larger prospective studies could benefit from systematic life-stage-related assessments of stressful events.

Moreover, childhood adversity was assessed retrospectively, bearing the risk for recall bias and pointing to the need for prospective cohort studies in this context. This would also allow to investigate the effects of childhood adversity on the risk of developing PMDD, and to contribute to the investigation of transitions from PMS to a full syndrome PMDD. Regarding the longer-term effects of childhood adversity on the cyclicity of mood, stress appraisal and cortisol, longer time intervals between bursts might be suitable to uncover clinically relevant and potentially slower contextual processes such as life transitions or marked clinical changes (e.g., Schricker et al., 2023c).

Conclusions

In conclusion, high levels of experienced childhood adversity appear to predict more pronounced premenstrual mood worsening and higher premenstrual increase of stress appraisal during daily life in women with PMDD. Women with higher childhood adversity further seem to differ from those with lower childhood adversity also in terms of saliva cortisol cyclicity by showing lower cortisol levels during the late luteal phase, possibly indicating a specific ecophenotype of PMDD. These identified affective-cognitive and neuroendocrine effects of childhood adversity in women with PMDD underscore the need for further research to delineate possible subgroups in PMDD. Understanding these distinctions can lead to more personalized interventions for women with PMDD, taking into account their unique experiences of childhood adversity.

CHAPTER VII: GENERAL DISCUSSION

7.1 Summary of the Present Findings

This dissertation comprises five studies aimed at understanding affective, cognitive and endocrinological (i.e. cortisol) processes and their interactions across the menstrual cycle in women with Premenstrual Dysphoric Disorder (PMDD). The findings can be summarised within a three-level model, including individual differences in affective and endocrinological cyclicity (macro-level), within-person variations across the cycle phases (meso-level) and within the cycle phases (micro-level) in affective, cognitive and endocrinological processes (micro-level) (see Figure 7.1).

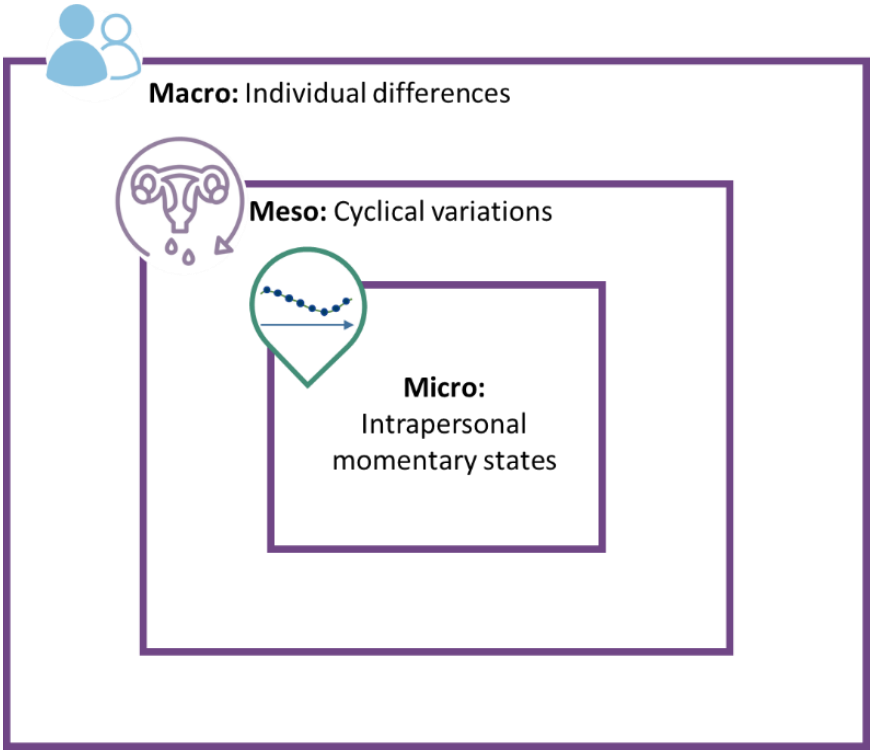

Figure 7.1 Multilevel Psychoendocrinological Model of Hypersensitivity

The macro-level covers findings related to trait-like psychosocial factors that may contribute to individual differences in variations in affective and endocrinological dynamics across the cycle in PMDD, subthreshold PMDD and healthy controls. Relatedly, Study 1 of this dissertation (Nayman et al., 2023a) demonstrated that women with PMDD displayed higher levels of habitual (trait) repetitive negative thinking and lower levels of habitual mindfulness and reappraisal than healthy women. In women with PMDD, those with favourable habitual cognitive emotion regulation strategies (i.e. lower trait repetitive negative thinking, higher trait mindfulness and reappraisal) showed better momentary mood during the non-symptomatic menstrual, follicular, and ovulatory

phases, whereas no associations with mood were found during the symptomatic late luteal phase. These findings were replicated in Study 2 (Nayman et al., 2024), which showed that lower trait repetitive negative thinking and higher trait mindfulness were associated with better momentary mood only during the follicular phase, but not during the late luteal phase. Thus, habitual cognitive emotion regulation strategies contributed to individual differences in mood during non-symptomatic cycle phases in PMDD, with favourable levels being associated with better mood. However, favourable levels of these strategies appeared to be decoupled from premenstrual mood, such that they did not protect affected women with PMDD from mood worsening during the late luteal phase (Nayman et al., 2023a, 2024). Study 2 further investigated associations between habitual cognitive emotion regulation strategies and momentary mood across the cycle in healthy controls, and showed that healthy controls with higher trait present-moment-awareness reported lower negative affect in both cycle phases, with a stronger association in the late luteal phase (Nayman et al., 2024). Trait aspects of repetitive negative thinking, mindfulness, and reappraisal were not linked to cortisol activity across the menstrual cycle in women with and without PMDD (Nayman et al., 2023a, 2024), except that lower habitual mindfulness was associated with lower menstrual cortisol levels in PMDD (Nayman et al., 2023a).

In Study 4 (Nayman et al., 2023b), which focused on individual differences in symptom severity in subthreshold PMDD, trait present-moment-awareness was associated with weaker increases in core, secondary, and somatic premenstrual symptoms and functional impairment from the follicular to the late luteal phase. Habitual acceptance was linked to lower premenstrual functional impairment. Taken together, these findings in subthreshold PMDD, which are contradictory to findings in full syndrome PMDD, emphasize that favourable habitual emotion regulation may serve as a protective factor for subthreshold PMDD and may represent a potential prevention target.

Study 5 (Nayman et al., 2023c) examined the effects of childhood adversity as a distal environmental risk factor for PMDD and found that higher levels of childhood adversity were associated with stronger mood deterioration and increased stress appraisal from the follicular to the late luteal phase in women with PMDD, even after controlling for recent stressful life events during the past 12 months. With regard to cortisol activity, the PMDD sample exhibited lower overall cortisol activity compared to healthy controls (Study 2, Nayman et al., 2024). In women with PMDD, experiences of childhood adversity were associated with additional cortisol reductions during the late luteal phase, suggesting that childhood adversity may represent a distal risk factor contributing to

individual differences in PMDD. This may reflect a specific ecophenotype of PMDD dependent on experiences of childhood adversity (Nayman et al., 2023c).

At the meso-level, which reflects within-person variations in affective, cognitive and endocrinological processes across the cycle phases, women with PMDD exhibited mood and cognitive cyclicity characterised by mood deterioration, exacerbation of momentary rumination and stress appraisal, and reductions in present-moment-awareness and self-acceptance during the late luteal phase compared to the follicular phase (Nayman et al., 2023c, 2024, in press). Women with subthreshold PMDD also showed increases in core affective symptoms and functional impairment during the late luteal phase compared to the follicular phase (Nayman et al., 2023b). In contrast, healthy women did not display mood but cortisol cyclicity, marked by lower cortisol levels during the late luteal compared to the follicular phase, whereas no cortisol cyclicity was found in women with PMDD (Nayman et al., 2024).

At the **micro level**, the focus is on affective, cognitive and endocrinological processes and their interplay within specific cycle phases. In contrast to trait emotion regulation, women with PMDD responded to moments of favourable cognitive states, specifically lower momentary rumination and higher momentary present-moment-awareness, with improved subsequent mood during the late luteal phase, but not during the follicular phase (Nayman et al., 2024). This suggests an even greater affective reactivity to momentary cognitive states in PMDD during the late luteal phase (Nayman et al., 2024), whereas habitual cognitive emotion regulation appeared to be decoupled from premenstrual mood (Nayman et al., 2023a, 2024). Similarly, in subthreshold PMDD, higher premenstrual symptoms were linked to increased daily states of rumination and perceived stress during the late luteal phase (Nayman et al., 2023b).

Study 3 (Nayman et al., in press), which involved a combined approach of ambulatory assessments and ambulatory inductions in daily life in women with and without PMDD showed more pronounced differential effects of induced ruminative versus mindful self-focus on positive affect in women with PMDD compared to healthy controls, especially during the late luteal phase (Nayman et al., in press). In particular, women with PMDD responded to mindful self-focus inductions during the late luteal phase with stronger increases in momentary positive affect, with no such group differences during the follicular phase. In addition, irrespective of clinical status and cycle phase, rumination inductions immediately increased momentary negative affect and rumination and decreased momentary present-moment-awareness in daily life, with no effect on self-acceptance. In contrast, mindful self-focus induction predicted immediate increases in

momentary self-acceptance with no effects on negative affect, rumination and present-moment-awareness (Nayman et al., in press).

With regard to cortisol activity, momentary cognitive states did not exhibit effects on momentary cortisol activity across the menstrual cycle in PMDD (Nayman et al., 2024). In contrast, healthy controls showed premenstrual decreases in cortisol levels following moments of lower than usual momentary rumination or higher than usual present-moment-awareness. The lack of intraindividual cortisol responses to momentary cognitive states in the late luteal phase may represent a biological marker of PMDD (Nayman et al., 2024).

7.2 Emotion Regulation in Premenstrual Dysphoric Disorder

Trait emotion regulation. Consistent with previous cross-sectional and longitudinal studies, we found that women with PMDD show higher unfavourable habitual emotion regulation strategies compared to healthy controls, including higher habitual rumination and lower habitual mindfulness and reappraisal tendencies (Nayman et al., 2023a, 2024). Similarly, previous studies have shown that women with severe PMS and PMDD tend to engage in higher levels of habitual rumination than healthy controls during both the follicular and late luteal phases (Craner et al., 2014, 2016; Eggert et al. 2017; Kappen et al. 2022). Furthermore, premenstrual laboratory-induced psychological and physiological stress elicited higher self-focused attention, including rumination, anxiety sensitivity, and body vigilance, in women with PMDD compared to healthy controls, despite experiencing the experimental tasks as similarly stressful (Craner et al. 2015). Thus, the present findings suggest a role for cognitive emotion regulation in PMDD symptom manifestation and highlight the need for further fine-grained research on emotion regulation in PMDD.

Higher habitual rumination has been shown to be associated with steeper increases in premenstrual depressive and eating symptoms and slower postmenstrual symptom clearance in the follicular phase in women with at least one clinically distressing affective core symptom (Dawson et al., 2018). These findings may emphasize that women who tend to use ruminative emotion regulation may not only experience exacerbations of premenstrual symptoms, but also difficulty returning to baseline during the follicular phase, increasing their susceptibility to prolonged distress across the entire menstrual cycle and narrowing the symptom-free window during the follicular phase (Dawson et al 2018). In particular, rumination on premenstrually neglected and piled up

tasks or ongoing interpersonal conflicts may cause potential carry-over effects of premenstrual distress into the postmenstrual follicular phase in untreated PMDD patients (as discussed in Nayman & Kuehner, in press).

In general, these findings might suggest that addressing habitual cognitive processes in psychotherapy could reduce premenstrual mood deterioration in women with PMDD. However, our longitudinal AA studies on cycle-phase-specific associations of habitual emotion regulation strategies with momentary mood in two independent PMDD samples (Study 1, Study 2; Nayman et al., 2023a, 2024) revealed that favourable cognitive traits, such as lower habitual rumination, and higher mindfulness and reappraisal, were associated with better mood during asymptomatic cycle phases, but not during the symptomatic late luteal phase. These findings suggest that favourable habitual cognitive emotion regulation strategies do not protect women with PMDD from premenstrual mood worsening (Nayman et al 2023a, 2024). Consistent with these findings, affected women report a perceived loss of control over their emotions and behaviour during the late luteal phase (with loss of control representing a DSM-5 criterion for PMDD, APA, 2013), despite their reported coping efforts, possibly due to a depletion of resources and ability to use familiar adaptive emotion regulation strategies (Nayman & Kuehner, in press). Thus, not only cognitive tendencies or knowledge of how to cope with distressing states, but also cycle-phase-specific characteristics may determine the effects of emotion regulation strategies in full syndrome PMDD. Nevertheless, it is noteworthy that the association of favourable habitual emotion regulation with better postmenstrual mood in the follicular phase may also be clinically relevant, given the possible delay in postmenstrual symptom clearance and consequent prolongation of premenstrual distress throughout the cycle in women with higher habitual rumination, as shown by Dawson et al. (2018).

Furthermore, the results of Study 4 on subthreshold PMDD supports the findings of Dawson et al. (2018) by showing that higher habitual mindfulness was associated with weaker premenstrual symptoms and impairment, and habitual acceptance with lower premenstrual functional impairment in subthreshold PMDD (Nayman et al., 2023b). The fact that these associations were not found for full syndrome PMDD (Nayman et al., 2023a, 2024) may suggest that favourable levels in habitual emotion regulation strategies may rather serve as protective factors for subthreshold PMDD and inform early, low-threshold intervention and prevention approaches for subthreshold PMDD to prevent progression to full syndrome PMDD (Nayman et al., 2023b). In contrast to women with full syndrome PMDD, women with subthreshold PMDD may have greater

access to their internal resources and adaptive strategies during the symptomatic luteal phase. Relatedly, higher habitual tendencies towards mindfulness (Lustyk et al., 2011) and reappraisal (Wu et al., 2016) also appear to be associated with lower premenstrual symptom severity in non-clinical samples. Thus, early interventions in subclinical but at risk stages may reduce or delay progression to full syndrome PMDD, as already shown for other mental disorders (e.g. Guidi et al., 2017; Poletti et al., 2024; Shah et al., 2020).

In the context of PMDD, possible difficulties in endorsing adaptive emotion regulation strategies during the late luteal phase (Nayman et al 2023a, 2024) may point to limitations of conventional psychotherapeutic interventions that target habitual emotion regulation strategies without considering the menstrual cycle as a contextual factor. It was therefore important to extend analyses on habitual emotion regulation strategies by examining potential cycle-phase-specific dynamic variations in states of rumination and mindfulness and their effects on momentary mood across the menstrual cycle in women with and without PMDD.

State emotion regulation. Women with PMDD appeared to exhibit not only affective cyclicity with premenstrual mood deterioration (Nayman et al., 2024), but also cyclicity in cognitive processes, reflected in higher state rumination as well as lower state present-moment-awareness and self-acceptance during the late luteal phase compared to the follicular phase, whereas such cyclicity was not found in healthy controls (Nayman et al., 2024, in press). These findings are consistent with previous limited research showing that state rumination in women with PMS and PMDD peaks during the luteal phase in another AA study (Beddig et al., 2020) and in a daily diary study (Craner et al., 2016) and contributes to higher premenstrual symptom severity (Craner et al., 2016). In women with subthreshold PMDD, higher daily rumination and perceived stress during the late luteal phase also predicted higher premenstrual symptom severity (Nayman et al 2023b). Overall, our findings extend previous research by additionally investigating the cyclicity of more adaptive cognitive states such as present-moment-awareness and self-acceptance, and suggest that time-varying state emotion regulation strategies may act as cycle-phase-specific micro-determinants that may intensify or attenuate premenstrual symptoms.

In fact, decreased within-person momentary rumination and increased within-person present-moment-awareness, particularly during the late luteal phase, predicted lower subsequent negative affect and higher subsequent positive affect in women with PMDD (Nayman et al., 2024), whereas the trait components of these cognitive factors

appeared to be decoupled from mood during this phase in PMDD (Nayman et al., 2023a, 2024). This highlights the importance of distinguishing between trait-like and state-like cognitive processes in PMDD and suggests heightened premenstrual sensitivity to cognitive states in PMDD (Nayman et al., 2024). As expected, no such cycle-phase-specific effects of cognitive states on momentary mood were found in healthy controls, suggesting that cycle-phase-specificity in emotion regulation is particularly characteristic of women with PMDD (Nayman et al., 2024). A late-luteal-phase-specific affective sensitivity towards cognitive states, especially towards ruminative thinking in PMDD with increased negative affect, has also been shown by Beddig et al. (2020). Similarly, state rumination appears to have a more detrimental effect on mood (i.e. reduced positive affect) in vulnerable individuals with other, noncyclical psychopathologies, such as those with remitted recurrent depression, compared to healthy controls (Schricker et al., 2023b). A stronger temporal association between rumination and affect has also been found in individuals with higher levels of depressive symptoms (Brose et al., 2015). This suggests that affective reactivity to cognitive states may be heightened in vulnerable individuals (e.g. Schricker et al., 2023b) or during vulnerable periods such as the luteal phase in PMDD (e.g. Nayman et al., 2024), with unfavourable cognitive states possibly exacerbating existing negative emotional states (Watkins & Roberts, 2020).

In previous AA studies, momentary negative mood (i.e. higher negative affect and lower positive affect; Beddig et al., 2020) and daily stressful appraisal (Beddig et al., 2019) in turn predicted more pronounced increased momentary rumination in women with PMDD compared to healthy controls, regardless of cycle phase. In contrast, reciprocal effects of momentary rumination and affect were restricted to the late luteal phase (Beddig et al., 2020). Our study in turn showed that negative momentary mood in women with PMDD predicted increased subsequent momentary rumination and decreased present-moment-awareness, particularly during the late luteal phase (Nayman et al., 2024). Relatedly, especially during the late luteal phase, negative mood in affected women may activate rumination and weaken present-moment-awareness, which in turn intensify negative mood, leading to a worsening of both affective and cognitive states and generating an upward spiral of negative mood and rumination that contributes to premenstrual symptom severity (Nayman & Kuehner, in press). Thus, this unfavourable upward spiral between rumination and negative affect, defined as a transdiagnostic process within the framework of the Response Styles Theory (Nolen-Hoeksema and Watkins 2011) appears to be valid especially during the late luteal

phase in PMDD (Nayman & Kuehner, in press, see Figure 7.2) and can be expanded to include other cognitive states, such as levels of state present-moment-awareness.

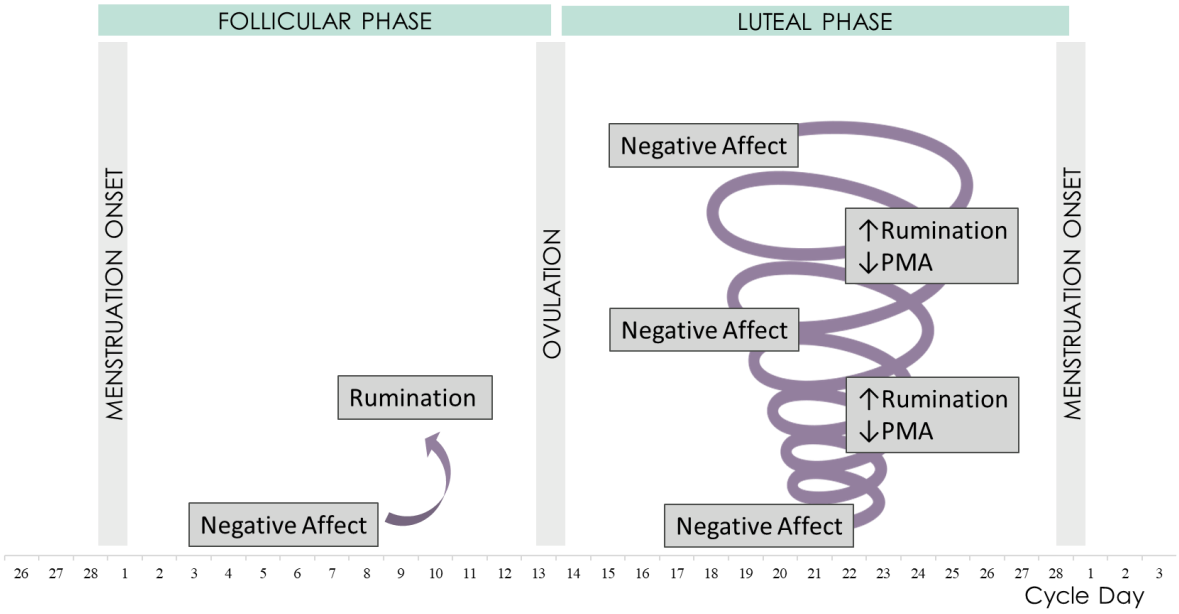

Figure 7.2 Premenstrual Upward Spiral of negative affect and cognitive states

Note. PMA = Present-Moment-Awareness.

Premenstrual increases in unfavourable cognitive states (i.e. high levels of rumination and low levels of present-moment-awareness) together with increased affective reactivity towards these states may also contribute to the documented risk of suicidality in PMDD (Eisenlohr-Moul et al 2022; Wikman et al 2023). Higher sensitivity to increased rumination and decreased present-moment-awareness in the late luteal phase may intensify feelings of hopelessness and loss of control, leading to internal entrapment (Nayman & Kuehner, in press).

Increased levels of and affective sensitivity to higher present-moment-awareness during the late luteal phase may also highlight the potential of mindfulness-based interventions for premenstrual affective states. Given the evidence indicating that mindfulness-based interventions reduce daily rumination (e.g. Li et al., 2022; Mao et al., 2023; Perestelo-Perez et al., 2017; Timm et al., 2018), the parallel cyclical changes in rumination and present-moment-awareness (Nayman et al., in press) may also point to potential interactions of rumination and present-moment-awareness. In this regard, decreases in present-moment-awareness may exacerbate rumination and/or vice versa, especially during the late luteal phase. However, in our recent study using ambulatory inductions of ruminative and mindful self-focus across the menstrual cycle during daily life, no late-luteal-phase-specific causal effects of ruminative self-focus on present-

moment-awareness or vice-versa were found in PMDD (Nayman et al., in press). Instead, regardless of clinical status (i.e. PMDD vs. healthy controls) and cycle phase (follicular vs. late luteal phase), induced ruminative self-focus predicted decreased present-moment-awareness with no effects of induced mindful self-focus on momentary rumination, possibly suggesting a stronger clinical role for rumination. However, induced mindful self-focus predicted stronger increases in positive affect during the late luteal phase in PMDD compared to healthy controls, with no group differences in the follicular phase (Nayman et al., in press), emphasising the potential of mindfulness-based interventions for premenstrual mood by possibly initiating an initial stage of an upward spiral of positive affect and positive cognitions, as proposed by Garland et al. (2015).

Taken together, trait (habitual) versus state (time-varying, momentary) rumination and present-moment-awareness appear to contribute differentially to the manifestation of premenstrual affective symptoms (Nayman et al., 2023a, 2024), thereby supporting approaches that conceptualize emotion regulation as a dynamic and iterative process with bidirectional links to affect (e.g. Gross, 2015). Our results suggest that in particular, cycle-phase-specific states of increased rumination and decreased mindfulness during the late luteal phase may exacerbate premenstrual mood deterioration (Beddig et al 2020; Nayman et al 2024). Thus, these cognitive states, and increased affective reactivity to them, may serve as warning signs of possible subsequent mood deterioration and represent targets for cycle-phase-specific interventions for PMDD.

7.3 Childhood Adversity in Premenstrual Dysphoric Disorder

Experiences of adversity, especially during sensitive developmental periods in childhood, can impair affective-cognitive and neuroendocrinological functions (Li et al., 2022; Pervanidou & Chrousos, 2018), thus contributing to later psychopathology in adulthood (Anda et al., 2010; Daníelsdóttir et al., 2024; Hughes et al., 2017; Lippard & Nemeroff, 2020). Childhood adversity is a risk factor for psychopathology in many mental disorders, including depressive, anxiety and substance use disorders (Anda et al., 2010; Daníelsdóttir et al., 2024; Lippard & Nemeroff, 2020), but also for higher symptom severity in PMDD. In this regard, Eisenlohr-Moul et al. (2016) showed that cyclical fluctuations in estradiol and progesterone and PMDD symptoms were stronger in women with a history of abuse. However, the study by Eisenlohr-Moul et al. (2016) did not define the timing of abuse experiences, whereas there may be differential or additive effects of childhood adversity and stressors during adulthood. Relatedly, there is

initial evidence suggesting that not only childhood adversity, but also recent perceived stress appears to exacerbate premenstrual symptom severity (Eisenlohr-Moul, 2019; Schweizer-Schubert et al., 2021). In this context, and in line with Beddig et al. (2019), we demonstrated that perceived stress in daily life peaks during the late luteal phase in PMDD (Nayman et al., 2023c). Thus, to understand the unique effects of childhood adversity, it was crucial to disentangle the effects of childhood adversity from recent stressors, and Study 5 consequently extended previous research by accounting for confounding effects of stressful life events during the past 12 months (Nayman et al., 2023c). Our study showed that in women with PMDD, childhood adversity was associated with stronger mood worsening and a higher increase in stress appraisal in daily life during the late luteal phase (Nayman et al 2023c). The identified increased premenstrual stress appraisal in affected women with higher childhood adversity suggests that early stress exposure may make women with PMDD more sensitive to daily life stress in their vulnerable late luteal phase. These findings point to individual differences in sensitivity to normal ovarian steroid changes in women with PMDD, depending on experiences of childhood adversity, and support the conceptualising of childhood adversity as a potential distal risk factor for PMDD, exacerbating premenstrual symptoms and daily perceived stress (Nayman et al., 2023c).

Notably, while childhood adversity has been shown to be associated with generally worse affective symptoms in other mental disorders (e.g. Lippard & Nemeroff, 2020), no main effects on general mood were identified in our PMDD sample (Nayman et al., 2023c). In contrast, the effects of childhood adversity on momentary mood and stress appraisal were restricted to the late luteal phase and possibly point to the moderating role of the HPG on the HPA axis in PMDD (Nayman et al., 2023c). In this context, further systematic research on childhood adversity and its pathways to later PMDD is warranted.

One pathway linking childhood adversity to the exacerbation of premenstrual mood deterioration and stress appraisal in women with PMDD may be difficulties in emotion regulation as a result of childhood adversity. In particular, rumination has been shown to be elevated in individuals with a history of childhood adversity and stressful life events (e.g. Watkins, 2022). Rumination appears to act as a common proximal mediator between these environmental risk factors and later psychopathology (Mansueto et al 2021; Watkins, 2022), thus serving as an important target for psychotherapy. The findings of elevated habitual rumination in women with PMDD compared to healthy controls (e.g. Craner et al., 2014; Eggert et al., 2017; Nayman et al., 2023a) as well as

increased state rumination during the late luteal phase compared to the follicular phase in PMDD (Beddig et al 2020; Nayman et al., in press) raises the question of whether cyclically varying emotion regulation may also moderate the association of childhood adversity and later premenstrual symptom severity.

Another pathway linking childhood adversity to later premenstrual symptoms may be alterations in HPA axis function, particularly in cortisol activity, which has already been suggested to be implicated in the psychopathology of PMDD, irrespective of childhood adversity.

7.4 Cortisol Activity in Premenstrual Dysphoric Disorder

Using an AA design, Study 2 (Nayman et al., 2024) showed that women with PMDD exhibited lower basal cortisol activity throughout the cycle compared to healthy controls (Nayman et al., 2024), thereby supporting previous evidence that cortisol activity is reduced in PMDD (e.g. Girdler et al., 1998, 2001, 2003). A previous AA study similarly suggested reduced dynamics of basal cortisol activity in PMDD, manifested by a flattened diurnal cortisol slope and a delayed CAR peak in PMDD compared to healthy controls, regardless of cycle phase (Beddig et al., 2019).

In addition to lower cortisol activity across the menstrual cycle, Study 2 revealed differential cycle-phase-specific dynamics in cortisol cyclicity as well as cortisol reactivity towards cognitive processes in women with PMDD compared to healthy controls (Nayman et al., 2024). While healthy women showed a cyclical pattern of cortisol with lower levels during the late luteal phase, women with PMDD did not show cortisol cyclicity (Nayman et al., 2024). The identified lower luteal phase levels of cortisol in healthy controls is consistent with two meta-analyses in in healthy women (Hamidovic et al., 2020; Klusmann et al., 2022). While these meta-analyses included studies with a variety of cortisol measurement methods, with the majority using a single measurement of total cortisol in the morning (Hamidovic et al., 2020; Klusmann et al., 2022), our study confirmed cortisol cyclicity by employing more fine-graded multiple cortisol measurements within a day to account for circadian effects on cortisol activity (Nayman et al., 2024). The premenstrual decrease in cortisol levels in healthy women may be explained by the premenstrual increase in ALLO, a metabolite of progesterone, which potentiates the GABAergic system and thereby negatively modulates HPA axis activity, leading to lower cortisol levels (Hamidovic et al., 2020; Klusmann et al., 2022). In contrast, the lack of cortisol cyclicity in PMDD may represent an endocrinological marker

for PMDD and point to a dysfunction in the interaction between the HPA axis and the GABAergic system in PMDD (cf. Schweizer-Schubert et al., 2021).

Furthermore, in healthy controls, favourable cognitive states during the late luteal phase (i.e. lower momentary rumination, higher present-moment-awareness) predicted lower subsequent cortisol activity, whereas no such cortisol reactivity during this phase was found in PMDD (Nayman et al., 2024). Similarly, Beddig et al. (2019) showed that healthy controls, but not women with PMDD, responded to momentary rumination with increased cortisol activity, but without cycle phase effects. These results suggest that he HPA axis appears to be less flexible in women with PMDD, with a lack of reactivity towards hormonal fluctuations as well as towards positive and negative cognitions throughout the cycle. Thus, lower total basal cortisol output and a lack of cortisol cyclicity and reactivity may indicate an endocrinological marker for PMDD. Further research is needed to replicate these findings and to examine associations between respective cortisol alterations and premenstrual symptoms in PMDD.

Accounting for childhood adversity added further nuances to the picture of cortisol dynamics in PMDD, suggesting potential subtypes of cortisol activity in PMDD. In particular, childhood adversity moderated cortisol cyclicity in PMDD, with experiences of higher childhood adversity being linked to further decreases in cortisol levels during the late luteal phase, thereby possibly indicating a specific ecophenotype resulting from childhood adversity (Nayman et al., 2023c).

Taken together, lower cortisol activity throughout the cycle as well as lack of cortisol cyclicity and reactivity appear to represent an endocrinological marker for PMDD (Nayman et al., 2024). In addition, there appear to be individual differences in cortisol cyclicity among women with PMDD, depending on experiences of childhood adversity (Nayman et al., 2023c).

7.5 Clinical Implications

The findings of this dissertation at multiple levels, covering individual differences at the macro-level as well as within-person variations over and within cycle phases at the meso- and micro level respectively (see Figure 7.1), add new insights to our knowledge of risk and protective factors for PMDD and may help to move towards a more personalised treatment of PMDD. The present findings particularly highlight the relevance of distinguishing between trait-like and state-like risk and protective factors, with trait-like factors contributing to a general vulnerability to premenstrual symptoms, and state-like factors (i.e. premenstrual rumination, present moment awareness, stress appraisal)

serving as proximal determinants and influencing premenstrual symptom severity (see Figure 7.3 for a proposed model for PMDD). Especially given the intercyclical variation in symptom severity in PMDD (Nappi et al., 2022; Nayman et al., 2023c; Potter et al., 2009), proximal risk factors represent important determinants of premenstrual symptom manifestations, may serve as targets for psychotherapy, and warrant further research.

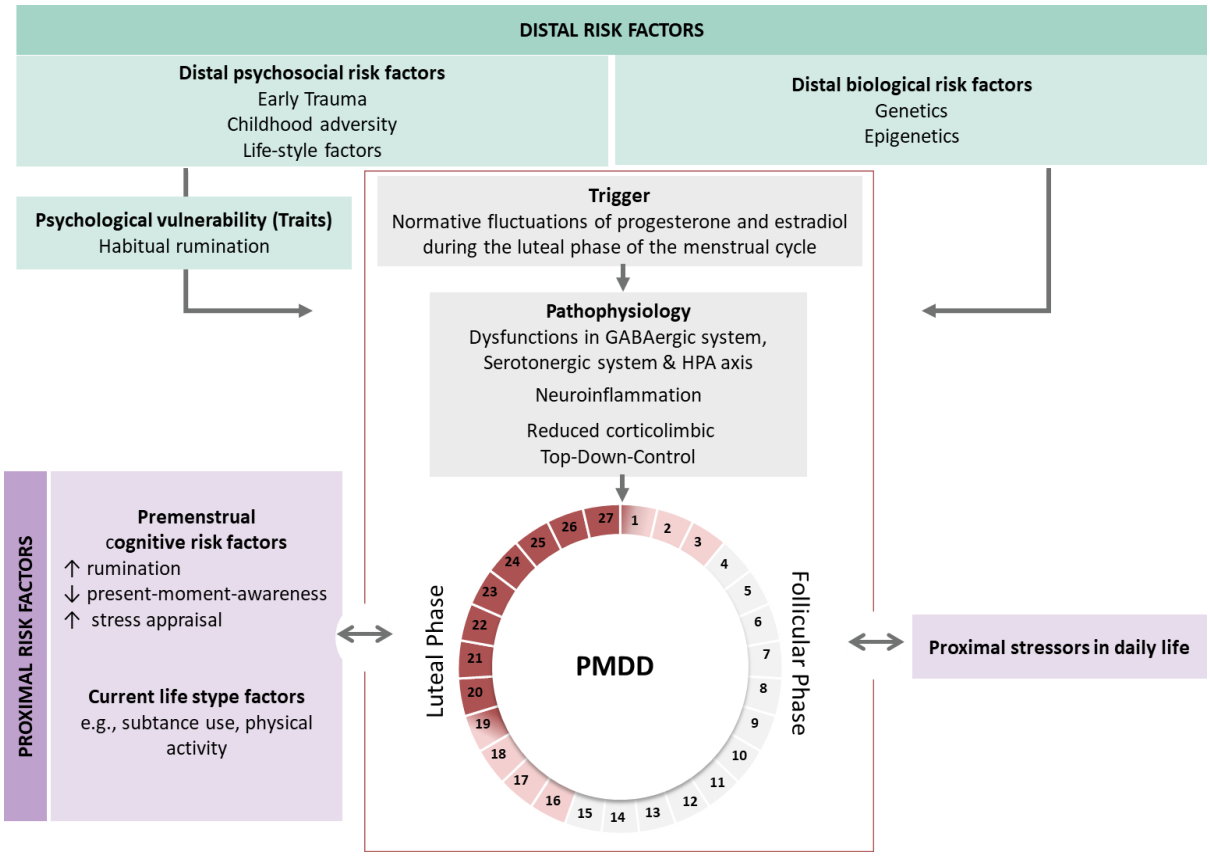

Figure 7.3 Biopsychosocial Model of Premenstrual Dysphoric Disorder

Note. The rose-red colour gradient represents the time window in which premenstrual symptoms can be present, with individual differences in onset und offset timing. PMDD = Premenstrual Dysphoric Disorder. This figure is adapted from Kuehner & Nayman (under review).

CBT has been suggested as a first-line treatment for PMDD (Hantsoo & Riddle, 2021) and appears to have low to moderate quality evidence (ACOG, 2023). Current evidence suggests that not only cognitive tendencies or knowledge of how to cope with distressing states, but in particular contextual factors may influence the dynamic use of emotion regulation strategies and their impact on subsequent mood (Beddig et al., 2020; Nayman et al., 2023a, 2023b, 2024). Relatedly, the observed stronger effects of cognitive states rather than traits on premenstrual mood point to potential limitations of generic psychotherapeutic interventions targeting habitual cognitions in PMDD and

support the validity of the situation-context fit theory (cf. Wenzel et al., 2020) with the menstrual cycle representing a main contextual factor in PMDD (Nayman et al., 2023a, 2024). Thus, cycle-phase-specific micro-interventions that target momentary dynamics of cognitive states (e.g. momentary rumination) and their micro-determinants, beyond targeting their habitual components, may be particularly beneficial for women with PMDD. Such micro-interventions are characterised by a specific timing of delivery and individually tailored content to meet cycle phase-specific needs.

In terms of the **timing of interventions**, negative emotional intensity has been suggested as a key contextual factor influencing the selection of emotion regulation strategies (Sheppes et al., 2011). In moments of low emotional intensity, long-term goals may be more easily accessed, and cognitively demanding strategies such as cognitive reappraisal may be more likely to be used, whereas in moments of high emotional intensity, less elaborative, attentional deployment strategies such as distraction may be more effective (Sheppes et al., 2011; Sheppes & Levin, 2013). Consequently, during the late luteal phase, which is characterised by intense negative emotions, less semantic-based strategies, such as attentional deployment or acceptance, rather than cognitive reappraisal, may prove more effective. Based on our results, I can speculate that the acquisition of cognitive and semantic-based strategies should be implemented particularly in the non-symptomatic follicular phase when higher cognitive capacity can be expected, whereas training these strategies throughout the cycle, with specifically intense, therapy-guided training during the luteal phase, may have the greatest benefit for women with PMDD. Systematic psychotherapy research on cycle-phase-targeted therapy programs for PMDD is warranted.

In terms of **intervention content**, high-arousal emotions have been shown to impair cognitive capacity (Fruzzetti & Shenk, 2020). Thus, by initially focusing on these high-arousal states and prioritising behavioural skills to reduce the arousal from high to moderate or low levels, patients may subsequently be able to use cognitive strategies (e.g. cognitive reappraisal), as proposed in Dialectical Behaviour Therapy (DBT; Linehan & Wilks 2015). DBT was originally conceptualised for individuals with chronic suicidality and borderline personality disorder (Linehan and Wilks 2015) and has been recently proposed for the treatment of PMDD (e.g. Eisenlohr-Moul 2019; Nayman et al. 2023a). A cycle-phase-specific training in experiential and present-moment-awareness to enable women to identify their moments of need for specific strategies, such as behavioural strategies (e.g. countering emotion-driven behaviour) with related skills training within the DBT program (Linehan & Wilks 2015), may be particularly beneficial.

The systematic consideration of possible childhood adversity as a distal risk factor may provide additional information regarding the specific content of interventions, as adversity-related core beliefs may be particularly activated during the vulnerable luteal phase in PMDD.

Furthermore, given the observed cyclicity of emotion regulation in PMDD (Nayman et al., 2024, in press), diagnostic symptom tracking can be extended to include monitoring of emotion regulation. This may open up the possibility of therapy-guided retrospective functional analyses of situations of emotion regulation difficulties in order to uncover individual cycle-phase-specific internal or external antecedents signalling possible mood deterioration and to derive alternative adaptive strategies, e.g. replacing impulsive behaviour with attentional deployment or ruminative reactivity with a concrete thinking style during the late luteal phase (cf. Nayman & Kuehner, in press). Repeated luteal-phase-targeted training of favourable emotion regulation strategies can then help to cultivate and strengthen behavioural and cognitive skills in response to varying affect and internal resources throughout the cycle.

Previous evidence, showing that high habitual mindfulness is associated with lower premenstrual symptom severity in non-clinical samples (Lustyk et al. 2011), and with less premenstrual impairment in women with subthreshold PMDD (Nayman et al. 2023b), suggests that Mindfulness-Based Stress Reduction (Kabat-Zin, 2003) may be particularly beneficial for non-clinical or subthreshold PMDD, potentially preventing the transition from prodromal premenstrual symptoms to full syndrome PMDD (as discussed in Nayman et al. 2023b). The lack of protective effects of habitual mindfulness (Nayman et al., 2023a, 2024), but mood-improving effects of luteal phase states (Nayman et al., 2024) and inductions (Nayman et al., in press) of present-moment-awareness in women with PMDD, may again highlight the need for cycle-phase-specific mindfulness training, including acceptance of thoughts and present-moment-awareness. In particular, Mindfulness-Based Cognitive Therapy (MBCT), which combines mindfulness with conventional CBT interventions (Li et al., 2022), may be tailored to the cycle-phase-specific characteristics of PMDD to teach self-regulation of attention and a non-judgmental focus on the present moment during the luteal phase, thereby training alternative responses to negative emotions and thoughts.

The transfer and practice of acquired therapeutic strategies outside the therapy session in daily life is a key goal in psychotherapy. For women with PMDD, the transfer of skills to daily life may be particularly challenging during the late luteal phase, especially if the cycle phase is not taken into account in emotion regulation training. Given that

distressing situations with high emotional demands may automatically activate habitually used behavioural or cognitive patterns (Schwabe & Wolf, 2009), as reflected by increased momentary rumination and decreased present-moment-awareness during the late luteal phase in PMDD (Beddig et al., 2019; Nayman et al., in press), mobile micro-interventions, such as Ecological Momentary Interventions (EMIs), can extend the therapy beyond the clinical setting and transfer the acquired skills into daily life (Myin-Germey et al., 2018), especially into the symptomatic luteal phase. To this end, the combination of in-session therapy and internet-based therapy, with digital interventions mainly scheduled during the luteal phase, may support the transfer of therapy effects to the high-risk cycle phase in daily life in PMDD.

7.6 Research Implications

Cycle-phase-specific interventions. The idea of cycle-phase-specific interventions warrants systematic research. Cycle-phase-specific ambulatory approaches, particularly EMIs or Just-in-Time Adaptive Interventions (JITAIs; Nahum-Shami et al., 2018), which are informed by AA of within-person affective, cognitive, behavioural and endocrinological dynamics across and within cycles, may allow to evaluate cycle-phase-specific effects of single interventions, thereby contributing to a contextual approach towards personalised psychiatric care for PMDD. AA can also improve the prediction of treatment outcomes due to its sensitivity to capture change (Myin-Germeys et al., 2018). In addition to the menstrual cycle as a contextual variable at the meso-level, further fine-grained assessments of intra- and interpersonal contextual variables within specific cycle phases at the micro-level (e.g. momentary stressors, emotional intensity, social activity, physical activity, heart rate variability, etc.) and across the menstrual cycle at the macro-level (e.g. life events, life transitions) can inform JITAI algorithms. Specifically, JITAI algorithms include (a) decision points (i.e. intervention delivery time), (b) tailoring variables (i.e. ambulatory inputs informing decisions when and which intervention is needed), (c) intervention options, and (d) decision rules (i.e. rules connecting decision points, tailoring variables and intervention options) as proposed by Nahum-Shani et al. (2018).

EMIs and JITAIs are based on the principle that affect, cognitions and behaviours are embedded in a given context and aim to address momentary needs, allowing for personalised interventions in patients' daily lives (Heron & Smyth, 2010; Myin-Germeys et al., 2018; Reininghaus et al., 2024; Schick et al., 2022; Seiferth et al., 2023). To date, EMIs have been developed and applied to several groups with subclinical and clinical

mental disorders, including anxiety, affective, psychotic and substance abuse disorders (Balaskas et al., 2021). They may also have the potential to address proximal psychological mechanisms that contribute to the development, exacerbation and maintenance of PMDD symptoms during the luteal phase. In future research, network analyses of PMDD symptoms (e.g. using Subgrouping within Group Iterative Multiple Model Estimation; Lane et al., 2019) may help to identify symptoms that may trigger and increase the likelihood of other symptoms, which in turn may help to tailor the temporal delivery of interventions.

Clinical Staging Model. In parallel with the growing evidence for dimensional diagnostic approaches, such as the Clinical Staging Model (Hartmann et al., 2021), which conceptualize mental health on a dimensional continuum, it has also been discussed that PMS and PMDD may lie on a continuum (Eisenlohr-Moul, 2019; Nayman & Kuehner, in press). The transdiagnostic Clinical Staging Model moves away from the traditional dichotomous diagnostic approach towards dynamic stages of psychopathology, ranging from asymptomatic (stage 0) to stages of severe mental disorders with variations in recurrence and severity (stages 2-4) (Hartmann et al., 2021). By identifying and recognising early stages of a condition, it also allows for the implementation of stage-specific early interventions aimed at preventing transition to higher clinical stages and the full syndrome. Using this approach, risk and resilience factors in the development of PMS and PMDD can be uncovered, as PMS and PMDD may develop from shared and dimensionally distributed risk processes (Eisenlohr-Moul, 2019). For instance, emotion regulation, particularly premenstrually increased rumination and decreased present-moment-awareness, may not only amplify premenstrual symptom severity in PMDD, but also potentially increase the risk of progression from prodromal or subthreshold PMDD to full syndrome PMDD (Nayman et al., 2023b). Prospective cohort studies investigating the predictive value of cycle-phase-specific AA phenotypes on the clinical course of premenstrual symptoms are therefore warranted.

Clinical Subtypes. It is important to recognize that PMDD is not a homogeneous clinical group but may present with several subtypes. Despite clear windows of symptom onset and offset, individual differences in the timing of symptom onset (e.g. early, mid- or late luteal phase) and symptom offset (e.g. rapid or gradual clearance after menstruation onset during the follicular phase) are possible (Eisenlohr-Moul, 2019). The potential subtypes could be characterised by different hypersensitivities to specific hor-

monal events (e.g. mid-luteal fluctuations in progesterone and ALLO, late luteal withdrawal in estradiol) (Peters et al., 2024), thereby carrying unique endocrinological or psychological (e.g. exposure to childhood adversity) mechanisms.

Findings from Study 5, suggesting that childhood adversity partially accounts for individual differences in the severity of premenstrual mood deterioration and cortisol cyclicity in women with PMDD (Nayman et al., 2023c), highlight the need for further research on possible ecophenotypes in PMDD resulting from environmental risk factors. It remains unclear how a) the specific timing of childhood adversity across developmental stages, b) the dose of exposure, and c) stressors in adolescence and adulthood moderate the effects of early adversity on the manifestation of PMDD, and which biological biomarkers may be involved. There is also a need to investigate the role of proximal and micro-risk factors (e.g. perceived stress) during the follicular phase for premenstrual symptoms in the subsequent luteal phase and for delayed postmenstrual symptom resolution, as well as their role in the clinical course over time, in order to better understand inter-cyclic variations in premenstrual symptom manifestations.

7.7 Limitations

It is important to acknowledge several limitations of the present studies.

First, to minimize participant burden and ensure high compliance within the intensive AA designs, PMDD diagnoses in Studies 1, 2, 4, and 5 were assessed using a retrospective structured and validated diagnostic interview (SCID-PMDD; Accortt et al., 2011). The diagnoses were not confirmed by prospective daily ratings over two symptomatic cycles, as required by the DSM-5 for a definite diagnosis, so the PMDD diagnoses in these studies must be considered provisional (APA, 2013). In turn, the use of an intensive AA design allowed the prospective investigation of variations in affective, cognitive and endocrinological micro-processes across the cycle with high temporal resolution, as well as differential effects of trait and state emotion regulation on mood and cortisol in daily life across the menstrual cycle.

While Studies 1, 2, 4 and 5 share the strength of using chromatographic ovulation tests to confirm the presence of an ovulatory cycle, Study 4 did not use an ovulation test and instead determined the cycle phases according to the counting method (Schmalenberger et al., 2021).

All studies were characterised by strict eligibility criteria that excluded individuals with certain psychiatric comorbidities and those taking psychotropic medication, with Study

4 being additionally restricted to university students. This in turn may have resulted in rather homogeneous samples and limited the generalizability of the findings.

Trait emotion regulation, in particular habitual repetitive negative thinking, mindfulness and reappraisal in Studies 1, 2 and 3, was assessed with global self-report measures, asking individuals how often they habitually use specific emotion regulation strategies to reflect broad tendencies in strategy use across time and contexts. However, given the weak to moderate correlations between trait and state levels of emotion regulation strategies (e.g. Koval et al., 2023), it remains unclear how well global self-reports capture how individuals identify, select and implement emotion regulation strategies, and whether these self-reports are more likely to assess *perceived* habitual emotion regulation strategies (e.g. Koval et al., 2023). Furthermore, the cycle phase during which the trait-related self-report measures were completed was not documented. Since the cycle phase in PMDD may impact perception, memory, affect, and behaviour (Rubinow & Schmidt, 1989), the possibility of cycle-phase effects on the trait-related self-reports cannot be ruled out. Future research should control for the cycle phase during which baseline measures are administered.

Moreover, cognitive states were measured with single items each. Relatedly, cognitive states of rumination and mindfulness were assessed unidimensionally by focusing on the process characteristic of uncontrollability of rumination and the present-moment-awareness facet of mindfulness. Additional facets, such as content-related aspects of rumination (Rosenkranz et al., 2020) and the non-judgmental acceptance component of mindfulness (Blanke & Brose, 2017), could shed more nuanced light on the role of cognitive emotion regulation in PMDD. In this respect, the Experience Sampling Method (ESM) item repository initiative (Kirtley et al. 2022) may help to generate reliable short scales for respective AA contexts in the future. In addition, further research investigating behavioural emotion regulation strategies (e.g. stress reduction skills) in PMDD may be particularly relevant to capture a broader range of emotion regulation strategies and to explore more treatment targets, particularly for states of high arousal symptoms during the luteal phase, when cognitive, sematic-based strategies may be less likely to be used. Thus, the inclusion of different classes of emotion regulation in basic research on PMDD may enrich the basis for the development of future prevention and intervention measures. Furthermore, in Studies 1, 2 and 3, we investigated emotion regulation with self-report measures, thereby focusing on conscious emotion regulation, whereas implicit assessments of emotion regulation (e.g. Eggert et al., 2017) may help to uncover automatic aspects of emotion regulation processes.

In Studies 1, 2, 3, which examined associations between cognitive traits and daily mood and endocrinological processes, no conclusions can be drawn about the causality of these associations because cognitive traits were assessed only once using self-report measures during the baseline session. In Study 2, cross-lagged multilevel analyses were performed to model within-subject associations, which is a good starting point to uncover potential causal associations, but experimental designs still represent the gold standard (Huffziger et al., 2013; Kuehner et al., 2023-Schmiedek & Neubauer, 2020). In this context, Study 3 is the first study to use an experimental approach in the daily lives of women with PMDD. Relatedly, Study 3 used ambulatory inductions, but screen-time-based compliance rates for these ambulatory inductions were low, which may have limited the statistical power to detect two-way or three-way interactions. The limitations of the present ambulatory induction design may have some implications for future research on ambulatory inductions. In Study 3, they were delivered at semi-random time points throughout the day, which may have disrupted momentary activities and led to disengagement (cf. Qian et al., 2022). In this regard, future research may benefit from tailoring these inductions to the dynamics of internal (e.g. moments of need) and external contextual states (e.g. outside of windows of intense responsibility within the day) (e.g. Qian et al., 2022).

Finally, although it was a strength of Study 5 to consider the effects of recent stressful life events when examining childhood adversity, childhood adversity was assessed across childhood without specifying the duration, timing, and developmental stage during exposure to childhood adversity, so that potential differential effects on psychological and neuroendocrinological outcomes could not be uncovered. Age of exposure to adversity has been suggested as an important moderator of HPA axis alteration (Hantsoo et al., 2023; Lippard et al., 2020). Further research is warranted to identify distinct critical developmental windows during which childhood adversity specifically affects the HPA-HPG interaction with long-term effects on premenstrual symptoms (Nayman et al., 2023c). In addition, the unique effects of childhood adversity and additional stressful life events in adulthood may be best investigated by designing larger prospective cohort studies that include systematic life-stage-related assessments of stressful life events to minimize recall bias and thus contribute to our understanding of the aetiological processes of PMDD (Nayman et al., 2023c).

7.8 Conclusions

Overall, the findings presented in this dissertation suggest that research and treatment of PMDD may benefit from a multilevel perspective. First, habitual (trait) and momentary (state) emotion regulation appear to contribute differentially to symptom manifestation in PMDD. While favourable habitual emotion regulation does not appear to protect women with PMDD from premenstrual mood deterioration, it is associated with weaker premenstrual symptoms and functional impairment in subthreshold PMDD and may represent a target for prevention of progression to full syndrome PMDD. In contrast, state components of favourable emotion regulation predict weaker mood deterioration in daily life during the late luteal phase in full syndrome PMDD, highlighting the importance of the menstrual cycle as a contextual factor in PMDD research, and the potential of cycle-phase-specific interventions for PMDD. Addressing individual windows of vulnerability throughout the menstrual cycle may help to move towards personalised psychiatric, psychotherapeutic and gynaecological care and increase the efficacy of psychotherapeutic interventions in PMDD. In addition, childhood adversity may serve as a distal risk factor with stronger premenstrual mood worsening, higher premenstrual stress appraisal and additional premenstrual reductions in cortisol activity in affected women with higher levels of childhood adversity. Further research on possible individual differences in PMDD may help to identify subtypes of PMDD, explore their underlying psychobiological mechanisms, and thus move towards mechanism-based treatment approaches for PMDD. With regard to cortisol activity, lower cortisol output throughout the cycle compared to healthy controls as well as lack of cortisol cyclicity and reactivity to momentary cognitive processes during the late luteal phase appear to reflect an endocrinological marker for PMDD. Cyclical characteristics have also been demonstrated in healthy controls, particularly with regard to cortisol activity and reactivity, with lower cortisol levels during the late luteal phase and a more pronounced premenstrual decline following moments of favourable cognitive states compared to the follicular phase. Thus, considering the menstrual cycle as a contextual factor in basic clinical research on psychopathology, regardless of clinical status, may lead to promising new approaches to understanding normative psychological and endocrinological processes across the cycle and markers of psychopathology in natural menstrual cycles.

SUMMARY

In this dissertation, I investigated the role of cognitive emotion regulation strategies on affective, cognitive, and cortisol trajectories across the menstrual cycle in women with and without Premenstrual Dysphoric Disorder (PMDD). PMDD has been included as a unique diagnostic entity in the ICD-11 and DSM-5 diagnostic systems and is characterised by at least one affective core symptom with additional cognitive or somatic symptoms that are restricted to the (late) luteal phase and resolve within a few days after the onset of menstruation in the follicular phase. Given the cyclical-dynamic course of symptoms in PMDD, longitudinal designs (e.g. using diary or ambulatory assessment data) over the menstrual cycle are of particular relevance. The overarching aim of this dissertation was to use such longitudinal methods to identify cycle-phase-specific risk and protective factors for premenstrual mood deterioration and endocrinological markers for PMDD.

Study 1 of my dissertation (Chapter II) examines the role of habitual (trait) tendencies of cognitive emotion regulation strategies for momentary mood across the menstrual cycle in women with PMDD. Compared to healthy controls, women with PMDD showed stronger tendencies towards unfavourable emotion regulation strategies (higher rumination and lower reappraisal and mindfulness tendencies). Multilevel analyses revealed that favourable manifestations of these habitual cognitive emotion regulation strategies in women with PMDD were associated with improved mood during the menstrual, follicular and ovulatory phases, but did not protect affected women against mood deterioration during the late luteal phase. This suggests possible cycle-phase-specific difficulties in the implementation of adaptive emotion regulation strategies and possible limitations of conventional psychotherapy methods that address emotion regulation across phases in the treatment of PMDD. The results of this study were replicated in Study 2 (Chapter III) in an independent sample. In contrast, favourable momentary cognitive states during the luteal phase predicted better premenstrual mood. Thus, this study points to the potential of cycle-phase-specific microinterventions in which luteal-phase-specific cognitive processes could act as therapeutic mechanisms. Furthermore, in Study 2, women with PMDD did not show cyclical fluctuations in cortisol activity, whereas healthy women had lower cortisol levels during the late luteal phase compared to the follicular phase, with additional cortisol reductions following

moments of favourable cognitive states. Lack of cortisol cyclicity and reactivity to premenstrual cognitive processes may therefore represent a possible endocrinological marker for PMDD.

In Study 3 (Chapter IV), I investigated affective and cognitive responses to induced ruminative and mindful self-focus across the menstrual cycle using experimental ambulatory inductions in the daily lives of women with and without PMDD. Women with PMDD responded to induced mindfulness with greater increases in positive affect than healthy controls, especially during the late luteal phase. Regardless of cycle phase and clinical status, induced rumination predicted greater momentary negative affect and momentary rumination and decreased momentary mindfulness, whereas induced mindfulness predicted greater momentary self-acceptance.

In Study 4 (Chapter V), I examined a sample with subthreshold PMDD. Here, adaptive habitual emotion regulation (mindfulness and acceptance) was associated with weaker increases in premenstrual symptoms and functional impairment. Stronger increases in premenstrual symptoms and functional impairment in turn predicted increases in rumination and perceived daily stress during the luteal phase. These findings point to the potential of dimensional approaches to investigate possible risk and protective factors for the transition from subclinical to clinical manifestations of premenstrual symptoms, as well as the potential of habitual mindfulness and acceptance as preventive measures for PMDD.

In Study 5 (Chapter VI), I showed that in women with PMDD, adverse childhood experiences were associated with stronger premenstrual mood deterioration and an additional cortisol decrease during the luteal phase. This suggests the clinical importance of childhood adversity for the cyclical course of symptoms and cortisol in PMDD.

Taken together, these studies point to the relevance of a multilevel approach that examines macro-processes (e.g. habitual emotion regulation, adverse childhood experiences) as well as meso- and micro-processes (cycle-phase-specific cognitive and endocrinological risk factors) of psychobiological factors in PMDD in order to identify their potential inter- and intra-individual variations. Evidence from this research approach may inform the development and advancement of personalised treatment approaches for PMDD.

ZUSAMMENFASSUNG

In dieser Dissertation untersuchte ich die Rolle kognitive Emotionsregulationsstrategien auf affektive, kognitive und Cortisolverläufe über den Zyklus hinweg bei Frauen mit und ohne Prämenstruelle Dysphorische Störung (PMDS). Die PMDS wurde als eigenständige Diagnoseeinheit in die Diagnosesysteme ICD-11 und DSM-5 aufgenommen und zeichnet sich durch mindestens ein affektives Kernsymptom mit zusätzlichen kognitiven oder somatischen Symptomen aus, das auf die (späte) Lutealphase beschränkt ist und sich innerhalb weniger Tage nach Menstruationsbeginn in der Follikelphase zurückbildet. Angesichts der zyklisch-dynamischen Symptomverläufe bei PMDS sind insbesondere Längsschnittdesigns (z.B. anhand von Tagebuch- oder Ambulatory-Assessment Daten) über den Zyklus von besonderer Bedeutung. Das übergeordnete Ziel dieser Dissertation war es, mit Hilfe solcher Längsschnittmethoden zyklusspezifische Risiko- und Schutzfaktoren für prämenstruelle Stimmungsverschlechterung sowie endokrinologische Marker für PMDS zu identifizieren.

Studie 1 (Kapitel II) meiner Dissertationsschrift befasst sich mit der Rolle habitueller (trait) Tendenzen kognitiver Emotionsregulationsstrategien für die momentane Stimmung über den Menstruationszyklus bei Frauen mit PMDS. Frauen mit PMDS wiesen im Vergleich zu gesunden Frauen stärkere Tendenzen zu ungünstigen Emotionsregulationsstrategien (höhere Ruminations- sowie niedrigere Neubewertungs- und Achtsamkeitstendenzen) auf. Multilevel-Analysen legten nahe, dass günstige Ausprägungen dieser habituellen kognitiven Emotionsregulationsstrategien bei Frauen mit PMDS mit besserer Stimmung während der Menstruations-, Follikel- und Ovulationsphase einhergehen, diese jedoch nicht vor einer Stimmungsverschlechterung in der späten Lutealphase schützen. Dies weist auf mögliche phasenspezifische Probleme bei der Umsetzung adaptiver Emotionsregulationsstrategien und auf Grenzen konventioneller Psychotherapieverfahren hin, die phasenübergreifende Emotionsregulation adressieren. Die Befunde dieser Arbeit wurden in Studie 2 (Kapitel III) an einer unabhängigen Stichprobe repliziert. Dagegen prädizierten günstige *momentane kognitive Zustände* während der Lutealphase bessere prämenstruelle Stimmung. Damit weist diese Studie auf das Potential phasenspezifischer Mikrointerventionen hin, bei denen lutealphasenspezifische kognitive Prozesse als Therapiemechanismen agieren könnten. Darüber hinaus zeigte Studie 2, dass Frauen mit PMDS keine zyklischen Schwankungen der Cortisolaktivität aufwiesen, während gesunde Frauen niedrigere Cortisolspiegel in der

späten Lutealphase im Vergleich zur Follikelphase aufwiesen, mit zusätzlicher Cortisolreduktion nach adaptiven momentanen kognitiven Zuständen. Fehlende Cortisolzyklizität und –reaktivität auf prämenstruelle kognitive Prozesse stellen somit einen möglichen endokrinologischen Marker für PMDS dar.

In Studie 3 (Kapitel IV) untersuchte ich anhand experimenteller Ambulatory Inductions im Alltag von Frauen mit und ohne PMDS affektive und kognitive Reaktionen auf induzierte ruminative und achtsame Selbstfokussierung über den Menstruationszyklus hinweg. Frauen mit PMDS reagierten auf induzierte Achtsamkeit speziell in der späten Lutealphase mit einem stärkeren Anstieg positiven Affekts als Gesunde. Unabhängig von Zyklusphase und klinischem Status prädizierte induziertes Grübeln stärkeren momentanen negativen Affekt und momentanes Grübeln sowie verminderte momentane Achtsamkeit, während induzierte Achtsamkeit stärkere momentane Selbstakzeptanz prädizierte.

In Studie 4 (Kapitel V) untersuchte ich eine Stichprobe mit subklinischer PMDS. Hier war adaptive habituelle Emotionsregulation (Achtsamkeit und Akzeptanz) mit schwächerer Zunahme von prämenstruellen Symptomen und Funktionseinschränkungen assoziiert. Stärkere prämenstruelle Symptome und Funktionseinschränkungen präzidierten wiederum eine Zunahme des Grübelns und der Stresswahrnehmung im Alltag während der Lutealphase. Diese Befunde weisen auf das Potential dimensionaler Ansätze zur Untersuchung möglicher Risiko- und Schutzfaktoren für den Übergang von subklinischen zu klinischen Ausprägungen prämenstrueller Symptome sowie auf das Potential von habitueller Achtsamkeit und Akzeptanz als Präventionsansätze für PMDS hin.

In Studie 5 (Kapitel VI) zeigte ich, dass bei Frauen mit PMDS adverse Kindheitserfahrungen mit stärkerer prämenstrueller Stimmungsverschlechterung und einer zusätzlichen Cortisolreduktion in der Lutealphase einhergehen. Dies verweist auf die klinische Bedeutung von Stresserfahrungen in der Kindheit für die zyklischen Symptom- und Cortisolverläufe bei PMDS.

Insgesamt weisen diese Studien auf die Relevanz eines Mehrebenenansatzes hin, der sowohl Makroprozesse (z.B. habituelle Emotionsregulation, adverse Kindheitserfahrungen) als auch Meso- und Mikroprozesse (zyklusphasenspezifische kognitive und endokrinologische Risikofaktoren) psychobiologischer Faktoren bei PMDS untersucht, um deren potenzielle inter- und intraindividuelle Variationen zu identifizieren. Die Erkenntnisse aus diesem Forschungsansatz können in die Entwicklung und Weiterentwicklung von personalisierten Behandlungsansätzen für PMDD einfließen.

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SUPPLEMENTARY MATERIAL

Supplementary materials Chapter III

Equation S1 – Exemplary equation

In the following, we present an exemplary equation for a cross-lagged MLM estimating how state rumination at time T-1 predicts NA at time T depending on the cycle phase.

$$NA_{ij} = \gamma_{00} + \gamma_{01} rumination_j^{B-S} + \gamma_{02} cycle\ phase_j + \gamma_{03} study\ day_j + \gamma_{10} rumination_{i(T-1)}^{W-S} + \gamma_{20} NA_{i(T-1)}^{W-S} + \gamma_{11} cycle\ phase_j * RNT_{i(T-1)}^{W-S} + \varepsilon_{ij} + u_{0j}$$

Here, γ_{00} represents the intercept, indicating the grand-mean across individuals and time points. γ_{01}, γ_{02} and γ_{03} represent fixed main effects of lagged and grand-mean-centered rumination as well as of cycle phase and study day at the between-subject (B-S) level. The equation further includes fixed effects of person-mean-centered (W-S) and time-lagged momentary rumination (γ_{10}) and NA (γ_{20}) of person *i* at time *T-1.* γ_{11} refers to the fixed effect of the cycle phase by rumination interaction. ε_{ij} denotes the residuals at level-1. At level 2, the intercepts were allowed to vary randomly across participants. Thus, u_{0j} denotes the residuals for person j at level-2 indicating the person-specific intercept deviation (Bolger & Laurenceau, 2013) and referring to random intercepts.

Table S1

Bivariate Between- and Within-Subject Correlations

	1	2	3	4	5	6	7
1) Momentary Negative Affect	1	-.78	.84	-.44	-.10	.46	-.46
2) Momentary Positive Affect	-.80	1	-.73	.47	.01	-.40	.40
3) Momentary Rumination	.65	-.64	1	-.54	-.05	.53	-.39
4) Momentary PMA	-.38	.43	-.46	1	-.06	-.19	.20
5) Cortisol	.05	-.04	.06	-.06	1	-.08	.14
6) Trait RNT						1	-.59
7) Trait PMA							1

Note. Between-subject correlations ($N_{individuals}$ = 120) are presented above the diagonal; within-subject correlations among momentary measures ($N_{measurement\ occasions}$ = 6974) are presented below the diagonal. Given that trait RNT and trait PMA represent single time-point scores as cross-sectional data, no within-subject correlations between the trait and state measures could be computed. RNT = Repetitive Negative Thinking; PMA = Present Moment Awareness.

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EDUCATION

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Apr 2015 – July 2015	**Tutor in Testtheory and Testconstruction** University of Ulm

AWARDS & RESEARCH GRANT

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CLINICAL EXPERIENCE

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PUBLICATIONS

Peer-Reviewed Publications

Nayman, S., Schricker, I. F., Reinhard, I., Grammatikos, I., & Kuehner, C. (in press). Induced Rumination and Mindful Self-focus in Daily Life across the Menstrual Cycle in Women with and without Premenstrual Dysphoric Disorder. Behaviour Research and Therapy. https://doi.org/10.1016/j.brat.2024.104630

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ACKNOWLEDGMENTS

I would like to express my deepest gratitude to my supervisor, **Prof. Dr. Christine Kühner**, for her exceptional support and guidance throughout my PhD journey. More than a supervisor, you have been a mentor who opened many doors for me, enriching both my professional and personal development. Your close supervision, coupled with continuous and constructive feedback, instilled confidence in my work and significantly contributed to my professional growth. I am especially thankful for your encouragement and support in translating this research into clinical practice, a pursuit that has been deeply meaningful to me. You struck an exceptional balance between providing guidance and allowing me the autonomy to develop new ideas and take on new challenges. Your unwavering support has been crucial to the success of this thesis and will undoubtedly serve as a strong foundation for my future academic endeavours.

To my colleague and friend, **Isabelle Schricker**, thank you for not only being a wonderful office mate whose humour had a "significant mood brightening effect" at many moments, but also for being a vital support throughout this project. Your contributions were invaluable, from taking on important tasks in the project to having crucial and fruitful discussions with me on both the content and methodological aspects of this work. To **Dr. Iris Reinhard**, I deeply appreciate your constant willingness to provide feedback and discuss solutions, especially on my complex analyses. To **Dr. Theresa Beddig**, I am deeply grateful for introducing me to PMDD research. Your previous work laid the essential foundation for this thesis.

I am also grateful to our student research assistants and Master of Science students, **Annika Richter**, **Ioanna Grammatikos**, and **Janina Dreer** who shared my enthusiasm for this project. Your assistance in data collection and curation has been invaluable. I would also like to extend my thanks to **Dr. Oliver Hennig** and **Dr. Maria Gilles** for providing the infrastructure that enabled me to set up the PMDD outpatient service at the Central Institute of Mental Health.

I would like to thank the **Empathique team**, especially **Julia Ruff, Şeyma Türk,** and **Miriam Çelebi** whose shared passion for research transfer led us to produce a psychoeducational video series on women's mental health.

This intense period would not have been the same without the friends with whom I share common values and whose company provided a much-needed balance! **Meryem**, **Yasemin**, **Ayla, Hatice** and **Nur**, thank you for your constant emotional support and the many joyful moments. Even though you live about 300 km away, **Rabia** and **Hanna**, your support and understanding were always felt, bridging the distance and reminding me that I was never alone.

Ebenso möchte ich meiner Familie meinen tief empfundenen Dank aussprechen. **Kaya Dayı**, Du warst es, der schon zu Beginn meines Bachelorstudiums den Gedanken an eine Promotion in mir geweckt und mir immer wieder deutlich sein Vertrauen vermittelt hat. **Hayati Dayı** und **Deniz Dayı**, seit meiner Kindheit habt ihr mich ganz klar spüren lassen, dass ich immer auf eure Unterstützung zählen kann.

Nazlı, meine Schwester, du besonderer Mensch – dein Dasein ist ein großer Segen für mich. Du bist die Erleichterung in jeder Erschwernis. Ohne dich wäre dieser Weg ungleich schwerer gewesen. An meine jüngeren Geschwister, **Hasan**, **Aişe Nur** und **Eslem**, eure Liebe und unser Zusammenhalt geben mir so viel Kraft.

Am Ende dieses langen Weges möchte ich meine tiefste Dankbarkeit den Menschen aussprechen, die mir die Grundlage für all meine Erfolge gegeben haben: meinen Eltern. **Mama**, ohne dich hätte ich als Kind die Hürden im Bildungssystem kaum überwinden können – du warst immer ein empowerndes Vorbild für mich. **Baba**, „İlim derya deniz, arayana“ [„Das Wissen ist ein unendliches Meer - für Suchende“] demiştin son mesajlarından birinde. Beni her zaman öğrenmeye ve kendimi geliştirmeye teşvik ettiğiniz ve sonsuz desteğiniz için size çok teşekkür ederim.