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# Stress, mood, and cortisol during daily life in women with Premenstrual Dysphoric Disorder (PMDD)

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ABSTRACT

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

## 1. Introduction

### 1.1. Premenstrual Dysphoric Disorder (PMDD)

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

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### 1.2. Subjective stress responses in PMDD

The mechanisms underlying PMDD are still insufficiently known, findings indicate a multifactorial genesis (Epperson et al., 2012; Beddig and Kuehner, 2017). An important factor might be stress. Higher levels of subjective and objective stress were identified as risk factors for the onset of PMDD (Perkonigg et al., 2004), PMDD exacerbates with stressful life events (Huang et al., 2015), and women suffering from severe premenstrual symptoms perceive more chronic stress (Kleinstauber et al., 2016). In an earlier study women with severe premenstrual syndromes perceived stressors as more severe and unpleasant than controls premenstrually, but not postmenstrually (Fontana and Badawy, 1997). Hoyer et al. (2013) identified higher subjective stress perception in the luteal phase in women with premenstrual symptoms during an emotional stroop task. Accordingly, PMDD women appear to show enhanced stress appraisal especially premenstrually. However, little is known about their stress responsivity during daily life, although this is important to determine generalizability and ecological validity of lab results and to identify potential mechanisms relevant to everyday life that can be targeted by appropriate therapeutic interventions. Subjective stress reactivity is mainly operationalized by negative affect (NA) towards stressors (Wichers et al., 2009). According to the circumplex affect model by Russell (1980), NA and positive affect (PA) can be further subdivided into low and high arousal states. Given that anger and irritability are the most prominent premenstrual symptoms (Hantsoo and Epperson, 2015; Owens and Eisenlohr-Moul, 2018) the distinction of arousal states might especially be important when studying mood states in PMDD. While low arousal NA states ($NA_{low}$) in response to stress could be more common for MDD, women with PMDD might more frequently react to stress especially with high arousal NA states ($NA_{high}$) such as being upset or irritated. Similarly, the differentiation between positive affect states high ($PA_{high}$) and low in arousal ($PA_{low}$) has not been addressed in PMDD research to date.

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

### 1.3. Basal and stress-reactive cortisol activity in PMDD

Sustained stressors can cause alterations in the activity of the hypothalamic–pituitary–adrenal axis (HPAA, Adam et al., 2017; Zorn et al., 2017), which is tightly controlled by GABAergic signaling (Maguire, 2019). Very few studies investigated basal and stress-reactive cortisol activity in women suffering from premenstrual symptoms, and these studies normally did not distinguish PMDD from the milder premenstrual syndrome (PMS). The cortisol awakening response (CAR) and the diurnal cortisol slope (DCS) are the two main indicators measuring basal cortisol activity during the day (cf. Kudielka et al., 2012; Adam et al., 2017), whereas cortisol stress reactivity is mainly being measured in experimental settings using standardized stressors (cf. Zorn et al., 2017). A review by Kiesner and Granger (2016) found no consistent evidence for a basal or stress-reactive cortisol dysregulation in women with PMS/PMDD. A small number of studies indicated blunted activation across the cycle, and there was only modest evidence that affected women would show blunted cortisol reactivity toward environmental stressors (Kiesner and Granger, 2016). However, included studies used heterogeneous methodology regarding types of stressors, cortisol measures and criteria for diagnosis. More recently, Huang et al. (2015) found attenuated cortisol activity in women with premenstrual syndromes when experiencing an experimental stressor. Taken together, previous studies give first but weak support for attenuated basal and reactive HPAA activity during daily life in women with PMDD (cf. Owens and Eisenlohr-Moul, 2018).

### 1.4. Ambulatory Assessment (AA) in PMDD

Introducing AA into the study of PMDD has been repeatedly called for (e.g. Bosman et al., 2016; Owens and Eisenlohr-Moul, 2018) because it has important advantages over retrospective approaches. First, due to the multiple real-time assessments recall bias is reduced (Trull and Ebner-Priemer, 2013). The latter represents a limitation particularly in mere retrospective studies but also in prospective daily rating studies when women are asked to summarize their symptoms over the past day (Bosman et al., 2016). Furthermore, AA enables to capture the variability of affect, cognitions, and physiological states within and across days and cycle phases, thereby allowing to study both between- and within person variability (cf. Bosman et al., 2016; Owens and Eisenlohr-Moul, 2018; Schlotz, 2019). The present study mainly focuses on within-person relations of stress with subjective and cortisol outcomes, thereby reflecting for example the extent to which an individual's negative affect increases when appraising stress and whether PMDD and control women differ with this regard. Using a longitudinal AA-design that includes all menstrual cycle phases does also allow to distinguish between possible state-like alterations in PMDD occurring only in the late luteal phase of the cycle and trait-like alterations occurring throughout the whole cycle. Moreover, the more detailed consideration of arousal in the assessment of affect states during daily life (cf. Hoyt et al., 2015) allows to identify possible distinct patterns of reactivity towards minor daily stressors within the PMDD context.

### 1.5. Study aims and hypotheses

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

## 2. Method

### 2.1. Participants

Women with PMDD were recruited using different sources (newspapers, local family doctors and gynecologists practices, homepage of the Central Institute of Mental Health (CIMH), social networks). After telephone screening, possible eligible women underwent a clinical baseline interview to assess study in- and exclusion criteria (see Section 2.2). Inclusion criteria were fulfilling the DSM-5 criteria for PMDD A to E using the Structured Interview for DSM-IV TR Defined PMDD (SCID-PMDD, Accortt et al., 2011 see Section 2.2) with the diagnostic

algorithm adapted for DSM-5. To avoid further participant burden, criterion F (prospective daily ratings during at least two symptomatic cycles before study inclusion) was not required. In parallel, age- and education-matched controls were recruited. Control participants were excluded if they met criteria for any affective core symptoms of PMDD (criterion B) according to DSM-5 (see Section 2.2). In contrast, premenstrual physical symptoms were not an exclusion criterion, given the fact that the majority of naturally cycling women are experiencing physical symptoms of varying degree during the late luteal and menstrual phase (Tschudin et al., 2010). Exclusion criteria for both samples included unfamiliarity with the German language, age < 20 and > 42, a reported cycle length of < 22 or > 34 days, a reported variation of cycle length of more than five days, use of hormonal contraceptives, antidepressants or other medication affecting the HPAA during the last three months, heavy exercise (≥1 h per day), late evening or night shifts, body mass index < 18 or > 35, birth of a child or lactation/breastfeeding during the last 6 months, history of gynecological diseases, bipolar or psychotic disorders, and substance dependence or current substance abuse (see Section 2.2). Consistent with DSM-5, other concurrent and past Axis-I disorders such as MDD and anxiety disorders were allowed, both in the PMDD and in the control sample. However, to differentiate PMDD from premenstrual exacerbation of another mental disorder, we included PMDD women with a current comorbid diagnosis only if their affective core symptoms for PMDD (A-criterion in DSM-5) differed noticeable from the affective core symptoms of the comorbid disorder, as suggested in DSM-5 (see APA, 2013). Of five women with a current comorbid depression diagnosis, we therefore had to exclude n = 2 women from the PMDD sample who reported depressed mood as the affective core symptom for PMDD, while we retained n = 3 women reporting irritability and mood lability as affective core symptoms for PMDD.

Of 138 women screened for PMDD, n = 22 were excluded due to insufficient severity of affective core symptoms or insufficient distress/impairment, n = 21 due to other exclusion criteria, and n = 25 refused to participate due to anticipated temporal overload linked to study participation. Of 118 screened controls, n = 15 did not meet the inclusion criteria, n = 8 were excluded due to the presence of affective core symptoms, n = 15 refused to participate due to anticipated temporal overload, and n = 10 could not be matched due to non-fitting matching criteria. Participants' data were analyzed if they had AA-assessments during at least three out of four menstrual cycle phases. Women who did not meet this criterion and did not repeat the missing assessment in the subsequent cycle were considered dropouts. In total, 18 women (9 PMDD, 9 controls) withdrew (12.9%). The reasons for discontinuating were: inconsistencies with menstrual cycle reports (n = 14), severe technical problems (n = 2), decision to start hormonal contraceptives (n = 1) and positive pregnancy test (n = 1). The final sample consisted of 61 PMDD women and 61 controls. The study protocol was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University. All participants gave written informed consent and received 100 € for participation.

### 2.2. Study Procedure and Measures

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

Individual calendars were then prepared for each woman based on the date of her last menstruation onset and the average length of her menstruation and of her menstrual cycle. The menstrual cycle was divided into the menstrual, follicular, ovulatory, and late luteal phase (see Wolfram et al., 2011). Assessments during the *menstrual phase* took place on the second and third day of menstruation (mean = 2.95 days, SD = 2.21). The *follicular phase* was examined on the second and third day after the end of menstruation (mean = 8.61 days, SD = 1.94). The *ovulatory phase* (mean = 17.15 days, SD = 2.0) was determined by a chromatographic ovulation test (gabControl hlH Ovulationsteststreifen, gabmed, Cologne) indicating a rise in luteinizing hormone levels in urine. Testing began a few days before the predicted ovulation and participants were instructed to continue the tests daily until a positive result occurred and then to perform the AA on the two days immediately following ovulation. If ovulation did not occur, participants were asked to repeat the test in the following menstrual cycle. Assessments of the *luteal phase* took place on the fourth and third day before the next menstruation was expected (mean = 26.38 days, SD = 3.02). The phases were validated according to the ovulation test and the exact time of the onset of the next menses. The calendar specified the exact days on which the AA were to be carried out and when to begin with the ovulation test. For example, if a woman's cycle had a regular duration of 28 days and bleeding lasted approximately five days, she assessed the menstrual phase at day 2 and 3 after menses onset, and the follicular phase at day 7 and 8. She began testing ovulation on day 11 and assessed the ovulation phase the day immediately after the test turned positive, and the late luteal phase at day 25 and 26 (i.e., days −4 and −3 before new menses onset). Participants were asked to repeat assessments during the next cycle if the assessment days were not accurate (e.g., if the actual time of menses onset was several days earlier or later than expected). To counteract potential sequential effects women started in different phases of their menstrual cycle, depending on the time point of the baseline session. Among women with PMDD 36.1% started in the menstrual, 24.6% in the follicular, 31.1% in the ovulatory and 8.2% in the late luteal phase, among controls 37.7% started in the menstrual, 26.2% in the follicular, 29.5% in the ovulatory and 6.6% in the late luteal phase. After three months of assessment we decided to stop women starting in the luteal phase to verify that the luteal phase was in fact assessed during an ovulatory cycle as confirmed by the ovulation test.[1]

### 2.3. Ambulatory assessment

The AA was carried out using Motorola Moto G 2nd Generation smartphones with the software My Experience movisensXS, Version

[1] Excluding women who started in the lutel phase did not significantly change any of the presented results.

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

1 Momentary NA and PA were assessed with 12 items based on the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) and previous AA studies (e.g. Kuehner et al., 2017; Timm et al., 2018) which were collapsed according to the circumplex model of affect (Russell, 1980) and in line with Nezlek (2005) and Hoyt et al. (2015) into $NA_{high}$ (upset, irritated, nervous, Cronbach's alpha = 0.80), $NA_{low}$ (listless, down, bored, $\alpha = 0.73$), $PA_{high}$ (cheerful, energetic, enthusiastic, $\alpha = 0.80$), and $PA_{low}$ (content, calm, relaxed, $\alpha = 0.88$) items. Outcomes were calculated by averaging the respective item scores, ranging from 1 (not at all) to 7 (very much).
2 Momentary rumination was measured with the item „right before the beep I was stuck on negative thoughts and could not disengage from them" (range 1–7, cf. Kuehner, 2017; Timm et al., 2018).
3 Recent event-related stress was conceptualized in terms of subjective appraisals of events that continually occur in the natural flow of daily life. Participants were instructed to describe via free-text the most important event they encountered since the last beep or, at the first beep, since waking up. Participants' appreciation of the event was rated on a 7-point bipolar Likert scale, ranging from "very unpleasant" to "very pleasant." This item was subsequently recoded to allow high scores to reflect stress (−3 = very pleasant, 0 = neutral, +3 = very unpleasant; cf. Wichers et al., 2009; van der Stouwe et al., 2019). The daily stressor types were coded subsequently according to the categorization by Gilbert et al. (2017).
4 Sleep quality and sleep duration were assessed by single items that were presented after awakening; sleep quality: "How did you sleep last night?" (1 = very bad; 7 = very good), sleep duration: "How many hours did you sleep last night approximately?".

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

### 2.4. Salivary measure of cortisol

Twenty minutes after each subjective rating, participants collected saliva cortisol samples with standard salivettes (Sarstedt, Germany). Subjects were instructed to refrain from strenuous exercise during the AA-day and not to eat, drink other than water, smoke, physically exercise or brush their teeth 20 min before completing saliva sampling. The smartphone briefly presented a random three-digit code which participants recorded on the label of the salivette tube they were using during each saliva collection (cf. Schlotz, 2019). After collection of the samples, participants indicated on the smartphone whether they had eaten, drunk, smoked or exercised during the last 20 min. By realizing a time-lag of 20 min between subjective assessments and cortisol samples, we could control for these possibly confounding effects and examine the actual influence of subjective variables on cortisol, since cortisol peaks with a time lag of 10–20 minutes (Schlotz, 2019). In addition, the CAR was measured by three saliva samples, directly after awakening before getting up, and 30 and 45 min later. Participants were instructed to wake before 8:00 and to refrain from eating, drinking (except water) and teeth brushing during the CAR assessment period. The DCS was assessed with the awakening sample and the eight samples following the subjective assessments, i.e. by excluding CAR samples 2 and 3. All samples were stored in the participant's home freezer until collection and subsequently frozen at −20 °C at the laboratory until biochemical analysis at the laboratory of Prof. Kirschbaum (Dresden, Germany). There, samples were centrifuged at 3000 rpm for 5 min, resulting in a clear supernatant of low viscosity. Saliva cortisol concentrations were measured using commercially available chemiluminescence-immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients for cortisol were < 8%.

### 2.5. Data analytic strategy

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

Cortisol data was log-transformed to adjust for skewness. Log data were examined for outliers, and outliers more than three standard deviations from the group mean were winsorized to 3 standard deviations (Stalder et al., 2016). In order to estimate basal cortisol secretion (CAR and DCS), time was centered at the waking time sample (i.e., higher values correspond to later times in the day). CAR compliance was defined as follows: Sample 1 had to be collected within 15 min of awakening, sample 2 30 ± 10 min and sample 3 45 ± 10 min after awakening. Samples extending these periods were excluded (25.9%). For reactive cortisol, samples were excluded if collected more than 10 min after the prompt (5.5%). The models estimating CAR and DCS indicated a significant effect of both time and time$^2$, and model comparisons (AIC, BIC) indicated a better fit for the quadratic model. Therefore, multilevel models assuming that CAR and DCS data followed a quadratic trend were applied. Possible confounders were analyzed in three separate models for CAR (1), diurnal slope (2), and reactive cortisol (3) in the total sample. Depending on the respective outcome we examined the effects of age, current medication use, early trauma, habitual smoking, time, time of awakening, sleep quality, sleep duration, whether it was a workday or not (models 1,2,3), and if participants had recently ingested

[2] For power reasons, we did not analyze different stressor types separately

drinks, smoked cigarettes, had eaten anything, brushed their teeth, and their level of physical activity (models 2,3) by including these variables as fixed effects. Possible confounders were only retained in the models if significant ($p < 0.05$), which applied to time$^2$ (models 1,2,3), time of awakening (2,3), workday (yes/no) (1), physical activity (3) and sleep duration (3).

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

## 3. Results

### 3.1. Compliance

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

### 3.2. Sample description

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

### 3.3. Stress appraisal

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

### 3.4. Momentary within-person effects of stress on mood and rumination

To examine effects of stress on mood states, $NA_{high}$, $NA_{low}$, $PA_{high}$, $PA_{low}$, and rumination were entered as dependent variables in five separate models (complete models with stepwise removal of non-significant interaction terms see Supplementary, Table S1). Multilevel analyses revealed a significant three-way interaction group*cycle phase*stress on momentary $NA_{high}$ ($F(3, 6364) = 2.83$, $p = 0.037$, see Table S1). Post hoc tests with separate models per group showed a significant two-way interaction stress*cycle phase in women with PMDD ($F(3, 3161) = 2.89$, $p = 0.034$). As shown in Fig. 1A and B, in PMDD women high within-person levels of stress appraisal were

**Table 1**
Demographic, clinical, and daily life characteristics for women with PMDD and controls.

| | PMDD (n = 61) %/mean (SD) | Controls (n = 61) %/mean (SD) | Test statistic | *p* |
|---|---|---|---|---|
| Demographic variables | | | | |
| Age | 29.4 (5.8) | 29.5 (5.1) | t = −0.03 | 0.977 |
| Education (% with high school degree | 72.1% | 75.4% | $Chi^2 = 0.17$ | 0.681 |
| Work situation (% in regular job or education) | 80.3% | 90.2% | $Chi^2 = 2.35$ | 0.126 |
| Marital status (% married or living together) | 60.7% | 59.0% | $Chi^2 = 0.03$ | 0.853 |
| Children (%) | 24.6% | 26.2% | $Chi^2 = 0.04$ | 0.835 |
| BMI | 23.6 (4.1) | 23.5(4.3) | t = 0.12 | 0.903 |
| Clinical variables | | | | |
| Lifetime diagnosis of Major Depressive Disorder (MDD, SCID-I) | 54.1% | 21.3% | $Chi^2 = 13.96$ | < 0.001 |
| Early trauma | 18.0% | 3.2% | $Chi^2 = 5.235$ | 0.022 |
| BDI-II[a] at baseline | 10.9 (8.9) | 4.8 (5.6) | t = 4.53 | < 0.001 |
| PSST[b] at baseline | 34.6 (9.8) | 6.6 (6.9) | t = 18.26 | < 0.001 |
| PSST[b] following the AA[c] | 32.3 (10.0) | 7.1 (8.4) | t = 13.04 | < 0.001 |
| Cycle-related variables | | | | |
| Previous use of hormonal contraceptives | 82.0% | 90.2% | $Chi^2 = 1.71$ | 0.191 |
| Duration (in days) of menstrual cycle during AA | 29.0 (3.1) | 29.4 (3.7) | t = −0.77 | 0.444 |
| Duration (in days) of period during AA | 5.3 (1.1) | 5.6 (1.7) | t = −0.85 | 0.399 |
| Momentary variables[d] (AA) | | | | |
| Stress appraisal | −0.7 (0.5) | −0.9 (0.6) | t = 1.89 | 0.062 |
| $NA_{high}$ | 2.8 (0.5) | 2.1 (0.7) | t = 5.64 | < 0.001 |
| $NA_{low}$ | 2.9 (0.6) | 2.4 (0.7) | t = 4.35 | < 0.001 |
| $PA_{high}$ | 3.9 (0.6) | 4.4 (0.8) | t = −3.85 | < 0.001 |
| $PA_{low}$ | 4.4 (0.7) | 5.0 (0.8) | t = −4.26 | < 0.001 |
| Rumination | 2.4 (0.8) | 1.9 (0.8) | t = 3.78 | < 0.001 |

[a] BDI-II = Beck Depression Inventory-Revised.
[b] PSST = Premenstrual Symptom Screening Tool.
[c] PMDD (n = 38), controls (n = 53).
[d] Aggregated mean at the person level.

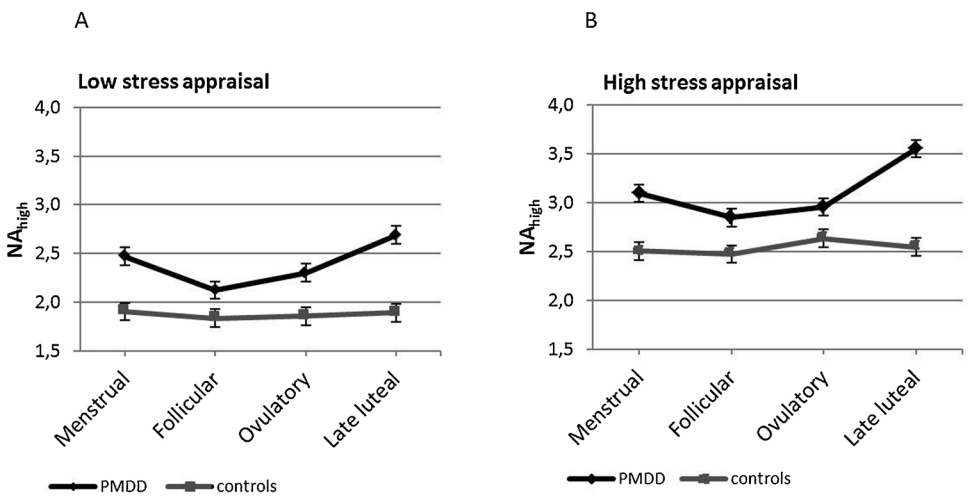


**Fig. 1.** Estimated mean values for $NA_{high}$ mean and standard errors per menstrual cycle phase toward situations with low (−1 SD, Fig. 1A), and high (+1 SD, Fig. 1B) individual stress appraisal for women with PMDD and controls. Note. Error bars represent standard error of the mean. Model includes time, time$^2$, assessment day, and aggregated stress as covariates.

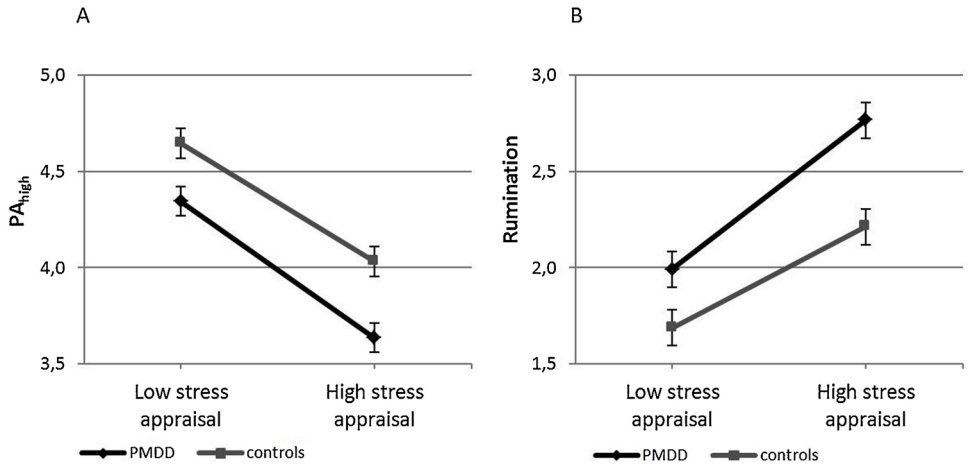


**Fig. 2.** Estimated mean values towards situations with low (–1 SD) and high (+1 SD) individual stress appraisal for $PA_{high}$ (Fig. 2A) and rumination (Fig. 2B). Note. Error bars represent standard error of the mean. Models include time, assessment day, cycle phase, and aggregated $PA_{high}$ (Fig.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

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

### 3.5. Cortisol diurnal rhythm

To examine whether women with PMDD would show a flattened profile of basal cortisol activity two separate models were calculated. For the CAR the multilevel model yielded no significant effect of group*cycle phase*time$^2$ ($p = 0.379$, see Table S2). After stepwise removal of non-significant interaction terms we identified a significant interaction group*time$^2$ ($F(1, 1547) = 5.87$, $p = 0.016$). Fig. 3A shows different CAR peaks in PMDD women and controls with highest values 30 min after awakening among controls and 45 min among PMDD women, indicating that PMDD was associated with a delayed peak. Similarly, no significant threefold interaction (group*cycle phase*time$^2$) was identified for the DCS ($p = 0.499$, see Table S2). After stepwise removal of non-significant interaction terms, the interaction group*time$^2$ demonstrated a significant effect on DCS ($F(1, 6277) = 7.53$, $p = 0.006$). As shown in Fig. 3B, PMDD was associated with a flatter DCS throughout the day.

### 3.6. Momentary within-person effects of stress, mood, and rumination on cortisol

To examine effects of stress, high and low affect states, and rumination on cortisol, we performed six separate models, one for each set of person mean-centered momentary daily-life predictors using cortisol secretion 20 min later as the dependent variable. In all models the interaction term predictor*group*cycle phase was non-significant (stress*group*cycle phase: $p = 0.787$, $NA_{high}$*group*cycle phase: $p = 0.484$, $NA_{low}$*group*cycle phase: $p = 0.945$, $PA_{high}$*group*cycle phase: $p = 0.922$, $PA_{low}$*group*cycle phase: $p = 0.740$, rumination*group*cycle phase: $p = 0.713$, see Table S3). After stepwise removal of non-significant interaction terms we identified a significant group*rumination effect ($F(1, 5517) = 4.21$, $p = 0.040$) revealing a different association of within-person rumination variability with HPAA activity in women with and without PMDD. Fig. 4 shows that higher within-person levels of rumination were linked to stronger cortisol activity in

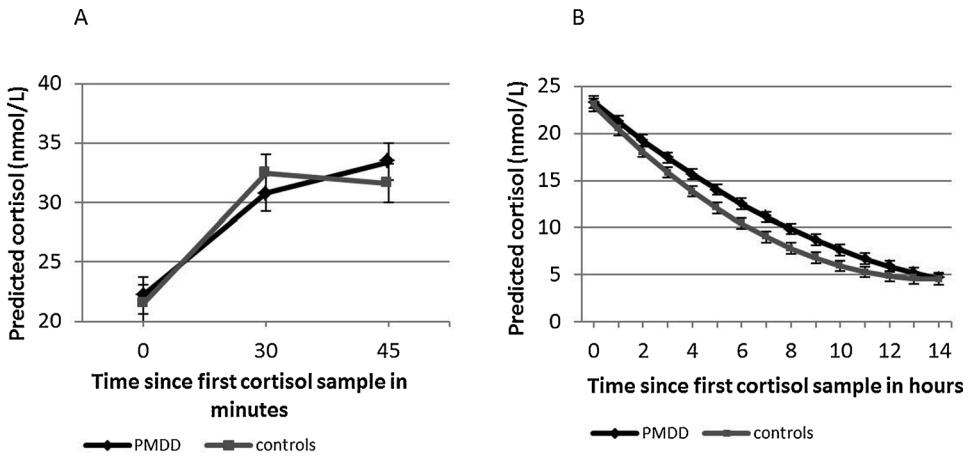


**Fig. 3.** Estimated CAR in women with PMDD and controls (Fig. 3A), and estimated DCS in women with PMDD and controls (Fig. 3B). Note. Error bars represent standard error of the mean. Models include cycle phase, workday (Fig. 3A), and time of awakening (Fig. 3B) as covariates.

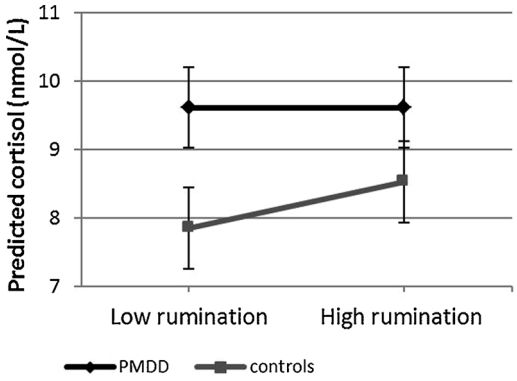


**Fig. 4.** Estimated mean cortisol levels for women with PMDD and controls for low (−1 SD) and high (+1 SD) individual momentary rumination scores. Note. Error bars represent standard error of the mean. Model includes time, time$^2$, cycle phase, time of awakening, physical activity, sleep duration, and aggregated rumination scores as covariates.

controls, while for women with PMDD momentary rumination and cortisol were uncoupled. In contrast no significant group*predictor interaction effect resulted for stress ($p = 0.853$), $NA_{high}$ ($p = 0.797$), $NA_{low}$ ($p = 0.268$), $PA_{high}$ ($p = 0.106$), and $PA_{low}$ ($p = 0.082$, see Table S3). After stepwise removal of non-significant interaction terms we identified main effects for $NA_{high}$ ($F\ (1, 5236) = 13.94$, $p < 0.001$, $B = 0.04$, $SE = 0.01$, $p < 0.001$), $PA_{high}$ ($F\ (1, 5201) = 4.58$, $p = 0.032$, $B = -0.02$, $SE = 0.01$, $p = 0.032$), and $PA_{low}$ ($F\ (1, 4901) = 9.26$, $p = 0.002$, $B = -0.03$, $SE = 0.01$, $p = 0.002$, see Table S3). Thus, across groups, higher within-person levels of momentary $NA_{high}$ and lower levels of momentary $PA_{low}$ and $PA_{high}$ were linked to higher cortisol secretion 20 min later. In contrast, no main effects were identified for stress ($p = 0.879$) and $NA_{low}$ ($p = 0.125$, see Table S3).

## 4. Discussion

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

Consistent with previous reports (for reviews see Epperson et al., 2012; Owens and Eisenlohr-Moul, 2018), women with PMDD rated stressors as more aversive in the late luteal compared to the follicular phase, whereas no respective cyclicity was found in healthy women. Our results furthermore highlight a specific response pattern toward daily life stressors in PMDD women. Women with PMDD showed a significant increase particularly in high-arousal negative affect states (upset, irritated, nervous) toward daily stressors in the late luteal phase compared to all other cycle phases and compared to healthy controls. Thereby, PMDD women appear to react with high intensity negative feelings of arousal towards stressors particularly during this phase, which may reciprocally contribute to a vicious circle between mood and interpersonal conflicts (the latter is also included in Criterion B2 of DSM-5 as “marked irritability or anger or increased interpersonal conflicts”). Interestingly, the preponderance of premenstrual high arousal negative emotions and mood lability over depressed mood in PMDD has led to a change in the respective listing of symptoms from DSM-IV to DSM-5 (Hantsoo and Epperson, 2015). In this context, some authors (Payne et al., 2009; Kuehner, 2017) propose a female-specific reproductive subtype of depression given that PMDD links to postpartum and perimenopausal depression due to specific symptom presentation, comorbidity, and biological response to hormonal changes. Additionally, there seems to be heterogeneity within the diagnosis of PMDD itself regarding treatment response, symptom content and symptom timing. In a large sample of PMDD women, Eisenlohr-Moul et al. (2019) observed different temporal subtypes and conclude that particularly those with late occurring symptoms might represent a hormone-*withdrawal-sensitive* subtype of PMDD, which may also indicate increased risk during postpartum and late menopausal transition, which are similarly characterized by neurosteroid withdrawal or deprivation. Here, AA-studies can importantly contribute to systematically examine possible different phenotypes underlying reproductive and nonreproductive subtypes of depression but also to identify possible more homogeneous subgroups of PMDD.

We further identified an enhanced within-subject effect of stress on rumination in PMDD women regardless of cycle phase. Affected women seem to cope with more stressful situations with stronger ruminative thoughts compared to controls. The missing cycle effect suggests that this reflects a trait-like feature. While retrospective studies have shown that women with severe premenstrual symptoms use more dysfunctional coping strategies such as rumination in general (e.g. Craner et al., 2014), the present study adds to previous research by showing specific accentuated within-subject stress-rumination associations in PMDD women in their everyday life. There is first indication that PMDD women show blunted basal HPAA function throughout the menstrual cycle (Owens and Eisenlohr-Moul, 2018), which is clearly supported by our results. First, their cortisol peak of the CAR was delayed. Although not entirely consistently, a blunted CAR (particularly the dynamic component) has been identified in various stress-related conditions such as posttraumatic stress disorder, chronic fatigue syndrome, atypical depression, in women having experienced early abuse (Tak et al., 2011; Kudielka et al., 2012; Powell et al., 2013), and in individuals with genetic or cognitive vulnerability to depression (Kuehner et al., 2007,

2011). Furthermore, hypoactivation of the CAR was most consistently predicted by a "burnout/fatigue/exhaustion" type of psychosocial stressors in a large meta-analysis (Boggero et al., 2017). Similarly, the DCS of PMDD women was flattened in the present study. In their recent review, Adam et al. (2017) identified significant associations between flatter DCS and poorer emotional and physical health across studies and conclude that flatter slopes may reflect or contribute to stress-related circadian mechanisms affecting multiple aspects of health. In the present study, delayed and flattened basal HPAA activation (CAR, DCS) was seen across the menstrual cycle, thereby again indicating a trait-like characteristic.

Our study further extends previous PMDD stress research by assessing cortisol reactivity towards stress, arousal facets of NA and PA, and rumination in everyday life. Contrary to expectation, we did not identify any main or interaction effect of stress on cortisol. Our current results therefore do not support research from laboratory settings showing a blunted cortisol response towards stressors in women with PMDD (Huang et al., 2015). One explanation for the missing effect of stress on cortisol in the present study might be that stressors were minor daily life events and thus may have had less impact on the HPAA compared to standardized laboratory stressors. Further, the interval between two assessments might have been too long in some cases (i.e., > 1 h, cf. Schlotz, 2019) for optimal peak cortisol detection in response to a stressor occurring during the interval. For power reasons, we also included all types of events that were mentioned during daily life, although specific event types such as interpersonal stressors might be stronger predictors for cortisol responses than others (Gilbert et al., 2017). Here larger studies are clearly needed to be able to subdivide daily life events in a more detailed way. In contrast, high scores of momentary high arousal NA and of high and low arousal PA were linked to high cortisol 20 min later regardless of group or cycle phase. While facets of PA have been understudied in daily life stress research so far, our results confirm earlier findings on within-subject associations between momentary NA and cortisol in different study populations (summarized in Schlotz, 2019). Here, specifically high arousal NA demonstrated a significant activating effect on HPA axis activity while the effect of low arousal NA was nonsignificant. Furthermore, our study revealed that in controls, but not in women with PMDD, high levels of momentary rumination were linked to high levels of momentary cortisol across the menstrual cycle. Therefore, while our results on healthy women are in line with earlier studies showing rather consistent positive associations between state measures of rumination and cortisol (Zoccola and Dickerson, 2012), momentary rumination and cortisol activity appear to be decoupled in PMDD women.

## 5. Clinical implications

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

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

## 6. Strengths and limitations

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

Our study has also some limitations. First, the study sample size was only modest. Although it clearly exceeds the recommended minimum size for estimating cross-level interactions (cf. Hox et al., 2017), statistical power may have been limited particularly for estimating three-way interactions. Therefore, the present results should be regarded as preliminary and validated in future studies with larger samples. Second, although the PMDD diagnosis was assessed with a reliable structured interview (SCID-PMDD, Accortt et al., 2011), this is nevertheless a retrospective measure, and confirmation by prospective daily ratings over at least two cycles was not required for study inclusion to prevent participant burden. Therefore, the PMDD-diagnoses in this study must be regarded as provisional (APA, 2013). However, our approach is in line with a majority of studies using retrospective reports to assess PMDD, and prevalence rates of moderate to severe premenstrual symptoms derived from retrospective epidemiological studies are consistent with those using prospective ratings (Cunningham et al., 2009). Furthermore, low consistency among daily symptom rating instruments has been observed, with a widely varying magnitude of symptom change between the pre- and postmenstrual week required for a PMDD diagnosis (Bosman et al., 2016). Future studies could profit from applying AA over two cycles (which was not possible for us due to financial restrictions) and combining them with daily symptom ratings. Third, our sample may have not been representative of patients with PMDD seeking for treatment, given the voluntary nature of the study. Even though the sample was heterogeneous regarding age, education, job and family situation, women with higher education levels were somewhat overrepresented. Further, since antidepressant medication and hormonal contraceptives are currently the most frequent treatments for PMDD (Epperson et al., 2012) the exclusion of women taking pharmaceutics and hormonal contraceptives - although necessary for our study purposes - may have led to the exclusion of patients suffering from particularly severe symptomatology. Fourth, to restrict participant burden only two assessment days per cycle phase were scheduled, which could be critical, however, especially with regard to the late luteal phase. Clinical studies have shown that women with PMDD have the peak of distress one to two days before menses onset (Epperson et al., 2012), though symptom timing and severitiy has been observed to be heterogeneous (Eisenlohr-Moul et al., 2019). The decision to schedule the third and fourth day was due to the fact that these days are

in the middle of the premenstrual week (as required for DSM-5) and therefore still within the acceptable range if menses had started one or two days earlier or later than expected. However it cannot be ruled out that thereby we missed days with the most severe premenstrual distress in some women. Fifth, although the PSST scores did not differ between a retrospectively assessed "typical" late luteal phase and the late luteal phase assessed by AA, our study design did not control whether an individual PMDD woman became asymptomatic or a control woman became symptomatic during the late luteal phase. Future studies could combine AA with daily ratings of premenstrual symptoms to investigate how the latter directly influence experiences measured by AA. Sixth, given the diurnal pattern of cortisol secretion, further studies should control for the possible influence of different chronotypes (morningness versus eveningness). Seventh, assessing daily life stress in AA studies in general presents some challenges (cf. Schlotz, 2019). In our semi-randomized design, the most important event could have occurred up to 120 min before the beep. With cortisol probes being sampled with a 20 min lag, we therefore might have missed some relevant cortisol peaks. Moreover, the addition of more objective stress measurements may be useful in future studies (Owens and Eisenlohr-Moul, 2018). Next, while we did not identify an effect of early trauma on cortisol, future PMDD studies should examine childhood trauma with more detailed measures (e.g. Bernstein et al., 2003). Furthermore, negative affect may have biased the recall of negative events and of stress appraisal to some extent. Finally, since all subjective constructs were assessed concurrently, a clear causal link from daily events to mood and rumination cannot be established with the present data.

## 7. Conclusions

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

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## Declaration of interest

None.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.104372.

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