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Associations of luteal phase changes in vagally mediated heart rate variability with premenstrual emotional changes

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Abstract

Background A recent meta-analysis revealed that vagally mediated heart rate variability (vmHRV; a biomarker of emotion regulation capacity) significantly decreases in the luteal phase of the menstrual cycle. As two follow-up studies suggest, these vmHRV decreases are driven primarily by increased luteal progesterone (P4). However, analyses also revealed significant interindividual differences in vmHRV reactivity to the cycle, which is in line with longstanding evidence for interindividual differences in *mood* sensitivity to the cycle. The present study begins to investigate whether these interindividual differences in vmHRV cyclicity can explain who is at higher risk of showing premenstrual emotional changes. We expected a greater degree of midluteal vmHRV decrease to be predictive of a greater premenstrual increase in negative affect.

Methods We conducted an observational study with a naturally cycling community sample ($N=31$, $M=26.03$ years). Over a span of six weeks, participants completed (a) daily ratings of negative affect and (b) counterbalanced lab visits in their ovulatory, midluteal, and perimenstrual phases. Lab visits were scheduled based on positive ovulation tests and included assessments of baseline vmHRV and salivary ovarian steroid levels.

Results In line with previous research, multilevel models suggest that most of the sample shows ovulatory-to-midluteal vmHRV decreases which, however, were *not* associated with premenstrual emotional changes. Interestingly, it was only the subgroup with luteal *increases* in vmHRV whose negative affect markedly worsened premenstrually and improved postmenstrually.

Conclusion The present study begins to investigate cyclical changes in vmHRV as a potential biomarker of mood sensitivity to the menstrual cycle. The results demonstrate a higher level of complexity in these associations than initially expected, given that only atypical midluteal *increases* in vmHRV are associated with greater premenstrual negative affect. Potential underlying mechanisms are discussed, among those the possibility that luteal vmHRV increases index compensatory efforts to regulate emotion in those with greater premenstrual negative affect. However, future studies with larger and clinical samples and more granular vmHRV assessments should build on these findings and further explore associations between vmHRV cyclicity and menstrually related mood changes.

Keywords Menstrual cycle, Progesterone, Vagally mediated heart rate variability, Negative affect

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Background

Heart rate variability (HRV) refers to the variation in time intervals between consecutive heartbeats, which is regulated by the autonomic nervous system. It is particularly the vagally mediated HRV (vmHRV) component that has been extensively studied in recent decades and emerged as a biomarker not only for *physical* [1, 2] but also for *mental* health [3–7]. According to the neurovisceral integration theory [8, 9], this predictive ability arises due to vmHRV being mainly generated by areas of the central autonomic network (e.g., prefrontal cortex, amygdala), which also play a central role in emotional and cognitive self-regulation. Consequently, high levels of connectivity and functional capacity in these regions contribute to both higher vmHRV and better psychological functioning. While most research has focused on exploring *interindividual* differences in vmHRV, less is known about systematic *within-person* fluctuations of vmHRV and their association with daily emotional and cognitive self-regulatory capacity.

Menstrual cycle and vmHRV

Given that important areas of the central autonomic network show a high density of ovarian steroid receptors [10–12], we recently studied the menstrual cycle with its fluctuations of estradiol (E2) and progesterone (P4) as a possible source for systematic within-person changes in vmHRV. Our recent meta-analysis [13] revealed a significant decrease in vmHRV from the follicular phase (i.e., onset of menses until after ovulation) to the luteal phase (i.e., after ovulation until the subsequent onset of menses). At the hormonal level, the follicular phase is characterized by generally low E2 and P4 levels with peaking E2 just before ovulation, while the luteal phase shows peaking P4 and E2 levels with rapidly falling levels prior to the subsequent onset of menses (Fig. 1a). Given these systematic E2 and P4 fluctuations, the meta-analytic comparisons of vmHRV in different cycle phases did not allow conclusions about which of the two ovarian steroids was associated with cyclical vmHRV changes. Subsequently, two within-person studies on the vmHRV-hormone association [14] revealed that it is *only* P4 – and
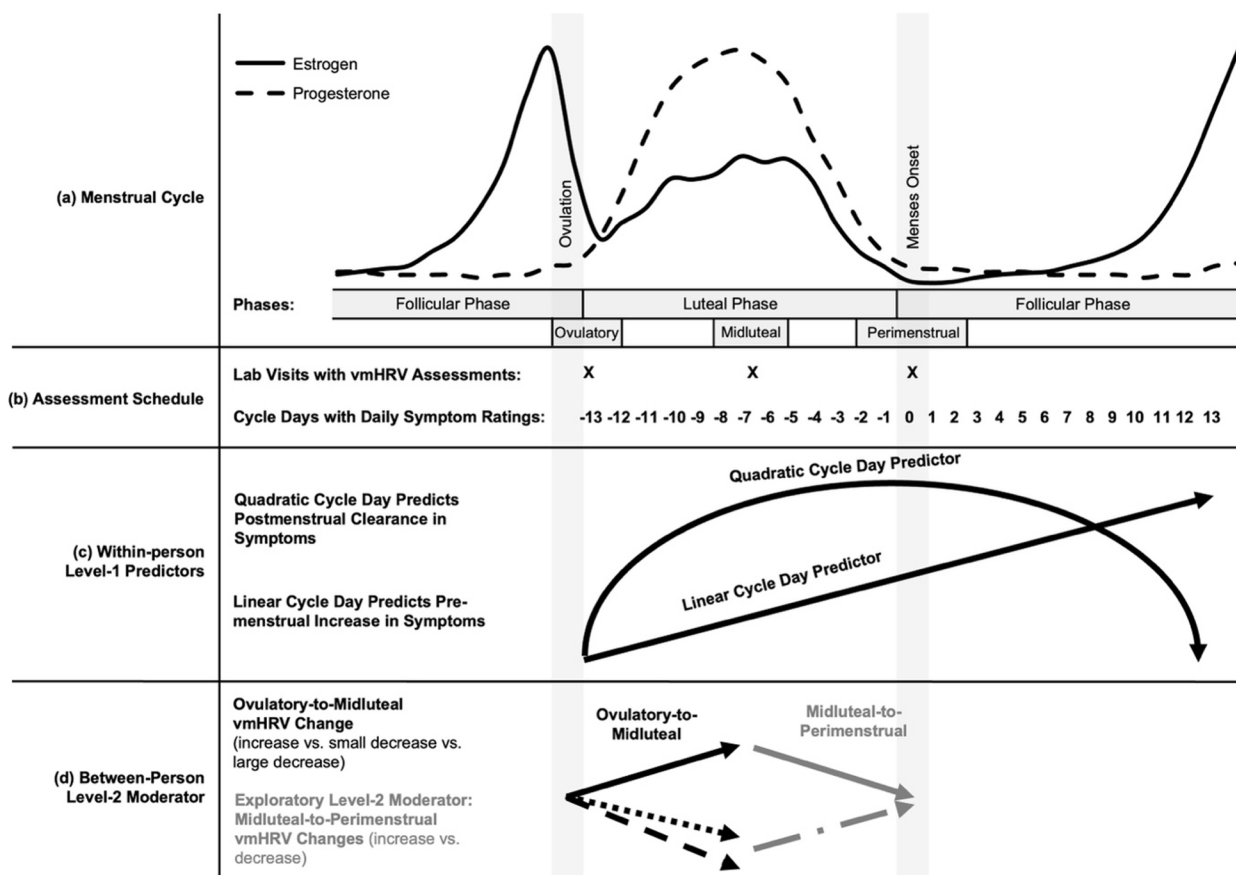

Fig. 1 Overview of the study's assessment schedule (of vmHRV and daily symptom ratings) and analytic approach (with level-1 predictors and level-2 moderators). Note that the pattern of lines indicating the vmHRV change group (level-2 moderator) is consistent throughout the figures (i.e., it matches with this group's symptom change depicted in Figs. 3– 5)

not E2 (nor the interaction of E2 and P4) – that is significantly correlated with cyclical vmHRV. Specifically, within a given subject, higher-than-usual P4 is associated with lower-than-usual vmHRV. However, analyses in both studies revealed interindividual differences in the association between P4 and vagally-mediated vmHRV, suggesting that *not all* naturally cycling individuals seem to show the same vmHRV sensitivity to the cycle. This is in line with decades of research on premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS), which consistently reveal that individuals also highly differ in their *mood* sensitivity to the cycle [15, 16].

Interindividual differences in hormone sensitivity

Rigorous longitudinal and experimental studies have demonstrated that the menstrual cycle and associated fluctuations in E2 and P4 are capable of exerting large effects on the *emotional* [17] and *behavioral* functioning (e.g., impulsive behavior, rumination; [18]) of susceptible individuals. In those individuals, distressing and impairing cyclical psychological symptoms typically emerge in the two premenstrual weeks and remit by the week after menses [19]. Seminal experimental research suggests that these symptoms may *not* be caused by abnormal ovarian hormone changes but rather by an abnormal *sensitivity* to normal changes in ovarian hormones and their metabolites across the cycle [17, 20]. This so-called hormone sensitivity is a dimension on which individuals differ. In strong expression, it can manifest in a primary cyclical mood disorder, for example PMDD, which affects approximately 5.5% [15], or emotional PMS, which occurs in approximately 10% of naturally cycling individuals [16].

To understand these interindividual differences, studies have started to identify markers of hormone sensitivity (indicated by the presence of clinically significant and cyclical mood symptoms). Some studies have found a history of trauma to be a *biographical* correlate of hormone sensitivity [21, 22], while a *genetic* correlate has been identified in the COMT Val158Met genotype [23]. We recently found interindividual differences in the degree of vmHRV reduction from the ovulatory (low P4) to the midluteal (high P4) phase [14], which is the same timeline associated with premenstrual symptom emergence in hormone-sensitive individuals; thus, the question arises whether vmHRV change across the cycle might function as a *physiological* marker of simultaneous emotional hormone sensitivity.

Present study and hypotheses

The present study uses the same sample previously described [14] to begin investigating cyclical changes in vagally mediated vmHRV as a potential physiological marker of emotional hormone sensitivity. We examined whether interindividual differences in vmHRV cyclicity are associated with interindividual differences in emotional changes in the perimenstrual window. In an observational study, a naturally cycling community sample completed daily negative affect ratings and counterbalanced lab visits with vmHRV assessments in three cycle phases (ovulatory, midluteal, perimenstrual). Irrespective of vmHRV cyclicity, we expected participants to differ in the degree of premenstrual emotional changes. Our first hypothesis thus aims to replicate previous findings in the literature showing that individuals vary in their emotional sensitivity to the menstrual cycle:

(1) Individuals differ in the cyclicity of negative affect: (a) In the days leading up to menses, some people will start to develop negative affect faster than others (i.e., have a more rapid premenstrual increase of negative affect), and (b) in the days after menses onset, some people's negative affect will take longer to return to baseline (i.e., slower postmenstrual reduction in negative affect).

Based on our preliminary work showing a normative midluteal vmHRV decrease [13] driven by the midluteal P4 peak [14], as well as the body of work finding that overall higher vmHRV levels are generally associated with better psychological functioning [5, 6, 7], we expected a greater degree of midluteal vmHRV decrease to be predictive of *a greater* premenstrual increase in negative affect. Our index for vmHRV cyclicity as a potential physiological marker of hormone sensitivity was thus conceptualized as the individual degree to which vmHRV decreases from the ovulatory (low P4) to the midluteal phase (high P4). We tested the following hypothesis:

(2) Higher levels of midluteal vmHRV decrease are associated with (a) a more rapid premenstrual increase and (b) a slower postmenstrual reduction in negative affect.

Methods

The present study was approved by the Ethics Committee of the Medical Faculty Heidelberg, University Hospital Heidelberg (approval code S-322/2017). All hypotheses and analytic strategies were preregistered on the Open Science Framework (https://osf.io/hsqpb).

Procedure

A detailed description of the recruitment and assessment procedures for this sample is given in Schmalenberger

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et al. [14]. Flyers, listservs, and social media were utilized to recruit a community sample of naturally cycling individuals for a study examining the "biology of female decision making," with full disclosure of the study's menstrual cycle focus. Interested individuals were prompted to a telephone screening assessing inclusionary criteria: (a) natural menstrual cycle, (b) BMI between 18 and 26, (c) between 18 and 45 years of age, and (d) being generally physically and mentally healthy (by confirming that they do not currently suffer from any chronic physical or mental health conditions). Exclusion criteria were (a) deviation from a natural menstrual cycle (e.g., due to hormonal contraceptives, amenorrhea, pregnancy, or breastfeeding), (b) cycle lengths shorter than 25 or longer than 35 days, (c) any psychopharmacological medication, (d) a past or present diagnosis of psychotic disorder (excluding dissociation), and/or (e) lack of German fluency.

Eligible individuals were invited to an enrollment visit during which the study procedures were thoroughly explained and at-home ovulation tests were handed out. During the enrollment visit, written informed consent was obtained from all the participants. Following their enrollment, participants completed an online battery of demographic and personality questionnaires. Beginning with their next menses onset, participants rated their daily negative affect each evening via a 3–5 min online questionnaire for an entire menses-to-menses cycle plus an additional two weeks (which resulted in a total of six weeks for a typical 28-day cycle). Starting in their mid-follicular phase, participants completed at-home urinary ovulation tests. Based on their reported onset of menses and positive ovulation test, each participant completed three counterbalanced lab visits in their (1) ovulatory phase (on the day of or day after the positive ovulation test), (2) mid-luteal phase (between days+6 to+8 after the day of the positive ovulation test), and (3) menstrual phase (between days+2 to+4 after onset of menses). To avoid diurnal effects, the time of day of lab visits was kept as consistent as possible within a participant. During each lab visit, we assessed vmHRV (Fig. 1b), ovarian hormone levels, and additional cognitive tasks (which are not part of the present study). After completing all daily symptom ratings and lab visits, participants were invited to a debriefing visit and received 80 Euros for time invested in the study. Finally, they informed the study team about when their next menstrual cycle began (information used for retrospective validation of cycle phase, see below). Data collection was carried out between March and August 2018.

Participants
Of the 86 interested individuals who contacted the study team, 67 were screened on the phone, and 53 were invited to an enrollment visit. During data collection, three individuals had to be excluded due to cycle irregularities ($N=2$ with an anovulatory cycle, $N=1$ with a luteal phase shorter than 6 days). The remaining 50 participants contributed three lab visits each ($N=150$). As described in detail below, for each lab visit, we used available cycle day and hormone assay information to retrospectively verify that the lab visits had occurred in the targeted phases of ovulatory cycles. Applying these retrospective validation criteria to the 150 lab visits of the 50 participants reduced the final sample to 31 participants. Table 1 provides an overview of the final sample's demographic and reproductive information.

Measures
Daily negative affect
Participants reported their daily negative affect each evening via an online questionnaire. The link was sent to them each night at approximately 7 pm. The study team followed up each morning to ensure questionnaire completion, sending email reminders if necessary. Daily negative affect was defined as the mean of the four core emotional symptoms of PMDD (depression,

Table 1 Demographic and reproductive information of the final sample ($N=31$)

Variables	Mean (*SD*), *n* (%)	Range
Demographic information		
Age (in years)	26.03 (5.52)	19–44
Female gender orientation	31 (100%)	-
Sexual orientation		
Heterosexual	27 (87%)	-
Homosexual	1 (3%)	-
Bisexual	1 (3%)	-
Prefer not to answer	2 (6%)	-
Relationship status		
In a relationship	21 (68%)	-
Single	10 (32%)	-
Highest education level		
High school diploma	15 (48%)	
University degree	16 (52%)	-
Employment status		
University student	27 (87%)	-
Employee	2 (6%)	-
Freelancer	1 (3%)	-
Unemployed	2 (6%)	-
Reproductive information		
Age at menarche (in years)	12.81 (1.62)	8–16
Having biological children	3 (10%)	-
Average menstrual cycle length (in days)	28.69 (2.85)	24–36

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anger/irritability, anxiety, mood swings) since decades of PMDD research revealed these symptoms to show cyclicity across the menstrual cycle in hormone-sensitive individuals [15–17]. The following 11 items were derived from a validated German symptom diary for PMDD diagnosis [24] and form the daily negative affect scale: (1) low mood, (2) hopelessness, (3) worthlessness, (4) anger, (5) irritability, (6) interpersonal conflicts, (7) anxiety, (8) being on edge, (9) sudden sadness, (10) sudden crying, and (11) rejection sensitivity. All items were rated on a 6-point Likert scale from 1-*not at all* to 6-*extreme.*

Ovulation
To determine ovulation, we utilized at-home urinary tests that identified the preovulatory surge of luteinizing hormone (LH). The LH tests were provided by Purbay® (Münster, Germany) and had a sensitivity of 10 mIU/mL. These tests required participants to compare the test and control lines themselves, as they did not have an electronic read-out device. During the enrollment visit, participants received training on how to use the LH tests effectively. To establish the appropriate cycle day for each participant to begin daily testing, we collected information on the length of their shortest menstrual cycle over the past six months. By subtracting 14 days (i.e., the relatively robust length of the luteal phase [25]) from this cycle length, we identified the earliest occurrence of ovulation within the past six months. To ensure that ovulation was not missed, participants were instructed to start ovulation testing five days prior to this calculated cycle day. Email reminders were sent out every morning at approximately 7 am during the testing period. Participants were instructed to take the tests each morning around the same time and contact the study team if they tested positive or had any uncertainties about the test results.

Ovarian steroids
Ovarian hormone levels were assessed from saliva samples collected via passive drool through a straw during lab visits. Participants provided a total of 3 mL saliva in two SaliCaps (IBL; Hamburg, Germany), which were stored at -80 °C in an upright freezer on site until being analyzed in the in-house hormone laboratory of the Institute of Medical Psychology, Heidelberg. After an initial 10-min centrifugation at 3540 rpm, salivary hormone levels were assessed in duplicate via luminescence immunoassay (IBL; Hamburg, Germany). The intra-assay coefficient of variation was 4.8% for E2 and 4.7% for P4; the interassay coefficient of variation was 5% for E2 and 4% for P4. Participants were instructed to *refrain* from the following behaviors in the two hours prior to lab visits: drink anything other than water or herbal tea, eat anything

with protein, smoke, and excessive exercise (for vmHRV assessment reasons). To further reduce the risk of adulteration by food or drink, saliva samples were collected at the end of the 75-min lab visit (during which only drinking water was allowed).

Vagally mediated heart rate variability
During each of the three lab visits, we assessed vmHRV with a 10-min baseline ECG that was sampled at a rate of 1000 Hz applying AcqKnowledge® 5 from Biopac Systems Inc. (Goleta, CA, USA). The ECG was amplified using the appropriate module (ECG100C). To attach the three ECG electrodes (located below the left and right collarbone and left rib), a study team member had to work with the participant and ask them to lift or slide their top to the side briefly, which created a social situation. Before leaving the participant alone in the room in a seated position, the study team member instructed them, "We will now take a baseline recording of your body's activity. Please sit very still until I come back in about 10 min." The first and last ~15 s (during which the study team member was still present in the room) were excluded from the ~10.5-min ECG, yielding 10 min of reliable ECG data. The ECG equipment failed in only one lab visit.

Data preparation and cleaning were conducted by trained personnel using Kubios HRV Premium 3.2.0 software (Kubios Oy; Kuopio, Finland). We utilized Kubio's automatic artifact correction feature to rectify artifacts and errors in the computerized marking of R-peaks (beats). Afterward, we manually inspected and adjusted the computerized marking of R-peaks according to the guidelines proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [26]. One 5-min epoch was removed from analyses as its artifacts exceeded 5%. Once each 5-min recording was cleaned, high frequency (HF) HRV (0.15–0.40 Hz) was calculated to index primarily vagally mediated HRV by spectral analysis. We opted for this frequency-domain measure over a time-based measure like RMSSD, as HF-HRV has been shown by some to be more robust to single artifacts [27]. For each lab visit of each participant, we averaged the two 5-min epochs to one vmHRV value. A log transformation was applied to better approximate a normal distribution.

Retrospective validation of menstrual cycle phase
After the completion of data collection, we evaluated whether the lab visits had occurred during the targeted phases (ovulatory, midluteal, perimenstrual) of ovulatory cycles. This retrospective validation process relied on several criteria: (1) the forward- and backward-count cycle days for the lab visits, (2) absolute P4 levels on the days of the lab visits, and (3) relative ovarian steroid

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levels between lab visits. *Cycle day* criteria were derived from the relatively robust luteal phase length of 14 days [25]. Consequently, ovulatory lab visits were required to fall between cycle days -17 and -12 before the next menses onset (where menses onset is day 1 and there is no day 0), midluteal lab visits were required to fall between cycle days -11 and -4 days, and perimenstrual lab visits were required to fall between cycle days -3 to +3 around menses onset (on day 1). In addition, we inspected *absolute P4 levels* during the ovulatory and midluteal lab visits to verify ovulation since P4 levels only rise significantly in the luteal phase of ovulatory cycles [28]. We used the cutoff value of 127 pg/mL for luteal P4 levels provided by the company distributing the hormone analyses kits (IBL; Hamburg, Germany) and required midluteal lab visits to show P4 $\geq$ 127 pg/mL and ovulatory lab visits to show P4 < 127 pg/mL. Finally, *relative hormone level* criteria were based on systematic E2 and P4 fluctuations across the menstrual cycle. As P4 levels start to rise around ovulation and peak in the midluteal phase, we required ovulatory P4 levels to be lower than midluteal P4 levels to retrospectively validate ovulatory and midluteal lab visits. Given the primary E2 peak in the ovulatory phase, the primary P4 peak in the midluteal phase, and the rapid E2 and P4 withdrawal in the perimenstrual phase, we retrospectively validated the perimenstrual phase by requiring perimenstrual E2 levels to be lower than ovulatory E2 levels and perimenstrual P4 levels to be lower than midluteal P4 levels (more detailed information can be found in [14], which used the same sample and in a recent methodological review [29]).

Out of the 150 lab visits by 50 participants, 104 lab visits by 39 participants met these validation criteria. Since the present study focuses on vmHRV cyclicity indicated by ovulatory-to-midluteal vmHRV changes, out of these 39 participants, only participants with both a validated ovulatory and midluteal lab visit could be included. This resulted in a final sample size of 31 participants and 87 lab visits (N = 31 ovulatory, N = 31 midluteal, N = 25 perimenstrual).

Analytic plan
Midluteal vmHRV decrease
The degree of midluteal vmHRV decrease describes the extent to which vmHRV levels decline from the ovulatory (low P4) to the midluteal phase (high P4) within a given participant. Using R-4.2.1 [30], we utilized *nlme* (package version 3.1.160; [31]) to predict vmHRV from categorical cycle phase (midluteal phase serving as the reference phase) in a multilevel model with lab visits (level 1; ovulatory vs. midluteal vs. perimenstrual) nested within participants (level 2). Random intercepts and slopes were included to account for interindividual differences in

mean vmHRV and vmHRV changes between phases. A participant's random slope of the ovulatory-vs-midluteal phase contrast was used to index their individual degree of midluteal vmHRV decrease. To make zero meaningful and ultimately ease interpretation of effects, the fixed slope was added to each random slope. Therefore, the degree of midluteal vmHRV decrease was a continuous, between-person variable calculated for each person as the fixed effect for the contrast (ovulatory vs midluteal; same for all participants) plus the random effect for the same contrast (variable across participants).

Cycle day predictors
To test our hypotheses on premenstrual increases and postmenstrual decreases in negative affect, we created a cycle day variable ranging from day -13 before the onset of menses until day + 13 after the onset of menses (on day 0; Fig. 1b). The primary outcome of the study is daily negative affect across these 27 days centered around menses. For the purposes of the analyses, this cycle day variable was recentered such that zero was placed at day -13 (making the cycle day variable now range from 0 to 26), which allows for more interpretable effects. In our models described below, including this cycle day variable as a predictor of daily negative affect allows for examining *premenstrual increases* in negative affect. In addition, we squared this linear cycle day variable and included it in the analyses, which allows for investigating *postmenstrual clearance* of symptoms. The squared cycle day variable thus captures the quadratic effects of cycle day (Fig. 1c).

Hypothesis testing
We tested our hypotheses on the primary outcome daily negative affect with a multilevel dataset with cycle days (level 1) nested within participants (level 2). Hypothesis 1 (interindividual differences in the perimenstrual increase and postmenstrual reduction in negative affect) centers around an unconditional multilevel model predicting negative affect from cycle day and squared cycle day. To test the hypothesized interindividual differences in the effect of cycle day and squared cycle day, we ran a likelihood ratio test to compare fit between models with and without including random effects for the predictors. Hypothesis 2 (more midluteal vmHRV suppression is associated with (a) a more rapid premenstrual increase and (b) slower postmenstrual decrease in negative affect) centers around a cross-level interaction between the individual degree of midluteal vmHRV decrease with cycle day (hypothesis 2a) and squared cycle day (hypothesis 2b). To test this, we ran a conditional multilevel model predicting negative affect from cycle day and squared cycle day (level 1), degree of midluteal vmHRV decrease

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(level 2), and the two cross-level interactions between cycle day predictors and vmHRV decrease. Again, we included random effects of both cycle day predictors. To account for interindividual differences in mean negative affect, we included random intercepts in all models described above. All multilevel models were run in the R-4.2.1 [30] *lme4* package (version 1.1.30; [32, 33]).

Results
Descriptives
The demographic and reproductive characteristics of the final sample ($N=31$) are presented in Table 1. The sample displayed diversity in terms of age and relationship status but was homogeneous with respect to gender identity and employment status. Regarding the primary outcome of the study, a total of 814 daily ratings of negative affect across 31 perimenstrual frames (i.e., 27 days ranging from cycle day -13 before the onset of menses

Table 2 Mean and SD of variables assessed during lab visits

	Cycle phase		
	Ovulatory	**Midluteal**	**Perimenstrual**
Backward-count cycle day	-13.48 (2.00)	-6.97 (1.74)	-
P4 (in ng/dL)	65.58 (30.98)	182.62 (84.83)	58.04 (30.76)
E2 (in pg/mL)	6.16 (3.06)	4.86 (2.89)	3.87 (3.02)
Vagally-mediated HRV (HFlog)	6.14 (1.03)	5.98 (1.35)	6.29 (0.97)
Percentage of artifacts during ECG assessment	.0028 (.0067)	.0051 (.0205)	.0029 (.0091)

until $+13$ days after the onset of menses, with menses onset on day 0) entered the analyses. Table 2 provides descriptive information on the variables assessed during lab visits ($N=87$). Both P4 and E2 levels show the expected cyclical variations. In line with previous meta-analytic findings [13], vmHRV levels are lowest in the midluteal phase compared to the ovulatory and perimenstrual phases. The highest percentage of artifacts during ECG assessments was observed in the midluteal phase. However, a multilevel model analysis did not reveal any significant differences in the artifacts between any of the three phase contrasts (ovulatory vs. midluteal, ovulatory vs. perimenstrual, midluteal vs. perimenstrual), with $p > 0.05$.

Ovulatory-to-midluteal vmHRV change
During preregistration, we planned to index vmHRV cyclicity via a linear variable reflecting the degree to which vmHRV drops midluteally. However, upon calculation, it became clear that the vmHRV decrease variable shows an almost normal distribution (skew=0.02) centered around a positive mean of 0.15 (with positive values reflecting the expected ovulatory-to-midluteal decrease) and a range between -1.40 and 1.87 (Fig. 2). The histogram thus revealed systematic differences in the *direction* of cyclical vmHRV change: While approximately two-thirds of the sample showed the expected *decrease* from ovulatory to midluteal vmHRV ($N=20$), one-third displayed a midluteal *increase.* Our initial theoretical concept of a variable indicating the degree of continuous vmHRV decrease was therefore not borne
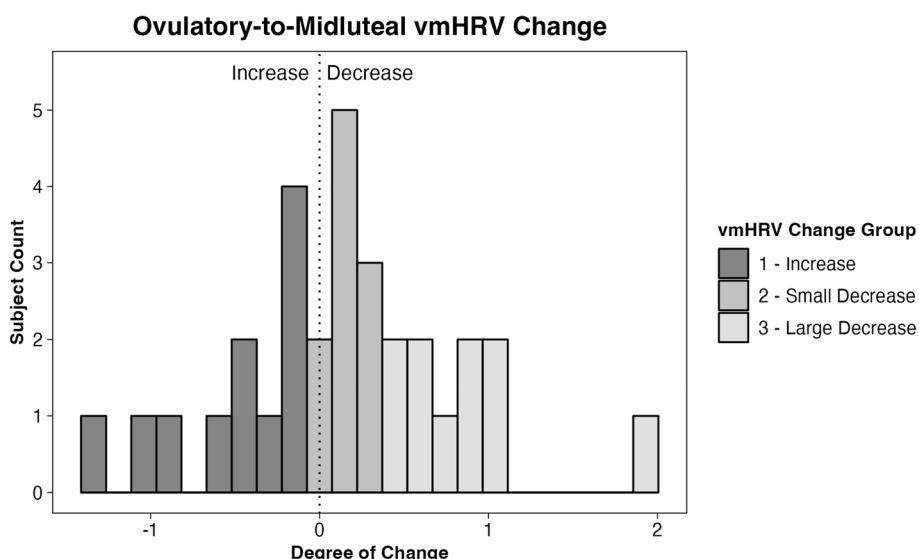
Fig. 2 Histogram of the continuous, between-person variable *midluteal vmHRV decrease* with higher values indicating more of the expected *decrease* from ovulatory to midluteal vmHRV. The three categories of the newly created vmHRV cyclicity variable (*increase*, *small decrease*, and *large decrease*) are marked by different shades of grey

out empirically, and the use of this continuous variable as a moderator would have led to great confusion and difficulty in the interpretation of results (i.e., a midluteal vmHRV *increase* would be difficult to interpret in this context). Therefore, a categorical variable named *vmHRV cyclicity* was generated. Each participant with a midluteal vmHRV decrease smaller than 0 (indicating a negative midluteal decrease, in other words, a midluteal *increase* in vmHRV) was assigned to the category *increase* (N=11). To keep category size equal, we dichotomized the remaining 20 participants with the expected midluteal *decrease* into two categories: *small decrease* (N=10) and *large decrease* (N=10). Note that the cutoff between small and large decreases is not theoretically founded but empirically chosen and might therefore be limited in its meaningfulness. The three categories of the newly created vmHRV cyclicity variable (increase, small decrease, large decrease from ovulatory to midluteal vmHRV) are depicted in Fig. 2 (histogram) and Fig. 1d (overview of analytic approach).

For each participant, we averaged vmHRV in all their available validated lab visits (including their perimenstrual lab visit) to yield the variable *individual mean vmHRV*. Across the three vmHRV cyclicity categories, individual mean vmHRV was the highest within the

increase group (N=11, M=6.59, SD=1.01), followed by the small decrease group (N=10, M=6.05, SD=0.78) and the large decrease group (N=10, M=5.75, SD=1.20). However, ANOVA tests revealed that these group differences were not statistically significant (p=0.17), meaning that the direction of ovulatory-to-midluteal vmHRV is not associated with general vmHRV levels.

Hypothesis 1: individuals differ in the cyclicity of negative affect

The results of the unconditional multilevel model predicting negative affect from cycle day and squared cycle day revealed a correlation of r=-1.0 between random effects of the linear and squared cycle day predictor. Given this conventionally high correlation [34], we adjusted all models to include only random effects for the linear cycle day predictor. The results of the adjusted model are presented in Table 3. The sample displayed a significant premenstrual increase (cycle day effect) and postmenstrual clearance (squared cycle day effect) of negative affect. We tested hypothesis 1 (significant interindividual differences in cyclicity of negative affect) with a likelihood ratio test that compared fit between models with and without including a random effect of linear cycle day. The models differed significantly ($\chi^2=35.6$,

Table 3 Multilevel models predicting negative affect from linear and squared cycle day (unconditional model) and from linear and squared cycle day, ovulatory-to-midluteal vmHRV change group, and their interaction (conditional model)

	Outcome: negative affect			
	Unconditional model		**Conditional model**	
	Estimates	*p*	*Estimates*	*p*
Fixed effects				
Intercept	1.38980	**<.001**	-0.00105	**<.001**
Cycle day	0.04692	**<.001**	0.02605	.140
Squared cycle day	-0.000185	**<.001**	-0.00105	.083
vmHRV change (increase)			-0.04599	.830
vmHRV change (small decrease)			-0.14436	.508
vmHRV change (increase) * cycle day			0.06601	**.007**
vmHRV change (small decrease) * cycle day			-0.00699	.779
vmHRV change (increase) * squared cycle day			-0.00233	**.006**
vmHRV change (small decrease) * squared cycle day			0.00003	.970
Random effects				
Intercept (τ_{00})	0.22		0.21	
Cycle day (τ_{11})	0.00		0.00	
Residual (σ^2)	0.28		0.28	
Intraclass correlation coefficient (ICC)	0.43		0.39	
Marginal R^2/conditional R^2	0.020/0.406		0.090/0.426	
N_{ID}	31		31	
$N_{observations}$	814		814	

vmHRV Change Categorical variable capturing ovulatory-to-midluteal vmHRV change (increase vs. small decrease vs. large decrease), with "large decrease" serving as the reference group. Statistically significant parameters are shown in bold

df = 2, $p < 0.001$), with the model including a random effect providing better fit. This suggests the presence of significant interindividual differences in premenstrual emotional changes, which confirms our hypothesis and replicates previous research.

Hypothesis 2: ovulatory-to-midluteal vmHRV change predicts premenstrual increase and postmenstrual clearance of negative affect

Predicting negative affect with categorical vmHRV predictor
Table 3 also presents results from a conditional multilevel model predicting negative affect from linear and quadratic cycle day (level 1), vmHRV cyclicity group (level 2), and the cross-level interactions between group and cycle day. As expected, we observed significant differences between the vmHRV cyclicity groups regarding their premenstrual symptom increases and postmenstrual symptom clearance (more specifically between the *large decrease* and the *increase* group); however, this was not in the direction we hypothesized. As depicted in Fig. 3, neither the *small decrease* nor the *large decrease* group (i.e., those with any midluteal drop in vmHRV) showed the expected linear and quadratic effects of cycle day on their negative affect severity (i.e., no marked premenstrual symptom increases and postmenstrual symptom clearance). Unexpectedly, it was the vmHRV *increase* group whose negative affect markedly increased premenstrually and decreased postmenstrually. In other words, only participants whose vmHRV levels increased from the ovulatory to the midluteal phase showed premenstrual negative affect.

Predicting single items with categorical vmHRV predictor
The primary outcome of our analyses (negative affect scale) covers the four core emotional PMDD symptoms (depression, anxiety, anger/irritability, and mood swings) and is therefore of heterogeneous nature. In addition, within each of these four symptoms, corresponding items show content variety. For example, anger/irritability is assessed with items (1) anger, (2) irritability, and (3) interpersonal conflict, which cover both emotional states and interactional behavior. In preregistered exploratory analyses, we also ran models predicting each of the 11 items comprising the negative affect scale. Detailed results of multilevel models are listed in Supplementary Materials 1 (Table S1A – S1E). In sum, 5 out of the 11 items showed the same result pattern observed in our primary outcome negative affect (Fig. 4). For (1) hopelessness, (2) worthlessness, (3) anxiety, (4) being on edge, and (5) rejection sensitivity, we found significant interactions between the vmHRV cyclicity group increase with both the linear and the squared cycle day predictor.

Predicting negative affect with continuous vmHRV predictor
The unexpected finding of people not only differing in the degree of their midluteal vmHRV decrease but also in the *direction* led us to create a categorical variable capturing ovulatory-to-midluteal vmHRV change (increase vs. small decrease vs. large decrease). However, as categorizing continuous variables can reduce statistical power, we additionally tested Hypothesis 2 using a more continuous approach. Two new variables were created to capture ovulatory-to-midluteal vmHRV changes:
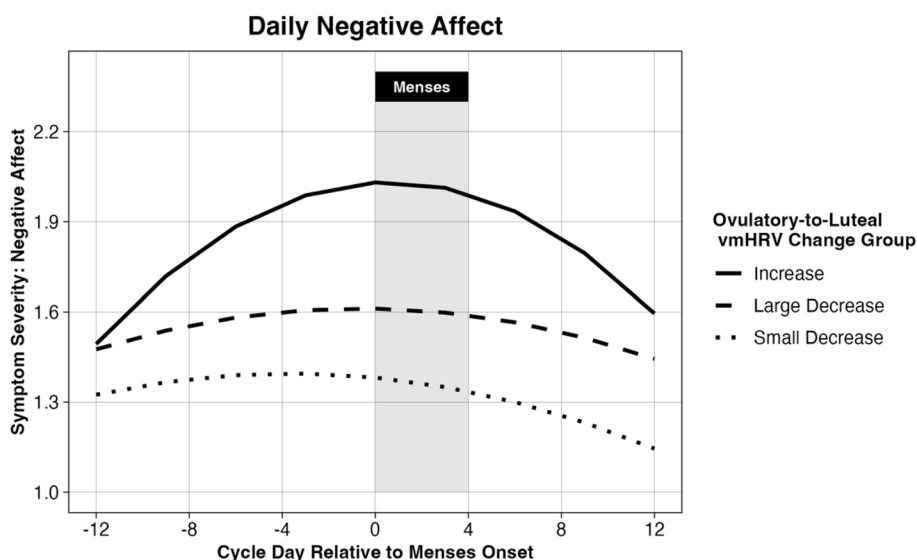

Fig. 3 Model implied values of daily negative affect across the perimenstrual frame from day -12 to +12 (with menses onset on day 0) in three ovulatory-to-midluteal vmHRV change groups (increase vs. small decrease vs. large decrease)
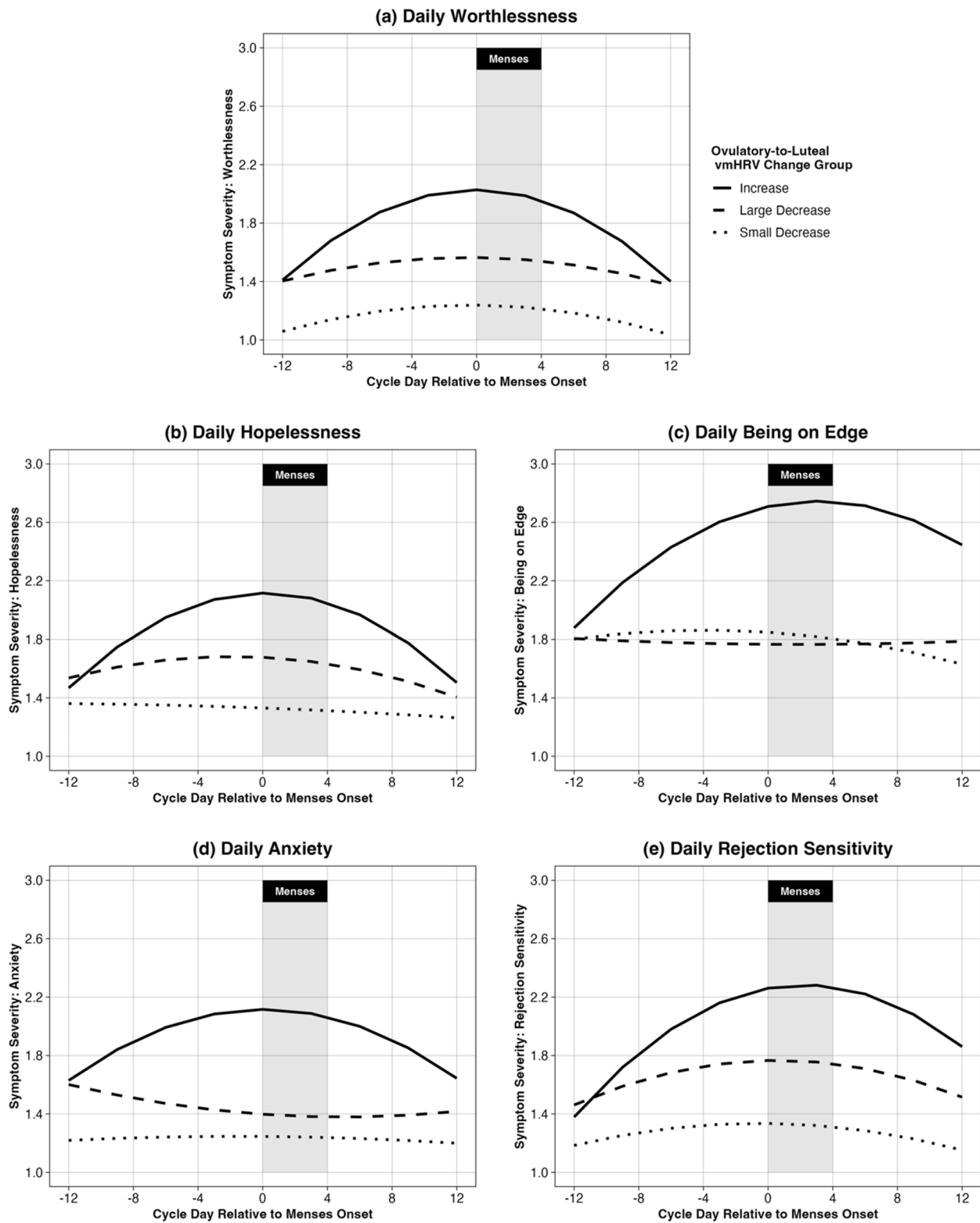
Fig. 4 Model implied values of daily (**a**) worthlessness, (**b**) hopelessness, (**c**) being on edge, (**d**) anxiety, and (**e**) rejection sensitivity across the perimenstrual frame from day -12 to + 12 (with menses onset on day 0) in three ovulatory-to-luteal vmHRV change groups (increase vs. small decrease vs. large increase)

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(1) *direction* (a dichotomous variable with the categories decrease vs. increase) and (2) *size* (a continuous variable describing the absolute vmHRV change between the two cycle phases). In a similar multilevel model as described above, we predicted daily negative affect in the perimenstrual phase (cycle day -13 to +13 centered around menses onset) with linear cycle day, quadratic cycle day, the two new variables direction and size, and their interactions with each other and the cycle day predictors. Model results revealed significant interactions between direction and cycle day and between direction and squared cycle day (Supplementary Table S2). As shown in Supplementary Figure S1, negative affect only increased premenstrually and cleared postmenstrually in the group of participants with an *increase* in midluteal vmHRV. Of note, our analyses using this continuous approach also revealed a significant interaction between size and direction in vmHRV change and a significant three-way-interaction between direction, size, and cycle day. However, given our sample size (with only 11 people in the increase group), the power to meaningfully interpret the effect of size in the two direction groups separately is most likely lacking. In summary, this more continuous approach broadly confirms our primary analysis using the categorical approach to measure changes in ovulatory-to-midluteal vmHRV. It reveals that midluteal vmHRV *increases* are riskier for concurrent cyclicity of negative affect than vmHRV decreases.

Exploratory analyses on midluteal-to-perimenstrual vmHRV change

Unexpectedly, the present study revealed that *deviating* from the normative ovulatory-to-midluteal vmHRV decrease was associated with cyclicity of negative affect. Given that previous work also showed a normative increase in vmHRV from the midluteal to perimenstrual phase [13, 14], the question arises whether the deviation from this increase might also be linked to cyclical negative affect. In an exploratory analysis, we expanded our investigation of ovulatory-to-midluteal vmHRV changes as a predictor of cyclical negative affect by analyzing midluteal-to-perimenstrual vmHRV changes, as shown in Fig. 1d.

Of the 31 participants, 25 completed a validated perimenstrual vmHRV assessment, allowing us to evaluate their individual level of midluteal-to-perimenstrual vmHRV change (similar to how we evaluated ovulatory-to-midluteal vmHRV change as described above). We observed that similar to the change in vmHRV from ovulation to the mid-luteal phase, participants varied not only in the magnitude but also in the *direction* of their vmHRV change. Once again, a small subgroup of the sample deviated from previous findings [13, 14] by

showing an atypical perimenstrual vmHRV *decrease.* Due to the smaller sample size of only 25 participants for the midluteal-to-perimenstrual vmHRV analysis, we avoided distinguishing between large and small increases/decreases (as we did for the ovulatory-to-midluteal vmHRV change), and instead, separated the sample only into midluteal-to-perimenstrual vmHRV increase vs. decrease. Table 4 shows the counts for each combination of vmHRV changes: Within the group of participants with an ovulatory-to-midluteal vmHRV decrease ($N=17$; i.e., participants without cyclicity of negative affect), the majority ($N=14$; 82%) showed the normative perimenstrual vmHRV increase. In contrast, within the atypical ovulatory-to-midluteal vmHRV increase group ($N=8$; i.e., participants with cyclicity of negative affect), the majority ($N=5$; 63%) showed an atypical perimenstrual vmHRV decrease.

In a similar multilevel model as described above, we predicted daily negative affect in the perimenstrual phase (cycle day -13 to +13 centered around menses onset) with linear cycle day, quadratic cycle day, midluteal-to-perimenstrual vmHRV change (categorical variable with increase vs. decrease), and their interactions. Model results revealed a significant interaction between midluteal-to-perimenstrual vmHRV group and both linear and quadratic cycle day (Supplementary Table S3). As shown in Fig. 5, only the group with the atypical perimenstrual vmHRV *decrease* (which consists mostly of people with the atypical ovulatory-to-midluteal *increase*) shows negative affect cyclicity. Potentially, the perimenstrual return to baseline vmHRV levels in this group might contribute to the postmenstrual improvements in negative affect. In contrast, the group with the normative perimenstrual vmHRV increase (consisting mostly of people with the normative midluteal vmHRV decrease) shows significantly lower cyclical negative affect. Taken together, while these exploratory analyses are technically not supportive of the specificity of the ovulatory-to-midluteal vmHRV change (given that the

Table 4 Counts for each combination of vmHRV change in the ovulatory-to-midluteal and midluteal-to-perimenstrual phase contrasts

		Midluteal-to-perimenstrual		
		Decrease	Increase	Total
Ovulatory-to-midluteal	Decrease (small and large)	3	14	17
	Increase	5	3	8
Total		8	17	25

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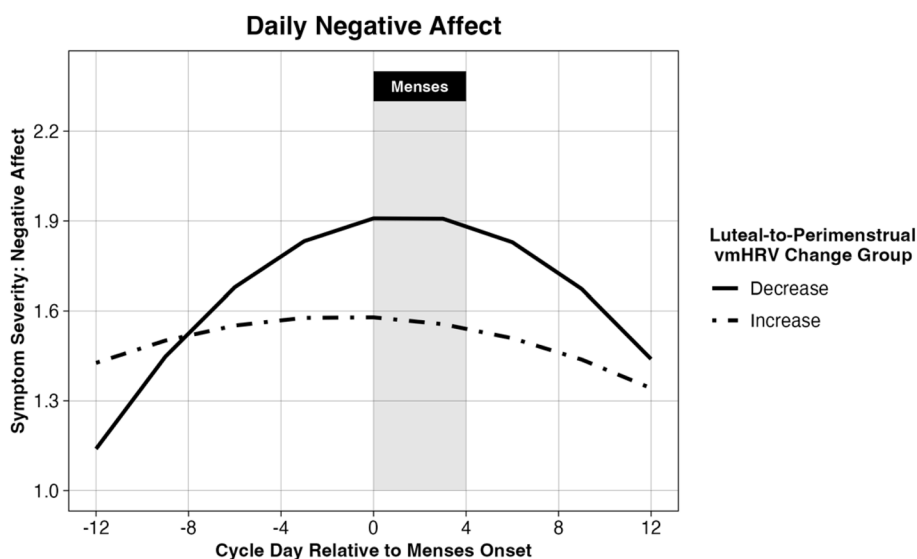
Daily Negative Affect

Fig. 5 Model implied values of daily negative affect across the perimenstrual frame from day -12 to + 12 (with menses onset on day 0) in the two midluteal-to-perimenstrual vmHRV change groups (decrease vs. increase)

midluteal-to-perimenstrual vmHRV change also served as a significant moderator of cyclicity of negative affect), they provide additional support for *midluteal vmHRV increase* as a potential physiological marker for concurrent emotional hormone sensitivity – whether midluteal vmHRV increase is framed as an ovulatory-to-midluteal increase or midluteal-to-perimenstrual decrease.

Discussion

Meta-analytic work points to the menstrual cycle as a source for systematic within-person changes in vmHRV, with lower vmHRV in the luteal phase than in the follicular phase [13]. Furthermore, prior work has shown that these cyclical vmHRV changes are driven primarily by increased luteal P4, with higher P4 (but not E2 or their interaction) predicting lower vmHRV [14]. However, given that analyses in these studies indicated interindividual differences in the effect of the cycle and P4 on vmHRV, not all naturally cycling individuals seem to show the same vmHRV reductions in the midluteal phase. The current study investigated whether interindividual differences in vmHRV cyclicity are predictive of interindividual differences in showing premenstrual increases in negative affect. In a community sample of naturally cycling individuals, we found that there was heterogeneity in the ovulatory-to-luteal change in vmHRV, with most participants showing the expected decrease but one-third revealing an *increase* in their midluteal vmHRV. Therefore, we trichotomized our sample into three equally sized subgroups of vmHRV: those with a large decrease, those

with a small decrease, and those with any increase. With these groups, the repeated measures design of the study allowed us to assess within-person associations of vmHRV and emotional changes. Contrary to our hypothesis that a robust midluteal vmHRV decrease would be associated with more robust premenstrual emotional symptoms, only the vmHRV *increase* group showed premenstrual emotional changes. This pattern was found in our primary outcome, a negative affect scale covering all four core emotional symptoms of PMDD (depression, anger/irritability, anxiety, and mood swings). Analyses on individual items replicated this finding in 5 out of the 11 items (worthlessness, interpersonal conflict, being on edge, anxiety, sudden crying, and rejection sensitivity). The association between midluteal vmHRV increases and cyclicity in negative affect received further empirical support by two sets of exploratory analyses: First, upon using a more continuous approach to probe ovulatory-to-midluteal vmHRV changes, we again found cyclical changes in negative affect only when vmHRV was increasing. Second, when approaching midluteal vmHRV levels not from the ovulatory but from the perimenstrual direction, it was found that only the group with midluteal-to-perimenstrual decreases (which mostly consisted of participants with ovulatory-to-midluteal increases) showed cyclicity of negative affect. Taken together, our results suggest that a less frequent form of vmHRV cyclicity (i.e., a midluteal vmHRV *increase*) was associated with premenstrual emotional symptoms and thus provides preliminary evidence for the possibility of

atypical midluteal vmHRV increases serving as a physiological marker of emotional hormone sensitivity.

Possible underlying mechanisms

Given the accumulated evidence that higher resting vagally mediated vmHRV typically correlates with better emotional and cognitive health [3–7], we were surprised to find that ovulatory-to-midluteal increases in vmHRV, which we had expected to be associated with *reduced* negative affect, predicted *greater* premenstrual negative affect. Two possible explanations for this finding should be evaluated in future efforts to replicate and extend this work. First, it is possible that the statistically abnormal [13] increase in vmHRV observed in participants with a greater increase in premenstrual negative affect indexes some as-yet-undefined pathological process that occurs in the midluteal phase for these individuals.

Second, and perhaps more likely, these luteal vmHRV increases may index efforts to regulate emotion in those with greater premenstrual negative affect. Experimental evidence suggests that, in the laboratory, instructions to use emotional regulation strategies (especially reappraisal) increase vmHRV relative to a control condition [4, 35, 36]. In most cases, these effects were observed in social contexts. This raises the possibility that the participants who experienced greater premenstrual negative affect were engaging in effortful emotion regulation during the midluteal lab visit (a social context) – whereas participants without such emotional symptoms did not need to engage these strategies. This compensatory need to regulate might have been especially pronounced during the ECG assessment (resulting in temporarily higher levels of vmHRV) since the ECG always followed the most social part of the lab visit (i.e., the welcoming of the participant and attachment of electrodes to the participant's body by a member of the staff requiring participants to briefly shift/lift their tops). In this explanation, elevated vmHRV in the midluteal phase could be viewed as an adaptive compensatory strategy among individuals experiencing elevated premenstrual negative affect.

Of note, the idea that higher vmHRV can be associated with *more* emotional symptoms and that the relationship between vmHRV and emotional functioning is not as linear as was long assumed received further empirical support from between-person studies. In these studies, participants with either very low or very high overall vmHRV levels reported *more* depression and *less* positive affect than participants with moderate vmHRV [37–40] indicating a U-shaped association between vmHRV and maladaptive emotional outcomes. One study found this quadratic relationship between vmHRV and depression to be unique to women [40]. The authors hypothesize that this might go back to women being more likely than

men to use tend-and-befriend coping strategies that promote greater emotion regulation and inhibitory control in the face of high distress. Through this lens, high levels of vmHRV in women (relative to men) might more strongly represent a compensatory neural response to heightened distress. Women on the very right side of the U-shaped function have heightened levels of depression and (either concurrently or subsequently) show greater emotion regulation efforts, which (in line with the neurovisceral integration theory [8, 9]) are reflected in high levels of vmHRV. In contrast, the low vmHRV levels of women on the very left side of the U-shaped vmHRV-depression function might indicate less self-regulatory resources, which might cause deficient emotion regulation and in turn heightened distress. Finally, women with moderate vmHRV (i.e., in the center of the function) might have more emotion regulation resources than women with lower vmHRV, which allows them to engage in context-appropriate emotion regulation and, in turn, experience less distress [40]. Although these studies focus on *interindividual* differences in vmHRV [37–40], they provide further empirical support for the idea that the atypical vmHRV increases in only the participants with premenstrual emotional symptoms might represent their compensatory efforts to regulate emotions in times of heightened distress. In conclusion, more work will be needed to disentangle these possibilities and understand the underlying mechanisms of the present findings. The use of longitudinal methods (e.g., daily monitoring of vmHRV across the cycle with wearable devices [41] that assess nightly vmHRV) and experimental designs (e.g., transcranial magnetic stimulation to increase vmHRV) in clinical samples may help to elucidate these vmHRV-symptom relationships.

Implications

Future studies should investigate the association between midluteal vmHRV increases and premenstrual negative affect in clinical samples of hormone-sensitive participants – ideally with daily testing of vagally mediated vmHRV with a consumer-grade wearable device to provide greater granularity and opportunities for testing directionality of effects. If our findings were replicated in these studies, this would further strengthen the role of midluteal vmHRV increases as a physiological marker of emotional hormone sensitivity. Having such a marker available in clinical and research settings would be advantageous in several ways. First and foremost, atypical vmHRV cyclicity as a marker of hormone sensitivity would aid our efforts to understand and treat the underlying pathophysiology of menstrually related mood changes and disorders. In addition, we would have a *physiological* correlate of hormone sensitivity next to

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the marker based on self-report (i.e., presence of self-reported PMDD symptoms), which would also be more cost-effective and less burdensome to detect than other physiological correlates based on genetic testing (i.e., the COMT genotype [23]). Finally, vmHRV cyclicity can be detected *faster* and with *less patient burden* than having participants assessed for hormone sensitivity via daily self-report of emotional symptoms across at least two menstrual cycles (as is required for PMDD diagnosis). One ovulation-to-ovulation cycle of vmHRV assessment (e.g., via a watch or ring [41]) would suffice.

Limitations

The present study has several limitations. First, we recruited a community sample, which naturally results in *lower* base rates of emotional hormone sensitivity and cyclicity of negative affect than we would expect in a sample recruited for PMDD (i.e., a primary cyclical mood disorder caused by high levels of hormone sensitivity). However, it is worth mentioning that even in this non-clinical sample, we were able to observe significant cyclicity of negative affect (as indicated by significant linear and quadratic cycle day effects) and interindividual differences in emotional hormone sensitivity (as indicated by a significant random effect of linear cycle day). This goes back to emotional hormone sensitivity being understood as a continuum on which people differ. Confirming our sample's interindividual differences in emotional hormone sensitivity (Hypothesis 1) allowed us to then test the idea that interindividual differences in vmHRV changes might be associated with them (Hypothesis 2) – even in this non-clinical sample. Nonetheless, not only should this result be replicated in a larger community sample, but also in a PMDD sample. Second, only 31 participants were included in the analyses since 19 participants were not successfully scheduled in both the targeted ovulatory and midluteal cycle phases. This was mostly due to challenges of the ovulation tests used in the study. We chose a relatively low LH cutoff of 10 mIU/mL (while other commercially available ovulation tests have cutoffs of 40–70 mIU/mL; [29]) given that ovulation typically occurs 10–12 h after the LH peak [42]. Theoretically, detecting the LH *rise* (rather than its peak) and scheduling lab visits for the same or the following day should yield lab visits occurring during ovulation. However, the low LH cutoff increased the risk for false positives due to higher baseline LH levels. In addition, manually interpreting test results (without an electronic read-out device) lacked standardization, which, in retrospect, might have also led to incorrect results. Third, our sample was homogeneous regarding educational background and gender identity, and we did not collect any information on race and ethnicity, which

limits our ability to generalize the results with regard to these variables. Fourth, we did not investigate whether participants had consistent circadian mood fluctuations, but we instructed everyone to report their daily symptoms at night. However, if participants experienced such fluctuations that potentially vary among them, nighttime symptom reports might be biased for some. Future studies should assess interindividual differences in circadian mood fluctuations in the context of hormone sensitivity. Fifth, our ovulatory-to-midluteal vmHRV change index was not linear, as expected, and required the creation of artificial groups (increase, small decrease, large decrease) to test hypotheses about the associations of directional vmHRV change with emotional hormone sensitivity. In addition, this vmHRV change index was based on only two vmHRV assessments; future work should use wearable technologies to capture continuous daily vmHRV and evaluate its temporal relationships to hormones and emotional symptoms. Sixth, we only utilized a frequency-domain parameter for vmHRV despite studies recommending the combination of time- and frequency-domain analyses [27]. Combining these methods will reduce risk as they differ in the types of errors, they are most prone to. Finally, by assessing cardiac regulation through standard ECG only, the current study was limited to investigating cardiac *vagal* activity (i.e., vmHRV) across the menstrual cycle as a potential physiological marker of emotional hormone sensitivity but could not investigate cardiac *sympathetic* regulation in a similar manner. Future studies should explore this further.

Conclusion

To the best of our knowledge, this is the first report of vagally mediated heart rate variability (vmHRV) potentially serving as a physiological marker of mood sensitivity to the menstrual cycle. While most naturally cycling individuals show vmHRV decreases in the luteal phase of the menstrual cycle (compared to both the ovulatory and perimenstrual phases), we provide preliminary evidence that a substantial midluteal *increase* in vagally mediated vmHRV might be associated with greater negative affect premenstrually. Future studies should replicate this finding in clinical samples and investigate whether this midluteal vmHRV increase is an attempt to cope with increased negative emotions (i.e., compensatory) or plays a paradoxical role in symptom development (i.e., pathological). Either way, this atypical form of vmHRV cyclicity as a physiological marker of between-person differences in hormone sensitivity to the menstrual cycle would aid our understanding and treatment of menstrually related mood changes and disorders such as PMDD.

Abbreviations
E2   Estradiol

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vmHRV   Vagally mediated heart rate variability
LH   Luteinizing hormone
P4   Progesterone
PMDD   Premenstrual dysphoric disorder
PMS   Premenstrual syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-024-03273-y.

Supplementary Material 1.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty Heidelberg, University Hospital Heidelberg (protocol code S-322/2017; date of approval 07/03/2017). Written informed consent was obtained from all the participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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