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Physical and mental fatigue across the menstrual cycle in women with and without generalised anxiety disorder

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ABSTRACT

Subjective, disabling fatigue is a common complaint and a key feature of numerous medical conditions, and is a transdiagnostic feature of psychiatric disorders. Despite physical and mental fatigue being associated with functional impairment and reduced quality of life, little is understood about its underlying mechanisms or modulating factors. Women commonly experience exacerbation of other (non-fatigue related) psychiatric symptoms during the luteal phase of the menstrual cycle, and report greater fatigue prevalence compared to men. It is therefore plausible that subjective fatigue may similarly fluctuate across the menstrual cycle. Here we compared physical and mental fatigue in the early-follicular (lower ovarian hormones) and mid-luteal (higher ovarian hormones) phases of a single menstrual cycle, while controlling for sleep disruption, in women with (n = 18) and without (non-anxious; n = 20) generalised anxiety disorder (GAD). As expected, women with GAD reported greater physical and mental fatigue than healthy women. Further, although there were no changes in physical fatigue from the early-follicular to mid-luteal phases in both groups, mental fatigue in non-anxious women increased to levels equivalent to those experienced by their GAD counterparts in the mid-luteal phase. Although salivary levels of estradiol and progesterone increased from the early-follicular to mid-luteal phase, hormones did not significantly predict fatigue in either phase. These findings are consistent with the exacerbations of state anxiety and mood disturbance recognised to occur in the luteal phase of the menstrual cycle. We speculate that increased mental fatigue in the luteal phase may represent a vulnerable period for the development and maintenance of psychiatric disorders, potentially via compromised emotional regulation.

The subjective complaint of fatigue is defined as difficulty in initiating and completing voluntary physical or cognitive tasks (physical and mental fatigue, respectively; Chaudhuri and Behan, 2004) and may be prolonged (> 1 month), chronic (1-6 months) or medically unexplained and debilitating to the point of diagnosis (chronic fatigue syndrome; CFS) (Fatt et al., 2019). Such subjective fatigue is a key feature in numerous medical disorders, and a transdiagnostic feature of psychiatric disorders, such as depression and anxiety (Chaudhuri and Behan, 2004). When experienced for prolonged durations (greater than one month), fatigue is associated with functional impairment, reduced quality of life and is a common complaint in general practice (Hickie et al., 1995). Current treatments assume that fatigue is mediated by other disorder specific symptoms (e.g., mood, sleep disturbance); however, its underlying mechanisms are largely undetermined.

Compared to men, women report a greater prevalence of fatigue and CFS, and are up to twice as likely to experience psychiatric conditions that feature fatigue, such as generalised anxiety disorder (GAD) (McLean et al., 2011; Mens-Verhulst and Bensing, 1998; Nacul et al., 2011). One factor that may contribute to the high prevalence of fatigue in women is variability in sex hormones across the menstrual cycle. Indeed, investigations have revealed that other (non-fatigue) transdiagnostic psychiatric symptoms, such as state anxiety and mood disturbance, are exacerbated during the luteal phase of the menstrual cycle when the ovarian hormones estradiol and progesterone are either high (mid-luteal phase) or declining (pre-menstrual phase). This effect is observed amongst women with psychiatric disorders (Labad et al., 2005; Sigmon et al., 2000; Van Veen et al., 2009) and also in non-clinical samples (Gonda et al., 2008). Consistent with this pattern of symptom fluctuation, it may be expected that subjective fatigue, being a transdiagnostic symptom of numerous psychiatric disorders, would similarly fluctuate. However, menstrual cycle-related variability in fatigue has not been investigated either in non-clinical samples or in

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women with conditions associated with prolonged fatigue.

Understanding menstrual cycle-related fluctuations in fatigue is important in facilitating our understanding of factors that contribute to increased comorbidity, symptom severity and burden of illness in psychiatric disorders. This understanding could inform sex-specific models of psychiatric disorders and their treatment. The primary purpose of this study was to examine the association between menstrual cycle phase and changes in fatigue (mental and physical) in a clinical sample with prolonged fatigue versus a non-clinical sample. For this purpose, we selected non-anxious women and women with generalised anxiety disorder (GAD), a condition experienced for > 6-months that is characterized by pathological levels of fatigue, along with alterations in mood and anxiety (Tyrer and Baldwin, 2006). Using a within-person study design, we compared fatigue in both groups of women at points in the menstrual cycle when ovarian hormones are lower (early-follicular phase) and higher (mid-luteal phase). It was hypothesised that fatigue would be exacerbated in both groups of women during the mid-luteal phase, consistent with previous reports of fluctuations in other transdiagnostic psychiatric symptoms (reviewed in Li and Graham, 2017).

1. Material and methods

1.1. Participants

Participants were 18 women with generalised anxiety disorder (GAD) and 20 non-anxious women aged between 18 and 35 years, who had regular menstrual cycles (range of 25–35 days), did not have medically diagnosed fertility problems or endocrine disorders, had not used hormonal contraceptives, or been pregnant or breastfeeding within the last 3-months, and who did not meet diagnostic criteria for premenstrual dysphoric disorder (PMDD). Comorbidity between GAD and depression is common so to ensure generalisability of results, women from neither group were excluded if they reported significant depressive symptoms during either assessment. Participants were recruited through university advertisements and via a public online participation system and received course credit or $AUD50 reimbursement for participation. All participants were screened for GAD using the GAD-7 (Spitzer et al., 2006) and PMDD via a questionnaire devised by the authors based on DSM-V PMDD criteria. The GAD-7 was administered to provide an indication of probable group allocation with a score of 10 or more used as an indicator of probable GAD, however, the presence or absence of a GAD diagnosis was confirmed using the GAD module of the Structured Clinical Interview for DSM-IV(SCID; First et al., 2002).

1.2. Measures

Self-reported mental and physical fatigue were measured at each assessment using the Fatigue and Energy Scale (FES; Keech et al., 2015). The FES measures current physical and mental fatigue severity by requiring participants to '*rate how much of each symptom you are feeling right now*' on an 11-point scale (0 = None, 10 = Absolute maximum). It contains 6 items such as 'heaviness in the limbs', 'brain fog/cloudy' and 'drained of mental energy', and has good psychometric properties (see Keech et al., 2015). Physical and mental fatigue scores were calculated by averaging the 3-items within each subscale (mental and physical fatigue). Previous applications of the FES in patient groups with debilitating fatigue suggest resting (baseline) scores of five and above represent clinically significant levels of fatigue (Cvejic et al., 2017; Keech et al., 2015; Sandler et al., 2016). Disrupted sleep was assessed at each assessment using item three of the Patient Health Questionnaire-9, "Trouble falling or staying asleep, or sleeping too much" (PHQ-9; Kroenke et al. (2001)).

1.3. Saliva analysis and materials

A saliva sample was collected at each assessment session via passive drool method using saliva collection aids and 2 mL cryovials from Stratech Scientific. Saliva samples were immediately stored in −17 °C for the duration of participation (maximum 4-weeks) and then transported in a frozen state to storage in −30 °C, before being transported via cold chain storage for assay by Stratech Scientific. Estradiol and progesterone were measured using commercially available ELISA assays (Salimetrics, USA), according to the manufacturer's instructions. Test sensitivity for estradiol and progesterone were 5.0 pg/mL (18.355 pmol/L) (intra-assay % CV 5.3; inter-assay % CV 5.8) and 0.1 pg/mL (0.367 pmol/L) (intra-assay % CV 6.1; inter-assay % CV 6.5), respectively.

1.4. Procedure

This study was conducted with the understanding and written consent of each participant, and all procedures were carried out in accordance with the Declaration of Helsinki and approved by the UNSW Human Research Ethics Committee (approval number: HC17257). Data was collected from February to May 2018 in the context of a larger study investigating menstrual cycle effects on repetitive negative thinking in women with and without GAD. Data for the current study was collected from the second cohort of participants recruited for the larger study by including the FES in the online survey, which contained questionnaires assessing repetitive negative thinking and GAD symptoms, at the early-follicular and mid-luteal assessments. Participants responding to study advertisements completed an online prescreening survey that assessed eligibility to participate, collected demographic and menstrual cycle information, and screened for possible GAD diagnosis. Two assessment sessions were scheduled to occur within a single menstrual cycle. Each participant's ovulation date was predicted via self-report, and subsequently confirmed using luteinizing hormone tests, using protocols described in Blake et al. (2016), with the exception that menstrual cycle length was determined via self-report. Assessment sessions were scheduled to occur during the early follicular (10–14 days prior to ovulation) and mid-luteal phases (5–10 days after ovulation) using ovulation date as the point of reference. Test order was counterbalanced across participants so that half completed the first assessment during the early-follicular phase and the other half during the mid-luteal phase. Prior to the first assessment, participants visited the lab to collect the study materials, complete the SCID and received study instructions. Each assessment session was identical and consisted of collecting a saliva sample between 8 and 11 pm and, immediately after, completing the online survey.

1.5. Data analysis

A repeated-measures ANOVA with a between factor of group (GAD v non-anxious) and a within factor of phase (early-follicular v mid-luteal) was conducted to assess changes in disrupted sleep, estradiol and progesterone across the menstrual cycle. As disrupted sleep differed between GAD and non-anxious women, a disrupted sleep score was calculated by averaging the two PHQ-9 item 3 scores from each assessment to use as a covariate in subsequent analyses. Repeated-measures ANCOVAs were conducted to determine whether physical and mental fatigue changed from the early-follicular to mid-luteal phases for each group while controlling for sleep disturbance. Planned paired-samples *t*-tests were conducted for each group to further investigate changes in physical and mental fatigue between menstrual phases. To investigate the contribution of estradiol and progesterone in predicting mental and physical fatigue, separate hierarchical linear regressions for physical and mental fatigue were conducted for each menstrual cycle phase. Mean-centered estradiol, progesterone and group (dummy variables: Treatment = 1, Control = 0) were entered in stage one, and group x estradiol and group x progesterone were entered into stage two.

Table 1
Sample characteristics of women with GAD and non-anxious women.

		Women with GAD	Non-anxious women	*P* value
Age, mean (SD)		19.55 (3.86)	20.95 (5.27)	ns
Menstrual cycle length, mean (SD)		29.35 (2.11)	30.20 (2.61)	ns
Estradiol pg/mL, mean (SD)	Early-follicular	0.99 (0.38)	0.92 (0.15)	ns
	Mid-luteal	1.07 (0.34)	1.18 (0.53)	ns
Progesterone pg/mL, mean (SD)	Early-follicular	156.39 (112.54)	129.15 (89.95)	ns
	Mid-luteal	351.14 (233.04)	345.07 (297.15)	ns
Ethnic representation, n (%)		Asian – 7 (39)	Asian – 10 (50)	ns*
		Caucasian – 10 (56)	Caucasian – 8 (40)	
		Other – 1 (5)	Other – 2 (10)	
Marital status, n (%)		Never married – 17 (94)	Never married – 19 (95)	ns*
		Married – 0	Married – 1 (5)	
		Divorced/separated – 1 (6)	Divorced/separated -	
Education attainment, n (%)		High school – 17 (94)	High school – 15 (75)	ns*
		Diploma – 0	Diploma – 3 (15)	
		Bachelor's degree – 1 (6)	Bachelor's degree – 2 (10)	
GAD-7, mean (SD)		13.63 (3.27)	3.35 (2.7)	P < .0001
Sleep disturbance, mean (SD)		1.80 (1.11)	0.90 (0.79)	*P* = .005
PHQ-9, mean (SD)		15.36 (4.09)	4.86 (2.81)	P < .0001

Note: GAD-7 scores during participant screening. PHQ-9 scores during first assessment. ns = not significant. * = Fischer's exact test used.

2. Results

Demographic details, hormone levels at each assessment and anxiety symptom severity are summarized in Table 1. Women with, and without, GAD did not differ in age, ethnic representation, menstrual cycle length, or estradiol and progesterone level at each assessment time point. Women with GAD reported significantly greater GAD and depressive symptoms compared to non-anxious women (t = 10.70, p < .001, Cohen's d = 3.44 and t = 9.67, p < .001, Cohen's d = 2.24, respectively). Three women in the GAD group and one in the non-anxious group did not have a positive LH test. Of the remainder, the percentage of women with positive LH tests within two days of predicted ovulation date was 80% for both groups, and all were within 4 days, suggesting menstrual phases were identified accurately.

For the repeated-measure ANOVAs there was a significant effect of phase for estradiol (F(1, 32) = 8.27, p = .007, η^2 = 0.21) and progesterone (F(1,32) = 21.76, p < .001, η^2 = 0.40) indicating that both hormones increased from the early-follicular to mid-luteal phases as expected. Hormone results were largely consistent with other studies, although increases in progesterone were slightly exaggerated, potentially due to collecting samples in the evening rather than the morning (e.g., Martel et al., 2017). There was no main effect of group or group by phase interaction for either hormone, indicating that increases in estradiol and progesterone did not differ between groups (ps > 0.05). There was a significant main effect of group for disrupted sleep (F = 29.33, p < .001, η^2 = 0.18), whereby women with GAD reported greater sleep disruption compared to non-anxious women. The lack of an effect of phase or group by phase interaction indicated sleep disruption did not change across the menstrual cycle for either group (ps > 0.05).

Fig. 1a and b show average physical and mental fatigue scores, respectively, for each group in the early-follicular and mid-luteal phases. The ANCOVAs revealed a main effect of group for physical fatigue, whereby women with GAD reported worse physical fatigue averaged across phases (F(1, 35) = 14.41, p = .001, η^2 = 0.13, but no effect of phase or group by phase interaction (ps > 0.05), indicating physical fatigue did not change from the early-follicular to mid-luteal phase in either group. This was confirmed using paired-samples t-tests that found no change between phases in either group (ps > 0.05). In contrast, the ANCOVA for mental fatigue, in addition to a main effect of group (women with GAD reporting worse mental fatigue averaged across phases, F(1,35) = 4.83, p = .035, η^2 = 0.05) also found a group by phase interaction (F(1,36) = 4.91, p = .033, η^2 = 0.12). Paired-samples t-tests found that mental fatigue significantly increased from the early-follicular to mid-luteal phase in non-anxious women (t = −2.23, p = .038, Cohen's d = 0.50), but did not change in women with GAD (p > .05). Visual inspection of Fig. 1b indicates that mental fatigue in non-anxious women elevated to levels consistent with their GAD counterparts. This was confirmed by post-hoc t-tests using Bonferroni's correction, which found mental fatigue was significantly higher in the GAD group compared to the non-anxious group in the early-follicular phase (t = 5.14, p < .0001, Cohen's d = 1.67), but there was no difference in mental fatigue between the groups in the mid-luteal phase (p > .05). Disrupted sleep was not a significant covariate in either analysis (ps > 0.05) suggesting no association between disrupted sleep and either physical or mental fatigue.

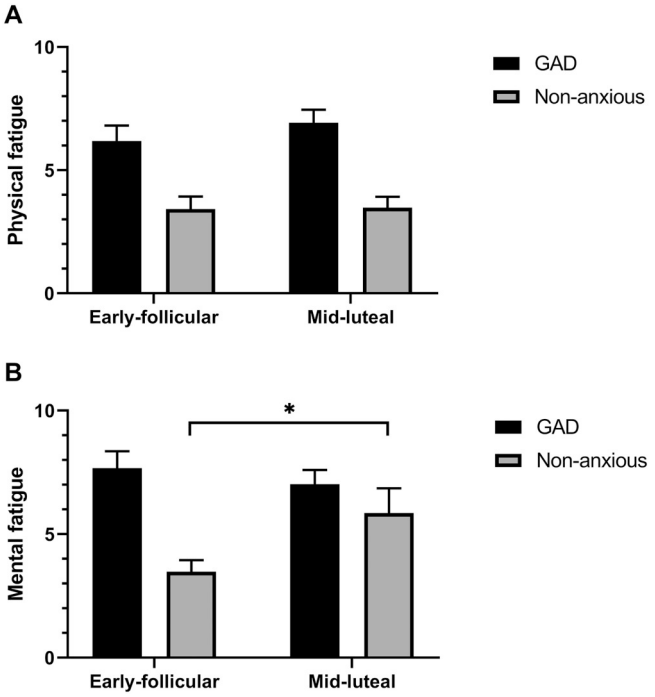

Fig. 1. Mean (± SEM) physical fatigue (A) and mental fatigue (B) scores for women with GAD and non-anxious women in the early-follicular and mid-luteal phases of the menstrual cycle (* significant difference).

Hierarchical linear regressions found that neither estradiol nor progesterone were significant predictors of physical or mental fatigue in the early-follicular or the mid-luteal phases of the menstrual cycle

Table 2
Linear regression model results using early-follicular and mid-luteal physical fatigue, and early-follicular and mid-luteal mental fatigue as the dependent variables.

Step	Variable	R^2	Δ R^2	B	SE B	β	t	p	95% CI
Prediction of physical fatigue in the early-follicular phase									
1	Estradiol	0.212	0.212	2.28	5.10	0.079	0.45	0.659	[−8.17, 12.72]
	Progesterone			−0.012	0.01	−0.15	−0.86	0.399	[−0.04, 0.02]
	Group*			7.80	2.86	0.47	2.73	0.011	[1.94, 13.66]
2	Estradiol	0.215	0.003	3.74	7.35	0.13	0.51	0.615	[−11.36, 18.85]
	Progesterone			−0.01	0.016	−0.15	−0.77	0.450	[−0.05, 0.02]
	Group*			7.92	3.00	0.48	2.64	0.014	[1.76, 14.08]
	Group × Estradiol			4.68	15.33	0.08	0.31	0.763	[−26.84, 36.20]
	Group × Progesterone			−0.004	0.03	−0.025	−0.13	0.900	[−0.07, 0.06]
Prediction of physical fatigue in the mid-luteal phase									
1	Estradiol	0.49	0.49	4.039	2.948	0.204	1.370	0.180	[−1.97, 10.04]
	Progesterone			−0.007	0.005	−0.221	−1.505	0.142	[−0.02, 0.00]
	Group*			11.800	2.167	0.707	5.447	0.000	[7.39, 16.21]
2	Estradiol	0.50	0.009	4.342	3.940	0.220	1.102	0.279	[−3.71, 12.39]
	Progesterone			−0.008	0.005	−0.244	−1.454	0.156	[−0.02, 0.00]
	Group*			11.884	2.312	0.712	5.139	0.000	[7.16, 16.61]
	Group × Estradiol			0.725	8.205	0.018	0.088	0.930	[−16.03, 17.48]
	Group × Progesterone			−0.007	0.011	−0.105	−0.619	0.541	[−0.03, 0.02]
Prediction of mental fatigue in the early-follicular phase									
1	Estradiol	0.42	0.42	−3.78	1.41	−0.11	−0.73	0.473	[−14.43, 6.86]
	Progesterone			0.002	0.02	0.02	0.13	0.897	[−0.03, 0.03]
	Group*			12.08	2.92	0.62	4.14	0.000	[6.10, 18.05]
2	Estradiol	0.43	0.02	−5.57	7.40	−0.16	−0.75	0.458	[−20.79, 9.64]
	Progesterone			−0.002	0.016	−0.017	−0.102	0.920	[−0.04, 0.03]
	Group*			11.969	3.019	0.613	3.964	0.001	[5.76, 18.18]
	Group × Estradiol			−7.855	15.448	−0.109	−0.508	0.615	[−39.61, 23.90]
	Group × Progesterone			0.025	0.031	0.129	0.784	0.440	[−0.04, 0.09]
Prediction of mental fatigue in the mid-luteal phase									
1	Estradiol	0.05	0.05	−0.283	5.342	−0.011	−0.053	0.958	[−11.17, 10.60]
	Progesterone			−0.004	0.008	−0.103	−0.515	0.610	[−0.02, 0.01]
	Group*			4.049	3.927	0.183	1.031	0.310	[−3.95, 12.05]
2	Estradiol	0.09	0.05	−0.542	7.021	−0.021	−0.077	0.939	[−14.88, 13.80]
	Progesterone			−0.006	0.009	−0.131	−0.584	0.564	[−0.03, 0.01]
	Group*			3.998	4.120	0.180	0.970	0.340	[−4.42, 12.41]
	Group × Estradiol			−1.634	14.620	−0.030	−0.112	0.912	[−31.49, 28.23]
	Group × Progesterone			−0.018	0.019	−0.205	−0.902	0.374	[−0.06, 0.02]

Note. *Significant variable.

(ps > 0.05; outcomes presented in Table 2). Consistent with the ANCOVA analyses, group was a predictor for physical fatigue in both the early-follicular and mid-luteal phases ($t = 2.73$, $p = .01$ and $t = 5.45$, $p < .0001$, respectively), and for mental fatigue in the early-follicular phase only ($t = 4.14$, $p < .0001$).

3. Discussion

Our study examined the association between menstrual cycle phase and mental and physical fatigue in women with prolonged, elevated fatigue (women with GAD) and non-anxious controls while controlling for sleep disruption. The results showed that physical fatigue was higher in women with GAD, and remained unchanged across the menstrual cycle for both groups. In contrast, while women with GAD reported high, unchanging levels of mental fatigue; non-anxious women reported an increase in mental fatigue to levels equivalent to their GAD counterparts in the mid-luteal phase (higher hormones, relative to the early-follicular phase). Elevation in mental fatigue to pathological levels in non-anxious women in the mid-luteal phase is concordant with the recognised sub-clinical exacerbations of state anxiety, depression and somatisation during the luteal phase of the menstrual cycle in non-clinical samples (Gonda et al., 2008). A lack of corresponding mid-luteal increases in mental fatigue in women with GAD may be due to a ceiling effect as the maximum score on the FES is 10, and women with GAD reported an average score of approximately eight. Indeed, the magnitude of mental fatigue reported by women with GAD in this study (measured under resting conditions) is higher than that reported by a sample of people with chronic fatigue syndrome following a fatigue exacerbation task in a previous study (Keech et al., 2015). Alternatively, the factors associated with fluctuations in fatigue may differ for healthy versus clinical populations, or the measure of fatigue may have mistakenly identified anxiety or depression in women with GAD (however, this seems unlikely given the FES-mental fatigue items: brain fog/cloudy; difficulties with memory of concentration; and drained of mental energy). Similarly, unchanging physical fatigue in both groups may reflect different modulating factors associated with mental and physical fatigue, however, the notion that distinct moderating features could exist for mental and physical fatigue requires further investigation.

The finding that mental fatigue was exacerbated to clinical levels in non-anxious women during the mid-luteal phase, when estradiol and progesterone levels were higher, raises the possibility that heightened ovarian hormone levels might in part contribute to increased mental fatigue. Although hormone levels were unrelated to mental fatigue within the early-follicular or the mid-luteal phases, this merely suggests that absolute levels of hormones (i.e., not taking into account relative levels of hormones across a cycle for a given woman) were unrelated to fatigue scores. It does not rule out the possibility that relative changes in these hormones across the cycle contribute, directly or indirectly, to changes in fatigue. For example, a potential mechanism by which ovarian hormones may indirectly moderate fatigue is via their effects on the hypothalamic-pituitary-adrenal (HPA) axis. HPA-axis

hyperactivity has been found in conditions characterized by pathological fatigue (for review see Kudielka and Kirschbaum (2005)) and has been associated with fatigue levels in people with multiple sclerosis, who experience debilitating fatigue (Gottschalk et al., 2005), suggesting an association between HPA-axis activity and fatigue severity (mental and physical fatigue were not differentiated in these studies). Since ovarian hormones, particularly estradiol, are associated with increased HPA-axis response following a stressor (Kudielka and Kirschbaum, 2005) it is possible that estradiol-elicited HPA-axis activity may be one mechanism influencing fatigue, although this possibility remains to be tested. Alternatively, it is possible that fluctuations in self-reported fatigue are indicative of menstrual-related fluctuations in the appraisal of fatigue, rather than the subjective experience of fatigue itself. For example, fatigue may be perceived to be more or less debilitating depending on menstrual cycle phase. However, it is unclear why appraisals of mental but not physical fatigue would vary across the menstrual cycle, and similarly, we did not find corresponding menstrual-related fluctuations in self-reported sleep disruption, which presumably would also be influenced by variations in appraisal. Regardless, this notion could be examined in future studies by assessing participant's appraisals of fatigue at each menstrual phase.

Mental fatigue has been found to impair emotion regulation (i.e., adaptive processes employed to influence emotions; Grillon et al. (2015)) and compromise higher order cognitive functioning (executive control; Van der Linden et al. (2003)). This raises the possibility that heightened mental fatigue during the mid-luteal phase could place women at heightened risk of emotion dysregulation and reduce control over perseverative and inflexible cognitions (e.g., repetitive negative thinking (see Ehring and Watkins (2008)). Such cognitive processes are characteristic of anxiety and depressive disorders, and indeed, it has been found that women with panic disorder use more maladaptive coping strategies, such as avoidance and rumination, which are associated with symptom exacerbation and maintenance, in the luteal phase (Sigmon et al., 2004). Similarly, we have found that non-anxious women show heightened rumination following a sad mood induction during periods of heightened estradiol (Graham et al., 2018). Therefore, we speculate that menstrual-cycle related shifts in mental fatigue, and its ensuing effect on the selection of coping strategies, could be one mechanism by which both healthy and clinical populations experience fluctuations in transdiagnostic psychiatric symptoms across the menstrual cycle. Future studies in which mental fatigue is experimentally manipulated are required to test this possibility.

It is possible that fluctuations in depressive symptoms across the menstrual cycle are responsible for the changes in mental fatigue found in non-anxious women. One limitation of the current study is that depressive symptoms were not measured at both assessments, preventing an examination of this possibility. However, we believe it is unlikely that the non-anxious group would have experienced significant fluctuations in depressive symptoms, and second, if the non-anxious women did experience menstrual-related fluctuations in depressive symptoms, it is unclear why this would influence mental, but not physical, fatigue. Another limitation of the current study was that a single item was used to measure sleep disturbance. Future studies could conduct a more thorough examination of sleep disturbance to confirm our finding that mental fatigue was not associated with the level of sleep disturbance.

Despite being a common complaint and a characteristic of numerous health disorders, little is understood about the mechanisms underlying subjective physical or mental fatigue, or the factors that are associated with its modulation. The results of this study suggest menstrual cycle phase is a biological factor associated with exacerbated mental but not physical fatigue in healthy women. Indeed, during the mid-luteal phase, non-anxious women reported levels of mental fatigue that were of a clinical magnitude and comparable to women with GAD, a condition that is associated with pathological, debilitating fatigue. Moreover, the interactive effects of mental fatigue exacerbation on cognitive coping strategies and psychiatric symptoms may be a promising area of future investigation in order to provide a more nuanced understanding of the phenomenon of menstrual-cycle related changes in anxiety and depression.

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Declaration of competing interest

None.

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