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Day-to-day co-variations of psychological and physical symptoms of the menstrual cycle: Insights to individual differences in steroid reactivity

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Summary The associations between physical and psychological symptoms of the menstrual cycle have not been carefully studied in past research, but may lead to a better understanding of the underlying mechanisms of these symptoms. The present study examines the day-to-day co-variations among physical and psychological symptoms of the menstrual cycle. These symptoms were evaluated on a daily basis across one entire menstrual cycle, with a non-clinical sample of 92 university students. Results showed that headaches, gastrointestinal problems, lower abdominal bloating, skin changes, and breast changes, were all significantly associated with higher levels of psychological symptoms; whereas back and joint pain, lower abdominal cramps, cervical mucous, and menstrual flow, were not associated with psychological symptoms. However, significant differences in these associations were observed across individuals for back and joint pain, headaches, lower abdominal cramps, skin changes, and menstrual flow: Whereas some women demonstrated higher levels of psychological symptoms associated with these physical symptoms, other women demonstrated lower levels of psychological symptoms. Finally, correlations among the associations between physical and psychological symptoms (slopes) demonstrated clear differences across the different physical symptoms. These results indicate that, although higher levels of *some* physical symptoms are associated with higher levels of psychological symptoms, there are significant differences in the *magnitude* and *direction* of these relations across individuals. Further consideration of physical symptoms may provide useful information for understanding individual differences in symptom profiles and response to steroid fluctuations, and for improving differential diagnosis and treatment planning and evaluation.

Higher prevalence rates of mood disorders among women, and an apparent link between mood disorders and events of the female reproductive cycle (e.g., menstrual cycle, post-partum, and menopause), have led scientists to study the associations between fluctuations in female reproductive

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steroids and psychological distress (e.g., Freeman, 2002). One important area of this research regards premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD, a severe form of PMS), which involve both psychological and physical symptoms that are temporally synchronous with the menstrual cycle (DSM-IV, American Psychiatric Association, 1994). Although PMS and PMDD are diagnostic entities with specific diagnostic criteria, the symptoms are not limited to women who meet these diagnostic criteria. For example, a recent review of the literature suggests that 50–80% of women of reproductive age experience at least a few premenstrual symptoms that range from mild to severe, that 13–18% may have premenstrual symptoms that create impairment and distress, and that 3–8% meet strict diagnostic criteria for premenstrual dysphoric disorder (PMDD; Halbreich et al., 2003). Although the causal mechanism of these problems is not understood, there is a general consensus that menstrual-cycle related symptoms have an hormonal etiology, and are the result of individual differences in *sensitivity* to normal serum levels of estrogen and progesterone, rather than abnormal levels of these steroids (Schmidt et al., 1998).

The study of menstrual-cycle related psychological changes would likely benefit from a more complete understanding of *all* symptoms of the menstrual cycle (e.g., physical and psychological), how these symptoms change across the cycle, and how these symptom changes co-vary with each other. For example, do the day-to-day changes in psychological symptoms correlate with the day-to-day changes in physical symptoms such as headaches and breast tenderness? A thorough study of these associations has never been conducted, and as a result, little remains known regarding the relevance of specific physical symptoms of the menstrual cycle in relation to psychological changes. In support of the relevance of physical symptoms for understanding psychological symptoms of the menstrual cycle, a recent study has demonstrated that significant associations exist between physical and psychological symptoms of the menstrual cycle (Kiesner, 2009).

The present study extends this research by examining how day-to-day variations in physical symptoms of the menstrual cycle co-vary with day-to-day variations in psychological symptoms, how these associations vary across individuals, and whether these associations are correlated among themselves. Because much of what has been learned about psychological symptoms of the menstrual cycle comes from research on PMS/PMDD, the following review of the literature will primarily consider research that has focused on these problems.

1. Physical symptoms of the menstrual cycle

The presence of physical symptoms throughout the menstrual cycle, and as part of PMS/PMDD, is widely recognized. For example, in one general population study (n = 1152), physical symptoms were the most common and severe of all DSM-IV symptoms of PMDD (Takeda et al., 2006). However, empirical research has generally not considered physical symptoms to be theoretically important for understanding the psychological symptoms of the menstrual cycle. For example, although physical symptoms are frequently assessed, these symptoms are rarely the central theoretical focus, and consideration of them is usually descriptive or diagnostic. Moreover, when physical symptoms are included, they are typically general in nature, or are grouped together into one single variable (e.g., Bloch et al., 1997; Freeman et al., 1985; Wittchen et al., 2002). Finally, although some research has examined specific physical symptoms of the menstrual cycle, including menstrual migraines (Martin, 2008) and dysmenorrhea (Dawood, 2006), research has failed to consider physical and psychological symptoms in a meaningfully integrated way. For example, do different physical symptoms show different types of associations with psychological symptoms? Thus, the data collected and analyses conducted have *not* focused on physical symptoms as theoretically important variables, and little remains known about the importance of these symptoms for understanding the psychological changes associated with the menstrual cycle.

An exception to this lack of integration of physical and psychological symptoms is a recent study by Kiesner (2009), who found that six physical symptoms (headaches, skin changes, gastrointestinal problems, breast changes, and coagulation and heaviness of menstrual bleeding) accounted for nearly 30% of the variance in premenstrual depressive symptoms, among a non-clinical sample of college-aged women. Thus, this previous research provides evidence that physical symptoms of the menstrual cycle may be theoretically important for understanding psychological symptoms of the menstrual cycle.

In addition to the lack of empirical research on the importance of physical symptoms, diagnostic criteria of PMDD also give little attention to physical symptoms. For example, although physical symptoms are included in DSM-IV criteria of PMDD, they are non-specific and are just one of the 11 items on the symptom list (listed as "other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of 'bloating,' weight gain", p. 717). As a result of these criteria, physical symptoms play a minimal role in diagnosis, which, considering the high levels of prevalence and severity of physical symptoms, may represent an under-recognition of their importance.

2. Tissue specificity of steroid effects

Because various physical symptoms are associated with different hormonal events affecting different tissues, understanding the specificity of the relations between physical and psychological symptoms may provide information on the endocrinological etiology of menstrual-cycle related psychological symptoms. Specific tissues that are affected by reproductive steroids include, for example, skin tissue (Hikima and Maibach, 2007; Oh and Smart, 1996), cervical/vaginal tissues (Gorodeski, 2000; Schmidt et al., 2002), breast tissue (Kimbro et al., 2008; Sunami et al., 2008), gastrointestinal tissue (Asarian and Geary, 2007; Di Leo et al., 2008), the endometrium (Ace and Okulicz, 1995), liver tissue (Grandien, 1996), and brain tissue (Bixo et al., 1997; Perlman et al., 2005).

The premise of the present study is that tissue-specific hormonal effects can be examined at a symptomatic level, and that examining the associations among specific physical and psychological symptoms will provide useful information regarding menstrual and premenstrual psychological difficulties. Because there are differences in which steroids affect each tissue, and at what point in the menstrual cycle different

tissues are affected, differential relations between physical and psychological symptoms may provide information on the underlying causes of the psychological symptoms.

3. Individual differences in response to steroid changes

Sensitivity to reproductive steroids varies across individuals as well as across tissues within individuals (see Rubinow and Schmidt, 2002, for a review and discussion of tissue and cellular specificity of gonadal steroid effects). For example, it is a common clinical observation that, whereas some women show improvement in PMS/PMDD symptoms with the use of oral contraceptives, other women experience the onset and/or a worsening of symptoms, with specific symptom profiles being heterogeneous across individuals (see Halbreich et al., 2006; Rapkin, 2003 for discussions). Idiosyncratic responses to other hormonal interventions have also been noted in treatment of PMS/PMDD. For example, in one study, including women with a diagnosis of PMS, the pharmacological suppression of ovarian activity resulted in symptom relief for half of the patients, but a worsening of symptoms for the other half (Schmidt et al., 1998). Those who had improved following ovarian suppression demonstrated a worsening of symptoms when hormones were pharmacologically reintroduced. However, women without PMS showed no changes in symptoms during ovarian suppression or hormonal replacement. Thus, some women respond positively, others negatively, and others show no change, to the same hormonal alterations. These individual differences are not understood.

4. Present study

Four main questions are addressed in this study. The first question is whether psychological and physical symptoms demonstrate systematic variations linked to the menstrual cycle in a non-clinical sample of college-aged women. These associations are tested using a general scale of psychological symptoms (including anxiety, depression, mood swings, and cognitive symptoms) and the following nine physical symptoms: back and joint pain, headaches, gastrointestinal problems, lower abdomen cramps, lower abdomen bloating, skin changes, breast changes, vaginal/cervical mucous, and menstrual flow and coagulation. Because changes in these symptoms should be expected across the menstrual-cycle, this question primarily addresses measurement validity. Differences in the strength of this association are expected across symptoms. Although the primary focus of this study will be on the general scale of psychological symptoms, these analyses will also be conducted separately for the four psychological symptom subscales.

The second question is whether the nine physical symptoms are associated with the general scale of psychological symptoms? That is to say, on average, across all subjects, are higher levels of each physical symptom associated with higher levels of psychological symptoms.

Third, are there significant differences across individuals in the associations between the physical symptoms and psychological symptoms? For example, do all individuals show similar associations between each physical symptom and psychological symptoms (e.g., higher levels of physical symptoms associated with higher levels of psychological symptoms), or are there individual differences in the magnitude and direction of these associations (e.g., some women show a positive association and other women a negative association)?

Fourth, are there correlations between mean level of psychological symptoms and the associations between the physical symptoms and psychological symptoms; and are there correlations between the associations between the physical and psychological symptoms? For example: Do women with a high average level of psychological symptoms tend to demonstrate a positive association between psychological symptoms and physical symptoms?; and Do women who show a positive association between psychological symptoms and breast changes tend also to demonstrate a positive association between psychological symptoms and lower abdominal cramps?

5. Methods

5.1. Participants

All first-year female undergraduate psychology students were given a general explanation of the study without providing information on specific variables or hypotheses. To minimize selection bias towards women with PMS symptoms, all potential participants were told that it was very important, for the success of the study, to include women both with and without menstrual difficulties. Individuals could not participate if they were using hormonal contraceptives or therapy, were pregnant, or not menstruating. Participants were asked to not participate, or to wait for a future cycle, if they were ill at the start of their next menstrual flow. However, it is possible that some participants experienced illness during the study. Participation was anonymous, voluntary, and did not result in compensation. The Ethics Committee of Psychological Research, of the University of Padova, approved this study.

Of the 98 women who initially agreed to participate, six did not complete the full study, resulting in a final sample of $n = 92$. The average age of these participants was $M = 20.80$ years ($SD = 3.71$). The six participants who did not complete the study provided various reasons for discontinuing their participation, including: use of oral contraceptives, lack of Internet access, and loss of interest in participation.

Research assistants met each participant individually to provide an explanation and demonstration of the on-line data collection procedure, to provide a password for access to the on-line questionnaire, and to review all questions and provide explanations when needed.

5.2. Measures

5.2.1. Online questionnaire and procedure

With the use of an individual password, participants had access to a 56-item online questionnaire. All scales and scale items used in the present study are presented in Appendix A. All questions referred to the last 24 h. Except for open ended questions (e.g., number of hygienic pad changes) all responses were given on a 5-point response scale ranging

from "*Not at all*" to "*Very much*". Participants were asked to begin completing questionnaires on the first day of their next menstrual flow, and to provide the specific date that their menstrual flow began.

Participants were asked to complete the on-line questionnaire each day for one entire menstrual cycle (i.e., from the first day of one menstruation to the first day of the following menstruation). When a questionnaire was skipped, that day was considered as missing data, and no imputation of missing data was conducted. Average cycle length was $M = 30$ days (range: 21—42 days), and the average number of questionnaires for each participant was $M = 27$ (range: 16—38). Thus, there was very little missing data. The total number of questionnaires completed across all participants was $N = 2483$. It should be noted that skipped days and different cycle length across participants does not present analytic problems for the analyses conducted.

The questionnaire used to assess psychological and physical symptoms was a modified version of a previously used menstrual-cycle symptom questionnaire (Kiesner, 2009). The items included in this questionnaire are based on DSM-IV symptoms of PMDD, other well recognized symptoms of the menstrual cycle not listed in the DSM-IV (e.g., skin changes, see Williams and Cunliffe, 1973; lower abdominal cramps, see Freeman et al., 1985), and symptoms of the menstrual cycle that are not typically considered in research (e.g., cervical mucous, coagulation in menstrual bleeding). Cervical mucous and coagulation in bleeding were included in this study because of possible links to hormonal changes (e.g., ovulation, build up and shedding of the endometrium). The format and response scale was similar to those used in other questionnaires on premenstrual symptoms (Freeman et al., 1996; Steiner et al., 2003). Empirical evidence for the validity of this questionnaire also comes from the present study (see Section 6).

5.2.2. Physical symptoms

The following nine physical symptoms were measured: "Back and Joint Pain", "Headaches", "Gastrointestinal Problems", "Lower Abdominal Cramps", "Lower Abdominal Bloating", "Skin Changes", "Breast Changes", "Vaginal/Cervical Mucous", "Menstrual Flow and Coagulation". All scale scores were either the mean of the relevant items, or simply the response to the single item. The exception was the score for menstrual flow and coagulation, which was coded as follows: if there was bleeding then menstrual flow and coagulation = mean of (1 + daytime pad changes + nighttime pad changes + coagulation in flow); if there was no bleeding then = 0.

5.2.3. Psychological symptoms

A general scale of psychological symptoms was composed of the following four subscales: "*Anxiety*", "*Depression*", "*Mood Swings*", and "*Cognitive*". These subscales represent the primary psychological components of PMDD in the DSM-IV. The general scale score was the mean of the four sub-scales.

5.2.4. Items not included in the present analyses

The on-line questionnaire included some items that are not analyzed in the present study. In some cases this was because the content of those questions was not directly relevant to these analyses (e.g., sexual interest and desire). Two questions that were not included, but deserve mention, regard upper abdominal cramps and bloating. Separate questions were asked regarding *upper* and *lower* abdominal cramps and bloating because it was expected that lower abdominal symptoms would be more strongly related to the menstrual cycle, and thus more relevant to this study. Preliminary analyses confirmed this, and thus upper abdominal cramps and bloating were not included in the present analyses.

5.3. Data analysis

Data analysis is divided into three sections. First, analyses tested for variations in physical and psychological symptoms across the menstrual cycle. To do this, the daily measures were recoded so that each individual's full menstrual cycle was divided into the following five segments of equal length: Early Follicular, Late Follicular, Mid-Cycle, Early Luteal, and Late Luteal. An average score was calculated for each symptom for each cycle phase. Because menstrual-cycle length varied across individuals, the number of days included in each menstrual-cycle phase also varied across individuals. This approach provides a meaningful division of the full cycle into separate phases, and provides a reliable estimate for each symptom within that phase. The first day of the second menstruation was maintained as a separate phase. Thus, a total of six phases are considered, extending from the menstruation of one cycle to the menstruation of a second cycle. Including the first day of the second menstruation completes the cycle by returning to the initial status of the first phase.

Repeated measures ANOVAs were then conducted treating psychological and physical symptoms as the dependent variables, and menstrual-cycle phase as the within subjects factor, testing specifically for a quadratic effect of menstrual-cycle phase (e.g., a curvilinear or U-shaped trend across time). Quadratic effects were tested because it was specifically hypothesized that all symptoms would follow a curvilinear trajectory across the course of the full cycle.

Regarding the division of the menstrual cycle, it should be noted that although past research has generally used hormonal assays to reliably establish the days of ovulation, variation exists across studies in how the menstrual cycle is divided. For example, some studies have divided the cycle into six phases (Rubinow et al., 1988) and others have divided the cycle into five phases (Schechter et al., 1989). Thus, although dividing the menstrual cycle into five phases is not unique, the present approach is limited by the fact that no hormonal assays were conducted, and thus lacks precision with regards to knowing the days of ovulation. For example, because the luteal phase is generally assumed to be approximately 14 days, regardless of cycle length (see Howards et al., 2009), individuals with long or short cycles may have ovulated during the second or fourth phase, rather than the third (mid-cycle) phase. To address this issue, we also tested for the effects of menstrual cycle phase after excluding those participants with short or long cycles. As will be seen in Section 6, the present analyses provide strong support for the validity of the current approach to dividing the menstrual cycle, in the absence of hormonal assays.

In the second set of analyses, the focus was on day-to-day variations and co-variations of symptoms rather than menstrual-cycle phase. Therefore, daily measures were used for these analyses rather than the cycle phases described above.

A Hierarchical Linear Model (HLM, Bryk and Raudenbush, 1992) was used to test for average effects of the physical symptoms, and for variations in intercepts and slopes, across individuals (see explanation in following paragraph). Hierarchical Linear Models are useful for analyzing data that have a hierarchical (nested) structure (Bryk and Raudenbush, 1992). In the present study, observations (each day, *Level-1*) are nested within individual subject (*Level-2*).

HLM analyses provide tests for average effects (also referred to as fixed effects) and individual differences in these effects (also referred to random effects). These different effects can be interpreted in the following way. The average or fixed effects are similar to normal multiple regression coefficients. Thus, what type of variation in the dependent variable can be expected with a change in each predictor, and is that association significant. With regards to individual differences in these effects, or random effects, there are two types. The first are referred to as random intercepts, and can be interpreted as mean level differences in the dependent variable across participants. Thus, one can think of each participant as a group within an ANOVA, and each individual (or group) has its own mean. The significance test for this effect tests whether the differences in average levels across individuals is significant (analogous to group differences in an ANOVA). Finally, the random slopes refer to individual differences in the associations between each of the physical symptoms (predictor variables) and psychological symptoms (the dependent variable). Specifically, this analysis estimates the association (slope) between each physical symptom and psychological symptoms, separately for each individual. The significance tests for these random slopes test whether differences exist in these slopes across individuals (e.g., do individuals differ from each other in the associations between physical and psychological symptoms?).

Finally, correlations among the intercepts and slopes were examined (i.e., correlations between the individuals' mean level of psychological symptoms and the individuals' slopes for each of the physical symptoms). In the HLM analyses described above, a separate regression line is estimated for each individual participant, including an individual mean level (intercept), and an individual slope for each physical symptom. In the present analyses we examine the correlations among these slopes and intercepts. For example, a correlation between the intercepts and the slopes for a specific physical symptom would indicate that individuals with a high average level of psychological symptoms (high intercept) also demonstrate a stronger association (slope) between psychological symptoms and that specific physical symptom. Similarly, a correlation between two slopes would indicate that individuals with a strong association between one physical symptom and psychological symptoms also demonstrate a strong association between a second physical symptom and psychological symptoms. This could be expected, for example, if two physical symptoms are caused by the same hormonal event.

To obtain a standardized solution for the HLM analysis, the psychological symptoms and all physical symptoms were standardized across the entire sample. The standardized physical symptom variables were also centered within each participant (subtracting the individual-level mean). The time variable was put on a scale ranging from −2 (first day of first menstruation) to +2 (first day of second menstruation), with the individuals' cycle midpoint set to 0.

Two important points should be made regarding the inclusion and interpretation of the time variable in the HLM analysis. First, it was important to include the time variable to statistically control for the expected U-shaped trend in psychological symptoms across the menstrual cycle. Doing so provides a conservative test of the effects of physical symptoms because they can be interpreted independently of a general menstrual-cycle effect on psychological symptoms. However, *individual* trajectories across time cannot be studied with only one month of individual data. For example, an individual may demonstrate a U-shaped trend in symptoms across one menstrual cycle that could be caused by other factors, and only coincidentally synchronized with that specific menstrual cycle. Therefore, the results regarding individual differences in trends across time are presented in Section 6, but they are not interpreted. Note, however, that this issue does *not* affect or limit any of the other analyses that are presented, and is only specific to *individual differences* in temporal trajectories across the menstrual cycle.

6. Results

6.1. Variability in physical and psychological symptoms across the menstrual cycle

Results from the repeated measures ANOVAs are presented in Fig. 1. As can be observed in the top left panel of this figure, a significant proportion of the variance in psychological symptoms was explained by the curvilinear (quadratic) effect of menstrual cycle phase $(\eta_p^2 = .46)$. Specifically, 46% of the variance in psychological symptoms was explained by a U-shaped trend across the menstrual cycle, with the lowest level of symptoms occurring during the mid-cycle phase. Similarly, all physical symptoms also showed a significant curvilinear trend across the menstrual cycle, although the proportion of variance explained varied a great deal across variables (see Fig. 1).

The above analyses were also conducted separately for the four psychological symptom subscales. All four symptoms demonstrated a significant curvilinear association with menstrual cycle phase: $F(1, 90) = 55.27$, $p < .001$, $\eta_p^2 = .38$, for anxiety; $F(1, 90) = 31.28$, $p < .001$, $\eta_p^2 = .26$, for depression; $F(1, 90) = 64.96$, $p < .001$, $\eta_p^2 = .42$, for mood swings; $F(1, 90) = 32.34$, $p < .001$, $\eta_p^2 = .26$, for cognitive symptoms. Thus, although differences appear to exist in the strength of this association across the different subscales, all four psychological symptoms showed a similar U-shaped trend across the menstrual cycle.

As noted in Section 5, the analyses presented in Fig. 1 were also conducted after excluding participants with short cycles (<24 days) or long cycles (>35 days). Eleven participants met these exclusionary criteria. There was no change in the variance explained (η_p^2) by the quadratic trend for lower abdominal cramps, breast changes, cervical mucous, and flow/coagulation. The changes observed for the remaining variables were very small, with the following results: $\eta_p^2 = .49$ for psychological symptoms, $\eta_p^2 = .27$ for headaches, $\eta_p^2 = .39$ for back and joint pain, $\eta_p^2 = .23$ for gastrointestinal problems, $\eta_p^2 = .68$ for lower abdominal bloating, $\eta_p^2 = .34$ for skin. Thus, the effect size was

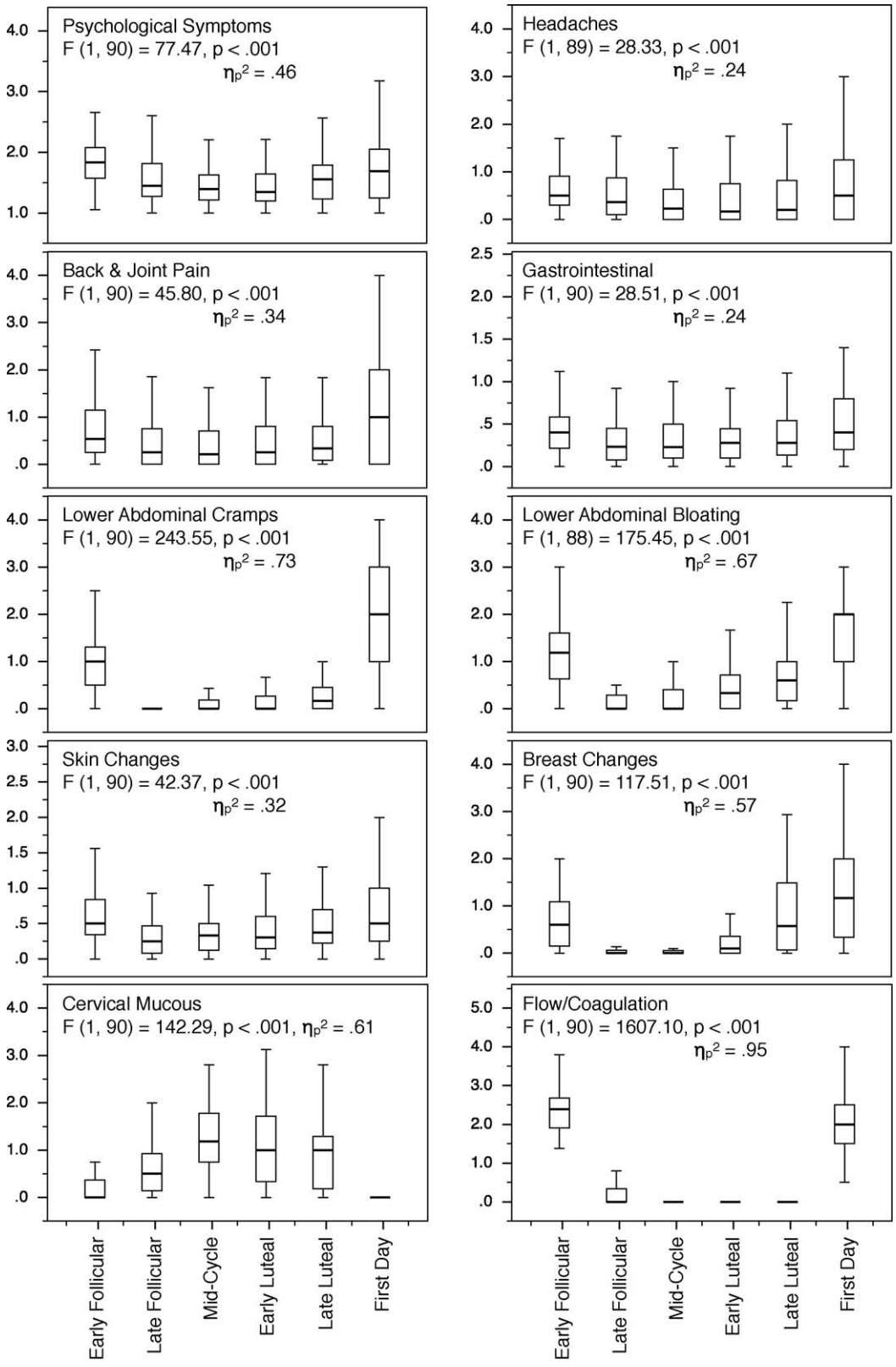

Figure 1 Box-plots presenting average symptom level for all variables during each menstrual-cycle phase (and first day of second cycle); and stattistical tests for repeated measures ANOVA's. All *F* tests and estimates of variance explained (η_p^2) are for the quadratic trends.

reduced only for gastrointestinal symptoms, but was a very small change (from 24% of the variance explained to 23% of the variance explained). Thus, these results were very robust even after excluding 11 participants with short or long cycles. Because anovulatory cycles are frequently associated with irregular cycles (see Norman et al., 2007), these analyses also minimize the plausibility of a bias created by anovulatory cycles.

Table 1 Coefficients and test statistics for the HLM model with random intercepts and slopes.

Predictor	β	Variance component	t $df = 91$	χ^2 $df = 81$
Fixed effects				
Intercept	−.08		−1.48	
Time	−.11		−4.08***	
Time^2	.07		2.78**	
Back and joint pain	.02		1.01	
Headache	.17		6.93***	
Gastrointestinal	.07		2.99**	
Cramps	.02		.88	
Bloating	.08		3.05**	
Skin changes	.10		3.29**	
Breast changes	.09		3.50***	
Cervical mucous	−.02		−.84	
Flow/coagulation	.01		.28	
Random effects				
Intercept		.22		148.67***
Time		.04		143.58***
Time^2		.02		82.25
Back and joint pain		.01		104.29*
Headache		.02		116.45**
Gastrointestinal		.01		75.12
Cramps		.02		103.63*
Bloating		.03		101.39†
Skin changes		.04		115.60**
Breast changes		.01		94.54
Cervical mucous		.01		73.13
Flow/coagulation		.05		121.75**
Residual		.43		

t-Tests for fixed effects are based on robust standard errors.
* $p < .05$.
** $p < .01$.
*** $p < .001$.
† $p = .06$

6.2. Hierarchical linear model

Results from the HLM model are presented in Table 1. Tests of significance for *average slopes* are presented in the top half of Table 1. These average effects can be interpreted similarly to results from a standard multiple regression. Both the linear and curvilinear (quadratic) effects of time were significant. The negative linear effect of time reflects the higher levels of psychological symptoms during the days of menstruation, which were concentrated at the beginning of the cycle. There is also a positive significant curvilinear slope, indicating a U-shaped trajectory of psychological symptoms over the course of the cycle, which is consistent with data presented in Fig. 1.

Five of the nine physical symptoms demonstrated significant associations with psychological symptoms. In all cases, higher levels of those physical symptoms were associated with higher levels of psychological symptoms. It should be noted that these "fixed" effects represent average slopes across individuals.

Significance tests for the random effects are presented in the bottom half of Table 1. These effects test for individual differences in the mean level of psychological symptoms, and in the associations between physical and psychological symptoms. Mean level differences (random intercepts) across individuals were significant, indicating that significant variability exists across individuals in their mean level of psychological symptoms. The linear effect of time demonstrated significant variability across individuals, whereas the curvilinear effect did not vary across individuals.

The associations between psychological symptoms and five of the nine physical symptoms showed significant variability across individual participants (random slopes, bottom half of Table 1). Specifically, individual differences were observed in the relations between psychological symptoms and (a) back and joint pain, (b) headaches, (c) lower abdominal cramps, (d) skin changes, and (e) menstrual flow/coagulation. On the other hand, there were no significant differences across individuals in the associations between psychological symptoms and (a) gastrointestinal problems, (b) breast changes, and (c) cervical mucous. The slopes for lower abdominal bloating showed close-to-significant variation across individuals ($p = .06$).

To graphically illustrate the differences across individuals in the associations between the psychological and physical symptoms, plots of individual slopes, for all physical symptoms, are presented in Fig. 2. Specifically, within each plot

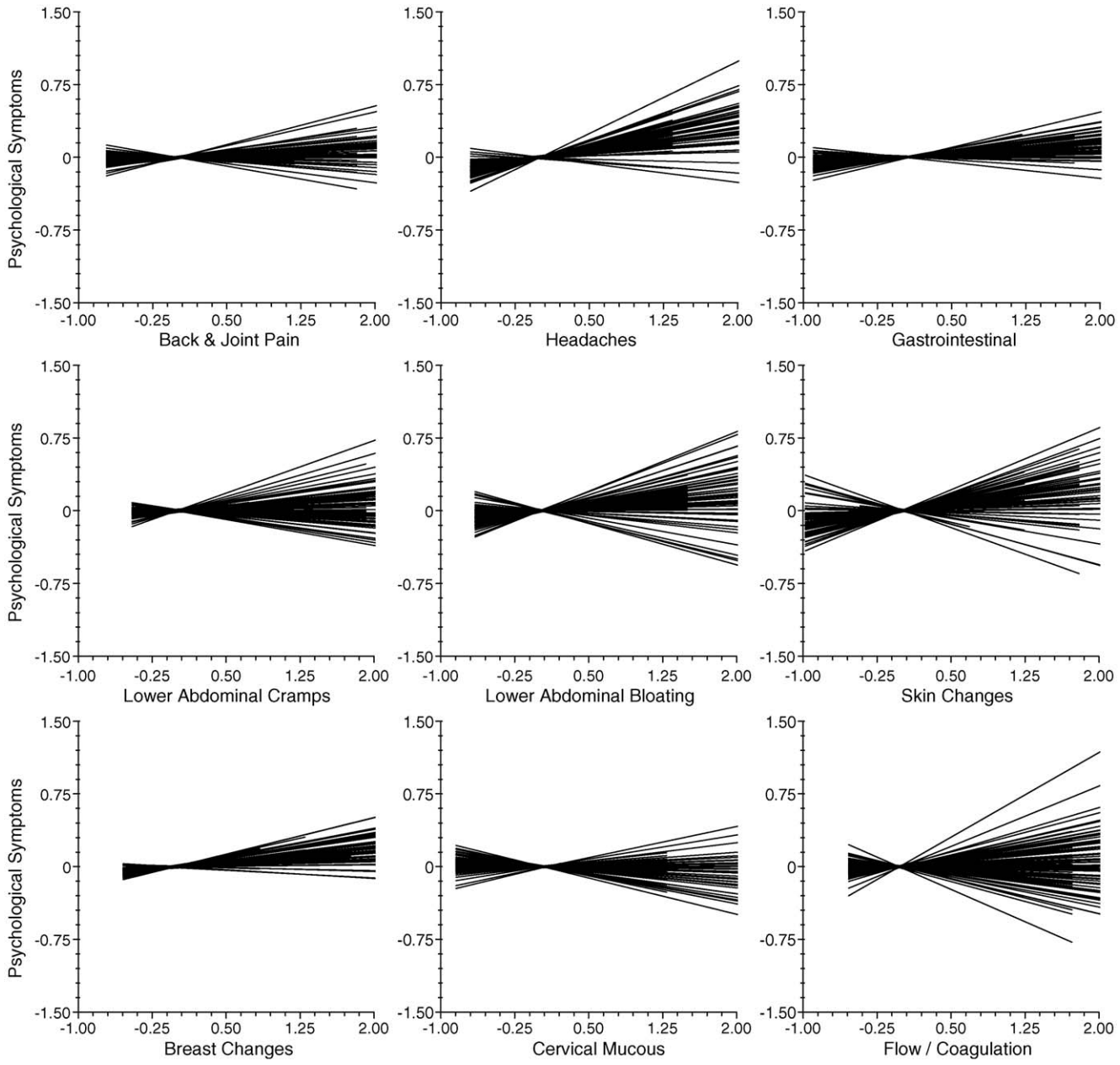

Figure 2 Random slopes for all physical symptoms. The psychological symptoms variable was centered within each individual (mean fixed to zero), thus removing mean level differences across individuals. This was done only for graphing purposes, and the distribution of slopes was invariant across the model used for the plots and the model presented in Table 1. The length of each line in these plots corresponds to the range for each participant on that predictor variable.

there is a separate line for each individual participant, and individual differences in these associations are illustrated by a fan-like effect of the lines. Thus, these plots present the variability across individuals in the relations between the psychological and physical symptoms—differences that are not easily perceived by reading the results in Table 1.

These plots illustrate the differences in these associations across individual participants as well as across the different physical symptoms. For example, for gastrointestinal symptoms and breast changes there is very little variation in the slopes across individuals, whereas for skin changes and flow/coagulation, there is a great deal of variability in the slopes. Moreover, for lower abdominal bloating, skin changes, and flow/coagulation, there is a wide range of slopes, including both positive and negative values; whereas, for headaches, the slopes are primarily positive. Overall, these results illustrate clear differences in average effects and individual slopes in the relations between psychological symptoms and the various physical symptoms.

6.3. Correlations among intercepts and slopes

The correlations between intercepts (mean individual level of psychological symptoms for each participant) and slopes (associations between the physical and psychological symptoms for each participant), are presented in Table 2. Because

Table 2 Correlations among intercepts (mean level for each participant) and slopes for all predictor variables.

	1	2	3	4	5	6	7	8	9	10	11	12
1. Intercept	—											
2. Time	−.07	—										
3. Time^2	.08	−.34**	—									
4. Back and joint	.05	−.56***	.65***	—								
5. Headaches	−.11	−.11	.06	−.40***	—							
6. Gastro	.06	.31**	−.39***	.01	−.58***	—						
7. Cramps	−.09	.19	−.15	−.21	−.47***	.38***	—					
8. Bloating	.11	−.62***	.21	.01	.59***	−.20	−.30**	—				
9. Skin	.01	−.07	−.15	−.11	.23*	.33**	−.39***	.47***	—			
10. Breast	.06	.29**	.19	.05	−.17	.17	−.37***	−.03	.55***	—		
11. Cervical mucous	−.16	−.33**	−.16	.13	−.19	.32**	−.20	.43***	.49***	.45***	—	
12. Flow/coagulation	−.29**	.65***	−.28*	−.17	−.14	.12	−.31**	−.66***	.19	.50***	−.09	—

	Number of correlations with all other variables			Number of correlations only with other physical symptoms								
Positive correlations	0	3	1	0	2	3	1	3	5	3	4	1
Negative correlations	1	4	3	1	3	1	5	2	1	1	0	2

$df = 81$ for significance tests.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

many of the correlations reach statistical significance, and many are relatively strong (13 are $|r| \geq .45$), we will highlight and discuss only the overall trends in these correlations. This is done considering the number of positive and negative correlations between the slopes and intercepts (see bottom of Table 2). For the intercepts and time variables, the number of significant correlations with all other slopes is presented. However, when considering the slopes for physical symptoms, only the number of significant correlations with the slopes of other physical symptoms is presented.

The correlations between the intercepts and all slopes are very weak, and overall do not suggest that high average levels of psychological symptoms are associated with steeper slopes for physical symptoms (the only exception was with menstrual flow).

With regards to the physical symptoms, several important differences among these correlations stand out. First, the slopes for back and joint pain are virtually uncorrelated with all other slopes. Thus, having a positive or negative slope for back and joint pain is not systematically associated with positive or negative slopes for the other variables. The only exception is for headaches: having a strong positive association between psychological symptoms and back and joint pain was associated with a weak association between psychological symptoms and headaches. Second, whereas the slopes for some variables showed a combination of positive and negative correlations (e.g., headaches, bloating), the slopes for other variables demonstrated a tendency to be either positively correlated with other slopes (skin changes, cervical mucous), or negatively correlated with other slopes (lower abdominal cramps).

6.4. Additional analyses

It has previously been found that coagulation in the menstrual flow, but not heaviness of the menstrual flow, was associated with premenstrual depressive symptoms (Kiesner, 2009). In the analyses presented above, however, these variables were combined into one variable. This was done because of the very high collinearity between these two variables when considered across the entire cycle (both variables could only be present during the days of menstrual bleeding). Therefore, an additional analysis was conducted testing for unique effects of these two variables, predicting psychological symptoms, focusing exclusively on the days of menstrual flow. In this analysis, across all participants, a total of 617 days of menstrual flow were considered. Results showed that, when controlling for mean level differences across participants (i.e., random intercepts), a significant effect was found for heaviness of menstrual flow ($F(1, 613.6) = 6.01$, $p = .015$) and a close-to-significant effect was found for coagulation in menstrual flow ($F(1, 613.9) = 3.39$, $p = .066$). Thus, although these results lead to a different conclusion than previous research, the more general conclusion that characteristics of menstrual bleeding are associated with psychological symptoms, is supported. This conclusion, however, must be interpreted in the context of the significant individual differences in the slopes of the flow/coagulation variable in the main analysis (Table 1).

7. Discussion

The main findings of the present study indicate that day-to-day fluctuations in physical symptoms of the menstrual cycle are significantly associated with day-to-day fluctuations in psychological symptoms, that these associations vary a great deal across physical symptoms and across individuals, and that the correlations among the associations between psychological and physical symptoms may provide a novel

approach for understanding the underlying mechanisms linking physical and psychological symptoms. Four specific sets of findings from this study, that lead to these general conclusions, will be addressed in the following section.

The first main finding was that all variables in this study were significantly determined by menstrual-cycle phase. Regarding the *physical symptoms*, these findings provide support for the validity of these measures as indirect indicators of fluctuations in reproductive steroids, and individual responsivity to these variations. As should be expected, large differences were observed in the strength of this association across the various physical symptoms. Regarding *psychological symptoms*, 46% of the variance in these symptoms was explained by the U-shaped curvilinear effect of menstrual-cycle phase. This is a very important finding because no research, to our knowledge, has ever quantified how much of the variance in psychological symptoms, among a non-clinical sample, can be attributed to the menstrual cycle.

The second set of findings regards the associations between physical and psychological symptoms. These associations were examined at the group level (average effect across all participants) as well as an individual-differences level. At a group level, the average association between psychological symptoms and five of the nine physical symptoms were significant, and positive, indicating that higher levels of those symptoms were associated with higher levels of psychological symptoms, controlling for the linear and curvilinear effects of time. These data support previous findings by Kiesner (2009), showing significant associations between physical and psychological symptoms.

The presence of these associations for some physical symptoms, but not all, is very important for interpretation. It was previously suggested that one explanation for the association between physical and psychological symptoms is that physical discomfort leads to psychological distress (Kiesner, 2009). If this *physical distress* hypothesis were true, it should be expected that physical symptoms associated with more severe physical discomfort (e.g., lower abdominal cramps) would be more strongly associated with psychological symptoms than physical symptoms that are associated with less severe physical discomfort (e.g., skin changes). Because this pattern of results was not found in the present study, the physical distress hypothesis was not supported.

It is particularly noteworthy that lower abdominal cramps showed no association with psychological symptoms (top half of Table 1). Lower abdominal cramps are among the most common physical symptoms associated with the menstrual cycle, they are generally associated with severe discomfort, and in the present study they were among the most strongly associated with menstrual-cycle phase (see Fig. 1). Nonetheless, they showed no average effect on psychological symptoms. One possible explanation is that this symptom is so common that the variable lacks variance. However, as can be observed in the box-plots in Fig. 1, lower abdominal cramps show a great deal of variability, and even during menstruation, the distribution was relatively symmetrical. Thus, this hypothesis does not seem plausible. Another possible explanation is that lower abdominal cramps are not the direct result of hormonal activity in local tissue, but are the result of local effects of prostaglandins and cytokines in the endometrium (this will be discussed below). This may differentiate lower abdominal cramps from other physical symptoms that may depend more specifically on local effects of reproductive hormones.

The third set of findings that support the general set of conclusions is that significant individual differences were observed in the associations between psychological and physical symptoms. For example, whereas some women showed higher levels of psychological symptoms associated with skin changes (positive slopes), others showed lower levels of psychological symptoms associated with skin changes (negative slopes). Two specific conclusions can be drawn from this finding. First, significant individual differences in the associations between psychological symptoms and physical symptoms are inconsistent with the *physical distress* hypothesis that was described above. Specifically, the *physical distress* hypothesis would predict that unpleasant physical symptoms would consistently lead to psychological distress, across individuals. Instead, the results showed that whereas some individuals demonstrated psychological distress associated with specific physical symptoms, others demonstrated lower levels of psychological symptoms associated with those same physical symptoms.

Second, by demonstrating individual differences in the associations between psychological symptoms and physical symptoms (physical symptoms that are caused by fluctuations in reproductive steroids), these results provide indirect support for the hypothesis that individual differences exist in *responsiveness* to changes in reproductive steroids (e.g., some women demonstrate a positive response and others a negative response). These results are consistent with past research suggesting that individual differences in response to fluctuations in reproductive steroids are the underlying cause of PMS (Schmidt et al., 1998). However, little is known about such individual differences and what contribution they make to menstrual-cycle related problems.

The fourth set of findings that support the general conclusions regards the correlations among the slopes. Clear differences in these correlations were observed across the different physical symptoms. For example, the slopes for back and joint pain were virtually uncorrelated with all other slopes, whereas the slopes for lower abdominal cramps demonstrated primarily negative correlations with the slopes of other physical symptoms, and the slopes for cervical mucous and skin changes demonstrated primarily positive correlations with the slopes of other physical symptoms. Consideration of how these slopes are differentially correlated with each other may provide insights to the underlying mechanisms linking these physical and psychological symptoms. For example, slopes for cervical mucous, bloating, and skin and breast changes, were consistently and positively correlated (5 of 6 correlations $> r = .43$), suggesting a common underlying cause linking each of these physical symptoms with psychological symptoms (e.g., direct effects of estrogen on local tissues). On the other hand, lower abdominal cramps, which showed negative correlations with other slopes, are believed to be caused by local variations of prostaglandins and cytokines in the endometrium (Kelly et al., 2001), which may then be indirectly related to psychological symptoms through, for example, afferent nerve stimulation to the brain (the relevance of cytokines is discussed in more detail below). Thus, the observed differences

in these correlations suggest that multiple processes may exist linking the different physical symptoms with psychological symptoms (e.g., direct effects of estrogen on local tissues and local effects of cytokines in the endometrium). However, why a positive slope for cramps would be associated with a negative slope for bloating, skin changes, breast changes, and menstrual flow, must be explained.

In previous work, Kiesner (2009) suggested two approaches to interpreting the associations between physical and psychological symptoms of the menstrual cycle. The first was the physical distress hypothesis. As described above, this hypothesis suggests that physical symptoms associated with more severe physical discomfort (e.g., lower abdominal cramps) should be more strongly associated with psychological symptoms than physical symptoms that are associated with less severe physical discomfort (e.g., skin changes). Given the pattern of associations observed in the present study, this hypothesis has not been supported.

The second approach is that physical symptoms are indices of sensitivity to reproductive steroids, and individuals who are physically sensitive are also neurologically sensitive. Thus, as with the physical symptoms, individual differences may exist in the neuroactive effects of these steroids (Dubrovsky, 2005). Moreover, metabolites of these steroids may also be involved. For example, neuroactive metabolites of progesterone and deoxycorticosterone are potent modulators of γ-aminobutyric acid (GABA) (Majewska et al., 1986), which is linked to depression (Hasler et al., 2007) and PMDD (Epperson et al., 2002).

The significant average effects for five of the physical symptoms are partially consistent with this *steroid sensitivity hypothesis*. However, two other findings suggest that the underlying causal mechanisms are more complicated. First, significant effects were not observed for all physical symptoms. Thus, that gastrointestinal problems and skin changes are associated with psychological symptoms, but back and joint pain and cervical mucous are not, is inconsistent with this explanation, and must be explained. Moreover, and possibly more important, are the individual differences in slopes (associations between psychological and physical symptoms). For some physical symptoms the range of slopes was large and included both positive and negative effects. This variability would not be predicted by a simple *steroid sensitivity hypothesis*. These data indicate that individual responsiveness to steroids should be considered both in terms of strength of effect (sensitivity) and direction of effect (valence). By considering these two individual-level parameters we will likely obtain a more complete understanding of menstrual-cycle related psychological changes (beneficial as well as deleterious).

A third mechanism that may contribute to the link between psychological and physical symptoms are proinflammatory cytokines. Cytokines are associated with physical and psychological symptoms that are termed "sickness behaviors" and include depression, muscle and joint pain, and fatigue (see Dantzer and Kelley, 2007). Cytokines are cyclically linked to the menstrual cycle through at least two mechanisms. First, changes in reproductive steroids result in differential up and down regulation of the two branches of the immune system, which may result in menstrually synchronous exacerbation of chronic infections alternating with up and down regulation of inflammatory processes (Doyle et al., 2007). Second, cytokines play a central role in regulation of the endometrial shedding during menstruation (Kelly et al., 2001). In support of the hypothesized relevance of proinflammatory cytokines, recent research has demonstrated that *highly sensitive C-reactive protein* (hs-CRP, a biomarker of inflammation) covaries with progesterone and estrogen, as well as with psychological and physical symptoms of the menstrual cycle (Puder et al., 2006). Also, in support of proinflammatory cytokine involvement in physical symptoms of the menstrual cycle, recent theorists have proposed that menstrual headaches are caused by inflammation of the trigeminovascular system (Mannix, 2008; Waeber and Moskowitz, 2005). Thus, because cytokines are known to induce sickness behaviors, and because they are linked to the menstrual cycle through at least two mechanisms, they may also provide insights for understanding fluctuations and covariations in physical and psychological symptoms of the menstrual cycle.

Finally, it is also possible that menstrual-cycle related symptoms result from various distinct mechanisms, or the combination of multiple mechanisms, and that individual differences exist in what mechanism, or set of mechanisms, is dominant for the observed symptom profile. Understanding and identifying these possible differences may help explain heterogeneity in clinical profiles and treatment response.

Four limitations of the present study should be noted. First, the sample is not large. Although the small sample size clearly did not present a problem with regards to statistical power, it does limit the generalizability of these results. Specifically, because 3—8% of women of reproductive age could be expected to meet diagnostic criteria for PMS/PMDD (Halbreich et al., 2003), with a sample of 92 we could not expect to have a large number of participants who would meet diagnostic criteria. Therefore the results from this study may not be specifically relevant for understanding PMS/PMDD etiology. However, the study of symptom variation and covariation in non-clinical samples, which include a full range of symptom severity, provides an important instrument for understanding the underlying processes linking the relevant symptoms. In fact, the specific research questions in the present study are optimally addressed with a non-clinical sample, which provides the best opportunity to capture the heterogeneity of these relations. Nonetheless, future research should apply similar assessment strategies using a larger sample that would allow the identification of a significant number of women with PMS/PMDD, thus allowing comparisons between cases and non-cases.

Second, the average age of this sample was relatively young, as compared to clinical samples of women with PMS or PMDD who typically participate in treatment studies. However, past research on community samples has not provided evidence for age differences in the prevalence of "menstrual-related problems" across the ages of 18—44 years old (Strine et al., 2005), or the prevalence of PMS/PMDD across the ages of 14—24 years old (Wittchen et al., 2002), or 20—49 years old (Takeda et al., 2006). Nonetheless, future research should consider a wider age range to test for age differences in the associations between physical and psychological symptoms.

Third, as noted in Section 5, efforts were taken to minimize selection bias towards women with PMS symptoms. Nonetheless, it is possible that selection occurred, either

in the direction of more symptomatic women or less symptomatic women. However, given the variability in symptoms and in the associations between physical and psychological symptoms, it is clear that this study captured the heterogeneity and variability in these associations that was the focus of the study. Thus, the results were clearly not biased by a homogeneous self-selected sample.

Fourth, the present study considered only one month of daily reports. Although this allowed valid tests of the research questions, many questions remain that will require a minimum of two months of daily questionnaires. For example, although in the present study a clear cyclical change in all symptoms was evident at the level of the full sample, individual trajectories linked to the menstrual cycle could not be examined without at least two months of individual data. As noted earlier, an individual may demonstrate a U-shaped trend in symptoms across one menstrual cycle that may be caused by other factors, and only coincidentally synchronized with that specific menstrual cycle. Thus, future research should extend measurement to include a minimum of two menstrual cycles. Note, however, that this limitation only applies to testing for individual differences in trends across time, and does not affect any of the conclusions presented in this paper.

The premise of this study was that research on menstrual-cycle related psychological changes would benefit from a more complete understanding of psychological *and* physical symptoms of the menstrual cycle, how these different symptoms change across the cycle, and how the changes in these symptoms co-vary with each other. The results demonstrated that day-to-day variations in physical symptoms of the menstrual cycle are significantly associated with day-to-day variations in psychological symptoms. However, these associations varied across the different physical symptoms, and across individuals. The differences across physical symptoms suggest that distinct causal mechanisms may link the different physical symptoms with psychological symptoms. The differences across individuals in these associations highlight the importance of understanding the idiosyncratic nature of individual response to changes in steroid hormones.

In conclusion, these results demonstrate that physical symptoms provide important information regarding individual differences in *response* to cyclical changes in reproductive steroids. Moreover, these findings suggest that the contribution of the menstrual cycle to changes in psychological symptoms, among a non-clinical sample of women, is substantial and must be more carefully examined and considered in all research considering psychological health of women.

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Conflict of interest

There are no conflicts of interest of any sort regarding the content of this report.

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Appendix A. Questionnaire scales and questions (all questions relative to the last 24 h)

Physical symptoms	
Back and joint pain	...did you have back pains? ...did you have joint pains?
Headaches	...did you have a headache? ...were you bothered by noise or light?
Gastrointestinal	...did you have gastrointestinal problems? ...did you have constipation? ...did you have more frequent bowel movements? ...did you have intestinal gas? ...did you have acidic or burning stomach?
Abdominal cramps	...did you have lower abdominal cramps?
Abdominal bloating	...did you have lower abdominal bloating?
Skin changes	...did you have changes in your sweat? ...did you have more acne? ...was your skin oily? ...was your skin dry?
Breast changes	...did you have changes in breast sensitivity? ...did you have breast swelling? ...did you have breast pain?
Cervical mucous	...did you have a clear vaginal mucous?

Appendix A (*Continued*)

Menstrual flow	...did you have any bleeding? (coded 0, 1) If yes, then ...how many times, during the day, did you need to change you pad? ...how many times, during the night, did you need to change your pad? ...did you have coagulation in your menstrual flow?
Psychological symptoms	
Anxiety	...did you feel anxious? ...did you feel tense or nervous?
Depression	...did you feel morally down? ...did you feel depressed? ...did you feel sad? ...did you have crying spells?
Mood swings	...did you feel like you lost control (e.g., an attack of anger)? ...were you irritable or easily upset? ...did you have mood swings?
Cognitive	...did you feel confused? ...did you have difficulty concentrating? ...were you forgetful? ...did you have difficulty making decisions? ...did you feel like your head was foggy?

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