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Effects of the menstrual cycle on mood, neurocognitive and neuroendocrine function in healthy premenopausal women

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ABSTRACT

Background. Neurocognitive functioning may be impaired in the luteal phase of the menstrual cycle due to associated changes in hypothalamic–pituitary–adrenal (HPA) axis function. This study examines the relationship between changes in neurocognition and HPA axis function in different phases of the menstrual cycle.

Method. Fifteen female volunteers, free from psychiatric history and hormonal medication were tested twice, during mid-follicular and late-luteal phases in a randomized, crossover design. Mood, neurocognitive function, and basal cortisol and dehydroepiandrosterone (DHEA) were profiled.

Results. Relative to the follicular phase, verbal fluency was impaired in the luteal phase and reaction times speeded on a continuous performance task, without affecting overall accuracy. 'Hedonic' scores on the UWIST-MACL scale were decreased in the luteal phase. There was also evidence of changes in the function of the HPA axis, with 24 h urinary cortisol concentrations and salivary DHEA levels being significantly lower during the luteal phase.

Conclusions. These data suggest that luteal phase HPA axis function is lower than in the follicular phase in premenopausal healthy women. This putative biological difference may be important for our understanding of the aetiopathogenesis of menstrually related mood change and neurocognitive disturbance.

INTRODUCTION

Many women experience changes in mood and cognition across the menstrual cycle (Frank, 1931). The increased use of oestrogen replacement therapies (ORT) in post-menopausal women has provided an opportunity to examine the effects of exogenous sex steroids on neurocognitive functions in humans. In a recent meta-analysis, Yaffe *et al.* (1998) concluded that oestrogen improves memory functions, but this may not be evident in asymptomatic subjects. LeBlanc *et al.* (2001) have reviewed the effects of ORT on specific neurocognitive domains and came to a similar conclusion, but suggested that the beneficial effects were specifically found on tests of verbal memory, vigilance, reasoning and motor speed.

The extrapolation between ORT in post-menopausal populations and the levels seen over the menstrual cycle in younger women may not be valid. An alternative approach has been to correlate directly endogenous fluctuations in hormone levels with cognitive task performance. Hausmann *et al.* (2000) reported decreased mental rotation performance during the mid-luteal phase. Changes in spatial ability correlated with sex hormone levels; testosterone having a positive effect and oestradiol a negative

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effect. A reduction in spatial working memory (WM) function in the luteal phase has been reported in women with premenstrual dysphoric disorder (PMDD) (Man *et al.* 1999) while increased verbal WM scores have been reported mid-cycle (Rosenberg & Park, 2002). Maki *et al.* (2002) found a dissociation in neurocognitive ability, with oestradiol levels being positively associated with verbal fluency and negatively associated with mental rotation and perceptual priming. However, such findings are not always consistent and it is unlikely that any single system would be entirely responsible for changes in cognition. For this reason, many researchers have sought other biological correlates of menstrual cycle-related cognitive change.

Elevated cortisol levels impair neurocognition in healthy subjects (Lupien *et al.* 1999; Young *et al.* 1999; de Quervain *et al.* 2000) and in conditions associated with a chronic elevation of endogenous cortisol levels, impairments are often reported (Starkman *et al.* 2001). Deficits are also found in MDD (Porter *et al.* 2003) and have been causally linked to hypercortisolaemia (van Londen *et al.* 1998). Importantly, patients with depression often exhibit an abnormal rhythm of cortisol secretion (Posener *et al.* 2000; Wong *et al.* 2000). As many women show depressive symptoms during the luteal phase, cyclical changes in cortisol levels may be causally related to changes in mood and cognition.

Odber *et al.* (1998) found that women who experienced slight physical and emotional premenstrual changes had significantly higher cortisol levels on pre- compared to post-menstrual days, whereas the opposite was true in women who were depressed pre-menstrually. Consistent changes in HPA axis function have been demonstrated using 'activating' challenges (Altemus *et al.* 1997; Kirschbaum *et al.* 1999). Attempts to relate directly changes in neurocognition across the menstrual cycle to changes in basal cortisol levels have been negative (McCormick & Teillon, 2001), however measurement of cortisol alone may provide an incomplete estimate of 'functional' hypercortisolism (Gallagher & Young, 2002; Young *et al.* 2002). A more precise assessment can be attained through the measurement of the ratio of cortisol to dehydroepiandrosterone (DHEA), an adrenal steroid with antiglucocorticoid properties (Kalimi *et al.* 1994). To our knowledge, no previous study has examined the cortisol-DHEA ratio in relation to cognition and mood across the menstrual cycle in healthy women.

The purpose of the present study was to assess neurocognitive functioning and basal HPA axis function, through the measurement of cortisol and DHEA, in follicular and luteal phases of the menstrual cycle in healthy premenopausal women. We predicted that HPA axis activity would be increased in the luteal phase, correlating with impaired neurocognitive functioning but not with mood effects.

METHOD

Subjects

Sixteen healthy female volunteers were recruited. Subjects had a mean age of 20·7 years (range, 18 to 25) and a mean IQ, estimated by the National Adult Reading Test (NART) (Nelson, 1982) of 114·5 points (range, 98 to 123). Mean BMI was 23·0 (range, 20 to 29·5). Subjects were interviewed regarding medical and psychiatric history and underwent physical examination. The psychiatric interview was semi-structured, based on DSM-IV criteria (American Psychiatric Association, 1994). All subjects were medication-free (including contraceptives) and had no current/past history of major medical illness, psychiatric illness (personally or in a first-degree relative) and a Beck Depression Inventory (BDI) score of <10. All were right-handed (Briggs & Nebes, 1975), not colour blind and had English as a first-language. The study received full approval from the local ethics committee and all subjects gave written informed consent.

Menstrual cycle history

Prospective menstrual cycle history was obtained using the Calendar of Premenstrual Experiences (CoPE) (Mortola *et al.* 1990). Subjects recorded length of menstruation, abnormal mid-cycle bleeding and length of cycle. The completed diaries were used to determine the dates of testing 8 ± 1 days after the start of menstruation (follicular phase) and 6 ± 1 days prior to onset of menstruation (luteal phase). Subjects with a CoPE score >10 were excluded. On day nine and on the last day of the cycle, subjects also completed a modified BDI (Keenan *et al.* 1992).

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Experimental design

A two-way crossover design was adopted, subjects being tested in follicular and luteal phases. Prior to testing, subjects were randomly allocated to one of two groups: one being tested in the follicular phase first and the other in the luteal phase first.

Neuroendocrine assessment

The day prior to testing, subjects were asked to collect a 24-h urine sample (total volume from midnight to midnight). Saliva samples were collected at 8 a.m. and 8 p.m. using salivettes (Sarstedt, Leicester, UK). Subjects were asked to refrain from eating, drinking or brushing their teeth 30 min prior to sampling.

Urinary cortisol analysis was performed on the 24 h samples without extraction using a cortisol solid-phase component system corti-cote (ICN Pharmaceuticals, California). The intra-assay coefficient of variance (CV) for the urinary cortisol assay was $\leqslant 9{\cdot}6\%$ across the quality control (QC) range. The sensitivity of the assay was 0·07 μg/dl. For salivary cortisol, the intra-assay CV for the assay was $\leqslant 12{\cdot}1\%$ across the assay range. The sensitivity of the assay was 0·07 μg/dl.

Salivary DHEA was analysed in two assays using standard radioimmunoassay techniques (Young *et al*. 2002). DHEA was extracted from saliva using hexane:ether (4:1) solvent. The intra-assay CV was $\leqslant 12{\cdot}3\%$ and inter-assay CV $\leqslant 9{\cdot}7\%$ across the QC range.

Self-rating mood scales

Prior to neurocognitive testing, the modified version of the BDI (Keenan *et al*. 1992) and the Altman Self-Rating Mania Scale (AMRS) (Altman *et al*. 1997) were administered to assess mood. The UWIST-MACL was also administered to assess arousal, stress and hedonia (Matthews *et al*. 1990).

Neurocognitive tests

Subjects were tested between 12.00 h and 16.00 h. Pen-and-paper tasks were administered according to standardized instructions (Lezak, 1995) and computerized tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) according to CANTAB manual protocols. A brief description of each test is given below.

Attention and executive function

Vigil Continuous Performance Test (Cegalis & Bowlin, 1991)

Over a period of 8 min, subjects are required to respond to the letter sequence of an 'A' followed by a 'K' and not to any other stimuli. Response latency and errors of omission and commissions are recorded.

Verbal fluency

Subjects are given a letter of the alphabet and are required to generate as many words as possible in 60 s according to a prescribed set of rules. The letters F, A and S were used on the first visit and T, R, W on the second.

Stroop Colour-Word Test (Stroop, 1935)

Trial 'C' requires subjects to read aloud a list of colour names in which none is printed in its matching colour. In the subsequent 'C–W' trial, subjects are required to name the colour of ink in which the colour names are printed. Total latency for each trial is recorded. The colour-word score is considered a measure of inhibitory control.

Trail Making Test

The first part of this test (Trails A) is primarily a visuomotor task. Trails B has an additional set-switching component (Spreen & Strauss, 1998). Total latency for each is recorded and a measure of 'shift' latency can be derived by subtracting total time to complete Trails B from Trails A.

Spatial Working Memory (*CANTAB*)

In this self-ordered search task, subjects search through an increasing number of boxes for a hidden token, without returning to a box which has already contained a token. Between- and within-search errors at levels 4, 6 and 8 are recorded. A strategy score is computed, with higher scores indicate less use of the strategy.

Verbal learning and memory

Rey-Auditory Verbal Learning Test

The test consists of two lists of 15 semantically and phonetically unrelated common, concrete nouns. List A is read to the subject five times in total, with a period of free recall after each presentation, providing a measure of immediate

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memory span (i.e. recall of the first list; List A1) and an overall learning index (List A1 to A5). A second list (List B) is then read out and the subject must then recall these new words, followed by recall of List A without further presentation of the words (List A6). After a 30 min delay, the subject is again asked to recall List A (List A7). On the second visit, alternate word lists were used (Lezak, 1995).

Visuospatial learning and memory

Pattern Recognition (*CANTAB*)

In this test of visual recognition memory subjects are required to identify from pairs of patterns the one that they recognize from a previous presentation sequence. Total percentage correct and response latency are recorded. An alternate set of patterns was used on visit 2.

Spatial Recognition (*CANTAB*)

In this test of spatial recognition memory, subjects must identify from a pair of boxes the one which is in the same location as one of those in a previous presentation sequence. Total percentage correct and response latency are recorded. Alternative presentation sequences were used on visit 2.

Spatial Span (*CANTAB*)

Subjects are presented with a screen containing irregularly placed squares that change colour in a particular order. Subjects must replicate the sequence in which the squares changed colour, up to a maximum of nine squares. The test terminates after the subject fails to recall three successive trials at a particular level.

Statistical analysis

Data were analysed using the Statistical Package for Social Science version 9 (SPSS, 1998). In order to ensure the data fulfilled the assumptions of the analysis of variance, the Kolmogorov–Smirnov test was used to verify normality of distribution, and Levene's test for homogeneity of variance. Where violations occurred, logarithmic transformations were applied. If data continued to violate test assumptions, the parametric analysis was confirmed using Wilcoxon ranked signs test.

Data were analysed using a repeated-measures ANOVA, with 'group' (i.e. the order in which the tests were administered) as a between subject factor. Menstrual cycle phase was used as a within subject factor, as well as difficulty 'level' or 'time' as appropriate. Within-subject degrees of freedom were corrected using the Huynh–Feldt epsilon and the adjusted P values are reported, although the original degrees of freedom are reported for clarity. For significant main effects, the mean or median difference between phases and the 95% confidence interval of the difference (95% CI) was calculated (Altman *et al.* 2000). Correlations were performed using Spearman's method.

RESULTS

Sixteen subjects were recruited, however one subject did not complete the whole study. Results are reported from the remaining 15.

Group allocation

There was no significant difference in age ($t=1{\cdot}04$, df$=13$, $P=0{\cdot}32$), NART score ($t=0{\cdot}78$, df$=13$, $P=0{\cdot}45$), BMI ($t=0{\cdot}75$, df$=13$, $P=0{\cdot}47$) or length of menstrual cycle ($t=0{\cdot}74$, df$=13$, $P=0{\cdot}47$) between subjects tested in the follicular phase first and those tested in the luteal phase first.

Neuroendocrine assessment

All neuroendocrine data are presented in Table 1.

Urinary cortisol (*see Fig.* 1)

A significant difference in 24 h urinary cortisol was detected, with levels being significantly lower in the luteal phase than the follicular phase ($F=6{\cdot}91$, df$=1,13$, $P=0{\cdot}021$). There was no main effect of group or interaction ($P>0{\cdot}4$).

Salivary cortisol

There was no significant main effect of phase on salivary cortisol levels ($F=0{\cdot}38$, df$=1,13$, $P=0{\cdot}55$), however a significant effect of time was observed ($F=153{\cdot}1$, df$=1,13$, $P<0{\cdot}0001$) with levels being lower at 20.00 h. There were no significant effects of group or other interactions ($P>0{\cdot}09$).

Salivary DHEA

A significant effect of phase was observed ($F=8{\cdot}07$, df$=1,12$, $P=0{\cdot}015$) with DHEA levels

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Table 1. *Mean* (±S.D.) *neuroendocrine measures and mood ratings in follicular and luteal phases* (*untransformed data are presented*; *see text for statistics*)

	Follicular		Luteal	
	Mean	(S.D.)	Mean	(S.D.)
24 h urinary cortisol (nmol)*	299·7	(181·6)	225·7	(112·7)
Cortisol (nmol/l)				
8 a.m.	23·4	(12·8)	22·9	(12·1)
8 p.m.	3·5	(2·8)	3·8	(6·1)
DHEA (nmol/l)†				
8 a.m.	5·4	(2·8)	4·3	(1·5)
8 p.m.	3·8	(1·3)	3·6	(1·6)
Cortisol-DHEA ratio				
8 a.m.	4·8	(2·7)	6·0	(3·2)
8 p.m.	0·9	(0·7)	0·9	(1·2)
BDI	1·9	(2·5)	2·9	(2·6)
AMRS	2·3	(1·5)	1·9	(1·9)
UWIST-MACL				
Stress	15·5	(4·2)	16·9	(4·6)
Arousal	21·7	(4·6)	21·3	(4·3)
Hedonia‡	26·9	(3·7)	24·1	(5·0)

* Mean difference (log transformed data) = 0·262, 95% CI = 0·055 to 0·469, $P = 0·021$.

† Mean difference of ANOVA main effect (log transformed data) = 0·151, 95% CI = 0·050 to 0·253, $P = 0·016$.

‡ Median difference (Wilcoxon method) = 3, 95% CI = 0 to 6, $P = 0·034$.

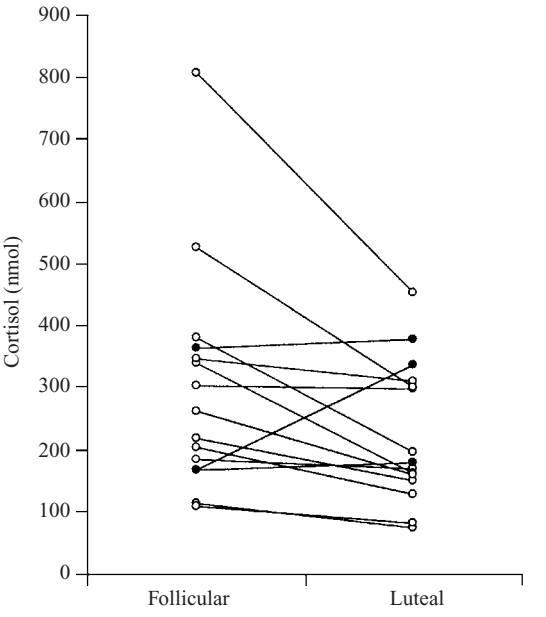

FIG. 1. Twenty-four hour urinary cortisol for each subject in follicular and luteal phases of the menstrual cycle. (○, Subjects demonstrating a decrease in cortisol levels in the luteal phase ($N = 12/15$; 80%); ●, subjects demonstrating an increase ($N = 3/15$; 20%). Mean difference = 74·03 nmol; 95% CI = 5·54 to 142·52.)

being lower in the luteal phase. An effect of time was also found, with DHEA levels being lower at 20.00 h ($F = 7·94$, df = 1,12, $P = 0·016$). No other main effects or interactions were present ($P > 0·1$).

Molar cortisol–DHEA ratio

The cortisol–DHEA ratio also exhibited significant diurnal variation, being lower at 20.00 h ($F = 146·1$, df = 1,12, $P < 0·0001$), however there was no effect of phase ($F = 0·15$, df = 1,13, $P = 0·70$). No other main effects or interactions were present ($P > 0·15$).

Mood ratings

The data are presented in Table 1. There was no significant difference in BDI scores (Wilcoxon $z = 1·86$, $P = 0·063$) or AMRS scores ($z = 1·10$, $P = 0·27$) across phases of the menstrual cycle. On the UWIST-MACL, there was no significant effect of phase on the stress ($z = 1·42$, $P = 0·16$) or arousal ($z = 0·39$, $P = 0·69$) subscales, however hedonic scores were significantly lower in the luteal phase ($z = 2·12$, $P = 0·034$).

Neurocognitive tests (Table 2)

Attention and executive function

Vigil Continuous Performance Test

A significant phase effect was observed for response latency, with response times being significantly faster in the luteal phase ($F = 10·47$, df = 1,13, $P = 0·007$) (see Fig. 2). A main effect of time was also observed, with response times being faster in the first quarter of the test and gradually slowing over time ($F = 3·59$, df = 3,39, $P = 0·022$). No other effects of group or interactions were found.

Because of the low occurrence of errors, errors of omission and commission were collapsed across the four time quarters of the test and the total error rate analysed. There was no significant effect of phase on the number of omissions ($F = 0·25$, df = 1,13, $P = 0·63$) or commissions ($F = 0·90$, df = 1,13, $P = 0·36$) and no significant phase by group interactions ($P > 0·08$). A significant group effect was also observed for omissions, with the group who were tested in the follicular phase first making significantly more errors ($F = 5·71$, df = 1,13, $P = 0·033$).

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Table 2. *Mean (±S.D.) outcome measures for all neurocognitive tests*

	Follicular		Luteal	
	Mean	(S.D.)	Mean	(S.D.)
Vigil CPT				
Total omissions	4·5	(9·0)	2·1	(3·0)
Total commissions	2·5	(3·5)	3·2	(4·3)
Average latency (ms)	355·3	(47·9)	329·2	(52·3)
Verbal Fluency				
Correct	44·2	(8·6)	40·5	(7·4)
Stroop				
Form 'C' latency (s)	53·5	(9·8)	55·5	(10·2)
Form 'CW' latency (s)	106·1	(13·8)	104·1	(13·9)
Trail Making Test				
Part 'A' latency (s)	25·8	(5·9)	26·9	(5·6)
Part 'B' latency (s)	47·1	(6·2)	50·3	(11·5)
Shift index (B−A)	21·3	(8·2)	23·4	(10·1)
Spatial Working Memory				
Between search errors	15·0	(10·0)	12·7	(11·7)
Within search errors	2·1	(5·1)	1·6	(5·1)
Strategy score	28·7	(5·3)	27·1	(6·2)
Rey-AVLT				
List 1 correct	9·1	(1·9)	9·1	(1·8)
Total (1 to 5) correct	61·3	(6·6)	63·3	(4·4)
List B correct	8·9	(1·8)	8·1	(1·6)
List 6 correct	12·8	(1·7)	13·6	(1·2)
List 7 correct	13·5	(1·5)	13·1	(1·8)
Pattern Recognition				
Correct (%)	96·4	(4·7)	95·8	(5·7)
Latency (ms)	1701·1	(248·3)	1608·6	(292·0)
Spatial Recognition				
Correct (%)	83·3	(15·3)	82·3	(11·0)
Latency (ms)	1748·6	(539·3)	1695·1	(431·5)
Spatial Span				
Total span	6·9	(1·2)	7·4	(1·1)

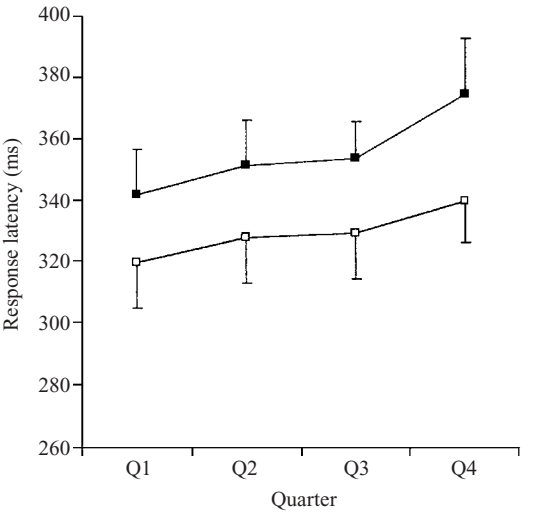

FIG. 2. Mean (±S.E.M.) Vigil reaction times for follicular (■) and luteal (□) phases across the four quarters of the test.

Verbal Fluency

A significant effect of phase was observed in the number of words correct, with lower scores in the luteal phase ($F=6·94$, df = 1,13, $P=0·021$). There was no main effect of group and no group by phase interaction ($P>0·1$).

Stroop Colour-Word Test

There was no significant main effect of phase on the total time to complete form C ($F=1·44$, df = 1,13, $P=0·25$), no effect of group and no interaction ($P>0·8$). For form CW, again there was no effect of phase ($F=0·74$, df = 1,13, $P=0·41$), however a phase by group interaction was observed ($F=6·91$, df = 1,13, $P=0·021$) suggestive of a learning or practice effect on the second administration. There was no main effect of group ($P>0·25$).

Trail Making Test

There was no significant main effect of phase on the total time to complete trails A ($F=0·37$, df = 1,13, $P=0·56$) or trails B ($F=1·16$, df = 1,13, $P=0·30$), and no effect of group or interaction ($P>0·28$). There was also no effect of phase on the derived 'shift' latency and no effect of group or interaction ($P>0·8$).

Spatial Working Memory

There was no significant effect of phase for the number of between search errors committed on levels 4 to 8 of the test ($F=1·17$, df = 1,13, $P=0·30$). As expected, a significant effect of level was observed, with the number of errors increasing with increasing problem complexity ($F=22·4$, df = 2,26, $P<0·0001$). There were no main effects of group or phase by group interactions ($P>0·4$).

Because of the number of subjects who did not make within search errors on the easier levels of the SWM test, the total within search error rate was calculated, however there was no significant effect of phase (Wilcoxon $z=1·12$, $P=0·26$). For the strategy score, there was no main effect of phase ($F=3·41$, df = 1,13, $P=0·09$), no phase by group interaction ($F=3·41$, df = 1,13, $P=0·09$) and no effect of group ($P>0·8$).

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Verbal learning and memory

Rey-Auditory Verbal Learning Test

There were no main effects of phase on immediate word span ($F=0{\cdot}01$, df=1,13, $P=0{\cdot}91$), total word recall ($F=1{\cdot}40$, df=1,13, $P=0{\cdot}26$), recall of the distractor list ($F=1{\cdot}94$, df=1,13, $P=0{\cdot}19$), list A6 recall ($F=3{\cdot}99$, df=1,13, $P=0{\cdot}07$) or list A7 delayed recall ($F=0{\cdot}57$, df=1,13, $P=0{\cdot}47$). No main effects of group or interactions were present for any measure ($P>0{\cdot}18$).

Visuospatial learning and memory

Pattern Recognition

There was no significant main effect of phase on the percentage correct ($F=0{\cdot}23$, df=1,13, $P=0{\cdot}64$) and the effect on response latency did not reach statistical significance ($F=4{\cdot}00$, df=1,13, $P=0{\cdot}067$). A phase by group interaction was present in latencies ($F=6{\cdot}88$, df=1,13, $P=0{\cdot}021$); subjects who were tested second in their luteal phase being significantly faster on that visit ($t=2{\cdot}92$, df=7, $P=0{\cdot}022$). No other significant effects were found ($P>0{\cdot}15$).

Spatial Recognition

There was no significant main effect of phase on the percentage correct ($F=0{\cdot}02$, df=1,13, $P=0{\cdot}90$) or response latency ($F=0{\cdot}25$, df=1,13, $P=0{\cdot}63$). No significant main effects of group or interactions were found ($P>0{\cdot}1$ for all).

Spatial Span

There was no significant effect of phase on total span ($F=3{\cdot}03$, df=1,13, $P=0{\cdot}11$) and no effect of group or interaction ($P>0{\cdot}1$).

Exploratory data analyses

Correlations between neuroendocrine and neurocognitive function

Twenty-four hour urinary cortisol during the follicular phase correlated negatively with Trails B reaction time ($r_s=-0{\cdot}595$, $P=0{\cdot}019$) and positively with spatial WM strategy scores ($r_s=0{\cdot}534$, $P=0{\cdot}041$). During the luteal phase there was a negative correlation between 24 h cortisol and Rey-AVLT list 6 ($r_s=-0{\cdot}526$, $P=0{\cdot}044$).

Correlations between mood and neurocognitive function

AMRS scores

Follicular phase scores correlated negatively with several indices of verbal learning: Rey-AVLT list A1 recall ($r_s=-0{\cdot}732$, $P=0{\cdot}002$), total words recalled ($r_s=-0{\cdot}764$, $P=0{\cdot}001$), list A6 recall ($r_s=-0{\cdot}612$, $P=0{\cdot}015$), and Stroop 'C' reaction time ($r_s=-0{\cdot}646$, $P=0{\cdot}009$) and Vigil reaction time ($r_s=-0{\cdot}566$, $P=0{\cdot}028$).

Luteal phase scores correlated with Vigil reaction time only ($r_s=-0{\cdot}559$, $P=0{\cdot}030$).

BDI scores

Follicular phase scores correlated with Rey-AVLT list 7 delayed recall only ($r_s=0{\cdot}541$, $P=0{\cdot}037$).

Luteal phase scores correlated with SWM between search errors ($r_s=0{\cdot}655$, $P=0{\cdot}008$), spatial span ($r_s=-0{\cdot}624$, $P=0{\cdot}013$) and Trails A reaction time ($r_s=0{\cdot}609$, $P=0{\cdot}016$).

UWIST-MACL

During the follicular phase, the only significant correlation was between 'hedonic' score and spatial recognition latency ($r_s=0{\cdot}538$, $P=0{\cdot}038$).

During the luteal phase, because of the strong negative correlation between BDI and 'hedonic' scores ($r_s=-0{\cdot}826$, $P<0{\cdot}0001$), the same variables were correlated but in an inverse manner: SWM between-search errors ($r_s=-0{\cdot}753$, $P=0{\cdot}001$), spatial span ($r_s=0{\cdot}527$, $P=0{\cdot}043$), also Trails B reaction time ($r_s=-0{\cdot}523$, $P=0{\cdot}045$). SWM between-search errors also correlated with the 'stress' subscale of the UWIST-MACL ($r_s=0{\cdot}585$, $P=0{\cdot}022$).

Correlations between mood and neuroendocrine function

The only significant correlation observed was between UWIST-MACL 'stress' subscale and 24 h urinary cortisol levels in the luteal phase ($r_s=-0{\cdot}527$, $P=0{\cdot}044$).

DISCUSSION

The present study demonstrates subtle and highly selective changes in mood, neurocognition and basal HPA axis function in different phases of the menstrual cycle in young, healthy, premenopausal women. Relative to

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the follicular phase, scores on the 'hedonic' subscale of the UWIST-MACL rating scale were significantly lower in the luteal phase. Verbal fluency was significantly reduced in the luteal phase, however response times for Vigil were speeded, without a concomitant change in target-detection. Pattern recognition latency was also speeded in the luteal phase, but only in subjects who were tested second on that visit. In addition, there was evidence of changes in basal HPA axis functions, but contrary to our hypothesis, 24 h urinary cortisol and salivary DHEA were significantly lower during the luteal phase.

The absence of detectable changes on clinical self-report scales such as the BDI and the AMRS in the present study is likely to be attributable to the screening criteria adopted, whereby subjects with any history of mood disorders or a BDI score >10 were excluded. Despite this, changes were detected on the 'hedonic' scale of the UWIST-MACL which is well suited to detect subtle changes in affect in non-clinical populations.

While studies of basal HPA axis function across the menstrual cycle have generally not shown a cycle related change (Leibenluft *et al.* 1994), the observed reduction in the luteal phase has been reported previously. Odber *et al.* (1998) found that subjects rating themselves as more depressed premenstrually had lower basal salivary cortisol levels on premenstrual compared to post-menstrual days. Therefore, although scores on the BDI did not change significantly, the lower 'hedonic' ratings in the luteal phase in the present study may be partly associated with HPA axis hypofunction. One major difference is that the present study found changes in urinary cortisol levels only, with no change in the levels in saliva. This contrasts a previous finding by Rabin *et al.* (1990) who examined women with PMS and found no change in urinary cortisol levels across the menstrual cycle, but decreased evening concentrations in plasma.

We also measured levels of DHEA. Both cortisol and DHEA are regulated by ACTH and a reduction in both these steroids suggests reduced hypothalamic or pituitary drive in the luteal phase. However, this is a somewhat tentative conclusion as previous work has demonstrated reduced rates of dexamethasone suppression and GR mRNA expression in the luteal phase (Altemus *et al.* 1997). Also, the majority of previous studies that have examined basal secretion have found no change over the cycle; those that have, reported increased cortisol in the luteal phase (Leibenluft *et al.* 1994). Studies that have measured DHEA have only assessed its sulphated form and again report no cycle-related change (Parker *et al.* 1981; Rubinow *et al.* 1988; Carandente *et al.* 1990).

Recent work suggests that the use of the citric acid-treated salivette device may lead to inaccurate estimates of steroid levels (Shirtcliff *et al.* 2001). This has only been demonstrated in assays that did not employ separation and extraction steps, and as such, is not directly applicable to the results of the present study, however our findings require replication using alternative procedures. Future studies should also consider a more frequent sampling schedule, to accurately assess the pulsatile nature of cortisol secretion. A final criticism is that menstrual cycle phase was ascertained by prospective self-report, which is not as accurate as other methods, such as monitoring basal body temperature or direct measurement of luteinizing hormone (Leibenluft *et al.* 1994).

A previous study examining verbal fluency found the opposite effect than we observed, reporting increased composite measures of fluency in the late-luteal phase, although the major contributory factor was 'rhyme' rather than 'category' or 'letter' fluency (Maki *et al.* 2002). Therefore, even with tests of a similar nature, the test sensitivity and specifics of its demands appear to be major factors in determining if an effect is seen. The improvement in Vigil in the luteal phase is consistent with studies that have demonstrated that ORT can improve performance on tests of attention (Smith *et al.* 2001), although others have reported no change across the menstrual cycle (Resnick *et al.* 1998). This latter study did however report subtle psychomotor slowing in the late follicular relative to the late-luteal phase therefore the effect observed in the present study may be due to increased motor speed. Cortisol levels have also been shown to affect attentional processing, but the relationship appears to be U-shaped. Elderly subjects who exhibit age-related increases in cortisol, in combination with current high basal cortisol levels, demonstrate impaired selective

attention (Lupien *et al*. 1994). Recent work in younger subjects found decreased salivary cortisol levels in response to pre-exam stress (despite a self-reported increase in stress levels) were associated with impaired selective attention (Vedhara *et al*. 2000). This may explain the present findings, although as yet the precise mechanisms underpinning these changes remain to be determined.

In summary, the present study found subtle changes in aspects of mood, neurocognitive and basal HPA axis function in different phases of the menstrual cycle. These data suggest that luteal phase HPA axis function is lower than in the follicular phase in premenopausal healthy women. This putative biological difference may be key to the understanding of the aetiopathogenesis of menstrually related mood change and neurocognitive disturbances.

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