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Functional cerebral asymmetries during the menstrual cycle: a cross-sectional and longitudinal analysis

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Abstract

This study aims at answering two basic questions regarding the mechanisms with which hormones modulate functional cerebral asymmetries. Which steroids or gonadotropins fluctuating during the menstrual cycle affect perceptual asymmetries? Can these effects be demonstrated in a cross-sectional (follicular and midluteal cycle phases analyzed) and a longitudinal design, in which the continuous hormone and asymmetry fluctuations were measured over a time course of 6 weeks? To answer these questions, 12 spontaneously cycling right-handed women participated in an experiment in which their levels of progesterone, estradiol, testosterone, LH, and FSH were assessed every 3 days by blood-sample based radioimmunoassays (RIAs). At the same points in time their asymmetries were analyzed with visual half-field (VHF) techniques using a lexical decision, a figure recognition, and a face discrimination task. Both cross-sectional and longitudinal analyzes showed that an increase of progesterone is related to a reduction in asymmetries in a figure recognition task by increasing the performance of the left-hemisphere which is less specialized for this task. Cross-sectionally, estradiol was shown to have significant relationships to the accuracy and the response speed of both hemispheres. However, since these effects were in the same direction, asymmetry was not affected. This was not the case in the longitudinal design, where estradiol affected the asymmetry in the lexical decision and the figural comparison task. Overall, these data show that hormonal fluctuations within the menstrual cycle have important impacts on functional cerebral asymmetries. The effect of progesterone was highly reliable and could be shown in both analysis schemes. By contrast, estradiol mainly, but not exclusively, affected both hemispheres in the same direction.

Keywords: Lateralization; Gonadal steroid hormones; Estradiol; Progesterone; Testosterone; FSH; LH; Sex differences

1. Introduction

Sex differences in functional cerebral asymmetries (FCA) are assumed to result from differences in underlying sex hormone levels. These individual and sex-related differences seem to be mediated by the organizing and activating effects of sex hormones [17]. These aspects of sex hormone-related modulations of FCA can best be investigated in women before menopause, because their natural steroid hormone levels fluctuate in relatively short time intervals during the menstrual cycle.

In a recent visual half-field (VHF) study [8], we could show concurrent shifts in FCA in a left-hemisphere dominated verbal task (lexical decision) as well as in two right-hemispheric non-verbal tasks (face discrimination and figural comparison) in spontaneously cycling women. For all tasks, we observed a greater FCA during menses and a more symmetrical functional organization during the midluteal phase. The second experiment of this study yielded that the FCA pattern in men and postmenopausal women remained stable over time for all these tasks and were similar to those of spontaneously cycling women during menses [8]. The control of carry-over effects due to the repeated measures design [7] as well as the validation of cycle phases using hormone assays were two important preconditions to reveal these results. Moreover, we could show the progesterone level to be an important agent that is significantly enhanced during the luteal phase, and that was significantly related to the degree of FCA. In the figural comparison task, progesterone had an enhancing effect on the less specialized left-hemisphere, and thus, had effected a reduction of the right hemisphere advantage [8].

The observation that spontaneously cycling women show greater FCA during menses compared to the high progesterone phase is supported by other studies using left (dichotic listening with verbal stimuli [11]) as well as right-hemispheric tasks (face decision [10], figural comparison [14]). Other studies revealed strongest lateralization

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Table 1
Mean, standard deviation (in parenthesis), and range (in braces) of different hormone levels during different cycle phases

Hormone	Menses	Follicular Phase	Luteal phase	Premenses
P (ng/ml)	0.55 (0.16) {0.20–0.70}	0.68 (0.27) {0.30–1.20}	18.52 (5.73) {8.90–25.70}	2.49 (2.33) {0.80–9.20}
E (pg/ml)	30.48 (14.40) {15.35–52.24}	167.43 (59.99) {70.44–272.38}	115.70 (17.57) {90.07–153.37}	39.43 (26.58) {9.34–107.45}
T (ng/ml)	0.28 (0.15) {0.07–0.57}	0.40 (0.14) {0.23–0.62}	0.30 (0.10) {0.15–0.41}	0.29 (0.14) {0.09–0.58}
LH (mlU/ml)	3.26 (1.25) {2.15–5.85}	21.40 (14.56) {6.59–50.10}	2.91 (1.58) {1.37–5.96}	2.18 (1.23) {0.48–4.31}
FSH (mlU/ml)	6.06 (1.88) {3.50–10.80}	8.04 (4.63) {3.00–17.60}	2.30 (1.04) {1.20–4.20}	2.80 (1.36) {1.00–5.10}

patterns in a non-lateralized chair identification task [3], and in various dichotic listening tasks [1,5,6] during cycle phases, which are defined by high levels of sex hormones. However, two of these studies [1,6] found differences in FCA pattern between premenses and the follicular phase, with greater FCA during high levels of estradiol without a concurrent progesterone peak. These results suggest that estradiol, rather than progesterone, possibly increases lateralization. However, direct examinations of the relationship between progesterone and estradiol levels and the degree of FCA during the menstrual cycle are rarely performed since most studies failed to include hormone assays.

One study [15] found complementary shifts in asymmetry with greater left-hemisphere advantage for the verbal task during midluteal phase and greater right hemisphere advantage for the music task during menses. Although this study failed to include hormonal assays, it showed that phase-related shifts in FCA seem to be task-specific. Although the results of our previous study showed that cycle-related modulation of lateralization pattern act independently of task or hemisphere, and appear in prototypical left as well as in right-hemispheric tasks, the hormone–asymmetry relationship was especially pronounced in the figural comparison task [8]. The degree of asymmetry [3] and the difficulty of a given task could possibly determine about the degree of cycle-related modulation of FCAs.

The aim of this study is to analyze the FCA during the individual menstrual cycle of each participating woman over a period of 6 weeks (15 testing sessions) and to clarify the hormone–asymmetry relationships. To determine FCAs, we used three VHF-field tasks which usually showed a clear left hemispheric (lexical decision task) or right-hemispheric advantage (figural comparison and face discrimination) in previous studies [7,8]. Moreover, the difficulty of these tasks differ. The face discrimination task is the most demanding and strongest lateralized task [7]. Levels of progesterone, estradiol, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) of each women were analyzed by radioimmunoassay (RIA) from blood-samples for each testing session.

All previous studies tested women only twice or three times. Thus, the individual cycle-length was only marginally considered. We aimed to perform cross-sectional and longitudinal analyzes of the relation between FCA and hormone levels over the entire length of a complete cycle. While cross-sectional analysis concentrates on distinct time points, and try to elucidate relationships in these limited time frames, a longitudinal analysis is able to provide additional information on the possible effects of the rise and fall of sex hormones levels on FCA. Additionally, a longitudinal design enables the analysis of smaller sex hormone fluctuation effects which occur outside the most prominent cycle phases.

Firstly, hormone–asymmetry relationships were analyzed cross-sectionally during the follicular and the midluteal cycle phase, when women show largest variation in different sex hormone levels (see Table 1). Secondary, we investigated the hormone–asymmetry relationships longitudinally over 6 weeks (15 sessions). With reference to our previous results [8], we expected a reduced FCA and a selective modulation of the task-related less specialized hemisphere during high progesterone levels. If peak progesterone levels have such effects, they should be observable in a cross-sectional as well as in a longitudinal design.

2. Methods

Twelve healthy, spontaneously cycling women who reported to have a regular menstrual cycle between 27 and 29 days participated in this study. Post-hoc analysis of three successive cycles revealed a median cycle-length of 29 days (mean = 30.45; S.D. = 6.25; range: 25–55 days). Although, for one women a cycle-length of 55 days could be observed, all women showed an ovulation which was detected from LH surges in the hormone assays. The handedness of all subjects were determined with the Edinburgh inventory [12]. The asymmetry-index (LQ) provided by this test is calculated by $[(R - L)/(R + L)] \times 100$, resulting in values between +100 and −100. Positive values indicate dextrality, while sinistrality results in negative values. The mean handedness-score was +82.0 (S.D. = 26.8; range from +9 to +100). The mean age of the spontaneously cycling women was 29.1 years (S.D. = 4.36; range: 23–38 years), and none of them had used hormonal contraceptives or any nervous system affecting medication during the last 6 months. All subjects had normal or corrected-to-normal visual acuity and were naive as to the hypothesis. They were recruited by announcement and were paid for their participation. Subjects of this study also participated in a study investigating the influence of sex hormones on spatial abilities during the menstrual cycle [9].

Prior to the first experimental session, one meeting was appointed to inform each woman about the general procedure of the study, to measure handedness and visual acuity and to collect data about the menstrual cycle. Subjects started with their first testing session at a time independent of their actual individual cycle day. They agreed to inform us about the first day of their actual and following cycles. To minimize the influence of the circadian rhythm in each subject, all experimental sessions of each subject were performed at the same time of the day over the course of the complete study. All 12 female participants completed 15 testing sessions with an inter-test interval of 3 days over a period of 6 weeks (180 sessions in total). Blood-samples were collected immediately after each testing session. Serum samples were stored at $-22\,^{\circ}C$ until all subjects had completed all tests. Estradiol (E), progesterone (P), testosterone (T), LH and FSH levels were assessed with radioimmunoassay (RIA) by an independent professional hormone analysis laboratory, with commercially available RIA kits (DPC Biermann GmbH, Bad Nauheim, Germany). The assessment of the serum sex hormone levels of each woman over a period of 6 weeks allowed a nearly perfect validation of the menstrual cycle phases, independent of the individual cycle-length.

Based on the hormone data of the serum samples, menstrual, follicular, midluteal, and premenstrual cycle phase were defined by a distinct point in time within each cycle phase for each woman. We used these distinct points in time to analyze cycle-dependent mood differences and to define points of interest for the cross-sectional analysis of the hormone-lateralization relationship. The menses were defined by the first testing session of a new cycle with low levels of estradiol and progesterone, and by reports of each woman about the onset of menstruation, while the premenstrual cycle phase was defined as the last testing session before menses. The follicular cycle phase was defined by highest estradiol levels before ovulation, which is particularly indicated by a clearly recognizable LH peak, while the midluteal phase is indicated by highest progesterone levels with concurrent high concentrations of estradiol after ovulation.

The VHF procedure was identical to previous studies [7,8]. The experiment started by placing the head of a subject to a chin rest at a distance of 68 cm from a monitor. All subjects were instructed to keep their head and body still during the whole test and to fixate a cross in the center of the screen. Thus, we ensured that lateralized stimulus presentation was more than 2° visual angle to the left or to the right of the fixation cross. We used an exposure time of 185 ms for all stimuli due to the more difficult face discrimination task [7]. All stimuli were presented within a frame of 4.8 cm wide and 4.5 cm high, 4.0 and 3.8° visual angle, respectively.

All three tasks included 70 trials. The first 10 practice-trials were eliminated. After 40 trials, the responding hand was changed in a balanced order. We tested all subjects with two parallel versions of each task in a balanced and alternate order. Additionally, the order of VHF tasks was balanced over all testing sessions. Frequency of correct answers and medial response times (RT) for both VHFs were used as dependent variables for all tasks.

Photographs for the face recognition task were taken from an US college album from the 1950s. The students on these pictures were all male, clean shaven, short haired, without glasses and in their early 20s. To avoid further non-facial characteristics, all photographs were framed with an ovoid overlay which covered the background and the clothes, with exception of the collar. After presentation of a fixation cross for 2 s, the stimuli appeared lateralized pseudo-randomly either in the left or the right VHF, while an empty frame was presented in the other VHF. The subjects were instructed to indicate as quickly and as correctly as possible whether the faces they saw were unchanged, ‘normal’ faces of male college students or altered, ‘monster’ faces by pressing a key with the fingers of their right- or left-hand. For the latter stimuli some facial characteristics were translocated. For example, the position of one eye and the mouth were swapped or everything was deleted except the nose, etc. All faces had the same orientation and an unemotional, neutral expression [7]. In previous studies [7,8], results of this task showed typically a very strong advantage for the left visual field (LVF), corresponding to the right hemisphere.

A pool of 120 German nouns was used for the lexical decision task. The words consisted of at least four letters up to maximum of seven. The stimuli were selected for a high degree of abstraction [2] to maximize the left-hemisphere advantage. Sixty stimuli were used for the first version, and the remaining 60 stimuli for the parallel version of the VHF procedure: the order of these two blocks of words was balanced amongst subjects. Each trial started by presentation of a fixation cross for 2 s. Next, a word appeared in the center of the monitor for 185 ms. Then, a fixation cross was presented for 2 s again, followed by a word for 185 ms pseudo-randomized in the LVF or RVF. A subsequent question-mark instructed the subject to decide by key press, if both words were the same or different. In the mismatching trials, words were identical with regard to the initial letter and to the number of letters. In previous studies [7,8] results of this task typically showed a better performance for words presented in the RVF, corresponding to the left-hemisphere.

For the figural comparison condition 120 (60 per version) black irregular polygons with at least eight edges were constructed with the Paintshop® software with the two stimulus blocks again being balanced. The procedure and timing was identical to the lexical decision task. Subjects had to decide by finger key press as fast and as correctly as possible if both polygons were the same or different. Normally, an advantage for the LVF, corresponding to the right hemisphere could be revealed in this task [7,8].

In order to control potential influences of mood which may influence cognitive performance, a German mood scale was applied to each of the 15 testing sessions [18]. Mood scores could range between 0 (euphoric) and 56 (extremely depressive). Scores are grouped into five mood classes: 0–6 (euphoric), 7–16 (well-balanced), 17–26 (depressed), 27–41 (moderately depressive), and 42–56 (extremely depressive).

3. Results

In the first step of the analysis, hormone data were standardized with respect to their mean and their variance. The results of the VHF tasks were first de-trended and then standardized accordingly. Plots of the results of the tasks showed a clear trend, indicating a practice effect for all three tasks. To analyze the results independently of practice, we de-trended the data according to Schlicht [16], decomposing the individual time series of task-related results into a smooth trend curve and differences from this curve. Then, we took these differences as the data of interest, again standardizing them to guarantee their comparability (see Fig. 1).

Evaluating the data by means of an analysis of variance (with repeated measures) would mean working with a three-way random effects model including interaction terms, where the factors are given by cycle phase (three levels), VHF (two levels) and type of processed task (three levels). Such an analysis clearly is not adequate for a sample size of 12. Hence, in contrast to previous investigations (cited above), we rejected this type of evaluation and analyzed our data using correlation statistics and non-parametric tests.

3.1. *Cross-sectional analyzes of hormone–lateralization relationships*

In the following, we present the correlation coefficients for the relationships between different sex hormones and the degree of asymmetry as well as the VHF-related performance during different cycle phases for each of the three tasks. At distinct hormonal points in time, the lateralization data (degree of FCA, and performance for each VHF) and the sex hormone levels were correlated using Pearson's product–moment-correlation statistics. During menstrual and premenstrual cycle phases estradiol and progesterone levels are very low and show only small individual variations. We therefore did not investigate the relationship between sex hormones and FCA data during these cycle phases. The largest individual variations in estradiol levels appear during the follicular and the midluteal cycle phases, when estradiol levels are significantly elevated. Progesterone levels show their largest variations only midluteally. For this reason, we focused on the cross-sectional lateralization/hormone relationship analyzes in these two cycle phases.

Identically to our previous study [8], we calculated performance differences between the RVF and the LVF (RVF minus LVF) as an indicator for the degree of FCA. With

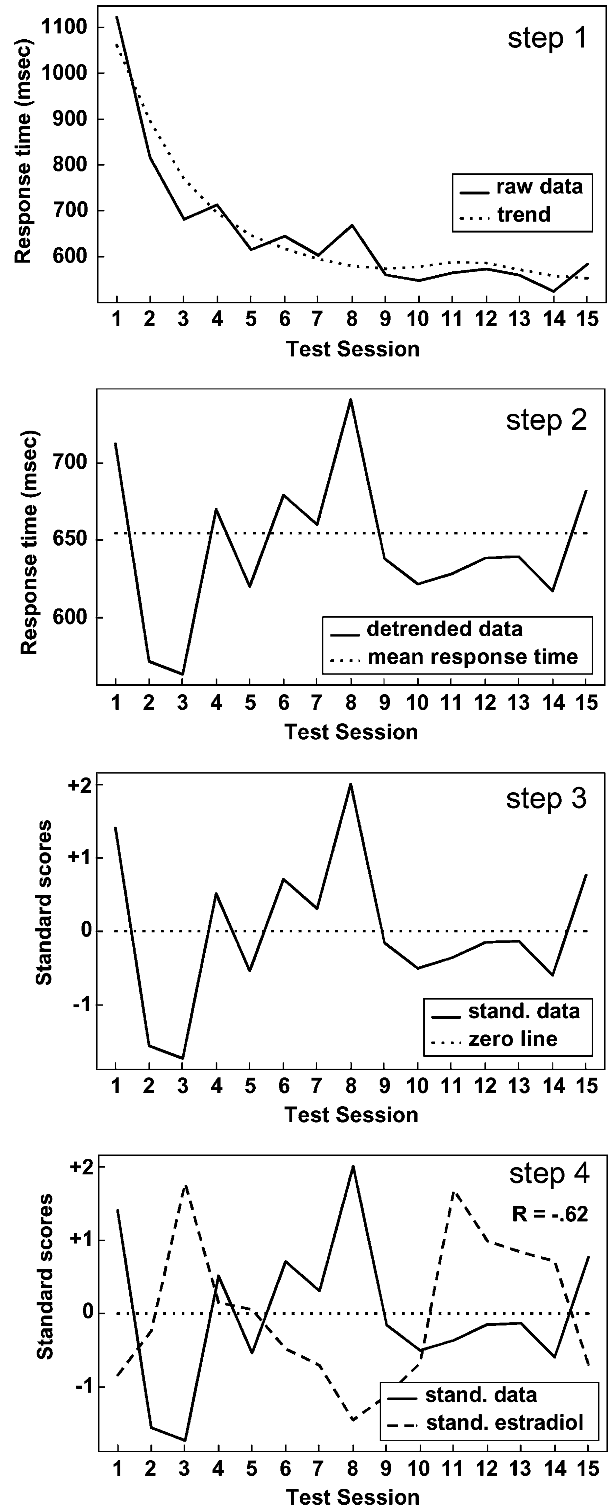

Fig. 1. De-trending procedure. Example data of one subject (no. 12) in the lexical decision task for the RVF over 15 sessions. Response times are getting faster from session 1–15. Firstly, the trend representing the practice effect is computed according to Schlicht [16] (step 1). Secondly, the raw data were de-trended by subtracting trend from raw data (step 2) and were then standardized (step 3). For the cross-sectional analysis, data from only session 11 (follicular phase) and session 14 (luteal phase) were selected. For the longitudinal analysis, data of all sessions were used and were cross-correlated with standardized estradiol level (time lag 0) (step 4).

Table 2
Correlation coefficients of the relationships between accuracy (%), and response times (RT) and progesterone (P) as well as estradiol (E) levels and mood in women during follicular as well as midluteal cycle phase (cross-sectional analyzes). Due to the directed hypothesis, one-tailed statistics were used for the progesterone–lateralization relationships

Task		P (luteal)	E (follicular)	E (luteal)	Mood (follicular)	Mood (luteal)
Figural comparison task	ASY (%)	0.55*	0.15	0.23	−0.61*	0.12
	LVF (%)	0.11	0.59*	0.55	−0.03	−0.22
	RVF (%)	0.52*	0.51	0.66*	−0.24	−0.10
	ASY (RT)	0.11	0.43	0.14	−0.40	−0.44
	LVF (RT)	−0.21	0.83**	−0.17	0.54	0.55
	RVF (RT)	−0.15	0.76**	−0.08	0.42	0.23
Lexical decision task	ASY (%)	0.02	−0.13	−0.18	−0.58*	0.65*
	LVF (%)	0.37	0.15	0.51	0.63*	−0.16
	RVF (%)	0.32	0.11	0.27	0.34	0.37
	ASY (RT)	−0.06	0.35	0.15	−0.25	−0.48
	LVF (RT)	−0.27	0.64*	−0.26	0.25	0.25
	RVF (RT)	−0.30	0.58*	−0.19	0.15	0.02
Face discrimination task	ASY (%)	−0.14	−0.14	−0.20	0.55	−0.19
	LVF (%)	0.42	−0.36	0.39	−0.59*	0.05
	RVF (%)	0.22	−0.44	0.14	0.17	−0.16
	ASY (RT)	−0.03	−0.02	0.25	−0.03	−0.42
	LVF (RT)	−0.31	0.67*	−0.50	0.36	0.41
	RVF (RT)	−0.27	0.65*	−0.26	0.34	0.09
Mood scale	T-score	0.27	0.20	−0.24		

* $P < 0.05$.
** $P < 0.01$.

reference to the results of this study, we expected a reduced FCA and a selective modulation of the task-related less specialized hemisphere due to high progesterone levels. Because of these directed hypotheses, we used one-tailed statistics when progesterone was analyzed in a cross-sectional design. All other statistical tests were two-tailed. Altogether, the correlation coefficients between five sex hormones (progesterone, estradiol, testosterone, LH, and FSH) and the asymmetry data (L and R differences and performance of the LVF and RVF) were evaluated for all three tasks (figural comparison, face discrimination and figural comparison). Correlation coefficients for estradiol and progesterone are shown in Table 2.

3.1.1. Figural comparison task

3.1.1.1. Progesterone. In the accuracy data, we found significant results only for the figural comparison task. As expected, progesterone showed a significant correlation with the degree of FCA in the figural comparison task ($r = 0.55$; $P < 0.05$). This result appeared as a consequence of the expected progesterone-modulated increase of accuracy in the RVF (left-hemisphere) ($r = 0.52$; $P < 0.05$), while no relationship between progesterone and the dominant right hemisphere could be revealed ($r = 0.11$, n.s.). The RT analysis of correct answers revealed no significant correlation coefficients of progesterone and the performance of either VHF as well as the degree of FCA (see Table 2).

3.1.1.2. Estradiol. In contrast, estradiol showed significant, or at least marginally significant, correlations with the accuracy in the figural comparison task during the follicular as well as during the midluteal phase. Since estradiol affected the accuracy of both VHFs in the same direction, estradiol levels were not correlated with the degree of FCA (follicular: $r = 0.15$, n.s.; midluteal: $r = 0.23$, n.s.) (see Table 2). A similar result is present in the RT analysis of correct answers. Despite these highly significant positive correlations between follicular estradiol and RVF ($r = 0.83$; $P = 0.001$) as well as LVF performance ($r = 0.76$; $P < 0.01$), no concomitant changes in degree of FCA could be observed (Table 2).

3.1.1.3. Other hormones. Additionally, the accuracy of the figural comparison task FSH showed high negative relationships with accuracy in the LVF ($r = -0.59$; $P < 0.05$) and RVF ($r = -0.57$; $P = 0.055$), but this result was only present during the follicular cycle phase. No further significant linear relationships appeared.

3.1.2. Lexical decision task

3.1.2.1. Progesterone. Accuracy as well as RT data were not significantly related to progesterone.

3.1.2.2. Estradiol. Similarly to the RT data of the figural comparison task, estradiol showed positive correlations with LVF ($r = 0.64$; $P < 0.05$) and RVF ($r = 0.58$; $P <$

0.05) during the follicular phase. Consequently, FCA was not affected (Table 2).

3.1.2.3. Other hormones. Testosterone was positively correlated with the degree of FCA in the RT of the lexical decision task during the midluteal phase ($r = 0.63$; $P < 0.05$). No significant linear relationships between any other sex hormones and FCA data appeared.

3.1.3. Face recognition task

3.1.3.1. Progesterone. Accuracy and RT data were not significantly related to progesterone.

3.1.3.2. Estradiol. In agreement with the RT data of both other VHF tasks, estradiol showed positive correlations with LVF ($r = 0.67$; $P < 0.05$) and RVF ($r = 0.65$; $P < 0.05$) during the follicular phase. Again, the degree of FCA was not affected (Table 2).

3.1.3.3. Other hormones. No significant linear relationships appeared.

3.2. Longitudinal analyzes of hormone-lateralization relationships

To analyze female FCAs in relation to the individual fluctuations of hormone concentrations, all data were considered in the second part of this study. Cross-correlations were calculated between hormone levels and the results of the VHF tasks during corresponding sessions. For each subject, we calculated separate Pearson's product–moment correlations between FCA data and hormone levels for time lags 0. For each of the three tasks, we then performed a one-sample two-sided Wilcoxon signed rank test to decide whether the mean correlation between the FCA results and the hormone under consideration differs significantly from 0. This was done for the degree of FCA and for the performance for each VHF. Contrary to the cross-sectional analysis, we had no clear hypothesis for the direction of the effect of progesterone levels in the longitudinal design. Thus, we performed the two-sided tests throughout.

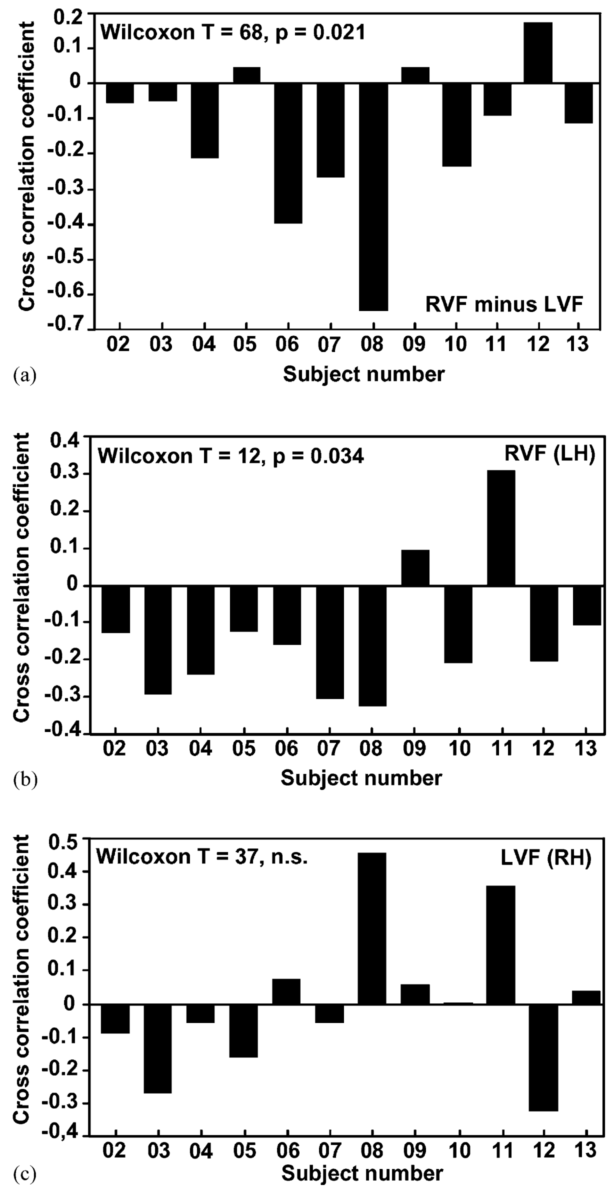

Fig. 2. Separate cross-correlations between progesterone levels and response times asymmetry (a), RVF (left-hemisphere) response times (b), and LVF (right hemisphere) response times (c) of all 12 subjects in the figural comparison task at time lag 0. These 12 individual correlations were then analyzed with a one-sample two-sided Wilcoxon signed rank test to decide whether the mean correlation between the lateralization results and progesterone levels differed significantly from 0. While there was no significant relation between progesterone levels and right hemisphere speed (c), progesterone decreased left-hemisphere speed (b), resulting in a reduced response times asymmetry during high progesterone levels (a).

3.2.1. Figural comparison task

3.2.1.1. Progesterone. For the RT of this task, the mean cross-correlation between progesterone and the degree of FCA was significantly different from 0 at time lag 0 ($W = 68$; $P < 0.05$). The individual correlation values of the women were mainly positive, indicating that high levels of progesterone reduced FCA, whereas low levels resulted in a larger right hemisphere advantage (see Fig. 2a). Additionally, we found a significant correlation for progesterone for the RVF only ($W = 12$; $P < 0.05$) (see Fig. 2b and c). These results suggest that the degree of FCA is significantly decreased during high levels of progesterone due to a modulation of the performance of the less specialized left-hemisphere (RVF). Although RT were affected here, the results correspond with the cross-sectional analysis and to our previous study [8].

3.2.1.2. Estradiol. The degree of FCA in accuracy data was significantly related to estradiol levels at time lag 0 ($W = 66$; $P < 0.05$). This is in contrast to the results of the

Table 3
T-scores (Wilcoxon signed rank test for one-sample) for longitudinal analyzes of the relationships between fluctuations of hormones, mood, and VHF performances

Task		P	E	T	LH	FSH	Mood
Figural comparison task	ASY (%)	50	33	55	38	49	38
	LVF (%)	52	56	38	52	46	34
	RVF (%)	49	52	23	58	32	41
	ASY (RT)	68*	66*	42	63	58	52
	LVF (RT)	37	32	41	44	57	60
	RVF (RT)	12*	19	38	23	42	40
Lexical decision task	ASY (%)	37	13*	37	29	32	42
	LVF (%)	45	20	24	20	21	24
	RVF (%)	37	48	31	43	30	39
	ASY (RT)	53	61	43	35	24	25
	LVF (RT)	35	41	28	38	54	35
	RVF (RT)	32	24	36	48	59	53
Face discrimination task	ASY (%)	46	37	32	33	31	56
	LVF (%)	56	36	28	30	24	45
	RVF (%)	43	44	33	38	41	26
	ASY (RT)	28	29	44	42	34	34
	LVF (RT)	32	30	45	41	43	58
	RVF (RT)	34	41	40	49	47	66*
Mood scale	T-score	61	56	56	26	19	

* $P < 0.05$.

cross-sectional analysis, where we found no such relationship. The individual correlations of the women were mainly positive, and the differences characterizing the degree of FCA were mainly negative. This means that for high levels of estradiol, the degree of FCA was reduced. Changes in the degree of FCA would suggest a differential effect of estradiol on VHFs. However, this was not the case. Although a stronger estradiol-mediated modulation of the less specialized right hemisphere (LVF) appeared, this effect did not reach significance ($W = 19$; $P = 0.13$).

3.2.1.3. Other hormones. We did not find a significant hormone–asymmetry relationship (Table 3).

3.2.2. Lexical decision task

3.2.2.1. Progesterone. No significant cross-correlations could be shown at either time lags (Table 3).

3.2.2.2. Estradiol. For the accuracy data, the only significant effect was the relation between estradiol and the degree of FCA in the lexical decision task ($W = 13$; $P < 0.05$). Since the correlations as well as the differences between LVF and RVF were mostly negative, higher levels of estradiol corresponded to a larger FCA for this left hemispheric task. An increase of FCA would suggest a differential effect of estradiol on the hemispheres. This, however, was not the case: although a stronger estradiol-mediated modulation of the less specialized right hemisphere (LVF) appeared, this effect did not reach significance ($W = 48$; $P = 0.151$).

3.2.2.3. Other hormones. Again, no significant hormone–asymmetry relationship appeared (Table 3).

3.2.3. Face discrimination task

3.2.3.1. Progesterone/estradiol/other hormones. No significant hormone–asymmetry relationships appeared (Table 3).

3.3. Cycle-dependent mood differences

3.3.1. Cross-sectional

To investigate potential mood changes during the menstrual cycle, we compared mood scale values (T-scores) during menstrual, follicular, midluteal, and premenstrual cycle phases (see Table 4). This analysis, using the non-parametric Friedman two-way analysis of variance by ranks, did not yield a significant difference between cycle phases ($\chi^2 = 3.21$; $N = 12$, d.f. $= 3$, n.s.). Moreover, correlation statistics between mood scores and sex hormones

Table 4
Means and standard deviations of mood scores for women during different menstrual cycle phases[a]

Cycle phase	Mean T-scores	S.D.
Menstrual	17.17	13.11
Follicular	12.83	10.23
Midluteal	17.42	10.86
Premenstrual	18.17	11.68

[a] Mood scale values range between euphoric (0) and extremely depressive (56).

showed no significant cross-sectional (Table 2) or longitudinally relationship (Table 3). By contrast, analyzes of the linear relationships between mood and asymmetry data revealed some significant results in both designs (see Tables 2 and 3). These effects strongly support controlling mood-related effects in future studies. However, in this study the relation between mood and asymmetry data were partly contradictory in direction and highly task-specific. Additionally, hormone–asymmetry relationships seem not to be affected by mood, because significant effects appeared in different dependent variables.

4. Discussion

The most important result of this study is the relationship between progesterone and the FCA. In agreement with our previous results [8], high levels of progesterone were related to a reduction of FCA at least in the figural comparison task due to a performance enhancement in the less specialized left-hemisphere. Despite the limitation due to the small sample size, but with a very accurate validation of the individual cycle phases, the result of the progesterone–asymmetry relationship reported here, appears in the cross-sectional as well as in the longitudinal design. Although in the latter case, the relationship between progesterone and FCA was small for each individual, they are in the same direction for most participants, and were thus, significant. It is still unclear why the significant correlation with progesterone is again only found for the figural comparison task, since cycle-dependent changes in FCA are, in principal, observable in all tasks used here [8]. However, it is known that the figural comparison task and other visuo-spatial lateralization experiments reveal especially pronounced interactions between VHF and sex [4,7,13].

The results related to progesterone fit to the hypothesis of the progesterone-mediated interhemispheric decoupling [8]. According to this assumption, progesterone reduces cortico-cortical transmission by suppressing the excitatory responses of neurons to glutamate as well as by enhancing their inhibitory responses to GABA. The combined effect would result, via a decrease of transcallosal neuronal activation, in a functional hemispheric decoupling, and thus, to a temporal reduction in FCA. According to this theoretical background, we expected and could show again that, if progesterone fluctuations during the menstrual cycle are related to changes in FCAs, it is particularly the less specialized hemisphere for a given task which is affected.

The activating effects of estradiol on FCA seem to be rather complex. In the cross-sectional analysis, estradiol revealed highly significant and task-independent influences on response times for both VHFs during the follicular cycle phase. According to these data, high levels of estradiol correspond with slower response times in LVF and RVF. For the accuracy data, high levels of estradiol enhanced the amount of correct answers during the figural comparison task in both VHFs during the follicular and the midluteal cycle phase. These effects were independent of concurrent progesterone levels. Since estradiol affected both VHFs, estradiol levels did not show any relationship with the degree of FCA during these distinct cycle phases. Instead, estradiol was found to affect the degree of FCA in the longitudinal design. For the response times of the figural comparison task estradiol reduced the degree of FCA, whereas, for the accuracy data of the lexical decision task estradiol, enlarged lateralization. The latter result corresponds to the findings of other studies, which showed greater FCA during follicular phase, compared to menses [1,6]. Similarly to our lexical decision task, where this result appeared, both studies used verbal stimuli. However, although Hampson [6] used hormone assays, she did not find a relationship between serum estradiol levels and asymmetry measures. Estradiol-related complementary changes in lateralization detected by the longitudinal design of this study, with an enlarged FCA in the left-dominated lexical decision task and a reduced FCA in the right-dominated figural comparison task correspond to the results of a dichotic listening study [15] and support an alternative explanation of cycle-related modulations of FCAs, as suggested by these authors. It is possible that similar task-related complementary shifts in FCAs during the midluteal phase (compared to menses), reported by this study, were due mainly to the activating effects of estradiol rather than modulated only by progesterone. These results make it likely that not only progesterone, but to some degree, also estradiol modulates FCA, although the detailed mechanisms have to be elucidated.

Effects of other sex hormones on FCA during the menstrual cycle were until now unknown. In the present study, we were unable to show that testosterone and gonadotropins display any significant relationships with the asymmetry data. The same is present in the relationship between mood and FCA. Hormone-related effects on mood could not be found.

A number of previous studies have encountered cycle phase-related lateralization differences in the analysis of accuracy data (e.g. [3,8,11,15]). This is in agreement with the cross-sectional results in this study. However, in the longitudinal analysis, hormonal fluctuations were primarily visible in the analysis of the response times. The reason could be that, due to the use of extensive repeated measures, practice effects resulted in a nearly perfect performance in terms of accuracy, especially during the last sessions. As a result, hormonal performance fluctuations are primarily visible in response times when analyzing the data with a longitudinal design. Thus, ceiling effects in accuracy are capable of influencing the hormone–lateralization relationship in response times.

Overall, fluctuations in sex hormones levels are related to changes in FCAs. During the prenatal ontogenetic development, this is mainly mediated by the organizing effects of testosterone (e.g. [17]). However, once the brain reaches a mature status, it seems to be mainly progesterone which modulates lateralization. Although highly significant activation effects of estradiol on performance in both VHFs occur, asymmetry patterns, as such, are affected to a much smaller extent. Of course, this does not mean that estradiol has no effects on cognition (e.g. [6,9]), but the impact of estradiol on perceptual asymmetries are not as clear-cut as those of progesterone, which seems to be a key agent of the dynamic asymmetry changes during the menstrual cycle.

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