



Steroid fluctuations modify functional cerebral asymmetries: the hypothesis of progesterone-mediated interhemispheric decoupling

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Received 4 August 1999; received in revised form 24 February 2000; accepted 7 March 2000

Abstract

This study examines the modulation of functional cerebral asymmetries by gonadal hormones in three distinct groups. Young, normally cycling women performed a prototypical left (lexical decision) and two prototypical right-hemispheric tasks (figural comparison and face discrimination) during the low steroid menses and the high steroid midluteal phase. Saliva progesterone levels were measured with radioimmunoassay (RIA). Parallel to younger females, young men, and postmenopausal women were tested at matching time intervals. Results revealed significant interactions between cycle phase and visual half-field in the accuracy of all three tasks for the younger women; stronger lateralization patterns occurring during menses, while a more bilateral or at least less asymmetric cerebral organization predominated the midluteal phase, when highest levels of progesterone appear. Progesterone seemed to have a significant influence on lateralization in the figural comparison task, with high hormone levels enhancing the performance of the left hemisphere (for this task subdominant), thereby decreasing asymmetry. After menopause, when the levels of gonadal hormones are lower and more stable, the lateralization patterns for all three tasks were similar to those of men and normally cycling women during menses. These results make it likely that steroids and especially progesterone are able to reduce cerebral asymmetries. We hypothesize that progesterone attenuates the effect of glutamate on non-NMDA receptors. This could diminish cortico-cortical transmission which is mostly dependent on a glutamate-induced initial EPSP in pyramidal neurons which receive transcallosal input. The reduction in callosal transfer could then suppress the functional asymmetries. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Menstrual cycle; Menopause; Lateralization; Corpus callosum

1. Introduction

A large number of studies have indicated that cerebral asymmetries of many functional systems are sex dependent (e.g. speech [12,33,73], spatial orientation [15,22,34,52,89], face recognition [10,66]). Although not all lateralization studies have shown this gender effect [5,11,44], the pattern of a more symmetrical lateralization in females but a more pronounced asymmetry in males pervades in many studies (for reviews

[13,29,37,51,87]). In addition to this more symmetrical lateralization, the data for women also show larger variance [33], supporting the assumption that females display a more heterogeneous pattern of functional cerebral organization [50].

The results of several recent studies make it likely that these sex effects are at least in part related to steroid differences between the genders. One implication of this finding is that alteration of steroid levels in transsexuals ([17,26], but see [74]), or during the continuous steroid fluctuations in normally cycling women, should lead to concomitant changes in cerebral asymmetries, a phenomenon which has repeatedly been observed [4,8,15,30,31,35,49,53,67,69]. Thus, if lateralization in women is to an important degree modulated by steroid fluctuations, it is very likely that

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female data are on the average less asymmetric and more variant, since women participating in lateralization experiments are very likely to be tested at different phases of their menstrual cycle.

However, different authors have meanwhile provided a remarkably controversial picture of the lateralized events during menstrual cycle [4,8,15,30,31,35,49,53,67,69]. Some studies have shown greatest asymmetries in figure recognition [8], dichotic listening [30,31,69], and spatial bisection [49] during the high steroid phase (mostly at the midluteal stage). But in other tasks no asymmetry in face processing [8] and lexical decision [15,35,67] were found during this hormonal status. Contrary to these, other studies have revealed strongest lateralization patterns during the low steroid menses in face decision [35], figural comparison [67] and dichotic listening with verbal [53] or with musical stimuli [69]. One study [69] found complementary shifts in asymmetry with a greater right ear advantage for the verbal task during midluteal phase, and a greater left ear advantage for the music task during menses. Additionally, it is unclear which hemisphere is more modulated by steroid hormones. Some studies report a suppression of the right hemisphere [30,31,35,53,69], whereas others indicate that especially the left hemisphere is activated by gonadal hormones [8,15,67].

Some contradictions arise due to the lack of hormone assessment in some studies, which inevitably increases the data pool with women tested outside the optimal time window. The extent of this problem is shown in a study by Gordon, Corbin, and Lee [28], in which half of the female subjects had to be eliminated from the analyses when post hoc hormone assays revealed these subjects not to have been in their expected cycle phase.

An important variable further confounding the issue is the repeated measures design itself. As we show elsewhere [34], although women show a significant right-hemisphere advantage in a figural comparison task, this lateralization can shift towards a more symmetrical (or even slightly inverted) pattern, from the first to the second session independently of the levels of gonadal hormones. As similar effects have also been reported in several previous studies [28,30,31,53], it is apparent that the session effect constitutes an important variable to be controlled in lateralized repeated measures designs with female subjects, if the true menstrual cycle effects on cerebral asymmetries are to be deduced. One possibility is to compare in session one the carry-over unaffected performance of menstrual versus midluteal subjects. However, the concomitant reduction in statistical power will reveal less statistically significant results [32]. We therefore conducted two experiments which controlled these possibly confounding variables, designed to reveal steroid effects

on cerebral asymmetries in three visual half-field tasks. Two of these tasks (face discrimination and figural comparison) typically reveal a left visual field advantage, while the third is a lexical decision task which usually yields a right visual field superiority [34]. A group of normally cycling women were tested with these three visual half-field tasks during their menstrual and midluteal cycle phases. We expected functional cerebral asymmetries only during menses, but less pronounced functional asymmetry during the midluteal phase, provided that other confounding variables could be eliminated. In the second experiment, men and postmenopausal women were tested twice with the same tasks, with an inter-test interval of 14 days. We expected stable functional cerebral asymmetries for both groups. Since the most prominent feature of the midluteal phase is the peak of progesterone concentration, we measured this steroid to validate the cycle phase of our subjects. We collected saliva samples at each test session for both female groups, and analyzed the levels of progesterone (P_4) by radioimmunoassay (RIA).

2. Methods

2.1. Subjects

Sixty-six subjects participated in this experiment. Apart from 19 young men, 26 were healthy, normally cycling women, with a regular (26–30 days) menstrual cycle, and 21 were postmenopausal women who had had their last menses at least 3 years before. All subjects were right-handed, as determined with the Edinburgh-Inventory [58]. The asymmetry-index (LQ) provided by this test is calculated as $(R-L/R+L) \times 100$, resulting in values between -100 and $+100$. This range describes the continuum from extreme sinistrality to extreme dextrality. The mean handedness score of our sample was $+93.2$ (range $+50$ to $+100$) for the normally cycling women, and $+97.9$ (range $+67$ to $+100$) for the postmenopausal women, and $+94.0$ (range $+79$ to $+100$) for the male subjects.

The mean age was 30.4 years (range 21–41 years) for the normally cycling women, 56.1 years (range 46–80 years) for the postmenopausal women and 29.3 years (range 24–45 years) for the men.

Women who had used, during the last 6 months oral contraceptives, hormonal replacements or any other medication which could effect the central nervous system were excluded from the study. All subjects had to have normal or corrected visual acuity, and were naive of the experimental hypothesis. Subjects were recruited by announcements, and were paid for their participation.

2.2. Procedure and materials

Prior to the experimental sessions, a meeting was arranged to inform female subjects about the general procedure, to measure handedness and visual acuity, and to collect data about the menstrual cycle of the normally cycling women. The women agreed to inform us of the first day of their next cycle, thus to plan the dates for the experimental sessions. Every normally cycling woman was tested twice, once during the menstrual phase (cycle day 2) and once during the midluteal phase (cycle day 21–23), to yield the largest differences in progesterone levels. The individual length of each woman's menstrual cycle was taken into account when planning the appointments for the experiments. Additionally, they were requested to confirm the onset of menses after the experiments. The men and postmenopausal women were tested in corresponding time intervals of 14 days. In order to balance the design for the normally cycling women, the two sessions were not conducted during a single menstrual cycle. Half of the normally cycling women were first tested during the midluteal phase, and later tested during the menstrual phase of the consecutive cycle. To minimize circadian rhythm influences, every experimental session was performed at the same time of the day. Directly after every session a sample of saliva was collected from the female subjects. Progesterone (P_4) levels were assessed by radioimmunoassay (RIA) to evaluate the menstrual cycle phases in normally cycling women, and to determine the stability of steroid hormone levels in postmenopausal women.

The measurement of steroid levels in the saliva is a valid and non-invasive method [64,65]. Salivary progesterone measurements reflect serum concentrations reliably and provide an attractive alternative to serum measurement [9,16]. Correlations between plasma and salivary progesterone levels measured in the same subject are generally very high [24]. Although the relative range of values obtained between the follicular and luteal phases are more compressed when measured in the saliva, compared to these in plasma [24], they suffice to reliably define hormone criteria for further analysis.

The determination of progesterone in the saliva was carried out by the RIA technique. Saliva samples were stored at -22°C until all female subjects had completed the tests. Progesterone was assayed using a ^{125}I Coat-A-Count[®] progesterone (Diagnostic Products, Los Angeles, CA). We adapted this method for the use with saliva by increasing tracer incubation (6 h, RT instead of 3 h, RT), and doubling the volume of the probe (200 μl). The intra-assay variability was about 10%.

Using conventional assays, the determination of estradiol in the saliva appear to be not as reliable,

since Choe, Khan-Dawood and Dawood [16] and Belkien et al. [7] were unable to show a correlation between saliva and plasma estradiol levels in normal menstrual cycles [61].

The visual half-field tests were started by placing the head of a seated subject on a chin rest, thus immobilizing the head, and the subjects were instructed to keep their head and body still during the whole test. This was an important measure to ensure that stimulus presentation was always more than 2° of visual angle to either left or right of the fixation cross. A pool of 120 German nouns was used for the lexical decision task, consisting of four to seven letters, selected for their high degree of abstraction [6] to maximize the left-hemisphere advantage. Sixty stimuli were used for the first, and 60 for the second experimental session, the order of the two blocks being balanced amongst the subjects. For the figural comparison condition, 120 black irregular polygons were constructed using a computer software (Paintshop[®]), within a white frame 4.8 cm wide by 4.5 cm high. Sixty polygons were presented per session, again the two stimulus blocks being balanced. Further details of the lexical decision and the figural comparison task have been described by Rode, Wagner, and Güntürkün [67]. Photographs for the face discrimination task were from a US college album of the 1950s. Students on these pictures were all males in their early 20 s, clean shaven, short haired and without spectacles. To mask all non-facial characteristics, all photographs were covered with an ovoid overlay covering the background and clothing, with exception of the collar.

In each trial the subject fixated a cross in the center of the monitor, after which the first stimulus appeared, either in the left or in the right visual half-field, while an empty frame appeared in the other half [67]. The exposure time was 185 ms, and all three tasks comprised of 70 trials each, excluding the first 10 practice trials, which were eliminated. In the lexical decision task, the subjects were instructed to indicate as quickly and as correctly as possible whether the stimulus shown was a word or a non-word. In the polygon task, the subjects had to memorize the centrally presented stimulus. Two seconds later one polygon was shown either to the left or the right of the fixation cross. Subjects had to decide whether the laterally shown pattern was identical to it or not. In the face discrimination task [34], subjects had to indicate whether the presented face was normal or an altered, 'monster' one. In the latter stimuli certain features were deleted or translocated. For example the positions of one eye and the mouth were swapped or everything was deleted except the nose etc. All faces had the same orientation and bore unemotional, neutral expressions. Subjects were tested with two parallel versions of each task. Although no differences between

these versions were found in the previous tests, we nevertheless balanced them over the two test sessions. Additionally the presentation of the tasks were pseudorandomized.

Two separate experiments were run with the same procedure but with different subjects. The first study tested young and normally cycling women. In the subsequent experiment men and postmenopausal women were tested. We did not combine the results, thus pooling the two data sets into a single large one, for one important reason: the statistical analysis of the results for the young women had to be different from the one for the other subjects. In normally cycling women the confounding effects of the two repeated measures (session and menstrual cycle effects) had to be controlled. By controlling the session effect, we were thus able to analyze the menstrual cycle effects. This is different from the postmenopausal and the male group, in which only the session effect had to be considered for no menstrual cycle effect existed. Here, the session effect had to be regarded. By retaining the testing order, we were then able to unequivocally analyze the stability of lateralization patterns over the time.

To control potential systematic variations in mood (which can influence performance levels for cognitive tasks), a German mood scale [90] was applied during each test session.

3. Results

3.1. Experiment 1

Twenty-six normally cycling female participants completed the two test sessions. The criteria for acceptance required P_4 values to be at least greater in midluteal than in menstrual samples, and seven subjects (27%) were excluded because their steroid samples did not meet these criteria. The mean values obtained for salivary P_4 in the remaining normally cycling women were 275.8 (SEM = 18.7) pg/ml in the menstrual and 422.1 (SEM = 27.7) pg/ml in the midluteal phases. A paired *t*-test revealed a significant mean salivary P_4 difference between the two phases ($t(18) = -7.16$, $P < 0.001$). The mean and standard error during the menstrual cycle of our female subjects are in the range of the normative data of Choe, Khan-Dawood and Dawood [16], who found a significant increase from 238.7 (SEM = 14.3) pg/ml in the proliferative phase to 475.3 (SEM = 39.8) pg/ml in the luteal phase ($P < 0.001$).

There were no significant mood differences between the mean *T*-scores for menstrual ($T = 55.07$) and midluteal ($T = 52.40$) cycle phases ($t(18) = 0.89$; n.s.).

The data of the 19 normally cycling women were analyzed using parametric statistics because the Kol-

mogorov–Smirnov Goodness-of-Fit test showed normal distributions for all variables. The medians of the reaction times for correct responses for all three tasks, and the frequency of the correct answers were analyzed with a two-by-two analysis of covariance (menses and luteal phase; right and left visual field) with repeated measurement and test order as a covariate, in order to control carry-over effects. Since we expected potential asymmetries in task-related directions (left hemisphere dominance for the lexical task and right hemisphere superiority for the figural comparison and the face discrimination tasks), we computed one-tailed *t*-tests in order to calculate only the strength of a task-related lateralization pattern during each cycle phase. For example, if a significant asymmetry in the lexical decision task appeared during one or both cycle phase(s), we expected an advantage for the left hemisphere (right visual field). The alpha adjustment of multiple test procedures were realized with the sequentially rejective Bonferroni test [38].

3.1.1. Lexical decision task

3.1.1.1. Correct responses. The frequency of the correct responses in the lexical decision task were analyzed with a two-by-two analysis of covariance with repeated measures. The first repeated measure was menses vs luteal phase, the second one was right vs left visual field. The test order acts as a covariate in order to control carry-over effects. In the lexical decision task, the analysis of the frequency of correct answers showed a highly significant interaction between visual half-field and cycle phase ($F(1,17) = 8.98$, $P < 0.01$). Additionally, the three-way interaction between visual half-field, cycle phase and the test order showed significance ($F(1,17) = 11.97$, $P < 0.01$). The analysis of the main effect, the ‘visual half-field’, was not significant, indicating a more symmetric lateralization pattern ($F(1,17) = 2.05$, n.s.). No further significances including the main effect of cycle phase ($F(1,17) = 1.60$, n.s.) were found. An analysis of changes in the performance of either the left or the right visual half-field from menses to midluteal cycle phase also revealed no significant alteration (LVF: ($t(18) = 0.004$, n.s.), RVF: ($t(18) = 1.66$, n.s.)). However, these last analyses could have been biased by carry-over effects of test order [34]. The overall level of performance in the lexical decision task was high (about 91% correct responses).

In order to describe the direction of interaction between visual half-field and cycle phase, independently of carry-over effects through the test order, we computed alpha adjusted paired *t*-tests (one-tailed) of visual half-field differences to indicate the strength of the lateralization during both cycle phases. This analysis was performed on the results of the first session only, and separately for women who had had their

first test session during their menses, and those who had done the first test during their midluteal phase. These data could not have been influenced by carry-over effects. Of course it should be noted that we were now dealing with only half of the data for analysis. The results indicated a marginally significant advantage of the expected right visual field (left hemisphere) during menses ($t(9) = -1.54$, $P = 0.079$), and no cerebral dominance during the luteal phase ($t(8) = -0.45$, n.s.) (Fig. 1).

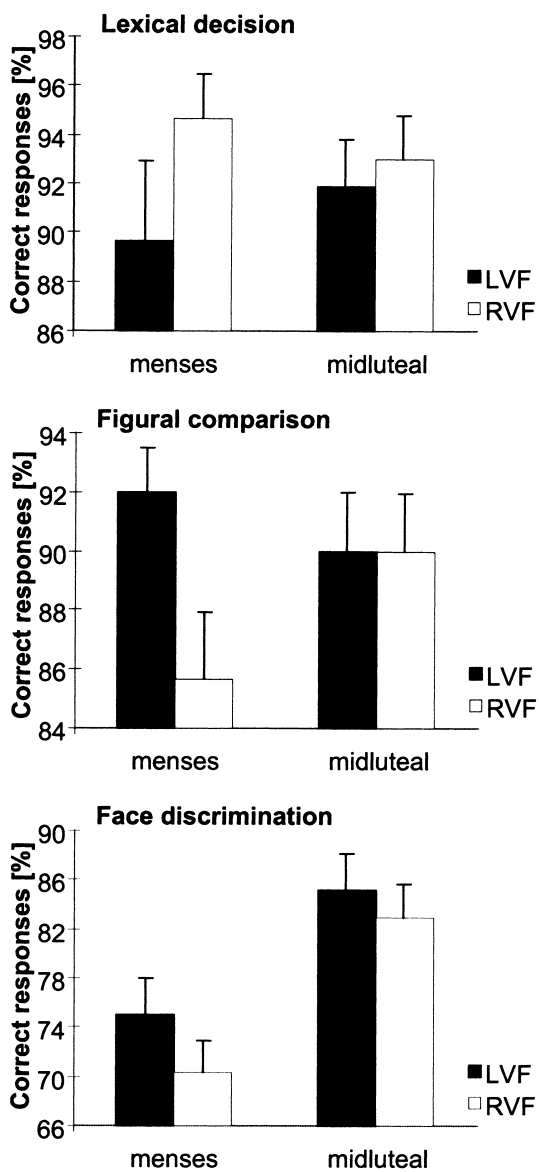


Fig. 1. Means of the correct responses for the normally cycling women at menstrual and midluteal cycle phase for the lexical, the figural, and the face stimuli, presented in the left (LVF) and right (RVF) visual half-field, in the carry-over unaffected session one.

3.1.1.2. Response times. For the response times the analysis yielded no significant main effects or interactions (all $F(1,17) < 2.00$, n.s.).

3.1.2. Figural comparison task

3.1.2.1. Correct responses. The frequency of the correct responses in the figural comparison task were analyzed with a two-by-two analysis of covariance with repeated measures. Again, the first repeated measure was cycle phase, the second one was visual half-field. The test order acts as a covariate in order to control carry-over effects. In this task, the analysis of the correct responses again indicated a significant interaction between visual half-field and cycle phase ($F(1,17) = 7.93$, $P < 0.05$). Also the three-way interaction (visual half-field \times cycle phase \times test order) was found to be significant ($F(1,17) = 5.97$, $P < 0.05$). In addition to these effects, significances were found for the main effect 'cycle phase', with a better performance during the menses ($F(1,17) = 11.29$, $P < 0.01$), and the interaction with the covariate 'test order' ($F(1,17) = 10.41$, $P < 0.01$). No other effects, including 'visual half-field' ($F(1,17) = 0.68$, n.s.), yielded significance. The overall performance in the accuracy of this task was high (about 87%).

To analyze the pattern of lateralization during both cycle phases which were not influenced by the test order, we computed alpha adjusted paired t -tests (one-tailed), only for the first test session. The results indicated a highly significant advantage of the expected left visual field (right hemisphere) during the menses ($t(9) = 3.23$, $P < 0.01$), in contrast to symmetrical performance during the luteal phase ($t(8) = -0.005$, n.s.) (Fig. 1).

3.1.2.2. Response times. The analysis of response times in the figural comparison task showed no significant main effect or interaction (all $F(1,17) < 2.21$, n.s.).

3.1.3. Face discrimination task

3.1.3.1. Correct responses. The frequency of the correct responses in the face discrimination task were analyzed with a two-by-two analysis of covariance with repeated measures. The first repeated measure was menses vs luteal phase, the second one was right vs left visual field. The test order acts as a covariate in order to control carry-over effects. In this task, the analysis of the frequency of correct responses revealed again a significant interaction between the visual half-field and the cycle phase ($F(1,17) = 4.45$, $P < 0.05$). Additionally, a strong lateralization with a superiority of the right hemisphere could be demonstrated ($F(1,17) = 5.29$, $P < 0.05$). Moreover, the covariate 'test order' was highly significant ($F(1,17) = 18.94$, $P < 0.001$). The

overall performance in the face discrimination experiment (79%) indicated this to be the most demanding of all three tasks.

To analyze the lateralization pattern during both cycle phases without the influence of carry-over effects of test order, alpha adjusted paired *t*-tests (one-tailed) of session one data were computed. Women showed a more bilateral organization during the luteal phase ($t(8)=0.88$, n.s.), in contrast to a marginally significant left visual field advantage (expected right hemisphere) during menses ($t(9)=1.41$, $P < 0.10$) (Fig. 1).

3.1.3.2. Response times. Similar to the other tasks, the analysis of response times demonstrated no significant main effects or interactions (all $F(1,17) < 2.18$, n.s.).

3.1.4. Correlations between saliva progesterone levels and RVF/LVF differences in normally cycling women

Since the ANOVA results indicated significant interactions between the visual half-field and cycle phase for the accuracy data only, we did not consider the analysis of the response times. Additionally, to avoid problems associated with repeated testing, only the carry-over unaffected data of session one were used. In order to examine the relationship between gonadal hormone levels and functional cerebral asymmetries, we computed differences of correct responses between the right and the left visual half-field (% correct responses RVF minus LVF). Negative values indicate a right, and positive values a left hemisphere dominance.

In view of the ANOVA results, which had depicted asymmetric lateralization patterns during the menses and a more bilateral organization during the midluteal phase, we expected a decrease of the functional cer-

ebal asymmetries during low levels of gonadal hormones, to a bilateral or slightly shifted pattern during higher levels of steroids. In order to test this hypothesis, we used multiple regression procedures to predict visual half-field differences from P_4 levels. This was done for all three tasks. Indeed, a significant linear model of the *R–L* differences in the figural comparison task could be revealed from saliva P_4 levels ($F(1,17)=4.70$, $P = 0.045$). The correlation between the two variables was $R = 0.47$. The best-fitting curve estimation was obtained with a logarithmic component entering the regression equation ($F(1,17)=5.25$, $P = 0.035$). The saliva concentration of P_4 explained about 22% of the variance of the *R–L* differences in the accuracy data of the figural comparison task. Fig. 2 shows the distribution of asymmetry scores as a function of measured P_4 level together with the best-fitting logarithmic function.

No further evidences was found for any significant relationships between P_4 and the asymmetry scores in the face discrimination or lexical decision tasks.

To decide which hemisphere is more modulated by P_4 in the figural comparison task, P_4 concentrations were correlated with the carry-over unaffected correct responses of right and left visual field data (session 1). There was a clear trend for a P_4 modulated accuracy in the right visual field (subdominant left hemisphere) ($F(1,17)=5.25$, $P = 0.057$) with a correlation of $R = 0.44$. There was no significant relationship ($R = -0.05$) between P_4 levels and left visual field accuracy ($F(1,17)=0.04$, n.s.).

3.1.4.1. Interim summary. The main result of the first experiment is that functional asymmetries in all three visual half-field tasks (lexical decision, figural comparison and face recognition) were modulated by the menstrual cycle. Regardless of whether the left or the right hemispheric systems were invoked, the extent of laterality was increased during the menses (low progesterone levels) and reduced during the midluteal phase (high progesterone levels).

3.2. Experiment 2

A prerequisite for the postmenopausal women was that they had to have low mean values of salivary P_4 measured at both sessions. Indeed, P_4 -levels were not significantly different between session one (295.2 pg/ml, SEM=20.4) and session two (314.4 pg/ml, SEM=32.6) ($t(20) = -0.67$, n.s.), and were additionally similar to the steroid levels of normally cycling women during their menses. This was the case for all 21 postmenopausal women tested and consequently all were included in the analyses. There were no significant mood variations between session one ($T = 48.14$) and session two ($T = 49.12$) in these subjects

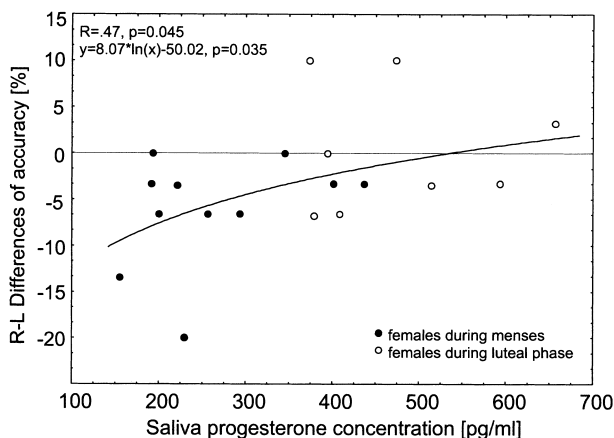


Fig. 2. Scatter plot of the right–left differences in the accuracy of the figural comparison task for session one, as a function of saliva P_4 level. Negative values indicate dominance of the right hemisphere, while superiority of the left hemisphere results in positive values. White points indicate values of the normally cycling women at midluteal phase, black points show values for other women during menses. The best-fitting polynomial function is shown.

($t(20) = -0.43$; n.s.). Male subjects were not monitored for mood changes or their progesterone levels.

The visual half field data of the 21 postmenopausal women and 19 men were analyzed using parametric statistics because the Kolmogorov–Smirnov Goodness-of-Fit test revealed normal distributions for all variables. For all three experiments, the medians of the reaction times for correct responses and the frequency of correct answers were analyzed with a two-by-two (first and second session; right and left visual field) analysis of variance with repeated measurement and ‘group’ as the between-subject variable.

3.2.1. Lexical decision task

For this task, the analysis of the frequency of correct answers in both groups showed a highly significant and well-known left hemispheric advantage (right visual field) for verbal stimuli ($F(1,37) = 17.07$, $P < 0.001$). This effect did not interact with ‘group’ (postmenopausal women vs men) ($F(1,37) = 2.78$, n.s.) and/or ‘time’ (first vs second session) ($F(1,37) = 0.18$, n.s.). However, we found a significant three-way interaction between visual half-field (VHF), ‘time’, and ‘group’, indicating a slightly increased asymmetry during the second session in males, in contrast to a slightly decreased cerebral asymmetry over time for the postmenopausal women. Male subjects showed a higher rate of correct responses (93.7%) compared to postmenopausal women (80.5%) ($F(1,37) = 23.94$, $P < 0.001$). The overall level of performance in the lexical decision task was high (87.1% correct responses for both groups and both sessions).

For the response times the analysis yielded no significant main effects or interactions (all $F(1,36) < 2.63$, n.s.).

3.2.2. Figural comparison task

For this task, the analysis of the correct responses indicated a significant difference between postmenopausal women (85.5%) and the male subjects (90.4%) in overall performance ($F(1,37) = 6.11$, $P < 0.05$). No other main effect or interaction reached significance. Overall level of performance in the figural comparison task was high (88.0% correct responses for both groups and both sessions).

The analysis of response times in the figural comparison task showed a highly significant dominance of the expected left visual-field (right hemisphere) ($F(1,37) = 11.58$, $P < 0.01$), but again this effect did not interact with ‘group’ ($F(1,37) = 2.05$, n.s.) and/or ‘time’ ($F(1,37) = 0.54$, n.s.), indicating stable functional cerebral asymmetries for both groups, independent of repeated measures. No other significant effects were found.

3.2.3. Face discrimination task

Also in this task, the analysis of the frequency of correct responses demonstrated a very strong superiority of the expected right hemisphere (left visual field advantage) ($F(1,37) = 33.99$, $P < 0.001$) for both groups, and again this effect did not interact with ‘time’ ($F(1,37) = 0.11$, n.s.) and/or ‘group’ ($F(1,36) = 0.51$, n.s.). Male subjects showed significantly better overall performance (80.2%) compared to the postmenopausal women (71.5%) ($F(1,37) = 7.95$, $P < 0.01$). No other main effect or interaction reached significance. The overall performance in the face discrimination task (75.8% correct responses) indicated that this task was the most demanding of the three experiments.

Also the analysis of the second dependent variable (response times) demonstrated a highly significant visual half-field effect ($F(1,37) = 10.28$, $P < 0.01$), indicating faster response times for the right hemisphere in both groups. Again this effect did not interact with ‘group’ ($F(1,37) = 0.16$, n.s.) and/or ‘time’ ($F(1,37) = 2.61$, n.s.). Additionally, only the differences in overall response times between the male subjects (934 ms) and postmenopausal women (1058 ms) reached significance ($F(1,37) = 4.81$, $P < 0.05$). No other significances were evident.

3.2.4. Correlations between saliva progesterone levels and RVF/LVF differences in postmenopausal women

There was no evidence of a curvilinear relationship between P_4 and visual field differences in the accuracy or response times of the different tasks. For these analyses we used only data of the first session, comparable to the normally cycling women.

3.2.4.1. Interim summary. The main result of the second experiment was that functional asymmetries for young men and postmenopausal women were stable over the two test sessions. In normally cycling women, on the other hand, these two test sessions revealed significant laterality changes for the same three visual half-field tasks.

4. Discussion

The most important results of the first experiment are the significant interactions between the menstrual cycle phase and visual half-field, shown by accuracy data of all three tasks. These results indicate that gonadal hormone modulation of lateralization patterns act independently of task or hemisphere, and appear in prototypical left as well as in right hemispheric tasks. The results of the second experiment show that the lateralization pattern in postmenopausal women has stayed remarkably stable over time for all of the

three visual half-field tasks. Although the overall performance level for men and postmenopausal women was quite different, the lateralization patterns for postmenopausal women were virtually identical to those of young men. Thus, the data of the two experiments make it likely that steroid fluctuations during the menstrual cycle are able to modify cerebral asymmetries to an important extent. The decrease of steroid levels appears to stabilize cerebral asymmetries, resulting in male-like lateralizations, whereas increases of steroid levels appear to reduce functional asymmetries.

In normally cycling women, a significant overall hemispheric dominance (LVF) appeared only for the most demanding face discrimination task. For the two other tasks no main effect of visual field was found, in line with the symmetrical organization often found in women [13,29,33,34,37,51,60,87]. The most important finding of the present study, however, is that this overall picture applies if the female asymmetry data are averaged over the entire menstrual cycle. Tested during low steroid periods alone, female asymmetries are similar to that of men. This conclusion is also strongly supported by results for the postmenopausal women, who showed significant and stable asymmetries in all three tasks, similar to those of the males.

It is rather unlikely that the differences between the two female groups could solely be a function of age. If this would be the case, asymmetric alterations would also accompany aging in males. Indeed, White, Green and Steiner [88] found no systematic age-related changes in the direction or degree of lateralization in males of three age groups (mean ages 21, 46 and 71 years). Thus we propose that specific steroid effects may be responsible for the asymmetry changes in postmenopausal women, and not their higher ages per se.

These results are in agreement with a number of previous reports on cycle-related asymmetry changes, while contradicting others. Similar to the results of Rode et al. ([67] figural comparison), Heister et al. ([35] face discrimination), Mead and Hampson ([53] dichotic listening with verbal stimuli), and Sanders and Wenmoth ([69] dichotic listening with musical stimuli), we found a more asymmetric lateralization during the menses, opposite to a more bilateral organization during the period of elevated gonadal hormones. This differs from the results of other authors who apparently obtained the greatest asymmetries during the high-steroid phases (figure recognition [8], dichotic listening [30,31,69], spatial bisection [49]). And finally, in accordance with Sanders and Wenmoth [69,70], our results also show that tasks that underlie robust hemispheric asymmetries, such as face discrimination, can be modulated by hormonal cycles, contrary to the assumption of Bibawi, Cherry and Hellige [8].

Also, our data do not support the assumption that asymmetries vary alternatingly with a left hemi-

sphere dominance during the luteal phase and a right-sided superiority during the menses [69]. Both, the hypothesis of alternating and reciprocal asymmetry changes during the cycle [69] and our data set have significant interactions between cycle phase and hemisphere in left and right hemisphere tasks in common. However, our data set also shows that the visual half-field differences in the left hemispheric lexical decision task were small during mid-luteal cycle phases and larger during menses. The asymmetry scores for lexical decision and face discrimination during menses were only significant at the 10% level, and thus mainly represent a trend. However, the whole pattern of cycle-related alterations of the lexical decision task is opposite to the view [69,70] of reciprocal asymmetry changes with a left-hemisphere superiority during midluteal time-points. If, in addition, low steroid levels would conjunct with low asymmetries in lexical decision [69], we should expect postmenopausal women to be less lateralized in this task. However, just the opposite was the case. Therefore, we are inclined to believe that all three asymmetry measures used, show a parallel increase and decrease of their asymmetry extent concomitant with low and high steroid levels.

The apparent contradictory findings of a number of studies cited above may in part have been caused by the omission of hormone assays, concomitant with the inclusion of subjects outside the appropriate phases of menstrual cycle. We had to exclude 27% normally cycling women, due to the hormone assay criteria, a rejection rate similar to several other studies (23% [53], 25% [55]). Another important prerequisite for the present analysis was the control of carry-over effects due to repeated testing. For the face discrimination task, the significant results of the testing order indicate better performance for women who had their first test during the luteal phase. For the figural comparison task, the interaction of test order with the cycle phase led to a stronger decrease of performance over time when the second session coincided with the luteal phase. Thus, the lateralization pattern of session one, unaffected by any carry-over effect, was virtually identical for all tasks for the normally cycling women, differing only between the menses and the luteal phase. These findings further illustrate the importance of controlling the hormonal status as well as session effects in such studies.

The cycle-related differences in lateralization shown here, appeared only in the analysis of the data on the accuracy but not on the reaction-times. Although we cannot rule out the possibility of a speed-accuracy trade-off, this should not affect the main result of these analyses, cycle-dependent laterality changes only in normally cycling women. A number of previous studies have also encountered cycle-related lateralization

differences in the analysis of data on accuracy (e.g. [8,53,69]).

In the figural comparison task, lateralization appeared largely to be under the direct influence of progesterone. This steroid had an enhancing effect on performance of the subdominant left hemisphere, such that high levels (monitored by the salivary P₄) led to a symmetrical lateralization pattern. The figural comparison task and other similar visuo-spatial lateralization tasks are known to reveal significant interactions between the visual half-field and sex [15,34,60]. This would support the assumption, that sex hormones primarily affect those cerebral asymmetries which have been shown to be sex-dependent. Up to now, some studies have reported functional effects of estradiol on lateralization (e.g. [30,31]), and some experiments

could reveal significant correlations between testosterone levels and cerebral asymmetries [79–82]. However, to our knowledge no study so far could reveal a significant correlation between dynamic, within-cycle changes of a sex hormone and lateralized cerebral function. Based on arguments presented below, we propose that levels of progesterone could indeed be an important factor in altering corticocortical transmission, and thereby the extent of lateralization.

4.1. The hypothesis of progesterone-mediated hemispheric decoupling

Our results demonstrate a reduction of lateralization during the luteal phase for all three tasks. Since both left and right hemispheric tests were used, it is unlikely that high levels of gonadal steroids have selectively inhibited or activated only a single cerebral hemisphere. More likely, cerebral asymmetries in general could have been reduced through a mechanism which altered processing in both hemispheres.

Since during the luteal phase plasma levels of both estradiol and progesterone are increased, it is possible that changes in lateralization are either due to one of these steroids or result from their combined action. But we have shown that progesterone had a significant impact on the increase in performance of the left hemisphere which ultimately resulted in a reduction of asymmetry at least for the figural comparison task. It is thus conceivable that progesterone may be at least one of the key factors in the modulation of cerebral asymmetries. However, it should be noted that other functions might, in principle, be induced also by other steroids, including estradiol [30,31,54]. We propose that 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 in the functional hemispheric decoupling and thus to a temporal reduction in functional asymmetry (Fig. 3).

The human corpus callosum contains at least 200 million fibers [1,83], which are mostly topographically organized [23]. Most callosal fibers arise from excitatory and glutamatergic pyramidal neurons [18,59]. Only a very small proportion of callosal fibres (probably far less than 5%) have been shown to be inhibitory and GABAergic [39,86]. In spite of this mainly excitatory cortico-cortical transmission, the main and longer lasting effect of callosal activation appears to be inhibitory [40], because most callosal fibers terminate on pyramidal neurons which then probably activate GABAergic interneurons [84,85]. These activated inhibitory cells could then induce a widespread inhibition in homotopic regions of the contralateral hemisphere [18]. Thus, the corpus callosum may not simply exert any excitatory or inhibitory action on the

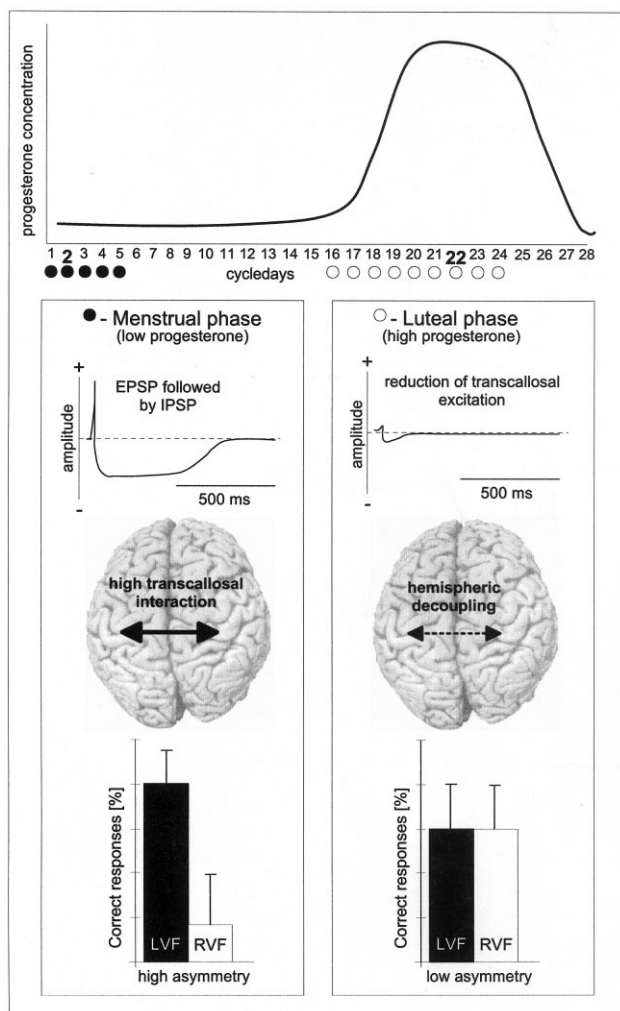


Fig. 3. The hypothesis of progesterone-mediated interhemispheric decoupling. It is assumed that a cycle-dependent increase in progesterone concentration during the luteal phase decreases glutamatergic non-NMDA and increases GABA receptor activation. These effects lead, via a decrease of transcallosal neuronal activation, to hemispheric decoupling, which then results in lesser functional asymmetries. See detailed explanation in the Discussion.

contralateral hemisphere, but rather to induce brief excitatory postsynaptic potentials (EPSP), followed by prolonged inhibition (IPSP) [43,72].

It has been demonstrated [43] that after callosal stimulation, the first excitatory response mainly depends on the activation of glutamatergic non-NMDA receptors. This initial EPSP is followed by a long-lasting IPSP, which has two components, with peak latencies of 30 ms and 185 ms respectively [18,43]. Differences in the pharmacological responses of these two components indicate the presence of two types of GABAergic interneurons, which possess two different types of receptors [43]. The GABA_A receptors mediate rapid inhibitory chloride currents, while the GABA_B receptors are coupled to slow inhibitory currents [48]. It is probable that most of these GABAergic neurons are excited by those pyramidal neurons which receive callosal input [41], since the blockage of the initial EPSP by kynurenic acid (a broad spectrum excitatory amino acid antagonist), and by CNQX (6-cyano-7-nitro-quinoline-2,3-dione, a highly specific non-NMDA antagonist), not only suppressed the initial excitatory response but also the following IPSPs [43].

Progesterone has been demonstrated to suppress in a dose dependent fashion the glutamate-induced excitatory responses of neurons [76,77]. Pharmacologically it could be shown that this effect is due to the attenuation of non-NMDA glutamate-receptors without being mediated by an increase of GABA inhibition [75]. Generally, physiological doses of progesterone reduce the excitatory glutamate responses by 87%, the magnitude of the change being directly proportional to the progesterone dose [77]. Progesterone is known to augment the inhibitory neuronal response to GABA [75]. In particular the 5- α -reduced metabolites of progesterone are potent positive allosteric modulators of GABA_A receptors [47], increasing channel openings of the GABA-gated chloride channel [68]. Additionally, an experimental or estrous-cycle dependent increase of progesterone concentration, up to the level of the rats' proestrus phase, increases neocortical GABA_B receptor density [2,3]. Presynaptically, GABA_B receptors are powerful regulators of transmitter release from GABAergic and glutamatergic synapses [3]. Thus, an increase of progesterone during the luteal phase could, after callosal activation, decrease the first excitatory EPSP, directly by decreasing non-NMDA receptor efficiency, and indirectly by augmenting the GABA responses, thereby additionally decreasing the effect of the glutamatergic callosal input. Together, these processes may result in a relative functional decoupling of the hemispheres due to high progesterone concentrations during the midluteal phase.

Estradiol exerts opposite effects with an increase to glutamate response by 86% [78]. If, however, neuronal

tissues are pretreated with estradiol before progesterone application, or if estradiol and progesterone are applied in a combined fashion, glutamate receptors are downregulated as with progesterone alone [77]. Thus, at least during midluteal cycle phase, the combined release of estradiol and progesterone would result in a decrease of non-NMDA glutamate receptor responsiveness. During the preovulatory cycle phase, in which estradiol peaks without progesterone, effects on interhemispheric interaction could be substantially different. Indeed, Altemus et al. [4] found greater asymmetry in follicular compared with luteal phase, while Hampson [31] reported asymmetry scores to be even more lateralized in the preovulatory phase than during menses.

Several neuropsychological models suggest that interhemispheric cross-talk is one of the most essential mechanisms in causing cerebral asymmetries (for review [14,36]). The most widespread view in explaining cerebral asymmetries by callosal mechanisms is reciprocal inhibition in which a stimulus-specific activation of one of the hemispheres inhibits the other one during task processing [19–21,25,56,62,63]. These assumptions which state that *non-static* functional mechanisms are able to cause asymmetries are difficult to reconcile with evidences for neuroanatomical and thus *static* asymmetries [42,71]. We propose that lateralized neural processes may probably emerge from anatomical asymmetries as well as from interhemispheric cross-talk. Thus, a steroid-induced reduction in interhemispheric transmission should reduce asymmetries to levels maintained by intrahemispheric mechanisms which do not depend on callosal transmission. The existence of these intrahemispheric asymmetry mechanisms are most evident in split-brain patients which lack a corpus callosum but still represent classic models to study the lateralization of different sensory, cognitive, or motor systems [27,45,46,57]. This is in line with our hypothesis. Indeed, lateralized performance in all three tasks of the present study was reduced, but with exception of the figural comparison task not completely abolished during midluteal phase. We are therefore inclined to believe that the data of this study resulted from a progesterone-induced alteration of interhemispheric interaction which then resulted in concomitant reductions of the degree of cerebral asymmetries.

Acknowledgements

The authors are grateful for grants from the MWF Nordrhein-Westfalen, the Deutsche Forschungsgemeinschaft, and the Alfried Krupp-Stiftung. They also acknowledge the help of Dr J. Kugler for radio-

immunoassay measurements, and of S. Rasmjou for linguistic improvements to the manuscript.

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