# Hemispheric asymmetry in spatial attention across the menstrual cycle

Markus Hausmann *

*Institute for Cognitive Neuroscience, Department of Biopsychology, GAFO 05/620, Ruhr-University Bochum, D-44780 Bochum, Germany*

## Abstract

Functional cerebral asymmetries (FCAs) are known to fluctuate across the menstrual cycle. The mechanisms of these sex hormonal modulations are poorly understood. It has been suggested that gonadal steroid hormones might suppress or specifically activate one hemisphere. However, recent studies suggest that high levels of gonadal steroid hormones reduce FCAs by its modulating effects on cortico-cortical transmission. To investigate the activating effects of gonadal steroid hormones on the interhemispheric interaction, a visual line-bisection task was administered to normally cycling women during menses and the midluteal cycle phase as well as to similar-aged healthy men. The results replicate previous findings of a sex difference in line-bisection as a function of hand-use and show that the hand-use effect fluctuates across the menstrual cycle. High levels of estradiol during the midluteal phase were related to a decrease of the hand-use effect. It is concluded that cycle-related fluctuations in levels of gonadal steroid hormones affect hemispheric asymmetry of spatial attention, presumably by interhemispheric spreading of neuronal activation.
© 2005 Elsevier Ltd. All rights reserved.

## 1. Introduction

Functional cerebral asymmetries (FCAs) are affected by organizing and activating effects of sex hormones (Wisniewski, 1998), and thus contribute to sex-related differences in functional cerebral organization. The activating effects of sex hormones on FCAs have been investigated in women with normal menstrual cycles because their natural sex hormone levels, e.g. progesterone and estradiol, fluctuate dramatically in relatively short-time intervals across the cycle. Plasma levels of progesterone and estradiol are low during menses (cycle days 1–5) and high during the luteal phase in the second half of the cycle after ovulation (cycle days 16–23). Plasma estradiol levels are highest preovulatory during the late follicular phase (cycle days 6–12).

Although contradictions exist, it has been shown that FCAs fluctuate over the menstrual cycle, presumably due to cycle-related hormonal variations (Bibawi, Cherry, &

Hellige, 1995; Hampson, 1990a, 1990b; Hausmann, Becker, Gather, & Güntürkün, 2002; Hausmann & Güntürkün, 2000; Heister, Landis, Regard, & Schroeder-Heister, 1989; McCourt, Mark, Radanovich, Willison, & Freeman, 1997; Mead & Hampson, 1996; Rode, Wagner, & Güntürkün, 1995; Sanders & Wenmoth, 1998). However, the underlying mechanisms for these dynamic cycle-related changes in the functional cerebral organization are still unknown.

It has been suggested that modulation by sex hormones is restricted to a single hemisphere (e.g. Hampson, 1990b), but there is dispute as to which one. Using the visual half-field paradigm, Bibawi et al. (1995) found a left hemisphere (LH) superiority in a chair-identification task during the midluteal phase and concluded that high levels of sex hormones selectively activate the LH. The idea of unilateral activation was supported by Sanders and Wenmoth (1998) in a dichotic-listening study, but in contrast to Bibawi et al. (1995), they found that it was mainly right hemisphere (RH) performance that was suppressed during the midluteal phase, which resulted in a stronger LH advantage for a verbal dichotic task during this phase and a stronger RH advantage for a mu-

* Tel.: +49 234 32 24323; fax: +49 234 32 14377.
*E-mail address:* Markus.Hausmann@ruhr-uni-bochum.de.

sic task during menses. An alternative mechanism has been proposed by McCourt et al. (1997), who have concluded from their data that both LH and RH might have been non-specifically activated midluteally, rather than a suppression of RH function. Thus, a slight FCA in a visuospatial task, favouring the RH, may have been promoted. Unfortunately none of these studies measured hormone levels from blood or saliva samples, and thus potential FCA/hormone relationships were not analysed directly. The absence of cycle validation using hormone assays, different properties of the task (modality, task difficulty, sex-sensitivity of the task), and carry-over effects due to repeated-measures (Hausmann & Güntürkün, 1999) are likely to be at least partly responsible for the inconsistencies in the literature.

In a previous study (Hausmann & Güntürkün, 2000), we took these methodological problems into account and found large FCAs in three visual half-field tasks during menses but reduced FCAs during the midluteal phase. In men and post-menopausal women, FCAs remained stable over time and were similar to those of normally cycling women during menses. Hormone analyses revealed that high levels of progesterone were related to an increase in the performance of the subdominant hemisphere, thus leading to concurrent shifts in FCAs on both verbal (lexical matching) and non-verbal tasks (face discrimination, figural comparison), assumed to tap LH and RH functions, respectively. These findings, which have been replicated in a cross-sectional and longitudinal study (Hausmann, Becker et al., 2002), suggest that sex hormones neither modulate specifically the LH or RH nor do they non-specifically activate both. Based on the assumption that interhemispheric inhibition results in a manifestation of FCAs (e.g. Chiarello & Maxfield, 1996; Cook, 1984), we hypothesized instead that progesterone modulates interhemisperic interaction (Hausmann, Becker et al., 2002; Hausmann & Güntürkün, 2000). According to this hypothesis, it is the less specialized hemisphere for a task that is particularly affected (for details: Hausmann & Güntürkün, 2000).

Estradiol, however, seems to affect both hemispheres similarly, and thus does not affect FCAs (Hausmann, Becker et al., 2002). Parallel estradiol-related changes in neuronal activity of the LH and RH are supported by a fMRI study carried out by Dietrich et al. (2001). This study investigated neuronal activity during motor and cognitive tasks in normally cycling women during menses and the follicular phase (high levels of estradiol). The results showed an estradiol-related increase in overall cortical activation of both hemispheres. However, the relative difference in cortical activation of the LH and RH was not affected. Due to the fact that this study focused on maximal differences in estradiol levels, no conclusions could be drawn about the neuromodulatory effects of progesterone. A recent fMRI study (Fernandez et al., 2003) mapped the cortical activity of women during menses and midluteal phase, and found cycle-dependent changes in the lateralization of cortical activation on a verbal task (synonym judgements) as a corollary of a symmetric increase of neuronal recruit-

ment during the midluteal phase, which is consistent with the reduced FCAs during the midluteal phase observed in previous behavioral studies (Hausmann, Becker et al., 2002; Hausmann & Güntürkün, 2000). Moreover, in line with those studies, Fernandez et al. (2003) showed that progesterone rather than estradiol was related to this effect. However, the additional recruitment during the midluteal phase found by Fernandez et al. was specifically located in the superior temporal gyrus and the medial wall of the superior frontal gyrus. The authors concluded that these findings cannot simply be explained by sex hormone effects on commissural transmission, because neither the superior temporal region nor the medial aspect of the superior frontal gyrus have a disproportional large number of commissural fibers (Pandya, Karol, & Heilbronn, 1971).

If cycle-related changes of FCAs are based on hormonal modulations of interhemispheric interaction, (sex-sensitive) tasks, which cannot be performed without interhemispheric interactions should be hormonally affected. Up to now, only one recent study exists that has addressed this question. Compton, Costello, and Diepold (2004) used a task (Banich & Belger, 1990) in which normally cycling women were required to match letters either within a single hemisphere or between hemispheres. The results did not support the hypothesis that progesterone leads to interhemispheric decoupling. The interhemispheric integration required by this task neither differ between cycle phases nor was related to progesterone levels. However, interhemispheric interaction is a multifaceted process, and the possibility that other interhemispheric processes fluctuate during the menstrual cycle, or that hormonal changes are related exclusively to FCAs, cannot be ruled out.

The present study addresses these questions by using the visual line-bisection task. The line-bisection task is usually used to quantify disorders in spatial attention. Patients with right-hemispheric lesions deviate to the right of the objective middle when bisecting horizontal lines, which has been called left hemineglect. In contrast, healthy right-handed people tend to bisect horizontal lines systematically to the left of the objective middle, called right pseudoneglect (Jewell & McCourt, 2000). A prominent interpretation for this phenomenon is that the two hemispheres differ with respect to the allocation of spatial attention. The LH is concerned almost exclusively with attention to the contralateral right hemispace, whereas the RH is capable of directing attention to both sides of space, although it tends to favor the contralateral left side (Heilman & Valenstein, 1979; Heilman & Van Den Abell, 1980; Mesulam, 1981). Several studies report that pseudoneglect in normal subjects is especially pronounced when the left hand, corresponding to the RH, is used to bisect the lines (e.g. Brodie & Pettigrew, 1996; Hausmann, Corballis, & Fabri, 2003; Hausmann, Ergun, Yazgan, & Güntürkün, 2002; Hausmann, Waldie, & Corballis, 2003; Luh, 1995; McCourt, Freeman, Tahmahkera-Stevens, & Chaussee, 2001; Scarisbrick, Tweedy, & Kuslansky, 1987; for review see

Jewell & McCourt, 2000). The hand-use difference has been interpreted within the framework of an activation-orientation hypothesis (Halligan & Marshall, 1989; Kinsbourne, 1970; McCourt et al., 2001; Reuter-Lorenz & Posner, 1990). Since each hand is controlled primarily by the contralateral hemisphere, the activation-orienting hypothesis (Halligan & Marshall, 1989; Reuter-Lorenz & Posner, 1990) states that the utilization of the left or right hands when bisecting lines should augment the activation of the RH or LH, and thus producing a greater degree of orientation toward the left or right hemispace, respectively (McCourt et al., 2001). However, the bias of both hands deviates towards the left of the veridical center, though more strongly when the left hand is used. This suggests that the hand effect is superimposed on an underlying hemispheric asymmetry, i.e. a RH superiority in visuospatial attention (McCourt et al., 2001).

It has been suggested that the robust and consistent leftward bias in neurotypical participants, even when the right hand is used to bisect lines, results from an inter-hemispheric communication between the RH, which dominates visuospatial attention, and the LH, which mainly controls the right-hand response (Failla, Sheppard, & Bradshaw, 2003; Hausmann, Corballis et al., 2003; Hausmann, Ergun et al., 2002; Hausmann, Waldie et al., 2003). According to the activation-orientation hypothesis (Halligan & Marshall, 1989; Kinsbourne, 1970; McCourt et al., 2001; Reuter-Lorenz & Posner, 1990), we might suggest that, in the right-hand condition, an interhemispheric spreading activation from LH motor areas to the dominant attention network in the RH is reduced relative to an intra-hemispheric spreading activation following left hand-use. An interhemispheric spreading activation probably involves the corpus callosum.

Although the line-bisection task is a rather indirect measure of callosal function, the importance of the corpus callosum in line-bisection, especially of posterior callosal areas (isthmus and splenium), is demonstrated by several studies. If an interhemispheric transfer is not possible or inefficient, the hemisphere controlling the responding hand seems to be responsible for the direction of the attentional bias (Failla et al., 2003), which results in a left bias with the left hand and a right bias with the right hand. This phenomenon, known as symmetrical neglect, is shown in children before puberty, when their posterior corpus callosums have not yet fully matured (Bradshaw, Nettleton, Wilson, & Bradshaw, 1987; Dellatolas, Coutin, & De Agostini, 1996; Dobler et al., 2001; Failla et al., 2003; Hausmann, Waldie et al., 2003; Roeltgen & Roeltgen, 1989), in patients with callosal infarction (Corballis, 1995; Kashiwagi, Kashiwagi, Nishikawa, Tanabe, & Okuda, 1990), and in split brain subjects (Hausmann, Corballis et al., 2003; Heilman, Bowers, & Watson, 1984). Moreover, the line-bisection task seems to be sex-sensitive. Women showed similar degrees of left bias with either hand, whereas men showed the left bias predominantly with the left hand (Hausmann, Ergun et al., 2002; Hausmann, Waldie et al., 2003). This might reflect a stronger interhemispheric connectivity in fe-

males, whose posterior corpus callosum is assumed to be larger on average than in males (DeLacoste-Utamsing & Holloway, 1982; Holloway, Anderson, Defendini, & Harper, 1993; Oka et al., 1999; Steinmetz et al., 1992; for review see, Driesen & Raz, 1995).

Based on these sex-related differences in the effects of hand-use on line-bisection, a stronger hand-use difference was expected for women during low steroid menses, whereas it should be reduced during the midluteal phase. The hand-use difference for men should differ from that of women in their midluteal phase, but should be similar to that of women during menses. Moreover, we expect progesterone to be the key agent affecting the interhemispheric interaction during the menstrual cycle.

## 2. Methods

### 2.1. Subjects

Twenty-four normally cycling women and 14 men were investigated. The mean age of women was 26.96 years (S.D. = 6.19; range: 19–42 years) and 33.93 years (S.D. = 10.02; range: 21–58 years) for men. All participants were right handed, as determined with the Edinburgh-Inventory (Oldfield, 1971). 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 LQ of female participants was 80.23 (S.D. = 18.02; range: 47.0–100) and 89.35 (S.D. = 14.38; range: 60.0–100) for men. The reading direction of all participants was left-to-right. Women who had used oral contraceptives or any other medication affecting the central nervous system during the last 6 months were excluded. All subjects had normal or corrected-to-normal visual acuity and were naive to the study's hypotheses. They were recruited by announcements, and were paid for their participation. Data were collected between February and August 2002 in Auckland, New Zealand. Female participants also took part in other experiments investigating the hormone effects on cognitive abilities and the functional cerebral organisation.

### 2.2. Procedure and materials

Prior to the experimental session, women were informed about the general procedure and data were collected about their individual menstrual cycles. All women agreed to inform us of the first day of their next cycle, in order to plan the dates for the experimental sessions. The normally cycling women were tested twice, once during the menstrual phase (cycle days 1–5) and once during the midluteal phase (cycle days 21–22), to yield the largest differences in estradiol and progesterone levels. Men were tested only once and no blood samples were taken. To control potential repeated-measures effects, half of the female group was first tested during the midluteal phase, and later tested during the men-

strual phase and vice versa. Directly after every session, a blood sample was collected. Serum estradiol and progestrone levels were determined with Chemiluminescent Microparticle Immunoassay (CMIA) by an independent professional medical laboratory, with commercially available CMIA kits.

The line-bisection task was identical to that used in previous studies (Hausmann, Corballis et al., 2003; Hausmann, Ergun et al., 2002; Hausmann, Waldie, Allison, & Corballis, 2003; Hausmann, Waldie et al., 2003). It comprised 17 horizontal black lines of 1 mm width on a white sheet of paper (21 cm × 30 cm). The lines ranged from 100 to 260 mm in their length in steps of 20 mm. The mean length was 183.5 mm. Since the position of the lines (left, center, or right) had important influences on the results of previous studies (Hausmann, Ergun et al., 2002; Hausmann, Waldie et al., 2003; Heilman et al., 1984; Luh, 1995; for review, Jewell & McCourt, 2000), line position was included in the experimental design and were pseudorandomly positioned so that seven lines appeared in the middle of the sheet, five lines appeared near the left and five lines near the right margin. The lateralized lines were 13 mm away from the margin. The line lengths for seven centred lines were 1 cm × 12 cm, 2 cm × 18 cm, 2 cm × 22 cm, and 2 cm × 24 cm (mean = 20 cm) and 10, 14, 16, 20, and 26 cm (mean = 17.2 cm) for five left- and five right-lateralized lines, respectively. The sheet was laid in front of the participant's midline. Participants were instructed to bisect all lines into two parts of equal length by marking the subjective midpoint of each line with a fine pencil. All participants completed the task with one hand and then repeated it with the other in a balanced order under each condition. Scan direction (left-to-right, right-to-left) was also included, because it has been proposed that inadvertent phasic LH or RH activation might result from uncontrolled visual scanning (McCourt et al., 1997). To control the effect of scan direction, all participants performed the task twice. They were instructed to scan each line from left-to-right or right-to-left by placing the pencil at the end of each line, moving the pencil along the line until the subjective center of the line was reached, and then to set the mark. The order of the two scan-direction conditions was counterbalanced. The experimenter covered each line after it was marked to ensure that the participants were not biased by their previous choices. There was no time restriction. The deviations to the left or to the right of each marked line were carefully measured to 0.5 mm accuracy. The percent deviation score for each line was computed as: ((measured left half − true half)/true half) × 100. This procedure is comparable to that used in other studies (Scarisbrick et al., 1987; Shuren, Wertman, & Heilman, 1994) and takes individual line length into account. Then, the mean score for all lines were computed separately for each hand used under each condition. Negative values indicate a left bias, positive values a right bias.

To control potential systematic variations in mood, which might influence performance levels for cognitive tasks, the State-Trait-Cheerfulness-Inventory (STCI-S18; Ruch,

Köhler, & van Thriel, 1996, 1997) was applied during each test session for women. The STCI-S18 is an instrument measuring the three concepts of cheerfulness, seriousness, and bad mood. The concept of 'cheerfulness' represents positive affect, such that subjects with a high score describe themselves, e.g. as being "in good spirits" or "in a mirthful mood". The concept of 'seriousness' is understood as the readiness to perceive, act, or communicate seriously (e.g. "I'm prepared to do a task in earnest"). The concept of 'bad mood' is defined by the two elements of sadness/melancholy and ill humour, such as "I am in a bad mood", "I am sad", "I am in a grumpy mood". Each concept included six items and the response was given on a 4-point rating-scale (strongly disagree, 1; moderately disagree, 2; moderately agree, 3, and strongly agree, 4).

## 3. Results

### 3.1. Hormone assays

Twenty normally cycling women completed two test sessions. Four women were excluded because they completed only one session and one woman was excluded because her progesterone levels were close to the detection limit in both sessions, which suggests an absence of ovulation in this participant. The mean level of serum progesterone in the remaining 19 women was 1.0 (S.E.M. = 0.1) nmol/L in the menstrual phase and 32.0 (S.E.M. = 3.7) nmol/L in the midluteal phase. The mean level of serum estradiol of 19 women was 182.0 (S.E.M. = 9.4) pmol/L in the menstrual phase and 564.4 (S.E.M. = 43.1) pmol/L in the midluteal phase. A paired $t$-test revealed a significant cycle-phase difference in mean serum progesterone, $t(18) = 8.34$, $p < 0.001$, and estradiol levels, $t(18) = 8.73$, $p < 0.001$.

### 3.2. Cycle-related effects (within-subjects)

The percentage deviation scores in line-bisection of normally cycling women were subjected to a $2 \times 2 \times 2 \times 3$ analysis of variance (ANOVA) with repeated-measures, with scan direction (right-to-left, left-to-right), cycle phase (menses, luteal phase), hand-use (left hand, right hand), and line position (left, centre, right) as within-subject factors. Greenhouse–Geisser procedure was used with epsilon-corrected degrees of freedom if data showed significant deviations from sphericity. As indicated by the intercept effect, an overall leftward bias ($-1.09 \pm 0.40$) was significant only when center lines were taken into account, $F(1, 18) = 7.30$, $p = 0.015$. None of the main effects of cycle phase, scan direction, hand-use or line position was significant, all $F < 3.26$, n.s. The interaction between cycle phase and hand-use (Fig. 1) was significant, $F(1, 18) = 4.73$, $p = 0.04$. Scheffé post hoc tests revealed only a significant hand-use difference in left bias during menses (right hand: $-0.07 \pm 0.39$, left hand: $-1.01 \pm 0.50$; $p = 0.01$), not during the midluteal phase (right hand: $-0.25 \pm 0.48$, left hand: $-0.45 \pm 0.44$; $p = 0.88$).
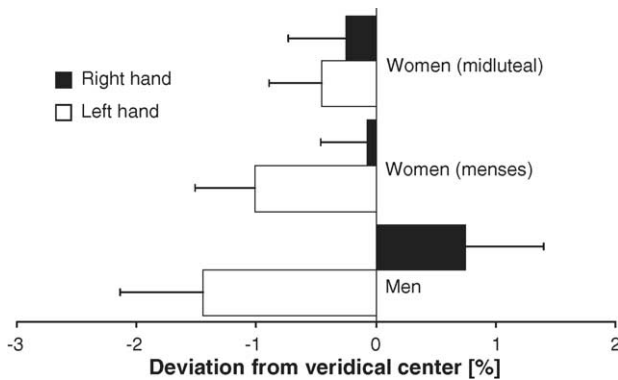
Fig. 1. Mean deviations from the true center (%) in visual line-bisection according to hand-use, sex, and cycle phase (menses vs. midluteal phase). Negative values indicate a bias towards the left and positive values indicate a bias towards the right of the objective middle.

Scheffé test yielded neither cycle-related differences for the left-hand bias, $p = 0.19$, nor for the right-hand bias, $p = 0.90$. Moreover, the interaction between scan direction and line position was significant, $F(1.97, 35.48) = 14.99$, $p = 0.001$. When the lines were scanned from right to left, participants showed a left bias particularly when the lines were located in the center ($-1.71 \pm 0.54$) or to the right ($-0.39 \pm 0.51$), and they showed a slight right bias when the lines were located to the left ($0.39 \pm 0.55$). In contrast, when the lines were scanned from left-to-right, participants showed a left bias especially when lines were located to the left ($-0.68 \pm 0.64$) or in the center ($-0.38 \pm 0.43$), and they showed a slight right bias when lines were located to the right ($0.18 \pm 0.46$). No other interaction was significant, all $F < 2.62$, n.s. When analysed the data by testing session, instead of cycle phase, neither the main effect of testing session, $F(1, 18) = 0.08$, n.s., nor the hand-use by testing session interaction approached significance, $F(1, 18) = 0.09$, n.s.

### 3.3. Male controls

Data from the male participants were analysed by $2 \times 2 \times 3$ analysis of variance with repeated-measures, with scan direction (right-to-left, left-to-right), hand-use and line position (left, center, right) as within-subject factors. The analysis revealed hand-use as the only significant main effect, $F(1, 13) = 8.63$, $p = 0.012$, indicating a strong left bias with the left hand ($-1.44 \pm 0.71$) and a right bias when the right hand is used to bisect the lines ($0.75 \pm 0.65$). Moreover, the interaction between scan direction and line position was significant, $F(1.92, 18.24) = 4.20$, $p = 0.026$. When the lines were scanned from right-to-left, men showed a left bias for the lines in the center ($-1.82 \pm 0.99$) and on the right ($-1.33 \pm 0.84$) and right bias for lines on the left ($0.62 \pm 0.91$), whereas in the left-to-right scan condition they showed a right bias for the lines on the left ($0.52 \pm 0.49$) and in the center ($0.42 \pm 0.58$), and a left bias only for the lines oriented to the right ($-0.49 \pm 0.78$). No other effects were significant, ($F < 3.21$, n.s.).

### 3.4. Sex differences (between-subjects)

Comparing the line-bisection data of men with those of women during menses, neither the main effect of sex nor any interaction with sex was significant, $F < 2.23$, n.s. In contrast, when comparing the data of men with those of women during the midluteal phase, the interaction between sex and hand-use (Fig. 1) was significant, $F(1, 31) = 6.41$, $p = 0.017$. Post hoc $t$-tests indicate a stronger difference between hands in males (left hand: $-1.44 \pm 0.60$, right hand: $0.75 \pm 0.60$, $t(13) = 2.94$, $p = 0.01$) than in females (left hand: $-0.45 \pm 0.52$, right hand: $-0.25 \pm 0.52$, $t(18) = 0.50$, n.s.). Moreover, the three-way interaction between hand-use, line position, and sex was significant, $F(1.69, 52.39) = 4.64$, $p = 0.018$. In the right-to-left scanning condition, the males showed the strongest bias (to the right) when the lines were on the left, and in the left-to-right scan condition they showed the strongest bias (to the left) when the lines were positioned on the right. In contrast, females showed the strongest bias (to the left) when the lines were positioned in the center, and this was independent of scanning direction. Neither the main effect of sex nor any other interaction with sex was significant, $F < 2.05$, n.s.

### 3.5. Sex hormones/behavior relationships

In view of significant interaction between cycle phase and hand-use, it was expected sex hormone levels to be significantly related to the hand-use difference. Due to the fact that estradiol and progesterone levels show only small individual variations during menses, the relationships between sex hormone levels and behavioral data were restricted to the midluteal phase. Three normally cycling women who participated only in one session, during the midluteal phase, were included in the analyses, raising the sample back to 22. Multiple regression with hand-use differences as dependent variable and midluteal estradiol and progesterone levels as predictors revealed a significant effect, $F(2, 21) = 3.95$, $p = 0.037$. However, only estradiol contributed significantly to the regression equation, $\beta = 0.67$, $p = 0.012$. The contribution of progesterone, although in the expected direction, did not reach significance, $\beta = -0.30$, n.s. Multiple regression for the right-hand bias revealed a significant model, $F(2, 21) = 3.56$, $p = 0.049$. However, the regression weights for both estradiol, $\beta = -0.47$, $p = 0.07$, and progesterone levels, $\beta = -0.09$, n.s., failed to reach significance. No significant effect was found with the left-hand bias as dependent variable, $F(2, 21) = 1.54$, n.s.

### 3.6. Effects of mood

Paired $t$-tests revealed no significant differences between menses and midluteal phase in cheerfulness, $t(18) = -0.42$, n.s.; seriousness, $t(18) = 1.43$, n.s.; and bad mood, $t(18) = -0.28$, n.s. Moreover, stepwise multiple regressions revealed the line-bisection bias of either hand or

the hand-use difference not to be significantly predicted by mood data.

## 4. Discussion

Overall, the left bias that is typically observed in neurologically normal individuals was also found in this study, although significant only when center lines were taken into account. The difference in the bias between the right and the left hand was especially pronounced in women during menses and in men. This hand-use difference was significantly reduced in women during the midluteal phase. Based on correlations, the hand-use difference was reduced when levels of estradiol were high. Although the right-hand bias is related to high levels of estradiol and progesterone during the midluteal phase, neither of these sex hormones alone contributes significantly to the right-hand bias. Mood did not affect the results of this study. The results are in agreement with a decrease in FCAs during the high-steroid midluteal phase (Hausmann, Becker et al., 2002; Hausmann & Güntürkün, 2000; Heister et al., 1989; Rode et al., 1995, but also see, e.g. Bibawi et al., 1995; McCourt et al., 1997).

Using a similar visuomotor task, a blind pointing task, McCourt et al. (1997) found opposite results to those reported here. Participants were instructed to raise a laser pointer, touching the sternum with the end of the pointer, and then extending the arm and hand so as to point toward a vertical line at a distance of 1 m, which coincided with the participants' midsagittal plane. When subjects agreed that the pointing direction was towards the midsagittal line, they activated the laser pointer. McCourt et al. found the strongest leftward pointing error during the luteal phase, which differed from all other phases (menses, follicular, premenstrual) and from male controls. Moreover, no main effect or interaction with hand-use was found. The authors concluded that the luteal phase may have non-specifically activated both hemispheres, and a slight functional asymmetry favoring the RH might have been promoted. Several task- and participant-related differences may have promoted the divergent results of McCourt et al.'s and the present study. For instance, McCourt et al. included left-handed participants. Up to now, no study exists that has investigated cycle-related effects on FCAs in sinistrals. Although the left bias in visual line-bisection of sinistrals seems to be only slightly reduced compared to dextrals (Jewell & McCourt, 2000), confounding effects based on the subject sample cannot be ruled out. Moreover, participants bisected large-scale space in the extrapersonal, not in the peripersonal space, which is again related to a smaller left bias (McCourt & Garlinghouse, 2000). Additionally, participants of McCourt et al.'s study had several practice trials and received visual feedback about their accuracy after each trial. This might be related to the large influence of testing session (four sessions were used), which often results in carry-over effects (Hausmann & Güntürkün, 2000; Mead & Hampson, 1996). The results of the present study did not show any

effects of testing session (only two sessions were used). Finally, McCourt et al. (1997) did not assess directly serum or saliva concentrations of sex hormones, which is the most accurate method of defining menstrual cycle phase (Epting & Overman, 1998). Thus, a limited cycle-phase validation and no analyses of hormone/behavior relationships were performed.

Previous studies investigating the hormone/behavior relationships directly suggest that it is mainly progesterone that modulates the interhemispheric interaction (Hausmann, Becker et al., 2002; Hausmann & Güntürkün, 2000; but see also Compton et al., 2004). Specifically, it has been hypothesized that high levels of progesterone reduce cortico-cortical transmission, and thus lead to a cycle phase-related reduction in FCAs (for details Hausmann & Güntürkün, 2000). This is partly supported by a fMRI study (Fernandez et al., 2003), which found cycle-dependent changes in FCAs of a verbal task as a corollary of a symmetric increase of neuronal recruitment during the midluteal phase. More specifically, bilateral superior temporal recruitment correlated positively with progesterone and medial superior frontal recruitment with both progesterone and estradiol levels. In contrast to Fernandez et al. (2003) and our previous behavioral experiments (Hausmann, Becker et al., 2002; Hausmann & Güntürkün, 2000), progesterone had only marginal effects in the present study.

There are behavioral studies which indicate that high estradiol levels increase FCAs (e.g. Altemus, Wexler, & Boulis, 1989; Hampson, 1990b). Others have shown that high levels of estradiol affect both hemispheres to a similar degree, and thus do not change the task-specific LH or RH superiority (Hausmann, Becker et al., 2002). Non-specific estradiol-related changes in neuronal activity of the LH and RH are supported by functional imaging data of Dietrich et al. (2001), who found an estradiol-related increase in overall activation of both hemispheres. Only one study showed a strong relationship between high estradiol levels and reduced FCAs. Mead and Hampson (1997) found a rightward turning preference that fluctuates across the menstrual cycle. At least among right-turning females, the rightward turning biases were significantly weaker during the midluteal phase. This reduction in motor asymmetry was significantly related to high estradiol levels, not to progesterone. Based on animal studies (e.g. Becker, Robinson, & Lorenz, 1982; Robinson, Camp, Jacknow, & Becker, 1982), Mead and Hampson (1997) concluded that higher estradiol levels are associated with a reduction of striatal dopamine activity. This effect might result from an asymmetrical influence of estradiol on the left- and right-striatal systems or a symmetrical modulation, thereby decreasing the relative disparity between both sides.

The estradiol-related reduction of the hand-use difference presented here might be based on similar mechanisms involving the motor system. It has been hypothesized (e.g. Kinsbourne, 1970; Halligan & Marshall, 1989) that the utilization of the left and right hands in line-bisection might augment the activation of the contralateral hemisphere, and thus

bias the orientation toward the ipsilateral hemispace. According to this activation-orientation hypothesis of attentional asymmetry (Halligan & Marshall, 1989; Kinsbourne, 1970; McCourt et al., 2001; Reuter-Lorenz & Posner, 1990), it might be argued that the estradiol-related reduction of hand-use difference results from a reduced activation of the left- and right-motor systems, thereby decreasing the relative disparity between both hemispheres, as supposed by Mead and Hampson (1997). However, asymmetrical effects of estradiol on the left- and right-motor systems are unlikely, because estradiol levels were not significantly related to the left- and right-hand bias. Further, the left- and right-hand bias did not change significantly across the menstrual cycle.

The reduced hand-use effect during the midluteal cycle phase might result from (a) a hormonal suppression of the RH superiority in spatial attention, (b) a hormonal activation of the less specialized LH, or (c) a hormonal modulation of interhemispheric interaction between the visuospatial attention-dominant RH and motor areas of the LH.

The results of the present study make it unlikely that sex hormones have specifically suppressed the RH because the left-hand bias did not fluctuate across cycle phases, nor was it clearly related to hormone levels. Rather it was virtually identical to that of men. It seems also rather unlikely that the LH was specifically activated by sex hormones. An activation of the LH predicts cycle-related differences in the right-hand bias, but the right-hand bias did not differ significantly between menses and the midluteal phase. Rather it was the difference between hands that was reduced in the midluteal phase, and which was strongly predicted by hormone levels. Estradiol levels were in this case a significant predictor. These results suggest that the interaction between the left and the right hemisphere assessed by this task fluctuates during the menstrual cycle. However, it should be noted that the right-hand bias was predicted by the combination of estradiol and progesterone (neither hormone was in fact a significant predictor). Thus, it can not fully ruled out that sex hormones have selectively activated the LH, as suggested by, e.g. Bibawi et al. (1995), thereby reducing the hand-use difference.

Previous studies (Failla et al., 2003; Hausmann, Ergun et al., 2002; Hausmann, Corballis et al., 2003; Hausmann, Waldie et al., 2003), which used the same or a similar line-bisection task, have suggested that the hand-use effect reflects an interhemispheric interaction between the visuospatial attention-dominant RH and motor areas of the LH. According to the activation-orientation hypothesis, the hand-use difference might result from a weaker spreading activation of the RH-dominant attention network when the right hand is used (interhemispheric pathway), compared to a spreading activation within the RH when the left hand is used to bisect lines (intrahemispheric pathway). Modulations of interhemispheric interaction should mainly involve the isthmus and splenium, because spatial attention mainly involves the right-posterior parietal cortex–or perhaps, as recent studies suggest, the right-superior temporal cortex (Karnath, Himmelbach, & Rorden, 2002; Karnath, Ferber, &

Himmelbach, 2001). These cortical areas are primarily connected with homotopic areas of the contralateral hemisphere via the posterior corpus callosum (Witelson, 1995). Note that the isthmus and splenium are known to affect the hand-use difference in line-bisection tasks (Hausmann, Corballis et al., 2003).

However, interhemispheric interaction is a multifaceted process. It includes the transfer of more or less specific activation from one hemisphere to the other, the integration of parallel processes, and interhemispheric inhibition, which has been suggested to result in a manifestation of FCAs (e.g. Chiarello & Maxfield, 1996; Cook, 1984). In previous visual half-field studies we have suggested that it might be interhemispheric inhibition, in particular, that is hormonally modulated (Hausmann, Becker et al., 2002; Hausmann & Güntürkün, 2000). However, interhemispheric processes which mainly involve transcallosal integration of specific stimuli, i.e. letter matching across visual fields, seem not to be under hormonal control (Compton et al., 2004). These findings, together with the results of the present study, suggest that sex hormones mainly affect interhemispheric transfer of less specific activation, whereas an interhemispheric transfer of specific information is not affected hormonally.

In summary, the hand-use difference in visual line-bisection fluctuates across the menstrual cycle and is reduced during the midluteal cycle phase. This reduction of hemispheric asymmetry in spatial attention is mainly related to high levels of estradiol. Although there is some evidence that sex hormones predict LH performance, activating effects of estradiol on one hemisphere seem to be rather unlikely. The results might be due to an estradiol-related reduction in the activation of the left- and right-motor systems, thereby decreasing the relative disparity between both hemispheres, or more likely to a cycle-related modulations of interhemispheric transfer of neuronal activation. If the latter is true, the hypothesis of progesterone-modulated interhemispheric decoupling (Hausmann & Güntürkün, 2000) needs to be extended in order to incorporate estradiol-related effects on specific aspects of interhemispheric interaction.

## References

Altemus, M., Wexler, B. E., & Boulis, N. (1989). Changes in perceptual asymmetry with the menstrual cycle. *Neuropsychologia*, 27, 233–240.

Banich, M. T., & Belger, A. (1990). Interhemispheric interaction: how do the hemispheres divide and conquer a task. *Cortex*, 26, 77–94.

Becker, J. B., Robinson, T. E., & Lorenz, K. A. (1982). Sex differences and estrous cycle variations in ampetamine-elicited rotational behavior. *European Journal of Pharmacology*, *80*, 65–72.

Bibawi, D., Cherry, B., & Hellige, J. B. (1995). Fluctuations of perceptual asymmetry across time in women and men: Effects related to the menstrual cycle. *Neuropsychologia*, *33*, 131–138.

Bradshaw, J. L., Nettleton, N. C., Wilson, L. E., & Bradshaw, C. S. (1987). Line bisection by left-handed preschoolers: A phenomenon of symmetrical neglect. *Brain and Cognition*, *6*, 377–385.

Brodie, E. E., & Pettigrew, L. E. L. (1996). Is left always right? Directional deviations in visual line bisection as a function of hand and initial scanning direction. *Neuropsychologia*, *34*, 467–470.

Chiarello, C., & Maxfield, L. (1996). Varieties of interhemispheric inhibition, or how to keep a good hemisphere down. *Brain and Cognition*, *30*, 81–108.

Compton, R. J., Costello, C., & Diepold, J. (2004). Interhemispheric integration durino the menstrual cycle: Failure to confirm progesterone-mediated interhemispheric decoupling. *Neuropsychologia*, *42*, 1496–1503.

Cook, N. D. (1984). Callosal inhibition: The key to the brain code. *Behavioral Science*, *29*, 98–110.

Corballis, M. C. (1995). Line bisection in a man with complete forebrain commissurotomy. *Neuropsychology*, *9*, 147–156.

DeLacoste-Utamsing, C., & Holloway, R. L. (1982). Sexual dimorphism in the human corpus callosum. *Science*, *216*, 1431–1432.

Dellatolas, G., Coutin, T., & De Agostini, M. (1996). Bisection and perception of horizontal lines in normal children. *Cortex*, *32*, 705–715.

Dietrich, T., Krings, T., Neulen, J., Willmes, K., Erberic, S., Thron, A., et al. (2001). Effects of blood estrogen level on cortical activation patterns during cognitive activation as measures by functional MRI. *Neuroimage*, *13*, 425–432.

Dobler, V., Manly, T., Atkinson, J., Wilson, B. A., Ioannou, K., & Robertson, I. H. (2001). Interaction of hand use and spatial selective attention in children. *Neuropsychologia*, *39*, 1055–1064.

Driesen, N. R., & Raz, N. (1995). The influence of sex, age, and handedness on the corpus callosum morphology: A meta analysis. *Psychobiology*, *23*, 240–247.

Epting, L. K., & Overman, W. H. (1998). Sex-sensitive tasks in men and women: A search for performance fluctuations across the menstrual cycle. *Behavioral Neuroscience*, *112*, 1304–1317.

Failla, C. F., Sheppard, D. M., & Bradshaw, J. L. (2003). Age and responding-hand related changes in performance of neurologically normal subjects on the line-bisection task and chimeric-faces task. *Brain and Cognition*, *52*, 353–363.

Fernandez, G., Weis, S., Stoffel-Wagner, B., Tendolkar, I., Reuber, M., Beyenburg, S., et al. (2003). Menstrual cycle-dependent neural plasticity in the adult human brain is hormone, task, and region specific. *Journal of Neuroscience*, *23*, 3790–3795.

Halligan, P. W., & Marshall, J. C. (1989). Line bisection in visuo-spatial neglect: Disproof of a conjecture. *Cortex*, *25*, 517–521.

Hampson, E. (1990a). Variations in sex related cognitive abilities across the menstrual cycle. *Brain and Cognition*, *14*, 26–43.

Hampson, E. (1990b). Estrogen-related variations in human spatial and articulatory-motor skills. *Psychoneuroendocrinology*, *15*, 97–111.

Hausmann, M., Becker, C., Gather, U., & Güntürkün, O. (2002). Functional cerebral asymmetries during the menstrual cycle: A cross-sectional and longitudinal analysis. *Neuropsychologia*, *40*, 808–816.

Hausmann, M., Corballis, M. C., & Fabri, M. (2003). Line bisection in the split brain. *Neuropsychology*, *17*, 602–609.

Hausmann, M., Ergun, G., Yazgan, Y., & Güntürkün, O. (2002). Sex differences in line bisection as a function of hand. *Neuropsychologia*, *40*, 235–240.

Hausmann, M., & Güntürkün, O. (1999). Sex differences in functional cerebral asymmetries in a repeated measures design. *Brain and Cognition*, *41*, 263–275.

Hausmann, M., & Güntürkün, O. (2000). Steroid fluctuations modify functional cerebral asymmetries: The hypothesis of progesterone-mediated interhemispheric decoupling. *Neuropsychologia*, *38*, 1362–1374.

Hausmann, M., Waldie, K. E., Allison, S. D., & Corballis, M. C. (2003). Line bisection following hemispherectomy. *Neuropsychologia*, *41*, 1523–1530.

Hausmann, M., Waldie, K. E., & Corballis, M. C. (2003). Developmental changes in line bisection: A result of callosal maturation? *Neuropsychology*, *17*, 155–160.

Heilman, K., Bowers, D., & Watson, R. (1984). Pseudoneglect in a patient with partial callosal disconnection. *Brain*, *107*, 519–532.

Heilman, K. M., & Valenstein, E. (1979). Mechanisms underlying hemispatial neglect. *Annals of Neurology*, *5*, 166–170.

Heilman, K. M., & Van Den Abell, T. (1980). Right hemisphere dominance for attention: The mechanism underlying asymmetries of attention (neglect). *Neurology*, *30*, 327–330.

Heister, G., Landis, T., Regard, M., & Schroeder-Heister, P. (1989). Shift of functional cerebral asymmetry during the menstrual cycle. *Neuropsychologia*, *27*, 871–880.

Holloway, R. L., Anderson, P. J., Defendini, R., & Harper, C. (1993). Sexual dimorphism of the human corpus callosum from three independent samples: Relative size of the corpus callosum. *American Journal of Physical Anthropology*, *92*, 481–498.

Jewell, G., & McCourt, M. E. (2000). Pseudoneglect: A review and meta-analysis of performance factors in line bisection task. *Neuropsychologia*, *38*, 93–110.

Karnath, H.-O., Himmelbach, M., & Rorden, C. (2002). The subcortical anatomy of human spatial neglect: Putamen, caudate nucleus and pulvinar. *Brain*, *125*, 350–360.

Karnath, H.-O., Ferber, S., & Himmelbach, M. (2001). Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature*, *411*, 950–953.

Kashiwagi, A., Kashiwagi, T., Nishikawa, T., Tanabe, H., & Okuda, J.-I. (1990). Hemispatial neglect in a patient with callosal infarction. *Brain*, *113*, 1005–1023.

Kinsbourne, M. (1970). The cerebral basis of lateral asymmetries in attention. *Acta Psychologica*, *33*, 193–201.

Luh, K. E. (1995). Line bisection and perceptual asymmetries in normal individuals: What you see is not what you get. *Neuropsychology*, *9*, 435–448.

McCourt, M. E., Freeman, P., Tahmahkera-Stevens, C., & Chaussee, M. (2001). The influence of unimanual response on pseudoneglect magnitude. *Brain and Cognition*, *45*, 52–63.

McCourt, M. E., & Garlinghouse, M. (2000). Asymmetries of visuospatial attention are modulated by viewing distance and visual field elevation: Pseudoneglect in peripersonal and extrapersonal space. *Cortex*, *36*, 715–731.

McCourt, M. E., Mark, V. W., Radonovich, K. J., Willison, S. K., & Freeman, P. (1997). The effects of gender, menstrual phase and practice on the perceived location of the midsagittal plane. *Neuropsychologia*, *35*, 717–724.

Mead, L. A., & Hampson, E. (1996). Asymmetric effects of ovarian hormones on hemispheric activity: Evidence from dichotic and tachistoscopic tests. *Neuropsychology*, *10*, 578–587.

Mead, L. A., & Hampson, E. (1997). Turning bias in humans is influenced by phase of the menstrual cycle. *Hormones and Behavior*, *31*, 65–74.

Mesulam, M.-M. (1981). A cortical network for directing attention and unilateral neglect. *Annals of Neurology*, *10*, 309–325.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia*, *9*, 97–113.

Oka, S., Miyamoto, O., Janjua, N. A., Honjo-Fujiwara, N., Ohkawa, M., Nagao, S., et al. (1999). Re-evaluation of sexual dimorphism in human corpus callosum. *Neuroreport*, *10*, 937–940.

Pandya, D. N., Karol, E. A., & Heilbronn, D. (1971). The topographical distribution of interhemispheric projections in the corpus callosum of the rhesus monkey. *Brain Research*, *32*, 31–43.

Reuter-Lorenz, P., & Posner, M. I. (1990). Components of neglect from right-hemisphere damage: An analysis of line bisection. *Neuropsychologia*, *28*, 327–333.

Robinson, T. E., Camp, D. M., Jacknow, D. S., & Becker, J. B. (1982). Sex differences and estrous cycle dependent variation in rotational behavior elicited by electrical stimulation of the mesostriatal dopamine system. *Behavioral Brain Research*, *6*, 273–287.

Rode, C., Wagner, M., & Güntürkün, O. (1995). Menstrual cycle affects functional cerebral asymmetries. *Neuropsychologia*, *33*, 855–865.

Roeltgen, M. G., & Roeltgen, D. P. (1989). Development of attention in normal children: A possible corpus callosum effect. *Developmental Neuropsychology*, *5*, 127–139.

Ruch, W., Köhler, G., & van Thriel, C. (1996). Assessing the "humorous temperament": Construction of the facet and standard trait forms of the State-Trait-Cheerfulness-Inventory—STCI. Measurement of the Sense of Humor. In W. Ruch (Ed.). *Humor: International Journal of Humor Research*, *9*, 303–339 [Special issue].

Ruch, W., Köhler, G., & van Thriel, C. (1997). To be in good or bad humor: Construction of the state form of the State-Trait-Cheerfulness-Inventory—STCI. *Personality and Individual Differences*, *22*, 477–491.

Sanders, G., & Wenmoth, D. (1998). Verbal and music dichotic listening tasks reveal variations in functional cerebral asymmetry across the menstrual cycle that are phase and task dependent. *Neuropsychologia*, *36*, 869–874.

Scarisbrick, D. J., Tweedy, J. R., & Kuslansky, G. (1987). Hand preference and performance effects on line bisection. *Neuropsychologia*, *25*, 695–699.

Shuren, J., Wertman, E., & Heilman, K. M. (1994). The neglected page. *Cortex*, *30*, 171–175.

Steinmetz, H., Jäncke, L., Kleinschmidt, A., Schlaug, G., Volkmann, J., & Huang, Y. (1992). Sex but no hand difference in the isthmus of the corpus callosum. *Neurology*, *42*, 749–752.

Wisniewski, A. B. (1998). Sexually-dimorphic pattern of cortical asymmetry, and the role of sex steroid hormones in determining cortical patterns of lateralization. *Psychoneuroendocrinology*, *23*, 519–547.

Witelson, S. F. (1995). Neuroanatomical basis of hemispheric functional specialization in the human brain: Possible developmental factors. In F. L. Kitterle (Ed.), *Hemispheric communication: mechanisms and models*. Hillsdale, NJ: Lawrence Erlbaum Associates, pp. 61–84.