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Transcallosal inhibition across the menstrual cycle: A TMS study

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Abstract

Objective: To determine if there are steroid-dependent changes in transcallosal transfer during the menstrual cycle in normal women.
Methods: We tested 13 normally cycling women during the menstrual, follicular and midluteal phases. Blood levels of estradiol (E) and progesterone (P) were determined by radioimmunoassay. Ipsilateral tonic voluntary muscle activity suppression, called ipsilateral silent period (iSP), was evoked by applying transcranial magnetic stimulation (TMS) over the left motor cortex and by measuring the EMG of the ipsilateral first dorsal interosseus (FDI) muscle. Both iSP-duration and transcallosal conduction times were measured and related to cycle phase and steroid levels.
Results: Duration of iSPs varied over the cycle with largest differences between follicular and midluteal phases. During the midluteal phase high levels of P were significantly related to short iSPs. This relation also applied to E levels and iSPs during the follicular phase.
Conclusions: Our study shows for the first time that the transcallosal transfer is modulated by E and P and changes over the menstrual cycle.
Significance: It is suggested that gonadal steroid hormones affect the interhemispheric interaction and change the functional cerebral organization sex dependently via its neuromodulatory properties on GABAergic and glutamatergic neurons.

Keywords: TMS; Ipsilateral silent period; Corpus callosum; Interhemispheric interaction; Sex hormones; Estradiol; Progesterone

1. Introduction

Gonadal steroid hormones have potent neuroactive properties and are known to affect various brain functions. The effects of gonadal steroid hormones such as estradiol (E) and progesterone (P) on mood (Compton and Levine, 1997), cognition (Hampson, 1990a,b; Hausmann et al., 2000; Kimura, 2002), and motor behaviour (Mead and Hampson, 1997) have been investigated in normally cycling women, because their natural plasma hormone levels fluctuate dramatically in relative short time intervals across the menstrual cycle. Plasma levels of P and E are low during menses (cycle day 1–5) and high during the luteal phase in the second half of the menstrual cycle after ovulation (cycle day 16–23). Plasma E levels reach the first peak preovulatory during the late follicular phase (cycle day 6–12).

Several behavioural studies have suggested that the neuromodulatory properties of E and P change the functional organization of the brain. Specifically, for instance, lateralised functions, e.g. language, spatial cognition, and face discrimination, are more lateralised during the low steroid menses than during the high steroid midluteal phase (Hausmann, 2005; Hausmann and Güntürkün, 2000; Hausmann et al., 2002; Heister et al., 1989; Holländer et al., 2005; Mead and Hampson, 1996; Rode et al., 1995). However, the underlying mechanisms for these hormone-related effects on cortical plasticity are rather unknown.

There is support that E changes the overall level of activation rather than modulating a specific activation pattern, which is related to a specific function. This has been shown by a fMRI study that investigated the neuronal activity during two cognitive tasks (word-stem completion and mental rotation) and a simple motor task during menses and late follicular phase at cycle day 11 and 12 (Dietrich et al., 2001). No assumptions could be made about

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the neuromodulatory effects of P, because this study focused on maximal differences in E levels.

Although studies suggest that also E affects functional cerebral asymmetries (Hausmann, in press; Holländer et al., 2005), high levels of P are related to a reduction of lateralisation (Hausmann and Güntürkün, 2000; Hausmann et al., 2002). Since this effect was present for both left and right hemispheric tasks, word matching and figural comparison, face discrimination, respectively, it is rather unlikely that high levels of P have selectively activated or suppressed a single hemisphere. It is more likely that P modulates the interhemispheric inhibition via the corpus callosum (Hausmann and Güntürkün, 2000; Hausmann et al., 2002), which is thought to be an essential mechanism in causing functional cerebral asymmetries (Chiarello and Maxfield, 1996; Cook, 1984). In line with these behavioural studies, a recent fMRI study (Fernandez et al., 2003) showed an increase of symmetrical activation in a semantic decision task which was positively related with P levels. However, the additional recruitment of areas on the contralateral right hemisphere during the midluteal phase was specifically located in the superior temporal gyrus and the medial wall of the superior frontal gyrus. The authors concluded that this cannot simply be explained by gonadal steroid hormone effects on commissural transmission (Fernandez et al., 2003), because neither the superior temporal region nor the medial aspect of the superior frontal gyrus have a disproportional many commissural fibres (Pandya et al., 1971). However, up to now, no study exists that investigates directly if gonadal steroid hormones affect the interhemispheric cross-talk. This study addresses this point by using transcranial magnetic stimulation (TMS), because this non-invasive neurophysiological technique has shown to be sensitive to detect activating effects of gonadal steroid hormones during the menstrual cycle and can be used to investigate mechanisms of motor-cortical excitability and inhibition of transcallosal processes.

TMS applied to the primary motor cortex evokes not only a response in muscles contralateral to the stimulation, but also a short period of suppression of ipsilateral tonic voluntary muscle activity (Ferbert et al., 1992; Wassermann et al., 1991). This phenomenon, called ipsilateral silent period (iSP), is assumed to be mediated cortically by excitatory transcallosal fibres targeting at inhibitory interneurons, and thus probably reflects the functional integrity of transcallosal fibres connecting homotopic areas of the left and right motorcortices (Buchmann et al., 2003; Chen, 2004; Daskalakis et al., 2002; Ferbert et al., 1992; Heinen et al., 1998; Meyer et al., 1995), though some evidence exists that iSP may be partially mediated subcortically through the brain-stem (Gerloff et al., 1998).

Moreover, TMS proved to be sensitive to detect neuromodulatory effects of gonadal steroid hormones in the motor system, as it was demonstrated by Smith and colleagues (Smith et al., 1999, 2002) using paired pulses TMS with a subthreshold conditioning and a suprathreshold test stimulus at different interstimulus intervals. In this paradigm, the response to the test stimulus is generally inhibited at short (1–5 ms) and facilitated at longer (6–20 ms) interstimulus intervals in healthy humans (Kujirai et al., 1993; Ziemann et al., 1996b). These phenomena are referred to as short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF), since they are thought to reflect the activity of inhibitory and facilitatory interneuronal circuits in the motor cortex. Studying a group of normally cycling women during the follicular (cycle day 7–12) and luteal cycle phase (cycle day 18–27), Smith and colleagues showed that the excitability of a cortical network changes with the menstrual cycle (Smith et al., 1999, 2002). The conditioning TMS produced more inhibition in the luteal phase than in the follicular phase, which was of similar magnitude to the effects of GABA agonists, or glutamate antagonists in previous experiments (Liepert et al., 1997; Schwenkreis et al., 1999; Ziemann et al., 1996a, 1998). Smith and colleagues included the menses (cycle day 2–5) in a follow-up study to detect the effects of E (Smith et al., 2002). The results showed an excitatory effect associated with E and confirmed the previous finding of inhibition associated with P. The E-related excitatory activation is supported by a repetitive TMS study which showed that the MEP did not increase during menses (cycle day 1), but increased progressively during ovulation at cycle day 14 (Inghilleri et al., 2004).

Beyond these findings of hormone-related changes of the inhibitory and facilitatory activity in the human cerebral cortex, the results of the present TMS study indicate that iSP, which is assumed to reflect interhemispheric, presumably transcallosal inhibition, fluctuates across the menstrual cycle. These results might help to elucidate the mechanisms which underlie hormone-related modulations of cortical plasticity and functional asymmetries of the human brain.

2. Methods

2.1. Subjects

Thirteen normally cycling women participated in this experiment. The mean age of the women was 23.62 years (SD = 4.11; range: 20–34 years). 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 consistent sinistrality to consistent dextrality. The mean LQ of participants was 91.35 (SD = 7.88; range: 75.0–100). Women who had used oral contraceptives or any other medication affecting the central nervous system during the last 6 months were excluded. Participants were recruited by announcements, and were paid for their participation. All participants gave written informed consent.

Experimental procedure was approved by the Local Ethical Committee.

2.2. Procedure and materials

Before the experimental session, women were informed about the general procedure and data were collected about the individual menstrual cycle. All women agreed to inform us of the first day of their next cycle, to plan the dates for the experimental sessions. The normally cycling women were tested triple, once during the menstrual phase (cycle day 2), once during the follicular phase (cycle day 8–10), and once during the midluteal phase (cycle day 21–22), to yield the largest differences in E and P levels. To control potential repeated-measures effects, women were tested in a balanced order, starting with the menses, the follicular, or the midluteal phase. Women were tested within one or two consecutive cycles. Directly after every TMS session a blood sample was collected. Serum E and P levels were determined with Radioimmunoassay (RIA) by an independent professional medical laboratory, with commercially available RIA kits.

2.3. TMS session

Focal TMS was performed using a Magstim 200 stimulator (Magstim Co., Whitland, Dyfed, UK). The stimuli were applied through a figure of eight coil (outside diameter 8.7 cm; peak magnetic field strength 2.2 T; peak electric field strength 660 V/m). Given the known influence of the induced current direction especially on the iSP duration (Chen et al., 2003), the grip of the coil was strictly pointing backwards (induced current in anterior direction) during all experimental procedures, with the coil held tangentially to the skull. Recordings were taken with Ag–AgCl surface electrodes from the first dorsal interosseus (FDI) muscle. They were stored on an EMG device (Neuropack 8, Nihon Kohden, Tokyo, Japan) for further analysis. The signals were amplified with a bandpass of 20 Hz–3 kHz, a sweep duration of 10–50 ms/div and a gain of 0.1–1 mV/div. For each subject, the stimulation point for eliciting maximal motor responses in the contralateral FDI muscle was determined individually over the left and the right motor cortex and marked on the skull. Motor threshold (MT) was determined at rest to the nearest 1% of the stimulator output, and was defined as the minimum intensity that produced five motor evoked potentials $>50\ \mu V$ out of 10 trials in the contralateral FDI muscle after stimulation of the right motor cortex (Rothwell et al., 1999). Muscle relaxation was controlled acoustically. Contralateral silent period (cSP) was evoked by applying TMS 50% above motor threshold over the right motor cortex while the subject was activating the contralateral FDI muscle with 20–30% of maximal force. Eight responses were rectified and superimposed. cSP duration was measured from the end of the MEP (onset of EMG suppression) until the first re-occurrence of voluntary EMG activity (Schwenkreis et al., 2002). For the assessment of the ipsilateral silent period (iSP), cortex stimulation was performed with maximally tonically contracted FDI muscles and 80% of the maximum stimulator output (Röricht et al., 1999). The left motor cortex was stimulated, and eight responses from the ipsilateral FDI muscle were rectified and superimposed. Onset latency and duration of the iSP were determined: The onset latency was measured from the stimulus to a point where the signal of the baseline EMG activity clearly fell under the mean amplitude of the EMG activity before the stimulus. Fig. 1 shows iSP during the follicular and midluteal phase for one subject. The duration of the iSP was measured from its onset to a point where the EMG activity reached the mean amplitude of the baseline EMG activity before the stimulus. Transcallosal conduction times (TCT) were determined by subtracting the onset latency of the MEP after stimulation of the contralateral motor cortex from the onset latency of the iSP in the same FDI muscle.

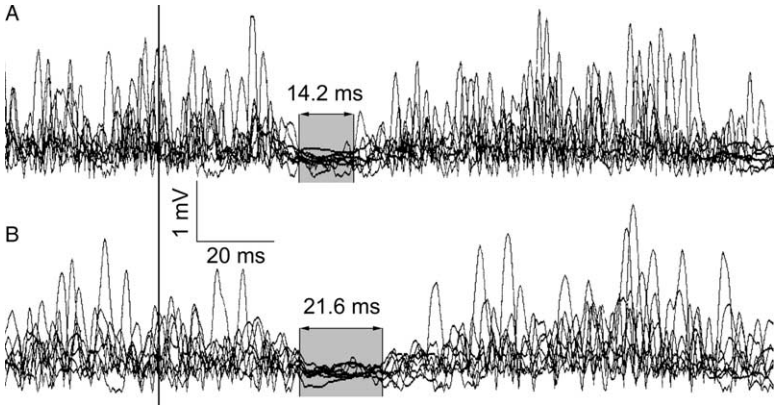

Fig. 1. Ipsilateral silent period (iSP) during the follicular (A) and midluteal phase (B) for one selected participant. A 40 ms prestimulus interval is registered; the time of stimulus application is marked by a vertical line. iSP is reduced during the follicular phase (iSP onset 36.4 ms post stimulus, iSP duration 14.2 ms), compared to the midluteal phase (iSP onset 36.6 ms post stimulus, iSP duration 21.6 ms), whereas the onset of the iSP is almost identical.

3. Results

3.1. Hormone assays

Thirteen normally cycling women completed three test sessions. Three women were excluded, because their P levels did not fluctuate during testing sessions. The mean levels of serum P and E in the remaining 10 women are shown in Table 1. Analyses of variance (ANOVA) with repeated measures, with Cycle phase as within-subject factor, revealed significant cycle-phase differences in serum P, $F(1.01,9.07)=53.65$, $P<0.0001$, and E levels, $F(2,18)=13.19$, $P<0.001$.

3.2. Cycle-related effects (within subjects)

Motor threshold (MT), duration of the contralateral (cSP) and ipsilateral silent period (iSP), and transcallosal conduction time (TCT) of normally cycling women were subjected to an analysis of variance (ANOVA) with repeated measures, with Cycle phase (menses, follicular, and luteal phase) as within-subject factor. Greenhouse-Geisser procedure was used with epsilon-corrected degrees of freedom, if data showed significant deviations from sphericity. Means and standard errors of all TMS measures are shown in milliseconds (ms). ANOVA revealed no differences in MTs between menses, follicular phase, and midluteal phase, $F(1.56,14.02)=0.99$, n.s. The analysis of iSP indicated a significant effect of cycle phase, $F(1.65,14.83)=5.50$, $P=.02$. Alpha-adjusted Bonferroni post hoc tests revealed only iSP's of the follicular (20.38 ± 3.82) and midluteal phase (23.30 ± 3.14) to be significantly different, $P=.01$ (Fig. 2). Post hoc comparisons of iSP's during menses (22.58 ± 4.00) and other cycle phase were not significant. ANOVA of cSP revealed no significant effect of cycle phase $F(1.16,10.41)=2.04$, n.s., indicating relatively stable cSP's across cycle phases. Moreover, no differences in TCT between menses, follicular phase, and luteal phase were found, $F(1.89,17.01)=0.81$, n.s.

Table 1
Means and standard deviations of progesterone (P) levels, estradiol (E) levels, motor threshold (MT), contralateral silent period (cSP), ipsilateral silent period (iSP) and transcallosal conduction time (TCT) during menses, follicular and midluteal cycle phase for women who fulfilled the inclusion criterion

	Menses	Follicular phase	Midluteal phase
P (μg/l)	1.52 ± 0.63	1.59 ± 0.83	12.59 ± 4.68
E (ng/l)	42.22 ± 15.95	64.00 ± 31.30	116.8 ± 48.78
MT (mV)	49.90 ± 8.41	48.10 ± 7.45	48.90 ± 7.95
CSP (ms)	152.07 ± 32.85	158.58 ± 49.56	142.29 ± 31.51
ISP (ms)	22.58 ± 4.00	20.38 ± 3.82	23.30 ± 3.14
TCT (ms)	16.96 ± 3.10	16.81 ± 2.80	16.02 ± 3.11

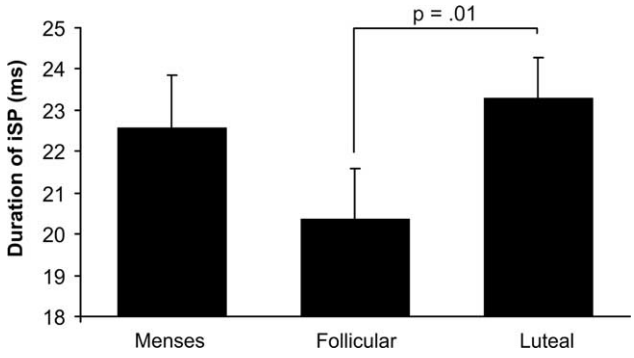

Fig. 2. Duration of the ipsilateral silent period (iSP) in ms across the menstrual cycle (menses, follicular, and luteal cycle phase). Largest differences in iSP appear between the follicular and luteal phase.

3.3. Sex hormones/iSP relationships

In view of the significant difference in iSP between follicular and midluteal phase, we expected sex hormone levels to be significantly related to iSP. The largest individual variations in E levels appear during the follicular and midluteal phase, when E levels are significantly elevated. P levels show their largest individual variation only midluteally. During menses and follicular phase P levels are minimal and close to detection level. Thus, in accordance with previous studies (Hausmann, 2005; Hausmann et al., 2002), stepwise multiple regression with P (and E) levels as predictors of iSP was restricted to the midluteal phase. To predict follicular iSP, only follicular levels of E were included in the regression. No regression has been performed for the menses.

During the midluteal phase, stepwise multiple regression revealed a significant model, $F(1,9)=5.44$, $P=0.048$, $R^2=0.41$, when absolute P levels, $\beta=-0.64$, $P=0.048$, entered the regression. Absolute E levels did not predict iSP in this model, $\beta=-0.024$, $P=0.95$. The P effect was even stronger, $F(1,8)=8.82$, $P=0.021$, $R^2=0.56$, when a ratio of luteal/follicular P levels, $\beta=-0.75$, $P=0.021$, was used in the regression. E level ratio did not predict luteal iSP, $\beta=-0.20$, $P=0.49$, and thus were excluded by the model. During the follicular phase, however, stepwise multiple regression revealed E, $\beta=-0.78$, to be a significant predictor of follicular iSP, $F(1,8)=10.56$, $P=0.014$, $R^2=0.60$ (Fig. 3).

4. Discussion

The results of the present study demonstrate that iSP fluctuates across the menstrual cycle. The iSP was especially reduced in the late follicular cycle phase and differed significantly from luteal iSP. iSP was significantly related to E and P levels within the follicular and luteal phase, respectively. Specifically, high levels of E were related to a reduced iSP during the follicular phase. During

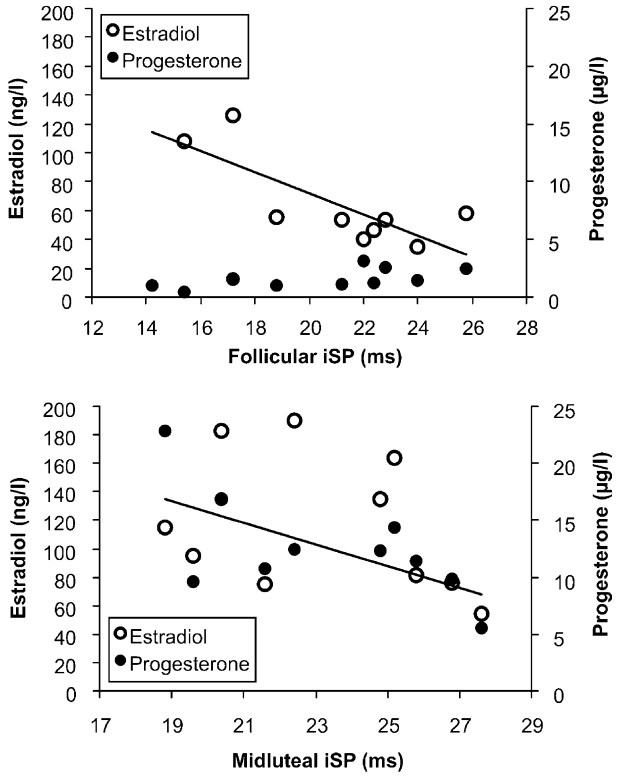

Fig. 3. Relationship between estradiol and progesterone levels and iSP during the follicular and the luteal phase. In the follicular phase, trend line represents the significant inverse relationship between iSP and estradiol levels. In the luteal phase, trend line represents the significant inverse relationship between iSP and progesterone levels.

the midluteal phase a reduced iSP appeared when high levels of P were present. No relationship between E levels and luteal iSPs was found. In contrast, cSP and MT did not fluctuate significantly across the menstrual cycle in this study. Moreover, TCT remained stable across the cycle, which suggests that latency of cortico-cortical transmission is not affected by gonadal steroid hormones. The results suggest that E and P affect primarily the degree of transcallosal inhibition in the human motor cortex.

In addition to iSP measurement, interhemispheric inhibition has been previously studied by applying a conditioning stimulus to the motor cortex, which reduced the size of the MEP produced by a test stimulus applied to the contralateral motor cortex at interstimulus intervals (ISI) between 6 and 50 ms (Chen et al., 2003, 2004; Ferbert et al., 1992; Hanajima et al., 2001). Using this method, at least two different phases of interhemispheric inhibition can be distinguished, one occurring at shorter ISI (about 10 ms), the other at longer ISI (about 40 ms). This interhemispheric inhibition at longer ISI is thought to be related to the iSP, whereas the interhemispheric inhibition at shorter ISI appears to be a different measure (Chen et al., 2003, Chen, 2004). Our present results support this assumption of two independent neuronal populations mediating interhemispheric inhibiton. Daskalakis et al. previously demonstrated that interhemispheric inhibition at an ISI of 10 ms reduces short-interval intracortical inhibition (SICI) as tested by paired-pulse TMS, an effect which is hypothesised to be mediated by presynaptic $GABA_B$ receptors (Daskalakis et al., 2002; Chen, 2004). On the other hand, SICI was shown to be reduced in the follicular phase and to be enhanced in the luteal phase of the cycle (Smith et al., 1999, 2002). Hence, if the underlying mechanisms of the iSP were related to the interhemispheric inhibition at 10 ms, one would expect an enhanced iSP in the follicular phase and a reduced iSP in the luteal phase. In contrast to this expectation, iSP was more pronounced in the luteal than in the follicular phase in our study, suggesting that it is based on a different neuronal population, reacting independently to variations in ovarian hormone levels.

Animal research has shown that physiological doses P suppresses the glutamate-induced excitatory responses of neurons by about 87% (Smith et al., 1987a,b), which is due to the attenuation of non-NMDA glutamate receptors without being mediated by an increase of GABA inhibition (Smith, 1991). The magnitude of this change is directly proportional to the P dose (Smith et al., 1987b). P and its metabolites tend to reduce neuronal excitability and raise the seizure threshold by augmenting the inhibitory neuronal response to GABA (Smith, 1991). In contrast, E exerts opposite effects with an increase to glutamate response by about 86% (Smith et al., 1988). If, however, neuronal tissues are pretreated with E before P application, or if E and P are applied in a combined fashion, glutamate receptors are downregulated as with P alone (Smith et al., 1987b). Thus, at least during the midluteal cycle phase, the combined release of E and P would result in a decrease of non-NMDA glutamate receptor responsiveness. These neuromodulatory effects of P and E might not only explain the modulations of cortical excitability in the human motor system during the menstrual cycle (Smith et al., 1999, 2002; Inghilleri et al., 2004), but are at least partly in line with hormone-related changes in iSP, which is assumed to represent a transcallosal inhibitory mechanism (Meyer et al., 1995), possibly mediated by transcallosal excitatory projections terminating on pyramidal neurons that activate inhibitory GABAergic interneurones (Kawaguchi, 1992; Toyama and Matsunami, 1976; Toyama et al., 1969). According to this model, iSP should be reduced when P levels are high, because a P-based reduction in the initial transcallosal excitatory activation, and thus, a reduced subsequent inhibition would lead to a reduced muscle response. In contrast, due to the P-agonistic effect of E (alone), iSP should be prolonged when E levels are high. However, the results of the regression analyses only revealed that high levels of P were significantly related to a reduction of iSP during the midluteal phase. About 41% of the variance in iSP is explained by the regression. The amount even increased up to 56% when the ratio of luteal/follicular P levels was taken into account, instead of absolute P concentrations. However, it is unclear why high E levels during the follicular phase are similarly related to

a reduced iSP, though E and P have obverse effects on non-NMDA and GABA receptors. The results suggest that both hormones affect specific aspects within the cascade of neurochemical processes related to transcallosal inhibition.

If it is correct that interhemispheric inhibition via the corpus callosum is an essential mechanism in causing functional cerebral asymmetries (e.g. Chiarello and Maxfield, 1996; Cook, 1984), a P-related reduction of transcallosal inhibition predicts reduced hemispheric asymmetries in motor functions and other functional domains which are asymmetrically organised in the brain. In line with this so-called hypothesis of P-modulated interhemispheric decoupling, a P-related reduction in functional cerebral asymmetries in favour of a more bilateral cerebral activation during the luteal phase has been reported previously by several studies using behavioural tasks (Hausmann et al., 2002; Hausmann and Güntürkün, 2000) and fMRI (Fernandez et al., 2003).

In sum, the results of the present study suggest that gonadal steroid hormones modulate transcallosal inhibition across the menstrual cycle. High levels of P and high levels of E (alone) seem to diminish the transcallosal inhibition, though hormonal effects on subcortical or spinal levels cannot be fully ruled out. Due to the fact that the neurophysiological mechanism of iSP is at least in some points speculative, we cannot fully explain how exactly P is reducing iSP. However, it is likely that P reduces iSP via its neuromodulatory effects on glutamatergic transcallosal fibres. The present study reveals the first direct physiological support of the idea that gonadal steroid hormones affect the interhemispheric interaction which has been assumed to be an essential mechanism in causing functional cerebral asymmetries.

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