Sex hormonal modulation of hemispheric asymmetry and interhemispheric crosstalk

Bayer, Ulrike

Sex hormonal modulation of hemispheric asymmetry and interhemispheric crosstalk

Ulrike Bayer

Thesis submitted for the degree of Doctor of Philosophy

Durham University, Psychology Department

2009

Declaration

I confirm that no part of the material offered has previously been submitted by me for a degree in this or in any other University. If material has been generated through joint work, my independent contribution has been clearly indicated. In all other cases material from the work of others has been acknowledged and quotations and paraphrases suitably indicated.

Copyright

Acknowledgements

Dr Markus Hausmann provided me with the opportunity to work with him on the exciting topic of sex hormonal effects on the brain. From the very beginning, until yesterday, he gave me his assistance and time, criticism and encouragement to finish this thesis. I sincerely thank him for his professional competence and his personal support at all stages of this work. I am glad our collaboration will continue.

I further thank Prof Charles Heywood for his valuable comments and suggestions on the thesis, especially at the final stage of this work.

I am especially grateful to Ingeborg and Hans Bayer for their continued support, and for understanding exactly what doing a PhD is all about.

I thank Aggy Gartner, Katja Morgenthal, and Reza Gartner, my friends in Berlin. They showed me what good friends are for, albeit mostly by telephone! It was essential to know that they were there for me while I was in Bochum and here in Durham. I especially thank Franziska Gniwotta for her patience and understanding when it was most required, both day and night.

Finally, I thank Marco Hirnstein as a colleague and friend. We shared not only an office and lots of stimulating discussions, but we also shared lots of English beers!

With deep respect and gratefulness, I dedicate this work to my father whose exceptional personality always inspires me.

Summary

Fluctuating levels of sex hormones (estrogen, E and progesterone, P) during the menstrual cycle have been shown to affect fundamental principles of brain organization, that is functional cerebral asymmetries (FCAs). Regarding a possible underlying mechanism, it seems likely that dynamics in FCAs are driven by hormonal modulations of interhemispheric crosstalk (i.e., interhemispheric inhibition). Whether other aspects of interhemispheric interaction, such as interhemispheric integration (IHI), are also susceptible to menstrual cycle-related hormonal changes has not yet been examined. Moreover, most of the findings come from studies investigating younger women during hormonal distinct cycle phases. This approach, however, does not allow conclusions about causal relationships between hormonal changes and functional brain organization. It seems, thus, necessary to direcly manipulate the hormonal status of participants *via* exogenous hormone therapy (HT).

The present thesis focused on sex hormonal changes in IHI and FCAs in normally cycling women and postmenopausal women with and without HT. Younger women were tested twice, once during the low-hormone menstrual phase and once during the high-P luteal phase. Postmenopausal women were tested in a between-participants design differentiating between postmenopausal women using E therapy (ET), those using E plus synthetic progestins, and postmenopausal controls without HT.

The results show that IHI in normally cycling women fluctuates across the menstrual cycle with an enhanced *inter*hemispheric processing during the luteal phase. Thus, it seems that aspects of interhemispheric interaction (i.e., IHI) other than those involved in FCAs are also affected by the menstrual cycle and cycle-related hormonal changes. In contrast, HT, and ET in particular, after the menopause seems to affect *intra*hemispheric processing whereas *inter*hemispheric was essentially unaffected by HT. A modulation of intrahemispheric functioning (i.e. right hemisphere functioning) which was related to estradiol-levels also became evident when postmenopausal women were tested on a right hemisphere dominated asymmetry task. The findings can be explained by a faster and more pronounced age-related decline in interhemispheric relative to intrahemispheric processing which seems to be accompanied by a higher sensitivity to HT. Aging processes together with differences in the hormonal status (exogenous changes as a result of HT vs. endogenous changes during the menstrual cycle) may also explain divergent behavioural outcomes in postmenopausal women and younger women.

Taken together, the findings show that the female brain retains its plasticity even after reproductive ages and remains susceptible to the effects of sex hormones throughout lifetime.

Table of contents

I Introduction

Gonadal steroids produce powerful neuromodulatory actions on the central nervous system. Besides affecting brain areas involved in reproduction (e.g., hypothalamus), the effects of gonadal hormones extend beyond their essential actions of modulating sexual behaviour, in that they can modulate cognitive behaviour. For example, sex hormones (e.g., estrogen) have been shown to affect cognitive abilities and particularly those which are known to differ between women and men that is, verbal and visuo-spatial abilities (e.g., Hampson, 1990a,b). Additionally, these cognitive abilities are asymmetrically organized in the brain. Specifically, language-related abilities are predominantly represented in the left hemisphere (LH) and hence, more efficiently processed by the LH. The right hemisphere (RH) typically shows a relative performance advantage in visuo-spatial abilities. Such an asymmetrical representation of cognitive processes in the two hemispheres is a fundamental aspect of human brain organization and is referred to as functional cerebral asymmetries (FCAs) (for review see Toga, 2003). Moreover, sex differences have not only been shown for specific cognitive abilities but also with respect to FCAs. That is, men, on average, exhibit pronounced and stable FCAs (e.g. Hiscock, Israelian, Inch, Jacek & Hiscock-Kalil, 1995). In contrast, women show a rather bilateral brain organization and a larger interindividual variability in the degree of FCAs (e.g., Hausmann, Behrendt-Körbitz, Kautz, Lamm, Radelt, & Güntürkün, 1998).

Women and men clearly differ in the concentration of sex hormones from early phases of development onwards until later life. Moreover, sex hormone levels are not stable but dramatically vary within relative short-term intervals in younger women during the menstrual cycle. Given these sex-specific hormonal environments, the impact of gonadal steroids on the brain seems to be the most plausible biological source of intra- and interindividual differences in brain organization and related functions. The present thesis focuses on estrogen and progesterone and their (direct) effects on the dynamics of the organization of the female brain.

Sex differences in functional cerebral asymmetries

Sex differences in human problem-solving have been consistently found in a number of studies over the past few decades (e.g., Kimura, 1992, 2002; Maccoby & Jacklin, 1974). Though these differences are average differences and the overlap between the two sexes on many tests is extensive (e.g., McKeever, 1995), men and women clearly display different patterns of abilities. Specifically, women are reported to excel in verbal tasks, perceptual

speed, articulation, and fine motor skills (e.g., Halpern, 2000; McGlone, 1980). Men, in contrast, tend to outperform women in visuo-spatial skills (e.g., mental rotation) and mathematical reasoning (e.g., Halpern, 1996; Voyer, Voyer, & Bryden, 1995).

As becomes evident, cognitive sex differences occur predominantly in those functions which have been associated with hemispheric specialization. Specifically, women show a superior performance in LH dependent functions whereas men perform better on tasks which mainly rely on RH functioning.

One early hypothesis put forward by Levy (1973) suggests that cognitive sex differences may arise from a sex-specific functional brain organization. According to this idea, the male superiority in RH-related functions results from a marked specialization of the RH for visuo-spatial processing and a marked specialization of the LH for language processes. In contrast, a more bilateral functional organization with some verbal abilities being represented in the RH has been suggested to account for both superior verbal processing and inferior visuo-spatial abilities in women (Levy, 1973).

In fact, sex differences in FCAs with men being more strongly lateralized than women are documented by two types of evidence. One source of evidence comes from people with brain injury. For example, one early study tested brain injured patients on a verbal comprehension test (Landsdell, 1962a,b). It was found that left temporal lobe lesions disrupted verbal abilities in males but not in females. This finding suggests that female patients were able to rely on residual language capabilities in the intact RH in order to perform the task. Another study examined the magnitude of IQ-impairment in patients with unilateral brain damages (McGlone, 1978, 1986). The author found that left-sided damage was associated with a decrease in performance on verbally weighted subtests of the IQ test. This, however, was only true for men but not for women. Again, this indicates a greater involvement of the RH in complex verbal functions in women than men.

The pattern of stronger and more pronounced left-right-differences in men than women has subsequently been confirmed by a number of studies testing healthy participants. For both verbal and visuo-spatial as well as face processing, it appears that women on average exhibit weaker hemispheric asymmetries (Halpern, 1996, 2000; Inglis & Lawson, 1981; McGlone, 1980). Further support comes from a meta-analysis which summarized tachistoscopic studies (Hiscock et al., 1995) and dichotic listening studies (Hiscock, Inch, Jacek, Hiscock-Kalil & Kalil, 1994) with respect to sex differences. Altogether, 31 out of 39 studies which reported a significant effect of sex on lateralization support the idea of greater FCAs in men than

women. Although the effects are rather small, Hiscock et al. (1994, 1995) concluded that on a population-level sex differences in laterality that accounts for one to two percent of the variance in laterality do exist. Moreover, there is some evidence of a larger interindividual variability in the degree of FCAs in women, whereas the prototypical lateralization in men is rather robust (Hausmann et al., 1998).

Many aspects of FCAs in relation to sex have been shown to be present early in infancy (e.g., Witelson, 1976). Given the distinct hormonal environments in males and females from early phases of development onwards, sex hormones and their impact on the brain seem to be a key factor to explain sex differences in FCAs.

Sex hormonal effects on functional brain organization

Sex hormones are biologically active substances that are mainly synthetized by the gonads (female ovaries and male testes) and, to a lesser extent, by the adrenal glands. The three main classes of sex hormones are estrogens (E), progestins, and androgens with their human principal derivatives estradiol, progesterone (P), and testosterone (T), respectively. Although all three classes of hormones are present in both sexes, men and women clearly differ in the concentration and fluctuation of specific hormones. In women, the two most prominent and potent steroids are 17β-estradiol (and its metabolites estrone and estriol) and P, while concentrations of T (as particularly synthesized by the adrenal-cortical glands) are rather low. Estradiol and P are products of the growing follicle in the ovaries of non-pregnant women. Secretion and plasma concentration of these steroids are primarily determined by the menstrual cycle. In men the most abundant steroid is T with levels around ten times higher than in women (e.g., Rupprecht, 2003).

As shown in Figure 1, all sex steroids are characterized by a specific chemical structure consisting of three six-carbon rings plus one five-carbon ring. They are synthesized *via* conversion of cholesterol into pregnenolone, the main precursor of sex hormones. Pregnenolone is then converted by specific enzymes into various types of sex hormones such as, P, T, and dihydrotestosterone (DHT). One key mechanism is that T but not DHT can be aromatized into estradiol via the enzyme aromatase. All steroids are fat soluble and pass easily through cell membranes. Sex hormonal effects can be mediated by slow genomic mechanisms through nuclear receptors as well as by fast nongenomic mechanisms through membrane-associated receptors and signaling cascades (e.g., McEwen & Alves, 1999). Thus,

genomic and non-genomic steroid effects within the central nervous system provide the molecular basis for a broad spectrum of steroid actions on neuronal function and plasticity.

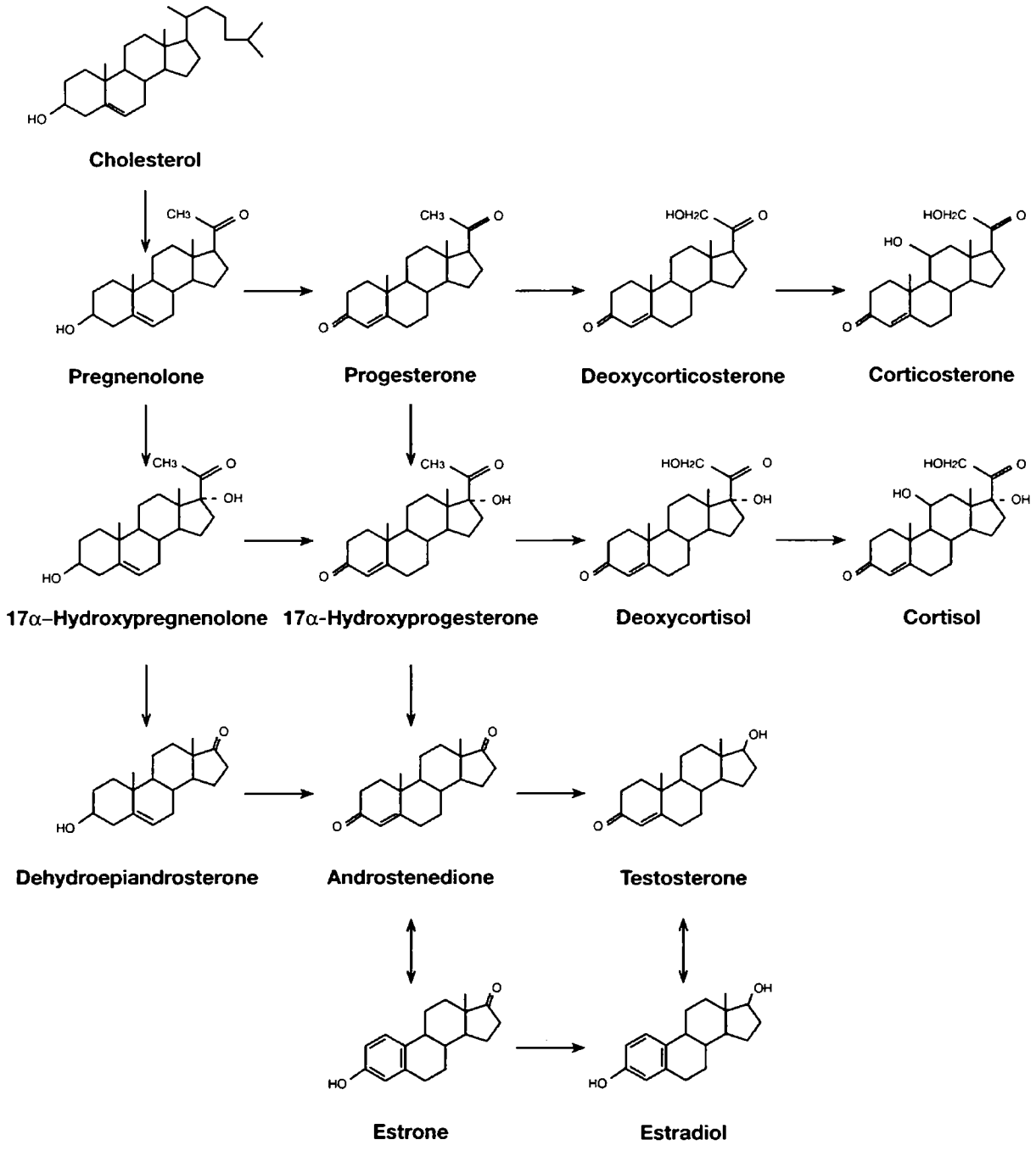

Fig. 1. Biosynthetic pathways of steroids. Adapted from Schumacher et al. (2007), *Endocrine Reviews, 28*(4), 414.

Organizing effects of sex hormones

Two types of sex hormonal effects have generally been distinguished: organizing and activating effects. Organizing effects of sex hormones are most likely to occur during early phases of development thereby permanently altering the construction and organization of the brain. Activating effects during later life are mediated by concurrent changes in circulating hormone levels, for example, those associated with the menstrual cycle, which can temporarily affect neural systems and related functions (e.g., Sherwin & Henry, 2008).

The organizing effects of sex hormones occur as an interaction between genetic and hormonal effects and are maximal during circumscribed sensitive periods. The exact periods for behavioural effects, however, are not known. Although weeks 8-24 of gestation have long been considered to be the key period, there is increasing evidence that there may be multiple sensitive periods during postnatal months (e.g., Cohen-Bendahan, van de Beek & Berenbaum, 2005).

In humans, sexual differentiation is controlled by androgens after the initial fetal stage where the presence (male development) or absence of the Y-chromosome and the SRY gene (female development) determine development. The role of prenatal androgens on the organization of the central nervous system including FCAs has been emphasized by one major framework provided by Geschwind and Behan in 1982 followed by three complex papers by Geschwind and Galaburda (1985a,b,c). The Geschwind-Behan-Galaburda theory (GBG) states that the presence of androgens, and T in particular, is associated with slowed growth within certain areas of the left hemispheres which is likely to result in an enlargement of homologous contralateral areas. These T-mediated alterations have been suggested to affect the development of language resulting in verbal disabilities (e.g., stuttering). Moreover, concomitant changes within the RH are assumed to alter various cognitive functions including visuospatial and musical abilities. Furthermore, the GBG model predicts a relationship between high levels of prenatal T and biological variables (e.g., immune disorders) caused by an influence of T on the thymus. Most importantly, in terms of hemispheric specialization, the GBG model suggests that changes within the LH lead to an anomalous dominance (AD) with alterations in verbal and visuo-spatial asymmetries and an atypical handedness. In their extensive review of the GBG model, Bryden, McManus and Bulman-Fleming (1994) assessed the empirical evidence coming from studies investigating possible relationships between these variables. Although there seem to be some associations between handedness and immune disorders as well as between AD and language disorders, the pattern of sex differences in AD,

language disabilities, and immune disorders is not always as predicted. Specifically, under the GBG model, men would be more likely to be left-handed, to have language impairments, and to be less lateralized than women. In fact, evidence exists that men are more often left-handed (e.g., Bryden, 1982) and more likely to be diagnosed as reading-disabled. However, the latter finding comes from school-aged boys and girls and might therefore be explained by sex differences in activity level and disruptive behaviour rather than with reading disability per se (Shaywitz, Shaywitz, Fletcher & Escobar, 1990). Most impoartantly within the present context, however, is the evidence stated above showing that men are not less lateralized but in fact more lateralized than women (e.g., Hiscock et al., 1994, 1995). Thus, as concluded by Bryden et al. (1994), none of the existing literature provides sufficiently compelling evidence for the GBG model.

Nonetheless, the fundamental impact of androgens for early development and organization of the brain has been highlighted by various studies in humans with an unusual hormonal environment, e.g. women with Congenital Adrenal Hyperplasia (CAH) (e.g., Collaer & Hines, 1995). Boys and girls with CAH are prenatally exposed to high levels of androgens. This hormonal condition results from an enzymatic deficiency which affects the feedback loop involving the production of cortisol. The consequence is the overproduction of androgens which is usually stopped by cortisol therapy after birth (e.g., Merke & Bornstein, 2005). Tirosh, Rod, Cohen and Hochberg (1993) have shown that LH language lateralization was more pronounced in CAH children, and female CAH patients in particular, compared with healthy right-handed controls. Although contradictions exist (e.g., Helleday, Siwers, Ritzen & Hugdahl, 1994; Mathews, Fane, Pasterski, Conway, Brook & Hines, 2004), this finding suggests an androgenic role in language lateralization.

Besides the assumption of a masculinizing role of T and its metabolite dihydrotestosterone (DHT), it has been suggested that E (as aromatized from T) plays a defeminizing role for male development. For example, Hines and Shipley (1984) examined FCAs in diethylstilbesterol (DES)-exposed women. DES is a synthetic E, prescribed for the purpose of pregnancy maintenance in cases of potential miscarriages. As a control group, their (unexposed) sisters were included. No differences in cognitive tests such as word fluency and spatial relation have been found. In a dichotic listening task, however, DES-exposed women showed higher right ear (LH) scores compared with controls whereas left ear scores were almost identical. This suggests that DES-exposed women exhibit greater verbal asymmetries similar to those in men as a result of early E exposure.

A feminizing role of early E exposure during sensitive periods in women, on the other hand, seems likely. This idea is mainly supported by findings from studies testing women with Turner's syndrome (TS). The TS is characterized by a gonadal dysgenesis as a result of a genetic aberration in women (X0-genotype). TS-women display a severe deficit in E. Studies on TS-patients have shown that these women showed reduced FCAs in a verbal dichotic listening task or even a reversed pattern of asymmetries in favour of the RH. In contrast, a healthy control group exhibit a typical LH advantage on this task (e.g., Netley & Rovet, 1982).

Activating effects of sex hormones

To investigate the phasic influences of circulating sex steroids (i.e., E and P) on FCAs during later life, two types of studies have commonly been conducted, that is studies testing younger women during the menstrual cycle and those testing transsexual patients receiving opposite-sex hormonal treatment. The latter approach provides an attractive opportunity to examine whether hemispheric differences are genetic sex-specific or affected by the actual hormonal environment (Forget & Cohen, 1994). Cohen and Forget (1995), for example, compared the lateralization pattern in men, genetic male transsexuals, and women on verbal and nonverbal dichotic listening tasks. A typical right ear (LH) advantage for verbal processing was found in all three groups. In the nonverbal task, however, only men revealed a significant left ear (RH) advantage whereas women and genetic male transsexuals showed similarly reduced hemispheric differences. Although contradictions exist (Herman, Grabowska & Dulko, 1993), this finding suggests that FCAs are not necessarily determined during the prenatal development.

A large number of studies have focused on the effects of sex hormones on FCA's in normally cycling women cycle because their endogenous hormone levels dramatically vary across the menstrual cycle (for review see Wiesniwski, 1998).

The menstrual cycle is a recurring cycle under hormonal control which is characterized by physiological changes in the ovaries and endometrium in reproductive-aged women. One cycle starting with menstruation lasts about 28 days and can be divided in several phases. The relative levels and timing of secretion of each hormone are displayed in Figure 2.

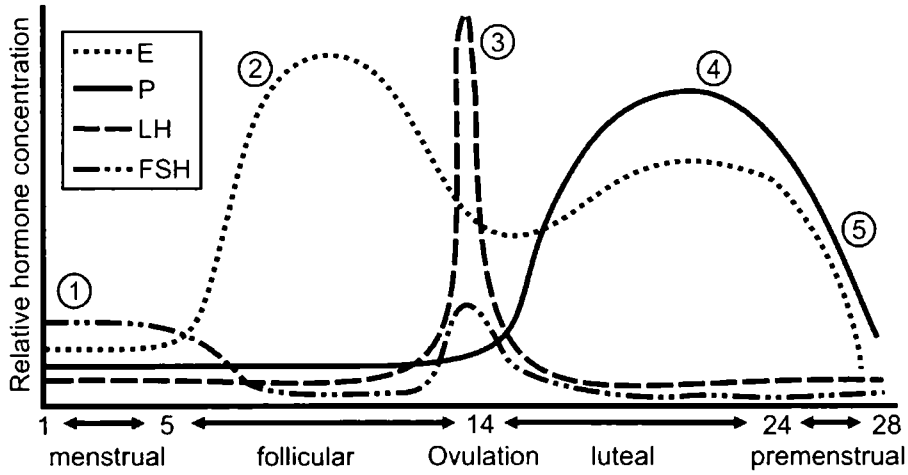

Fig. 2. The menstrual cycle. Schematic illustration of fluctuations in sex hormone (estradiol, E; progesterone, P) and gonadotropin levels (luteinizing hormone, LH; follicle-stimulating hormone, FSH) during an average 28-day menstrual cycle. Adapted from Hausmann & Bayer (submitted).

During the menstrual phase (1), the secretion of gonadotropin-releasing-hormone (GnRH) from the hypothalamus increases and leads to the release of follicle-stimulating hormone (FSH) from the anterior pituitary into the bloodstream. During this phase, E- and P-levels are lowest (1). In response to FSH, the ovary begins steroid production that is, mainly, E production (follicular phase, 2). An increasing E-level exerts a negative feedback which results in a decreased release of FSH. As soon as E-levels reach a critical threshold, however, the negative feedback turns into a positive feedback causing a massive release of luteinizing hormone (LH) which leads to ovulation (3). The following luteal phase is characterized by the synthesis of large quantities of P by the corpora luteum, a transient endocrine gland. At the same time E reaches its second peak (4). In the event of no fertilization, P- and E-levels rapidly decrease (5) leading to the menstruation. In response to low E- and P-levels, a new menstrual cycle starts with an increase in FSH release (e.g., Asso, 1983).

Functional cerebral asymmetries during the menstrual cycle

In recent years, a number of studies have demonstrated that FCAs fluctuate across the menstrual cycle (Bibawi, Cherry, & Hellige, 1995; Hampson, 1990a, 1990b; Heister, Landis, Regard, & Schroeder-Heister, 1989; McCourt, Mark, Radanovich, Willison, & Freeman, 1997; Mead & Hampson, 1996; Rode, Wagner, & Güntürkün, 1995; Sanders &Wenmoth, 1998). With regard to the direction of the observed changes, the results are somewhat

controversial as are the proposed hypotheses about a possible influence of gonadal steroids on FCAs.

Based on evidence from cycle-related changes in auditory asymmetries, one hypothesis, originally presented by Hampson (1990a,b; see also Mead & Hampson, 1996; Sanders & Wenmoth, 1998) suggests that high levels of sex hormones, and particulary E, are related to an enhancement of LH verbal performance and a suppression of RH visual-spatial performance. This idea predicts *task-dependent* changes in FCAs, i.e. an increase in hemispheric differences in LH dominated verbal tasks, but an attenuation in RH dominated tasks.

An alternative conceptualization has been suggested by Heister et al. (1989) who assume that low levels of sex hormones as present during menses are related to typical hemispheric differences whereas an increase in E- and P-levels is accompanied by a *task-independent* attenuation of FCAs. This assumption is based on the logic that the hormonal conditions during the menstrual phase are similar to that in men and hence, women show a more "male-like" functional brain organization with enhanced FCAs. However, this idea does not make specific assumptions about which steroid (i.e, E and/or P) might be relevant in modulating the performance of the LH and/or RH.

A third idea has been presented by McCourt et al. (1997). The authors assume a hormone-related nonspecific activation of both hemispheres which lowers the threshold for a task-specific phasic activation (Kinsbourne, 1983; Reuter-Lorenz, Kinsbourne, & Moscovitch, 1990). Accordingly, higher levels of sex hormones should result in enhanced asymmetries for both LH and RH dominated tasks. Although not explicitly stated by the authors, the activating effects of E on the central nervous system as opposed to the depressant actions of P, which are known to enhance GABA-ergic transmission, would suggest E as the relevant agent. It should be noted here, that this hypothesis was originally based on findings in a blinding pointing task to assess the perceived location of the midsagittal plane and hence, does not directly refer to menstrual cycle-related changes in perceptual asymmetries.

Regarding the empirical evidence (Table 1), the majority of findings for RH dominated tasks favour the assumption of an attenuation in FCAs when sex hormones are high which is in line with the hypotheses of Heister (1989) and Hampson (e.g. visual half-field studies for face decision: Heister et al, 1989; Rode et al., 1995; dichotic listening studies with musical material: Sanders & Wenmoth, 1998). There are, however, also studies which reported the opposite finding with reduced asymmetries during menses (e.g., Mead & Hampson, 1996) or

which did not find any differences in perceptual asymmetry to RH dominated tasks between high and low steroid phases of the cycle (e.g. for line orientation: Chiarello, McMahon, & Schaefer, 1989; for face perception: Bibawi et al., 1995; for face recognition: Compton & Levine, 1997).

With regard to LH dominated verbal tasks, most of the visual half-field studies did not find any changes in FCAs (for lexical decision: Chiarello et al., 1989; Compton & Levine, 1997; Heister et al., 1989; word matching: Rode et al., 1995). A few studies using lateralized auditory stimuli reported findings of an enhanced verbal asymmetry during high-hormone phases (Alexander et al., 2002; Altemus et al., 1989; Hampson, 1990b; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008; Weekes & Zaidel, 1996) which partly support Hampson 's (1990) and McCourt et al.'s (1997) predictions. Additionally, the observation of a right visual field (LH) advantage for a nonlateralized chair recognition task during the midluteal phase (Bibawi et al., 1995) might be explained by Hampson's idea of a specific activation of the LH by high levels of sex hormones, although which hormone is implicated remains unclear.

Dichotic listening studies

Study	Participants	Cycle phases (cycle days)	Hormone assay	Main results
Altemus et al. (1989)	39 normally cycling women (mean age = 30 years)	Follicular phase (6-12) Premenstrual phase (21-28)	No	Fused rhymed words tests (three versions) and emotional words test (two versions): Reduced REA during follicular phase (degree of asymmetry, accuracy).
Hampson (1990a)	45 normally cycling women (mean age = 23.7 years)	Menses (3-5) Midluteal phase (18-23)	No	Dichotic words test: No significant effects of cycle phase on REA.
Hampson (1990b)	50 normally cycling women (mean age = 26.4 years)	Menses (3-5) Follicular phase (12-13)	E, P, LH (blood)	Dichotic words test: Reduced REA during menses (accuracy). E positively related to degree of asymmetry (accuracy).
Mead & Hampson (1996)	36 normally cycling women (mean age: 23.7 years)	Menses (3-5) Midluteal phase (18-23)	E (saliva)	Emotional words test – verbal component: Reduced REA during midluteal phase (accuracy, only for women tested first during the midluteal phase). Emotional words test – nonverbal component: Reduced LEA during menses (accuracy).
Weekes & Zaidel (1996)	45 normally cycling women	Menses Luteal phase	No	Verbal task: Reduced REA in women during menses (accuracy, between-participants analysis).
Sanders & Wenmoth (1998)	32 normally cycling women (mean age = 24 years)	Menses (3-5) Midluteal phase (20-22)	No	Consonant-vowel identification task: Reduced REA during menses (accuracy). Musical chord recognition task: Reduced LEA during midlueal phase (accuracy).
Alexander et al. (2002)	30 normally cycling women (mean age = 32 years) 12 men (mean age = 32 years)	Menses (1-7) Follicular phase (8-14) Midcycle phase (15-21) Premenstrual phase (22-28)	No	Fused rhymed words tests (three versions) and emotional words test (two versions): Reduced REA during premenstrual phase compared with follicular phase (degree of asymmetry, accuracy). Men revealed stable but generally smaller REAs.
Wadnerkar et al. (2008)	25 normally cycling women (mean age = 22.6 years) 20 men (mean age = 22.2 years)	Menses (2-5) Midluteal phase (18-25)	No	Consonant-vowel test: Reduced REA during menses (accuracy). Men (tested once) revealed a strong REA different to that in women during menses.

Visual half-field studies

Study	Participants	Cycle phases (cycle days)	Hormone assay	Main results
Heister et al. (1989)	12 normally cycling women (age range = 22-39 years)	Menses (1-3) Follicular phase (8-14) Luteal phase. (15-22) Premenstrual phase (23-28)	No	Lexical decision: No significant effects of cycle phase on RVFA. Face discrimination task: Reduced LVFA during premenstrual phase compared with menses (response times).
Chiarello et al. (1989)	24 normally cycling women (mean age = 23.5 years) 24 men (mean age = 23.0 years)	Menses (2-3) Follicular phase (10-12) Midluteal phase (23-25)	No	Lexical decision: Reduction in typical response bias (β)-asymmetry (stricter criterion for LVF than RVF) during menses. Men revealed stable VHF effects in β-asymmetries during corresponding time intervals which were different to that in women during menses. Line orientation task: No significant effects of cycle phase on LVFA.
Bibawi et al. (1995)	13 normally cycling women 16 men	Menses (3-5) Midluteal phase (17-19)	No	Chair identification (non-lateralized): Significant RVFA during the luteal phase but not during menses (accuracy). Men revealed no VHF effect during either testing session. Face processing: No significant effects of cycle phase on LVFA.
Rode et al. (1995)	17 normally cycling women (mean age = 26.3 years)	Menses (2) Luteal phase (22-25)	E, P (blood)	Word matching: No significant effects of cycle phase on RVFA. Figural comparison: Reduced LVFA during luteal phase (response times). E and/or P were not significantly related to performance measures.
Mead & Hampson (1996)	36 normally cycling women (mean age = 23.7 years)	Menses (3-5) Midluteal phase (18-23)	E (saliva)	Rhyming words task (producing a RVFA): Significant decrease in LVF performance during midluteal phase (accuracy, within-participants analysis, simple comparisons). Face recognition: Reduced LVFA during menses (response times, between-participants analysis). Significant decrease in LVF performance during midluteal phase (accuracy, within-participants analysis, simple comparisons).
Weekes & Zaidel (1996)	45 normally cycling women	Menses Luteal phase	No	Lexical decision: No significant differences in RVFA between groups (between-participants analyses).

Compton & Levine (1997)	24 normally cycling women (mean age = 24 years)	Menses (2-5) Follicular phase (8-11) Midluteal phase (19-22)	No	Lexical decision: No significant effects of cycle phase on RVFA. Face decision (two versions): No significant effects of cycle phase on LVFA.
Hausmann & Güntürkün (2000)	26 normally cycling women (mean age = 30.4 years) 9 men (mean age = 29.3 years) 21 postmenopausal women (mean age = 56.1 years)	Menses (2) Midluteal phase (21-23)	P (saliva)	Word matching: Reduced RVFA during midluteal phase (accuracy): Figural comparison: Reduced LVFA during midluteal phase (accuracy). P negatively related to degree of asymmetry (accuracy). Face discrimination and Reduced LVFA during midluteal phase (accuracy). Controls revealed stable VHF effects in all tasks during corresponding time intervals.
Hausmann et al. (2002)	12 normally cycling women	15 testing sessions over 6 weeks in consecutive intervals of 3 days	E, P, T, LH, FSH (blood)	Word matching: E positively related to degree of asymmetry (accuracy, longitudinal design). Figural comparison: P negatively related to degree of asymmetry (accuracy and response times) and positively/negatively related to RVF-accuracy/RVF-response times (longitudinal design). E negatively related to degree in asymmetry (response times, longitudinal design).

Functional magnetic resonance imaging studies

Study	Participants	Cycle phases (cycle days)	Hormone assay	Main results
Dietrich et al. (2000)	6 normally cycling women (age range = 21-31 years) 6 men (age range = 22-29 years)	Menses Follicular phase (11-12)	E, T (blood)	Word stem completion task, Mental rotation task, Motor task: No significant effects of cycle phase on performance of any task. Cognitive tasks and brain activity: Reduced cortical activation during menses. Larger areas of activation in women during follicular phase than men.
Fernandez et al. (2003)	12 normally cycling women	Menses (2-4) Midluteal phase (21)	E, P, T, LH, FSH, SHBG, DHEA (blood)	Synonym judgement task: No significant effects of cycle phase on performance. Brain activity: Reduced left lateralized activation pattern during midluteal phase. P negatively related to degree of asymmetry.
Weis et al. (2008)	14 normally cycling women (mean age = 26.8 years) 14 men (mean age = 27.4 years)	Menses (1-3) Follicular phase (9-11)	E, P (blood)	Word matching: Reduced RVFA (response times) which was related to reduced inhibitory influence on the right inferior frontal gyrus (IFG) during follicular phase. E negatively related to degree of interhemipsheric inhibition. Men revealed stable RVFA and no change in inhibitory influence on the right IFG during corresponding time intervals.

Table 1. Studies on menstrual cycle-related changes in functional cerebral asymmetries. Adapted from Hausmann & Bayer (submitted). *Note.* Right ear advantage (REA), Left ear advantage (LEA), Left visual half-field advantage (LVFA), Right visual half-field advantage (RVFA), Estradiol (E), Progesterone (P), Tesosterone (T), Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Sex hormone binding globulin (SHBG), Dehydroepiandrosterone (DHEA).

The controversial findings of the studies cited above might partly arise from a number of methodological differences in, for example, the modality and type of tasks used and the kind of performance measures (accuracy and/or speed of responses). The most critical point, however, is that most of these studies did not control for the predicted cycle phase by measuring hormone levels. It has been shown that only about 60% of young women ovulate during each cycle (e.g., Metcalf & MacKenzie, 1980) and the timing of hormone fluctuations varies between as well as within subjects. Moreover, no assumptions about a specific role of either steroid by correlating hormone levels to performance measures can be made. Finally, it should be noted that none of the ideas based on the above cited findings provides any assumptions about possible neural mechanisms underlying hormone-related changes in FCAs.

With respect to the issues discussed above, two later studies conducted by Hausmann and Güntürkün (2000, Hausmann, Becker, Gather & Güntürkün, 2002) are of particular relevance. In the first study, Hausmann and Güntürkün (2000) tested normally cycling women during menses and during the high-P luteal phase on a prototypical LH dominated visual half-field (VHF) task (word matching) and two prototypical RH dominated VFH-tasks (figural comparison, face discrimination). Cycle-phases were validated by measuring P-levels from saliva samples. Additionally, younger men and postmenopausal women without hormone therapy (HT) were tested in corresponding time intervals. The authors found significant interactions between cycle-phase and VHF for all three tasks indicating a decrease in asymmetries during the high-P luteal phase as a result of a performance enhancement of the subdominant hemisphere, respectively. Notably, hemispheric differences in men and postmenopausal women were similar to those in women during menses and remained stable over time. Moreover, P-levels in normally cycling women were significantly related to the decrease in asymmetry in the figural comparison task. This finding has been replicated by a follow-up study using the same tasks, in which normally cycling women were tested 15 times in subsequent time intervals of three days (Hausmann et al., 2002). This approach allowed for longitudinal analyses of FCA-hormone relationships over more than an entire duration of a complete cycle. In both the cross-sectional and the longitudinal analyses, the authors found significant relationships between high P-levels and reduced FCAs as a result of a performance enhancement of the less specialized LH in the figural comparison task. In contrast, estradiol-levels were related to performance measures of both VHFs, and hence did not affect FCAs.

The hypothesis of progesterone-mediated interhemispheric decoupling

Based on their findings of task-independent changes in FCAs (Hausmann & Güntürkün, 2000), Hausmann and Güntürkün concluded that sex hormones, and P in particular, do not selectively modulate either one of the two hemispheres but rather that it is the interaction between both hemispheres which is affected by sex hormones. This idea is based on the assumption that interhemispheric interaction, that is interhemispheric inhibition, is a fundamental prerequisite for the manifestation of FCAs (Maxfield & Chiarello, 1996). Specifically, interhemispheric inhibition as a dynamic mechanism in causing FCAs has been assumed to be a result of callosal suppresion in which a stimulus-specific activation of one of the hemispheres inhibits homotopic areas in the other during task processing (e.g., Cook, 1984). Although the cortico-cortical transmission is mainly excitatory, the longer lasting effect of callosal activation seems to be inhibitory (e.g., Innocenti, 1980), because most callosal fibers terminate on pyramidal neurons which then probably activate GABAergic interneurons (e.g., Toyama & Matsunami, 1976; Toyama, Tokashiki & Matsunami, 1969). Thus, it seems that the corpus callosum induces a short excitatory postsynaptic potential followed by a sustained inhibition (e.g., Kawaguchi, 1992).

According to the *hypothesis of progesterone-mediated interhemispheric decoupling* (Hausmann & Güntürkün, 2000, Hausmann et al., 2002), high levels of P as present during the luteal phase attenuate these inihibitory processes leading to a functional decoupling of the two hemispheres. This, then, finally results in reduced FCAs with an enhancement of the performance of the subdominant hemisphere (Figure 3).

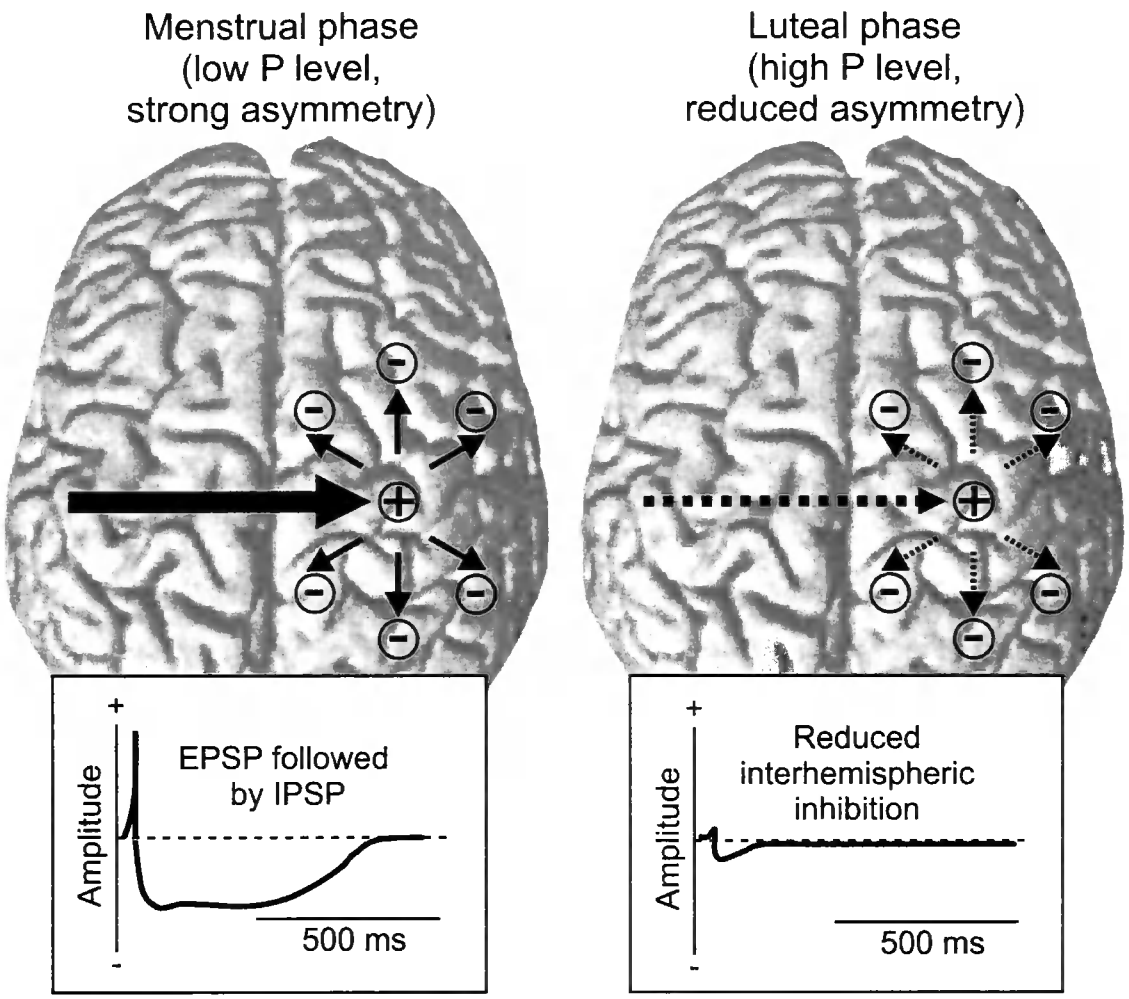

Fig. 3. Schematic illustration of the hypothesis of progesterone-modulated interhemispheric inhibition. Adapted from Hausmann & Bayer (submitted).

Left figure illustrates the process of interhemispheric inhibition during the low-P menstrual phase. It is assumed that increasing P-levels during the luteal phase attenuate interhemispheric inhibition via modulations of glutaminergic and GABAergic receptor activation. This effect could result in a temporal decoupling of the two hemispheres leading to reduced functional asymmetries (right figure) (Hausmann and Güntürkün, 2000; Hausmann et al., 2002).

At a physiological level, it was proposed that P reduces interhemispheric inhibition by suppressing the excitatory responses of neurons to glutamate as well as by enhancing their inhibitory responses to GABA (Hausmann & Güntürkün, 2000; Hausmann et al., 2002). In fact, pharmacological studies have demonstrated that P suppresses the excitatory neural responses to glutamate, an effect which was due to an attenuation of non-NMDA glutamate receptors (e.g., Smith, 1991; Smith, Waterhouse & Woodward, 1987). The magnitude of decrease was directly proportional to the dose of P. At the same time, P has been shown to increase GABA-induced inhibitory responses of neurons by modulating $GABA_A$-receptors. By contrast, estradiol exerts the opposite effect and increases neuronal responses to glutamate.

The combined action of P and estradiol, however, is similar to that of P alone (e.g., Smith et al., 1988). Thus, it was assumed that during the luteal phase of the menstrual cycle, increased estradiol- and P-levels exert P-like effects which might temporarily lead to a functional decoupling of the two hemispheres resulting in reduced FCAs (Hausmann & Güntürkün, 2000; Hausmann et al., 2002).

With respect to the studies discussed above, it is important to note that the majority of VHFT-findings can be explained by the hypothesis of Hausmann and Güntürkün (2000, Hausmann et al., 2002) according to which FCAs are mostly pronounced during menses but reduced when sex hormone levels, and P-levels in particular, are high (e.g., Heister et al., 1989; Rode et al., 1995).

Menstrual cycle- and hormone-related changes in FCAs have also been demonstrated by functional magnetic resonance imaging (fMRI) studies (see Table 1). Fernandez et al. (2003), for example, used a verbal synonym judgements task and found an increase in bilateral neuronal activity in women during the midluteal phase compared with menses. In line with the hypothesis of Hausmann and Güntürkün (2000; Hausmann et al., 2002), the decrease in asymmetry was related to P-levels whereas estradiol-levels seem not to affect FCAs. This assumption finds further support by an imaging study conducted by Dietrich et al. (2001). Using several cognitive and motor tasks, the authors reported a general increase in brain activation during the high-estradiol follicular phase compared with menses which did not affect lateralization pattern (Dietrich et al., 2001, see also Table 1). However, the two imaging studies presented here do not allow any conclusions about possible mechanisms underlying cycle- and hormone-related changes in FCAs.

In this respect, a most recent study significantly contributes to the understanding of sex hormonal effects on functional asymmetries (Weis, Hausmann, Stoffers, Vohn, Kellermann & Sturm, 2008). Based on the hypothesis of hormone-mediated interhemispheric decoupling (Hausmann & Güntürkün, 2000; Hausmann et al., 2002), which claims interhemispheric inhibition to be the central process in generating FCAs, this study used a connectivity analyses to directly determine the inhibitory influence of the dominant hemisphere on homologous brain areas of the subdominant hemisphere. Normally cycling women were tested during the low steroid menstrual phase and during the high E follicular phase on a verbal VHF-task (word matching). Additionally, a male control group was tested at corresponding time intervals. At the behavioural level, the authors found reduced asymmetries during the high-hormone follicular phase compared with menses whereas men exhibited

substantial FCAs during both testing sessions. The connectivity analyses additionally revealed estradiol-related fluctuations in the inhibitory influence of the dominant on the non-dominant hemisphere. In contrast, interhemispheric inhibition in male controls remained stable over time. It is important to note that significant differences between the menstrual and follicular phase were only found when the analyses were restricted to the comparison of activation in the right inferior frontal gyrus (IFG). The results were interpreted as showing that in women during the menstrual phase and in men, the left IFG exerts an inhibitory effect on homotopic areas within the RH which was not evident in women during the follicular phase.

This study provides two major implications. First, in line with the model of Hausmann and Güntürkün (2000; Hausmann et al., 2002), the findings indicate that the process of interhemispheric inhibition is in fact a key mechanism in generating FCAs. Most importantly, however, they indicate that rising levels of sex hormones are related to an attenuation of interhemispheric inhibition and thus reduced FCAs which is in line with the proposed mechanism underlying hormone-related changes in asymmetries (Hausmann & Güntürkün, 2000). In the study of Weis et al. (2008), however, it was estradiol and not P which was related to the effects. This might be due to the fact that the authors focussed on the menstrual phase during which estradiol- but not P-levels are highest. Thus, it does not necessarily imply that P is unrelated to interhemispheric inhibition. The authors rather concluded that both estradiol and P might exert similar effects on interhemispheric cross-talk during the follicular and luteal phase, respectively. Since estradiol and P have been shown to have partly opposite neuromodulatory properties on glutamate and GABA receptors, it seems likely that either estradiol and P induce similar neuromodulatory processes *via* different pathways or both estradiol and P serve as precursors of the same directly acting steroid (Weis et al., 2008).

The latter assumption is in line with the findings of a recent neurophysiological study (Hausmann, Tegenthoff, Sänger, Janssen, Güntürkün & Schwenkreis, 2006). This study employed transcranial magnetic stimulation (TMS) to investigate the neuromodulatory properties of E and P on transcallosal inhibition. TMS was applied to the primary motor cortex evoking a short suppression of tonic voluntary muscle activity in the corresponding contralateral and ipsilateral hand muscle. The ipsilateral silent period (iSP) is mediated by transcallosal fibers, and thus, iSP is assumed to reflect transcallosal inhibition. Normally cycling women were tested during menses as well as during follicular and luteal phases. The authors found that E and P-levels during follicular and luteal phases, respectively, were negatively related to iSP. In accordance with Weis et al. (2008), this finding indicates similar effects of high estradiol- and P-levels on specific interhemispheric processes, though both

hormones are known to exert partly opposing effects on GABA and glutamate receptors. Moreover, in line with the hypothesis of progesterone-mediated interhemispheric decoupling (Hausmann & Güntürkün, 2000; Hausmann et al., 2002), the authors concluded that a reduced interhemispheric motor inhibition would predict an attenuation of hemispheric differences in the motor system which is also asymmetrically organized.

Interhemispheric interaction during the menstrual cycle

In subsequent years, the hypothesis of progesterone-mediated interhemispheric decoupling (Hausmann & Güntürkün, 2000; Hausmann et al., 2002) has initiated further research on the more general idea that sex hormones modulate cortico-cortical transmission.

For example, Hausmann (2005) tested normally cycling women during menses and during the luteal phase using a visual line-bisection task. In such tasks, subjects are required to manually bisect a line drawn on paper by marking with a pen. It has been shown that healthy subjects systematically misbisect space, generally erring to the left veridical centre, a phenomenon which is referred to as "pseudoneglect". This pseudoneglect has been assumed to constitute a behavioural manifestation of an underlying attentional asymmetry with an advantage of the right hemisphere in allocating attention. Although this pseudoneglect is especially pronounced when the left hand (corresponding to the right hemisphere) is used to bisect the lines (e.g., Hausmann, Ergun, Yazgan & Güntürkün, 2002; Hausmann, Waldie & Corballis, 2003), it is also present, albeit reduced, for the right hand (left hemisphere) (e.g., Jewell & McCourt, 2000). This hand-use difference has been assumed to reflect transcallosal spreading activation from the line-bisection bias-dominating right hemisphere to the left hemisphere, controlling the left and right hand, respectively. Hausmann (2005) found a reduced hand-use difference in women during the luteal phase compared with menses. Moreover, the hand-use difference in women during the luteal phase, but not during menses, significantly differed from that found in male controls. This finding was interpreted as a hormone-dependent modulation of interhemispheric transfer of neuronal activation. This effect was mainly related to high E levels suggesting that specific transcallosal processes might be differentially affected by estradiol and P. It must be noted, however, that the line bisection task used by Hausmann (2005) gives a rather indirect measure of interhemispheric interaction and hence, the findings do not provide direct evidence of a sex hormonal modulated transcallosal crosstalk.

One paradigm which provides a direct measure of interhemispheric crosstalk is the Banich-Belger paradigm (Banich & Belger, 1990). In this paradigm, within-hemisphere processing is compared with across-hemisphere processing which allows the possibility of estimating the relative efficiency of interhemispheric integration. Specifically, participants are asked to match stimuli which are presented in either one visual half-field (within-hemisphere condition) or across both visual half-fields (across-hemisphere condition). A number of studies have demonstrated that the cooperation between the two hemispheres facilitates the performance in complex tasks but not in easier tasks. For example, relatively simple tasks such as deciding whether two letters are physically identical (e.g., 'A' and 'A') are usually performed better when the relevant information (matching stimuli) are directed to one hemisphere rather than both hemispheres (within-field advantage). By contrast, in more complex tasks such as deciding whether two letters have the same name (e.g., 'a' and 'A'), a performance advantage becomes evident when the matches are directed to both hemispheres rather than to only one hemisphere. This phenomenon is referred to as "across-field advantage" (AFA) and has been assumed to change gradually with increasing task demands. That is, a large within-field advantage shifts to a reduced within-field advantage or no within-across difference rather than to a significant AFA. A small AFA, on the other hand, changes to a significant AFA when the task becomes more complex. Thus, regardless of the baseline (i.e., AFA in the less demanding task), the efficiency of across-hemisphere processing relative to within-hemisphere processing increases under increasing task demands (e.g., Weissman & Banich, 2000).

This dynamic change of interhemispheric effects on performance has been suggested to result from the interaction between two opposing forces. Specifically, it seems likely that interhemispheric integration produces time costs because the information needs to be integrated across both hemispheres *via* the corpus callosum. On the other hand, the division of labour between hemispheres can increase the computational power because both hemispheres can process a part of the information relatively independent. When task demands are low, the benefits of across-hemisphere integration are not efficient enough to outweigh the costs associated with interhemispheric crosstalk. As task complexity increases, however, the benefits of having the resources of both hemispheres available are greater than the costs which results in an AFA. Thus, it seems that the relative efficiency of interhemispheric integration as determined by the across-within-difference changes as a function of task difficulty (e.g., Weissman & Banich, 2000).

In line with this idea, functional imaging studies have demonstrated that highly demanding tasks elicit a more bilateral activation pattern than simpler tasks (e.g., Klingberg, O'Sullivan & Roland, 1997). A more recent imaging study used a variation of the Banich-Belger paradigm and found a greater bilateral activation in the occipital cortex in the more demanding letter name task compared with an easier letter shape task indicating an increase in bilateral resource sharing as task demands increase (Pollmann, Zaidel & Cramon, 2003).

So far, only one study has used the Banich-Belger paradigm to determine sex hormonal effects on interhemispheric integration (Compton, Costello & Diepold, 2004). Specifically, this study tested normally cycling women during the menstrual and the luteal phase on a more demanding version of the task in which participants were required to match letters according to their name identity (e.g., 'a' and 'A'). Referring to the hypothesis of progesterone-mediated decoupling (Hausmann & Güntürkün, 2000; Hausmann et al., 2002), Compton et al. (2004) predicted that interhemispheric integration becomes less efficient (i.e., smaller AFA) with increasing P-levels during the luteal phase compared with menses. The results, however, did not reveal any cycle- or hormone-related changes in the AFA. The authors concluded that their findings failed to confirm the hypothesis of progesterone-mediated interhemispheric decoupling.

It must be noted, however, that the model put forward by Hausmann and Güntürkün (2000; Hausmann et al., 2002) specifically refers to the process of interhemispheric inhibition as a dynamic regulatory mechanism coordinating the simultaneous and partly conflicting outputs of the lateralized system. Thus, the hypothesis of progesterone-mediated decoupling does not provide specific assumptions about cycle- and hormone-related changes in interhemispheric integration (i.e., AFA). The proposed decoupling of the two hemispheres during the high-P luteal phase may imply a less efficient interhemispheric integration. It seems also likely, however, that a reduced interhemispheric suppression of homotopic brain areas relates to a more efficient processing within each hemisphere which might finally contribute to an enhanced interhemispheric integration.

Summary and conclusions

There is substantial evidence that FCAs fluctuate across the menstrual cycle. Although contradictions exist, it seems that FACs are mostly pronounced during the low-hormone menstrual phase, whereas they are reduced during cycle phase of high-hormones, and during the high-P luteal phase in particular. Regarding a possible mechanism, it is likely that

menstrual cycle- and hormone-related changes in asymmetries are driven by sex hormonal modulations in interhemispheric inhibition.

Regarding the more general idea of a sex hormonal modulation of interhemispheric interaction, the behavioural evidence with one study providing a rather indirect measure (Hausmann, 2005) and another study which did not find cycle-related changes in interhemispheric integration (Compton et al., 2004) is far less clear. One critical point in the Compton et al. study is that the authors used only one version of a letter matching task. As stated above, interhemispheric effects clearly interact with task difficulty. Thus, it seems likely that hormonal effects on interhemispheric integration become particularly evident under varying task demands, an aspect which has not yet been investigated.

Most importantly, however, seems the fact that the evidence of sex hormonal effects on FCAs and interhemispheric interaction discussed so far comes exclusively from studies testing younger women across the menstrual cycle. This correlative approach does not allow for conclusions about causal relationships between hormonal fluctuations and changes in the functional brain organization. Moreover, it has been demonstrated that repeated measurements as applied in menstrual cycle-studies can affect functional brain organization (Hausmann & Güntürkün, 1999). Although in the majority of studies the order of cycle phase was counterbalanced across participants or control groups (e.g., age-matched men, postmenopausal women without hormone therapy) were included, potential carry-over effects cannot completely be ruled out.

To significantly emphasize the idea of dynamic changes in the brain organization and related functions as a result of sex hormonal fluctuations, it is necessary to directly manipulate participants' hormonal status. One possible approach is the investigation of postmenopausal women receiving different hormonal substitution.

Hormone therapy and Cognition

Hormone therapy (HT) in postmenopausal women consists of E therapy (ET) alone or with the addition of synthetic progestins and was initially prescribed to relieve menopausal symptoms, such as hot flushes and changes in mood. Additionally, it has widely been demonstrated that HT can affect cognition in postmenopausal women. Specifically, it has been suggested that HT, and ET in particular, improves cognitive functioning (see Hogervorst, Williams, Budge et al., 2000, for a review) probably by its modulatory effects on neurotransmitters (e.g., Bethea, Lu, Gundlah & Streicher, 2002), neuroconnectivity (e.g.,

Toran-Allerand, 1991), and neuroprotection (e.g., McEwen, 2002). Specifically, it has been suggested that E stimulates neurogenisis in the temporal and prefrontal lobe which might explain positive effects of ET on some aspects of memory functioning. There are, however, also studies indicating no (e.g., Low & Anstey, 2006) or even negative effects of HT on the global cognitive status (e.g., Craig, Maki & Murphy, 2005; Rapp, Espeland, Shumaker et al., 2003).

Notably, most of the studies reporting positive relationships between HT-use and cognition are cross-sectional observational studies. Longitudinal studies and randomised-controlled trials rather reported negative effects (e.g., Low & Anstey, 2006). One limitation of observational studies, however, is the "healthy-user-bias" reflecting the tendency of on average healthier and better educated women to elect receiving HT. Positive effects of HT on cognition could then be explained by characterstics of these women rather than the physiological properties of E.

Furthermore, differences between studies in the behavioural outcome may arise from differences in age among participants. In their recent review, Sherwin and Henry (2008) suggested that there might be a window of opportunity closely around the time of menopause in which ET protects against cognitive aging. This critical period hypothesis (Sherwin & Henry, 2008) is supported by animal studies which demonstrated an attenuated increase in spine density after E administration in older compared with younger rats (e.g., Adams, Shah, Janssen & Morrison, 2001). This suggests a decrease in the morphological plasticity with increasing age, probably as a result of a decrease in sensitivity of neurons following a prolonged absence of E exposure (e.g., Sherwin & Henry, 2008).

Finally, differences in cognitive domains that have been assessed might significantly contribute to differences in the outcome between studies. Specifically, it seems that only some aspects of cognition are sensitive to the effects of HT. For example, a specific enhancement of verbal but not visual memory has been reported by Maki, Zonderman and Resnick (2001, see also Wolf & Kirschbaum, 2002). In contrast, another study found the opposite pattern with better performances in a visuo-spatial task (i.e., figural memory) in postmenopausal women receiving HT (Resnick, Maki, Rapp, Espeland, Brunner &Coker, 2006). These findings suggest that HT differentially affect the verbal and visuo-spatial domain. Since verbal and visuo-spatial processing mainly relies on the LH and RH, respectively, these controversial findings might indicate that HT in postmenopausal women differentially affects the functional brain organization, and FCAs in particular.

Hormone therapy and functional cerebral asymmetries

So far, only one study investigated the effects of different HTs in postmenopausal women on FCAs in a quasi-experimental design (Bayer & Erdmann, 2008). Specifically, the authors tested postmenopausal women using either a single ET, a combined HT (cHT) containing E and synthetic progestins, or no HT. The results showed reduced verbal asymmetries in postmenopausal women receiving E, suggesting that HT, and E therapy in particular, indeed affects FCAs. Yet, Bayer and Erdmann (2008) did not control for participants' hormonal status from blood or saliva samples. Although HT is known to affect the E- and P-metabolism, it remains unclear whether postmenopausal women with HT did show the expected increase in estradiol- and P-levels, respectively, as typically measured in hormone studies. Especially cHT, which contains synthetic progestins, does not necessarily leads to an increase in P-levels (e.g., Kuhl, 2006). Since no hormone-behaviour-relationships could be revealed, the interpretation of the findings remains limited. Moreover, no direct comparisons between sex hormone-related changes in FCAs during the menstrual cycle on the one hand, and as a result of HT on the other hand, can be made.

Aim of the present thesis

The purpose of the present thesis is to answer two major questions. First, as to whether sex hormonal changes across the menstrual cycle can affect interhemispheric integration under varying task demands. Second, as to whether both interhemispheric integration and FCAs are sensitive to direct hormonal manipulations *via* hormone therapy.

The first question will be addressed by chapter II describing a study which tested normally cycling women on interhemispheric integration using two different versions of the Banich-Belger task. In an easier version, participants were asked to match letters according to their physical identity (physical-identity task, e.g., 'A' and 'A'). In a more demanding task, participants had to decide whether to letters had the same name (name-identity task, e.g., 'a' and 'A'). Normally cycling women were tested during the menstrual phase and the luteal phase. Additionally, a group of postmenopausal women without HT and men were included as control groups. To validate the cycle phases in normally cycling women, sex hormone-levels were measured from saliva samples.

The second question will be addressed by chapter III and IV presenting 2 studies which tested postmenopausal women receiving different hormone therapies (ET, cHT, and no HT) in a cross-sectional design. Both studies used well-validated paradigms to determine HT-related

effects on interhemispheric integration and FCAs. Specifically, interhemispheric integration was measured by the Banich-Belger paradigm using an easier physical-identity task and a more demanding name-identity task. FCAs were measured with a prototypical LH dominated verbal task (word matching) and a RH dominated visuo-spatial task (figure matching) which have previously been demonstrated to reveal LH and RH advantages, respectively, but which are otherwise sensitive to hormonal effects (e.g., Hausmann & Güntürkün, 2000). In both studies sex hormone-concentrations were assessed from saliva samples, providing the possibility of directly relating hormone-levels to performance levels which has not been done previously.

References

Adams, M. M., Shah, R. A., Janssen, W. G. M. & Morrison, J. H. (2001). Different modes of hippocampal plasticity in response to estrogen in young and aged female rats, *Proceedings of the National Academy of Sciences of the United States of America*, 98, 8071-8076.

Alexander, G. M., Altemus, M., Peterson, B. S. & Wexler, B. E. (2002). Replication of a premenstrual decrease in right-ear advantage on language-related dichotic listening tests of cerebral laterality. *Neuropsychologia*, 40, 1293-1299.

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

Asso, D. (1983). The real menstrual cycle. Chichester: John Wiley & Sons.

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

Bayer, U. & Erdmann, G. (2008). The influence of sex hormones on functional cerebral asymmetries in postmenopausal women. *Brain and Cognition*, 67, 140-149.

Beaumont, J. G. (1982). Studies with verbal stimuli. In J. G. Beaumont (Ed.), *Divided visual field studies of cerebral organisation* (58-86). London: Academic Press.

Bethea, C. L., Lu, N. Z., Gundlah, C. & Streicher, J. M. (2002). Diverse actions of ovarian steroids in the serotonin neural system. *Frontiers in Neuroendocrinology*, 23, 41-100.

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.

Bryden, M. P. (1982). *Laterality: Functional asymmetry in the Intact Brain.* New York: Academic Press.

Bryden, M. P., McManus, I. C. & Bulman-Fleming, M. B. (1994). Evaluating the empirical support for the Geschwind-Behan-Galaburda model of cerebral lateralization. *Brain and Cognition*, 26, 103-167.

Chiarello, C., McMahon, M. A. & Schaefer, K. (1989). Visual cerebral lateralization over phases of the menstrual cycle: a preliminary investigation. *Brain and Cognition*, 11, 18-36.

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

Cohen, H. & Forget, H. (1995). Auditory cerebral lateralization following cross-gender hormone therapy. *Cortex*, 31, 565-573.

Cohen-Bendahan, C. C., van de Beek, C. & Berenbaum, S. A. (2005). Prenatal sex hormone effects on child and adult sex-typed behavior: methods and findings. *Neuroscience and Biobehavioral Reviews*, 29, 353-384.

Collaer, M. L. & Hines, M. (1995). Human behavioral sex differences: a role for gonadal hormones during early development? *Psychological Bulletin*, 118, 55-107.

Compton, R. J. & Levine, S. C. (1997). Menstrual cycle phase and mood effects on perceptual asymmetry. *Brain and Cognition*, 35, 168-183.

Compton, R.J., Costello, C. & Diepold, J. (2004). Interhemispheric integration during 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.

Craig, M. C., Maki, P. M. & Murphy, D. G. (2005). The Women's Health Initiative Memory Study: findings and implications for treatment. *Lancet Neurology*, 4, 190-194.

Dapretto, M. & Bookheimer, S. Y. (1999). Form and content: dissociating syntax and semantics in sentence comprehension. *Neuron*, 24, 427-432.

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

Fernandez, G., Weis, S., Stoffel-Wagner, B., Tendolkar, I., Reuber, M., Beyenburg, S., Klaver, P., Fell, J., de Greiff, A., Ruhlmann, J., Reul., J. & Elger, C. E. (2003). Menstrual cycle-dependent neural plasticity in the adult human brain is hormone, task, and region specific. *Journal of Neuroscience*, 23, 3790-3795.

Fiez, J. A. & Petersen, S. E. (1998). Neuroimaging studies of word reading. *Proceedings of*

the National Academy of Science U S A, 95, 914-921.

Forget, H. & Cohen, H. (1994). Life after birth: the influence of steroid hormones on cerebral structure and function is not fixed prenatally. *Brain and Cognition*, 26, 243-248.

Geschwind, N. & Behan, P. (1982). Left-handedness: association with immune disease, migraine, and developmental learning disorder. *Proceedings of the National Academy of Sciences of the United States of America*, 79, 5097-5100.

Geschwind, N. & Galaburda, A. M. (1985a). Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. *Archives of Neurology*, 42, 428-459.

Geschwind, N. & Galaburda, A. M. (1985b). Cerebral lateralization. Biological mechanisms, associations, and pathology: II. A hypothesis and a program for research. *Archives of Neurology*, 42, 521-552.

Geschwind, N. & Galaburda, A. M. (1985c). Cerebral lateralization. Biological mechanisms, associations, and pathology: III. A hypothesis and a program for research. *Archives of Neurology*, 42, 634-654.

Halpern, D.F. (1996). Sex, brains, hands, and spatial cognition. *Developmental Review*, 16, 261-270.

Halpern, E. (2000*). Sex differences in cognitive abilities*. Mahawah, NJ: Lawrence Erlbaum Associates.

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. (2005). Hemispheric asymmetry in spatial attention across the menstrual cycle. *Neuropsychologia*, 43, 1559-1567.

Hausmann, M. & Bayer, U. Sex hormonal effects on hemispheric asymmetry and interhemispheric interaction. Submitted.

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., Behrendt-Körbitz, S., Kautz, H., Lamm, C., Radelt, F. & Güntürkün, O. (1998). Sex differences in oral asymmetries during word repetition. *Neuropsychologia*, 36, 1397-1402.

Hausmann, M., Ergun, G., Yazgan, Y. & Gunturkun, O. (2002). Sex differences in line

bisection as a function of hand. *Neuropsychologia*, 40, 235-240.

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

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., Tegenthoff, M., Sanger, J., Janssen, F., Güntürkün, O. & Schwenkreis, P. (2006) Transcallosal inhibition across the menstrual cycle: a TMS study. *Clinical Neurophysiology*, 117, 26-32.

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

Helleday, J., Siwers, B., Ritzen, E.M. & Hugdahl, K. (1994). Normal lateralization for handedness and ear advantage in a verbal dichotic listening task in women with congenital adrenal hyperplasia (CAH). *Neuropsychologia*, 32, 875–880.

Herman, A., Grabowska, A. & Dulko, S. (1993). Transsexualism and sex-related differences in hemispheric asymmetry. *Acta Neurobiologiae Experimentalis*, 53, 269-274.

Hines, M. & Shipley, C. (1984). Prenatal exposure to diethylstilbestrol (DES) and the development of sexually dimorphic cognitive abilities and cerebral lateralization. *Developmental Psychology*, 20, 81–94.

Hiscock, M., Inch, R., Jacek, C., Hiscock-Kalil, C. & Kalil, K. M. (1994). Is there a sex difference in human laterality? I. An exhaustive survey of auditory laterality studies from six neuropsychology journals. *Journal of Clinical and Experimental Neuropsychology*, 16, 423-435.

Hiscock, M., Israelian, M., Inch, R., Jacek, C. & Hiscock-Kalil, C. (1995). Is there a sex difference in human laterality? II. An exhaustive survey of visual laterality studies from six neuropsychology journals. *Journal of Clinical and Experimental Neuropsychology*, 17, 590-610.

Hogervorst, E., Williams, J., Budge, M., Riedel, W. & Jolles, J. (2000). The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. *Neuroscience*, 101, 485-512.

Inglis, J. & Lawson, J. S. (1981). Sex differences in the effects of unilateral brain damage on intelligence. *Science*, 212, 693-695.

Innocenti, G. M. (1980). The primary visual pathway through the corpus callosum: morphological and functional aspects in the cat. *Archives Italiennes de Biologie*, 118, 124-188.

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

Kawaguchi, Y. (1992). Receptor subtypes involved in callosal-induced postsynaptic potentials in rat frontal agranular cortex in vitro. *Experimental Brain Research*, 88, 33-40.

Kimura, D. (1992). Sex differences in the brain. *Scientific American*, 267, 119-125.

Kimura, D. (2002). Sex hormones influence human cognitive pattern. *Neuroendocrinology Letters*, 23, 67-77.

Klingberg, T., O'Sullivan, B. T. & Roland, P. E. (1997). Bilateral activation of fronto-parietal networks by incrementing demand in a working memory task. *Cerebral Cortex*, 7, 465-471.

Kolb, B. & Wishaw, I. Q. (1996). *Neuropsychologie*. (2th Ed.), Heidelberg: Spektrum Akademischer Verlag.

Landsdell, H. (1962a). Laterality of verbal intelligence in the brain. *Science*, 135, 922-923.

Landsdell, H. (1962b). A sex difference in effect of temporal-lobe neurosurgery on design preference. *Nature*, 194, 852-854.

Levy, J. (1973). Lateral specialization of the human brain. Behavioural manifestations and possible evolutionary basis. In: Kiger, J. (Ed). *The Biology of Behaviour*. Oregon State University Press, Corvallis.

Low, L. F. & Anstey, K. J. (2006). Hormone replacement therapy and cognitive performance in postmenopausal women--a review by cognitive domain. *Neuroscience and Biobehavioral Reviews*, 30, 66-84.

Maccoby, E. E. & Jacklin, C. N. (1974). *The Psychology of Sex Differences*. Stanford University Press, Stanford CA.

Maki, P. M., Zonderman, A. B. & Resnick, S. M. (2001). Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. *American Journal of Psychiatry*, 158, 227-233.

Mathews, G. A., Fane, B. A., Pasterski, V. L., Conway, G. S., Brook, C. & Hines, M. (2004). Androgenic influences on neural asymmetry: Handedness and language lateralization in individuals with congenital adrenal hyperplasia. *Psychoneuroendocrinology*, 29, 810-822.

McEwen, B. (2002). Estrogen actions throughout the brain. *Recent Progress in Hormone Research*, 57, 357-384.

McEwen, B. S. & Alves, S. E. (1999). Estrogen actions in the central nervous system. *Endocrine Reviews*, 20, 279-307.

McGlone, J. (1977). Sex differences in the cerebral organization of verbal functions in patients with unilateral brain lesions. *Brain*, 100, 775-793.

McGlone, J. (1980). Sex differences in functional brain asymmetry: a critical survey. *Behavioral and Brain Sciences*, 3, 215-263.

McGlone, J. (1986). The neuropsychology of sex differencesin human brain organization. In Goldstein, G., Tarter, R. E. (Eds). *Advances in Clinical Neuropsychology*, Vol 3 Plenum Press, New York.

McKeever, W. F. (1995). Hormone and hemisphericity hypotheses regarding cognitive sex differences: Possible future explanatory power, but current empirical chaos. *Learning and Individual Differences*, 7, 323-340.

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

Merke, D. P. & Bornstein, S. R. (2005). Congenital adrenal hyperplasia. *Lancet*, 365, 2125-2136.

Metcalf, M. G. & Mackenzie, J. A. (1980). Incidence of ovulation in young women. *Journal of Biosocial Science*, 12, 345-352.

Netley, C. & Rovet, J. (1982). Atypical hermispheric lateralization in turner syndrome Subjects. *Cortex*, 18, 377-384.

Pollmann, S., Zaidel, E., & von Cramon, D. Y. (2003). The neural basis of the bilateral distribution advantage. *Experimental Brain Research*, 153, 322-333.

Rapp, S. R., Espeland, M. A., Shumaker, S. A., Henderson, V. W., Brunner, R. L., Manson, J. E., et al. (2003). Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *Jama*, 289, 2663-2672.

Resnick, S. M., Maki, P. M., Rapp, S. R., Espeland, M. A., Brunner, R., Coker, L. H., et al. (2006). Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *Journal of Clinical Endocrinology and Metabolism*, 91, 1802-1810.

Reuter-Lorentz, P., Moscovitch, M. & Kinsbourne, M. (1990). Hemispheric control of spatial attention. *Brain and Cognition*, 12, 20-266.

Rizzolatti, G., Umilta, C. & Berlucchi, G. (1971). Opposite superiorities of the right and left cerebral hemispheres in discriminative reaction time to physiognomical and alphabetical material. *Brain*, 94, 431-42.

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

Rupprecht, R. (2003). Neuroactive steroids: mechanisms of action and neuropharmacological properties. *Psychoneuroendocrinology*, 28, 139-168.

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.

Schumacher, M., Guennoun, R., Ghoumari, A., Massaad, C., Robert, F., El-Etr, M. et al. (2007). Novel perspectives for progesterone in hormone replacement therapy, with special reference to the nervous system. *Endocrine Reviews*, 28, 387-439.

Sergent, J. & Bindra, D. (1981). Differential hemispheric processing of faces: Methodological considerations and reinterpretation, *Psychological Bulletin*, 89, 541-554.

Shaywitz, S. E., Shaywitz, B. A., Fletcher, J. M. & Escobar, M. (1990). Prevalence of reading disability in boys and girls: Results of the Connecticut Longitudinal Study. *Journal of the American Medical Association,* 264, 998-1002.

Sherwin, B. B. & Henry, J. F. (2008). Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: a critical review. *Frontiers in Neuroendocrinology*, 29, 88-113.

Smith, S. S. (1991). Progesterone administration attenuates excitatory amino acid responses of cerebellar Purkinje cells. *Neuroscience*, 42, 309-320.

Smith, S. S., Waterhouse, B. D. & Woodward, D. J. (1987). Locally applied progesterone metabolites alter neuronal responsiveness in the cerebellum. *Brain Research Bulletin*, 18, 739-747.

Smith, S. S., Waterhouse, B. D. & Woodward, D. J. (1988) Locally applied estrogens potentiate glutamate-evoked excitation of cerebellar Purkinje cells. *Brain Research*, 475, 272-282.

Springer, S. P. & Deutsch, G. (1998). *Linkes – rechtes Gehirn.* (4th Ed.), Heidelberg: Spektrum Akademischer Verlag.

Tirosh, E., Rod, R., Cohen, A. & Hochberg, Z. (1993). Congenital adrenal hyperplasia and cerebral lateralizations. *Pediatric Neurology*, 9, 198-201.

Toga, A. W. & Thompson, P. M. (2003). Mapping brain asymmetry. *Nature Reviews.* Neuroscience, 4, 37-48.

Torand-Allerand, C. D. (1991). Organotypic culture of the developing cerebral cortex and hypothalamus: relevance to sexual differentiation. *Psychoneuroendocrinology*, 16, 7-24.

Toyama, K. & Matsunami, K. (1976). Convergence of specific visual and commissural impulses upon inhibitory interneurons of the cat's visual cortex. *Neuroscience*, 1, 107-112.

Toyama, K., Tokashiki, S. & Matsunami, K. (1969). Synaptic action of commissural impulses upon association efferent cells in the cat visual cortex. *Brain Research*, 14, 518-520.

Voyer, D., Voyer, S. & Bryden, M. P. (1995). Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. *Psychological Bulletin*, 117, 250-270.

Wadnerkar, M. B., Whiteside, S. P., Cowell, P. E. (2008). Dichotic listening asymmetry: sex differences and menstrual cycle effects. *Laterality*, 13, 297-309.

Weekes, N. Y. & Zaidel, E. (1996). The influence of menstrual stage on interhemispheric interactions: Converging results from two lateralized tasks. *Brain and Cognition*, 32, 278-282.

Weis, S., Hausmann, M., Stoffers, B., Vohn, R., Kellermann, T. & Sturm, W. (2008). Estradiol modulates functional brain organization during the menstrual cycle: an analysis of interhemispheric inhibition. *Journal of Neuroscience*, 28, 13401-13410.

Weissman, D. H. & Compton, R. J. (2003). Practice makes a hemisphere perfect: The advantage of interhemispheric recruitment is eliminated with practice. *Laterality*, 8, 361-375.

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. (1976). Sex and the single hemisphere: right hemisphere specialization for spatial processing. *Science*, 193, 425-427.

Wolf, O. T. & Kirschbaum, C. (2002). Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. *Hormones and Behavior*, 41, 259-266.

II Interhemispheric interaction during the menstrual cycle

Ulrike Bayer [1], Nina Kessler [2], Onur Güntürkün, [2] & Markus Hausmann [1]

[1] Department of Psychology, Durham University, Durham, United Kingdom
[2] Department of Biopsychology, Institute for Cognitive Neuroscience, Ruhr-University Bochum, Bochum, Germany

Abstract

Fluctuating levels of sex hormones and high levels of progesterone (P), in particular, have been suggested to reduce interhemispheric inhibition. The present study focuses on hormone-dependent modulation of interhemispheric integration. In two versions of the Banich-Belger task, participants were asked to match letters according to their physical (e.g., A vs. A) and semantic identity (e.g., A vs. a). Matches were presented either within or across visual half-fields. Moreover, a simple reaction-time task (Poffenberger task) that is assumed to estimate interhemispheric transfer time (IHTT) was used. Seventeen normally cycling women were tested during low P menses and high P midluteal phase. Saliva levels of P were analyzed using chemiluminescence assays. Fifteen postmenopausal women performed the same tasks in corresponding time intervals. Additionally, 28 younger male controls were tested once. In agreement with previous results, the more demanding (semantic) interhemispheric integration task revealed a typical across-field advantage (AFA) for all three groups. However, in normally cycling women, the AFA was significantly reduced during menses. IHTT did not change across the cycle phases. The results indicate that interhemispheric integration fluctuates across the menstrual cycle and is reduced during menses. During the luteal phase, however, the AFA is increased, suggesting that accompanying hormonal conditions favour an efficient interhemispheric integration. We conclude that transcallosal mechanisms involved in interhemispheric integration are profoundly altered when sex hormones are permanently reduced as in men and postmenopausal women. This difference enables an efficient interhemispheric integration without modulatory effects of P.

Neuropsychologia, 2008, 46(9), 2415-2422.

Introduction

Sex hormones are capable of changing the functional cerebral organization by organizing and activating effects (Wiesniewski, 1998). The effects of sex hormones have been particularly investigated in normally cycling women because their endogenous hormone levels fluctuate dramatically across the menstrual cycle. Although contradictions exist (e.g., Chiarello, McMahon, & Schaefer, 1989; Compton & Levine, 1997), the majority of studies testing women during different cycle phases reported cycle-dependent fluctuations in functional cerebral asymmetries (FCA) (Bibawi, Cherry, & Hellige, 1995; Hampson, 1990a,b; Hausmann, 2005; 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). Some of these studies suggest that it is especially the left hemisphere which is affected by sex hormone-related changes across the menstrual cycle (e.g., Hampson, 1990a,b; Bibawi et al., 1995), while others propose the opposite, and suggest that the right hemisphere is particularly sensitive for hormonal fluctuations (e.g., Sanders & Wenmoth, 1998).

A different approach has been proposed by others (Hausmann et al., 2002; Hausmann & Güntürkün, 2000) who hypothesized that the interaction between both hemispheres is affected by the activating effects of sex hormones. This idea is based on the assumption that interhemispheric interaction that takes place as interhemispheric inhibition between homotopic structures is a fundamental prerequisite for the manifestation of FCAs (e.g., Chiarello & Maxfield, 1996). Specifically, the hypothesis of progesterone-modulated interhemispheric decoupling (Hausmann et al., 2002; Hausmann & Güntürkün, 2000) assumes that high levels of progesterone (P) and its metabolites attenuate interhemispheric inhibition by decreasing glutamatergic callosal synaptic efficiency. This then leads to a functional decoupling of both hemispheres which finally results in reduced FCAs when P-levels are high. In these studies, the typical left-hemispheric superiority in word matching as well as the right-hemispheric advantage in polygon matching and face discrimination was reduced during the midluteal phase (Hausmann & Güntürkün, 2000; Hausmann et al., 2002), suggesting that a sex-hormones-related reduction of FCAs is relatively task-independent.

Although the hypothesis of P-modulated interhemispheric decoupling (Hausmann & Güntürkün, 2000; Hausmann et al., 2002) refers to a specific process of interhemispheric inhibition and hence, may only account for P-related changes of FCAs, the general idea that

sex hormones affect interhemispheric interaction has received some support from studies using tasks which cannot be performed without interhemispheric crosstalk. For example, during the midluteal phase, Hausmann (2005) found a reduced hand-use difference in a visual line-bisection task which has been assumed to be affected by transcallosal interactions. The reduced hand-use difference has been suggested to reflect transcallosal spreading activation from the line-bisection bias-dominating right hemisphere to the left hemisphere, controlling the left and right hand, respectively. In this study, the reduced hand-use difference was mainly related to high estradiol (E) levels. Even though this task provides a rather indirect measure of interhemispheric interaction, these findings suggest that different transcallosal processes might be differentially affected by E and P.

The first direct physiological support of the idea that gonadal hormones affect interhemispheric interactions comes from a recent study (Hausmann, Tegenthoff, Sänger, Janssen, Güntürkün, & Schwenkreis, 2006) using transcranial magnetic stimulation (TMS). Hausmann et al. (2006) examined transcallosal motor inhibition in normally cycling women during menses, follicular, and midluteal cycle phase. The results revealed a negative relationship between transcallosal inhibition and E- and P-levels during the follicular and luteal phase, respectively, which underlines their neuromodulatory properties on glutamatergic and GABAergic neurons. Since motor functions have been shown to be asymmetrically organized in the brain, these findings can be interpreted in terms of the hypothesis of P-modulated interhemispheric decoupling (Hausmann & Güntürkün, 2000; Hausmann et al., 2002) according to which a P-related reduction of interhemispheric inhibition should result in a more bilateral organization of motor functions (see Hausmann et al., 2006, for details).

A different aspect of interhemispheric interaction has been considered by Compton, Costello, and Diepold (2004) who investigated whether sex hormones modulate interhemispheric integration in women during the menstrual cycle. The authors used a prominent paradigm by Banich and Belger (1990) which can hardly be performed without an integration of information between the hemispheres (e.g., Zaidel, 1995). In the Banich-Belger task, individuals must decide whether a target item matches either one of two probes. If the target and matching probe are positioned in the same visual half-field (VHF, within-field trials), and hence directed to the same hemisphere, no interhemispheric interaction is required to make the decision. In contrast, on across-field trials, the target and matching probe are directed to different hemispheres. Thus, the brain must integrate the information across hemispheres to identify the match. To this end, both hemispheres must be able to actively

participate without being inhibited by the other side. Thus, the Banich and Belger task measures the ability for bihemispheric activation and integration of information across hemispheres by comparing bi-hemisphere processing to within-hemisphere processing. It has been shown that across-field integration allowing for a division of labour between the hemispheres enhances performance when task complexity increases (across-field advantage, AFA), but impedes performance on less demanding tasks (Banich & Belger, 1990). Compton et al. (2004) used a more complex version of the Banich-Belger task in which normally cycling women were required to determine whether two letters had the same name (e.g., "A" and "a"). Since a match decision in this task cannot be made on physical characteristics alone, it requires the transformation of letters into their semantic code. This is considerably more demanding and hence should produce an advantage in performance when the two hemispheres must communicate (AFA).

It is important to note that the type of interhemispheric interaction required by the Banich and Belger task deviates from the previously used perceptual asymmetry experiments. The Banich-Belger task requires a bihemispheric activation and interhemispheric integration and thus both hemispheres contribute to the output. In contrast, the perceptual asymmetry tasks employed by Hausmann and Güntürkün require an inhibitory coupling to achieve meta-control of the dominant side during task performance (only one hemisphere dominates the output) (Cook, 1984; Chiarello & Maxfield, 1996). Referring to the hypothesis of progesterone-mediated interhemispheric decoupling, Compton et al. (2004) expected a P-related reduction in AFA during the midluteal phase compared to menses, which is based on interhemispheric decoupling. Given the view presented above, this is not necessarily the case. One might also hypothesize that P leads to a greater integration between the hemispheres due to less interhemispheric inhibition. In fact, behavioural data did not reveal any hormonal effects on interhemispheric integration (Compton et al., 2004). The authors concluded that P might modulate interhemispheric inhibition but not interhemispheric integration.

As stated above, task difficulty seems to be an important factor in tasks that require interhemispheric integration. The AFA is particularly present when the benefit of interhemispheric integration is sufficient to overweigh its costs, a situation that is usually given on highly demanding across-field trials (Weissman, Banich & Puente, 2000). In contrast, on less demanding across-field trials the benefit of interhemispheric integration is too small to outweigh the costs leading to no or even a negative AFA, indicating a within-field advantage. Thus, regardless whether the AFA is positive or negative, it reflects the efficiency of interhemispheric integration relative to intrahemispheric processing. Since it has

been shown that the relative efficiency of interhemispheric processing gradually changes as a function of task difficulty (Weissman & Banich, 2000), the present study investigates the influence of task difficulty on cycle-related changes in AFA. Normally cycling women were tested during the midluteal and the menstrual phase in a less and a more demanding version of the Banich-Belger paradigm, the physical- and name-identity task, respectively. Given that interhemispheric integration indeed changes across the menstrual cycle, it seems likely that sex hormones mainly affect interhemispheric processes on a higher processing level. Thus, we hypothesize that menstrual cycle-related fluctuations in AFA are particularly pronounced in the more demanding name-identity task.

Men and postmenopausal women not taking any hormonal replacements were used as controls. Due to stable and low P-levels in postmenopausal women, we predict the AFA to be relatively stable across time and similar to the AFA in men and women during menses.

Additionally, we used a simple reaction-time task (Poffenberger task) to investigate whether interhemispheric transfer times (IHTT) fluctuate across the menstrual cycle. In this task, participants must respond to visual stimuli presented either in the left (LVF) or right visual field (RVF) with the right and the left hand. The crossed-uncrossed difference (CUD), in which median RT under the two uncrossed conditions (stimuli presented in the VHF ipsilateral to the responding hand) is subtracted from median RT under the crossed conditions (stimuli presented in the VHF opposite to the responding hand), can be used as an estimate of IHTT (Poffenberger, 1912). Compared to the Banich-Belger task, the Poffenberger task was assumed to be the least demanding task since it only requires a transfer of visuo-motor information. A recent study has shown sex differences in IHTT as measured by event related potentials (Moes, Brown, & Minnema, 2007). Specifically, this study found more symmetric and shorter overall IHTTs in females than in males. Up to now, no study has investigated whether sex hormones affect IHTT across the menstrual cycle.

Method

Participants

Twenty normally cycling women with a mean age of 24.9 years (SD = 5.42, age range: 20 - 40), and a regular menstrual cycle between 25-30 days participated in the present study. Additionally, 15 postmenopausal women with a mean age of 58.7 years (SD = 5.79, age range: 48 – 68) who had their last menses at least one year before testing, and 28 younger men with a mean age of 26.3 years (SD = 4.15, age range: 18 - 36) were investigated. All

participants were right handed as determined with the Edinburgh Inventory (Oldfield, 1971). The asymmetry-index provided by this test is calculated as ((R-L)/(R+L)) x 100, resulting in values between -100 (consistent left-handedness) and +100 (consistent right-handedness). The mean handedness score for normally cycling women was 93.8 (SD = 7.05; range: 80.0-100), 83.4 (SD = 26.19; range: 10.0-100) for the postmenopausal women, and 68.2 (SD = 25.16; range: 25.0-100) for men. All statistical analyses including postmenopausal women were additionally performed with LQ as a covariate because of participants' large variability in right-handedness. Since the pattern of results was not affected, these data are not reported.

Female participants who had used hormonal contraceptives/replacements or any other medication during the last 6 months which could affect the central nervous system were excluded. All participants had normal or corrected to normal visual acuity. They were naïve for the experimental hypotheses. All participants were recruited by announcements, and were paid for their participation.

Procedure

Sex hormone-related effects on interhemispheric integration and interhemispheric transfer time were investigated with two versions of the Banich-Belger task, and the Poffenberger task, respectively. Normally cycling women were tested twice, once during the menstrual phase (cycle days 1-2) and once during the midluteal phase (cycle days 18-23), to yield the largest differences in P-levels. Before the first experimental session, normally cycling women were informed about the general procedure and data were collected about the individual length of their menstrual cycle. All women agreed to inform us about the first day of their next cycle. The individual cycle length was taken into account when planning the appointments for the experiments. To control for repeated-measures effects, women were tested in a balanced order, starting during menses or the midluteal phase. Normally cycling women were tested within one or two consecutive cycles.

Postmenopausal women were tested twice in corresponding time intervals of about two weeks. Before and after each session, a saliva sample was collected from all female participants. Saliva P-levels were determined with Chemiluminescence assay (CLIA) by an independent professional hormone laboratory, with commercially available hormone assays. Male controls were tested only once. For the analyses of interhemispheric integration (Banich-Belger task), five male participants had to be excluded because they performed only

one task condition. For the analyses of interhemispheric transfer times (Poffenberger task), one male had to be excluded because he did not finish the task.

Interhemispheric integration (Banich-Belger task)

The interhemispheric-integration task was identical to that used by Banich and Belger (1990). Participants were asked to fixate a cross in the middle of the screen. Then, an array of three stimuli arranged in "V" formation was presented around a central fixation cross. The top two stimuli were always two different uppercase letters, one on either side of the fixation cross. These letters were presented 2.8 degree of visual angle lateral from the midline and 1.4 degree visual angle above fixation cross. A third letter was centred 1.4 degree visual angle below the fixation point and 1.4 degree visual angle either to the right or left of the centre. In the less demanding physical-identity task, the third letter was an uppercase letter, and participants were asked to indicate whether the bottom letter was the same as either of the top two letters. In the more demanding name-identity task, the bottom letter was a lowercase letter, and participants determined whether this had the same name as either of the top two letters. Letter stimuli were A, B, E, G, H, Q, R, T, and, in the name-identity task, their lowercase equivalents. Each trials started by presentation of a fixation cross for 200 ms, followed by a stimulus array for 200 ms and then by an inter-trial interval of randomized length between 500 and 2000 ms in which responses were recorded. Both tasks comprised of 224 trials divided into four blocks of 56 trials each with brief breaks between blocks. The participants responded with either the right or left index finger on alternating blocks. The order of hand use was balanced between subjects. Prior to each task, participants performed 28 practice trials which were excluded from the analyses. Within each block, half of the trials were match trials and half were mismatch trials. Half of the match trials were within-field matches and the other half were across-field matches. Within both types of matches, the bottom letter appeared equally often in the RVF and LVF. Median reaction times (RT) of only correct trials and accuracy were used as dependent variables. For RT and accuracy only match trials were analyzed, because mismatch trials cannot be categorized as across- or within-field trials.

Interhemispheric transfer time (Poffenberger task)

The Poffenberger task used in the present study was identical to Corballis (2002). The stimuli were filled circular disks, 0.86 degree visual angle, placed 2.5 degree visual angle

either to the left or right of a central fixation cross, or simultaneously on both sides. Responses were made with the index finger of either the right or the left hand on a keyboard placed at the participant's midline. The stimuli were presented in two blocks of 100 trials per each hand with a brief break after 50 trials. On a given block of trials, participants used the same hand. The order of response hand was balanced between participants. Within each block, there were 30 trials in which the disks were presented in the LVF, 30 in which they were in the RVF, 30 in which stimuli were presented simultaneously in both VHF (bilateral), and 10 "catch trials" in which no stimulus was presented. Catch trials and trials with simultaneous stimulus presentation were not analysed. At the beginning of each trial a fixation cross appeared in the middle of the screen followed by two consecutive stimuli presented for 135 ms, with inter-stimulus intervals of 300, 400, 500, 600, or 700 ms. Each of the five intervals was paired six times with each stimulus configuration. Participants were instructed to press the response key as quickly as possible when they detected the stimulus, but refrain from responding if no stimulus appeared. The experiment started by placing the head of a seated participant to a chin rest at a distance of 57 cm from a monitor. Participants were instructed to keep their head and body still during the whole test. Median RT for the left and right hand on stimulus presentation in LVF and RVF were recorded. IHTT was estimated by calculating the difference of median RTs in the crossed and uncrossed conditions (CUD).

Mood questionnaire

To control for potential cycle-dependent variations in mood, a German mood scale (Befindlichkeits-Skala, BFS, Zerssen, 1976) was applied to all normally cycling women before each test session. BFS mood scores can range between 0 (euphoric) and 56 (extremely depressive). To avoid confounding effects of strong variations in mood between the two sessions which can influence performance on interhemispheric integration (Compton & Mintzer, 2001), normally cycling women who showed a difference of more than 25 points between cycle phases were excluded from further analyses.

In postmenopausal women, potential variations in mood between sessions were measured with the State-Trait-Cheerfulness-inventory (STCI-S18; Ruch, Köhler & van Thriel, 1997). The STCI-S18 measures three different concepts of mood: cheerfulness, seriousness, and bad mood. Each concept included six items. Written response was given on a 4-point rating-scale (strongly disagree, 1; moderately disagree, 2; moderately agree, 3, and strongly agree, 4).

Results

Mood scales

Since cycle-dependent fluctuations in mood can affect interhemispheric processes (Compton & Mintzer, 2001), German mood scales were applied. Three normally cycling women were excluded from further analysis, because their BFS mood scores differed largely (≥ 25 point) between cycle phases. For the remaining 17 normally cycling women, a paired *t*-test revealed no significant difference in mood between menses (M = 13.5, SD = 8.02) and the midluteal phase (M = 16.0, SD = 7.46), $t(16) = 1.53$, n.s.. Similarly, mood scores did not differ between normally cycling women tested during menses (M = 10.3, SD = 4.71) and midluteal phase (M = 16.3, SD = 7.28), $t(15) = 2.01$, n.s., when only the first session was taken into account (between-participants analysis). For postmenopausal women, mood scores did not differ between test sessions 1 and 2. In neither of the three STCI-S18 subscales (Ruch, Köhler & van Thriel, 1997) paired *t*-tests revealed significant differences in mood between sessions: cheerfulness ($t(14) = -.47$, n.s.), seriousness ($t(14) = -.37$, n.s.), and bad mood ($t(14) = -.53$, n.s.).

Hormone assay

For normally cycling women, the mean P-level was 38.6 pg/ml (SD = 22.72, range: 10.0-89.0 pg/ml) in the menstrual phase and 193.6 pg/ml (SD = 147.44, range: 14.5-514.0 pg/ml) in the midluteal phase. A paired *t*-test revealed this difference in mean P-levels to be significant, $t(16) = 4.77$, $p<.0001$. For postmenopausal women, the mean P-level did not significantly differ between session 1, 42.7 pg/ml (SD = 24.88, range: 14.0-92.0) and session 2, 34.4 pg/ml (SD = 25.37, range: 9.0-111.0), $t(14) = 1.08$, n.s..

Interhemispheric integration (Banich-Belger task)

Normally cycling women: Median RTs were subjected to a 2 x 2 x 2 x 2 analysis of variance (ANOVA) with repeated measures, with Cycle phase (menses, luteal), Task (physical-identity, name-identity), Trial type (within-field, across-field), and VHF (LVF, RVF) as within-participants factors. AFA was calculated as the difference between trial types (AFA: within-field RT minus across-field RT). The ANOVA revealed a significant main effect of Task, $F(1,16) = 47.33$, $p<.0001$, $\eta^2 = .75$, with faster response times in the physical- than name-identity task. The Task by Trial type interaction was also significant, $F(1,16) =$

8.10, $p<.05$, $\eta^2 = .34$, indicating an advantage on across-field trials (mean ± SEM: M = 524 ± 24.0 ms) compared to within-field trials (M = 554 ± 24.4 ms) in the more demanding name-identity task but not in the physical-identity task (across-field trials: M = 389 ± 18.8 ms; within-field trials: M = 381 ± 16.6 ms). Moreover, there was a significant Cycle phase by Trial type interaction, $F(1,16) = 7.30$, $p<.05$, $\eta^2 = .31$ (see Table 1).

Phase		**Menstrual**			**Luteal**	
Task	**Within**	**Across**	**AFA**	**Within**	**Across**	**AFA**
Physical ID	384 ± 20.5	399 ± 22.2	-15.1 ± 8.79	378 ± 19.2	380 ± 19.6	-1.6 ± 8.16
Name ID	557 ± 29.9	549 ± 29.4	7.1 ± 17.31	552 ± 30.2	499 ± 29.0	**52.9 ± 13.10** ***
Total	470 ± 19.2	474 ± 19.1	-4.0 ± 9.96	465 ± 23.0	439 ± 22.2	**25.6 ± 7.62** **

Table 1. Mean reaction time (in ms ± SEM) of normally cycling women in the Banich-Belger task (within-participants analysis) as a function of Cycle Phase (menses, luteal), Task (physical-identity, name-identity), and Trial type (within-field, across-field) and AFA (in ms ± SEM) in the physical-identity task (AFA PI), the name-identity task (AFA NI), and across both tasks (AFA). * marks simple effects between trial types per cycle phase with ***: $p \leq .001$; **: $p \leq .01$

Alpha-adjusted post hoc paired *t*-tests (see Table 1) revealed a significant difference between trial types in the luteal phase. Midluteal RTs on across-field trials were significantly reduced compared to within-field trials, $t(16) = 3.36$, $p<.01$. The effect of Trial type during the menstrual phase did not approach significance ($t(16) = -.40$, n.s). Simple comparisons between the two cycle phases per trial type, however, did not reveal significant differences either in within-field trials ($t(16) = -.23$, n.s.) or across-field trials ($t(16) = -1.64$, n.s.).

Although the 2-way interaction was mainly driven by the name-identity task, the 3-way interaction did not approach significance ($F(1,16) = 2.21$, n.s.). Neither the main effect of Cycle phase nor any other interaction with Cycle phase approached significance, all $F < 3.68$, n.s..

The results were virtually identical when Cycle phase was treated as a between-participants factor. In this analysis, only data of the first session were included. However, in contrast to the within-participants design, the Cycle phase x Task x Trial type interaction was significant ($F(1,15) = 5.00$, $p<.05$, $\eta^2 = .25$, see Table 2). Alpha-adjusted post hoc paired *t*-tests (Table 2) revealed a significant difference between trial types in the name-identity task

during the midluteal phase ($t(8) = 3.73$, $p<.01$) but not during menses ($t(7) = -.05$, n.s.). An unpaired t-test, revealed the luteal and menstrual AFA in the name-identity task to be significantly different, $t(15) = 2.72$, $p<.05$ (Fig. 1). In agreement to the within-participants analysis, neither the main effect of Cycle phase nor any other interaction with Cycle phase approached significance, all $F < .08$, n.s..

Phase	**Menstrual**			**Luteal**		
Task	**Within**	**Across**	**AFA**	**Within**	**Across**	**AFA**
Physical ID	378 ± 30.6	392 ± 31.7	-13.8 ± 11.09	365 ± 28.8	361 ± 29.9	3.6 ± 5.08
Name ID	482 ± 45.7	483 ± 38.8	-0.8 ± 16.64	538 ± 43.1	472 ± 36.6	**65.9 ± 17.69 ****
Total	430 ± 33.1	437 ± 29.7	-7.3 ± 13.21	451 ± 31.3	416 ± 28.0	**34.7 ± 8.99 ****

Table 2. Mean reaction time (in ms ± SEM) of normally cycling women in the Banich-Belger task (between-participants analysis) as a function of Cycle Phase (menses, luteal), Task (physical-identity, name-identity), and Trial type (within-field, across-field) and AFA (in ms ± SEM) in the physical-identity task (AFA PI), the name-identity task (AFA NI), and across both tasks (AFA). * marks simple effects between trial types per cycle phase with **: $p \leq .01$

The corresponding 2 x 2 x 2 x 2 ANOVA for accuracy (within-participants analysis) revealed a main effect of Task, indicating a higher performance in the physical- than name-identity task ($F(1,16) = 5.86$, $p<.05$, $\eta^2 = .27$). Neither the main effect of Cycle phase nor any interaction with Cycle phase approached significance, all $F < 1.83$, n.s..

In the between-participants analysis of accuracy, only the Cycle phase x VHF interaction was significant ($F(1,15) = 18.67$, $p<.01$, $\eta^2 = .55$). During the luteal phase, the number of correct responses on stimuli presented in the LVF was higher than to stimuli presented in the RVF (LVF: M = 93.2 ± 1.9 %; RVF: M = 91.2 ± 1.8 %). The inverted pattern was evident for women during menses (LVF: M = 88.7 ± 3.4 %; RVF: M = 91.3 ± 2.8 %). No other main effect or interaction approached significance, all $F < 2.64$, n.s..

Postmenopausal women: The median RTs on matching trials of postmenopausal women were subjected to a 2 x 2 x 2 x 2 ANOVA with Session (session 1, session 2), Task, Trial type, and VHF as within-participants factors. Overall, postmenopausal women showed a better performance in session 2 than session 1, resulting in a significant main effect of Session

($F(1,14) = 8.65, p<.05, \eta^2 = .38$). As indicated by the significant main effect of Task ($F(1,14) = 96.94, p<.0001, \eta^2 = .87$), RTs were faster in the physical- than name-identity task. This effect did significantly interact with Trial type ($F(1,14) = 10.22, p<.01, \eta^2 = .42$). Alpha-adjusted post hoc paired t-tests revealed a significant Trial type effect only in the name-identity task ($t(14) = 2.62, p<.05$), not in the physical-identity task ($t(14) = -0.23$, n.s.). All interaction with Session did not approach significance (all $F < 2.92$, n.s.). Descriptive statistics are shown in Table 3.

Session	**Session 1**			**Session 2**		
Task	**Within**	**Across**	**AFA**	**Within**	**Across**	**AFA**
Physical ID	712 ± 66.2	732 ± 51.0	-20.0 ± 30.23	672 ± 68.3	663 ± 51.3	9.2 ± 21.99
Name ID	962 ± 84.5	899 ± 66.3	63.4 ± 32.23	864 ± 54.0	789 ± 50.9	**74.8 ± 28.83** *
Total	837 ± 74.0	815 ± 56.7	21.7 ± 29.05	768 ± 58.7	726 ± 50.1	42.0 ± 20.23

Table 3. Mean reaction time in ms ± SEM of postmenopausal women in the Banich-Belger task as a function of Session (session 1, session 2), Task (physical-identity, name-identity), and Trial type (within-field, across-field) and AFA (in ms ± SEM) in the physical-identity task (AFA PI), the name-identity task (AFA NI), and across both tasks (AFA). * marks simple effects between trial types per session with *: $p \leq .05$

The analysis of the accuracies revealed a significant main effect of Task with higher performances in the physical- than name-identity task ($F(1,14) = 14.18, p<.01, \eta^2 = .50$). This effect did not interact with Trial type and/or Session (all $F < 0.09$, n.s.).

Interhemispheric transfer time (Poffenberger task)

Normally cycling women: The 2 x 2 x 2 ANOVA with repeated measures with Cycle phase, Hand-use (right hand, left hand), and VHF as within-participants factors did not reveal any significances (all $F < 3.5$, n.s.). Response time differences between uncrossed- and crossed trials did not significantly differ between menses (CUD = 4.9 ± 4.84 ms) and midluteal phase (CUD = 4.8 ± 5.57 ms), $t(16) = -.02$, n.s.. Similarly, no significant effects were found in the between-participants analysis (all $F < 2.58$, n.s.).

Postmenopausal women: Median RTs were subjected to a 2 x 2 x 2 ANOVA with repeated measures, with Session, Hand-use, and VHF as within-participants factors. Neither the main effects of Session, Hand-use, or VHF nor any interaction between these factors approached significance (all $F < 4.5$, n.s.). The crossed-uncrossed difference did not change significantly between session 1 (CUD = 8.9 ± 3.61 ms) and session 2 (CUD = 5.5 ± 5.07 ms), $t(14) = .66$, n.s..

Sex differences in interhemisperhic integration (Banich-Belger task)

When response times in the Banich-Belger task of normally cycling women during the midluteal phase were compared to those of male controls, neither the main effect of Sex nor any interaction with Sex was significant (all $F < 1.48$; n.s.). Similarly to women during the luteal phase (see Table 1), male controls showed a significant difference between within- and across-field trials (overall AFA = 23.4 ± 9.70 ms; $t(22) = 2.41$, $p<.05$). This effect was particularly pronounced in the more demanding name-identity task (AFA = 52.0 ± 15.12 ms, $t(22) = 3.44$, $p<.01$) and was virtually identical to that of normally cycling women during the midluteal phase (see Table 1). Although the effect of Trial type was significant in men but not in women during menses (see Table 1), the comparison between these two groups did not reveal a significant interaction between Sex and Trial type ($F(1,38) = 3.72$, $p<.07$). The difference between AFA in men and women during menses was also not significant ($t(38) = 1.91$; $p<.06$). Neither the main effect of Sex nor any other interaction with Sex approached significance (all $F < 1.48$; n.s.).

The comparison between postmenopausal women (session 1) and men revealed faster responses in males ($F(1,36) = 29.50$, $p<.001$, $\eta^2 = .45$). Moreover, the interaction between Sex and Task was significant ($F(1,36) = 4.76$, $p<.05$, $\eta^2 = .12$) which suggests that an increase of response times in the more demanding semantic task was more evident in postmenopausal women than in men. No other interaction with Sex was significant (all $F < 2.73$, n.s.). AFA in the name-identity task was virtually identical in both groups (postmenopausal women: AFA = 63.4 ± 32.23 ms), $t(36) = -.36$, n.s..

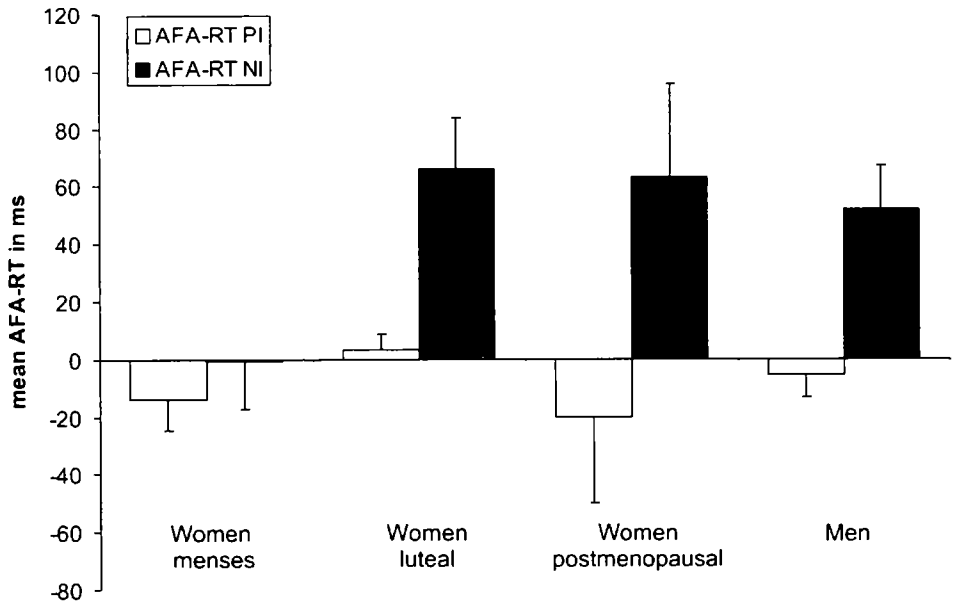

Fig. 1. Mean AFA in ms (± SEM) in normally cycling women during menses and the luteal phase (between-participants analysis), postmenopausal women (session 1), and men in the physical-identity task (white bars) and name-identity task (black bars).

Sex differences in interhemispheric transfer time (Poffenberger task)

Comparing the overall response times of women during the midluteal phase with those of men, the main effect of Sex was significant ($F(1,42) = 6.78$, $p<.05$, $\eta^2 = .14$). Men revealed faster responses than women during the luteal phase. However, the CUD did not differ between women during the luteal phase (CUD = 4.8 ± 5.57 ms) and men (CUD = 4.0 ± 1.85 ms), $t(42) = -.16$, n.s.. No other interaction with Sex approached significance (all $F < 1.13$, n.s.). Comparing response times of women during menses and men, again only the main effect of Sex was significant ($F(1,42) = 6.31$, $p<.05$, $\eta^2 = .13$) with faster responses in men. All other interactions with Sex were not significant, $F < 1.26$, n.s.. The CUD in men was virtually identical to the CUD in women during menses (CUD = 4.9 ± 4.84 ms, $t(42) = -.21$, n.s.).

The comparison between postmenopausal women at session 1 and men revealed a significant main effect of Sex with faster responses in men than in postmenopausal women ($F(1,40) = 26.05$, $p<.0001$, $\eta^2 = .39$). Moreover, the main effect of VHF ($F(1,40) = 4.71$, $p<.05$, $\eta^2 = .11$) and the interaction between Hand use and VHF ($F(1,40) = 12.45$, $p<.01$, $\eta^2 = .24$) were significant. Participants responded particularly faster on stimuli presented in RVF than LVF. This pattern was especially pronounced when the right hand was used. Although

CUDs in postmenopausal women (CUD = 8.9 ± 3.61 ms) were slightly larger than in men (CUD = 4.0 ± 1.85 ms), this difference did not approach significance ($t(40) = 1.36$, n.s.).

Relationships between progesterone and interhemispheric tasks

In view of the significant interaction between Cycle phase and Trial type in interhemispheric integration (Banich-Belger task), P-levels were expected to be significantly related to AFA. However, P-levels were not significantly related to AFA, neither when normally cycling women from both cycle phases (session 1) were included in the analysis (r = .18, n = 17, n.s.) nor when the correlation was restricted to women in the luteal phase (session 1 and 2) (r = -.18, n = 17, n.s.). Moreover, P-levels were not significantly related to RTs and accuracies on within- and across-field trials (all $r < \pm .43$, n.s.). The relationship between P-levels and CUD (Poffenberger task) was also not significant (all $r < \pm .24$, n.s.).

Finally, we analysed the relationship between AFA and CUD. Although the correlation between both measures of interhemispheric interaction was always positive, it did not approach significance. This insignificant effect was found for AFA based on the physical and name-identity task and was present for all participating groups (all $r < .27$, n.s.).

Discussion

In line with previous findings (Banich & Belger, 1990; Weissmann et al., 2000), the results of the present study support the idea that interhemispheric integration becomes advantageous with increasing task demands. Men, normally cycling women, and postmenopausal women revealed an AFA in the more demanding name-identity task but not in the less demanding physical-identity task. Moreover, the present study revealed the first evidence for cycle-dependent fluctuations in interhemispheric integration. Normally cycling women during the luteal phase showed a strong AFA for the more demanding name-identity task, in particular, a finding which was significant in the between-participants analysis. In contrast to our predictions, the AFA of normally cycling women during the luteal phase was virtually identical to that of aged-matched men and postmenopausal women who showed a robust AFA in both testing sessions. However, no advantage of interhemispheric integration was found in normally cycling women during menses. The results suggest that in younger women, the menstrual cycle and concomitant changes in sex-hormone levels are related to dynamic changes in interhemispheric integration. Interactions across the hemispheres seem to

be differently organized in postmenopausal women. Here, a stable hormonal environment with low gonadal hormones seems to promote a stable interhemispheric integration. Although men of the present study were tested only once, we assume the AFA of men to be similarly stable as it is in postmenopausal women because both groups have comparably low and stable sex hormone-levels.

The present finding is in contrast to a previous study (Compton et al., 2004) which did not find cycle-related fluctuations in interhemispheric integration. The conflicting finding cannot simply be explained by the fact that Compton et al. (2004) used only the name-identity task. Both studies were also similar with respect to participants' age and selected cycle phases. However, normally cycling women in Compton et al. (2004) and the present study differed substantially in the participants' hormonal status. Participants' mean luteal P-level in Compton et al. (2004) was approximately twice as high as the mean P-level during menses, whereas in the present study, luteal P-levels were about five times higher than during menses. Moreover, in Compton et al.'s study, normally cycling women showed higher P-levels during menses (72.8 pg/ml) than the present study (38.59 pg/ml), whereas P-levels were lower during the midluteal phase (131.0 pg/ml) than those reported here (193.55 pg/ml). If cycle-related fluctuations in hormone levels are indeed related to a cycle-dependent modulation of interhemispheric integration, the present study is more likely to find significant effects. It should be noted, however, that P itself was unrelated to interhemispheric integration in both studies. This might indicate that these effects are not directly mediated by sex hormones. An alternative hormonal explanation might be that cycle-related fluctuations in interhemispheric integration, as measured by the Banich-Belger task, are affected by sex hormones other than P but also increase during the midluteal phase, e.g. E and/or P-metabolites. Although there is evidence that P-levels are related to other interhemispheric processes, i.e. interhemispheric inhibition (Hausmann & Güntürkün, 2000; Hausmann et al., 2002; Hausmann et al., 2006), it is rather unlikely that such a inhibition is also involved in interhemispheric integration.

The key finding that only normally cycling women during menses did not show a strong AFA clarifies two different but intertwined aspects, namely the nature of interhemispheric interactions, and the difference between cycle-related effects in younger women on one side, and men and postmenopausal women on the other. We will discuss these two points separately.

The Nature of Interhemispheric Interactions

Interhemispheric inhibition refers to mechanisms that suppress a concurrent processing in the opposite hemisphere by activation of GABAergic interneurons in homotopic areas (Toyama & Matsunami, 1976; Toyama, Tokashiki & Matsunami, 1969). This inhibitory coupling between hemispheres can take place at a very early level of cortical processing (Bergert, Windmann, & Güntürkün, 2006), possibly already between the occipital cortices (Miniussi, Girelli, & Marzi, 1998). As a result, one hemisphere dominates the task. In contrast, interhemispheric integration involves parallel processing in both hemispheres by activating common resources, probably mainly at later processing stages (Mohr, Landgrebe, & Schweinberger, 2002). It requires a more decoupled interhemispheric state that allows both sides to independently process the relevant stimuli. Although the mechanisms underlying the AFA are not fully clear, it has been suggested that it does not simply reflect a processing load division effect but rather a reduction of mutual interference between hemispheres during perceptual processing (e.g., Sohn, Liederman & Tippens-Reinitz, 1996).

Our findings suggest that different interhemispheric processes are differentially affected by sex-hormonal fluctuations across the menstrual cycle. Tasks that mainly rely on interhemispheric inhibition seem to be affected by P (and E), and thus modulate FCAs (Hausmann & Güntürkün, 2000; Hausmann et al., 2002; Hausmann et al., 2006). Tasks which require a bihemispheric activation of common resources with a subsequent integration are also affected by the menstrual cycle, without P being directly relevant.

IHTT seems not to be affected by the menstrual cycle and cycle-related hormonal changes, at least when measured behaviourally. The present study showed that CUD in the Poffenberger task as an estimate of IHTT did not fluctuate across the menstrual cycle and did not differ between men and women, regardless which cycle phase was taken into account. However, due to the fact that sex differences in IHTT can be measured by event-related potentials (Moes, Brown & Minnema, 2007), it seems possible that CUD based on response times is not sensitive enough to detect sex and sex-hormonal effects. This assumption is also supported by the non-significant overall difference between crossed and uncrossed trials, suggesting that CUDs as measured by the Poffenberger task do not provide a reliable estimate of IHTT.

Sex- and Age-Specific Differences of Interhemispheric Interactions

Previous perceptual asymmetry studies focusing on cycle-related fluctuation in FCAs have shown that men, postmenopausal women, and normally cycling women during menses show similar asymmetry patterns, probably because their levels of relevant sex hormones, i.e., P and E, are similarly low (Hausmann & Güntürkün, 2000; Hausmann et al., 2002). Only few studies that did not use interhemispheric-inhibition tasks suggest a more male-like functional cerebral organisation in women during the luteal phase rather than for women during menses (e.g. McCourt et al., 1997). This is similar to the present study which also found virtually identical results in women during the luteal phase and in men. The enhanced interhemispheric integration in women during the luteal phase suggests that high levels of sex hormones, others than P, might temporally optimize parallel processing in tasks that demand interhemispheric integration.

However, why did postmenopausal women and men show a robust AFA although they reveal low sex hormone levels, comparable to those of women during menses? To understand this paradoxical finding it is important to stress the profound effect of sex hormones, such as E and P, on many aspects of neuronal processing, ranging from synaptic adjustments up to neurotrophic factors that alter cellular morphology. The low level of these hormones in men and their loss in postmenopausal women requires a difference in neural functional architecture, including interhemispheric interactions. These neural differences are by far not understood.

In older adults, several neuromorphological changes have been shown with increasing age (e.g., Sowell, Peterson, Thompson, Welcome, Henkenius & Toga, 2003), including changes in frontal and parieto-occipital brain regions which are known to be critical for visual letter processing and interhemispheric integration (e.g., Puce; Allison, Asgari, Gore & McCarthy, 1996; Pollmann, Zaidel & von Cramon, 2003). In contrast, age-related changes in corpus callosum morphology seem to be relatively small, particularly in older women (Cowell, Allen, Zalatimo & Denenberg, 1992; Cowell, Turetsky, Gur, Grossman, Shtasel & Gur, 1994; Dubb, Gur, Avants & Gee, 2003; Suganthy, Raghuram, Antonisamy, Vettivel, Madhavi & Koshi, 2003; Sullivan, Rosenbloom, Desmond & Pfefferbaum, 2001). Thus, given that the costs associated with communication between the hemispheres are virtually the same in women during menses and postmenopausal women, we are inclined to believe that an AFA in the latter group occurred in part because the relative performance on within-field trials versus across-field trials was reduced due to an age-related decline.

This assumption is in line with the idea that additional recruitment of brain areas via callosal pathways serves as a compensatory mechanism to counteract age-related deficits in cognitive functions (e.g., Cabeza, Anderson, Locantore & McIntosh, 2002). It has been shown that older adults relative to younger adults benefit more from interhemispheric interaction even when task demands are relatively low (Reuter-Lorenz, Stanczak & Miller, 1999, Banich & Brown, 2000). A greater bilateral involvement with increasing age was also reported in several neuroimaging studies showing bilateral activity in frontal and parietal sites in older adults but a more lateralized activity in younger adults (e.g., Reuter-Lorenz, Jonides et al., 2000; Cabeza et al., 2002). Thus, according to the present results, it seems reasonable to assume that different neuronal conditions in younger and postmenopausal women ensure an effective interhemispheric integration, particularly when the task becomes more demanding.

Summary

In summary, the present study provides the first evidence that the AFA in the Banich-Belger task changes dynamically in women across the menstrual cycle, whereas it remains relatively stable in postmenopausal women without HRT. Although no relationship between P-levels and interhemispheric integration was found, modulating effects of E or other cycle-related hormones cannot be ruled out. However, IHTT, estimated by response time CUDs, was not affected by the menstrual cycle, and thus seems not to be under sex-hormonal control.

The idea that the interhemispheric crosstalk is hormonally affected and fluctuates across the menstrual cycle is based on the hypothesis of P-modulated interhemispheric decoupling, referring to interhemispheric inhibition (Hausmann & Güntürkün, 2000; Hausmann et al., 2002). The present study focuses on a complementary interhemispheric process that requires bihemispheric processing with subsequent interhemispheric integration. Thus, the present study importantly extends the theory of Hausmann and Güntürkün by clarifying two aspects:

1. In normally cycling women, the hormonal condition during menses is associated with increases in interhemispheric coupling via inhibition, and subsequently enhances FCAs. However, this hormonal state concomitantly decreases the AFA in the Banich-Belger task. During the luteal phase, interhemispheric inhibition is reduced, resulting in low FCAs and a condition that favours bihemispheric processing and thus, increases AFAs.

2. The system of bihemispheric activation is profoundly altered when gonadal steroid hormones, such as E and P, are drastically reduced, as in men and postmenopausal

women. We assume that permanently low levels of such important neuroactive agents are accompanied by a different architecture of interhemispheric communication that is presently not properly understood. This different architecture ensures successful interhemispheric integration without the modulatory effects of sex hormones.

Acknowledgements

The authors thank all participating women for their cooperation. This work is supported by grant HA 3285/4-1 of the Deutsche Forschungsgemeinschaft (DFG) to M.H.

References

Banich, M. T., & Belger, A. (1990). Interhemispheric interaction: how do the hemispheres divide and conquer a task? *Cortex, 26*(1), 77-94.

Banich, M. T., & Brown, W. S. (2000). A life-span perspective on interaction between the cerebral hemispheres. *Developmental Neuropsychology, 18*(1), 1-10.

Bergert, S., Windmann, S., & Güntürkün, O. (2006). Is interhemispheric communication disturbed when the two hemispheres perform on separate tasks? *Neuropsychologia, 44*, 1457-1467.

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*(1), 131-138.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Chiarello, C., & Maxfield, L. (1996). Varieties of interhemispheric inhibition, or how to keep a good hemisphere down. *Brain and Cognition, 30*(1), 81-108.

Chiarello, C., McMahon, M. A., & Schaefer, K. (1989). Visual cerebral lateralization over phases of the menstrual cycle: a preliminary investigation. *Brain and Cognition, 11*(1), 18-36.

Compton, R. J., Costello, C., & Diepold, J. (2004). Interhemispheric integration during the menstrual cycle: failure to confirm progesterone-mediated interhemispheric decoupling. *Neuropsychologia, 42*(11), 1496-1503.

Compton, R. J., & Levine, S. C. (1997). Menstrual cycle phase and mood effects on perceptual asymmetry. *Brain and Cognition, 35*(2), 168-183.

Compton, R. J., & Mintzer, D. A. (2001). Effects of worry and evaluation stress on interhemispheric interaction. *Neuropsychology, 15*(4), 427-433.

Cook, N. D. (1984). Homotopic callosal inhibition. *Brain and Language, 23*(1), 116-125.

Corballis, M. C. (2002). Hemispheric interactions in simple reaction time. *Neuropsychologia, 40*(4), 423-434.

Cowell, B., Allen, L., Zalatimo, N., & Denenberg, V. (1992). A developmental study of sex by age interaction in human corpus callosum. *Developmental Brain Research, 66*, 187-192.

Cowell, P. E., Turetsky, B. I., Gur, R. C., Grossman, R. I., Shtasel, D. L., & Gur, R. E. (1994). Sex differences in aging of the human frontal and temporal lobes. *Journal of Neuroscience, 14*(8), 4748-4755.

Dubb, A., Gur, R., Avants, B., & Gee, J. (2003). Characterization of sexual dimorphism in the human corpus callosum. *Neuroimage, 20*(1), 512-519.

Hampson, E. (1990). Estrogen-related variations in human spatial and articulatory-motor skills. *Psychoneuroendocrinology, 15*(2), 97-111.

Hampson, E. (1990). Variations in sex-related cognitive abilities across the menstrual cycle. *Brain and Cognition, 14*(1), 26-43.

Hausmann, M. (2005). Hemispheric asymmetry in spatial attention across the menstrual cycle. *Neuropsychologia, 43*(11), 1559-1567.

Hausmann, M., Becker, C., Gather, U., & Güntürkün, O. (2002). Functional cerebral asymmetries during the menstrual cycle: a cross-sectional and longitudinal analysis. *Neuropsychologia, 40*(7), 808-816.

Hausmann, M., & Güntürkün, O. (2000). Steroid fluctuations modify functional cerebral asymmetries: the hypothesis of progesterone-mediated interhemispheric decoupling. *Neuropsychologia, 38*(10), 1362-1374.

Hausmann, M., Tegenthoff, M., Sanger, J., Janssen, F., Güntürkün, O., & Schwenkreis, P. (2006). Transcallosal inhibition across the menstrual cycle: A TMS study. *Clinical neurophysiology: Official journal of the International Federation of Clinical Neurophysiology, 117*(1), 26-32.

Heister, G., Landis, T., Regard, M., & Schroeder-Heister, P. (1989). Shift of functional cerebral asymmetry during the menstrual cycle. *Neuropsychologia, 27*(6), 871-880.

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*(5), 717-724.

Mead, L. A., & Hampson, E. (1997). Turning bias in humans is influenced by phase of the menstrual cycle. *Hormones and Behavior, 31*(1), 65-74.

Miniussi C., Girelli M., & Marzi, C. A. (1998). Neural site of the redundant target effect: electrophysiological evidence. *Journal of Cognitive Neuroscience, 10*, 216-230.

Moes, P. E., Brown, W. S., & Minnema, M. T. (2007). Individual differences in interhemispheric transfer time (IHTT) as measured by event related potentials. *Neuropsychologia, 45*(11), 2626-2630.

Mohr, B., Landgrebe, A., & Schweinberger, S. R. (2002). Interhemispheric cooperation for familiar but not unfamiliar face processing. *Neuropsychologia, 40*, 1841-1848.

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

Poffenberger, A.T. (1912). Reaction time to retinal stimulation with special reference to the time lost in conduction through nerve centres. *Archives of Psychology, 23*, 1-73.

Pollmann, S., Zaidel, E., & von Cramon, D. Y. (2003). The neural basis of the bilateral distribution advantage. *Experimental Brain Research, 153*(3), 322-333.

Puce, A., Allison, T., Asgari, M., Gore, J. C., & McCarthy, G. (1996). Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. *Journal of Neuroscience, 16*(16), 5205-5215.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., et al. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *Journal of Cognitive Neuroscience, 12*(1), 174-187.

Reuter-Lorenz, P. A., & Stanczak, L. (2000). Differential effects of aging on the functions of the corpus callosum. *Developmental Neuropsychology, 18*(1), 113-137.

Rode, C., Wagner, M., & Güntürkün, O. (1995). Menstrual cycle affects functional cerebral asymmetries. *Neuropsychologia, 33*(7), 855-865.

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*(9), 869-874.

Sohn, Y. S., Liederman, J., & Tippens Reinitz, M. (1996). Division of inputs between hemispheres eliminates illusory conjunctions. *Neuropsychologia, 34*(11), 1057-68.

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga,

A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience, 6*(3), 309-315.

Suganthy, J., Raghuram, L., Antonisamy, B., Vettivel, S., Madhavi, C., & Koshi, R. (2003). Gender- and age-related differences in the morphology of the corpus callosum. *Clinical Anatomy, 16*(5), 396-403.

Sullivan, E. V., Rosenbloom, M. J., Desmond, J. E., & Pfefferbaum, A. (2001). Sex differences in corpus callosum size: relationship to age and intracranial size. *Neurobiology of Aging, 22*(4), 603-611.

Toyama, K., & Matsunami, K. (1976). Convergence of specific visual and commissural impulses upon inhibitory interneurons of the cat's visual cortex. *Neuroscience, 1*, 107-12.

Toyama, K., Tokashiki, S., & Matsunami, K. (1969). Synaptic action of commissural impulses upon association e.erent cells in the cat visual cortex. *Brain Research, 14*, 518-20.

Weissman, D. H., & Banich, M. T. (2000). The cerebral hemispheres cooperate to perform complex but not simple tasks. *Neuropsychology, 14*(1), 41-59.

Weissman, D. H., Banich, M. T., & Puente, E. I. (2000). An unbalanced distribution of inputs across the hemispheres facilitates interhemispheric interaction. *Journal of the International Neuropsychological Society, 6*(3), 313-321.

Wisniewski, A. B. (1998). Sexually-dimorphic patterns of cortical asymmetry, and the role for sex steroid hormones in determining cortical patterns of lateralization. *Psychoneuroendocrinology, 23*(5), 519-547.

Zaidel, E. (1995). Interhemisphesric transfer in the split brain: Long-term status following complete cerebral commissurotomy. In R. J. Davidson, & K. Hugdahl (Eds.), *Brain Asymmetry* (pp. 491–532). Cambridge, MA: MIT Press.

Zerssen, D. von, *Die Befindlichkeits-Skala*, Beltz-Verlag, Weinheim, 1976.

III Effects of sex hormone therapy on interhemispheric crosstalk in postmenopausal women

Ulrike Bayer & Markus Hausmann

Department of Psychology, University of Durham, Durham, UK

Abstract

Evidence exists that fluctuating levels of sex hormones affect interhemispheric interaction in women during the menstrual cycle. The present study investigated whether interhemispheric interaction is susceptible to direct hormonal manipulations via hormone therapy (HT). Sixty-eight postmenopausal women who received HT either with estrogen alone (n=15), an estrogen-gestagen combination (n=22) or without HT (n=31) were investigated. Participants were asked to match letters according to their physical or name identity. Matches were presented either within or across visual half-fields. Additionally, a simple reaction-time task, assumed to estimate interhemispheric transfer time (IHTT), was used. Overall, postmenopausal women showed an across-field advantage in the more demanding name-identity task but not in the less demanding physical-identity task. However, across both tasks, the groups differed in responses to within- and across- field trials: the control group performed better on across- than within-field trials, whereas both HT groups showed faster responses on within- than across-field trials. IHTT did not differ between groups. The findings suggest that postmenopausal E-therapy affects the relative efficiency of interhemispheric integration via modulating within-hemisphere functioning.

Neuropsychology, 2008, in press.

Introduction

Neuropsychological and neurophysiological evidence exists that sex hormones affect various brain functions (Wiesniewski, 1998). Specifically, it has been suggested that changes in estradiol (E) and progesterone (P) levels across the menstrual cycle modulate different aspects of interhemispheric interaction. For example, several studies have reported cycle-related changes in functional cerebral asymmetries (FCAs) (e.g., Bibawi, Cherry, & Hellige, 1995; Hampson, 1990a, 1990b; Heister, Landis, Regard, & Schroeder-Heister, 1989; McCourt, Mark, Radanovich, Willison, & Freeman, 1997; Mead & Hampson, 1996; Rode, Wagner, & Güntürkün, 1995; Sanders & Wenmoth, 1998). However, none of these studies suggests a potential neural mechanism underlying sex hormonal changes in FCAs during the menstrual cycle. The first attempt has been made by Hausmann and Güntürkün (Hausmann, Becker, Gather, & Güntürkün, 2002; Hausmann & Güntürkün, 2000). The authors hypothesized that the interaction between the two hemispheres is affected by the activating effects of sex hormones. This idea is based on the assumption that interhemispheric interaction that takes place as interhemispheric inhibition between homotopic structures is a fundamental prerequisite for the manifestation of FCAs (e.g., Chiarello & Maxfield, 1996). The authors found a P-related reduction of FCAs in left- (word matching) as well as in right-hemispheric tasks (face discrimination, polygon matching) during the midluteal phase when gonadal sex hormone levels are relatively high compared with menses. Specifically, it has been proposed that high levels of P during the luteal phase attenuate interhemispheric inhibition, probably via its neuromodulatory effects on GABAergic interneurons. A decrease in the degree of interhemispheric inhibition might subsequently lead to a functionally more independent processing within each hemisphere. This so-called hemispheric decoupling finally results in reduced FCAs (see Hausmann & Güntürkün 2000; Hausmann et al., 2002, for details).

Further support for the idea that sex hormones affect different aspects of interhemispheric interaction comes from a study using a visual line-bisection task (Hausmann, 2005). In visual line-bisection tasks, subjects are required to manually bisect a line drawn on paper by marking with a pen. It has been shown that healthy subjects systematically misbisect space, generally erring to the left veridical centre, a phenomenon has been assumed to arise from an advantage of the right hemisphere in allocating attention. The leftward bias is also present, albeit reduced, for the right hand, corresponding to the left hemisphere) (e.g., Jewell & McCourt, 2000). This hand-use difference has been assumed to reflect transcallosal spreading activation

from the line-bisection bias-dominating right hemisphere to the left hemisphere, controlling the left and right hand, respectively. Hausmann (2005) found a reduced hand-use difference in women during the luteal phase compared with menses. This effect was mainly related to high E levels, suggesting that different transcallosal processes are differentially affected by E and P.

The neuromodulatory effects of both E and P on interhemispheric interaction have also been shown in a neurophysiological study using transcranial magnetic stimulation (TMS; Hausmann, Tegenthoff, Sänger, Janssen, Güntürkün, & Schwenkreis, 2006). This study reported a negative relationship between transcallosal inhibition and E and P levels during the follicular and luteal phase, respectively, which underlines their neurmodulatory properties on glutamatergic and GABAergic neurons. These findings are in line with the hypothesis of P-modulated interhemispheric decoupling (Hausmann & Güntürkün, 2000; Hausmann et al., 2002), according to which a P-related reduction of interhemispheric inhibition should result in a reduced hemispheric asymmetry and more bilateral organization of motor functions (see Hausmann et al., 2006, for details).

Two previous studies (Bayer, Kessler, Güntürkün & Hausmann, 2008; Compton, Costello & Diepold, 2004) focused on menstrual cycle-related changes in interhemispheric integration, another important aspect of interhemispheric crosstalk. Both studies used a prominent paradigm developed by Banich and Belger (1990) which requires interhemispheric integration (e.g. Zaidel, 1995). The Banich-Belger task measures specific aspects of interhemispheric communication by comparing bihemispheric processing with within-hemisphere processing. In this paradigm, individuals must decide whether a target item matches either one of two probes. If the target and matching probe are positioned in the same visual half-field (VHF, within-field trials), and hence directed to the same hemisphere, no interhemispheric interaction is required to make the decision. In contrast, on across-field trials, the target and matching probe are directed to different hemispheres. In these trials, the brain must integrate information across VHFs to identify the match. It has been shown that across-field integration, allowing for a division of labour between hemispheres, enhances the performance when task complexity increases (across-field advantage, AFA), but impedes the performance on less demanding tasks (Banich & Belger, 1990). In contrast to Compton et al. (2004), who did not reveal cycle-related fluctuations in AFA, Bayer et al. (2008) reported a significantly enhanced AFA during the high-P luteal phase compared with menses. It is important to note that the luteal AFA was similar in size to that found in age-matched men and postmenopausal women without hormone therapy (HT). This finding seems somewhat controversial, given

that the majority of studies reported a similar functional brain organisation in women during menses, men, and postmenopausal women without HT, probably as a result of similarly low levels of sex hormones (e.g., Hausmann & Güntürkün, 2000). Bayer et al (2008) concluded that the hormonal conditions during the luteal phase seem to promote a substantial AFA. A virtually identical AFA in men and postmenopausal controls, who show permanently reduced sex hormone-levels, seems to be the result from fundamental differences in the functional neural architecture (e.g., interhemispheric interactions) between these groups and normally cycling women, rather than from hormonal differences. In contrast to cycle-related dynamic changes in interhemispheric integration in younger women, the AFA of postmenopausal women was stable across corresponding time intervals, probably as a result of a stable hormonal environment which maintains stable interhemispheric integration. In this study, however, fluctuations in AFA in normally cycling women were not directly related to P levels, suggesting that other sex hormones than P might be relevant.

One approach to determine whether the AFA in normally cycling women is affected by E or P might be to control for the hormonal status of normally cycling women with leuprolide acetate (Lupron), a gonadotropin-releasing hormone (GnRH) agonist (e.g., Berman, Schmidt, Rubinow, Danaceau, Van Horn, Esposito, et al., 1997). An alternative approach which also allows for a direct manipulation of sex hormone levels has been followed by the present study which investigated postmenopausal women receiving different hormone therapies (HT). Specifically, we have investigated whether E-therapy (ET) and a combined E plus gestagen HT (cHT) might differentially affect interhemispheric integration. Synthetic gestagens are compounds that are chemically derived from either testosterone or progesterone and possess progestational activity. Within the context of postmenopausal therapy, they cause a secretory transformation of an E-primed endometrium and inhibit further proliferation (e.g., Wiegratz & Kuhl, 2004). Besides these actions on peripheral target tissues, however, gestagens have also been shown to exert neuromodulatory effects on the brain. Whether these effects are similar to those of P is not yet understood (e.g., Schumacher, Guennoun, Ghoumari, Massaad, Robert, El-Etr, et al., 2007).

A number of studies suggest that HT in postmenopausal women (and in younger women with artificial menopause as a result of gynecological operations) positively affects various cognitive functions, e.g. verbal memory, specific aspects of attention, processing speed, and response speed (see Hogervorst, Williams, Budge, Riedel, & Jolles, 2000, for a review). However, conflicting findings have also been reported which suggest either neutral or even negative effects of HT (e.g., Craig et al., 2005; Hogervorst et al., 2000; Low and Anstey,

2006). These inconsistencies may partly arise from pre-existing group differences in age, education level, premenopausal hormonal state, and menopausal symptoms (e.g., mood) which are particularly relevant in studies testing women on the basis of the regular treatment regimen (e.g., Barrett-Connor, 1998; Maki, Zonderman & Resnick, 2001).

Although these problems cannot be completely ruled out by matching groups, the approach of investigating postmenopausal women allows for a separate determination of the effects of E and E-gestagen combination on functional brain organization. So far, only one study specifically investigated the effects of HT on FCAs in postmenopausal women (Bayer & Erdmann, 2008). The authors found an enhanced performance of the right hemisphere in women taking E only (estrogen therapy, ET) suggesting an important role of postmenopausal ET in modulating FCAs.

The present study investigates HT-related effects in postmenopausal women on interhemispheric integration. This has not been investigated previously. To separate the effects of E alone from those of E plus gestagen, women undergoing HT were further subdivided into two groups namely, those receiving ET and those receiving a combined HT (cHT) including E and gestagens. To investigate the efficiency of interhemispheric integration, participants performed two versions of the Banich-Belger task which differed in task demands and were identical to those used by Bayer et al. (2008). Based on previous results (e.g., Bayer et al, 2008; see also Reuter-Lorenz & Stanczak, 2000), we expected postmenopausal women without HT to reveal an AFA that is particularly pronounced in the more demanding name-identity task. Postmenopausal women with HT (i.e. ET or cHT) were expected to differ in AFA from the control group. If HT indeed affects interhemispheric integration, it seems likely that E and/or gestagens mainly affect interhemispheric processes at a higher processing level. Thus, we hypothesize that group differences in AFA will be particularly pronounced in the more demanding name-identity task.

To investigate whether the interhemispheric transfer of visuomotor information might be affected by HT, we additionally used a simple reaction-time task in which participants must respond to visual stimuli presented either in the left (LVF) or right visual field (RVF) with the right and the left hand. As an estimate of interhemispheric transfer times (IHTT), the crossed-uncrossed difference (CUD) was calculated by subtracting the median RT under the two uncrossed conditions (stimuli presented in the VHF ipsilateral to the responding hand) from median RT under the crossed conditions (stimuli presented in the VHF opposite to the responding hand; Poffenberger, 1912). It has been shown that IHTT can differ between sexes

with women showing more symmetric and shorter overall IHTT than men (Nowicka & Fersen. 2001; Moes, Brown, & Minnema, 2007). Up until now, it has not been investigated whether interhemispheric integration and IHTTs are susceptible to direct hormonal manipulations induced by HT.

Method

Participants

Sixty-eight postmenopausal women with a mean age of 58.1 years (SD = 6.30, age range: 46-71 years) participated in this study. All participants were right-handed as determined by the Edinburgh Inventory (Oldfield, 1971). The asymmetry-index provided by this test is calculated as ((R-L)/(R+L)) x 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 87.6 (SD = 18.59).

All participants were native German speakers. Women did not use any medication which might have affected the central nervous system during the previous 6 months. All participants had normal or corrected-to-normal visual acuity. They were naïve of the experimental hypotheses. Participants were recruited by announcements, and were paid for their participation.

Experimental groups

Based on their regular hormonal treatment, participants were assigned to one of three groups: (1) the control group consisted of 31 women who had been in their menopause for at least one year (mean duration = 6.8 years, SD = 4.92, range: 1.0-20.0) and did not receive any hormonal treatment. Menopause was defined as the time point of last menstruation; (2) the ET group consisted of 15 women who received E only; and (3) the cHT group consisted of women (n = 19) who received either a continuous cHT or a cyclic cHT (n = 3). Participants in the cyclic cHT subgroup were tested during the second phase of the cyclic treatment, at the earliest on the fourth day of additional gestagen treatment. This approach is based on a recent study, which strongly supports the assumption that continuous and cyclic HT do not differ in their effects on functional brain organization (Bayer & Erdmann, 2008).

For the ET group, mean duration of hormonal treatment was 6.8 years (SD = 5.90, range: 0.8 – 18.0 years). For the cHT group, mean duration was 4.5 years (SD = 4.15, range: 0.3 –

14.0). There was no difference between the two hormone groups in HT duration, $t(35) = 1.41$, n.s. Details about hormonal therapies are shown in Table 1.

Group	Hormone regimen	dosage	Route of administration	treatment	N
	CE	0.6 mg	oral	continous	2
	CE	1.25 mg	oral	continous	2
	estradiol	25 µg	transdermal	continous	2
ET	**estradiol**	37.5 µg	transdermal	continous	1
	estradiol	50 µg	transdermal	continous	3
	estradiol	100 µg	transdermal	continous	1
	estradiol	0.6 mg	percutane	continous	2
	estradiolvalerate	4 mg	intramuscular	continous	2
	estradiol + NEA	1 mg + 0.5 mg	oral	continous	7
	estradiol + NEA	2 mg + 1.0 mg	oral	continous	3
	estradiol + dienogest	1 mg + 2 mg	oral	continous	3
	estradiol + drospirenon + NEA	1 mg + 2 mg + 1mg	oral	continous	1
cHT	**estradiol + NEA**	25 µg + 125 µg	transdermal	continous	3
	estradiol + NEA	0.5 mg + 5 mg	percutane + oral	continous	1
	estradiol + progesterone	0.6 mg + 100 mg	percutane + oral	continous	1
	CE + medrogestone	0.3 mg + 5 mg	oral	cyclic	2
	CE + MPA	0.6 mg + 5 mg	oral	cyclic	1

Table 1. Number of postmenopausal women, types of hormone therapy, dosages, and route of administration in the estrogen therapy (ET) and the combined HT (cHT) group. Note. Conjugated estrogens (CE), norethisterone acetate (NEA), medroxyprogesterone acetate (MPA).

Groups did not differ with respect to age, handedness, and years of education (Table 2).

	C group n = 31	ET group n = 15	cHT group n = 22	$F(2,65)$	p
Mean age (in years)	58.7 (5.69)	58.9 (6.85)	56.7 (6.80)	0.81	n.s.
Mean handedness (EHI score)	86.5 (20.25)	83.7 (18.72)	91.8 (15.86)	0.94	n.s.
Mean years of education	14.1 (2.86)	13.0 (2.70)	14.0 (2.59)	0.87	n.s.

Table 2. Age, handedness, and years of education (means and standard deviations) for the control (C) group, the estrogen therapy (ET) group, and the combined HT (cHT) group and the ANOVA results for the between-subjects factor Group (control, ET, and cHT group) on each of the parameters.

Procedure

Sex hormone-related effects on interhemispheric integration and IHTT were investigated using two different tasks: (1) the Banich-Belger task, and (2) the Poffenberger task. Before and after the testing session, saliva samples were taken from each participant. Saliva estradiol- and P-levels were determined with chemiluminescence assay by an independent professional hormone laboratory, with commercially available hormone assays. For estradiol, intra-assay coefficients of variations (CVs) were 3.7% and 7.9%, inter-assay CVs were 5.9% and 13.9% for high and low estradiol-samples, respectively. For P, intra and inter-assay CVs were 2.3% to 6.0% and 8.4% to 18.8% for high and low P-samples, respectively. The assay sensitivity was 0.3 pg/ml for estradiol and 2.6 pg/ml for P.

The experiment started by placing the head of a seated participant in a chin rest at a distance of 57 cm from a monitor. Participants were instructed to keep their head and body still during the whole test. For the analysis of interhemispheric integration, one woman from the control group had to be excluded because she performed only one task.

Interhemispheric integration

The interhemispheric integration task was identical to that used in a previous study (Bayer et al., 2008). In the two versions of the task, adopted from Banich and Belger (1990), participants were presented with an array of three letters arranged in "V" formation and presented around a central fixation cross. The top two stimuli were always two different uppercase letters. These letters were presented 2.8 degrees of visual angle to the left and right

of the midline and 1.4 degrees above a fixation cross. A third letter was centred 1.4 degrees below the fixation point and 1.4 degrees either to the right or left of the centre. In the less demanding physical-identity task, the third letter was an uppercase letter, and participants determined whether the bottom letter was the same as either of the top two letters. In the more demanding name-identity task the third letter was a lowercase letter, and participants decided whether this had the same name as either of the top two letters. Letter stimuli were A, B, E, G, H, Q, R, T, and, in the name-identity task, their lowercase equivalents.

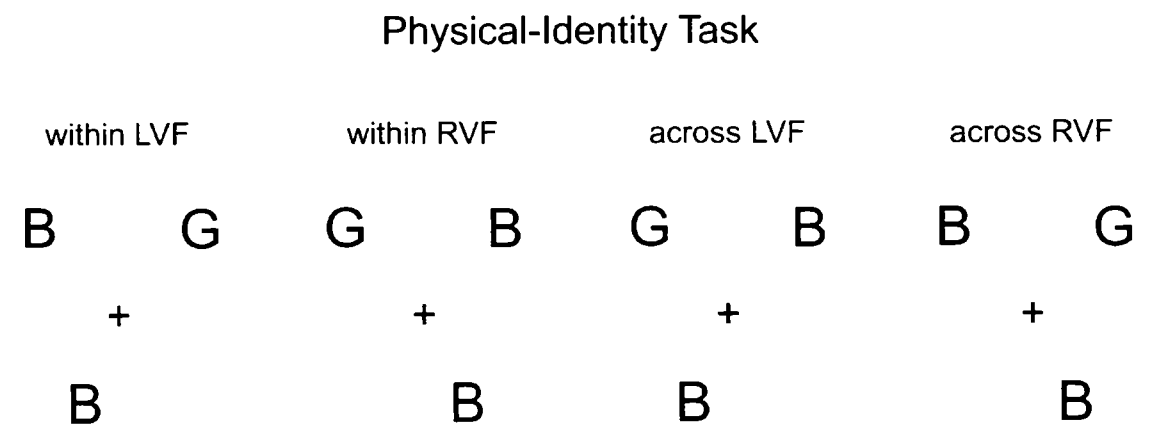

Fig 1. Sample match trials for the physical-identity task.

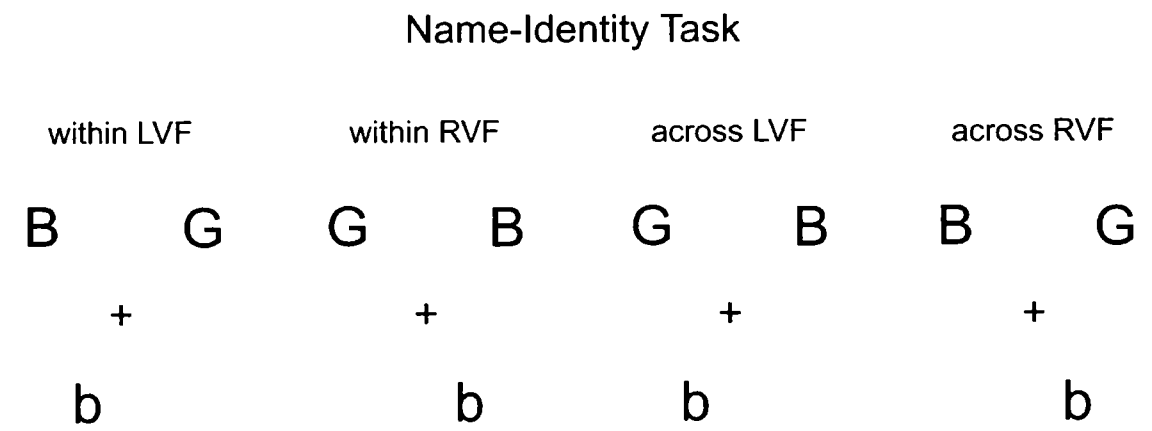

Fig 2. Sample match trials for the name-identity task.

Each trial started by the presentation of a fixation cross for 200 ms, followed by a stimulus array for 200 ms and then by an inter-trial interval of randomized length between 500 and 2000 ms in which responses were recorded.

Both tasks were composed of 224 trials divided into four blocks of 56 each with short breaks between blocks. The participants responded with either the right or left index finger on alternating blocks. The order of hand use was balanced between participants. Prior to each task, participants performed 28 practice trials which were excluded from the analyses. Within each block, half of the trials were match trials and half were mismatch trials. Half of the match trials were within-field matches and the other half were across-field matches. Within both types of matches, the bottom letter appeared equally often in the right and left visual fields. Response accuracy and corresponding median reaction time (RT) on match trials were used as dependent variables. Mismatch trials were not analyzed since they cannot be categorized as within- or across-field trials.

Poffenberger task

The Poffenberger task was identical to that used by Bayer et al. (2008). The stimuli were filled circular disks, 0.86 degrees in visual angle, flashed with their centres 5 degrees either to the left or right of a central fixation cross, or simultaneously on both sides. Responses were made with the index finger of either the right or left hand on a keyboard placed at the participants' midline.

Stimuli were presented in two blocks of 100 trials per each hand with a short break after 50 trials. On a given block, participants used the same hand. The order of response hand was balanced between participants. Within each block, there were 30 trials in which stimuli were presented in the left visual field (LVF), 30 on which they were in the right visual field (RVF), 30 in which stimuli were presented simultaneously in both fields (bilateral), and 10 "catch" trials in which no stimulus was presented. Each trial started with the presentation of a fixation cross located in the centre of the monitor followed by two consecutive stimuli presented for 135 ms, with inter stimulus intervals of 300, 400, 500, 600, or 700 ms. Each of the five intervals was paired six times with each stimulus configuration. Participants were instructed to press the response key as soon as they detected a stimulus, but refrain from responding if no stimulus appeared. Median RT for the left and right hand on stimulus presentations in LVF and RVF were taken. "Catch" trials and bilateral trials were not analysed. IHTT was

estimated by calculating the differences of median RTs in the crossed and uncrossed conditions (CUD).

Control Measures

To control for potential systematic variations in mood which can affect interhemispheric interaction (e.g., Compton & Mintzer, 2001), self reports on present mood state were assessed at the beginning of the testing session. Participants completed the Sate-Trait-Cheerfulness-inventory (STCI-S18; Ruch, Köhler & van Thriel, 1997) which measures three different concepts of mood: cheerfulness, seriousness, and bad mood. Each concept included sex items. Written responses were given on a 4-point rating scale, from *1* = *strongly disagree* to *4* = *strongly agree*.

Results

Hormone assay

Three participants, two from the ET group and one from the cHT group, were excluded from further analyses. Despite the hormonal treatment, these participants did not show the expected increase in estradiol-levels. In fact, estradiol-levels were even below the detection limit (0.8 pg/ml) of the assay. Thus, sixty-five participants entered the statistical analysis.

Estradiol-levels were subjected to an analysis of variance with Group as between-participants factor Group (ET group, cHT group, and control group). The ANOVA revealed a significant effect of Group ($F(2,62) = 7.47$, $p<.01$) Alpha-adjusted post hoc paired t-tests indicated estradiol-levels in the ET group ($t(42) = -2.88$, $p<.01$) and the cHT group ($t(50) = -4.54$, $p<.001$) to be significantly higher compared with those in postmenopausal controls without HT. Both HT groups did not differ in estradiol-levels ($t(32) = -0.46$, n.s.). Descriptive statistics are shown in Table 3.

	Estrogen	Progesterone
	Mean (SD)	Mean (SD)
C group (n = 31)	2.1 (2.16)	55.8 (45.29)
ET group (n = 13)	12.7 (20.51)	43.5 (31.04)
cHT group (n = 21)	15.6 (16.36)	43.6 (27.10)

Table 3. Mean and SD of E- and P-levels (pg/ml) in the control (C) group, the estrogen therapy (ET) group, and the combined HT (cHT) group.

The corresponding analysis for P-levels did not reveal significant differences between groups ($F(2,62) = 0.86$, n.s., see Table 3). The missing differences in P-levels between the cHT group and the control and ET group can be explained by the fact that women of the cHT group received synthetic gestagens which are unrelated to endogenous P-levels as measured by a highly specific P assay (Kuhl, 2006), and hence are not detectable using commercially available P assays.

Interhemispheric integration (Banich-Belger task)

Median RTs were subjected to a 3 x (2 x 2 x 2) analysis of variance (ANOVA) with repeated measures, with Group (control, ET, and cHT group) as a between-participants factor, and Task (physical-identity, name-identity), Trial type (within-field, across-field), and VHF (LVF, RVF) as within-participants factors. Additionally, AFAs were calculated as the difference between trial types for each task (AFA: within-field RT minus across-field RT). The analysis revealed a significant main effect of Task, $F(1,61) = 179.41$, $p<.0001$, with faster responses in the physical- than name-identity task. The Task by Trial type interaction was also significant ($F(1,61) = 34.91$, $p<.001$) indicating an advantage on across-field trials (mean ± SEM: M = 928 ± 33.3 ms) compared with within-field trials (M = 969 ± 35.7 ms) in the name-identity task but not in the physical-identity task (across-field trials: M = 744 ± 29.9 ms; within-field trials: M = 693 ± 31.6 ms). Additionally, there was a significant interaction between Group and Trial type, $F(2,61) = 3.54$, $p<.05$, (see Table 4).

Group	control group			ET group			cHT group		
Task	**Within**	**Across**	**AFA**	**Within**	**Across**	**AFA**	**Within**	**Across**	**AFA**
PI	747	763	-17.0	628	707	**-78.8**	704	763	**-59.0**
	±43.5	±41.2	±18.19	±66.1	±62.6	**±17.37****	±52.0	±49.3	**± 14.02*****
NI	1026	959	**66.8**	955	924	31.8	925	902	23.5
	±49.3	±45.9	**±19.84****	±74.8	±69.7	±23.54	±58.9	±54.8	±17.66
Total	886	861	25.6	792	815	**-23.5**	815	832	-17.8
	±44.6	±41.6	±15.81	±67.8	±63.19	**±10.58***	±53.4	±49.7	± 11.24

Table 4. Mean reaction time (in ms ± SEM) for each trial type (within-field and across-field) and the AFA in the Banich-Belger task as a function of Group (control, ET, and cHT group) and Task (physical-identity = PI, name-identity = NI). * marks simple effects between trial types per group with ***p ≤ .001; **p ≤ .01; *p ≤ .05

As shown in Table 4, postmenopausal women without HT showed a performance advantage on across-field trials compared with within-field trials across both tasks, whereas both HT groups responded faster on within-field trials than across-field trials. Alpha-adjusted post hoc paired t-tests revealed the difference between trial types to be significant in the ET group ($t(12) = 2.22$, $p<.05$) but not in the cHT group ($t(20) = -1.58$, n.s.). The effect of Trial type was also not significant in postmenopausal controls ($t(29) = 1.62$, n.s.). The comparison between groups per trial type revealed no significant differences (all $t < 1.1$, n.s.). No other effects including the factor Group approached significance (all $F < 2.3$, n.s.).

It has been suggested that age might affect interhemispheric integration (e.g., Bayer et al., 2008; Reuter-Lorenz & Stanczak, 2000). Although all three groups of the present study did not differ in age, we additionally calculated the ANOVA including the factor age as a covariate. However, the effect of HT on interhemispheric integration as reflected by the significant Group by Trial type interaction remained the same. Moreover, a median-split based on age for each group did also not change this result.

To examine the change in AFA with increasing task demands, as an estimation of efficiency of interhemispheric integration (e.g., Weissman & Banich, 2000), AFAs were separately calculated for both tasks within each group (Table 4 and Figure 1). A significant AFA in the more demanding name-identity task was evident in the control group ($t(29) =$

3.37, $p<01$). No difference was found for the less demanding physical-identity task ($t(29) = -0.93$, n.s.). In contrast, both HT groups showed a significant within-field advantage (WFA) in the physical-identity task (ET group: $t(12) = -4.53$, $p<.001$; cHT group: $t(20) = -4.21$, $p<.0001$) which shifted towards a slight but non-significant AFA in the name-identity task (ET group: $t(12) = 1.35$, n.s.; cHT group: $t(20) = 1.33$, n.s.).

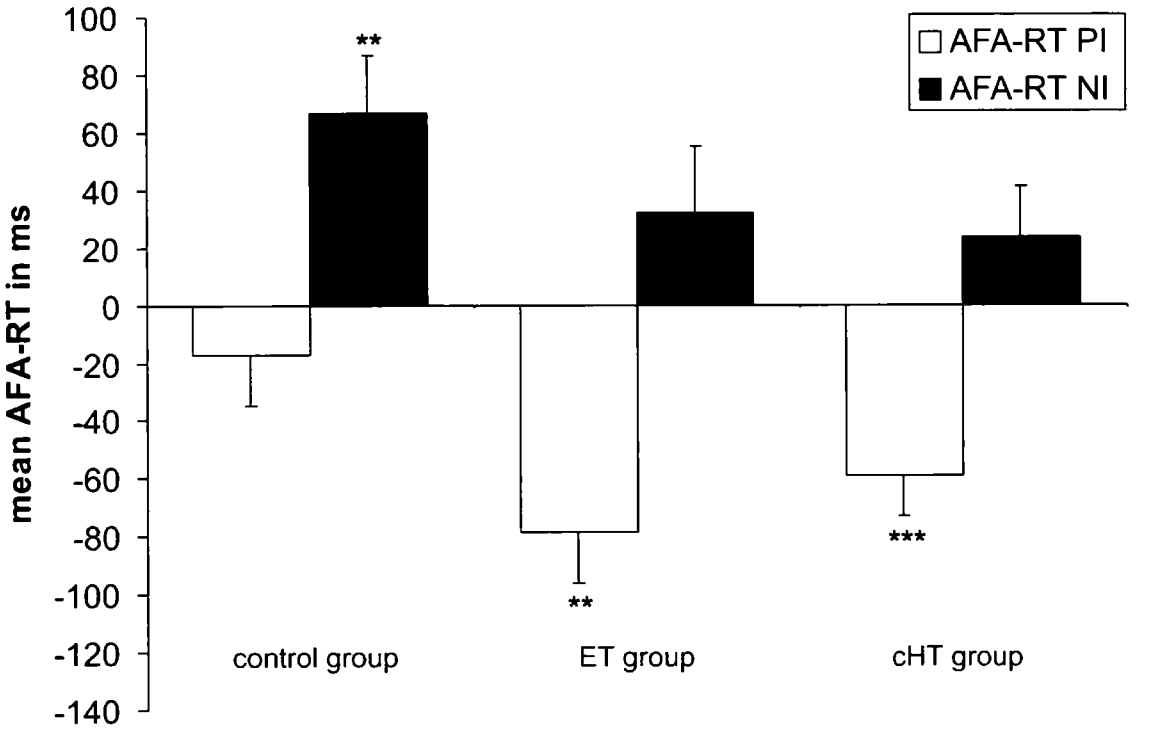

Fig. 3. Mean AFA in ms (± SEM) for the control group, ET group, and cHT group in the physical-identity task (white bars) and name-identity task (black bars). * marks simple effects between trial types per group and per task with *** $p \leq .001$; ** $p \leq .01$.

The corresponding analysis of accuracy revealed a significant main effect of Task with higher performance in the physical- than name-identity task ($F(1,61) = 20.96$, $p<.001$). This effect did not interact with Trial type and/or Group (all $F < 1.65$, n.s.).

Interhemispheric transfer time (Poffenberger task)

Median RTs were subjected to a 3 x 2 x 2 ANOVA with repeated measures, with Group (control, ET, and cHT group) as a between-participants factor, and Hand-use (right hand, left hand), and VHF (LVF, RVF) as within-participants factors. CUD was calculated as difference

between uncrossed and crossed trials. The analysis revealed a significant main effect of VHF ($F(1,62) = 35.47, p<.001$), with faster responses to stimuli presented in the RVF (M = 307.0 ± 6.31 ms) than to those presented in the LVF (M = 322.3 ± 6.56 ms). This effect was particularly pronounced when the right hand was used to respond ($F(1,62) = 6.07, p<.05$). Neither the main effect of Group nor any interaction with Group approached significance (all $F < 1.92$, n.s.). Although the mean CUD in the ET group (CUD = 2.2 ± 3.56 ms) was half the amount compared with the other groups (control group: CUD = 5.1 ± 2.30 ms; cHT group: CUD = 5.3 ± 2.80 ms), group differences in CUD did not approach significance ($F(2,62) = 0.28$, n.s.).

Relationships between sex hormones and interhemispheric tasks

To examine potential linear relationships between estradiol levels and interhemispheric integration (AFA), regression analyses were calculated. Including all three groups, the analyses neither revealed estradiol-levels to be significantly related to AFA across both tasks, nor AFA in the physical identity task nor AFA in the name-identity task (all $r < \pm.19$, n.s.). Significant relationships were also not found when regressions were restricted to the ET and cHT group (all $r < \pm .04$, n.s.). Similarly, estradiol-levels were also unrelated to CUD in the Poffenberger task (all $r < \pm .24$, n.s.).

Since an association between IHTT and the efficiency of interhemispheric integration has been suggested (e.g., Cherbuin & Brinkman, 2006), we also analyzed the relationship between CUD and AFA in the physical-identity task and the name-identity task. Again, none of the relationships was significant (all $r \pm .40$, n.s.).

Mood

Analyses of variance with Group (control, ET, and cHT group) as the between-participants factor revealed a significant difference between groups in seriousness ($F(2,62) = 4.53, p<.05$). The mean score in seriousness was marginally higher in the cHT group (M = 15.6 ± 1.85) than in the control group (M = 14.3 ± 2.32; $t(50) = -1.99, p<.06$). This difference was significant when compared with the ET group (M = 13.2 ± 2.42; $t(31) = -3.12, p<.01$). Group differences were not significant for cheerfulness and bad mood (both $F < 2.54$, n.s.).

Previous research has shown that mood can affect efficiency of interhemispheric processing (Compton & Mintzer, 2001). Moreover, it might be assumed that performance

differences between the cHT and the control group were a result of differences in seriousness. However, ANOVA results for interhemispheric integration and IHTT reported above remained the same if 'seriousness' was included in the analyses as a covariate. The results did not reveal any significant interactions with seriousness (all $F < 3.36$, n.s.). Moreover, mood scores were neither related to AFA nor IHTT (all $r \pm .11$, n.s.).

Discussion

In line with a recent previous study which also included postmenopausal women without HT (Bayer et al., 2008), postmenopausal women in the present study showed an AFA in the more demanding name-identity task but not in the less demanding physical-identity task. This finding is also in agreement with previous findings in younger samples which showed that interhemispheric integration becomes advantageous as task demands increase (e.g., Weissman & Banich, 2000; Weissman, Banich & Puente, 2000). However, as indicated by the significant interaction between Group and Trial type, groups of the present study responded differently on within- and across-field trials. Specifically, across both tasks, postmenopausal women using HT performed better on within- than across-field trials (WFA) whereas the control group without HT showed the opposite pattern with faster responses on across- than within-field trials (AFA). The IHTT as estimated by CUD in the Poffenberger task did not differ between groups. Thus, the present findings revealed only the AFA but not IHTT to be affected by HT in postmenopausal women.

The two HT groups in the present study did not differ in interhemisphric integration but rather showed an almost identical AFA under all conditions. In line with the results of Bayer and Erdmann (2008) who found an effect of ET on FCAs, this finding suggest that exogenous E is the key agent in modulating the functional brain organization in postmenopausal women. However, estradiol-levels were not directly related to performance measures in the present study. This might be because the estradiol assay used in the present study has a minimal cross-reactivity to other E-metabolities and thus does not reflect total E exposure. Yet, ET affects a wide range of E-metabolites (e.g., Mueck, Seeger, Gräser, Oettel, & Lippert, 2001; Mueck, Seeger & Wallwiener, 2002). For example, estrone levels are known to increase as result of ET (e.g., Gleason, Carlsson, Johnson, Atwood, & Asthana, 2005). Although the neurobiology of estrone is not completely clear, findings from animal studies indicate that estrone can also exert neuromodulatory effects via cell membrane-mediated pathways

(Shughrue & Merchenthaler, 2003). This suggests that differences in AFA between groups of the present study result from differences in E-metabolites other than estradiol.

The additional administration of gestagens in the cHT group revealed almost identical results, suggesting that P is not directly involved in modulating the AFA. This is in agreement with a recent study which found P levels not to be related to cycle-related fluctuations in AFA in normally cycling women (Bayer et al., 2008). However, the conclusion about possible P-related effects in the present study has its limitations. Except for one participant, all women of the cHT group received synthetic gestagens (see Table 1). It has been shown that these substances are not metabolised to P and hence cannot be detected by commercial available P assays (e.g., Kuhl, 2006). Although P metabolism is affected by administration of synthetic gestagens, it is unclear as to whether possible central effects are similar to those of endogenous P.

The results of the present study make it unlikely that interhemispheric integration as such is affected by HT. An efficient interhemispheric integration is reflected by changes in AFA with varying task demands rather than by an overall AFA per se (e.g., Banich & Belger, 1990; Weissman & Banich, 2000). For example, it has been shown that a large WFA can shift task-dependently to a strongly reduced difference between within- and across-field performance rather than to a significant AFA (Weissman & Banich, 2000). This is exactly what has been found in both HT groups of the present study, indicating an increase in benefits of interhemispheric integration as task demands increase. Thus, regardless of the within/across difference in the less demanding task, all three postmenopausal groups of the present study showed an efficient interhemispheric integration which becomes advantageous in the more demanding task.

The present study rather suggests that it is the *intra*hemispheric processing, in particular, which is enhanced in postmenopausal women taking HT. Specifically, the present results suggest a HT-related improvement of cognitive processing within each hemisphere which seems to be accompanied by a smaller need to recruit additional brain resources in the contralateral hemisphere, reducing the relative benefits of across-hemisphere processing. This might explain why no AFA occurred in both HT groups. Thus, in contrast to our prediction, our results suggest that sex hormonal therapy in postmenopausal women increases the efficiency of *intra*hemispheric processing, whereas *inter*hemispheric integration seems to be essentially unaffected by HT.

It could be assumed that beneficial effects of HT become especially pronounced at higher levels of task demands. However, this has not been found in the present study. The present findings rather suggest that postmenopausal women benefit from HT even when task demands are relatively low.

The idea of HT-related effects on intrahemispheric processing finds further support by two recent studies investigating the effects of HT on FCAs in postmenopausal women (Bayer & Erdmann, 2008; Bayer & Hausmann, in press). In both studies it was the intrahemispheric functioning, and right hemispheric functioning in particular, which was affected by HT leading to reduced asymmetries in the verbal and visuo-spatial domain, respectively. Although it has been suggested that interhemispheric integration and FCAs rely on different callosal processes (Bayer et al., 2008), these findings indicate that changes in functional brain organization in postmenopausal women are mediated by HT-related alterations in intrahemispheric processing.

A recent study examined interhemispheric integration in younger women across the menstrual cycle and postmenopausal women without HT (Bayer et al., 2008). Postmenopausal women without HT in the present and the previous study revealed a robust AFA in the Banich-Belger task. Notably, AFA in younger women fluctuated across the menstrual cycle. Specifically, Bayer et al. (2008) found a substantial AFA in normally cycling women during the luteal phase in which E and P levels are high, whereas the AFA was strongly reduced during menses when sex hormone levels are similarly low as in postmenopausal women without HT (Bayer et al., 2008). This difference has been explained by age-related neuromorphological changes including a decrease in efficiency of intrahemispheric rather than interhemispheric processing (Bayer et al., 2008). Consistent with this idea, within-field performance seems disproportionately impaired compared with across-field performance in postmenopausal women without HT in the present study, resulting in a substantial AFA in the more demanding task. In fact, it has been shown that older adults benefit more from interhemispheric interaction than younger adults (Reuter-Lorenz & Stanczak, 2000; Banich & Brown, 2000), indicating that additional recruitment of brain areas via transcallosal pathways serves as a compensatory mechanism to counteract age-related deficits in cognitive functions (e.g., Cabeza, Anderson, Locantore & McIntosh, 2002).

In contrast to the HT-related effects reported in the present study, an increase in sex hormones in younger women during the luteal phase seems to modulate across-hemisphere processing, resulting in an enhanced AFA. Thus, the AFA is affected by both menstrual cycle-

and HT-related changes in sex hormone levels, but probably through different mechanisms. The comparison between sex hormonal effects in normally cycling women and postmenopausal women, however, must be tentative. For example, in normally cycling women levels of endogenous estradiol are increased. However, in postmenopausal women, exogenous E, for example conjugated E (CE), is mainly metabolized to estrone which might differently affect neural networks underlying interhemispheric integration. Moreover, synthetic gestagens as used within a cHT are known to have pharmacological characteristics different from those of endogenous P in normally cycling women. For example, norethisterone acetate (NEA) and medroxyprogesterone acetate (MPA) are endowed with an affinity to androgen-receptors (AR) thereby exerting androgenic effects. Furthermore, all synthetic gestagens used in the cHT group of the present study are known to exhibit anti-estrogenic effects (e.g., Schumacher et al., 2007). Such properties have not been demonstrated for endogenous P. In addition, synthetic gestagens differentially affect sex hormone-binding globulin (SHBG)- levels which in turn influence circulating hormone levels (e.g., Campagnoli 2005, Kuhl, 2006, Wiegratz & Kuhl, 2004). These differences in sex hormonal exposure between normally cycling women and postmenopausal women taking HT might explain divergent behavioural outcomes. Finally, it should be noted that the brain of postmenopausal women may respond differently to changing levels of sex hormones compared with the younger female brain (e.g., Spencer, Waters, Romeo, Wood, Milner, & McEwen, 2008). For example, animal research has shown that aging might be accompanied by a loss of estrogen receptors resulting in a lower sensitivity to estrogen (e.g., Adams, Fink, Shah, Janssen, Hayashi, Milner, et al., 2002). Similar changes in receptor densitiy with increasing age might also account for differences in menstrual cycle-related and HT-related changes in AFA between younger (Bayer et al., 2008) and postmenopausal women (present study), respectively.

It is possible that HT-related effects in postmenopausal women are a result of organizing effects of HT rather than activating effects. For example, it has been suggested that the duration of RT affects cognitive performance in postmenopausal women (e.g., Jacobs, Tang, Stern, et al., 1998). In the present study, however, HT-duration and AFA were not related (all $r \pm 2.5$, n.s.).

Compton & Mintzer (2001) have shown that mood, i.e. worry and evaluation stress, can affect the AFA. However, such effects did not apply to the present findings for several reasons. Although the present study revealed group differences in one mood scale, i.e. seriousness, it was the cHT group that differed in seriousness from both the ET group (and

controls). However, the AFA was almost identical between both HT groups for all conditions. Moreover, Seriousness as a covariate in the statistical analyses did not change the pattern of results. In addition, the AFA in postmenopausal women was unrelated to any of the applied mood scales.

Finally all three postmenopausal groups were matched according to age. This is important to note because women taking ET were hysterectomized. In a number of cases, this surgery is applied to younger women before reaching natural menopause. The ET group of the present study, however, did not differ in age from the cHT group and controls, indicating that age effects are not confounded with the results. This is further supported by an additional analysis including age as a covariate which did not change the results. All three groups did also not differ in handedness and education level, precluding the possibility that differences in these factors were responsible for group differences in interhemispheric integration. Because several confounding variables were controlled, the present study strongly suggests that differences between postmenopausal women occur as a consequence of HT and its activating effects on functional brain organization.

IHTT as estimated by CUD was not affected by HT. This result also suggests that interhemispheric processes are not affected by HT. Bayer et al. (2008) investigated IHTT in younger women across the menstrual cycle and also found no sex hormonal effects on IHTT. However, it is unclear whether these negative findings indicate that IHTT is not under sex hormonal control or whether CUDs based on response times are simply not sensitive enough to detect hormonal effects. In fact, it has been shown that IHTT as measured by event-related potentials can differ between sexes with women showing more symmetric and shorter overall IHTT than men (Nowicka & Fersen. 2001; Moes, Brown, & Minnema, 2007) which might indicate that sex hormones can modulate IHTT.

In sum, the present study provides the first evidence that HT in postmenopausal women affects the relative efficiency of interhemispheric integration as measured by the Banich-Belger task, probably as a result of HT-related enhancement of within-hemisphere functioning. Although E- and P-levels were not directly related to interhemispheric integration, our results suggest an important mediating role of HT. These findings indicate that HT in postmenopausal women may protect against a normal age-related decrease in the efficiency of intrahemispheric processing, and hence, provide further support for the controversial idea that HT improves various brain functions.

Acknowledgements

The authors thank Charles A. Heywood for his valuable comments and all participating women for their cooperation. This work is supported by grant HA 3285/4-1 of the Deutsche Forschungsgemeinschaft (DFG) to M.H.

References

Adams, M. M., Fink, S. E., Shah, R. A., Janssen, W. G., Hayashi, S., Milner, T. A., et al. (2002). Estrogen and aging affect the subcellular distribution of estrogen receptor-alpha in the hippocampus of female rats. *Journal of Neuroscience, 22*(9), 3608-3614.

Banich, M. T., & Belger, A. (1990). Interhemispheric interaction: how do the hemispheres divide and conquer a task? *Cortex, 26*(1), 77-94.

Banich, M. T., & Brown, W. S. (2000). A life-span perspective on interaction between the cerebral hemispheres. *Developmental Neuropsychology, 18*(1), 1-10.

Barrett-Connor, E. (1998). Rethinking estrogen and the brain. *Journal of American Geriatrics Society, 46*(7), 918-920.

Bayer, U., Kessler, N., Güntürkün, O., & Hausmann, M. (2008). Interhemispheric interaction during the menstrual cycle. *Neuropsychologia, 46*, 2415-2422.

Bayer, U., & Erdmann, G. (2008). The Influence of Sex Hormones on Functional Cerebral Asymmetries in Postmenopausal Women. *Brain and Cognition, 67*, 140-149.

Bayer, U., & Hausmann, M. (2008). Estrogen therapy affects right hemisphere functioning in postmenopausal women. *Hormones and Behavior*. in press.

Berman, K. F., Schmidt, P. J., Rubinow, D. R., Danaceau, M. A., Van Horn, J. D., Esposito, G., et al. (1997). Modulation of cognition-specific cortical activity by gonadal steroids: a positron-emission tomography study in women. *Proceedings of the National Academy of Sciences of the United States of America, 94*(16), 8836-8841.

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*(1), 131-138.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Campagnoli, C., Abba, C., Ambroggio, S., & Peris, C. (2005). Pregnancy, progesterone and progestins in relation to breast cancer risk. *Journal of Steroid Biochemistry and Molecular*

Biology, 97(5), 441-450.

Compton, R. J., Costello, C., & Diepold, J. (2004). Interhemispheric integration during the menstrual cycle: failure to confirm progesterone-mediated interhemispheric decoupling. *Neuropsychologia, 42*(11), 1496-1503.

Compton, R. J., & Mintzer, D. A. (2001). Effects of worry and evaluation stress on interhemispheric interaction. *Neuropsychology, 15*(4), 427-433.

Corballis, M. C. (2002). Hemispheric interactions in simple reaction time. *Neuropsychologia, 40*(4), 423-434.

Craig, M. C., Maki, P. M., & Murphy, D. G. (2005). The Women's Health Initiative Memory Study: findings and implications for treatment. *Lancet Neurology, 4*(3), 190-194.

Gleason, C. E., Carlsson, C. M., Johnson, S., Atwood, C., & Asthana, S. (2005). Clinical pharmacology and differential cognitive efficacy of estrogen preparations. *Annals of the New York Academy of Sciences, 1052*, 93-115.

Hampson, E. (1990a). Estrogen-related variations in human spatial and articulatory-motor skills. *Psychoneuroendocrinology, 15*(2), 97-111.

Hampson, E. (1990b). Variations in sex-related cognitive abilities across the menstrual cycle. *Brain and Cognition, 14*(1), 26-43.

Hausmann, M. (2005). Hemispheric asymmetry in spatial attention across the menstrual cycle. *Neuropsychologia, 43*(11), 1559-1567.

Hausmann, M., Becker, C., Gather, U., & Güntürkün, O. (2002). Functional cerebral asymmetries during the menstrual cycle: a cross-sectional and longitudinal analysis. *Neuropsychologia, 40*(7), 808-816.

Hausmann, M., & Güntürkün, O. (2000). Steroid fluctuations modify functional cerebral asymmetries: the hypothesis of progesterone-mediated interhemispheric decoupling. *Neuropsychologia, 38*(10), 1362-1374.

Hausmann, M., Tegenthoff, M., Sanger, J., Janssen, F., Güntürkün, O., & Schwenkreis, P. (2006). Transcallosal inhibition across the menstrual cycle: A TMS study. *Clinical neurophysiology: Official journal of the International Federation of Clinical Neurophysiology, 117*(1), 26-32.

Heister, G., Landis, T., Regard, M., & Schroeder-Heister, P. (1989). Shift of functional cerebral asymmetry during the menstrual cycle. *Neuropsychologia, 27*(6), 871-880.

Hogervorst, E., Williams, J., Budge, M., Riedel, W., & Jolles, J. (2000). The Nature of the Effects of Female Gonadal Hormone Replacement Therapy on Cognitive Function in Postemnopausal Women: A Meta-Analysis. *Neuroscience 101*(3), 485-512.

Jacobs, D. M., Tang, M. X., Stern, Y., Sano, M., Marder, K., Bell, K. L., et al. (1998). Cognitive function in nondemented older women who took estrogen after menopause. *Neurology, 50*(2), 368-373.

Jäncke, L. (2002). Does "callosal relay" explain ear advantage in dichotic monitoring? *Laterality, 7*(4), 309-320.

Jewell, G., & McCourt, M. E. (2000). Pseudoneglect: a review and meta-analysis of performance factors in line bisection tasks. *Neuropsychologia, 38*(1), 93-110.

Kuhl, H. (2006). *Klimakterium, Postmenopause und Hormonsubstitution.* Bremen, London, Boston: UNI-MED Verlag AG.

Low, L. F., & Anstey, K. J. (2006). Hormone replacement therapy and cognitive performance in postmenopausal women--a review by cognitive domain. *Neuroscience and Biobehavioral Reviews, 30*(1), 66-84.

Maki, P. M., Zonderman, A. B., & Resnick, S. M. (2001). Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. *American Journal of Psychiatry, 158*(2), 227-233.

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*(5), 717-724.

Mead, L. A., & Hampson, E. (1997). Turning bias in humans is influenced by phase of the menstrual cycle. *Hormones and Behavior, 31*(1), 65-74.

Moes, P. E., Brown, W. S., & Minnema, M. T. (2007). Individual differences in interhemispheric transfer time (IHTT) as measured by event related potentials. *Neuropsychologia, 45*(11), 2626-2630.

Mueck, A. O., Seeger, H., Gräser, T., Oettel, M., & Lippert, T. H. (2001). The Effects of Postmenopausal Hormone Replacement Therapy and Oral Contraceptives on the Endogenous Estradiol Metabolism. *Hormone and Metabolic Research, 33*, 744-747.

Mueck, A. O., Seeger, H., & Wallwiener, D. (2002). Impact of hormone replacement therapy on endogenous estradiol metabolism in postmenopausal women. *Maturitas, 43*(2), 87-93.

Nowicka, A., & Fersen, E (2001). Sex-related differences in interhemispheric transmission time in the human brain. *Neuroreport, 12*(18), 4171-4175.

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

Poffenberger, A.T. (1912). Reaction time to retinal stimulation with special reference to the time lost in conduction through nerve centres. *Archives of Psychology, 23*, 1-73.

Reuter-Lorenz, P. A., & Stanczak, L. (2000). Differential effects of aging on the functions of the corpus callosum. *Developmental Neuropsychology, 18*(1), 113-137.

Rode, C., Wagner, M., & Güntürkün, O. (1995). Menstrual cycle affects functional cerebral asymmetries. *Neuropsychologia, 33*(7), 855-865.

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*(9), 869-874.

Schumacher, M., Guennoun, R., Ghoumari, A., Massaad, C., Robert, F., El-Etr, M., et al. (2007). Novel perspectives for progesterone in hormone replacement therapy, with special reference to the nervous system. *Endocrine Reviews, 28*(4), 387-439.

Shughrue, P. J., & Merchenthaler, I. (2003). Estrogen prevents the loss of CA1 hippocampal neurons in gerbils after ischemic injury. *Neuroscience, 116*(3), 851-861.

Spencer, J. L., Waters, E. M., Romeo, R. D., Wood, G. E., Milner, T. A., & McEwen, B. S. (2008). Uncovering the mechanisms of estrogen effects on hippocampal function. *Frontiers in Neuroendocrinology, 29*(2), 219-237.

Weissman, D. H., & Banich, M. T. (2000). The cerebral hemispheres cooperate to perform complex but not simple tasks. *Neuropsychology, 14*(1), 41-59.

Weissman, D. H., Banich, M. T., & Puente, E. I. (2000). An unbalanced distribution of inputs across the hemispheres facilitates interhemispheric interaction. *Journal of the International Neuropsychological Society, 6*(3), 313-321.

Wiegratz, I., & Kuhl, H. (2004). Progestogen therapies: differences in clinical effects? *Trends in Endocrinology and Metabolism, 15*(6), 277-285.

Wisniewski, A. B. (1998). Sexually-dimorphic patterns of cortical asymmetry, and the role for sex steroid hormones in determining cortical patterns of lateralization. *Psychoneuroendocrinology, 23*(5), 519-547.

Zaidel, E. (1995). Interhemisphesric transfer in the split brain: Long-term status following complete cerebral commissurotomy. In R. J. Davidson, & K. Hugdahl (Eds.), *Brain Asymmetry* (pp. 491–532). Cambridge, MA: MIT Press.

IV Estrogen therapy affects right hemisphere functioning in postmenopausal women

Ulrike Bayer & Markus Hausmann

Department of Psychology, Durham University, Durham, United Kingdom

Abstract

It has been suggested that hormone therapy (HT) in postmenopausal women differentially affects verbal and visuo-spatial abilities which mainly rely on left hemisphere (LH) and right hemisphere (RH) functioning, respectively. Thus, it seems likely that HT-related effects on cognition are driven by associated hormonal changes and their impact on functional brain organization, and functional cerebral asymmetries (FCAs) in particular. The present study investigated HT-related effects on FCAs in sixty-seven postmenopausal women who received hormone therapy either with estrogen (E) alone (n=14), an E-gestagen combination (n= 22) or without HT (control group, n=31). Saliva levels of free E and progesterone (P) were analyzed using chemiluminescence assays. FCAs were measured with the visual half-field (VHF) technique using a word matching and a figural comparison task. In agreement with previous results, a postmenopausal control group showed a left hemisphere (LH) advantage in the verbal task and a right hemisphere (RH) advantage in visuo-spatial processing. In contrast, both HT groups revealed significantly reduced FCAs in the figural comparison task as a result of an E-related decrease in RH performance. The findings suggest that E-therapy in postmenopausal women can affect visuo-spatial abilities by modulating the functional brain organization and RH functioning in particular.

Hormones and Behavior, 2008, 55, 228-234.

Introduction

Hormone therapy (HT) in postmenopausal women has been shown to affect various cognitive functions. However, there is an ongoing debate about the direction of these effects. While some studies reported positive effects of HT on cognition (see Hogervorst et al., 2000, for a review), others found no effect (e.g., Low and Anstey, 2006) or even negative effects (e.g., Craig et al., 2005; Hogervorst et al., 2000; Low and Anstey, 2006). These inconsistencies are most likely a result of differences in study design, participant's age and general health status (e.g., Barrett-Connor, 1998; Maki et al., 2001), and most importantly, the cognitive domains that have been assessed. For example, some studies revealed detrimental effects of HT in postmenopausal women on the global cognitive status (e.g., Rapp et al., 2003; Shumaker et al., 2004). Studies which have differentiated between specific cognitive domains generally found only some cognitive abilities to be sensitive to HT, including verbal and visuo-spatial abilities (for review see Maki and Hogervorst, 2003). However, these studies have also yielded inconsistent findings, with some studies rather suggesting a specific enhancement in verbal but not visual-spatial cognition (e.g., Maki et al., 2001, Wolf and Kirschbaum, 2002). One study reported beneficial effects of HT in a visuo-spatial task, i.e., figural memory, but deleterious effects on verbal processing, i.e., verbal learning and memory (Resnick et al., 2006). These findings suggest that HT affects verbal and visuo-spatial domains differently. Due to the fact that verbal and visuo-spatial processing respectively rely on left hemisphere (LH) (e.g., Beaumont, 1982) and right hemisphere (RH) functioning (e.g., Kimura, 1966), it seems likely that sex hormonal treatment in postmenopausal women has diverse effects on functional brain organization, and hemispheric asymmetries in particular. In fact, a number of imaging studies indicate that HT modulates functional brain organization during cognitive task performance (see Maki and Resnick, 2001, for a review). For example, differences in brain activation pattern between postmenopausal women with and without HT have been shown for brain regions that are involved in memory processing, e.g. the parahippocampal gyrus and the inferior and dorsal frontal gyrus (e.g., Maki and Resnick, 2001). Since these studies have mainly focused on specific cognitive tasks, they are, however, less revealing as to which hemisphere is more affected by HT in postmenopausal women.

A large body of evidence has shown that changing levels of sex hormones, i.e. estrogen (E) and progesterone (P), in particular, affect functional cerebral asymmetries (FCAs) (Wiesniewski, 1998). This has been specifically investigated in younger normally cycling women because their endogenous hormone levels fluctuate dramatically across the menstrual

cycle (Bibawi et al., 1995; Hampson, 1990a, 1990b; Hausmann et al., 2002; Hausmann and Güntürkün, 2000; Heister et al., 1989; McCourt et al., 1997; Mead and Hampson, 1996; Rode et al., 1995; Sanders and Wenmoth, 1998). Although contradictions exist (Chiarello et al., 1989; Compton and Levine, 1997; Hampson, 1990a, 1990b;), the majority of findings indicate cycle-related decreases in FCAs, suggesting a more bilateral lateralization during phases of high levels of E and/or P in the follicular and luteal phase and enhanced FCAs during menses when sex hormone levels are low (Hausmann and Güntürkün, 2000; Hausmann et al., 2002; Heister et al., 1989; Rode et al., 1995). This observation is in line with the results of one study which additionally included postmenopausal women without HT as a control group (Hausmann and Güntürkün, 2000). Postmenopausal women who have similarly low levels of E and P as younger women during menses showed similarly strong FCAs. Notably, in contrast to cycle-related dynamic changes in FCAs in younger women, FCAs in postmenopausal women remained stable over corresponding time intervals, probably as a result of a stable hormonal environment.

The question as to whether FCAs might be affected by postmenopausal HT has so far been addressed by only one study (Bayer and Erdmann, 2008). The authors tested postmenopausal women with and without HT on a word-matching task using the visual half-field technique. Interestingly, this study found reduced verbal asymmetries in women taking E only (estrogen therapy, ET) due to an improvement of right hemisphere (RH) performance. According to these results, a beneficial effect of E on verbal processing might be explained by an additional recruitment of RH verbal capacities. However, this study did not measure E- and P-levels from saliva or blood samples, and thus, no direct relationship between sex hormone levels and LH and/or RH performance has been investigated.

To investigate HT-related effects on hemispheric differences, the present study tested postmenopausal women who did or did not receive HT. To separate the effects of E alone from those of E plus P in combination, women with HT were further subdivided into two groups receiving either ET or a combined hormone therapy (cHT) containing E and a synthetic gestagen. Additionally, free estradiol- and P-levels were measured using chemiluminescence assays from saliva samples. To investigate FCAs, participants performed a word matching task and a figural comparison task that are known to predominantly involve LH and RH processes, respectively (e.g., Hausmann and Güntürkün, 2000; Hausmann et al., 2002; Rode et al., 1995). Based on previous findings (Bayer and Erdmann, 2008; Hausmann and Güntürkün, 2000), women without HT were expected to show typically strong hemispheric differences. According to previous findings in normally cycling women (e.g.,

Hausmann and Güntürkün, 2000; Hausmann et al., 2002; Heister et al, 1989; Rode et al., 1995) and postmenopausal women using HT (Bayer and Erdmann, 2008), we expected a HT-related reduction in FCAs.

Method

Participants

Sixty-seven postmenopausal women aged between 46 and 71 years (M = 58.1 years, SD = 6.35) participated in this study. All participants were right-handed as determined by the Edinburgh-Inventory (Oldfield, 1971). The asymmetry-index provided by this test is calculated as ((R-L)/(R+L)) x 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 87.4 (SD =18.66; range: 10.0 – 100.0).

All participants were native German speakers. Women who had used any medication which could have affected the central nervous system during the last 6 months before testing were excluded. All participants had normal or corrected to normal visual acuity and were naïve as to the experimental hypotheses. Participants were recruited by announcements and were paid for their participation.

Experimental Groups

Based on their regular use or non-use of HT, women were assigned to either one of three groups: (1) the control group consisted of 31 women who had been in their menopause for at least one year (M = 6.8 years, SD = 4.92) and were not using any form of hormone therapy; (2) the ET group consisted of 14 women who were currently undergoing a continuous estrogen therapy (ET); and (3) the cHT group consisted of women who received either a continuous (n = 19) or a cyclic cHT (n = 3). Participants of the latter subgroup were tested during the second phase of treatment no earlier than the fourth day of additional gestagen treatment. For the ET group, mean duration of hormonal treatment was 6.7 years (SD = 6.11, range: 0.8 – 18.0 years). For the cHT group, mean duration was 4.5 years (SD = 4.15, range: 0.3 – 14.0). There was no difference between the two hormone groups in HT duration, $t(34) = 1.31$, n.s. Details about hormonal therapies are shown in Table 1.

Group	Hormone regimen	dosage	Route of administration	treatment	N
	CE	0.6 mg	oral	continous	2
	CE	1.25 mg	oral	continous	2
	estradiol	25 µg	transdermal	continous	2
ET	**estradiol**	37.5 µg	transdermal	continous	1
	estradiol	50 µg	transdermal	continous	3
	estradiol	100 µg	transdermal	continous	1
	estradiol	0.6 mg	percutane	continous	1
	estradiolvalerate	4 mg	intramuscular	continous	2
	estradiol + NEA	1 mg + 0.5 mg	oral	continous	7
	estradiol + NEA	2 mg + 1.0 mg	oral	continous	3
	estradiol + dienogest	1 mg + 2 mg	oral	continous	3
	estradiol + drospirenon + NEA	1 mg + 2 mg + 1mg	oral	continous	1
cHT	**estradiol + NEA**	25 µg + 125 µg	transdermal	continous	3
	estradiol + NEA	0.5 mg + 5 mg	percutane + oral	continous	1
	estradiol + progesterone	0.6 mg + 100 mg	percutane + oral	continous	1
	CE + medrogestone	0.3 mg + 5 mg	oral	cyclic	2
	CE + MPA	0.6 mg + 5 mg	oral	cyclic	1

Table 1. Number of participants and types of hormone therapy in the estrogen therapy (ET) group and the combined HT (cHT) group. *Note.* Conjugated estrogens (CE), norethisterone acetate (NEA), medroxyprogesterone acetate (MPA).

Groups did not differ with respect to age, handedness, years of education, and years after menopause (Table 2).

	C group	ET group	cHT group	$F(2,64)$	p
Mean age (in years)	58.7 (5.69)	58.9 (7.11)	56.7 (6.79)	0.79	n.s.
Mean handedness (EHI score)	86.5 (20.25)	82.5 (18.85)	91.8 (15.87)	1.12	n.s.
Mean years of education	14.1 (2.86)	13.0 (2.80)	14.0 (2.50)	0.82	n.s.
Mean years after menopause	6.8 (4.92)	11.4 (8.29)	7.7 (6.46)	2.70	n.s.

Table 2. Descriptives (mean and standard deviation) for the control (C) group, the estrogen therapy (ET) group, and the combined HT (cHT) group and results of the analyses of variance with the between-participants factor Group (control, ET, and cHT group) for each of the parameters.

Tasks

Two visual half-field (VHF) tasks were used in the present study: a word matching task and a figural comparison task which respectively are known to reveal a robust advantage for the right visual field (RVF), corresponding to the LH, and the left visual field (LVF), corresponding to the RH (Hausmann et al., 2002, Hausmann and Güntürkün, 1999, 2000; Hausmann et al., 2003). The VHF technique provides a valid and reliable measure of FCAs (e.g., Krach et al., 2006). This is supported by recent functional neuroimaging data which indicate a high correlation between FCA patterns assessed by the tachistoscopic VHF technique and the asymmetrical BOLD responses as revealed by functional magnetic resonance imaging (fMRI) (e.g., Hunter and Brysbaert, 2008). The word matching task and figural comparison task used here have been previously shown to dominantly activate cortical areas in the left and right hemisphere. For example, fMRI revealed the left inferior frontal gyrus (IFG) as the central functional area for the word matching task, both in female and in male subjects (Weis et al., submitted). The IFG has been shown to be selectively involved with the processing of semantic aspects of verbal information, word reading and internal speech (Dapretto and Bookheimer, 1999; Fiez and Petersen, 1998; Hinke et al., 1993).

A pool of 60 German nouns was used for the word matching task, consisting of four to seven letters, and selected for a high degree of abstraction (Baschek et al., 1977) to maximise the left hemisphere advantage. For the figural comparison task, 60 black irregular polygons with at least eight edges were constructed using the Paintshop® software. All stimuli were presented in a white frame. Each task comprised 60 trials which were performed in two

blocks of 30 trials with a brief resting period between blocks. Within each block stimuli were arranged pseudorandomly, with the limitation that each condition involving the type of trial (same vs. different) and VHF (LVF vs. RVF) were presented equally often used and no more than 3 consecutive trials were in any given condition. Prior to each block the participants performed 10 practice trials which were excluded from the analysis. The order of the two tasks was balanced across participants.

Procedure

Before and after each session a sample of saliva was collected from all participants. Saliva estradiol- and P-levels were determined with chemiluminescence assay (CLIA) by an independent professional hormone laboratory, with commercially available hormone assays. For estradiol, intra-assay coefficients of variations (CVs) were 3.7% and 7.9%, inter-assay CVs were 5.9% and 13.9% for high and low estradiol-samples, respectively. For P, intra and inter-assay CVs were 2.3% to 6.0% and 8.4% to 18.8% for high and low P-samples, respectively.

Both tasks were presented by means of visual half-field (VHF) technique which was identical to that of previous studies (e.g. Hausmann et al., 2002; Hausmann and Güntürkün, 1999, 2000; Hausmann et al., 2003). The experiment started by placing the head of the seated participant on a chin rest at a distance of 57 cm from a monitor. Participants were instructed to keep head and body still during the whole experiment and to fixate a cross positioned at the center of the screen. All stimuli were presented for 185 ms within a frame 4.8 cm wide and 4.5 cm high (4.0° and 3.8° visual angle, respectively). The distance between the fixation cross and the inner edge of the frame was 2.6 cm (2.2° visual angle), which ensured a lateralised stimulus presentation to the left or to the right of the fixations cross.

Each trial began with presentation of a central fixation cross for 2 s followed by a centrally presented stimulus for 185 ms. Then, the fixation cross was presented again for 2 s. Next, a second stimulus was laterally presented in either the left or the right visual field. A subsequent question mark instructed the participants to decide as accurately and as quickly as possible with the index finger of one hand whether the two stimuli were same or different by pressing one of two predefined buttons on a keyboard. In mismatch trials of the word matching task, stimuli were identical with respect to the initial letter and to the number of letters. Response hand was changed after the first block of each task. The order of hand was balanced across participants.

For each task, FCA in accuracy and median response time (RT) of correct responses were analyzed using 3 x 2 analysis of variance (ANOVA) with repeated measures, with Group (control, ET, and cHT group) as the between-participants factor and VHF (left visual field, LVF and right visual field, RVF) as the within-participants factor.

Mood questionnaire

To control potential systematic variations in mood which might not only influence the performance on cognitive tasks but also FCAs (e.g., Compton and Levine, 1997), the State-Trait-Cheerfulness-Inventory (STCI-S18; Ruch et al., 1997) was administered to all participants prior to cognitive testing. The STCI-S18 measures three components of mood, i.e., cheerfulness, seriousness, and bad mood. The STCI-S18 includes six items for each these concepts. Response is given on a 4-point rating-scale (strongly disagree, 1; moderately disagree, 2; moderately agree, 3, and strongly agree, 4).

Results

Hormone assay

Three participants, two from the ET group and one from the cHT group, were excluded from further analyses. Despite of HT treatment, these participants did not show the expected increase in estradiol-levels. In fact, estradiol-levels were even below the detection limit (0.8 pg/ml) of the hormone essay. Sixty-four participants were included in the statistical analysis.

Estradiol- and P-levels were analyzed by analyses of variance (ANOVA) with the between-participants factor Group (control group, ET group, and cHT group). As expected, the ANOVA for estradiol-levels revealed a significant effect of Group ($F(2,61) = 9.03$, $p<.001$). Alpha-adjusted post hoc unpaired t-tests (Bonferroni) indicated estradiol-levels in the ET group ($t(41) = -2.45$, $p=.019$, one-tailed) and the cHT group ($t(50) = -4.54$, $p<.001$) to be significantly higher compared to the control group. The two HT groups did not differ in estradiol-levels ($t(31) = -1.27$, n.s.). Descriptive statistics are shown in Table 3.

	Estrogen	Progesterone
	M (SEM)	M (SEM)
C group (n = 31)	2.1 (0.39)	55.8 (8.14)
ET group (n = 12)	7.3 (3.55)	38.6 (8.23)
cHT group (n = 21)	14.9 (3.47)	42.4 (5.75)
Reference range	0.5 – 10.8	18.0 – 51.0

Table 3. Mean (M) and SEM of E- and P-levels (pg/ml) in the control (C) group, the estrogen therapy (ET) group, the combined HT (cHT) group, and reference range for salivary assay for postmenopausal women without HT.

The corresponding analysis for P-levels did not reveal significant differences between groups ($F(2,61) = 0.92$, n.s.). The cHT group revealed similarly low P levels as the control group and the ET group (see Table 3). The lack of group differences in P-levels can be explained by the fact that, with the exception of one woman, all participants of the cHT group received synthetic gestagens. It has been shown that these substances are neither transformed to endogenous P nor related to P-levels as measured by the P-assay (e.g., Kuhl, 2006).

Word matching task

Analysis of accuracy in the word matching task revealed a significant main effect of VHF ($F(1,61) = 66.38$, $p<.0001$) indicating a strong advantage for the RVF (mean ± SEM: M = 87.1 ± 1.18 %, LVF: 73.3 ± 1.29 %), corresponding to a predicted superior LH performance in this task. Neither the main effect of Group nor the interaction between VHF and Group approached significance (both $F < 0.33$, n.s., see Figure 1). Using the same task in postmenopausal women without HT, Hausmann and Güntürkün (2000) reported an overall accuracy of 80.5%. Similarly, the control group of the present study revealed an overall performance of 79.6%. Overall performance in the two hormone groups was 80.7%.

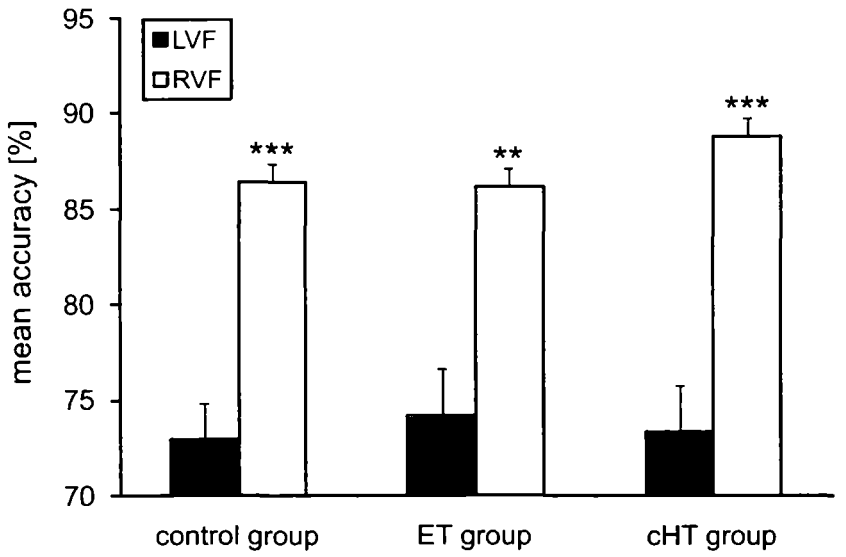

Fig. 1. Mean accuracy (± SEM) in the word matching task as a function of Group (control group, ET group, and cHT group) and VHF (LVF and RVF). * marks simple effects between VHFs per group with *** $p \leq .001$ and ** $p \leq .01$

The corresponding analysis for RTs did not reveal any significant effects (all $F < 0.24$, n.s.).

Figural comparison task

ANOVA for accuracy in the figural comparison task revealed a significant Group x VHF interaction ($F(2,61) = 3.22$, $p<.05$; see Figure 2).

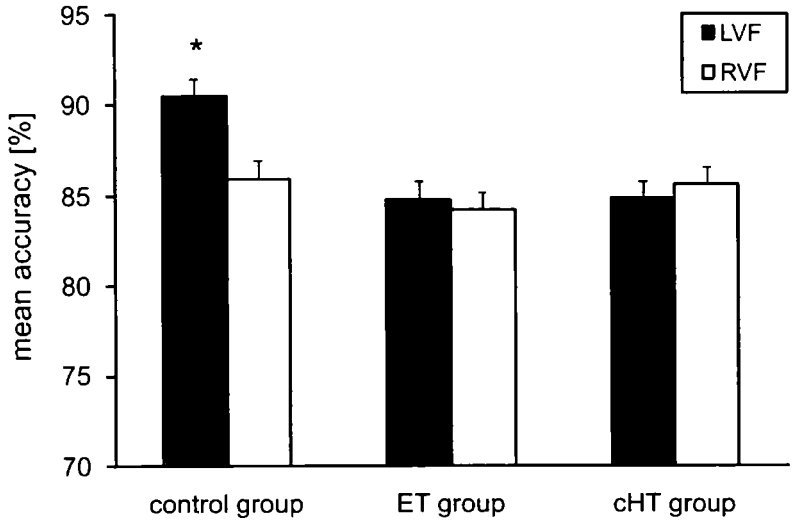

Fig. 2. Mean accuracy (± SEM) in the figural comparison task as a function of Group (control group, ET group, and cHT group) and VHF (LVF and RVF). * marks simple effects between VHFs per group with * $p \leq .05$

Alpha-adjusted post-hoc paired *t*-tests indicated a significant LVF advantage only in the control group ($t(30) = 3.92$, $p<.001$) but not in the ET group ($t(11) = 0.24$, n.s.) or cHT group ($t(20) = -0.39$, n.s.). Simple comparisons between groups for each VHF (alpha adjusted unpaired *t*-tests) revealed a significantly stronger LVF-advantage in the control group compared to the cHT group ($t(50) = 2.66$, $p=.011$). Although the LVF-advantage of the control group was also stronger than it was in the ET group, this effect only approached significance ($t(41) = 2.34$, $p=0.024$). The overall performance in the control group (88.2%) and the two HT groups (85.0%) was almost identical to that for postmenopausal women without HT on the identical task (85.5%) as previously reported by Hausmann & Güntürkün (2000).

The corresponding analysis for RTs also revealed a significant main effect of VHF (LVF: M = 1075.5 ± 26.48 ms, RVF: M = 1119.6 ± 23.24 ms; $F(1,61) = 7.41$, $p<.01$) with faster responses to stimuli presented in the LVF than to those presented in the RVF, corresponding to an expected superior RH performance in this task. For response times, no other effect approached significance (both $F < 0.31$, n.s.).

Relationships between sex hormones and behaviour

With respect to the significant interaction between Group and VHF for accuracies in the figural comparison task, sex hormone levels, and estradiol-levels in particular, were expected to be significantly related to performance measures. Pearson analyses revealed a significant negative relationship between estradiol and LVF/RH accuracy (r = -.25, n = 64, p<.05), indicating a decrease of LVF performance with increasing estradiol-levels. Estradiol-levels were not significantly related to accuracies in the RVF (r = -.11, n = 64, n.s.). Relationships between P-levels and accuracies in the figural comparison task were not significant (both r > -1.4, n = 64, n.s.).

Mood

The ANOVA with Group (control group, ET group and cHT group) as between-participants factor for the three concepts of mood revealed a significant difference between groups in seriousness (F(2,61) = 5.03, p<.01) but not in cheerfulness and bad mood (both F < 2.29, n.s.). The mean score in seriousness was higher in the cHT group (M = 15.5 ± 0.40) compared to the control group (M = 14.3 ± 0.42; t(50) = -1.91, p<.07) and the ET group (M = 13.0 ± 0.69; t(31) = -3.35, p<.01).

Previous research has shown that mood can affect perceptual asymmetries (e.g., Compton and Levine, 1997). Thus, it might be assumed that performance differences between the cHT and the control group were due to differences in seriousness. However, a reanalysis of the 3 x 2 ANOVA including the factor Seriousness as a covariate did not reveal a significant interaction between VHF and seriousness (all F(1,61 = 0.84, n.s.). Moreover, mood scores were neither significantly correlated with LVF/RH or RVF/LH performance (all r ± .14, n.s.).

Discussion

Overall, postmenopausal women in the present study revealed the expected LH and RH superiorities in the word matching (accuracy) and the figural comparison task (response time), respectively. Moreover, we found reduced FCAs, i.e., increased bilaterality, in the figural comparison task for both the ET and cHT group. Notably, estradiol levels were negatively related to accuracy in the dominant LVF/RH. Thus, the present results suggest that FCAs in postmenopausal women, and particularly RH functioning, as measured by the figural comparison task, are affected by HT and concomitant increases in estradiol. Although the

VHF technique gives only an estimate of FCAs, the present findings strongly suggest that HT-related behavioural changes are accompanied by alterations in brain activity. Using similar tasks, Weis et al. (submitted) found corresponding effects for behavioural measures and neuronal activity as measured with functional imaging (fMRI) as a result of sex hormonal changes across the menstrual cycle.

Our finding of significant hemispheric differences for word matching (accuracy) and figural comparison (accuracy and RT) in the control group is in line with previous findings in postmenopausal women without HT (e.g., Bayer and Erdmann, 2008; Hausmann and Güntürkün, 2000) which also showed LH and RH advantages for verbal and nonverbal processing, respectively. The permanent decrease in E and P levels after menopause seems to stabilize FCAs and corresponding VHF differences. The results of the present study also support the hypothesis of dynamic changes in FCA in younger women across the menstrual cycle which proposes that low levels of sex hormones are associated with typical lateralization patterns (e.g., Hausmann et al., 2002, Hausmann and Güntürkün, 2000; Heister et al., 1989).

The result of an estradiol-related reduction in hemispheric asymmetry in both the ET and the cHT group indicates that P might not be involved in modulating FCAs in postmenopausal women. This is in contrast to previous studies investigating younger women across hormonally distinct cycle phases. These studies have shown a P-related attenuation of asymmetries in normally cycling women during the midluteal phase (Hausmann and Güntürkün, 2000; Hausmann et al., 2002). It should be noted, however, that the conclusion about possible P-related effects and the comparison between single ET and cHT in the present study have limitations. Except for one participant, all women of the cHT group received synthetic gestagens (see Table 1). It has been shown that these substances are not metabolised to P and hence cannot be detected by commercial available P assays (e.g., Kuhl, 2006). Although P metabolism is affected by administration of synthetic gestagens, it is unclear whether possible central effects are similar to those reported for endogenous P. Moreover, women of the cHT group differed in the particular gestagens used (see Table 1). Different gestagens are known to have different pharmacological properties. For example, norethisterone acetate (NEA) and medroxyprogesterone acetate (MPA) are endowed with a similar affinity to androgen-receptors (AR) thereby exerting androgenic effects. Other gestagens (e.g., dionegest and medrogeston) show anti-androgenic effects with lower or even absent AR-affinity (e.g., progesterone). In addition, different gestagens can differentially affect sex hormone-binding globulin (SHBG)- levels which in turn influences circulating

hormone levels (e.g., Campagnoli 2005, Kuhl, 2006). Thus, we cannot rule out the possibility that P-related effects on FCAs are confounded by the heterogeneity of gestagen treatment in the cHT group.

The present study revealed estradiol levels to be related to changes in RH performance, leading to reduced FCAs for figural comparison in the two HT groups. Notably, the estradiol assay used in the present study has a minimal cross-reactivity to other E-metabolities and thus does not reflect total E exposure. However, ET affects a wide range of E-metabolites (e.g., Gleason et al., 2005; Mueck et al., 2002). For example, estrone has been shown to exert neuromodulatory effects via cell membrane-mediated pathways similarly to those of estradiol (Shughrue and Merchenthaler, 2003). Thus, we cannot rule out the possibility that other E-metabolites might also have contributed to the present results.

Our finding can be explained by an ET-mediated and estradiol-related modulation of either intra- or interhemispheric processing. The latter idea is based on the hypothesis that an attenuation of FCAs as found in younger women during the luteal phase of the menstrual cycle are a result of P-related modulations of interhemispheric inhibition (Hausmann and Güntürkün, 2000; Hausmann et al., 2002) which has been assumed to be a fundamental prerequisite for the manifestation of FCAs (e.g., Chiarello and Maxfield, 1996). In fact, one recent imaging study reported a reduced interhemispheric inhibition between homotopic brain areas along with reduced behavioural asymmetries in women during the follicular phase compared to menses (Weis et al., submitted) with the strength of interhemispheric inhibition to be significantly related to E-levels indicating that interhemispheric inhibition can be similarly affected by different sex hormones, i.e., E and P. This idea corresponds with the results of a transcranial magnetic stimulation (TMS) study which found a negative relationship between transcallosal inhibition and E- and P-levels during the follicular and luteal phase, respectively (Hausmann et al., 2006).

The present findings, however, are more suggestive of an HT-related modulation of intrahemispheric processing, and RH processing in particular. A selective modulation of RH processing due to HT has recently been proposed by one study which also tested postmenopausal women with and without HT (Bayer and Erdmann, 2008). The authors reported an enhanced RH performance for verbal processing leading to reduced FCAs in postmenopausal women using ET. At first glance, the finding from Bayer and Erdmann (2008) seems contradictory to the results of present study. However, this is not necessarily the case. It is possible that an enhanced verbal performance of the RH (Bayer and Erdmann,

2008) might be accompanied by a decrease in visuo-spatial processing (present study). This idea suggests that E-related effects on different functional domains do not occur independently. Rather, it is conceivable that a reorganization of the verbal domain also leads to modifications in another cognitive domain, e.g. in visuo-spatial cognition - a principle of functional brain organisation that has been proposed previously in a different context (Hausmann et al., 2004). In other words, ET after menopause seems to enhance verbal processing within the RH at the expense of visuo-spatial processing.

In contrast to Bayer and Erdmann (2008) however, the present study did not reveal HT-related changes in the verbal task. Although this contradicts our previous argument, it should be noted that the LH advantage in the word matching task was much more pronounced than the RH advantage in the figural comparison task. This is in line with the observation that particularly strongly lateralized tasks are less susceptible to hormone-related changes (e.g., Bibawi et al., 1995, Hausmann and Güntürkün, 2000). Moreover, the figural comparison task used in the present study has shown the most responsiveness to participant's sex and sex-hormonal changes (Hausmann and Güntürkün, 1999, 2000; Hausmann et al., 2002).

Nevertheless, the present results together with those reported by Bayer and Erdmann (2008) suggest that it is the RH in particular which is susceptible to E-therapy in postmenopausal women. The idea of divergent effects of HT on the RH suggests that ET enhances verbal abilities in general while suppressing visuo-spatial skills. Based on the present results, however, this conclusion must be tentative because the tasks used here are specifically designed to estimate relative performance differences between the two hemispheres and do not reflect an overall measure of visuo-spatial abilities.

The results of the present study can best be explained within the context of age-related neuromorphological changes (e.g., Sowell et al., 2003). For example, age-related changes have been found in parieto-occipital brain regions which are known to be involved in visuo-perceptual tasks (e.g., Puce et al., 1996). These changes have been suggested to be particularly pronounced within the RH and hence affect functions associated with the RH to a greater degree than those associated with the LH (e.g., Ellis and Oscar-Berman, 1989; Goldstein and Shelly, 1981). In line with this idea, several studies using visual-perceptual tasks found that the RH performance was more affected by aging than LH performance (e.g., Gerhardtstein et al., 1998; Rastatter and McGuire, 1990). In contrast, age-related changes in the morphology of the corpus callosum and associated alterations in interhemispheric integrity seem to be relatively small, particularly in older women (Cowell et al., 1992; Cowell et al.,

1994; Dubb et al., 2003; Suganthy et al., 2003; Sullivan et al., 2001). These findings suggest that RH functions are especially affected by aging and age-related effects. This is perhaps one reason why the RH is also more susceptible to HT-effects.

Age-related neuromorphological changes in postmenopausal women might also explain differences between the present study (see also Bayer and Erdmann, 2008) and studies of younger women during the menstrual cycle which tend to suggest sex hormonal modulation of interhemispheric interaction as the key mechanism for cycle-related changes in FCAs (e.g., Hausmann and Güntürkün, 2000; Hausmann et al., 2002, Weis et al., submitted). Thus, it seems that the functional brain organization is affected by both menstrual cycle- and HT-related changes in sex hormone levels, but probably through different underlying neural mechanisms.

We cannot rule out the possibility that HT-related effects in postmenopausal women in the present study are a result of long-term effects of HT. In fact, it has been suggested that length of HT exposure affects cognitive performance in postmenopausal women (e.g., Jacobs et al., 1998). Such long-term effects, usually referred to as the organizational effects, are likely to induce neuromorphological changes in specific brain structures and related functions (e.g., Sherwin and Henry, 2008). In the present study, however, HT duration was not significantly related to LH- and/or RH-performance in the figural comparison task (all $r \pm .08$, n.s.) This is in line with Bayer and Erdmann (2008) who also failed to find a relationship between length of HT exposure and performance parameters. Thus, it seems rather likely that HT-related effects on FCAs in postmenopausal women are transient and depend on the specific sex hormone levels present. These so-called activating effects of sex hormones, and E in particular, have been shown to act on the brain via multiple pathways. For example, it has been shown that E can modulate cerebral glucose metabolism and blood flow during the resting state in postmenopausal women (e.g., Maki and Resnick, 2001). An alteration in brain activity, i.e. resting frontal activity, has also been demonstrated in younger women during menses as compared to the high-E ovulatory phase (Hwang et al., 2008). These findings suggest that estradiol-related changes in FCAs in the present study might be a result of a hormonal modulation of the baseline activity. This has previously been suggested by McCourt et al. (1997) who assumed that high levels of sex hormones, and E in particular, tonically enhance overall cerebral function which may lower the threshold for phasic activation as induced by a given task (McCourt et al., 1997). However, this idea implies a general effect on both hemispheres rather than a task-specific effect on the RH as indicated by the present results (see also, Bayer and Erdmann, 2008). We are therefore inclined to believe that the ET-

mediated decrease in RH performance as found in the present study reflects a specific modulation of neuronal circuitries underlying visual-spatial processing within the RH.

Using a prototypical verbal and a visuo-spatial task which dominantly rely on the LH and RH respectively, the present study found a HT-related effect particularly for RH processing. Whether such an effect extends to other lateralized functions or is implicated only in specific RH processes has to be clarified. However, given the characteristic right hemispheric superiority in the visuo-spatial task used here, we are inclined to believe that other RH dominated functions might be similarly affected by HT in postmenopausal women.

Compton and Levine (1997) reported that cycle-related changes in mood can affect perceptual asymmetries. However, although groups differed on one mood subscale, i.e. seriousness, this cannot account for the present results. Firstly, it was the cHT group that differed in seriousness from both the ET group and the controls: However, the FCA patterns in both tasks were almost identical between HT groups. Moreover, seriousness used as a covariate in the statistical analyses did not change the pattern of results. Finally, relationships between mood scores and cognitive performance did not approach significance. Also, all three groups were well-matched for age, handedness, and education level, precluding the possibility that differences in these factors might be responsible for any group differences.

In sum, the present study revealed an E-related decrease in RH superiority in a visuo-spatial task leading to a reduced FCA. Together with previous results (Bayer and Erdmann, 2008), this finding suggests that HT differentially affects verbal and visuo-spatial processing within the RH. Due to the fact that several confounding variables were controlled, the present study further suggests that HT, and ET in particular, dominantly affects RH functioning in postmenopausal women via its activating effects on functional brain organisation. These changes in functional brain organization may be at least partly responsible for HT-related affects on specific cognitive abilities.

Acknowledgements

The authors thank Prof. Anne Campbell for her helpful comments on the manuscript and all participating women for their cooperation. This work is supported by grant HA 3285/4-1 of the Deutsche Forschungsgemeinschaft (DFG) to M.H.

References

Barrett-Connor, E., 1998. Rethinking estrogen and the brain. J Am Geriatr Soc. 46, 918-20.

Baschek, I. L., et al., 1977. Bestimmung der Bildhaftigkeit, Konkretheit und der Bedeutungshaltigkeit von 800 Substantiven. Z Exp Angew Psychol. 24, 353-96.

Bayer, U., Erdmann, G., 2008. The influence of sex hormones on functional cerebral asymmetries in postmenopausal women. Brain Cogn. 67, 140-9.

Bibawi, D., et al., 1995. Fluctuations of perceptual asymmetry across time in women and men: effects related to the menstrual cycle. Neuropsychologia. 33, 131-8.

Campagnoli, C., et al., 2005. Pregnancy, progesterone and progestins in relation to breast cancer risk. J Steroid Biochem Mol Biol. 97, 441-50.

Chiarello, C., Maxfield, L., 1996. Varieties of interhemispheric inhibition, or how to keep a good hemisphere down. Brain Cogn. 30, 81-108.

Compton, R. J., Levine, S. C., 1997. Menstrual cycle phase and mood effects on perceptual asymmetry. Brain Cogn. 35, 168-83.

Cowell, P. E., et al., 1992. A developmental study of sex and age interactions in the human corpus callosum. Brain Res Dev Brain Res. 66, 187-92.

Cowell, P. E., et al., 1994. Sex differences in aging of the human frontal and temporal lobes. J Neurosci. 14, 4748-55.

Craig, M. C., et al., 2005. The Women's Health Initiative Memory Study: findings and implications for treatment. Lancet Neurol. 4, 190-4.

Dapretto, M., Bookheimer, S.Y., 1999. Form and content: dissociating syntax and semantics in sentence comprehension. Neuron 24, 427-32.

Dolcos, F., et al., 2002. Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. Neurosci Biobehav Rev. 26, 819-25.

Dubb, A., et al., 2003. Characterization of sexual dimorphism in the human corpus callosum. Neuroimage 20, 512-9.

Ellis, R. J., Oscar-Berman, M., 1989. Alcoholism, aging, and functional cerebral asymmetries. Psychol Bull. 106, 128-47.

Fiez, J.A., Petersen, S.E., 1998. Neuroimaging studies of word reading. Proc. Natl. Acad. Sci. U S A 95, 914-21.

Gerhardstein, P., et al., 1998. Age-related hemispheric asymmetry in object discrimination. J Clin Exp Neuropsychol. 20, 174-85.

Gleason, C. E., et al., 2005. Clinical pharmacology and differential cognitive efficacy of estrogen preparations. Ann N Y Acad Sci. 1052, 93-115.

Goldstein, G., Shelly, C., 1981. Does the right hemisphere age more rapidly than the left? J Clin Neuropsychol. 3, 65-78.

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

Hampson, E., 1990. Variations in sex-related cognitive abilities across the menstrual cycle. Brain Cogn. 14, 26-43.

Hausmann, M., 2005. Hemispheric asymmetry in spatial attention across the menstrual cycle. Neuropsychologia. 43, 1559-67.

Hausmann, M., et al., 2002. Functional cerebral asymmetries during the menstrual cycle: a cross-sectional and longitudinal analysis. Neuropsychologia. 40, 808-16.

Hausmann, M., et al., 2004. Evidence for reduced hemispheric asymmetries in non-verbal functions in bilinguals. J. Neurolinguistics 17, 285-299.

Hausmann, M., Güntürkün , O., 1999. Sex differences in functional cerebral asymmetries in a repeated measures design. Brain Cogn. 41, 263-75.

Hausmann, M., Güntürkün , O., 2000. Steroid fluctuations modify functional cerebral asymmetries: the hypothesis of progesterone-mediated interhemispheric decoupling. Neuropsychologia. 38, 1362-74.

Hausmann, M. et al., 2003. Age-related changes in hemispheric asymmetry depend on sex. Laterality. 8, 277-90.

Hausmann, M., et al., 2006. Transcallosal inhibition across the menstrual cycle: A TMS study. Clin Neurophysiol. 117, 26-32.

Heister, G., et al., 1989. Shift of functional cerebral asymmetry during the menstrual cycle. Neuropsychologia. 27, 871-80.

Hinke, R.M., et al., 1993. Functional magnetic resonance imaging of Broca's area during internal speech. Neuroreport 4, 675-8.

Hogervorst, E., et al., 2000. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience. 101, 485-512.

Hunter, Z. R., Brysbaert, M., 2007. Visual half-field experiments are a good measure of cerebral language dominance if used properly: Evidence from fMRI. Neuropsychologia.

Hwang, R. J., et al., 2008. The resting frontal alpha asymmetry across the menstrual cycle: a magnetoencephalographic study. Horm Behav. 54, 28-33.

Jacobs, D. M., et al., 1998. Cognitive function in nondemented older women who took estrogen after menopause. Neurology. 50, 368-73.

Krach, S., et al., 2006. Comparison between visual half-field performance and cerebral blood flow changes as indicators of language dominance. Laterality. 11, 122-40.

Kuhl, H., 2006. Klimakterium, Postmenopause und Hormonsubstitution. Bremen, London, Boston: UNI-MED Verlag AG.

Low, L. F., Anstey, K. J., 2006. Hormone replacement therapy and cognitive performance in postmenopausal women--a review by cognitive domain. Neurosci Biobehav Rev. 30, 66-84.

Maki, P., Hogervorst, E., 2003. The menopause and HRT. HRT and cognitive decline. Best Pract Res Clin Endocrinol Metab. 17, 105-22.

Maki, P. M., Resnick, S. M., 2001. Effects of estrogen on patterns of brain activity at rest and during cognitive activity: a review of neuroimaging studies. Neuroimage. 14, 789-801.

Maki, P. M., et al., 2001. Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. Am J Psychiatry. 158, 227-33.

McCourt, M. E., et al., 1997. The effects of gender, menstrual phase and practice on the perceived location of the midsagittal plane. Neuropsychologia. 35, 717-24.

Mead, L., Hampson, E., 1996. Asymmetric effects of ovarian hormones on hemispheric activity: Evidence from dichotic and tachistoscopic tests. Neuropsychology. 10, 578-87.

Mueck, A. O., et al., 2002. Impact of hormone replacement therapy on endogenous estradiol metabolism in postmenopausal women. Maturitas. 43, 87-93.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia. 9, 97-113.

Puce, A., et al., 1996. Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. J Neurosci. 16, 5205-15.

Rapp, S. R., et al., 2003. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. Jama. 289, 2663-72.

Rastatter, M. P., McGuire, R. A., 1990. Some effects of advanced aging on the visual-language processing capacity of the left and right hemispheres: evidence from unilateral tachistoscopic viewing. J Speech Hear Res. 33, 134-40.

Resnick, S. M., et al., 2006. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J Clin Endocrinol Metab. 91, 1802-10.

Rode, C., et al., 1995. Menstrual cycle affects functional cerebral asymmetries. Neuropsychologia. 33, 855-65.

Ruch, W., et al., 1997. To be in good or bad humor: Construction of the state form of the

Stait-Trait-Cheerfulness-Inventory – STCI. Pers Individ Dif. 22, 477-91.

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, 869-74.

Sherwin, B. B., Henry, J. F., 2008. Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: a critical review. Front Neuroendocrinol. 29, 88-113.

Shughrue, P. J., Merchenthaler, I., 2003. Estrogen prevents the loss of CA1 hippocampal neurons in gerbils after ischemic injury. Neuroscience. 116, 851-61.

Shumaker, S. A., et al., 2004. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. Jama. 291, 2947-58.

Sowell, E. R., et al., 2003. Mapping cortical change across the human life span. Nat Neurosci. 6, 309-15.

Suganthy, J., et al., 2003. Gender- and age-related differences in the morphology of the corpus callosum. Clin Anat. 16, 396-403.

Sullivan, E. V., et al., 2001. Sex differences in corpus callosum size: relationship to age and intracranial size. Neurobiol Aging. 22, 603-11.

Weis, S., et al., 2008. Estradiol modulates functional brain organization during the menstrual cycle: An analysis of interhemispheric inhibition. submitted.

Wisniewski, A. B., 1998. Sexually-dimorphic patterns of cortical asymmetry, and the role for sex steroid hormones in determining cortical patterns of lateralization. Psychoneuroendocrinology. 23, 519-47.

Wolf, O. T., Kirschbaum, C., 2002. Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. Horm Behav. 41, 259-66.

V General Discussion

The present thesis aimed to investigate sex hormonal effects on specific aspects of functional brain organization. Using different behavioural paradigms in younger women during the menstrual cycle and postmenopausal women receiving different hormone therapies (HT), all three studies indicate that interhemispheric interaction and functional cerebral asymmetries (FCAs) are affected by both the menstrual cycle and HT.

Menstrual cycle and interhemispheric interaction

Chapter II describes a study using two different paradigms to investigate specific aspects of interhemispheric interaction, namely interhemispheric integration and interhemispheric transfer times (IHTTs) in younger women during the menstrual cycle.

Interhemispheric integration was measured by the Banich-Belger paradigm consisting of two differentially demanding tasks. To demonstrate interhemispheric effects (i.e., an across-field advantage, AFA, in a more demanding task) it was important that the two tasks clearly differ in their task demands. Banich and Belger (1990) have argued that it is the complexity of a task rather than its overall difficulty that predicts whether across-hemisphere processing will aid the overall performance. For example, one study using dim vs. bright stimuli found no AFA in the more demanding dim-stimuli task, probably because the dim-bright manipulation did not change the number of computational steps or operations involved in performing the task (e.g., Weissman & Banich, 2000). In contrast, the physical- and name-identity tasks used in study 1 were expected to differ in their computational complexity with the name-identity task requiring more processing steps, that is transforming the information into a higher semantic code in order to reveal an AFA.

In line with this idea, study 1 shows that normally cycling women, similar-aged men, and postmenopausal women without HT exhibit a typical performance advantage of having the resources of both hemispheres available when tasks demands increase. In all three groups, an AFA was evident in the name-identity task but not in the physical-identity task. This result indicates that the tasks used here constitute a valid measure to assess interhemispheric effects on performance which was an important prerequisite to reveal potential sex hormonal influence on interhemispheric integration.

In fact, study 1 provides the first evidence that interhemispheric integration fluctuates across the menstrual cycle. Specifically, women showed an AFA during the high-P luteal

phase but not during menses. In the within-participants analyses, this effect was found across both the easier and the more demanding task. However, when data were analyzed in a between-participants design which is unaffected by practice effects, the difference in the AFA between menses and the luteal phase was particularly pronounced in the more demanding name-identity task.

Although P-levels were not related to changes in the AFA, it seems rather unlikely that factors other than the menstrual cycle and cycle-related hormonal changes have contributed to the results for several reasons. First, all normally cycling women included in the analyses showed the expected increase in P-levels during the luteal phase compared with menses. The importance of cycle phase validation has been indicated by previous research. For example, based on salivary estradiol assays, Mead and Hampson (1996) had to exclude 23% of women because they did not reach the expected increase in estradiol-levels during the midluteal phase. Similarly, Hausmann and Güntürkün (2000) reported an exclusion ratio of about 27 % of participating women which is in line with published reports of the proportion of younger women who are likely to show an anovulatory cycle (e.g., Metcalf & Mckenzie, 1980). Yet, as confirmed by the salivary assays, this does not apply to study 1.

Second, previous research has suggested that functional brain organization (e.g., Hausmann & Güntürkün, 1999) including interhemispheric effects on performance (Weissman & Compton, 2003) is not only modulated by the nature of the task but also by the participant's prior experience with the task. However, the control group of postmenopausal women without HT did not exhibit differences in the AFA between the two testing sessions. This indicates that the AFA represents a reliable measure of the efficiency of interhemispheric integration which remains stable over time. Thus, changes in the AFA over time as found in normally cycling women seem to result from menstrual cycle-related changes rather than from repeated measure effects.

Finally, it has been suggested that the AFA is sensitive to individual differences in mood (e.g., Compton & Mintzer, 2001). To preclude the possibility of an impact of mood changes on interhemispheric integration, study 1 only included women who did not exhibit large variations in mood state between the menstrual and the luteal phase. Moreover, subsequent analyses did not reveal significant relationships between mood scales and performance measures. Thus, because several confounding variables were controlled, the findings strongly suggest that differences in the AFA between women during menses and during the luteal phase occur as a consequence of menstrual cycle-related hormonal changes.

The hormonal conditions during the luteal phase, but not during menses, seem to promote an efficient interhemispheric integration function which finally leads to a substantial AFA. It remains open whether other sex steroids or their metabolites might have mediated this effect. For example, Hausmann (2005) found changes in the hand-use difference in a line bisection task which was assumed to depend on transcallosal interaction in normally cycling women between menses and the luteal phase, an effect which was mainly related to high estradiol- but not P-levels. This might also apply to the present findings. Furthermore, it seems possible that E and/or P are not directly involved but rather serve as precursors for the relevant neurosteroid (e.g., Weis, Hausmann, Stoffers, Vohn, Kellermann & Sturm, 2008). For example, animal studies have demonstrated that P is rapidly converted by 5α-reductase into neurosteroids (i.e., 5α-dihydroprogesterone and 5α-dihydrodeoxycorticosterone) which exert allosteric actions on the $GABA_A$ receptor (e.g., Rupprecht, 2003), an effect which has been suggested to be crucial in modulating interhemispheric inhibition (e.g., Hausmann & Güntürkün, 2000). Similar neurosteroid-actions on callosal processes underlying interhemispheric integration might contribute to a stable AFA during the luteal phase without P being directly involved.

Notably, younger men as well as postmenopausal women without HT, who show permanently reduced sex hormone levels, exhibited an AFA which was virtually identical to that in women during the luteal phase. Thus, it is likely that the functional neural architecture including interhemispheric integration is fundamentally different in these groups compared with younger women. Here, an efficient interhemispheric integration is ensured without the neuromodulatory effects of sex hormones.

Previous research on cycle-related changes in FCAs mainly reported similar lateralization pattern in women during menses, men, and postmenopausal women without HT, probably as a result of similarly low levels of sex hormones (e.g., Hausmann & Güntürkün, 2000). This is in contrast to the results of study 2 and suggests that FCAs and interhemispheric integration rely on different callosal mechanisms.

FCAs have been assumed to arise from transcallosal inhibition processes. Specifically, three varieties of interhemispheric inhibition have been proposed (e.g., Chiarello & Maxfield, 1996). Interhemispheric *suppression* describes an inhibitory process suppressing the concurrent processing of information in the opposite hemisphere by activation of GABAergic interneurons in homotopic areas. In contrast, interhemispheric *isolation* has been proposed to suspend information transfer between the two hemispheres thereby insulating each

hemisphere without suppressing any other function. This process may prevent potentially harmful interhemispheric intrusions. The third model of interhemispheric inhibition assumes that the processing within one hemisphere impedes the processing within the other hemisphere via *interference* which may lead to a disadvantage of hemispheric interaction. Thus, all three models provide a theoretical account of cerebral laterality.

The potential mechanisms underlying the AFA are far less clear. However, some authors have attributed the AFA as measured by the Banich-Belger task to the specific process of interhemispheric *isolation* (e.g., Liederman, 1986). Liederman and Meehan (1986), for example, argued that inhibitory processes which reduce interhemispheric crosstalk and interference may constitute optimal conditions for each hemisphere to process a part of the information. According to this idea, the AFA does not simply reflect an effect of the division of processing load but rather a reduction of mutual interference between hemispheres during perceptual processing (e.g., Sohn, Liederman & Tippens-Reinitz, 1996).

In contrast, the manifestation of FCAs at a behavioural level seems to be mainly a result of interhemispheric *suppression* between hemispheres which has been assumed to be attenuated by high levels of sex hormones (Hausmann & Güntürkün, 2000; Hausmann, Becker, Gather & Güntürkün, 2002). As it becomes clear, this model does not make specific assumptions about sex hormonal changes in the AFA. Considering the rationale presented above, however, one might assume that a functional decoupling of the two hemispheres as a result of high P-levels during the luteal phase (Hausmann & Güntürkün, 2000; Hausmann et al., 2002) relates to a more efficient interhemispheric integration because both hemispheres can process the information somewhat independently. Yet, "decoupled hemispheres" may also imply a reduced capability of the two hemispheres to integrate and combine the bilateral output. However, in study 1, both high sex hormone levels during the luteal phase (i.e., in normally cycling women) and low sex hormone levels (i.e., in men and postmenopausal women) were accompanied by a substantial AFA. The results presented here are therefore much more complex and difficult to reconcile with findings of sex hormonal changes in FCAs. Thus, the present findings clearly suggest that interhemispheric integration and FCAs constitute two different and rather independent aspects of interhemispheric interaction.

Taken together, study 1 demonstrates cycle-related changes in the relative efficiency of interhemispheric integration, probably as a result of hormonal changes. This finding extends previous research on sex hormonal effects on FCAs, in that it provides the first direct evidence as measured at the behavioural level that interhemispheric interaction (i.e.,

interhemispheric integration) is sensitive to the menstrual cycle and cycle-related changes in the hormonal environment. IHTTs, on the other hand, did not differ between hormonal distinct cycle phases. Thus, it seems that different callosal processes are differently affected by the menstrual cycle and cycle-related hormonal changes. That is, interhemispheric inhibition as a mechanism underlying FCAs has been shown to be modulated by high estradiol- and P-levels during the follicular and luteal phase, respectively (e.g., Hausmann & Güntürkün, 2000; Hausmann et al., 2002; Weis et al., 2008). In contrast, interhemispheric integration does fluctuate across the menstrual cycle, but without direct effects of P. Finally, the simple process of transferring visuo-motor information between hemispheres seems not to be under sex hormonal control, at least when measured behaviourally.

Hormone therapy and functional brain organization

Hormone therapy and interhemispheric interaction

Study 2 was designed to investigate whether interhemispheric interaction is also susceptible to direct hormonal manipulations *via* HT. Therefore, postmenopausal women receiving either a single estrogen therapy (ET), a combined E plus synthetic progestins therapy (cHT), or no HT were tested using the same tasks as in study 1. Overall, the findings in the interhemispheric integration tasks replicate the results from study 1 showing that across-hemisphere processing becomes advantageous in postmenopausal women as task demands increase. Moreover, study 2 revealed a significant impact of HT on interhemispheric integration. Specifically, the ET and the cHT group differed from postmenopausal controls in *intra*hemispheric processing which was improved across both tasks. However, in all three groups, the benefits of *inter*hemispheric processing equally increased in the more demanding task indicating an efficient interhemispheric integration in both postmenopausal women with and without HT. Thus, although the absolute increase in the AFA from the easier to the more demanding task was similar in all groups, women using HT showed a reduced *relative* efficiency of interhemispheric integration (i.e., strongly reduced AFA) as a result of an enhanced within-hemisphere performance. This finding suggests that HT positively affects *intra*hemispheric processing. Specifically, the missing AFA in the two hormone groups indicates that HT enhances intrahemispheric performance at a processing stage critical for the manifestation of an AFA.

A recent imaging study (Pollmann, Zaidel & von Cramon, 2003), using similar interhemispheric integration tasks, found that the AFA in a more demanding task went along with increased activation in the lateral occipital and fusiform gyri in the contralateral hemisphere. These activations, in turn, were associated with a spreading activation of homotopic brain areas in the ipsilateral hemisphere indicating a bilateral resource sharing. Notably, these effects were restricted to the occipital cortex which suggests the visual letter processing as the most likely processing stage at which the resources of a single hemisphere become taxed, leading to the need to recruit bilateral brain areas (Pollmann et al., 2003). With respect to the findings from study 2, it thus seems likely that HT, and ET in particular, specifically modulates neuronal circuitries within the occipital cortex underlying unilateral visual processing.

In contrast, *inter*hemispheric processing is essentially unaffected by HT. This idea is further supported by the finding that IHTTs, as another aspect of interhemispheric interaction, did not differ between the two hormone groups and the control groups of study 2.

Compared with study 1, it seems that both the menstrual cycle and HT affect interhemispheric integration, but through fundamentally different mechanisms. While cycle-related changes seem to result from hormonal modulations of interhemispheric processing, HT after menopause mainly affects within-hemisphere processing. However, these differences between younger and postmenopausal women might be partly a result of differences between endogenous hormonal changes during the menstrual cycle and those associated with exogenous hormonal manipulations. Moreover, the findings in postmenopausal women are likely to be confounded by age-related neuromorphological and functional changes. These issues will be further addressed in a subsequent section.

Hormone therapy and functional cerebral asymmetries

Despite the large body of evidence showing that fluctuating levels of sex hormones during the menstrual cycle affect FCAs (e.g., Hausmann & Güntürkün, 2000; Hausmann et al., 2002; Heister, Landis, Regard & Schroeder-Heister, 1989; Rode, Wagner & Güntürkün, 1995), the impact of HT in healthy participants has so far been neglected. Using the same approach as in study 2, study 3 investigated the effects of HT on FCAs in postmenopausal women receiving either ET, cHT, or no HT. FCAs were measured by a prototypical LH dominated verbal (word matching) and a RH dominated visuo-spatial task (figural comparison).

In line with previous studies (Bayer & Erdmann, 2008; Hausmann & Günturkün, 2000), the control group with no HT showed typical hemispheric differences with a LH advantage in the verbal task and a RH advantage in the visuo-spatial task. Thus, it seems that the loss of sex hormones after menopause stabilize functional asymmetries. Moreover, the results show an estradiol-related decrease in RH performance in the visuo-spatial task leading to reduced FCAs. As in study 2, this effect was evident in both the ET and the cHT group.

One recent study also reported a decrease in asymmetries in postmenopausal women using HT. In this study, however, RH verbal functioning was enhanced in postmenopausal women using ET, leading to reduced hemispheric differences in the verbal domain. The results from study 3 together with the findings of Bayer and Erdmann (2008) therefore suggest that ET in postmenopausal women exerts a task-specific effect on RH functioning. Moreover, the reciprocal changes in RH performance in verbal and visuo-spatial functioning indicate that modulations in functional asymmetries across different domains do not occur independently. It is rather assumed that HT improves RH verbal processing at the expense of visuo-spatial abilities.

The findings of study 3 have an important impact on the understanding of HT-related effects on cognition in general. Particularly, the results from study 3 and Bayer and Erdmann's study (2008) suggest a RH mechanism that might account for differential HT effects on verbal and visuo-spatial abilities which mainly rely on LH and RH functioning, respectively (e.g., Maki, Zonderman & Resnick, 2001; Resnick et al., 2006; Wolf & Kirschbaum, 2002).

The idea of estradiol-related modulation of interhemispheric processing, and RH processing in particular, challenges the notion that changes in FCAs occur as a result of hormonal modulations of interhemispheric interaction as it has been suggested for normally cycling women (e.g., Hausmann & Güntürkün, 2000; Hausmann et al., 2002; Weis et al., 2008). Contradictions between findings in normally cycling women and postmenopausal women can best be explained by age-related neuromorphological changes which will be addressed in detail in the next section.

Methodological issues

Estrogen- vs combined hormone therapy. In both study 2 and study 3, the combined E plus synthetic progestins substitution did not differently affect functional brain organization compared with the single ET, indicating a pivotal role of E in mediating the observed effects.

This assumption is directly supported by the result of estradiol-related changes in FCAs (study 3). However, an additional role of synthetic progestins, which may differ from the effects of ET, cannot be completely ruled out. Rather, it seems that differences in the specific kind of synthetic progestin between postmenopausal women receiving cHT might have covered systematic effects on performance measures.

In their recent review on the clinical effects of progestins, Wiegratz & Kuhl (2004) stated that "the only indication for the addition of progestins to estrogen-replacement therapy is endometrial protection" (Wiegratz & Kuhl, 2004). In fact, synthetic progestins are only considered with respect to their effectiveness in preventing uterine hyperplasia and malignancy in response to E. Since the natural P is inactivated very rapidly, a wide variety of synthetic progestins with an enhanced hormonal potency has been developed.

Generally, all synthetic progestins are derived from either C19 testosterone or P and have in common the so-called progestogenic effect. That is, the induction of a characteristic change in the E-primed endometrium. However, according to their origin and specific chemical structures, synthetic progestins differently affect the P-metabolism and exert different pattern of hormonal actions which are, in terms of central effects, far less well understood (e.g., Schindler et al., 2003). An overview of biological activities of synthetic progestins relative to P is given in Table 1.

	P	E	A-E	And	A-And
Progesterone	+	-	+	-	±
NEA	+	+	+	+	-
MPA	+	-	+	±	-
Dienogest	+	±	±	-	+
Drospirenone	+	-	+	-	+
Medrogestone	+	-	+	-	±

Table 1. Biological activities of synthetic progestins used in study 2 and 3 compared with endogenous P. Adapted from Schindler et al. (2003), *Maturitas,* 46, 7-16. *Note.* Norethisterone acetate (NEA), Medroxyprogesterone acetate (MPA), progestogenic (P), estrogenic (E), anti-estrogenic (A-E), androgenic (And), anti-androgenic (A-And). **(+) effective, (±) weakly effective, (-) not effective.**

Differences in the biological activity are mainly based on variations among synthetic progestins in the ability to bind to the P-receptor. This is also true in relation to binding to other steroid receptors (i.e., estrogen and androgen receptors; ER and AR). For example,norethisterone acetate (NEA), as the most used synthetic progestin in postmenopausal women of study 2 and 3 receiving cHT, has been shown to upregulate ERα-activity thereby exerting estrogenic effects (e.g., Campagnoli, Clavel-Chapelon, Kaaks, Peris & Berrino, 2005b). This effect is not evident for other synthetic progestins such as Drosperinon. Medroxyprogesterone acetate (MPA) and Drosperinone. On the other hand, NEA and also MPA are endowed with an affinity to AR which may result in androgenic properties and thus, antagonize the action of estrogens *via* an increase in insulin-like growth factor-1 (IFG-1) (e.g., Campagnoli, Abba, Ambroggio & Peris, 2005a). Moreover, androgenic progestins also oppose the E-induced increase in sex hormone-binding globulin (SHBG)-levels. In contrast, Dienogest, Drosperinone and Medrogestone exert opposing (i.e., anti-androgenic) effects (e.g., Schindler et al., 2003). Thus, differences in the pharmacological properties between several synthetic progestins are likely to confound possible effects on functional brain organization.

Influence of task on hormone therapy-related effects. The results of study 2 and 3 make it likely that HT-mediated (i.e., ET-mediated) changes in functional brain organization are a result of modulations of intrahemispheric processing rather than interhemispheric crosstalk.

With respect to the direction of these effects, the finding of an estradiol-related decrease in RH performance (study 3) seems contradictory to the results from study 2 indicating positive effects of HT on both hemispheres. One has to bear in mind, however, that the interhemispheric integration tasks (study 2) and the functional asymmetries tasks (study 3) clearly differ in several respects. For example, the interhemispheric integration tasks are non-lateralized tasks in which within-hemisphere processing is compared with across-hemisphere processing. The impact of interhemispheric crosstalk on performance (i.e., AFA) has been shown to become evident using different kinds of stimuli (i.e., letters and digits; Banich & Belger, 1990) with the lateral occipital and fusiform gyri as a potential neural basis (e.g., Pollmann et al., 2003). In contrast, the figural comparison task as a prototypical RH lateralized task (study 3) measures relative performance differences between the two hemispheres. An RH advantage reflecting the RH specialization for tasks involving a visuo-spatial component has been demonstrated by various means and seems highly task- and

stimulus-specific. Moreover, functional imaging data indicate a lateralized activation particularly in the right inferior temporal cortex during the figural comparison task (unpublished data).

Thus, both kinds of tasks seem not only to differ in the underlying callosal mechanisms (see above) but also in the specific neuronal circuitries within each hemisphere involved in visual letter matching and figural comparison, respectively. The estradiol-related effect in the lateralized task (study 3) has been assumed to reflect a modulation of specific neuronal networks underlying the RH advantage in figural matching, probably at a higher processing stage. In contrast, the HT-mediated improvement of within-hemisphere letter matching (study 2) is likely to result from an increased efficiency at the very early level of visual perception. This effect seems less specific with respect to the kind of stimuli and processing steps being involved. Thus, it is reasonable to assume that HT-related effects on within-hemisphere processing strongly depend on the nature of the task and stimuli being used.

Menstrual cycle versus hormone therapy effects

The investigation of postmenopausal women using different HTs allows the direct determination of changes in functional brain organization as a result of different hormonal environments. This approach, however, also comprises critical aspects which will subsequently be discussed in further detail.

Endogenous vs. exogenous hormonal changes

The divergent behavioural outcomes in younger women and postmenopausal women as a result of sex hormonal changes during the menstrual cycle and after HT, respectively, are likely to result from fundamental differences between endogenous and exogenous hormonal fluctuations.

To date, no HT is available that can adequately simulate the hormonal changes as they occur during the menstrual cycle. For example, hormone levels in normally cycling women are dynamically changing whereas the use of synthetic hormones results in steady hormone levels. Furthermore, synthetic E and progestins differently affect the E- and P-metabolism as compared with endogenous E and P (e.g., Kuhl, 2006). In fact, during the menstrual cycle it is mainly estradiol which is increased. In contrast, conjugated estrogens (CE) which are widely used in HT are predominantly converted into estrone resulting in a shift of estradiol/estrone

ratio favouring estrone (e.g., Gleason, Carlsson, Johnson, Atwood & Asthana, 2005). The neurobiology of estrone is not fully clear. Given that estrone is biologically weaker than estradiol, effects of HTs including CE might not be equivalent to either endogenous or exogenous estradiol. Specifically, variations in receptor binding affinitiy (e.g., Kuiper, Carlsson, Grandien et al., 1997) and potency for cell membrane-mediated pathways (e.g., Deecher, Swiggard, Frail & O'Connor, 2003) make it likely that CE and estradiol exhibit differential effects on the brain.

The most significant differences, however, is the use of synthetic progestins in a cHT which clearly differ in their hormonal properties from endogenous P. This might be the main reason why, in neither study 2 nor study 3, possible P-related effects could be revealed. Endogenous P, for example, is converted to the $GABA_A$ receptor-active metabolite allopregnanolone whose importance in mediating central effects has been outlined earlier (e.g., Campagnoli et al., 2005a,b; Schumacher et al., 2007; Wiegratz & Kuhl, 2004). Though synthetic progestins are also extensively metabolized, their metabolites are not well characterized. Some of the P-derived progestins may have the potential to be converted to neuroactive metabolites (e.g., Schumacher et al., 2007). Specifically, NEA has been shown to exert anxiolytic-like actions in rats, an effect that might have been mediated by $GABA_A$–receptor modulations. Whether some metabolites of NEA *directly* act on $GABA_A$–receptors, however, still needs to be clarified. MPA, on the other hand, which does not exhibit $GABA_A$–receptor actions has been demonstrated to enhance the inhibitory transmission mediated by this receptor type by inhibiting the metabolism of allopregnanolone (e.g., Belelli & Herd, 2003) and hence, might be assumed to exert P-like effects. Such effects have not yet been demonstrated for other specific progestins. In addition, most of the synthetic progestins differ from endogenous P in that, they interact with ARs and ERs which is associated with agonistic or antagonistic effects (e.g., Campagnoli et al., 2005a,b; see also Table 1). Moreover, as already discussed, differences in synthetic progestin-use in postmenopausal cHT women in study 2 and 3 exacerbates the comparison between the effects of endogenous P and exogenous progestins.

Age-related effects

In general, studies on hormonal manipulations are almost exclusively carried out in clinical populations or in participants older than those with natural hormonal fluctuations. Likewise, studies 2 and 3 investigated women after the menopause with a mean age of about

60 years. In contrast, the mean age of participants in menstrual cycle-studies is about 25 years. Thus, age-related changes in brain structures and functions in postmenopausal women are likely to confound sex hormonal effects on functional brain organization which limits the direct comparison between menstrual cycle- and HT-related effects.

The conclusion drawn from study 2 and 3, that HT affects intrahemispheric processing disagrees with the idea of sex hormonal modulations of interhemispheric interaction during the menstrual cycle (e.g., Hausmann & Güntürkün, 2000, Hausmann et al., 2002; Weis et al., 2008, see also study 1). These differences can be explained by neuromorphological changes with increasing age in postmenopausal women, including white and gray matter atrophy, a reduction of synaptic spine density, and neurochemical alteraltions (e.g., Cabeza, Anderson, Locantore & McIntosh, 2002).

For example, a significant age-related loss in gray matter density has been found in specific brain areas such as frontal and parieto-occipital brain regions (e.g., Sowell, Peterson, Thompson, Welcome, Henkenius & Toga, 2003). It is important to note that these brain areas are known to be critical for visual letter processing as is required in the Banich-Belger tasks used in study 2 (e.g., Puce; Allison, Asgari, Gore & McCarthy, 1996; Pollmann et al., 2003). In contrast, the corpus callosum and associated interhemispheric processes seem to be relatively robust against an age-related decline (Cowell, Allen, Zalatimo & Denenberg, 1992; Cowell et al., 1994; Dubb, Gur, Avants & Gee, 2003; Suganthy et al., 2003; Sullivan, Rosenbloom, Desmond & Pfefferbaum, 2001). Evidence even suggests that the recruitment of contralateral brain resources *via* the corpus callosum serves as a compensatory strategy to counteract age-related decrements in the efficiency of specialized unilateral brain regions (e.g., Cabeza et al., 2002). In fact, a number of imaging studies found a more bilateral brain activity during cognitive task performance in older compared with younger adults (e.g., Cabeza, Anderson, Houle, Mangels & Nyberg, 2000, Cabeza et al., 2002; Reuter-Lorenz et al., 2000). Likewise, postmenopausal women without HT (study 1 and 2) showed a substantial AFA reflecting a performance advantage under conditions of bilateral resource sharing, probably as a result of a decrease in the efficiency of within-hemisphere processing as tasks demands increase. Thus, differential aging effects within and across hemispheres might explain why an influence of HT on performance becomes particularly evident in intrahemispheric processing.

In terms of hemispheric specialization, it has been suggested that aging affects the RH and associated functions more than the LH (e.g., Ellis & Oscar-Berman, 1989). This idea is

originally based on observations that older adults showed a decline in the performance IQ of the Wechsler Adult Intelligence Scale (WAIS) while their verbal abilities remained relatively stable (e.g., Goldstein & Shelly, 1981). This, however, might also result from the fact that the performance tests of the WAIS are performed under time constrains whereas the verbal tests are not. In fact, a general decrease in processing speed with increasing age has been demonstrated in a variety of ways (e.g., Reuter-Lorentz & Stanczak, 2000). However, domain-specific dissociations in performance decrement similar to those in older adults also apply to patients with RH injuries leading to the assumption of a greater loss of RH capabilities with increasing age. Likewise, several studies using visual-perceptual tasks found that a performance decline was more pronounced for RH than LH (e.g., Gerhardtstein, Peterson & Rapcsak, 1998; Rastatter & McGuire, 1990). This might explain why the RH was more sensitive to HT-related effects in both study 3 presented here and the Bayer & Erdmann's study (2008).

Thus, it seems that detrimental effects associated with increasing age, and especially those affecting brain structures and functions within each hemisphere, contribute to differences between normally cycling women and postmenopausal women in sex hormone-mediated changes in inter- vs. intrahemispheric processes.

Final conclusions

In summary, the present thesis extends prior knowledge about sex hormonal effects on functional brain organization in three major ways. First, study 1 indicates that menstrual cycle- and hormone-related changes are not restricted to interhemipsheric inhibition as it has been initially suggested by Hausmann & Güntürkün (2000; Hausmann et al., 2002). The findings rather suggest that other aspects (i.e., interhemispheric integration) than those involved in FCAs are also affected by sex hormonal changes during the menstrual cycle. Moreover, the results emphasize the idea put forward by several authors (e.g., Hausmann, 2005; Hausmann, Tegenthoff, Sanger, Janssen, Güntürkün & Schwenkreis, 2006; Weis et al., 2008) that not only P but also estradiol and metabolites of these hormones can potentially modulate interhemispheric processes. Secondly, as suggested by the findings in postmenopausal women, sex hormonal effects do not exclusively modulate interhemispheric crosstalk but also apply to neuronal processes within each hemisphere. Finally, study 2 and 3 demonstrate that changes in the functional organization of the female brain do not exclusively occur in relation to endogenous hormonal variations but can also be induced by exogenous

hormonal manipulations *via* HT in postmenopausal women. These findings significantly emphasize the assumption of a direct influence of sex hormones on the brain. Furthermore, they show that the female brain retains its plasticity after reproductive ages and remains susceptible to the influence of sex hormones, and E in particular, throughout the lifetime.

References

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

Bayer, U. & Erdmann, G. (2008). The influence of sex hormones on functional cerebral asymmetries in postmenopausal women. *Brain and Cognition*, 67, 140-149.

Belelli, D. & Herd, M. B. (2003). The contraceptive agent Provera enhances GABA(A) receptor-mediated inhibitory neurotransmission in the rat hippocampus: evidence for endogenous neurosteroids? *Journal of Neuroscience*, 23, 10013-10020.

Cabeza, R., Anderson, N. D., Houle, S., Mangels, J. A. & Nyberg, L. (2000). Age-related differences in neural activity during item and temporal-order memory retrieval: a positron emission tomography study. *Journal of Cognitive Neuroscience*, 12, 197-206.

Cabeza, R., Anderson, N. D., Locantore, J. K. & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage*, 17, 1394-1402.

Campagnoli, C., Abba, C., Ambroggio, S. & Peris, C. (2005a). Pregnancy, progesterone and progestins in relation to breast cancer risk. *The Journal of Steroid Biochemistry and Molecular Biology*, 97, 441-450.

Campagnoli, C., Clavel-Chapelon, F., Kaaks, R., Peris, C. & Berrino, F. (2005b). Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. *The Journal of Steroid Biochemistry and Molecular Biology*, 96, 95-108.

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. & Mintzer, D. A. (2001). Effects of worry and evaluation stress on interhemispheric interaction. *Neuropsychology*, 15, 427-433.

Cowell, P. E., Allen, L. S., Zalatimo, N. S. & Denenberg, V. H. (1992). A developmental study of sex and age interactions in the human corpus callosum. *Developmental Brain Research*, 66, 187-192.

Cowell, P. E., Turetsky, B. I., Gur, R. C., Grossman, R. I., Shtasel, D. L. & Gur, R. E. (1994). Sex differences in aging of the human frontal and temporal lobes. *Journal of*

Neuroscience, 14, 4748-4755.

Deecher, D. C., Swiggard, P., Frail, D. E. & O'Connor, L. T. (2003). Characterization of a membrane-associated estrogen receptor in a rat hypothalamic cell line (D12). *Endocrine*, 22, 211-223.

Dubb, A., Gur, R., Avants, B. & Gee, J. (2003). Characterization of sexual dimorphism in the human corpus callosum. *Neuroimage*, 20, 512-519.

Ellis, R. J. & Oscar-Berman, M. (1989). Alcoholism, aging, and functional cerebral asymmetries. *Psychological Bulletin*, 106, 128-147.

Gerhardstein, P., Peterson, M. A. & Rapcsak, S. Z. (1998). Age-related hemispheric asymmetry in object discrimination. *Journal of Clinical and Experimental Neuropsychology*, 20, 174-185.

Gleason, C. E., Carlsson, C. M., Johnson, S., Atwood, C. & Asthana, S. (2005). Clinical pharmacology and differential cognitive efficacy of estrogen preparations. *Annals of the New York Academy of Sciences*, 1052, 93-115.

Goldstein, G. & Shelly, C. (1981). Does the right hemisphere age more rapidly than the left? *The Clinical Neuropsychologist*, 3, 65-78.

Hausmann, M. (2005). Hemispheric asymmetry in spatial attention across the menstrual cycle. *Neuropsychologia*, 43, 1559-1567.

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. & 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., Tegenthoff, M., Sanger, J., Janssen, F., Güntürkün, O. & Schwenkreis, P. (2006). Transcallosal inhibition across the menstrual cycle: A TMS study. *Clinical Neurophysiology: Official journal of the International Federation of Clinical Neurophysiology*, 117, 26-32.

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

Kuhl, H. (2006). *Klimakterium, Postmenopause und Hormonsubstitution*. Bremen, London, Boston: UNI-MED Verlag AG.

Kuiper, G. G., Carlsson, B., Grandien, K., Enmark, E., Haggblad, J., Nilsson, S. et al. (1997). Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. *Endocrinology*, 138, 863-870.

Liederman, J. (1986). Subtraction in addition to addition: dual task performance improves when tasks are presented to separate hemispheres. *Journal of Clinical and Experimental Neuropsychology*, 8, 486-502.

Liederman, J. & Meehan, P. (1986). When is between-hemisphere division of labor advantageous? *Neuropsychologia*, 24, 863-874.

Maki, P. M., Zonderman, A. B. & Resnick, S. M. (2001). Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. *The American Journal of Psychiatry*, 158, 227-233.

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

Metcalf, M. G. & Mackenzie, J. A. (1980). Incidence of ovulation in young women. *Journal of Biosocial Science*, 12, 345-352.

Pollmann, S., Zaidel, E. & von Cramon, D. Y. (2003). The neural basis of the bilateral distribution advantage. *Experimental Brain Research*, 153, 322-333.

Puce, A., Allison, T., Asgari, M., Gore, J. C. & McCarthy, G. (1996). Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. *Journal of Neuroscience*, 16, 5205-5215.

Rastatter, M. P. & McGuire, R. A. (1990). Some effects of advanced aging on the visual-language processing capacity of the left and right hemispheres: evidence from unilateral tachistoscopic viewing. *Journal of Speech and Hearing Research*, 33, 134-140.

Reuter-Lorenz, P. A. & Stanczak, L. (2000). Differential effects of aging on the functions of the corpus callosum. *Developmental Neuropsychology*, 18, 113-137.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C. et al. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *Journal of Cognitive Neuroscience*, 12, 174-187.

Resnick, S. M., Maki, P. M., Rapp, S. R., Espeland, M. A., Brunner, R., Coker, L. H. et al. (2006). Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *The Journal of Clinical Endocrinology and Metabolism*, 91, 1802-1810.

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

Rupprecht, R. (2003). Neuroactive steroids: mechanisms of action and neuropharmacological

properties. *Psychoneuroendocrinology*, 28, 139-168.

Schindler, A. E., Campagnoli, C., Druckmann, R., Huber, J., Pasqualini, J. R., Schweppe, K. W. et al. (2003). Classification and pharmacology of progestins. *Maturitas*, 46 Suppl 1, S7-S16.

Schumacher, M., Guennoun, R., Ghoumari, A., Massaad, C., Robert, F., El-Etr, M. et al. (2007). Novel perspectives for progesterone in hormone replacement therapy, with special reference to the nervous system. *Endocrine Reviews*, 28, 387-439.

Sohn, Y. S., Liederman, J. & Reinitz, M. T. (1996). Division of inputs between hemispheres eliminates illusory conjunctions. *Neuropsychologia*, 34, 1057-1068.

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L. & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience*, 6, 309-315.

Suganthy, J., Raghuram, L., Antonisamy, B., Vettivel, S., Madhavi, C. & Koshi, R. (2003). Gender- and age-related differences in the morphology of the corpus callosum. *Clinical Anatomy*, 16, 396-403.

Sullivan, E. V., Rosenbloom, M. J., Desmond, J. E. & Pfefferbaum, A. (2001). Sex differences in corpus callosum size: relationship to age and intracranial size. *Neurobiology of Aging*, 22, 603-611.

Weis, S., Hausmann, M., Stoffers, B., Vohn, R., Kellermann, T. & Sturm, W. (2008). Estradiol modulates functional brain organization during the menstrual cycle: an analysis of interhemispheric inhibition. *Journal of Neuroscience*, 28, 13401-13410.

Weissman, D. H. & Banich, M. T. (2000). The cerebral hemispheres cooperate to perform complex but not simple tasks. *Neuropsychology*, 14, 41-59.

Weissman, D. H. & Compton, R. J. (2003). Practice makes a hemisphere perfect: The advantage of interhemispheric recruitment is eliminated with practice. *Laterality*, 8, 361-375.

Wiegratz, I. & Kuhl, H. (2004). Progestogen therapies: differences in clinical effects? *Trends in Endocrinology and Metabolism*, 15, 277-285.

Wolf, O. T. & Kirschbaum, C. (2002). Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. *Hormones and Behavior*, 41, 259-266.