Hodgetts, S., **Hausmann, M.** (2018). The neuromodulatory effects of sex hormones on functional cerebral asymmetries and cognitive control: An update. *Zeitschrift für Neuropsychologie (Journal of Neuropsychology)*, 29, 127-139.

The neuromodulatory effects of sex hormones on functional cerebral asymmetries and cognitive control: An update

Der Einfluss von Sexualhormonen auf funktionelle Hirnasymmetrien und kognitive Kontrolle: Eine aktualisierte Neuauflage

Sophie Hodgetts[1] and Markus Hausmann*[2]

1. School of Psychology, Faculty of Health Sciences and Wellbeing, University of Sunderland, Shackleton House, Silksworth Row, Sunderland SR1 3QR, UK.
2. Department of Psychology, Durham University, South Road, Durham DH1 3LE, UK.

*Correspondence to: Dr. Markus Hausmann, Department of Psychology, Durham University, South Road, Durham DH1 3LE, United Kingdom. E-mail: markus.hausmann@durham.ac.uk

Abstract (English)

In 2000, Hausmann and Güntürkün (2000a,b) published a target article in the Journal of Neuropsychology / Zeitschrift für Neuropsychologie on the influences of sex hormones on functional cerebral asymmetries (FCAs). They presented a neuroendocrinological model (Hausmann & Güntürkün, 2000c) that could potentially explain how sex hormones modulate FCAs. The model proposed that high levels of progesterone reduce the synaptic efficiency of cortico-cortical transmission, leading to a reduction of FCAs. However, empirical data testing their hypothesis directly were missing. Using different approaches, we have now gathered behavioural, electrophysiological and neuroimaging data partly supporting the original idea, but also pointing towards estradiol modulating FCAs. The current review will give an update on this fascinating topic and briefly explores clinical applications.

Abstract (deutsch)

Vor fast 20 Jahren veröffentlichten Hausmann und Güntürkün (2000a,b) einen Übersichtsartikel in der Zeitschrift für Neuropsychologie zu den Einflüssen von Sexualhormonen auf funktionelle cerebrale Asymmetrien (FCAs). Die Autoren präsentierten ein neuroendokrinologisches Modell (Hausmann & Güntürkün, 2000c), das potentiell erklären konnte wie Sexualhormone FCAs modulieren. Das Modell ging davon aus, dass hohe Progesteronspiegel die synaptische Effizienz der cortico-corticalen Übertragung vermindern und so FCAs reduzieren. Empirische Daten die diese Modellannahmen direkt testen existierten damals jedoch nicht. Mit verschiedenen neurowissenschaftlichen Ansätzen haben wir nun zahlreiche Daten erheben können, die die ursprünglichen Modellannahmen teilweise stützen und darüber hinaus Östradiol als bedeutenden Neuromodulator ausweisen. Mit diesem Übersichtsartikel möchten wir ein Update zu diesem faszinierenden Forschungsbereich geben sowie dessen potentielle klinische Relevanz kurz diskutieren.

1. Background

Sex is one of the most frequently investigated factors with respect to individual differences in functional brain organisation, and in functional cerebral asymmetries (FCAs) in particular (Hausmann & Bayer, 2010). Sex differences in FCAs have been reported in tasks related to language (Hausmann et al., 1998; Shaywitz et al., 1995), spatial ability (Chiarello et al., 1989; Corballis & Sidey, 1993; Hausmann & Güntürkün, 2000), and face recognition (Borod et al., 1983, Rizzolatti & Buchtel, 1977). While contradictions exist (e.g. Ashton & McFarland, 1991; Sommer et al, 2004), these studies suggest that women show reduced FCAs (i.e., increased bilaterality), relative to men.

Several reviews and meta-analyses have been conducted in an attempt to quantify the size of sex differences in FCAs across a range of lateralised cognitive processes (e.g., Hiscock et al., 1994; 1995; 1999; 2001; Vogel et al., 2003; Voyer, 1995). Taken together, these meta-analyses conclude that small but reliable sex differences in FCAs exist at the population level, with males yielding larger asymmetries than women do. Given the small effect sizes reported by these meta-analyses, it follows that only studies with large sample sizes will yield consistent and significant sex differences in FCAs. Hirnstein et al. (2013) supported this notion in a study using behavioural data compiled from 1782 participants (885 females). The data were acquired using a behavioural measure of language lateralisation (i.e., the Bergen dichotic listening task, Hugdahl et al., 2009). The results showed that sex differences in the degree of language lateralisation were dependent on age, and the effect of sex was largest during adolescence (Cohen's d = 0.31).

A large body of evidence suggested that the distinct hormonal profiles of men and women are key to the generation and maintenance of such sex differences in FCAs and cognition. However, sex hormone levels are not stable in women. Instead, they fluctuate both across the lifespan (e.g., menopause) and across shorter time intervals (e.g., the menstrual cycle). As such, menstrual cycle related hormone fluctuations might at least to some extent underpin the larger degree of inter- and intra-individual variation in women.

2. Sex hormonal effects on the brain

There are three main groups of gonadal steroid hormones: estrogens, progestins, and androgens. The human principle derivatives are estradiol, progesterone, and testosterone, respectively. Sex steroids can cross the blood-brain barrier, despite being synthesised primarily by the gonads (e.g. testes, ovaries) and adrenal glands (Rupprecht, 2003). However, there is increasing evidence that sex hormones can be synthesised locally in specific brain regions (e.g. hippocampus, prefrontal cortex; Luine, 2014; Rupprecht, 2003).

Organising and activating effects of sex hormones

Sex hormonal effects on the brain are broadly categorised as either organising or activating effects. Organising effects result from interactions between hormones and genes, and occur primarily during early ontogenesis and puberty. These effects result in permanent sex differences in brain structure. Activating effects are the result of hormonal fluctuations that occur throughout life and, in contrast to organising effects, are transient and reflect dynamic changes in functional brain organisation (for a review, see Cohen-Bendahan et al., 2005).

Organising effects are maximal during certain sensitive periods. The precise sensitive periods for organising effects are not known, however, it is generally accepted that gestation weeks 8-24 are a key period during ontogenesis, although increasing evidence suggests additional sensitive periods exist (Cohen-Bendahan et al., 2005). Activating effects refer to the transient effects of fluctuations in sex hormone levels on brain activity, functional brain organisation, and cognitive function (Luine, 2014). To investigate the activating effects of sex hormones (i.e., estradiol and progesterone), a large number of studies have taken advantage of the endogenous fluctuations in hormone levels that occur in young women during the menstrual cycle (Wisniewski, 1998).

The menstrual cycle is a recurring reproductive cycle, characterised by hormonal fluctuations and physiological changes in the ovaries and uterus. Each cycle begins with menstruation, and lasts approximately 28 days. The cycle can be divided into several phases, each characterised by a different hormonal profile. Throughout the menstrual phase (cycle days 1-5), circulating levels of estradiol and progesterone are low. At cycle day 6, estradiol begins to increase, reaching a peak just prior to ovulation; progesterone levels remain low throughout this phase (the follicular phase, cycle days 6-12). Ovulation typically occurs around cycle day 14, following the secretion of luteinising hormone. At this point, estradiol levels drop slightly. Following ovulation, the cells surrounding the egg undergo luteinisation. During this phase, estradiol and progesterone are secreted by the luteinised cells and estradiol levels reach a second, smaller peak while progesterone levels reach their maximum (luteal phase, cycle day 22). Estradiol and progesterone levels both fall rapidly (premenstrual phase, cycle days 24 - 28) before a new cycle begins. See Hausmann & Bayer (2010) for more details.

3. Sex hormones and lateralisation

Organising effects of sex hormones on lateralisation

Several clinical studies suggest that estrogen can influence FCAs during early development (Hines & Shipley, 1984). In a behavioural study, Hines and Shipley (1984) examined language lateralisation in women exposed to diethylstilbesterol (DES) during gestation. Diethylstilbesterol is a synthetic estrogen, administered to pregnant women to lower risk of miscarriage. These authors showed that language lateralisation was significantly increased in the offspring of DES-exposed women, compared to their unexposed sisters. Although contradictions exist (e.g. Smith & Hines, 2000), this finding suggests that high levels of prenatal estradiol may play a defeminising role in male development (Hausmann & Bayer, 2010).

Lateralisation across the menstrual cycle

Since 2000, a large body of evidence has developed, using a range of behavioural, electrophysiological, and neuroimaging techniques, demonstrating that lateralisation fluctuates across the menstrual cycle (Alexander et al., 2002; Bayer & Hausmann, 2011; Cowell et al., 2011; Hausmann, 2005; Hausmann & Güntürkün, 2000a, b, c; Hausmann et al., 2013; Hjelmervik et al., 2012; Hodgetts et al., 2015; 2017; Wadnerkar et al., 2008; Weis et al., 2008; 2011, but also see Dietrich et al., 1999; Kranczioch et al., 2016). However, the literature is inconsistent with respect to the direction of the laterality change and, subsequently, the mechanisms underlying the effects.

Several studies using lateralised tasks such as verbal dichotic listening (Cowell et al., 2011; Wadnerkar et al., 2008; Hampson, 1990a; Hampson, 1990b; Hjelmervik et al., 2012; Sanders & Wenmoth, 1998, Weekes & Zaidel, 1996) and spatial bisection (McCourt et al.,

1997) have shown that lateralisation increases during high-hormone phases as compared to low-hormone phases. However, other studies have demonstrated reductions in FCAs in high-hormone phases, relative to low-hormone phases using similar tasks, including verbal dichotic listening (Alexander et al., 2002; Altemus et al., 1989; Hodgetts et al., 2015; Mead & Hampson, 1996); music dichotic listening (Sanders & Wenmoth, 1998); line bisection (Hausmann, 2005; Hausmann et al., 2002), lexical decision (Hausmann & Güntürkün, 2000; Hausmann et al., 2002), figural comparison (Weis et al., 2011; Hausmann & Güntürkün, 2000), word matching (Weis et al., 2008), and face perception (Hausmann & Güntürkün, 2000; Hausmann et al., 2002).

Critically, a number of potential mechanisms underlying cycle effects on FCAs have been proposed. One suggestion is that sex hormones selectively influence activity of a specific hemisphere, although there is debate regarding which one. For example, using a visual-half field paradigm, Bibawi et al. (1995) presented normally cycling women with images of chairs, presented in pairs (one to the left and one to the right visual field). Participants were then required to identify which chairs had been presented from a 12-item array. Results showed that during the high-hormone luteal phase, women correctly identified more chairs presented to the right visual field than the left, indicative of a left hemispheric advantage. However, there was no hemispheric advantage during the low-hormone menstrual phase. Subsequently, the authors concluded that sex hormones selectively activate the left hemisphere. Using two dichotic listening paradigms (language and music, lateralised to the left and right hemispheres, respectively), Sanders and Wenmoth (1998) demonstrated greater language lateralisation during the luteal phase compared to the menstrual phase, but a greater FCA for music processing during the menstrual phase. Thus, these authors

concluded that right hemispheric activity was selectively suppressed during high-hormone cycle phases.

Critically, several studies (e.g. Wadnerkar et al., 2008; Sanders & Wenmoth, 1998; Weekes & Zaidel, 1996; Bibawi et al., 1995; McCourt et al., 1997) did not objectively verify participants' reported cycle phase by directly measuring hormone levels. Such measures are critical for menstrual cycle research, as evidence suggests that a significant proportion of menstrual cycles in young women aged 20-24 years (approx. 40%, Metcalf & Mackenzie, 1980) are non-ovulatory. Thus, these women may not experience the expected fluctuations of estradiol and/or progesterone. Indeed, many studies that did include hormone measures report a high rate of post-hoc participant exclusion on account of their hormone levels not falling into the expected ranges for each cycle phase (e.g., up to 46% participants were excluded in Gordon et al., 1986). As such, if some participants were tested just before or after the expected peaks in estradiol and progesterone levels, there would be greater variability in the degree of FCAs across participants.

In the early study by Hausmann and Güntürkün (2000) investigating FCAs across the menstrual cycle, direct hormone measurements were included. In this study, normally cycling women completed left-hemispheric (word matching) and right-hemispheric (figure matching, face discrimination) tasks, during both the low-hormone menstrual phase and the high-progesterone luteal phase. Cycle phase was verified by salivary hormone assays. In addition, a sample of men and a sample of post-menopausal women were tested at corresponding time intervals. The authors identified an interaction between cycle phase and FCAs in all tasks, indicative of a general reduction in FCAs during the high-progesterone luteal phase. In contrast, FCAs were stable across time in post-menopausal women and men. A second study

replicated these findings with the same tasks (Hausmann et al., 2002). In this study, normally cycling women were tested 15 times at three-day intervals. This allowed for a longitudinal analysis of the relationship between sex hormones and FCAs for longer than one menstrual cycle, as well as a cross-sectional analysis. For the figure-matching task, both analyses indicated a significant relationship between progesterone and reduced FCAS, resulting from an enhanced performance of the sub-dominant left hemisphere.

As these studies demonstrated FCAs for both left- and right-hemispheric tasks were reduced when levels of progesterone were high, it was suggested that sex hormones were not selectively influencing the activity of a particular hemisphere. Instead, Hausmann and Güntürkün (2000c) proposed that sex hormones affect FCAs by modulating interhemispheric interaction, a physiological process that affects both hemispheres. This mechanism is based on the assumption that the lateralisation of a cognitive process, to either hemisphere, arises due to inhibition of the non-dominant hemisphere by the dominant hemisphere (i.e. interhemispheric inhibition) via the corpus callosum (Chiarello & Maxfield, 1996; Cook, 1984). Specifically, Hausmann and Güntürkün (2000) argued that although cortico-cortical transmission is primarily excitatory, interhemispheric inhibition occurs because the lasting effect of callosal activity is inhibition of the contralateral hemisphere (Innocenti, 1980). This inhibition occurs because the majority of callosal projections terminate on pyramidal neurons, which subsequently activate GABAergic interneurons (Toyama & Matsunami, 1976). Moreover, it has been shown that callosal projections may also terminate directly on GABAergic interneurons (Conti & Manzoni, 1994). Both of these mechanisms would result in widespread inhibition of homotopic regions of the non-dominant hemisphere by the dominant hemisphere (Kawaguchi, 1992).

In the hypothesis of progesterone-mediated hemispheric decoupling, Hausmann and Güntürkün (2000c) proposed that high levels of progesterone during the luteal phase leads to a reduction of interhemispheric inhibition. This leads, in turn, to a functional decoupling of the two hemispheres and a reduction in lateralisation. Specifically, it was proposed that progesterone and metabolites, such as allopregnanolone, can reduce interhemispheric inhibition by suppressing the excitatory neural response to glutamate and increasing the inhibitory neural response to GABA (Hausmann & Güntürkün, 2000; Hausmann et al., 2002; Hausmann & Bayer, 2010). This view was supported by a number of physiological studies, demonstrating that progesterone suppresses the excitatory response of neurons to glutamate, while also increasing the inhibitory response of neurons to GABA (Smith et al., 1987a, 1987b). Further studies have shown that similar effects are obtained with combined estradiol and progesterone administration (Smith et al., 1987b). Thus, it was proposed that high levels of progesterone in the luteal phase might lead to a transient reduction in interhemispheric inhibition, and in turn, a reduction in lateralisation (Hausmann & Güntürkün, 2000; Hausmann et al., 2002).

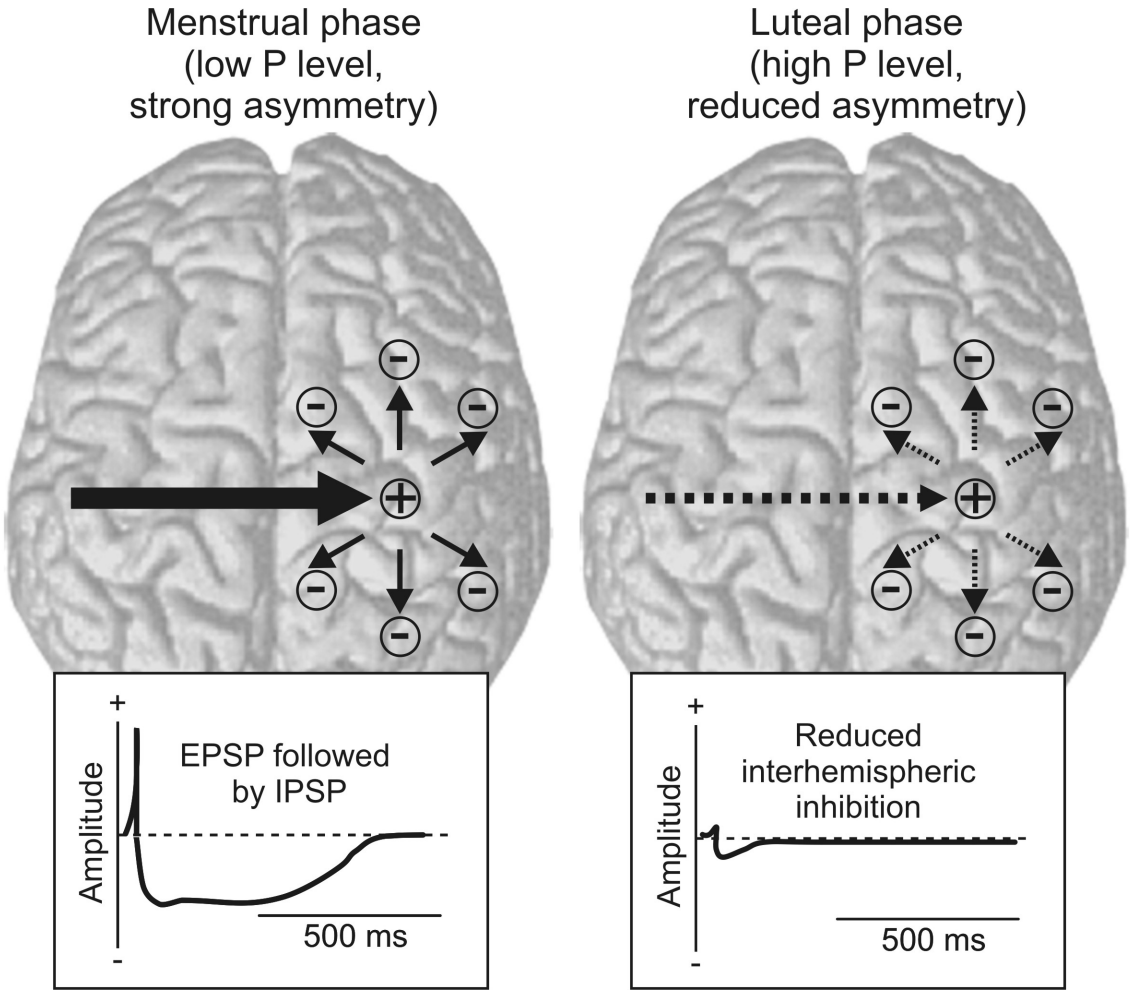

Figure 1. Schematic illustration of the original hypothesis of progesterone-modulated interhemispheric inhibition. Left figure illustrates the process of interhemispheric inhibition. Although the cortico-cortical transmission is mainly excitatory, the main and longer lasting effect in the contralateral hemisphere appears to be inhibitory, probably because most excitatory (glutamatergic) callosal fibers terminate on pyramidal neurons which then activate inhibitory (GABAergic) interneurons. These activated inhibitory interneurons could then induce a widespread inhibition in homotopic regions of the contralateral hemisphere. According to Hausmann and Güntürkün (2000; Hausmann et al., 2002), progesterone reduces cortico-cortical transmission during the midluteal phase by suppressing the excitatory responses of neurons to glutamate and by enhancing their inhibitory responses to GABA. The combined effect would result in the functional hemispheric decoupling, and thus to a temporal reduction in functional asymmetry (right figure). Adopted from Hausmann and Bayer (2010) and reprinted with permission from MIT Press.

A similar mechanism aiming to explain cycle-related effects of sex hormones to FCAs was previously proposed by Bianki and Filippova (1996, 2000), who were the first to investigate

the link between changes in FCAs in motor activity in the open field and stages of the estrous cycle in rats. Based on their findings, however, Bianki and Filippova (1996, 2000) suggested that higher levels of estrogen levels in the proestrus phase, during which ovarian follicles in rats mature, increased interhemispheric inhibition from the left hemisphere to the right hemisphere. This interhemispheric inhibition was significantly reduced in this study when estrogen levels dropped.

In line with Bianki and Filippova (1996, 2000), Weis et al. (2008) also reported evidence for the notion that estradiol levels can influence inter-hemispheric inhibition and FCAs. In this study, normally cycling women underwent functional magnetic resonance imaging (fMRI) while completing a word-matching task, identical to that used by Hausmann and Güntürkün (2000c). All women were tested during both the low-hormone menstrual phase and the high-estradiol follicular phase. A control group of males was tested at corresponding time intervals. Functional connectivity was assessed using psychophysical interaction analysis (PPI) to determine the inhibitory influence of the dominant left hemisphere on the non-dominant right hemisphere. Behaviourally, a significant left-hemispheric advantage was found in the menstrual phase, which was reduced in the follicular phase. In addition, PPI analysis revealed that the inhibitory influence of the left hemisphere over the right hemisphere fluctuated according to estradiol levels. Specifically, high levels of estradiol during the follicular phase were associated with reduced interhemispheric inhibition, and in turn, reduced FCAs. In contrast, no change in FCAs or interhemispheric inhibition was found in the male controls. Moreover, no significant difference was found when activity in left inferior frontal gyrus (a region critically involved in the word-matching task) was directly compared between the menstrual and follicular phases.

In contrast to Hausmann and Güntürkün (2000) who found that high progesterone levels (in combination with high estradiol levels) can reduce interhemispheric inhibition, Weis et al. (2008) showed that it was estradiol alone, not progesterone, which was associated with a reduction in interhemispheric inhibition. This finding is in line with other studies investigating the sex hormonal modulation of interhemispheric processes. For example, Hausmann et al. (2006) employed transcranial magnetic stimulation (TMS) to investigate the effect of sex hormones on transcallosal transfer. In this study, TMS was applied to the primary motor cortex to elicit suppression of tonic voluntary muscle activity in both the contralateral and ipsilateral side. The ipsilateral suppression (the ipsilateral silent period) is thought to be cortically mediated via excitatory transcallosal fibers that terminate on inhibitory interneurons (Hausmann et al., 2006). Therefore, the ipsilateral silent period can be used as an indirect measure of the connectivity between homotopic regions of the left and right motor cortices. Hausmann et al. (2006) showed that the ipsilateral silent period fluctuates across the menstrual cycle, with the largest suppression/inhibition during the luteal phase (high levels of estradiol and progesterone) compared to the follicular phase (high levels of estradiol only). Hausmann et al. (2013) reported additional evidence in support of this view. In this study, electroencephalography (EEG) was used to directly measure interhemispheric connectivity by using visual-evoked potentials to estimate interhemispheric transfer time (IHTT). The results showed that IHTT from right-to-left was longer during the luteal phase as compared to the menstrual phase. Additional analyses revealed that this effect was related to high levels of estradiol, as opposed to progesterone, suggested the different interhemispheric processes are modulated by different sex hormones (Hausmann et al., 2013).

In recent years, research into sex hormonal effects in the brain has expanded to investigate other aspects of functional connectivity, such as intrahemispheric connectivity (Weis et al., 2011). For example, using a figure-matching task, Weis et al. (2011) investigated whether reductions in FCA for this task were similar to those seen for the verbal task (Weis et al., 2008). Behaviourally, women demonstrated reduced FCAs during the luteal phase. In addition, fMRI data revealed cycle-phase related changes in functional connectivity *within* the task dominant hemisphere. Specifically, activation of right-hemispheric networks was reduced during the luteal phase, as compared to both the menstrual and the follicular phase. In addition, PPI analysis revealed cycle-related changes in functional connectivity, such that stronger functional connectivity between a right temporal seed region (fusiform gyrus) and heterotopic regions of the left hemisphere (e.g. precuneus, postcentral gyrus, inferior parietal lobule) was found during the luteal phase. Consequently, the authors suggest that sex hormones modulate not only interhemispheric inhibition between homotopic areas (Weis et al., 2008) but can also influence intrahemispheric integration, and interhemispheric connectivity between heterotopic brain regions (Weis et al., 2011). For a recent review on the potential neuroendocrine mechanisms underlying the effects of estradiol and progesterone on FCAs, see Hausmann (2017).

Top-down versus bottom-up effects

Several previous studies (Cowell et al., 2011; Hampson, 1990a,1990b; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008) suggested that left hemispheric language dominance was increased during cycle phases associated with high levels of estradiol. However, this was not a consistent finding, with other studies suggesting that high levels of estradiol led to a reduction in FCAs (Alexander et al., 2002; Altemus et al., 1989; Mead & Hampson, 1996;

Sanders & Wenmoth, 1998). Still further research showed that estradiol influenced language lateralisation, in particular when a high level of cognitive (top-down) control was required (Hjelmervik et al., 2012).

Hjelmervik et al. (2012) investigated hormonal effects on the top-down processes related to language lateralisation using a forced-attention dichotic listening paradigm. This task is a robust tool used to provide a behavioural measure of language lateralisation. It involves the simultaneous presentation of two different auditory stimuli, separately to the left and right ear. Participants are required to report which one of the stimuli they heard the most clearly. Typically, in healthy right-handed adults, this task reveals a bias favouring the right ear, indicative of left-hemispheric language lateralisation. However, the so-called right-ear advantage (REA) can be modulated by instructing participants to selectively attend to and report from either the left or the right ear specifically. In contrast to the non-forced condition, the forced-left condition requires a high level of cognitive control, as participants must override their bias towards the dominant right ear. In this study, normally cycling women completed the dichotic listening task three times across the cycle. A cycle-related effect was found only in the forced-left condition. In this condition, women demonstrated a greater left-ear advantage during the high-estradiol follicular phase, as compared to both the menstrual and luteal phases. The authors interpreted this finding as evidence of an active role of estradiol on cognitive control, and not on language lateralisation per se (Hjelmervik et al., 2012).

A recent study (Hodgetts et al., 2015) aimed to disentangle the effects of estradiol on top-down/bottom-up aspects of FCAs. It was predicted that if gonadal steroid hormones primarily affected the bottom-up processes related to language lateralisation (e.g. inter-hemispheric inhibition), estradiol and/or progesterone would reduce the dichotic listening bias across all

attention conditions. However, if high levels of gonadal hormones selectively affect top-down cognitive control, estradiol-related changes were expected only in the forced-left dichotic listening condition (Hjelmervik et al., 2012).

This study showed that language lateralisation was reduced when estradiol and progesterone levels were high, across all attention conditions. This suggests that the effect of sex hormones on cognitive control is marginal, and that the neuromodulatory properties of sex hormones on FCAs are due primarily to their influence over bottom-up processes. Given that the same effect was present for both right ear and left ear advantages, it is unlikely that the general reduction in language lateralisation is due to sex hormones selectively affecting one hemisphere. Instead, it was argued that this effect was due to the effect of sex hormones over interhemispheric inhibition. In line with this hypothesis, it was argued that the reduced REA in the non-forced and forced-right condition in participants with a relatively high level of estradiol might be due to reduced inhibition of the subdominant right hemisphere by the dominant left hemisphere. This would facilitate right hemisphere processing of stimuli presented to the left ear. Moreover, during the forced-left condition, it was argued that the top-down control process, required to successfully divert attention away from the dominant right ear in favour of the left ear, results in a shift of activation from the left hemisphere to the right hemisphere. As such, if estradiol is exacting a neuromodulatory effect on interhemispheric inhibition, the reduced LEA in the forced-left condition may be due to a reduction of inhibition from the right hemisphere over the left hemisphere. This would lead to an increase in left-hemispheric processing of stimuli presented to the right ear, and a reduction in the LEA.

Given that interhemispheric inhibition is a universal physiological process that underpins

lateralisation, it follows that high estradiol levels should also reduce biases for tasks lateralised to the right hemisphere. Therefore, a follow-up study (Hodgetts et al., 2017) was designed to investigate this notion, using two differently lateralised dichotic listening tasks. In this study, a linguistic and an emotional prosody dichotic listening task were used, designed to assess left and right hemispheric FCAs, respectively. For this study, it was hypothesised that if estradiol influenced the bottom-up processes of lateralisation (i.e., interhemispheric inhibition), reduced dichotic listening biases should be found in both tasks, regardless of the attention condition, when estradiol levels are high. In contrast, if estradiol influenced cognitive control, increased biases should be found in the forced-left and forced-right conditions of the linguistic and emotional dichotic listening tasks, respectively. However, no modulatory effect of sex hormones on language lateralisation was found. Moreover, in the emotional prosody task, high estradiol levels were marginally associated with a reduction in FCAs in the forced-right condition, suggesting that estradiol had a small effect on the top-down aspect of FCAs in this task.

Critically, in this study, the degree of lateralisation yielded in both tasks was considerably larger than those in either Hodgetts et al. (2015) or Hjelmervik et al. (2012). It was argued that this was due to a strong, stimulus-driven (bottom-up) effect, which resulted in the task being less cognitively demanding. As such, it was suggested that the stimulus-driven effect was so strong that any sex hormonal effects on FCAs were masked. It was also noted that the only dichotic listening condition to show any estradiol-related trends was the cognitive control (forced-right) condition of the emotional task. Moreover, this condition yielded the smallest bias and the lowest target detection rate of all the forced-attention conditions. Thus, it was argued that these dichotic listening tasks associated with high target detection rates

and large laterality biases, are less susceptible to the modulatory effects of sex hormones which may be due to particularly strong stimulus-driven effects masking any sex hormone-related effect on FCAs.

These studies, in conjunction with Hjelmervik et al. (2012) suggest that estradiol (and potentially progesterone) are, in principle, capable of modulating both top-down and bottom-up processes related to FCAs. Specifically, while these studies suggest that sex hormones do possess neuromodulatory properties that can influence FCAs, these effects may be reduced when task demands are low.

4. Sex hormones and resting state connectivity

In light of evidence showing that sex hormones can affect task-related functional connectivity, recent research has begun to investigate sex hormonal effects on functional connectivity in the brain at rest. In the absence of a specific cognitive task, the brain exhibits a pattern of low-frequency oscillations in the BOLD signal (approx. 0.01-0.1Hz, Damoiseaux et al., 2006). Biswal et al. (1995) were the first to demonstrate the resting state fMRI (rs-fMRI) approach, revealing temporally correlated time courses of low frequency oscillations within the sensory motor cortex. Subsequent research using rs-fMRI has identified a number of networks that are spatially comparable to task-related activations (Damoiseaux et al., 2006), such as executive function (Laird et al., 2011; Seeley et al., 2007), language (Laird et al., 2011; Tie et al., 2014) and memory (Laird et al., 2011; Vincent et al., 2006) resting state networks. Given that functional connectivity is susceptible to endogenous hormone fluctuations across the menstrual cycle (Weis et al., 2008; Weis et al., 2011), sex hormones may also be capable of influencing resting state connectivity. This is a critical issue, as it would suggest that sex hormone effects on task performance and functional brain organisation may not be due to an

effect on task-related brain activity, but reflective of their effect on task-independent intrinsic connectivity.

Five recent studies have investigated the effect of cycle-related hormone fluctuations on resting state network connectivity but with inconsistent results (Arélin et al., 2015; De Bondt et al., 2015; Hjelmervik et al., 2014; Weis et al., 2017; Petersen et al., 2014). Using a between-subjects design, Petersen et al. (2014) investigated resting state functional connectivity under different hormonal conditions, across the menstrual cycle in normally cycling women, and in oral contraceptive pill users. Normally cycling women were tested either in the menstrual phase (termed early follicular by the authors) or the luteal phase. This study reported increased functional connectivity between the right anterior cingulate cortex (ACC) and the executive control network, and reduced functional connectivity between the left angular gyrus and the anterior default mode network (DMN) during the luteal as compared to the menstrual phase. Using a repeated-measures design, Weis et al. (2017) investigated functional connectivity of the auditory and default mode networks in normally cycling women, and a control sample of men. This study demonstrated increased connectivity between regions of left prefrontal cortex (PFC) and the DMN in women during the menstrual phase, compared to the follicular and luteal phases. In contrast, DMN connectivity was stable in men. In the auditory network, no effect of cycle phase/session was found, and no interaction between cycle phase/session and sex was found. In contrast, Hjelmervik et al. (2014) investigated four fronto-parietal cognitive control networks, using a repeated measures design. No cycle-related effect on functional connectivity was found. Similarly, De Bondt et al. (2015) did not find any effect of sex hormones in fronto-parietal networks (termed 'executive control networks' by the authors). However, analysis of the DMN revealed

an increase in functional connectivity in the luteal phase, relative to the follicular phase, between the cuneus and the network. Arélin et al. (2015) conducted 32 resting state scans in a single subject across four menstrual cycles. Results showed that high progesterone levels were associated with increased connectivity of the dorsolateral PFC and the sensorimotor cortex to the resting state network. Further analysis revealed that high progesterone levels were associated with higher functional connectivity between right dorsolateral prefrontal cortex bilateral sensorimotor cortex, and the hippocampus, as well as between the left dorsolateral PFC and bilateral hippocampi.

The finding of a menstrual cycle effect on DMN connectivity (e.g. Petersen et al., 2014; Weis et al., 2017) presents a number of implications, for both task-based and rs-fMRI. Specifically, this study suggests that DMN connectivity is not stable in women, and is confounded by sex hormonal fluctuations across the menstrual cycle. However, this cannot be generalised to other cognitive networks. This finding also has implications for behavioural studies. Critically, this finding suggests that the effect of gonadal steroid hormones on behaviours underpinned by regions of DMN, such as the medial PFC, orbitofrontal cortex and cingulate cortex, might at least to some extent depend on resting-state connectivity, as opposed to task-related activity.

5. Estrogen and the prefrontal cortex

As mentioned earlier, there is empirical evidence suggesting that estradiol is capable of modulating both top-down and bottom-up processes related to FCAs. In line with this assumption, a number of physiological studies, in both humans and non-human primates, have shown that estrogen receptors are present in the PFC. For example, Wang et al. (2010) demonstrated that estrogen receptor alpha (ERα) was present in excitatory synapses of the

dorsolateral PFC of female rhesus monkeys. In a human post-mortem study, Bixo et al. (1995) demonstrated that the concentration of estradiol in frontal cortex is higher compared to other cortical regions, such as temporal cortex and cingulate cortex.

Estrogen and cognitive control processes

As mentioned earlier in this review, using the dichotic listening paradigm, Hjelmervik et al. (2012) demonstrated that cognitive control improved during the high-estradiol follicular phase, and that this was directly associated with an increase in estradiol levels compared to the menstrual phase. This finding was in line with a number of menstrual cycle studies which have similarly demonstrated the enhancing influence of estrogen on cognitive control (Colzato et al., 2012; Hampson, 1990a, 1990b; Hampson & Morley, 2013; Hjelmervik et al., 2012; Rosenberg & Park, 2002). Rosenberg and Park (2002) demonstrated that verbal working memory ability fluctuated across the menstrual cycle, with participants' best performance occurring during high estradiol phases. However, this study did not include any direct hormone measurements (see also Craig et al., 2007). Hampson and Morley (2013) investigated estradiol effects on working memory by comparing performance between groups of women with naturally differing levels of estradiol. In this study, women were classified as high/low in estradiol via a post-hoc median split based on saliva assays. It was found that women with relatively high levels of estradiol committed significantly fewer errors in a spatial working memory task. Similarly, Colzato et al. (2012) demonstrated that inhibitory control varies across the menstrual cycle, with women in the high-estradiol follicular phase exhibiting better inhibitory control relative to the menstrual and the luteal phases (but see Colzato et al., 2010).

Due to the link between aging, the menopause, and cognitive decline (Henderson, 2008), the majority of evidence suggesting that estradiol can improve executive functioning has been conducted in post-menopausal women receiving hormone therapy. Indeed, it has been suggested that it is particularly frontally mediated functions that show decline following menopause (Fuh et al., 2006; Thilers et al., 2010). Following a systematic review, Maki and Sundermann (2009) concluded that estradiol therapy has beneficial effects on several cognitive control processes, including working memory (Duff & Hampson, 2000), problem solving (Erickson et al., 2007) and source memory (Wegesin & Stern, 2007).

In addition to these behavioural studies, evidence for an enhancing effect of estrogen therapy on PFC functioning and cognitive control processes has been found in neuroimaging studies. Joffe et al. (2006) conducted a randomised, double-blind, placebo-controlled fMRI study of estradiol effects on prefrontal cognitive functioning in 52 peri-/post-menopausal women using a battery of executive function tasks. Behaviourally, the enhancing effect of estradiol was restricted to an improvement in response inhibition only. However, the fMRI data revealed increased activation in several frontal cortical regions associated with cognitive control, including inferior frontal gyrus, dorsolateral PFC and posterior parietal regions. Subsequently, the authors conclude that estradiol therapy increases the "functional capacity" of the PFC, via the recruitment of additional frontal regions, leading to improvements in executive functioning.

Critically, the enhancing effect of estradiol on executive functions is inconsistent (Colzato & Hommel, 2014). For example, a high level of estradiol during the follicular phase has been associated with impaired response inhibition in a stop-signal reaction time task, as compared to both the luteal and the menstrual phases (Colzato et al., 2010). This is in direct

contrast to the enhancing effect of estradiol on response inhibition demonstrated by Colzato et al. (2012). Additional studies have linked high levels of estradiol to detriments in working memory (Gasbarri et al., 2008) and increased susceptibility to interference in the Stroop task (Hatta & Nagaya, 2009). Moreover, a recent study reported no effect of cycle-related estradiol fluctuations on a range of tasks requiring cognitive control, including working memory and verbal learning (Mihalj et al., 2014).

In light of these inconsistencies, it has recently been suggested that the effect of estradiol on cognition is dependent on individual differences in baseline dopaminergic function (Colzato & Hommel, 2014). Dopaminergic effects on cognition tasks follow an "inverted-U" function, such that performance improves with medium dopamine levels, and deteriorates with high/low levels. Given that estradiol is associated with increased dopamine turnover rates, Colzato and Hommel (2014) speculated that participants with low baseline dopamine levels, and thus poor cognitive performance, might benefit from high levels of estradiol and concurrent increases in dopamine. In contrast, those with high baseline dopamine levels, and good cognitive performance, would experience detrimental effects with high estradiol levels, as dopamine increases beyond an optimal point. A study by Jacobs and D'Esposito (2011) supports this notion. In this study, the authors demonstrated an interactive effect of baseline dopamine levels (indexed by variation associated with the catechol-O-methyltransferase $Val^{158}Met$ genotype) and menstrual cycle phase on a working memory task. Specifically, women with low baseline dopamine exhibited poor working memory during the menstrual phase (low estradiol), but improved during the follicular phase (high estradiol). In contrast, participants with high baseline dopamine demonstrated the opposite pattern, good performance when estradiol was low, and impairments when estradiol was high. Taken together, these findings suggest that while estradiol can have an enhancing effect on

executive functioning and cognitive control abilities, this effect is subject to individual differences in neurophysiology.

6. Clinical implications

The findings also in this research area also have some tentative clinical implications as well, particularly for the notion that estradiol acts as an antipsychotic in schizophrenia (Häfner, 2005; Riecher-Rössler et al., 1994; Kulkarni et al., 2013; for a review: Riecher-Rössler & Kulkarni, 2010). As schizophrenia and psychosis have consistently been associated with extensive deficits in executive function (Aas et al., 2014; Gold, 2004; Johnson-Selfridge & Zalewski, 2001; Roiser et al., 2013; Weisbrod et al., 2000), it is possible that estradiol could be beneficial to the cognitive symptoms of the illness. Interestingly, a recent study suggested that newly diagnosed patients with schizophrenia yielded higher levels of progesterone, compared to healthy controls (Bicikova et al., 2013). However, it is not clear yet whether progesterone alone can also modulate schizophrenic symptomatology, or if this is due to an interactive effect with estradiol (Ko et al., 2006).

In a similar manner, the present literature on sex hormonal effects on the brain and cognition also has some tentative implications for the notion of stratified medicine, which features highly in, for example, the current National Health Service (NHS) strategy in the United Kingdom or in the prevention and health care system in Germany. This notion has evolved from earlier conceptualisations of personalised or tailored treatment programmes, referred to as *gender-specific medicine* (Legato, 2017) or *sex-sensitive psychiatry* (e.g. Riecher-Rössler & Rohde, 2001). Both concepts refer to the practice of medical care in such a way that the planning, delivery, and method of treatment have been tailored to take sex differences into account. For example, with reference to schizophrenia and psychosis, this

might involve the tailoring of medication regimens to account for changes in symptom severity across the menstrual cycle. Indeed, a number of early clinical studies that have demonstrated greater improvement in psychotic symptoms in patients given an adjunctive estradiol treatment (e.g. Kulkarni et al., 1996; 2001; Riecher-Rössler & Kulkarni, 2010). However, given that a number of studies not yielding an "enhancing" effect of estradiol on cognition, it could be argued that adjunctive hormonal therapies may not be suitable for all patients. As such, the additional of such therapies may require a "trial and error" approach to treatment planning. This would involve altering medication regimens until the best combination is found for that particular patient. Such an approach has the obvious benefit of leading to a successful outcome for that particular patient. However, this approach could prove costly, both economically (time spent by clinicians working with individual cases, cost of multiple medications being administered in the short term) and personally for the patient. Critically, hormone therapies are characterised by a range of side effects, and it is currently not clear how they might interact with standard antipsychotic treatments. As such, there is a high need for further clinical research in order to fully determine how such treatments might be implemented.

Schizophrenia has also been consistently associated with atypical FCAs (Løberg et al., 1999; Løberg et al., 2004; Oertel et al., 2010; Oertel-Knochel & Linden, 2011). Given that sex hormones are capable of influencing a number of processes related to FCAs, a possible question for future research concerns the relationship between the modulation of FCAs by gonadal hormones in atypically lateralised patients. Schizophrenia is also characterised aberrant functional connectivity in the DMN (Broyd et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Garrity et al., 2007; Whitfield-Gabrieli et al., 2008). As such, the findings of a

menstrual cycle effect on the DMN (Petersen et al., 2014; Weis et al., 2017) raises questions regarding how this network is affected by sex hormones in patients, and the potential behavioural consequences of this.

7. Conclusions and future directions.

In conclusion, despite growth in the number of studies in the area since 2000, several ongoing debates concerning the mechanisms by which gonadal steroid hormones can affect brain lateralisation and cognition remain. At present, it may be argued that are three potential mechanisms by which hormones influence FCAs: (1) sex hormones affect one hemisphere exclusively, (2) sex hormones affect the activity of either hemisphere, or (3) sex hormones affect the processes related to interhemispheric interaction. Indeed, it is unlikely that only one mechanism can fully account for the range of hormonal effects reported throughout the literature (Hausmann, 2017). For example, recent studies from our group suggest that estradiol effects on FCAs are task-dependent, and that tasks which yield a large degree of asymmetry due to low task demands might be less likely to demonstrate sex hormonal effects (Hodgetts et al., 2015; 2017). Taken together, these findings suggest that differences in the degree of asymmetry produced by an individual task might account for some of the inconsistencies in the literature regarding the effect of sex hormones on FCAs. Similarly, the results across a number of behavioural studies, from our group and others, have important implications for our understanding of estradiol-related effects on executive function and cognitive control. Perhaps most importantly, they suggest that the notion of estradiol enhancing cognitive control (Colzato et al., 2012; Hampson, 1990a, 1990b; Hampson & Morley, 2013; Hjelmervik et al., 2012; Rosenberg & Park, 2002) is too simplistic. Rather, the current literature seems to indicate that the enhancing effect of estradiol is sensitive to

individual differences, potentially due to underlying differences in neurophysiology. Whether the effect of estradiol is similarly selective for all aspects of executive function (e.g., response inhibition, set-switching) remains a question for future research, however, such a selective effect might help explaining the presence of inconsistencies.

References

Aas, M., Dazzan, P., Mondelli, V., Melle, I., Murray, R. M., & Pariante, C. M. (2014). A systematic review of cognitive function in first-episode psychosis, including a discussion on childhood trauma, stress, and inflammation. *Frontiers in Psychiatry, 4*. doi:10.3389/fpsyt.2013.00182

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*(8), 1293-1299. doi:10.1016/s0028-3932(01)00220-2

Altemus, M., Wexler, B. E., & Boulis, N. (1989). Changes in perceptual asymmetry with the menstrual-cycle. *Neuropsychologia, 27*(2), 233-240. doi:10.1016/0028-3932(89)90174-7

Arelin, K., Mueller, K., Barth, C., Rekkae, P. V., Kratzsch, J., Burmann, I., . . . Sacher, J. (2015). Progesterone mediates brain functional connectivity changes during the menstrual cycle-a pilot resting state MRI study. *Frontiers in Neuroscience, 9*. doi:10.3389/fnins.2015.00044

Ashton, R., & McFarland, K. (1991) A simple dual-task study of laterality, sex-differences and handedness. Cortex, 27(1), 105-109.

Bayer, U., & Hausmann, M. (2011). Estrogen treatment affects brain functioning after menopause. *Menopause international, 17*(4), 148-152. doi:10.1258/mi.2011.011105

Bianki, V. L., Filippova, E. B. (1996). Influence of the estral phases on the hemispheric asymmetry in rats. Nauchnye Doklady Vysshei Shkoly. Biologicheskie Nauki, 46, 753-761.

Bianki, V. L., Filippova, E. B. (2000). Sex differences in lateralization in the animal brain. Newark, NJ Harwood Academic Publishers.

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. doi:10.1016/0028-3932(94)00103-v

Bicikova, M., Hill, M., Ripova, D., Mohr, P., & Hampl, R. (2013). Determination of steroid metabolome as a possible tool for laboratory diagnosis of schizophrenia. *Journal of Steroid Biochemistry and Molecular Biology, 133*, 77-83. doi:10.1016/j.jsbmb.2012.08.009

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine, 34*(4), 537-541. doi:10.1002/mrm.1910340409

Bixo, M., Backstrom, T., Winblad, B., & Andersson, A. (1995). Estradiol and testosterone in specific regions of the human female brain in different endocrine states. *Journal of Steroid Biochemistry and Molecular Biology, 55*(3-4), 297-303. doi:10.1016/0960-0760(95)00179-4

Borod, J. C., Koff, E., & White, B. (1983). Facial asymmetry in posed and spontaneous expressions of emotion. *Brain and Cognition*, *2*(2), 165-175. http://doi.org/10.1016/0278-2626(83)90006-4

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S. (2009). Default-mode brain dysfunction in mental disorders: A systematic review. *Neuroscience and Biobehavioral Reviews, 33*(3), 279-296. http://doi.org/10.1016/j.neubiorev.2008.09.002

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network:

Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences, 1124*, 1-38. http://doi.org/10.1196/annals.1440.011

Chiarello, C., & Maxfield, L. (1996). Varieties of interhemispheric inhibition, or how to keep a good hemisphere down. *Brain and Cognition, 30*(1), 81-108. doi:10.1006/brcg.1996.0006

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.

Cohen-Bendahan, C. 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*(2), 353-384. doi:10.1016/j.neubiorev.2004.11.004

Colzato, L. S., Hertsig, G., Van Den Wildenberg, W. P. M., & Hommel, B. (2010). Estrogen modulates inhibitory control in healthy human females: evidence from the stop-signal paradigm. *Neuroscience, 167*(3), 709-715. doi:10.1016/j.neuroscience.2010.02.029

Colzato, L. S., Pratt, J., & Hommel, B. (2012). Estrogen modulates inhibition of return in healthy human females. *Neuropsychologia, 50*(1), 98-103. doi:10.1016/j.neuropsychologia.2011.11.003

Conti, F., & Manzoni, T. (1994). The neurotransmitters and postsynaptic actions of callosally projecting neurons. *Behavioural Brain Research, 64*(1-2), 37-53. doi: 10.1016/0166-4328(94)90117-1

Cook, N. D. (1984). Callosal inhibition - the key to the brain code. *Behavioral Science, 29*(2), 98-110. doi:10.1002/bs.3830290203

Corballis, M. C., & Sidey, S. (1993). Effects of concurrent memory load on visual-field differences in mental rotation. *Neuropsychologia, 31*(2), 183-197.

Cowell, P. E., Ledger, W. L., Wadnerkar, M. B., Skilling, F. M., & Whiteside, S. P. (2011).

Hormones and dichotic listening: Evidence from the study of menstrual cycle effects. *Brain and Cognition, 76*(2), 256-262. doi:10.1016/j.bandc.2011.03.010

Craig, M. C., Fletcher, P. C., Daly, E. M., Rymer, J., Cutter, W. J., Brammer, M., . . . Murphy, D. G. M. (2007). Gonadotropin hormone releasing hormone agonists alter prefrontal function during verbal encoding in young women. *Psychoneuroendocrinology, 32*(8-10), 1116-1127. doi:10.1016/j.psyneuen.2007.09.009

Damoiseaux, J. S., Rombouts, S., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America, 103*(37), 13848-13853. doi:10.1073/pnas.0601417103

De Bondt, T., Smeets, D., Pullens, P., Van Hecke, W., Jacquemyn, Y., & Parizel, P. M. (2015). Stability of resting state networks in the female brain during hormonal changes and their relation to premenstrual symptoms. *Brain Research, 1624*, 275-285. doi:10.1016/j.brainres.2015.07.045

Dietrich, T., Krinks, T., Willmes, K., Neulen, J., Kemeny, S., Erberich, S., Thron, A., & Sturm, W. (1999). Cortical activation pattern of two neuropsychological tasks during different phases of the menstrual cycle: A preliminary fMRI study. *NeuroImage*, *9*, p. S331.

Duff, S. J., & Hampson, E. (2000). A beneficial effect of estrogen on working memory in postmenopausal women taking hormone replacement therapy. *Hormones and Behavior, 38*(4), 262-276. doi:10.1006/hbeh.2000.1625

Erickson, K. I., Colcombe, S. J., Elavsky, S., McAuley, E., Korol, D. L., Scalf, P. E., & Kramer, A. F. (2007). Interactive effects of fitness and hormone treatment on brain health in postmenopausal women. *Neurobiology of Aging, 28*(2), 179-185. doi:10.1016/j.neurobiolaging.2005.11.016

Fuh, J. L., Wang, S. J., Lee, S. J., Lu, S. R., & Juang, K. D. (2006). A longitudinal study of cognition change during early menopausal transition in a rural community. *Maturitas, 53*(4), 447-453. doi:10.1016/j.maturitas.2005.07.009

Garrity, A. G., Pearlson, G. D., McKiernan, K., Lloyd, D., Kiehl, K. a., & Calhoun, V. D. (2007). Aberrant "default mode" functional connectivity in schizophrenia. *American Journal of Psychiatry, 164*(3), 450-457. http://doi.org/10.1176/appi.ajp.164.3.450

Gasbarri, A., Pompili, A., d'Onofrio, A., Cifariello, A., Tavares, M. C., & Tomaz, C. (2008). Working memory for emotional facial expressions: Role of the estrogen in young women. *Psychoneuroendocrinology, 33*(7), 964-972. doi:10.1016/j.psyneuen.2008.04.007.

Gold, J. M. (2004). Cognitive deficits as treatment targets in schizophrenia. *Schizophrenia Research, 72*(1), 21-28. doi:10.1016/j.schres.2004.09.008

Gordon, H. W., Corbin, E. D., & Lee, P. A. (1986). Changes in specialized cognitive function following changes in hormone levels. *Cortex, 22*(3), 399-415.

Häfner, H. (2005). Gender differences in schizophrenia. *Estrogen Effects in Psychiatric Disorders*, *28*, 53-94. http://doi.org/10.1007/3-211-27063-9_3

Hampson, E. (1990a). Estrogen-related variations in human spatial and articulatory-motor skills. *Psychoneuroendocrinology, 15*(2), 97-111. doi:10.1016/0306-4530(90)90018-5

Hampson, E. (1990b). Variations in sex-related cognitive-abilities across the menstrual-cycle. *Brain and Cognition, 14*(1), 26-43. doi:10.1016/0278-2626(90)90058-v

Hampson, E., & Morley, E. E. (2013). Estradiol concentrations and working memory performance in women of reproductive age. *Psychoneuroendocrinology, 38*(12), 2897-2904. doi:10.1016/j.psyneuen.2013.07.020

Hatta, T., & Nagaya, K. (2009). Menstrual Cycle Phase Effects on Memory and Stroop Task Performance. *Archives of Sexual Behavior, 38*(5), 821-827. doi:10.1007/s10508-008-9445-7

Hausmann, M. (2005). Hemispheric asymmetry in spatial attention across the menstrual cycle. *Neuropsychologia, 43*(11), 1559-1567. doi:10.1016/j.neuropsychologia.2005.01.017

Hausmann, M. (2017). Why sex hormones matter for neuroscience: a very short review on sex, sex hormones, and functional brain asymmetries. *Journal of Neuroscience Research, 95*(1-2), 40-49. doi:10.1002/jnr.23857

Hausmann, M., Bayer, U., 2010. Sex hormonal effects on hemispheric asymmetry and interhemispheric interaction, in: Hugdahl, K., Westerhausen, R. (Eds.), The two halves of the brain: Information processing in the cerebral hemispheres. Cambridge, MA: MIT Press. 287-312.

Hausmann, M., Becker, C., Gather, U., & Gunturkun, O. (2002). Functional cerebral asymmetries during the menstrual cycle: a cross-sectional and longitudinal analysis. *Neuropsychologia, 40*(7), 808-816. doi:10.1016/s0028-3932(01)00179-8

Hausmann, M., Behrendt-Körbitz, S., Kautz, H., Lamm, C., Radelt, F., & Güntürkün, O. (1998). Sex differences in oral asymmetries during wordrepetition. Neuropsychologia, 36(12), 1397-1402. http://doi.org/10.1016/S0028-3932(98)00027-X

Hausmann, M., Günürkün, O. (2000a). Der Einfluss von Sexualhormonen auf funktionelle cerebrale Asymmetrien. Zeitschrift für Neuropsychologie, 11(4), 203-215.

Hausmann, M., Günürkün, O. (2000b). Progesteron und die interhemisphärische Interaktion. Zeitschrift für Neuropsychologie, 11(4), 229-232.

Hausmann, M., & Güntürkün, O. (2000c). Steroid fluctuations modify functional cerebral

asymmetries: The hypothesis of progesterone-mediated interhemispheric decoupling. *Neuropsychologia, 38*(10), 1362-1374. http://doi.org/10.1016/S0028-3932(00)00045-2

Hausmann, M., Hamm, J. P., Waldie, K. E., & Kirk, I. J. (2013). Sex hormonal modulation of interhemispheric transfer time. *Neuropsychologia, 51*(9), 1734-1741. doi:10.1016/j.neuropsychologia.2013.05.017

Hausmann, M., Tegenthoff, M., Sanger, J., Janssen, F., Gunturkun, O., & Schwenkreis, P. (2006). Transcallosal inhibition across the menstrual cycle: A TMS study. *Clinical Neurophysiology, 117*(1), 26-32. doi:10.1016/j.clinph.2005.08.022

Hines, M., & Shipley, C. (1984). Prenatal exposure to diethylstilbestrol (des) and the development of sexually dimorphic cognitive-abilities and cerebral lateralization. *Developmental Psychology, 20*(1), 81-94. doi:10.1037/0012-1649.20.1.81

Hirnstein, M., Hugdahl, K., & Hausmann, M. (2014). How brain asymmetry relates to performance - a large-scale dichotic listening study (vol 4, 997, 2014). *Frontiers in Psychology, 5*. doi:10.3389/fpsyg.2014.00058

Hiscock, M., Inch, R., Hawryluk, J., Lyon, P. J., & Perachio, N. (1999). Is there a sex difference in human laterality? 3. An exhaustive survey of tactile laterality studies from six neuropsychology journals. *Journal of Clinical and Experimental Neuropsychology, 21*(1), 17-28. doi:10.1076/jcen.21.1.17.944

Hiscock, M., Inch, R., Jacek, C., Hiscockkalil, C., & Kalil, K. M. (1994). Is there a sex difference in human laterality? 1: An exhaustive survey of auditory laterality studies from 6 neuropsychology journals. *Journal of Clinical and Experimental Neuropsychology, 16*(3), 423-435. doi:10.1080/01688639408402653

Hiscock, M., Israelian, M., Inch, R., Jacek, C., & Hiscockkalil, C. (1995). Is there a sex difference

in human laterality? 2. An exhaustive survey of visual laterality studies from 6 neuropsychology journals. *Journal of Clinical and Experimental Neuropsychology, 17*(4), 590-610. doi:10.1080/01688639508405148

Hiscock, M., Perachio, N., & Inch, R. (2001). Is there a sex difference in human laterality? 4. An exhaustive survey of dual-task interference studies from six neuropsychology journals. *Journal of Clinical and Experimental Neuropsychology, 23*(2), 137-148. doi:10.1076/jcen.23.2.137.1206

Hjelmervik, H., Hausmann, M., Osnes, B., Westerhausen, R., & Specht, K. (2014). Resting States Are Resting Traits - An fMRI Study of Sex Differences and Menstrual Cycle Effects in Resting State Cognitive Control Networks. *Plos One, 9*(7). doi:10.1371/journal.pone.0103492

Hjelmervik, H., Westerhausen, R., Osnes, B., Endresen, C. B., Hugdahl, K., Hausmann, M., & Specht, K. (2012). Language lateralization and cognitive control across the menstrual cycle assessed with a dichotic-listening paradigm. *Psychoneuroendocrinology, 37*(11), 1866-1875. doi:10.1016/j.psyneuen.2012.03.021

Hodgetts, S., Weis, S., & Hausmann, M. (2015). Sex hormones affect language lateralisation but not cognitive control in normally cycling women. *Hormones and Behavior, 74*, 194-200. doi:10.1016/j.yhbeh.2015.06.019

Hodgetts, S., Weis, S., & Hausmann, M. (2017). Estradiol-related variations in top-down and bottom-up processes of cerebral lateralization. *Neuropsychology, 31*(3), 319-327. doi:10.1037/neu0000338

Hugdahl, K., Westerhausen, R., Alho, K., Medvedev, S., Laine, M., & Hamalainen, H. (2009). Attention and cognitive control: Unfolding the dichotic listening story. *Scandinavian Journal of Psychology, 50*(1), 11-22. doi:10.1111/j.1467-9450.2008.00676.x

Innocenti, G. M. (1980). The primary visual pathway through the corpus-callosum - morphological and functional-aspects in the cat. *Archives Italiennes De Biologie, 118*(2), 124-188.

Jacobs, E., & D'Esposito, M. (2011). Estrogen Shapes Dopamine-Dependent Cognitive Processes: Implications for Women's Health. *Journal of Neuroscience, 31*(14), 5286-5293. doi:10.1523/jneurosci.6394-10.2011

Joffe, H., Hall, J. E., Gruber, S., Sarmiento, I. A., Cohen, L. S., Yurgelun-Todd, D., & Martin, K. A. (2006). Estrogen therapy selectively enhances prefrontal cognitive processes: a randomized, double-blind, placebo-controlled study with functional magnetic resonance imaging in perimenopausal and recently postmenopausal women. *Menopause-the Journal of the North American Menopause Society, 13*(3), 411-422. doi:10.1097/01.gme.0000189618.48774.7b

Johnson-Selfridge, M., & Zalewski, C. (1998). Moderator variables of executive functioning in schizophrenia: Meta-analytic findings. *Archives of Clinical Neuropsychology, 13*(1), 59-59.

Ko, Y. H., Joe, S. H., Cho, W., Park, J. H., Lee, J. J., Jung, I. K., . . . Kim, S. H. (2006). Effect of hormone replacement therapy on cognitive function in women with chronic schizophrenia. *International Journal of Psychiatry in Clinical Practice, 10*(2), 97-104. doi:10.1080/13651500500526235

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

Kranzcioch, C., Lindig, A., Hausmann, M. (2016). Sex hormones modulate neurophysiological correlates of visual temporal attention. *Neuropsychologia, 91*, 86-98.

Kulkarni, J., deCastella, A., Smith, D., Taffe, J., Keks, N., & Copolov, D. (1996). A clinical trial of

the effects of estrogen in acutely psychotic women. *Schizophrenia Research, 20*(3), 247-252. doi:10.1016/0920-9964(96)82949-5

Kulkarni, J., Gavrilidis, E., Worsley, R., Van Rheenen, T., & Hayes, E. (2013). The role of estrogen in the treatment of men with schizophrenia. *International journal of endocrinology and metabolism, 11*(3), 129-136. doi:10.5812/ijem.6615

Kulkarni, J., Riedel, A., de Castella, A. R., Fitzgerald, P. B., Rolfe, T. J., Taffe, J., & Burger, H. (2001). Estrogen - a potential treatment for schizophrenia. *Schizophrenia Research, 48*(1), 137-144. doi:10.1016/s0920-9964(00)00088-8

Laird, A. R., Fox, P. M., Eickhoff, S. B., Turner, J. A., Ray, K. L., McKay, D. R., . . . Fox, P. T. (2011). Behavioral Interpretations of Intrinsic Connectivity Networks. *Journal of Cognitive Neuroscience, 23*(12), 4022-4037.

Legato, M. J. (2017). *Principles of gender-specific medicine.* (3. Aufl.). London: Elsevier Inc.

Loberg, E. M., Hugdahl, K., & Green, M. F. (1999). Hemispheric asymmetry in schizophrenia: A "dual deficits" model. *Biological Psychiatry, 45*(1), 76-81. doi:10.1016/s0006-3223(98)00219-4

Loberg, E. M., Jorgensen, H. A., & Hugdahl, K. (2004). Dichotic listening in schizophrenic patients: effects of previous vs. ongoing auditory hallucinations. *Psychiatry Research, 128*(2), 167-174. doi:10.1016/j.pschres.2004.01.011

Luine, V. N. (2014). Estradiol and cognitive function: Past, present and future. *Hormones and Behavior, 66*(4), 602-618. doi:10.1016/j.yhbeh.2014.08.011

Maki, P. M., & Sundermann, E. (2009). Hormone therapy and cognitive function. *Human Reproduction Update, 15*(6), 667-681. doi:10.1093/humupd/dmp022

McCourt, M. E., Olafson, C., & Sackmann, C. (1996). Cognitive and perceptual influences on visual line bisection in normal observers: Psychophysical and chronometric analyses

of pseudoneglect. *Investigative Ophthalmology & Visual Science, 37*(3), 2383-2383.

Mead, L. A., & Hampson, E. (1996). Asymmetric effects of ovarian hormones on hemispheric activity: Evidence from dichotic and tachistoscopic tests. *Neuropsychology, 10*(4), 578-587.

Metcalf, M . G. & Mackenzie, J. A. (1980). Incidence of ovulation in young women. *Journal of Biosocial Science, 12,* 345-352. https://doi.org/10.1017/S002193200001289X

Mihalj, M., Drenjančević, I., Včev, A., Šumanovac, A., Čavka, A., & Gmajnić, R. (2014). Basic cognitive functions across the menstrual cycle in a controlled female cohort. *Med Glas (Zenica), 11*(1), 177-185.

Oertel, V., Knöchel, C., Rotarska-Jagiela, A., Schönmeyer, R., Lindner, M., van de Ven, V., … Linden, D. E. J. (2010). Reduced laterality as a trait marker of schizophrenia--evidence from structural and functional neuroimaging. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 30*(6), 2289-2299. http://doi.org/10.1523/JNEUROSCI.4575-09.2010

Oertel-Knöchel, V., & Linden, D. E. J. (2011). Cerebral asymmetry in schizophrenia. http://doi.org/10.1177/1073858410386493

Petersen, N., Kilpatrick, L. A., Goharzad, A., & Cahill, L. (2014). Oral contraceptive pill use and menstrual cycle phase are associated with altered resting state functional connectivity. *Neuroimage, 90*, 24-32. doi:10.1016/j.neuroimage.2013.12.016

Riecher-Rössler, A., Hafner, H., Stumbaum, M., Maurer, K., & Schmidt, R. (1994). Can estradiol modulate schizophrenic symptomatology. *Schizophrenia Bulletin, 20*(1), 203-214.

Riecher-Rössler A., Kulkarni J. (2010) Estrogens and Gonadal Function in Schizophrenia and Related Psychoses. In: Neill J., Kulkarni J. (eds) *Biological Basis of Sex Differences in Psychopharmacology. Current Topics in Behavioral Neurosciences*, vol 8. Springer,

Berlin, Heidelberg, pp. 155-171.

Riecher-Rössler A., Rohde, A. (2001). *Psychische Erkrankungen bei Frauen*. Basel: Karger.

Rizzolatti, G., & Buchtel, H.A. (1977) Hemispheric superiority in reaction time to faces: a sex difference. *Cortex, 13*(3), 300-305

Roiser, J. P., Wigton, R., Kilner, J. M., Mendez, M. a., Hon, N., Friston, K. J., & Joyce, E. M. (2013). Dysconnectivity in the frontoparietal attention network in schizophrenia. *Frontiers in Psychiatry*, *4*(DEC), 1-13. http://doi.org/10.3389/fpsyt.2013.00176

Rosenberg, L., & Park, S. (2002). Verbal and spatial functions across the menstrual cycle in healthy young women. *Psychoneuroendocrinology, 27*(7), 835-841. doi:10.1016/s0306-4530(01)00083-x

Rupprecht, R., & Holsboer, F. (1999). Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. *Trends in Neurosciences, 22*(9), 410-416. doi:10.1016/s0166-2236(99)01399-5

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. doi:10.1016/s0028-3932(98)00022-0

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., . . . Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience, 27*(9), 2349-2356. doi:10.1523/jneurosci.5587-06.2007

Smith, L. L., & Hines, M. (2000). Language lateralization and handedness in women prenatally exposed to diethylstilbestrol (DES). *Psychoneuroendocrinology, 25*(5), 497-512. doi:10.1016/s0306-4530(00)00005-6

Sommer, I. E. C., Aleman, A., Bouma, A., & Kahn, R. S. (2004). Do women really have more

bilateral language representation than men? A meta-analysis of functional imaging studies. *Brain, 127*(8), 1845-1852. http://doi.org/10.1093/brain/awh207

Thilers, P. P., MacDonald, S. W. S., Nilsson, L. G., & Herlitz, A. (2010). Accelerated postmenopausal cognitive decline is restricted to women with normal BMI: Longitudinal evidence from the Betula project. *Psychoneuroendocrinology, 35*(4), 516-524. doi:10.1016/j.psyneuen.2009.08.018

Vincent, J. L., Snyder, A. Z., Fox, M. D., Shannon, B. J., Andrews, J. R., Raichle, M. E., & Buckner, R. L. (2006). Coherent spontaneous activity identifies a hippocampal-parietal memory network. *Journal of Neurophysiology, 96*(6), 3517-3531. doi:10.1152/jn.00048.2006

Vogel, J. J., Bowers, C. A., & Vogel, D. S. (2003). Cerebral lateralization of spatial abilities: A meta-analysis. *Brain and Cognition, 52*(2), 197-204. doi:10.1016/s0278-2626(03)00056-3

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*(2). doi:10.1037/0033-2909.117.2.250

Wadnerkar, M. B., Whiteside, S. P., & Cowell, P. E. (2008). Dichotic listening asymmetry: Sex differences and menstrual cycle effects. *Laterality, 13*(4), 297-309. doi:10.1080/13576500701821106

Weekes, N. Y., & Zaidel, E. (1996). The effects of procedural variations on lateralized stroop effects. *Brain and Cognition, 31*(3), 308-330. doi:10.1006/brcg.1996.0049

Wegesin, D. J., & Stern, Y. (2007). Effects of hormone replacement therapy and aging on cognition: Evidence for executive dysfunction. *Aging Neuropsychology and Cognition, 14*(3), 301-328. doi:10.1080/13825580600802893

Weis, S., Hausmann, M., Stoffers, B., & Sturm, W. (2011). Dynamic changes in functional

cerebral connectivity of spatial cognition during the menstrual cycle. *Human Brain Mapping, 32*(10), 1544-1556. doi:10.1002/hbm.21126

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*(50), 13401-13410. doi:10.1523/jneurosci.4392-08.2008

Weis, S., Hodgetts, S., & Hausmann, M. (2017). Sex differences and menstrual cycle effects in cognitive and sensory resting state networks. *Brain and Cognition.* doi:https://doi.org/10.1016/j.bandc.2017.09.003

Weisbrod, M., Kiefer, M., Marzinzik, F., & Spitzer, M. (2000). Executive control is disturbed in schizophrenia: Evidence from event-related potentials in a Go/NoGo task. *Biological Psychiatry, 47*(1), 51-60. doi:10.1016/s0006-3223(99)00218-8

Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J.D., & Seidman, L.J. (2009) Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proceedings of the National Academy of Sciences, 106*(4), 1279-1284. doi: http:// 10.1073/pnas.0809141106

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. doi:10.1016/s0306-4530(98)00019-5