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Why sex hormones matter for neuroscience – A very short review on sex, sex hormones and functional brain asymmetries

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Abstract

Biological sex and sex hormones are known to affect *Functional Cerebral Asymmetries* (FCAs). Men are generally more lateralised than women. The effect size of this sex difference is small but robust. Some of the inconsistencies in the literature may be explained by sex-related hormonal differences. The majority of studies focussing on neuromodulatory properties of sex hormones on FCAs have investigated women during the menstrual cycle. Although contradictions exist, these studies typically find that levels of estradiol and/or progesterone correlated with the degree of FCAs, suggesting that sex differences in FCAs partly depend on hormonal state and the day of testing. The results indicate that FCAs are not fixed but are hormone-dependent, and as such they can dynamically change within relative short-time periods throughout life. Many issues raised in this mini review refer not only to FCAs but also to other aspects of functional brain organization, such as functional connectivity within and between the cerebral hemispheres. If more studies were to routinely take sex and sex hormones into account, this would significantly improve our understanding of sex differences in brain and behavior as well as their clinical relevance.

Keywords: gender, hemispheric asymmetries, estradiol, progesterone, menstrual cycle, functional connectivity, brain plasticity

Significance

Sex differences in structural and functional brain organization are generally considered to be small but robust, but there are considerable inconsistencies between studies. Some of these inconsistencies occur because within-sex variation in sex hormonal factors has been largely ignored. Using studies of functional cerebral asymmetries, as an example of a fundamental principle of functional brain organization, this mini review aims to show that sex differences in the brain, and their clinical relevance, will not be fully understood, if sex hormonal factors are neglected.

Introduction

Functional Cerebral Asymmetries (FCAs) refer to the relative differences between the left and right hemisphere in some neural functions and cognitive processes, and represent a relatively simple model to investigate the functional connectivity in the brain. Although FCAs are a fundamental principle of brain organization (e.g., the vast majority of human individuals are left lateralized for language), about half of the variation in FCAs is attributable to individual differences (Kim et al., 1990). This variation was simply treated as random error and usually ignored in the past (Hellige, 1993). The aim of this mini review is to focus on sex and sex hormones as a major reason of inter- and intraindividual variation in FCAs and the functional connectivity between cerebral hemispheres.

Sex differences in FCA

The idea that sex differences in FCAs exist is not new. Apart from handedness, sex is one of the most frequently investigated factors of interindividual variation in FCAs. Early clinical data showed that men are more likely to display verbal and non-verbal deficits after left and right hemisphere lesions, respectively, whereas the deficits are less hemisphere-specific for women (Lansdell, 1961; McGlone, 1977; 1978; McGlone and Kertesz, 1973; Wechsler, 1955).

In healthy adults, sex differences in FCAs have been reported for many cognitive domains, including language (e.g. Bryden, 1979; Franzon and Hughdahl, 1986; Shaywitz et al., 1995), spatial orientation (e.g. Chiarello et al., 1989; Corballis and Sidey, 1993; Witelson, 1976), spatial attention (Hausmann et al., 2002), and face

recognition (Borod et al., 1983; Rizzolatti and Buchtel, 1977). Although contrary findings exist (e.g., Ashton and McFarland, 1991; Sommer et al., 2004), the majority of studies which report sex differences reveal reduced FCAs in females when compared with males (e.g. Corballis and Sidey, 1993; Hausmann et al., 2002; Hausmann and Güntürkün, 1999; Hausmann, Waldie, et al., 2003; Inglis and Lawson, 1981; Juarez and Corsi-Cabrera, 1995; Liu et al., 2009; McGlone, 1980; Meinschaefer et al., 1999; Rasmjou et al., 1999; Shaywitz et al., 1995; Voyer, 1996). Moreover, there is some evidence that women exhibit a larger degree of interindividual variability in FCAs, whereas FCAs in males are rather robust (Hausmann et al., 1998).

Numerous meta-analyses have aimed to quantify the nature and magnitude of sex differences in FCAs (e.g., Hiscock, et al., 1994; 1995; 1999; 2001; Vogel et al., 2003; Voyer, 1996; 2011). Merrill Hiscock found stronger hemispheric asymmetry in males across a range of auditory (Hiscock et al., 1994), visual (Hiscock et al., 1995), tactile (Hiscock et al., 1999) and dual task interference laterality tasks (Hiscock et al., 2001) and concluded that, on the population level, sex difference in FCAs (i.e., larger FCAs in men than women) are small but reliable (Hiscock et al., 2001). Daniel Voyer (1996, 2011) came to the same conclusion in his meta-analyses. Small effect sizes imply that only studies using a large sample size will reliably find sex differences in FCAs. Hirnstein et al. (2013) compiled behavioral data from 1782 participants (885 females) and found that sex differences in the degree of language lateralization, as measured with a well-established verbal dichotic listening task (Hugdahl, 1995), were dependent on age, with the largest effect size (Cohen's d = 0.31) in adolescents. In this task, participants receive two auditory stimuli (usually syllables or words) simultaneously presented via headphones to the left and right ear and report the

stimulus they hear the most clearly. A bias towards verbal stimuli presented to the right ear is typically revealed, indicative of left-hemispheric language lateralization. This so-called right ear advantage (REA) results from bottom-up factors relating to contralateral auditory projections from the ear to the primary auditory cortex while ipsilateral projections are inhibited (Kimura, 1967; for a review see Westerhausen and Hugdahl, 2010). The sex difference in this task observed by Hirnstein et al. (2013) was in line with a recent study (Bless et al., 2015) which assessed language lateralization in over 4,000 participants with a smartphone application (*iDichotic*). This study also revealed larger language lateralization in men than women with a small effect size of Cohen's d = 0.18. Although effect sizes in sex differences of language lateralization are small, they are consistent with, for example, recent anatomical findings showing larger leftward asymmetry of the planum temporale (which overlaps with Wernicke's area) in men than women (e.g., Guadelupe et al., 2015), which are established very early in ontogenesis (Li et al., 2014). However, as mentioned earlier, not all studies revealed sex differences in FCAs (e.g., Sommer, 2010). Voyer (1996) concluded that even in the majority of studies focusing on FCAs, no interactions of hemisphere with sex occurred.

Sex differences in the functional connectivity within and between hemispheres

Sex differences in FCAs also tell us something about the structural and functional connectivity between the left and right cerebral hemispheres. In spite of interhemispheric connections being mainly excitatory, the main and longer lasting effect of callosal activation appears to be inhibitory (Innocenti, 1980; 1986; Kawaguchi, 1992). The dominant hemisphere inhibits the non-dominant hemisphere resulting in FCAs for a given tasks and the reduction of interhemispheric inhibition

results in an increase in bilateral activation and reduced FCAs (e.g. Cook, 1984; Regard et al., 1994).

Early studies of sex differences in structural and functional interhemispheric interaction more directly, investigated the size and shape of the corpus callosum, the largest commissure in the human brain. However, there is an ongoing debate as to whether sex differences in the macro- and microanatomy of the corpus callosum truly exist and, if they do, what the functional relevance of this is (for a critical review: Bishop and Wahlsten, 1997). On the functional level, there is evidence that the interhemispheric transfer time (IHTT), as measured by visual-evoked potentials, is faster in the right-to-left direction than left-to-right direction (Marzi, 2010; Nowicka and Tacikowski, 2011). However, this directional asymmetry in conduction velocities between hemispheres seems to be less pronounced in women who show more symmetrical IHTT than men (Moes et al., 2007; Nowicka & Fersten, 2001). Although IHTT is directly related to the structural integrity of the corpus callosum (e.g. Westerhausen et al., 2006; Whitford et al., 2011), the extent to which interhemispheric inhibition (related to FCAs) and IHTT share the same transcallosal mechanisms is not entirely clear (Hausmann et al., 2013). A larger corpus callosum might explain the more symmetrical IHTT in women than men, but it is less clear how this might explain reduced FCAs in women than men, if the main role of corpus callosum is interhemispheric inhibition.

Recently, many studies investigated sex differences in the structural connectivity with diffusion tensor imaging (DTI) (e.g., Duarte-Carvajalino et al., 2012; Dunst et al., 2014; Gong et al., 2009; Ingalhalikar et al., 2013; Satterthwaite et al., 2015; Sun et al., 2015; Szeszko et al., 2003; Tomasi and Volkow, 2012; Westerhausen et al., 2003, 2011; see Gong et al., 2011, for a review). For example, Ingalhalikar et al.

(2013) investigated the diffusion-based structural connectome in a sample of 949 youths (428 males and 521 females) aged between 8–22 years. In line with previous studies indicating greater overall cortical connectivity in women (e.g., Gong et al., 2009) and higher probability of inter-hemispheric connections in women than men (e.g., Duarte-Carvajalino et al., 2012), and similar to earlier studies that used neurofunctional (e.g., Wood et al., 1991) and anatomical approaches (e.g., Hagmann et al., 2006), Ingalhalikar et al. (2013) found that in all supratentorial regions, males had greater structural connectivity *within* hemispheres, whereas *between*-hemispheric connectivity predominated in females, leading the authors to questionable speculation that male brains are structured to facilitate connectivity between perception and coordinated action, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes. Although the extent to which developmental trajectories of sexual dimorphisms in the human connectome (e.g., Ingalhalikar et al., 2013) and sex differences in, for example language lateralization (Hugdahl, 1995) coincide is currently unknown, sex hormone changes during adolescence are likely to play an important role (e.g., Neufang et a., 2009).

The functional relevance of these findings was followed-up by the same group (Tunc et al., 2016) investigating functionally defined subnetworks. They found higher structural connectivity for men between motor, sensory (auditory and visual) and default mode subnetworks associated with executive control tasks (fronto-parietal and cingulo-opercular), whereas the structural connectivity in women was higher among subcortical, sensory and attention subnetworks. Finally, a recent structural connectivity study in a sample of 312 males and 362 females aged between 9–22 years suggested that “the degree to which a given participant’s cognitive profile was

“male” or “female” was significantly related to the masculinity or femininity of their pattern of brain connectivity” (Satterthwaite et al., 2015, p. 2383). Although these studies found clear sex differences in the structural and functional connectivity, the overall picture is inconsistent because some connectivity studies with large sample sizes revealed no sex differences (e.g., Nielsen et al., 2013) as well as substantial variability and overlap within and between the sexes, respectively (Joel et al., 2015).

Given that some individual studies reveal sex differences in FCAs, and especially the functional connectivity, while others do not, this may indicate the existence of sex-related interindividual factors which have been largely ignored. In line with this view, it has been suggested that sex should be viewed as “an imperfect, temporary proxy for yet-unknown factors, such as hormones or sex-linked genes, that explain variation better than sex” (Manely, 2016). Indeed, studies investigating fluctuations in sex hormone levels, for example in women during the menstrual cycle, revealed that sex hormones partly account for inter- and intraindividual variations in FCAs. If sex hormones affect FCAs and other interhemispheric interaction, sex differences in both aspects of functional brain organization should depend to some extent on the hormonal state, and consequently, time of testing.

Sex hormonal effects on FCA

Sex hormones not only have *organizational effects* on the brain, for example during prenatal brain development, but also *activational effects* which are seen as acute and reversible (Arnold, 2009) and which can dynamically change FCAs, the functional connectivity in the brain, and consequently (cognitive) behavior (Wisniewski, 1998). Although the distinction between organizational and activational effects are not clear-cut, it is the latter which is in the focus of this mini review.

Sex hormones are mainly synthesized by the ovaries in women and testes in men and by the adrenal glands in both sexes. Some sex hormones, so-called neurosteroids, are directly produced within the brain (Rupprecht, 2003). The effects of sex hormones 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 and Alves, 1999). Thus, sex hormones have a broad spectrum of effects on brain functioning and plasticity. Rather than being restricted to sexual and reproductive behavior, sex hormones have more general effects such as on higher cognitive functioning. However, the underlying hormonal mechanisms that modulate FCAs and cognitive behavior are generally unclear (Wisniewski, 1998).

Several studies investigating the activating effects of sex hormones on brain and behavior have focused on women because women's sex hormone levels, such as estradiol and progesterone, fluctuate within relative short-time periods, and within physiologically normal ranges, during the menstrual cycle (Figure 1).

Moreover, it has been shown in behavioral (e.g., Bibawi et al., 1995; Hampson, 1990a; 1990b; Hausmann, 2005; Hausmann and Güntürkün, 2000; Hausmann et al., 2002; Heister et al., 1989; Holländer et al., 2005; Mead and Hampson, 1996; McCourt et al., 1997; Rode et al., 1995; Sanders and Wenmoth, 1998) and neuroimaging studies (e.g., Fernandez et al., 2009; Weis et al., 2008; Weis et al., 2011; Thimm et al., 2014) that FCAs and/or the functional connectivity in the brain change across the menstrual cycle. However, the results are somewhat controversial (Compton et al., 2004; see Hausmann and Bayer, 2010, for a review).

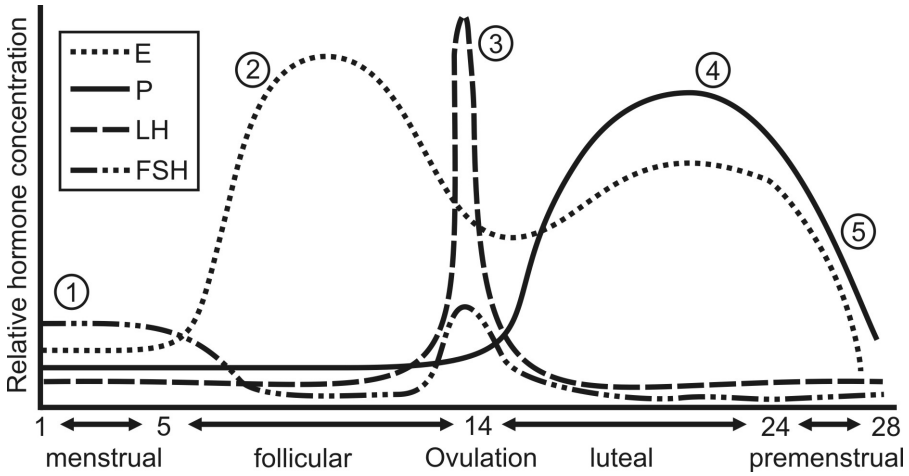

Figure 1. The menstrual cycle. Schematic illustration of fluctuations in sex hormone (estradiol, E; progesterone, P) and gonadotropin levels (luteinizing hormone, LH; follicle-stimulating hormone, FSH) during an average 28-day menstrual cycle. LH and FSH secretion by the pituitary gland determines the menstrual cycle. Cycle day 1 is defined by the discharge of blood from the non-pregnant uterus. During the menstrual phase (1), cycle day 1-5, the concentrations of E and P are lowest. Beginning with cycle day 6, E level continuously increases, approaching its maximum about one day before ovulation (follicular phase; 2). P level remains low during the follicular phase. About 14 days after menstruation begins, LH secretion initiates ovulation (3). E level drops slightly. After ovulation, the small cells that surround the egg undergo chemical changes (luteinization). During this luteal phase, E and P are secreted by the luteinized cells. About 7-8 days postovulatory, E level approaches its second maximum together with P. P level reaches its peak at around cycle day 22 (midluteal phase, 4). Levels of E and P fall rapidly between cycle day 24-28 (premenstrual phase, 5) and a new cycle begins (adopted from Hausmann and Bayer, 2010; reprinted with permission from MIT Press).

Several of these studies (e.g., Altemus et al., 1989; Fernandez et al., 2003; Hausmann et al., 2002; Hausmann and Güntürkün, 2000; Mead and Hampson, 1996; Rode et al., 1995; Sanders and Wenmoth, 1998; Weis et al., 2008) revealed that FCAs are reduced in the pre-ovulatory follicular phase during which follicles in the ovary mature (high levels of estradiol) and/or during post-ovulatory luteal phase which begins with the formation of the corpus luteum (high levels of progesterone and estradiol), whereas FCAs were significantly larger during menstruation (sometimes also referred to as early follicular phase) when levels of estradiol and progesterone are lowest. In contrast, other studies found the opposite, that is,

significant FCAs during the follicular and/or luteal phase in combination with reduced FCAs during menstruation (e.g., Hampson, 1990b; Mead and Hampson, 1996; Sanders and Wenmoth, 1998; Wadnerkar et al., 2008; Weekes and Zaidel, 1996). The conflicting findings, sometimes even occuring in the same study (e.g., Mead & Hampson, 1996; Sanders & Wenmoth, 1998), indicate that size and direction of the effects partly depend on the specific task and test modality (Hausmann and Bayer, 2010; Hodgetts et al., 2015).

One major issue, especially in many earlier studies investigating sex-hormonal effects on FCAs (and cognition), was that cycle phases estimates were based on day-counting techniques rather than determining levels of sex hormones directly from blood or saliva samples. This is highly problematic because only about 60% of younger women ovulate during each menstrual cycle (Metcalf and MacKenzie, 1980) and the length of distinct cycle phases as well as fluctuations in sex hormone levels can vary substantially between and within women. Studies including hormone assays usually exclude up to about 50% of their participants (e.g., Gordon et al., 1986; Hodgetts et al., 2015) because post hoc-measured sex hormone levels did not match the expected cycle phase.

The search for underlying mechanisms

Inconsistencies in the results as well as methodological issues and differences between studies make it particularly difficult to disentangle the mechanisms by which sex hormones modulate FCAs in humans. Some studies suggest that hormonal influences are restricted to a single hemisphere (e.g., a facilitative effect of high estrogen levels on the left hemisphere, Hampson, 1990b), but there is dispute as to which one. Using the visual half-field paradigm, Bibawi et al. (1995) found left

hemisphere superiority in a non-lateralized chair-identification task during the midluteal phase and also concluded that high levels of sex hormones selectively activate the left hemisphere. The idea of unilateral activation by sex hormones was supported by Sanders and Wenmoth (1998) in a dichotic-listening study. In contrast to Bibawi et al. (1995), they found that mainly right hemisphere performance was suppressed during the midluteal phase, resulting in a stronger left hemispheric advantage for a verbal task during this phase and a stronger right hemispheric advantage for a music task during menses. An alternative mechanism was proposed by McCourt et al. (1997) who concluded that the increase of a leftward bias in a visuomotor task during the luteal phase as compared to menstrual phase might indicate that both the left and right hemisphere might have been non-specifically activated midluteally, and a slight functional asymmetry favoring the right hemisphere may have been promoted.

A different approach to explain cycle-related effects of sex hormones to FCAs was proposed by Bianki and Filippova (1996; 2000) who were 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, they postulated that increased estrogen levels during the phase of proestrus increasing interhemispheric inhibition from the left hemisphere to the right hemisphere, whereas the inhibitory action from the left hemisphere to the right hemisphere weakens during the estrus due to lower estrogen levels.

Similarly, the first attempt to explain the cycle-related effects on FCAs in humans within a physiological framework also proposed that sex hormones affect the *interaction* between hemispheres (Hausmann and Güntürkün, 2000). This idea was based on findings that FCAs in left- (word matching) *and* right-hemispheric tasks

(face recognition, figure matching) were reduced during the midluteal phase compared to the menstrual phase, albeit with different effect sizes. Based on the idea that the main role of callosal communication is inhibition (see above), it was hypothesized that progesterone reduces interhemispheric inhibition by suppressing the excitatory responses of neurons to glutamate (Smith et al., 1987a; 1987b), as well as by enhancing their inhibitory responses to GABA (Smith, 1991). This combined effect would result in an increase in bilateral activation and a temporal reduction in FCAs (e.g. Cook, 1984; Regard et al., 1994). This hypothesis of progesterone-mediated interhemispheric decoupling (Hausmann and Güntürkün, 2000) has received some empirical support by different studies and various techniques, including behavioral experiments (e.g., Hausmann et al., 2002; Hausmann & Güntürkün, 2000), transcranial magnetic stimulation (Hausmann et al., 2006), and functional magnetic resonance imaging (Weis et al., 2008, 2011).

Although the fMRI study by Weis et al. (2008) found significant cycle-related changes in language lateralization in both response times and number of correct responses (i.e., reduced FCA in the follicular phase compared with the menstrual phase), cycle-related changes in the asymmetrical activation of the left inferior frontal gyrus (i.e. Broca's area) were not significant. However, a connectivity analysis of the same data revealed that the inhibitory influence of the dominant on the non-dominant hemisphere fluctuated across the menstrual cycle. Specifically, Weis et al. (2008) found that interhemispheric inhibition was reduced during the follicular phase compared with the menstrual phase. In contrast to Hausmann and Güntürkün (2000), who hypothesized that high levels of progesterone are related to reduced FCAs, however, Weis et al. found estradiol levels to be related to the reduction in the functional connectivity between hemispheres.

The role of estradiol and progesterone

Behavioral findings similar to Weis et al. (2008), reduced FCAs when estradiol levels were high, have also been shown by other studies (e.g., Hausmann, 2005; Hausmann et al., 2006; Holländer et al., 2005) and are difficult to explain partly because estradiol and progesterone have mainly opposite effects on glutamate and GABA receptors, though synergistic effects have also been reported (e.g., Smith, 1994; Smith et al., 1987c; Csakvari, 2007). Progesterone and the 5-alpha-reduced metabolites of progesterone are especially potent positive allosteric modulators of $GABA_A$ receptors (Majewska et al., 1986) and have mainly inhibitory effects, while estrogens have mainly excitatory effects on neuronal excitability (for a review: Taubol et al., 2015). Other studies have shown that background steroid milieu modulates the effectiveness of estradiol in regard to excitatory transmission (Smith 1994). For instance, administration of estradiol prior to progesterone administration rendered the system refractory to neuromodulation by progesterone (Smith, 1994), indicating that the mutual effects of estradiol and progesterone are very complex. Consequently, several studies have concluded that cycle-related changes in FCAs are related to the interaction of at least two sex hormones (e.g., Hodgetts et al., 2015).

The original model (Hausmann and Güntürkün, 2000) assumed that excitatory callosal fibers activated GABA-initiated inhibition in homotopic areas of the contralateral hemisphere and that high progesterone levels inhibit the interhemispheric inhibition, thereby increasing activation in the non-dominant hemisphere for a given task. If estradiol has mainly excitatory effects on glutamate receptors, we would assume an increase in interhemispheric inhibition and larger FCAs when estradiol levels are high, for example, in the follicular phase. Although

there is evidence for both, it has been shown that high estradiol levels generally increase neural activity in both hemispheres (Dietrich et al., 2001; Hausmann et al., 2002), suggesting that high levels of progesterone and high levels of estradiol can increase activation in the non-dominant hemisphere. In contrast to progesterone, however, GABA-ergic mechanisms seem to be unaffected by estradiol as an acute response (Taubol et al., 2015). Maybe it is the combined effects of progesterone on the glutamtergic- and GABA-ergic system that is required to inhibit interhemispheric inhibition, whereas the acute excitatory effect of estradiol on the glutamatergic system increases activation in both hemispheres, and especially in the less active non-dominant hemisphere for a given task. However, the mechanisms involved in the excitatory effect of estrogens are generally complex, and in some circumstances estrogens may even reduce excitation (Taubol et al., 2015).

It is difficult to tease apart the effects of estradiol and progesterone in menstrual cycle studies, because estradiol levels are always elevated when progesterone levels are increased during the luteal phase. One avenue to disentangle both processes in future studies might be to investigate women who take different hormonal contraceptives (e.g., progestogen-only pill users) or to examine women who receive selective estrogen-receptor modulators (e.g., tamoxifen), a hormone therapy that blocks estrogen action to treat and prevent some types of breast cancer. So far, only few studies have investigated the effects of direct exogenous hormonal manipulations on FCAs and interhemispheric interaction. These studies include experiments with postmenopausal women receiving estrogen therapy or combined estrogen plus gestagen therapy (Bayer & Erdmann, 2008; Bayer & Hausmann, 2009a, 2009b, 2010; for a review: Bayer and Hausmann, 2011). The results suggest that in postmenopausal women, estrogen therapy specifically affects

*intra*hemispheric processes, mainly in the right hemisphere, rather than *inter*hemispheric interaction. However, the results are difficult to compare to normally cycling women, because of age-related neuromorphological and neurochemical differences between both groups (e.g., Cabeza et al., 2002).

The effects of estrogen on prefrontal functioning

In addition to the bottom-up effects of estradiol on FCAs and the functional connectivity, which were discussed in the previous sections, recent laterality research has also investigated the top-down effects of estradiol on FCAs. This research was partly stimulated by a large number of studies showing that the influence of estrogen on prefrontal functioning (e.g., working memory) in normally cycling women was especially strong when high level of cognitive control was required (Jacobs & D'Esposito, 2011) and the observation that cycle-related effects of estradiol on cognition might depend mainly on its influence on the prefrontal cortex (Keenan et al., 2001), a cortical area that has a particular high concentration of estrogen receptors in the human brain (Bixo et al., 1995).

The hypothesis that estradiol affects FCAs via its effects on cognitive control was first tested by Hjelmervik et al. (2012) with a dichotic listening task commonly used to investigate FCAs related to language (Hugdahl, 1995, 2003). As discussed earlier, previous research has shown that language lateralization measured with dichotic listening tasks is sensitive to sex (i.e., robust but small sex differences, with larger REA in men than women, e.g., Hirnstein et al., 2013) and sex hormones fluctuating across the menstrual cycle (e.g., Alexander et al., 2002; Altemus, et al., 1989; Cowell et al., 2011; Hampson, 1990a, 1990b; Mead and Hampson, 1996; Sanders and Wenmoth, 1998; Wadnerkar et al., 2008).

To investigate the top-down effects of estradiol on FCAs, Hjelmervik et al. (2012) manipulated cognitive control by forcing participants (i.e., normally cycling women, repeatedly tested during the menstrual, follicular and luteal phase and men) to shift their attention to either the left or right ear. In contrast to the stimulus-driven (bottom-up) non-forced attention condition, the forced-left condition requires top-down cognitive control, because participants need to actively override the tendency to report stimuli presented to the dominant right ear (Hugdahl, 2003; Loberg et al., 1999; Hugdahl et al., 2009). The results revealed cycle-related changes only in the cognitive control condition that required participants to shift attention to stimuli presented to the left ear. In this condition, women in the follicular phase (high estradiol levels) showed an increased left-ear advantage compared to both the menstrual and the luteal phase. As no menstrual cycle effect was observed in the non-forced attention condition, Hjelmervik et al. (2012) concluded that estradiol influences cognitive control as opposed to language lateralisation per se.

A recent study (Hodgetts et al., 2015) aimed to replicate this finding in a between-subjects design. Naturally cycling women were tested only once in all three forced-attention conditions. Although this study originally aimed to test each woman during the menstrual, follicular *or* luteal phase, hormone assays for estradiol and progesterone revealed many women were not in the expected cycle phase. Therefore the entire sample was divided (based on a median split) into two groups high and low in estradiol levels. In contrast to Hjelmervik et al. (2012), this study found reduced FCAs in women with high estradiol levels across all attention conditions and regardless of cognitive control demands leading to the conclusion that estradiol reduces the stimulus-driven (bottom-up) aspect of language lateralisation, rather than the cognitive control (top-down) component. Although both studies were

methodologically similar, there were also some important differences. For example, in contrast to the within-subject design in Hjelmervik et al. (2012), Hodgetts et al. (2015) adopted a between-subject design (which is less susceptible to repeated measures effects), investigated more women (N = 73 as compared to 15 participants tested three times), revealed consistently larger FCAs across all conditions, and showed generally higher estradiol levels.

Concluding remarks

In this mini review, I have discussed three potential mechanisms of hormone action on FCAs: (a) only one hemisphere is hormonally affected (e.g., Hampson, 1990b), (b) neural activity of both hemispheres is affected, thereby promoting existing FCAs (McCourt et al., 1997), and (c) steroid hormones affect the interaction/inhibition between hemispheres (Hausmann & Bayer, 2010). Although this mini review has focused on the latter, all mechanisms have revealed at least some empirical support. In fact, it is unlikely that only one mechanism can account for all findings. A combination of the above mechanisms (and maybe additional mechanisms) may be required to account for some task-related effects and, for instance, the increase in FCAs during high hormone states of the menstrual cycle.

The title of this mini review was chosen in recognition of a comprehensive review by Larry Cahill (2006) who concluded that “the effects of circulating sex hormones cannot fully account for all sex differences observed in the adult brain” (Cahill 2006, p. 478). This statement also applies to cycle-related changes in FCAs and the functional connectivity in the brain although even when significant relationships between sex hormone and FCAs have been found, the effects are usually relatively small.

Furthermore, other cycle-related factors, for example changes in mood (e.g., Compton and Levine, 1997) have been found to modulate FCAs and interhemispheric interaction. Thus, even if medium to large correlations between estradiol and/or progesterone levels and the degree in FCAs are found, it does not necessarily mean that these sex hormones are directly involved. Additionally, it is not always clear whether observed neural effects are based on sex hormones or their metabolites. The relationship between sex, sex hormones, and FCAs is complex and it is probably naïve to assume that relationships are always linear or that only one sex hormone is involved.

This mini review focuses on women and sex hormone fluctuations across the menstrual cycle. Some studies controlled for these fluctuations by including only men (e.g., Kono et al., 2007; Ortigue et al., 2004), an approach which is relatively common in animal research. This means, conclusions drawn by these studies are based on samples that represent only about half the population. Other studies which have included both sexes, compared men to women in only one phase of the menstrual cycle (e.g., Bonenberger et al., 2013; Galea et al., 2005; Gizewski et al., 2006; Halari et al., 2006). Although the latter approach is more favorable, it means that neuroscientists are implicitly defining a hormonal baseline in normally cycling women, while acknowledging that sex and sex hormones are potential confounds.

Finally, men are also known to show fluctuations in sex hormones levels (i.e., testosterone) on a diurnal and seasonal basis (e.g., Smith et al., 2013). However, only very few studies have investigated hormonal variations in men (e.g., Moffat and Hampson, 1996, 2000). Sex-sensitive neuroscience research should assess potential hormonal variations in both sexes. If more studies were to include sex and levels of sex hormone more routinely into account, we would develop a much better

understanding of true sex differences in brain and behavior, the size of the effects, the mechanisms underlying these differences, and their clinical relevance.

Conflict of Interest Statement

The author has no conflicts of interest.

Role of Authors

The author takes full responsibility for the conceptualization and drafting of this Review.

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