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Mini-Review

Why Sex Hormones Matter for Neuroscience: A Very Short Review on Sex, Sex Hormones, and Functional Brain Asymmetries

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Biological sex and sex hormones are known to affect functional cerebral asymmetries (FCAs). Men are generally more lateralized 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. Most studies focusing on neuromodulatory properties of sex hormones on FCAs have investigated women during the menstrual cycle. Although contradictions exist, these studies have typically shown that levels of estradiol and/or progesterone correlate with the degree of FCAs, suggesting that sex differences in FCAs partially depend on hormonal state and day of testing. The results indicate that FCAs are not fixed but are hormone dependent, and as such they can dynamically change within relatively short 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. Our understanding of sex differences in brain and behavior as well as their clinical relevance will improve significantly if more studies routinely take sex and sex hormones into account. © 2016 Wiley Periodicals, Inc.

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Functional cerebral asymmetries (FCAs) refer to the relative differences between the left and the right hemispheres in some neural functions and cognitive processes and represent a relatively simple model for investigating 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 was usually ignored in the past (Hellige, 1993). This Mini-Review focuses on sex and sex hormones as major reasons for 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 nonverbal deficits after left and right hemisphere lesions, respectively, whereas the deficits are less hemisphere-specific for women (Wechsler, 1955; Lansdell, 1961; McGlone and Kertesz, 1973; McGlone, 1977, 1978).

In healthy adults, sex differences in FCAs have been reported for many cognitive domains, including language (see, e.g., Bryden, 1979; Franzon and Hughdahl, 1986; Shaywitz et al., 1995), spatial orientation (see, e.g., Witelson, 1976; Chiarello et al., 1989; Corballis and Sidey, 1993), spatial attention (Hausmann et al., 2002b), and face recognition (Rizzolatti and Buchtel, 1977; Borod et al.,

SIGNIFICANCE

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

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1983). Although contrary findings exist (see, e.g., Ashton and McFarland, 1991; Sommer et al., 2004), most studies reporting sex differences have revealed reduced FCAs in females compared with males (see, e.g., McGlone, 1980; Inglis and Lawson, 1981; Corballis and Sidey, 1993; Juarez and Corsi-Cabrera, 1995; Shaywitz et al., 1995; Voyer, 1996; Hausmann and Güntürkün, 1999; Meinschaefer et al., 1999; Rasmjou et al., 1999; Hausmann et al., 2002b, 2003; Liu et al., 2009). Moreover, there is some evidence that women exhibit a greater degree of interindividual variability in FCAs, whereas FCAs in males are rather robust (Hausmann et al., 1998).

Numerous meta-analyses have sought to quantify the nature and magnitude of sex differences in FCAs (see, e.g., Hiscock, et al., 1994, 1995, 1999, 2001; Voyer, 1996, 2011; Vogel et al., 2003). Merrill Hiscock and colleagues 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 (Hiscock et al., 2001) laterality tasks and concluded that, on the population level, sex differences in FCAs (i.e., larger FCAs in men than in 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 will reliably find sex differences in FCAs. Hirnstein et al. (2013) compiled behavioral data from 1,782 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 (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 ears and report the stimulus that they hear the most clearly. A bias toward 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, whereas ipsilateral projections are inhibited (Kimura, 1967; for review see Westerhausen and Hugdahl, 2010). The sex difference in this task observed by Hirnstein et al. (2013) is in line with a recent study by Bless et al. (2015) that assessed language lateralization in over 4,000 participants with a smartphone application (iDichotic). This study also revealed greater language lateralization in men than in women, with a small effect 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 greater leftward asymmetry of the planum temporale (which overlaps with Wernicke's area) in men than in women (e.g., Guadelupe et al., 2015), which is established very early in ontogenesis (Li et al., 2014). However, as mentioned previously, 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 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 nondominant hemisphere, resulting in FCAs for a given task, and the reduction of interhemispheric inhibition results in an increase in bilateral activation and reduced FCAs (see, e.g., Cook, 1984; Regard et al., 1994).

Early studies of sex differences in structural and functional interhemispheric interaction investigated more directly the size and shape of the corpus callosum, the largest commissure in the human brain. However, there is an ongoing debate with regard 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 see 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 in the 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 (Nowicka and Fersten, 2001; Moes et al., 2007). Although IHTT is directly related to the structural integrity of the corpus callosum (see, 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 in men, but it is less clear how this might explain reduced FCAs in women compared with men if the main role of the corpus callosum is interhemispheric inhibition.

Recently, many studies have investigated sex differences in the structural connectivity with diffusion tensor imaging (e.g., Szeszko et al., 2003; Westerhausen et al., 2003, 2011; Gong et al., 2009; Duarte-Carvajalino et al., 2012; Tomasi and Volkow, 2012; Dunst et al., 2014; Ingalhalikar et al., 2014; Satterthwaite et al., 2015; Sun et al., 2015; for review see Gong et al., 2011). For example, Ingalhalikar et al. (2014) investigated the diffusion-based structural connectome in a sample of 949 youths (428 males and 521 females) aged 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 interhemispheric connections in women than in 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. (2014) found that, in all supratentorial regions, males had greater structural connectivity *within* hemispheres, whereas *between-*

hemisphere connectivity predominated in females, leading the authors to the 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 (Ingalhalikar et al., 2014) and sex differences in, for example, language lateralization (Hugdahl, 1995) coincide is currently unknown, sex hormone changes during adolescence are likely to play important roles (Neufang et al., 2009).

The functional relevance of these findings was followed by the same group (Tunc et al., 2016) investigating functionally defined subnetworks. They found higher structural connectivity for men among motor, sensory (auditory and visual), and default-mode subnetworks associated with executive control tasks (frontoparietal 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 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 indicated clear sex differences in structural and functional connectivity, the overall picture is inconsistent because some connectivity studies with large samples revealed no sex differences (e.g., Nielsen et al., 2013) as well as substantial variability and overlap within and between the sexes (Joel et al., 2015).

Some individual studies have revealed sex differences in FCAs, and especially functional connectivity, whereas others have not; this may indicate the existence of sex-related interindividual factors that 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" (Manley, 2016). Indeed, studies investigating fluctuations in sex hormone levels, for example, in women during the menstrual cycle, revealed that sex hormones partially 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 FCAS

Sex hormones not only have organizational effects on the brain, such as during prenatal brain development, but also activational effects that are seen as acute and reversible (Arnold, 2009) and that can dynamically change FCAs, functional connectivity in the brain, and consequently (cognitive) behavior (Wisniewski, 1998). Although the distinctions between organizational and activational effects are not clearcut, the latter are in the focus of this Mini-Review.

Sex hormones are synthesized mainly by the ovaries in women, the testes in men, and 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 (see, e.g., McEwen and Alves, 1999). Thus, sex hormones have a broad spectrum of effects on brain function and plasticity. Rather than being restricted to sexual and reproductive behavior, sex hormones also have more general effects, such as on higher cognitive function. 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 relatively short time periods and within physiologically normal ranges during the menstrual cycle (Fig. 1).

Moreover, it has been shown in behavioral (e.g., Heister et al., 1989; Hampson, 1990a,b; Bibawi et al., 1995; Rode et al., 1995; Mead and Hampson, 1996; McCourt et al., 1997; Sanders and Wenmoth, 1998; Hausmann and Güntürkün, 2000; Hausmann et al., 2002a; Hausmann, 2005; Holländer et al., 2005) and neuroimaging (e.g., Weis et al., 2008; Fernandez et al., 2003; Weis et al., 2011; Thimm et al., 2014) studies that FCAs and functional connectivity in the brain change across the menstrual cycle. However, the results are somewhat controversial (Compton et al., 2004; for review see Hausmann and Bayer, 2010).

Several of these studies (e.g., Altemus et al., 1989; Rode et al., 1995; Mead and Hampson, 1996; Sanders and Wenmoth, 1998; Hausmann and Güntürkün, 2000; Hausmann et al., 2002a; Fernandez et al., 2003; Weis et al., 2008) revealed that FCAs were reduced in the preovulatory follicular phase, during which follicles in the ovary mature (high levels of estradiol) and/or during the postovulatory luteal phase that begins with the formation of the corpus luteum (high levels of progesterone and estradiol), whereas FCAs were significantly greater during menstruation (sometimes also referred to as the *early follicular phase*), when levels of estradiol and progesterone are lowest. In contrast, other studies showed 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; Weekes and Zaidel, 1996; Sanders and Wenmoth, 1998; Wadnerkar et al., 2008). The conflicting results, sometimes occurring even in the same study (e.g., Mead and Hampson, 1996; Sanders and Wenmoth, 1998), indicate that size and direction of the effects partially 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), is that cycle phase estimates were based on day-

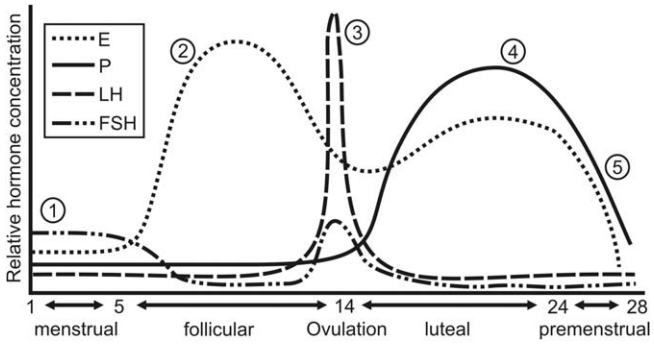

Fig. 1. The menstrual cycle. Schematic illustration of fluctuations in sex hormones (E, estradiol; P, progesterone) and gonadotropin levels (LH, luteinizing hormone; FSH, follicle-stimulating hormone) during an average 28-day menstrual cycle. LH and FSH secretion by the pituitary gland determines the menstrual cycle. Cycle day 1 is defined by the discharge of blood from the nonpregnant uterus. During the menstrual phase (1; cycle days 1–5), the concentrations of E and P are lowest. Beginning with cycle day 6, E level continuously increases, approaching its maximum about 1 day before ovulation (2; follicular phase). 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 or 8 days postovulation, E level approaches its second maximum, together with P. P level reaches its peak at about cycle day 22 (4; midluteal phase). Levels of E and P fall rapidly between cycle days 24 and 28 (5; premenstrual phase), and a new cycle begins. Adopted from Hausmann and Bayer (2010) and reprinted with permission from MIT Press. (Hugdahl, K. and R. Westerhausen, Eds., The Two Halves of the Brain: Information Processing in the Cerebral Hemispheres, Figure 9.2, p. 258, ©2010 Massachusetts Institute of Technology, published by the MIT Press).

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 lengths of distinct cycle phases as well as fluctuations in sex hormone levels can vary substantially among and within women. Studies including hormone assays have usually excluded 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 among studies make it particularly difficult to disentangle the mechanisms by which sex hormones modulate FCAs in humans. Some studies have suggested 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 with regard to which one. Using the visual half-field paradigm, Bibawi et al. (1995) found left hemisphere superiority in a nonlateralized 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 musical 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 compared with the menstrual phase might indicate that both the left and the right hemispheres are nonspecifically activated midluteally and that a slight functional asymmetry favoring the right hemisphere might have been promoted.

A different approach for explaining cycle-related effects of sex hormones to FCAs was 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, they postulated that increased estrogen levels during the phase of proestrus increase interhemispheric inhibition from the left hemisphere to the right hemisphere, whereas the inhibitory action from the left hemisphere to the right hemisphere weakens during estrus because of 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 hemispheric (word matching) *and* right hemispheric tasks (face recognition, figure matching) were reduced during the midluteal phase compared with the menstrual phase, albeit with different effect sizes. Based on the idea that the main role of callosal communication is inhibition (see previous discussion), it was hypothesized that progesterone reduces interhemispheric inhibition by suppressing the excitatory responses of neurons to glutamate (Smith et al., 1987a,b) 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 (see, e.g., Cook, 1984; Regard et al., 1994). This hypothesis of progesterone-mediated interhemispheric decoupling (Hausmann and Güntürkün, 2000) has received some empirical support in different studies with various techniques, including behavioral experiments (e.g., Hausmann and Güntürkün, 2000; Hausmann et al., 2002a), transcranial magnetic stimulation (Hausmann et al., 2006), and functional magnetic resonance imaging (fMRI; Weis et al., 2008, 2011).

Although the fMRI study by Weis et al. (2008) showed 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 nondominant 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 had hypothesized that high levels of progesterone are related to reduced FCAs, Weis and colleagues found estradiol levels to be related to the reduction in functional connectivity between hemispheres.

ROLES OF ESTRADIOL AND PROGESTERONE

Behavioral results similar to those of Weis et al. (2008), i.e., reduced FCAs when estradiol levels were high, have also been shown in other studies (e.g., Hausmann, 2005; Holländer et al., 2005; Hausmann et al., 2006) and are difficult to explain, partially because estradiol and progesterone have mainly opposite effects on glutamate and GABA receptors, although synergistic effects have also been reported (e.g., Smith, 1994; Smith et al., 1987c; Csakvari, et al., 2007). Progesterone and the 5α-reduced metabolites of progesterone are especially potent positive allosteric modulators of $GABA_A$ receptors (Majewska et al., 1986) and have mainly inhibitory effects, whereas estrogens have mainly excitatory effects on neuronal excitability (for review see Taubøll et al., 2015). Other studies have shown that background steroid milieu modulates the effectiveness of estradiol with 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 groups 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 inhibited the interhemispheric inhibition, thereby increasing activation in the nondominant 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., 2002a), suggesting that high levels of progesterone and high levels of estradiol can increase activation in the nondominant hemisphere. In contrast to progesterone, however, GABAergic mechanisms seem to be unaffected by estradiol as an acute response (Taubøll et al., 2015). Maybe it is the combined effects of progesterone on the glutamatergic and GABAergic systems that are required to inhibit interhemispheric inhibition, whereas the acute excitatory effect of estradiol on the glutamatergic system increases activation in both hemispheres, especially in the less active nondominant 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 (Taubøll 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, 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 and Erdmann, 2008; Bayer and Hausmann, 2009a,b,; for review see Bayer and Hausmann, 2011). The results suggest that, in postmenopausal women, estrogen therapy specifically affects intrahemispheric processes, mainly in the right hemisphere, rather than interhemispheric interaction. However, the results are difficult to compare with normally those of cycling women because of age-related neuromorphological and neurochemical differences the two groups (see, e.g., Cabeza et al., 2002).

EFFECTS OF ESTROGEN ON PREFRONTAL FUNCTION

In addition to the bottom-up effects of estradiol on FCAs and functional connectivity that have been discussed in the previous sections, recent laterality research has investigated the top-down effects of estradiol on FCAs. This research was partially stimulated by a large number of studies showing that the influence of estrogen on prefrontal function (e.g., working memory) in normally cycling women was especially strong when a high level of cognitive control was required (Jacobs and D'Esposito, 2011) and by 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 particularly 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 previously, prior 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 in women; see, e.g., Hirnstein et al., 2013) and sex hormones fluctuating

across the menstrual cycle (see, e.g., Altemus, et al., 1989; Hampson, 1990a,b; Mead and Hampson, 1996; Sanders and Wenmoth, 1998; Alexander et al., 2002; Wadnerkar et al., 2008; Cowell et al., 2011).

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 phases, and men) to shift their attention to either the left or the right ear. In contrast to the stimulus-driven (bottom-up) nonforced attention condition, the forced-left condition requires top-down cognitive control because participants must actively override the tendency to report stimuli presented to the dominant right ear (Løberg et al., 1999; Hugdahl, 2003; 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 with both the menstrual and the luteal phases. Because no menstrual cycle effect was observed in the nonforced attention condition, Hjelmervik et al. (2012) concluded that estradiol influences cognitive control as opposed to language lateralization per se.

A recent study (Hodgetts et al., 2015) sought 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 sought to test each woman during the menstrual, follicular, *or* luteal phase, hormone assays for estradiol and progesterone revealed that 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), Hodgetts et al. (2015) found reduced FCAs in women with high estradiol levels across all attention conditions regardless of cognitive control demands, leading to the conclusion that estradiol reduces the stimulus-driven (bottom-up) aspect of language lateralization rather than the cognitive control (top-down) component. Although the studies were methodologically similar, there were also some important differences. For example, in contrast to the within-subject design of Hjelmervik et al. (2012), Hodgetts et al. (2015) adopted a between-subject design (which is less susceptible to repeated-measures effects), investigated more women ($n = 73$ compared with 15 participants tested three times), revealed consistently larger FCAs across all conditions, and showed generally higher estradiol levels.

CONCLUSIONS

This Mini-Review discusses three potential mechanisms of hormone action on FCAs: 1) only one hemisphere is hormonally affected (e.g., Hampson, 1990b); 2) neural activity of both hemispheres is affected, thereby promoting existing FCAs (McCourt et al., 1997); and 3) steroid hormones affect the interaction/inhibition between hemispheres (Hausmann and Bayer, 2010). Although this Mini-Review focuses on the latter, there is at least some empirical support for all mechanisms. In fact, it is unlikely that only one mechanism can account for all findings. A combination of the these mechanisms (and possibly 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" (p. 478). This statement also applies to cycle-related changes in FCAs and functional connectivity in the brain, although, even when significant relationships between sex hormones and FCAs have been found, the effects have usually been relatively small.

Furthermore, other cycle-related factors, such as changes in mood (see, e.g., Compton and Levine, 1997), have been shown to modulate FCAs and interhemispheric interaction. Thus, even if medium-sized 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 relationships among sex, sex hormones, and FCAs are 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., Ortigue et al., 2004; Kono et al., 2007), an approach that is relatively common in animal research. This means that conclusions drawn from these studies are based on samples that represent only about half the population. Other studies that included both sexes compared men with women in only one phase of the menstrual cycle (e.g., Galea et al., 2005; Gizewski et al., 2006; Halari et al., 2006; Bonenberger et al., 2013). 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 hormone levels (i.e., testosterone) on a diurnal and seasonal basis (Smith et al., 2013). However, 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 take 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 Mini-Review.

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