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Chapter 28

Sex hormonal effects on brain lateralization

Markus Hausmann & D. Michael Burt

Department of Psychology, Durham University, United Kingdom

Address for correspondence:

Dr Markus Hausmann

Department of Psychology, Durham University,

South Road, Durham DH1 3LE, United Kingdom,

Phone: +44-(0)191-33-43286

Fax: +44-(0)191-33-14377,

E-mail: Markus.Hausmann@durham.ac.uk

Abstract

Functional cerebral asymmetries (FCAs) refer to variation in neural function between the left and right cerebral hemisphere. Small but robust sex differences in FCAs are frequently observed. However, there are considerable inconsistencies between studies due to between- and within-sex variation in sex hormonal environments, i.e., during prenatal development and across the menstrual cycle, respectively. FCAs have been studied mainly in cognitive domains, with FCAs related to affective and social behaviour largely ignored, especially in the context of neuroendocrinology. We propose that the underlying hormonal mechanisms by which FCAs are organized during early ontogenesis and modulated later in life show similarities between affective, cognitive and social processes.

Introduction

Brain lateralization or *Functional Cerebral Asymmetries* (FCAs) refer to the relative differences between the left and right cerebral hemisphere in some neural functions including cognitive and emotional processing. Within the cognitive domain it is well established that the left hemisphere predominates in different language processes and complex motor coordination, whereas the right dominates in spatial abilities, non-verbal memory and face recognition (Hellige, 1993).

In addition to these well-established FCAs, emotional and social processes also appear to be asymmetrically organized in the brain. There is convincing empirical evidence that emotions are asymmetrically processed although the pattern of asymmetry is debated. The *right-hemisphere hypothesis* (Borod et al., 1998) states that all six basic emotions are exclusively processed in the right hemisphere. In contrast, the *valence model* of emotion lateralization (e.g., Stafford & Brandaro, 2010) suggests that the right hemisphere dominates processing of negatively valenced emotions (sadness, anger, fear and disgust), whereas positively valenced emotions (happiness and surprise) are dominantly processed by the left. This model was originally based on studies of patients with unilateral lesions, but later received support from neurologically intact participants (e.g., Silberman & Weingartner, 1986). A variation of the valence model categorizes emotions in terms of approach and avoidance rather than positive and negative valence (e.g., Davidson, 1995). The valence and approach-avoidance models overlap but differ, for example, anger is associated with approach behavior but is negative in valence.

Behavioral approach and avoidance tendencies have been associated with both the experience and the expression of emotion (e.g., Davidson, 1992) and studies

indicate that the left frontal area is associated with behaviors facilitating approach, such as fine motor behavior, language, and the expression of certain positive emotions (e.g., Fox & Davidson, 1984). In contrast, the right frontal area is associated with behaviors facilitating avoidance from novel or stressful stimuli, such as gross motor movement, autonomic reactivity, and the expression of certain negative emotions (Fox & Davidson, 1984).

One frequent approach to investigate the relationship between FCAs and both affective and social behavior is to explore the perception of emotional facial expressions using behavioral paradigms such as the visual half-field technique (Bourne, 2006) and the emotional chimeric faces test (e.g., Sackheim & Gur, 1978). Typically, in the emotional chimeric faces test, participants are presented with two mirror image faces, one which displays an emotion on the left and the other on the right (see Figure 28.1)

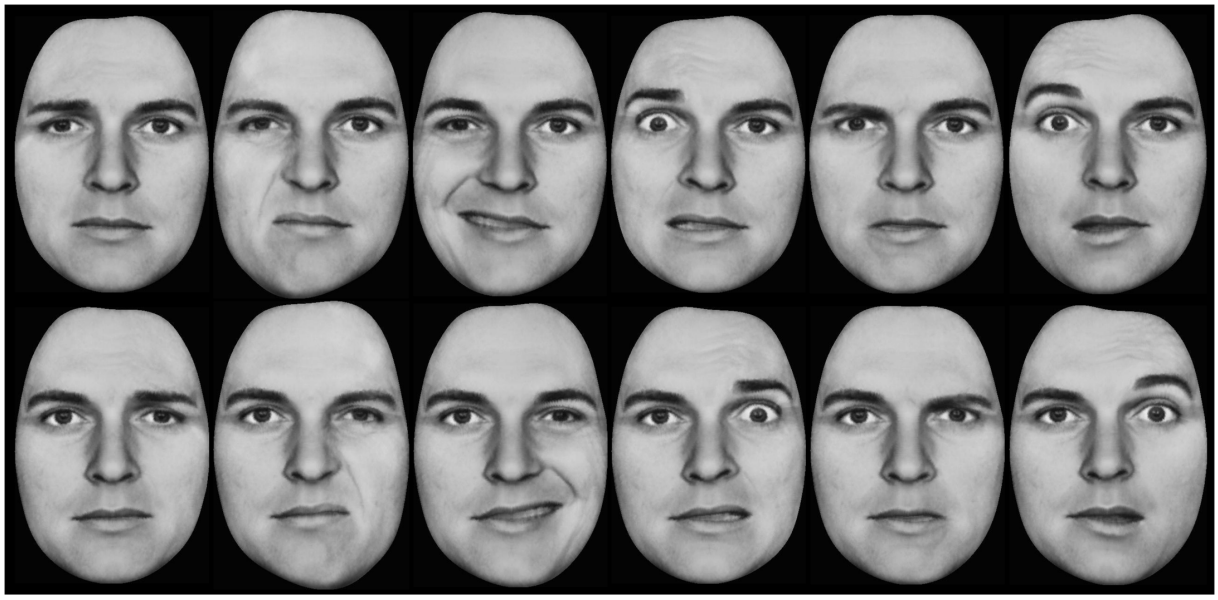

Figure 28.1. Which image looks more emotional? The upper and lower chimeric faces are mirror versions with the left of the upper face and right of the lower face being emotional.

Although the contents of the stimuli are identical mirror images, participants tend to find the face presenting the emotional expression on the left hemiface more emotional, a finding that is generally interpreted as support for the right hemisphere hypothesis (Innes et al., 2016). In a typical visual half-field technique, an emotional and a neutral face are presented briefly (to avoid eye movement) to either side of fixation and participants decide which face displays an emotional facial expression. Results of the visual half-field technique sometimes support the right hemisphere hypothesis (e.g., Alves, Aznar-Casanova, & Fukusima, 2009) but at other times the related valence and approach/avoidance models (e.g., Reuter-Lorenz & Davidson, 1981). Both paradigms appear to measure somewhat different aspects of emotion lateralization and face processing with the visual half-field technique showing greater variation in findings. This variation may be related to emotion, as recent research using music to induce emotion altered FCAs for facial expressions (e.g., Hausmann, Hodgetts, & Eerola, 2016), possibly due to the music affecting the lateralized patterns of frontal brain activity.

Frontal alpha asymmetry offers another approach to understanding emotion lateralization as Wheeler, Davidson and Tomarken's (1993) found that individuals with greater left frontal activation reported more intense feelings to positive stimuli whereas individuals with greater right frontal activation reported more intense feelings to negative stimuli. Their findings have led to a body of research implicating asymmetry in frontal alpha activity as reliable electrophysiological marker of trait affective style (Davidson, 2004). However, such frontal alpha asymmetry does not only reflect traits but also states of affective style (Harmon-Jones & Gable, 2017; Coan & Allen, 2003).

Sex-Related Variation in FCAs

There is substantial variation between individuals in the magnitude and direction of FCAs with about half of the variation in FCAs attributable to individual differences (Kim et al., 1990). Such variation has generally been ignored as random error (Hellige, 1993). However, there are many inter- *and* intra-individual factors contributing to the variation in FCAs including longstanding factors such as age, handedness and biological sex, but also factors which vary within an individual such as hormonal and emotional states. In the section that follows, we will outline evidence that sex and sex hormones are two important factors which contribute to inter- and intra-individual variations in FCAs in the cognitive domain.

Early clinical findings suggested that unilateral lesions are more likely to result in severe cognitive deficits for males than females, for whom deficits are less hemisphere-specific (e.g., McGlone, 1977; 1978). Meta-analyses of data from neurotypical participants revealed generally larger FCAs in males than females (Voyer, 1996, 2011) leading to the conclusion that, at the population level, larger FCAs in males than females are small but reliable. However, Voyer (1996) noted that the majority of studies focusing on FCAs found no significant interaction of hemisphere with sex. In addition to sex differences in the magnitude and direction of cognitive FCAs there is evidence that females demonstrate greater variation in FCAs than males (Hausmann et al., 1998).

Until recently, research focused mainly on sex differences in FCAs in cognitive domains, but current research has found that several key neural correlates of emotion and decision making show sex-related variation in FCAs (Reber & Tranel, 2017), particularly in the ventromedial prefrontal cortex and the amygdala, “in which

males with right-side lesions and females with left-side lesions display significant behavioral impairments, yet males with left-side lesions and females with right-side lesions display relatively unimpaired performance on emotion and decision-making tasks" (p. 270). The ventromedial prefrontal cortex is known to be significantly involved in emotion regulation, decision making, and social functioning (e.g., Damasio et al., 1994).

Patterns of activation for emotionally arousing memories reveal sex differences in FCAs with a stronger relationship between memory of emotionally arousing stimuli and right amygdala activation in males but left amygdala activation in females (e.g., Cahill et al., 2001). In line with this, extensive social conduct deficits in males after unilateral right amygdala damage but in females after left amygdala damage were found (Tranel & Bechara, 2009). These asymmetries in the social domain appear paralleled in patterns of neural connectivity of the amygdala with males showing higher connectivity in the right than left amygdala but the opposite pattern in females (Kilpatrick et al., 2006).

For FCAs to develop, be maintained and vary, interhemispheric connections appear to be vital (e.g., Chiarello & Maxfield, 1996). Despite interhemispheric connections being mainly excitatory, their long-lasting effect is inhibitory (Innocenti, 1986; Kawaguchi, 1992) with inhibition by the dominant hemisphere, resulting in FCAs, and the reduction of interhemispheric inhibition, resulting in increased bilateral activation (e.g. Cook, 1984; Regard et al., 1994).

Early studies aiming to link sex differences in structural and functional interhemispheric interaction directly to the size and shape of the corpus callosum but instead led to an ongoing debate as to whether sex differences in the macro- and microanatomy of the corpus callosum exist and their potential functional relevance

(see Bishop & Wahlsten, 1997, for review). Interhemispheric transfer time (IHTT) of visual-evoked potentials is faster in the right-to-left direction than left-to-right direction (e.g., Marzi, 2010) and this directional asymmetry appears less pronounced in females than males (Moes et al., 2007; Nowicka & Fersten, 2001). However, the extent to which interhemispheric inhibition related to FCAs and IHTT share the same transcallosal mechanisms is not entirely clear (Hausmann et al., 2013).

The patterns of neutral connectivity discussed above might be revealed with Diffusion Tensor Imaging (DTI) which has recently been used to investigate sex differences (see Gong et al., 2011, for a review). Studies generally find greater overall cortical connectivity in females (e.g., Gong et al., 2009) and greater *inter*-hemispheric connectivity in females than males (e.g., Duarte-Carvajalino et al., 2012; Ingalhalikar et al., 2013), but greater structural connectivity in males *within* hemispheres, leading Ingalhalikar et al. to speculate that male brains' structure facilitates connectivity between perception and coordinated action, whereas female brains 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 fluctuations during adolescence are likely to play an important role (e.g., Neufang et al., 2009).

The pattern of interhemispheric connectivity may vary depending upon functions, with for example Tunc et al. (2016) finding higher structural connectivity between motor, sensory (auditory and visual) and default mode subnetworks associated with executive control tasks (fronto-parietal and cingulo-opercular) in males but higher structural connectivity in females among subcortical, sensory and attention

subnetworks. However, not all studies find such functional specificity. For example, Satterthwaite et al. (2015) found no evidence of functional specificity despite finding differences in structural connectivity which were robust to the extent that they predicted participant's biological sex better than the participant's cognitive profile of between- versus within-module connectivity in males than in females. Variation between studies may be due to differences in DTI techniques, which whilst advanced, are still developing and debated (Björnholm et al., 2017).

However, sex alone does not explain the large variation in FCAs between studies. Instead, sex may be "an imperfect, temporary proxy for yet-unknown factors, such as hormones or sex-linked genes, that explain variation better than sex" (Maney, 2016). In line with this, variation in sex hormone levels, such as during the menstrual cycle, reveal that hormones account for inter- and intra-individual variation in FCAs.

Organizing effects of sex hormones effects on FCAs

Sex hormones are categorized as having either organizing effects, affecting neuronal development, or activating effects, modulating functional interactions within existing neuronal structures (Phoenix, Goy, Gerall, & Young, 1959), but these effects overlap rather than being highly distinct (Arnold & Breedlove, 1985).

The organizing effects of sex hormones have, for example, been assessed in individuals exposed to atypical (prenatal) hormonal environments, such as those with Congenital Adrenal Hyperplasia (CAH) which causes prenatal overproduction of androgens (that are normally medically corrected after birth). Although, Tirosh, Rod, Cohen and Hochberg (1993) found significantly enhanced FCAs in verbal tasks, particularly in CAH females, suggesting an androgenic role in language lateralization,

their finding has not been replicated (e.g., Helleday, Siwers, Ritzen, & Hugdahl, 1994; Mathews, Fane, Pasterski, Conway, Brook, & Hines, 2004). Studies of FCAs in individuals with hormonal atypicalities due to chromosomal aberrations have, for example, found that males with XXY Klinefelter syndrome, which results typically in decreased androgens levels but increased follicle-stimulating hormone and luteinizing hormone levels, have reduced FCAs for language and a related decreased asymmetries in the superior temporal gyrus and the supramarginal gyrus (part of Wernicke's area) (Van Rijn, Alemann, Swaab, Vink, Sommer, & Kahn, 2008). Thus, although the results are mixed, possibly due to variation in androgen supplementation later in life, evidence from individuals with atypical hormonal levels points to androgens increasing FCAs.

Activating effects of sex hormones on FCAs

In comparison to the *organizing effects* of sex hormones on the brain, *activating effects* are acute and reversible (Arnold, 2009), enabling dynamic changes in FCAs, functional connectivity, and consequently behavior (Wisniewski, 1998). It is the activating effects which are in the focus of our own research and the current review.

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 signalling cascades (e.g., McEwen & Alves, 1999). Thus, sex hormones have many varied effects on both 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). The well-known relatively short-time

fluctuations in estradiol and progesterone levels of the menstrual cycle have led to a focus on these hormones in females (Figure 28.2).

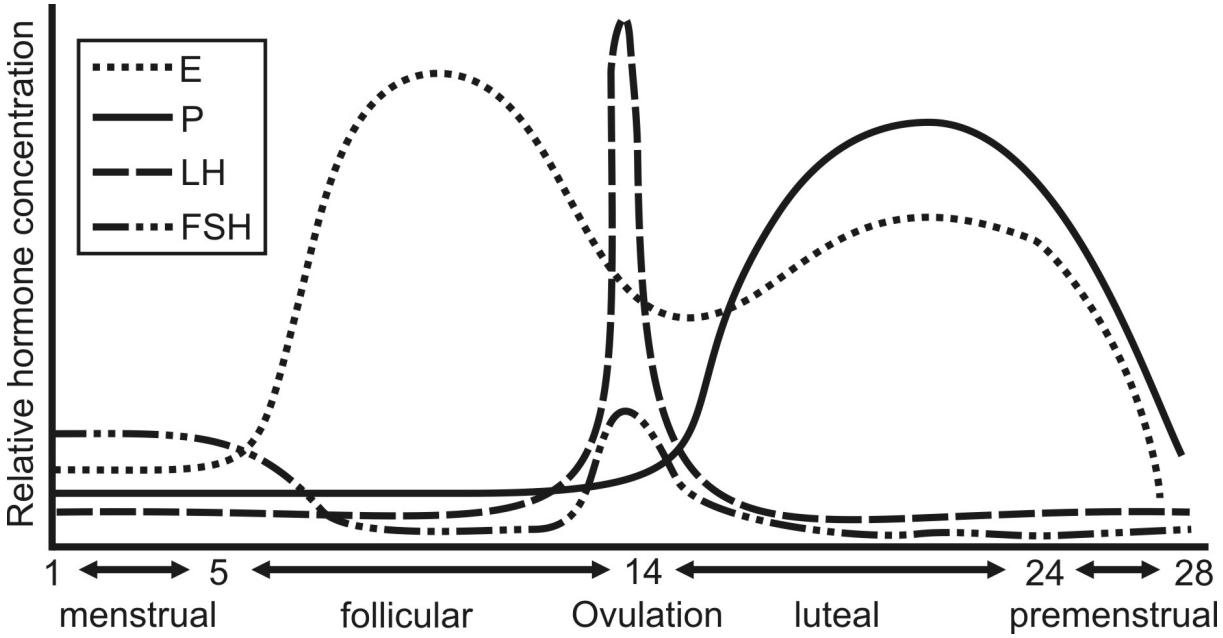

Figure 28.2. Schematic figure of the menstrual cycle, illustrating fluctuations in sex hormones (estradiol, E; progesterone, P) and gonadotropin levels (luteinizing hormone, LH; follicle-stimulating hormone, FSH) during an average 28-day menstrual cycle (adopted from Hausmann & Bayer, 2010; reprinted with permission from MIT Press).

Moreover, it has been shown in behavioral (e.g., Bibawi et al., 1995; Hampson, 1990; Hausmann, 2005; Hausmann and Güntürkün, 2000; Hausmann et al., 2002; Mead & Hampson, 1996; McCourt et al., 1997; Sanders & Wenmoth, 1998) and neuroimaging studies (e.g., Weis et al., 2008; Weis et al., 2011; Thimm et al., 2014) that FCAs and the functional connectivity related to cognitive processes change across the menstrual cycle. However, results are controversial (Compton et al., 2004; see Hausmann, 2017, Hausmann and Bayer, 2010, for review) as some studies

(e.g., Hausmann et al., 2002; Hausmann & Güntürkün, 2000; Mead & Hampson, 1996; Sanders & Wenmoth, 1998; Weis et al., 2008) found a reduction in FCAs related to high estradiol levels and/or progesterone levels, whereas other studies found the opposite, significant and larger FCAs related to high estradiol levels and/or progesterone levels in comparison to reduced FCAs during menstruation (e.g., Hampson, 1990; Mead & Hampson, 1996; Sanders & Wenmoth, 1998). Such conflicting results sometimes even occurred in the same study (e.g., Mead & Hampson, 1996; Sanders & Wenmoth, 1998), indicating that size and direction of the effects partly depend on the specific task and test modality (Hausmann & Bayer, 2010; Hodgetts et al., 2015).

The search for underlying mechanisms

The mechanisms by which sex hormones modulate FCAs appear to be complex with some inconsistencies occurring due to methodological differences between studies, such as the task and hormone assessment method used. Some studies found that hormones affect only one hemisphere but some implicated the left (e.g., Hampson, 1990, Bibawi et al., 1995) and others the right (e.g., Sanders & Wenmoth, 1998). 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 FCA favoring the right hemisphere may have been promoted.

Findings from work with rats led Bianki and Filippova (2000) to a different approach centered on hemispheric interaction to explain cycle-related effects of sex hormones on FCAs in which increased estrogen levels during proestrus increased left

hemisphere interhemispheric inhibition on the right hemisphere, whereas lower estrogen levels weakened this inhibitory action. In humans, based upon findings that FCAs were reduced for both for left and right hemisphere tasks during the midluteal phase, Hausmann and Güntürkün (2000) proposed that it was the interaction between hemispheres that was hormonally medicated rather than influence on one or both hemispheres. The authors suggested that the hormonal effect on FCAs was caused by progesterone reducing interhemispheric inhibition via suppressing the excitatory responses of neurons to glutamate (e.g., Smith et al., 1987), as well as by enhancing their inhibitory responses to GABA (Smith, 1991), resulting in hemispheric decoupling. This hypothesis of progesterone-mediated interhemispheric decoupling (Hausmann & Güntürkün, 2000) has received empirical support from studies using various techniques, including behavioral experiments (e.g., Hausmann et al., 2002; Hausmann & Güntürkün, 2000), transcranial magnetic stimulation (Hausmann et al., 2006), and fMRI (Weis et al., 2008, 2011). Weis et al (2008) also found reduced FCAs in the behavioral data when hormonal levels were high, however, the effect occurred in the follicular phase when only levels of estradiol were high. In addition, and in line with the hypothesis, the functional connectivity analysis based upon the same participants found an inhibitory influence of the dominant over the non-dominant hemisphere that varied with the menstrual cycle, but again with estradiol levels relating to the reduction in functional connectivity between hemispheres.

Estradiol, progesterone or both?

The reduction in FCAs during high estradiol levels found by Weis et al. (2008) has also been found in other studies (e.g., Hausmann, 2005; Hausmann et al., 2006). Such findings are difficult to explain in terms of progesterone-mediated

interhemispheric decoupling mainly because estradiol typically has an excitatory effect (but one which is complex and may occasionally be inhibitory, Taubol et al., 2015) whereas progesterone's effects are mainly inhibitory (Majewska et al., 1986). However, the neuromodulatory effects of estrogen and progesterone appear to interact, for example, prior estradiol administration weakens the subsequent excitatory effect of progesterone (Smith, 1994). Thus, explanations of cycle-related FCAs must at least take into account the interaction between estrogen and progesterone (Hodgetts et al., 2015).

The model of progesterone-mediated interhemispheric decoupling initially 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 (Hausmann & Güntürkün, 2000). If the effect of estradiol on glutamate receptors is mainly excitatory then we would assume both an increase in interhemispheric inhibition and larger FCAs when estradiol levels are high 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 the combination of high levels of progesterone together with high levels of estradiol results in increased activation in both the non-dominant and dominant hemispheres. In contrast to progesterone, however, GABA-ergic mechanisms seem to be unaffected by estradiol in isolation as an acute response (Taubol et al., 2015). The combined effect of progesterone on the glutamtergic- and GABA-ergic systems may be required to inhibit interhemispheric inhibition, whereas the acute excitatory effect of estradiol on the glutamatergic

system increases activation in both hemispheres with a significant effect on the less active, non-dominant hemisphere.

The effects of estrogen on prefrontal functioning

The effects discussed so far have predominantly been in areas involved in fairly low level perceptual processing and may therefore be thought of as bottom-up effects of estradiol. However, recent studies have shown effects of estrogen on prefrontal function such as working memory and tasks requiring high levels of cognitive control (Jacobs & D'Esposito, 2011). Thus, cycle-related effects of estradiol may affect cognition via prefrontal cortex (Keenan et al., 2001), an area with a particularly high estrogen receptor concentration in humans (Bixo et al., 1995). This hypothesis that estradiol affects FCAs via its effects on cognitive control was first tested by Hjelmervik et al. (2012) using a dichotic listening task (Hugdahl, 1995) that had been previously demonstrated both larger left hemispheric bias in males than females (e.g., Hirnstein et al., 2013) and fluctuations in language lateralization across the menstrual cycle (e.g., Hampson, 1990; Sanders & Wenmoth, 1998). Results revealed high estradiol levels during the follicular phase were associated with an increased left-ear advantage but only when participants were cued to shift attention to stimuli presented to the non-dominant left ear. As no menstrual cycle effect was observed when participants were not cued to shift their attention, Hjelmervik et al. (2012) concluded that the influence of estradiol was on cognitive control rather than language lateralization per se.

However, a subsequent replication attempt (Hodgetts et al., 2015) found reduced FCAs in females with high estradiol levels regardless of level of cognitive control, leading to the conclusion that estradiol reduces the stimulus-driven (bottom-up)

aspect of language lateralization, rather than the cognitive control component. Notably, Hjelmervik et al. (2012) used a within subject design repeatedly testing the same individuals whereas Hodgetts et al.'s design was between subjects comparing individuals who were higher and lower than median levels of estradiol. Thus, different findings may be due to differences in the study design and sample size. However, a cycle-related modulation of the top-down aspect of FCAs was recently found in an emotional prosody task, in which participants were asked to identify the emotional tone of a target (Hodgetts, Weis & Hausmann, 2017), supporting the potential role of estradiol in the modulation of cognitive control.

Hormonal effects on FCAs related to affective and social behavior

Menstrual cycle-related effects of estradiol on cognition and FCAs are likely to involve the prefrontal cortex (Keenan et al., 2001; Hjelmervik et al., 2012, respectively), probably due to its high concentration of estrogen receptors (Bixo et al., 1995). Since asymmetries in frontal activation have been linked to approach and withdrawal tendencies (Davidson, 1992), we might expect fluctuations in estradiol levels to alter approach and withdrawal tendencies which are likely to be critical for social interactions (Coan & Allen, 2003).

Although fontal alpha asymmetry as neural marker of approach and avoidance tendencies are assumed to be relatively robust over a lifetime, there is still variation due to environmental/situational factors (Harmon-Jones & Gable, 2017; Coan & Allen, 2003), such as changes in the hormonal environment as discussed previously. In line with the idea of sex hormones affecting emotion by modulating asymmetry in frontal activation, females suffering from premenstrual dysphoric disorder showed greater right (than left) frontal alpha activity during the luteal phase (Baehr et al.,

2004). In healthy females, a different pattern has been found with MEG, revealing higher activation over left than right frontal electrodes during the menstrual phase, when levels of estradiol and progesterone are relatively low, compared to the periovulatory phase, when especially estradiol levels are high (Hwang et al., 2008). In contrast, Solis-Ortiz et al. (1994) found no menstrual cycle-related variation in frontal alpha asymmetries possibly due to a small sample, but did find significantly higher interhemispheric correlation in $alpha_1$ (8-10 Hz) activity between frontal electrodes (F3 and F4) during ovulation and for occipital electrodes (O1 and O2) during the premenstrual phase supporting the idea that hormonal fluctuations modulate interhemispheric oscillations. This is in line with the suggestion that the corpus callosum may provide a neuroanatomical correlate for frontal cortical asymmetries and that interhemispheric crosstalk plays a significant role in approach-avoidance motivation and behavior (Schutter & Harmon-Jones, 2013). Inconsistent findings may be due to the fact that previous studies did not distinguish between healthy females who are susceptible and unsusceptible to emotion-related symptoms of the menstrual cycle (Huang et al., 2015). Huang et al. hypothesized that females high in neuroticism are more susceptible and are more likely to experience cycle-related fluctuations in resting frontal alpha asymmetry. Indeed, their results revealed lower relative left prefrontal alpha during the midlate luteal phase in high-neuroticism females than lower-neuroticism females, implying that progesterone plays a role. The authors concluded that resting frontal alpha asymmetry is a reliable neural marker of positive versus negative affective styles that is influenced by the state of the female (i.e., the menstrual cycle).

Little research has been conducted on the hormonal effects on FCAs in the perception of social emotional cues such as facial expressions. This is surprising not

only because such cues are important but also because similar sex differences with reduced FCAs in females have been found for facial expression perception (e.g., Bourne, 2005, 2008) as have been found in the cognitive domain (Voyer, 1996, 2011). Recently, Bourne and Vladeanu (2017) found more socially anxious females to show a reduced right hemisphere bias in the emotional chimeric faces task that used six emotions. The similar pattern was also found in more socially anxious males but to a less extent. Using the chimeric faces task with expressions of only happiness and anger, Bourne and Gray (2009) found the second-to-fourth finger (2D:4D) ratio, which is assumed to reflect prenatal testosterone and estradiol exposure (e.g., Manning et al., 1998), to be associated with a stronger right hemisphere bias, suggesting that higher levels of prenatal testosterone exposure and low levels of estrogen exposure result in a stronger right hemisphere bias in the perception of happy and angry facial expressions. However, the 2D:4D ratio is a very indirect and highly controversial measurement of the prenatal hormonal environment and further research is needed to understand hormonal effects on FCAs involved in social perception. We are currently starting to address this by investigating females across different cycle phases (Birch, Burt, & Hausmann, in progress).

Concluding remarks

Until now research has mainly focused on the hormonal effects of sex and sex hormones on FCAs in the cognitive domain. While further work is needed to clarify the relationship and mechanisms in the cognitive domain, our understanding of the relationship between emotion lateralization and approach and avoidance behavior, though of key importance to social behavior, is in its infancy.

The organizing and activating effects of sex hormones modulate FCAs underlying cognitive processing. As similar FACs have been found related to emotional and social behavior, it is likely that these will also be modulated by hormonal fluctuation. While sex hormones are certainly not the exclusive cause of variations in FCAs, including those responsible for sex differences, the lack of control for potential hormonal effects is likely to explain some of the inconsistencies in reports of FCAs in the current literature.

The mechanisms underlying the organizing and activating effects of sex hormones on FCAs are unclear. Three potential activating mechanisms on FCAs have been suggested: (i) sex hormones affect only one hemisphere (e.g., Hampson, 1990), (ii) both hemispheres are nonspecifically activated hormonally, accentuating slight asymmetries, and (iii) sex hormones affect the interhemispheric crosstalk, probably via the corpus callosum (e.g., Hausmann & Güntürkün, 2000). In line with the latter hypothesis, a direct relationship between the corpus callosum and emotion has been reported, highlighting the importance of considering the direction of signal transfer between the cerebral hemispheres in studying approach- and avoidance- related motivation (Schutter & Harmon-Jones, 2013). These authors concluded that the corpus callosum provides a possible neuroanatomical correlate for frontal cortical asymmetries and that interhemispheric signal transfer plays a role in the emergence of approach-related motivation and behavior. However, for FCAs in general, all proposed mechanisms have received some empirical support and a combination of these mechanisms is likely (Hausmann, 2017).

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