Antipsychotic effects of sex hormones and atypical hemispheric asymmetries

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Abstract:

Functional cerebral asymmetries (FCAs) are a fundamental principle of brain organisation. While specific patterns of asymmetry are characteristic of healthy human brains, atypical or reduced FCAs have been reported for several psychotic disorders, including schizophrenia and mood disorders. However, it is unclear whether atypical FCAs reflect a predisposition to psychotic disorders or a compensatory neural strategy for the progressive structural and functional changes in the brain associated with psychosis. A separate stream of research has demonstrated the antipsychotic effects of sex hormones in clinical populations. Moreover, modern neuroscience has shown that sex hormones, particularly estrogen and progesterone, can affect FCAs due to their organising effects (e.g. during prenatal development), and also by their activating effects throughout life (e.g. in younger women during the menstrual cycle or in post-menopausal women as a consequence of hormone therapy). By combining these research streams, this narrative literature review explores the relationship between the neuromodulatory properties of estrogen, FCAs and psychotic and psychotic-like symptoms. This research is not only of theoretical interest for the understanding of FCAs and psychotic symptoms, but might also be of clinical relevance for the development of stratified treatment approaches for women and men suffering from psychosis and mood disorders.

Keywords: Hemispheric asymmetry; Sex hormones; Estrogen, Schizophrenia; Psychotic disorders

1. Introduction

Cerebral lateralisation is a fundamental principle of functional brain organisation, referring to the asymmetrical representation of a specific cognitive process in a cerebral hemisphere (i.e., functional cerebral asymmetries, FCAs). Although it has been shown that FCAs are relatively stable over time (e.g., Vingerhoets, 2019), a number of factors have been shown to contribute to variations in FCAs (e.g., Hausmann, 2019), including biological sex and sex hormones (e.g., Hausmann, 2017). Moreover, a significant body of research has demonstrated different patterns of FCAs in patients with psychiatric conditions, primarily psychotic disorders (i.e., schizophrenia) and mood disorders (i.e., bipolar disorder and major depressive disorder) (Bruder, Stewart, & McGrath, 2017; Ocklenburg, Güntürkün, Hugdahl, & Hirnstein, 2015; Oertel-Knöchel & Linden, 2011). Furthermore, several clinical studies suggest that sex hormones have therapeutic benefits for such patients. This narrative literature review aims to synthesise the main findings from each of these research streams, to explore the theoretical relationship between sex hormones, FCAs, and psychiatric conditions.

2. Functional cerebral asymmetries in psychiatric disorders

In the healthy adult human brain, the left hemisphere is typically dominant for language, while the right hemisphere is dominant for visuo-spatial processes (Broca, 1861; Kimura, 1967). Research in clinical populations has demonstrated differences in patterns of FCAs, as compared to healthy controls. Compared to healthy human brains, atypical (i.e. reduced or reversed) FCAs have been reported for disorders characterised by psychosis (e.g. schizophrenia, Ocklenburg et al., 2015; Oertel-Knöchel & Linden, 2011), as well as mood disorders (e.g. major depressive disorder, Bruder et al., 2017, and bipolar disorder, Altshuler et al., 2008; Royer et al., 2015). However, it is important to note that no clear criterion exist regarding the degree at which FCAs should be considered *atypical*, as laterality index-based

cut-offs differ quite substantially across studies (Vingerhoets, 2019; Hausmann, 2019). However, the majority of studies of patients with psychotic disorders consider FCAs *atypical* when the functional difference between hemispheres does not approach significance (i.e., bilateral representation of functions, Alary et al., 2013; Bleich-Cohen et al., 2012; Dollfus et al., 2005), or when they are reversed (Sommer, Aleman, Ramsey, Bouma, & Kahn, 2001; Sommer, Ramsey, Mandl, & Kahn, 2003).

2.1. *Schizophrenia*

Schizophrenia is a severe psychiatric disorder characterised by positive symptoms (e.g. hallucinations, delusions), negative symptoms (e.g. blunted affect, anhedonia) and cognitive deficits (e.g. cognitive disorganisation). A plethora of evidence suggests that the brains of patients with schizophrenia are characterised by atypical FCAs when compared to healthy controls (Crow, Chance, Priddle, Radua, & James, 2013; Ocklenburg et al., 2015; Oertel-Knöchel & Linden, 2011). One of the most extensively investigated FCAs in schizophrenia are those associated with language processing.

Several studies have linked structural or morphological asymmetries to FCAs. For example, in healthy participants, the planum temporale (PT), an area in the temporal cortex involved in language processing, is generally larger in the left hemisphere when compared to the right hemisphere (Geschwind & Levitsky, 1968). However, in patients with schizophrenia, this structural asymmetry is either reduced or reversed. Evidence demonstrating this atypical asymmetry has been found in post mortem studies (Falkai et al., 1992) as well as studies that have used structural MRI (Hasan et al., 2011; Hu et al., 2013; Kasai et al., 2003; Oertel et al., 2010). Moreover, significantly reduced asymmetry of the PT has been reported in two meta-analyses (Shapleske, Rossell, Woodruff, & David, 1999; Sommer, Aleman, Ramsey, Bouma, & Kahn, 2001), although contradictory results exist (Smiley et al., 2013, 2011). In addition, a

recent study did not find a significant relationship between PT asymmetry and FCAs in the functional magnetic resonance (fMRI) response of core language areas in 287 healthy adults (Tzourio-Mazoyer, Crivello, & Mazoyer, 2018), questioning the role of PT asymmetry as a marker of language lateralisation. However, further research has demonstrated reduced structural asymmetries in other language areas, besides the PT. For example, in an MRI study of first-episode psychosis patients, Sheng et al., (2013) demonstrated reduced grey matter volume compared to healthy controls in a number of language related areas (e.g. left middle temporal cortex, left insula, and left fusiform cortex).

In line with advances in the capabilities of neuroimaging, more recent evidence concerning structural asymmetries has investigated white matter structure and structural connectivity in patients with schizophrenia. However, findings so far are inconsistent. Miyata et al. (2012) reported an atypical asymmetry in white matter integrity in patients with schizophrenia. In this study, patients showed a rightward shift of white matter integrity in two regions: the external capsule and the posterior limb of the internal capsule. Moreover, Miyata et al. (2012) found that these atypical asymmetries correlated positively with negative symptom severity. Similar findings were also found by Ho et al. (2017), Gómez-Gastiasoro et al. (2019) and Joo et al. (2018), but no correlations with symptom measures were found in the latter study. In contrast, Sun, Chen, Collinson, Bezerianos, and Sim (2017) demonstrated reduced leftward asymmetry in the structural connectivity of several regions in patients with schizophrenia, including the inferior and superior frontal gyrus and superior temporal gyrus. Moreover, these asymmetries were positively associated with severity of positive symptomatology. However, it should be noted that contradictions exist, for example Takao et al. (2010) reported no significant effect of diagnosis on asymmetries in white matter integrity or grey matter volume asymmetry.

Neuroimaging studies in schizophrenia have demonstrated atypical asymmetries at the structural level and functional level, although the relationship between both is not always clear-

cut. As with structural asymmetries, most research to date has focused on FCAs related to language processes. Consequently, reduced activation of the left hemisphere during language processing and/or production has been demonstrated in patients with schizophrenia across a range of studies, including fMRI (Alary et al., 2013; Bleich-Cohen et al., 2012; Dollfus et al., 2005; Leroux, Delcroix, & Dollfus, 2015; Oertel et al., 2010; Razafimandimby et al., 2007; Weiss et al., 2004, 2006; Zhang et al., 2008) electroencephalography (Angrilli et al., 2009; Jalili et al., 2010) and positron emission tomography (Artiges et al., 2000). Moreover, some of these studies have demonstrated a relationship between reduced language lateralisation and psychotic symptoms (e.g. auditory hallucinations, Zhang et al., 2008). Further studies have investigated asymmetries in the functional connectivity of language networks in patients using resting state fMRI. Son et al. (2017) reported that schizophrenia patients showed reduced functional connectivity within the language network compared to controls, but no difference in asymmetry (i.e. both patients and controls were left lateralised). In contrast, Mueller, Wang, Pan, Holt, and Liu (2015) found reduced FCA in language processing in patients, albeit in a different network. Again, it should be noted that null findings exist suggesting no difference in FCAs for language between patients and controls (Narr et al., 2001; Razafimandimby, Tzourio-Mazoyer, Mazoyer, Maïza, & Dollfus, 2011).

A number of behavioural laterality studies have yielded evidence supporting the notion that language FCAs are reduced in patients with schizophrenia (Hahn et al., 2011; Hugdahl et al., 2012; Løberg, Hugdahl, & Green, 1999; Løberg, Jørgensen, & Hugdahl, 2004; Rossell & Boundy, 2005). The paradigm most commonly used to assess language lateralisation at the behavioural level is dichotic listening. This paradigm involves the simultaneous presentation of two auditory stimuli, one to the left and one to the right ear. Participants are required to verbally report whichever stimuli they heard the most clearly. In healthy right-handed adults, this task typically reveals a bias towards stimuli presented to the right ear (i.e., right ear

advantage), indicative of left-hemispheric language lateralisation (Kimura, 1967). A number of studies using this paradigm have revealed reduced right ear advantage (or a left ear advantage) in patients with schizophrenia (Hahn et al., 2011; Løberg, Hugdahl, & Green, 1999; Løberg, Jørgensen, & Hugdahl, 2004; meta-analysis by Ocklenburg, Westerhausen, Hirnstein, & Hugdahl, 2013), although some contradictions exist (Løberg, Jørgensen, & Hugdahl, 2002). Interestingly, some of these studies have suggested that the right ear advantage (and language asymmetry in general) is altered specifically in patients with hallucinations (Hugdahl et al., 2012; Løberg et al., 2004; Rossell & Boundy, 2005). This suggests that reduced FCAs for language may reflect a disposition towards psychosis characterised specifically by auditory hallucinations.

The previous sections focused on left hemispheric language FCAs in patients with schizophrenia. However, it is important to note that, although less researched, FCAs in other functional domains are also known to be reduced or reversed in patients with schizophrenia as compared to healthy adults. Some studies have investigated FCAs for emotional processing in patients with schizophrenia using facial emotional recognition paradigms. For example, Champagne, Mendrek, Germain, Hot, and Lavoie (2014) recorded event-related potentials (ERPs) in patients with schizophrenia and healthy controls while they viewed images of emotional facial expressions. The results demonstrated reduced right hemispheric activation in patients with schizophrenia. Similar results have been reported using behavioural measures of FCAs for emotion processing (Gooding, Luh, & Tallent, 2001; Gooding & Tallent, 2002; Kucharska-Pietura, David, Dropko, & Klimkowski, 2002). Moreover, language functions that are typically lateralised to the right hemisphere in healthy participants, such as emotional prosody processing, have been shown to differ in patients with schizophrenia, with some studies demonstrating reduced/reversed FCAs (Alba-Ferrara, Hirnstein, Weis, & Hausmann,

2012; Mitchell, Elliott, Barry, Cruttenden, & Woodruff, 2004) while others have demonstrated increased FCAs in patients compared to controls (Bach et al., 2009).

In light of the considerable amount of evidence suggesting an association between FCAs and schizophrenia, a number of researchers have begun to question whether atypical FCAs reflect a genetic predisposition to psychosis (i.e. a trait marker), or a neurocompensatory strategy for the progressive structural and functional changes in the brain associated with psychosis (i.e. state dependent). Evidence in support of the former hypothesis has been provided by studies demonstrating reduced or reversed language lateralisation in both the relatives of patients with schizophrenia (Bhojraj et al., 2009; Hu et al., 2013; Park et al., 2013; Qiu et al., 2009, but see Deep-Soboslay et al., 2010), and in 'ultra-high risk' populations (e.g. participants potentially in the prodromal phase of schizophrenia (Dean, Orr, Newberry, & Mittal, 2016; Natsubori et al., 2014). Furthermore, a recent genome-wide association study by Wiberg et al. (2019) identified a polymorphism associated with several psychiatric diagnoses, including schizophrenia/psychosis, as well as left-handedness and the integrity of several white matter tracts associated with language lateralisation. Given that a considerable number of studies have demonstrated a higher incidence of left-handedness in patients with schizophrenia compared to healthy controls (see meta-analysis by Hirnstein & Hugdahl, 2014), Wiberg et al. (2019) argued that this particular polymorphism may at least partly represent a genotype for a range of psychiatric diagnoses. On the other hand, a number of longitudinal/cross-sectional studies have been conducted to investigate whether atypical FCAs are the result of progressive neural changes following diagnosis. Evidence here is inconsistent, however, with some studies suggesting that atypical FCAs develop concurrently with illness progression (e.g. Clark et al., 2010) while others show them to be stable across time (e.g., Bakalar et al., 2009). Recently, Wang et al., (2019) conducted a meta-analysis on fMRI data from a large sample of patients across various stages of illness progression (first episode, chronic, and healthy controls). The

results showed that males who were left lateralised at first episode experienced a reduction in FCAs as they progressed into chronic illness. In contrast, female patients demonstrated reduced FCAs that were stable during illness progression. Consequently, the authors purport the aetiology of schizophrenia is likely due a genetic factor located on the sex chromosomes that influences the development of language lateralisation.

2.2. *Mood and anxiety disorders*

Disorders characterised by psychosis, such as schizophrenia, are not the only severe mental disorders associated with atypical FCAs. Indeed, a number of studies have suggested that mood disorders, such as bipolar disorder (Bruder et al., 1994; Caligiuri et al., 2004; Jogia, Haldane, Cobb, Kumari, & Frangou, 2008; Killgore, Gruber, & Yurgelun-Todd, 2008; Najt, Bayer, & Hausmann, 2013; Najt & Hausmann, 2014) and major depressive disorder (Allen, Urry, Hitt, & Coan, 2004; Bruder et al., 2017; Gotlib, 1998; Henriques & Davidson, 1991; Stewart, Bismark, Towers, Coan, & Allen, 2010) especially with co-morbid anxiety disorders (Bruder, Wexler, Stewart, Price, & Quitkin, 1999) are also associated with atypical FCAs.

Bipolar disorder is a dynamic mood disorder characterised by a cyclic pattern of mood states including, mania, severe depression, hypomania, as well as mixed states. It is generally accepted that bipolar disorder is associated with dysfunctional emotion regulation (Phillips et al., 2008), which in turn is associated with atypical FCAs. In particular, a number of studies using facial emotion recognition paradigms have demonstrated a reduction or reversal of the typical right hemispheric advantage found in healthy participants, when patients are in a manic state (Jogia, Haldane, Cobb, Kumari, & Frangou, 2008; Killgore, Gruber, & Yurgelun-Todd, 2008). Similar findings were reported in euthymic patients using an emotional prosody dichotic listening task (Najt & Hausmann, 2014) and a visual line bisection task (Najt, Bayer, & Hausmann, 2013), which are typically both lateralised in healthy controls due to the relative

dominance of the right hemisphere in emotion processing and visuospatial attention, respectively (Broca, 1861; Hellige, 1993; Kimura, 1967). Atypical FCAs have also been reported during depressive episodes in bipolar disorder, but these neuroimaging studies suggest dysfunction of the left rather than right hemisphere (Allen, Iacono, Depue, & Arbisi, 1993; Altshuler et al., 2008; Lawrence et al., 2004). Together, these studies suggest that FCAs for emotion processing in patients with bipolar disorder are state dependent, and not trait markers of the disorder, supporting the notion that atypical FCAs, for example in emotion lateralisation may not be the cause but the consequence of impaired emotion regulation/processing. In contrast to the majority of functional data, Wang et al. (2018) demonstrated a number of structural differences in bipolar patients that were indicative of reduced left hemispheric function, but increased right hemispheric efficiency compared to controls. Moreover, Wang et al. (2018) reported that these atypical asymmetries significantly correlated with clinical measures of mania, suggesting that atypical asymmetries are potential biomarkers for the clinical presentation of bipolar disorder (see also Ho et al., 2017).

A comparatively small number of studies have investigated FCAs for non-emotional processes in patients with bipolar disorder. However, those that have identified increased FCAs in bipolar disorder for tasks involving the right hemisphere, such as spatial attention (Rao, Arasappa, Reddy, Venkatasubramanian, & Gangadhar, 2010) and handedness (Savitz, Van Der Merwe, Solms, & Ramesar, 2007), compared to healthy controls. Given that, in practice, many clinicians conceptualise bipolar disorder and schizophrenia as similar diagnoses (Laursen, Agerbo, & Pedersen, 2009), and also given the aforementioned studies concerning language FCAs in schizophrenia, it is important to consider studies of language FCAs in bipolar disorder. However, few such studies exist, and those that do suggest that language FCAs in bipolar disorder do not differ from those of healthy controls. For example, using structural MRI (Ratnanather et al., 2013) demonstrated similar asymmetries in the volume of the planum

temporale in bipolar patients compared to controls. In addition, using fMRI during a language processing task, Royer et al. (2015) reported that bipolar patients show lateralised activation of the left hemisphere that did not differ from healthy controls.

Similarly, studies of major depressive disorder (i.e. unipolar depression without mania or psychosis) have also reported atypical FCAs in patients compared to healthy controls. Many studies of this population show atypical FCAs in primarily frontal areas (Bruder et al., 2017). Studies using resting state EEG to investigate frontal alpha asymmetry have found that patients with major depression are characterised by reduced activity in the left hemisphere, as compared to the right hemisphere (Allen, Urry, Hitt, & Coan, 2004; Gotlib, 1998; Henriques & Davidson, 1991; Stewart, Bismark, Towers, Coan, & Allen, 2010; for a meta-analysis see Thibodeau, Jorgensen, & Kim, 2006). Furthermore, Allen et al. (2004) purport that this FCA is stable (i.e. a trait marker), as the same pattern is found regardless of whether the patient is symptomatic or euthymic during testing. Similarly, resting state PET studies have reported reduced blood flow in the left dorsolateral prefrontal cortex in depressed patients (Baxter et al., 1985; Bench, Friston, Brown, Frackowiak, & Dolan, 1993) but contradictory findings also exist (Sacher et al., 2012). Bruder et al. (2017) suggest that these inconsistencies may reflect difference in the diagnostic subtypes included in each sample. Resting state fMRI studies have also reported decreased activity in the left hemisphere of patients with depression, albeit across a number of cortical and subcortical regions (for review see the meta-analysis by Fitzgerald, Laird, Maller, & Daskalakis, 2008).

A smaller number of studies have investigated FCAs in non-frontal areas in patients with depression (Bruder et al., 2017). Moreover, a number of behavioural laterality studies using the dichotic listening paradigm have yielded inconsistent findings, with some studies reporting a significantly larger right-ear advantage in patients with depression (Bruder et al., 1989; Pine et al., 2000), and others reporting no difference between patients and controls (Hugdahl et al.,

2003; Moscovitch, Strauss, & Olds, 1981; Wale & Carr, 1990). As previously mentioned, Bruder et al. (2017) suggest that this inconsistency may reflect differences between the samples with respect to patient characteristics. Indeed, Bruder, Wexler, Stewart, Price, and Quitkin (1999) reported findings that suggest the REA is only reduced in MDD patients with a comorbid anxiety disorder (Bruder et al., 1999). Consequently, Bruder et al. (2017) suggests that anxious arousal is associated with increased right parietotemporal activity, which results in a reduced left hemisphere advantage for dichotic listening.

3. Sex hormone effects on functional cerebral asymmetries

In healthy adults, a body of research has demonstrated sex differences in FCAs in tasks related to language (Hausmann et al., 1998), spatial ability (Chiarello, McMahon, & Schaefer, 1989; Hausmann & Güntürkün, 2000), and face recognition (Borod et al., 2005; Rizzolatti & Buchtel, 1977). While contradictions exist (e.g. Boles, 2005; Frost et al., 1999; Knecht et al., 2000; Sommer, Aleman, Bouma, & Kahn, 2004), these studies suggest that women show slightly reduced FCAs (i.e. increased bilaterality) or even stronger asymmetry (Kaiser, Kuenzli, Zappatore, & Nitsch, 2007; Ladavas, Umiltà, & Ricci- Bitti, 1980), relative to men. Several reviews, meta-analyses and large-scale studies have been conducted to quantify the size of sex differences in FCAs across a range of lateralised cognitive processes (e.g., Bless et al., 2015; Hirnstein et al., 2014; Hiscock et al., 1994; 1995; 1999; 2001; Vogel et al., 2003; Voyer, 1995). Taken together, these meta-analyses and large-scale studies conclude that small but reliable sex differences in FCAs exist at the population level, with males yielding larger FCAs than women do.

Additional evidence has suggested that the distinct sex hormonal profiles of men and women are one important factor to the generation and maintenance of such sex differences in FCAs and cognition (e.g. Hodgetts & Hausmann, 2018; Weis & Hausmann, 2010). However,

sex hormone levels are not stable but fluctuate in women both across the lifespan (e.g., menopause) and across shorter time intervals (e.g., during the menstrual cycle). As such, menstrual cycle related hormone fluctuations might at least to some extent underpin the larger degree of inter- and intra-individual variation in FCAs in women. Sex hormonal fluctuations (seasonal) are also known in men but their potential effects on atypical FCAs were hardly studied (e.g. Moffat & Hampson, 2000).

3.1. *Organising and activating effects*

Sex hormonal effects on brain and behaviour are broadly categorised as either organising or activating effects (Phoenix, Goy, Gerall & Young, 1959). Organising effects result from interactions between hormones and genes, and occur primarily during early ontogenesis and puberty. These effects result in permanent sex differences in brain structure (for a recent review, see Jäncke, 2018). Activating effects are the result of hormonal fluctuations that occur throughout life and, in contrast to organising effects, are transient and reflect dynamic changes in functional brain organisation (for a review, see Cohen-Bendahan, Beek, & Berenbaum, 2005). Activating effects are typically investigated in naturally cycling women, by assessing changes in FCAs across the menstrual cycle that occur in line with fluctuating hormone levels.

3.1.1. *Organising effects of sex hormones on FCAs*

Organising effects of sex hormones are typically investigated in clinical populations affected by atypical sex hormonal conditions during gestation or childhood. One such condition is congenital adrenal hyperplasia (CAH), a genetic condition that, in both males and females, is characterised by an underproduction of cortisol and a consequential overproduction of androgens, including testosterone. While contradictions exist (Helleday, Siwers, Ritzen, & Hugdahl, 1994; Mathews et al., 2004), several studies in CAH patients have suggested a role

for androgens in handedness (e.g. Kelso, Nicholls, Warne, & Zacharin, 2000) and language lateralisation (e.g. Tirosh, Rod, Cohen, & Hochberg, 1993).

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

Sex hormones have also been shown to influence FCAs later in life, throughout adulthood (Forget & Cohen, 1994). Studies on lateralization in transsexuals who underwent a gender-affirming hormone therapy for several months provide an interesting opportunity to investigate whether asymmetries are determined by genetic sex or by the current hormonal environment (Forget & Cohen, 1994). The observation that men and transwomen (male-to-female) reveal differences in lateralisation strongly suggests that the influence of sex hormones on cerebral structures and functions is not fixed prenatally. Specifically, it has been shown that women and transwomen have similar patterns of FCAs (Cohen & Forget, 1995).

However, this finding is not consistent. For example, using fMRI, Sommer et al. (2008) showed that, although cerebral activation was related to sex hormonal changes, lateralisation in a verbal and spatial task was not affected by gender-affirming hormonal treatment. Another study (Cohen-Kettenis, van Goozen, Doorn, & Gooren, 1998) investigated transmen and transwomen, who were not yet receiving hormone therapy and found the degree of

lateralisation in both groups to be between those of male and female controls. This suggests that transgender identity can affect lateralisation and cognitive behaviour even before hormonal treatment, perhaps as a result of organisational hormonal influences.

3.1.2. *Activating effects of sex hormones on FCAs*

A large body of evidence has developed, incorporating a range of behavioural, electrophysiological, and neuroimaging techniques, demonstrating that FCAs fluctuate within relatively short-term periods across different phases of the menstrual cycle, in line with hormone fluctuations (Alexander, Altemus, Peterson, & Wexler, 2002; Bayer & Hausmann, 2011; Cowell, Ledger, Wadnerkar, Skilling, & Whiteside, 2011; Hausmann, Hamm, Waldie, & Kirk, 2013; Hausmann & Güntürkün, 2000; Hodgetts, Weis, & Hausmann, 2015, 2017; Weis et al., 2008; Weis, Hausmann, Stoffers, & Sturm, 2011). However, the literature is inconsistent with respect to the direction of the laterality change and, subsequently, the mechanisms underlying these activating effects.

Several behavioural studies which used well-established laterality tasks, such as verbal dichotic listening (Cowell et al., 2011; Hampson, 1990a; Hampson, 1990b; Hjelmervik et al., 2012; Sanders & Wenmoth, 1998; Wadnerkar, Whiteside, & Cowell, 2008) and line bisection (McCourt & Olafson, 1997) have shown that FCAs increase during high hormone phases (i.e. high estradiol and progesterone levels) relative to low hormone phases (low estradiol and progesterone levels). However, other studies have shown reduced FCAs in high-hormone phases, relative to low hormone phases using similar tasks, including verbal dichotic listening (Alexander et al., 2002; Altemus & Wexler, 1989; Hodgetts et al., 2015; Mead & Hampson, 1996); music dichotic listening (Sanders & Wenmoth, 1998); line bisection (Hausmann, 2005; Hausmann, Becker, Gather, & Güntürkün, 2002), lexical decision (Hausmann & Güntürkün, 2000; Hausmann et al., 2002), figure-matching (Hausmann & Güntürkün, 2000; Weis et al.,

2011), word matching (Weis et al., 2008), and face perception (Hausmann & Güntürkün, 2000; Hausmann et al., 2002).

A potential mechanism of sex hormonal effects on FCAs in humans was initially proposed by Hausmann and Güntürkün (2000). In that study, normally cycling women completed left-hemispheric (word-matching) and right-hemispheric (figure-matching, face discrimination) tasks, during both the low-hormone menstrual phase and the high-progesterone luteal phase. Menstrual cycle phase was verified by salivary hormone assays. In addition, a sample of men and a sample of postmenopausal women were tested at corresponding time intervals. The authors identified an interaction between cycle phase and FCAs in all tasks, indicative of a general reduction in FCAs during the high progesterone luteal phase. In contrast, FCAs were stable across time in postmenopausal women and men. Because this study (see also Hausmann et al., 2002) demonstrated a general reduction in FCAs, for both right and left hemispheric tasks, when levels of progesterone were high, it was suggested that sex hormones could not be selectively influencing only one hemisphere. Instead, Hausmann and Güntürkün (2000) proposed that sex hormones affect FCAs by modulating interhemispheric interaction, a physiological process that affects both hemispheres.

In their hypothesis of progesterone-mediated interhemispheric decoupling, Hausmann and Güntürkün (2000) proposed that high levels of progesterone during the luteal phase leads to a reduction of interhemispheric inhibition. This, in turn, leads to a functional decoupling of the two hemispheres and a reduction in FCAs. Specifically, they proposed that progesterone can reduce interhemispheric inhibition by suppressing the excitatory neural response to glutamate and by increasing the inhibitory neural response to GABA (Hausmann & Güntürkün, 2000; Hausmann et al., 2002; Hausmann & Bayer, 2010). This view was supported by several physiological studies demonstrating that progesterone suppresses the excitatory response of neurons to glutamate, while also increasing the inhibitory response of neurons to GABA

(Smith, Waterhouse, & Woodward, 1987a, 1987b). A further study showed that similar effects may be obtained with combined estradiol and progesterone administration (Smith, Waterhouse, & Woodward, 1987c). Thus, it was proposed that high levels of progesterone in the luteal phase might lead to a transient reduction in interhemispheric inhibition and, in turn, to a reduction in lateralisation (Hausmann & Güntürkün, 2000; Hausmann et al., 2002).

This hypothesis was further investigated in an fMRI study (Weis et al., 2008) in which normally cycling women completed a word-matching task, identical to that used by Hausmann and Güntürkün (2000). All women were tested during both the low hormone menstrual phase and the high estradiol follicular phase; a control group of males was tested at corresponding time intervals. Functional connectivity was assessed using psychophysical interaction analysis (PPI) to determine the inhibitory influence of the dominant left hemisphere on the nondominant right hemisphere. In addition to a significant left hemispheric advantage in accuracy and response times found in the menstrual phase, which was reduced in the follicular phase, PPI analysis revealed that the inhibitory influence of the left hemisphere over the right hemisphere fluctuated according to estradiol levels. Specifically, high levels of estradiol during the follicular phase were associated with reduced interhemispheric inhibition and, in turn, reduced FCAs. No significant changes in FCAs or interhemispheric inhibition were found in the male controls.

While Hausmann & Güntürkün (2000) found that high progesterone levels (in combination with high estradiol levels) can reduce interhemispheric inhibition, Weis et al. (2008) showed that estradiol alone could reduce interhemispheric inhibition. Similar results were found in a transcranial magnetic stimulation (TMS) study by Hausmann et al. (2006). In this study, TMS was applied to the primary motor cortex to elicit suppression of tonic voluntary muscle activity in both the contralateral and ipsilateral side. Ipsilateral suppression (i.e., ipsilateral silent period) is thought to be cortically mediated via excitatory transcallosal fibres, and thus can be

seen as an indirect measure of the connectivity between homotopic regions of the left and right motor cortices. Hausmann et al. (2006) showed that the ipsilateral silent period fluctuates across the menstrual cycle, with the largest suppression/inhibition taking place during the luteal phase (high levels of estradiol and progesterone) compared to the follicular phase (high levels of estradiol only). Hausmann et al. (2013) reported additional evidence in support of this view, in an electroencephalography study of interhemispheric transfer time (IHTT). This study showed that IHTT from right to left was longer during the luteal phase compared to the menstrual phase. Additional analyses revealed that this effect was related to high levels of estradiol, as opposed to progesterone, which suggested that the different interhemispheric processes are modulated by different sex hormones (Hausmann et al., 2013).

Hjelmervik et al. (2012) investigated hormonal effects in normally cycling women on the top-down processes related to language lateralisation using a forced-attention dichotic listening paradigm. In this task, participants have to selectively attend to and report from either the left or the right ear specifically. In contrast to the non-forced condition, the forced-left condition requires a high level of cognitive control, as participants must override their bias toward the dominant right ear. A cycle-related effect was found only in the forced-left condition. Here, women demonstrated a greater left-ear advantage during the high-estradiol follicular phase, compared to both the menstrual and luteal phases. The authors interpreted this finding as evidence of an active role of estradiol on cognitive control, and not on language lateralisation *per se* (Hjelmervik et al., 2012). In contrast to Hjelmervik et al. (2012), Hodgetts et al. (2015) found that language lateralisation was reduced across all attention conditions when estradiol and progesterone levels were high, suggesting that the neuromodulatory properties of sex hormones on FCAs primarily affected the bottom-up processes, maybe via the mechanism suggested by Hausmann & Gunturkun (2000). In a follow-up study, Hodgetts et al. (2017) used a linguistic and an emotional prosody dichotic listening task to investigate whether high levels

of estradiol were related to reduced dichotic listening biases in both tasks and influenced the bottom-up processes of lateralisation (i.e., interhemispheric inhibition) in all three attention conditions and irrespectively of the left or right dominance of the task. Although no modulatory effect of sex hormones on language lateralisation was replicated, Hodgetts et al. (2017) found in the right-hemispheric emotional prosody task that high estradiol levels were associated with a reduction in FCAs in the forced-right condition. This suggests that estradiol can affect the top-down aspect of FCAs in a right-hemispheric task. Although task-related differences in the degree of lateralisation might explain some of the inconsistency between studies, these studies, in conjunction with Hjelmervik et al. (2012), suggest that estradiol (and potentially progesterone) are capable of modulating both top-down *and* bottom-up processes related to FCAs.

The majority of studies investigating the relationship between FCAs and sex hormones have been investigated samples of premenopausal women. However, a comparatively small number of studies have investigated the effect of direct manipulations of hormone levels on FCAs and interhemispheric communication by focusing on post-menopausal women taking hormone therapy (HT; for a review see Bayer & Hausmann, 2011). These studies typically compare measures of lateralisation between postmenopausal women using estrogen therapy, combined estrogen plus progestin therapy, and those not taking any hormonal substitution (Bayer and Erdmann, 2008; Bayer and Hausmann, 2009). For example, using the visual half-field technique Bayer and Erdmann (2008) and Bayer and Hausmann (2009a, b) demonstrated reduced FCAs in postmenopausal women using HT, compared to postmenopausal women without HT. Moreover, Bayer and Hausmann (2009a) demonstrated that right hemisphere processing was negatively related to estradiol levels. As such, it was concluded that while the effect of sex hormones on FCAs across the menstrual cycle is likely underpinned by hormonal

effects on interhemispheric transmission, the effect of HT on FCAs appears to underpinned by hormonal effects on within hemisphere connectivity (Bayer & Hausmann, 2011).

4. Sex hormones and psychosis

So far, we have shown that (1) psychotic disorders are linked with atypical FCAs, although causation is not entirely clear, and (2) FCAs are affected by sex hormones during early ontogenesis (organising effects) and later in life due to their neuromodulatory properties (activating effects). A third stream of research involving clinical populations has demonstrated the neuroleptic effects of sex hormones, across a range of psychiatric diagnoses including psychotic disorders (primarily schizophrenia) and mood disorders (bipolar disorder, major depressive disorder). Research in this area includes a number of epidemiological and clinical studies, indicating a higher incidence of schizophrenia in men compared to women (Aleman, Kahn, & Selten, 2003; McGrath, Saha, Chant, & Welham, 2008; van der Werf et al., 2014, but also see Häfner et al., 1989; Jablensky et al., 1992), and an earlier onset in men than women (Angermeyer & Kuhn, 1988; Häfner, Maurer, Loffler, & Riecher-Rossler, 1993; Häfner et al., 1989; Häfner et al., 1998). Moreover, while both sexes show peak incidence rates in their 20s (men in their early 20s, women in their late 20s), several studies revealed a second, smaller peak of first episode incidence in women at age 45-49 years (Häfner et al. 1998; Kirkbride et al., 2012; Riecher-Rossler, Loffler, & Munk-Jorgensen, 1997; Riecher-Rössler et al., 1994), an age range consistent with menopausal onset, and a subsequent decrease in estrogen production.

Emil Kraepelin (1893) first implicated an imbalance of estrogens in the aetiology of dementia praecox more than 100 years ago and it took nearly a century until this idea was reflated and a number of studies investigated whether sex hormones, particularly estrogens, can have antipsychotic effects that reduce women's vulnerability to psychotic illnesses (Riecher-Rössler & Kulkarni, 2011). Riecher-Rössler and Häfner (1993) formally proposed

two separate but related hypotheses concerning the role of estrogen in schizophrenia. Firstly, it was proposed that estrogens exert a protective effect against psychosis (*estrogen protection hypothesis*). Secondly, it was proposed that patients with psychosis would show hypoestrogenism and gonadal dysfunction (*hypoestrogenism hypothesis*). In fact, several studies have shown that psychotic symptoms fluctuate across the menstrual cycle, such that they are more severe during low estrogen phases (Bergemann, Parzer, Runnebaum, Resch, & Mundt, 2007a; Bergemann, Abu-Tair, & Strowitzki, 2007b; Choi, Kang, & Joe, 2001; Harris, 1997; Ko et al., 2006; Markham, 2012; Riecher-Rössler, Häfner, Stumbaum, Maurer, & Schmidt, 1994; Riecher-Rössler et al., 1994), and that psychotic symptoms reduce during pregnancy, when estrogen levels are high, but relapse following delivery, when estrogen levels return to normal (Howard, Goss, Leese, Appleby, & Thornicroft, 2004; Munk-Olsen et al., 2009; Vigod & Ross, 2010). In addition, several studies have demonstrated reduced average levels of circulating estradiol and progesterone levels in blood, and as opposed to during specific cycle phases (Canuso et al., 2002; Howard, 2005; Oades & Schepker, 1994; Riecher-Rössler et al., 2013), as well as menstrual irregularities (e.g. anovulation and reduced fertility, Bundy, Stahl, & MacCabe, 2011) in women with psychotic symptoms. Critically, these findings have been replicated in first-episode, antipsychotic-naïve patients (González-Blanco et al., 2016; Petrikis et al., 2016; Riecher-Rössler et al., 2013), suggesting that hypoestrogenism is not due to the effects of medication. Finally, direct evidence comes from intervention studies, showing neuroprotective effects of 17β-estradiol administration for women with schizophrenia (Akhondzadeh et al., 2006; Bergemann et al., 2007b; Ghafari et al., 2013; Kulkarni et al., 2001; Kulkarni, 2009; Kulkarni et al., 2008; Liao et al., 2002; Riecher-Rössler, Butler, & Kulkarni, 2018, for a review see Begemann, Dekker, van Lunenburg, and Sommer, 2012). However, as noted by Riecher-Rössler et al. (2018) postmenopausal women with schizophrenia are most likely to benefit from estrogen augmentation therapy, because schizophrenia and psychosis

have consistently been associated with extensive deficits in executive function (Aas et al., 2014; Gold, 2004; Johnson-Selfridge & Zalewski, 1997; Roiser et al., 2013; Weisbrod, Kiefer, Marzinzik, & Spitzer, 2000) and there is some evidence showing that high estradiol levels can have positive effects on executive function (Jacobs & D'esposito, 2011; Keenan et al., 2001; Maki & Sundermann. 2009).

Table 1 Studies investigating the direct (i.e. sex hormone administration) and indirect effect (i.e. comparing different phases of the menstrual cycle) of sex hormones (estradiol, progesterone) on psychotic symptoms.

Study	Participants	Mean age (± S.D.)	Cycle phases (cycle days)/Hormone adjunct	Outcome measures	Main results
Bergemann et al. (2007a)	125 women with schizophrenia	35.0 (8.3)	Proliferative (2–4) Peri-ovulatory (10–12) Luteal (20–22)	PANSS BPRS	Significant improvement in psychotic symptoms during the luteal phase, relative to other phases
Bergemann et al., (2007b)	Case report, 1 women with late-onset schizophrenia	51.0	Transdermal estradiol monotherapy 50 μg estradiol hemihydrate, 250 μg norethisteronacetate, 4.80 mg norethisteronacetate	PANSS	Remission of psychotic symptoms during the treatment course.
Choi et al. (2001)	24 women with schizophrenia	36.1 (6.4)	Menstrual phase (3-4) Postmenstrual (6-7 days following menstruation) Premenstrual (week before menstruation)	BPRS	No change in psychotic symptoms across the cycle, higher anxiety/depression scores in premenstrual phase, no correlation with estrogen levels.
Ghafari et al., 2013	32 women with schizophrenia	34.5 (8.7)	Adjunctive daily oral conjugated estrogen 0.625 mg/day for 4 weeks	PANSS	Significant reduction in severity of positive symptoms, negative symptoms, and general psychopathology following estrogen administration
Harris (1997)	39 women with schizophrenia	34.8 (S.D. not reported)	Premenstrual (5 days before menstruation) Menstrual Postmenstrual (5 days after menses cessation)	BPRS	Significant worsening of affective symptoms during menstruation
Ko et al. (2006)	35 women with schizophrenia, classified as	34.0 (6.1)	Follicular (1 – 14)	SANS Immediate Visual Recognition Scale	Significant negative correlation between SANS scores and estradiol levels

	high or low estradiol post-hoc			List Recall Scale List Acquisition Scale Oral Fluency Test Trail Making Test A and B Wechsler Adult Intelligence Scale-Revised Digit Symbol Test	Low estradiol group showed significantly poorer cognitive performance compared to high estradiol group
Kulkarni et al. (2001)	36 women with schizophrenia	34.0 (8.47)	Transdermal estradiol 50mcg (n =12) Transdermal estradiol 100mcg (n =12) Placebo (n = 12)	PANSS	Significant clinical improvement with 100mcg estradiol compared to 50mcg and placebo (antipsychotics only)
Kulkarni et al. (2008)	102 women with schizophrenia	33.65 (8.25)	Transdermal estradiol 100-µg (n = 56) Placebo (n = 46)	PANSS	Significant clinical improvement with 100mcg estradiol compared to placebo (antipsychotics only)
Kulkarni et al. (2014)	51 women with schizoaffective disorder or bipolar disorder	38.91 (9.6)	Tamoxifen (n = 15) Medroxyprogesterone acetate (MPA, n = 18) Placebo (n =18)	CARS-M	MPA group showed significantly reductions in symptom severity compared to both the tamoxifen and placebo groups.
Liao et al. (2002)	Case reports, 4 women with schizophrenia	40, 35, 34, and 50.	Adjunctive daily oral dose of conjugated estrogen (Premarin 0.625 mg) for 3 months	NOSIE	Significant reduction of psychotic symptoms in 2 cases.

Louzã et al. (2004)	40 women with acute schizophrenia	32.3 (8.2)	Adjunctive dose of conjugated estrogens 0.625 mg/day (n = 21) Adjunctive placebo (n = 19)	BPRS	Similar rate of improvement in both groups for positive, negative, and general symptomology.
Riecher-Rössler et al. (1994)	32 women with schizophrenia	30.5 (6.5)	Cycle days 2, 7, 13, 14, 21, 28	BPRS NOSIE	Significant relationship between estradiol level and symptom severity; low estradiol levels associated with increased symptom severity
Thompson et al. (2000)	29 women with psychosis 31 healthy controls	30.76 (7.84)	Cycle days 1-14, and 14-28	PANSS Arithmetic Block design Mental rotation Trail Making Test A and B Counting Digit span Digit symbol Pegboard composite Tapping composite	No change in symptom severity between the two cycle phases. Both groups showed improved mental rotation when estrogen levels were low. High estrogen levels were associated with poor motor performance in psychotic women only.

Note: Brief Psychiatric Rating Scale/BPRS; Clinician Administered Rating Scale for Mania/CARS-M; Nurses' Observation Scale for In-patient Evaluation/NOSIE; Positive and Negative Syndrome Scale/PANSS; Scale for the Assessment of Negative Symptoms/SANS)

In addition to the many studies implicating estrogen in psychosis and schizophrenia, a small but significant body of research has investigated the potential role of progesterone. This is primarily due the relationship between the two hormones; when estradiol levels are naturally low, progesterone levels are also low, making it difficult to rule out an effect of progesterone, or an interactive estrogen/progesterone effect on psychotic symptoms (Sun, Walker, Dean, van den Buuse, & Gogos, 2016). However, studies investigating the role of progesterone in schizophrenia are limited (Ko et al., 2006; Sun et al., 2016). For example, although a number of studies have suggested that progesterone levels are lower in women with schizophrenia compared to healthy controls (Bergemann et al., 2005, 2007; Rubin et al., 2010; Thompson, Sergejew, & Kulkarni, 2000), patients in these studies were not medication naïve, and so medication effects cannot be ruled out.

Studies investigating the role of sex hormones in other psychiatric conditions have focused primarily on bipolar disorder and major depressive disorder (Soria et al., 2018). However, the number of studies here is quite limited compared to schizophrenia (Gogos, Ney, Seymour, Van Rheenen, & Felmingham, 2019). Similar to schizophrenia, bipolar disorder is associated with fluctuations in symptom severity in line with naturally occurring hormone fluctuations, with low hormone cycle phases being characterised by more severe manic/depressive symptoms (Rasgon, Bauer, Glenn, Elman, & Whybrow, 2003; Shivakumar, Bernstein, & Suppes, 2008). Further evidence has demonstrated increased severity of manic symptoms in the post-partum period (Heron, Haque, Oyebode, Craddock, & Jones, 2009), and decreased mood stability both during and after menopause (Marsh, Gershenson, & Rothschild, 2015; Marsh et al., 2012). As such, a limited number of small clinical trials have been conducted to investigate sex hormones as adjunctive therapies in bipolar disorder (Meinhard, Kessing, & Vinberg, 2014). Kulkarni et al. (2014) demonstrated that both adjunctive medroxyprogesterone and tamoxifen, a selective estrogen receptor modulator (SERM) that lacks the possible negative effects of estrogen on

breast and uterine tissue, were associated with greater symptom improvement, and medroxyprogesterone was associated with faster improvements in symptoms compared to adjunctive tamoxifen and mood stabilisers alone. Other studies also found anti-manic effects in women with bipolar disorder after SERM treatment (Amrollahi et al., 2011; Yildiz, Guleryuz, Ankerst, Öngür, & Renshaw, 2008; Zarate et al., 2007). A small number of studies investigating the use of estrogen as an adjunct to antidepressant therapy specifically for peri-menopausal women and reported positive results (e.g., Kulkarni et al., 2018; for a review see Worsley et al., 2012).

5. Integrating atypical asymmetries, sex hormones and psychotic symptoms.

It has been argued that FCAs are double-coded by stable characteristics (traits) and temporary situational aspects (states) (e.g., Hausmann, 2019). Sex hormones are assumed to contribute to the establishment of FCAs during early development (via organising effects) and also dynamically change FCAs in certain constraints throughout life, for example in younger women during different cycle phases (Hausmann, 2017), and in postmenopausal women in response to hormone therapy (Bayer & Hausmann, 2011). The question arising from this, and the three research streams discussed in this review, is whether there is a functional link between the effects of FCAs, sex hormones and psychotic symptoms. Although it is currently not clear whether atypical FCAs are cause or consequence of psychotic symptoms, one might speculate that sex hormonal modulations of FCAs will also modulate psychotic symptoms.

One important issue in this context that has been neglected so far is that it is not always clear whether atypical FCAs observed in schizophrenia and other psychotic disorders are due to the disorder itself or a consequence of the neuroleptic treatment patients with schizophrenia receive. For example, Tomer and Flor-Henry (1989) found that neuroleptic treatment can reverse the attention asymmetry in patients with schizophrenia; unmedicated patients showed

inattention to the right hemisphere in the Mesulam Cancellation Test (Weintraub & Mesulam, 1985), which changed to more prominent left-sided inattention in medicated patients. This suggests that neuroleptics may normalise left hemisphere performance, at the expense of deteriorated right hemisphere performance. Other studies have also suggested that in male and female patients with schizophrenia, neuroleptic medication can restore typical lateralisation (Harvey, Nelson, Haller, & Early, 1993; Mohr, Landis & Brugger, 2006; Sapir, Dobrusin, Ben-Bashat, & Henik, 2007; Seidman et al., 1993; Wigal, Swanson, & Potkin, 1997).

Regarding state-trait aspects of atypical FCAs in schizophrenia, it is interesting to note that both symptomatic *and* non-symptomatic patients yield reduced FCAs during the forced-left attention condition of the consonant-vowel DL task (Løberg et al., 2004). In this study, Løberg et al. (2004) recruited patients with schizophrenia who were currently experiencing auditory hallucinations, patients with a history of auditory hallucinations who were not symptomatic, and a healthy control group to complete three DL conditions. In the non-forced attention condition, only patients currently experiencing hallucinations demonstrated a reduced FCA compared to healthy controls. Non-symptomatic patients with a history of hallucinations did not show a reduced language asymmetry, leading the authors to conclude that reduced language lateralisation is likely to be a state marker for psychotic symptoms. In contrast, both patient groups exhibited difficulties modulating attention during the forced-attention DL conditions, suggesting that attentional control ability is a trait marker of psychosis.

This is particularly interesting in the context of Hjelmervik et al.'s (2012) study, which showed that attention control in healthy women improved in line with higher levels of estradiol, as indicated by an increase in FCA in the forced-left attention condition during the follicular phase. Taking these research streams together, it is possible that the mechanism by which sex hormones exert neuroleptic effects in schizophrenia concerns both state *and* trait aspects of the disorder. Specifically, high levels of estradiol lead to improved cognitive control by increasing

activity within prefrontal areas in a compensatory manner, resulting in a reduction of the severity of psychotic symptoms during high estradiol cycle phases, as seen in a number of clinical studies (Bergemann, Parzer, Runnebaum, Resch, & Mundt, 2007; Choi, Kang, & Joe, 2001; Harris, 1997; Ko et al., 2006; Markham, 2012; Riecher-Rössler, Häfner, Stumbaum, Maurer, & Schmidt, 1994; Riecher-Rössler et al., 1994). This is in line with a specific mechanism put forward in a recent review by McGregor, Riordan, and Thornton (2017). Amongst other potential mechanisms, McGregor et al. (2017) purport that GABA dysfunction localised specifically to parvalbumin (PV) expressing neurons in the prefrontal cortex and hippocampus is characteristic of the brains of patients with schizophrenia. Moreover, McGregor et al. (2017) argue that a loss of PV neurons underpins the cognitive impairments consistently demonstrated by patients with schizophrenia, including those related to cognitive control. Amongst other actions at this level, estradiol has been shown to exert a protective effect over PV expression in the brain, as well as increasing the number PV expressing neurons in the prefrontal cortex. McGregor et al. (2017) go on to argue that estradiol has been shown to increase GABA receptor number and binding affinity in several animal models. Taken together, it is argued that the interaction with GABAergic pathways may be one mechanism by which estradiol exerts a beneficial effect in schizophrenia, particularly where cognitive aspects of the disorder are concerned. A recent review by Moraga-Amaro et al. (2018) suggested that future studies should employ positron emission tomography (PET) in order to fully identify how estradiol interacts with other neurotransmitter systems in order to exert its neuroprotective effects. Indeed, although PET studies of estrogen effects on monoaminergic activity have been conducted in samples of patients with depression (for a review see Zsido et al., 2017), no such studies exist in patients with schizophrenia (Moraga-Amaro et al., 2018).

It is also generally accepted that estradiol (and progesterone) can reduce left hemispheric language asymmetries in healthy women (Alexander et al., 2002; Altemus & Wexler, 1989;

Hodgetts et al., 2015; Mead & Hampson, 1996). What is currently unclear, however, is whether the effect of sex hormones on FCAs is also related to the antipsychotic effects of estradiol. Bayer and Hausmann (2011) suggested that estradiol may produce an antipsychotic effect in schizophrenia by modulating the atypical FCAs demonstrated in such patients. However, given that patients with schizophrenia typically demonstrate reduced FCAs (Hahn et al., 2011; Løberg, Hugdahl, & Green, 1999; Løberg, Jørgensen, & Hugdahl, 2004; meta-analysis by Ocklenburg, Westerhausen, Hirnstein, & Hugdahl, 2013) and atypical interhemispheric interaction, such as excessive callosal information (e.g., David, 1993; Narr et al., 2003) or longer interhemispheric transfer (IHTT) (Henshall et al., 2012), compared to healthy controls, it seems unlikely that high levels of estradiol reduce psychotic symptoms by 'normalising' FCAs (i.e. increasing lateralisation to a level comparable with healthy controls). Instead, estradiol might enhance bilateral brain organisation in patients with schizophrenia and thereby increasing the difference in lateralisation seen between patients and controls. Several studies provided evidence to suggest that reduced FCAs (i.e., more bilateral brain organisation) are a marker of neurocompensatory functions in specific populations including healthy elderly people (Bracco et al., 2011; Cabeza, 2002; for a review see Wingfield & Grossman, 2006) and people with neurodevelopmental conditions (e.g. autism, Whitehouse & Bishop, 2008; dyslexia, Bishop, 2013; Illingworth & Bishop, 2009; Shaywitz et al., 2007). Additionally, as women tend to demonstrate more bilateral brain organisation compared to men, this might also explain why women are generally less likely to be diagnosed with a psychotic disorder such as schizophrenia (Aleman, Kahn, & Selten, 2003; McGrath, Saha, Chant, & Welham, 2008; van der Werf et al., 2014) and also show less severe psychotic symptoms (Goldstein, Tsuang & Faraone, 1989). Taken together with evidence demonstrating a beneficial effect of estradiol on prefrontal functions (Hjelmervik et al., 2012; Jacobs & D'Esposito, 2011), this supports the

notion that there are at least two different mechanisms by which sex hormones, and high estradiol levels in particular, can exert beneficial effects in patients with psychiatric disorders.

6. Conclusions and future directions

Research to date supports the notion that atypical patterns of FCA in men and women are associated with a number of psychiatric diagnoses, including schizophrenia, bipolar disorder, and major depressive disorder. What is less clear, is whether there is a functional relationship between of FCAs, sex hormones and psychotic symptoms and, if these is, in which directions causation flows. For example, whether atypical FCAs are a cause or a consequence of psychotic symptoms remains a matter of debate. However, in light of the evidence presented in this review, it seems plausible that sex hormonal modulations of FCAs can contribute to the modulation of psychotic symptoms.

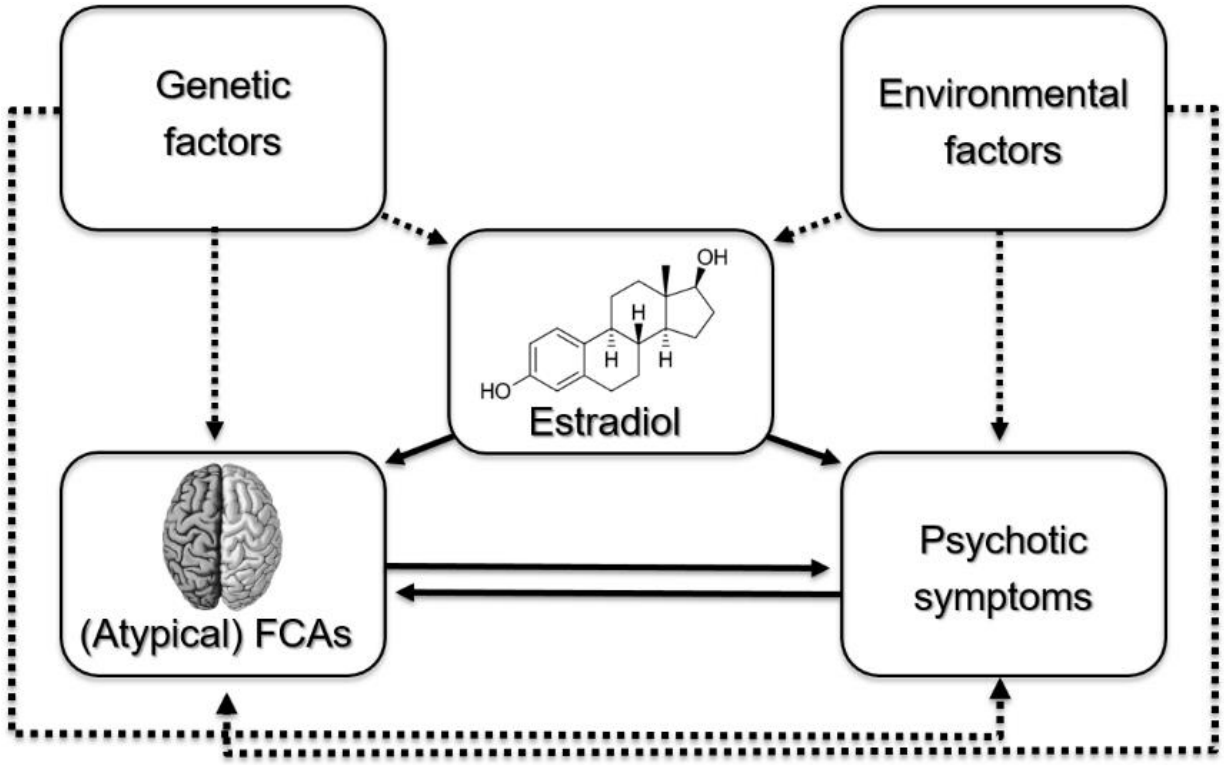

Fig. 1 – The influence of estradiol on functional cerebral asymmetries (FCAs) and psychotic symptoms in schizophrenia and other mental disorders, such as major depression, bipolar disorder, anxiety and neurodevelopmental disorders. Estradiol can affect functional asymmetries and cognitive control and can reduce psychotic symptoms. The causality of the relationship between atypical asymmetries and psychotic symptoms is still unclear. There is empirical evidence for both atypical asymmetries as a trait marker of the disorder and as a neurocompensatory mechanism. The main focus of the current review is indicated by the solid arrows.

As previously mentioned, it has been suggested that FCAs are, in general, double-coded by both stable characteristics (traits) and temporary situational aspects (states) (e.g., Hausmann, 2019). Related to this notion, this review also discussed the state-trait aspects of atypical FCAs, particularly with respect to schizophrenia, in order to consider the potential mechanisms underpinning the beneficial effect of estradiol on psychotic symptoms. Although limited to a relatively small number of studies, there is evidence to suggest that reduced FCAs (e.g., for language) are a state marker of schizophrenia, while reduced cognitive control ability is a trait maker for the disorder. Similarly, findings to date support the notion that there are at least two potential mechanisms by which estradiol exerts antipsychotic effects. Firstly, amongst other

mechanisms, McGregor et al. (2017) argue that schizophrenia is associated with a loss of GABAergic PV neurons in the prefrontal cortex, and estradiol has a protective influence over PV expression, resulting in a beneficial effect on cognitive aspects of the disorder. Secondly, given that high estradiol levels are associated with reduced FCAs (increased bilaterality), it is possible that estradiol might enhance bilateral brain activity in patients with schizophrenia, facilitating the recruitment of additional brain regions in a neurocompensatory manner. However, it should be noted that the proposed mechanisms are speculative, as they are yet to be directly investigated.

The findings presented in this review, although sometimes contradictory, do at least suggest tentative clinical implications worthy of further investigation. In particular, the idea sex hormones may act as an antipsychotic agent against schizophrenia (Häfner, 2005; Kulkarni et al., 2013; McGregor et al., 2017; Riecher-Rössler et al., 1994; Riecher-Rössler & Kulkarni, 2011) requires further investigation in clinical populations in order to identify optimal sex-sensitive treatment strategies for women *and* men. However, it is important to note that not all clinical studies report positive therapeutic effects of adjunctive estrogen (e.g. Louza et al., 2004) as well as experimental studies reporting negative SERM effects on the healthy brain. For example, Chen et al. (2017) investigated the effect of tamoxifen on premenopausal women and found significant deficits in working memory and general executive function performance and significantly lower functional connectivity of the right dorsolateral prefrontal cortex with the right hippocampus compared with controls. Also, this study did not find significant changes in functional connectivity in the left dorsolateral prefrontal cortex within the whole brain between the tamoxifen group and healthy control women.

Most of the evidence reported in this review is based on sex hormonal effects in women, with very little on men. However, we are inclined to believe that the mechanisms underlying antipsychotic effects of sex hormones and FCAs in women and men might be similar.

Unfortunately, there are only very few studies that investigated the effects of SERMs on brain functions in men. One of these is the fMRI study by Goekoop et al. (2006) who found that raloxifene treatment in elderly men lead to an increase in activation in bilateral parietal, mediotemporal and prefrontal areas. The authors concluded that a SERM-induced increase in cortical arousal can potentially enhance activation in brain areas involved in several different cognitive domains, including attention, working memory, executive functioning and verbal abilities. However, the underlying neural mechanisms of SERM-related effects on cognition and functional brain organisation remain unclear and further research is needed that investigate the suggested link between FCAs, sex hormones, and psychotic symptoms directly.

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