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Sex differences in schizophrenia, bipolar disorder and PTSD: Are gonadal hormones the link?

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Abstract

In this review, we describe the sex differences in prevalence, onset, symptom profiles and disease outcome that are evident in schizophrenia, bipolar disorder and post-traumatic stress disorder. Women with schizophrenia tend to exhibit less disease impairment than men; by contrast, women with post-traumatic stress disorder are more affected than men. The most likely candidates to explain these sex differences are gonadal hormones. This review details the clinical evidence that estradiol and progesterone are dysregulated in these psychiatric disorders. Notably, existing data on estradiol, and to a lesser extent, progesterone, suggest that low levels of these hormones may increase the risk of disease development and worsen symptom severity. We argue that future studies require a more inclusive, considered analysis of gonadal steroid hormones and the intricacies of the interactions between them, with methodological rigour applied, to enhance our understanding of the roles of steroid hormones in psychiatric disorders.

Keywords: schizophrenia; bipolar disorder (BD); posttraumatic stress disorder (PTSD); estradiol; progesterone

Abbreviations

BD: bipolar disorder

CNS: central nervous system

DHEA: dehydroepiandrosterone

HPA: hypothalamic-pituitary-adrenal

HPG: hypothalamic-pituitary-gonadal

PACAP: pituitary adenylate cyclase-activating peptide

PTSD: post-traumatic stress disorder

1. Introduction

Sex differences are prevalent in disorders affecting the central nervous system (CNS). Schizophrenia, bipolar disorder (BD), post-traumatic stress disorder (PTSD), major depressive disorder, autism spectrum disorder, Alzheimer's disease, multiple sclerosis, motor neuron disease and Parkinson's disease are examples of such conditions that report sexually dimorphic incidence rates, symptomology or prognosis (Christiansen *et al.*, 2015; Diflorio *et al.*, 2010; Gogos *et al.*, 2015; Pinares-Garcia *et al.*, 2018; Sanchez *et al.*, 2010). While there are a number of biological, cultural and environmental factors that may underlie these sex differences, the important role of gonadal steroid hormones has become increasingly evident in recent decades. Steroids have potent and widespread effects in the brain and the role of gonadal hormones have been of particular interest (Gogos *et al.*, 2015; Pinares-Garcia *et al.*, 2018). Accumulating evidence demonstrates the influence of gonadal steroid hormones on cognition and various pathophysiological pathways, in addition to their therapeutic potential. Throughout the lifespan, mammalian females experience various endogenous fluctuations in ovarian hormone levels, which can influence the symptom profile of CNS disorders. Such fluctuations include the recurring oscillations of estradiol and progesterone across the reproductive cycle (i.e. the menstrual cycle), the dramatic changes throughout pregnancy and post-partum that orchestrate reproduction, and the overall decline in circulating hormone levels associated with reproductive senescence (i.e. menopause) (Sbisa *et al.*, 2017; Sun *et al.*, 2016). Researchers have utilised these natural variations in estradiol and progesterone to investigate their effects on the expression of psychiatric disorders and subsequently glean insight into the mechanisms of endogenous gonadal hormones and how they may act in concert with each other. More recently, the impact of exogenous hormone administration has been investigated, highlighting their therapeutic potential (Kulkarni *et al.*, 2014; Kulkarni *et al.*, 2012). In this review, therefore, we summarise the literature describing sex differences in certain psychiatric disorders, and then probe whether these differences are due to the influence of selected steroid hormones. We outline the evidence of steroid hormone dyregulation in each disorder, emphasising the similarities across disorders. The integral role of estradiol and progesterone in psychiatry is highlighted and a number of unanswered questions are posed as improvements for further studies are suggested.

This review will focus on schizophrenia, BD and PTSD, three sexually dimorphic psychiatric disorders that show similarities in clinical/cognitive symptomatology, aetiology and neurobiology.

In the next section we detail evidence of sex differences in these three disorders, focussing on the differences between men and women in disease incidence, onset and symptom expression.

2. Sex differences in psychiatric disorders

2.1 Schizophrenia

Schizophrenia is a chronic disorder characterised by multiple symptom categories, including positive psychotic symptoms, negative symptoms, disordered thoughts/speech, and cognitive deficits (APA, 2013). Sex differences in schizophrenia are widely documented in the literature, reportedly affecting several domains including disease onset, course of illness, and symptom profiles (Gogos *et al.*, 2015; Ochoa *et al.*, 2012; Sun *et al.*, 2016). The incidence of schizophrenia is greater in men (1.4:1 male:female ratio) (McGrath *et al.*, 2004), who typically experience peak onset between the ages of 18-25, approximately 4 years earlier than women (Galderisi *et al.*, 2012; Hafner, 2003). Additionally, women uniquely exhibit a second surge of disease onset around 45-49 years, suggested to be attributed to the decline of ovarian hormones due to menopause (Hafner, 2003; Sun *et al.*, 2016). Sex differences in disease progression and prognosis have also been observed, with men showing less responsiveness to antipsychotic medication (Szymanski *et al.*, 1995), and longer, more frequent hospitalisations (Szymanski *et al.*, 1995; Usall *et al.*, 2003). Men also exhibit greater substance abuse (Koster *et al.*, 2008; Ochoa *et al.*, 2012), social isolation, and withdrawal than women (Koster *et al.*, 2008; Zhang *et al.*, 2012), who have better social prognoses, including retainment of marriages, interpersonal relationships (Hafner, 2003; Vila-Rodriguez *et al.*, 2011), and employment (Cotton *et al.*, 2009; Vila-Rodriguez *et al.*, 2011). Furthermore, women experience higher rates of remission and recovery than men (Carpiniello *et al.*, 2012). Whilst the sex differences in schizophrenia are typically observed post-diagnosis, a recent review suggests their presence prior to the onset of clinically detectable symptoms, with men displaying poorer premorbid functioning than women, including greater social withdrawal, isolation, and poor self-care (Mendrek *et al.*, 2016).

In addition to the sex differences in social and behavioural domains, men with schizophrenia experience more brain morphological abnormalities than women. For example, gross anatomical studies show greater ventricular enlargement (Narr *et al.*, 2001), and more severe frontal and

temporal lobe atrophy in men (Bryant *et al.*, 1999; Narr *et al.*, 2001). Furthermore, men also show greater abnormalities in white matter microstructure (Kanaan *et al.*, 2012; Kelly *et al.*, 2018).

Research regarding sex differences in symptomology in schizophrenia remains less clear. Some studies report that women suffer more positive (Thorup *et al.*, 2007) and affective symptoms than men (Ochoa *et al.*, 2012; Zhang *et al.*, 2012), and several studies suggest milder symptoms overall in women, including fewer cognitive deficits (Han *et al.*, 2012), and less severe negative symptoms (Bakhshi *et al.*, 2015; Galderisi *et al.*, 2012; Grossman *et al.*, 2008; Koster *et al.*, 2008). By contrast, others failed to identify any sex differences in positive or negative symptoms (Han *et al.*, 2012; Ochoa *et al.*, 2012; Szymanski *et al.*, 1995). Furthermore, both men (Morgan *et al.*, 2008) and women (Szymanski *et al.*, 1995) have been reported as suffering greater depressive symptoms, and women experience worse negative symptoms than men (Galderisi *et al.*, 2012). There are several possible explanations for these discrepancies, including inconsistent methodology, sampling variation and size, and the use of different symptom evaluation tools, particularly when comparing earlier versus recent studies. Sex-specific differences in comorbid and psychosocial factors including substance abuse (Riecher-Rössler *et al.*, 2018), and access to, or engagement with social supports may also explain some of the sex differences observed (Grossman *et al.*, 2008). These issues highlight the need for further investigation into sex differences using a systematic approach to control for confounding variables.

2.2 Bipolar Disorder

BD is a complex disorder characterised by extreme fluctuations in mood, from manic highs to depressive lows (APA, 2013). Two diagnostic subtypes are recognised; BD I – characterised by at least one episode of full blown mania that impacts functioning, or BD II – characterised by a more short-lived and less severe form of mania, called hypomania, that occurs alongside episodes of depression. The lifetime incidence of BD is approximately 1:1 in men and women, although the incidence of manic episodes and unipolar mania is higher in men with the disease (Diflorio *et al.*, 2010). Research suggests an increased prevalence of BD II and hypomania in women, with general functioning being significantly better for men with this BD subtype (Diflorio *et al.*, 2010). Women with BD also report increased rates of rapid cycling in some but not all studies (Baldassano *et al.*, 2005; Diflorio *et al.*, 2010; Robb *et al.*, 1998). Reports of sex differences in psychosis symptoms

are inconsistent; with some studies finding an increased prevalence in men versus women (Morgan *et al.*, 2005) or vice-versa (Bräunig *et al.*, 2009), and others finding no differences at all (Kessing, 2004). Comorbid phobia, panic disorder, PTSD, eating disorders and borderline personality disorder are more frequently reported in women than men with BD, while higher rates of comorbid conduct and substance use disorders are reported in men (Diflorio *et al.*, 2010; Suominen *et al.*, 2009).

Most extant studies indicate an equivocal age of onset across the sexes, although some have reported that women may be slightly older than men when the disease manifest (Diflorio *et al.*, 2010; Kawa *et al.*, 2005; Robb *et al.*, 1998; Suppes *et al.*, 2001). Recurrent depressive polarity and a depressive or mixed onset has been shown to predominate in women with BD (Kessing, 2004; Viguera *et al.*, 2001), while mania may be more prevalent in men at first onset (Kawa *et al.*, 2005; Suppes *et al.*, 2001). Owing to inconsistent literature, it is not clear if there are sex differences in the *number* of depressive or manic episodes (Baldassano *et al.*, 2005; Diflorio *et al.*, 2010; Robb *et al.*, 1998). However, some studies do show an increased use of antidepressant treatment in women with BD, as well as of benzodiazepines, electroconvulsive therapy and psychotherapy (Baldassano *et al.*, 2005; Karanti *et al.*, 2015). On the other hand, men appear to be treated with lithium more often (Karanti *et al.*, 2015), but sex differences in its clinical response are not evident (Viguera *et al.*, 2001). Women with BD have far increased rates of hypothyroidism (when lithium-treated) and are at increased risk of migraine, compared to men; while rates of metabolic syndrome appear to be equivocal across the sexes (Diflorio *et al.*, 2010; Saunders *et al.*, 2014).

Sex-specific effects on cognitive profiles have been largely unexplored in the BD literature. However, there is some evidence to show that men with BD perform worse on visuospatial construction (Gogos *et al.*, 2010) and better on spatial memory and sustained attention tasks (Bücker *et al.*, 2014) compared to women with BD but not controls. Men with BD have also been found to have worse verbal memory performance (Carrus *et al.*, 2010), worse recognition of happy prosody (Van Rheenen *et al.*, 2013) and reduced sensorimotor gating (Gogos *et al.*, 2009) compared to male controls; while worse recognition of surprise and fear prosody (Bozikas *et al.*, 2007) and increased sensorimotor gating (Gogos *et al.*, 2009) has been seen in women with BD compared to female controls. One study showed that women with BD experience greater cognitive benefit from vigorous physical activity than men with BD (Fellendorf *et al.*, 2017).

In terms of brain morphology, there is no evidence of sex differences in global grey or white matter, limbic, or ventricular and sulcal volumes (Jogia *et al.*, 2012). Reduced grey matter volume of the medial prefrontal cortex however, has been reported in men with BD compared to male controls (Almeida *et al.*, 2009; Jogia *et al.*, 2012). Further, right hippocampal volume loss is evident in women versus men with BD (Shi *et al.*, 2018) but not controls. Women with BD also exhibit abnormal neural engagement of the caudate and prefrontal cortex during social-cognitive tasks compared to female controls (Jogia *et al.*, 2012). Overall, compared to schizophrenia there is very little research investigating sex differences in BD. However, the available data show that there are sex differences in a number of domains of BD, supporting the idea that sex is an important consideration in BD.

2.3 Post-Traumatic Stress Disorder

PTSD is a common disorder that occurs after experiencing a traumatic event involving threat to life or physical integrity (APA, 2013). It is characterised by re-experiencing symptoms including intrusive memories and nightmares of the trauma, avoidance of trauma reminders, hyper-arousal and dysregulation in mood, cognition and in the hypothalamic-pituitary axis (Pitman *et al.*, 2012). There are several known risk factors for PTSD, including previous psychiatric or trauma history, family psychiatric history, and age at trauma onset. One of the most robust known risk factors of PTSD is being female. Large scale epidemiological and prospective studies consistently report that women develop PTSD at approximately twice the rate of men following trauma (Christiansen *et al.*, 2015; Kessler *et al.*, 2017; Olff, 2017; Tolin *et al.*, 2006). Longitudinally, the PTSD sex difference is highest between the ages of 21 and 25, with men and women reporting their highest rates of PTSD in their 40s and 50s, respectively (Ditlevsen *et al.*, 2010).

Sex differences in the risk of PTSD are not attributable to measurement errors, reporting bias or methodological issues (Christiansen *et al.*, 2015; Tolin *et al.*, 2006). A multiplicity of factors (social, cognitive, biological and genetic) may contribute to this sex difference; for example, women are exposed to greater interpersonal and sexual violence, which lead to greater rates of PTSD (Christiansen *et al.*, 2015; Forbes *et al.*, 2014; Kessler *et al.*, 2017; Olff, 2017). In contrast, men are typically exposed to more industrial accidents, war and combat trauma and physical assaults (Kessler *et al.*, 2017). This raises the question, if women are associated with more toxic

forms of trauma exposure such as sexual violence, might this explain their heightened risk of developing PTSD? The most definitive test of whether sex differences in PTSD can be attributed to sex differences in prevalence of exposure to different types of trauma was in the largest study in a US sample of >34,000 participants (Blanco *et al.*, 2018). Lifetime prevalence for PTSD was 9.48% in women and 5.97% in men, and women experienced childhood maltreatment and assaultive violence more often than men. However, differences in the prevalence of exposure to varying trauma types did not explain the differential risk of PTSD in women and men. In fact, most types of trauma (17 out of 19) were associated with greater risk of PTSD in women than in men. A key finding of this study was that a difference in reactivity to trauma, regardless of the type of trauma, explained more than 60% of the differential PTSD risk in women and men (Blanco *et al.*, 2018).

In epidemiological studies, there are sex differences in initial reactivity to trauma with increased peri-traumatic dissociation and perception of life threat reported as more prevalent immediate responses in women than men (Bryant *et al.*, 2003; Irish *et al.*, 2011; Norris *et al.*, 2002; Solomon *et al.*, 2005). Differences in symptom presentation appear to dissipate somewhat over time, with studies reporting similar symptomology between men and women, albeit women reporting stronger intensity across all symptoms (Carragher *et al.*, 2016; Murphy *et al.*, 2018). There are few studies reporting sex differences in standard experimental tasks that assess PTSD mechanisms and risk factors. In one imaging study, however, increased blood-oxygen-level dependent (BOLD) activation was observed in the right amygdala and anterior cingulate cortex of healthy women compared to men during a fear conditioning task, a task where reduction in arousal to analogue trauma (e.g. electric shock) is measured physiologically (Lebron-Milad *et al.*, 2012). Further, we showed that women have greater negative memory consolidation than men in response to stress-induction, suggesting a potential mechanism for the greater female susceptibility to developing PTSD (Felmingham *et al.*, 2012c). In this study, participants viewed negative, neutral and positive images and were then exposed to a stress-induction test (i.e. cold-pressor stress task) immediately following encoding and stress hormones (cortisol and salivary alpha amylase) were recorded. Although women and men showed similar stress-induced increases in cortisol, women showed significantly greater recall of negative images which suggests greater negative memory consolidation following stress in women (Felmingham *et al.*, 2012c).

Women appear to be more responsive to PTSD treatment than men, with studies reporting better treatment gains and maintenance to exposure and behavioural therapies in female patients (Felmingham *et al.*, 2012a; Galovski *et al.*, 2013; Stenmark *et al.*, 2014). Most recently, a meta-analysis of 48 of these studies confirmed that women indeed have better treatment responses than men, though this primarily examined studies employing behavioural interventions, and differences in responses to pharmacological treatment were not reported (Wade *et al.*, 2016). Interestingly, it is also reported that women with, but not without, PTSD express higher fear responses to a conditioned stimulus than men (Inslicht *et al.*, 2013), which may explain the success during exposure therapy, due to the reliance of the technique on effective reactivation of trauma memories. However, there has not been sufficient research to identify why treatment responses are better in women, with tentative explanations involving increased learning capacity in females during both trauma experience and extinction training (Felmingham *et al.*, 2012a).

3. Are gonadal steroid hormones the mediating factor?

The neurobiological complexity of the psychiatric disorders described above contributes to the fact that the exact mechanisms underlying the aetiology of these disorders remain elusive. However, the most commonly attributed candidate to explain the sex differences described above, is the dysfunction of neuroactive steroid systems (Gogos *et al.*, 2015; Sun *et al.*, 2016). For example, the above observations underpin the *estrogen hypothesis of schizophrenia*, which postulates a protective role of estrogens against the development and severity of the disorder (Gogos *et al.*, 2015; Seeman *et al.*, 1990). Similarly, in relation to PTSD, evidence of sex differences has led to the hypothesis that low estradiol results in poor extinction recall. The reproductive life cycle in women makes them particularly sensitive to rapid and/or cyclical variation in levels of circulating ovarian hormones at different time periods. In this section, we briefly describe the two primary ovarian hormones and then detail evidence of gonadal steroid dysfunction in each of the psychiatric disorders of interest.

3.1 The main female steroid hormones: Estrogens and Progesterone

The ovarian hormones, estrogens and progesterone, are also neuroactive steroids which play a crucial role in glial and neuronal development, structure, and function (Barth *et al.*, 2015). Of these, progestogens are a class of neuroactive steroids that bind to, and activate progesterone receptors. In humans, endogenous progesterone (P4) is the most potent and abundant progestogen subtype. It is synthesised both centrally and peripherally via catalysis of pregnenolone, a cholesterol-derived steroid precursor (Sun *et al.*, 2016; Tsutsui, 2008) (Figure 1). As a precursor to estrogens, testosterone (the main male gonadal hormone), and various glucocorticoids and mineralocorticoids, progesterone plays a crucial role in both male and female health and development. In adult males, serum progesterone levels reportedly range between 1-3 nM with little change relative to age (Oettel *et al.*, 2004; Sun *et al.*, 2016). In contrast, non-pregnant premenopausal women experience variable serum progesterone levels relative to their menstrual cycle (Figure 2), with lowest concentrations reported during the early follicular phase (0.3-2 nM) and maximum concentrations during the mid-luteal phase (20-55 nM) (Mumford *et al.*, 2010; Sun *et al.*, 2016). Progesterone levels are highest during pregnancy, with serum progesterone steadily increasing throughout the gestational period, and reaching peak concentrations of up to 4-fold non-pregnant levels at term (Byrns, 2014; Schock *et al.*, 2016). By contrast, serum progesterone levels dramatically decline following menopause (Santoro, 2005).

The term *estrogen* describes a class of structurally and functionally similar compounds, the most common of which are estrone (E1); 17β estradiol, or 'estradiol' (E2); and estriol (E3) (Thomas *et al.*, 2013). Of these, estradiol is the most potent endogenous estrogen in humans (Gogos *et al.*, 2015; Jeyakumar *et al.*, 2011), and the focal estrogen of this review. The synthesis of estrogens occurs both centrally and peripherally, and is mediated via aromatisation of testosterone (Figure 1). Estradiol is present in both males and females, however adult males show considerably lower total serum estradiol than females (140 pM) (Sun *et al.*, 2016; Yamamoto *et al.*, 1995), with minimal fluctuations or age-related decline (Greenblatt *et al.*, 1976; Orwoll *et al.*, 2006). Conversely, non-pregnant premenopausal women exhibit biphasic cyclic variation in serum estradiol during their 28-day menstrual cycle (Figure 2); lowest estradiol levels during the early follicular phase (median ~150 pM), highest levels during ovulation (median ~670 pM), and a second, smaller peak during the mid-luteal phase (median ~500 pM) (Stricker *et al.*, 2006; Sun *et al.*, 2016). During pregnancy, estradiol levels increase up to 9-fold, but drop dramatically post-partum (Schock *et al.*, 2016).

Similarly, estradiol levels decline dramatically following menopause, reaching levels ≤100 pM (Burger *et al.*, 1998).

Steroid hormones may work via either organisational or activational effects. Organisational mechanisms refer to the effects of steroid hormones during prenatal and early postnatal development that result in permanent effects on the brain. Whilst activational mechanisms are the receptor-mediated transient actions of steroid hormones that occur predominantly in adulthood. Throughout the brain, progesterone and estradiol function by directly binding to receptors that act via genomic and non-genomic mechanisms (Gogos *et al.*, 2015; Newton-Mann *et al.*, 2017; Petersen *et al.*, 2013). Of these, the most common of the genomic receptors are ligand-modulated transcription factors known as progesterone receptor-A and -B, and estrogen receptor-α and -β. Following the diffusion of the steroid hormone across the cellular membrane, it then activates its cytoplasmic receptor, triggering conformational changes that result in receptor homo- or hetero-dimerisation. The dimerised receptors then translocate to the nucleus where they bind to promoter regions of target genes and regulate transcription (Ellmann *et al.*, 2009). Dimerised estrogen receptors specifically bind to activator protein 1 sites or estrogen response elements, enabling transcription of estrogen-responsive genes (Newton-Mann *et al.*, 2017). The non-genomic effects of progesterone are primarily mediated via several membrane-bound receptors; estrogenic signalling also occurs via membrane-bound receptors, and G protein-coupled estrogen receptor 1. The non-genomic effects of these steroids are rapid and involve activation of a range of downstream effects (Newton-Mann *et al.*, 2017; Petersen *et al.*, 2013).

To summarise, in women, estradiol and progesterone levels fluctuate throughout the reproductive lifespan. Further, these levels are much higher in women than in men. Whilst progesterone primarily exerts its effects via activating its receptors, it also has significant indirect effects via its conversion into a number of neuroactive molecules, including testosterone and estrogens. This constant, complex interaction between steroid hormones needs to be recognised before one can consider the effects of hormones across the reproductive life cycle.

3.2 Evidence of gonadal steroid hormone dysregulation in Schizophrenia

Women with schizophrenia often experience symptom fluctuation relative to their menstrual cycle phase, and also experience high rates of irregular menses – a common symptom of gonadal

hormone dysfunction (Gleeson *et al.*, 2016). Further, the cyclical exacerbation of symptoms corresponds to periods of low levels of estradiol and progesterone in the menstrual cycle (Bergemann *et al.*, 2007; Hoff *et al.*, 2001; Kumari *et al.*, 2010), during which times women also experience increased rates of hospitalisation (Bergemann *et al.*, 2002). Similarly, symptom improvements during pregnancy, and worsening of symptoms post-partum correspond to increased and decreased gonadal hormone levels, respectively (Riecher-Rössler, 2017). This is also true for the mid-life surge of female diagnoses, which correspond with menopause (Ochoa *et al.*, 2012), with women over the age of forty receiving new diagnoses at approximately twice the rate of men (Riecher-Rössler, 2017).

The above findings may be explained, at least in part, to chronic hypoestrogenism in schizophrenic patients. Low serum estradiol has been reported in both male (Belvederi Murri *et al.*, 2016; Doğan Bulut *et al.*, 2016) and female (Bergemann *et al.*, 2002; Bergemann *et al.*, 2007) patients with schizophrenia and first-episode psychosis with serum estradiol varying relative to menstrual phase in females. Women showed reduced estradiol levels throughout the entire menstrual cycle, with hypoestrogenism identified during the follicular phase (defined as serum estradiol below 110 pM), as well as the peri-ovulatory phase (defined as serum estradiol below 370 pM) (Bergemann *et al.*, 2005). It is important to note that these effects are thought to be unrelated to antipsychotic drug treatment-induced hyperprolactinemia, which can itself induce a hypoestrogenic state (McGregor *et al.*, 2017). Similarly, compared to healthy controls, lower serum progesterone has been reported in both male and female patients with schizophrenia (Bicikova *et al.*, 2013; Doğan Bulut *et al.*, 2016; Ritsner *et al.*, 2007). Antipsychotic medications were reported to significantly increase pregnenolone levels in the brain, suggesting that correction of aberrant progesterone signalling may be partially involved in their efficacy (Ritsner, 2011). A recent meta-analysis found elevated levels of circulating dehydroepiandrosterone sulphate (DHEA-S) and testosterone levels in both male and female patients with schizophrenia or first-episode psychosis (Misiak *et al.*, 2018). Numerous studies report a negative correlation between serum testosterone and the severity of negative symptoms and cognitive deficits in male patients with schizophrenia (Akhondzadeh *et al.*, 2006; Ko *et al.*, 2007; Shirayama *et al.*, 2002; Sisek-Sprem *et al.*, 2015). Whilst further research is needed, these findings suggest dysfunction at multiple levels of the neurosteroid biosynthetic pathway.

At present, research into the use of hormonal therapies in schizophrenia is providing promising results (reviewed in (Gogos *et al.*, 2015; Sbisa *et al.*, 2017)). Studies by Kulkarni and colleagues demonstrated that combined antipsychotic and estradiol therapy significantly improved symptoms in premenopausal female patients, particularly the positive symptoms, and improved general psychopathology in male patients, without causing feminising side-effects (reviewed in (Kulkarni *et al.*, 2012)). Similarly, a double-blind placebo-controlled trial found that combined administration of haloperidol and a synthetic estradiol significantly improved both positive and negative symptoms in premenopausal women with chronic schizophrenia (Akhondzadeh *et al.*, 2003). Unfortunately, long-term use of estradiol may be associated with side-effects including increased cardiovascular and cancer risk (reviewed in (Sbisa *et al.*, 2017)). Additionally, the ligand-binding domains for estrogen receptor-α and -β are highly homologous (Newton-Mann *et al.*, 2017), making it difficult to selectively target these receptors using orthosteric ligands. In an attempt to subvert these issues, researchers are exploring the therapeutic potential of selective estrogen receptor modulators, such as raloxifene, that elicit tissue-dependent and/or receptor-dependent agonist or antagonist effects (Sbisa *et al.*, 2017). While the exact mechanism of action of raloxifene in the CNS is unclear, it has high affinity for both estrogen receptor-α and -β (Newton-Mann *et al.*, 2017). However, depending on sex, reproductive status, and hormone levels, the clinical efficacy of raloxifene is likely to vary (Sbisa *et al.*, 2017). Nevertheless, reviews have concluded that combined antipsychotic and raloxifene therapy improves both positive and negative symptoms in women with schizophrenia, and improves negative symptoms in men with schizophrenia (Bratek *et al.*, 2016; McGregor *et al.*, 2017). In perimenopausal and postmenopausal women (aged 40-70 years) with treatment-resistant schizophrenia, raloxifene reduced symptom severity and improved likelihood of clinical response (Kulkarni *et al.*, 2016). By contrast, another study found that severely ill, postmenopausal women with schizophrenia receiving adjunct raloxifene did not show symptom improvement, and in fact experienced worsened positive and negative symptoms (Weiser *et al.*, 2017). The authors concluded that whilst raloxifene may be beneficial for some patients, further research is needed to identify suitable subgroups for safe administration.

Interestingly, one study found that adjunctive low-dose pregnenolone improved positive symptoms, extrapyramidal side effects, and several measures of executive function in chronically ill male and female patients (Ritsner, 2010). Furthermore, progesterone administration has been

shown to improve cognition in healthy women (Berent-Spillson *et al.*, 2015) suggesting it may be of benefit for the cognitive deficits in schizophrenia. However, progesterone and its receptors have received considerably less attention than estradiol in the neuropsychiatric community, thus further research is needed to better understand the role of progesterone, as well as other neuroactive compounds, in schizophrenia (Sun *et al.*, 2016). Overall, there is strong evidence for a role of steroid hormones in schizophrenia and in particular, that reduced estradiol levels may be a predisposing factor to disease development and symptom severity in at-risk populations.

3.3 Evidence of gonadal steroid hormone dysregulation in Bipolar Disorder

A large proportion of women with BD have menstrual abnormalities that precede diagnosis (Rasgon *et al.*, 2005). There are a number of studies providing evidence that reproductive life cycle events associated with hormonal fluctuations, specifically a reduction in hormone levels, can influence the course of BD. For example, perimenstrual mood changes are reported in 40-65% of BD women (Blehar *et al.*, 1998; Teatero *et al.*, 2014), and those women who experience perimenstrual mood changes are at higher risk for post-partum relapse (Perich *et al.*, 2017), a worse course of illness and increased symptom severity (Dias *et al.*, 2011). Rapid cycling, comorbid anxiety and mixed mood episodes, as well as an earlier age of mania or depression onset are also more frequently reported in BD women who have reported reproductive life cycle associated mood changes (Perich *et al.*, 2017). The luteal phase of the menstrual cycle (both early and late luteal, i.e. low hormone levels) has been associated with greater manic/depressive symptoms compared to other phases (Rasgon *et al.*, 2003; Shivakumar *et al.*, 2008). An elevation of mood and psychosis symptoms post-partum is common (Blehar *et al.*, 1998; Jones *et al.*, 2014), with one study reporting an 8-fold increase in the prevalence of mania symptoms in BD women in the week following childbirth compared to during pregnancy (Heron *et al.*, 2009). Some clinical studies also show high rates of emotional disturbance with an onset in pregnancy, although epidemiological studies indicate that the prevalence rate for first time hospitalisations for a mood episode during pregnancy is low (Jones *et al.*, 2014). The risk of BD relapse during the post-partum period is estimated at 35%, with higher relapse rates in women who are medication naïve during pregnancy compared to those that aren't (Wesseloo *et al.*, 2015). Notably, conversion from major depressive disorder to BD also appears to be several fold higher in the first six months post-partum than

typically seen annually (Sharma *et al.*, 2014). Transition to menopause is also commonly characterised by an increase in mood disturbance in women with BD (Blehar *et al.*, 1998; Marsh *et al.*, 2015). Longitudinal evidence indicates that progression from pre to postmenopausal stages is associated with a decrease in mood stability associated with increasing depressive and decreasing mania symptoms (Marsh *et al.*, 2012).

While this clinical evidence implicates fluctuations in gonadal hormones in the phenomenology of BD in women, research on gonadal hormone and neurosteroid profiles in the disorder is sparse. One study reported significantly decreased cerebrospinal fluid levels of pregnenolone in BD patients irrespective of sex, that was driven by patients who were depressed rather than euthymic at the time of testing (George *et al.*, 1994). Another study reported that relative to controls, euthymic BD women had increased circulating progesterone and allopregnanolone (active metabolite of progesterone) but not cortisol concentrations during the luteal phase of the menstrual cycle (Hardoy *et al.*, 2006). In contrast, two other studies found that the progesterone and estradiol levels of women with BD (either rapid cycling or with post-partum BD relapse) did not differ from control women during either the mid-luteal or follicular phases of the menstrual cycle (Karadag *et al.*, 2004; Wieck *et al.*, 2003). Finally, testosterone levels were lower in depressed men with BD, but higher in depressed women with BD, compared to their respective controls (Wooderson *et al.*, 2015). Higher testosterone levels during a depressive or mixed episode have been associated with an increased incidence of mania and suicide attempts in BD patients, irrespective of sex (Sher *et al.*, 2012), with baseline testosterone predictive of future suicidal behaviour in depressed or mixed episode BD women (Sher *et al.*, 2014).

Further evidence for the involvement of gonadal hormones in BD comes from studies where women were receiving exogenous estrogenic treatments. A small study reported that there were no significant mood changes in women with BD who were taking oral contraceptives (containing combined synthetic estradiol and progesterone) on the active versus inactive (placebo) days, but there was a slight but significant worsening of mood in BD women *not* taking oral contraceptives (first seven days of cycle versus last seven days) (Rasgon *et al.*, 2003). Several small clinical trials also highlight the efficacy of the selective estrogen receptor modulator, tamoxifen, and one study showed benefits using the synthetic progesterone, medroxyprogesterone, for the treatment of acute mania (Kulkarni *et al.*, 2014; Meinhard *et al.*, 2014). In a study of women with post-partum psychosis and estrogen deficiency, psychosis symptoms were ameliorated with daily estradiol

treatment (Ahokas *et al.*, 2000). Pregnenolone has also been shown to be efficacious for the treatment of BD depression, although the mechanism of action is unclear given that changes in depressive symptoms did not correlate with changes in serum pregnenolone or other neurosteroids (Brown *et al.*, 2014). The evidence for steroid hormone dysregulation in women with BD is supported by studies showing a worsening of symptoms during times of low levels of gonadal hormones, and by clinical trials suggesting that certain steroid hormones can improve specific symptoms of BD.

3.4 Evidence of gonadal steroid hormone dysregulation in Post-Traumatic Stress Disorder

Gonadal hormones are thought to be a critical factor in the contrasting rates of PTSD diagnoses between men and women (Ney *et al.*, 2018; Rasmusson *et al.*, 2017). Human studies have identified estradiol as an important regulator of the recall of extinction memories (Glover *et al.*, 2015), which is the quintessential process underlying recovery from a traumatic experience. This may be expected, given the known importance of estradiol on memory, learning and cognitive processes more generally (Frick *et al.*, 2015; Gogos *et al.*, 2014; Sbisa *et al.*, 2017). In studies of fear extinction in healthy women, it has been found that higher estradiol levels are associated with improved task performance, where participants learn that a previously aversive stimulus is no longer associated with an aversive experience (for example, an electric shock) with success gauged by change in physiological arousal upon presentation of the stimulus (Graham *et al.*, 2013; Milad *et al.*, 2010; Wegerer *et al.*, 2014; Zeidan *et al.*, 2011). Similar studies have found that women with higher levels of endogenous estradiol more successfully extinguish fear memories compared to women using hormonal contraceptives (Graham *et al.*, 2013; Li *et al.*, 2016; White *et al.*, 2016). The effect of menstrual cycle phase on fear extinction in healthy women is less consistent, with a large scale study finding no significant differences between phases (Lonsdorf *et al.*, 2015).

Although no study has examined long-term estradiol levels in PTSD patients, there has been some research measuring gonadal hormones in PTSD. One study found that women with PTSD and low estradiol levels had intensified physiological responses to an aversive laboratory stimulus, compared to non-PTSD women with low estradiol levels. This effect was absent in women with high estradiol levels, where PTSD and non-PTSD participants displayed similar responding to the aversive stimulus, strongly suggesting a protective effect of estradiol on fear learning (Glover *et*

al., 2012). Women with PTSD were also shown to exhibit increased phobic anxiety and depression during the early follicular, compared to mid-luteal, phase of the menstrual cycle (Nillni *et al.*, 2015). In another study, women with PTSD in the mid-luteal phase of the menstrual cycle exhibited impaired fear extinction compared to women in the early follicular phase (Pineles *et al.*, 2016), which is the reverse finding of healthy participants. Whilst it is unclear what the mechanistic implications of these findings might be, recent genetic studies have identified estradiol-related risk factors for PTSD, with estrogen-response elements on the pituitary adenylate cyclase-activating peptide (PACAP) receptor gene, PAC1R, associated with PTSD severity in women but not men (Lind *et al.*, 2017). This is a significant finding since PACAP deficiency is associated with impaired production of transcriptional factors underlying both the HPA and sympathetic stress responses in mice (Stroth *et al.*, 2010). The recent meta-analysis by Lind and colleagues (2017) therefore provides evidence of hormone influences on stress reactivity at the genetic level, and a possible diverging factor in prevalence and severity of PTSD between the sexes. Further, estrogen-dependent effects on DNA methylation of on the HDAC4 gene may be associated with fear learning and memory in PTSD (Maddox *et al.*, 2018).

Whereas estrogenic signalling is implicated in effective recovery following a traumatic experience, consolidation of emotional memories may instead be associated with progesterone levels at the time of trauma. Studies of real-world trauma have shown that increased reports of flashback memories and increased PTSD symptomology are associated with hospitalisation during the mid-luteal phase (Bryant *et al.*, 2011), which is characterised by peak progesterone levels as well as elevated estradiol. Similarly, survivors of sexual assault who neglected to take emergency contraception (which contains high dose progesterone) were significantly more likely to report higher PTSD symptomology compared to those who did take emergency contraception (Ferree *et al.*, 2012). In the laboratory, healthy women who are in the mid-luteal phase report more intrusive memories of negative stimuli (Ertman *et al.*, 2011; Wassell *et al.*, 2015), and this effect is correlated with levels of progesterone but not estradiol at encoding (Ertman *et al.*, 2011; Felmingham *et al.*, 2012b; Wassell *et al.*, 2015). Only one study has found that estradiol was associated with increased reports of intrusive memories (Cheung *et al.*, 2013); conversely another study found that estradiol was associated with decreased reports of intrusions (Wegerer *et al.*, 2014). Overall, a number of studies support a facilitative effect of progesterone levels on intrusive

memories of emotionally negative stimuli during encoding, with inconsistent or negligible effects of estradiol.

4. Future directions and implications

The exact mechanisms underlying the sex differences in the severe psychiatric disorders described above are unclear, but likely involve genetic factors, biological, cognitive and social influences. In this review, we have focussed on the role of gonadal and neuroactive hormones, particularly estradiol and progesterone, to explain the sex differences. Whilst it is common for researchers to investigate the role of gonadal hormones in women, what about men? Estradiol and progesterone may also play an important role on symptom severity in men (Kulkarni *et al.*, 2013), conversely it may be that testosterone is the key hormone influencing disease development and severity in men (Ko *et al.*, 2007). Further, there is a strong link between testosterone and estrogens, whereby the enzyme aromatase regulates the conversion of testosterone to estradiol (Figure 1). The role of hormones in men is an important issue and yet an understudied area; again highlighting that future research should always consider both males and females.

Based on the evidence presented here, it is clear that female hormone variation informs similar symptom profiles across schizophrenia, BD, and PTSD. In both schizophrenia and BD, low levels of estradiol are associated with increased manic and psychotic-like symptoms, as demonstrated in both experimental and observational studies (Gogos *et al.*, 2015; Meinhard *et al.*, 2014). In PTSD, low estradiol levels are associated with poorer recovery following a traumatic experience and continuity of PTSD symptoms (Glover *et al.*, 2015), while progesterone levels may influence the consolidation of emotional memories at the time of trauma. In all of these disorders, higher estradiol is generally associated with improved symptomology; this is most relevant to the cognitive domain and represents a significant novel treatment avenue (Glover *et al.*, 2015; Gogos *et al.*, 2015; Meinhard *et al.*, 2014).

An intriguing contradiction between symptom profiles of these three disorders is that, despite high estradiol being recognised as a key protective factor explaining lower rates of schizophrenia and BD-II in women, low estradiol is conversely believed to drive higher prevalence of PTSD in women. Given that women have higher estradiol levels than men, were estradiol a primary aetiological protective factor in all three disorders it might have been expected that women would

have lower, rather than higher, rates of PTSD as is observed in schizophrenia. This phenomenon is likely explainable by the differential influence of gonadal hormone fluctuation during different stages of PTSD. In PTSD, trauma causes an extreme biological stress response resulting in downregulation of the hypothalamic-pituitary-gonadal (HPG) axis and lower production of estradiol and progesterone that results in impaired extinction learning long-term (Ney *et al.*, 2018; Toufexis *et al.*, 2014). Restoration of these hormones in PTSD, and similarly upregulation in schizophrenia and BD, therefore appears to be a promising treatment option for similar reasons between the disorders, including through augmentation of cognition. However, high levels of gonadal hormones may similarly be a risk factor for PTSD through facilitation of learning, which acts to enhance consolidation of trauma memories at the time of trauma. The differential effect of hormones in this case reflects PTSD as a delayed disorder, characterised by an initial stressor and a later onset of symptomology (APA, 2013).

It is important to recognise that steroid hormones show dynamic interactions, meaning that treatment target options may include more than just estradiol. For example, in PTSD, downregulation of the HPG axis coincides with interruption of cortisol production in the hypothalamic-pituitary-adrenal (HPA) axis following extreme stress created during trauma (Ney *et al.*, 2018; Pitman *et al.*, 2012; Toufexis *et al.*, 2014). Restoration of either of these pathways can improve PTSD symptomology through the cognitive aspects of fear extinction learning (Glover *et al.*, 2015; Ney *et al.*, 2018; Pitman *et al.*, 2012). It is necessary to consider that these axes, as with all steroid hormone production, are inseparable and are dual effectors in disorders that are stress-related; not only in PTSD, but cortisol production is chronically dysregulated in both schizophrenia and BD (Girshkin *et al.*, 2014). Similarly, the effects attributed to estradiol and progesterone in each of these disorders might be better explained by the increasingly recognised influence of other neuroactive steroids (which include precursors and metabolites of estradiol and progesterone; Figure 1) in psychiatric disorders, such as pregnenolone, allopregnanolone, testosterone and DHEA (Melcangi *et al.*, 2011; Rasmusson *et al.*, 2017; Ritsner, 2011; Sun *et al.*, 2016; Zheng, 2009). For instance, research has highlighted the importance of allopregnanolone and DHEA for fear extinction learning and PTSD symptomology (Rasmusson *et al.*, 2017). Unlike progesterone, allopregnanolone is a potent allosteric modulator of the GABA-A receptor, a receptor implicated in psychiatric disorders (Melcangi *et al.*, 2011; Sun *et al.*, 2016). A recent study showed that men with psychotic features of schizophrenia, BD or major depression had

elevated DHEA levels compared to those without a history of psychosis (Buoli *et al.*, 2016). Given the known interactions between neuroactive steroids, it is important to identify the underlying imbalances in steroid levels for each disorder. For example, in women, PTSD was associated with lower levels of 5α-dihydroprogesterone, the primary metabolite of progesterone and precursor of allopregnanolone (Pineles *et al.*, 2018), suggesting that pharmacological targeting of 5α-dihydroprogesterone, rather than allopregnanolone or progesterone, may be beneficial. Findings of an imbalance of various neuroactive steroids in these psychiatric disorders underscores the importance of further research into steroid interactions instead of isolated targets such as estradiol.

Overall, this review provides compelling evidence for cross-disorder estradiol-related protective mechanisms, which may be expected given the known importance of both genomic and non-genomic effects of estrogens on cognitive processes more generally (Frick *et al.*, 2015). However, estradiol and progesterone have broad functional diversity in the brain, with both types of receptor implicated in multiple processes such as neurogenesis, microglia expression, inflammation, and bioenergetics (Gogos *et al.*, 2015; Rettberg *et al.*, 2014; Sun *et al.*, 2016). Given this diversity, it is unlikely that steroid hormones play a single role in the pathogenesis and pathophysiology of PTSD, schizophrenia, or BD – rather, their role is likely to regulate various signalling, neurodevelopmental, neuroplastic, and epigenetic processes. As an example, all three disorders are characterised by reductions in hippocampal volume and functioning (Lieberman *et al.*, 2018; Pitman *et al.*, 2012; Shi *et al.*, 2018), which is attributable to various neurobiological mechanisms associated with learning and memory. Estradiol has been shown to modulate phosphorylation of ERK, mTOR and PKA pathways (Fortress *et al.*, 2013; Hasegawa *et al.*, 2015; Kim *et al.*, 2016) and can increase dendritic spine density of hippocampal neurons (Luine *et al.*, 2013). Phosphorylation of these pathways in turn mediate estrogenic genomic actions including DNA methylation and histone acetylation in the hippocampus, subsequently affecting levels of proteins such as brain-derived neurotrophic factor (Zhao *et al.*, 2010), which is a potent effector of learning and memory and recognised as a critical factor in psychiatric disorders (Luine *et al.*, 2013; Pitman *et al.*, 2012; Wu *et al.*, 2013). Given the well-established role of neurotransmitter dysfunction in psychiatric disorders, it is important to note that both estradiol and progesterone modulate the activity of dopaminergic, serotonergic, glutamatergic and GABAergic systems (for example, (Kokras *et al.*, 2018); reviewed in (Barth *et al.*, 2015; Gogos *et al.*, 2015; Sun *et al.*, 2016)). Neurobiological pathways involved in the pathophysiology of these disorders, specifically the

prefrontal and limbic networks and their connectivity, have also been shown to have sex specificity (Felmingham *et al.*, 2010). Estradiol receptors are expressed throughout the hippocampus (Österlund *et al.*, 2000), as well as the dorsolateral prefrontal cortex (Montague *et al.*, 2008), for which cross-talk is involved in increasing psychotic symptomology (Lieberman *et al.*, 2018) as well as being critical to fear circuitry (Pitman *et al.*, 2012). Based on this converging evidence, it is likely that the similarities in symptomology between these three disorders is attributed to dysfunction across similar estrogenic-mediated mechanisms. In support, the most recent clinical studies have detected large genome-wide association overlaps in heritability of vulnerability towards PTSD and schizophrenia, with a moderate shared effect between these disorders and BD (Duncan *et al.*, 2018). Future research will need to assess the extent to which similar mechanisms mediate symptomology across disorders and lessons may be learnt by combining methodologies and theoretical models between fields.

Finally, there are some common limitations across studies. Examining the specific effects of gonadal hormones in a naturalistic human setting is particularly difficult. Inconsistencies in the literature are likely due to varied methodologies in the population selection (e.g. women in different reproductive life stages), and the symptom/task/hormone measures (e.g. estimated cycle phase compared to blood levels or saliva assays). To compound this, the lack of methodological detail makes it very difficult to compare across studies. For example, when one discusses differences across the menstrual cycle, it is often unclear what the effects observed are actually due to – is it really a change in estradiol level? Or is it the accompanying increase in progesterone (Sun *et al.*, 2016) or testosterone levels that are the mediating factors? To complicate matters further, it is unknown whether the differences observed in blood hormone levels correspond to CNS hormone levels; therefore, using changes in blood levels as evidence for these hormones mediating the sex differences in psychiatric disorders should be treated with caution. Another issue is the increasing prevalence of hormonal contraceptive use by women; studies need to report on contraceptive use, including type of contraception, duration of use, and so on. This is particularly important given the known influence of contraceptives, containing synthetic estrogen and progestin, on cognition (Gogos *et al.*, 2014). Using animal models of psychiatric disorders is one way we can control for many of the confounding variables (Gogos *et al.*, 2015; Sbisa *et al.*, 2017). Future studies require a more inclusive, considered effort of steroid hormones and the intricacies

of the interactions between them, with methodological rigour applied, to enhance our understanding of the roles of steroid hormones in psychiatric disorders.

5. Conclusions

Psychiatric disorders such as schizophrenia, BD and PTSD are chronic and debilitating diseases that have no easy treatment and in some cases, they are incurable. Current medications are inadequate; they do not treat all patients of all symptoms, nor are they side-effect free. Thus, the need for the development of better treatments, or perhaps adjunctive treatments, is clearly important. Could gonadal hormones, such as estradiol, provide the framework for the development of future therapeutics? In this review, three different psychiatric disorders were examined, however, there are a number of similarities between them, such as cognitive impairment, genetic predisposition, neurotransmitter dysfunction, inflammation, and so on. It has been proposed that a mechanism uniting the genetic and neurobiological factors implicated in psychiatric disorders might be endocrine responses, specifically estradiol, which has been described as the 'master regulator' of these systems (Rettberg *et al.*, 2014). Given the fact that the steroid receptors are wide-spread throughout the CNS (Newton-Mann *et al.*, 2017), and that steroid hormones have wide-ranging effects on the CNS (Gogos *et al.*, 2015), it is not surprising that estradiol and progesterone can modulate the expression of psychiatric disorders. Although, whether the influence of steroid hormones requires organisational or activational effects or genomic or non-genomic actions is not clear, but likely involves a combination of these. One thing is obvious, there are marked sex differences across multiple disorders; women with schizophrenia tend to exhibit less disease impairment than men (Gogos *et al.*, 2015), but women with PTSD are more affected than men (Blanco *et al.*, 2018). We implore to researchers and clinicians to, at the very least, acknowledge that sex differences exist. Thus future studies should be balanced for sex, and in the clinic, women may need to be classified according to their hormone status before starting treatment. Illuminating the extent to which steroid hormones facilitate these purported sex differences, and the associated mechanisms, may lead to avenues for novel therapeutic approaches, and allow for precision medicine for men as well as women. This has important potential therapeutic implications for the preponderance of neuropsychiatric diseases with sexually dimorphic incidence, symptomology and treatment responses.

Figure legends

Figure 1: Simplified biosynthesis pathway for progesterone and estradiol.

HSD: hydroxysteroid dehydrogenase P450: cytochrome P450; P450scc: cholesterol side-chain cleavage enzyme; (adapted from Sun *et al.*, 2016).

Figure 2: Fluctuating circulating levels of 17β-estradiol and progesterone in women across the menstrual cycle (adapted from (Sun *et al.*, 2016; Widmaier *et al.*, 2014)).

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017).

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Competing Interests

None

Did not involve animal experimentation, does not include Western blots or immunohistochemistry

Declaration of transparency and scientific rigour

This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the *BJP* guidelines for Design & Analysis, and as recommended by funding agencies, publishers and other organisations engaged with supporting research.

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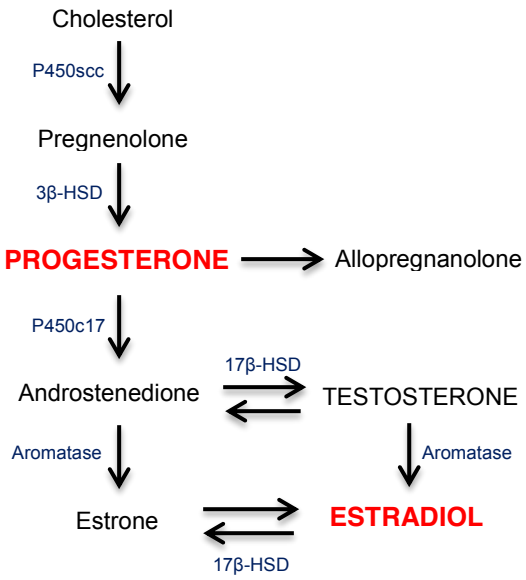
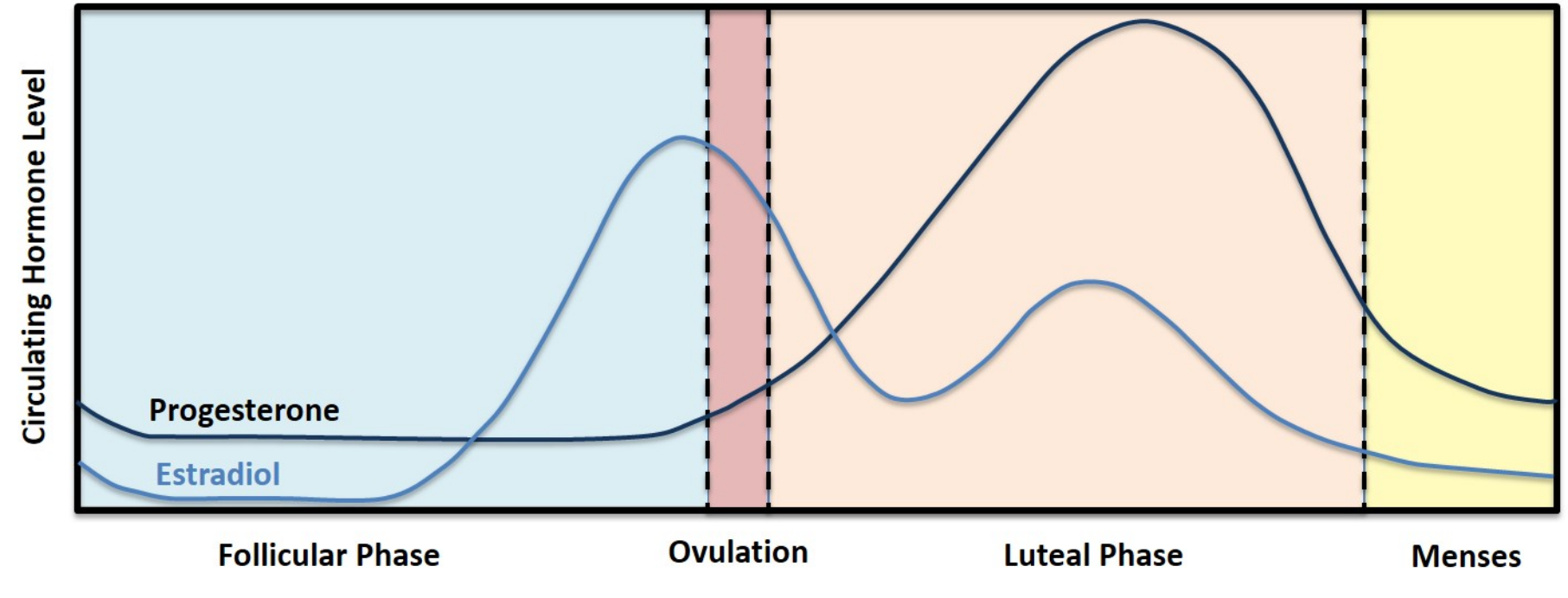

Cholesterol
P450scc
Pregnenolone
3β-HSD
PROGESTERONE
Allopregnanolone
P450c17
17β-HSD
Androstenedione
TESTOSTERONE
Aromatase
Aromatase
Estrone
ESTRADIOL
17β-HSD


Circulating Hormone Level
Progesterone
Estradiol
Follicular Phase
Ovulation
Luteal Phase
Menses