Psychoneuroendocrinology 109 (2019) 104416

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

An alternative theory for hormone effects on sex differences in PTSD: The role of heightened sex hormones during trauma

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ARTICLE INFO

Keywords:
Sex differences
Sex hormones
Posttraumatic stress disorder
Stress hormones
Emotional memory
Memory consolidation

ABSTRACT

Women are at least twice as susceptible to developing post-traumatic stress disorder (PTSD) compared to men. Although most research seeking to explain this discrepancy has focussed on the role of oestradiol during fear extinction learning, the role of progesterone has been overlooked, despite relatively consistent findings being reported concerning the role of progesterone during consolidation of emotional and intrusive memories. In this review article, we outline literature supporting the role of progesterone on memory formation, with particular emphasis on potential memory-enhancing properties of progesterone when subjects are placed under stress. It is possible that progesterone directly and indirectly exerts memory-enhancing effects at the time of trauma, which is an effect that may not be necessarily captured during non-stressful paradigms. We propose a model whereby progesterone's steroidogenic relationship to cortisol and brain-derived neurotrophic factor in combination with elevated oestradiol may enhance emotional memory consolidation during trauma and therefore present a specific vulnerability to PTSD formation in women, particularly during the mid-luteal phase of the menstrual cycle.

1. Background

Post-traumatic stress disorder (PTSD) is a psychiatric condition that may develop following exposure to a traumatic experience, and is characterised by re-experiencing trauma, avoidance of trauma reminders, hyperarousal, and negative cognition and mood. A core feature of the PTSD profile is the repeated reliving of traumatic memories. Impaired retrieval of explicit memories of trauma and distressing, spontaneous recollections of trauma, known as intrusive memories, are among the most common and troubling symptoms in PTSD (American Psychiatric Association, 2013; Brewin, 2011). Intrusive memories in PTSD are usually distressing and involuntary in nature, are difficult for patients to voluntarily recall with specificity and contribute to the ongoing state of hyper-arousal that is also characteristic of PTSD (Brewin et al., 2010; Ehlers, 2010; Kleim et al., 2008). Intrusive memories are thought to develop during memory consolidation, which is the stage of memory retention where a brief representation in the brain of an event is enhanced and stabilised through multiple neural and hormonal functions for the purpose of long-term preservation (McGaugh, 2000). Inadequate contextualisation and integration of traumatic experiences into autobiographical memory during the consolidation process is a key part of a leading theory of how disjointed memories result in fragmented intrusions characteristic of distressing aspects of the trauma (Brewin et al., 2010; Conway and Pleydell-Pearce, 2000; Ehlers and Clark, 2000). Excessive activation of various hormones due to the extreme stress of trauma exposure is proposed to contribute to an overly strong memory trace of traumatic experiences (Brewin et al., 2010; Pitman, 1989; Pitman and Delahanty, 2005; Pitman et al., 2012).

Women are twice as likely to be diagnosed with PTSD than men (McLean et al., 2011; Silove et al., 2017; Wittchen et al., 2011), a difference that remains significant even after differences in trauma types experienced by each sex is accounted for (Blanco et al., 2018; Olff et al., 2007; Tolin and Foa, 2006). Specifically, women with a history of trauma exposure, including those with PTSD, reported more intrusive memories than men; while the non-trauma-exposed controls did not show such sex difference (Hsu et al., 2018). Unfortunately, much of our understanding of the role of sex hormones in PTSD, and psychopathology more generally, lags behind our broader understanding of psychopathology despite gender differences being a pressing issue for many conditions (Gogos et al., 2019; Kokras and Dalla, 2014; Sun et al., 2016). In PTSD, some human research has investigated the role of ovarian sex hormones – primarily oestradiol – in the consolidation of fear extinction memories, which is thought to be a key mechanism involved in the development of PTSD following trauma (for reviews see

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https://doi.org/10.1016/j.psyneuen.2019.104416
Received 14 May 2019; Received in revised form 5 July 2019; Accepted 22 August 2019

Glover et al., 2015; Lebron-Milad and Milad, 2012; Li and Graham, 2017; Ney et al., 2018). Specifically, several studies in healthy controls have found that low oestradiol levels are associated with impaired fear extinction recall (Glover et al., 2012; Graham and Milad, 2013; Milad et al., 2010; White and Graham, 2016; Zeidan et al., 2011). Oestradiol levels are therefore believed by some authors to represent a significant treatment target for PTSD (Glover et al., 2012, 2015). However, these findings are not consistent with findings in women with PTSD, suggesting that more research is needed to understand the effect of hormones (Pineles et al., 2016). Further, there is no current evidence for a low-oestradiol phenotype underlying PTSD in clinical populations.

The low-oestradiol narrative is also largely contained to the role of oestradiol in the months and years after the trauma has occurred. In the current review, we discuss evidence that both progesterone and oestradiol are associated with learning and memory, and postulate that higher levels of these hormones at the time of trauma, rather than lower hormonal levels following trauma, may explain the heightened prevalence of trauma-related disorders in women. We discuss in depth that, despite a large literature examining the relationship between progesterone and memory more generally (Barros et al., 2015; Luine and Frankfurt, 2013), limited attention has been paid to the role of progesterone in underlying PTSD mechanisms. We therefore pay particular attention to the molecular mechanisms underlying the relationship between progesterone, stress hormones, and emotional memory, and provide a novel interpretation for how high female sex hormones – particularly progesterone – at the time of trauma may be a risk factor for PTSD due to the potential for progesterone to elevate stress hormones. This is discussed with reference to existing evidence concerning the relationship between progesterone, oestradiol, and the prevalence of intrusive memories.

2. Cortisol, emotional memories and intrusive memories

Memories with an emotional charge are selectively enhanced over neutral memories through neural and hormonal interactions (McGaugh, 2000). This is a consequence of inhibition of γ-aminobutyric acid (GABA)ergic terminals by stress-induced adrenergic and glucocorticoid signalling in the basolateral amygdala (BLA), the centre of emotional salience, which enhances the consolidation of emotional experiences through afferent projections to the hippocampus and nucleus accumbens (McGaugh, 2004; Roozendaal et al., 2009a, 2009b; Roozendaal and McGaugh, 2011). This is a well-established mechanism whose key principles have been demonstrated in many animal studies. For instance, administration of a glucocorticoid receptor agonist into the BLA, but not the adjacently positioned central nucleus of the amygdala, enhanced memory retention in rats, whereas glucocorticoid antagonism of the BLA, but not the central nucleus, impaired memory retention (Roozendaal and McGaugh, 1997). Similarly, it has been shown in animal studies that memory-enhancement occurs in interactions between the prefrontal cortex and BLA, with enhancement of emotional memories through corticotrophin-releasing factor as well as corticosterone relying on glucocorticoid receptor integrity (Roozendaal et al., 2009a, 2009b; Roozendaal et al., 2008).

Human studies have confirmed that stress-induced (Bryant et al., 2013; Chou et al., 2014; Nicholson et al., 2014) or exogenously administered cortisol (Rombold et al., 2016), in conjunction with other stress hormones, positively predicts the number of reported intrusions following exposure to emotional or traumatic stimuli, which is consistent with preclinical memory literature (Roozendaal and McGaugh, 2011). Further, carriers of high-risk FKBP5 genotypes, associated with maladaptive cortisol basal and stress-induced reactivity, reported more intrusive memories of emotional images and had higher salivary alpha amylase (a biomarker for norepinephrine) at baseline than low-risk FKBP5 carriers (Cheung and Bryant, 2015).

Although there are several approaches to describing the nature of intrusions, biological development of intrusive memories is generally theorised to be a product of over-consolidation of emotional memories due to excessive glucocorticoid and adrenergic hormone release at the time of trauma (Brewin et al., 2010; Pitman, 1989; Pitman et al., 2012). In the dual representation theory of intrusions (Brewin et al., 2010), for instance, it is stated that intrusive memories are a break-down of the integration of perceptual and bottom-up processing of memory with contextual, or autobiographical, memory. Break-down of this integration of these two categories of memory components is due to loss of hippocampal volume in PTSD, which is negatively affected due to the extreme stress of trauma (Shin et al., 2006). Recent research has identified that stress-responsive genes (eg. *COMT*) associated with hippocampal reduction following trauma (Hayes et al., 2017), and genes involved in glucocorticoid sensitivity (eg. *FKBP5*) increase the risk of developing PTSD in those exposed to trauma (Cheung and Bryant, 2015; Mehta et al., 2011). Similarly, considerable research suggests that influx of stress hormones at the time of trauma results in enhanced encoding of situational stimuli that becomes associated with an overly-consolidated trauma memory trace (Pitman and Delahanty, 2005; Pitman et al., 2012). These memories may be experienced as intrusive, given their ties with situational reminders that may be directly or indirectly related to the traumatic experience.

3. Progesterone and steroid hormones

Progesterone and its neuroactive metabolites are involved in memory through many different mechanisms that are only beginning to be understood (Barros et al., 2015). Progesterone is a steroid hormone, along with the other sex hormones (eg. oestradiol and testosterone), which also are classified in the same category as glucocorticoids, such as corticosterone and cortisol (Miller and Auchus, 2011; Payne and Hales, 2004). However, as noted previously, there is some confusion over the terminology ‘steroid hormone’ and the steroidogenic pathway more generally (Schumacher et al., 2014). All steroid hormones are synthesised through hydroxylation of cholesterol to pregnenolone by the enzymes in the P450 cholesterol side-chain cleavage cytochrome (P450c) category, as well as the steroidogenic acute regulatory protein (StAR) (Fig. 1). For instance, hydroxylation of 17OH-progesterone by P450c21 results in 11-deoxycortisol, which is the precursor to cortisol. Similarly, both testosterone and oestradiol are end products of the steroidogenic pathway with pregnenolone or progesterone as intermediate precursors (Miller and Auchus, 2011). Progesterone is also the mediating hormone between pregnenolone and allopregnanolone, which has potent influence over the hypothalamic-pituitary-adrenal (HPA)axis through GABAergic signalling (Crowley and Girdler, 2014). Progesterone, whilst being a primary female sex hormone, is also present in males at lower levels that do not cyclically fluctuate (Oettel and Mukhopadhyay, 2004). It is important to note that biosynthesis of cortisol, as well as testosterone and corticosterone, occurs in both males and females through mediating hormones pregnenolone and progesterone. This is important because cortisol has a key role in emotional memory consolidation. Cortisol can be synthesised by hydroxylation of progesterone to 17OH-hydroxyprogesterone through P450c17, however, is also largely mediated by cataclysm of 17OH-pregnenolone by 3β-hydroxysteroid dehydrogenase (3βHSD) (Miller and Auchus, 2011). Testosterone, on the other hand, is an end product of pregnenolone or progesterone catabolism through 3βHSD and 17βHSD enzyme catabolism of androstenediol and androstenedione, respectively. Progesterone is synthesised not only in the ovaries but also in the adrenal gland and brain, which can occur as part of the stress response (Crowley and Girdler, 2014). Examination of the steroidogenic pathway at this level of detail can help us to understand why progesterone and other sex hormones may interact with cortisol in the aetiology of PTSD symptoms.

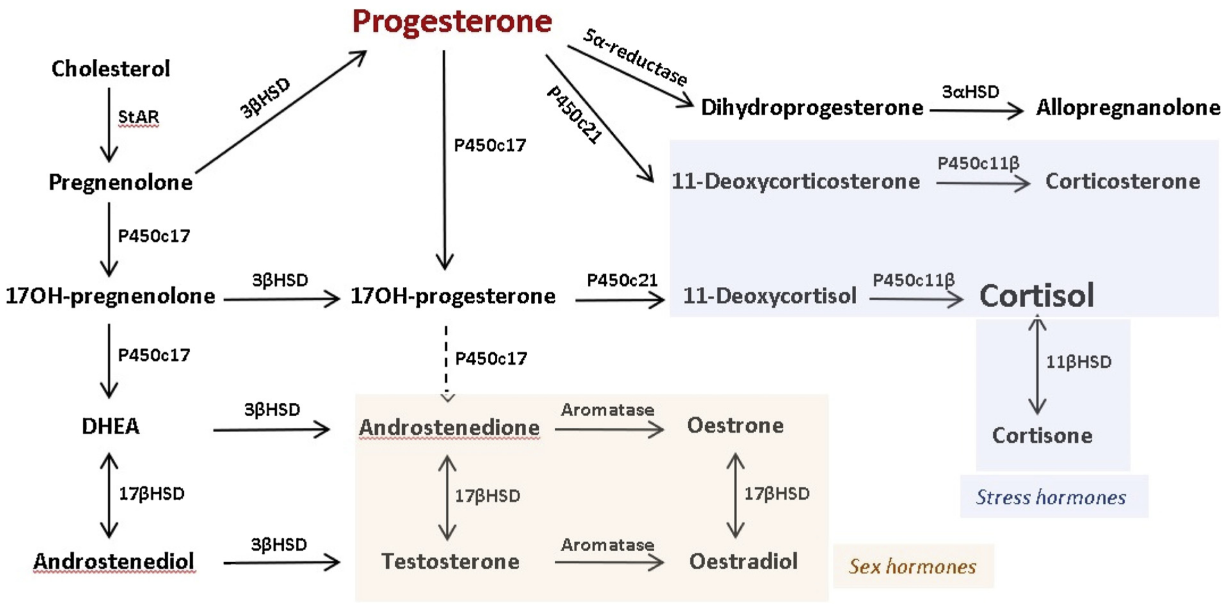

Fig. 1. Simplified steroidogenic pathway (adapted from Miller and Auchus, 2011). Progesterone is the precursor for the 'stress hormones' including cortisol and the 'sex hormones' including oestradiol.

3.1. *The human menstrual cycle*

The human menstrual cycle lasts an average of approximately 28 days and can be divided into the periods prior to and following ovulation which occurs on day 14 (called the follicular and luteal phases, respectively, Fig. 2). During the early follicular phase (days 1–7), both progesterone and oestradiol levels are initially low while follicle stimulating hormone produces ovarian follicles. The late follicular phase occurs as ovulation approaches (days 10-14) and is characterised by peak oestradiol levels, though progesterone levels remains low. Progesterone levels begin to rise after ovulation; this is initiated by a rapid spike in luteinizing hormone and oestradiol at the end of the late follicular phase, as well as a decrease in follicle stimulating hormone (Becker et al., 2005). The mid-luteal phase (days 18–24) is characterised by peak progesterone levels and a second smaller peak of oestradiol, during and after which both oestradiol and progesterone slowly decrease over the luteal phase to reach base levels at menstruation and the beginning of a new follicular phase and new cycle.

Fluctuation of these ovarian hormones throughout the menstrual cycle, whilst primarily responsible for regulating reproductive processes, are also recognised to influence cognitive, stress-related, and emotional outcomes (Becker et al., 2005; Gogos et al., 2019; Jang and Elfenbein, 2018; Kokras and Dalla, 2014). For instance, women with PTSD report higher depression and phobic anxiety symptoms during the early follicular phase (when progesterone and oestradiol levels are at the lowest) compared to the mid-luteal phase (Nillni et al., 2015).

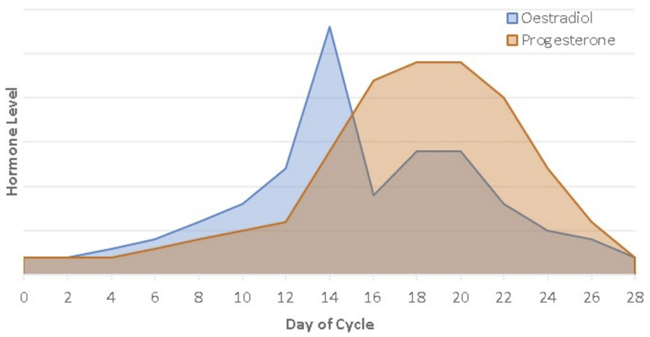

Fig. 2. The human menstrual cycle, adapted from Sun, et al. (2016). Oestradiol rapidly peaks at midcycle immediately prior to ovulation. Progesterone peaks more gradually in the midluteal phase following ovulation.

4. Progesterone and memory

The direction of the effect of progesterone on memory in the absence of stress is generally inconsistent (Barros et al., 2015). In some studies, progesterone has been shown to have impairing effects on different aspects of memory. For instance, progesterone compared to placebo administration in healthy women impaired recognition accuracy for faces, possibly by decreasing recruitment of the fusiform gyrus, prefrontal cortex, and amygdala as shown by fMRI during encoding and retrieval (van Wingen et al., 2007). Further, in a clinical trial, four weeks of progesterone therapy had detrimental effects on memory improvements that had followed from oestradiol treatment in female Alzheimer's patients (Honjo et al., 2005). The inhibitory effects of progesterone on memory are largely attributed to its metabolite, the neuroactive steroid allopregnanolone, which has high affinity for $GABA_A$ receptors. In early studies, young women who received high doses of progesterone performed worse on working memory and delayed recall tasks and allopregnanolone was most highly correlated with the memory outcome measures (Freeman et al., 1993, 1992). More recently, a single dose of allopregnanolone compared to placebo in healthy women impaired episodic memory (Kask et al., 2008). The effects observed in these studies are believed to be due to allopregnanolone binding to $GABA_A$ receptors of which activation produces potent downregulation of memory consolidation as shown in benzodiazepine studies (Chapouthier and Venault, 2002). Similarly, increased GABAergic inhibition of the HPA cortisol response during negative feedback is associated with decreased memory consolidation with glucocorticoids as a key mechanism in stress-mediated memory enhancement (Roozendaal et al., 2009a, 2009b), and allopregnanolone is known to increase HPA negative feedback through binding to $GABA_A$ receptors during stress (Crowley and Girdler, 2014; Wirth, 2011). Progesterone is also reported to have an impairing effect on long term potentiation, which otherwise alters synaptic plasticity to enhance memory consolidation (Foy et al., 2008). Therefore, there are multiple proposed mechanisms that explain how progesterone might impair memory encoding and consolidation of memories (Barros et al., 2015).

Progesterone also appears to have memory enhancing properties.

Progesterone was associated with significantly improved performance on verbal working memory tasks, as well as trending improvements on verbal recall in menopausal women (Berent-Spillson et al., 2015). Similarly, the addition of progesterone to an oestradiol-only hormone replacement therapy in post-menopausal women resulted in significant improvement on verbal learning and verbal memory tests (Maki et al., 2001; Natale et al., 2001). Progesterone has been studied primarily in animal models of brain injury and aging with potential clinical application to patients with dementia. Progesterone administrated to elderly rats improved performance on hippocampal- and cortical-dependent memory tasks (Frye and Walf, 2008), and has been more generally shown to enhance performance in healthy rat models to improve memory decline (Frye et al., 2009; Harburger et al., 2008; Lewis et al., 2008). One mechanism by which memory may be enhanced by progesterone is through neuroprotection (Barros et al., 2015; Singh and Su, 2013). For instance, progesterone has shown neuroprotective properties by reducing oxidative injury due to glutamate toxicity (Kaur et al., 2007), and reducing loss of hippocampal pyramidal neurons following induced ischemia in rats (Morali et al., 2005), among others (see Singh and Su, 2013).

How progesterone exerts concurrent positive and impairing effects on memory may be through increased expression of brain-derived neurotrophic factor (BDNF), which is a known catalyst of memory enhancement (Minichiello, 2009) and is found to be a risk factor for PTSD development following trauma due to its critical role in memory development (Andero and Ressler, 2012; Bekinschtein et al., 2014; Bruenig et al., 2016; Pitts et al., 2019). Animal studies have shown that progesterone increases BDNF gene and protein expression (Jiang et al., 2016; Kaur et al., 2007). At the molecular level, this may occur through progesterone receptor membrane component-1 mediated extracellular-signal-regulated kinase 5 (ERK-5) signalling, which was shown to facilitate BDNF release in rodent glial cells (Kaur et al., 2007; Su et al., 2012). BDNF then plays a critical role in consolidating memories in the hippocampus, amygdala, and insular cortex through facilitation of synaptic plasticity in these areas (Bekinschtein et al., 2014).

Overall, progesterone-mediated effects on memory consolidation are inconsistent, and the underlying mechanisms are yet to be fully understood. However, and as we will review later in this article, the role of progesterone in emotional memories is likely to interact with cortisol reactivity, such that higher progesterone will enhance cortisol bioavailability and memory consolidation more readily in stressful situations. Progesterone, then, may be key to understanding sex differences in PTSD prevalence, particularly in the development of intrusive memories following trauma.

4.1. Progesterone and emotional memory

In intrusive memory paradigms, violent and emotional images or films are viewed by participants in the laboratory (James et al., 2016). Participants will record the nature and quantity of emotional and intrusive memories that they experienced after viewing of, and/or related to, these images over a number of days following the testing session. It has been recently shown that women report increased levels of intrusive memories compared to men (Rattel et al., 2019). A reliable finding that may explain sex differences in this literature is that progesterone levels are associated with variability in emotional memory encoding and consolidation (Bayer et al., 2014; Ertman et al., 2011; Felmingham et al., 2012a, 2012b; Ferree et al., 2011; Wassell et al., 2015; Wegerer et al., 2014). The relationship between progesterone and intrusive memories is observed in both laboratory (Andreano et al., 2008; Bayer et al., 2014; Ferree and Cahill, 2009; Soni et al., 2013) and naturalistic settings (Bryant et al., 2011; Ferree et al., 2012) when analogue trauma or trauma respectively, is experienced during the mid-luteal menstrual phase when progesterone is at its peak. As with much of the progesterone-memory literature, however, there is some lack of a consistent direction for this effect (Garcia et al., 2018).

4.1.1. The effect of stress induction on progesterone modulation of emotional memory

We have observed that when studies are separated by presence or absence of stress induction, the effects of progesterone are far more consistent. Specifically, most studies that have not used stress induction have found that higher progesterone levels (Ertman et al., 2011; Ferree et al., 2011; Soni et al., 2013; Wassell et al., 2015), or being in the mid-luteal phase compared to early follicular phase (Ertman et al., 2011; Ferree and Cahill, 2009; Ferree et al., 2011; Soni et al., 2013), is associated with increased negative emotional memories. Only two studies have reported that the early follicular phase compared to the luteal phase was (Bayer et al., 2014), or lower oestradiol levels were (Wegerer et al., 2014), associated with increased negative intrusive or emotional memories upon recall compared to the luteal phase. Conversely, those that have used a stress induction prior to or during memory consolidation have consistently reported that higher progesterone levels (Felmingham et al., 2012a), or being in the mid-luteal phase of the menstrual cycle (Andreano et al., 2008; Bryant et al., 2011; Ferree et al., 2012), is associated with increased negative emotional memories which is similar to the findings of the majority of non-stress studies. This pattern has important implications for the PTSD literature as it points to a sex-specific vulnerability that appears to enhance memory consolidation following a stressful experience for women when progesterone is high. This finding has also been reported by one of the two studies recruiting PTSD women in the fear extinction literature (Pineles et al., 2016, but see Glover et al., 2012).

4.2. Relationship between Progesterone and Cortisol: possible mechanism underlying intrusive memories in PTSD

There are a number of human studies reporting that increased progesterone is associated with increased cortisol responsiveness to stress (Herrera et al., 2016; Kirschbaum et al., 1999; Roca et al., 2003). Several emotional memory studies measuring progesterone have also reported that free cortisol level is associated with increased progesterone but not oestradiol and is associated with increased memory for emotional stimuli following stress induction (Andreano et al., 2008; Felmingham et al., 2012a). That increased cortisol is observed in menstrual phases typified by heightened progesterone, the mid-luteal phase, might imply that there is increased basal cortisol levels more generally during these menstrual phases. Unfortunately, there is not enough research for understanding basal cortisol level fluctuation across the menstrual cycle. Current evidence is mixed, with suggestions of no variation across cycles (McCormick and Teillon, 2001), trending variation across the cycle (Walder et al., 2012), variation in longer than average cycles (Nepomnaschy et al., 2011) and variation depending on whether the female has previously given birth (Fanson et al., 2014).

Conversely, research examining the bioavailability of cortisol in different menstrual phases when under stress suggests that cortisol is more readily available – although maybe not generally heightened in basal levels – during the luteal phase. For instance, Herrera et al. (2016) most recently measured salivary cortisol following acute laboratory stress induction, the cold pressor task, in naturally cycling women. They found that women with high progesterone had significantly higher salivary cortisol response to the stressor, compared to women with low progesterone. This finding is replicated in other studies using social stress with ACTH administration, cold pressor stress and exercise stress (Felmingham et al., 2012a; Kirschbaum et al., 1999; Roca et al., 2003), however was contradicted in Maki et al. (2015) who found lower cortisol responsiveness to social stress in women in the luteal compared to follicular phase. This anomalous finding is not easily reconcilable with the previous literature, as previous studies used similar stress tasks and general procedures yet found opposite results. However, Maki et al. (2015) reported a relatively high proportion of cortisol non-responders to their stress manipulation (over 50%). It is possible that physical stressors, or social stress combined with ACTH administration, may be necessary to elicit a strong enough stress response to make cortisol reactivity differences evident.

Although there is some inconsistency in the relationship between progesterone levels during the luteal phase, presumably synthesised by the ovaries, and cortisol availability, progesterone synthesised elsewhere also show a relationship with cortisol. Firstly, it is well known that adrenal progesterone is at least released as part of the adrenocortical downregulating mechanism concurrently with cortisol under stress, and that release of these hormones is closely correlated (Crowley and Girdler, 2014; Wirth, 2011; Wirth et al., 2007). This is because both adrenal progesterone and cortisol are under the control of adrenocorticotropic hormone (ACTH), which is a key mediating hormone in the activation of the HPA response to stress. This has been established by over 50 years of research, where administration of ACTH to both male and female humans and animals has resulted in significantly increased circulating cortisol and progesterone, verifying that progesterone is part of the adrenal stress response (Chatdarong et al., 2006; De Geyter et al., 2002; De Silva et al., 1983).

Progesterone is therefore considered to be part of the stress response and is best known for its role in termination of the HPA response through negative feedback, through its metabolite allopregnanolone. Briefly, the HPA axis maintains basal status through an inhibitory GABAergic tone in the hypothalamus and anterior pituitary gland. The HPA stress response is activated by disinhibition of this GABAergic tone and renewal of this tone through negative feedback of glucocorticoids restores the basal status of the HPA axis (Fig. 3) (Keller-Wood and Dallman, 1984; Tasker and Herman, 2011). Allopregnanolone, through its affinity to the GABA$_A$ receptor, is therefore widely believed to facilitate the termination of the HPA response to stress through restoration of the inhibitory tone at hypothalamic and pituitary sites of the HPA axis (Bali and Jaggi, 2014; Crowley and Girdler, 2014; Schumacher et al., 2014; Wirth, 2011). Although this has mostly been shown in animal studies (Crowley and Girdler, 2014), administration of progesterone in humans reduced cortisol responsiveness to subsequent acute stress tasks (Childs et al., 2010) and allopregnanolone levels were found to increase in response to acute stress (Droogleever Fortuyn et al., 2004).

Aside from the classical view where cortisol and progesterone are synthesised on demand in the adrenal glands (Schumacher et al., 2014), there is also evidence that stress-induced steroid hormones are synthesised outside of the adrenal glands in the peripheral and central nervous systems, including the brain (Compagnone and Mellon, 2000; Do Rego et al., 2009; Taves et al., 2011). For progesterone, this was demonstrated in one study where increased circulating progesterone levels were observed following spinal cord injury in rats following castration and adrenalectomy (Labombarda et al., 2006). Similarly, human neuronal cell lines express 3βHSD (Brown et al., 2000) and other enzymes needed for the synthesis of progesterone from cholesterol are present in the brain and peripheral nervous system (Do Rego et al., 2009). The human brain also expresses mRNA for hydroxylases involved in glucocorticoid synthesis (Beyenburg et al., 2001; Guennoun et al., 1995; Kishimoto et al., 2004; Rupprecht et al., 2010; Yu et al., 2002) and animal research clearly shows that cortisol and corticosterone may be synthesised de novo in the brain and peripheral nervous system (Taves et al., 2011).

We know that: (a) ovarian progesterone levels that peak during the mid-luteal phase reach circulation, as shown by routine peripheral hormonal assays; and (b) cortisol and progesterone may both be synthesised de novo and in the adrenal glands; thus it is important to consider that progesterone is an partial intermediate step in cortisol biosynthesis (Fig. 1). Specifically, hydroxylation of progesterone metabolite 17OH-hydroxyprogesterone produces cortisol through several intermediator steps (Miller and Auchus, 2011; Payne and Hales, 2004). The exact biosynthetic relationship between progesterone and cortisol during stress is difficult to discern from animal studies, since glucocorticoid effects in most routinely studied animals are produced by corticosteroids rather than cortisol, of which corticosterone is more fully catalysed from progesterone than pregnenolone. There is some literature, such as in fish and other animals, whereby P450c gene transcription is heightened acutely during stress, resulting in on-demand cortisol rather than corticosterone synthesis for regulation of the stress response (Geslin and Auperin, 2004; Hagen et al., 2006; Sandhu and Vijayan, 2011). There is currently limited evidence that 17OH-hydroxyprogesterone may be synthesised de novo in mammalian brains (Compagnone and Mellon, 2000); however this has been shown in birds (Matsunaga et al., 2001). Therefore, it has been demonstrated both in classical steroidogenic research that progesterone affects cortisol synthesis, and this has been more recently observed in vivo and de novo.

Ultimately, it is clear that: (a) progesterone is a stress hormone and is active during the stress response; and (b) progesterone release during stress is correlated with cortisol, which is potentially explainable by it being a precursor in cortisol synthesis.

5. The role of oestradiol in facilitating memory

Oestradiol is also a prominent regulator of brain BDNF levels (Carbone and Handa, 2013; Luine and Frankfurt, 2013; Scharfman and MacLusky, 2006). When administered to mice or rats, oestradiol increases the expression of BDNF protein levels, subsequently inducing dendritic growth, spinogenesis, and synaptogenesis (Bimonte-Nelson et al., 2004; Sasahara et al., 2007). BDNF expression may be regulated by oestradiol due to the presence of an oestradiol response element on the BDNF gene as part of the well-characterised genomic functions of oestradiol (Bjrnstrm and Sjberg, 2005; Sohrabji et al., 1995). Rapid increases in spinogenesis, dendritic growth, and synaptogenesis are observed in animals administered oestradiol or synthetic oestradiols, and these increases are associated with enhanced memory consolidation (Inagaki et al., 2012; Kramár et al., 2009; Luine, 2016; Luine and Frankfurt, 2013). The role of oestradiol in facilitating memory consolidation and learning has attracted attention in clinical domains such as dementia and schizophrenia (Gogos et al., 2015; Sherwin, 2012). In particular, oestradiol displays robust enhancing effects on verbal memory (Maki et al., 2002; Sherwin, 2012) as well as cognitive enhancement in tasks such as prepulse inhibition and higher order cognitive functioning (Gogos, 2013; Gogos et al., 2015). Similarly, women

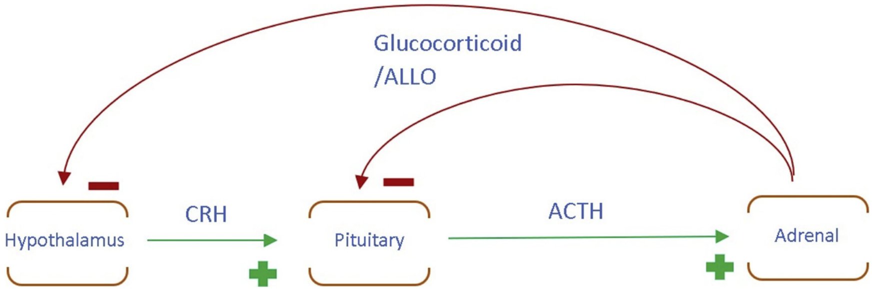

Fig. 3. HPA axis and negative feedback, including allopregnanolone (ALLO).

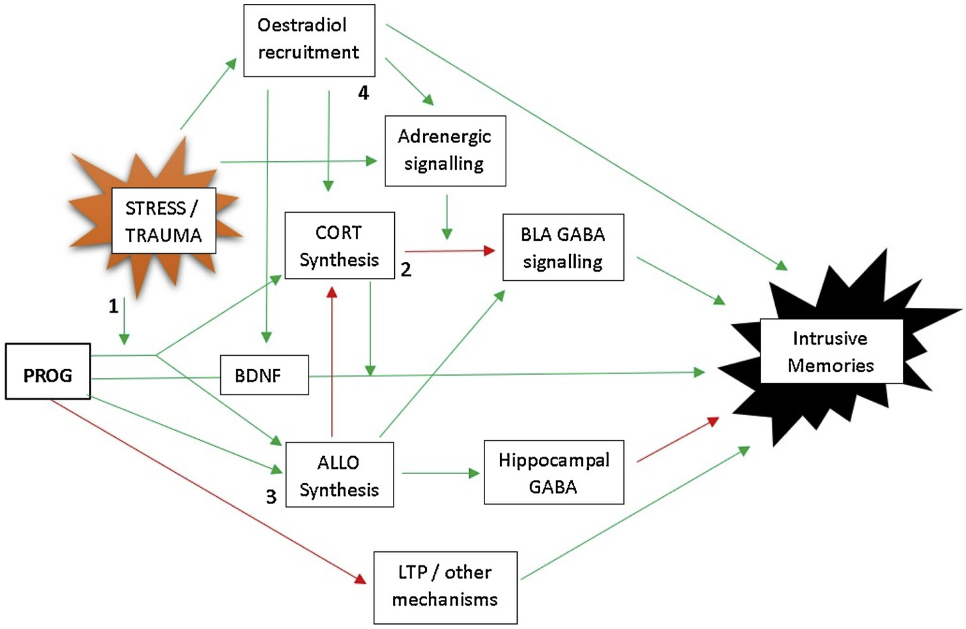

Fig. 4. The effect of progesterone on intrusive memories. Green arrows are excitatory pathways, red arrows are inhibitory pathways. 1. Presence of stress/trauma moderates the effect of progesterone (PROG) on cortisol (CORT) synthesis. 2. Under stress, progesterone-mediated increased cortisol synthesis increases brain derived neurotrophic factor (BDNF) signalling and reduces inhibitory basolateral amygdala (BLA) signalling, which increases intrusive memory consolidation. 3. In the absence of stress/trauma, progesterone levels result in less intrusive memories through allopregnanolone (ALLO), hippocampal γ-aminobutyric acid (GABA), and other pathways. 4. Stress/trauma may result in intrusive memories when oestradiol levels are higher (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

in menstrual cycle phases associated with heightened oestradiol perform better across a range of cognitive and memory measures, including verbal memory and fluency (Baker et al., 2018; Gogos et al., 2014; Sattari et al., 2017).

5.1. Relationship between oestradiol, cortisol and emotional images

Oestradiol is also a potent effector of the HPA stress response. In animal studies oestradiol has been found to facilitate expression of corticotrophin-releasing factor (CRF) in the paraventricular nucleus of hypothalamus during acute stress (Hu et al., 2016; Liu et al., 2012), and both CRF and oestradiol are increased following stress (Liu et al., 2011). Oestradiol appears to exert these effects by impairing negative feedback of the HPA axis in the hypothalamus, with studies showing that glucocorticoid feedback is specifically impaired by oestradiol during stress (Bangasser and Valentino, 2014; Burgess and Handa, 1992; Weiser and Handa, 2009). Similarly, oestradiol is known to enhance memory consolidation, learning, and cognition (Luine, 2016, 2014), with particularly strong effects on fear extinction learning, the literature for which will not be covered here due to being extensively reviewed elsewhere (Glover et al., 2015; Lebron-Milad et al., 2012; Li and Graham, 2017). Despite this, there is little evidence to our knowledge for a low oestradiol phenotype associated with predisposition to PTSD. It is more likely to be the case that, due to the known effect of stress which can downregulate the hypothalamic-pituitary-gonadal (HPG) axis and subsequent production of endogenous sex hormones (Rasmusson et al., 2017; Toufexis et al., 2014), a low oestradiol phenotype may develop following traumatic experience. This proposition is supported by documents of elevated rates of acute stress disorder in women compared to men (Bryant and Harvey, 2003), suggesting sex differences are prevalent before the onset of PTSD, which is a chronic condition. There is some current evidence for oestradiol response elements on the PACAP gene – a regulator of the HPA stress response – that may influence outcomes in PTSD for women but not men (Lind et al., 2017; Ressler et al., 2011). These studies suggest that an oestradiol-genotype may predispose certain women to PTSD following stress; however, whether the role of this polymorphism expresses this disposition at stages of learning, memory or stress responses is unclear.

Further, despite consistent results from animal studies of the effects of oestradiol on stress responding and emotional memories, findings from human studies have been far less consistent. Stress-potentiating effects of oestradiol have been observed in human stress tasks (Kirschbaum et al., 1996; Kudielka and Kirschbaum, 2005), but not in others (Andreano and Cahill, 2010; Felmingham et al., 2012a), and a role for oestradiol in emotional memories under stress is generally not supported (Ertman et al., 2011; Felmingham et al., 2012a; Soni et al., 2013; Wassell et al., 2015; Wegerer et al., 2014), but see Cheung et al. (2013).

6. A model for intrusive memory vulnerability during the luteal phase

Based on the evidence reviewed above, a likely explanation for a lack of enhanced emotional memory during the mid-luteal phase in studies that did not employ a stressor could be that progesterone and/or oestradiol are associated with enhanced cortisol bioavailability on demand, rather than with enhanced basal levels of cortisol more generally. Indeed, multiple human studies have found that, in healthy women, viewing emotional images is associated with lower cortisol responsiveness (Corbett et al., 2017; Holsen et al., 2013; Nicholson et al., 2014; van Stegeren et al., 2008), which suggests that paradigms consisting merely of viewing of emotional images are often not perceived as stressful enough to consistently elicit a biological stress response (hence the move towards emotional or traumatic films as an analogue for trauma and intrusions, see James et al., 2016).

Conversely, studies that have purposefully elicited a stress response have found that increased progesterone is associated with both enhanced cortisol and memory recall for emotional stimuli (Andreano et al., 2008; Felmingham et al., 2012a). This effect is mimicked in real world studies of female trauma survivors, who are by nature the subjects of extreme stress (Bryant et al., 2011; Ferree et al., 2012, but see Maki et al., 2015). Specifically, increased flashback memories were reported by women who presented to hospitals following traumatic experiences that occurred during their mid-luteal menstrual phase (Bryant et al., 2011). Similarly, hormonal contraceptives are known to lower endogenous levels of sex hormones. In one study, women who presented to hospital following sexual assault and who refused to take hormonal contraceptives reported more intrusive memory symptoms at a follow-up interview compared to those who did take emergency hormonal contraceptives (Ferree et al., 2012). Therefore, it is possible that, during times of enhanced progesterone availability, progesterone has minimal enhancing effects on emotional memories in the absence of stress, though during stress this response rapidly activates memory enhancement through heightened cortisol bioavailability (Fig. 4). In support, one other study found that females who underwent a stressor during memory consolidation had higher memory for emotional stimuli than men, though had significantly lower memory for emotional stimuli if they underwent a non-stressful control condition (Felmingham et al., 2012b). Although not measured in this particular study, this interaction effect may have been at least partially moderated by the presence of enhanced progesterone in women, which is elevated relative to men for half of the menstrual cycle. This study was supported by a similar study which found that the effect of stress-induced cortisol on emotional memory consolidation was significantly more prominent in women with high, compared to women with low, progesterone levels (Felmingham et al., 2012a).

Therefore, we propose that progesterone may aid the consolidation of emotional memories during stressful experiences, with evidence of enhanced likelihood of developing intrusive memories of a traumatic experience if encoding and consolidation occurs when progesterone is high (Fig. 4). In our model, we have also incorporated a potential role of increased progesterone on BDNF, due to the increasingly recognised relationship between the two (Jiang et al., 2016; Kaur et al., 2007). It is possible that both adrenal and non-adrenal progesterone might enhance BDNF signalling to enhance memory consolidation, given that BDNF is known to be a risk factor for over-consolidation of traumatic memories (Bekinschtein et al., 2014; Bruenig et al., 2016). Similarly, recent studies have found that acute but not chronic stress upregulates BDNF mRNA levels (Molteni et al., 2008; Shi et al., 2010), but not all studies have replicated this (Lakshminarasimhan and Chattarji, 2012; Murakami et al., 2005).

We have also included a potential role of oestradiol, as preclinical research shows that oestradiol may also facilitate enhanced stress responsiveness (Bangasser and Valentino, 2014). Similarly, as oestradiol plays a critical role during memory formation through regulation of BDNF protein levels, we expect that heightened oestradiol is associated with enhanced memories regardless of the stress condition. For instance, in a recent report, we showed that higher oestradiol in a group of healthy women was associated with acquisition of conditioned responding – a key indicator of fear learning and subsequent fear-related PTSD symptoms – during a standard fear learning and extinction task. In contrast, lower oestradiol was associated with no differentiation between aversive and non-aversive stimuli during this learning phase of the study (Ney, McKay, To, & Felmingham, under review). These findings are similar to memory effects reported in related literature, albeit these other studies reported beneficial effects of oestradiol on consolidation and recall of extinction, rather than fear, memories (reviewed in Ney et al., 2018).

Another consequence of the proposed model is that, following extreme stress, interactions between the HPA and HPG axes causes downregulation of hormone recruitment, which results in the low-oestradiol phenotype believed to be most vulnerable to PTSD through impaired fear extinction learning (Glover et al., 2015; Lebron-Milad et al., 2012; Li and Graham, 2017). Similarly, downregulation of the HPG axis, leading to decreased allopregnanolone synthesis (Pineles et al., 2018; Rasmusson et al., 2017), results in an enduring hormonal PTSD phenotype characterised by reduced extinction learning capacity driven by downregulated sex hormones. However, it is critical to firstly note that there is very little existing evidence for this phenotype in clinical populations, aside from a small collection of genetic studies such as Ressler et al. (2011). It is also important to consider that women are more responsive to psychological treatment for posttraumatic disorders than men, which appears to contradict a low-oestradiol phenotype hypothesis for PTSD (Felmingham and Bryant, 2012; Galovski et al., 2013; Stenmark et al., 2014; Wade et al., 2016). Under our model here increased treatment responsiveness in females likely reflects hormonally-driven learning and memory mechanisms that are advantageous during treatment. These same hormone-driven improvements in learning and memory contribute towards vulnerability to developing the disorder at the time of trauma by the same mechanism, as well as through facilitation of stress hormone bioavailability. This approach is particularly compelling given evidence that rates of acute stress disorder are also significantly higher in women than men (Bryant and Harvey, 2003; Dai et al., 2018). This finding is replicated in symptom cluster studies, where women have also reported greater number of intrusions in the acute aftermath of trauma than men (Carragher et al., 2016; Hourani et al., 2015), suggesting that sex differences in PTSD symptoms and intrusive memories are evident immediately following trauma and before the expected course of recovery is expected to occur.

6.1. Pregnancy, labour, PTSD and sex hormones

Based on this model, PTSD should be more prevalent during pregnancy, another natural stage of life characterised by fluctuation in sex hormone levels. However, current research is insufficient to provide support for or against our model. During pregnancy, progesterone and oestradiol levels increase dramatically until midway through pregnancy and stay elevated until the few weeks before childbirth (Csapo et al., 1971; Tulchinsky and Hobel, 1973; Tulchinsky et al., 1972). Notably, increases in 17OH-progesterone levels, which is an intermediate between progesterone and cortisol, is not consistent throughout pregnancy and in the second half of pregnancy does not increase until the final weeks (Tulchinsky and Hobel, 1973; Tulchinsky et al., 1972). Labour is initiated by decreased levels of progesterone and increased levels of oestrogens, though this is primarily oestriol rather than oestradiol (Smith et al., 2009). CRF, which is critical to the release of cortisol in the HPA axis, also increases as labour approaches (Smith et al., 2009). During labour there are also heightened levels of cortisol (Benfield et al., 2014); this seems to be oestrogen- rather than progesterone-driven (Smith et al., 2009). Levels of sex and stress hormones decrease dramatically in the days following delivery (Hendrick et al., 1998; Mastorakos and Ilias, 2003), and these hormone changes are frequently cited as causes of postpartum mood and other psychiatric disorders (Ahokas et al., 2000; Hendrick et al., 1998; Schiller et al., 2015).

There are many epidemiological studies that examine PTSD symptomatology during pregnancy and following labour. Overall, pregnancy is associated with PTSD rates similar to that found in the general population (Khoramroudi, 2018; Soderquist et al., 2009); however, most studies have examined existing cases of PTSD or trauma exposure and have not measured traumas that occur during pregnancy itself. In this vein, given the high levels of sex hormones during pregnancy, most women experience relief from PTSD symptoms as pregnancy progresses (Muzik et al., 2016; Onoye et al., 2013; Smith et al., 2006). Towards the end of pregnancy and during labour, however, there are increased rates of PTSD symptomatology compared to during pregnancy (Khoramroudi, 2018; Onoye et al., 2013; Seng et al., 2010). These increased rates continue postpartum, when development of PTSD following childbirth is recognised as a clinical risk, especially in at-risk populations such as those with complicated pregnancies or with trauma histories (Grekin and O'Hara, 2014; Wijma et al., 1997). However, when risk factors such as these are accounted for PTSD rates postpartum have been found in most studies to be only marginally, if at all, higher than in women in the general population (Alcorn et al., 2010; Polachek et al., 2016, 2012; Soderquist et al., 2006).

Given the changes in sex hormones throughout pregnancy, it may be expected based on our theory that PTSD may be more prevalent during pregnancy, and potentially less prevalent following labour due to decreased progesterone levels. However, it is known that cortisol and CRF levels are high during labour; this is not driven by progesterone but by oestrogens, which arguably necessitates an oestrogen pathway in our model. It is also notable that 17OH-progesterone, the intermediate hormone between progesterone and cortisol, does not increase significantly until the few weeks prior to labour (Tulchinsky et al., 1972).

This pattern of 17OH-progesterone fluctuation does coincide with increasing levels of PTSD prevalence during pregnancy (Khoramroudi, 2018); however, the link between these changes is largely speculative due to the lack of research on this specific topic. Progesterone's varying role throughout pregnancy also highlights the complex nature of hormonal activation that leads to PTSD – clearly it cannot be attributed to only one or only a few hormones. Further to this, no studies to our knowledge have performed laboratory testing on PTSD symptomology in pregnant women, and clearly none have been performed during labour. It is therefore impossible based on the current evidence to differentiate how a pregnant, compared to a non-pregnant, women may respond to a traumatic experience. Future studies may wish to explore this; however, research methods such as analogue trauma or aversive stimulations will be limited by the necessity of protecting the health of pregnant women.

7. Limitations and future directions

Several caveats to this model must be considered in future research. Firstly, some studies using emotional stimuli without stress induction have found a relationship between progesterone levels and emotional memory (Ertman et al., 2011; Ferree et al., 2011). This remaining discrepancy is not well described by our model, however it is consistent with the broader progesterone memory literature, where progesterone effects are directionally inconsistent in absence of stress (Barros et al., 2015). One potential explanation for this inconsistency may be the lack of rigorous control in these studies of trauma or psychiatric history, which has a strong influence on memory consolidation. Interestingly, the same research that shows that healthy participants do not have cortisol responsiveness when viewing emotional stimuli also suggests that trauma and psychiatric populations exhibit increased cortisol to viewing the same emotional stimuli (Holsen et al., 2013; Nicholson et al., 2014). This implies that trauma exposure, and particularly psychiatric history and condition, enhances sensitivity to stress such that even a mild stressor such as viewing emotional content can trigger a biological cortisol response. Therefore, trauma and psychiatric history should be factored into future studies of emotional memory. In line with the rest of the progesterone-memory literature, these apparent inconsistencies may be due to utilisation of contrasting memory mechanisms and contexts or may simply be due to differences in research design and statistical issues due to generally underpowered research. Future studies should also aim to replicate the progesterone-stress findings to see if our model extends to different demographics and wider populations, with implications for PTSD and other disorders.

Similarly, more rigorous human studies are required to understand the influence of oestradiol on memory consolidation at the time of stress, particularly given the recent genetic evidence of involvement of the PACAP gene, which is a key regulator of the HPA axis (Lind et al., 2017; Ressler et al., 2011). Future studies might explore this model using genetic techniques, rather than acute levels and responses. Another theoretical note might be that sex differences, particularly in the brain, are often not a product of sex hormones but of more proximal mechanisms such as inflammatory mediators and immune cells (McCarthy et al., 2015). For instance, an alternative explanation for the relationship between luteal phase and cortisol responsiveness might be that luteinizing hormone, which is responsible for the progesterone surge and is most prevalent during the luteal phase, also can stimulate steroidogenesis in the adrenal cortex through activation of luteinizing receptors (Kero et al., 2000; Pabon et al., 1996; Rao et al., 2004; Schoemaker et al., 2002). Therefore, increased luteinizing hormone availability during the luteal phase might enhance stress responsiveness, and some human studies have found it to be correlated with increased cortisol in women (Alevizaki et al., 2006; Harlow et al., 1997; Saxena and Seely, 2012; Tock et al., 2014). Other differences between the sexes might be attributable to differences in rates of PTSD and other psychiatric conditions (Cahill, 2006) including gender roles, socialization, and cognitive factors that should be explored concurrently with biological indicators in future studies.

8. Summary and conclusions

In this article we have discussed the multi-faceted role of progesterone in emotional and non-emotional memory consolidation, with special relevance to its potential role in the formation of intrusive memories in PTSD. We have also briefly considered the role that oestradiol may play during stress and during memory consolidation of a stressful event. Intrusive memories in PTSD are believed to develop due to excessive stress hormone activation at the time of trauma, which leads to over-consolidation and poor contextualisation of emotional memories. Importantly, progesterone is an indirect intermediate in cortisol biosynthesis, and has relationships to BDNF and FKBP5 which may increase both stress responding and memory consolidation during a traumatic event. However, both naturalistic and experimental human studies have consistently reported that, when under stress, progesterone is associated with enhanced emotional memory consolidation and is correlated with cortisol activation.

We have therefore proposed a model (Fig. 4) whereby progesterone acts indirectly through cortisol and BDNF to enhance consolidation of emotional memories into intrusive memories and note that this may only happen when an experience is sufficiently stressful to elicit a biological stress response. Specifically, heightened progesterone at the time of trauma can increase the cortisol response to stress, which, in conjunction with heightened BDNF levels, enhances memory consolidation to a maladaptive level. Similarly, oestradiol may also enhance the magnitude of the stress response and consequent memory consolidation through similar mechanisms. We therefore propose that the same learning and memory mechanisms that drive heightened recovery of PTSD following treatment in women also underlie the increased prevalence of this disorder in women following trauma. We have presented several lines of evidence to support this model, including laboratory studies, field reports, and clinical trials. Further, there is evidence that sex differences in symptomology are evident even before PTSD can be diagnosed such that women display higher rates of acute stress disorder than men. A particular strength of this model is that it is consistent with evidence from existing theories of PTSD aetiology, including excessive stress activation and the role of oestradiol in recovery from the disorder, whilst proposing a putative explanation for why women may be more vulnerable to increased symptomology and diagnosis. This model also challenges the existing theory that sex differences in PTSD aetiology are attributable to low oestradiol levels by emphasising high levels at the time of trauma as the vulnerability factor. Whilst we believe there is a large amount of existing evidence for our theory, there is more research needed.

In conclusion, it is clear that women are more susceptible to stress-related disorders, including PTSD. Despite increasing efforts to understand this discrepancy, however, a comprehensive explanation is still lacking. Most of the recent efforts have focussed on low oestradiol during PTSD development and maintenance following trauma. Our approach here is to model risk factors for PTSD at the exact time of trauma, such as progesterone. This model needs validation from further empirical studies, and clinical applications may include 'first aid' treatments for men and women immediately following trauma, as well as potential identification of risk gene variants in progesterone, and possibly stress-related oestradiol, regulation.

Declaration of Competing Interest

None.

Acknowledgement

This work was supported by an National Health and Medical

Research Council project grant to KLF (APP1073041).

References

Ahokas, A., Aito, M., Rimon, R., 2000. Positive treatment effect of estradiol in postpartum psychosis: a pilot study. J. Clin. Psychiatry 61 (3), 166–169.

Alcorn, K.L., O'Donovan, A., Patrick, J.C., Creedy, D., Devilly, G.J., 2010. A prospective longitudinal study of the prevalence of post-traumatic stress disorder resulting from childbirth events. Psychol. Med. 40 (11), 1849–1859. https://doi.org/10.1017/s0033291709992224.

Alevizaki, M., Saltiki, K., Mantzou, E., Anastasiou, E., Huhtaniemi, I., 2006. The adrenal gland may be a target of LH action in postmenopausal women. Eur. J. Endocrinol. 154 (6), 875–881. https://doi.org/10.1530/eje.1.02165.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association, Washington DC.

Andero, R., Ressler, K.J., 2012. Fear extinction and BDNF: translating animal models of PTSD to the clinic. Genes Brain Behav. 11 (5), 503–512. https://doi.org/10.1111/j.1601-183X.2012.00801.x.

Andreano, J.M., Arjomandi, H., Cahill, L., 2008. Menstrual cycle modulation of the relationship between cortisol and long-term memory. Psychoneuroendocrinology 33 (6). https://doi.org/10.1016/j.psyneuen.2008.03.009.

Andreano, J.M., Cahill, L., 2010. Menstrual cycle modulation of medial temporal activity evoked by negative emotion. Neuroimage 53 (4), 1286–1293. https://doi.org/10.1016/j.neuroimage.2010.07.011.

Baker, F.C., Sattari, N., de Zambotti, M., Goldstone, A., Alaynick, W.A., Mednick, S.C., 2018. Impact of sex steroids and reproductive stage on sleep-dependent memory consolidation in women. Neurobiol. Learn. Mem. https://doi.org/10.1016/j.nlm.2018.03.017.

Bali, A., Jaggi, A.S., 2014. Multifunctional aspects of allopregnanolone in stress and related disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 48, 64–78. https://doi.org/10.1016/j.pnpbp.2013.09.005.

Bangasser, D.A., Valentino, R.J., 2014. Sex differences in stress-related psychiatric disorders: neurobiological perspectives. Front. Neuroendocrinol. 35 (3), 303–319. https://doi.org/10.1016/j.yfrne.2014.03.008.

Barros, L.A., Tufik, S., Andersen, M.L., 2015. The role of progesterone in memory: an overview of three decades. Neurosci. Biobehav. Rev. 49, 193–204. https://doi.org/10.1016/j.neubiorev.2014.11.015.

Bayer, J., Schultz, H., Gamer, M., Sommer, T., 2014. Menstrual-cycle dependent fluctuations in ovarian hormones affect emotional memory. Neurobiol. Learn. Mem. 110, 55–63. https://doi.org/10.1016/j.nlm.2014.01.017.

Becker, J.B., Arnold, A.P., Berkley, K.J., Blaustein, J.D., Eckel, L.A., Hampson, E., et al., 2005. Strategies and methods for research on sex differences in brain and behavior. Endocrinology 146 (4), 1650–1673. https://doi.org/10.1210/en.2004-1142.

Bekinschtein, P., Cammarota, M., Medina, J.H., 2014. BDNF and memory processing. Neuropharmacology 76 (Pt C), 677–683. https://doi.org/10.1016/j.neuropharm.2013.04.024.

Benfield, R.D., Newton, E.R., Tanner, C.J., Heitkemper, M.M., 2014. Cortisol as a biomarker of stress in term human labor: physiological and methodological issues. Biol. Res. Nurs. 16 (1), 64–71. https://doi.org/10.1177/1099800412471580.

Berent-Spillson, A., Briceno, E., Pinsky, A., Simmen, A., Persad, C.C., Zubieta, J.-K., Smith, Y.R., 2015. Distinct cognitive effects of estrogen and progesterone in menopausal women. Psychoneuroendocrinology 59, 25–36. https://doi.org/10.1016/j.psyneuen.2015.04.020.

Beyenburg, S., Watzka, M., Clusmann, H., Blumcke, I., Bidlingmaier, F., Elger, C.E., Stoffel-Wagner, B., 2001. Messenger RNA of steroid 21-hydroxylase (CYP21) is expressed in the human hippocampus. Neurosci. Lett. 308 (2), 111–114.

Bimonte-Nelson, H.A., Singleton, R.S., Williams, B.J., Granholm, A.C., 2004. Ovarian hormones and cognition in the aged female rat: II. Progesterone supplementation reverses the cognitive enhancing effects of ovariectomy. Behav. Neurosci. 118 (4), 707–714. https://doi.org/10.1037/0735-7044.118.4.707.

Björnström, L., Sjöberg, M., 2005. Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. Mol. Endocrinol. 19 (4), 833–842. https://doi.org/10.1210/me.2004-0486.

Blanco, C., Hoertel, N., Wall, M.M., Franco, S., Peyre, H., Neria, Y., et al., 2018. Toward understanding sex differences in the prevalence of posttraumatic stress disorder: results from the national epidemiologic survey on alcohol and related conditions. J. Clin. Psychiatry 79 (2). https://doi.org/10.4088/JCP.16m11364.

Brewin, C.R., 2011. The nature and significance of memory disturbance in posttraumatic stress disorder. Annu. Rev. Clin. Psychol. 7, 203–227. https://doi.org/10.1146/annurev-clinpsy-032210-104544.

Brewin, C.R., Gregory, J.D., Lipton, M., Burgess, N., 2010. Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. Psychol. Rev. 117 (1), 210–232. https://doi.org/10.1037/a0018113.

Brown, R.C., Cascio, C., Papadopoulos, V., 2000. Pathways of neurosteroid biosynthesis in cell lines from human brain: regulation of dehydroepiandrosterone formation by oxidative stress and beta-amyloid peptide. J. Neurochem. 74 (2), 847–859.

Bruenig, D., Lurie, J., Morris, C.P., Harvey, W., Lawford, B., Young, R.M., Voisey, J., 2016. A case-control study and meta-analysis reveal BDNF Val66Met is a possible risk factor for PTSD. Neural Plast. 2016, 10. https://doi.org/10.1155/2016/6979435.

Bryant, R.A., Felmingham, K.L., Silove, D., Creamer, M., O'Donnell, M., McFarlane, A.C., 2011. The association between menstrual cycle and traumatic memories. J. Affect. Disord. 131 (1–3), 398–401. https://doi.org/10.1016/j.jad.2010.10.049.

Bryant, R.A., Harvey, A.G., 2003. Gender differences in the relationship between acute stress disorder and posttraumatic stress disorder following motor vehicle accidents. Aust. N. Z. J. Psychiatry 37 (2), 226–229. https://doi.org/10.1046/j.1440-1614.2003.01130.x.

Bryant, R.A., McGrath, C., Felmingham, K.L., 2013. The roles of noradrenergic and glucocorticoid activation in the development of intrusive memories. PLoS One 8 (4), e62675. https://doi.org/10.1371/journal.pone.0062675.

Burgess, L.H., Handa, R.J., 1992. Chronic estrogen-induced alterations in adrenocorticotropin and corticosterone secretion, and glucocorticoid receptor-mediated functions in female rats. Endocrinology 131 (3), 1261–1269. https://doi.org/10.1210/endo.131.3.1324155.

Cahill, L., 2006. Why sex matters for neuroscience. Nat. Rev. Neurosci. 7 (6), 477–484. https://doi.org/10.1038/nrn1909.

Carbone, D.L., Handa, R.J., 2013. Sex and stress hormone influences on the expression and activity of brain-derived neurotrophic factor. Neuroscience 239, 295–303. https://doi.org/10.1016/j.neuroscience.2012.10.073.

Carragher, N., Sunderland, M., Batterham, P.J., Calear, A.L., Elhai, J.D., Chapman, C., Mills, K., 2016. Discriminant validity and gender differences in DSM-5 posttraumatic stress disorder symptoms. J. Affect. Disord. 190, 56–67. https://doi.org/10.1016/j.jad.2015.09.071.

Chapouthier, G., Venault, P., 2002. GABA-A receptor complex and memory processes. Curr. Top. Med. Chem. 2 (8), 841–851.

Chatdarong, K., Ponglowhapan, S., Karlsson, A., Linde-Forsberg, C., 2006. The effect of ACTH stimulation on cortisol and progesterone concentrations in intact and ovariohysterectomized domestic cats. Theriogenology 66 (6-7), 1482–1487. https://doi.org/10.1016/j.theriogenology.2006.01.005.

Cheung, J., Bryant, R.A., 2015. FKBP5 risk alleles and the development of intrusive memories. Neurobiol. Learn. Mem. 125, 258–264. https://doi.org/10.1016/j.nlm.2015.09.008.

Cheung, J., Chervonsky, L., Felmingham, K.L., Bryant, R.A., 2013. The role of estrogen in intrusive memories. Neurobiol. Learn. Mem. 106, 87–94. https://doi.org/10.1016/j.nlm.2013.07.005.

Childs, E., Van Dam, N.T., de Wit, H., 2010. Effects of acute progesterone administration upon responses to acute psychosocial stress in men. Exp. Clin. Psychopharmacol. 18 (1), 78–86. https://doi.org/10.1037/a0018060.

Chou, C.Y., La Marca, R., Steptoe, A., Brewin, C.R., 2014. Biological responses to trauma and the development of intrusive memories: an analog study with the trauma film paradigm. Biol. Psychol. 103, 135–143. https://doi.org/10.1016/j.biopsycho.2014.08.002.

Compagnone, N.A., Mellon, S.H., 2000. Neurosteroids: biosynthesis and function of these novel neuromodulators. Front. Neuroendocrinol. 21 (1), 1–56. https://doi.org/10.1006/frne.1999.0188.

Conway, M.A., Pleydell-Pearce, C.W., 2000. The construction of autobiographical memories in the self-memory system. Psychol. Rev. 107 (2), 261–288. https://doi.org/10.1037//0033-295X.

Corbett, B., Weinberg, L., Duarte, A., 2017. The effect of mild acute stress during memory consolidation on emotional recognition memory. Neurobiol. Learn. Mem. 145, 34–44. https://doi.org/10.1016/j.nlm.2017.08.005.

Crowley, S.K., Girdler, S.S., 2014. Neurosteroid, GABAergic and hypothalamic pituitary adrenal (HPA) axis regulation: what is the current state of knowledge in humans? Psychopharmacology (Berl.) 231 (17), 3619–3634. https://doi.org/10.1007/s00213-014-3572-8.

Csapo, A.I., Knobil, E., van der Molen, H.J., Wiest, W.G., 1971. Peripheral plasma progesterone levels during human pregnancy and labor. Am. J. Obstet. Gynecol. 110 (5), 630–632. https://doi.org/10.1016/0002-9378(71)90242-0.

Dai, W., Liu, A., Kaminga, A.C., Deng, J., Lai, Z., Yang, J., Wen, S.W., 2018. Prevalence of acute stress disorder among road traffic accident survivors: a meta-analysis. BMC Psychiatry 18 (1). https://doi.org/10.1186/s12888-018-1769-9. 188-188.

De Geyter, C., De Geyter, M., Huber, P.R., Nieschlag, E., Holzgreve, W., 2002. Progesterone serum levels during the follicular phase of the menstrual cycle originate from the crosstalk between the ovaries and the adrenal cortex. Hum. Reprod. 17 (4), 933–939. https://doi.org/10.1093/humrep/17.4.933.

De Silva, M., Kaltenbach, C.C., Dunn, T.G., 1983. Serum cortisol and progesterone after administration of adrenocorticotropin and(or) prolactin to sheep. J. Anim. Sci. 57 (6), 1525–1529.

Do Rego, J.L., Seong, J.Y., Burel, D., Leprince, J., Luu-The, V., Tsutsui, K., et al., 2009. Neurosteroid biosynthesis: enzymatic pathways and neuroendocrine regulation by neurotransmitters and neuropeptides. Front. Neuroendocrinol. 30 (3), 259–301. https://doi.org/10.1016/j.yfrne.2009.05.006.

Droogleever Fortuyn, H.A., van Broekhoven, F., Span, P.N., Backstrom, T., Zitman, F.G., Verkes, R.J., 2004. Effects of PhD examination stress on allopregnanolone and cortisol plasma levels and peripheral benzodiazepine receptor density. Psychoneuroendocrinology 29 (10), 1341–1344. https://doi.org/10.1016/j.psyneuen.2004.02.003.

Ehlers, A., 2010. Understanding and treating unwanted trauma memories in posttraumatic stress disorder. J. Psychol. 218 (2), 141–145. https://doi.org/10.1027/a000001].

Ehlers, A., Clark, D.M., 2000. A cognitive model of posttraumatic stress disorder. Behavior Research and Therapy 38, 319–345.

Ertman, N., Andreano, J.M., Cahill, L., 2011. Progesterone at encoding predicts subsequent emotional memory. Learn. Mem. 18 (12), 759–763. https://doi.org/10.1101/lm.023267.111.

Fanson, K.V., Keeley, T., Fanson, B.G., 2014. Cyclic changes in cortisol across the estrous cycle in parous and nulliparous Asian elephants. Endocr. Connect. 3 (2), 57–66. https://doi.org/10.1530/EC-14-0025.

Felmingham, K.L., Bryant, R.A., 2012. Gender differences in the maintenance of response to cognitive behavior therapy for posttraumatic stress disorder. J. Consult. Clin. Psychol. 80 (2), 196–200. https://doi.org/10.1037/a0027156.

Felmingham, K.L., Fong, W.C., Bryant, R.A., 2012a. The impact of progesterone on memory consolidation of threatening images in women. Psychoneuroendocrinology 37 (11), 1896–1900. https://doi.org/10.1016/j.psyneuen.2012.03.026.

Felmingham, K.L., Tran, T.P., Fong, W.C., Bryant, R.A., 2012b. Sex differences in emotional memory consolidation: the effect of stress-induced salivary alpha-amylase and cortisol. Biol. Psychol. 89, 539–544. https://doi.org/10.1016/j.biopsycho.2011.12.006.

Ferree, N.K., Cahill, L., 2009. Post-event spontaneous intrusive recollections and strength of memory for emotional events in men and women. Conscious. Cogn. 18 (1), 126–134. https://doi.org/10.1016/j.concog.2008.11.008.

Ferree, N.K., Kamat, R., Cahill, L., 2011. Influences of menstrual cycle position and sex hormone levels on spontaneous intrusive recollections following emotional stimuli. Conscious. Cogn. 20 (4), 1154–1162. https://doi.org/10.1016/j.concog.2011.02.003.

Ferree, N.K., Wheeler, M., Cahill, L., 2012. The influence of emergency contraception on post-traumatic stress symptoms following sexual assault. J. Forensic Nurs. 8 (3), 122–130. https://doi.org/10.1111/j.1939-3938.2012.01134.x.

Foy, M.R., Akopian, G., Thompson, R.F., 2008. Progesterone regulation of synaptic transmission and plasticity in rodent hippocampus. Learn. Mem. 15 (11), 820–822. https://doi.org/10.1101/lm.1124708.

Freeman, E.W., Purdy, R.H., Coutifaris, C., Rickels, K., Paul, S.M., 1993. Anxiolytic metabolites of progesterone: correlation with mood and performance measures following oral progesterone administration to healthy female volunteers. Neuroendocrinology 58 (4), 478–484. https://doi.org/10.1159/000126579.

Freeman, E.W., Weinstock, L., Rickels, K., Sondheimer, S.J., Coutifaris, C., 1992. A placebo-controlled study of effects of oral progesterone on performance and mood. Br. J. Clin. Pharmacol. 33 (3), 293–298. https://doi.org/10.1111/j.1365-2125.1992.tb04038.x.

Frye, C.A., Llaneza, D.C., Walf, A.A., 2009. Progesterone can enhance consolidation and/or performance in spatial, object and working memory tasks in Long–Evans rats. Anim. Behav. 78 (2), 279–286.

Frye, C.A., Walf, A.A., 2008. Progesterone enhances performance of aged mice in cortical or hippocampal tasks. Neurosci. Lett. 437 (2), 116–120. https://doi.org/10.1016/j.neulet.2008.04.004.

Galovski, T.E., Blain, L.M., Chappuis, C., Fletcher, T., 2013. Sex differences in recovery from PTSD in male and female interpersonal assault survivors. Behav. Res. Ther. 51 (6), 247–255. https://doi.org/10.1016/j.brat.2013.02.002.

Garcia, N.M., Walker, R.S., Zoellner, L.A., 2018. Estrogen, progesterone, and the menstrual cycle: a systematic review of fear learning, intrusive memories, and PTSD. Clin. Psychol. Rev. 66, 80–96. https://doi.org/10.1016/j.cpr.2018.06.005.

Geslin, M., Auperin, B., 2004. Relationship between changes in mRNAs of the genes encoding steroidogenic acute regulatory protein and P450 cholesterol side chain cleavage in head kidney and plasma levels of cortisol in response to different kinds of acute stress in the rainbow trout (Oncorhynchus mykiss). Gen. Comp. Endocrinol. 135 (1), 70–80. https://doi.org/10.1016/S0016-6480(03)00283-1.

Glover, E.M., Jovanovic, T., Mercer, K.B., Kerley, K., Bradley, B., Ressler, K.J., Norrholm, S.D., 2012. Estrogen levels are associated with extinction deficits in women with posttraumatic stress disorder. Biol. Psychiatry 72 (1), 19–24. https://doi.org/10.1016/j.biopsych.2012.02.031.

Glover, E.M., Jovanovic, T., Norrholm, S.D., 2015. Estrogen and extinction of fear memories: implications for posttraumatic stress disorder treatment. Biol. Psychiatry 78 (3), 178–185. https://doi.org/10.1016/j.biopsych.2015.02.007.

Gogos, A., 2013. Natural and synthetic sex hormones: effects on higher-order cognitive function and prepulse inhibition. Biol. Psychol. 93 (1), 17–23. https://doi.org/10.1016/j.biopsycho.2013.02.001.

Gogos, A., Ney, L.J., Seymour, N., Van Rheenen, T., Felmingam, K.L., 2019. Sex differences in schizophrenia, bipolar disorder and PTSD: Are gonadal hormones the link? Br. J. Pharmacol. https://doi.org/10.1111/bph.14584.

Gogos, A., Sbisa, A.M., Sun, J., Gibbons, A., Udawela, M., Dean, B., 2015. A role for estrogen in schizophrenia: clinical and preclinical findings. Int. J. Endocrinol. 2015, 615356. https://doi.org/10.1155/2015/615356.

Gogos, A., Wu, Y.C., Williams, A.S., Byrne, L.K., 2014. The effects of ethinylestradiol and progestins (“the pill”) on cognitive function in pre-menopausal women. Neurochem. Res. 39 (12), 2288–2300. https://doi.org/10.1007/s11064-014-1444-6.

Graham, B.M., Milad, M.R., 2013. Blockade of estrogen by hormonal contraceptives impairs fear extinction in female rats and women. Biol. Psychiatry 73 (4), 371–378. https://doi.org/10.1016/j.biopsych.2012.09.018.

Grekin, R., O’Hara, M.W., 2014. Prevalence and risk factors of postpartum posttraumatic stress disorder: a meta-analysis. Clin. Psychol. Rev. 34 (5), 389–401. https://doi.org/10.1016/j.cpr.2014.05.003.

Guennoun, R., Fiddes, R.J., Gouézou, M., Lombès, M., Baulieu, E.E., 1995. A key enzyme in the biosynthesis of neurosteroids, 3β-hydroxysteroid dehydrogenase/Δ5-Δ4-isomerase (3β-HSD), is expressed in rat brain. Mol. Brain Res. 30 (2), 287–300. https://doi.org/10.1016/0169-328X(95)00016-L.

Hagen, I.J., Kusakabe, M., Young, G., 2006. Effects of ACTH and cAMP on steroidogenic acute regulatory protein and P450 11β-hydroxylase messenger RNAs in rainbow trout interrenal cells: relationship with in vitro cortisol production. Gen. Comp. Endocrinol. 145 (3), 254–262. https://doi.org/10.1016/j.ygcen.2005.09.014.

Harburger, L.L., Pechenino, A.S., Saadi, A., Frick, K.M., 2008. Post-training progesterone dose-dependently enhances object, but not spatial, memory consolidation. Behav. Brain Res. 194 (2), 174–180. https://doi.org/10.1016/j.bbr.2008.07.014.

Harlow, C.R., Jenkins, J.M., Winston, R.M., 1997. Increased follicular fluid total and free cortisol levels during the luteinizing hormone surge. Fertil. Steril. 68 (1), 48–53.

Hayes, J.P., Logue, M.W., Reagan, A., Salat, D., Wolf, E.J., Sadeh, N., et al., 2017. COMT Val158Met polymorphism moderates the association between PTSD symptom severity and hippocampal volume. J. Psychiatry Neurosci. 42 (2), 95–102.

Hendrick, V., Altshuler, L.L., Suri, R., 1998. Hormonal changes in the postpartum and implications for postpartum depression. Psychosomatics 39 (2), 93–101. https://doi.org/10.1016/s0033-3182(98)71355-6.

Herrera, A.Y., Nielsen, S.E., Mather, M., 2016. Stress-induced increases in progesterone and cortisol in naturally cycling women. Neurobiol. Stress 3, 96–104. https://doi.org/10.1016/j.ynstr.2016.02.006.

Holsen, L.M., Lancaster, K., Klibanski, A., Whitfield-Gabrieli, S., Cherkerzian, S., Buka, S., Goldstein, J.M., 2013. HPA-axis hormone modulation of stress response circuitry activity in women with remitted major depression. Neuroscience 250, 733–742. https://doi.org/10.1016/j.neuroscience.2013.07.042.

Honjo, H., Iwasa, K., Kawata, M., Fushiki, S., Hosoda, T., Tatsumi, H., et al., 2005. Progestins and estrogens and Alzheimer’s disease. J. Steroid Biochem. Mol. Biol. 93 (2), 305–308. https://doi.org/10.1016/j.jsbmb.2004.12.001.

Hourani, L., Williams, J., Bray, R., Kandel, D., 2015. Gender differences in the expression of PTSD symptoms among active duty military personnel. J. Anxiety Disord. 29, 101–108. https://doi.org/10.1016/j.janxdis.2014.11.007.

Hsu, C.-M.K., Kleim, B., Nicholson, E.L., Zuj, D.V., Cushing, P.J., Gray, K.E., et al., 2018. Sex differences in intrusive memories following trauma. PLoS One 13 (12), e0208575. https://doi.org/10.1371/journal.pone.0208575.

Hu, P., Liu, J., Yasrebi, A., Gotthardt, J.D., Bello, N.T., Pang, Z.P., Roepke, T.A., 2016. Gq protein-coupled membrane-initiated estrogen signaling rapidly excites corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus in female mice. Endocrinology 157 (9), 3604–3620. https://doi.org/10.1210/en.2016-1191.

Inagaki, T., Frankfurt, M., Luine, V., 2012. Estrogen-induced memory enhancements are blocked by acute bisphenol A in adult female rats: role of dendritic spines. Endocrinology 153 (7), 3357–3367. https://doi.org/10.1210/en.2012-1121.

James, E.L., Lau-Zhu, A., Clark, I.A., Visser, R.M., Hagenaars, M.A., Holmes, E.A., 2016. The trauma film paradigm as an experimental psychopathology model of psychological trauma: intrusive memories and beyond. Clin. Psychol. Rev. 47, 106–142. https://doi.org/10.1016/j.cpr.2016.04.010.

Jang, D., Elfenbein, H.A., 2018. Menstrual cycle effects on mental health outcomes: a meta-analysis. Arch. Suicide Res. 1–21. https://doi.org/10.1080/13811118.2018.1430638.

Jiang, C., Zuo, F., Wang, Y., Lu, H., Yang, Q., Wang, J., 2016. Progesterone changes VEGF and BDNF expression and promotes neurogenesis after ischemic stroke. Mol. Neurobiol. 54 (1), 571–581. https://doi.org/10.1007/s12035-015-9651-y.

Kask, K., Backstrom, T., Nilsson, L.G., Sundstrom-Poromaa, I., 2008. Allopregnanolone impairs episodic memory in healthy women. Psychopharmacology (Berl.) 199 (2), 161–168. https://doi.org/10.1007/s00213-008-1150-7.

Kaur, P., Jodhka, P.K., Underwood, W.A., Bowles, C.A., de Fiebre, N.C., de Fiebre, C.M., Singh, M., 2007. Progesterone increases brain-derived neuroptrophic factor expression and protects against glutamate toxicity in a mitogen-activated protein kinase- and phosphoinositide-3 kinase-dependent manner in cerebral cortical explants. J. Neurosci. Res. 85 (11), 2441–2449. https://doi.org/10.1002/jnr.21370.

Keller-Wood, M.E., Dallman, M.F., 1984. Corticosteroid inhibition of ACTH secretion. Endocr. Rev. 5 (1), 1–24.

Kero, J., Poutanen, M., Zhang, F.-P., Rahman, N., McNicol, A.M., Nilson, J.H., et al., 2000. Elevated luteinizing hormone induces expression of its receptor and promotes steroidogenesis in the adrenal cortex. J. Clin. Invest. 105 (5), 633–641. https://doi.org/10.1172/JCI7716.

Khoramroudi, R., 2018. The prevalence of posttraumatic stress disorder during pregnancy and postpartum period. J. Family Med. Prim. Care 7 (1), 220–223. https://doi.org/10.4103/jfmpc.jfmpc_272_17.

Kirschbaum, C., Kudielka, B.M., Gaab, J., Schommer, N.C., Hellhammer, D.H., 1999. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-Adrenal Axis. Psychosom. Med. 61 (2), 154–162. https://doi.org/10.1097/00006842-199903000-00006.

Kirschbaum, C., Schommer, N., Federenko, I., Gaab, J., Neumann, O., Oellers, M., et al., 1996. Short-term estradiol treatment enhances PituitaryAdrenal Axis and sympathetic responses to psychosocial stress in healthy young men. J. Clin. Endocrinol. Metab. 81 (10), 3639–3643.

Kishimoto, W., Hiroi, T., Shiraishi, M., Osada, M., Imaoka, S., Kominami, S., et al., 2004. Cytochrome P450 2D catalyze steroid 21-hydroxylation in the brain. Endocrinology 145 (2), 699–705. https://doi.org/10.1210/en.2003-1109.

Kleim, B., Wallott, F., Ehlers, A., 2008. Are trauma memories disjointed from other autobiographical memories in posttraumatic stress disorder? An experimental investigation. Behav. Cogn. Psychother. 36 (2), 221–234. https://doi.org/10.1017/S1352465807004080.

Kokras, N., Dalla, C., 2014. Sex differences in animal models of psychiatric disorders. Br. J. Pharmacol. 171 (20), 4595–4619. https://doi.org/10.1111/bph.2014.171.issue-20.

Kramár, E.A., Chen, L.Y., Brandon, N.J., Rex, C.S., Liu, F., Gall, C.M., Lynch, G., 2009. Cytoskeletal changes underlie estrogen’s acute effects on synaptic transmission and plasticity. J. Neurosci. 29 (41), 12982–12993. https://doi.org/10.1523/JNEUROSCI.3059-09.2009.

Kudielka, B.M., Kirschbaum, C., 2005. Sex differences in HPA axis responses to stress: a review. Biol. Psychol. 69 (1), 113–132. https://doi.org/10.1016/j.biopsycho.2004.11.009.

Labombarda, F., Pianos, A., Liere, P., Eychenne, B., Gonzalez, S., Cambourg, A., et al., 2006. Injury elicited increase in spinal cord neurosteroid content analyzed by gas chromatography mass spectrometry. Endocrinology 147 (4), 1847–1859. https://doi.org/10.1210/en.2005-0955.

Lakshminarasimhan, H., Chattarji, S., 2012. Stress leads to contrasting effects on the levels of brain derived neurotrophic factor in the Hippocampus and amygdala. PLoS One 7 (1), e30481. https://doi.org/10.1371/journal.pone.0030481.

Lebron-Milad, K., Graham, B.M., Milad, M.R., 2012. Low estradiol levels: a vulnerability factor for the development of posttraumatic stress disorder. Biol. Psychiatry 72, 6–7. https://doi.org/10.1016/j.biopsych.2012.04.029.

Lebron-Milad, K., Milad, M.R., 2012. Sex differences, gonadal hormones and the fear extinction network: implications for anxiety disorders. Biol. Mood Anxiety Disord. 2 (3). https://doi.org/10.1186/2045-5380-2-3.

Lewis, M.C., Orr, P.T., Frick, K.M., 2008. Differential effects of acute progesterone administration on spatial and object memory in middle-aged and aged female C57BL/6 mice. Horm. Behav. 54 (3), 455–462. https://doi.org/10.1016/j.yhbeh.2008.05.010.

Li, S., Graham, B.M., 2017. Why are women so vulnerable to anxiety, trauma-related and stress-related disorders? The potential role of sex hormones. Lancet Psychiatry 4 (1), 73–82. https://doi.org/10.1016/s2215-0366(16)30358-3.

Lind, M.J., Marraccini, M.E., Sheerin, C.M., Bountress, K., Bacanu, S.A., Amstadter, A.B., Nugent, N.R., 2017. Association of posttraumatic stress disorder with rs2267735 in the ADCYAP1R1 gene: a meta-analysis. J. Trauma. Stress 30 (4), 389–398. https://doi.org/10.1002/jts.22211.

Liu, J., Bisschop, P.H., Eggels, L., Foppen, E., Fliers, E., Zhou, J.N., Kalsbeek, A., 2012. Intrahypothalamic estradiol modulates hypothalamus-pituitary-adrenal-axis activity in female rats. Endocrinology 153 (7), 3337–3344. https://doi.org/10.1210/en.2011-2176.

Liu, J., Hu, P., Qi, X.R., Meng, F.T., Kalsbeek, A., Zhou, J.N., 2011. Acute restraint stress increases intrahypothalamic oestradiol concentrations in conjunction with increased hypothalamic oestrogen receptor beta and aromatase mRNA expression in female rats. J. Neuroendocrinol. 23 (5), 435–443. https://doi.org/10.1111/j.1365-2826.2011.02123.x.

Luine, V., 2016. Estradiol: mediator of memories, spine density and cognitive resilience to stress in female rodents. J. Steroid Biochem. Mol. Biol. 160, 189–195. https://doi.org/10.1016/j.jsbmb.2015.07.022.

Luine, V., Frankfurt, M., 2013. Interactions between estradiol, BDNF and dendritic spines in promoting memory. Neuroscience 239, 34–45. https://doi.org/10.1016/j.neuroscience.2012.10.019.

Luine, V.N., 2014. Estradiol and cognitive function: past, present and future. Horm. Behav. 66 (4), 602–618. https://doi.org/10.1016/j.yhbeh.2014.08.011.

Maki, P.M., Mordecai, K.L., Rubin, L.H., Sundermann, E., Savarese, A., Eatough, E., Drogos, L., 2015. Menstrual cycle effects on cortisol responsivity and emotional retrieval following a psychosocial stressor. Horm. Behav. 74, 201–208. https://doi.org/10.1016/j.yhbeh.2015.06.023.

Maki, P.M., Rich, J.B., Rosenbaum, R.S., 2002. Implicit memory varies across the menstrual cycle: estrogen effects in young women. Neuropsychologia 40 (5), 518–529.

Maki, P.M., Zonderman, A.B., Resnick, S.M., 2001. Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. Am. J. Psychiatry 158 (2), 227–233. https://doi.org/10.1176/appi.ajp.158.2.227.

Mastorakos, G., Ilias, I., 2003. Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. Ann. N. Y. Acad. Sci. 997, 136–149. https://doi.org/10.1196/annals.1290.016.

Matsunaga, M., Ukena, K., Tsutsui, K., 2001. Expression and localization of cytochrome P450 17 alpha-hydroxylase/c17,20-lyase in the avian brain. Brain Res. 899 (1–2), 112–122.

McCarthy, M.M., Pickett, L.A., VanRyzin, J.W., Kight, K.E., 2015. Surprising origins of sex differences in the brain. Horm. Behav. 76, 3–10. https://doi.org/10.1016/j.yhbeh.2015.04.013.

McCormick, C.M., Teillon, S.M., 2001. Menstrual cycle variation in spatial ability: relation to salivary cortisol levels. Horm. Behav. 39 (1), 29–38. https://doi.org/10.1006/hbeh.2000.1636.

McGaugh, J.L., 2000. Memory-a century of consolidation. Science 287 (5451), 248–251.

McGaugh, J.L., 2004. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu. Rev. Neurosci. 27, 1–28. https://doi.org/10.1146/annurev.neuro.27.070203.144157.

McLean, C.P., Asnaani, A., Litz, B.T., Hofmann, S.G., 2011. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J. Psychiatr. Res. 45 (8), 1027–1035. https://doi.org/10.1016/j.jpsychires.2011.03.006.

Mehta, D., Gonik, M., Klengel, T., Rex-Haffner, M., Menke, A., Rubel, J., et al., 2011. Using polymorphisms in FKBP5 to define biologically distinct subtypes of posttraumatic stress disorder: evidence from endocrine and gene expression studies. Arch. Gen. Psychiatry 68 (9), 901–910. https://doi.org/10.1001/archgenpsychiatry.2011.50.

Milad, M.R., Zeidan, M.A., Contero, A., Pitman, R.K., Klibanski, A., Rauch, S.L., Goldstein, J.M., 2010. The influence of gonadal hormones on conditioned fear extinction in healthy humans. Neuroscience 168 (3), 652–658. https://doi.org/10.1016/j.neuroscience.2010.04.030.

Miller, W.L., Auchus, R.J., 2011. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr. Rev. 32 (1), 81–151. https://doi.org/10.1210/er.2010-0013.

Minichiello, L., 2009. TrkB signalling pathways in LTP and learning. Nat. Rev. Neurosci. 10 (12), 850–860. https://doi.org/10.1038/nrn2738.

Molteni, R., Calabrese, F., Cattaneo, A., Mancini, M., Gennarelli, M., Racagni, G., Riva, M.A., 2008. Acute stress responsiveness of the neurotrophin BDNF in the rat Hippocampus is modulated by chronic treatment with the antidepressant duloxetine. Neuropsychopharmacology 34, 1523. https://doi.org/10.1038/npp.2008.208.

Morali, G., Letechipia-Vallejo, G., Lopez-Loeza, E., Montes, P., Hernandez-Morales, L., Cervantes, M., 2005. Post-ischemic administration of progesterone in rats exerts neuroprotective effects on the hippocampus. Neurosci. Lett. 382 (3), 286–290. https://doi.org/10.1016/j.neulet.2005.03.066.

Murakami, S., Imbe, H., Morikawa, Y., Kubo, C., Senba, E., 2005. Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. Neurosci. Res. 53 (2), 129–139. https://doi.org/10.1016/j.neures.2005.06.008.

Muzik, M., McGinnis, E.W., Bocknek, E., Morelen, D., Rosenblum, K.L., Liberzon, I., et al., 2016. PTSD symptoms across pregnancy and early postpartum among women with lifetime PTSD DIAGNOSIS. Depress. Anxiety 33 (7), 584–591. https://doi.org/10.1002/da.22465.

Natale, V., Albertazzi, P., Zini, M., Di Micco, R., 2001. Exploration of cyclical changes in memory and mood in postmenopausal women taking sequential combined oestrogen and progestogen preparations. Br. J. Obstet. Gynaecol. 108 (3), 286–290. https://doi.org/10.1016/S0306-5456(00)00070-X.

Nepomnaschy, P.A., Altman, R.M., Watterson, R., Co, C., McConnell, D.S., England, B.G., 2011. Is cortisol excretion independent of menstrual cycle day? A longitudinal evaluation of first morning urinary specimens. PLoS One 6 (3), e18242. https://doi.org/10.1371/journal.pone.0018242.

Ney, L.J., Matthews, A., Bruno, R., Felmingham, K.L., 2018. Modulation of the endocannabinoid system by sex hormones: implications for Posttraumatic Stress Disorder. Neurosci. Biobehav. Rev. 94, 302–320. https://doi.org/10.1016/j.neubiorev.2018.07.006.

Nicholson, E.L., Bryant, R.A., Felmingham, K.L., 2014. Interaction of noradrenaline and cortisol predicts negative intrusive memories in posttraumatic stress disorder. Neurobiol. Learn. Mem. 112, 204–211. https://doi.org/10.1016/j.nlm.2013.11.018.

Nillni, Y.I., Pineles, S.L., Patton, S.C., Rouse, M.H., Sawyer, A.T., Rasmusson, A.M., 2015. Menstrual cycle effects on psychological symptoms in women with PTSD. J. Trauma. Stress 28 (1), 1–7. https://doi.org/10.1002/jts.21984.

Oettel, M., Mukhopadhyay, A.K., 2004. Progesterone: the forgotten hormone in men? Aging Male 7 (3), 236–257.

Olff, M., Langeland, W., Draijer, N., Gersons, B.P., 2007. Gender differences in posttraumatic stress disorder. Psychol. Bull. 133 (2), 183–204. https://doi.org/10.1037/0033-2909.133.2.183.

Onoye, J.M., Shafer, L.A., Goebert, D.A., Morland, L.A., Matsu, C.R., Hamagami, F., 2013. Changes in PTSD symptomatology and mental health during pregnancy and postpartum. Arch. Womens Ment. Health 16 (6), 453–463. https://doi.org/10.1007/s00737-013-0365-8.

Pabon, J.E., Li, X., Lei, Z.M., Sanfilippo, J.S., Yussman, M.A., Rao, C.V., 1996. Novel presence of luteinizing hormone/chorionic gonadotropin receptors in human adrenal glands. J. Clin. Endocrinol. Metab. 81 (6), 2397–2400. https://doi.org/10.1210/jcem.81.6.8964884.

Payne, A.H., Hales, D.B., 2004. Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. Endocr. Rev. 25 (6), 947–970. https://doi.org/10.1210/er.2003-0030.

Pineles, S.L., Nillni, Y.I., King, M.W., Patton, S.C., Bauer, M.R., Mostoufi, S.M., et al., 2016. Extinction retention and the menstrual cycle: different associations for women with posttraumatic stress disorder. J. Abnorm. Psychol. 125 (3), 349–355. https://doi.org/10.1037/abn0000138.

Pineles, S.L., Nillni, Y.I., Pinna, G., Irvine, J., Webb, A., Arditte Hall, K.A., et al., 2018. PTSD in women is associated with a block in conversion of progesterone to the GABAergic neurosteroids allopregnanolone and pregnanolone measured in plasma. Psychoneuroendocrinology 93, 133–141. https://doi.org/10.1016/j.psyneuen.2018.04.024.

Pitman, R.K., 1989. Post-traumatic stress disorder, hormones, and memory. Biol. Psychiatry 26, 221–223.

Pitman, R.K., Delahanty, D.L., 2005. Conceptually driven pharmacological approaches to acute trauma. CNS Spectr. 10 (2), 99–106. https://doi.org/10.1017/S109285290001943X.

Pitman, R.K., Rasmusson, A.M., Koenen, K.C., Shin, L.M., Orr, S.P., Gilbertson, M.W., et al., 2012. Biological studies of post-traumatic stress disorder. Nat. Rev. Neurosci. 13 (11), 769–787. https://doi.org/10.1038/nrn3339.

Pitts, B.L., Whealin, J.M., Harpaz-Rotem, I., Duman, R.S., Krystal, J.H., Southwick, S.M., Pietrzak, R.H., 2019. BDNF Val66Met polymorphism and posttraumatic stress symptoms in U.S. Military veterans: protective effect of physical exercise. Psychoneuroendocrinology 100, 198–202. https://doi.org/10.1016/j.psyneuen.2018.10.011.

Polachek, I.S., Dulitzky, M., Margolis-Dorfman, L., Simchen, M.J., 2016. A simple model for prediction postpartum PTSD in high-risk pregnancies. Arch. Womens Ment. Health 19 (3), 483–490. https://doi.org/10.1007/s00737-015-0582-4.

Polachek, I.S., Harari, L.H., Baum, M., Strous, R.D., 2012. Postpartum post-traumatic stress disorder symptoms: the uninvited birth companion. Isr. Med. Assoc. J. 14 (6), 347–353.

Rao, C.V., Zhou, X.L., Lei, Z.M., 2004. Functional luteinizing Hormone/Chorionic gonadotropin receptors in human adrenal cortical H295R cells. Biol. Reprod. 71 (2), 579–587. https://doi.org/10.1095/biolreprod.104.027300.

Rasmusson, A.M., Marx, C.E., Pineles, S.L., Locci, A., Scioli-Salter, E.R., Nillni, Y.I., et al., 2017. Neuroactive steroids and PTSD treatment. Neurosci. Lett. 649, 156–163. https://doi.org/10.1016/j.neulet.2017.01.054.

Rattel, J.A., Wegerer, M., Miedl, S.F., Blechert, J., Grünberger, L.M., Craske, M.G., Wilhelm, F.H., 2019. Peritraumatic unconditioned and conditioned responding explains sex differences in intrusions after analogue trauma. Behav. Res. Ther. 116, 19–29. https://doi.org/10.1016/j.brat.2019.01.009.

Ressler, K.J., Mercer, K.B., Bradley, B., Jovanovic, T., Mahan, A., Kerley, K., et al., 2011. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature 470 (7335), 492–497. https://doi.org/10.1038/nature09856.

Roca, C.A., Schmidt, P.J., Altemus, M., Deuster, P., Danaceau, M.A., Putnam, K., Rubinow, D.R., 2003. Differential menstrual cycle regulation of hypothalamic-pituitary-adrenal axis in women with premenstrual syndrome and controls. J. Clin. Endocrinol. Metab. 88 (7), 3057–3063. https://doi.org/10.1210/jc.2002-021570.

Rombold, F., Wingenfeld, K., Renneberg, B., Hellmann-Regen, J., Otte, C., Roepke, S., 2016. Influence of the noradrenergic and glucocorticoid system on the formation of intrusive memories: an experimental approach with a trauma film paradigm. Psychol. Med. 46 (12), 2523–2534. https://doi.org/10.1017/S0033291716001379.

Roozendaal, B., McEwen, B.S., Chattarji, S., 2009a. Stress, memory and the amygdala. Nat. Rev. Neurosci. 10 (6), 423–433. https://doi.org/10.1038/nrn2651.

Roozendaal, B., McGaugh, J.L., 1997. Glucocorticoid receptor agonist and antagonist administration into the basolateral but not central amygdala modulates memory storage. Neurobiol. Learn. Mem. 67, 176–179.

Roozendaal, B., McGaugh, J.L., 2011. Memory modulation. Behav. Neurosci. 125 (6), 797–824. https://doi.org/10.1037/a0026187.

Roozendaal, B., McReynolds, J.R., Van der Zee, E.A., Lee, S., McGaugh, J.L., McIntyre, C.K., 2009b. Glucocorticoid effects on memory consolidation depend on functional interactions between the medial prefrontal cortex and basolateral amygdala. J. Neurosci. 29 (45), 14299–14308. https://doi.org/10.1523/JNEUROSCI.3626-09.2009.

Roozendaal, B., Schelling, G., McGaugh, J.L., 2008. Corticotropin-releasing factor in the basolateral amygdala enhances memory consolidation via an interaction with the beta-adrenoceptor-cAMP pathway: dependence on glucocorticoid receptor activation. J. Neurosci. 28 (26), 6642–6651. https://doi.org/10.1523/JNEUROSCI.1336-08.2008.

Rupprecht, R., Papadopoulos, V., Rammes, G., Baghai, T.C., Fan, J., Akula, N., et al., 2010. Translocator protein (18 kDa) (TSPO) as a therapeutic target for neurological and psychiatric disorders. Nat. Rev. Drug Discov. 9 (12), 971–988. https://doi.org/10.1038/nrd3295.

Sandhu, N., Vijayan, M.M., 2011. Cadmium-mediated disruption of cortisol biosynthesis involves suppression of corticosteroidogenic genes in rainbow trout. Aquat. Toxicol.

103 (1), 92–100. https://doi.org/10.1016/j.aquatox.2011.02.011.

Sasahara, K., Shikimi, H., Haraguchi, S., Sakamoto, H., Honda, S., Harada, N., Tsutsui, K., 2007. Mode of action and functional significance of estrogen-inducing dendritic growth, spinogenesis, and synaptogenesis in the developing Purkinje cell. J. Neurosci. 27 (28), 7408–7417. https://doi.org/10.1523/jneurosci.0710-07.2007.

Sattari, N., McDevitt, E.A., Panas, D., Niknazar, M., Ahmadi, M., Naji, M., et al., 2017. The effect of sex and menstrual phase on memory formation during a nap. Neurobiol. Learn. Mem. 145, 119–128. https://doi.org/10.1016/j.nlm.2017.09.007.

Saxena, A.R., Seely, E.W., 2012. Luteinizing hormone correlates with adrenal function in postmenopausal women. Menopause 19 (11), 1280–1283. https://doi.org/10.1097/gme.0b013e31825540c4.

Scharfman, H.E., MacLusky, N.J., 2006. Estrogen and brain-derived neurotrophic factor (BDNF) in hippocampus: complexity of steroid hormone-growth factor interactions in the adult CNS. Front. Neuroendocrinol. 27 (4), 415–435. https://doi.org/10.1016/j.yfrne.2006.09.004.

Schiller, C.E., Meltzer-Brody, S., Rubinow, D.R., 2015. The role of reproductive hormones in postpartum depression. CNS Spectr. 20 (1), 48–59. https://doi.org/10.1017/S1092852914000480.

Schoemaker, N.J., Teerds, K.J., Mol, J.A., Lumeij, J.T., Thijssen, J.H., Rijnberk, A., 2002. The role of luteinizing hormone in the pathogenesis of hyperadrenocorticism in neutered ferrets. Mol. Cell. Endocrinol. 197 (1–2), 117–125.

Schumacher, M., Mattern, C., Ghoumari, A., Oudinet, J.P., Liere, P., Labombarda, F., et al., 2014. Revisiting the roles of progesterone and allopregnanolone in the nervous system: resurgence of the progesterone receptors. Prog. Neurobiol. 113, 6–39. https://doi.org/10.1016/j.pneurobio.2013.09.004.

Seng, J.S., Rauch, S.A., Resnick, H., Reed, C.D., King, A., Low, L.K., et al., 2010. Exploring posttraumatic stress disorder symptom profile among pregnant women. J. Psychosom. Obstet. Gynaecol. 31 (3), 176–187. https://doi.org/10.3109/0167482x.2010.486453.

Sherwin, B.B., 2012. Estrogen and cognitive functioning in women: lessons we have learned. Behav. Neurosci. 126 (1), 123–127. https://doi.org/10.1037/a0025539.

Shi, S.S., Shao, S.H., Yuan, B.P., Pan, F., Li, Z.L., 2010. Acute stress and chronic stress change brain-derived neurotrophic factor (BDNF) and tyrosine kinase-coupled receptor (TrkB) expression in both young and aged rat hippocampus. Yonsei Med. J. 51 (5), 661–671. https://doi.org/10.3349/ymj.2010.51.5.661.

Shin, L.M., Rauch, S.L., Pitman, R.K., 2006. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann. N. Y. Acad. Sci. 1071 (1), 67–79. https://doi.org/10.1196/annals.1364.007.

Silove, D., Baker, J.R., Mohsin, M., Teesson, M., Creamer, M., O'Donnell, M., et al., 2017. The contribution of gender-based violence and network trauma to gender differences in Post-Traumatic Stress Disorder. PLoS One 12 (2), e0171879. https://doi.org/10.1371/journal.pone.0171879.

Singh, M., Su, C., 2013. Progesterone, brain-derived neurotrophic factor and neuroprotection. Neuroscience 239, 84–91. https://doi.org/10.1016/j.neuroscience.2012.09.056.

Smith, M.V., Poschman, K., Cavaleri, M.A., Howell, H.B., Yonkers, K.A., 2006. Symptoms of posttraumatic stress disorder in a community sample of low-income pregnant women. Am. J. Psychiatry 163 (5), 881–884. https://doi.org/10.1176/ajp.2006.163.5.881.

Smith, R., Smith, J.I., Shen, X., Engel, P.J., Bowman, M.E., McGrath, S.A., et al., 2009. Patterns of plasma corticotropin-releasing hormone, progesterone, estradiol, and estriol change and the onset of human labor. J. Clin. Endocrinol. Metab. 94 (6), 2066–2074. https://doi.org/10.1210/jc.2008-2257.

Soderquist, J., Wijma, B., Thorbert, G., Wijma, K., 2009. Risk factors in pregnancy for post-traumatic stress and depression after childbirth. Bjog 116 (5), 672–680. https://doi.org/10.1111/j.1471-0528.2008.02083.x.

Soderquist, J., Wijma, B., Wijma, K., 2006. The longitudinal course of post-traumatic stress after childbirth. J. Psychosom. Obstet. Gynaecol. 27 (2), 113–119.

Sohrabji, F., Miranda, R.C., Toran-Allerand, C.D., 1995. Identification of a putative estrogen response element in the gene encoding brain-derived neurotrophic factor. Proc. Natl. Acad. Sci. U.S.A. 92 (24), 11110–11114.

Soni, M., Curran, V.H., Kamboj, S.K., 2013. Identification of a narrow post-ovulatory window of vulnerability to distressing involuntary memories in healthy women. Neurobiol. Learn. Mem. 104, 32–38. https://doi.org/10.1016/j.nlm.2013.04.003.

Stenmark, H., Guzey, I.C., Elbert, T., Holen, A., 2014. Gender and offender status predicting treatment success in refugees and asylum seekers with PTSD. Eur. J. Psychotraumatol. 5https://doi.org/10.3402/ejpt.v5.20803. 10.3402/ejpt.v3405.20803.

Su, C., Cunningham, R.L., Rybalchenko, N., Singh, M., 2012. Progesterone increases the release of brain-derived neurotrophic factor from glia via progesterone receptor membrane component 1 (Pgrmc1)-Dependent ERK5 signaling. Endocrinology 153 (9), 4389–4400. https://doi.org/10.1210/en.2011-2177.

Sun, J., Walker, A.J., Dean, B., van den Buuse, M., Gogos, A., 2016. Progesterone: the neglected hormone in schizophrenia? A focus on progesterone-dopamine interactions. Psychoneuroendocrinology 74, 126–140. https://doi.org/10.1016/j.psyneuen.2016.08.019.

Tasker, J.G., Herman, J.P., 2011. Mechanisms of rapid glucocorticoid feedback inhibition of the hypothalamic-pituitary-adrenal axis. Stress 14 (4), 398–406. https://doi.org/10.3109/10253890.2011.586446.

Taves, M.D., Gomez-Sanchez, C.E., Soma, K.K., 2011. Extra-adrenal glucocorticoids and mineralocorticoids: evidence for local synthesis, regulation, and function. American Journal of Physiology - Endocrinology and Metabolism 301 (1), E11–E24. https://doi.org/10.1152/ajpendo.00100.2011.

Tock, L., Carneiro, G., Pereira, A.Z., Tufik, S., Zanella, M.T., 2014. Adrenocortical production is associated with higher levels of luteinizing hormone in nonobese women with polycystic ovary syndrome. Int. J. Endocrinol. 2014, 620605. https://doi.org/10.1155/2014/620605.

Tolin, D.F., Foa, E.B., 2006. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. Psychol. Bull. 132 (6), 959–992. https://doi.org/10.1037/0033-2909.132.6.959.

Toufexis, D., Rivarola, M.A., Lara, H., Viau, V., 2014. Stress and the reproductive axis. J. Neuroendocrinol. 26 (9), 573–586. https://doi.org/10.1111/jne.12179.

Tulchinsky, D., Hobel, C.J., 1973. Plasma human chorionic gonadotropin, estrone, estradiol, estriol, progesterone, and 17α-hydroxyprogesterone in human pregnancy: III. Early normal pregnancy. Am. J. Obstet. Gynecol. 117 (7), 884–893. https://doi.org/10.1016/0002-9378(73)90057-4.

Tulchinsky, D., Hobel, C.J., Yeager, E., Marshall, J.R., 1972. Plasma estrone, estradiol, estriol, progesterone, and 17-hydroxyprogesterone in human pregnancy: I. Normal pregnancy. Am. J. Obstet. Gynecol. 112 (8), 1095–1100. https://doi.org/10.1016/0002-9378(72)90185-8.

van Stegeren, A.H., Wolf, O.T., Kindt, M., 2008. Salivary alpha amylase and cortisol responses to different stress tasks: impact of sex. Int. J. Psychophysiol. 69 (1), 33–40. https://doi.org/10.1016/j.ijpsycho.2008.02.008.

van Wingen, G., van Broekhoven, F., Verkes, R.J., Petersson, K.M., Backstrom, T., Buitelaar, J., Fernandez, G., 2007. How progesterone impairs memory for biologically salient stimuli in healthy young women. J. Neurosci. 27 (42), 11416–11423. https://doi.org/10.1523/JNEUROSCI.1715-07.2007.

Wade, D., Varker, T., Kartal, D., Hetrick, S., O'Donnell, M., Forbes, D., 2016. Gender difference in outcomes following trauma-focused interventions for posttraumatic stress disorder: systematic review and meta-analysis. Psychol. Trauma 8 (3), 356–364. https://doi.org/10.1037/tra0000110.

Walder, D.J., Statucka, M., Daly, M.P., Axen, K., Haber, M., 2012. Biological sex and menstrual cycle phase modulation of cortisol levels and psychiatric symptoms in a non-clinical sample of young adults. Psychiatry Res. 197 (3), 314–321. https://doi.org/10.1016/j.psychres.2011.09.009.

Wassell, J., Rogers, S., Felmingham, K.L., Pearson, J., Bryant, R.A., 2015. Progesterone and mental imagery interactively predict emotional memories. Psychoneuroendocrinology 51, 1–10. https://doi.org/10.1016/j.psyneuen.2014.09.005.

Wegerer, M., Kerschbaum, H., Blechert, J., Wilhelm, F.H., 2014. Low levels of estradiol are associated with elevated conditioned responding during fear extinction and with intrusive memories in daily life. Neurobiol. Learn. Mem. 116, 145–154. https://doi.org/10.1016/j.nlm.2014.10.001.

Weiser, M.J., Handa, R.J., 2009. Estrogen impairs glucocorticoid dependent negative feedback on the hypothalamic-pituitary-adrenal axis via estrogen receptor alpha within the hypothalamus. Neuroscience 159 (2), 883–895. https://doi.org/10.1016/j.neuroscience.2008.12.058.

White, E.C., Graham, B.M., 2016. Estradiol levels in women predict skin conductance response but not valence and expectancy ratings in conditioned fear extinction. Neurobiol. Learn. Mem. 134 (Pt B), 339–348. https://doi.org/10.1016/j.nlm.2016.08.011.

Wijma, K., Soderquist, J., Wijma, B., 1997. Posttraumatic stress disorder after childbirth: a cross sectional study. J. Anxiety Disord. 11 (6), 587–597.

Wirth, M.M., 2011. Beyond the HPA axis: progesterone-derived neuroactive steroids in human stress and emotion. Front. Endocrinol. (Lausanne) 2 (19), 373–386. https://doi.org/10.3389/endo.2011.00019.

Wirth, M.M., Meier, E.A., Fredrickson, B.L., Schultheiss, O.C., 2007. Relationship between salivary cortisol and progesterone levels in humans. Biol. Psychol. 74 (1), 104–107. https://doi.org/10.1016/j.biopsycho.2006.06.007.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., et al., 2011. The size andburden of mental disorders and other disorders of thebrain in Europe 2010. Eur. Neuropsychopharmacol. 21 (9), 655–679. https://doi.org/10.1016/j.euroneuro.2011.07.018.

Yu, L., Romero, D.G., Gomez-Sanchez, C.E., Gomez-Sanchez, E.P., 2002. Steroidogenic enzyme gene expression in the human brain. Mol. Cell. Endocrinol. 190 (1), 9–17. https://doi.org/10.1016/S0303-7207(02)00041-2.

Zeidan, M.A., Igoe, S.A., Linnman, C., Vitalo, A., Levine, J.B., Klibanski, A., et al., 2011. Estradiol modulates medial prefrontal cortex and amygdala activity during fear extinction in women and female rats. Biol. Psychiatry 70 (10), 920–927. https://doi.org/10.1016/j.biopsych.2011.05.016.