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Neuroendocrine pathways underlying risk and resilience to PTSD in women

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ABSTRACT

Women are twice as likely than men to suffer from posttraumatic stress disorder (PTSD). While women have increased exposure to traumatic events of many types and have greater prevalence of comorbid psychiatric disorders compared to men, these differences do not account for the overall sex difference in the prevalence of PTSD. The current review summarizes significant findings that implicate the role of estradiol, progesterone, and allopregnanolone in female risk for PTSD symptoms and dysregulation of fear psychophysiology that is cardinal to PTSD. We also discuss how these steroid hormones influence the stress axis and neural substrates critical for the regulation of fear responses. Understanding the role of ovarian steroid hormones in risk and resilience for trauma-related adverse mental health outcomes across the lifespan in women has important translational, clinical, and intergenerational implications for mitigating the consequences of trauma exposure.

1. Introduction

Post-traumatic stress disorder (PTSD) is a debilitating psychiatric condition that occurs after exposure to a psychological traumatic event (Dedert et al., 2010). Epidemiological studies indicate that approximately 70% of the general population will experience a traumatic event in their lifetime, but only 7.8% of the general population in the United States will go on to develop PTSD (Keane et al., 2009). Prospective studies indicate that while the majority of trauma victims experience the cardinal symptoms of PTSD, including re-experiencing, avoidance, and hyperarousal, immediately following trauma (Rothbaum et al., 1992), for most trauma survivors these symptoms subside and eventually disappear (Rothbaum et al., 1992). For a significant minority, however, the symptoms persist and develop into syndromal PTSD that is associated with significant comorbidities including major depression (Rytwinski et al., 2013), substance and alcohol abuse (Pietrzak et al., 2011), suicide (Thibodeau et al., 2013), and cardiometabolic disease (Boscarino, 2008; Weiss et al., 2011).

PTSD is a heterogeneous psychiatric syndrome that is characterized by re-experiencing, avoidance, hyperarousal symptoms, and negative cognitions (Apa, 2013). The etiology and maintenance of PTSD is linked to deficits in fear regulation, including increased fear response and deficits in fear extinction (Jovanovic et al., 2012; Norrholm et al., 2015, 2011), that are assessed in humans and in rodents by objectively measuring psychophysiological changes, such as skin conductance or startle responses, in response to fear conditioning paradigms (Davis, 1992; Fendt and Fanselow, 1999; Maren, 2001; Jovanovic et al., 2005). Classical fear conditioning paradigms typically consist of a habituation phase, a fear conditioning (acquisition) phase, and a fear extinction phase (Fig. 1. In the habituation phase, subjects become familiar with the study environment. In the fear-conditioning phase (acquisition), a neutral stimulus (conditioned stimulus; CS) is paired with an aversive unconditioned stimulus (such as a mild shock or aversive air blast; US). In the fear extinction phase, the CS is no longer presented with the aversive US, and participants should be able to dissociate the CS from danger. An extinction recall phase is sometimes used to assess the presence of fear extinction learning acquired during the extinction phase of the paradigm. Some paradigms have multiple neutral stimuli, where only one (CS+) is paired with the US (danger cue) while the other (CS−) is not (safety cue). These fear-conditioning paradigms can assess stimulus (CS+ vs. CS−) and context discrimination (environment or cue-based), as well as fear generalization, the expression of fear in inappropriate contexts. Deficits in fear inhibition during fear conditioning are analogous to the fear generalization symptoms seen in PTSD, while deficits in fear extinction and extinction recall point to the re-experiencing and hyperarousal symptoms characteristic of PTSD in traumatized individuals (Jovanovic et al., 2012).

Many studies over the last few decades have identified

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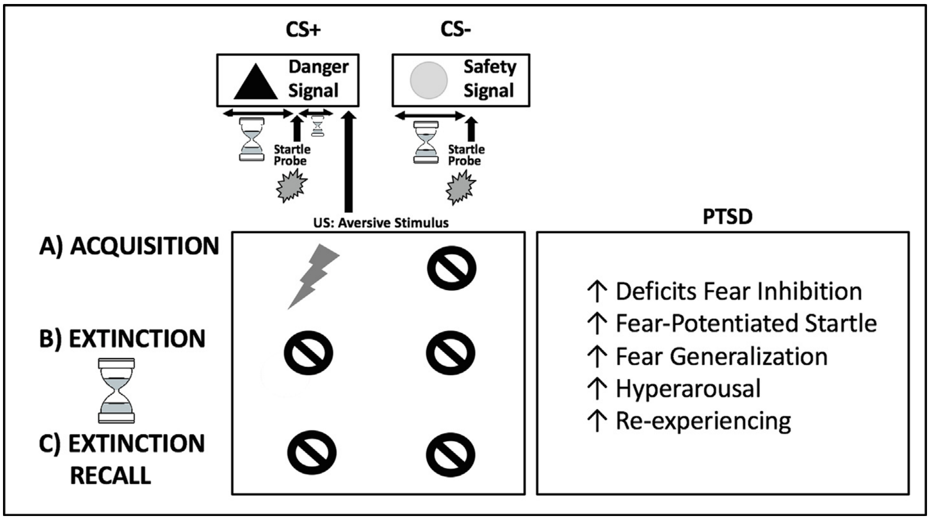


Fig. 1. *Illustration of fear conditioning paradigms and fear responses related to PTSD.* Classical fear conditioning paradigms typically consist of a (A) conditioning (acquisition) phase, an (B) extinction phase, and sometimes an (C) extinction recall phase. In the conditioning phase (acquisition), a neutral stimulus (conditioned stimulus; CS) is paired with an aversive unconditioned stimulus (US; such as a mild shock or aversive air blast). Some paradigms have multiple neutral stimuli, where only one (CS+; danger cue) is paired with the aversive US while the other (CS−; safety cue) is not. In the extinction phase, the CS+ is no longer presented with the aversive US, and participants should learn to dissociate the CS from danger. In some paradigms, recall of the extinction memory (dissociation of the CS+ from danger) is assessed at a later time (extinction retention phase). Fear potentiated startle is another paradigm used, in which the startle response is measured in response to a loud but harmless tone (startle probe) in the presence of the CS+ and CS−. Deficits in fear inhibition during fear conditioning are analogous to the increased fear and fear generalization symptoms seen in PTSD, while deficits in extinction and extinction recall point to the re-experiencing and hyperarousal symptoms characteristic of PTSD.

environmental risk factors for individual vulnerability to the development of PTSD in trauma survivors, including severity and duration of trauma, childhood abuse and lack of family and social support (Breslau, 2001; Roberts et al., 2012). Recent work has also identified genetic factors that influence individual susceptibility to PTSD, as PTSD is 30–40% heritable (Stein et al., 2002). Candidate gene studies suggest that genetic polymorphisms at loci that influence the activity of biological mechanisms, including the stress axis and fear circuitry, increase individual vulnerability to the development of PTSD (Michopoulos et al., 2015).

One factor known to affect risk for and severity of PTSD is biological sex, as women are twice as likely than men to suffer from PTSD (Breslau, 2001; Kessler et al., 1995; Olff et al., 2007; Tolin and Foa, 2006). While women have increased exposure to traumatic events that confer greater risk for PTSD and have greater prevalence of comorbid psychiatric disorders compared to men, these differences do not account for the overall sex difference in the prevalence of PTSD (Breslau et al., 1999; Kessler et al., 1995; Olff et al., 2007). In the current non-systematic review, we will summarize significant findings that implicate the role of ovarian steroid hormones in female risk for PTSD symptoms and dysregulation of fear psychophysiology that is cardinal to PTSD. More specifically, we will summarize how natural fluctuations in estradiol, progesterone and its metabolite allopregnanolone, the primary endogenous female steroid hormones, over the ovarian cycle of women are associated with changes in PTSD symptoms and how these hormones influence neural substrates critical for the regulation of fear responses. In parallel, we will highlight translational and preclinical animal model studies that manipulate ovarian steroid hormones to assess their mechanistic role in PTSD pathophysiology. Understanding the role of ovarian steroid hormones in risk and resilience for trauma-related adverse mental health outcomes has important translational, clinical, and intergenerational implications for mitigating the consequences of trauma exposure.

2. Physiology of ovarian hormone fluctuations over the menstrual cycle

Estradiol (E2) is the primary endogenous estrogen that is produced by the aromatase enzyme, which converts testosterone into E2. E2 acts primarily via estrogen receptors alpha (ERα) and beta (ERβ), both nuclear steroid hormone receptor transcription factors that are localized within the cell nucleus where once the ligand binds, dimerize to bind estrogen response elements within promoter regions of DNA to influence gene transcription (Nilsson et al., 2001). While ERα and ERβ mediate most central E2 effects, it is important to note that these two receptors can also interact with other transcription factors when they are not bound to E2 (Kushner et al., 2000). These non-classical effects of E2 receptors have been labeled as ligand-independent (Blaustein, 2004).

Progesterone (P4) is the primary endogenous progestin that is synthesized from cholesterol and pregnanolone by cytochrome P45017 and 3β-hydroxysteroid-dehydrogenase (3β-HSD), respectively (Pineles et al., 2018). P4 influences gene transcription via its own steroid hormone receptor transcription factor, the progesterone receptor (PR) (Schumacher et al., 2014), whose expression is increased by E2 (Leavitt et al., 1977). Progesterone can have fast-acting, neuroactive effects via its conversion to its metabolite, 3α-5α- tetrahydroprogesterone, more commonly known as allopregnanolone. Allopregnanolone is a positive allosteric modulator of γ-aminobutyric acid ($GABA_A$) receptors that is ten times more potent than benzodiazepines (Majewska et al., 1986). This conversion of progesterone to allopregnanolone is a two-step process, requiring 5α-reductase to convert progesterone into 5α-dihydroprogesterone (5α-DHP), and 3α-hydroxysteroid-dehydrogenase (3α-HSD) to convert 5α-DHP into allopregnanolone (Majewska et al., 1986).

Importantly, concentrations E2 and P4 vary over the course of the menstrual cycle in women and non-human primates, and the estrus cycle in rodents. The fluctuations of E2 and P4 are regulated by the fine-tuned control of the hypothalamic-pituitary-gonadal (HPG) axis. More specifically, gonadotropin-releasing hormone (GnRH) is secreted from neurons in the medialbasal hypothalamus in a pulsatile manner (Ordog et al., 1997; Clarke and Cummins, 1982), that in turns binds GnRH receptors in the anterior pituitary to induce the secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) into the vasculature. LH acts on receptors in the theca cells of the ovaries to stimulate androgen synthesis, follicle rupture, and ovulation, while FSH acts to stimulate follicle maturation and increase aromatase activity for E2 biosynthesis from the granulosa cells (Channing et al., 1980).

At the beginning of the ovarian cycle in the early follicular (women) or estrus (rodent) phase, concentrations of E2 are at their with lowest levels due to negative feedback inhibition of the HPG axis (Yamaji et al., 1972). However, over the course of the follicular phase, E2 levels increase steadily due to continued GnRH, and subsequent LH, and FSH release. A switch from negative to positive inhibition of the HPG axis occurs after E2 levels reach a threshold wherein they excite rather than inhibit GnRH neurons (via kisspeptin, reviewed in Kauffman et al.

(2007)), inducing the LH surge that is critical for the induction of ovulation at mid-cycle (Karsch et al., 1973). In the luteal (women) or diestrus (rodent) phase of the ovarian cycle, the ruptured follicle degenerates into the corpus luteum, a body that secretes progesterone in preparation for embryo implantation in the uterus (Channing et al., 1980). Thus, the luteal phase is characterized by an increase in P4 concentrations that wanes slowly over time (Rubinow et al., 1988). E2 concentrations decline following ovulation but rise again following the mid-luteal increase in P4 (Rubinow et al., 1988). In parallel with P4 concentrations, plasma concentrations of allopregnanolone increase in the luteal compared to the follicular phase in women (Pineles et al., 2018; Martinez et al., 2016). Peripheral concentrations of E2, P4, and allopregnanolone all decrease if pregnancy does not occur, triggering menses and the beginning of the next cycle (Rubinow et al., 1988).

Fluctuations in steroid hormones concentrations over the menstrual cycle have been associated with changes in affective symptoms in women, as approximately 20% of reproductive-aged women in the United States experience significant increases in mood and anxiety symptoms in the premenstrual (luteal) phase of the cycle (Strine et al., 2005). Decreasing levels of E2 (Douma et al., 2005; Pigott, 2003; Rapkin et al., 2002) and P4/allopregnanolone (Nappi et al., 2001; Monteleone et al., 2000; Rapkin et al., 1997) in the luteal phase have all been implicated in the etiology of mood dysregulation and premenstrual dysphoric disorder (PMDD), a mood disorder described in the DSM-5 whose onset is defined by menstrual cycle phase (Apa, 2013). Although PMDD is characterized primarily by increases in depressed mood and anhedonia, it is also associated with increased anxiety symptoms (Apa, 2013; Epperson et al., 2012). While low levels of E2 and diminishing concentrations of P4/allopregnanolone have been associated with increased risk for anxiety disorders in the premenstruum (Hantsoo and Epperson, 2017), the role of ovarian steroids in the etiology and maintenance of PTSD in women is less clear.

3. Ovarian hormones influence fear responses in women and rodents

3.1. Menstrual cycle phase impacts memory and fear responses in healthy women

Studies probing memory for emotionally-arousing stimuli demonstrate that menstrual cycle phase is associated with changes in memory across both declarative and non-declarative forms of memory (Table 1). Work across a number of studies leveraging classical fear-conditioning and list-learning tasks links phases of the menstrual cycle with high E2 levels with facilitated learning in humans, particularly for emotionally-arousing stimuli. For example, healthy women in the luteal phase of the menstrual cycle are more likely to experience spontaneous intrusive memories after watching an emotional film and to remember details of an emotional story compared to hearing a neutral story, relative to the early follicular phase (Ferree et al., 2011; Ferree and Cahill, 2009; Nielsen et al., 2013). Women in the early luteal phase are also more likely to experience intrusive memories for several days after watching a stressful film compared to women in the late luteal phase (low E2) or mid-follicular phase (high E2) of the cycle (Soni et al., 2013). Such effects of menstrual cycle phase on emotional declarative memory may not be specific to negative or threatening stimuli, as women in the late-follicular phase of the menstrual cycle are more likely to remember positive images compared to women in the early-follicular phase, but found no effect of cycle phase on memory for negative images (Pompili et al., 2016). However, the findings are not entirely consistent across the literature, as data from at least one study showed that women in the early-follicular phase (low E2 levels) were more likely to remember negative picture stimuli compared to women in the mid-luteal phase (Bayer et al., 2014).

The above-mentioned results from studies assessing the effects of menstrual cycle phase on emotional declarative memory are also not in full concordance with studies leveraging fear-conditioning paradigms to assess menstrual cycle effects on fear memory. For the majority of studies, there was no effect of menstrual cycle phase on the initial learning or acquisition of the fear memory (Milad et al., 2006; Pineles et al., 2016; Lonsdorf et al., 2015). Only one study found an effect on fear acquisition, such that healthy women in the luteal phase of the menstrual cycle displayed stronger acquisition of fear to a threat versus non-threat-linked stimulus (fear discrimination between danger and safety signals), while women in the follicular phase did not (Glover et al., 2013).

Instead, in classical conditioning paradigms, menstrual cycle appears to have stronger effects on fear extinction and particularly the long-term retention of extinction memory (“extinction recall”), which likely rely upon different neural substrates than the initial acquisition of fear. As in the case of emotional declarative memory, fear extinction and extinction recall require the participation of the hippocampus, medial prefrontal cortex, and amygdala, whereas the associations formed during fear acquisition primarily reside within the amygdala (Dunsmoor and Kroes, 2019). Perhaps more importantly, the most consistent effects of cycle phase are observed for extinction recall, such that high-E2 phases of the menstrual cycle are associated with better recall (Pineles et al., 2016; Milad et al., 2010; White and Graham, 2016; Li and Graham, 2016). Such recall paradigms are conducted 24 h after the initial formation of the extinction memory, entailing consolidation processes that depend upon genetic effects for the formation of new stable synapses via transcriptional regulation by ERα, ERβ, and/or PR receptors. Together, such findings suggest that menstrual cycle phase has its strongest effects on transcription-dependent memory consolidation processes.

Discrepancies between studies may also arise from possible confounding of when memory learning, consolidation and recall where assessed relative to menstrual cycle phase at the time of each assessment, as well as methodological differences between studies, such as the specific phenotypes assessed (emotional memory vs. conditioning), and methods of assessment of menstrual cycle phase (Table 1). For example, some studies use self-report measures of menstrual cycle phase based on recall of first day of menses (Milad et al., 2006; Glover et al., 2013), while others measure salivary E2 and P4 concentrations to verify menstrual cycle phase and categorize into follicular vs. luteal (Ferree et al., 2011; Ferree and Cahill, 2009; Nielsen et al., 2013; Soni et al., 2013; Pompili et al., 2016; Bayer et al., 2014). Also contributing to the noise in menstrual cycle influences on fear responses and memory in women is the inherent variation in concentrations of E2 and P4 within menstrual cycle phases themselves (e.g. low E2 during early follicular vs. moderate E2 during mid-follicular vs. high E2 during ovulation/late follicular).

3.2. Menstrual cycle phase influences on PTSD and fear responses in traumatized women

A handful of studies have linked PTSD symptoms with menstrual cycle-related changes in ovarian hormones. Among recently traumatized women, flashback memories—a hallmark symptom of PTSD—were significantly higher during the luteal phase compared to other cycle phases (Bryant et al., 2011). This study also showed that women who reported having experienced the initial trauma during the luteal phase additionally reported greater difficulties with flashbacks (Bryant et al., 2011). However, the evidence must be considered preliminary as the measurement of cycle timing relied on self-report of last menstrual period, a notoriously unreliable timing method (Wilcox et al., 2000), in a relatively small cohort of women ($N = 138$). The only other study assessing the effects of menstrual cycle phase (confirmed by E2/P4 hormone assays) on PTSD symptoms ($N = 49$) found that some PTSD symptoms are exacerbated in the early follicular phase of the menstrual cycle as opposed to the mid-luteal phase (Nillni et al., 2015). More specifically, women with PTSD show higher depression and

Table 1
Summary of clinical data assessing the effects of menstrual cycle phase and E2 levels on fear acquisition, extinction, extinction recall and inhibition in women.

Clinical status	Reference	Sample size	Phenotype assessed	Menstrual cycle phase or hormone assessment	Effect of E2 or higher-E2 cycle phase
Healthy	Feree et al.	40 (19 follicular phase, 21 luteal phase); 48 (16 follicular phase, 16 luteal phase, 16 men)	Emotional declarative memory	Menstrual cycle phase confirmed by salivary E2/P4	↑ intrusive recollection of negative stimuli
Healthy	Nielsen et al.	98 (28 follicular phase, 31 luteal phase, 39 men)	Emotional declarative memory	Menstrual cycle phase confirmed by salivary E2/P4	↑ arousal-related enhancement of recall
Healthy	Soni et al.	42 (11 late luteal phase, 15 early luteal phase, 15 mid-follicular phase)	Emotional declarative memory	Menstrual cycle phase confirmed by salivary E2/P4	↑ intrusive recollection of negative stimuli
Healthy	Bayer et al.	22 (early follicular, and mid-luteal)	Emotional declarative memory	Menstrual cycle phase confirmed by salivary E2/P4	↓ declarative memory for negative emotional stimuli
Healthy	Pompili et al.	38 (20 early follicular phase, 18 peri-ovulatory phase)	Emotional declarative memory	Menstrual cycle phase confirmed by salivary E2/P4	No effect on declarative memory for negative stimuli;↑ declarative memory for positive stimuli
Healthy	Glover et al.	28 (14 follicular phase, 14 luteal phase)	Classical conditioning	Menstrual cycle phase (self-report based on first day of menses)	↑ fear acquisition to danger signal; ↑ fear discrimination
Healthy	Milad et al.	28 (14 early follicular phase, 14 late follicular phase)	Classical conditioning	Menstrual cycle phase (self-report based on first day of menses)	No cycle effect on fear acquisition; ↓ extinction recall
Healthy	Lonsdorf et al.	337 (18 follicular, 22 luteal, 172 hormonal contraceptives, 116 men)	Classical conditioning	Menstrual cycle phase, self-report; Hormonal contraceptive use	No cycle effect on fear inhibition; No cycle effect on extinction; Contraceptives (low E2/P4) ↓ fear inhibition
Healthy*	Pineles et al.	16 (repeated-measures in early follicular and mid-luteal phases)	Classical conditioning	Menstrual cycle phase, assessed by ovulation kit, confirmed by plasma E2/P4	No effect on acquisition; ↑ extinction recall
Healthy	Wegerer et al.	37 (16 early follicular phase, 21 luteal phase)	Classical conditioning (violent film clips as US)	Salivary E2	No effect on acquisition; ↑ fear extinction; ↓ memory for negative stimuli
Healthy*	Glover et al.	49 (24 low E2, 25 high E2)	Classical conditioning	Serum E2	No effect on acquisition; no effect on fear inhibition; no effect on extinction
Healthy	Milad et al.	54 (18 low E2, 18 high E2, 18 men)	Classical conditioning	Serum E2	No effect on acquisition; no effect on extinction training; ↑ extinction recall
Healthy	White & Graham	73 (20 high E2, 19 low E2, 16 hormonal contraceptives, 18 males)	Classical conditioning	Serum E2	No effect on fear inhibition; ↑ extinction recall
Healthy & Spider Phobic	Li & Graham	60 (30 high E2, 30 low E2; 26 healthy, 34 spider phobic)	Classical conditioning (pictures of spiders as CS)	Serum E2	No effect on extinction training; ↑ fear inhibition to CS-; ↑ extinction recall
PTSD*	Glover et al.	44 (22 high E2, 22 low E2); 32 (17 low E2, 15 high E2)	Classical conditioning	Serum E2	No effect on acquisition; ↑ fear inhibition to CS-; ↑ extinction
PTSD*	Pineles et al.	16 (repeated-measures in early follicular and mid-luteal phases)	Classical conditioning	Menstrual cycle phase, assessed by ovulation kit, confirmed by plasma E2/P4	No effect on acquisition; ↓ extinction recall

* Studies that found differences between a healthy group and a patient group are listed twice to distinguish the separate results of E2 in each group.

phobic anxiety during the early follicular phase as compared to the mid-luteal phase confirmed by E2 and P4 concentrations (Nillni et al., 2015). While these limited available data on menstrual cycle phase and PTSD symptoms suggest that different aspects of PTSD symptomology change over the varying phases of the menstrual cycle (with memory-related symptoms such as intrusive recall increasing during the early/mid luteal phase, and anxiety symptoms peaking during the early follicular phase), a more comprehensive, large cohort study is necessary to better describe menstrual cycle effects on PTSD symptomology in traumatized women.

Laboratory-based studies of fear conditioning and extinction show that extinction recall in women with PTSD is impaired during the early luteal phase of the menstrual cycle as confirmed by tracking of the ovulatory LH surge (Pineles et al., 2016). Such findings suggest that the hormonal changes shortly after ovulation (decrease in E2, increase in P4) negatively impact the consolidation and/or post-encoding stabilization of the extinction memory in women with PTSD, with relatively little effect on the initial formation and extinction of fear memory. These results contrast somewhat with the findings from healthy participants, who show greater fear acquisition to threat (Glover et al., 2013), and greater extinction memory (Milad et al., 2006), and worse extinction recall during the follicular phase (Pineles et al., 2016). Together these limited data suggest that menstrual cycle stage influences PTSD symptoms and fear psychophysiology in traumatized women. However, given that there has only been one fear conditioning study in women to assess menstrual cycles effects on PTSD (Pineles et al., 2016), additional work is needed to better understand the effects of ovarian hormone fluctuations on PTSD and fear responses in traumatized women over the menstrual cycle, as well as other periods of significant hormonal change (i.e. menopause, postpartum). Furthermore, the above studies linking menstrual cycle phase to alterations in PTSD symptoms and fear learning do not examine the direct association between steroid hormones concentrations themselves, and PTSD symptoms and fear responses (Table 1). However, many studies in women suggest that concentrations of E2 and P4/allogpregnanolone (independent of menstrual cycle phase) are associated with risk for PTSD and altered fear-learning outcomes.

3.3. Ovarian hormone concentrations are associated with PTSD and fear responses in women

In healthy women, low E2 concentrations are associated with greater intrusive memories after fear conditioning with short and violent film clips as the unconditioned stimuli (Wegerer et al., 2014). Similarly, low E2 concentrations in women are associated with higher PTSD symptoms compared to women with high E2 levels (Glover et al., 2012). Furthermore, low E2 levels are associated with poorer extinction recall, even though women with low E2 levels report a conscious expectation that the CS+ was no longer associated with threat (Milad et al., 2010; White and Graham, 2016; Li and Graham, 2016). In fact, women with high E2 levels do not differ from men in extinction recall, suggesting that E2 is at least partly responsible for the increased vulnerability for PTSD in women (Milad et al., 2010). Use of hormonal contraceptives, which inhibit endogenous E2 production and reduce overall E2 concentrations, is also associated with poorer extinction recall (White and Graham, 2016; Graham and Milad, 2013). Although little experimental work has been conducted, initial evidence suggests that this deficit in extinction recall is rescued by a single oral dose of E2 (Graham and Milad, 2013).

Estradiol levels influence fear extinction training in women as well (Table 1). Healthy women with high endogenous E2 concentrations demonstrate fear stimulus discrimination, lower fear potentiated startle to a safety cue, and lower skin conductance responses during extinction recall, while women with low endogenous E2 levels do not (Glover et al., 2013; Li and Graham, 2016). Healthy women with lower E2 concentrations also display higher skin conductance responses during fear extinction than women with higher E2 concentrations (Wegerer et al., 2014). In women with PTSD, low E2 levels are associated with greater fear potentiated startle during extinction (Glover et al., 2012). Together, these data suggest that lower E2 concentrations may increase vulnerability for PTSD symptoms and poorer fear learning outcomes in traumatized women (Table 1). This notion is supported by a systematic review of the literature on E2 and menstrual cycle phase on fear learning and PTSD (Garcia et al., 2018), as well as data showing that the suppression of endogenous E2 concentration via hormonal contraceptives in healthy women leads to lower stimulus discrimination during extinction recall (Lonsdorf et al., 2015).

While a substantial literature on the effects of E2 on fear-related outcomes exists as described above in women, P4 concentrations have more reliably been used as a way to confirm menstrual cycle phase as opposed to assessing their relationships to PTSD symptoms and fear psychophysiology (Garcia et al., 2018). Thus, only a handful of studies assess the association between P4 concentrations on similar outcomes in healthy women (Garcia et al., 2018), and the results have been equivocal. P4 concentrations are not associated with emotion regulation of psychophysiological fear responses (Graham et al., 2017) or intrusive memories after fear conditioning (Wegerer et al., 2014) in healthy women. P4 levels are also not associated with changes in conditioned fear extinction and recall in healthy women over the menstrual cycle (Zeidan et al., 2011; Milad et al., 2010; White and Graham, 2016). However, salivary P4 concentrations in the luteal phase of the cycle predict spontaneous intrusive memories after exposure to emotional films in healthy women (Ferree et al., 2011), and high P4 concentrations in healthy women during the early-luteal phase predict intrusive memories for several days after watching a stressful film (Soni et al., 2013).

Very few studies assess the relationship between P4/allopregnanlone and PTSD-related outcomes in women with PTSD. Data from a singular study focused on fear extinction showed that extinction recall during the midluteal phase is associated with high P4 concentrations in women with PTSD (Pineles et al., 2016). Plasma and cerebral spinal fluid (CSF) concentrations of allopregnanolone are lower in women with PTSD (Pineles et al., 2018; Rasmusson et al., 2006). This decrease in allopregnanolone occurs in parallel with an increase of its precursor, 5α-DHP (5α-dihydroprogesterone), consistent with the notion of a deficiency in the activity of the allopregnanolone synthetic enzyme 3α-hydroxysteroid dehydrogenase (3α-HSD) (Pineles et al., 2018). PTSD symptom severity is associated with lower allopregnanolone to 5α-DHP ratio in women during the early luteal phase (Pineles et al., 2018). Although these studies indicate that P4 and allopregnanolone impact PTSD-related symptoms and fear extinction, the ability to assess the unique effects of high P4/allopregnanolone on outcomes on interest is difficult due to the fact that P4/allopregnanolone concentrations are high when E2 concentrations are as well (Becker et al., 2005). Significant work in rodent models has addressed this issue by not only assessing the effects of estrus cycle phase on fear-related outcomes, but also by directly manipulating hormones levels.

3.4. Ovarian hormones concentrations are associated with altered fear responses in rodents

Preclinical studies in rodent models highlight the associations between estrus cycle phase and fear psychophysiology. For example, naturally cycling rats in the proestrus phase (high E2 and P4) show better extinction recall compared to rats in the metestrus phase (low E2 and P4) (Graham and Milad, 2013). Rats in the proestrus phase of the estrus cycle also display less freezing behavior (indicative of less fear) during extinction recall compared to rats in the metestrus phase (Milad et al., 2009). This enhanced recall during the proestrus phase in female rats is extinguished when E2 and/or P4 receptor antagonists are administered before extinction training (Milad et al., 2009). Likewise, exogenous administration of E2 and/or P4 prior to extinction training during the metestrus phase results in less freezing during extinction recall, suggesting that differences in extinction recall due to differences in estrus cycle phase are directly influenced by ovarian hormones (Milad et al., 2009).

The above notion is highlighted by data showing that E2 administration 24-hours prior to fear conditioning improves extinction (Rivas-Arancibia and Vazquez-Pereyra, 1994). Furthermore, direct manipulation of endogenous ovarian hormones in female rats via hormonal contraceptive treatment results in more freezing during extinction training and extinction recall compared to naturally cycling rats (Graham and Milad, 2013). This effect is dose-dependent, as higher doses of hormonal contraceptives exacerbate this effect, increasing freezing during extinction and augmenting poorer extinction recall (Graham and Milad, 2013). While these data indicate that high E2 levels may confer resilience by facilitating fear extinction learning, E2 administration during proestrus phase when endogenous E2 concentrations are high results in an impairment of extinction (Graham and Scott, 2018), suggesting that the effects of E2 on extinction processes may work as an inverted U function wherein low and high E2 levels impair extinction and moderate E2 levels facilitate extinction in females (Graham and Scott, 2018). It is important to note however, that the findings of the above studies are limited due to presence of hormonal fluctuations of both E2 and P4. To assess the direct effects of E2 and P4 on fear psychophysiology, studies in rodent models have used hormone replacement following ovariectomy (to remove endogenous hormones) to assess the direct effects of these steroid hormones on fear processes.

Table 2 summarizes findings on direct E2 manipulation and fear learning processes while highlighting methodological differences between studies. Chronic E2 administration over 16 days also facilitates fear extinction of conditioned taste aversion in both gonadectomized male and female rats (Yuan and Chambers, 1999). Replacement of E2 in ovariectomized (OVX) female rats results in fast fear generalization (Lynch et al., 2013), in facilitation of extinction recall (Graham and Daher, 2016), and in decreased freezing in a novel context after contextual fear conditioning (Barker and Galea, 2010; Gupta et al., 2001). While this result suggests that E2 may increase the ability to discriminate between novel and threatening contexts for female rats (Barker and Galea, 2010), other studies provide evidence that high E2 concentrations are associated with poorer fear learning outcomes. For example, OVX mice supplemented with estradiol benzoate for 10 days display greater anxiety-like behavior and more freezing after fear conditioning compared to OVX mice without E2 replacement (Morgan and Pfaff, 2001). This increased freezing after fear conditioning appears when OVX mice are treated with E2 both acutely (two days) and chronically (two weeks) at high doses (Matsumoto et al., 2018). The equivocal nature of these results may be due to alterations in estrogen dosage administered, type of estrogen administered, or type of fear conditioning assessed (contextual versus cue-based). For example, low doses of 17β-estradiol and 17α-estradiol enhance contextual fear conditioning, while high doses impair contextual fear conditioning (Barha et al., 2010). High and low doses of estrone do not have an effect on contextual fear conditioning in old female rats, but a middle dose impairs contextual fear conditioning (Barha et al., 2010).

Studies in female rats indicate that P4 facilitates the recall of fear extinction (Milad et al., 2009), corroborating data showing that replacement of P4 to OVX female mice enhances more general cognitive performance (Frye and Walf, 2008). However, another study showed that fear extinction recall is potentiated by P4 replacement six hours following extinction training in E2-replaced OVX rats, whereas P4's potentiating effects on extinction recall is abolished if extinction training occurs 24 h after P4 is administered (Graham and Daher, 2016). These studies indicate that P4's ability to modulate fear extinction recall in E2-treated OVX rodents is biphasic and dependent on the time interval between P4 replacement and fear extinction training (Graham and Daher, 2016). This notion that timing from maximal P4 concentrations is important for its influence on affective symptoms is further highlighted by data in women showing that withdrawal from high levels of P4/allopregnanolone during the menstrual cycle and in the postpartum period are associated with increased depressive symptoms (Smith, 2002).

Although concentrations of allopregnanolone also fluctuate with those of P4 across the menstrual and estrus cycles, much less research has directly manipulated allopregnanolone levels in preclinical models to assess the neuroactive steroid's influence on fear responses. However, data from translational rodent models of PTSD show that decreases in allopregnanolone are induced by exposure to either prolonged social isolation or a single-prolonged stressor and associated with risk for PTSD-like phenotypes, including enhanced contextual fear condition and deficits in contextual fear extinction and recall (Pibiri et al., 2008; Pinna and Rasmusson, 2014; Zhang et al., 2014). Importantly, these fear deficits in rodents are normalized upon exogenous treatment with allopregnanolone itself (Pibiri et al., 2008), a synthetic analog (ganaxolone) (Pinna and Rasmusson, 2014), and other pharmaceutical agents that increase endogenous allopregnanolone levels in the brain (Zhang et al., 2014), suggesting that allopregnanolone may be an effective treatment for PTSD (Rasmusson et al., 2017).

3.5. Summary, synthesis and caveats

Overall, available preclinical, translational, and clinical data suggest that low levels of E2 in pre-menopausal, reproductive aged women confer risk for increased PTSD symptoms and dysregulation of fear responses, whereas high concentrations of E2 bestow resilience to PTSD and maladaptive alterations in fear psychophysiology in traumatized women by facilitating fear extinction learning and recall (Table 1). This notion that high E2 levels confer resilience to dysregulation of fear responses is corroborated by translational rodent studies (Table 2). Available cross-sectional data also suggest that the effects of E2 and P4 on fear regulation are impacted by the presence of PTSD in women. This is exemplified by findings showing that low E2 is associated with fear extinction deficits only in women with PTSD (Glover et al., 2012), and data showing that fear extinction recall is enhanced in healthy women, but impaired in women with PTSD during the early luteal phase of the menstrual cycle (Pineles et al., 2016).

Although findings from many studies indicate that high E2 status confers resilience from PTSD symptoms and deficits in fear psychophysiology in women (Table 1), there are some inconsistencies in results, including null findings, that may be attributable to methodological differences between studies. For example, Milad and colleagues found that healthy women in the middle of the menstrual cycle (when E2 levels are high) have impaired extinction recall (Milad et al., 2006), while several other studies have found that high E2 is associated with enhanced extinction recall in women (Milad et al., 2010; White and Graham, 2016; Li and Graham, 2016) or that E2 has no effect on extinction (Glover et al., 2012). Subtle differences in the conditioning paradigms used, such as the number of conditioning trials assessed in extinction and how early and late extinction were defined between studies, may contribute to inconsistent results between studies and null findings. Furthermore, the study by Milad and colleagues compared women in different phases of the menstrual cycle and relied solely on self-reporting of menstrual cycle phase by participants, while the other studies assessed absolute E2 concentrations and compared participants based on E2 level (Milad et al., 2010; White and Graham, 2016; Li and Graham, 2016). Finally, it is also important to note that differences in results may arise due to difference in whether ovarian hormone concentrations were assessed in saliva or blood, as salivary levels are a better reflection of free and bioactive levels, whereas blood levels also include bound and inactive steroid hormone levels (Bellem et al., 2011). Another factor that may contribute to the equivocal nature of existing data are the nuisances of different fear conditioning paradigms used by investigators. For instance, Barker and Galea found that E2 reduces fear generalization (Barker and Galea, 2010), while Lynch and

Table 2
Summary of preclinical studies assessing the effects of direct E2 manipulation on fear acquisition, extinction, extinction recall and inhibition in ovariectomized (OVX) and orchidectomized (ODX) rodents.

Reference	Species	Sex	Sample size	Type of fear conditioning	Hormone replacement used	Hormone dosage	Effects of E2
Yuan & Chambers	Rat	Male & Female	~10 animals per group	Conditioned taste aversion	OVX/ODX animals implanted with capsule containing crystalline E2 for 8 days, 16 days, or 20 days before conditioned taste aversion occurred.	0 mm, 10 mm, or 30 mm capsule filled with crystalline E2	No effect on acquisition; ↑ extinction
Graham & Daher	Rat	Female	11–16 per group	Auditory fear conditioning	OVX females administered E2 benzoate 24 h after conditioning and again 24 h before extinction training	10 μg in 150 μL sesame oil	No effect on extinction training; ↑ extinction recall
Morgan & Pfaff	Mouse	Female	15–17 animals per group	Auditory fear conditioning	OVX females implanted with capsule containing E2 benzoate 2 weeks before fear conditioning	25, 50, or 75 μg in 0.03 mL sesame oil	↑ acquisition
Graham & Scott	Rat	Female	7–17 animals per group	Auditory fear conditioning	Estrous cycle phase confirmed by daily vaginal smears, low or high dose of β-E2 administered 30 min before extinction training	15 μg/kg (low dose) or 100 μg/kg (high dose) of β-E2	No effect on extinction training in proestrus; ↑ extinction training in metestrus; Low dose ↑ extinction recall when endogenous E2 is low; Low dose ↓ extinction recall or has no effect when endogenous E2 is high; High dose ↓ extinction recall when endogenous E2 is high
Barker & Galea	Rat	Male & Female	8 per group	Contextual/ auditory fear conditioning	OVX/ODX animals received E2 benzoate for 15 days, ending the day before the conditioning procedure began	33 μg/kg in 0.1 mL sesame oil	No effect on acquisition; ↑ fear inhibition
Lynch et al.	Rat	Male & Female	9–12 per group	Contextual fear conditioning	OVX females implanted with capsule containing 17β-E2 9 days before conditioning	5 mm capsule filled with 17β-E2	↓ fear inhibition
Gupta et al.	Rat	Male & Female	25 or 29 females, 12 males	Contextual fear conditioning	OVX animals administered E2 benzoate 48 h before conditioning and again 4 h before conditioning	10 μg in 0.1 mL peanut oil	↓ consolidation of acquisition
Matsumoto et al.	Mouse	Female	4–9 animals per group	Contextual fear conditioning	OVX females administered different doses of E2 benzoate either 2 days or 2 weeks before conditioning	0.5 μg, 5 μg, or 50 μg injection in 0.1 mL oil, or 0.03 μg, 0.3 μg, 3 μg, or 30 μg in implanted capsule	↑ acquisition
Barha et al.	Rat	Female	7–9 animals per group	Contextual fear conditioning	OVX females administered 17β-E2, 17α-E2, or estrone 30 min before conditioning	0.3 μg/0.1 mL, 1 μg/0.1 mL, or 10 μg/0.1 mL 17β-E2, 17α-E2, or estrone in sesame oil	No effect on fear inhibition; No effect on cued fear acquisition;, Low levels (β and α) ↑ contextual fear acquisition; High levels ↓ contextual fear acquisition
Lynch et al.	Rat	Female	5–10 animals per group	Contextual fear conditioning	OVX females acutely administered E2 benzoate 24 h, 6 h, or 1 h before training and were tested 24 h or 6 days post training. Other OVX females acutely administered E2 benzoate 24 h after training and 6 days, 2 days, 24 h, 6 h, or 1 h before testing. Other OVX females were given ERα agonist or ERβ agonist 24 h following training (24 h before testing)	15 μg E2 benzoate in 0.1 mL sesame oil, 1 mg/kg or 2.5 mg/kg of ERα agonist or ERβ agonist	↓ fear inhibition
Lynch et al.	Rat	Female	5–16 animals per group	Contextual fear conditioning	OVX females acutely administered cytosolic ER antagonist, E2 benzoate (subcutaneous injection or intracranial infusion), or ER agonists 24 h post-training and 24 h before testing	15 μg/0.1 mL E2 benzoate (subcutaneous injection), 2 μL of 10 mM solution of E2 benzoate and dimethylsulfoxide (DMSO) (intracranial infusion), 100 μg in 2 μL DMSO of cytosolic ER antagonist, 0.2 pg/μL ERα agonist in DMSO, 40 pg/μL ERβ agonist in DMSO	↓ fear inhibition
Chang et al.	Rat	Male & Female	6–18 animals per group	Contextual fear conditioning	OVX females administered E2 benzoate (subcutaneous injection) 24 h before conditioning. Other OVX females administered E2 benzoate (hippocampal infusion), ERα agonist, or ERβ agonist 1 h before conditioning	10 μg or 20 μg E2 benzoate dissolved in sesame oil (subcutaneous injection) , 0.5 μM E2 benzoate in DMSO (hippocampal infusion), 5 μM ERα agonist, 5 μM ERβ agonist	No effect on acquisition, ↑ extinction recall

colleagues reported that E2 increases fear generalization (Lynch et al., 2013, 2014, 2016). Barker and Galea assessed fear by measuring freezing in a novel context (Barker and Galea, 2010), while Lynch and colleagues measured latency to cross to another part of the conditioning chamber (Lynch et al., 2013, 2014, 2016).

Robust studies implicating P4 role in modulating risk and resilience for PTSD in women are generally lacking due to being used more as confirmatory maker of cycle phase and high co-linearity with E2 concentrations in the luteal phase (Becker et al., 2005). However, fluctuations, withdrawal, and reductions of P4/allopregnanolone have been associated with increased risk for deficits in contextual fear conditioning and fear extinction and recall in rodents (Pibiri et al., 2008; Pinna and Rasmusson, 2014; Zhang et al., 2014) and in women with PTSD (Pineles et al., 2018, 2016). In the next section, we discuss two mechanisms by which E2 and P4/allopregnanolone influence fear psychophysiology and PTSD-related symptoms, via the modulation of fear neurocircuitry and the activity of the hypothalamic–pituitaryadrenal (HPA) axis.

4. Mechanisms of ovarian hormone action on fear and PTSD symptoms

4.1. Ovarian hormone actions on fear neurocircuitry

Neurocircuitry models of the regulation of fear involve the amygdala, insula, hippocampus, and sub-regions of the prefrontal cortex, including the medial prefrontal cortex (mPFC) and anterior cingulate cortex (for reviews see (Hartley and Phelps, 2010; Sehlmeyer et al., 2009). Dysfunction in various aspects of these circuits has been implicated in the pathophysiology of PTSD. For example, PTSD has been consistently linked with amygdala hyper-reactivity accompanied by reduced functional (Stevens et al., 2013; Jin et al., 2014) and structural (Costanzo et al., 2016; Koch et al., 2017) connectivity with ventromedical PFC (vmPFC) subregions containing putative inhibitory projections to the amygdala, such as Brodmann Area 25. Individuals with PTSD also show increased functional connectivity between the amygdala and components of the salience network including dorsal ACC/dmPFC and the insula (Brown et al., 2014; Fonzo et al., 2010; Sripada et al., 2012).

Fluctuations in steroid hormones are very likely to influence the neurocircuitry supporting acute threat reactivity and extinction learning. The human amygdala, hippocampus, and prefrontal cortex are densely populated with E2 receptors (ERα, ERβ) (Ostlund et al., 2003; Pilgrim and Hutchison, 1994). E2 activation of ERβ has broad influences on synaptic plasticity (facilitating dendritic growth) (Woolley, 1998; Bi et al., 2001) as well as amygdala-mediated anxiolytic effects (Oyola et al., 2012). The amygdala, hippocampus, and vmPFC show relatively low progesterone receptor (PR) expression, but do show high levels of membrane-expressed progesterone receptors (mPR) (Pang et al., 2013). Although steroid binding and biological functions of mPRs are only beginning to be explored in humans, these membrane-expressed receptors may be a critical component of how P4 influences cellular function. For example, these receptors have been implicated the precipitous drop in P4 that is responsible for stimulating labor in humans (Karteris et al., 2006). Interestingly, post-mortem concentrations of P4 are highest in the amygdala, hypothalamus, and cerebellum relative to other brain regions (Bixo et al., 1997). The post-mortem concentration of allopregnanolone also appears to be relatively low within the amygdala, hippocampus, and vmPFC (Bixo et al., 1997), with greater expression in the substantia nigra and basal hypothalamus. However, even very low concentrations of allopregnanolone are known to potentiate the GABAa receptor (Puia et al., 1990), producing a number of neuroprotective effects such as stimulating the proliferation of human neural progenitor cells in the hippocampus (Wang et al., 2005).

Furthermore, anatomical MRI studies in women indicate that effects of female hormonal fluctuations during a single menstrual cycle have surprisingly gross global effects on the brain that can be observed at the coarse spatial resolution (~1 mm^3) observable with MRI neuroimaging. For example, a study mapping brain-wide gray matter, white matter, and CSF at 4 longitudinal timepoints within a cycle showed a 1.8% increase in gray matter volume concurrent with the peak in blood serum E2 (at ovulation), relative to other cycle timepoints (Hagemann et al., 2011). The hippocampus, in particular, shows structural changes over the menstrual cycle in healthy women. During the mid-follicular phase of the cycle, hippocampal volume increases relative to the late luteal phase when E2 is low, with corresponding increases in declarative memory performance (Protopopescu et al., 2008; Pletzer et al., 2010). A systematic review of structural neuroimaging studies shows that effects of both E2 and P4 are consistently observed within the fear neurocircuitry, particularly in the amygdala, hippocampus, nearby medial temporal lobe regions, and the anterior cingulate cortex (Catenaccio et al., 2016).

The menstrual cycle and steroid hormone levels have similarly been linked with changes in human brain function. E2 appears to be linked with greater connectivity and activation in the vmPFC and hippocampus, and facilitates their modulatory influence on amygdala reactivity. For example, healthy women in the mid-follicular phase of the menstrual cycle show greater resting state activity (measured via glucose metabolism) in the prefrontal cortex and medial temporal lobe (including the hippocampus) compared to when they were in the early follicular phase (Reiman et al., 1996). Women with higher E2 levels concentrations show greater resting state amygdala-prefrontal cortex connectivity compared to women with low E2 levels (Engman et al., 2016). E2 concentrations positively correlate with vmPFC activity in healthy women during the presentation of highly-arousing unpleasant film clips (Miedl et al., 2018), and these findings have been interpreted as reflecting a beneficial prefrontal modulation of arousal responses to a potentially traumatizing stimulus.

In contrast, P4 appears to have opposing effects on the amygdala and its connections with the vmPFC and hippocampus. One particularly powerful neuroimaging study actively manipulated P4 levels (van Wingen et al., 2008), giving a single oral dose of micronized P4 during the early follicular phase when endogenous P4 and E2 are typically low. This was contrasted with a within-subjects placebo condition at the same phase of the next menstrual cycle. Blood assays confirmed that P4 and allopregnanalone increased to a level biologically expected during the mid-luteal phase or during early pregnancy. P4 produced an increase in the reactivity of the right basolateral amygdala to negative emotional face stimuli, and had no effect on any other brain region. Furthermore, P4 administration decreased the functional connectivity between the amygdala and the fusiform gyrus (involved in face perception) and increased connectivity with dACC. Similar findings have been observed in naturally-cycling women in the mid-luteal phase when endogenous P4 is high, who show increased amygdala and hippocampal responses to negative emotional stimuli relative to the early follicular phase (Andreano and Cahill, 2010), potentially indicating increased arousal or vigilance. Such P4-related alterations in human brain function closely parallel many of the neuroimaging correlates of PTSD.

A growing body of literature has addressed the effects of E2 on neural circuit function during fear conditioning and extinction. Women display greater activation of the right amygdala during fear acquisition compared to men (Lebron-Milad et al., 2012). A more detailed look at the contribution of E2 to this sex difference shows that only those women with high E2 concentrations display this heightened pattern of amygdala reactivity, whereas women with low E2, and women taking oral contraceptives did not differ from men (Lebron-Milad et al., 2012), and a similar pattern has been observed for hypothalamic activation (Hwang et al., 2015). E2 concentrations in women appear to be linearly associated with activity in the amygdala and hypothalamus (Hwang et al., 2015).

During fear extinction, successful extinction is expected to produce a reduction in amygdala reactivity to the CS+ (given that it is no longer associated with threat), accompanied by activation in the vmPFC and hippocampus which both facilitate the formation and expression of extinction memories. In one study of cycling women, those with low levels of E2 showed lower activation of vmPFC during extinction learning, and of vmPFC and hippocampus during extinction recall, compared to those with high levels of E2 (Zeidan et al., 2011; Hwang et al., 2015). Similarly, women taking oral contraceptives with resulting suppression of endogenous hormones show heightened amygdala reactivity to the CS+ during extinction (relative to men and naturally cycling women), reflecting a potential failure or slowing of extinction (Merz et al., 2012). Together, the findings suggest that when E2 is lower, amygdala reactivity during fear acquisition is also lower, but there is also a (potentially maladaptive) decrease in vmPFC and hippocampal activation during fear extinction and recall and a corresponding increase in the amygdala response to the extinguished CS+. It may thus be hypothesized that, during times of low or fluctuating E2, trauma-exposed women may fail to engage the vmPFC and hippocampus in extinguishing the fear associated with the trauma memory in the weeks and months following the trauma. While no neuroimaging study has yet investigated the direct effects of steroid hormone manipulation on fear neurocircuitry in women with PTSD, preclinical studies in rodent models have informed our understanding of how ovarian hormones affect the neurocircuitry regulating fear responses.

Estrogens influence the structure and function of the neurocircuitry regulating learning and cognition (for review please see (Spencer et al., 2008)). In the regards to contextual fear learning known to be impaired in individuals with PTSD and linked to function of the hippocampus (Hartley and Phelps, 2010; Sehlmeyer et al., 2009), E2 replacement in OVX rats in reduces hippocampal long-term potentiation (LTP) while concurrently attenuating freezing behavior, suggesting that E2 reduces consolidation of the contextual fear memories (Gupta et al., 2001). This effect of E2 on hippocampal consolidation of the contextual fear is mediated via E2 actions on ERβ, as male and female mice lacking ERβ (BERKO) display less freezing in the context in which fear conditioning occurred (Day et al., 2005) and OVX rats injected with an ERβ agonist in the dorsal hippocampus show enhanced retrieval of a contextual fear extinction memory (Chang et al., 2009). ERβ in the dorsal CA1 region of the hippocampus also mediates the fear generalization enhancing effects of E2 in OVX rats by affecting retrieval of the fear memory (Lynch et al., 2014, 2016).

Estradiol also affects fear conditioning in a rodent model of PTSD wherein rats undergo a single prolonged stress that induces deficits in fear extinction and other PTSD-like phenotypes (Armario et al., 2008). Supplementation of E2 in females who underwent a single prolonged stress show less freezing after contextual freezing compared to animals not given E2 (Saffari et al., 2015). This beneficial effect of E2 supplementation occurs concomitantly with E2-induced increases in levels of brain derived neurotrophic factor (BDNF; a neurotrophin that promotes cell generation and survival) and increased cell density in the hippocampus compared to animals supplemented with vehicle alone (Saffari et al., 2015). These data suggest that E2 promotes neurogenesis and cell survival in the hippocampus to reduce fear behaviors.

Estrogens can also impact the function of the amygdala to modulate fear psychophysiology in a sub-region specific manner. For instance, the activity in the basolateral amygdala (BLA) is higher in female than male rats, and varies over the course of the estrus cycle in female rats (Blume et al., 2017). Similar to effects seen in the hippocampus, E2 affects synaptic plasticity in the amygdala. Inhibition of aromatase, the enzyme that converts testosterone into E2, in the BLA reduces spine density and blocks LTP in female rats (Bender et al., 2017). The ability of E2 to affect the activity and plasticity of the amygdala has direct ramifications for the amydala's capacity to regulate fear learning and extinction. For example, naturally cycling rats administered an ERβ agonist systemically 30 min prior to fear extinction training show less freezing during fear extinction recall compared to animals who received an ERα agonist or vehicle, suggesting ERβ facilitates extinction consolidation (Zeidan et al., 2011). Additionally, systemic E2 administration immediately following extinction training (during the metestrus phase) show better fear extinction recall (less freezing) the next day compared to animals administered E2 four hours after extinction training. This systemic E2 administration following extinction training induces lower c-fos expression (an immediate early gene that marks neuronal activation) in the amygdala, suggesting that ERβ activation immediately following extinction training may modify synaptic plasticity in the amygdala to improve extinction memory consolidation (Zeidan et al., 2011).

The actions of E2 on modulating synaptic plasticity within the amygdala to improve the consolidation of fear extinction training are also sub-region specific. E2 treatment reduces c-fos expression in the lateral amygdala and increases c-fos expression in the central nucleus of the amygdala (CeA) during extinction learning (Maeng et al., 2017). However, during extinction recall, E2 treatment reduces c-fos expression in the central amygdala (Maeng et al., 2017). These results suggest that the E2-induced reduction of lateral amygdala activity during extinction learning results in the dissociation between the CS and the US (Maeng et al., 2017), and that the E2-incuded reduction of CeA activity during extinction recall reduces the expression of fear behaviors (Zeidan et al., 2011; Maeng et al., 2017).

One mechanism by which E2 may be impacting the structure and function of the amygdala is by modulating the expression, and thus actions, of HDAC4, a histone deacetylase implicated in learning and memory (Fitzsimons et al., 2013; Kim et al., 2012; Sando et al., 2012; Wang et al., 2011). Female mice in metestrus when E2 concentrations are low show increased HDAC4 expression in the amygdala after fear conditioning compared to females that remained in their home cage and did not undergo fear conditioning (Maddox et al., 2017). A similar increase in HDAC4 expression in the amygdala is also seen in fear-conditioned OVX females. However, fear-conditioning in intact female mice during proestrus when E2 concentrations are high and in OVX females treated with E2 does not result in increased HDAC4 expression, suggesting that beneficial effects of E2 on fear learning and extinction may be mediated by its effects on HDAC4 (Maddox et al., 2017). This notion is supported by evidence that alterations in methylation within the *HDAC4* gene are association with PTSD in women (Maddox et al., 2017). Furthermore, a single nucleotide polymorphism (SNP) within the *HDAC4* gene is associated with greater expression of fear, deficits in fear extinction, increased resting state functional connectivity of the amygdala in traumatized women (Maddox et al., 2017). Overall, these data suggest that E2's ability to modulate HDAC4 may contribute to PTSD in women (Maddox et al., 2017).

Another area critical for fear learning whose structure and function shows sex differences (Garrett and Wellman, 2009; Kolb and Stewart, 1991) and whose activity is modulated by E2 in females is the PFC, including the mPFC and the vmPFC (known as the infralimbic cortex in rodents) (Maeng et al., 2017). E2 administration immediately following fear extinction training in female rats results in greater activation of infralimbic cortex as indicated by increased c-fos expression in the infralimbic cortex (Zeidan et al., 2011). Because the infralimbic cortex typically acts to inhibit the amygdala, these results suggest that E2's ability to reduce amygdala activity and decrease fear behaviors is mediated by increasing the activity of the infralimbic cortex (Zeidan et al., 2011; Maeng et al., 2017). Overall, these data recapitulate findings from women showing that natural variation in E2 concentrations over the menstrual cycle influence fear extinction recall and vmPFC/amygdala activation (Zeidan et al., 2011).

Although P4 replacement in aged, OVX mice increases freezing in a contextual fear conditioning task mediated by the hippocampus and the mPFC, reports of the effects of P4 on the neurocircuitry of fear are more rare than findings focused on E2, mostly due to the inability to disentangle the effects of E2 from P4 in gonadally-intact systems in reproductive aged females. However, because allopregnanolone acts as a positive allosteric modulator of $GABA_A$ receptors independent of the progesterone receptor, its ability to modulate the activity of fear neurocircuitry is better defined. Indeed, fluctuations in allopregnanolone over the estrus cycle in rodents can modulate both the phasic and tonic inhibitory tone of neurons within fear neurocircuitry in a manner that is dependent on the reorganization $GABA_A$ receptor subunits (Maguire and Mody, 2007, 2009). Allopregnanolone's ability to facilitate fear extinction in mice with stress-induced decreases in central allopregnanolone concentrations is thought to be mediated by inhibition of LTP or enhancement of long-term depression (LTD) within the hippocampus (Rasmusson et al., 2017).

4.2. Ovarian hormone actions on stress axis regulation and function in females

Another mechanism by which E2 and P4/allopregnanolone confer risk and resilience to PTSD is their modulation of activity and regulation of the hypothalamic-pituitaryadrenal (HPA) axis, which has also been implicated in the pathophysiology of PTSD (Yehuda, 2005). Individuals with PTSD show lower levels of basal cortisol (Yehuda, 2005), enhanced glucocorticoid negative feedback inhibition of the HPA axis as assessed by a dexamethasone suppression test (DST) (Yehuda et al., 1995), increased glucocorticoid sensitivity (Yehuda et al., 2004), heightened levels of central and peripheral concentrations of corticotropin-releasing factor (CRF) (Baker et al., 2005; de Kloet et al., 2008), and decreased levels of FKBP5, a co-chaperone of the glucocorticoid receptor (GR) that prevents cortisol from binding and thus inhibits the translocation of GRs into the nucleus (Yehuda et al., 2009). Importantly, preclinical and translational work has shown that E2 and P4/allopregnanolone can modulate the function of the HPA axis.

Basal (unprovoked, resting) cortisol and ACTH concentrations can be augmented by E2 in rats (Viau and Meaney, 1991; Burgess and Handa, 1992; Carey et al., 1995), monkeys (Stavisky et al., 2003; Wood et al., 2004; Giussani et al., 2000; Smith and Norman, 1987), and replacement of E2 in postmenopausal women increases cortisol (Gudmundsson et al., 1999; Burleson et al., 1998). Estradiol increases the expression of CRF mRNA in the CeA (Jasnow et al., 2006; Li et al., 2003) and paraventricular nucleus (PVN) of the hypothalamus in OVX female rats and mice, respectively (Paulmyer-Lacroix et al., 1996). Replacement of E2 in OVX rhesus monkeys results in augmented CRH mRNA levels in the PVN (Roy et al., 1999) as well increased CRF peptide levels in the hypothalamus (Kerdelhue et al., 1995). These effects of E2 on CRH, ACTH and cortisol are linked to E2's enhancement of glucocorticoid negative feedback inhibition of the HPA axis via modulation of GR and mineralocorticoid receptors (Carey et al., 1995; Patchev and Almeida, 1996). Indeed, replacement of E2 in OVX monkeys increases the responsiveness of the HPA axis by diminishing glucocorticoid negative feedback in response to a DST (Wilson et al., 2005). Taken together, these data suggest that E2 facilitates HPA responsivity under basal, unprovoked conditions.

Replacement of E2 in OVX female rodents also increases ACTH and corticosterone release following exposure to a novel environment (Carey et al., 1995) and restraint stress (Handa et al., 1994). This increase in stress-induced ACTH and corticosterone by E2 occurs concomitantly with stress-induced increases in CRF within the PVN (Lund et al., 2004). Although these preclinical studies also suggest that E2 facilitates HPA responsiveness during stress exposure, a handful of studies also support the notion that E2 attenuates stress-induced activity of the HPA axis. For instance, E2 replacement in OVX rats attenuates stress-induced release of ACTH but not corticosterone (Young et al., 2001). Similarly, E2 supplementation in perimenopausal women reduces increases in cortisol and ACTH induced by a cognitive, arithmetic challenge (Komesaroff et al., 1999). The equivocal nature of these results suggests that other factors may influence E2's ability to modulate HPA responsiveness.

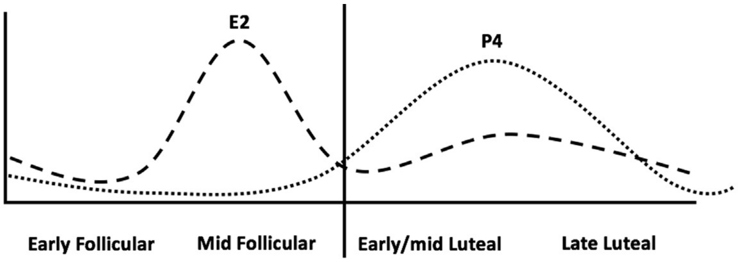
One such factor is a background of chronic stress exposure, as chronic psychosocial stress in female macaques exacerbates the effects of E2 on glucocorticoid negative feedback in response to a DST (Wilson et al., 2005). Furthermore, chronic stress exposure itself can result in low E2 concentrations due to hypogonadism induced by suppression of the HPG axis due to cortisol and CRF actions (CITES) (Galea et al., 1997). Another factor that may influence E2's ability to influence HPA function is genetic variability in genes critical for regulation. For example, a single nucleotide polymorphism (SNP) in the *ADCYAP1R1* gene is associated with dysregulation of fear responses, greater PTSD symptoms, increased odds for a PTSD diagnosis in women (Ressler et al., 2011; Almli et al., 2013), as well as increases reactivity of the hippocampus and amygdala to threat stimuli and decreased functional connectivity between hippocampus and amygdala in traumatized women (Stevens et al., 2014). This SNP lays within an estrogen response element within the *ADCYAP1R1* gene, thus influencing E2's ability to modulate the downstream actions of PACAP (pituitary adenylate cyclase-activating polypeptide) (Mercer et al., 2016), an important regulator of the HPA axis (Legradi et al., 1998).

Another factor that influences E2's effects on the HPA axis is whether P4 is on board. For instance, the facilitating effects of E2 on activity within the PVN of OVX female rodents is reversed if P4 is replacement concurrently with E2 (Figueiredo et al., 2003). Similarly, replacement of E2 in combination with P4 in OVX monkeys abrogates the increase in CRH mRNA levels in the PVN induced by E2 replacement alone (Roy et al., 1999), as well as the facilitation of glucocorticoid negative feedback by E2 replacement alone (Wilson et al., 2005). These effects of P4 on HPA axis function are mediated via allopregnanlone, as GABAergic inhibition is critical for modulating the activity of CRH neurons within the PVN (Cullinan et al., 2008) and microinfusion of neuroactive steroids similar to allopregnanolone decrease circulating levels of corticosterone in mice (Sarkar et al., 2011). These data, and findings showing that allopregnanolone concentrations increase following acute stress and act to restore homeostasis by inhibiting the release of CRH and cortisol (Purdy et al., 1991; Patchev et al., 1996, 1994) indicate that decreases in allopregnanolone over the menstrual cycle in women with PTSD who also show lower levels of central allopregnanolone (Rasmusson et al., 2006) may facilitate the activity of the HPA axis and exacerbate PTSD symptoms and deficits in fear responses by heightening amygdala activity.

5. Conclusions and future directions

To date, a significant amount of data indicates that low concentrations of E2 and P4/allopregnanolone (early follicular phase) are associated with increased PTSD-related symptoms and deficits in fear regulation in healthy and traumatized women, and that high or increasing levels of E2 and P4/allopregnanolone (mid follicular and early luteal phase) may be protective for traumatized women (Fig. 2). However, it is important to note that not all studies assessing the relationships between these steroid hormones and PTSD symptoms and fear responses are congruent. The equivocal nature of some of the findings highlight the importance of accounting for factors that may influence the association and our interpretation of the data (Tables 1 and 2), including (but not limited to) the sample assessed (clinical versus community based), the context of fear conditioning paradigms used, species studied, whether studies were done in gonadally-intact or OVX condition, and type, timing, dosing, and absolute concentrations of hormone replacement regimes administered.

In human studies, race is another critical factor to consider, as concentrations of E2 and P4 during the menstrual cycle are greater in AA compared to Caucasian women (Setiawan et al., 2006; Haiman et al., 2006). Furthermore, race may influence skin conductance that is assessed as an outcome measure for fear learning paradigms. This notion is highlighted by the study by Pineles and colleauges that found that only 28% of skin conductance responders (participants who had an



	Low E2/P4	High E2	Increasing E2/P4	Declining E2/P4
Acquisition	—	—	—	?
Extinction	—	—	—	?
Extinction Recall	⬇	⬆	⬆	?
Fear Inhibition	⬇	⬆	⬆	?

Fig. 2. *Relationship between cycle phase, ovarian hormones, and fear conditioning.* Existing studies in women indicate no relationship between menstrual cycle phase/ovarian hormone levels on acquisition or extinction processes. Low E2/P4 concentrations (as seen in the early follicular phase) are associated with impaired extinction recall and fear inhibition. High E2 concentrations (seen in the late follicular phase) and high E2/P4 concentrations (seen in the early to mid luteal phase) are associated with enhanced extinction recall and fear inhibition. The effects of declining E2/P4 concentrations during the late luteal phase on fear conditioning processes remain to be assessed.

adequate skin conductance response to the unconditioned stimulus) were African-American, while 71% of skin conductance non-responders were African-American (Pineles et al., 2016). It therefore may be problematic to rely on skin conductance as a measure of fear if the measure does not adequately report fear responses in African-Americans. Given that African-Americans are at the highest risk for PTSD (Gillespie et al., 2009), it is critical that studies modeling processes that go awry in PTSD use measures that are effective in the African-American population. To date, the majority of studies examining the role of ovarian hormones on fear learning and/or PTSD symptoms in humans feature overwhelmingly white populations, or fail to report racial demographics of the sample.

Some critical gaps in knowledge that currently exist regarding the influences of E2 and P4/allopregnanolone on risk and resilience to PTSD stem from the lack of studies assessing these relationships throughout the lifespan, when dramatic changes in concentrations of these steroid hormones occur concomitantly with increased risk for anxiety symptoms (reviewed in (Hantsoo and Epperson, 2017). The sex difference in stress- and trauma-related disorders favoring females to males by two to one emerges during puberty (Garza and Jovanovic, 2017), highlighting the need to better understand how menarche interacts with stress and trauma exposure to impact the neurobehavioral development of neurocircuitry implicated in fear in girls and young women.

Another period in the female reproductive lifespan whose effects on risk and resilience to PTSD has been largely understudied is pregnancy, a period of nine months characterized by a profound increase in ovarian steroid hormones, as concentrations of E2 and P4 increase by tenfold (Soldin et al., 2005; Jung et al., 2011). Results from the few existing studies assessing the effects of pregnancy on PTSD symptoms are equivocal in nature (Seng et al., 2009; Smith et al., 2006; Seng et al., 2010), as some studies show that lower levels of PTSD symptoms in pregnant compared to non-pregnant women (Smith et al., 2006; Onoye et al., 2013) and another shows greater hyperarousal and deficits in fear inhibition (Michopoulos et al., 2015). Because epidemiological studies show that rates of PTSD are 4–5% higher in pregnant compared to non-pregnant women (Seng et al., 2010) and that stress exposure during gestation impacts risk for adverse birth outcomes (Koen et al., 2016; Kertes et al., 2016) and intergenerational risk for adverse health outcomes in offspring (Sack et al., 1995; Yehuda et al., 2005, 2008), it is important to determine the mechanisms by which changes in E2 and P4/allopregnanolone during pregnancy may impact PTSD and dysregulation of fear responses.

Significant changes in circulating E2 and P4/allopregnanolone also occur during reproductive senescence, as the menopausal transition has also been associated with increased risk for affective disruption in women, including augmented symptoms of depression and anxiety (Hantsoo and Epperson, 2017). While some studies assessing the effects of E2 on PTSD symptoms and fear extinction in traumatized women have included postmenopausal women due to the upper limit of their inclusion criteria (Glover et al., 2012), to our knowledge there are no studies that specifically assess the effects of menopause on PTSD symptoms and fear psychophysiology in traumatized women. Similarly, there are a lack of studies systematically assessing the effects of different hormone replacement regimens on PTSD symptoms and fear psychophysiology in traumatized post-menopausal women. Because chronic PTSD is linked to accelerated aging (Wolf et al., 2018) and heightened risk for physical health condition linked to increased morbidity and mortality (such as cardiometabolic disorders) (Rosenbaum et al., 2015), this should be a focus of future research in women's health.

Similarly, future studies are necessary to better understand the long-term consequences of hormonal oral contraceptive use on PTSD symptoms in reproductive aged women. The data from preclinical and clinical studies showing that the inhibition of endogenous E2 and P4/allopregnanolone with hormonal contraceptive use is associated with poorer fear response regulation (Lonsdorf et al., 2015; White and Graham, 2016; Graham and Milad, 2013) and increased amygdala reactivity (Merz et al., 2012) suggest that taking such contraceptives may exacerbate PTSD in traumatized women. Largely unexplored is also the effect of hormonal contraceptive use, cycle phase, and E2 and P4/allopregnanolone concentrations at the time of trauma exposure on prospective risk for developing PTSD. A singular study assessing the effects of emergency contraceptive on PTSD symptom development following sexual assault supports the notion that manipulation of ovarian hormones in the immediate aftermath of trauma alters risk for PTSD development (Ferree et al., 2012).

In summary, ovarian steroid hormones and their fluctuations over the course of the menstrual cycle confer risk and resilience to PTSD-related symptoms and deficits in fear psychophysiology in females. These data underscore the notion that supplementation of E2 and/or P4/allopregnanolone during times when these levels of these hormones are endogenously low and in concert with evidence-based treatment for PTSD, such as prolonged exposure therapy (Maples-Keller et al., 2017; Powers et al., 2010), may serve as novel therapeutic interventions for traumatized women with PTSD. The promise of the therapeutic potential of such interventions is highlighted by the recent demonstration in a phase III clinical trial that a positive allosteric modulator of the $GABA_A$ receptor is efficacious in the treatment post-partum depression (Meltzer-Brody et al., 2018). Future studies are clearly warranted to assess such hormonal intervention as therapies, and to better understand the impact of ovarian steroid hormones on risk for PTSD across the lifespan in women. Results from these studies will also have important implications for transgender individuals with PTSD (Nguyen et al., 2019). The recent mandate by the National Institutes of Health that requires investigators to address sex as a biological variable in their proposals and studies will help expedite our understanding of female risk and resilience to PTSD and other adverse trauma-related sequelea (Clayton, 2018).

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