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Sex differences in fear extinction

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Abstract

Despite the exponential increase in fear research during the last years, few studies have included female subjects in their design. The need to include females arises from the knowledge gap of mechanistic processes underlying the behavioral and neural differences observed in fear extinction. Moreover, the exact contribution of sex and hormones in relation to learning and behavior is still largely unknown. Insights from this field could be beneficial as fear-related disorders are twice as prevalent in women compared to men. Here, we review an up-to-date summary of animal and human studies in adulthood that report sex differences in fear extinction from a structural and functional approach. Furthermore, we describe how these factors could contribute to the observed sex differences in fear extinction during normal and pathological conditions.

Keywords

Fear; Extinction; Human; Rodent; Sex; Male; Female

1. Introduction

1.1. Fear learning: Fear conditioning and fear extinction processes

Fear is a neurological process aimed at executing rapid behaviors to preserve ones individual integrity in the presence of a threat (LeDoux, 2014). All fear responses can be categorized as innate or acquired, and those acquired are usually added to the behavioral repertoire of the organism through classical (or Pavlovian) conditioning (Davis 1994). Classical conditioning is the procedure by which, after a series of repeated matches of a safe stimulus, known as

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neutral stimulus, with a naturally threatening one, the unconditioned stimulus (US), the neutral stimulus becomes a conditioned stimulus (CS) with the ability to elicit a fearful response, conditioned response (CR) (Pavlov, 1927). The CR can be specific to the tone, showing an effective discrimination, or might occur in presence of different tones, demonstrating generalization of the CR (Dunsmoor et al. 2009; Dunsmoor et al. 2011; Huckleberry et al. 2016). Other stimuli can be used as a CS rather than a tone, as in the case of contextual fear conditioning (FC). Fear memory consolidation is the process by which recent fearful associations are stabilized through the storage in a long-term reservoir (Dudai et al. 2015). Typically, this process is carried out in three temporally segregated stages with some overlap between them (Dudai et al. 2015): first, during synaptic consolidation, synaptic buttons strengthen in response to Ca2+ dependent pathways activation after CS presentations (Long Term Potentiation, LTP) (Lynch, 2004; McKenzie & Eichenbaum, 2011). Concurrently, in system consolidation other structures (such as the extended amygdala or the medial prefrontal cortex (mPFC)) are recruited permitting the long term recall of fear memories (Winocur and Moscovitch, 2011). Lastly, fear memories undergo reconsolidation during the recall of the CR and are integrated with new environmental information, permitting the creation of an updated fear memory representation (Schiller et al. 2010). Fear extinction (FE) refers to the process in which the CRs decline by the successive presentation of a fear-eliciting CS in the absence of an aversive US (Myers and Davis, 2007). This process is also time segregated, and involves the weakening (Long Term Depression, LTD) of previous potentiated synapses, and LTP of other inhibitory pathways (Myers et al., 2006). According to classical LTP studies (Miserendino et al., 1990), FE is mediated by N-methyl-D-aspartate–receptor (NMDA-R) and the signaling action of protein kinases and phosphatases (Michael Davis, 2011; Myers et al. 2006). Furthermore, the extinguished CR might reappear in a different context from that in which FE took place, showing renewal of the CR. Also, the CR might show spontaneous recovery if the animal is presented the CS some time after FE acquisition took place. Moreover, the CR can also be recovered by merely presenting the US sometime after extinction, in a process called reinstatement. These three processes (spontaneous recovery, reinstatement and renewal of the CR) highlight that the undergoing processes of FE are aimed towards the acquisition of a new inhibitory learning rather than the weakening of a previously potentiated one.

1.2. Fear related disorders

In this review we will refer to fear-based disorders as the group of psychiatric conditions that share pathological fear processing and prominent anxiety symptoms as core features in their development, or maintenance (Flores et al., 2018). We will specifically focus on posttraumatic stress disorder (PTSD), phobic disorders and panic disorder. Patients suffering from these conditions show alterations in fear learning that include: a greater conditioning to danger cues, impairments in FE and impairments in inhibitory conditioning to safety signals (Garfinkel et al., 2014; Jovanovic et al., 2012; Jovanovic and Norrholm, 2011; Lissek et al., 2005; Milad et al., 2009; Rougemont-Bücking et al., 2011). In addition, the main psychological treatment available for these patients includes FE procedures (i.e., exposure therapy), thus providing a model with good face validity for exposure therapy (Scheveneels et al., 2016; Vervliet et al., 2013).

Anxiety and fear-based disorders are increasingly recognized as conditions producing a great disease burden and economic impact, also being projected as one of the leading causes of disability and healthcare costs for the next decade (Kessler et al., 2012; Whiteford et al., 2013; Wittchen et al., 2011). Notably, these disorders affect men and women disproportionately. Women are double the risk for panic attacks, specific and social phobias compared to men, and PTSD can reach three times the prevalence in women (de Jonge et al., 2016; Gradus et al., 2017; Steel et al., 2014; Wardenaar et al., 2017). Women are also more likely to have a long disease course, and to present comorbidities (Kessler et al., 2015; McLean et al., 2011; Pigott, 2003). Although the reasons for this biased burden remain largely unknown, they are thought to arise from multiple interactions between physiological, neurobiological, environmental and socio-cultural factors (Kessler et al., 2017; McCutcheon et al., 2010; Olff, 2017; Tolin and Foa, 2006). Due to the the high economical and social burdens of fear-related disorders, there is a need to increase research in this field, especially in translational studies, since current treatments work for most, but not all patients. Besides, a considerable proportion of patients drops out of treatment or experiences relapses of symptoms, even after medicial completion (Batelaan et al., 2017; Edlund et al., 2002; Hofmann and Smits, 2008; Imel et al., 2013; Koen and Stein, 2011; Loerinc et al., 2015; Roshanaei-Moghaddam et al., 2011). Research aimed at identifying novel molecular targets and markers of circuit dysfunction will lead to improved interventions, and better quality of life for the people suffering from these disorders.

1.3. Sex differences and similarities: a change in the framework

In most mammals, including humans, sex is the biological trait determined genetically by the presence of XX or XY chromosomes. Soon after the XX or XY genotype is set, genes like the *Sry* or *Xist* promote sexo-dimorphic processes that influence brain structure, cellular function, gene expression and a wide range of behaviors (Arnold, 2017, 2009; Davies and Wilkinson, 2006; Du et al., 2004; McCarthy and Arnold, 2011; Sanchis-Segura and Becker, 2016). Apart from these influences, sex hormones shape the organism in three different ways: first, by defining wiring patterns and brain structures during neurodevelopment, also regarded as “organizational effects” (Wallen, 2005). Later, by altering intrinsic functions in the brain depending on their cyclic or sustained presence; like the modulation of hippocampal spines by fluctuating estradiol (E2) levels (Woolley, 1998). The last source of influence arises from the interaction of these sexually determined traits with the environment, making men and women shape their behavior according to social norms, other individuals or their personal adequacy (Berenbaum and Beltz, 2016; Springer et al., 2012). Still, most brain areas are not strictly sexually dimorphic, rather they appear as a continuum of characteristics, or what some authors have described as a mosaic, with several degrees of variability attributable to sex (Joel and McCarthy, 2017). Notably, it must be accounted that many of these differences manifest in the framework of compensation, meaning that organisms of opposite sex use different neurobiological substrates to solve the same problem and converge on the same behavior (De Vries, 2004; Wang et al., 1994). For this reason, once a sex difference is found, it must be contextualized depending on the setting where it is detected (Joel and McCarthy, 2017).

The study of sex differences (or similarities) is not fully considered in the field of neuroscience. In the last years, researchers have produced 5.5 studies in males per 1 in females (Zucker and Beery, 2010); pointing out the evident and growing need to change our approach to science by including female subjects at all levels of research (Clayton and Collins, 2014; Prendergast et al., 2014). Undoubtedly, scientists will need to adapt their approach to research questions (Fields, 2014), but the benefits will overcome the costs by providing improvements in the generalizability of results, increasing the control over data variability and prompting the possibility to develop personalized or even sex-based interventions. Lastly, human research often interchangeably uses the term sex or gender as one variable. Gender is now defined as the social, environmental, cultural and behavioral factors, or choices that influence a person's self-identity and health (Clayton and Tannenbaum, 2016). From all the reviewed studies here, if any, none performed further confirmation of sex by genotype, or specific analyses of gender preference. For these reasons, we will focus only on studies reporting sex differences.

1.4. The study of sex differences in fear extinction

Mixed results are reported when comparing males and females upon cued-FE tasks, with some studies finding impairments for females and others not (Baker-Andresen et al., 2013; Baran et al., 2010, 2009; Fenton et al., 2014; Gruene et al., 2015; Maeng and Milad, 2015; Milad et al., 2009; Voulo and Parsons, 2017). A more consistent picture emerges when the influence of hormones or the estrous (animal)/menstrual (human) cycle is considered: females undergoing FE training during proestrus (high E2/ high progesterone (P4)) have similar FE recall than males. In contrast, females undergoing FE during metestrus (low E2/ low P4) have impairments in FE recall compared to proestrus females or males (Gruene et al., 2015; Lebrón-Milad et al., 2013; Milad et al., 2009; Colin D. Rey et al., 2014). Fear learning studies that focused on contextual fear conditioning (FC) usually detect that females have lower freezing levels during FE training, and greater extinction rates when compared to males (Maren et al. 1994; Gupta et al. 2001; Dalla and Shors 2009; Barker and Galea 2010; Daviu et al. 2014; Bangasser and Wicks 2017 but see Matsuda et al., 2015, Baran et al., 2009). Although these studies do not control for the estrous cycle, rather they administered E2 or ovariectomized females, finding improvements and impairments in FE respectively. In human studies, men and women acquire fear and extinction similarly but sex differences are observed for FE recall. Women undergoing FE training during the mid-phase of their menstrual cycles, with low E2 levels, or women taking hormonal contraceptives (HC) have less FE recall. In contrast, women with high E2 levels demonstrate better FE recall (Graham and Milad, 2013; Hwang et al., 2015; Lebron-Milad and Milad, 2012; Milad et al., 2010, 2006; Zeidan et al., 2011). In sum, these studies point at important influences of sex hormones over fear memories that could be directly influencing FE consolidation (Lebron-Milad and Milad, 2012). Also, the spontaneous recovery of the CR is more likely to happen in female individuals (Fenton et al., 2016; Matsuda et al., 2015).

1.5. Limitations in the study of sex differences in FE

Before reviewing the pertinent studies, it is worth noting some of the limitations found when studying FC and FE. It is possible that the observed sex differences in FE may arise from inherent differences in fear acquisition, fear memory consolidation or fear expression

(Dachtler et al., 2011; Dalla and Shors, 2009; Keiser et al., 2017). This is the case of studies finding significant sex differences in contextual fear acquisition (Blume et al., 2017; Chang et al., 2009). In fact, it is known that males and females possess differently weighted molecular mechanisms for fear memory formation including synaptic kinases, transcription factors and activated genes (Dachtler et al., 2011; Keiser and Tronson, 2016; Mizuno and Giese, 2010; Tronson, 2018). However, just some of these mechanisms are known for FE or FE recall. Also, the molecular signatures of FE in each sex may reflect the engagement of specific cognitive and behavioral strategies used to approach and learn from threats (Mizuno and Giese, 2010; Shansky, 2018; Silva et al., 2013; Tronson, 2018). Researchers have pointed out, that females are more likely to engage in active responses, like darting in rats or the tend-and-befriend response in humans (Gruene et al., 2015; Olff, 2017; Taylor et al., 2000). Therefore, studies in rats relying just on freezing behavior, may be not capturing the full behavioral response of females. Notably, there are no studies to date suggesting that female mice present darting behavior. Additional factors like the dynamics of sex hormones or social interactions leave ample room for methodological differences that could influence results. Examples of this include the techniques and timing used to monitor the estrous cycle, or the effects of social interaction between males (Kikusui, 2013; Maeng et al., 2015; Prendergast et al., 2014). Furthermore, we must account for all the inherent limitations of FC, which include the inability to assess the organism's subjective response, the nature and type of conditioned responses, or the considerable methodological discrepancies between animal and human studies. As an example, most human studies perform FE immediately after FE training, while in animal studies, FE is assessed after a time lapse usually longer than 6 hours, being known that both processes recruit specific molecular signatures (Myers and Davis, 2007). Some of these elements are covered in depth elsewhere (Sevenster et al. 2014; Cook et al. 2014; Top Jr. et al. 2016) but call for the adaptation of FC and FE methodologies in human and animal studies in order to improve the translationability of results (Flores et al., 2018). Below, we will review FE studies that report sex differences and unless stated, they do not detect significant differences in fear acquisition. Nevertheless, we must encourage readers to make careful considerations given the aforementioned limitations.

2. Sex differences in brain systems and molecular pathways involved in fear extinction

2.1. Brain structures and neuronal circuits

The structures and circuits implicated in FC and FE act as a dynamic network of connections, with some areas being essential for fear acquisition or fear expression, while others work as relay stations or parallel processing points (Anglada-Figueroa and Quirk, 2005; Nader et al., 2001). Therefore, the correct interaction within this circuitry, and the integrity of its components, are major determinants of the behavioral output. Moreover, circuits involved in fear acquisition, fear expression, FE and anxiety overlap, although using different neuronal substrates. For example, microcircuits in the central amygdala (CeA) or the projections from the basolateral amygdala (BLA) to the mPFC promote fear learning but are also involved in FE and can induce anxiogenic or anxiolytic states (Tovote et al., 2015). The neuroanatomical and functional correlates help us identify key nodes in this distributed

network where FE memories are encoded and stored; we review them here considering studies performed in both sexes.

2.1.1. Amygdaloid complex—The amygdala is a key hub for fear processing that is mainly composed of a cortical-like structure, the BLA, and a striatum-like structure, the CeA. During FC, auditory (CS) and nociceptive (US) inputs converge in the lateral amygdala (LA) triggering plastic changes (Herry and Johansen, 2014; McGaugh, 2004). The basal amygdala (BA) has prominent connections with the hippocampus and cortical structures, being able to integrate relevant contextual information and internal states (Calandreau et al., 2005; Gründemann et al., 2018; Phillips and LeDoux, 1992). Information flows from these nuclei to the CeA, which is the essential output station that triggers behavioral and homeostatic responses. Besides this, the CeA is also involved in plasticity, nociception and the hierarchical organization of defensive behaviors (Balleine and Killcross, 2006; Cardinal et al., 2002; Ehrlich et al., 2009; Fadok et al., 2017; Isosaka et al., 2015; Li et al., 2013). During FE, different neuronal populations in the BLA signal the CS-US contingency, and partially encode prediction errors (Herry and Johansen, 2014). Moreover, BA projections to the ventral hippocampus, or the prelimbic cortex (PrL) promote fear expression, while BA projections to the infralimbic cortex (IL) promote fear inhibition (Herry et al., 2008; Knapska et al., 2012; Senn et al., 2014). FE requires plastic changes in the amygdala, that can further reduce fear expression by increasing the perisomatic inhibition of fear neurons and by potentiating inhibitory synapses from intercalated cells under IL influence (Amano et al., 2010; Davis et al., 2017; Herry et al., 2008, 2006; Sotres-Bayon et al., 2007; Trouche et al., 2013). Thus, the interactions within these circuits modulate fear expression and enable FE encoding and consolidation (Adhikari et al., 2015; Bukalo et al., 2015; Herry et al., 2010). Recent evidence points out additional functions of the amygdala, specifically the CeA, in valence assignment, feeding behavior, and reward-related actions that could render this structure, as an integrator of internal states promoting the engagement into different behaviors (Beyeler et al., 2018; Fadok et al., 2018; Gründemann et al., 2018; Herry and Johansen, 2014; Kim et al., 2017; Paré and Quirk, 2017; Xu et al., 2016). In humans, neuroimaging studies show that the amygdala has restricted activity during FC, and inconsistently activated during FE training (Alvarez et al., 2008; Fullana et al., 2016; Knight et al., 2004; LaBar et al., 1998; Milad et al., 2007b; Phelps et al., 2004). During FE recall, most studies do not report activity in the amygdala (but see Zeidan et al. 2011). However, studies that have observed amygdala activations usually report it to be correlated with activity in the dorsal anterior cingulate cortex (dACC) and greater fear expression (Linnman et al., 2012c).

Anatomical comparisons reveal that males have larger and denser medial amygdalas, whereas females demonstrate more GABAergic neurons and fluctuations in the density of its dendritic spines across the estrous cycle. Notably these differences are not present in the BLA or CeA (Cooke and Woolley, 2005; Morris et al., 2008; Rasia-Filho et al., 2004; Stefanova and Ovtscharoff, 2000). At the functional level, females present a more inhibited LA during proestrus and a more inhibited BA during diestrus that correlate with faster cued-FE and contextual-FE respectively (Blume et al., 2017). Studies that have focused on humans report mixed findings when comparing the amygdala of males and females

(Goldstein et al., 2001; Marwha et al., 2017; Ruigrok et al., 2014). However, sex differences are evident when assessing functional activations and resting state functional connectivity (rsFC). The rsFC refers to the spatiotemporal patterns of coupled brain activity that integrate a variety of intrinsic networks involved in cognitive function, memory or salient stimuli detection (Damoiseaux et al., 2006). Regarding fear behavior, there are increases in amygdala-dACC/dorsomedial prefrontal cortex (dmPFC) rsFC after fear learning, that are positively correlated with behavioral and autonomic measures of fear (Schultz et al., 2012). Likewise, drug-induced decrements in the amygdala-hippocampal rsFC after FE learning relate to greater hippocampal activation and thus enhancements in FE recall (Rabinak et al., 2018). Therefore, it is hypothesized that rsFC changes observed after fear procedures may reflect ongoing memory consolidation, also relating to several behavioral impairments observed in patients with fear-related disorders such as PTSD (Zhu et al., 2017). At rest, men have higher amygdala-ventromedial prefrontal cortex (vmPFC) rsFC and women with low E2 show increased rsFC with the dACC (Engman et al., 2016). When presented with threatening cues, women show greater amygdala reactivity during low E2 phases of the menstrual cycle and this activity is not correlated with arousal measures or cortical activity (Goldstein et al., 2005). A finding that may be explained by the attenuating effects of E2 over the activation of subcortical structures of the arousal system (Goldstein et al., 2010). Most FC-FE studies that include both sexes report no sex differences for the CRs during FE training (Knight et al. 2004; Gottfried and Dolan 2004; but see Fullana et al. 2018), but some differences are observed for the activity in the amygdala during fear acquisition (Hwang et al., 2015; Lebron-Milad and Milad, 2012). Only one study has found greater activations in the left amygdala and vmPFC during FE recall in women with high E2 compared to women with low E2 (Zeidan et al., 2011).

In the clinical field, PTSD and phobic patients have structural and functional alterations in the amygdala, commonly presenting hyperactivity that is coupled with hippocampal and vmPFC hypoactivity (Engel et al., 2009; Etkin and Wager, 2007a; Ipser et al., 2013; McLaughlin et al., 2014; Michael et al., 2007; Sripada et al., 2012a; Stevens et al., 2013). Likewise, their FE recall impairments correlate with hyperactivations in the amygdala (Milad et al., 2009). In summary, the amygdala is a relevant structure for processing and eliciting conditioned responses regardless of sex. Its basal function seems to be influenced by hormonal levels, with some studies showing decreased reactivity during high E2 states and hyperactivity during low E2 states; although, this effect may be restricted to specific subnuclei. The CeA, along with the extended amygdala, are under heavy neuromodulatory control and they may be able to integrate multiple inputs to set internal states that facilitate appropriate and scalable behaviors (Fadok et al., 2018; Herry and Johansen, 2014; Paré and Quirk, 2017)

2.1.2. mPFC—The mPFC is a region implicated in fear learning that integrates sensory and contextual information to elicit flexible behavioral adaptations (Giustino and Maren, 2015). Two subdivisions of the mPFC receive the most attention when studying FE in rodents, the IL and the PrL, and they are thought to work as functional homologues of the human vmPFC and dACC respectively (Milad and Quirk, 2012). The IL cortex is involved in the formation of FE memories, activated during FE recall and its IL-BLA projections are

necessary for extinction-related plasticity, but its function can be spared during FE recall (Adhikari et al., 2015; Bloodgood et al., 2018; Bukalo et al., 2015; Do-Monte et al., 2015; Herry et al., 2010; Kalisch et al., 2006; Lissek et al., 2013). In comparison, the PrL is implicated in the acquisition and expression of conditioned fear responses by integrating inputs from the BLA, hippocampus and thalamus into cortical networks (Courtin et al., 2014; Do-Monte et al., 2015; Sotres-Bayon et al., 2012). Further detail is discussed in Sotres-Bayon and Quirk 2010; Giustino and Maren 2015. In humans, the dorsal parts of the ACC and mPFC (dACC, dmPFC) are relevant for attention, negative emotional responses and the expression and evaluation of fear (Etkin et al., 2011; Milad et al., 2007a). While the ventral parts of the ACC and mPFC (sgACC, pgACC, rACC, vmPFC) exert an inhibitory control over subcortical structures and promote the consolidation of emotional memories, including FE memories (Milad et al., 2007b; Pace-Schott et al., 2015). FE training activates both, the dorsal and ventral parts, from which the vmPFC shows gradual increases (Delgado et al., 2008; Etkin et al., 2011; Fullana et al., 2018). In contrast, during FE recall, prefrontal activations are observed mostly in the ventral ACC and vmPFC when comparing the CR to a CS that underwent FE training against the CR to an unextinguished CS (Fullana et al., 2018; Lebron-Milad et al., 2012; Milad et al., 2007b, 2005).

The mPFC portrays intrinsic and extinction-related sex differences: structurally, the pyramidal neurons in the PrL of female rodents have smaller and less complex apical dendritic arbors (Koss et al., 2014). Also, pre-training electrolytic damage to the IL impairs FE acquisition and its maintenance in females, but in males it only impairs FE recall. Interestingly, this lesion also makes females acquire fear faster (Baran et al., 2010). Successful FE recall induces IL activations in males and females, but females with FE recall impairments (trained during low E2 phases) show persistent PrL activity and hypoactivation of the IL (Gruene et al., 2014; Knapska and Maren, 2009). By measuring prefrontal activity with local field potentials, researchers showed that females have greater freezing levels that correlate with persistent theta (4-12 Hz) and gamma (30-120 Hz) activity in the PrL during FE training. In addition, they fail to produce gamma activations in the IL during FE recall compared to males (Fenton et al., 2016, 2014). Animal studies have revealed that synchronized theta rhythms in the amygdala, mPFC and hippocampus are observed after FC and during fear expression. Moreover, gamma oscillations are involved in cognitive and attentional functions mediated by the prefrontal cortex (PFC) (Karalis et al., 2016; Likhtik et al., 2014; Seidenbecher et al., 2003). These oscillations are important for encoding information, long-range network synchronization, cognitive function, allowing the formation of neuronal ensembles in the short recurring time windows that facilitate synaptic interactions (Herry and Johansen, 2014; Pelletier and Paré, 2004). Thus, the observed sex differences in prefrontal synchronization may contribute to the distinct behavioral responses of males and females during FE.

In humans, anatomical and functional differences result in greater amygdala-vmPFC rsFC in men and greater amygdala-dACC rsFC in women with low E2 levels (Engman et al., 2016; Goldstein et al., 2005, 2001; Ruigrok et al., 2014). Prefrontal activity seems to be more prominent in women during FE training (dACC and mPFC) and men show higher vmPFC activity during FE recall (Lebron-Milad et al., 2012). However, if hormonal levels are considered, women with high E2 have greater activations in prefrontal structures (rACC,

MCC) during FE training and FE recall compared to men and women with low E2 (Hwang et al., 2015; Zeidan et al., 2011). These studies do not report significant differences in fear acquisition but find diverging prefrontal activations among sexes. Notably, women taking hormonal contraceptives (HC) have impairments in FE that relate to greater activations in the ACC, vmPFC, amygdala and thalamus compared to men or women in the luteal phase (high E2/ high P4) (Merz et al., 2012).

In the clinics, PTSD patients exhibit basal and functional alterations in prefrontal function; with additional impairments in FE recall that relate to hypoactivations in the vmFPC-hippocampus and hyperactivations in the dACC (Bluhm et al., 2009; Etkin and Wager, 2007; Milad et al., 2009; Rougemont-Bücking et al., 2011; Shvil et al., 2014). A tractographic study performed in traumatized women reported a positive correlation between FE and the integrity of the cingulum, the main white tract connecting the cingulate and the entorhinal cortex, so that better hippocampal-ACC connectivity predicted lower fear responses during FE (Fani et al., 2015). In sum, the reviewed studies suggest that mPFC function, specifically IL signaling, is important to trigger FE memory formation in both sexes but females are more likely to show persistent PrL activity and lower IL activity resulting in lower FE recall. The observed differences in theta and gamma oscillations may relate to a differential coupling between mPFC-hippocampus-amygdala that render females unable to switch between fear and safety states (Courtin et al., 2014; Lesting et al., 2013; Likhtik et al., 2014; Pelletier and Paré, 2004; Stujenske et al., 2014). However, these studies did not account for hormonal status and it is still unknown if low E2 states influence amygdala-dACC connectivity like suggested by human studies (Engman et al., 2016; Goldstein et al., 2005). For example, high E2 or estrogen receptor beta (ER-β) activation can influence excitatory transmission and synaptic plasticity in the IL through glutamatergic mechanisms (Galvin and Ninan, 2014). Still, it remains to be explored if E2 or P4 levels can influence prefrontal interneurons and thus promote a differential engagement of cortical networks that eventually impacts FE memory encoding or its consolidation (Burgos-Robles et al., 2009, 2007; Courtin et al., 2014).

2.1.3. Hippocampus—FE memory is time and context-dependent, and the hippocampus relays information regarding the location and time where FE learning took place. Its role is crucial for memory processes, and the spatial and non-spatial representation of environmental stimuli (Maren et al., 2013). It enables organisms to encode internal or external contexts to generate optimal predictions and adjustments in their behavior. Moreover, fear reinstatement, renewal and spontaneous recovery implicate time and space-dependent contextual changes that trigger the reappearance of fear behavior (Ji and Maren, 2007). The dorsal hippocampus is involved in the acquisition, contextual encoding and context-dependent retrieval of FE memories (Corcoran et al., 2005; Lissek et al., 2013; Maren et al., 2013; Sierra-Mercado et al., 2011). In comparison, the circuits arising from the ventral hippocampus contribute to fear renewal and promote fear relapse (Knapska et al., 2012; Marek et al., 2018). Human neuroimaging studies that evaluated hippocampal activation during FE find mixed results, probably because of the different degrees of contextual involvement. Deactivations during FE training and activations during FE recall

are observed, mostly when FE recall takes place in safe contexts (Fullana et al., 2018; Hatch et al., 2013; Kalisch, 2006; Knight et al., 2004; Milad et al., 2007b).

Sex differences in hippocampal function are found in a variety of tasks (Koss and Frick, 2017). In fear paradigms, males show greater freezing to context which has been related to NMDA-R mediated mechanisms (Maren et al., 1994). An effect that is likely related to the estrogen actions on hippocampal function. Estrogen-dependent positive modulation of hippocampal spines may result in females having increased spines during high E2 states of their estrous cycle, and ovariectomized rats without estrogen replacement having decreased hippocampal spines (Gupta et al., 2001; Li et al., 2004; Woolley, 1998). In addition, hippocampal NMDA-R activated downstream signaling could be important for these sex differences in FE, because phosphorylation of extracellular signal-regulated kinase (ERK) 2 appears to be less sensitive in female mice (Matsuda et al., 2015). A rodent study focused in contextual fear conditioning found that an ER-β agonist dosed in the hippocampus of females enhanced FE recall, thus providing a mechanism for E2 actions in this structure (Chang et al., 2009). Likewise, a human study that considered E2 levels found a positive correlation between E2 levels and FE recall. Also, better FE recall was related to greater activations in the hippocampus, vmPFC, dACC and amygdala (Zeidan et al., 2011).

Regarding clinical populations, PTSD patients have prominent structural and functional hippocampal abnormalities. Men with PTSD show lower amygdala-hippocampus rsFC and women with panic disorder have decreases in hippocampal metabolism (Bisaga et al., 1998; Etkin and Wager, 2007b; Garfinkel and Liberzon, 2009; SHIN et al., 2006; Sripada et al., 2012b; Trzesniak et al., 2010; van Rooij et al., 2015). These hippocampal dysfunctions coupled with an overactive amygdala and dACC result in a failure to inhibit fear responses when safety cues or safe contexts are presented (Garfinkel et al., 2014; Jovanovic et al., 2012; Rougemont-Bücking et al., 2011). In conclusion, the encoding of temporal and contextual stimuli is vastly influenced by hormonal states. Females undergo constant shifts in hippocampal function, so that the formation of FE memories using safe contexts as a trigger may be hindered in restricted periods or upon damage, ft remains to be determined if hormone-dependent shifts in hippocampal function can influence circuits relevant for FE (Åhs et al., 2015; Knapska et al., 2012; Marek et al., 2018) or the hippocampal inputs to structures that integrate internal states like the CeA, PrL or BNST (Rozeske et al., 2018; Xu et al., 2016; Zelikowsky et al., 2014).

2.1.4. Periaqueductal gray (PAG)—The PAG, also called “central gray”, is a region in the midbrain that coordinates functions like anxiety, fear learning, pain modulation and the onset of rapid defensive responses (Bandler and Shipley, 1994; Rabellino et al., 2016; Tovote et al., 2016). It is recognized as the central output pathway of threat processing, and involved in complex functions, such as the encoding of prediction errors and the relay of expectancy information to higher-order structures (Arico et al., 2017; McNally et al., 2011; Ozawa et al., 2017; Watson et al., 2016). Sex differences in the PAG are documented for sexual behavior, anxiolysis and antinociception (Linnman et al., 2012a; Loyd and Murphy, 2009; Schwartz-Giblin and McCarthy, 1995). Moreover, E2 can enhance GAB Aergic transmission and induce μ-opioid receptor (MOR) internalization, while drops in P4 can alter $GABA_A$ receptor subunit composition, decreasing its inhibitory output (Griffiths and

Lovick, 2005; Lovick, 2012; Loyd et al., 2008; Schwartz-Giblin and McCarthy, 1995). In humans, PAG activity is observed in relation to the anticipation of pain, imminent threat confrontation and during FE training (Fullana et al., 2018; Linnman et al., 2012b; Qi et al., 2018). Sex differences exist for PAG's basal rsFC, with less activation observed in women with high E2 upon fearful stimuli presentation (Goldstein et al., 2010; Kong et al., 2010). Moreover, in FC-FE tasks it is specifically activated to cues that signal danger or anticipate pain (CS+) (Lindner et al., 2015). In the clinics, PTSD patients have shown to have a greater recruitment of the PAG at rest and during threatening or non-threatening situations compared with controls (Harricharan et al., 2016; Rabellino et al., 2016; Steuwe et al., 2014). Overall, the PAG is involved in pain modulation and the execution of behavioral responses, some of which are the main outcomes measured in FE. Sex differences in the PAG are largely understudied, and it is still unknown if hormonal regulation of opioid and GABAergic transmission can influence FE or nociceptive encoding (Ozawa et al., 2017). Moreover, it must be explored if hormonal cycling results in shifting functional states in the PAG that impact how inputs are integrated and behaviors are selected (Fadok et al., 2018; Li et al., 2013).

2.1.5. Hypothalamic nuclei—The hypothalamus regulates autonomic, endocrine and behavioral responses to learned and innate threats (Keifer et al., 2015; LeDoux et al., 1988; Myers et al., 2014; Silva et al., 2016, 2013). It portrays extensive anatomical and functional sex differences related to parenting and sexual behaviors (Bailey and Silver, 2014; Cheung et al., 2015; Forger et al., 2004; Rhodes and Rubin, 1999; Simerly, 2002; Yang et al., 2013). However, the hypothalamus's involvement in FE is largely unexplored. The expression of estrogen receptors in several hypothalamic nuclei fluctuate throughout the estrous cycle possibly altering its intrinsic activity (Acevedo-Rodriguez et al., 2015; Brown et al., 1992; Frank et al., 2014). When fearful stimuli are presented, the ventromedial hypothalamus (VMH), lateral hypothalamus, and the left amygdala are more activated in men, than women. But when the menstrual cycle phase is considered, women in the late follicular/ mid cycle phase (high E2/ low P4) have attenuations in the stress response circuitry, including the paraventricular hypothalamus, VMH, PAG, dACC and CeA compared to women in the early follicular phase (low E2/ low P4) (Goldstein et al., 2010, 2005). Furthermore, VMH activity may relate to some behavioral alterations seen in patients with fear-based disorders, since electrical stimulation of the VMH elicits panic attacks in humans and some animal models (Kunwar et al., 2015; Wang et al., 2015; Wilent et al., 2010). In line with this, knocking down the vesicular glutamate transporter 2 in the VMH results in decreased fear expression in males only (Cheung et al., 2015). Just few studies have addressed the hypothalamus during FE learning reporting mixed results for its activation (Lebron Milad 2012, Hwang et al. 2015). One study found greater activity in the left-hypothalamus in women, whereas greater activity in the right-hypothalamus was found in men during FE learning, but no further differences were detected during FE recall (Lebron-Milad et al., 2012). In contrast, another study reported no sex differences in hypothalamic activation during FE training or recall, but found that the hypothalamus was highly active along with the threat detection system (amygdala, insular cortex, medial cingulate cortex) in women undergoing FC during high E2 states compared to men or women taking HC (Hwang et al., 2015). Future studies examining the role of the hypothalamus will add to the understanding

of the sex differences in fear and FE learning. For example, the VMH is regulated by hormones, but also integrates sensory (medial amygdala, basomedial amygdala) and nociceptive inputs (parabrachial nucleus) to influence relevant structures (dorsal PAG, BNST) that elicit and maintain CRs (Bester et al., 1997; Kunwar et al., 2015; Yang et al., 2013).

2.1.6. Bed Nucleus of the Stria Terminalis (BNST)—The BNST, part of the extended amygdala, acts as an integration node between external sensory information and internal homeostatic or autonomic states (Avery et al., 2014). It can activate the hypothalamus when facing stress, and its multiple subnuclei are strongly regulated by neuropeptides and sex hormones (Glangetas and Georges, 2016; Jennings et al., 2013; Kash et al., 2015; Marcinkiewcz et al., 2016; Tillman et al., 2018). Its function has been related to a sustained state of apprehension or fear, usually defined as anxiety, but it is also implicated in threat processing and responds to phasic and sustained stimuli (Alvarez et al., 2011; Fox et al., 2015; Gungor and Pare, 2016; Lebow and Chen, 2016; Shackman and Fox, 2016; Torrisi et al., 2018). In fear learning tasks, the BNST contributes to the acquisition, expression, reinstatement and some forms of contextual fear (Fullana et al., 2018; Goode and Maren, 2017; Hammack et al., 2015), but its role in FE is largely unexplored (Ranjan et al., 2017). There is a big gap in research regarding the influence of the sex differences in the BNST upon fear learning (Allen and Gorski, 1990; Avery et al., 2014). This structure undergoes a sexually dimorphic masculinization early in life and its function is also influenced by hormones in a state-dependent manner (Bangasser and Shors, 2008; Chung et al., 2002; de Vries and Forger, 2015; Kelly et al., 2013; Morishita et al., 2017; Pol et al., 2006; Zhou et al., 1995). Little is known regarding BNST's role in phasic threat response or fear inhibition processes, but its involvement is possibly under reported, at least in human studies (Fox et al., 2015; Shackman and Fox, 2016). Few studies have observed greater BNST activations in phobic orPTSD female patients (Brinkmann et al., 2017; Münsterkötter et al., 2015; Straube et al., 2007). Furthermore, its role in FE may be of importance due to its capacity to integrate internal states with contextual stimuli, future research will delineate the specific influences of hormones upon its function and how they may relate to FE (Chung et al., 2002; Cooke and Simerly, 2005; Oler et al., 2017).

2.1.7. Insula—The insula is located beneath the lateral sulcus, having an important function detecting salient stimuli and integrating somatosensory, motor and autonomic information with cognitive functions (Craig, 2009; Menon and Uddin, 2010; Namkung et al., 2017; Uddin, 2015). Therefore, it is not surprising that FC studies find it consistently activated during fear acquisition, upon the anticipation of pain or during the delivery of different types of USs (Benson et al., 2014, 2012; Fullana et al., 2016; Gramsch et al., 2014; Sehlmeyer et al., 2009). FE training activates the insular cortex, especially when it takes place in the same context where FC took place (Fullana et al., 2018; Gramsch et al., 2014; Sehlmeyer et al., 2009). Likewise, activations during FE recall are mostly seen when comparing CS+ vs CS− (Fullana et al., 2018). Basal differences in its structure and function are described for men and women (Kann et al., 2016; Ruigrok et al., 2014). Importantly, men receiving electric shocks have greater activations in the insula-hippocampus, whereas women taking HC seem to have this activation dampened (Hwang et al., 2015). During FE

recall, women have higher insular activity compared to men, but the difference seems to be driven by women with high E2 levels (Hwang et al., 2015; Lebron-Milad and Milad, 2012). Notably, insular dysfunctions are related to several psychiatric disorders, including anxiety and fear-based disorders (Etkin and Wager, 2007; Goodkind et al., 2015; Shin and Liberzon, 2010; Stein et al., 2007). For example, PTSD patients show insular hyperactivity at rest, and during exposure to traumatic and non-traumatic stimuli (Bruce et al., 2013; Fonzo et al., 2010; Simmons et al., 2008; Sripada et al., 2012a, 2012b; Stevens et al., 2013). Only one FE study reported increased insular blood flow during FE training in women with PTSD compared to women without (Bremner et al., 2005). Altogether, the insula plays a crucial role in salient stimuli detection regardless of sex; with some evidence indicating that its function may be modulated by endogenous and exogenous hormones (Hwang et al., 2015; Lebron-Milad and Milad, 2012). Insights into insular dysfunction mechanisms will be of uttermost value to several psychiatric disorders (Goodkind et al., 2015; Menon, 2011).

2.1.8. Summary—In summary, we can conclude that the amygdala, mPFC and hippocampus are implicated in the sex differences observed in FE, but more research is needed to examine the potential role of the BNST, hypothalamus, PAG and insula. The amygdala is consistently shown to react to threats regardless of sex, although it seems that some of its subnuclei may be overactive in females during low E2 phases. Moreover, its role as an integrator of internal states is relevant for FE, allowing females to switch and engage into different response patterns. Regarding the mPFC, IL function is relevant for FE memory formation-consolidation, and females demonstrate persistent PrL and lower IL activations during FE compared to males, which also correlate with greater freezing levels. According to the reviewed studies, mPFC function may follow the menstrual/ estrous cycle shifts rendering it hypoactive in low E2 phases. However, it is not clear if these effects are related to circuits displaying sexual dimorphism, distinct neuromodulation, or changes in connectivity with other structures (e.g., amygdala, hippocampus). Furthermore, the hippocampus is an important structure for the contextual embedding of FE memories receiving a large hormonal influence. E2 positively regulates its dendritic spines and can enhance FE through ER-β activation. The integrity of the hippocampus and its connectivity with the mPFC may be pivotal components of FE memory formation, especially in women and patients with fear-based disorders. Regarding the PAG, it seems that fluctuations in E2 and P4 can promote changes in GABAergic and opioid signaling that further impact its intrinsic activation and inhibitory output. Nevertheless, these effects are largely understudied. Concerning the other reviewed structures, the insula signals and detects salient stimuli regardless of sex but some evidence suggests that women may activate it differently depending on their hormonal levels. Lastly, the BNST and hypothalamus are understudied structures that receive a strong hormonal modulation, which could be relevant for the integration of internal states that impact the appearance and magnitude of the CRs during FE.

2.2. Sex Differences in Molecular Mechanisms of Fear Extinction

FE memory signals the safety of a previously conditioned stimulus in a specific context and this process is highly regulated by several neurotransmitters and intercellular signals at precise time points (Ehrlich et al., 2009). Depending on the temporal characteristics of FE

training, immediate or delayed, and the molecular signals presented prior or after training, different mechanisms can be recruited (Maren and Chang, 2006; Myers et al., 2006). The adequate coordination of neurochemical signals allows organisms to learn and ensure that future threats are adequately faced. Nevertheless, dysregulations under certain genetic and environmental conditions can give rise to pathological behavioral responses. Here we will review studies exploring some of these systems in FE, as well as their interaction with sex and hormones.

2.2.1. Glutamate and GABA—Glutamate is an excitatory neurotransmitter that belongs to the family of aminoacidic neurotransmitters. It is synthesized from glutamine in a wide variety of neurons (Meldrum, 2000). γ-Aminobutyric Acid (GABA), an aminoacidic neurotransmitter with inhibitory actions, is produced from the degradation of glutamate by the enzyme Glutamic-Acid Decarboxylase (GAD), which is presented in two isoforms: GAD65 and GAD67 (Meldrum, 2000; Petroff, 2002). The excitatory effects of glutamate are typically produced through ionotropic NMDA-R, α-amino-3-hydroxy-5-methyl-4-isoxazole Propionic Acid receptor (AMPA/ Kainate receptor) or metabotropic receptors (mGluR 1-8) (Sanacora et al. 2008); whereas GABA hyperpolarizes neurons acting on $GABA_A$, $GABA_B$ or $GABA_C$ receptors (Enz, 2001).

Sex differences have been identified within the glutamatergic system in both rodents and humans. First, concentrations of glutamate and GABA are sexually dimorphic in discrete brain nuclei important for FC, such as the nucleus accumbens or the VMH (Frankfurt et al., 1984). Further, concentrations of these neurotransmitters also differ across the estrous cycle in healthy adult female rats. Glutamate presents higher concentrations within the nucleus accumbens in males, but females possess higher levels in the diagonal bands of Broca and the VMH. On the other hand, GABA is more concentrated in the lateral hypothalamus, the habenular nuclei and the VMH of male rats. Notably, these differences arise during the metestrus stage of the estrous cycle, but not in proestrus. Also, there is an increased GABAergic function in response to E2 and the regulation of female sexual behavior by the VMH (Frankfurt et al., 1984). Furthermore, these nuclei are involved in different traits of fear processing, such as predator fear memory by the VMH (Silva et al., 2016) or freezing behavior during the exposure to a CS by the dorsal habenula (Agetsuma et al., 2010). Although the specific contribution to FE of each of the previous structures is still to be elucidated, they are known to be necessary for normal threat processing. Disruption of GABAergic and glutamatergic neurotransmission, especially during low sex-hormone states in females, might contribute to the prevalent phenotype in fear pathology.

Glutamate is of special interest to FE research due to its implication in LTP. During LTP, glutamate binds to AMPA-R producing a tetanic pulse necessary for the activation of NMDA-R. Further, glutamate binds to NMDA-R allowing Ca^{2+} influx only after magnesium leaves the cation channel in response to a tetanic stimulation. During the early 90's, it was demonstrated that NMDA-R antagonism within the amygdala, but not other areas, blocked the acquisition of the CR in a dose-dependent manner (Miserendino et al., 1990). Upon consideration of the extinction of the CR as a LTP of remote inhibitory synapses, new studies were carried out to examine the involvement of NMDA-R in FE. Surprisingly, pretraining administration of NMDA-R antagonists blocks the acquisition of extinction,

while AMPA-R antagonist infusions before FE training have no effect (Zimmerman and Maren, 2010). The AMPA-R is essential for NMDA-R activation and subsequent LTP that leads to memory formation. Interestingly, GluA1, one of the most common AMPA-R subunits, is essential for FC in male mice, but not in females (Dachtler et al., 2011), although it is more expressed in females' hippocampus compared to males (Katsouli et al., 2014). In regards to NMDA-R, female rodents usually perform poorer in NMDA-R dependent tasks, presumably because of a lower activation of NMDA-R during LTP when compared to males (Maren et al., 1994). Notwithstanding, aging produces a downregulation of Glu2N NMDA-R subunit, causing slight LTP decline in males; while this effect is not reported in females (Monfort and Felipo, 2007).

In contrast, the GABAergic system oppositely regulates fear memory formation. While glutamate is involved in depolarization of postsynaptic neuron and associative learning (Riedel et al., 2003), GABA hyperpolarizes postsynaptic membranes (Kalueff and Nutt, 1996). $GABA_A$-R has been widely studied due to its involvement in fear memory within the amygdala, hippocampus and PFC (Davis and Myers, 2002; Makkar et al., 2010). From all GABA receptors, $GABA_A$-R is the main target of a wide variety of available drugs, with their potential anxiolytic effects well described (Holmes and Chen, 2015). In the IL cortex, the pharmacological enhancement of $GABA_A$-R transmission before FE training increases FE acquisition and consolidation in the long term. Also, pre-training infusions of a $GABA_A$-R agonist in the BLA, as well as post-training infusion in the IL cortex, facilitate within-session FE, but produce no effects in successive recalls of that FE memory (Akirav et al., 2006). Particularly, α4-$GABA_A$-R and α5-$GABA_A$-R subunits of the $GABA_A$-R are the most reported sex-dependent mediators of fear memories within the GABAergic system. In males, α4-$GABA_A$-R knockout (KO) present increased fear to context in delay, but not trace auditory FC. In contrast, females lacking α4-$GABA_A$-R subunit express increased fear to context in trace auditory FC, but not delayed (Moore et al., 2010). Additionally, hippocampal deletion of α5-$GABA_A$-R subunit disrupts auditory FC in male and female mice; but producing lower fear expression in males with trace FC, while females display similar fear expression levels in trace and no trace conditions (Yee et al., 2004). Unfortunately, we are not aware of more studies exploring the involvement of these subunits in FE.

2.2.2. Cholinergic and Monoaminergic systems

2.2.2.1. Noradrenaline: Noradrenergic neurons in the locus coeruleus (LC) portray heterogeneous responses during fear and extinction learning that can strongly influence FE processes through its wide projections to the amygdala and mPFC (Quirk and Mueller, 2008; Uematsu et al., 2017). NA acts upon β-adrenergic receptors to increase neuronal excitability and upregulate protein kinase A (PKA) which are crucial processes for neuronal plasticity and FE memory formation (Berlau and McGaugh, 2006; Mueller et al., 2008). Moreover, NA promotes the retrieval of contextual fear memories and rodents with genetic NA depletion, or injected with propranolol (non-selective β-receptor antagonist), have deficits in fear memory retrieval (Murchison et al., 2004; Ouyang and Thomas, 2005). In addition, NA signaling is implicated in the "immediate extinction deficit", an impairment in extinction learning observed when FE is performed immediately after fear acquisition (Giustino et al.,

2017). The pharmacological blockade of NA signaling confirms its necessity for normal FE acquisition and FE consolidation (Mueller et al., 2008; Rodriguez-Romaguera et al., 2009). Nevertheless, enhancing NA signaling less consistently improves FE and instead promotes anxiety (Lonsdorf et al., 2014; Morris and Bouton, 2007; Tuerk et al., 2018).

Regardless of the multiple effects of NA on fear acquisition and FE, we are not aware of any study addressing specific sex differences. This is unexpected because it is known that testosterone regulates monoaminergic neonatal development in a sex dependent manner (Stewart and Rajabi, 1994) and that anatomical and functional sex differences exist in the LC (Bangasser et al., 2016, 2011; Mulvey et al., 2018; Valentino et al., 2012). Notably, females are more sensitive to the arousal-enhancing effects of corticotropin-releasing factor (CRF) due to a decreased ability to desensitize CRF1 receptors and differential receptor coupling and trafficking (Bangasser et al., 2018, 2010; Curtis et al., 2006; Valentino et al., 1991). In addition, females present decreases in μ-opioid receptor (MOR) function in the LC compared to males, that can render it overactive specially in stressful situations (Curtis et al., 2012; Guajardo et al., 2017). Besides this, cyclic surges of E2 increase NA synthesis, decrease its degradation but also promote adrenergic receptor internalization; pointing at a plausible mechanism by which females maintain arousal levels at the expense of a decreased ability to influence downstream signaling (Bangasser et al., 2016). The increases in NA tone and the greater LC function in females may confer a heightened susceptibility to develop NA dysregulations and hyperarousal symptoms after increased CRF exposure (Bangasser et al., 2018). Studies in humans performing adrenergic manipulations have found sex-specific effects for emotional processing, amygdala activation and patients' response to treatments (Cahill and van Stegeren, 2003; Kornstein et al., 2000; Lonergan et al., 2013; Poundja et al., 2012; Schwabe et al., 2013) but some others have not (Rothbaum et al., 2008; Steenen et al., 2016). With these data we can assume that FE-related increases in NA may synergize with higher NA levels during high E2 phases, together inducing a stronger recruitment of structures relevant for FE encoding or its consolidation. It is also possible that retrieved fear memories undergo a weaker reconsolidation due to decreased NA influence over intracellular processes, altogether resulting in stronger FE memory formation (Isiegas et al., 2006; Johansen et al., 2011). It remains to be explored if there is a differential recruitment of LC neurons in males and females that could impact its influence over target structures like the mPFC or amygdala.

2.2.2.2. Dopamine: DA is involved in arousal, motor control, stress response and several learning theories implicate it in the formation of fear and extinction memories (Abraham et al., 2014; Menezes et al., 2015; Mueller et al., 2010; Rodriguez-Romaguera et al., 2012; Shi et al., 2017). D1 and D2 receptors in the mPFC are involved in FE memory consolidation, and D1 receptor in the BLA is important for within-session FE (Hikind and Maroun, 2008; Mueller et al., 2010). Neuronal activity in the ventral tegmental area is necessary for normal FE learning, likewise promoting mitogen-activated protein kinase (MAPK) phosphorylation in the IL and LA (Brischoux et al., 2009; Gore et al., 2014; Luo et al., 2018). Pharmacological manipulations show that L-dopa and D1 agonists generally enhance FE and FE recall whereas D1 antagonists impair them, and D2 manipulations produce mixed results (Abraham et al., 2016; Haaker et al., 2015; Hikind and Maroun, 2008; Mueller et al., 2010;

Zbukvic et al., 2017). Sex differences in DA system are described for baseline or drug-induced DA release, receptor dynamics, DA levels, catechol-O-metyltransferase (COMT) activity and mesocortical projections (Harrison and Tunbridge, 2008; Kritzer and Creutz, 2008; Munro et al., 2006; Paolo, 1994; Riccardi et al., 2011). Additionally, the COMT gene polymorphism ($Val^{158}Met$), enhances DA levels and cortical function alongside interactions with E2. Women with the met/met genotype show improvements in working memory and dorsolateral prefrontal cortex function during the early phase of their cycle (low E2 levels), while val/val women have impairments. This relationship changes in phases near ovulation (high E2 levels), so that met/met women now show impairments, and val/val women have improvements (Jacobs and D'Esposito, 2011). In line with this data, a study reports that D1 agonism in females during low E2 phases reverts their usual FE recall impairment, while females trained during high E2 phases have their FE recall impaired by the drug (Colin D. Rey et al., 2014). Together pointing out that DA signaling follows E2 dynamics and influences PFC function, including FE, as an "inverted U-shape"; exerting a positive influence during low E2 phases and impairing an "optimal" signaling in high E2 phases (Jacobs and D'Esposito, 2011; Colin D. Rey et al., 2014). The basis of this effect is unknown but can relate to the observed differences in mesocortical projections or to a lower DA function that protects females from prefrontal overactivation during high reactivity states, like in low E2 phases. Finally, it must be accounted that DA may also act upon the striatum and influence the cortico-subcortical network connectivity relevant for FE (Correia et al., 2016; Luo et al., 2018; Myers and Davis, 2007).

2.2.2.3. Serotonin: Serotonin (5-HT) is produced in the raphe nuclei of the brainstem and implicated in several fear memory processes (Bauer, 2015; Gaspar et al., 2003). Selective serotonin reuptake inhibitors (SSRIs) are one of the most prescribed drugs in psychiatric practice and the first-line pharmacological treatment for mood, anxiety and fear-based disorders (Ravindran and Stein, 2010). When dosed acutely, they inhibit the serotonin transporter (SERT) and lead to a net increase in 5-HT, enhancing anxiety symptoms and increasing fear expression (Marcinkiewcz et al., 2016). On the contrary, chronic doses are needed to obtain clinically significant effects and anxiolysis (Invernizzi et al., 1996; Krishnan and Nestler, 2008). The effects of SSRIs upon FE vary depending on the type of drug, treatment duration and timing of administration. Chronic fluoxetine or escitalopram facilitate FE (Arce et al., 2008; Bui et al., 2013; Deschaux et al., 2013, 2011; Karpova et al., 2011), but chronic citalopram impairs fear acquisition and FE through NR2B NMDA-R subunit downregulation in the BLA (Burghardt et al., 2013). Sex differences in this system include 5-HT receptor distribution, SERT binding potential and the regulation of 5-HT synthesis by E2 through ER-β receptors (Donner and Handa, 2009; Jovanovic et al., 2008; Rubinow et al., 1998; Suzuki et al., 2013). Moreover, studies in animal models report mixed findings for E2-SSRIs interactions. For example, E2 can negatively impact the efficacy of fluvoxamine, but provides benefits for women in the perimenopause (Benmansour et al., 2012; Damoiseaux et al., 2014). A fear learning study found that acute doses of fluoxetine increased fear responses in both sexes during FE training and FE recall. But 14 days of chronic fluoxetine enhanced FE learning and FE recall in females only during low E2 phases (Lebrón-Milad et al., 2013). This effect is similar to the one obtained with D1 agonism and highlights the possibility that increases in monoaminergic signaling may enhance mPFC

function during low E2 phases, thus facilitating FE formation. However, this assumption may be overgeneralized, as each monoamine is implicated in discrete processes of FE learning and their interactions with other systems should be considered (Jolas and Aghajanian, 1997; Nestler et al., 1990; West et al., 2009). It will be important to delineate the magnitude of monoaminergic FE enhancement during low E2 phases because they may act as adjuvants to exposure therapy under restricted conditions but may also promote greater fear retrieval.

2.2.2.4. Acetylcholine (ACh): ACh binds to muscarinic and nicotinic receptors to regulate several physiologic functions in the central nervous system that include arousal, attention and cognition. Cholinergic transmission is also implicated in neuronal activity synchronization, thereby improving the “signal-to-noise” ratio in the amygdala and facilitating memory encoding in the PFC (Hasselmo, 2006; Unal et al., 2015). Within the FE network, cholinergic neurons act as a relay of sensory pathways and regulate FC and FE by altering synaptic plasticity, firing patterns and neuronal excitability (Knox, 2016). Increases in muscarinic signaling are related to improvements in FE learning and FE recall, while decreased muscarinic signaling usually impairs FE processes (Jiang et al., 2016; Knox and Keller, 2016; Santini et al., 2012; Wilson and Fadel, 2017; Zelikowsky et al., 2013). The role of cholinergic neurotransmission through nicotinic receptors in FE is less clear, since the effects are highly dependent on the length of administration and the hippocampal involvement during a task (Elias et al., 2010; Kutlu and Gould, 2015, 2014).

A contextual fear learning study that explored sex differences reports that muscarinic blockade in males impairs fear memory recall, while females seem unaffected. Nevertheless, animals were exposed to the context only for 5 minutes and it would be desirable to explore if this male-specific impairment in fear retrieval extends into FE learning (Rashid et al., 2017). Sex differences are observed for nicotinic receptor dynamics, with males (and men) upregulating nicotinic receptors after chronic nicotine exposure, but remaining unaltered in females (Koylu et al. 1997). Moreover in women, P4 levels are associated with lower β_2-nicotinic receptor expression in cortical and cerebellar areas (Cosgrove et al., 2012). A FC study demonstrated that nicotine exposure affects males and females differently. Males showed impairments in FE when acute low or high doses of nicotine were used, whereas females only were affected by high doses. In contrast, chronic nicotine exposure increased the spontaneous recovery of fear in females only (Oliver et al., 2018; Tumolo et al., 2018). To summarize, although it has been demonstrated that muscarinic and nicotinic receptor activity can modulate fear learning and FE, it is not well defined how they specficially influence FE in each sex. Some studies point out that cholinergic signaling can act upon cortical and BLA interneurons to promote fear learning through disinhibition, but the contribution of this mechanism to FE is largely unexplored (Gozzi et al., 2010; Letzkus et al., 2015). Moreover, tobacco smoking is highly prevalent in patients with psychiatric disorders (Cook et al., 2014; Lawrence et al., 2009) and some of the reviewed studies suggest that chronic nicotine exposure may produce a resistance to FE in men, whereas women are more vulnerable to the spontaneous recovery of fear.

2.2.3. Neuropeptides and Neurotrophins

2.2.3.1. Cannabinoids: Endocannabinoid (eCB) signaling is crucial for FC and FE. Research has shown that the manipulation of eCBs can alter the acquisition and expression of contextual, but not cued fear memories (Chhatwal and Ressler, 2007; Marsicano et al., 2002). Studies in animals and humans support the notion that agonizing eCB signaling facilitates FE learning (Chhatwal et al. 2005; Lutz 2007; Das et al. 2013; Dincheva et al. 2015 but see Bowers and Ressler 2015; Soria-Gómez et al. 2015). Proposed mechanisms for this positive effect include the modulation of synapses in an activity-dependent manner and the stimulation of plasticity at inhibitory synapses (Hill et al., 2010; Trouche et al., 2013; Vogel et al., 2016). In contrast, deletions or blockade of CB1 receptor produces severe impairments in FE due to the blockade of kinase and phosphatase activity (Cannich et al., 2004; Hill et al., 2010; Marsicano et al., 2002; Papini et al., 2015). Also, human studies show that dronabinol (synthetic THC) decreases amygdala reactivity during FE training, whereas increasing hippocampal and vmPFC activity during FE recall (Das et al., 2013; Rabinak et al., 2014, 2013). Notably, the positive effects of eCBs over FE are only demonstrated with acute administrations, as chronic dosing impairs between and within-session FE and threat-safety discrimination (Lin et al., 2008; Papini et al., 2017).

There are several region-specific sex differences in eCB levels and CB1 receptor expression. Compared to naturally cycling females, males and ovariectomized females have higher density of CB1 receptors in the hippocampus, greater CB1 receptor binding in the hypothalamus and lower CB1 binding in the amygdala. Interestingly, the increased hippocampal CB1 expression in ovariectomized females is negatively regulated by the administration of E2 (Bradshaw et al., 2006; Reich et al., 2009; Riebe et al., 2010). Further, cycling females are reported to have fluctuations of eCB levels throughout the estrous cycle in several brain regions (Bradshaw et al., 2006). And various studies accounted cycling females as being more sensitive to the effects of eCBs over nociception, motor movements and neurogenesis (Craft et al., 2013; Krebs-Kraft et al., 2010). Functionally, high E2 levels can potentiate CA1 excitatory transmission in a sex-dependent manner by increasing eCB signaling through the activation of ER-α and promoting a retrograde suppression of GABAergic inhibition (Huang and Woolley, 2012). Lastly, the administration of an eCB antagonist in males can induce differences in the activity of the hypothalamic-pituitary-adrenal (HPA) axis, producing a greater and longer ACTH-dependent corticosteorne diurnal peak (Atkinson et al., 2010). Despite these findings, little research has specifically addressed for sex differences during FE. One study investigated the effects of CB1 agonism and antagonism in females, showing that FE was enhanced with eCB agonists and impaired with antagonists, concluding that eCB effects on FE are not sex-dependent (Simone et al., 2015). Finally, increases in eCB signaling can reverse the stress-dependent alterations in FE in both sexes, but producing different effects in the hippocampus (Zer-Aviv and Akirav, 2016). In sum, few studies have addressed eCB-hormonal interactions upon FE, probably fueled by the positive results obtained with cannabinoid signal enhancements (Gunduz-Cinar et al., 2013). Studies exploring the pharmacokinetics and sex-divergent effects of chronic usage would be useful if considering cannabinoids as adjuvants to exposure therapy.

2.2.3.2. Opioids: Opioid peptides are classically involved in pain regulation; and for this reason, used as first line drugs to treat physical trauma. However, they are also consumed as drugs of abuse because of their addictive properties. Several areas of the fear circuitry expressing opiate receptors are also involved in the processing of aversive, cognitive and physiological aspects of pain (Sandkühler and Lee, 2013). For example, opioids act on the intercalated cells of the amygdala and on the PAG to promote FE, hence regulating the encoding of prediction errors and the inhibition of aversive stimuli processing (Ozawa et al., 2017; Roy et al., 2014). Notably, dynorphin and μ opioid receptor (MOR) signaling are implicated in the formation of FE memories in rodents and humans (Bilkei-Gorzo et al., 2012; Likhtik et al., 2008; McNally et al., 2005; Parsons et al., 2010). Gonadal hormones, specifically E2, can interact with the opioid system promoting their release, inducing receptor internalization and altering the rates of receptor homo-heterodimerization (Loyd et al., 2008; Loyd and Murphy, 2009). MOR expression is higher in males compared to cycling females in the ventrolateral PAG, with the lowest expression found during the proestras phase (Loyd et al., 2008). Moreover, some studies point out that sex and hormones are factors that can influence how painful stimuli are perceived or processed (Chartoff and Mavrikaki, 2015; Craft, 2008; Eckersell et al., 1998; Kelly et al., 2003; Liu et al., 2011; Torres-Reveron et al., 2009).

A study that administered intra-LC doses of a MOR agonist found that females had decreased sensitivity to MOR-mediated inhibition of LC neuronal activity, along with an overall decreased expression of MOR. Also, researchers measured behavioral outcomes using an operant set shifting task, showing that females made more preservative errors, whereas males made more the total errors and premature responses (Guajardo, Synder et al., 2017). This study highlights an important sex dimorphism in opioid function in the LC of females. Opioids are known to counteract the effects of stress-induced LC activation, and to promote the recovery of LC activity to pre-stress levels (Valentino and Van Bockstaele, 2015). A decreased ability to diminish LC hyperactivity after facing stressful events would leave females prone to develop hyperarousal states. A study that focused on the effects of opioid administration on fear learning showed that dosing subcutaneous morphine after fear acquisition resulted in increased fear responses during FE only in females that had low E2 levels. This effect was absent in males, proestrus females or when dosed prior to FE training, demonstrating that acute morphine shortly after trauma can enhance fear responses in a subset of females. However, no further differences were observed during FE recall in any group (Perez-Torres et al., 2015). In sum, the decreased sensitivity of MOR in the LC of females, may hinder their capacity to downregulate LC hyperactivity after facing stressful events. Also, the fluctuation of E2 levels during the estrous cycle can impact the expression of MOR in the PAG; an essential structure that encodes expectancy errors and processes painful stimuli during fear learning tasks. Studies exploring the intracellular mechanisms underlying sex differences in FE will be valuable, opioid receptor activation can influence cAMP expression, and it is known that increased cAMP can delay FE memory formation (Myers and Davis, 2007). Additionally, morphine is commonly dosed after acute trauma and it may promote adverse behavioral outcomes in a subset of women.

2.2.3.3. Corticotropin-releasing factor (CRF): CRF is a peptide hormone involved in the activation of the HPA axis, also regulating neuroendocrine, behavioral and emotional adaptations to stressors (Sherin and Nemeroff, 2011). Localized CRF increases in the BLA during FE training, impair further FE recall but without affecting FE acquisition. On the contrary, CRF decrements improve FE recall (Abiri et al., 2014; Hollis et al., 2016). Fear learning processes are tightly regulated by this peptide, CRF can induce hyperexcitability of principal neurons in the BLA and decrease eCB signaling (Gray et al., 2015; Rainnie et al., 2004). Further, specific impairments of NMDA or $GABA_A$-R function in CRF neurons increase fear expression and impair FE respectively (Gafford et al., 2012; Gilman et al., 2015). Interestingly, CRF is related to the "immediate extinction deficit", pointing out actions over NA transmission, but also a possible convergence of their intracellular signaling cascades (Hollis et al., 2016; Isogawa et al., 2013; Roozendaal et al., 2008). The transcription of CRF is modulated by E2. Higher basal CRF is found in the PVN of females during the proestrus phase, demonstrating also greater upregulation after physical (foot shock) or emotional stressors (Bingaman et al., 1994; Iwasaki-Sekino et al., 2009). Moreover, CRF1 and CRF2 receptors undergo sexually dimorphic changes after puberty, and differences in CRF1 dynamics in the LC are related to an enhanced sensitivity to CRF in females. Specifically, females have a greater coupling of CRF1 receptor with the GTP-binding protein, Gs in unstressed conditions. Also, the association of CRF1 receptor with β-arrestin2, a molecule promoting receptor internalization, occurs in the LC of males only, compromising CRF1 receptor internalization in females (Bangasser and Shors, 2010; Bangasser and Wicks, 2017; Weathington and Cooke, 2012). When administered centrally, CRF induces similar activations in males and females, except for the LC and lateral PAG which are activated only in females (Wiersielis et al., 2016). Nevertheless, another study that evaluated neuronal activity after central CRF administration found negative correlations for E2 levels and c-fos activation in the extended amygdala (Salvatore et al., 2018). In addition, KO of NMDA-R subunit NR1 (*Grin1*) in CRF neurons increased CRs during FE session only in males (Gilman et al., 2015). In sum, CRF enhancements of neuronal excitability seem to be detrimental for FE probably by encouraging an internal state of increased alertness and mobilization of resources (Binder and Nemeroff, 2010). Also, its signaling produces greater activations in the LC of females that are related to a different modulation of CRF1 which may posit females prone to develop arousal dysregulations under high or constant CRF secretion (Bangasser et al., 2018; Bangasser and Wicks, 2017; Curtis et al., 2006). Moreover, it remains to be explored if CRF projections from structures like the CeA or BNST can influence FE learning or its consolidation in a sex-dependent manner (Ehrlich et al., 2009; McCall et al., 2015; Sanford et al., 2017). The stress-induced sex differences in FE are reviewed somewhere else (Maren and Holmes, 2016; Merz et al., 2018; Merz and Wolf, 2017; ter Horst et al., 2012; Wolf et al., 2015).

2.2.3.4. Brain-derived neurotrophic factor (BDNF): BNDF is a neurotrophin that influences neuronal function and survival, also playing roles in neurodevelopment, stress response and memory (Andero and Ressler, 2012). It promotes neuronal excitability (Minichiello, 2009), fear acquisition (Andero et al., 2011) and it is important for FE consolidation (Chhatwal et al., 2006; Choi et al., 2010; Heldt et al., 2007; Peters et al., 2010). Remarkably, intra-hippocampal BDNF produces cue-dependent FE even in the

absence of training (Peters et al., 2010). Studies have revealed that BDNF acts as a signaling mediator of estrogen in the brain (Carrer et al., 2003; Scharfman and MacLusky, 2006). High E2 levels upregulate BDNF mRNA and protein levels in the hippocampus, which also fluctuate across the estrous cycle (Gibbs, 1998). The VAL66Met polymorphism in the pro-region of BDNF decreases its secretion, produces deficits in FE, and lower amygdala habituation to emotional stimuli (Gasic et al., 2009; Hariri et al., 2003; Lonsdorf et al., 2015; Soliman et al., 2010). Furthermore, male and female mice with the $BDNF^{Met/Met}$ genotype have impairments in hippocampal function, with females showing additional alterations in the normal fluctuation of plasticity molecules in the hippocampus (Spencer et al., 2010).

Sex differences exist for BDNF function; females with a resistance to FE have lower basal BDNF mRNA levels in the IL and greater methylation at exon IV (Baker-Andresen et al. 2013). In comparison, males subjected to FE have increased BDNF exon I and exon IV mRNA in the mPFC (Bredy et al., 2007). A study that performed a conditional KO of TrkB receptor in parvalbumin interneurons found impairments in FE consolidation for males compared to littermate controls or females (Lucas et al., 2014). Moreover, the authors emphasized on the importance of this differential TrkB-dependent effect, because SSRIs are known to upregulate BDNF in the BLA and promote greater plasticity in parvalbumin interneurons (Karpova et al., 2011). Although the specific mechanism is not known yet, it may follow secondary impairments of NMDA-R function due to the bidirectional glutamatergic-BDNF interactions (Andero and Ressler, 2012; Minichiello, 2009). It remains to be tested if females are endowed with a compensatory mechanism to consolidate FE even in the absence of TrkB signaling. The association of BDNF with psychiatric disorders and its interaction with inter-individual factors like genotype or hormonal status place this neurotrophin at a central point for further studies, especially the ones addressing mental disorders with a sex-biased prevalence (Andero et al., 2014).

2.2.3.5. Oxytocin-Vasopressin: Oxytocin (OXT) and vasopressin (AVP) are molecules that act as neuropeptides and neurohormones exerting central and peripheric effects. They regulate stress, social behavior and can shape defensive responses, especially to unpredictable threats (Dębiec, 2005; Grillon et al., 2013; Leppanen et al., 2018; Meyer-Lindenberg et al., 2011; Neumann, 2008). Moreover, central OXT promotes weaker fear memory formation, but can also impair FE if dosed prior to FE training (Toth et al., 2012). Nevertheless, the effects of OXT over FE are influenced by factors like the strength of fear memories, the timing of OXT doses and the targeted structures, sometimes producing opposite effects (Huber et al., 2005; Knobloch et al., 2012; Lahoud and Maroun, 2013; Viviani et al., 2011; Zoicas et al., 2014) (Campbell-Smith et al., 2015). Interestingly, in the centro lateral amygdala, OXT can activate a subpopulation of neurons that feedforward inhibit the centro medial amygdala, thereby reducing passive fear responses (freezing, fear potentiated startle) and promoting active fear responses (Terburg et al., 2018; Viviani et al., 2011). In humans, intranasal OXT enhances FE recall but producing transient increases in the CRs of men during FE training (Acheson et al., 2013; Eckstein et al., 2015).

OXT and AVP systems portray structure and species-specific sex differences, with the AVP system usually being more prominent in males and the OXT system in females (de Vries, 2008; De Vries and Panzica, 2006; Dumais and Veenema, 2016; Lee et al., 2009;

MacDonald, 2013). Also, both systems are regulated by sex hormones in an organizational and state-dependent manner, but the positive influence of E2 upon OXT is the most notorious (de Vries and Södersten, 2009; Gimpl et al., 2002; Grazzini et al., 1998; Meyer-Lindenberg et al., 2011; Olff et al., 2013; Sippel et al., 2017). Intranasal OXT produces sex-dependent activations in the amygdala and changes in its rsFC (Bethlehem et al., 2017; Domes et al., 2010, 2007; Ebner et al., 2016; Eckstein et al., 2017; Kovács and Kéri, 2015; Lischke et al., 2012; Petrovic et al., 2008; Sripada et al., 2013). In addition, OXT can modulate PFC activity in a sex dependent manner, possibly through actions of interneurons (Li et al., 2016; Luo et al., 2017; Nakajima et al., 2014). It is notable that the effects of OXT are influenced by inter-individual factors such as lifetime experiences and genotype (Bartz et al., 2011; Bradley et al., 2013; Heim et al., 2009; Meinlschmidt and Heim, 2007; Sippel et al., 2017). In the clinics, intranasal OXT exerts positive effects in PTSD patients by activating different neuronal substrates in men and women, also showing beneficial effects for a subset of people after trauma (Koch et al., 2016a, 2016b; Sack et al., 2017; van Zuiden et al., 2017). Unfortunately, these benefits do not seem to generalize to other anxiety disorders (Acheson et al., 2015). Overall, it seems that OXT is a neuropeptide that can influence fear retrieval, acute CRs to threats and FE memory consolidation. Some evidence indicates that OXTR expression is different in males and females in structures like the VMH, but not in the CeA (Uhl-Bronner et al., 2005). However, its functional role in FE, especially in females, remains to be elucidated. When exploring the effects of OXT over FE, researchers must account for sex, hormonal status, genotype and lifetime experiences in order to define the specific conditions under which OXT can positively regulate FE memories (Meyer-Lindenberg et al., 2011)

2.2.4. Regulation of fear extinction by gonadal hormones—Fear processes, especially FE, have shown to be strongly regulated by circulating sex hormones. Despite the higher life prevalence of stress and fear related disorders in women, the specific influence of sex hormones on FE remains poorly understood (Bangasser and Valentino, 2014). E2 has proved to enhance FE, either when administered systemically in ovariectomized rats or in the putatively high E2 stages across the estrous cycle (Graham and Daher, 2016; Milad et al., 2009). Further, inhibition of E2 synthesis during FE has shown to reduce auditory FE (Graham and Milad, 2014). In contrast, P4, another hormone that also peaks with E2 during the proestrus phase, is hypothesized to exert opposite functions on FE compared to E2, but mixed results are commonly reported. Allopregnanolone, a P4 metabolite, acts as a positive allosteric modulator of $GABA_A$-R with the capacity to alter its subunit composition. In addition, studies have described a concentration-dependent biphasic effect over $GABA_A$-R that can lead to an allopregnanolone tolerance at high concentrations (Andréen et al., 2009; Pinna et al., 2000; Turkmen et al., 2011). In naturally cycling rats, systemic administration of a P4 receptor antagonist prevents the impairment in FE recall observed in females undergoing FE training during metestrus (Graham and Daher, 2016). Interestingly, if allopregnanolone is artificially infused in the BNST before both, fear acquisition and FE training, it no longer enhances FE. This outcome reflects that the BNST may integrate the temporal profile of internal hormonal states with other ongoing processes (Acca et al., 2017). Altogether, these findings suggest that in naturally cycling females, E2 may exert facilitating effects over FE, while P4 exerts the contrary, probably by involving genetic and

epigenetic mechanisms regulating the synthesis of proteins necessary for FE memory consolidation.

Low circulating E2 has shown to be a vulnerability factor for the development of PTSD (Lebron-Milad and Milad, 2012). Moreover, the chronic suppression of E2 synthesis by monophasic hormonal contraceptives in women or by the administration of progestin in rats, results in a low-extinction phenotype, which can be easily reverted by terminating treatments or by systemically administering an E2 receptor agonist (Graham and Milad, 2013). Additionally, women with low salivary E2 present higher skin conductance response during FE training in comparison to women with high E2 (Wegerer et al., 2014). Serum E2 concentrations can predict exposure therapy efficacy in women with spider phobia (Graham et al., 2018). Moreover, women with fear-based disorders taking HC display reductions in treatment efficacy and increased post-treatment symptoms (Li and Graham, 2016). Little research has been conducted regarding E2 role in other fear-based disorders such as panic disorder. Women at high risk for panic attacks have shown precipitation of panic disorder after taking HC (Deci et al., 1992). In contrast, estrogen replacement therapy is reported to be effective at reducing panic symptoms (Chung et al., 1995). Likewise, in men, pentagastrin-induced panic symptoms are reduced after a 3-day pretreatment with ethinyl E2 (an estrogen receptor agonist) (McManus et al., 2001).

The role of testosterone, the primary sex hormone in males which lacks fluctuating properties, in regard to FE remains controversial. On the one hand, some studies report testosterone does not play a role in male rodents in FC, FE or FE recall (Anagnostaras et al. 1998; McDermott et al. 2012). On the other hand, several studies report a strong modulation of FE acquisition and retention by male and female gonadal hormones. Further, blocking aromatase enzyme with fadrozole during FE training impairs FE recall 24 hours later in males (Graham and Milad, 2014). Also, dosing males with a GnRH agonist that increases the synthesis of testosterone enhances FE memory consolidation (Maeng et al., 2017). One hypothesis for this effect is that testosterone acts by its conversion to E2, producing over FE all the facilitating effects that were previously described (Graham and Milad, 2014). This could explain why FE appears more stable in males, while it presents disruptions in females during low E2 stages. Although it’s controversial, the current literature on E2 in males is hypothesized to be as important as in females for the consolidation of the FE memory. Testosterone levels seem unaltered in male patients with PTSD, but when analyzing a subset of PTSD patients without any comorbidity, higher testosterone levels are observed in comparison to controls and males with comorbid PTSD (Karlović et al., 2012). In line with this study, abnormalities in testosterone concentration have also been found in American survivors of the Iranian Hostage Crisis, presenting higher salivary testosterone than healthy controls (Rahe et al., 1990). In contrast, some other studies report lower testosterone in cerebrospinal fluid of combat veterans with current PTSD (Mulchahey et al., 2001). The existence of a SNP within the gene encoding for the 5-α-reductase (SRD5A2), an enzyme that degrades testosterone into dihydrotestosterone, correlates with more serious PTSD symptoms in men, but not women (Gillespie et al. 2013).

2.2.5. Summary—There are several molecular mechanisms implicated in the sex differences observed in FE, some of which are directly influenced by the dynamics of

gonadal hormones. E2 and testosterone emerge as crucial elements in FE memory formation with the capacity to positively regulate its consolidation. As reviewed here, women with high E2 levels, or rodents undergoing FE training during the proestrus phase, have better FE memory recall compared to women with low E2 levels or rodents trained during other estrous phases. Studies also show that glutamatergic transmission is crucial for fear learning and FE acquisition, although GluA1 seems to be essential for fear acquisition in males. Furthermore, several sex dimorphisms are reported for $GABA_A$-R subunits that may impact fear acquisition and FE learning, having additional interactions with P4 metabolites. However, studies exploring the glutamatergic and GABAergic mechanisms of FE in both sexes are scarce. Neurotransmission in the LC is tightly modulated by sex and hormones. Differences in CRF1 receptor dynamics and MOR sensitivity leave females vulnerable to the effects of sustained CRF signaling, and prone to NA overactivation under stressful situations. Further, the effects of CRF over target structures may interact with hormonal levels, because females with high E2 have shown less activation of the extended amygdala in response to CRF. Neurotransmission by eCBs and BDNF generally improves FE in both sexes, from which the latter is positively regulated by E2 and may be related to the enhanced FE recall in females undergoing FE training during high E2 phases. In the case of DA and 5-HT transmission, studies have shown differential effects over FE that depend on the type of drug and the targeted receptor. However, females benefit from increases in DA and 5-HT transmission only during stages with low E2 levels. The other reviewed neurotransmitters produce different effects over FE in each sex, but not always following the same direction. It seems that their actions are subject to factors like the dose, timing of administration and specific effects over target structures.

3 Future directions

Our knowledge about FE and the implicated neural circuits will be greatly improved with the arrival of revolutionary technologies. The combination of tools that determine specific neuronal profiles, with others that track neuronal dynamics *in vivo,* will enable researchers to precisely manipulate neuronal populations driving FE behavior. Additional factors like age, social interactions and the environment have not received much focus despite their powerful impact on health and behavior. Future studies must target these variables and provide evidence for additional within-sex effects that have not been accounted in detail yet, potentially improving our understanding of when and how sex differences arise in FE. Examples include, female's reproductive status (Milligan-Saville and Graham, 2016), the role of social interactions in males (Horii et al., 2017), and the changes in fear learning across the lifespan (Kim and Richardson, 2010; Remmes et al., 2016). In humans, accounting for gender as a research variable is gaining recognition in psychiatric and behavioral research (The Lancet Psychiatry, 2016). Gender and gender conformity may be considered as an additional context (i.e. socioeconomic status, marital status) in which a person develops with the capacity to influence perceptions, choices, health and behavior (Short et al., 2013). Its role upon FE is fairly unrecognized, but its inclusion as a 2-step approach questionnaire where participants are asked for their sex assigned at birth and their current gender identity may provide insights about its contributions to fear learning (Clayton and Tannenbaum, 2016).

Research frontiers will expand by the translation of basic research into the clinics. FE mimics exposure therapy procedures and it can be regarded as an useful model to test novel approaches to treat fear-based disorders despite its intrinsic limitations (Milad et al., 2014). Drugs that increase BNDF or cannabinoid signaling could be beneficial interventions for exposure therapy regardless of sex. In the case of hormonal interventions, males have shown to improve their FE with the use of a GnRH agonist (Maeng et al., 2017), while females may benefit from exogenous E2 or an ER-B agonist during their naturally low E2 stages (Maeng and Milad, 2015). However, a tight monitoring of the menstrual cycle/ hormonal levels is necessary since adverse outcomes are possible if E2 dosing is not timely constrained (Cover et al., 2014). Drugs increasing monoaminergic function in the mPFC during low E2 stages in females may render similar benefits as E2 (Inagaki et al., 2010).

Other aspects that may be relevant for women undergoing exposure therapy include the acknowledgement of SSRIs intake and a high nicotine consumption. Furthermore, hormonal contraception seems to be related with lower levels of FE, altered rsFC and changes in HPA axis reactivity (Engman et al., 2018; Graham and Milad, 2013; Hertel et al., 2017; Petersen et al., 2014). Thus, it seems urgent to explore the specific outcomes of exposure therapy in women using hormonal contraception. Lastly, the tailored timing of exposure therapy sessions during putatively high E2 phases may result in better clinical outcomes. Nevertheless, we lack studies that track fear learning in a within-subjects design throughout the menstrual cycle. It is still necessary to define the exact time windows in which E2 benefits FE as it is not known if the benefits can be obtained during the peri-ovulatory phase, the mid luteal phase or following drastic hormonal shifts? (Maeng and Milad, 2015). Future studies performing a systematic control of the menstrual/estrous cycle and the hormonal status will inform about the specific factors to account for when performing fear research in women and females.

4 Conclusions

Here we have discussed all the studies on sex differences in FE that we are aware of. Despite an exponential growth in the number of papers focused on FE during the last 20 years, few studies using animal models have included both sexes in their design. Moreover, studies in humans and FE scarcely test for sex differences or systematically control for hormonal status. During the last years, this research bias has started to change, and now more studies are focused on sex differences in FE in both animals and humans. The main reason fueling this change implies the consensus about the need to focus on the female brain. For example, it is evident that including sex as a variable in FE is giving us a better understanding of the mechanistic processes underlying it, either by delineating the influence of sex hormones, or by revealing different brain connectivity patterns, among others. In addition, actual medical interventions begin to focus on personalized treatments. Thus, the understanding of how sex and hormonal status alter FE will be beneficial for designing specific treatments for men and women when appropriate.

The need to account for sex and the hormonal status when performing fear research is highlighted by studies that demonstrated women and female rodents seem to be generally hyper-responsive to threats during low E2 hormonal phases, also presenting impairments in

FE. The results from this review can be summarized into 5 points: 1) Sex hormones modulate FE and its consolidation but the exact underlying molecular mechanisms remain largely unknown. Seemingly, putative high E2 levels and P4 shifts exert positive and negative effects on FE respectively. 2) Hormonal fluctuations may determine different functional states in females, as some neurotransmitter/ neuropeptides follow these hormonal shifts, potentially influencing neuronal circuits relevant for FE. Examples include the changes in hippocampal spine density, differences in PAG's inhibitory output, and the persistence of CeA/BNST-mediated behaviors. 3) The prominent sex differences in LC function, render it overactive in females under certain conditions. Moreover, greater NA signaling can impact fear retrieval, FE encoding, and FE consolidation. 4) PFC function seems to be regulated differently by monoamines throughout the menstrual/estrous cycle, so that increases in monoaminergic transmission during low E2 phases generally exert a positive influence over FE and the opposite occurs in phases with high E2. An observation that warrants further research since most drugs used to treat fear-based disorders target these systems. 5) There are apparent sex differences in the molecular mechanisms of FE consolidation related to glutamate, males with impaired glutamatergic function are unable to consolidate FE while females seem unaffected. The possibility of an alternative compensatory mechanism for FE consolidation in females should be explored.

Besides the small amount of research focused on females in FE, we must also account for the additional limitations in this review: There are considerable gaps in the mechanisms and circuits implicated in the retrieval of memories, specially FE memories. This is a crucial factor since memories become embedded into distributed networks with the passage of time and much of the reviewed studies are focused on the retrieval of FE in the short term. For example, it seems that FE memories are weakly stored into long-lasting engrams and the role of the striatum, thalamus and dorsolateral prefrontal cortex remains to be explored. Added to this, molecular signatures for FE and FE recall are scarce, and some of the conflicting findings may be explained by mechanisms applying only to a subset of neurons e.g. interneurons vs pyramidal neurons. Thus, the polymodal profiling of the studied neurons along with technical improvements in single-cell research will increase our understanding about their role in the micro and macrocircuits that regulate fear learning. Coupled with these theoretical frontiers, the ample methodological differences make it difficult to directly compare studies. Immediate and delayed FE are known to recruit specific molecular machinery, making them not completely interchangeable. Also, most studies submit subjects to non-naturalistic tasks or scenarios and rely solely on freezing response to measure fear learning. Thus, improvements in fear research will be achieved by the measurement of multiple CRs, the standardization and inclusion of subject's hormonal status and the increased use of pathological fear learning animal models. Overall, the analysis of the sex differences in FE can give important insights about possible circuit and molecular dysregulations underlying the pathophysiology of fear-based disorders.

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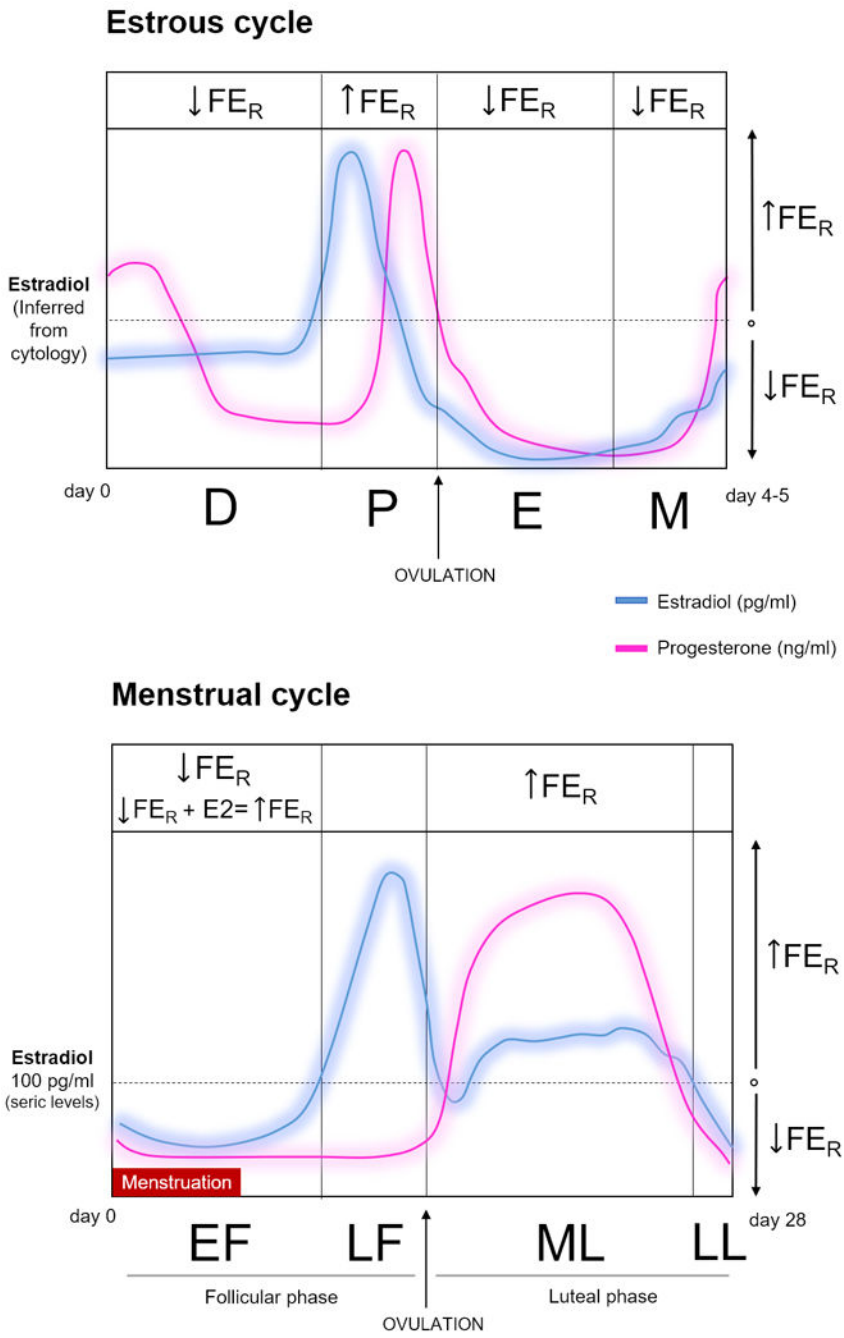

Figure 1.

Scaled representation of estradiol and progesterone levels during the distinct phases of the estrous (rodent) and menstrual cycle (human). The result of subjecting females to Fear Extinction (FE) training during each phase is shown at the top as fear extinction recall (FE_R). The FE_R of females undergoing FE training under high or low estrogen states appears on the right. * denotes additional within-session effects of the cycle during FE training. D: diestrus, E: estrus, E2: estradiol, EF: early follicular phase, LF: late follicular phase, LL: late luteal phase, M: metestrus, ML: mid luteal phase, P: proestrus. Information obtained from:

1. Milad et al., 2009, 2. Gruene et al., 2015, 3. Rey et al., 2014, 4. Milad et al., 2010, 5. Zeidan et al., 2011, 6 Pineles et al., 2016, 7. Graham & Milad 2013

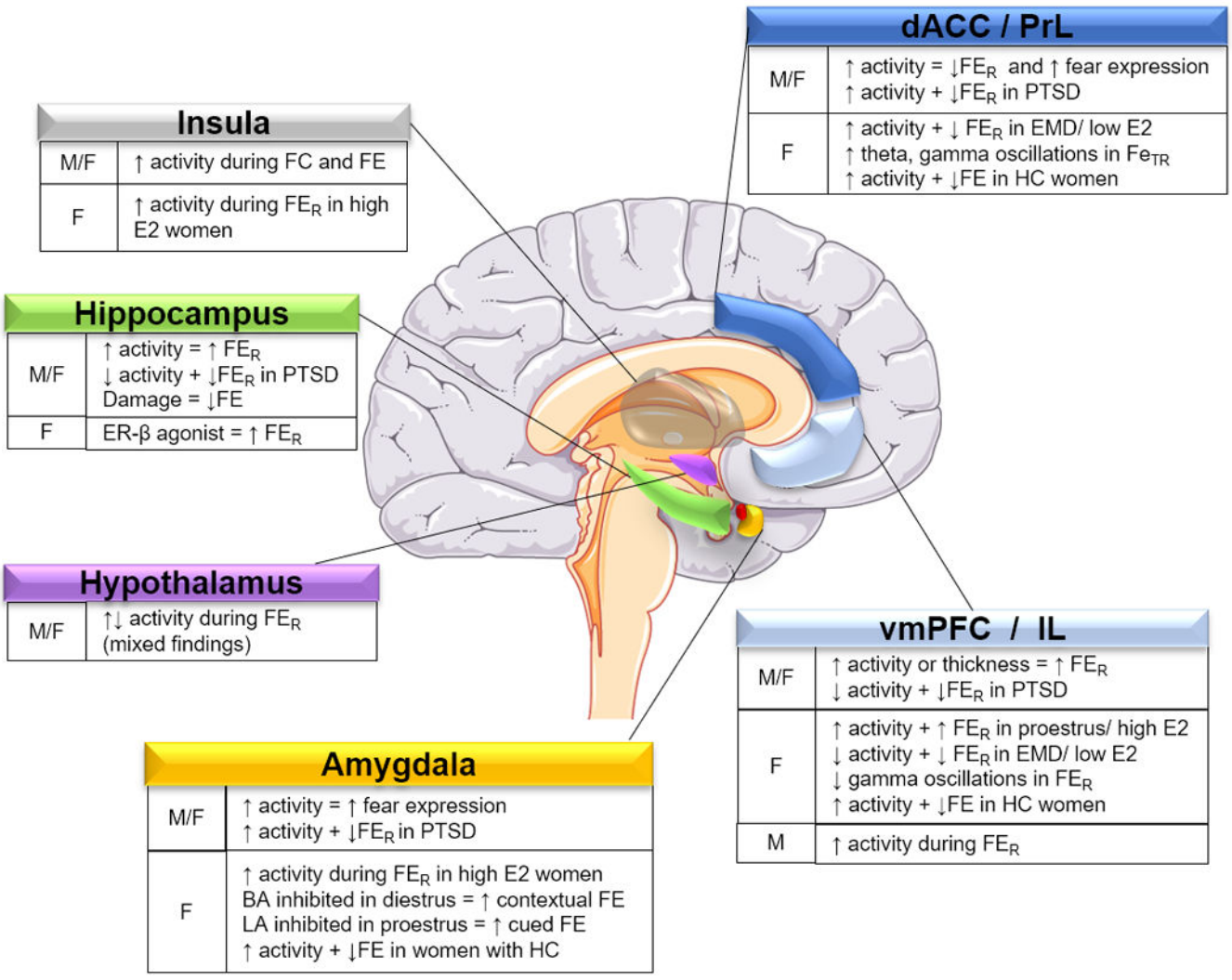

Figure 2.

Schematic representation of the brain structures where sex differences in fear extinction are reported. The main findings of animal and human research appear enlisted under each structure. BA: basal amygdala, dACC: dorsal anterior cingulate cortex, E2: estradiol, EMD: estrus, metestrus, diestrus phases of estrous cycle, ER-β: estrogen receptor beta, F: females, FC: fear conditioning, FE: fear extinction: FE_R: fear extinction recall, FE_{TR}: fear extinction training, HC: hormonal contraceptives, IL: infralimbic cortex, LA: lateral amygdala, M: male, M/ F: male and female, PrL: prelimbic cortex, PTSD: posttraumatic stress disorder, vmPFC: ventromedial prefrontal cortex.

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Table 1.

Selected studies that compare sex differences during fear extinction training and fear extinction recall in cued fear conditioning paradigms. Some methodological details that could influence behavioral responses are depicted.

STUDY			METHODOLOGY						RESULTS		
Author	**Species**	**Groups**	**Test sex diff**	**Manipulation**	**via**	**Timing**	**Behavioral paradigm**	**FE recall test**	**Outcome measures**	**FE training**	**FE recall**	**Functional/ anatomical correlates**
Merz et al., 2012	*H*	M, F(Lut), F(HC)	Y	basal	-	-	Diff-cued, imm FE	-	SCR, BOLD	F=M		F(HC) > M, F(Lut) in AMY, dACC and vmPFC
Blume et al., 2017	*R*	M, F(d), F(p) in FC and FE_{TR}	Y	basal	-	-	S-cued, 4d FE	-	freezing	M=F, F(p) > F(d)		F(p) with greater LA inhibition
Knapska & Maren 2009	*R*	just males	N	basal	-	-	S-cued, 24h FE	24h	freezing, c-fos		M enhanced in FE context, impaired in diff context	Increased c-fos in IL, ITC, DG for FE recall. Increased in BLA, PrL, CeM for fear renewal. CA1 & CA3 c-fos in both
Gruene et al., 2014	*R*	just females	N	basal*	-	-	S-cued, 24h FE	24h	freezing, c-fos		F enhanced in diff context	Increased c-fos in IL for FE recall
Lindner et al., 2015	*H*	just females	N	basal	-	-	Diff-cued, imm FE	-	FPS, BOLD			PAG, vmPFC activation to CS in FE training. Activation to startle probe in CS+ during FE training for insula, ACC, thalamus &PAG
Baran et al., 2009	*R*	M, F	N	basal	-	-	S-cued, 1h and 24h FE	24h	freezing	F fail to extinguish	F fail to extinguish	
Voulo & Parsons 2017	*R*	M, F	Y	basal	-	-	S-cued, 24h FE	24h	freezing FPS	F=M	M > F only in FPS	
Nagaya et al., 2015	*R*	M, F	Y	Allo / Allo inhibitor / Allo antagonist	Intra-BNST	PRE-FE	S-cued, 24h FE	24h	freezing	F=M		
Antov & Stockhorst 2014	*H*	M, F(Ef), F(Lf)	Y	basal	-	-	Diff-cued, imm FE	24h	SCR	F > M*	F=M	
Zeidan et al., 2011	*R*	just females, F(m) in FE_{TR}	N	ER-α/ ER-β agonist / E2	SC	PRE-FE/ E2 POST-FE	S-cued, 24h FE	24h	freezing, c-fos		Enhanced in F(m)	E2 increased c-fos in IL-vmPFC and decreased in amygdala

STUDY		METHODOLOGY								RESULTS		
Author	**Species**	**Groups**	**Test sex diff**	**Manipulation**	**via**	**Timing**	**Behavioral paradigm**	**FE recall test**	**Outcome measures**	**FE training**	**FE recall**	**Functional/ anatomical correlates**
	H	just females, F(HE2), F(LE2)	N	basal	-	-	Diff-cued, imm FE	24h	SCR, BOLD		F(HE2) > F(LE2)	F(HE2) greater activation in amygdala HPC, dACC and vmPFC for FE recall, & greater vmPFC for FE training
Milad, Zeidan et al., 2010	*H*	M, F(HE2), F(LE2)	Y	basal	-	-	Diff-cued, imm FE	24h	SCR, EXT ret index	F(HE2) =F(LE2). M=F	F(HE2) > F(LE2). M, F(HE2) > F(LE2)	
Milad, Igoe et al., 2009	*R*	M, F(p), F(m) in FE_{TR}	Y	E2/ P/ E2 antagonist/ P antagonist	SC	PRE-FE	S-cued, 24h FE	24h	freezing	F=M. F(m) +E2&PG > F(m), F(m) +E, F(m)+P	F=M. F(p), M > F(m). Enhanced in F(m)+E2	
Milad, Goldstein et al., 2006	*H*	M, F(Ef), F(Lf)	Y	basal	-	-	Diff-cued, imm FE	24h	SCR, EXT ret index	F=M	F(Ef), M > F(Lf)	
Hwang et al., 2015	*H*	M, F(HC), F(HE2), F(LE2)	Y	basal	-	-	Diff-cued, imm FE	24h	BOLD			F(HE2) > F(LE2) in insula, F(HE2) > M in rACC and insula in FE training. F(HE2) > M in insula and MCC in FE recall
Graham & Milad 2013	*H*	just FEM F(HC), F(Ef) in FE_{TR}	N	E2	PO	PRE-FE	Diff-cued, imm FE/ 24h FE	24h	SCR		Impaired in F(HC). Rescued in F(Ef)+E2	
	M	just females, F	N	ER-α/ ER-β agonist/ Progestin	SC	PRE-FE	S-cued, 24h FE	24h	freezing		Impaired in F +P. Rescued with ER agonists	
Graham & Daher 2016	*R*	just FEM. F(OVX), F(d) in FC & FE_R	N	P / E2 / P antagonist	SC	PRE-FE	S-cued, vary FE	24h	freezing		Enhanced in F(m)+P antagonist	
Graham & Milad 2014	*R*	just males	N	E2 / aromatase inhibitor	SC	PRE-FE, POST-FE	S-cued, 24h FE	24h	freezing		Impaired by aromatase inhibitor. Rescued by E2	
Maeng & Cover 2017	*R*	just females,	N	E2	SC	PRE-FE	S-cued, 24h FE	24h	freezing, c-fos		Enhanced in F(m)+E2	E2 increase CEl c-fos and decrease LA c-fos in FE training.

STUDY		METHODOLOGY								RESULTS		
Author	**Species**	**Groups**	**Test sex diff**	**Manipulation**	**via**	**Timing**	**Behavioral paradigm**	**FE recall test**	**Outcome measures**	**FE training**	**FE recall**	**Functional/ anatomical correlates**
		F(m) in FE_{TR}										Decrease CeM c-fos in FE recall
Baran et al., 2010	*R*	M, F	Y	Bilateral electrolytic lesion IL-PrL	Intra-mPFC	PRE-FC	S-cued, 1h or 24h FE	24h	freezing	M > F	F > M	
Fenton et al., 2014	*R*	M, F	Y	basal	-	-	S-cued, 24h FE	13d	Local field potentials	M > F	M > F	F have persistent theta activation in the PrL during FE training and FE recall
Fenton et al., 2016	*R*	M, F	Y	basal	-	-	S-cued, 24h FE	13d	Local field potentials	M > F	M > F	F persistent gamma in PrL in FE training and failure to increase IL gamma in FE recall
Lebron-Milad et al., 2013	*R*	M, F(p,e), F(m,d) in FE_{TR}	Y	Fluoxetine acute or chronic	IP/PO	PRE-FE	S-cued, 24h or 14d FE	24h	freezing	Acute impaired in M, F. Chronic enhanced in F(m,d)	Chronic enhanced in F(m,d)	
Lebron-Milad et al., 2012	*H*	M, F	Y	basal	-	-	Diff-cued, imm FE	24h	SCR, BOLD	F=M	F=M	FE tr: F > M dACC, mPFC, l-hypothalamus; M > F r-hypothalamus. FE recall: M >F rACC; F>M insula
Gruene et al., 2015	*R*	M, F(p), F(e,m,d) in FE_{TR}	Y	basal	-	-	S-cued, 24h FE	24h	freezing	F=M. F(p) > F(e,m,d)	F=M. F(p) > F(e,m,d)	High freezing M have neuroanatomical alterations
Mueller et al., 2014	*H*	M, F	N	basal	-	-	Diff-cued, imm FE	24h	EEG			dACC theta activity in FE training, vmPFC changes in gamma activity in FE recall
Moore et al., 2010	*M*	M, F	Y	GABAa-α4 KO	-	-	s-cued: trace/ delay ed, 24h FE	-	freezing	F > M with delayed FC. M > F with trace FC		
Wiltgen et al., 2005	*M*	M, F	Y	GABAa-δ subunit KO	-	-	s-cued: trace/ delay ed, 24h FE	-	freezing	M>F in delayed and trace FC		
Morris & bouton 2007	*R*	F	N	Yohimbine	IP	PRE-FE	S-cued, 24h FE	24h	freezing	Enhanced	Enhanced	
Mueller et al., 2009	*R*	M	N	Yohimbine	IP	PRE-FE	S-cued, 24h FE	24h	freezing	Enhanced		

STUDY				METHODOLOGY						RESULTS		
Author	**Species**	**Groups**	**Test sex diff**	**Manipulation**	**via**	**Timing**	**Behavioral paradigm**	**FE recall test**	**Outcome measures**	**FE training**	**FE recall**	**Functional/ anatomical correlates**
Cain et al., 2004	*M*	M	N	Yohimbine / Propranolol	SC	PRE-FE	S-cued, 24h FE spaced/massed	24h	freezing	Yohimbine enhances. Propranolol impairs	Yohimbine enhances	
Rey et al., 2014	*R*	M, F(p), F(e,m,d) in FE_{TR}	Y	D1 agonist	IP	PRE-FE	S-cued, 24h FE	24h	freezing, c-fos	F=M	Impaired in F(p), enhanced in F(e,m,d)	c-fos in IL-BLA projecting neurons was unchanged after FE but correlated with freezing in F(e,m,d)
Simone, Malivore et al., 2015	*R*	F, F(OVX)	N	CB1 agonist / antagonist	IP	PRE-FE	S-cued, 24h FE	-	freezing	Agonist low dose enhance, high dose impairs		
Simone, Green et al., 2015	*R*	M	N	CB1 agonist / antagonist	IP	PRE-FE	S-cued, 24h FE	-	freezing	Agonist enhance		
Perez-Torres et al., 2015	*R*	M, F(p), F(m) in FC	Y	Morphine	SC	imm POST-FC	S-cued,24h FE	-	freezing	M, F(p) + morphine > F(m) +morphine		morphine increased MOR in amygdala of F(p) & M but not F(m)
Gilman et al., 2015	*M*	M, F	Y	Grin1 KO in CRF neurons	-	-	Diff-cued, 24h FE	-	freezing	F > M		
Lucas et al., 2014	*M*	M, F	Y	TrkB in PV cells KO	-	-	S-cued, 24h FE	24h/7d	freezing		Impaired in M	
Baker-Andersen et al., 2013	*M*	M, F	Y	BDNF agonist	IP	PRE-FE	S-cued: + retrieval, 24h FE	24h	freezing	M > F. Rescued in F by BDNF agonist	Impaired in F	F with lower BDNF mRNA and greater exon IV methylation

* = additional sex differences during fear acquisition or basal outcome measures.

ACTH- adrenocorticotropic hormone, Allo- allopregnanolone, BA- basal amygdala, BDNF- brain derived neurotrophic factor, BLA- basolateral amygdala, BNST- bed nucleus of the stria terminalis, BOLD- blood oxygen level dependent, CB1- cannabinoid receptor type 1, CEl- centro lateral amygdala, CeM- central amygdala, CFC- contextual fear conditioning, d- days, D1- dopamine receptor D1, dACC- dorsal anterior cingulate cortex, DG- dentate gyrus, dHPC- dorsal hippocampus, diff- different, Diff-cued- differential-cued fear conditioning, E2- estradiol, EEG- electroencephalogram, ER-α - estrogen receptor alpha, ER-β- estrogen receptor beta, EXT ret index- extinction retention index, F- female, F(d)- female diestrus, F(e)- female estrus, F(Ef)- female early follicular phase, F(HC)- Female hormonal contraceptives, F(HE2)- female high estradiol, F(LE2)- female low estradiol, F(Lf)- female late follicular phase, F(Lut)- Female luteal phase, F(m)- female metestrus, F(OVX)- female ovariectomized, F(p)- female proestrus, FC - fear conditioning, FE- fear extinction, FE_R- fear extinction recall, FE_{TR}- fear extinction training, FPS- fear potentiated startle, h- hours, *H*- human, HPC- hippocampus, IL- infralimbic cortex, imm- immediate, IP- intraperitoneal administration, ITC- intercalated cells of the amygdala, LA- lateral amygdala, l-hypothalamus- left hypothalamus, LTP- long term potentiation, M- male, *M*- mouse, M(TESTX)- male orchiectomized, MCC- mid cingulate cortex, MOR- mu opioid receptor, N- no, NMDAr- NMDA receptor, P-progesterone, PAG- periaqueductal gray, PO- oral administration, PRE-FC- previous to fear conditioning, PRE- FE_R - previous to fear extinction recall, PRE- FE_{TR} - previous to fear extinction training, PrL- prelimbic cortex, PV- parvalbumin , *R* – rat, rACC- rostral anterior cingulate cortex, r-hypothalamus- right hypothalamus, SC- subcutaneous administration, SCR- skin conductance response, S-cued- single-cued fear conditioning, SR- spontaneous recovery, TrkB- tropomyosin receptor kinase B, vmPFC- ventromedial prefrontal cortex, Y- yes

Table 2.

Selected studies that compare sex differences during fear extinction training and fear extinction recall for contextual fear conditioning paradigms. Some methodological details that could influence behavioral responses are depicted.

STUDY		METHODOLOGY								RESULTS		
Author	**Species**	**Groups**	**Test sex diff**	**Manipulation**	**via**	**Timing**	**Behavioral paradigm**	**FE recall test**	**Outcome measures**	**FE training**	**FE recall**	**Functional/ anatomical correlates**
Maren et al., 1994	*R*	M, F	Y	basal	-	-	CFC,24h FE	24h	freezing	F > M		M>F HPC LTP & NMDAr activation
Gupta et al., 2001	*R*	M, F, F(OVX)	Y	E2	SC	PRE-FC	CFC, 24h FE	24h	freezing & FE rates	F(OVX+E2) > F(OVX)	F > F(OVX), M	F(OVX) had greater LTP in DG of HPC, reversed in F(OVX)+E2
Barker & Galea 2010	*R*	M(TESTX), F(OVX)	Y	E2	SC	15 d PRE-FC	CFC, 24h FE	24h	freezing	F(OVX) > M(TESTX)	F(OVX +E2)>F(OVX) , M(TESTX+/−E2)	
Daviu et al., 2014	*R*	M, F	Y	basal	-	-	CFC, 9d FE	24h	freezing	F > M	F > M	F>M ACTH & corticosterone levels
Chang et al., 2009	*R*	M, F(p), F(e), F(d) in FC	Y	basal	-	-	CFC, 24h FE	24h	freezing & FE rates	F(p) > M	F(e), F(p) > M	
		F(OVX+E2), F(OVX+P)	N	basal	-	-	CFC, 24h FE	24h	freezing & FE rates		F(OVX+E2) > F(OVX+P)	
		F(OVX)	N	ER-α/ ER-β agonist	IP	PRE-FC	CFC, 24h FE	24h	freezing & FE rates		F(OVX+ER-β) > F(OVX+ER-α)	
		F(OVX)	N	ER-β agonist / E2	Intra-HPC	PRE-FE recall	CFC, 24h FE	24h	freezing & FE rates		Enhanced for F(OVX+E2/ER-β)	
Blume et al., 2017	*R*	M, F(d), F(p) in FC and FE_{TR}	Y	basal	-	-	CFC, 4d FE	-	freezing	M=F, F(d) > F(p)		F(d) with greater BA inhibition
Matsuda et al., 2015	*M*	M, F, F(OVX)	Y	basal	-	-	CFC, 24h	28d	freezing	F > F(OVX)	M > F	ERK phosphorylation in dHPC appeared sooner in males
Matsuda et al., 2018	*M*	M, F	Y	Basal, 1-week isolation	-	PRE-FC	CFC, 24h FE	35d	freezing	(Fear expression) F grouped > F isolated		
Dachtler et al., 2011	*M*	M, F	Y	GLUR1 KO	-	-	CFC, 24h FE	-	freezing	Enhanced in M *		

STUDY				METHODOLOGY						RESULTS		
Author	**Species**	**Groups**	**Test sex diff**	**Manipulation**	**via**	**Timing**	**Behavioral paradigm**	**FE recall test**	**Outcome measures**	**FE training**	**FE recall**	**Functional/ anatomical correlates**
Oliver et al., 2018	*M*	M, F	Y	Nicotine acute & chronic	IP/SC	PRE-FE / PRE-FC	CFC, 24h FE	24h	freezing		Acute impaired F & M. Chronic impaired in M	
Tumolo et al., 2018	*M*	M, F	Y	Nicotine chronic	SC	POST-FE	CFC, 24h FE	24h	freezing		SR: M > F. Nicotine decreases SR in M and enhances in F	

*= additional sex differences during fear acquisition or basal outcome measures.

ACTH- adrenocorticotropic hormone, Allo- allopregnanolone, BA- basal amygdala, BDNF- brain derived neurotrophic factor, BLA- basolateral amygdala, BNST- bed nucleus of the stria terminalis, BOLD- blood oxygen level dependent, CB1- cannabinoid receptor type 1, CEl- centro lateral amygdala, CeM- central amygdala, CFC- contextual fear conditioning, d- days, D1- dopamine receptor D1, dACC- dorsal anterior cingulate cortex, DG- dentate gyrus, dHPC- dorsal hippocampus, diff- different, Diff-cued- differential-cued fear conditioning, E2- estradiol, EEG- electroencephalogram, ER-α - estrogen receptor alpha, ER-β- estrogen receptor beta, EXT ret index- extinction retention index, F- female, F(d)- female diestrus, F(e)- female estrus, F(Ef)- female early follicular phase, F(HC)- Female hormonal contraceptives, F(HE2)- female high estradiol, F(LE2)- female low estradiol, F(Lf)- female late follicular phase, F(Lut)- Female luteal phase, F(m)- female metestrus, F(OVX)- female ovariectomized, F(p)- female proestrus, FC - fear conditioning, FE- fear extinction, FE_R- fear extinction recall, FE_{TR}- fear extinction training, FPS- fear potentiated startle, h- hours , *H*- human, HPC- hippocampus, IL- infralimbic cortex, imm- immediate, IP- intraperitoneal administration, ITC- intercalated cells of the amygdala, LA- lateral amygdala, l-hypothalamus- left hypothalamus, LTP- long term potentiation, M- male, *M*- mouse, M(TESTX)- male orchiectomized, MCC- mid cingulate cortex, MOR- mu opioid receptor, N- no, NMDAr- NMDA receptor, P- progesterone, PAG- periaqueductal gray, PO- oral administration, PRE-FC- previous to fear conditioning, PRE- FE_R - previous to fear extinction recall, PRE- FE_{TR} - previous to fear extinction training, PrL- prelimbic cortex, PV- parvalbumin , *R* – rat, rACC- rostral anterior cingulate cortex, r-hypothalamus- right hypothalamus, SC- subcutaneous administration, SCR- skin conductance response, S-cued- single-cued fear conditioning, SR- spontaneous recovery, TrkB- tropomyosin receptor kinase B, vmPFC- ventromedial prefrontal cortex, Y- yes