Behaviour Research and Therapy 129 (2020) 103615

Contents lists available at ScienceDirect

Behaviour Research and Therapy

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

A review on how stress modulates fear conditioning: Let's not forget the role of sex and sex hormones

Clémence Peyrot[a,b,1], Alexandra Brouillard[a,c,1], Simon Morand-Beaulieu[a,d,e], Marie-France Marin[a,b,c,*]

[a] Research Center, Institut universitaire en santé mentale de Montréal, 7331 Hochelaga Street, Montreal, Quebec, Canada, H1N 3J4
[b] Department of Psychiatry and Addictology, Université de Montréal, 2900 Édouard-Montpetit Boulevard, Montreal, Quebec, Canada, H3T 1J4
[c] Department of Psychology, Université du Québec à Montréal, 100 Sherbrooke Street W, Montreal, Quebec, Canada, H2X 2P3
[d] Department of Neuroscience, Université de Montréal, 2960 de la Tour Rd, Montreal, Quebec, Canada, H3T 1J4
[e] Currently with the Child Study Center, Yale University School of Medicine, 230 S Frontage Rd, New Haven, CT, 06519, USA

ARTICLE INFO

Keywords:
Stress
Stress hormones
Fear conditioning
Sex differences
Sex hormones

ABSTRACT

Stress and fear are two fields of research that have evolved simultaneously. It was not until the eighties that these domains converged in order to better characterize the impact of stress on fear memory formation. Here, we reviewed the effects of stress occurring before fear acquisition on the main phases of fear conditioning protocols (acquisition training, extinction training, extinction retention test), with a specific focus on sex and sex hormones. We also paid close attention to methodological aspects in order to better understand and characterize discrepant findings across studies. In men, stress appears to potentiate fear acquisition at a physiological level but induces lower activations of fear-related brain regions. In women, results are inconsistent. Although some studies have shown that stress lowers physiological fear responses and heightens brain activations in women during fear acquisition, many studies report no significant effects. Irrespective of sex, pre-acquisition stress seems to induce fear extinction learning resistance. Overall, few studies have taken into account sex hormones, despite their impact on both the fear and stress brain networks. As methodological variability makes it complex to draw strong conclusions, several methodological aspects are discussed with the aim of orienting future research.

1. Introduction

As part of this special edition on fear conditioning, this review aims to understand how stress exposure or modulation of stress hormones before a fear conditioning protocol may affect fear learning, extinction learning and extinction retention, as a function of sex and sex hormones. The first section will offer a historical perspective of the fields of stress, fear, and sex. We will also describe the clinical relevance to further studying these three topics together. We will then review the studies that have assessed the impact of pre-acquisition stress on the various phases of the fear conditioning protocol. We will finally conclude with a discussion pertaining to methodological differences and some suggestions and guidelines for future studies in the field.

1.1. Fear mechanisms

1.1.1. History of fear research

The concept of conditioning was inadvertently discovered by Ivan Pavlov at the end of the 19th century. After pairing food (an appetitive stimulus) with a neutral stimulus (such as the sound of a metronome), Pavlov discovered that the single presentation of the neutral stimulus was enough to induce salivation in dogs. He called this process *conditioned reflex* (Pavlov, 1927), which is now well-known as classical or Pavlovian conditioning.

In parallel, in 1920, John B. Watson and Rosalie Rayner designed an experimental protocol to study fear responses in infants (Watson & Rayner, 2000). In their famous Little Albert experiment, they exposed a toddler to several pairings between a white rat and a loud noise. Consequently, Little Albert developed a generalized fear to all rats' features,

* Corresponding author. Department of Psychology, Université du Québec à Montréal, 100 Sherbrooke Street W, Montreal, Quebec, H2X 2P3, Canada.
E-mail addresses: clemence.peyrot@umontreal.ca (C. Peyrot), brouillard.alexandra@courrier.uqam.ca (A. Brouillard), simon.morand-beaulieu@yale.edu (S. Morand-Beaulieu), marin.marie-france@uqam.ca (M.-F. Marin).
[1] These authors contributed equally to the manuscript.

https://doi.org/10.1016/j.brat.2020.103615
Received 30 September 2019; Received in revised form 27 March 2020; Accepted 5 April 2020
Available online 10 April 2020
0005-7967/

such as white fur (Watson & Rayner, 2000). This study added an emotional component to classical conditioning and contributed to develop the field of fear conditioning research.

1.1.2. Studying fear processes in the laboratory

Over the years, experimental paradigms were developed to study the physiological, psychological, and neuronal processes involved in fear conditioning in humans. In this type of experimental paradigm, participants are usually first exposed to a habituation phase in order to allow them to become acquainted with the neutral innocuous stimuli (NS) used in the experiment (e.g., geometric figure, picture, colored light, noise). During the fear acquisition phase, an aversive unconditioned stimulus (US; e.g., electric shock, loud noise, airblast to the larynx) is linked to one NS (Craske, Hermans, & Vansteenwegen, 2006; Lipp, 2006). As the US induces an unconditioned response, several pairings between the NS and the US generate an associative learning. The NS itself is then enough to generate a conditioned fear response and is thereafter referred to as a conditioned stimulus (CS) or threat cue (LeDoux, 2014; Lonsdorf et al., 2017). The associative fear acquisition corresponds to an emotional memory process, which will then undergo memory consolidation and could later be recalled (Kandel, Dudai, & Mayford, 2014; Sangha, Diehl, Bergstrom, & Drew, 2019). In fear conditioning paradigms, two CSs are usually presented, one CS is reinforced by a US (CS+), whereas the other is not (CS-; safety cue). Depending on the methodology used, the CS+ presentations can be completely reinforced (100% of the trials) or partially (not all CS + trials are followed by the US) (Lonsdorf et al., 2017).

Fear acquisition training is often followed by fear extinction training, where the same CSs are presented without any association with the US. As a result, participants learn that the CS+ no longer predicts the aversive stimulus and a decrease in fear responses to the CS + is observed as extinction learning occurs. As it was the case for fear acquisition, the fear extinction process creates a new memory trace, which implies that both the fear memory and the extinction memory traces coexist and compete for expression (Myers & Davis, 2002, 2007). Several hours later, or a day after, an extinction retention test (extinction recall) could take place in order to evaluate fear extinction memory consolidation (for reviews see: Bouton, 2004; Milad & Quirk, 2012; Myers & Davis, 2007).

1.1.3. Measuring fear responses

In the laboratory, fear can be assessed through physiological, psychological, and neural measures. Physiological measures such as skin conductance (SC) and fear-potentiated startle reflex (FPS) are regularly used to record variations of the sympathetic nervous system activity in response to threat stimuli (Fridlund & Cacioppo, 1986; Grings, 1960; Lonsdorf et al., 2017). Other measures such as heart rate (HR) and pupillary dilatation are also employed, but less frequently (Lonsdorf et al., 2017). A differential score is often used to measure physiological fear acquisition. This method consists of subtracting the CS- responses from the CS+ responses, which allows to quantify the amplitude of discrimination between threat and safety cues (Lonsdorf et al., 2017).

Fear could also be assessed by psychological measures. Indeed, subjective responses allow to evaluate cognitive process, such as US expectancy and contingency learning, and/or affective processes, such as valence or arousal ratings (Boddez et al., 2013; Lipp, 2006; Lonsdorf et al., 2017). Regarding cognitive processes, US expectancy is defined as the expectancy to receive an US after a CS presentation, whereas contingency awareness allows to determine if the participant can explicitly tell which CS is paired with a US and which one is not (Boddez et al., 2013; Craske et al., 2006; Lipp, 2006; Lonsdorf et al., 2017). Regarding affective responses, valence is usually evaluated by asking the participant to rate the stimulus as unpleasant/negative, neutral, or pleasant/positive, whereas arousal is usually measured on a continuous scale, from low to high arousal (Lipp, 2006; Lonsdorf et al., 2017).

Neural measures can also be collected with functional magnetic resonance imaging (fMRI), which offers an insight into the brain structures involved in fear learning processes. Over the years, a wealth of fMRI investigations have allowed identifying key regions implicated in fear acquisition and its regulation, which is now referred to as the fear circuitry: the amygdala, the hippocampus, the dorsal anterior cingulate cortex (dACC), the ventromedial prefrontal cortex (vmPFC), and the insular cortex (for reviews see: McGaugh, 2004; Milad & Quirk, 2012; Milad, Rauch, Pitman, & Quirk, 2006; Pitman et al., 2012; Quirk & Mueller, 2008; Sangha et al., 2019; Shin & Liberzon, 2010). The amygdala is involved in fear acquisition, fear extinction, and extinction memory and is interconnected with other regions of the fear circuitry. The hippocampus plays a key role in processing relevant contextual information, whereas the dACC and insular cortex are involved in fear acquisition. The vmPFC is a crucial brain structure involved in fear extinction learning and retention (Milad, Rosenbaum, & Simon, 2014; Tovote, Fadok, & Luthi, 2015).

1.2. Stress mechanisms

1.2.1. Characterization of the stress response

Alongside the early days of fear conditioning, endocrinology research also started to blossom by the end of the 19th century, which has led to the concept of stress as we know it nowadays. Claude Bernard was the first to describe the importance to maintain the body's inner balance (Bernard, 1865), which was later conceptualized as homeostasis. A few decades later, Walter Cannon showed that a threat to the homeostasis generates the secretion of catecholamines (adrenaline and noradrenaline) by the adrenal medulla (Cannon, 1915). These responses also lead to physiological adaptations such as an increase of blood pressure, heart rate, and respiration (Cannon & Lissak, 1939; Selye, 1950). It also activates brain structures, in particular the hippocampus, the amygdala, as well as the cingulate, insular, and frontal cortices, which are fear-related regions that all express a high density of adrenaline receptors called β-adrenoreceptors (Reznikoff, Manaker, Rhodes, Winokur, & Rainbow, 1986; Roozendaal, 2000, 2003; Roozendaal & McGaugh, 2011). This physiological response characterized by the activation of the sympathetic–adrenal–medullary (SAM) axis corresponds to the first wave of a stress response (Sapolsky, Romero, & Munck, 2000).

Afterwards, Hans Selye further detailed bodily reactions when facing a stressful situation. Using the term ‘stress’ in humans for the first time, he described the hormonal cascade generating the liberation of glucocorticoids (GCs) (Selye, 1950). In the sixties, researchers discovered that stress hormones could cross the blood-brain-barrier and bind to receptors. Indeed, corticosteroids receptors were found on a vast number of brain regions, particularly located in the hypothalamus and in limbic structures such as the amygdala and the hippocampus, as well as in the prefrontal cortex (Joels & Baram, 2009; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, Weiss, & Schwartz, 1968), which are also involved in the fear network. GCs secretion results from the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which corresponds to the second wave of a stress response (Miller, 2018; Sapolsky et al., 2000). It takes its origin in the hypothalamus, which produces and releases the corticotropin-releasing hormone (CRH). CRH stimulates the secretion of the adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH is then released in the systemic blood circulation and stimulates the adrenal cortex glands, which in turn secrete GCs (the most common GCs in humans being cortisol) (for reviews see: Gunnar & Vazquez, 2006; Heim, Owens, Plotsky, & Nemeroff, 1997; Lopez, Akil, & Watson, 1999).

By binding to their receptors, GCs have various effects through non-genomic and genomic mechanisms. Rapidly activated, non-genomic effects of cortisol involve changes in intracellular communication, but not pertaining to genes. On the other hand, genomic effects are produced after a certain amount of time (approximately 1 h), when cortisol induces a specific gene expression. Both of these mechanisms allow to

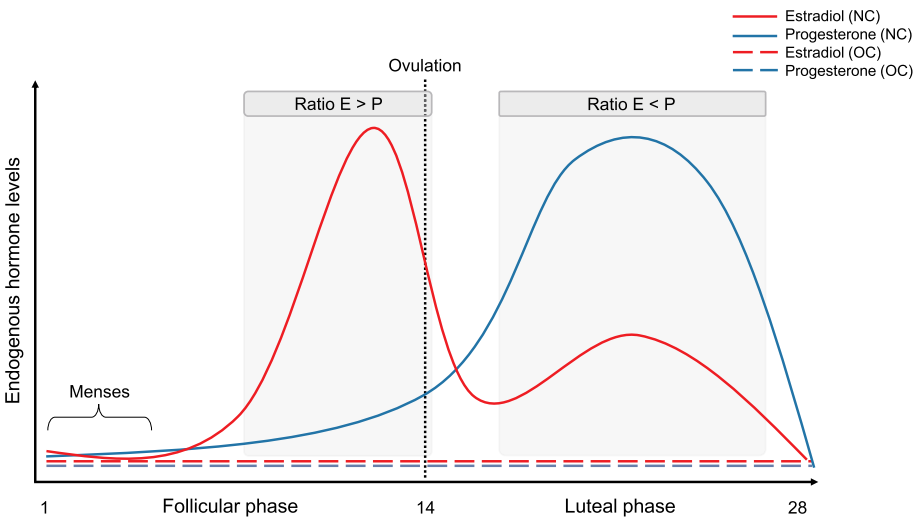

Fig. 1. Schematic representation of endogenous sex hormone levels in naturally cycling women and women using oral contraceptives. Menstrual cycle variations of naturally cycling (NC) women are illustrated by full lines, where estradiol levels (red line) are low in the early follicular phase and increase just before ovulation time, around midcycle. In the luteal phase, estradiol levels remain moderately high and then decrease before the onset of a new cycle. Progesterone levels (blue line) are low in the follicular phase and begin to rise after ovulation. They peak in the mid-luteal phase to finally decline to low concentrations before the onset of a new cycle. Hormonal milieu of women using oral contraceptives (OC) is represented by dashed lines, where both endogenous estradiol (red line) and progesterone (blue line) levels remain low and stable. Illustrations of the estradiol (E) and progesterone (P) ratio (gray boxes) highlight how the E/P ratio could fluctuate across menstrual cycle phases. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

induce molecular changes such as neurogenesis, epigenetic and structural plasticity, which contribute to the reduction of the stress response as well as to the formation of the stress-related memory trace (de Kloet, Karst, & Joels, 2008; McEwen, Nasca, & Gray, 2016).

For a long time, stress was only defined by its biological stress response. It was only in 1975 that John W. Mason brought to light the psychological aspects of stress (Mason, 1975). He showed that factors such as uncontrollability, unpredictability, novelty, and/or threat to one's ego are necessary to induce a stress response (Dickerson & Kemeny, 2004; Mason, 1968, 1975).

1.2.2. Inducing stress in the laboratory

Past research has set the bases for the stress field, which has greatly flourished throughout the years. A stress response is now defined as a threat perception activating psychobiological reactions (Joels & Baram, 2009). Knowing the different components of stress, several strategies can be implemented to induce it at an experimental level. Participants can be exposed to a physical stressor, such as the Cold Pressor Test (CPT; Hines & Brown, 1936), a psychosocial stressor, such as the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) or a physical stressor with a psychological component, such as the Socially Evaluated Cold Pressor Test (SECPT; Schwabe, Haddad, & Schachinger, 2008). These methods induce an increase of endogenous levels of stress hormones, thereby activating both the SAM and the HPA axes. To mimic some physiological aspects of a stress response, synthetic hormones could be used to specifically target one axis (for example, yohimbine for the SAM axis or hydrocortisone for the HPA axis).

1.3. How sex modulates stress and fear

1.3.1. Sex differences

Sex has been shown to be an important modulator of both fear and stress processes (Maeng & Milad, 2015; Ramikie & Ressler, 2018; Sze & Brunton, 2019). In line with this review's topics of interest, both fields seem to be influenced independently by sex. Indeed, men and women differ from each other with regards to their reactivity to stress (Bale & Epperson, 2015; Kinner, Het, & Wolf, 2014; Oyola & Handa, 2017). The type of stressor used in stress studies has also been shown to influence the differences between men and women. For instance, women show greater reactivity to social rejection, while men react more to achievement challenges (Stroud, Salovey, & Epel, 2002). However, results pertaining to sex differences in fear conditioning have been inconsistent, but some evidence suggests that men generally exhibit larger fear responses to both CS+ and CS- than women during fear acquisition training, fear extinction training, and extinction retention test (Cover, Maeng, Lebron-Milad, & Milad, 2014; Day & Stevenson, 2019; Lebron-Milad et al., 2012; Milad, Goldstein, et al., 2006).

However, it is crucial to take into account the fact that women have sex hormone variations due to their menstrual cycle, and that this recurrent cyclicity is not present in men. Thus, it is very likely that the variability induced by pooling hormonally different women into a single group considerably decreases the statistical power to detect sex differences. That being said, we will dwell on a more precise way to look at sex differences, where sex hormones will be examined as a potential moderator of stress and fear.

1.3.2. The importance of sex hormones

Sex hormones, most importantly estradiol, progesterone, and testosterone, are produced by both men and women, but at different levels. These steroid hormones not only have an organizational role in the developing brain of boys and girls (Blakemore, Burnett, & Dahl, 2010; Sinclair, Purves-Tyson, Allen, & Weickert, 2014), but they are also important in the modulation of physiological and cognitive processes (for reviews see: Hamson, Roes, & Galea, 2016; Kimura, 1996; Luine, 2008). Comparable to the HPA axis, the hypothalamic-pituitary-gonadal (HPG) axis is a specific neuroendocrine system that controls the secretion of sex hormones (Atwood et al., 2005). Its mechanism involves the hypothalamus, which produces gonadotropin-releasing hormone (GnRH). GnRH binds to the anterior pituitary and leads to the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These two hormones are responsible for the stimulation of gonads (ovaries in females and testes in males) and to a lesser extent the adrenal cortex, in order to produce sex hormones such as estrogens (estradiol), progestins (progesterone), and androgens (testosterone) (Handa & Weiser, 2014; Merz & Wolf, 2017).

While men's hormonal milieu remains relatively stable through time, women's sex hormones are fluctuating through their menstrual cycle (see Fig. 1). Premenopausal naturally cycling women have an average cycle length of 28 days, where day 1 corresponds to the first menstruation day. In the follicular phase, which corresponds to the first half of the cycle, low levels of endogenous estradiol and progesterone are circulating, with a surge of estradiol before ovulation. Ovulation occurs at midcycle and is followed by the luteal phase, the second half of the cycle. While estradiol declines to moderate levels, progesterone levels rise and peak at mid luteal phase. In the last days of the cycle, both hormones drop to their lowest levels. In women taking hormonal oral contraceptives (OC), their menstrual cycle is inhibited through the intake of low doses of exogenous hormones. Most OC formulas combine

synthetic estradiol (ethinylestradiol) and progesterone (e.g., levonogestrel), which prevent ovulation by chronically maintaining low levels of endogenous sex hormones (Golobof & Kiley, 2016). Interestingly, a large number of gonadal receptors are located in many fear- and stress-related structures such as the amygdala, the hippocampus, the anterior cingulate cortex, and the prefrontal cortex (Cover et al., 2014; Goldstein et al., 2001; Maeng & Milad, 2015).

Given that sex hormone levels differ between men and women, but also between women depending on their menstrual cycle phase or the use of OC, it became essential not only to recruit men and women, but also to distinguish hormonal phases of the menstrual cycle in order to homogenize subgroups and refine analyses.

The impact of sex hormones on the stress system has been largely documented in the literature. It is known that the HPA and the HPG axes interact together, which enforces the relevance of studying the interaction of both systems. Animal evidence shows a bidirectional influence of HPA and HPG axes (Toufexis, Rivarola, Lara, & Viau, 2014), but interestingly, very few human studies examined the impact of sex hormones on the HPA axis, and vice-versa. Among them, it has been shown that estradiol administration enhances HPA axis activity by increasing levels of ACTH and cortisol in healthy men after a psychosocial stress (Kirschbaum et al., 1996). When comparing hormonal profiles instead of dichotomous sex, Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer (1999) found that both women in the luteal phase and men had greater cortisol reactivity in response to a psychosocial stressor relative to women in the follicular phase and OC users (for reviews see: Kirschbaum et al., 1999; Kirschbaum, Wust, & Hellhammer, 1992; Merz, 2017). Enhanced cortisol response in luteal women, relative to follicular women or those using OC, has been documented several times (for a review see Kajantie & Phillips, 2006). Moreover, women taking OC have been shown to exhibit a blunted salivary cortisol response after a stress induction. This effect may be due to higher expression of the cortisol binding globulin (an important cortisol's transport protein) in OC women than in naturally cycling women (Fujimoto, Villanueva, Hopper, Moscinski, & Rebar, 1986; Kirschbaum et al., 1999; Moore, Kawagoe, Davajan, Mishell, & Nakamura, 1978; Reynolds et al., 2013). Altogether, these findings highlight the importance of using precise methodological designs in order to assess the mechanisms by which sex hormones impact stress reactivity.

In fear conditioning, human studies focusing on sex hormones are quite limited (Garcia, Walker, & Zoellner, 2018). Although the impact of sex hormones on fear conditioning is less studied, it appears that gonadal hormones modulate neuronal activity of regions involved in the fear circuitry. In fact, compared to OC users, low-estradiol women, and men, women with high levels of estradiol exhibit higher activation in several fear-related brain structures such as the insular cortex, the amygdala, and the cingulate cortex during fear acquisition training (Hwang et al., 2015).

Therefore, studies investigating the relationship between stress and sex hormones and those investigating the impact of sex hormones on fear conditioning tend to suggest that higher estradiol levels are associated with greater cortisol reactivity (Kirschbaum et al., 1992, 1999; Merz, 2017) and with higher activation of fear-promoting regions during fear learning (Hwang et al., 2015).

1.4. Clinical relevance of studying stress, fear, and sex

Studying the impact of stress on fear memory is also relevant for various psychopathologies, notably post-traumatic stress disorder (PTSD). In fact, exposure to a traumatic event (e.g., sexual or physical abuse, a serious car accident) induces a massive secretion of stress hormones, which modulates the brain regions involved in the fear circuitry. This undoubtedly has an impact on the fear learning processes. The formation of traumatic memories involves fear conditioning processes, as a strong association between the sensory cues (NS) and the traumatic event occurs (Lissek & van Meurs, 2015). After experiencing a traumatic event, certain individuals will develop a pathological fear, which could contribute to the development of various psychopathologies, such as PTSD (de Quervain, Schwabe, & Roozendaal, 2017; Shin & Liberzon, 2010). Importantly, the traumatic fear memory trace, formed under very stressful conditions, is sometimes resistant to extinction. In fact, exposure-based therapy, which is the gold standard therapy for fear-based disorders such as PTSD, relies on extinction learning principles (Maples-Keller et al., 2019; McLean & Foa, 2011; Rauch, Eftekhari, & Ruzek, 2012). Although its efficacy has been proven, some patients remain symptomatic and others relapse after a certain time (Bradley, Greene, Russ, Dutra, & Westen, 2005; Najavits, 2015; Steenkamp, Litz, Hoge, & Marmar, 2015). In the laboratory, patients suffering from PTSD express difficulties to regulate fear, with higher fear expression in acquisition training and deficits in fear extinction (learning and retention) (Jovanovic, Kazama, Bachevalier, & Davis, 2012; Lissek & van Meurs, 2015; Milad et al., 2008).

As we have outlined here, the impact of stress during a traumatic event on fear acquisition and consolidation is still not well defined. A better understanding of the genesis of traumatic memory is thus crucial to improve treatments and to specifically address the deficits in fear extinction observed in PTSD patients. Moreover, women are twice more likely than men to develop PTSD (Kornfield, Hantsoo, & Epperson, 2018; Ramikie & Ressler, 2018), a statistic that highlights the importance of taking into account sex differences when investigating the impact of stress on fear.

1.5. The current review: a focus on the interaction between stress, fear and sex

We reviewed the literature on stress, fear and sex separately and we will now focus our attention on the interaction between these three fields of research. In contrast to prior reviews on the impact of acute stress on conditioned fear (Raio & Phelps, 2015), or stress and sex hormones effects on emotional memory (Merz & Wolf, 2017), the current review has a specific focus on how sex and sex hormones modulate the impact of pre-acquisition stress on fear conditioning in humans. Our objectives are to review the impact of pre-acquisition stress on 1) fear acquisition, 2) fear extinction, and 3) extinction retention, as function of sex differences and sex hormone profiles. Finally, we pay a particular attention to the methodological differences that could explain discrepancies between studies and provide methodological recommendations for future studies.

2. The impact of pre-acquisition stress on fear learning

2.1. Stress and fear acquisition in men

In men, the effects of stress on fear acquisition have been studied with a wide variety of paradigms and measures. The first study investigating this question showed that psychosocial stress exposure 60 min before fear acquisition induced an increase of the skin conductance responses (SCR) to the CS+ but not to the CS- in men (Jackson, Payne, Nadel, & Jacobs, 2006). They also reported a positive correlation between changes in cortisol levels induced by the stressor and SCR differential, suggesting that higher stress responses promoted better discrimination between the CS+ and the CS- at a physiological level. In a recent study from Simon-Kutscher, Wanke, Hiller, and Schwabe (2019), it was found that psychosocial stress exposure 17 min before fear learning disrupted context-dependent fear acquisition, as assessed by SCRs. However, null results regarding the impact of pre-acquisition stress have also been reported in men. For instance, administering a psychosocial stressor 20 or 24 min before fear acquisition training did not modulate fear acquisition in men, as assessed by SCRs (Antov & Stockhorst, 2014; Antov, Wolk, & Stockhorst, 2013). The study by Antov et al. (2013) also reported the mere opposite of Jackson

Table 1
Experimental details and main results.

Study	Total n	Mean age	Sex ratio	OC intake	Group composition	Stressor type/ cortisol measure	Task duration (minutes)	Interval between end of stress task/ cortisol administration and beginning of fear acquisition training (minutes)	Data collected	Experimental phase tested	Results for fear acquisition training	Results for fear extinction training	Results for retention test
Antov et al. (2013)	Exp 1: 24	22.8	24M:0W	N/A	Stress (n = 12) vs control (n = 12)	Psychosocial stressor	20	24	SCR	Fear acquisition training, extinction training	Psychosocial stressor had no impact on SCR differentials. In the stress group, trend-level negative correlation between SCR differentials and changes in cortisol levels.	Psychosocial stressor had no impact on SCR differentials. In the stress group, trend-level negative correlation between SCR differentials and changes in cortisol levels.	N/A
	Exp 2: 38	22.5	38M:0W	N/A	Stress (n = 20) vs control (n = 18)	CPT	3	6	SCR	Fear acquisition training, extinction training	CPT had no impact on SCR differentials.	CPT induced an extinction resistance. In the CPT group, the peak of diastolic and systolic blood pressure was positively correlated with the SCR differentials.	N/A
Antov and Stockhorst (2014)	72	23.9	24M:48W	All women were naturally cycling	Stress (12 men, 12 EF, 12 MC) vs control (12 men, 12 EF, 12 MC)	Psychosocial stressor	20	20	SCR	Fear acquisition training, extinction training, retention test	Psychosocial stressor exposure or sex hormone status had no impact on fear acquisition, as assessed with SCRs.	Psychosocial stressor exposure or sex hormone status had no impact on fear extinction, as assessed with SCRs.	In EF women, SCR differentials were larger in the psychosocial stressor group (vs. the control group) during the retention test. The opposite pattern was found in MC women.
Cornelisse et al. (2014)	63 (62 EXT)	21.4	63M:0W	N/A	Hydrocortisone 4 h before fear acquisition (n = 21) vs hydrocortisone 1 h before fear acquisition (n = 21) vs placebo (n = 21)	Hydrocortisone 10 mg	N/A	60 or 240	FPS, SCR, US expectancy	Fear acquisition training, extinction training	Hydrocortisone administration had no impact on fear acquisition, as assessed with FPS responses, SCRs, and US expectancy ratings.	Only hydrocortisone administration 4 h prior to fear acquisition testing induced fear extinction resistance, as assessed with FPS responses.	N/A
Jackson et al. (2006)	94	19.6	49M:45W	19/45 women were taking OCs	Stress (22 women, 24 men) vs control (23 women, 25 men)	Psychosocial stressor	20	60	SCR	Fear acquisition training, extinction training	Psychosocial stressor exposure enhanced SCRs to the CS+ in men, but not in women	Psychosocial stressor exposure enhanced SCRs to the CS+ in men, during both early and late extinction. In women, psychosocial stressor exposure reduced the SCR differential, only	N/A

(*continued on next page*)

Table 1 (*continued*)

Study	Total n	Mean age	Sex ratio	OC intake	Group composition	Stressor type/ cortisol measure	Task duration (minutes)	Interval between end of stress task/ cortisol administration and beginning of fear acquisition training (minutes)	Data collected	Experimental phase tested	Results for fear acquisition training	Results for fear extinction training	Results for retention test
												during early extinction.	
Merz et al. (2010)	39	23.2	20M:19W	Half of the women were taking OCs	Hydrocortisone (10 women, 10 men) vs placebo (9 women, 10 men) (contingency unaware sample)	Hydrocortisone 30 mg	N/A	45	fMRI, SCR	Fear acquisition training	Hydrocortisone administration reduced SCR differentials in women, but it had no impact in men. It also reduced the insula differential activation in men but enhanced it in women.	N/A	N/A
Merz et al. (2012)	122	23.1[a]	32M:90W	30/90 women were taking OCs (separate group)	Hydrocortisone (17 men, 15 EF, 15 LU, 15 OC) vs placebo (15 men, 15 EF, 15 LU, 15 OC) (contingency unaware sample)	Hydrocortisone 30 mg	N/A	45	fMRI, SCR	Fear acquisition training	No impact of sex or hydrocortisone on SCRs. Hydrocortisone administration enhanced the differential activation of the hippocampus and the anterior parahippocampal gyrus in OC users, but reduced it in men, follicular women, and luteal women.	N/A	N/A
Merz, Stark et al. (2013)	50	34.3	20M:30W	15/30 women were taking OCs (separate group)	Within-subjects design (20 men, 15 LU, 15 OC)	Endogenous cortisol	N/A	N/A	fMRI, SCR	Fear acquisition training	Endogenous cortisol was negatively correlated to SCR differentials in OC women only. In men and OC women, endogenous cortisol was positively correlated to differential activation in the amygdala	N/A	N/A
Merz, Wolf et al. (2013)	96	23.2	48M:48W	All women were taking OCs	Stress (24 women, 24 men) vs control (24 men, 24 women)	Psychosocial stressor	15	25	fMRI, SCR	Fear acquisition training	Psychosocial stressor exposure reduced SCRs to the CS + in men, but not in OC women. Stress reduced the differential activation of the nucleus accumbens during early acqusition in men, but enhanced it in OC women. The same pattern was observed during late acquisition in the	N/A	N/A

(*continued on next page*)

Table 1 (*continued*)

Study	Total n	Mean age	Sex ratio	OC intake	Group composition	Stressor type/ cortisol measure	Task duration (minutes)	Interval between end of stress task/ cortisol administration and beginning of fear acquisition training (minutes)	Data collected	Experimental phase tested	Results for fear acquisition training	Results for fear extinction training	Results for retention test
											amygdala and the ACC.		
Riggenbach et al. (2019)	141	19.4	68M:73W	All women were naturally cycling	Stress (28 women, 39 men) vs control (45 women, 29 men)	SECPT	3	0	FPS, US expectancy	Fear acquisition training, extinction training, retention test	SECPT exposure enhanced FPS responses to the CS+, irrespective of participants' sex. Stressed men had lower US expectancy ratings for the CS+ and higher US expectancy ratings for the CS- than non-stressed men. Stress had no impact on US expectancy in women.	No impact of SECPT on FPS responses, but stressed participants showed a slower reduction of US expectancy ratings for the CS+. FPS differentials were positively corelated to cortisol changes in response to the stressor. Sex did not modulate the impact of stress on extinction.	SECPT exposure enhanced FPS responses to the CS+. FPS differentials were positively corelated to cortisol changes in response to the stressor. Sex did not modulate the impact of stress on extinction retention.
Simon-Kutscher et al. (2019)	72	25.5	31M:41W	All women were naturally cycling	Stress (16 men, 20 women) vs control (15 men, 21 women)	Psychosocial stressor	13	17	SCR, US expectancy	Fear acquisition training, extinction training	Psychosocial stress exposure disrupted context-dependant fear acquisition, as assessed with SCRs. Stress had no impact on US expectancy. Sex did not modulate the impact of stress on fear acquisition.	Psychosocial stress exposure induced an extinction resistance for cue-dependant fear responses, as assessed with SCRs. Stress had no impact on US expectancy. Sex did not modulate the impact of stress on extinction.	N/A
Stark et al. (2006)	34	24.2	17M:17W	All women were taking OCs	Hydrocortisone (8 women, 9 men) vs placebo (9 women, 8 men)	Hydrocortisone 30 mg	N/A	15	fMRI, SCR	Fear acquisition training	Hydrocortisone administration reduced SCRs to the CS+ in men but not in OC women. In men, it also reduced the CS+ vs. CS- contrast in the ACC, the lateral OFC, and the mPFC, while it had the opposed effect in women taking OCs (increase of the CS+ vs CS- contrast).	N/A	N/A
Tabbert et al. (2010)	20	23.2	0M:20W	All women were taking OCs	Hydrocortisone (n = 10) vs placebo (n = 10)	Hydrocortisone 30 mg	N/A	45	fMRI, SCR	Fear acquisition training, extinction training	Hydrocortisone administration had no impact on fear acquisition as assessed with SCRs. It however enhanced the activation of the	Hydrocortisone administration induced higher SCRs for both CS+ and CS- during extinction. It also enhanced the	N/A

(*continued on next page*)

Table 1 (*continued*)

Study	Total n	Mean age	Sex ratio	OC intake	Group composition	Stressor type/ cortisol measure	Task duration (minutes)	Interval between end of stress task/ cortisol administration and beginning of fear acquisition training (minutes)	Data collected	Experimental phase tested	Results for fear acquisition training	Results for fear extinction training	Results for retention test
											hippocampus and the anterior parahippocampal gyrus to the CS+ (vs CS-) in OC users.	activation of the hippocampus and the amygdala to the CS- (vs CS+) in OC users.	
van Ast et al. (2012)	43	21.3	21M:22W	All women were taking OCs	Hydrocortisone (11 women, 10 men) vs placebo (11 women, 11 men)	Hydrocortisone 20 mg	N/A	45	FPS, SCR, US expectancy	Fear acquisition training	Hydrocortisone administration impaired the contextualization of fear expression, which led to increased fear generalization in women, as assessed by FPS responses. Men displayed the opposite pattern. Hydrocortisone administration tended to reduced SCR differentials in men but not in women. Hydrocortisone administration had no impact on US expectancy, irrespective of participants' sex.	N/A	N/A
Zorawski et al. (2005)	45	24.7	23M:22W	No report of OC intake	Within-subjects design	Endogeneous cortisol	N/A	N/A	SCR	Fear acquisition training, extinction training	SCR differentials were correlated with endogenous cortisol levels in men but not in women.	Endogenous cortisol was not associated to SCRs during extinction, irrespective of participants' sex.	N/A

Abbreviations: N/A, not applicable; M, men; W, women; OC, oral contraceptives; EF, early follicular; MC, mid-cycle; LU, luteal; CPT, Cold Pressor Test; SECPT, Socially-evaluated Cold Pressor Test; SCR, skin conductance response; FPS, fear-potentiated startle; fMRI, functional magnetic resonance imaging; US, unconditioned stimulus; CS, conditioned stimulus; ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex.

Note.

[a] Mean age in each group was between 21.3 and 24.8.

et al. (2006) (i.e., a negative correlation between changes in cortisol levels induced by a psychosocial stress and CS+/CS- differentiation). Nevertheless, Antov et al. (2013) and Jackson et al. (2006) both used the same method to operationalize cortisol changes, by using the difference between the peak in cortisol levels obtained after the stress exposure and the baseline levels. Both of these studies therefore used a change in cortisol levels, rather than absolute levels. One important difference between these two studies however is the timing of the psychosocial stressor with regards to the conditioning procedure. In fact, in the study by Jackson and collaborators (2006), participants were stressed 1 h before fear learning, while in the study by Antov et al. (2013), there was a 24-min interval between the end of the psychosocial stressor and the beginning of the fear learning procedure (see Table 1). Because cortisol rapidly activates non-genomic effects and produces genomic effects after approximately 1 h, the timing of the psychosocial stressor with regards to the fear acquisition training is an important factor to consider. It is therefore possible that the results observed in the study by Jackson et al. (2006) reflect genomic effects, whereas the results obtained by Antov et al. (2013) rather reflect non-genomic effects.

When interpreting the discrepant findings between these two studies, one must also keep mind that only 12 participants from the study of Antov et al. (2013) were involved in the stress condition, and that the reported correlation only reached trend level. Finally, Merz, Wolf, et al. (2013) found that psychosocial stress exposure reduced SCRs to the CS + in men. Here, participants were stressed 25 min before fear acquisition, suggesting that cortisol levels peaked during fear acquisition training.

Physical stressors, such as the CPT or SECPT, were not extensively used to assess the impact of stress on fear conditioning in men. On the one hand, Antov et al. (2013) reported that a physical stressor (CPT) 6 min before fear learning had no impact on SCR differentials during fear acquisition, but they found that changes in diastolic and systolic blood pressure induced by the stressor were positively correlated with SCR differentials. On the other hand, Riggenbach et al. (2019) found that the SECPT immediately before fear acquisition training enhanced fear FPS responses to the CS+, but they did not find a relationship between heart rate and FPS differentials. They also reported that stressed men had lower US expectancy ratings for the CS+ and higher US expectancy ratings for the CS- than non-stressed men.

Regarding endogenous cortisol levels, Zorawski, Cook, Kuhn, & LaBar (2005) showed that men with high cortisol levels had greater SCR differential relative to their counterparts with low endogenous cortisol levels. They also found a positive association between endogenous cortisol levels and SCR differential in men. This association between endogenous cortisol levels and SCR differential was however not replicated by Merz et al. (2013).

Negative results regarding the impact of hydrocortisone administration on fear acquisition has been reported in men, as assessed by SCRs (Cornelisse, van Ast, Joels, & Kindt, 2014; Merz et al., 2010, 2012), FPS (Cornelisse et al., 2014), or US expectancy ratings (Cornelisse et al., 2014). Stark et al. (2006) even reported that it induced a decrease in SCRs to the CS+ in men. van Ast, Vervliet, and Kindt (2012) found a trend in the same direction. These effects are however in contradiction to those of some studies described above, where stress exposure or endogenous cortisol levels were associated with larger SCR differentials.

In the aforementioned studies, the timing of the fear acquisition training relative to the end of the stressor/cortisol administration ranged from 6 to 240 min (see Table 1). Such methodological variations may explain this discrepancy observed between studies, as stress may trigger genomic effects in some studies but not others. Also, the fact that negative results were obtained with hydrocortisone administration suggests that the psychological aspect associated with a stressor might be responsible for the enhancing effect of stress on fear responses in men.

At the neural level, hydrocortisone administration 15 or 45 min prior to fear acquisition training in men reduced the differential activation (CS+ vs. CS- contrast) in the insular cortex (Merz et al., 2010), the hippocampus, the anterior parahippocampal gyrus (Merz et al., 2012), the anterior cingulate cortex (ACC), the lateral orbitofrontal cortex, and the medial prefrontal cortex (Stark et al., 2006). Psychosocial stress exposure 25 min before fear acquisition training had similar effects, with reduction of the differential activation in the nucleus accumbens during early acquisition, and in the amygdala and the ACC during late acquisition, in comparison with the control group (Merz, Wolf, et al., 2013). However, basal cortisol levels were positively correlated with differential activation in the amygdala (Merz, Stark, et al., 2013). This points towards an inverted-U shape relationship between cortisol levels and amygdala activation during fear learning in men, where basal cortisol levels are associated to better fear acquisition (i.e., greater differentiation between CS+ and CS-, as measured by amygdala activation) but increases in cortisol levels past a certain point could lead to disrupted fear acquisition (i.e., lower differential amygdala activation).

All in all, some evidence suggests that the physiological correlates of fear could be enhanced by stress exposure in men. At the neural level, hydrocortisone administration seems to have the opposite effect, with a reduced differential activation of brain regions during the CS+ vs. CS- contrast.

2.2. Stress and fear acquisition in women

In women, multiple studies reported that sex did not modulate the impact of stress on fear acquisition. For instance, psychosocial stress exposure 60 min before fear learning was found to have no impact on fear acquisition in women, as assessed by SCRs (Jackson et al., 2006). However, as mentioned previously, women tend to differ from men with regard to their physiological reactivity to stress (Bale & Epperson, 2015; Kinner et al., 2014; Kirschbaum et al., 1992; Oyola & Handa, 2017). In the study by Jackson and colleagues, women reported similar augmentation of subjective stress levels than men, but exhibited no significant increase of cortisol levels in response to the psychosocial stressor (Jackson et al., 2006). The fact that women did not respond as much as men at the endocrine level might account for the lack of significant effect of stress on fear acquisition. Also, findings from Simon-Kutscher et al. (2019), which suggested that a psychosocial stress exposure 17 min before fear acquisition training disrupted context-dependent fear acquisition, came from a mixed sample of men and women. In that study, the authors specifically tested whether sex modulated the impact of stress on fear acquisition, which was not the case. This suggests that the impact of stress on context-dependent fear learning seems to be similar for both sexes.

To our knowledge, only one study investigated the impact of a physical stressor on fear acquisition in women. Similar to their findings in men, Riggenbach et al. (2019) found that physical stress exposure enhanced FPS responses to the CS+ in women, as it was the case in men. However, while stressed men had lower US expectancy ratings for the CS+, physical stress exposure had no impact on US expectancy ratings in women. Yet, this study administered a stressor immediately before fear acquisition training, which suggests that cortisol did not have time to reach its peak levels at the beginning of the fear protocol. Because stress increased baseline startle responses, this suggests that the SAM axis activation provoked physiological alterations and could potentially have driven the effects found later during the fear acquisition training. Additional biological measures such as salivary alpha-amylase (sAA) concentrations, which represent a proxy measure of the SAM axis activation (Strahler, Skoluda, Kappert, & Nater, 2017), could allow a clearer interpretation of these findings.

Furthermore, the correlation found by Zorawski et al. (2005) between endogenous cortisol levels and SCR differential was found in men, but not in women. Merz et al. (2010) found that hydrocortisone

administration 45 min before fear acquisition training reduced SCR differentials in women. Here again, the sample of women assigned to the hydrocortisone condition was quite small (n = 10).

This being said, these studies were conducted without taking into account the variations of sex hormone levels pertaining to the menstrual cycle. Furthermore, they did not assess the specific impact that OC intake can have on stress and fear levels. To circumvent this issue, some studies have formed experimental groups by taking into account the menstrual cycle and/or OC intake, allowing a better characterization of the impact of stress on fear conditioning in women.

2.2.1. Stress and fear acquisition in women taking oral contraceptives

Contrary to what many studies reported in men, psychosocial stress exposure (Merz, Wolf, et al., 2013) or hydrocortisone administration (Merz et al., 2012; Stark et al., 2006; Tabbert et al., 2010; van Ast et al., 2012) had no impact on SCRs to the CS+ in OC women when induced 15–45 min prior fear acquisition training (see Table 1). It also had no impact on US expectancy ratings in OC women (van Ast et al., 2012). Yet, this study reported that hydrocortisone administration impaired the contextualization of fear expression in OC women, which led to increased fear generalization, as assessed by FPS responses. Another study found that endogenous cortisol levels were negatively correlated with SCR differentials in OC women (Merz, Stark, et al., 2013), which is the opposite of what was reported in men (Zorawski et al., 2005).

At the neural level, basal cortisol levels (Merz, Stark, et al., 2013), psychosocial stress exposure (Merz, Wolf, et al., 2013), and hydrocortisone administration (Merz et al., 2010; Tabbert et al., 2010) performed 25–45 min before fear acquisition training were all associated with enhanced differential activation in many brain structures, such as the amygdala, insula, nucleus accumbens, anterior cingulate gyrus, hippocampus, anterior parahippocampal gyrus, lateral orbitofrontal cortex, and medial prefrontal cortex.

2.2.2. Stress and fear acquisition in naturally cycling women

Very few studies have assessed how the different phases of the menstrual cycle modulate the impact of stress or stress hormones on fear acquisition. Antov and Stockhorst (2014) reported that men, early follicular women, and mid-cycle women all showed similar SCRs during fear acquisition following psychosocial stress exposure. In the same vein, Merz et al. (2012) reported similar SCRs during fear acquisition following hydrocortisone administration in men, follicular women, luteal women, and OC women. This last result appears to contradict the ones described earlier in section 1.3.2, where women with low sex hormone levels, such as those in the follicular phase or taking OC, tend to react relatively the same way to fear and stress procedures and distinguish themselves from women with high gonadal hormone levels and men (Hwang et al., 2015; Kirschbaum et al., 1999). A possible explanation for this divergence is the lack of sex hormone discrimination between the two naturally cycling women groups in the study of Merz et al. (2012). All expected between-group differences were confirmed regarding salivary progesterone and testosterone levels (as depicted in Fig. 2). However, follicular and luteal women did not statistically differ with regard to their salivary estradiol levels, which is unexpected. This suggests that both naturally cycling women groups were not as distinct as expected at an endocrine level. Yet, it is the first study that has examined the relationship between stress and fear learning in various sex hormone profiles. Therefore, the influence of gonadal hormones on the relationship between stress hormones and fear learning remains unclear. Overall, the fact that OC users stand out from naturally cycling women (either in their follicular or their luteal phase) suggests that most of gonadal influence on stress may not come from endogenous sex hormone concentrations (otherwise follicular and OC women would have displayed similar fear responses under stress given that their endogenous levels of sex hormones are both very low). In other words, it seems that the effects of stress on fear acquisition observed in the OC group might be better explained by the use of synthetic hormones contained in OC and/or by the fact of having chronically low levels of endogenous sex hormones.

3. The impact of pre-acquisition stress on fear extinction

3.1. Stress and fear extinction in men

Researchers have also investigated the long-lasting effects of stress on fear learning (i.e., if memory modulation can still be observed when stress hormone levels are back to baseline).

Regarding the impact of a pre-acquisition psychosocial stressor on fear extinction in men, Antov and Stockhorst (2014) reported that it had no impact on fear extinction (conducted immediately after fear acquisition), as assessed by SCRs. On the other hand, Jackson et al. (2006) found that it enhanced SCRs to the CS+ during fear extinction training. This discrepancy could be due to higher statistical power in the study by Jackson et al. (2006), where the sample was twice as large as the one in Antov and Stockhorst's (2014) study. Similarly, Simon-Kutscher et al. (2019) found that psychosocial stress exposure 17 min before fear acquisition induced an extinction resistance, where SCRs for the CS+ did not decrease in stressed participants as opposed to the control group. However, stress had no impact on US expectancy and sex did not modulate the impact of stress on extinction learning, which suggests that these results are comparable for both men and women.

As for basal cortisol levels, Zorawski et al. (2005) found that endogenous levels were unrelated to SCRs during extinction training conducted 24 h after the fear acquisition training, irrespective of participants' sex.

In men, while it had no impact on fear acquisition, hydrocortisone administration 4 h prior to fear acquisition training induced an extinction resistance as measured by FPS (Cornelisse et al., 2014). This fear extinction resistance may be explained by the genomic pathway of cortisol: gene-related mechanisms may have contributed to a stronger consolidation of the fear acquisition memory, which then contributed to undermine extinction learning. A similar extinction resistance process, as measured by SCRs, was found following the activation of SAM axis through a physical stressor (Antov et al., 2013). In that study, fear acquisition and fear extinction trainings took place six and 14 min after the physical stressor, respectively. However, the control group did not exhibit the expected decrease in fear levels throughout extinction learning, making it difficult to conclude that is was indeed the long-term effects of stress that impaired the fear extinction process. Riggenbach et al. (2019) found that SECPT administered immediately before fear acquisition had no impact on FPS responses during fear extinction training conducted 24 h later. However, stressed participants showed a slower reduction of US expectancy ratings for the CS+ during extinction learning relative to the control group. FPS differentials were positively correlated with cortisol changes in response to the stressor. In their study, sex did not modulate the impact of stress on extinction learning, suggesting that these results should be similar for both men and women.

Taken together, these studies suggest an impact of pre-acquisition stress extinction resistance in men. Importantly, altough the timing and the method used to increase cortisol levels seem to have different effects on fear acquisition, this does not seem to be the case with fear extinction. In fact, effects were found with different timings of stressor/hydrocortisone administration and various methods. However, no study to our knowledge evaluated the impact of a pre-acquisition stress or hydrocortisone administration on the neural correlates of fear extinction in men.

3.2. Stress and fear extinction in women

In women, results are somewhat less clear. As stated previously, some studies reported that stress could induce an extinction resistance that was not modulated by participants' sex (Riggenbach et al., 2019;

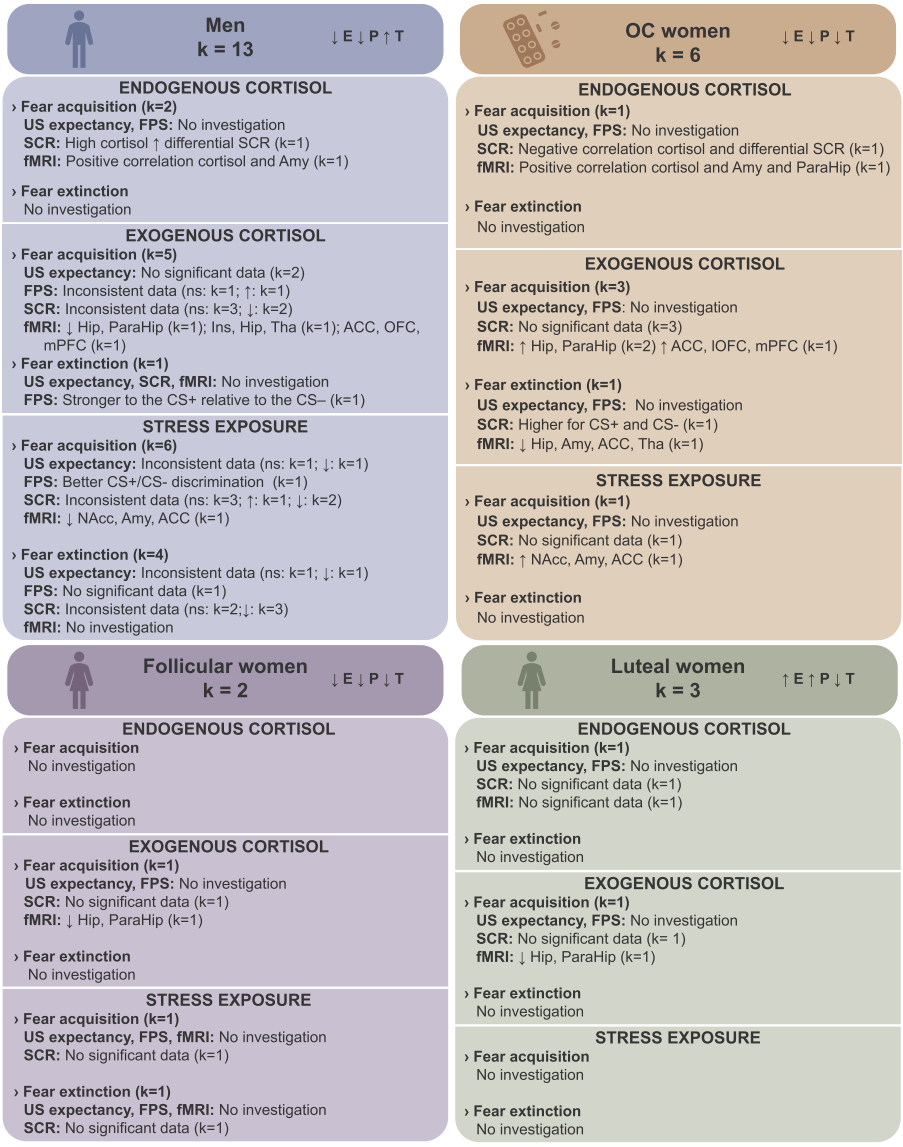

Fig. 2. Summary of findings related to stress and fear acquisition pertaining to sex hormone profiles. Each profile is characterized by specific sex hormone levels (concentrations are represented by either downward arrow for low levels or upward arrow for high levels; and hormones are expressed as T for testosterone, E for estradiol, and P for progesterone). Results are summed up with regards to the main stress protocols used in fear research (endogenous cortisol corresponds to naturally fluctuating cortisol levels (basal levels), exogenous cortisol refers to the administration of hydrocortisone, and stress exposure refers to a stressful psychosocial or physical task). For physiolgical measures, downward arrows represent impaired performance in fear acquisition and fear extinction, whereas upward arrows imply a better performance. For fMRI, downward arrows correspond to reduced brain activations whereas upward arrows represent increased brain activations.
Abbreviations: SCR, skin conductance response; fMRI, functional magnetic resonance imaging; US, unconditioned stimulus; Amy, amygdala; Hip, hippocampus; ParaHi, parahimpocampal gyrus; NAcc, nucleus accumbens; ACC, anterior cingulate cortex; Tha, thalamus; lOFC, lateral orbitofrontal cortex; mPFC, medial prefrontal cortex; ns, non-significant.

Simon-Kutscher et al., 2019). However, and opposed to their findings in men, Jackson et al. (2006) reported that 60 min pre-acquisition stress reduced women's SCR differential during early extinction training, which was conducted 24 h after fear acquisition training.

In OC women, 45 min pre-acquisition hydrocortisone administration induced higher SCRs for both the CS+ and CS- during fear extinction training (conducted immediately after fear acquisition) (Tabbert et al., 2010). Compared to a placebo, the hydrocortisone group exhibited lower activation in the amygdala and the hippocampus to the CS+ relative to the CS-. By comparing different stages of the menstrual cycle, Antov and Stockhorst (2014) reported that similar to men, there was no impact of 20 min pre-acquisition psychosocial stress exposure on fear extinction learning for both follicular and mid-cycle women. Therefore, evidence for a role of pre-acquisition stress or stress hormone administration on extinction learning resistance is scarcer in women than in men.

4. The impact of pre-acquisition stress on extinction retention

Very few studies have assessed the impact of pre-acquisition stress on extinction memory. Riggenbach et al. (2019) reported that SECPT exposure immediately before fear acquisition training enhanced FPS responses to the CS+ during the extinction retention test and that FPS differentials were positively correlated to cortisol changes in response to the stressor. Moreover, sex did not modulate the impact of stress on extinction retention. However, when taking the menstrual cycle into account, Antov and Stockhorst (2014) found that stress exposure 20 min before fear acquisition training enhanced SCR differentials during extinction retention test in early follicular women, while it had the opposite effect in mid-cycle women. The latter results suggest that estradiol levels play an important role in modulating the effects of stress, applied before fear acquisition, on extinction memory. Yet, the literature on this matter remains scarce and such results merit replication.

5. Discussion and future directions

Of all studies evaluating the impact of pre-acquisition stress on fear conditioning, most of them revealed an enhancing effect of stress on physiological reactivity (e.g., skin conductance responses) and a decreased activation of the neural fear network in men during fear acquisition training. In women, findings are less consistent. Few studies were conducted in naturally cycling women, making it difficult to draw conclusions. However, there is more converging evidence in OC users, where stress seems to act by increasing activations in the brain regions of the fear network (see Table 1 for a summary of each study). The

opposite pattern was found in men, which highlights the need to take into consideration the contribution of sex hormones, and in this particular case, the use of synthetic hormones.

At a structural level, OC use has been linked to differences in various brain structures, such as larger prefrontal and temporal cortices, parahippocampal and fusiform gyri (Pletzer et al., 2010; Pletzer, Kronbichler, & Kerschbaum, 2015), and lower cortical thickness in orbitofrontal and cingulate cortices (Petersen, Touroutoglou, Andreano, & Cahill, 2015). The duration of OC use also seems to be an important factor, as longer duration of use has been associated with larger hippocampus and basal ganglia (Pletzer, Harris, & Hidalgo-Lopez, 2019). This suggests that OC intake impacts women's brain anatomy, particularly in regions important for emotional and memory processes. Altogether, these alterations may alter one's vulnerability to the development of various pathologies. It has in fact been proposed that OC intake (which acts by lowering endogenous sex hormone levels) might make women more vulnerable to develop psychopathologies such as PTSD and anxiety disorders (Glover et al., 2012; Glover, Jovanovic, & Norrholm, 2015; Kornfield et al., 2018). At a pre-clinical level, it has been shown that inhibition of sex hormone levels, notably estradiol's, impairs extinction memory consolidation (Graham & Milad, 2013, 2014; Milad et al., 2010; White & Graham, 2016). Given the important parallel between fear extinction learning and exposure-based therapy in clinical populations (see section 1.4), these data suggest that extinction memories are less likely to be consolidated in women with natural or OC-induced low estradiol concentrations (Graham & Milad, 2013; Milad et al., 2010; White & Graham, 2016). Importantly, this result has also been found in a clinical sample. Indeed, women suffering from spider phobia who were using hormonal contraceptives (OC, implant, intra-uterine device) exhibited less improvement in response to an exposure therapy than their naturally cycling counterparts, echoing deficits in fear extinction (Graham, Li, Black, & Ost, 2018). Although various mechanisms such as reduction of dendritic spine density, and down-regulation of genomic and non-genomic effects have been proposed (Glover et al., 2015; Graham & Milad, 2013), more research is needed to fully understand whether and how OC could affect women's mental health.

The findings reviewed here also showed that pre-acquisition stress could induce extinction learning resistance. Interestingly, this suggests that the fear memory trace acquired under elevated stress hormones levels might hamper the subsequent formation of the extinction learning trace. This finding seems to hold in both men and women, although sex hormone profiles have not been investigated with regards to this question (see Table 1 and Fig. 2). As for extinction retention, the impact of pre-acquisition stress remains scarcely studied. Pre-acquisition stress seems to lead to enhanced fear responses during the extinction retention test for men and women, but sex hormones also appear to be modulating this relationship. Indeed, high estradiol levels were shown to facilitate extinction retention performance in naturally cycling women who were exposed to a stressor, while the opposite pattern was found relative to low estradiol levels.

All in all, fear conditioning protocols have been proposed as valid experimental models to mimic the formation of the fear or traumatic memory association, an inherent part of psychopathologies such as PTSD and anxiety (Briscione, Jovanovic, & Norrholm, 2014; Pitman, 1989; Pitman et al., 2012; Southwick et al., 1999). It is nonetheless important to highlight that this model is not perfectly suited to examine these disorders. Indeed, this type of protocol uses a CS-US association to mimic the conditioned fear acquired from a traumatic experience. Clearly, the intensity of a traumatic event could not be compared to the aversive stimuli used in the laboratory. The various fear associations that could be formed during a traumatic event are likely complex and therefore, one could argue that the laboratory models are overly simplified (for a discussion, see Beckers, Krypotos, Boddez, Effting, & Kindt, 2013). Moreover, PTSD criteria A of the DSM-V requires the occurrence of a highly stressful event (American Psychiatric Association, 2013), which in fact corresponds to an US. In experimental models, the stressor is temporally conducted *before* the associative learning in order to obtain elevated stress hormone levels at the time of learning the fear association. As it surely does not mimic the exact same mechanism as in PTSD, fear conditioning protocols nonetheless allow to study the effects of stress on fear memory processes. By stressing participants before fear acquisition training, cortisol levels are still heightened at the time of the associative learning (Merz & Wolf, 2017; Schwabe, Joels, Roozendaal, Wolf, & Oitzl, 2012). This still allows to investigate the modulatory effects of stress on fear learning in a laboratory setting, even if it is exerted rather differently than in reality.

Additionally, the utility of using experimental fear protocols is clinically relevant (Duits et al., 2015; Graham & Milad, 2011; Rothbaum & Davis, 2003). While translational value has been shown between an experimental fear protocol and the clinical treatment of exposure (Scheveneels, Boddez, Vervliet, & Hermans, 2016), predictive validity of fear patterns in mental health patients remains to be largely investigated (Duits et al., 2015; Scheveneels et al., 2016). Interestingly, some studies have shown a promising value of using stress- and fear-related biomarkers in the aftermath of trauma in order to predict PTSD development. Indeed, both higher heart rate and skin conductance responses in the aftermath of trauma have been associated with subsequent PTSD diagnosis (Bryant, Harvey, Guthrie, & Moulds, 2000; Hinrichs et al., 2019; Shalev et al., 2000). Laboratory- and therapy-based extinction performance have also been used to help determine treatment prognosis (Forcadell et al., 2017; Post et al., 2017). While these examples plead towards a predictive value of either the fear or stress system on psychopathology development and treatment response, no studies to our knowledge have evaluated the joint influence of these two systems (i.e., how fear is learned under elevated levels of stress) on predicting therapeutic outcomes. Evaluating how stress impacts fear learning and its subsequent extinction in a laboratory setting might help in identifying therapy responsiveness profiles.

In short, despite its limitations, the use of the fear conditioning protocol remains a highly relevant model to examine neurobiological and behavioral components of fear and stress pathologies, notably in humans. This model offers a great range of adaptations and can be a useful tool for investigating various populations. However, many inconsistencies are reported in the literature of stress, fear, and sex hormones. For studies integrating these three research domains, we here review specific recommendations from each field in order to promote state-of-the-art research on stress, fear, and sex differences and sex hormone profiles.

5.1. Stress-related recommendations

Methodologies used to study the impact of stress vary largely from one study to another, making it difficult to draw general conclusions. Many factors may account for these discrepancies, such as the temporal period between stress exposure and fear learning, the type of stressor used, and the targeted stress wave.

The time between stress exposure and fear learning is crucial, given that GCs have effects through non-genomic (rapid pathway of actions) and genomic mechanisms (slower pathway of gene-mediated actions) (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Schwabe et al., 2012). This raises the importance of considering the time lapse between stress exposure or stress hormone modulation and fear acquisition in order to identify which mechanisms are at play and modulate fear learning.

Furthermore, different stress protocols have been used in fear conditioning studies, providing distinct information. A physical stressor is generally used in order to activate the first stress wave, allowing to study the effect of the SAM axis activation on fear responses (Antov et al., 2013). However, such procedure does not consider the cognitive load of stress, which usually accompanies a stress reaction. In fact, psychosocial stressors lead to the activation of both stress waves and also adds a psychological burden (Antov & Stockhorst, 2014; Antov

et al., 2013; Jackson et al., 2006; Merz, Wolf, et al., 2013), which could in turn have an influence on the emotional and cognitive processes at play. That being said, this type of stressor makes it difficult to isolate the contribution of each stress system (HPA and SAM axes) on memory processes. Pharmacological protocols were found to be helpful when one wants to isolate some specific components. Not only pharmacological protocols could be applied alone (e.g., hydrocortisone administration), they could also be relevant in the context of stress exposure (e.g., administrating a beta-blocker to decrease SAM activation and study the impact of reactive cortisol along with the cognitive load induced by the stressor). Note that these various methods aim to assess the impact of reactive cortisol (in response to a stressor) on fear. Although the majority of studies reviewed in this manuscript considered reactive cortisol, it is also possible to assess the impact of endogenous cortisol (basal levels under non-stressful conditions) on fear conditioned responses (Merz et al., 2013a; Zorawski et al., 2005).

Additionally, cortisol levels have been shown to modulate memory performance, following an inverted-U shaped relationship, where memory performance (y axis) varies according to cortisol levels (x axis) (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). Both very low and very high levels of cortisol have been shown to be deleterious for memory performance, whereas moderate cortisol levels provide optimal memory performance (Lupien et al., 2007). In this manuscript, the reviewed evidence suggests that during fear acquisition, high endogenous cortisol levels (basal levels) in men increase fear brain responses, while these responses decrease following high doses of exogenous cortisol (Merz, Stark, et al., 2013; Merz, Wolf, et al., 2013). Obviously, endogenous cortisol levels are considerably lower than cortisol levels reached with an exogenous administration protocol (i.e., hydrocortisone). Higher endogenous cortisol levels may therefore increase activations of certain brain regions from moderate to optimal levels, while exogenous cortisol administration may decrease brain activations, as it induces a shift on the right end of the inverted-U shaped curve. One must also keep in mind the different doses used with such pharmacological protocols, which could sometimes represent supraphysiological doses (Cornelisse et al., 2014; Merz et al., 2012, 2010; Stark et al., 2006; Tabbert et al., 2010; van Ast et al., 2012). Taken together, these data suggest that fear-related brain activations may follow a similar relationship with cortisol variations than memory performance does. In the future, it would be interesting to pharmacologically decrease or increase cortisol levels to understand the impact of cortisol variations on the fear network activation.

5.2. Fear-related recommendations

Studies investigating fear conditioning largely used SCR and fMRI as their indices of fear, although other studies have also extended their investigation by including more indicators, such as FPS, US expectancy, and brain imaging. Combining multiple systems, such as physiology, psychology, and brain imaging clearly represents a strength, as combined data could provide a better comprehension of fear outcomes. Knowing the disparity between self-reports and biology concerning emotional stimuli (Polackova Solcova & Lacev, 2017; White & Graham, 2016), examining subjective fear responses can add an extra layer of informative data. At this moment, it is sometimes difficult to reconcile some of the discrepant results. A more systematic investigation of multiple indices of fear could definitely be beneficial for the field in the long-term as it would facilitate the comparison between studies and will undoubtedly allow to have a better comprehension of the field with the necessary nuances.

These methods all provide information about responses to the fearful and safety cues. Two main methods are used to analyze these responses. Some studies look at both CSs independently, while others use differential scores (subtracting the response to the CS- from the CS + response). A large differential score can be interpreted as a successful fear learning, reflecting higher reactivity to the threat-signaling cue. However, using this differential analytic approach can sometimes hinder some effects. Indeed, a low differential score during fear acquisition training could suggest an unsuccessful fear acquisition where fear responses are low to both the CS+ and the CS-, but it can also be explained by fear generalization, where fear responses are high and similar to all stimuli. At a clinical level, fear generalization is often observed in populations who have difficulty in discriminating what is threatening than what is safe (Duits et al., 2015). Looking at both cue types (CS+ and CS-) can therefore facilitate the interpretation of the fear conditioning data. Thereby, if one favors the differential analytic approach, it could still be relevant to present the data of the CS+ and the CS- separately in order to have a better grasp of these nuances.

Finally, many protocols have been designed for different purposes. While most studies use contingency understanding as an inclusion criterion (Hamm & Vaitl, 1996; Hamm & Weike, 2005; Lovibond & Shanks, 2002; Tabbert et al., 2011), contingency unaware samples are sometimes used to investigate implicit fear learning (Merz et al., 2010, 2012). This method allows the examination of fear activations in the brain by using supraliminal stimuli procedure, where distractors are displayed during fear acquisition training to prevent the declarative learning. Thereby, the distraction task used to hamper the CS-US relationship could be a focus of attention for participants during fear acquisition training. This could ultimately blur the results at both the physiological and neural levels. In other words, data obtained could not only be due to the fear conditioning protocol, but also to the additional cognitive task used in this type of procedure. As discussed by Mertens and Engelhard (2019), numerous factors are important when considering the validity of unaware fear conditioning results, notably individual differences (in cognition and perception), the interference task, and the awareness measure. Other studies have used different types of fear conditioning paradigm as well. For instance, an instructed fear conditioning protocol was adopted by Merz et al. (2013), where all participants were explicitly told the contingency (e.g., this geometrical shape will be followed by an electric shock). While it was done to obtain a contingency aware sample, some studies did not specify any contingency inclusion criterion (Antov & Stockhorst, 2014; Stark et al., 2006). Thus, it appears essential to consider the instructions provided to the participants, due to their potential influence on the outcomes of interest (Lonsdorf et al., 2017) and to also take into account the criteria (e.g., contingency awareness) used to include or exclude participants. For an extensive review on the subject see Lonsdorf et al. (2017).

5.3. Recommendations for sex hormone assessment

So far, only few studies have considered the interaction between stress and sex hormones in the context of fear conditioning. The phases of the menstrual cycle have been less investigated in that context (see Fig. 2), therefore knowledge regarding gonadal profiles is rather limited. This calls for further investigation of stress impact on fear as a function of women's hormonal milieu. That being said, recruiting women on the basis of a particular phase of the menstrual cycle is clearly a challenge. Moreover, the definition of menstrual cycle phases often varies from one research study to another. As gonadal levels fluctuate within the two main phases of the menstrual cycle, researchers must pay particular attention to what they want to assess. Indeed, the early follicular phase, ranging from day 1–8 according to different studies (Antov & Stockhorst, 2014; Kirschbaum et al., 1999; Merz et al., 2012; Wharton et al., 2008), is frequently used to examine the impact of low levels of estradiol and progesterone. On the other hand, the (mid)luteal phase, characterized by higher levels of progesterone and estradiol, varies from around day 20–26 (Kirschbaum et al., 1999; Merz et al., 2012; Mordecai, Rubin, & Maki, 2008). To investigate the effect of estradiol changes only, the early follicular should be compared to the mid-cycle phase (high levels of estradiol and low levels of progesterone; which occurs around ovulation time, from day 11–16; Antov & Stockhorst, 2014). Targeting with more precision a specific

phase would definitely contribute to disentangle the contribution of sex hormones when studying the impact of stress on fear. However, only relying on the women's self-report to target a specific period within the menstrual cycle might induce some bias. When possible, both self-report data and sex hormone concentrations should be considered when studying naturally cycling women, where sex hormone levels could be used to support the self-report data.

In addition, comparing three to four sex hormone subgroups in either stress or control conditions can be an issue for feasibility and/or statistical power. The reported non-significant and inconsistent results do indeed reflect this reality, where many studies using SCR had less than 20 participants per group (Merz, Stark, et al., 2013; Merz et al., 2010; Stark et al., 2006; Tabbert et al., 2010). Knowing the high between-subject variability in physiological experiments, subgroup multiplication implies a substantially greater sample size in order to overcome underpowered analyses (Ney et al., 2018). Importantly, this could prevent statistical errors that are more likely to occur when statistical power is low (Gelman & Carlin, 2014).

In this vein, studies where large samples are hard to recruit could focus on sex hormone profiles treated as a continuous variable. Beyond small sample sizes, this method can overcome other limitations associated with the grouping approach such as miscategorization (e.g., a woman with rising estradiol levels that is classified in early follicular). Additionally, looking at the estradiol (E)/progesterone (P) ratio could also represent an interesting approach to analyze women subgroups, reflecting a more standardized perspective (Hernandez-Lopez, Garcia-Granados, Chavira-Ramirez, & Mondragon-Ceballos, 2017). When using this ratio, the relative weight of each hormone is taken into account. Unlike using self-reports, it can provide a more objective manner to classify women through cycle phase categories (e.g., follicular = low E/low P, ovulation = high E/low P, luteal = moderate E/high P). When considering it as a continuous measure, the ratio provides useful information by quantifying the (im)balance between these two hormones, notably at ovulation versus luteal phase where the E/P ratio becomes totally inversed (see Fig. 1). For example, a woman at day 8 and day 20 of her menstrual cycle might have similar estradiol concentrations but will display different progesterone levels. The E/P ratio could reduce interindividual variability and provide a more complete measure, giving information about the dynamic between the two hormones.

5.4. Future perspectives: A drift towards clinical data

Most studies examined the question on how stress impacts fear conditioning in healthy participants, generally with the intention of understanding mechanisms behind the etiology of certain psychopathologies such as PTSD. However, few studies were conducted in clinical populations. Due to the frequent associations between dysregulations of the stress system and various mental health disorders (Adam et al., 2017; Agorastos, Pervanidou, Chrousos, & Kolaitis, 2018; Berger et al., 2016; Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013), exploring stress mechanisms in fear conditioning among clinical samples is valuable, and could further inform on the maintenance of some symptoms that characterize these psychopathologies.

So far, the impact of acute stress on fear has rarely been studied in populations with dysregulated stress levels such as PTSD, major depressive disorder (MDD) and anxiety disorders (Dunlop & Wong, 2019; Faravelli et al., 2012; Stetler & Miller, 2011; Steudte-Schmiedgen, Kirschbaum, Alexander, & Stalder, 2016). Among the few studies, it has been shown that cortisol suppression leads to reduced physiological fear responses in PTSD patients (Jovanovic et al., 2011). Kuehl and collaborators (2020) recently investigated the effects of yohimbine-induced SAM axis activation on fear responses in MDD patients with or without childhood adversity. While yohimbine increased fear responses, no effect of MDD was found. However, the activation of the SAM axis worsened CS differentiation in individuals without a history of adverse childhood experiences. The opposite pattern was found (at a trend level) in individuals with a history of adverse childhood experiences. Taken together, these data call for the importance of considering the population type when assessing the impact of stress exposure and stress hormones on fear memory formation and consolidation. More studies are therefore needed in order to better characterize the effects of stress on the etiology, severity, and maintenance of fear- and stress-related psychopathologies.

6. Conclusion

Stress is an inherent component in the formation of traumatic fear memories. Fear conditioning protocols allow to evaluate the acquisition and extinction of fear. By combining them with a stress exposure protocol, they offer the possibility to investigate how stress can impact emotional memory. Given that fear- and stress-related pathologies are marked by considerable sex differences, this review hence described the effects of pre-acquisition stress on fear conditioning, by considering the contribution of sex and sex hormone levels. In men, stress hormones seem to enhance physiological threat differentiation, while reducing fear network activation. In women, considering sex hormone profiles allows to draw a clearer picture of how the stress and fear networks interact. In women taking oral contraceptives, cortisol appears to increase activation in several fear-related brain regions. As for naturally cycling women, few data are available regarding their gonadal hormone levels and many inconsistencies are reported. This review also unveiled extinction impairments induced by pre-acquisition stress, a finding that seems to hold irrespective of sex.

We focused on result disparity and tried to understand which aspects might be underlying it. Results appear not only to be influenced by sex hormone grouping, but also by methodological differences pertaining to both fear conditioning and stress protocols. Importantly, other factors have been identified in the literature as key modulators of the main concepts reviewed here (stress, fear, and sex differences) (Lonsdorf & Merz, 2017). As an example, ethnicity (Asnaani, Richey, Dimaite, Hinton, & Hofmann, 2010; Lewis-Fernandez et al., 2010; Martinez, Franco-Chaves, Milad, & Quirk, 2014), education (Rosenbaum et al., 2015), and some personality traits (Indovina, Robbins, Nunez-Elizalde, Dunn, & Bishop, 2011; Otto et al., 2007; Rauch et al., 2005) have been shown to influence conditioned fear. While some of these factors are often considered in the study recruitment to balance groups or statistically account for them (e.g., age, ethnicity), others might be less often examined and may distribute unevenly between the groups studied. For example, sex differences have been reported in anxiety-like traits. Women endorse more neuroticism (De Bolle et al., 2015; Lynn & Martin, 1997), and have a greater tendency to ruminate (Johnson & Whisman, 2013). As such, isolating the contribution of each factor could be a challenge. Future studies should therefore pay particular attention to such variables and to factor them in their analyses when needed.

In sum, this review provided an overview of the various studies assessing the impact of stress on fear learning as a function of sex differences and sex hormones. The interaction between these three domains is complex and could be influenced by several methodological factors. Paying attention to these factors will hopefully allow a better understanding of the question and will make significant contributions in clinical settings.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

MFM holds a salary award from the Fonds de recherche du Québec –

Santé (FRQS) and is the PI of a Discovery Grant from the Natural Sciences and Engineering Research Council of Canada (NSERC). AB holds a M.Sc. Scholarship from the Canadian Institutes of Health Research (CIHR). SMB is supported by a postdoctoral fellowship award from the CIHR.

References

Adam, E. K., Quinn, M. E., Tavernier, R., McQuillan, M. T., Dahlke, K. A., & Gilbert, K. E. (2017). Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. *Psychoneuroendocrinology, 83*, 25–41. https://doi.org/10.1016/j.psyneuen.2017.05.018.

Agorastos, A., Pervanidou, P., Chrousos, G. P., & Kolaitis, G. (2018). Early life stress and trauma: Developmental neuroendocrine aspects of prolonged stress system dysregulation. *Hormones (Athens), 17*(4), 507–520. https://doi.org/10.1007/s42000-018-0065-x.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC.

Antov, M. I., & Stockhorst, U. (2014). Stress exposure prior to fear acquisition interacts with estradiol status to alter recall of fear extinction in humans. *Psychoneuroendocrinology, 49*, 106–118. https://doi.org/10.1016/j.psyneuen.2014.06.022.

Antov, M. I., Wolk, C., & Stockhorst, U. (2013). Differential impact of the first and second wave of a stress response on subsequent fear conditioning in healthy men. *Biological Psychology, 94*(2), 456–468. https://doi.org/10.1016/j.biopsycho.2013.08.007.

Asnaani, A., Richey, J. A., Dimaite, R., Hinton, D. E., & Hofmann, S. G. (2010). A cross-ethnic comparison of lifetime prevalence rates of anxiety disorders. *The Journal of Nervous and Mental Disease, 198*(8), 551–555. https://doi.org/10.1097/NMD.0b013e3181ea169f.

van Ast, V. A., Vervliet, B., & Kindt, M. (2012). Contextual control over expression of fear is affected by cortisol. *Frontiers in Behavioral Neuroscience, 6*, 67. https://doi.org/10.3389/fnbeh.2012.00067.

Atwood, C. S., Meethal, S. V., Liu, T., Wilson, A. C., Gallego, M., Smith, M. A., et al. (2005). Dysregulation of the hypothalamic-pituitary-gonadal axis with menopause and andropause promotes neurodegenerative senescence. *Journal of Neuropathology & Experimental Neurology, 64*(2), 93–103. https://doi.org/10.1093/jnen/64.2.93.

Bale, T. L., & Epperson, C. N. (2015). Sex differences and stress across the lifespan. *Nature Neuroscience, 18*(10), 1413–1420. https://doi.org/10.1038/nn.4112.

Beckers, T., Krypotos, A. M., Boddez, Y., Effting, M., & Kindt, M. (2013). What's wrong with fear conditioning? *Biological Psychology, 92*(1), 90–96. https://doi.org/10.1016/j.biopsycho.2011.12.015.

Berger, M., Kraeuter, A. K., Romanik, D., Malouf, P., Amminger, G. P., & Sarnyai, Z. (2016). Cortisol awakening response in patients with psychosis: Systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews, 68*, 157–166. https://doi.org/10.1016/j.neubiorev.2016.05.027.

Bernard, C. (1865). *Introduction à l'étude de la médecine expérimentale.* Paris, France: J.B. Baillière & Fils.

Blakemore, S. J., Burnett, S., & Dahl, R. E. (2010). The role of puberty in the developing adolescent brain. *Human Brain Mapping, 31*(6), 926–933. https://doi.org/10.1002/hbm.21052.

Boddez, Y., Baeyens, F., Luyten, L., Vansteenwegen, D., Hermans, D., & Beckers, T. (2013). Rating data are underrated: Validity of US expectancy in human fear conditioning. *Journal of Behavior Therapy and Experimental Psychiatry, 44*(2), 201–206. https://doi.org/10.1016/j.jbtep.2012.08.003.

Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning & Memory, 11*(5), 485–494. https://doi.org/10.1101/lm.78804.

Bradley, R., Greene, J., Russ, E., Dutra, L., & Westen, D. (2005). A multidimensional meta-analysis of psychotherapy for PTSD. *American Journal of Psychiatry, 162*(2), 214–227. https://doi.org/10.1176/appi.ajp.162.2.214.

Briscione, M. A., Jovanovic, T., & Norrholm, S. D. (2014). Conditioned fear associated phenotypes as robust, translational indices of trauma-, stressor-, and anxiety-related behaviors. *Frontiers in Psychiatry, 5*, 88. https://doi.org/10.3389/fpsyt.2014.00088.

Bryant, R. A., Harvey, A. G., Guthrie, R. M., & Moulds, M. L. (2000). A prospective study of psychophysiological arousal, acute stress disorder, and posttraumatic stress disorder. *Journal of Abnormal Psychology, 109*(2), 341–344. https://doi.org/10.1023/A:1025750209553.

Cannon, W. B. (1915). *Bodily changes in pain, hunger, fear, and rage: An account of recent researches into the function of emotional excitement.* New York, NY: D. Appleton & Co.

Cannon, W. B., & Lissak, K. (1939). Evidence for adrenaline in adrenergic neurones. *American Journal of Physiology-Legacy Content, 125*(4), 765–777. https://doi.org/10.1152/ajplegacy.1939.125.4.765.

Cornelisse, S., van Ast, V. A., Joels, M., & Kindt, M. (2014). Delayed effects of cortisol enhance fear memory of trace conditioning. *Psychoneuroendocrinology, 40*, 257–268. https://doi.org/10.1016/j.psyneuen.2013.11.013.

Cover, K. K., Maeng, L. Y., Lebron-Milad, K., & Milad, M. R. (2014). Mechanisms of estradiol in fear circuitry: Implications for sex differences in psychopathology. *Translational Psychiatry, 4*, e422. https://doi.org/10.1038/tp.2014.67.

Craske, M. G., Hermans, D. E., & Vansteenwegen, D. E. (2006). *Fear and learning: From basic processes to clinical implications.* Washington, DC: American Psychological Association.

Day, H. L. L., & Stevenson, C. W. (2019). The neurobiological basis of sex differences in learned fear and its inhibition. *European Journal of Neuroscience*. https://doi.org/10.1111/ejn.14602.

De Bolle, M., De Fruyt, F., McCrae, R. R., Lockenhoff, C. E., Costa, P. T., Aguilar-Vafaie, M. E., ... Terracciano, A. (2015). The emergence of sex differences in personality traits in early adolescence: A cross-sectional, cross-cultural study. *Journal of Personality and Social Psychology, 108*(1), 171–185. https://doi.org/10.1037/a0038497.

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin, 130*(3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355.

Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., ... Baas, J. M. (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and Anxiety, 32*(4), 239–253. https://doi.org/10.1002/da.22353.

Dunlop, B. W., & Wong, A. (2019). The hypothalamic-pituitary-adrenal axis in PTSD: Pathophysiology and treatment interventions. *Progress In Neuro-Psychopharmacology & Biological Psychiatry, 89*, 361–379. https://doi.org/10.1016/j.pnpbp.2018.10.010.

Faravelli, C., Lo Sauro, C., Lelli, L., Pietrini, F., Lazzeretti, L., Godini, L., ... Ricca, V. (2012). The role of life events and HPA axis in anxiety disorders: A review. *Current Pharmaceutical Design, 18*(35), 5663–5674. https://doi.org/10.2174/138161212803530907.

Forcadell, E., Torrents-Rodas, D., Vervliet, B., Leiva, D., Tortella-Feliu, M., & Fullana, M. A. (2017). Does fear extinction in the laboratory predict outcomes of exposure therapy? A treatment analog study. *International Journal of Psychophysiology, 121*, 63–71. https://doi.org/10.1016/j.ijpsycho.2017.09.001.

Fridlund, A. J., & Cacioppo, J. T. (1986). Guidelines for human electromyographic research. *Psychophysiology, 23*(5), 567–589. https://doi.org/10.1111/j.1469-8986.1986.tb00676.x.

Fujimoto, V. Y., Villanueva, A. L., Hopper, B., Moscinski, M., & Rebar, R. W. (1986). Increased adrenocortical responsiveness to exogenous ACTH in oral contraceptive users. *Advances in Contraception, 2*(4), 343–353. https://doi.org/10.1007/bf02340051.

Garcia, N. M., Walker, R. S., & Zoellner, L. A. (2018). Estrogen, progesterone, and the menstrual cycle: A systematic review of fear learning, intrusive memories, and PTSD. *Clinical Psychology Review, 66*, 80–96. https://doi.org/10.1016/j.cpr.2018.06.005.

Gelman, A., & Carlin, J. (2014). Beyond power calculations: Assessing type S (sign) and type M (magnitude) errors. *Perspectives on Psychological Science, 9*(6), 641–651. https://doi.org/10.1177/1745691614551642.

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

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

Goldstein, J. M., Seidman, L. J., Horton, N. J., Makris, N., Kennedy, D. N., Caviness, V. S., Jr., ... Tsuang, M. T. (2001). Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cerebral Cortex, 11*(6), 490–497. https://doi.org/10.1093/cercor/11.6.490.

Golobof, A., & Kiley, J. (2016). The current status of oral contraceptives: Progress and recent innovations. *Seminars in Reproductive Medicine, 34*(3), 145–151. https://doi.org/10.1055/s-0036-1572546.

Graham, B. M., Li, S. H., Black, M. J., & Ost, L. G. (2018). The association between estradiol levels, hormonal contraceptive use, and responsiveness to one-session-treatment for spider phobia in women. *Psychoneuroendocrinology, 90*, 134–140. https://doi.org/10.1016/j.psyneuen.2018.02.019.

Graham, B. M., & Milad, M. R. (2011). The study of fear extinction: Implications for anxiety disorders. *American Journal of Psychiatry, 168*(12), 1255–1265. https://doi.org/10.1176/appi.ajp.2011.11040557.

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

Graham, B. M., & Milad, M. R. (2014). Inhibition of estradiol synthesis impairs fear extinction in male rats. *Learning & Memory, 21*(7), 347–350. https://doi.org/10.1101/lm.034926.114.

Grings, W. W. (1960). Preparatory set variables related to classical conditioning of autonomic responses. *Psychol Rev, 67*, 243–252. https://doi.org/10.1037/h0046852.

Gunnar, M. R., & Vazquez, D. (2006). Stress neurobiology and developmental psychopathology. In D. Cicchetti, & D. J. Cohen (Eds.). *Developmental Psychopathology, 2nd ed. Volume Two: Developmental Neuroscience* (pp. 533–577). Hoboken, NJ: John Wiley & Sons, Inc. https://doi.org/10.1002/9780470939390.ch13.

Hamm, A. O., & Vaitl, D. (1996). Affective learning: Awareness and aversion. *Psychophysiology, 33*(6), 698–710. https://doi.org/10.1111/j.1469-8986.1996.tb02366.x.

Hamm, A. O., & Weike, A. I. (2005). The neuropsychology of fear learning and fear regulation. *International Journal of Psychophysiology, 57*(1), 5–14. https://doi.org/10.1016/j.ijpsycho.2005.01.006.

Hamson, D. K., Roes, M. M., & Galea, L. A. (2016). Sex hormones and cognition: Neuroendocrine influences on memory and learning. *Comparative Physiology, 6*(3), 1295–1337. https://doi.org/10.1002/cphy.c150031.

Handa, R. J., & Weiser, M. J. (2014). Gonadal steroid hormones and the hypothalamo-pituitary-adrenal axis. *Frontiers in Neuroendocrinology, 35*(2), 197–220. https://doi.org/10.1016/j.yfrne.2013.11.001.

Heim, C., Owens, M. J., Plotsky, P. M., & Nemeroff, C. B. (1997). The role of early adverse life events in the etiology of depression and posttraumatic stress disorder. Focus on corticotropin-releasing factor. *Annals of the New York Academy of Sciences, 821*, 194–207. https://doi.org/10.1111/j.1749-6632.1997.tb48279.x.

Hernandez-Lopez, L., Garcia-Granados, D. M., Chavira-Ramirez, R., & Mondragon-Ceballos, R. (2017). Testosterone, the progesterone/estradiol ratio, and female ratings of masculine facial fluctuating asymmetry for a long-term relationship.

Physiology & Behavior, 175, 66–71. https://doi.org/10.1016/j.physbeh.2017.03.033.
Hines, E. A., & Brown, G. E. (1936). The cold pressor test for measuring the reactibility of the blood pressure: Data concerning 571 normal and hypertensive subjects. *American Heart Journal, 11*(1), 1–9. https://doi.org/10.1016/S0002-8703(36)90370-8.
Hinrichs, R., van Rooij, S. J., Michopoulos, V., Schultebraucks, K., Winters, S., Maples-Keller, J., ... Jovanovic, T. (2019). Increased skin conductance response in the immediate aftermath of trauma predicts PTSD risk. *Chronic Stress (Thousand Oaks), 3*. https://doi.org/10.1177/2470547019844441.
Hwang, M. J., Zsido, R. G., Song, H., Pace-Schott, E. F., Miller, K. K., Lebron-Milad, K., ... Milad, M. R. (2015). Contribution of estradiol levels and hormonal contraceptives to sex differences within the fear network during fear conditioning and extinction. *BMC Psychiatry, 15*, 295. https://doi.org/10.1186/s12888-015-0673-9.
Indovina, I., Robbins, T. W., Nunez-Elizalde, A. O., Dunn, B. D., & Bishop, S. J. (2011). Fear-conditioning mechanisms associated with trait vulnerability to anxiety in humans. *Neuron, 69*(3), 563–571. https://doi.org/10.1016/j.neuron.2010.12.034.
Jackson, E. D., Payne, J. D., Nadel, L., & Jacobs, W. J. (2006). Stress differentially modulates fear conditioning in healthy men and women. *Biological Psychiatry, 59*(6), 516–522. https://doi.org/10.1016/j.biopsych.2005.08.002.
Joels, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature Reviews Neuroscience, 10*(6), 459–466. https://doi.org/10.1038/nrn2632.
Joels, M., Pu, Z., Wiegert, O., Oitzl, M. S., & Krugers, H. J. (2006). Learning under stress: How does it work? *Trends in Cognitive Sciences, 10*(4), 152–158. https://doi.org/10.1016/j.tics.2006.02.002.
Johnson, D. P., & Whisman, M. A. (2013). Gender differences in rumination: A meta-analysis. *Personality and Individual Differences, 55*(4), 367–374. https://doi.org/10.1016/j.paid.2013.03.019.
Jovanovic, T., Kazama, A., Bachevalier, J., & Davis, M. (2012). Impaired safety signal learning may be a biomarker of PTSD. *Neuropharmacology, 62*(2), 695–704. https://doi.org/10.1016/j.neuropharm.2011.02.023.
Jovanovic, T., Phifer, J. E., Sicking, K., Weiss, T., Norrholm, S. D., Bradley, B., et al. (2011). Cortisol suppression by dexamethasone reduces exaggerated fear responses in posttraumatic stress disorder. *Psychoneuroendocrinology, 36*(10), 1540–1552. https://doi.org/10.1016/j.psyneuen.2011.04.008.
Kajantie, E., & Phillips, D. I. (2006). The effects of sex and hormonal status on the physiological response to acute psychosocial stress. *Psychoneuroendocrinology, 31*(2), 151–178. https://doi.org/10.1016/j.psyneuen.2005.07.002.
Kandel, E. R., Dudai, Y., & Mayford, M. R. (2014). The molecular and systems biology of memory. *Cell, 157*(1), 163–186. https://doi.org/10.1016/j.cell.2014.03.001.
Kimura, D. (1996). Sex, sexual orientation and sex hormones influence human cognitive function. *Current Opinion in Neurobiology, 6*(2), 259–263. https://doi.org/10.1016/s0959-4388(96)80081-x.
Kinner, V. L., Het, S., & Wolf, O. T. (2014). Emotion regulation: Exploring the impact of stress and sex. *Frontiers in Behavioral Neuroscience, 8*, 397. https://doi.org/10.3389/fnbeh.2014.00397.
Kirschbaum, C., Kudielka, B. M., Gaab, J., Schommer, N. C., & Hellhammer, D. H. (1999). Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosomatic Medicine, 61*(2), 154–162. https://doi.org/10.1097/00006842-199903000-00006.
Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology, 28*(1–2), 76–81. https://doi.org/10.1159/000119004.
Kirschbaum, C., Schommer, N., Federenko, I., Gaab, J., Neumann, O., Oellers, M., ... Hellhammer, D. H. (1996). Short-term estradiol treatment enhances pituitary-adrenal axis and sympathetic responses to psychosocial stress in healthy young men. *Journal of Clinical Endocrinology & Metabolism, 81*(10), 3639–3643. https://doi.org/10.1210/jcem.81.10.8855815.
de Kloet, E. R., Karst, H., & Joels, M. (2008). Corticosteroid hormones in the central stress response: Quick-and-slow. *Frontiers in Neuroendocrinology, 29*(2), 268–272. https://doi.org/10.1016/j.yfrne.2007.10.002.
Kirschbaum, C., Wust, S., & Hellhammer, D. (1992). Consistent sex differences in cortisol responses to psychological stress. *Psychosomatic Medicine, 54*(6), 648–657. https://doi.org/10.1097/00006842-199211000-00004.
Kornfield, S. L., Hantsoo, L., & Epperson, C. N. (2018). What does sex have to do with it? The role of sex as a biological variable in the development of posttraumatic stress disorder. *Current Psychiatry Reports, 20*(6), 39. https://doi.org/10.1007/s11920-018-0907-x.
Kuehl, L. K., Deuter, C. E., Hellmann-Regen, J., Kaczmarczyk, M., Otte, C., & Wingenfeld, K. (2020). Enhanced noradrenergic activity by yohimbine and differential fear conditioning in patients with major depression with and without adverse childhood experiences. *Progress In Neuro-Psychopharmacology & Biological Psychiatry, 96*, 109751. https://doi.org/10.1016/j.pnpbp.2019.109751.
Lebron-Milad, K., Abbs, B., Milad, M. R., Linnman, C., Rougemount-Bucking, A., Zeidan, M. A., ... Goldstein, J. M. (2012). Sex differences in the neurobiology of fear conditioning and extinction: A preliminary fMRI study of shared sex differences with stress-arousal circuitry. *Biology of Mood & Anxiety Disorders, 2*, 7. https://doi.org/10.1186/2045-5380-2-7.
LeDoux, J. E. (2014). Coming to terms with fear. *Proceedings of the National Academy of Sciences of the U S A, 111*(8), 2871–2878. https://doi.org/10.1073/pnas.1400335111.
Lewis-Fernandez, R., Hinton, D. E., Laria, A. J., Patterson, E. H., Hofmann, S. G., Craske, M. G., ... Liao, B. (2010). Culture and the anxiety disorders: Recommendations for DSM-V. *Depression and Anxiety, 27*(2), 212–229. https://doi.org/10.1002/da.20647.
Lipp, O. V. (2006). Human fear learning: Contemporary procedures and measurement. In M. G. Craske, D. Hermans, & D. Vansteenwegen (Eds.). *Fear and learning: From basic processes to clinical implications* (pp. 37–51). Washington, DC: American Psychological Association.
Lissek, S., & van Meurs, B. (2015). Learning models of PTSD: Theoretical accounts and psychobiological evidence. *International Journal of Psychophysiology, 98*(3 Pt 2), 594–605. https://doi.org/10.1016/j.ijpsycho.2014.11.006.
Lonsdorf, T. B., Menz, M. M., Andreatta, M., Fullana, M. A., Golkar, A., Haaker, J., ... Merz, C. J. (2017). Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neuroscience & Biobehavioral Reviews, 77*, 247–285. https://doi.org/10.1016/j.neubiorev.2017.02.026.
Lonsdorf, T. B., & Merz, C. J. (2017). More than just noise: Inter-individual differences in fear acquisition, extinction and return of fear in humans - biological, experiential, temperamental factors, and methodological pitfalls. *Neuroscience & Biobehavioral Reviews, 80*, 703–728. https://doi.org/10.1016/j.neubiorev.2017.07.007.
Lopez, J. F., Akil, H., & Watson, S. J. (1999). Neural circuits mediating stress. *Biological Psychiatry, 46*(11), 1461–1471. https://doi.org/10.1016/s0006-3223(99)00266-8.
Lovibond, P. F., & Shanks, D. R. (2002). The role of awareness in pavlovian conditioning: Empirical evidence and theoretical implications. *Journal of Experimental Psychology: Animal Behavior Processes, 28*(1), 3–26. https://doi.org/10.1037/0097-7403.28.1.3.
Luine, V. N. (2008). Sex steroids and cognitive function. *Journal of Neuroendocrinology, 20*(6), 866–872. https://doi.org/10.1111/j.1365-2826.2008.01710.x.
Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition, 65*(3), 209–237. https://doi.org/10.1016/j.bandc.2007.02.007.
Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience, 10*(6), 434–445. https://doi.org/10.1038/nrn2639.
Lynn, R., & Martin, T. (1997). Gender differences in extraversion, neuroticism, and psychoticism in 37 nations. *The Journal of Social Psychology, 137*(3), 369–373. https://doi.org/10.1080/00224549709595447.
Maeng, L. Y., & Milad, M. R. (2015). Sex differences in anxiety disorders: Interactions between fear, stress, and gonadal hormones. *Hormones and Behavior, 76*, 106–117. https://doi.org/10.1016/j.yhbeh.2015.04.002.
Maples-Keller, J. L., Rauch, S. A. M., Jovanovic, T., Yasinski, C. W., Goodnight, J. M., Sherrill, A., ... Norrholm, S. D. (2019). Changes in trauma-potentiated startle, skin conductance, and heart rate within prolonged exposure therapy for PTSD in high and low treatment responders. *Journal of Anxiety Disorders, 68*, 102147. https://doi.org/10.1016/j.janxdis.2019.102147.
Martinez, K. G., Franco-Chaves, J. A., Milad, M. R., & Quirk, G. J. (2014). Ethnic differences in physiological responses to fear conditioned stimuli. *PloS One, 9*(12), e114977. https://doi.org/10.1371/journal.pone.0114977.
Mason, J. W. (1968). A review of psychoendocrine research on the sympathetic-adrenal medullary system. *Psychosomatic Medicine, 30*(5), https://doi.org/10.1097/00006842-196809000-00022 Suppl:631-653.
Mason, J. W. (1975). A historical view of the stress field. *Journal of Human Stress, 1*(1), 6–12. https://doi.org/10.1080/0097840x.1975.9940399 contd.
McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress effects on neuronal structure: Hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology, 41*(1), 3–23. https://doi.org/10.1038/npp.2015.171.
McEwen, B. S., Weiss, J. M., & Schwartz, L. S. (1968). Selective retention of corticosterone by limbic structures in rat brain. *Nature, 220*(5170), 911–912. https://doi.org/10.1038/220911a0.
McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience, 27*, 1–28. https://doi.org/10.1146/annurev.neuro.27.070203.144157.
McLean, C. P., & Foa, E. B. (2011). Prolonged exposure therapy for post-traumatic stress disorder: A review of evidence and dissemination. *Expert Rev Neurother, 11*(8), 1151–1163. https://doi.org/10.1586/ern.11.94.
Mertens, G., & Engelhard, I. M. (2019). A systematic review and meta-analysis of the evidence for unaware fear conditioning. *Neuroscience & Biobehavioral Reviews, 108*, 254–268. https://doi.org/10.1016/j.neubiorev.2019.11.012.
Merz, C. J. (2017). Contribution of stress and sex hormones to memory encoding. *Psychoneuroendocrinology, 82*, 51–58. https://doi.org/10.1016/j.psyneuen.2017.05.002.
Merz, C. J., Stark, R., Vaitl, D., Tabbert, K., & Wolf, O. T. (2013a). Stress hormones are associated with the neuronal correlates of instructed fear conditioning. *Biological Psychology, 92*(1), 82–89. https://doi.org/10.1016/j.biopsycho.2012.02.017.
Merz, C. J., Tabbert, K., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., et al. (2010). Investigating the impact of sex and cortisol on implicit fear conditioning with fMRI. *Psychoneuroendocrinology, 35*(1), 33–46. https://doi.org/10.1016/j.psyneuen.2009.07.009.
Merz, C. J., Tabbert, K., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., et al. (2012). Oral contraceptive usage alters the effects of cortisol on implicit fear learning. *Hormones and Behavior, 62*(4), 531–538. https://doi.org/10.1016/j.yhbeh.2012.09.001.
Merz, C. J., & Wolf, O. T. (2017). Sex differences in stress effects on emotional learning. *Journal of Neuroscience Research, 95*(1–2), 93–105. https://doi.org/10.1002/jnr.23811.
Merz, C. J., Wolf, O. T., Schweckendiek, J., Klucken, T., Vaitl, D., & Stark, R. (2013b). Stress differentially affects fear conditioning in men and women. *Psychoneuroendocrinology, 38*(11), 2529–2541. https://doi.org/10.1016/j.psyneuen.2013.05.015.
Milad, M. R., Goldstein, J. M., Orr, S. P., Wedig, M. M., Klibanski, A., Pitman, R. K., et al. (2006a). Fear conditioning and extinction: Influence of sex and menstrual cycle in healthy humans. *Behavioral Neuroscience, 120*(6), 1196–1203. https://doi.org/10.1037/0735-7044.120.5.1196.
Milad, M. R., Orr, S. P., Lasko, N. B., Chang, Y., Rauch, S. L., & Pitman, R. K. (2008).

Presence and acquired origin of reduced recall for fear extinction in PTSD: Results of a twin study. *Journal of Psychiatric Research, 42*(7), 515–520. https://doi.org/10.1016/j.jpsychires.2008.01.017.
Milad, M. R., & Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. *Annual Review of Psychology, 63*, 129–151. https://doi.org/10.1146/annurev.psych.121208.131631.
Milad, M. R., Rauch, S. L., Pitman, R. K., & Quirk, G. J. (2006b). Fear extinction in rats: Implications for human brain imaging and anxiety disorders. *Biological Psychology, 73*(1), 61–71. https://doi.org/10.1016/j.biopsycho.2006.01.008.
Milad, M. R., Rosenbaum, B. L., & Simon, N. M. (2014). Neuroscience of fear extinction: Implications for assessment and treatment of fear-based and anxiety related disorders. *Behaviour Research and Therapy, 62*, 17–23. https://doi.org/10.1016/j.brat.2014.08.006.
Milad, M. R., Zeidan, M. A., Contero, A., Pitman, R. K., Klibanski, A., Rauch, S. L., et al. (2010). The influence of gonadal hormones on conditioned fear extinction in healthy humans. *Neuroscience, 168*(3), 652–658. https://doi.org/10.1016/j.neuroscience.2010.04.030.
Miller, W. L. (2018). The hypothalamic-pituitary-adrenal Axis: A brief history. *Horm Res Paediatr, 89*(4), 212–223. https://doi.org/10.1159/000487755.
Moore, D. E., Kawagoe, S., Davajan, V., Mishell, D. R., & Nakamura, R. M. (1978). An in vivo system in man for quantitation of estrogenicity. I. Physiologic changes in binding capacity of serum corticosteroid-binding globulin. *American Journal of Obstetrics and Gynecology, 130*(4), 475–481. https://doi.org/10.1016/0002-9378(78)90293-4.
Mordecai, K. L., Rubin, L. H., & Maki, P. M. (2008). Effects of menstrual cycle phase and oral contraceptive use on verbal memory. *Hormones and Behavior, 54*(2), 286–293. https://doi.org/10.1016/j.yhbeh.2008.03.006.
Myers, K. M., & Davis, M. (2002). Behavioral and neural analysis of extinction. *Neuron, 36*(4), 567–584. https://doi.org/10.1016/S0896-6273(02)01064-4.
Myers, K. M., & Davis, M. (2007). Mechanisms of fear extinction. *Molecular Psychiatry, 12*(2), 120–150. https://doi.org/10.1038/sj.mp.4001939.
Najavits, L. M. (2015). The problem of dropout from "gold standard" PTSD therapies. *F1000Prime Rep, 7*, 43. https://doi.org/10.12703/P7-43.
Ney, L. J., Wade, M., Reynolds, A., Zuj, D. V., Dymond, S., Matthews, A., et al. (2018). Critical evaluation of current data analysis strategies for psychophysiological measures of fear conditioning and extinction in humans. *International Journal of Psychophysiology, 134*, 95–107. https://doi.org/10.1016/j.ijpsycho.2018.10.010.
Otto, M. W., Leyro, T. M., Christian, K., Deveney, C. M., Reese, H., Pollack, M. H., et al. (2007). Prediction of "fear" acquisition in healthy control participants in a de novo fear-conditioning paradigm. *Behavior Modification, 31*(1), 32–51. https://doi.org/10.1177/0145445506295054.
Oyola, M. G., & Handa, R. J. (2017). Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes: Sex differences in regulation of stress responsivity. *Stress: The International Journal on the Biology of Stress, 20*(5), 476–494. https://doi.org/10.1080/10253890.2017.1369523.
Pavlov, I. P. (1927). *Conditioned reflexes.* Oxford, England: Oxford University Press.
Petersen, N., Touroutoglou, A., Andreano, J. M., & Cahill, L. (2015). Oral contraceptive pill use is associated with localized decreases in cortical thickness. *Human Brain Mapping, 36*(7), 2644–2654. https://doi.org/10.1002/hbm.22797.
Pitman, R. K. (1989). Post-traumatic stress disorder, hormones, and memory. *Biological Psychiatry, 26*(3), 221–223. https://doi.org/10.1016/0006-3223(89)90033-4.
Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., ... Liberzon, I. (2012). Biological studies of post-traumatic stress disorder. *Nature Reviews Neuroscience, 13*(11), 769–787. https://doi.org/10.1038/nrn3339.
Pletzer, B., Harris, T., & Hidalgo-Lopez, E. (2019). Previous contraceptive treatment relates to grey matter volumes in the hippocampus and basal ganglia. *Scientific Reports, 9*(1), 11003. https://doi.org/10.1038/s41598-019-47446-4.
Pletzer, B., Kronbichler, M., Aichhorn, M., Bergmann, J., Ladurner, G., & Kerschbaum, H. H. (2010). Menstrual cycle and hormonal contraceptive use modulate human brain structure. *Brain Research, 1348*, 55–62. https://doi.org/10.1016/j.brainres.2010.06.019.
Pletzer, B., Kronbichler, M., & Kerschbaum, H. (2015). Differential effects of androgenic and anti-androgenic progestins on fusiform and frontal gray matter volume and face recognition performance. *Brain Research, 1596*, 108–115. https://doi.org/10.1016/j.brainres.2014.11.025.
Polackova Solcova, I., & Lacev, A. (2017). Differences in male and female subjective experience and physiological reactions to emotional stimuli. *International Journal of Psychophysiology, 117*, 75–82. https://doi.org/10.1016/j.ijpsycho.2017.04.009.
Post, L. M., Michopoulos, V., Stevens, J. S., Reddy, R., Maples, J. L., Morgan, J. R., ... Rothbaum, B. O. (2017). Psychological and psychobiological responses to immediate early intervention in the emergency department: Case report of one-session exposure therapy for the prevention of PTSD. *Pract Innov (Wash D C), 2*(2), 55–65. https://doi.org/10.1037/pri0000043.
de Quervain, D., Schwabe, L., & Roozendaal, B. (2017). Stress, glucocorticoids and memory: Implications for treating fear-related disorders. *Nature Reviews Neuroscience, 18*(1), 7–19. https://doi.org/10.1038/nrn.2016.155.
Quirk, G. J., & Mueller, D. (2008). Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology, 33*(1), 56–72. https://doi.org/10.1038/sj.npp.1301555.
Raio, C. M., & Phelps, E. A. (2015). The influence of acute stress on the regulation of conditioned fear. *Neurobiol Stress, 1*, 134–146. https://doi.org/10.1016/j.ynstr.2014.11.004.
Ramikie, T. S., & Ressler, K. J. (2018). Mechanisms of sex differences in fear and post-traumatic stress disorder. *Biological Psychiatry, 83*(10), 876–885. https://doi.org/10.1016/j.biopsych.2017.11.016.
Rauch, S. A., Eftekhari, A., & Ruzek, J. I. (2012). Review of exposure therapy: A gold standard for PTSD treatment. *Journal of Rehabilitation Research and Development, 49*(5), 679–687. https://doi.org/10.1682/jrrd.2011.08.0152.
Rauch, S. L., Milad, M. R., Orr, S. P., Quinn, B. T., Fischl, B., & Pitman, R. K. (2005). Orbitofrontal thickness, retention of fear extinction, and extraversion. *NeuroReport, 16*(17), 1909–1912. https://doi.org/10.1097/01.wnr.0000186599.66243.50.
Reynolds, R. M., Hii, H. L., Pennell, C. E., McKeague, I. W., de Kloet, E. R., Lye, S., ... Foster, J. K. (2013). Analysis of baseline hypothalamic-pituitary-adrenal activity in late adolescence reveals gender specific sensitivity of the stress axis. *Psychoneuroendocrinology, 38*(8), 1271–1280. https://doi.org/10.1016/j.psyneuen.2012.11.010.
Reznikoff, G. A., Manaker, S., Rhodes, C. H., Winokur, A., & Rainbow, T. C. (1986). Localization and quantification of beta-adrenergic receptors in human brain. *Neurology, 36*(8), 1067. https://doi.org/10.1212/WNL.36.8.1067.
Riggenbach, M. R., Weiser, J. N., Mosley, B. E., Hipskind, J. J., Wireman, L. E., Hess, K. L., ... Zoladz, P. R. (2019). Immediate pre-learning stress enhances baseline startle response and fear acquisition in a fear-potentiated startle paradigm. *Behavioural Brain Research, 371*, 111980. https://doi.org/10.1016/j.bbr.2019.111980.
Roozendaal, B. (2000). 1999 Curt P. Richter award. Glucocorticoids and the regulation of memory consolidation. *Psychoneuroendocrinology, 25*(3), 213–238. https://doi.org/10.1016/s0306-4530(99)00058-x.
Roozendaal, B. (2003). Systems mediating acute glucocorticoid effects on memory consolidation and retrieval. *Progress In Neuro-Psychopharmacology & Biological Psychiatry, 27*(8), 1213–1223. https://doi.org/10.1016/j.pnpbp.2003.09.015.
Roozendaal, B., & McGaugh, J. L. (2011). Memory modulation. *Behavioral Neuroscience, 125*(6), 797–824. https://doi.org/10.1037/a0026187.
Rosenbaum, B. L., Bui, E., Marin, M. F., Holt, D. J., Lasko, N. B., Pitman, R. K., ... Milad, M. R. (2015). Demographic factors predict magnitude of conditioned fear. *International Journal of Psychophysiology, 98*(1), 59–64. https://doi.org/10.1016/j.ijpsycho.2015.06.010.
Rothbaum, B. O., & Davis, M. (2003). Applying learning principles to the treatment of post-trauma reactions. *Annals of the New York Academy of Sciences, 1008*, 112–121. https://doi.org/10.1196/annals.1301.012.
Sangha, S., Diehl, M. M., Bergstrom, H. C., & Drew, M. R. (2019). Know safety, no fear. *Neuroscience & Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2019.11.006.
Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews, 21*(1), 55–89. https://doi.org/10.1210/edrv.21.1.0389.
Scheveneels, S., Boddez, Y., Vervliet, B., & Hermans, D. (2016). The validity of laboratory-based treatment research: Bridging the gap between fear extinction and exposure treatment. *Behaviour Research and Therapy, 86*, 87–94. https://doi.org/10.1016/j.brat.2016.08.015.
Schwabe, L., Haddad, L., & Schachinger, H. (2008). HPA axis activation by a socially evaluated cold-pressor test. *Psychoneuroendocrinology, 33*(6), 890–895. https://doi.org/10.1016/j.psyneuen.2008.03.001.
Schwabe, L., Joels, M., Roozendaal, B., Wolf, O. T., & Oitzl, M. S. (2012). Stress effects on memory: An update and integration. *Neuroscience & Biobehavioral Reviews, 36*(7), 1740–1749. https://doi.org/10.1016/j.neubiorev.2011.07.002.
Selye, H. (1950). Stress and the general adaptation syndrome. *British Medical Journal, 1*(4667), 1383–1392. https://doi.org/10.1136/bmj.1.4667.1383.
Shalev, A. Y., Peri, T., Brandes, D., Freedman, S., Orr, S. P., & Pitman, R. K. (2000). Auditory startle response in trauma survivors with posttraumatic stress disorder: A prospective study. *American Journal of Psychiatry, 157*(2), 255–261. https://doi.org/10.1176/appi.ajp.157.2.255.
Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology, 35*(1), 169–191. https://doi.org/10.1038/npp.2009.83.
Simon-Kutscher, K., Wanke, N., Hiller, C., & Schwabe, L. (2019). Fear without context: Acute stress modulates the balance of cue-dependent and contextual fear learning. *Psychological Science, 30*(8), 1123–1135. https://doi.org/10.1177/0956797619852027.
Sinclair, D., Purves-Tyson, T. D., Allen, K. M., & Weickert, C. S. (2014). Impacts of stress and sex hormones on dopamine neurotransmission in the adolescent brain. *Psychopharmacology (Berl), 231*(8), 1581–1599. https://doi.org/10.1007/s00213-013-3415-z.
Southwick, S. M., Bremner, J. D., Rasmusson, A., Morgan, C. A., 3rd, Arnsten, A., & Charney, D. S. (1999). Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biological Psychiatry, 46*(9), 1192–1204. https://doi.org/10.1016/s0006-3223(99)00219-x.
Stark, R., Wolf, O. T., Tabbert, K., Kagerer, S., Zimmermann, M., Kirsch, P., ... Vaitl, D. (2006). Influence of the stress hormone cortisol on fear conditioning in humans: Evidence for sex differences in the response of the prefrontal cortex. *NeuroImage, 32*(3), 1290–1298. https://doi.org/10.1016/j.neuroimage.2006.05.046.
Staufenbiel, S. M., Penninx, B. W., Spijker, A. T., Elzinga, B. M., & van Rossum, E. F. (2013). Hair cortisol, stress exposure, and mental health in humans: A systematic review. *Psychoneuroendocrinology, 38*(8), 1220–1235. https://doi.org/10.1016/j.psyneuen.2012.11.015.
Steenkamp, M. M., Litz, B. T., Hoge, C. W., & Marmar, C. R. (2015). Psychotherapy for military-related PTSD: A review of randomized clinical trials. *Jama, 314*(5), 489–500. https://doi.org/10.1001/jama.2015.8370.
Stetler, C., & Miller, G. E. (2011). Depression and hypothalamic-pituitary-adrenal activation: A quantitative summary of four decades of research. *Psychosomatic Medicine, 73*(2), 114–126. https://doi.org/10.1097/PSY.0b013e31820ad12b.
Steudte-Schmiedgen, S., Kirschbaum, C., Alexander, N., & Stalder, T. (2016). An integrative model linking traumatization, cortisol dysregulation and posttraumatic stress disorder: Insight from recent hair cortisol findings. *Neuroscience & Biobehavioral Reviews, 69*, 124–135. https://doi.org/10.1016/j.neubiorev.2016.07.015.
Strahler, J., Skoluda, N., Kappert, M. B., & Nater, U. M. (2017). Simultaneous

measurement of salivary cortisol and alpha-amylase: Application and recommendations. *Neuroscience & Biobehavioral Reviews, 83*, 657–677. https://doi.org/10.1016/j.neubiorev.2017.08.015.

Stroud, L. R., Salovey, P., & Epel, E. S. (2002). Sex differences in stress responses: Social rejection versus achievement stress. *Biological Psychiatry, 52*(4), 318–327. https://doi.org/10.1016/s0006-3223(02)01333-1.

Sze, Y., & Brunton, P. J. (2019). Sex, stress and steroids. *European Journal of Neuroscience*. https://doi.org/10.1111/ejn.14615.

Tabbert, K., Merz, C. J., Klucken, T., Schweckendiek, J., Vaitl, D., Wolf, O. T., et al. (2010). Cortisol enhances neural differentiation during fear acquisition and extinction in contingency aware young women. *Neurobiology of Learning and Memory, 94*(3), 392–401. https://doi.org/10.1016/j.nlm.2010.08.006.

Tabbert, K., Merz, C. J., Klucken, T., Schweckendiek, J., Vaitl, D., Wolf, O. T., et al. (2011). Influence of contingency awareness on neural, electrodermal and evaluative responses during fear conditioning. *Social Cognitive and Affective Neuroscience, 6*(4), 495–506. https://doi.org/10.1093/scan/nsq070.

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

Tovote, P., Fadok, J. P., & Luthi, A. (2015). Neuronal circuits for fear and anxiety. *Nature Reviews Neuroscience, 16*(6), 317–331. https://doi.org/10.1038/nrn3945.

Watson, J. B., & Rayner, R. (2000). Conditioned emotional reactions. 1920. *American Psychologist, 55*(3), 313–317. https://doi.org/10.1037/0003-066X.55.3.313.

Wharton, W., Hirshman, E., Merritt, P., Doyle, L., Paris, S., & Gleason, C. (2008). Oral contraceptives and androgenicity: Influences on visuospatial task performance in younger individuals. *Experimental and Clinical Psychopharmacology, 16*(2), 156–164. https://doi.org/10.1037/1064-1297.16.2.156.

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

Zorawski, M., Cook, C. A., Kuhn, C. M., & LaBar, K. S. (2005). Sex, stress, and fear: Individual differences in conditioned learning. *Cognitive, Affective, & Behavioral Neuroscience, 5*(2), 191–201. https://doi.org/10.3758/cabn.5.2.191.