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Let's talk about sex . . . differences in human fear conditioning

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Fear conditioning represents an experimental paradigm ideally suited to investigate aversive learning and memory mechanisms that are fundamental to the development, maintenance and treatment of mental disorders. Men and women seem to differ in their capability to learn and retrieve fear and extinction memories. This review outlines how sex may influence human fear conditioning, with an emphasis on the sex hormones and oral contraceptives. Available evidence suggests women with high estrogen levels to acquire fear more readily, but also to extinguish fear more easily, leading to an enhanced extinction memory trace. By contrast, women with low estrogens (e.g. due to oral contraceptives) seem to show deficits in extinction recall. These findings are highly relevant for future basic and applied studies alike.

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Introduction

Anxiety and stress-related disorders occur twice as likely and with a higher severity in women compared to men [1•,2,3]. Fear conditioning represents an important model for the development, maintenance and treatment of these disorders [4–6]. However, surprisingly few fear conditioning studies have been conducted in females questioning the generalizability of the obtained results [1•,7]. Proper research in females faces some methodological challenges such as the fluctuation of sex hormones over the menstrual cycle or the intake of hormonal contraceptives [cf. 8], which requires multiplying the sample sizes per experiment when compared to a study conducted in men only. For this reason, such a strategy has not been pursued systematically as evident by a substantially reduced number of fear conditioning studies investigating female compared to male brains [9].

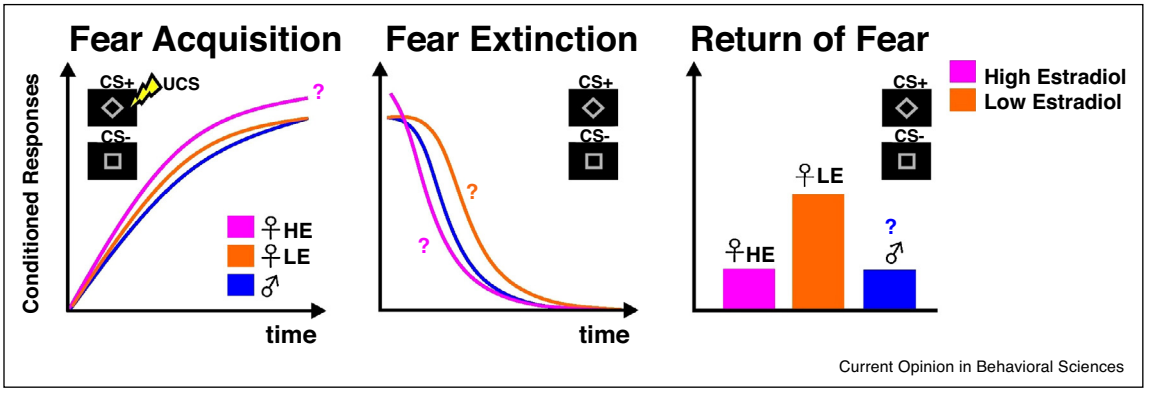
In this review, we will selectively focus on the available literature reporting sex differences in human fear conditioning. We present evidence for sex and sex hormone effects on the different phases of fear conditioning, separated into fear acquisition, extinction and the return of fear. After that, current trends will be highlighted and an outlook will be given before coming to concluding remarks.

Sex differences in fear acquisition

During fear acquisition training, the paired presentation of a stimulus (conditioned stimulus, CS+) with an innately aversive event (unconditioned stimulus, UCS, e.g. an electrical stimulation) leads to fear learning as indexed by conditioned fear responses to the CS+ on different outcome measures [for methodological details, see 10]. Most human studies employ differential fear conditioning designs, in which a second CS (CS−) is added without coupling with the UCS, usually acting as a safety signal (cf. Figure 1). Fear learning is proposed to be associated with the development of anxiety and stress-related disorders, such as posttraumatic stress disorder (PTSD; 5,6).

One study observed women to exhibit deficits in CS+/CS− discrimination relative to men as evident in skin conductance responses (SCRs) or subjective reports of fear [11]. By contrast, on the neural level, another study reported higher CS+/CS− differentiation in women in structures of the fear network (amygdala and anterior cingulate cortex [12]). Women also reported more fear and displayed more insula activation to the cue predicting pain in comparison to men [13,14]. These organizational effects of sex hormones seem to result from long-term consequences of differential sex hormone availability on physiology and morphology during the development of the male and female brain [15]. Complementing activational effects of sex hormones reflect physiological and morphological changes over the entire life due to variations of circulating sex hormones [15]. Indeed, a closer look at the influence of the menstrual cycle and the intake of oral contraceptives (OCs; cf. Box 1 for details on the menstrual cycle and OCs) revealed evidence for activational effects: a higher differential activation of the amygdala, cingulate cortex, hippocampus, hypothalamus and insula was found in women with high levels of the female sex hormone estradiol in comparison to men, or women

Figure 1

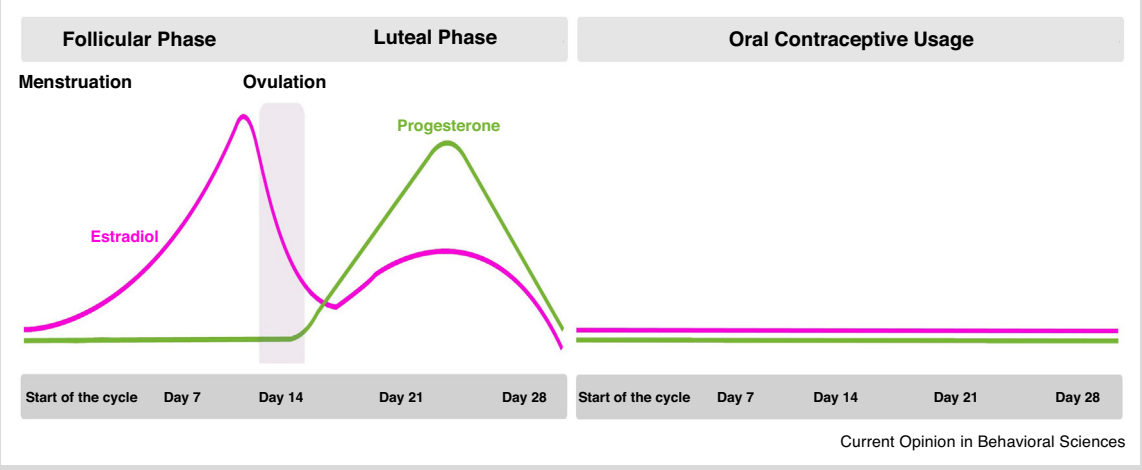


Schema on the influence of sex hormones on different fear conditioning processes. During fear *acquisition*, women (♀) with high estradiol (HE) concentrations seem to show higher conditioned responses (difference between CS+ and CS−) compared to women with low estradiol (LE) concentrations and men (♂). During fear *extinction*, high estradiol seems to be related to better extinction learning, whereas low estradiol seems to be associated with worse extinction learning and worse extinction consolidation. As a result women with low estradiol display a stronger *return of fear*. ? indicates that the available data do not lead to conclusive results.

Box 1 Schema on sex hormone availability over the course of the menstrual cycle and during intake of oral contraceptives (OCs).

The release of the female sex hormones estradiol and progesterone varies over the course of the menstrual cycle (mean cycle length: 28 days). During the early follicular phase, low levels of both hormones can be observed. During ovulation, estradiol concentrations peak and also reach high levels during the luteal phase together with a rise in progesterone. The release of both hormones declines before onset of the menstruation.

OCs typically contain synthetic forms of the female sex hormones estradiol and progesterone in differing concentrations. The exogenous intake of these synthetic sex hormones suppresses the endogenous production of sex hormones via a negative feedback mechanism, reducing the activation of the hypothalamus–pituitary–gonadal (HPG) axis, which releases female sex hormones from the gonads and the adrenal cortex under normal conditions [55•]. Variations in the capacity of OCs to inhibit the HPG axis can be observed when OC type and brand are taken into account [56–58]. In general, OC intake leads to constantly elevated levels of synthetic sex hormones, but low levels of endogenous sex hormones as well as absent fluctuations over the course of the menstrual cycle.



taking OCs or women with low estradiol levels [16,17]. Thus, periods of high estradiol levels, as observed during ovulation or during the luteal phase, seem to be related to enhanced learning processes, potentially representing a vulnerability factor for the development of anxiety disorders.

Without considering the influence of circulating sex hormone levels, female patients with a diagnosis of PTSD showed a higher CS+/CS− differentiation in SCRs during fear learning compared to male PTSD patients [18]. However in children with PTSD, pre-pubertal and pubertal, 8–13 years old girls displayed less CS-discrimination

in SCRs and fear-potentiated startle (FPS) compared to boys [19], calling for more developmental studies in this area.

Notably, in samples including men and women with differing sex hormone status [e.g. 20,21], no differences in SCRs have been reported for fear acquisition or even men showed a higher CS+/CS− differentiation in comparison to free-cycling women [22]. Thus, it remains to be shown if women with high estrogens consistently show increased fear acquisition in studies properly designed to compare them with men and women with low estrogen availability. Moreover, if the used CS depicted male and female faces, stronger differential SCRs occurred for same sex stimulus in a sample of 10–17 years old children [23]. This approach should be pursued to disentangle interactions between participants' sex and sex-associated CS (and UCS).

Sex differences in extinction and the return of fear

During extinction training, repeated presentations of the CS without further pairings with the UCS lead to decreasing conditioned fear responses (cf. Figure 1). Extinction learning is considered to mediate exposure-based treatments in cognitive-behavioral therapy [24; but see 25].

However, even after successful extinction, conditioned responding may reoccur (cf. Figure 1) as a function of time (spontaneous recovery), after a contextual change (renewal) or unsignalled presentations of the UCS or other aversive events (reinstatement; [26,27]). Current models emphasize that a new memory trace is generated during extinction learning, which competes with the fear memory trace for retrieval [26,28,29]. Successive responding is therefore guided by the winning memory trace: low conditioned fear responses during a return of fear test and relative to the end of extinction training indicates a dominance of the extinction over the fear memory trace. This is, interpreted as good extinction recall (or poor fear recall).

By contrast to the rather mixed literature on sex differences in fear acquisition, there is accumulating evidence from healthy humans that sex and sex hormones potently modulate fear extinction processes [8,9,30]. Organizational effects of sex hormones point to a larger differential activation of the insular cortex in women during extinction recall, whereas men showed greater activation in the rostral anterior cingulate cortex [12]. Activational effects localize especially estrogens to play a key role, with high levels of estradiol typically enhancing extinction and extinction recall. Free-cycling women displaying high estradiol levels showed increased activation of the inhibition-related ventromedial prefrontal cortex (vmPFC) during extinction learning relative to women with low estradiol levels [31••]. Correspondingly, elevated estradiol levels during extinction facilitated subsequent extinction recall, as evident by reduced differential SCRs and enhanced activations of the vmPFC and amygdala. Importantly, a positive correlation between estradiol and vmPFC activation was observed, pointing to a direct link between estrogens and extinction processes [31••]. Congruently, Graham and Milad [20••] found free-cycling women with high estradiol levels to exhibit enhanced extinction recall compared to both, women with naturally low circulating estradiol levels or women taking OCs. Furthermore, pre-extinction estradiol administration prevented extinction impairments in women in the early follicular phase (normally characterized by low sex hormone levels, cf. Box 1), resulting in a reduced return of fear when compared to placebo-treated women [20••]. By contrast, one study found a higher insula activation during late extinction and extinction recall in women with high estradiol levels when compared to men and OC women, which was interpreted as enhanced extinction memory consolidation [16].

By contrast, low levels of circulating female sex hormones (either resulting from natural fluctuations across the menstrual cycle or due to OC intake, cf. Box 1) seem to impair extinction processes and promote fear recovery during subsequent recall [32]. For instance, deficient extinction learning was found in OC women, but not in men or free-cycling women in the luteal phase, as indicated by higher differential fear responses in the amygdala, vmPFC, thalamus, and anterior cingulate cortex [33]. OC women furthermore showed an attenuated activation of the posterior cingulate cortex during extinction learning, but higher differential responses in the hippocampus, thalamus, and cerebellum after reinstatement when compared to men [13]. Additionally, low estradiol was also associated with greater fear recovery in SCRs during extinction recall. For OC women however, a stronger return of fear was observed in SCRs compared to women with high estradiol levels [34].

Importantly, similar results have been recently obtained in clinically anxious women suggesting that healthy as well as phobic women with low estradiol display deficient extinction recall, that is, exhibiting a stronger recovery of differential SCRs when compared to women with high estradiol concentrations [21•]. Interestingly, low estradiol women exhibited increased threat expectancy ratings and SCRs also during the presentation of safety cues, pointing to a generally impaired fear inhibition. It has thus been proposed that low estradiol concentrations may represent a vulnerability factor for the development of PTSD and anxiety disorders [32].

However, contrary to that notion, it has been recently reported that women with PTSD, compared to those without PTSD, displayed impaired extinction retention in the midluteal phase (when estradiol and progesterone levels peak) relative to the early follicular phase of the

menstrual cycle [35]. In addition to this cycle-phase specific analysis, regression analyses including plasma estradiol and progesterone levels rather indicated reduced extinction retention in women with PTSD to be associated with high progesterone and low estradiol. Another study suggests a deficient extinction recall among male but not female patients with PTSD, resulting in enhanced differential SCRs and increased neural activity in the rostral anterior cingulate cortex during recall, whereas no such sex difference occurred in healthy controls [36]. Speculatively, PTSD symptomatology might vary as a function of different variables, for example cause, onset and severity of the trauma, for which estrogens do not seem to be as central as for extinction processes in healthy humans (and recently translated to phobic women; [21•]). Moreover, specific analysis strategies (comparison between different menstrual cycle stages vs. direct associations tested by sex hormone levels) might also account for the different results.

In sum, the existing literature in healthy humans provide growing evidence for a facilitating effect of female sex hormones, especially of estrogens, on extinction processes, raising considerations regarding the coordination of exposure-based treatments within specific phases of the menstrual cycle. Certainly, more studies with clinical samples are warranted to disentangle potential differences between patients and healthy controls that ultimately will aid translating experimental findings into clinical practice.

Methodological considerations

Important methodological considerations need to be taken into account when trying to draw a conclusive picture of the presented results. First, we provided a selective overview of recent fear conditioning studies reporting sex differences. However, while available data are still limited due to the overrepresentation of results derived from research including males only [1•], the existing literature including both sexes with null or not reported results concerning sex differences is hard to identify. Second, findings in women without consideration of the influence of circulating sex hormones can lead to wrong conclusions, given that opposing result patterns might exist in different subgroups, which may cancel each other out. Thus, sex differences might be especially apparent when differing sex hormones are considered. Third, sex differences in extinction learning and the return of fear need to be interpreted in light of the sex differences being already present during fear acquisition in order to understand the selective impact of sex hormones on the subsequent processes. Fourth, rather small methodological differences between studies (e.g. CS or UCS modality, timing between experimental phases) might nevertheless result in non-comparable findings [10,37•]. These considerations call for a meta-analysis of the existing data including methodological details as potential moderators (in addition to menstrual cycle phase and intake of hormonal contraceptives).

Sex differences in fear conditioning: current trends and outlook

Stress is another important risk factor for the development, maintenance and relapse of anxiety disorders [38,39]. In response to stress, the adrenal cortex releases glucocorticoids (GCs), which typically enhance memory consolidation but impair memory retrieval [40,41]. These effects might explain why stress is often associated with symptom relapse [38]. At the same time, GCs appear to be able to boost the success of exposure based therapy presumably by impairing the retrieval of previously established fear memories and by enhancing extinction consolidation [42,43]. Important for the current review is the increasing evidence from laboratory studies investigating the impact of sex and stress hormones on fear conditioning. For example, work from our group has repeatedly demonstrated that stress or GC treatment impairs the neural correlates of CS+/CS− differentiation during fear acquisition in men but enhances it in women [8,44–46]. The latter effect appears to be restricted to women using OCs [47•,48]. Stress induction before fear acquisition and immediate extinction has also been shown to reduce extinction recall 24 hour later in women tested in the early follicular phase compared to men [49]. More recently, we observed impairing effects of GCs on extinction recall, which again occurred in men but not in women using OCs [50]. Thus, sex differences observed in the laboratory during relatively stress-free fear learning conditions might disappear or even reverse in stressful situations (for comprehensive reviews, please see [8,51]).

Periods with varying sex hormone concentrations such as puberty, pregnancy, delivery or menopause are associated with greater changes in sex hormone levels compared to rather small changes over the menstrual cycle or due to OC intake. Indeed, recent data suggests that the positive association between estradiol levels and extinction recall is mitigated after delivery in female rats and free-cycling women [52]. Aside from these findings, almost nothing is known about possible modulations of fear conditioning processes during these sensitive periods. Thus, future research should fill these gaps, optimally using longitudinal designs. Besides, the underlying mechanisms should be investigated by systematically manipulating endogenous sex hormones with specific agonists and antagonists in order to pave the way for more personalized treatment approaches.

Despite relatively good evidence of estrogens to play a major role in fear conditioning processes [51], gestagens such as progesterone and its derivatives should not be neglected, since prior research in rodents [53,54] and humans [35; but see 22], already found some evidence for their involvement.

Additionally, more studies are needed translating basic findings to clinical populations, for example comparing success of exposure therapy across the menstrual cycle and during OC intake. The idea would be to perform exposure therapy at a time with high estrogen availability (e.g. during the luteal phase, cf. Box 1) in order to enhance exposure therapy and facilitate consolidation of the acquired extinction memory. With this approach, relapses might be reduced in the long run.

Conclusion

The present review highlights sex hormones as an important modulator of different fear conditioning processes. Whereas high estrogen levels are associated with enhanced extinction and extinction memory recall, they also seem to facilitate initial fear acquisition. Thus, it might be assumed that high estrogens play an essential role in emotional learning processes in general, ultimately leading to unfavorable effects during fear acquisition, whereas being beneficial during extinction processes. Based on this line of evidence, it might be assumed that activational effects of sex hormones also play a critical role in other basic emotional and cognitive processes — an area which clearly calls for paying close attention in future research.

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Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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