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# Hormonal contraceptive usage influences stress hormone effects on cognition and emotion

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ABSTRACT

Men and women partially differ in how they respond to stress and how stress in return affects their cognition and emotion. The influence of hormonal contraceptives (HCs) on this interaction has received little attention, which is surprising given the prevalence of HC usage. This selective review illustrates how HC usage modulates the effects of stress hormones on cognition and emotion. As three examples, we discuss stress hormone effects on episodic memory, fear conditioning and cognitive emotion regulation. The identified studies revealed that stress effects on cognitive-emotional processes in women using HCs were at times reduced or even absent when compared to men or naturally cycling women. Especially striking were the few examples of reversed effects in HC women. As underlying neuroendocrine mechanisms, we discuss influences of HCs on the neuroendocrine stress response and effects of HCs on central glucocorticoid sensitivity. The summarized findings emphasize the need for additional translational research.

## 1. Introduction

Hormonal contraceptives (HCs) are used for birth control by millions of women worldwide. A recent survey from the United Nations revealed that more than 18% of women between the ages of 15 and 49 in North America and Europe (approximately 44 million) and more than 8% worldwide (approximately 151 million) are current HC users (United Nations, 2019). These compounds contain synthetically derived estrogens and/or progestins suppressing the natural fluctuation of sex hormones orchestrated by the hypothalamus-pituitary gonadal (HPG) axis (e.g., estradiol and progesterone; Montoya and Bos, 2017). Given the prevalence and length of HC usage it is surprising how little information is available regarding its impact on how women respond to stress and how HCs interact with stress to influence cognitive and emotional processes in turn. This is particularly remarkable since many stress-related mental disorders are more prevalent in women. For instance, women compared to men have a higher lifetime prevalence of posttraumatic stress disorder, major depression and several anxiety disorders, whereas men have a higher prevalence for alcoholism and autism (Cover et al., 2014; Kessler et al., 2005). Accumulating evidence further indicates that sex hormones and HCs critically alter behavior and brain function underlying proper cognitive and emotional processing (Brønnick et al., 2020; Lewis et al., 2019; Montoya and Bos, 2017; Rehbein et al., 2021). Yet, despite its broad relevance for women's mental health very little is known about the association between HC usage and the vulnerability for mental disorders (Lewis et al., 2019; Raeder et al., 2019; Sundström Poromaa et al., 2020) as well as the underlying cognitive-emotional mechanisms that may pave the way to aberrant behaviors in the first place.

Our selective review will illustrate how HC usage influences the effects of stress hormones on cognition and emotion. As examples stimulated by our own work and others, we will focus on stress hormone effects on emotional learning and memory processes exemplified with episodic memory and fear conditioning as well as cognitive emotion regulation. Finally, we will outline important open questions and possible next steps for basic, translational and clinical research.

### 1.1. The stress response and stress paradigms in humans

Stress hormone release in response to (potential) threats is essential for the adaptation to critical life events and ongoing, every-day challenging situations (McEwen, 2004). While the acute stress response is

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mostly adaptive, repeated or chronic stress constitutes a major risk factor for the development and maintenance of a whole range of mental and physical disorders (Cohen et al., 2016; McEwen, 2004; McEwen and Akil, 2020; Sanacora et al., 2022). In humans, uncontrollable situations containing a threat to the social self, represent potent stressors (Dickerson and Kemeny, 2004). This can be realized in the laboratory in order to test the impact of stress on subsequent cognitive and emotional processes (see Box 1 for an overview of some of the human stress induction paradigms relevant for the current review). A broader and in-depth review of different laboratory and online stressors is given by Pfeifer et al. (2021).

The endocrine system responds to a stressor by activating two major stress systems: the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. The SNS initiates a rapid response mediated by (nor)adrenaline released by the adrenal medulla, resulting in rapid increases in blood pressure and heart rate. This first stress response has been conceptualized as the fight-or-flight response (Cannon, 1932). The second and somewhat slower response comprises the release of glucocorticoids (mainly cortisol in humans). Glucocorticoid secretion is orchestrated by the HPA axis releasing corticotropin-releasing hormone from the hypothalamus to initiate the secretion of adrenocorticotropic hormone from the anterior pituitary into the bloodstream. Adrenocorticotropic hormone in turn stimulates glucocorticoid release from the adrenal cortex. Glucocorticoids can easily cross the blood-brain-barrier and target many brain structures expressing mineralocorticoid and glucocorticoid receptors. In particular, glucocorticoids influence regions critically involved in emotional learning and memory as well as emotion regulation processes such as the medial temporal lobe (hippocampus and amygdala) and prefrontal areas (Arnsten, 2009; Joëls and Baram, 2009; Rodrigues et al., 2009; Roozendaal et al., 2009).

### 1.2. Interactions between the HPA and HPG axes and the role of HCs

In general, men and women differ in endocrine and behavioral stress responses (Kudielka and Kirschbaum, 2005; Taylor et al., 2000). The close and bidirectional interaction between one of the major stress systems (the HPA axis) and the sex hormone system (the HPG axis) is, at least in part, responsible for these sex differences. To create an even greater challenge, there is ample evidence that stress responsiveness of the HPA axis changes over the course of the menstrual cycle. A more pronounced glucocorticoid release can be observed during the luteal phase (compared to the follicular phase; Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005) characterized by elevated estradiol and progesterone concentrations. Of special importance for the current review is the observation that HCs substantially influence the response of the HPA axis to stress (see Gervasio et al., 2022 for a recent meta-analysis; Kirschbaum et al., 1999). Typically, HCs dampen the free (unbound, biologically active) cortisol stress response by increasing cortisol-binding globulin levels and changing the proportion of total to free cortisol (Hellhammer et al., 2009; Kirschbaum et al., 1999; van der Vange et al., 1990). Thus, while total cortisol concentrations are increased in HC women which might have effects on HPA targeted systems throughout the body (see Hertel et al., 2017) their free cortisol

**Box 1**
Stress induction methods and pharmacological challenges in humans.

The elements of social evaluative threat and uncontrollability lead (on average) to a robust HPA response (Dickerson and Kemeny, 2004). In the laboratory, stress can be experimentally induced with public speaking tasks such as the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). The paradigm combines a public speech in front of a cold and non-responsive committee with a mental arithmetic task (Labuschagne et al., 2019).

In recent years, virtual reality versions (Zimmer et al., 2019) as well as online versions of the paradigm (Gunnar et al., 2021) have been developed (for a review, see Pfeifer et al., 2021). Moreover, some elements of the TSST have been used during the creation of fMRI compatible stressors such as the ScanSTRESS paradigm (Lederbogen et al., 2011).

Alternatively, physiological stressors can be used, such as an immersion of the hand into ice-cold water as realized in the cold pressor test (CPT; Hines and Brown, 1932).

The CPT has been further developed into the socially evaluated cold pressor test (SECPT; Schwabe et al., 2008b) by adding a standardized social evaluative component to it (monitoring by a neutral experimenter and video recording). The SECPT is more powerful than the CPT in stimulating the HPA axis, even though the responses are typically lower than those observed in studies using the TSST (Giles et al., 2014).

The specific effects of cortisol can also be tested in pharmacological studies by administering the hormone in a double-blind design. Importantly in these studies, participants experience neither subjective stress nor an activation of the SNS. Furthermore, participants cannot reliably identify if they received cortisol or a placebo. The oral cortisol dosages administered range between 5 and 100 mg (Het et al., 2005), with a dosage of 10 to 30 mg being usually given. This exogenous administration leads to cortisol concentrations in the upper physiological to supraphysiological range which are substantially higher than those induced by the laboratory stressors mentioned above (Abercrombie et al., 2012; Jentsch et al., 2019; Kinner et al., 2018; Langer et al., 2021).

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concentrations are typically not elevated and their free cortisol response to a stressor is, in fact, blunted (Gervasio et al., 2022; Hellhammer et al., 2009). In contrast, other stress systems (e.g., the SNS) appear to be less influenced by HC usage (Kirschbaum et al., 1999).

Importantly, the bidirectional interaction between the HPA and HPG axes might underlie the different vulnerabilities for distinct stress-associated mental disorders as outlined before.

The influence of HCs on stress effects on cognitive and emotional processes might be caused by at least two possible mechanisms: First, the impact of HCs might occur due to differences in the endocrine response to a stressor. As mentioned above, HC usage causes a blunted free cortisol response to acute stress (Gervasio et al., 2022; Kirschbaum et al., 1999), which in turn might reduce or even reverse the cognitive and emotional stress effects in these women. Second, and not mutually exclusive to the first explanation, HC effects might occur due to a different responsiveness of the female brain under HC usage to the same neuroendocrine stress signals. In support of this hypothesis we observed that the same pharmacological administration of the stress hormone cortisol caused different and in part opposing effects on neural networks involved in fear learning (Merz et al., 2012; cf. 3.1) and emotion regulation (Jentsch et al., 2019; cf. 4).

The goal of this manuscript is to review experimental studies in humans, which have investigated the potential influence of HC usage on stress effects on episodic memory, fear conditioning and cognitive emotion regulation. We therefore focused on experiments that specifically tested HC women and compared the stress effects with men and/or naturally cycling (NC) women. Combined oral contraceptives containing an ethinylestradiol and a gestagenic component are the most frequently prescribed type of HCs (Burkman et al., 2011; Christin-Maitre, 2013) and therefore predominantly represented in the studies discussed here.

After a general introduction to episodic memory and the typical paradigms used to probe memory, we briefly outline potential factors mediating or influencing stress and HC effects on episodic memory. Thereafter, we selectively review experimental studies illustrating the impact of HCs on stress effects on episodic memory with a particular focus on memory encoding, memory consolidation, and memory retrieval.

## 2. Episodic memory

Episodic memory enables us to remember personally experienced events from the past and defines us as individual beings with individual experiences (Tulving, 1993). In the laboratory, a variety of paradigms have been established to investigate the underlying mechanisms and varying influencing factors. In a typical memory paradigm (as implemented in stress research; Shields, 2020), participants intentionally or incidentally (Preuss et al., 2009) encode a series of words (Espin et al., 2013; Merz, 2017; Schwabe and Wolf, 2014; Smeets et al., 2007), pictures (Abercrombie et al., 2012; Cornelisse et al., 2011; Hidalgo et al., 2015; Nielsen et al., 2013), objects (Wiemers et al., 2013) or videos (Echterhoff and Wolf, 2012; Smith et al., 2019). After a certain consolidation period (typically 24 h; Mordecai et al., 2017; Schwabe et al., 2008a; Smeets et al., 2007), retrieval is tested either using a recognition (Brown and Aggleton, 2001), a cued and/or a free recall task (Carpenter et al., 2006).

As already mentioned, stress and stress hormones exert a substantial impact on learning and memory processes. Unraveling the relevant mechanisms cannot only be helpful in educational contexts or at court, but also for a better understanding and treatment of mental disorders such as posttraumatic stress disorder (de Quervain et al., 2017; Merz et al., 2016). Critically, the timing between stress and the relevant memory phase (encoding, consolidation and retrieval) needs to be considered. Here, we only focus on studies that clearly differentiate between these phases.

In addition to the timing of the stressor or cortisol administration, there are several factors mediating the effects of stress on episodic memory, for example, valence (Shields et al., 2017; Wolf, 2009) or HC usage, which we will emphasize in the following sections. Indeed, initial evidence suggests that HC women might not exactly fit into the general picture sketched above, but most studies either study a rather heterogeneous group of participants or exclude HC women from their sample. Importantly, stress effects on episodic memory seem to be even more prominent when HC women are excluded (Shields et al., 2017).

### 2.1. Memory encoding

Stress in the context of encoding typically results in better memory performance (Shields et al., 2017) especially for objects central to the stressful episode (Bierbrauer et al., 2021; Wiemers et al., 2013) as well as stimulus material that is linked to the stressor (Trammell and Clore, 2014). If the stressor however is not part of the encoding context such that it is experienced a long time before the stressor or in another environment, it usually has an impairing effect on memory (Shields et al., 2017). In contrast, cortisol administration prior to encoding appears to be time-of-day dependent. While pre-encoding cortisol administration in the morning often leads to impaired memory performance, it seems to cause an improvement in the evening (Het et al., 2005). This picture might result from the circadian cortisol fluctuation in interaction with the distinct affinity and distribution of glucocorticoid and mineralocorticoid receptors (de Kloet et al., 1998; Het et al., 2005; for more information on the circadian rhythm in HC women see chapter 6).

When comparing stress hormone effects on memory encoding between men and HC women, no differences were observed in two studies using the CPT followed by a word recall task (Schwabe et al., 2008a) and a cortisol injection prior to a picture recall task (Abercrombie et al., 2012). In the former study, stress enhanced memory performance in both groups dependent on the valence of the stimulus (Schwabe et al., 2008a), whereas in the latter study, no stress hormone effects on memory were observed in general (Abercrombie et al., 2012). In addition, exposure to a modified TSST during encoding led to better memory of context-congruent personality words in men, HC and NC women (Smeets et al., 2007).

However, there is also some evidence for HC-specific stress effects on encoding processes. For instance, the encoding of pictures after undergoing the TSST improved memory performance for emotional pictures only in a group of men, while the group of women, of which more than two thirds were taking HCs, did not show these effects (Cornelisse et al., 2011). Moreover, exposure to the SECPT before encoding tended to facilitate cued recall of neutral words in HC women only, while NC women tested in the follicular or luteal phase were not affected and men showed an enhanced retrieval of negative words (Merz, 2017). In conclusion, the few available findings point to a dampening as well as potentially valence-specific HC influence on stress hormone effects on encoding processes.

### 2.2. Memory consolidation

In most prior studies post-encoding stress generally enhanced memory consolidation (Roozendaal et al., 2007). Only two studies examining the effects of stress on consolidation processes controlled for HC intake. Both of them investigated the influence of the CPT on the consolidation of gist and detail in NC versus HC women (Nielsen et al., 2014; Nielsen et al., 2013). In the first study, HC women showed a blunted cortisol response to the stressor, as well as an attenuated noradrenergic reaction to the images. Nevertheless, an increase in cortisol levels as a result of the stressor led to improved recognition of positive images solely in HC women and only when the noradrenergic response to the images was low (Nielsen et al., 2013). In the second study, stress enhanced the retrieval of gist and peripheral details of an emotional versus a neutral story in NC women in their luteal phase, while no effect was observed for HC women (Nielsen et al., 2014). Together, the two available studies also indicate a weakening and

valence-specific influence of HCs on stress hormone effects on consolidation processes.

### 2.3. Memory retrieval

Regardless of the participant's sex hormone status, pre-retrieval stress and cortisol administration typically impair memory performance, particularly in response to emotional material and during free recall tasks (Gagnon and Wagner, 2016; Het et al., 2005; Shields et al., 2017; Wolf, 2017).

When sex hormone differences were explicitly examined, pre-retrieval cortisol administration was shown to affect word retrieval in NC women tested in their luteal phase and during their menses, but not in HC women (see Fig. 1; Kuhlmann and Wolf, 2005). Furthermore, stress equally reduced retrieval of negative items in the active and inactive pill phase for HC women, despite a missing cortisol response to the stressor in HC women compared to NC women (Mordecai et al., 2017). Consequently, the already mentioned valence-specific and dampening stress effects of HCs can also be observed during retrieval.

Altogether, the state of facts concerning the influence of stress and HCs on episodic memory is still relatively sparse. Yet, it indicates that the effects on encoding, consolidation and retrieval are quite similar. On the one hand HCs appear to reduce stress (hormone) effects on episodic memory processes, on the other hand they seem to elicit valence-specific effects, which should yet be interpreted with caution due to the limited availability of data.

Besides episodic memory tasks, emotional memory can also be investigated by using fear conditioning paradigms. In the following section, we briefly illustrate the typical laboratory human fear conditioning procedure before presenting empirical findings regarding the impact of stress and HCs on its distinct phases fear acquisition, extinction, and retrieval, respectively.

## 3. Fear conditioning

Fear conditioning represents a valuable translational model for the development, maintenance, relapse and treatment of anxiety disorders and posttraumatic stress disorder (e.g., Milad and Quirk, 2012; Mineka and Oehlberg, 2008). Different learning and memory mechanisms occur during the phases of a typical fear conditioning paradigm, which are all

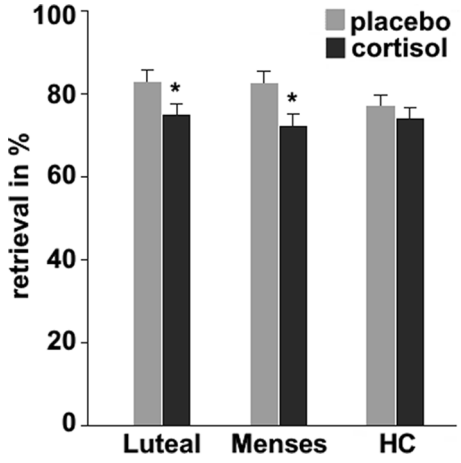


**Fig. 1.** Cortisol administration (30 mg) 1 h before retrieval testing resulted in impaired memory retrieval (defined as the percentage of words remembered from the encoding list) in women tested in the luteal phase and during menses, but not in women taking hormonal contraceptives (HC). *$p < 0.05$. Reprinted in a modified version from Kuhlmann, S., & Wolf, O. T. (2005). Cortisol and memory retrieval in women: Influence of menstrual cycle and oral contraceptives. *Psychopharmacology*, *183*(1), 65–71, with permission from Springer Nature.

prone to effects of stress in interaction with sex hormones and HCs (Merz and Wolf, 2017, 2015). In the following section, specific effects of stress and sex hormones on fear acquisition training, extinction training and exposure therapy as well as retrieval will be presented.

### 3.1. Fear acquisition

During fear acquisition training an unconditioned stimulus such as an electric stimulation is repeatedly coupled with a neutral stimulus such as a picture of a blue lamp, whereas another stimulus, for example a picture of a yellow lamp is not paired with the unconditioned stimulus. This differential procedure leads to the occurrence of higher conditioned responses towards the blue lamp (conditioned stimulus, CS+) compared to the yellow lamp (CS-). This CS+/CS- differentiation constitutes the relevant fear learning index and can be measured using methods such as skin conductance responses (SCRs), brain activation (in the fear network comprising the amygdala, insula and dorsal anterior cingulate cortex (dACC)) or ratings of expectancy of the unconditioned stimulus (Lonsdorf et al., 2017).

The sex hormone-dependent impact of stress or glucocorticoid administration on fear learning (also extending to subsequent phases) has been extensively and recently reviewed elsewhere (Peyrot et al., 2020), thus, just the key findings will be reported here. Cortisol administration and the TSST reduced CS+/CS- differentiation in the amygdala or hippocampus in men (Merz et al., 2013; Merz et al., 2010; Stark et al., 2006), NC women (Merz et al., 2012), but increased neural responding in HC women (Merz et al., 2013; Merz et al., 2012; Stark et al., 2006; Tabbert et al., 2010). This response pattern was partly confirmed in SCRs at least in men (Merz et al., 2013; Stark et al., 2006; van Ast et al., 2012), but not always (Jackson et al., 2006). In addition, no stress effect was found in men and NC women tested in the follicular and midcycle phase (Antov and Stockhorst, 2014). Importantly, a direct comparison of cortisol effects on fear learning in men, NC women tested in the follicular and luteal phase and HC women was realized in only one study so far (Merz et al., 2012). In this study, HC intake seems to specifically increase CS+/CS- differentiation in the anterior parahippocampal gyrus and hippocampus during fear learning after cortisol administration (see Fig. 2). In men and both NC women groups, cortisol reduced neural responding in the same contrast.

Thus, stress hormones appear to decrease fear learning in men and NC women but increase CS+/CS- differentiation in HC women in particular regarding the neural correlates.

### 3.2. Extinction training and exposure therapy

When the unconditioned stimulus is no longer presented while the CS are shown, conditioned responding declines, a process called extinction learning (Lonsdorf et al., 2017). During extinction training, a second memory trace is formed inhibiting the original fear memory trace (Bouton, 2004). Extinction learning constitutes the underlying mechanism of exposure therapy, in which patients with anxiety disorders are confronted with their fearful stimuli or situations (Graham and Milad, 2011). Thus, augmenting strategies to increase extinction and exposure therapy success seem highly warranted. One promising avenue revealed that stress hormones generally facilitate extinction learning and exposure therapy (de Quervain et al., 2019; de Quervain et al., 2017) as also summarized in the Stress Timing affects Relapse model (Meir Drexler et al., 2020, 2019). Mechanistically, stress hormones impair fear retrieval at the onset of extinction training (Merz et al., 2018) and facilitate the consolidation of the inhibitory extinction memory trace (Bentz et al., 2010).

A closer look at the extinction literature revealed only two studies explicitly including men and HC women undergoing a stress or a pharmacological manipulation before extinction training. First, pre-extinction cortisol administration reduced conditioned SCRs during extinction training in male and female patients with posttraumatic stress

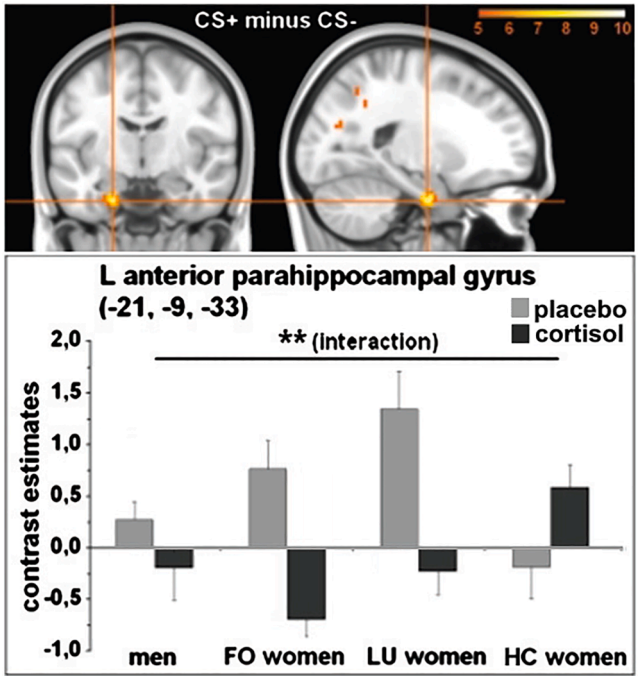


**Fig. 2.** Cortisol administration (30 mg) reduces CS+/CS- differentiation in the anterior parahippocampal gyrus in men, women tested in the follicular (FO) and luteal (LU) phase, but increases neural responding in women using hormonal contraceptives (HC). ** $p < 0.005$ for the treatment × sex hormone status interaction. Reprinted from Merz CJ, Tabbert K, Schweckendiek J, Klucken T, Vaitl D, Stark R, Wolf OT. 2012. Oral contraceptive usage alters the effects of cortisol on implicit fear learning. Horm Behav 62:531–538, with permission from Elsevier.

disorder (Inslicht et al., 2021). Even though female patients with post-traumatic stress disorder were either naturally cycling or using HCs, sex hormone related effects were not mentioned. Second and more importantly, exposure to the CPT before extinction training reduced expectancy of the unconditioned stimulus during extinction and retrieval in men, but rather increased expectancy of the unconditioned stimulus in HC women (Bentz et al., 2013).

Importantly, cortisol administration also enhances exposure therapy success in patients with spider phobia, social phobia and acrophobia (de Quervain et al., 2011; Soravia et al., 2014; Soravia et al., 2006). In all of these patient studies, no sex differences were reported and a further characterization of the women group in terms of sex hormones and HC intake was not reported. At least in one study in spider phobia, only HC women were included (Lass-Hennemann and Michael, 2014): Results revealed that exposure sessions conducted in the morning (high cortisol levels) enhanced exposure therapy success compared to sessions in the evening (low cortisol levels). Especially relevant for the current review are recent findings showing that the SECPT increased exposure therapy success in spider phobic NC women tested during the follicular phase, but this beneficial effect was highly reduced in HC women (Raeder et al., subm.).

In sum, stress hormones seem to facilitate extinction learning and exposure therapy, whereas HC intake mostly either reduces or even reverses this beneficial effect, as far as the current data suggest.

### 3.3. Retrieval

When CS are presented again after fear acquisition and extinction training during a retrieval test, conditioned responding typically reoccurs due to different phenomena, including renewal (context change between extinction training and retrieval) or reinstatement (unsignaled presentations of the unconditioned stimulus; Lonsdorf et al., 2017), proving the existence of a fear and an extinction memory trace competing with each other (Bouton, 2004). Stress hormone effects on fear and extinction memory retrieval have been rarely investigated in general (in men only: Merz et al., 2020; Merz et al., 2014) and even less regarding the interaction with sex hormones.

Only two relevant studies for possible HC effects were identified: Firstly, the CPT seems to inhibit the extinction memory trace resulting in a higher return of conditioned SCRs in both men and women (Raio et al., 2014). However, no data on women's hormonal status was reported in this study. Secondly, the most critical retrieval study compared men and HC women after cortisol administration (Kinner et al., 2018): cortisol increased conditioned SCRs and amygdala activation during extinction memory retrieval in men, but cortisol decreased amygdala activation in HC women.

All in all, a rather limited amount of data speaks for stress hormones to inhibit extinction memory retrieval (thus, leading to a return of conditioned responses) in general. HC intake might reduce or even reverse this stress hormone effect as also observed for fear acquisition and extinction training.

Another cognitive-emotional process, which is modulated by stress hormones and appears to differ between men and women, constitutes the ability to regulate one's emotions. In the next section, we will first outline the general concept of cognitive emotion regulation and its neural underpinnings. Then, we introduce a typical laboratory paradigm with which emotion regulation processes are tested, before we discuss the few available studies that explicitly investigated the effects of stress and HCs on cognitive emotion regulation.

## 4. Cognitive emotion regulation

Cognitive emotion regulation refers to all deliberate and implicit processes whereby one monitors, evaluates or modifies the occurrence, quality, magnitude, duration or expression of an emotion (Gross, 2015). It heavily relies on a cognitive system, involving dorsolateral and ventrolateral prefrontal brain regions that exert top-down control on limbic structures such as the amygdala (Etkin et al., 2015; Morawetz et al., 2017). Importantly, these regions are modulated by stress and sex hormones and are therefore also sensitive to the influences of HCs (Arnsten, 2009; Montoya and Bos, 2017; van Wingen et al., 2011). Cognitive reappraisal and distraction are two of the most frequently studied cognitive emotion regulation strategies and considered as being most effective for the downregulation of negative emotions (Webb et al., 2012). While distraction involves directing attention away from the emotional stimulus toward non-emotional aspects of the situation, cognitive reappraisal aims at reinterpreting the emotional situation in order to change its emotional impact (Gross, 2015).

Difficulties in emotion regulation have been implicated in the development, maintenance and treatment of various forms of psychopathology (Berking and Wupperman, 2012), including mood and anxiety disorders, which occur twice as likely in women than in men (Cover et al., 2014). Moreover, first experimental studies have shown that the influence of stress on cognitive emotion regulation may differ between men and women (Kinner et al., 2014; Ma et al., 2017). However, despite the above mentioned, well-known sex differences and impact of HC on stress reactivity (Gervasio et al., 2022; Kudielka and Kirschbaum, 2005) and accumulating evidence for sex differences in emotion regulation effectivity (McRae et al., 2008; Nolen-Hoeksema, 2012), there is only a limited number of studies investigating the modulatory role of stress hormones on cognitive emotion regulation, with even fewer studies exploring the interactive effects of stress and sex and only a handful considering the impact of HC usage.

In the laboratory, cognitive emotion regulation is typically tested with a picture-based paradigm, in which participants are confronted with negative and neutral scenes and instructed to either view and naturally respond to them or to regulate their emerging emotions using different predefined emotion regulation strategies. Employing such a

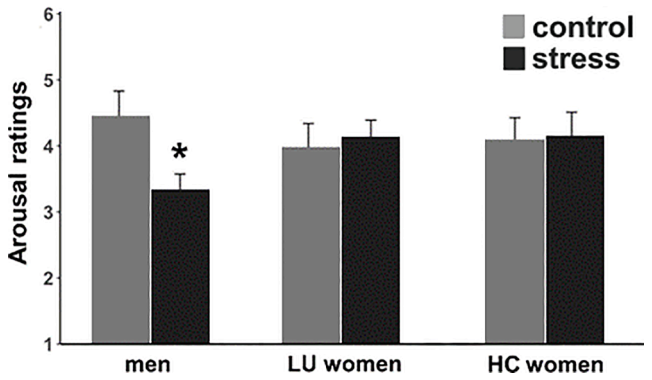


**Fig. 3.** Exposure to the TSST (stress) as compared to the Placebo-TSST (control) improves downregulation of negative emotions via cognitive reappraisal in men, but not in women tested in the luteal phase (LU) or women using hormonal contraceptives (HC), as indicated by significantly reduced arousal ratings. * $p < 0.05$ for Bonferroni-corrected post-hoc t-tests (data taken from Langer et al., 2020).

paradigm in an fMRI environment, Jentsch et al. (2019) investigated the effects of cortisol administration on the behavioral and neural correlates of cognitive reappraisal and distraction in men and HC women. On the neural level, cortisol increased regulatory activity in the ventrolateral prefrontal cortex when using distraction and attenuated emotion-related activation in the amygdala when regulating negative emotions via cognitive reappraisal in both, men and HC women. Interestingly however, on the behavioral level, cortisol administration diminished subjective emotional responses only in men, while leaving emotional ratings in HC women unaffected. Consistently, Langer and colleagues (2020) found acute stress induced by the TSST to improve emotion regulatory performance in men, but neither in NC women tested in the luteal phase nor in HC women (see Fig. 3). In particular, stress facilitated the application of cognitive reappraisal but not distraction, indicated by reduced emotional arousal as well as enhanced valence and regulatory success ratings in men. Stressed men also displayed stronger pupil dilations during reappraisal attempts suggesting enhanced cognitive regulatory engagement, which ultimately may have led to better regulatory outcomes. Importantly, cortisol secretion was positively linked to subjective reappraisal success again in men, but not in NC or HC women. By contrast, in a recent neuroimaging study from Sandner et al. (2021), exposure to a compact version of the Scan*STRESS* did not affect cognitive emotion regulation at all, neither on a behavioral, nor on a neural level and neither in men, nor in HC women.

Notably, a closer look at the cortisol reactivity in both stress studies revealed that in the study by Langer et al. (2020) stressed men exhibited a significantly larger cortisol increase when compared to the stressed group of NC or HC women, while no such sex difference was found in the study by Sandner and colleagues (2021). Supposing that the beneficial stress effects on emotion regulatory performances in men are mainly driven by cortisol, it is therefore reasonable to assume that the presence or absence of sex-specific stress effects on emotion regulation may at least in parts be explained by the presence or absence of sex differences in the initial neuroendocrine stress response.

Taken together, the limited data tentatively suggest that stress hormones (in particular cortisol) promote cognitive emotion regulation. This beneficial effect seems to prevail in men, leaving emotion regulation mostly unaffected in both NC and HC women. It has to be noted though that the findings have to be interpreted with caution until more data is available.

## 5. Integration of the findings regarding HC effects on cognition and emotion

Our selective review summarizes the current evidence for a modulatory influence of HCs on the impact of acute stress on human cognition and emotion. The identified studies revealed that stress effects on different cognitive-emotional processes in women using HCs were at times reduced or even absent. Even more striking were the few examples of reversed effects in the HC group. HCs potentiating stress (hormone) effects were not observed so far. Strong conclusions can, however, not be drawn at the moment due to the sparsity of studies addressing this highly relevant issue, which was also remarkable.

On the one hand, HCs appear to reduce stress (hormone) effects on episodic memory processes. Beneficial effects of stress on encoding and/or consolidation as well as negative effects of stress or cortisol on memory retrieval were weaker or missing in HC users (Cornelisse et al., 2011; Kuhlmann and Wolf, 2005; Nielsen et al., 2014). On the other hand, there is initial evidence that HCs seem to elicit valence-specific effects. HC women exerted improved memory for neutral and positive stimuli during encoding and consolidation (Merz and Wolf, 2017; Nielsen et al., 2013), and impaired memory for negative stimuli during retrieval (Mordecai et al., 2017). Thus, with respect to acute stress effects on episodic memory, HC users might not only experience the beneficial effects on encoding and consolidation but also appear to be protected from impairments and negativity biases.

A partially similar picture emerged for fear conditioning, even though some differences were notable. Cortisol administration impaired the neural correlates of fear learning in men (Merz et al., 2010; van Ast et al., 2012) and NC women, but had the opposite effect in HC users (Merz et al., 2012; Stark et al., 2006; Tabbert et al., 2010), which was also observed after stress induction (Merz et al., 2013). This is as of today the most striking finding of an opposing (and not just reduced) effect of stress or cortisol in HC users. For extinction consolidation and extinction retrieval, the empirical picture is more similar to the episodic memory findings: HC women benefit less from stress with respect to an enhancement of extinction consolidation (Bentz et al., 2013) or exposure-based psychotherapy (Raeder et al., subm.). At the same time, they appear less vulnerable to a cortisol induced return of fear due to a reduced extinction retrieval impairment (Kinner et al., 2018).

Only a limited number of studies has addressed the impact of HCs on stress hormone effects regarding cognitive emotion regulation. The current evidence suggests that stress induced cortisol elevations or cortisol administration enhance cognitive emotion regulation in men (Jentsch et al., 2019; Langer et al., 2021). In women (NC women as well as HC users), this effect appears to be weaker, which at least in part might reflect changes in HPA reactivity.

Interestingly as summarized above, we found examples for both mechanistic scenarios which we had outlined in the introduction. On the one hand, there is evidence that HCs lead to a blunted free cortisol stress response which in turn reduced the cognitive and/or affective impact of the stressor (e.g., Cornelisse et al., 2011; Langer et al., 2020). On the other hand, there are examples (especially derived from pharmacological cortisol studies) which illustrate that the behavioral and neural response to cortisol differs between women using HCs and other studied groups (e.g., NC women or men, see Kinner et al., 2018; Merz et al., 2012). We will discuss possible neuroendocrine mechanisms underlying those two scenarios in the following sections.

### 5.1. *Possible neuroendocrine mechanisms: HC effects mediated via altered HPA responsivity*

As mentioned in the introduction, oral HCs enhance cortisol-binding globulin concentrations (e.g. van der Vange et al., 1990), which in turn leads to a blunted free (e.g., as measured in salivary samples) cortisol response to acute stress (Hellhammer et al., 2009; Kirschbaum et al., 1999). In parallel, basal (plasma derived) cortisol concentrations are increased (e.g., Hertel et al., 2017). In line with this interpretation, cortisol-binding globulin concentrations in HC women were found to be negatively associated with the free salivary cortisol response but positively correlated with total cortisol concentrations (Kumsta et al., 2007;

for an additional review, see Lewis et al., 2019). This effect occurs only for those compounds which trigger cortisol-binding globulin production in the liver. In contrast, for example, the use of a progestin-releasing intrauterine device (not triggering cortisol-binding globulin production) was associated with an increased salivary cortisol response to acute stress, which apparently was centrally mediated (Aleknaviciute et al., 2017).

Importantly, recent research has illustrated a widespread HC influence on the brain with effects on the amygdala, hippocampus and prefrontal cortex (for a review, see Brønnick et al., 2020), which are also involved in HPA axis regulation (Arnsten, 2009; Joëls and Baram, 2009). Moreover, HCs change the activity and action of monoamines, gamma-aminobutyric acid or neurosteroids in the brain (for a review, see Porcu et al., 2019). It is therefore very likely that HC effects on the brain might exert additional modulatory influence on basal HPA activity and stress reactivity beyond the cortisol-binding globulin effect described above, which will be described in the following section.

### *5.2. Possible neuroendocrine mechanisms: HC effects mediated via altered brain responsivity to glucocorticoids*

Another potential mechanism explaining the reduced or even reversed stress effects in HC women comprises a generally altered or reduced central glucocorticoid sensitivity. Exogenous sex hormones contained within HCs bind to estrogen and progestin receptors and thereby act peripherally and centrally to suppress the production of endogenous sex hormones (Lewis et al., 2019). Yet, the continuous binding of synthetic estradiol and/or progesterone after regular HC intake might lead to a subsequent downregulation or desensitization of these receptors in brain regions crucial for cognitive-emotional processing. In support of this idea, converging lines of evidence from the human neuroimaging literature revealed functional and structural changes in amygdala, hippocampal and prefrontal regions as well as decreased functional connectivity between these structures in HC users relative to NC women and men (Brønnick et al., 2020; Lewis et al., 2019; Rehbein et al., 2021). Notably however, stress was just recently found to enhance amygdala-prefrontal coupling especially during the active relative to the inactive phase of HC intake (Nasseri et al., 2020). It is therefore reasonable that acute stress or cortisol administration could unchain the proposed reduced receptor excitability in HC women, which in turn might trigger mechanisms promoting cognition and emotion. By contrast, these receptors are not continuously occupied in men and NC women, prompting cognitive-emotional processes to operate properly when glucocorticoid levels are rather low (Merz and Wolf, 2017).

Alternatively, it is conceivable that differences in the affinity and/or binding capacities of mineralocorticoid and glucocorticoid receptors in HC women caused the diverging stress effects. Estradiol for instance decreases mineralocorticoid receptor binding, whereas progesterone can substantially reduce mineralocorticoid receptor affinity for glucocorticoids (Turner, 1997) and directly competes with glucocorticoids for glucocorticoid receptor binding. This competition inhibits glucocorticoid receptor action, whereas estradiol appears to decrease both, glucocorticoid receptor expression and action (Bourke et al., 2012). Accordingly, mineralocorticoid and glucocorticoid receptor binding capacities have been shown to differ between sexes as well as in women depending on menstrual cycle phase (ter Horst et al., 2012; Turner, 1997; Turner and Weaver, 1985).

Moreover, HPG axis functioning is altered in HC women (Fleischman et al., 2010). Sex hormones also affect HPA axis activity, and stress hormones affect HPG axis activity (Viau, 2002). For instance, the HPA axis can be stimulated by estradiol (Toufexis et al., 2014), which also seems to depend on which estrogen receptor type is activated (Handa et al., 1994; Handa and Weiser, 2014). Thus, endogenous and synthetic sex hormones might occupy or stimulate different receptor types and interact differently with stress hormones in the brain.

In the next two sections, we will outline some challenges and future directions which should be considered when designing and translating future experiments for cross-disciplinary research in humans and animals.

## 6. Challenges and future directions for research in humans

Although there is evidence that HCs critically influence the stress response and various cognitive processes, HC women are often ignored or at least not analyzed separately in the discussed research fields. Most of the results reported here were related to oral contraceptives, which need to be distinguished from other types of HCs like hormonal patches, vaginal rings, subdermal implants or intrauterine devices. Critically, their respective effects on the stress system (Aleknaviciute et al., 2017) and mood (disorders; Poromaa and Segebladh, 2012; Skovlund et al., 2018; Skovlund et al., 2016; Zettermark et al., 2018) can differ.

Furthermore, HC effects are dependent on the specific compounds. The most common oral contraceptive type consists of a combination of a synthetic estrogen (mostly ethinylestradiol) and a synthetic progestin. To date, there is a large number of different HC compositions, differing in type and dosage of the concerning synthetic hormones (Christin-Maitre, 2013; Herrera et al., 2019), leading to a great variety of potential neurobiological effects (Porcu et al., 2019). Depending on the structure, certain types of progestins cannot only bind to progesterone receptors, but also to androgen and estrogen receptors and even to mineralocorticoid or glucocorticoid receptors (Kuhl, 2005). Binding affinity as well as agonistic and antagonistic actions to the specific receptor determine the resulting effects of the progestins and estrogens (Kuhl, 2005; Sitruk-Ware and Nath, 2010). As already mentioned above and of special relevance for the stress effects on cognitive-emotional processes, mineralocorticoid and glucocorticoid receptor binding can for example differ in women depending on the menstrual cycle phase (ter Horst et al., 2012; Turner, 1997; Turner and Weaver, 1985). However, the exact impact of synthetic sex hormones on mineralocorticoid and glucocorticoid receptor expression and action and whether it is similar to the effects of endogenous sex hormones remains to be explored. Likewise, we do not know whether endogenous and exogenous sex hormones might stimulate different receptor types or interact differently with stress hormones in the brain. One approach that could provide essential insight into this complex neurobiological intersection is to target, visualize and quantify HC and glucocorticoid receptor binding in the brain with means of positron emission tomography. Studying this interaction will not only help to clarify potential neurochemical changes accompanying HC use but will also open new avenues for stress research in human and animal models alike. This technology could not only provide an important insight into the consequences of acute stress hormone secretion, but also into the circadian dynamics of cortisol release. As mentioned above, stress hormone effects on cognition might underlie time-of-day dependent effects, which can eventually have an impact on cognitive processes (Het et al., 2005). In a healthy person, the cortisol concentration rises sharply immediately after awakening (cortisol awakening response) and falls at first rapidly and thereupon more slowly during the day (Adam et al., 2017; Pruessner et al., 1997). However, one study found a blunted cortisol awakening response in HC women, although the average cortisol levels were higher at awakening (Høgsted et al., 2021). Since a flatter cortisol drop and an overall enhanced cortisol concentration are often associated with mental illness, an explicit investigation of the circadian rhythm of HC women appears to be very important (Adam et al., 2017; Het et al., 2005).

Another important factor to consider is the dosage level of the HC components. Combined HCs either contain daily estrogen and progestin in constant dosages (monophasic contraceptives) or vary the dosages of estrogen and progestin over time (multi-phasic contraceptives; Christin-Maitre, 2013). All of these different factors might exert an impact on stress effects on cognitive-emotional functioning. For this reason, researchers in this field should not consider HC in general as a critical factor, but rather commit to one type of HC composition or even

compare different compositions with each other. At the very least, information about the specific HC type or its components should be collected and reported.

Aside from HC compounds, the duration of HC intake or HC phase should be considered in the future. HC regimens typically include both an active (when synthetic hormones are taken) and an inactive (when synthetic hormones are not taken) pill phase. Some studies reported differences in memory performance (Mordecai et al., 2008), working-memory related brain activation (Herrera et al., 2020) and resting state functional connectivity (Petersen et al., 2014) between the active and inactive pill phase in HC users. Interestingly, such phase-dependent alterations in resting state functional connectivity were not only observed under baseline conditions but also after exposure to a stressor in the ventromedial prefrontal cortex, amygdala and parahippocampus (Nasseri et al., 2020). Critically, these alterations occurred, even though the free cortisol response to the stressor was comparable across pill phases, providing additional evidence for the idea that the female brain's responsiveness to neuroendocrine stress signals differs under HC usage. In order to enhance our understanding of HC– and HC-phase-related effects on the brain's response to stress, more studies using within-subjects designs (testing women repeatedly in different pill phases) are clearly needed.

In addition, it remains unclear how long HCs need to be taken in order to exert effects on brain and behavior and whether HC-related changes persist over months (Balogh et al., 1981) or even years (Chan et al., 2008) after pill discontinuation. Longitudinal designs investigating women before they start to take HCs and testing them again under HC intake and ideally also later when they stop using HCs could shed light on the long-term effects of HC usage and its interaction with stress in modulating cognitive-emotional processes. Particularly, longitudinal studies represent well-suited designs to test if and how HC usage is associated with the development of psychopathological conditions, for which cognitive-emotional processes play a crucial role, for example anxiety disorders or posttraumatic stress disorder. Also available treatment options such as exposure therapy might work differently under HC intake as already shown in women with anxiety disorders (Graham et al., 2018; Raeder et al., 2019). In light of first experimental studies on the influence of HCs on trauma processing (Miedl et al., 2018), an exploration of HC usage in the context of therapeutic interventions in posttraumatic stress disorder also seems highly needed. More generally, large-scaled and longitudinal clinical studies should be realized including HC intake, early childhood adversity with its known long-lasting impact on mental health (Hakamata et al., 2022; Rudd et al., 2021) as well as comprehensive measures of different psychopathologies.

Moreover, the menstrual cycle phase of the NC control group needs to be considered. While NC women in the follicular phase exhibit relatively low endogenous sex hormone levels most likely resembling those of HC users, NC women in the luteal phase display higher endogenous levels of estradiol and progesterone (Fleischman et al., 2010; Frye, 2006; Montoya and Bos, 2017). It has thus been argued that HC users should ideally be contrasted to NC women in the follicular phase in order to better 'isolate' the effects of HCs because differences in endogenous sex hormones are minimized between these groups (Montoya and Bos, 2017). In this case, but also generally, it would be desirable to assess serum levels of endogenous and exogenous sex hormones to verify the experimental group assignment. Furthermore, a more fine-grained subdivision of menstrual cycle phases should be considered as recommended before (Schmalenberger et al., 2021).

In addition to manifold hormonal influences, HC usage may also be related to personality traits such as risk aversion, conscientiousness, general anxiety (Priestnall et al., 1978; Ross et al., 2001), social biases including education, religiosity, socialization, age, relationship status, sexual activity or the general attitude towards medication (Priestnall et al., 1978). These factors could also contribute to systematic differences between women who choose to take HCs and those who do not (see also Brønnick et al., 2020). However, systematic explorations of these factors in relation to cognitive and emotional processes and their modulation by stress are lacking so far. While within-subjects and longitudinal designs can overcome these potential confounders and self-selection biases, it is still important for future studies using between-subjects designs with HC and NC women to collect data on them to be able to control for these factors as far as possible.

All things considered, more studies systematically comparing men, NC and HC women as well as within-subjects and longitudinal approaches in HC women are clearly needed to provide causal insights into the impact of HC treatment on stress effects on cognition and emotion. In designing these studies, future researchers are strongly encouraged to thoroughly characterize participants' demographics, including HC formulation and regimen, HC initiation and duration of use, as well as lifetime history of HC use. Some of the proposed methodological issues indeed require enhancing sample sizes to allow proper investigation. For example, when calculating effect sizes for designing a study, effect sizes of stress effects on retrieval were reported as overall g+=-0.215 (Shields et al., 2017), but no longer significant (and even in the opposite direction: g+=0.101) when HC women were included, and increased (to g+=-0.294) when HC women were excluded.

Focusing on the stress side, different approaches exist to test the impact of stress hormones on cognitive-emotional processing (cf. Box 1). They do not necessarily have to lead to identical results, but can shed light into the relevant underlying mechanisms. In more detail, a less potent stressor such as the CPT more strongly activates the SNS compared to the HPA axis, for which only marginally elevated cortisol concentrations can be observed. Stressors with a social-evaluative component (cf. Dickerson and Kemeny, 2004) such as the SECPT or the TSST typically lead to higher cortisol increases along with SNS activation. In contrast, glucocorticoid administration selectively enhances cortisol concentrations from mildly elevated to supra-physiological cortisol levels (dependent on the dosage) and leaves the SNS untouched. Thus, on the one hand, HC effects on cognitive-emotional processes only emerging when using the CPT would argue for a selective HC effect on the SNS. On the other hand, if HCs exert differential effects only when administering glucocorticoids, a selective cortisol effect might be assumed. Most likely, the SNS and HPA axis exert joint effects in modulating cognition and emotion (Roozendaal et al., 2006a) calling for further elaborated experiments directly comparing different stress protocols amongst each other and in comparison with glucocorticoid administration studies (also implementing possible dose–response approaches; cf. Lupien et al., 1999; Schilling et al., 2013).

## 7. Challenges and future directions for research in animals

Methodological approaches in laboratory animals greatly differ from human experiments (Haaker et al., 2019), but they can particularly shed light onto the relevant underlying mechanisms, for example regarding the interactive HC and glucocorticoid effects on different brain structures or on the HPA axis at the peripheral but also central level. Particularly, dose–response studies testing different cortisol dosages should be realized in animal studies targeting specific cortisol receptors in critical brain areas such as the amygdala or the hippocampus along with antagonizing them (e.g., Khaksari et al., 2007; Roozendaal et al., 2006b). Using agonists and antagonists in a similar manner, different HC compounds, including estrogens and progestins need to be explored in their ability to downregulate or desensitize sex as well as stress hormone receptors. Moreover, co-expression of these sex and stress hormone receptors in relevant brain regions need to be more closely identified in future animal work.

In addition, longitudinal and causality-related approaches should be implemented in animals by using a baseline test of the relevant process, a test after HC administration as well as a follow-up test after HC treatment has stopped. Critically, the duration of HC administration and/or discontinuation could be experimentally varied to make causal

inferences regarding the direct and long-lasting impact of HCs on cognitive-emotional processing. This approach can overcome the above-mentioned typical limitations in human research, for example regarding personality traits differing between HC and NC women.

We should keep in mind that the very methodology substantially differs between animal and human studies (Haaker et al., 2019), thus, results do not necessarily converge. For example, implementation of a stress protocol may include life-threatening situations in animals (e.g. underwater trauma), whereas the combination of a challenge (such as putting a hand in ice-cold water) with social evaluation is used in humans. Still, both approaches are highly needed to advance the field (maybe at best directly combining them, e.g. Fouquet et al., 2010; Graham and Milad, 2013; Haaker et al., 2013). In particular, animal researchers should include females in their protocols (cf. Clayton and Collins, 2014; Shansky and Murphy, 2021), since they are highly underrepresented in the learning and memory field (Cover et al., 2014; Lebron-Milad and Milad, 2012). In this respect, a critical challenge consists of the exact handling of the estrus cycle covering only four days in rodents (accompanied with rapidly changing sex hormone levels) compared to the menstrual cycle in women lasting 28 days, especially in multiple-day experiments as realized in episodic memory or fear conditioning paradigms. The interaction of stress and sex hormone effects has already been established in animals for classical and operant conditioning (Dalla and Shors, 2009; Shors, 2004), which needs to be extended to other relevant fields such as extinction learning and retrieval or episodic memory.

Apart from the mentioned acute effects of stress hormones, another important future direction for the animal field comprises the investigation of early life adversity and chronic stress effects on cognitive-emotional processes, which cannot be experimentally tested in humans due to ethical reasons. Still, early life adversity as well as chronic stress are both associated with long-lasting changes in brain functioning and structure as well as psychopathology (Herzog and Schmahl, 2018; McEwen et al., 2016; Teicher et al., 2016). How HCs interact with adverse events in early life or chronic stress conditions to modulate cognition and emotion should be clarified in animal studies.

## 8. Conclusions and clinical relevance

In this review, we summarized and discussed the current literature on HCs modulating stress hormone effects on episodic memory, fear conditioning and cognitive emotion regulation. Indeed, HCs seem to attenuate, nullify, or even reverse stress hormone effects in these cognitive-emotional domains, whereas a potentiation effect has so far not been identified. Different underlying mechanisms might account for these specific HC effects, which need to be tested in further human and animal experiments as outlined above.

Critically, the identification of the direct HC impact on many brain structures and functions steadily increased in recent years (Brønnick et al., 2020; Lewis et al., 2019; Rehbein et al., 2021), but the interaction with stress hormones is still in its infancy. In the face of high numbers of women using HCs (United Nations, 2019) and the higher prevalence of many stress-related mental disorders in women (Cover et al., 2014; Kessler et al., 2005), future research must identify if and how exactly HCs in combination with acute or chronic stress contribute to the development, maintenance, treatment, and relapse phenomena in different mental disorders. A closer look at the underlying basic learning and memory as well as emotion regulation processes might provide important insights into the critical underlying mechanisms, brain structures and functions relevant to be translated for clinical purposes. Eventually, this endeavor could set the stage for a personalized medicine approach (Hamburg and Collins, 2010), thus, possibly varying treatment options between sexes and between NC and HC women.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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