



Review

Sex Differences in Stress Effects on Emotional Learning

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Stress influences emotional learning and memory processes. These effects are thought to underlie stress-associated mental disorders. Sex differences in stress reactivity and in central nervous system stress sensitivity illustrate the important modulatory role of sex hormones. This Review outlines how stress hormones influence different stages of the fear conditioning process, such as fear acquisition, extinction, and retrieval. Results will be compared with findings on the impact of stress on episodic memory. The focus is on the available human data on sex differences and the impact sex hormones have on the stress effects on emotional learning and memory. It will become apparent that the menstrual cycle but also the intake of hormonal contraceptives modulates the impact of stress on brain and behavior. Additional basic research is needed for a deeper insight regarding the interplay between stress and sex hormones in emotion and cognition. In addition, new treatment options might be derived to optimize existing strategies such as exposure therapy, which relies on the principles of fear conditioning. © 2016 Wiley Periodicals, Inc.

Key words: cortisol; extinction; fear conditioning; glucocorticoids; hormonal contraceptives; memory retrieval

The release of stress hormones in the face of a (potential) threat is essential for the adaptation to major life events as well as to ongoing, everyday challenges, a process called *allostasis* (McEwen, 2004). In humans, a threat to the social self in combination with uncontrollability of a situation represents a strong stressor (Dickerson and Kemeny, 2004). An experimental realization of such a stressor can be implemented with public-speaking paradigms such as the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) or with physiological stressors such as an immersion of the hand in ice-cold water as in the cold pressor test (CPT; Hines and Brown, 1932) or the socially evaluated cold pressor test (SECPT) developed later (Schwabe et al., 2008b).

Men and women differ in their stress responses on the endocrinological and behavioral levels (Taylor et al., 2000; Kudielka and Kirschbaum, 2005), which might underlie the different vulnerabilities for distinct stress-

associated mental disorders. Women compared with men have a higher lifetime incidence of posttraumatic stress disorder (PTSD), major depression, and several anxiety disorders (Kessler et al., 2005; Cover et al., 2014).

Sex differences in stress effects on learning and memory processes might be caused by two possible mechanisms: First, sex differences might occur as a result of differences in the endocrinological response to a stressor. Second, and not mutually exclusive to the first explanation, sex differences might occur as a result of a different responsiveness of the male and the female brains to the same neuroendocrine stress signals.

NEUROENDOCRINE REGULATION OF THE STRESS RESPONSE

The endocrinological response to a stressor is conveyed by the activation of two major stress axes, the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenocortical (HPA) axis (see Fig. 1). The SNS triggers a rapid response to stress initiated by the effects of (nor)-adrenaline secreted from the adrenal medulla, leading to

SIGNIFICANCE:

We highlight the interaction between stress and sex hormones in the domain of episodic memory and fear conditioning in humans. These effects might help to explain the different vulnerabilities for men and women regarding the development and maintenance of stress-related mental disorders. Moreover, it becomes apparent that sex hormone variations over the course of the menstrual cycle and the intake of oral contraceptives represent critical variables to consider in future basic science studies.

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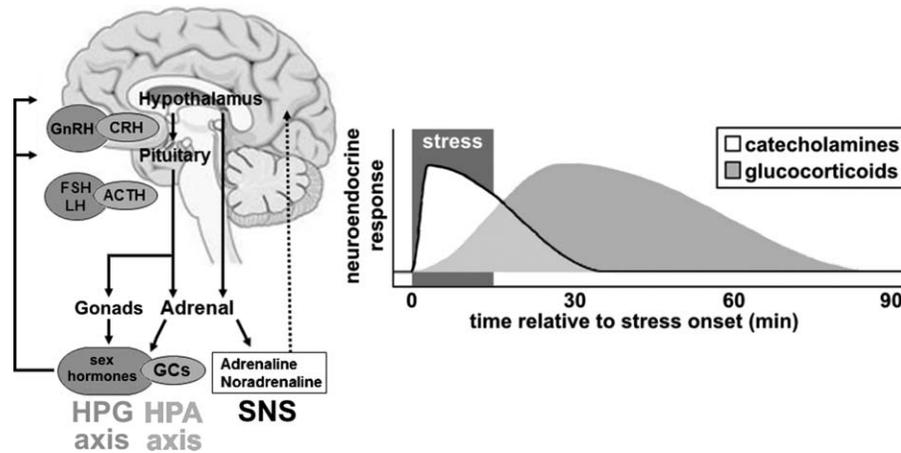


Fig. 1. Stress initiates two lines of defense mechanisms in humans, the rapidly acting sympathetic nervous system (SNS) and the slower hypothalamic–pituitary–adrenocortical (HPA) axis. Activation of the hypothalamus stimulates the SNS to secrete the catecholamines adrenaline and noradrenaline from the adrenal medulla. The hypothalamus also secretes corticotropin-releasing hormone (CRH), which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland into the blood stream. ACTH prompts the adrenal cortex to release glucocorticoids (GCs), which can readily pass the blood–brain barrier and modulate brain functions involved in learning

and memory. Furthermore, GCs exert negative feedback on the hypothalamus and pituitary gland reducing HPA axis activity.

The hypothalamus also controls the release of sex hormones via the hypothalamic–pituitary–gonadal (HPG) axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland into the blood stream. The gonads and adrenal cortex secrete sex hormones that exert negative feedback on the hypothalamus and pituitary gland.

increases in blood pressure, heart rate, and breathing frequency. This first stress response wave, which occurs in seconds, is interpreted as the fight-or-flight response (Cannon, 1932). The second, slightly delayed stress response consists of the release of glucocorticoids (GCs; mainly cortisol in humans) and reaches its peak ~20–30 min after stress onset (Dickerson and Kemeny, 2004). Cortisol secretion is governed by the HPA axis, which releases corticotropin-releasing hormone (CRH) from the hypothalamus to stimulate the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH finally stimulates the synthesis and release of GCs from the adrenal cortex, which can readily enter the brain to impact structures involved in learning and memory processes (Joëls and Baram, 2009). GCs exert negative feedback on the hypothalamus and the pituitary gland as well as on the hippocampus and prefrontal areas to ensure a fine-tuned regulation of the HPA axis and the stress response (De Kloet et al., 2005; Ulrich-Lai and Herman, 2009).

The cortisol stress response is usually measured at different time points, including a baseline sample and a sample around the peak of the cortisol response, whereas the time course can also be combined in the area under the curve measure (cf. Prüssner et al., 2003). In addition to laboratory stressors (see above) or real-life stressors such as an oral presentation at the university (Merz and Wolf, 2015), cortisol concentrations can be manipulated by using pharmacological approaches, e.g., by the administration of synthetic GCs such as hydrocortisone or dexamethasone. However, GC application mimics only the cortisol release and not the secretion of CRH and ACTH

or the activation of the SNS accompanying the stress response.

Two types of intracellular receptors are occupied by circulating GCs, mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs), which differ in their affinity and distribution within the brain. MRs are located in the hypothalamus, hippocampus, amygdala, and locus coeruleus, whereas GRs are expressed ubiquitously in the brain. GCs bind to MRs with a high affinity and to GRs with a low affinity. GCs thus prominently occupy MRs under basal conditions, whereas GRs are occupied mainly after increases in GC concentrations, for instance, after exposure to stress (Joëls and Baram, 2009). In addition to these intracellular receptors, membrane-located GRs and MRs have recently been described that can mediate rapid GC effects (Joëls et al., 2008; Roozendaal et al., 2010). Via these receptors, GCs can substantially modulate (emotional) learning and memory processes. The effects of GCs on learning and memory have been attributed mostly to their impact on GRs, but evidence suggesting a role of membrane-located MRs is accumulating (Joëls et al., 2008; Vogel et al., 2016).

NEUROENDOCRINE REGULATION OF THE RELEASE OF SEX HORMONES

In addition to the control by the HPA axis, a regulation of the release of sex hormones is also governed by another neuroendocrine system, the hypothalamic–pituitary–gonadal (HPG) axis (Meethal and Atwood, 2005; see Fig. 1). The hypothalamus is responsible for the release of gonadotropin-releasing hormone (GnRH) which leads to a secretion of follicle-stimulating hormone (FSH) and

luteinizing hormone (LH) from the anterior pituitary gland into the blood stream. LH and FSH stimulate cells in the gonads (ovaries and testes) and the adrenal cortex to produce sex hormones such as estrogens (e.g., estradiol), gestagens (e.g., progesterone), and androgens (e.g., testosterone). Similar to the HPA axis, the HPG axis is also controlled by a negative feedback loop involving sex hormones to reduce HPG axis activity on the level of the hypothalamus and the pituitary gland.

Over the course of the typical menstrual cycle (~28 days in duration), sex hormone concentrations vary greatly, with LH, FSH, and estradiol peaking midcycle around ovulation (day 14), although progesterone concentrations increase in the second half of the cycle (the luteal phase). The onset of menstrual bleeding marks the beginning of a new cycle, with sex hormone concentrations dropping and reaching low levels during the follicular phase.

Sex hormones influence the brain and the periphery through activational and organizational effects. Organizational effects reflect long-term influences of sex hormones on morphology and physiology during development, whereas activational effects refer to circulating sex hormones prompting morphological and physiological changes over the entire life span (Gillies and McArthur, 2010). Activational effects can be investigated in free-cycling women during different stages of the menstrual cycle with the associated varying sex hormone concentrations and altered HPG axis activity.

INTERACTIONS BETWEEN THE HPA AND THE HPG AXES

The HPG axis is interconnected with the HPA axis on different levels, allowing for neuroendocrine communication and adaptation to environmental changes to maintain homeostasis. For example, a stress-induced activation of the HPA axis leads to an inhibition of estrogen and testosterone release (Toufexis et al., 2014; Lu et al., 2015). In turn, estrogens can enhance HPA axis functioning, whereas testosterone inhibits it (Kirschbaum et al., 1996; Handa and Weiser, 2014). Psychosocial laboratory stressors such as the TSST induce a stronger HPA axis stress response in men than in women (Kudielka and Kirschbaum, 2005; Kajantie and Phillips, 2006). However, this sex difference might depend on the specific paradigm used; women seem to react more to social rejection and men more to tasks involving achievement challenges (Stroud et al., 2002). In a large meta-analysis (Dickerson and Kemeny, 2004), no strong overall influence of sex on the cortisol response to laboratory stressors could be detected; however, a possible influence of menstrual cycle and hormonal contraceptives was not taken into account. Indeed, fluctuations of sex hormones during the menstrual cycle seem to modulate the HPA axis response in women. A more pronounced HPA axis stress response can be observed during the luteal phase (Kudielka and Kirschbaum, 2005; Kajantie and Phillips, 2006) characterized by elevated estradiol and progesterone concentra-

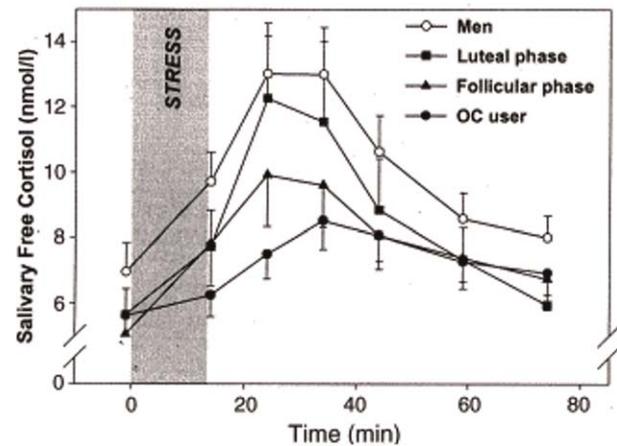


Fig. 2. Exposure to a standardized psychosocial stress protocol (Trier Social Stress Test, TSST) leads to increases in mean (\pm SEM) free salivary cortisol concentrations over time. Women in the luteal phase of the menstrual cycle exhibit increases comparable to those of men, whereas women in the follicular phase show less pronounced cortisol releases. Women taking oral contraceptives (OC user) display a blunted cortisol stress response in saliva. Slightly modified from Kudielka BM, Kirschbaum C. 2005. Sex differences in HPA axis responses to stress: a review. *Biol Psychol* 69:113–132, with permission from Elsevier.

tions. Additionally, oral contraceptives (OCs) appear to dampen the free (unbound, i.e. biologically active) cortisol stress response by increasing cortisol-binding globulin (Kirschbaum et al., 1999; Rohleder et al., 2003). The typical blunted free salivary cortisol stress response in OC women compared with men as well as with women in the follicular and luteal phases is displayed in Figure 2. In line with the findings on experimentally induced stress, OC women also exhibit a reduced free cortisol release during an oral presentation at the university, even though the effect might be somewhat less pronounced for these real-life stressors (Merz and Wolf, 2015).

Taken together, sex hormones critically affect HPA axis activity, and vice versa, as a result of the complex interactions between the HPG and the HPA axes. Additionally, hormones released by both axes can enter the brain and modulate cognition and emotion. However, until now, many experimental stress studies in humans have focused exclusively on men. Furthermore, in studies including women, information about menstrual cycle phase and/or hormonal contraception are often not taken into account in the experimental design but may explain a critical amount of variance.

The present Review summarizes the literature concerning the impact of stress hormones on emotional learning and memory processes in humans. After a general introduction to episodic memory and fear conditioning, we briefly outline the impact of stress on episodic memory. Emotionally arousing stimuli are especially affected by stress hormones because of the interactive effects of circulating GCs and an activated SNS on the amygdala and the hippocampus (Roosendaal et al., 2009). We focus

particularly on fear conditioning, for which some data are available on the influence of sex hormones and the intake of hormonal contraceptives.

Episodic Memory and Fear Conditioning

Past personal events, such as the birth of a child, are stored in episodic memory, which critically depends on the medial temporal lobes, including the hippocampus (Nadel and Moscovitch, 1997). In general, three stages of memory processing can be distinguished (Tulving, 1983): 1) encoding, transformation of an incoming information into a memory representation; 2) consolidation, modification and stabilization of this representation; and 3) retrieval, reactivation of the stored memory trace. Emotional information is preferentially stored in episodic memory, relying on an interplay between the hippocampus and the amygdala (Cahill and McGaugh, 1998; Phelps and LeDoux, 2005).

In addition to episodic memory tasks, emotional learning processes can also be investigated by using fear conditioning paradigms (including processes depending on procedural but also on episodic memory), which offer important translational aspects (Milad and Quirk, 2012). Similar to episodic memory, fear conditioning can consist of different stages, acquisition, extinction, and retrieval and the consolidation processes between them. During fear acquisition, individuals learn that a (typically neutral) stimulus is coupled with an aversive event (unconditioned stimulus; UCS) such as an electrical shock that elicits an unconditioned response (e.g., fear; Pavlov, 1927). After a few pairings, the originally neutral stimulus becomes a conditioned stimulus (CS) able to trigger parts of the unconditioned response reflected in the conditioned fear response. Fear acquisition processes are assumed to play a significant role in the development of anxiety disorders as well as PTSD (Mineka and Oehlberg, 2008; Graham and Milad, 2011).

During exposure therapy, phobic patients are repeatedly confronted with their feared stimuli or situations, which typically leads to a reduction of phobic fear. Exposure therapy represents the most effective strategy to treat anxiety disorders or PTSD and relies on fear extinction principles (Vervliet et al., 2013). After initial fear memory formation, recurrent presentations of the CS without the UCS result in fear extinction, during which conditioned fear vanishes. However, extinction does not erase the conditioned response forever; fear is just temporarily not expressed. For example, patients often experience a relapse of phobic fear when confronted with their specific CS after a change in context (Bouton, 2004; Vervliet et al., 2013). Thus, two competing memory traces must be distinguished after extinction, one excitatory memory trace referring to the acquired fear memory and one inhibitory memory trace referring to extinction memory (Bouton, 2004).

The amygdala plays a special role in fear conditioning in rodents and humans (LeDoux, 2000; Phelps and LeDoux, 2005). Additionally, the anterior cingulate,

(ventral and anterior parts of the) insula, ventromedial prefrontal cortex (vmPFC), and hippocampus are integrated in the neuronal network mediating fear and extinction (Sehlmeyer et al., 2009; Mechias et al., 2010; Greco and Liberzon, 2016). Abnormalities in this circuitry can be found in patients with anxiety disorders or PTSD (Etkin and Wager, 2007; Graham and Milad, 2011), along with altered resting-state connectivity between the amygdala and the hippocampus (Sripada et al., 2012a,b). A deeper understanding of the neurobiological underpinnings of fear conditioning processes is essential to providing treatment options tailored to men and women, for which different prevalence rates are described for anxiety disorders and PTSD, for example (Kessler et al., 2005; Cover et al., 2014). The impact of stress and sex hormones on the fear and extinction circuit might serve as a helpful model in investigating these sex differences in prevalence rates.

First, we outline results on the sex-dependent impact of stress hormones on episodic memory encoding and consolidation as well as on fear memory formation. Second, we provide an overview of the influence of these factors on episodic memory retrieval as well as on extinction learning and retrieval and their clinical applications. We refer the reader to Table I to find experimental details of the studies mentioned below concerning the influence of sex and stress hormones on emotional learning and memory processes and to Table II for details to be considered in future studies.

Effects of Stress and Sex Hormones on Episodic Memory Encoding and Consolidation

Experimental studies investigating pre-encoding stress have reported mixed findings. Important moderators are the timing of the stressor relative to encoding (Joëls, 2006; Schwabe and Wolf, 2013), the time of day (Het et al., 2005) and the emotionality of the stimulus material. Pre-encoding stress or cortisol application facilitates encoding and/or consolidation of emotionally arousing information (Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006; Payne et al., 2007), whereas nonarousing, neutral material is often stored less efficiently under stress or after cortisol administration (Kuhlmann and Wolf, 2006; Smeets et al., 2006; but see Rimmele et al., 2003).

Sex differences have been reported, with men showing enhanced memory for emotional pictures when stressed at encoding. Women in contrast did not display a stress effect on memory in this study (Cornelisse et al., 2011). Similarly, exposure to stress before encoding led to enhanced memory performance in men, whereas no change was observed in the women tested in the follicular or luteal phase or taking OCs (Espin et al., 2013; but see Schwabe et al., 2008a). In sum, pre-encoding stress seemingly exerts an effect on episodic memory for emotional material in men but not as consistently in women.

Stress or cortisol administration *after* encoding typically enhances episodic memory consolidation, and

TABLE I. Overview of Experimental Details of the Studies Mentioned on the Influence of Sex and Stress Hormones on Different Emotional Learning Processes*

Study	Stressor/GC administration	Timing stress – memory phase	Sex	Time of day
Effects of stress on episodic memory encoding				
Buchanan and Lovallo (2001)	Hydrocortisone 20 mg	60 Min before encoding	Men + women	N/A
Cornelisse et al. (2011)	TSST	9 Min before encoding	Men + women (OC + FO + LU)	12–6 PM
Espin et al. (2013)	TSST	15 Min before encoding	Men + women (OC + FO + LU)	2–5 PM
Kuhlmann and Wolf (2006)	Hydrocortisone 30 mg	10 Min before encoding	Men	11 AM–1 PM
Payne et al. (2007)	TSST	Immediately before encoding	Men + women	N/A
Kimmele et al. (2003)	Hydrocortisone 25 mg	75 Min before encoding	Men + women	4–6 PM
Smeets et al. (2006)	TSST	Immediately before encoding	Men + women	2–5 PM
Schwabe et al. (2008b)	CPT	10 Min before encoding	Men + women (OC)	2–5:30 PM
Effects of stress on episodic memory consolidation				
Andreano and Cahill (2006)	CPT	Immediately after encoding	Men + women	12–5 PM
Andreano et al. (2008)	CPT	Immediately after encoding	Women (FO + LU)	12–5 PM
Felmingham et al. (2012)	CPT	Immediately after encoding	Women (FC: LU + non-LU)	1–6 PM
McCullough and Yonelinas (2013)	CPT	10 Min after encoding	Men + women (OC + FC)	11 AM–3 PM
Nielsen et al. (2013)	CPT	Immediately after encoding	Women (OC + FO + LU)	12–6 PM
Nielsen et al. (2014)	CPT	After encoding	Women (OC + FC + LU)	12–6 PM
Yonelinas et al. (2011)	Skydiving	57 Min after encoding	Men + women (OC)	9:30 AM–1:30 PM
Effects of stress on episodic memory retrieval				
de Quervain et al. (2000)	Cortisone 25 mg	60 Min before retrieval	Men + women	N/A
Kuhlmann and Wolf (2005a,b)	Hydrocortisone 30 mg	60 Min before retrieval	Women (OC + ME + LU)	10 AM–5 PM
Kuhlmann et al. (2005a)	Hydrocortisone 30 mg	60 Min before retrieval	Women (FO)	10 AM–4 PM
Kuhlmann et al. (2005b)	TSST	10 Min before retrieval	Men	10 AM–12 PM
Maki et al. (2015)	TSST	10 Min before retrieval	Women (FO + LU)	1–5 PM
Merz et al. (2010b)	Modified TSST	30 Min before retrieval	Men + women (OC)	3–6:30 PM
Rohleder et al. (2009)	Hydrocortisone 30 mg	60 Min before retrieval	Men + women (FC)	10 AM–3 PM
Schoofs and Wolf (2009)	TSST	10 Min before retrieval	Women (OC + LU)	10–11 AM
Smeets et al. (2008)	CPT	10 Min before retrieval	Men + women	1–6 PM
Tollenaar et al. (2008)	TSST	First retrieval during stress (15 min after onset) Second retrieval 15 min after stress	Men	11:30 AM–3 PM
Effects of stress on fear memory formation				
Antov and Stockhorst (2014)	Psychosocial stressor	45 Min before acquisition	Men + women (FO + midcycle)	10 AM–5:30 PM
Antov et al. (2013)	Exp. 1: psychosocial stressor Exp. 2: CPT	Exp.1: 18 min before acquisition Exp.2: 6 min before acquisition	Men	Exp. 1: 10 AM–4 PM Exp. 2: 0:30–4:30 PM
Jackson et al. (2006)	Psychosocial stressor	60 Min before acquisition	Men + women (OC)	N/A
Merz et al. (2010a)	Hydrocortisone 30 mg	45 Min before acquisition	Men + women (OC + LU)	2–5 PM
Merz et al. (2012)	Hydrocortisone 30 mg	45 Min before acquisition	Men + women (OC + FO + LU)	2–5 PM
Merz et al. (2013)	TSST	25 Min before acquisition	Men + women (OC)	2–5 PM
Merz et al. (2014b)	Hydrocortisone 30 mg	Immediately after acquisition, 45 min before extinction	Men	2–5 PM
Soeter and Kindt (2011)	Yohimbine hydrochloride 20 mg	30 Min before acquisition	Men + women	N/A
Stark et al. (2006)	Hydrocortisone 30 mg	15 Min before acquisition	Men + women (OC)	12–2 PM
Tabbert et al. (2010)	Hydrocortisone 30 mg	45 Min before acquisition	Women (OC)	2–5 PM
van Ast et al. (2012)	Hydrocortisone 20 mg	45 Min before acquisition	Men + women (OC)	12–7 PM
Zorawski et al. (2005)	Endogenous cortisol	N/A	Men + women	2–4 PM

TABLE I. Continued

Study	Stressor/GC administration	Timing stress – memory phase	Sex	Time of day
Zorawski et al. (2006)	Mental arithmetic + public speech	Immediately after acquisition	Men + women	2–6 PM
Effects of stress on fear extinction/exposure therapy				
Bentz et al. (2013)	CPT	20 Min before extinction	Men + women (OC)	10 AM–6 PM
de Quervain et al. (2011)	Hydrocortisone 20 mg	60 Min before exposure therapy	Men + women	N/A
Lass-Hennemann and Michael (2014)	Endogenous cortisol	Measured immediately before exposure therapy and every 30 min during exposure therapy	Women (OC)	8 AM or 6 PM
Meyeroeker et al. (2012)	Yohimbine hydrochloride 10 mg	60 Min before exposure therapy	Men + women	N/A
Powers et al. (2009)	Yohimbine hydrochloride 10.8 mg	60 Min before exposure therapy	Men + women	N/A
Smits et al. (2014)	Yohimbine hydrochloride 10.8 mg	60 Min before exposure therapy	Men + women	N/A
Soravia et al. (2006)	Exp. 1: cortisone 25 mg Exp. 2: hydrocortisone 10 mg	60 Min before exposure therapy	Men + women	Exp. 1: 2–5 PM Exp. 2: 5–7 PM
Soravia et al. (2014)	Hydrocortisone 20 mg	60 Min before exposure therapy	Men + women (LU)	6–9 PM
Effects of stress on fear memory retrieval				
Hamacher-Dang et al. (2015)	SECPT	Immediately after extinction and 24 hr before retrieval	Men	12:30–5:45 PM
Merz et al. (2014a)	SECPT	20 Min before retrieval	Men	1:30–4:30 PM
Raio et al. (2014)	CPT	12 Min before retrieval	Men + women	12–5 PM
Suris et al. (2010)	Hydrocortisone sodium succinate 4 mg/kg i.v.	Immediately after reactivation	Men	N/A

*OC, oral contraceptives; ME, mensis; FO, follicular phase; LU, luteal phase; FC, free-cycling; TSST, Trier Social Stress Test; CPT, cold pressor test; SECPT, socially evaluated cold pressor test). Please note that this review and this table only contain a selection of studies conducted in this area.

emotionally arousing information is affected especially (Wolf, 2009). Again, stress effects seem to be more pronounced in men than in women (Andreano and Cahill, 2006; Yonelinas et al., 2011; McCullough and Yonelinas, 2013). In more detail, Andreano and Cahill (2006) report that stress induction after encoding of a neutral story led to enhanced memory retrieval in men but not in women. In addition, a quadratic relationship between cortisol release and memory retrieval was observed only in men. However, in two studies, stress facilitated episodic memory consolidation in women tested in the midluteal phase, in which estradiol and progesterone concentrations are high and HPA responsivity might be most pronounced (Andreano et al., 2008; Felmingham et al., 2012). Women taking hormonal contraceptives seem to have a better memory when the SNS, but not the HPA axis, is activated after initial encoding (Nielsen et al., 2013; but see Nielsen et al., 2014). All in all, postencoding stress and its associated rise in cortisol facilitate memory consolidation; women examined in the luteal phase as well as men appear to benefit from increases in stress hormone concentrations after learning.

Effects of Stress and Sex Hormones on Fear Memory Formation

As with the findings for episodic memory encoding, it is not yet clear how stress hormones affect fear acquisition, but here again the timing of stress exposure also appears to be important. Exposure to stress leads rapidly to an activation of the SNS and the accompanying release of (nor)adrenaline (see Fig. 1), which seems to be associated with increased conditioned fear (Antov et al., 2013). In accordance with this, enhanced noradrenergic stimulation by the α 2-adrenoreceptor antagonist yohimbine increased fear memories as evidenced by slower extinction learning, heightened reinstatement, and facilitated fear reacquisition (Soeter and Kindt, 2011).

The cortisol stress response, in contrast, appears to be negatively correlated with fear acquisition (Antov et al., 2013). This is in line with findings showing that, 30 min after exposure to stress, cortisol responses are negatively associated with amygdala activation (Oei et al., 2012). However, it has to be noted that all of these studies were conducted in men only. In line with animal data on eye-blink and fear conditioning (Shors, 2004; Dalla and Shors, 2009), accumulating evidence in humans suggests sex differences in stress effects on fear memory formation. For example, exposure to stress 1 hr before fear acquisition increased fear responses in men but inhibited fear learning in women (Jackson et al., 2006). Stress-induced cortisol elevations observed after fear acquisition consistently facilitated fear memory consolidation in men (Zorawski et al., 2005, 2006; Merz et al., 2014b) but not in women (Zorawski et al., 2005, 2006). When fear acquisition took place 45 min after stress onset, no differences between groups differing in sex hormone status occurred in fear acquisition and subsequent extinction (Antov and Stockhorst, 2014).

TABLE II. Overview of Experimental Details To Be Considered in Future Research Projects on the Impact of Sex and Stress Hormones on Emotional Learning Processes

Women specific	<p>For free-cycling women: validation of sex hormone status by analyses of sex hormones (if possible) and subjective report (day of onset of the last/next menstruation; cf. Allen et al., 2016; Merz et al., 2012) to allocate them to the correct stage of the menstrual cycle (menses, follicular phase, ovulation, luteal phase)</p> <p>For OC women: consider scheduling testing days during the pill-intake phase, inclusion of monophasic preparations vs. bi-/tri-/quattrophasic preparations with increasing concentrations of sex hormones, preparations containing a gestagen with an MR-antagonistic profile (cf. Genazzani et al., 2007)</p> <p>Consider hormonal contraceptive methods apart from OCs such as vaginal contraceptive rings, hormone spirals, hormone rods, or injectable depot contraceptives</p> <p>Consider age as a confounding factor due to varying sex hormone concentrations across different stages of life (e.g. before/during/after puberty, adulthood, after menopause)</p>
Stress specific	<p>Consider the time course of the neuroendocrine stress response relative to the experimental task (cf. Fig. 1)</p> <p>Consider the experimental stressor to be used</p> <p>Consider the pharmaceutical to be used to manipulate the stress reaction (e.g., based on affinity and/or half-life) and the exact dosage (same dosage for all participants vs. individually adjusted)</p> <p>Consider the following sources of variance: age; nicotine, coffee, alcohol, and medication intake; genetic factors; personality factors; time of day (cf. Kudielka et al., 2009)</p>

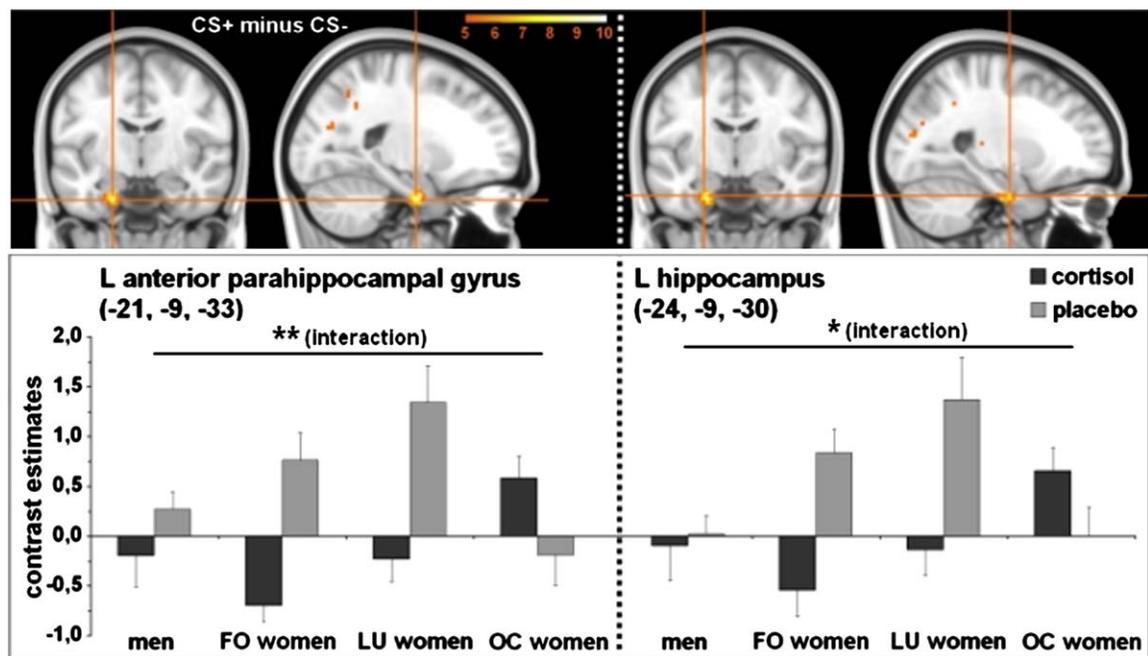


Fig. 3. Administration of 30 mg cortisol leads to a sex hormone-dependent effect on fear memory formation (contrast CS+ minus CS-) in the left (L) anterior parahippocampal gyrus and the hippocampus. For demonstration purposes, a threshold of $F \geq 5.0$ was applied to the data (see color bar for exact F values), which are displayed on the standard MNI brain template. In the bar graphs, mean (\pm SEM) contrast estimates for CS+ minus CS- are depicted for men, women in the follicular (FO) and in the luteal (LU) phases, and women taking oral contraceptives (OC). They are shown in separate

panels for the cortisol and the placebo groups in the peak voxel of the anterior parahippocampal gyrus and the hippocampus. Cortisol reduced the CS+/CS- differentiation in both brain regions in men, FO, and LU women but enhanced it in OC women. $*P < 0.05$; $**P < 0.005$ for the treatment \times 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.

Pharmacological studies also showed that GCs differentially modulate fear learning and memory processes in men and women. Cortisol administration reduced activation of the fear network in men and free-cycling women (tested in the follicular and luteal phases) but heightened fear-related brain activity in OC women

(Stark et al., 2006; Merz et al., 2010a, 2012; Tabbert et al., 2010; see Fig. 3). Notably, exposure to a psychosocial laboratory stressor (the TSST) led to the same pattern of results: whereas stress attenuated the fear circuit in men, it increased neural fear responses in OC women, e.g., in the amygdala (Merz et al., 2013; see Fig. 4).

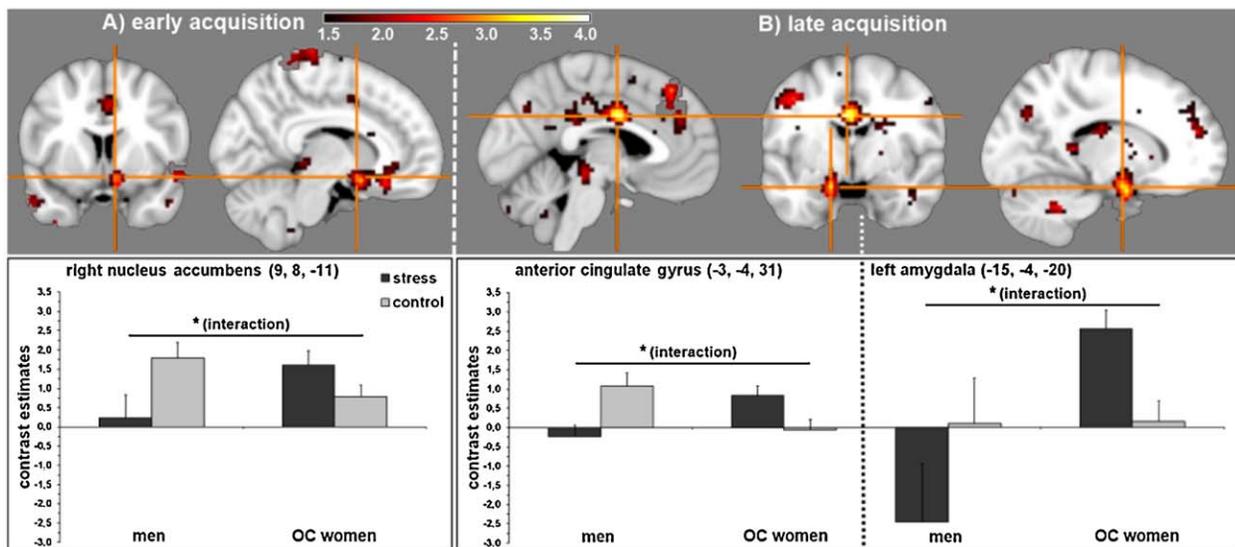


Fig. 4. Exposure to the TSST leads to a sex-dependent effect on fear memory formation (contrast CS+ minus CS-) in the right nucleus accumbens during early acquisition (A) and in the anterior cingulate gyrus and the left amygdala during late acquisition (B). Stress reduced the CS+/CS- differentiation in all three brain regions in men but enhanced it in women taking oral contraceptives (OC). A threshold of $T \geq 1.5$ was applied to the data (see color bar for exact T values), which are displayed on the standard MNI brain template. In the bar graphs,

mean (\pm SEM) contrast estimates for CS+ minus CS- are depicted for men and OC women in the peak voxels, with separate panels for the stress and the control group. $*P < 0.05$ for the treatment \times sex interaction. Reprinted from Merz CJ, Wolf OT, Schweckendiek J, Klucken T, Vaitl D, Stark R. 2013. Stress differentially affects fear conditioning in men and women. *Psychoneuroendocrinology* 38:2529–2541, with permission from Elsevier.

Moreover, cortisol reduced fear contextualization and intensified fear generalization in OC women, whereas the opposite pattern was observed in men (van Ast et al., 2012). Such cortisol-induced deficits in fear contextualization could enhance the vulnerability for anxiety disorders and PTSD, as discussed elsewhere with respect to low estrogen levels (Lebron-Milad and Milad, 2012; Lebron-Milad et al., 2012).

In conclusion, activation of the SNS typically enhances fear memory formation. When cortisol concentrations peak shortly before or during fear acquisition, they might inhibit the fear network surrounding the amygdala in men and free-cycling women. However, stress or cortisol administration seems to increase fear-associated brain activation in OC women. The influence of stress on basic emotional learning mechanisms (just as in episodic memory) hence appears to vary substantially in women as a function of sex hormone status at the time of testing. Clinically, these altered fear learning processes might translate into vulnerability factors for the acquisition of an anxiety disorder or PTSD, which should be properly investigated in future studies. However, it is still largely unknown how exactly stress and sex hormones interact in different brain areas influencing fear memory consolidation.

Effects of Stress and Sex Hormones on Episodic Memory Retrieval, Fear Extinction and Retrieval, and Their Clinical Applications

Episodic memory retrieval. Impaired episodic memory retrieval is observed after stress induction (Kuhl-

mann et al., 2005b; Smeets et al., 2008; Tollenaar et al., 2008; Merz et al., 2010b) or cortisol administration (de Quervain et al., 2000; see Het et al., 2005, for a meta-analysis), in particular for emotionally arousing material (Wolf, 2009). With regard to a possible interaction with sex hormones, this cortisol-induced retrieval deficit was also shown in women tested in the follicular phase (Kuhlmann et al., 2005a), in the luteal phase, and during menses but not in OC women (Kuhlmann and Wolf, 2005). Presumably, exogenous sex hormones contained in OCs can directly or indirectly reduce central GC sensitivity. In addition, exposure to stress also reduces memory retrieval in women examined in the follicular or luteal phase, even though the association between cortisol increase and memory was evident only in the follicular phase (Maki et al., 2015). In partial agreement, stress did not affect retrieval performance in women tested in the luteal phase (Schoofs and Wolf, 2009). Stress-induced increases in free cortisol concentrations are heightened in the luteal phase (Kirschbaum et al., 1999) in which HPA axis feedback and peripheral GC sensitivity are decreased (Altemus et al., 1997; Rohleder et al., 2001). This reduced peripheral GC sensitivity might go along with a slightly reduced central GC sensitivity (cf. Rohleder et al., 2009) and explain the absence of a stress-induced retrieval deficit in women in the luteal phase (cf. Schoofs and Wolf, 2009). However, the attenuated GC sensitivity in the luteal phase does not seem capable of abolishing the effects of supraphysiological cortisol concentrations on memory retrieval after pharmacological administration (Kuhlmann and Wolf, 2005).

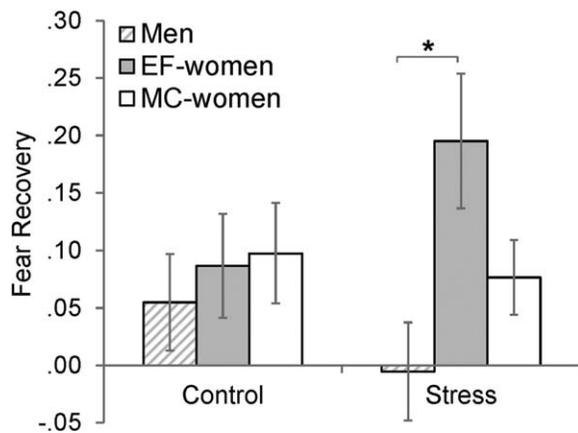


Fig. 5. Exposure to stress prior to fear acquisition and extinction leads to a sex hormone-dependent fear recovery on the next day. Fear recovery represents the difference between mean differential skin conductance responses (CS+ minus CS-) during early recall on day 2 and late extinction on day 1. Bar graphs depict mean (\pm SEM) fear recovery for men as well as women tested during the early follicular phase (EF) and midcycle (MC), with separate panels for the control and the stress groups. * $P < 0.05$ stress enhanced fear recovery in EF-women compared with men. Slightly modified from Antov MI, 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, with permission from Elsevier.

Fear extinction and retrieval. These findings regarding the influence of stress and sex hormones on episodic memory may help in interpreting results from fear extinction and retrieval studies, in which similar mechanisms might be involved (Nees et al., 2015). Notably, the effects of stress hormones, particularly in interaction with sex hormones, on fear extinction and retrieval processes can be made only cautiously because only a few experiments on this topic have been carried out so far. In a study including only OC women, cortisol administration before fear acquisition enhanced fear-related neuronal activation during fear acquisition but attenuated amygdala and hippocampus activation during subsequent extinction learning (Tabbert et al., 2010). In addition, psychosocial stress before acquisition and subsequent extinction also had a differential impact on fear retrieval on the next day in men and women depending on the women's menstrual cycle stage (early follicular vs. midcycle phase; Antov and Stockhorst, 2014). Fear retrieval in the stress group was higher in women in the early follicular phase compared with men (see Fig. 5), suggesting low levels of circulating female sex hormones (either from low levels during the follicular phase or from OC intake) in combination with stress to contribute to resistance to extinction (cf. Maeng and Milad, 2015).

However, the direct impact of stress mediators on extinction or retrieval could not be ascertained in these studies, because stress hormones might also have strengthened consolidation of the previously acquired fear. For a less confounded assessment, extinction and prior stress hormone increases must be separated from fear acquisition,

as was realized by Bentz and colleagues (2013). They report acute stress to reduce fear retrieval (observed during early extinction, which was maintained at early fear retrieval the next day) in the form of UCS expectancy in men but not in OC women. Again, OC women might not be influenced by stress hormone effects on emotional memory retrieval, as in the case of episodic memory, because of a direct and/or indirect reduction of central GC sensitivity (see above; Kuhlmann and Wolf, 2005).

Clinical applications. Because extinction learning is the experimental analogue to exposure therapy, patient studies can shed light on translational and applied aspects of using stress hormones as an adjunct to exposure sessions. Indeed, clinical studies showed beneficial effects of cortisol on extinction-based interventions. Male and female patients with spider, heights, or social phobia (Soravia et al., 2006, 2014; de Quervain et al., 2011) reported less fear after exposure sessions as well as at followup without medication. These important findings can be explained with the help of the literature on episodic memory (see above; de Quervain and Margraf, 2008; Bentz et al., 2010): although cortisol reduced fear retrieval when patients encountered their feared stimulus during exposure therapy, they could simultaneously consolidate the corrected information better (less fear). In addition to the HPA axis marker cortisol, pharmacologically increased noradrenergic (SNS) activity before exposure therapy also attenuated fear at followup in male and female patients with claustrophobia (Powers et al., 2009) or social phobia (Smits et al., 2014) but not in patients with fear of flying when exposure took place in virtual reality (Meyerbroeker et al., 2012). However, none of these clinical studies differentiated according to different phases of the menstrual cycle or OC usage (except for Soravia et al., 2014, who did not include OC women). It seems that clinical findings indicate cortisol to be a beneficial adjunct for exposure therapy applying to both men and women. However, opposing or null effects in distinct phases of the menstrual cycle or under OC usage cannot be excluded.

A recent study extended these findings to OC women with spider phobia (Lass-Hennemann and Michael, 2014), making use of the circadian cortisol rhythm. Exposure therapy was conducted either in the morning with the associated high cortisol levels or in the afternoon when cortisol levels are low. Indeed, exposure during high endogenous cortisol concentrations led to a more pronounced reduction of phobic fear. Another study in male and female patients with panic disorder and agoraphobia observed an association between high cortisol levels after awakening and better exposure-therapy outcome (Meuret et al., 2015).

A mechanistic interpretation of these intervention studies is hindered by the fact that the effects of stress or cortisol administration might have both reduced fear retrieval during the first encounter with the phobic stimulus and enhanced extinction consolidation simultaneously; thus, a distinct separation between these different learning phases cannot be made. This question can, however, be

addressed in laboratory studies. In a recent study, we tested the influence of stress on extinction consolidation in a 3-day renewal design (Hamacher-Dang et al., 2015). During retrieval, the group exposed to stress after extinction showed an increased return of fear in the acquisition but not in the extinction context. We hypothesized that stress facilitated the integration of contextual cues into long-term memory. With the same design, the effects of stress on fear retrieval were tested, changing the timing of stress from postextinction to preretrieval (Merz et al., 2014a). Now, stress attenuated fear retrieval in the acquisition context and also generally lowered skin conductance responses in the extinction context. This finding is in line with a stress-induced retrieval impairment of emotional memories. Results support the aforementioned clinical observations (Soravia et al., 2006, 2014; de Quervain et al., 2011; Lass-Hennemann and Michael, 2014; but see Raio et al., 2014). A similar effect was found in patients with PTSD: exposure therapy followed by GC infusion beneficially affected symptoms at 1 week but not at 1 month later (Suris et al., 2010). However, male participants only were investigated in this study. In a recent study conducted in our laboratory using a predictive learning task, cortisol administration disrupted vmPFC functioning during the retrieval of previously acquired associations in men but not in OC women (Kinner et al., 2016), suggesting effects of OC usage similar to those observed during fear acquisition (see above).

SUMMARY

Altogether, clinical studies suggest a fear-reducing effect of high cortisol concentrations on phobic fear, a finding mirrored in data from healthy men. Mechanistically, stress hormones appear to reduce fear retrieval and enhance the consolidation of extinction, similar to the impact of stress on episodic memory. It remains to be shown whether these effects extend to all phobias and which boundary conditions have to be considered. In addition, low endogenous levels of circulating estradiol have been linked to deficient extinction learning as evidenced by increased fear retrieval, which might be interpreted in terms of a vulnerability factor for developing PTSD (cf. Lebron-Milad and Milad, 2012; Lebron-Milad et al., 2012). Future studies should thus particularly focus on the investigation of the menstrual cycle and OC intake (cf. Maeng and Milad, 2015) but also on the exact timing of cortisol application/stress induction/time of day and the specific increase in cortisol concentrations necessary for beneficial effects to occur as well as the complex interactions between these critical variables.

GENERAL CONCLUSIONS AND OUTLOOK

Stress influences episodic memory as well as fear conditioning. Stress hormones inhibit retrieval and enhance consolidation in episodic memory, particularly for emotionally arousing information. Similar effects are observed in fear conditioning paradigms, which also induce emotional arousal. In both cases, existing data suggest that OC

intake either weakens the observed effects of stress or cortisol administration (such as in episodic memory) or even reverses them (such as in fear conditioning) in OC women compared with men.

A possible hypothesis explaining these effects might be as follows: OCs contain ethinylestradiol, binding to estrogen receptors, and a gestagenic component, binding to progesterin receptors. The greater binding of estradiol and/or progesterone after continuous OC intake might lead to a subsequent downregulation and/or desensitization of these receptors in various brain structures mediating emotional learning and memory processes. Stress or cortisol administration, however, could reverse this reduced excitability, allowing more pronounced learning processes compared with conditions without stress. In contrast, these receptors are not continuously stimulated in men and free-cycling women, consequently allowing learning and memory processes to function properly in the absence of stress.

However, the influence of stress and sex hormones has largely been neglected in research on emotional learning and memory processes, even though initial studies have found important interactions between the HPA and the HPG axes. Occasionally, opposing effects in different groups of women have been observed, which should be considered when trying to understand the basic mechanisms of stress-related mental disorders such as PTSD as well as everyday stressful events such as giving an oral presentation (cf. Merz and Wolf, 2015).

Prospectively, we must disentangle whether the observed memory effects are based on differing stress responses or on an altered central GC sensitivity (or both). Future studies should focus on the investigation of women in different stages of the menstrual cycle and of OC women (cf. Table II). For OC women, the existence of quite different hormonal regimes adds another level of complexity. Critical factors facilitating extinction learning should be identified, such as stress hormones (de Quervain and Margraf, 2008; Bentz et al. 2010) or fluctuating sex hormone concentrations over the course of the menstrual cycle (Lebron-Milad and Milad, 2012; Maeng and Milad, 2015) and their interactions (see Stockhorst and Antov, 2016, for a review including additional mediators). Such future experiments are clearly needed to explain the differences between men and women in the prevalence for acquiring and maintaining stress-associated disorders such as PTSD on the neurobiological level. These insights into emotional learning and memory processes are also crucial for the improvement of therapy strategies in the context of an individualized treatment (personalized medicine; cf. Hamburg and Collins, 2010) of patients with anxiety disorders or PTSD.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

ROLE OF AUTHORS

Drafting of the manuscript: CJM, OTW; critical revision of the manuscript for important intellectual content: CJM, OTW.

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