Sex Differences in the Central Nervous System

Edited by
Rebecca M. Shansky

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Edited by

REBECCA M. SHANSKY
Northeastern University, Boston, MA, USA

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CHAPTER 7

Stress and Emotional Learning in Humans: Evidence for Sex Differences

Christian J. Merz, Oliver T. Wolf
Ruhr-University Bochum, Institute of Cognitive Neuroscience, Department of Cognitive Psychology, Bochum, Germany

1 INTRODUCTION

Stress has been conceptually defined as a response to a threat to homeostasis. In humans, psychosocial stressors are especially powerful. A threat to the social self (social evaluative threat) in combination with uncontrollability of the situation is especially potent in prompting stress (Dickerson and Kemeny, 2004). In the laboratory, stress can be induced by means of public speaking paradigms such as the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), or by painful manipulations (immersion of the hand into ice water) such as the cold pressor test (CPT) or the later-developed socially evaluated CPT (Schwabe et al., 2008).

It has been suggested that women and men differ in how they respond to stressors, based upon endocrinological and behavioral responses (Taylor et al., 2000). These differences might translate into vulnerabilities for distinct stress-associated psychiatric disorders. Compared with men, women have, for example, a higher risk for major depression, posttraumatic stress disorder (PTSD), and several anxiety disorders, but a lower prevalence in schizophrenia, substance abuse, and autism (Cover et al., 2014).

When discussing possible sex differences in how stressors affect learning and memory, two possible scenarios should be considered. On the one hand, sex differences might occur because the two sexes differ in their endocrinological response to a stressor. Alternatively, or additionally, sex differences might reflect a different responsivity of the brain to the same neuroendocrine stress signal (e.g., glucocorticoids).

Endocrinologically, both sexes generally respond to stressors with an activation of the two major stress systems, the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenocortical (HPA) axis (see Figure 7.1). The SNS initiates a rapid first stress response wave, which is dominated by the effects of (nor)adrenaline released from the adrenal medulla. Increases in heart rate and breathing frequency prepare the body for action. This initial response has been conceptualized as the fight or flight response (Cannon, 1932).

Slightly delayed, at least with respect to its adrenal end product, the HPA axis also responds. Corticotropin-releasing hormone (CRH), released from the hypothalamus, works to stimulate the secretion of adrenocorticotropin (ACTH) in conjunction with

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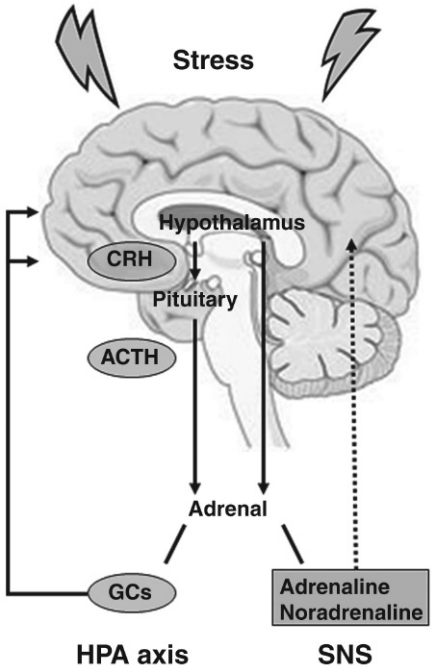

Figure 7.1 ***Stress activates two lines of defense mechanisms: the rapidly acting sympathetic nervous system (SNS) and the slower hypothalamic–pituitary–adrenocortical (HPA) axis.*** Activation of the hypothalamus stimulates the SNS to secrete (nor)adrenaline from the adrenal medulla. The hypothalamus also releases CRH, which stimulates the secretion of adrenocorticotropin (ACTH) from the anterior pituitary gland into the blood stream. ACTH stimulates the adrenal cortex to release glucocorticoids (GCs), which can easily pass the blood–brain barrier and modulate brain functions involved in learning and memory. GCs exert negative feedback effects on the hypothalamus and the pituitary gland, leading to reduced activity of the HPA axis.

arginine vasopressin (Joëls and Baram, 2009). ACTH in turn stimulates the synthesis and release of glucocorticoids (GCs; mainly cortisol in humans) from the adrenal cortex. The neuroendocrine stress response is regulated by circulating GCs via negative feedback mechanisms targeting the pituitary, the hypothalamus, the hippocampus, and prefrontal areas (Ulrich-Lai and Herman, 2009). This negative feedback loop is essential for the regulation of both the HPA axis and the stress response (De Kloet et al., 2005). GCs mediate their effects by binding to two subtypes of intracellular receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). These two receptors differ in their affinity and distribution within the brain: while MRs are mainly located in the hippocampus, GRs are expressed throughout the brain, for example, in the prefrontal cortex. In addition, membrane-bound GRs and MRs have also been identified (Joëls et al., 2008; Roozendaal et al., 2010). Due to their prominence throughout the brain, corticoid receptors modulate several cognitive processes, including memory. While most

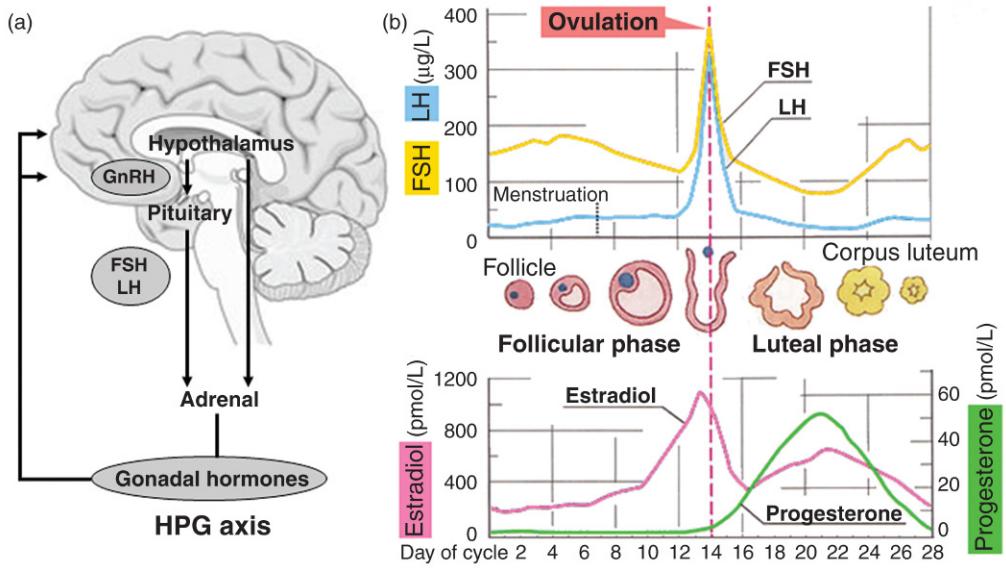

Figure 7.2 (a) The hypothalamus controls the release of gonadal hormones via the hypothalamic–pituitary–gonadal (HPG) axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland into the blood stream. The gonads secrete gonadal hormones, which exert negative feedback effects on the hypothalamus and the pituitary gland. (b) In women, secretion of hormones from the HPG axis is subject to changes over the menstrual cycle. In the follicular phase, low levels of the gonadal hormone estradiol are present, which rise midcycle to initiate ovulation. After that, the following luteal phase is characterized by higher estradiol as well as progesterone concentrations. The pituitary hormones LH and FSH show peak concentrations during ovulation.

of the effects associated with GCs – especially when related to stress – have been attributed to GR, the importance of MRs has also been emphasized (Joëls et al., 2008). The newly discovered membrane bound MR in particular might be responsible for some of the rapid effects of acute stress on memory discussed in the present chapter.

The hypothalamic–pituitary–gonadal (HPG) axis controls the release of the gonadal hormones estradiol, progesterone, and testosterone from the ovaries and testes. Regarding the course of the menstrual cycle, estradiol concentrations peak in the middle of the cycle around ovulation, while progesterone concentrations increase in the second half of the cycle (in the luteal phase; see Figure 7.2). The HPG axis is influenced by acute and, even more pronounced, chronic stress. In turn, it also influences the HPA axis.

It is well established that the HPA axis response is modulated by gonadal steroids (Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005; Taylor et al., 2000). Experimental studies in humans using psychosocial laboratory stressors such as the TSST have often observed that men show a stronger HPA axis response to the stressor than women (Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005). However, this

might depend on the specific paradigm used (Stroud et al., 2002). No strong overall influence of sex on the cortisol response to laboratory stressors could be detected in a large meta-analysis, which, however, was not able to investigate a possible influence of menstrual cycle and hormonal contraceptives (Dickerson and Kemeny, 2004).

In women, fluctuations of gonadal hormones during the menstrual cycle seem to modulate the HPA axis response. A more pronounced HPA axis response to stressors is observed during the luteal phase (Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005), characterized by elevated progesterone and estradiol levels. The situation in humans is further complicated by the fact that hormonal contraceptives 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 salivary free cortisol response of women using hormonal contraceptives is displayed in Figure 7.3.

In conclusion, gonadal steroids impact HPA axis reactivity in humans as a result of the complex interaction between the HPA and HPG axes. Furthermore, hormones released by both axes can influence the brain and cognition. However, many experimental studies in humans have been conducted exclusively with men. Moreover, in studies with

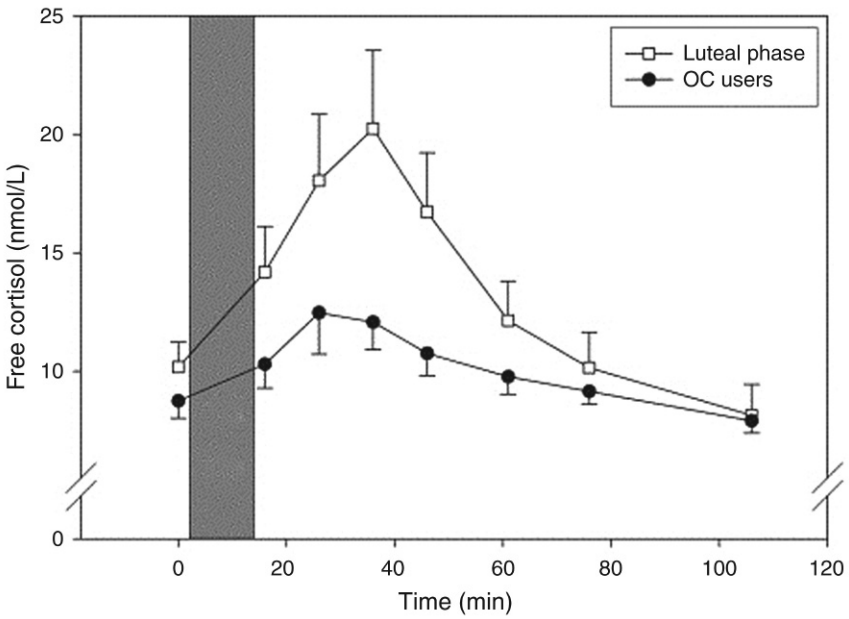

Figure 7.3 ***Exposure to a standardized psychosocial stress protocol (Trier Social Stress Test, TSST) leads to increases in free cortisol concentrations over time.*** Women in the luteal phase of the menstrual cycle exhibit higher cortisol increases compared with women taking oral contraceptives (OCs) who typically show blunted cortisol responses in saliva. *(Reprinted from Rohleder et al. (2003). With permission from Elsevier.)*

women, information about menstrual cycle phase and/or hormonal contraception is often not taken into account in the experimental design (Beckner et al., 2006; Smeets et al., 2006). Similarly, most studies in rodents focus exclusively on males when examining stress effects on memory.

In the present chapter, we will review the literature concerning the impact of stress hormones on learning and memory processes in humans. Particularly, we will focus on episodic memory and fear conditioning, two forms of long-term memory, for which some data are available on the influence of gonadal hormones and the intake of hormonal contraceptives.

2 EPISODIC MEMORY

Episodic memory relies heavily on intact medial temporal lobes, including the most recognized structure for memory: the hippocampus (Nadel and Moscovitch, 1997). Personal individual events of the past, such as the party on your 18th birthday or the day of your driving test, are stored in your episodic memory. In general, three stages of memory processing can be identified (Tulving, 1983): (1) encoding: transformation of incoming information into a memory representation, (2) consolidation: modification and stabilization of this representation, and (3) retrieval: reactivation of the stored memory trace.

Stress and stress hormones exert numerous effects on these memory stages in humans. Typically, stress impairs memory retrieval, but enhances consolidation processes. The effects on encoding seem to depend on various factors. Emotionally arousing stimuli in particular are affected by stress, which is explained by an interaction between GCs and an activation of the SNS affecting the amygdala and the hippocampus (Roozendaal et al., 2009). In the following sections, we will delineate these different effects. After brief introductions to the overall picture in each memory stage, we will concentrate on experimental studies focusing on sex differences in episodic memory after exposure to stress or administration of cortisol.

2.1 Encoding

Generally, findings on pre-encoding stress have revealed enhancing, impairing, and absent effects of stress. Several ideas have been proposed to explain these results. The first refers to the timing of the stressor relative to the learning session. Exposure to stress a relatively long time before encoding exerts detrimental effects on memory, whereas stress taking place directly before or as part of the learning session facilitates memory encoding (for reviews see Joëls, 2006; Schwabe and Wolf, 2013). Stress within the learning context situation helps the individual to better retrieve this memory at a later point in time. The second idea is time of day: a meta-analysis found impaired memory when acute cortisol administration was set before encoding in the morning, but the

reversed effect was found when cortisol administration took place in the afternoon (Het et al., 2005). Since cortisol concentrations are subject to a circadian rhythm, with high levels in the morning declining over the course of the day, adding cortisol to these already relatively high endogenous concentrations in the morning seems to have negative effects on memory. The third idea concerns emotionality of the stimulus material: pre-encoding stress or cortisol application leads to a superior encoding and/or consolidation of emotionally arousing material (Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006; Payne et al., 2007; Rimmele et al., 2003; Wolf, 2012), whereas nonarousing information is stored less efficiently (Kuhlmann and Wolf, 2006; Payne et al., 2007; Rimmele et al., 2003; Smeets et al., 2006). Thus, a stressor can potentiate the impact of stimulus emotionality on long-term memory.

Now let us turn to those studies reporting sex differences and the impact of circulating gonadal hormones. Cornelisse et al. (2011) investigated men and women encoding neutral and emotional pictures after stress induction using the TSST. One week later, men in the stress condition showed better memory for emotional pictures compared with men in the control condition. This effect was not found for neutral pictures or in the female group. The latter fact is interesting – why should women not display a stress effect? One explanation could be that more than two-thirds of the female participants used hormonal contraceptives, which are associated with a substantially blunted free cortisol stress response (see "Introduction"). In both sexes, the cortisol stress response was correlated with the enhanced emotional memory recognition suggesting that indeed differences in cortisol concentrations underlie the observed sex differences in this study rather than different effects of cortisol on the brain.

In general, pooling groups of women with and without hormonal contraceptive usage into one group might cancel out potential effects of circulating (endogenous and exogenous) gonadal hormones. Indeed, a separation of women into different groups of free-cycling women and women taking hormonal contraceptives is needed to allow for a more detailed understanding of the influence of circulating gonadal hormones. Unfortunately, only few studies have included a closer description of their female sample up to now, so that the picture remains inconclusive, at least at the moment.

One experiment in men and women taking oral contraceptives was able to show that cold pressor stress before the learning session increased memory in men and women taking oral contraceptives (Schwabe et al., 2008), suggesting that, regarding cognitive performance, both groups might respond to stress in a similar fashion. However, this pattern was not confirmed in a study clearly differentiating women according to the stage of their menstrual cycle (follicular and luteal phase) and the intake of oral contraceptives (Espin et al., 2013). Under control conditions, all of these female groups remembered more neutral words compared with men. Exposure to stress before encoding and directly following retrieval disrupted this sex difference, which could be traced back to an enhanced performance after stress in men, but no change after stress in the three groups

of women. However, stress induction only increased cortisol concentrations in women in the luteal phase (limiting the conclusions to be drawn from this study). In the same group of women, a correlation was found between the cortisol increase after stress and poorer performance. This finding contrasts a previous study showing that stress-induced cortisol increases were negatively correlated with memory performance in men, but not in women tested in the luteal phase (Wolf et al., 2001).

In conclusion, many studies investigating stress effects on encoding have investigated men only (Nater et al., 2007; Quaedflieg et al., 2013; Tops et al., 2003) or men and women but without reporting details regarding the female sample and also without explicitly testing for sex differences (Rimmele et al., 2003; Zoladz et al., 2011). Only a small number of experiments have outlined details on menstrual cycle or usage of hormonal contraceptives in women and at the same time looked at potential group differences, but these studies do not yield a consistent picture. A tentative conclusion based on the available data is that the effects of stress on encoding are more robust in men compared with women.

2.2 Consolidation

Experimental elevation of stress hormones after a learning episode typically leads to enhanced memory for this information, especially for emotionally arousing material (Wolf, 2009). This effect can be observed when female and male participants are exposed to stress (Beckner et al., 2006; Cahill et al., 2003; Preuss and Wolf, 2009; Smeets et al., 2006). From an evolutionary point of view, the facilitation of memory consolidation after a stressful event clearly serves adaptation: better memory for a dangerous situation helps individuals to initiate adequate survival mechanisms when later encountering a comparable threatening situation (De Kloet et al., 2005; McEwen, 1998).

Looking closer at potential underlying sex differences, the positive effect of postencoding stress on later familiarity-based recognition has been reported by one research group to occur in men, but not in women (McCullough and Yonelinas, 2013; Yonelinas et al., 2011). It is worth mentioning that men and women exhibited similar cortisol increases in response to stress in both of the studies mentioned, so an explanation for the above-mentioned discrepancy cannot be derived from differing cortisol responses. Thus, differences in the sensitivity to stress hormones appear to be the most likely explanation.

In addition, another study found an inverted U relationship between a stress-induced cortisol increase and memory for a neutral story in men (Andreano and Cahill, 2006), while no relationship was evident in women. Felmingham et al. (2012b) found a similar enhancing effect of postlearning stress for nonarousing images in men. In free-cycling women, on the other hand, the increase in stress hormones after encoding was positively related to later memory recall of emotionally arousing images. Again, cortisol responses to the stressor were comparable in men and women. A similar study revealed that stress enhances memory consolidation for emotionally arousing images when women are tested

in the midluteal phase, in which estradiol and progesterone concentrations are high, but not in women tested in other phases of the menstrual cycle, when progesterone is low (Felmingham et al., 2012a). In line with these results, a positive relationship between cortisol concentrations after encoding and an enhanced memory performance was only observed in women tested in the midluteal phase (Andreano et al., 2008; see Figure 7.4), but not in the early or late follicular phase. Thus, progesterone might represent an important player in modulating stress effects on memory consolidation in women. Of course, it cannot be ruled out that the effects observed in the midluteal phase are not solely due to progesterone increases in this phase. Relatively high estradiol levels might exert their effects only in the presence of high progesterone concentrations; both are present in the midluteal phase. Pharmacological interventions directly manipulating progesterone and/or

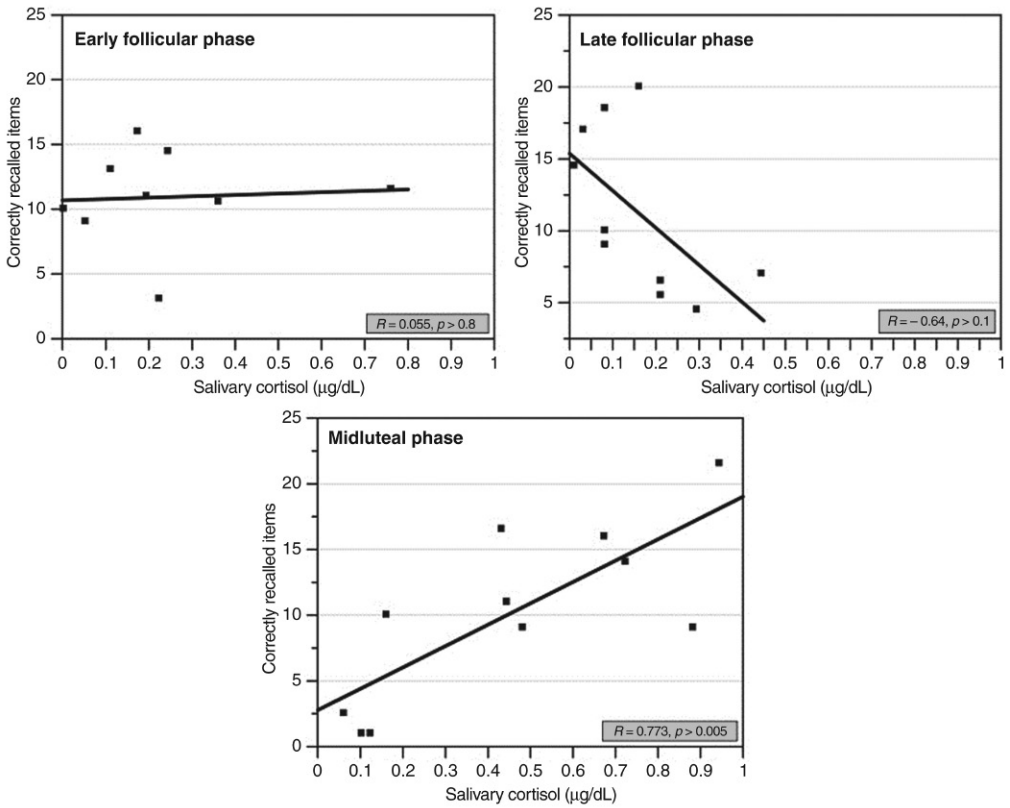

Figure 7.4 ***Association between salivary cortisol concentrations after stress induction (postlearning stress) and memory retrieval 1 week later in women in the early follicular, late follicular, and midluteal phases.*** A significant positive relationship occurred in the midluteal phase, whereas a trend toward the negative direction was observed in the early follicular phase. *(Slightly modified from Andreano et al. (2008). With permission from Elsevier.)*

estradiol levels would be desirable in order to understand the exact underlying gonadal hormone-related mechanisms.

Apart from differences due to gonadal hormones, the impact of oral contraceptives in stress effects on consolidation processes has also been investigated recently. In a study by Nielsen et al. (2013), free-cycling women and women taking hormonal contraceptives viewed neutral and emotionally arousing images before being exposed to cold pressor stress or a control procedure. The stressor was more effective in increasing cortisol concentrations in free-cycling women than in women taking hormonal contraceptives, who typically display relatively blunted free cortisol responses (Kirschbaum et al., 1999; Rohleder et al., 2003). Stress hormones did not facilitate memory consolidation of emotional pictures in any free-cycling women, but recall of nonarousing pictures 1 week later was heightened in those free-cycling women responding to the stressor with increased SNS and HPA axis activation. Women taking hormonal contraceptives tended to retrieve more emotionally arousing images when the SNS, but not the HPA axis, was activated. This rather complex pattern at least suggests that, in addition to the particular menstrual cycle phase, the interplay between the SNS and the HPA axis needs to be taken into account when trying to understand stress effects on memory consolidation in women. The second study on this issue once again confirmed that stress leads to enhanced memory consolidation for emotional material in free-cycling women (Nielsen et al., 2014). However, women taking hormonal contraceptives were not influenced in their memory performance by stress exposure at all. It seems that consolidation processes are subject to modulatory influences of stress and gonadal hormones in complex ways. This issue certainly needs to be investigated in future studies to gain greater insight into how memory is differentially consolidated in men and women under stressful conditions, which will also contribute to the understanding of factors leading to psychopathology after confrontation with a traumatic situation.

Taken together, stress hormones enhance memory consolidation, especially for emotionally arousing material. With regard to the potential influence of gonadal hormones, the limited literature on this issue assumes an enhancing effect of stress on consolidation in women with higher progesterone concentrations as present in the midluteal phase. In contrast, postencoding stress might cause a detrimental influence on memory performance in women in the late follicular phase. These presumably opposing effects could explain why sometimes no impact of stress on memory consolidation has been reported in women: the negative and positive effects of postlearning stress across the cycle may have cancelled each other out. These opposing influences occurring in different stages of the menstrual cycle must be further examined since they rely on studies with rather small sample sizes. In addition, the impact of hormonal contraceptives needs to be investigated in future studies; first findings indicate a differential effect of stress on memory consolidation in free-cycling women and in women taking hormonal contraceptives.

2.3 Retrieval

Generally, memory retrieval is reduced when persons are stressed (Kuhlmann et al., 2005b; Merz et al., 2010b; Smeets et al., 2006; Tollenaar et al., 2008) or when cortisol is administered prior to retrieval (De Quervain et al., 2000; see Het et al., 2005 for a meta-analysis). As in consolidation, emotionally arousing material is particularly affected (Wolf, 2009). From an evolutionary point of view, this stress-induced retrieval deficit might serve an adaptive purpose (Roozendaal, 2002): retrieval processes for prior information interfere with the encoding of new information (Allan and Allen, 2005); thus, a temporary reduction in retrieval allows for appropriate and efficient encoding and consolidation of the stressful and potentially threatening new event itself.

What do we know about the potential impact of sex differences and gonadal hormones on stress effects on memory retrieval? When men and free-cycling women across the whole menstrual cycle are studied together, there does not seem to be much of a difference in the overall picture (Rohleder et al., 2009; Schönfeld et al., 2014; Schwabe and Wolf, 2009; Smeets, 2011; Young et al., 2011). When women are tested in the follicular phase, the finding of cortisol-induced memory reduction of emotional material stays the same (Kuhlmann et al., 2005a). One study demonstrated that cortisol reduces the retrieval of emotional and neutral information in women investigated in the luteal phase and during menses but not in women taking oral contraceptives (Kuhlmann and Wolf, 2005; see Figure 7.5). These data have been interpreted to support the notion that

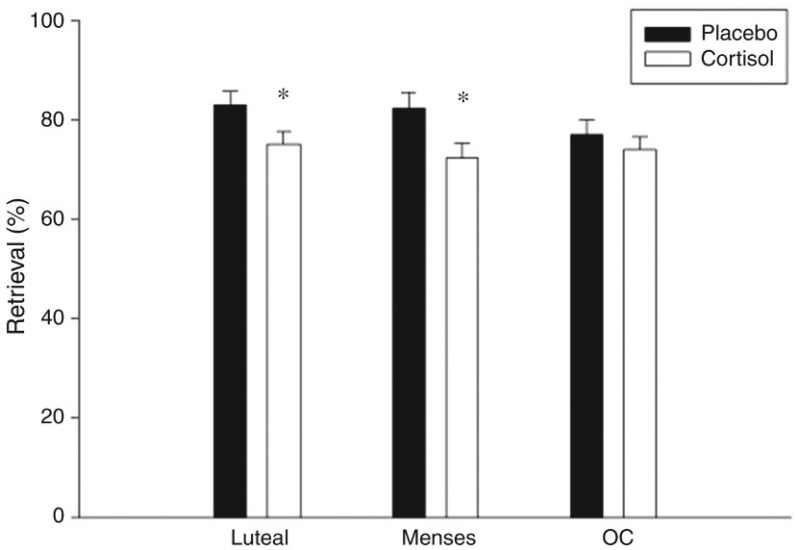

Figure 7.5 ***Effects of an oral administration of 30 mg cortisol on delayed free retrieval of words in women tested in the luteal phase, during menses, and in women taking oral contraceptives (OC).*** Cortisol significantly reduced memory retrieval in women in the luteal phase and during menses, but not in OC women. *$p < 0.05$. *(Reprinted from Kuhlmann and Wolf (2005). With kind permission from Springer Science and Business Media.)*

women using oral contraceptives exhibit a slightly reduced central GC sensitivity to cortisol. Oral contraceptives contain exogenous gonadal hormones, which could either directly or indirectly affect the sensitivity of the brain to GCs. This issue needs to be tackled in future work.

Apart from cortisol administration, exposure to stress also led to an interesting result in one study challenging some of the previously made conclusions. This study failed to observe the adverse effect of stress on memory retrieval in a group of women tested in the luteal phase (Schoofs and Wolf, 2009). In the luteal phase, stress-induced increases in free cortisol concentrations are heightened (Kirschbaum et al., 1999), while HPA feedback and peripheral GC sensitivity are decreased (Altemus et al., 1997; Rohleder et al., 2001). In light of results obtained by Schoofs and Wolf (2009), it could be speculated whether these reductions in peripheral GC sensitivity also transfer to central GC sensitivity (Rohleder et al., 2009). The absent effects of stress on memory retrieval in women investigated in the luteal phase can be interpreted as a reduced central sensitivity to stress-induced cortisol effects (Schoofs and Wolf, 2009). Cortisol administration inhibited memory retrieval in the luteal phase (Kuhlmann and Wolf, 2005), whereas stress did not (Schoofs and Wolf, 2009). Thus, GC sensitivity in women in the luteal phase might be slightly reduced thereby abolishing effects on memory retrieval induced by stress-related cortisol increases while not affecting effects induced by supraphysiological cortisol elevations after pharmacological administration.

All in all, it has been found that stress is typically associated with poorer memory retrieval, especially for emotionally arousing information. A small number of studies support the idea that the menstrual cycle and the intake of contraceptives might modulate the observed findings. In one of these studies, cortisol administration did not influence retrieval performance in women taking oral contraceptives, while in the other women in the luteal phase were not affected in memory retrieval after stress induction. Of course, these findings need to be replicated, but they emphasize the importance of paying attention to the modulatory impact of gonadal steroids on retrieval processes.

2.4 Interim conclusion on episodic memory

Taken together, we can conclude that stress differentially affects the three stages of episodic memory processing. Stress enhances the encoding of emotionally arousing material, whereas, at the same time, it might impair the encoding of nonarousing information. The timing of the stressor relative to the encoding is also critical for stress effects to occur. On the one hand, stress facilitates memory when applied shortly before or during learning, and on the other hand, it deteriorates memory when applied before encoding (e.g., at the peak of cortisol concentrations). Few studies have addressed the issue of possible sex differences of pre-encoding stress. The usage of hormonal contraceptives and its associated blunted free cortisol stress response appears to cause weaker effects of stress on memory.

Stress enhances consolidation processes but typically reduces retrieval, particularly retrieval of emotional material. Regarding consolidation, it has been suggested that

progesterone plays a critical role in the enhancing effects of stress; thus, women seem to benefit from postencoding stress especially when they are in the midluteal phase. At the same time, a different study reported that women in the luteal phase are not susceptible to the impairing effects of psychosocial stress (but not cortisol administration) on memory retrieval. Thus, women in the luteal phase benefit from the positive effect of stress on consolidation, but also from not being affected by the stress-inhibiting effect on memory retrieval. In addition, the usage of hormonal contraceptives appears to weaken the effects of cortisol on memory retrieval.

All in all, the existing literature indicates that stress and cortisol administration lead to more variable and smaller effects on long-term memory in women compared with men. The use of hormonal contraceptives, as well as elevated progesterone levels during the luteal phase, are important mediators. Interestingly, there is little overall evidence for an enhanced sensitivity to stress or stress hormones in women when it comes to hippocampal-based episodic memory. In Chapter 8, we will proceed to fear conditioning, another form of long-term memory relying on amygdala activity.

3 FEAR CONDITIONING

During classical conditioning, individuals learn that a typically neutral stimulus is paired with an aversive or pleasant event (unconditioned stimulus, UCS), which leads to an unconditioned response (e.g., fear; Pavlov, 1927). As a result of a couple of pairings of both stimuli, the originally neutral stimulus alone can trigger parts of the unconditioned response and is now termed the conditioned stimulus (CS). In this section, only fear conditioning studies using aversive events as the UCS (such as an electrical stimulation) will be presented. Fear conditioning processes are assumed to play a major role in the development of anxiety disorders as well as PTSD (Graham and Milad, 2011; Mineka and Oehlberg, 2008).

After initial fear memory formation with repeated couplings of the CS with the UCS, recurrent presentations of the CS without the UCS result in fear extinction leading to the suppression of conditioned fear. The most effective psychotherapeutic strategy to treat anxiety disorders, namely exposure therapy, in which patients are confronted with their phobic stimuli or situations, relies on fear extinction processes (Vervliet et al., 2013). But extinction training does not erase fear forever – fear is just temporarily not expressed. Individuals often experience a relapse of (pathological) fear, for example, after a change in context (renewal) (Bouton, 2004).

The amygdala is assumed to be the interspecies, core structure responsible for fear conditioning (LeDoux, 2000). In addition, the anterior cingulate cortex, the insula, the ventromedial prefrontal cortex, and the hippocampus constitute integral parts of the fear and extinction network (Mechias et al., 2010; Sehlmeyer et al., 2009). Intriguingly, patients with anxiety disorders or PTSD exhibit abnormalities in this fear circuitry

(Etkin and Wager, 2007; Graham and Milad, 2011). Because the prevalence of anxiety disorders and PTSD is substantially different in men and women (Cover et al., 2014), it is important to understand the neurobiological mechanisms of these sex differences in the underlying fear conditioning processes. Moreover, the impact of stress and stress hormones on the fear and extinction network as a function of sex needs to be elucidated. Generally, sex hormones seem to influence cortisol effects on fear learning. Additionally, high cortisol concentrations also inhibit fear retrieval. First, we will present results on the sex-dependent impact of stress hormones on fear memory formation and consolidation, and second, on extinction learning and the return of fear.

3.1 Fear memory formation and consolidation

Controversial findings exist regarding the question of whether and how stress and stress hormones affect fear learning; some studies have reported increased, others have reported reduced, conditioned fear memory after exposure to stress. Again, the timing of the stress exposure appears to be important. For example, exposure to stress rapidly leads to SNS activity and the accompanying release of (nor)adrenaline, which seems to be associated with increased conditioned fear (Antov et al., 2013). In line with these results, enhanced noradrenergic stimulation by the α2-adrenoreceptor antagonist, yohimbine, strengthens subsequent fear memory as shown by slower subsequent extinction learning, heightened fear retrieval after reinstatement, and augmented fear reacquisition (Soeter and Kindt, 2011).

In contrast to the influence of the rapidly developing SNS response, the slower cortisol response to a stressor appears to be negatively correlated with fear acquisition (Antov et al., 2013). This is consistent with findings showing that the cortisol response 30 min after stress exposure is negatively associated with amygdala activation (Oei et al., 2012). However, the above-mentioned results were obtained in men only, and there is, in line with animal data on eye-blink and fear conditioning (Dalla and Shors, 2009), accumulating evidence for significant sex differences in stress effects on fear conditioning. Exposure to stress 1 h before fear conditioning increased fear conditioned responses in men, but seemed to inhibit fear learning in women (Jackson et al., 2006). Correspondingly, stress-induced cortisol elevations observed after fear conditioning strengthened fear memory consolidation in men, but not in women (Zorawski et al., 2005, 2006). Critically, information on the usage of oral contraceptives was not given in these studies. Nevertheless, the same effect was also seen when cortisol was administered after fear acquisition in men (Merz et al., 2014b). When fear learning takes place at a time when stress-induced cortisol concentrations are back to baseline, no differences between groups with differing gonadal hormone status occurred in fear acquisition and subsequent extinction (Antov and Stockhorst, 2014). However, on the next day, stress led to higher fear recovery in women tested in the follicular phase compared with men. Extinction memory was also reduced in women in the follicular phase compared with women investigated midcycle.

In addition, pharmacological studies propose that GCs may further modulate fear learning and memory processes differently in men and women. Pharmacological elevations of cortisol diminish neuronal fear responses in men and free-cycling women (tested in the follicular and luteal phase), but heighten fear-related brain activity in women taking oral contraceptives (Merz et al., 2010a, 2012; Stark et al., 2006; Tabbert et al., 2010; see Figure 7.6). Importantly, psychosocial stress induction led to the same pattern of results: whereas stress attenuated conditioned brain activation in men, it increased fear responses in women taking oral contraceptives, for example, in the amygdala (Merz et al., 2013). These studies using functional neuroimaging discovered that GC administration and exposure to stress influenced the fear network sex hormone dependently, affecting, among others, the amygdala and the hippocampus, critical for emotional memory formation. In the case of the fear conditioning study using psychosocial stress induction (Merz et al., 2013), it needs to be mentioned that women taking oral contraceptives showed significantly lower increases in cortisol concentrations than men (Kirschbaum et al., 1999; Rohleder et al., 2003). Because the pattern of results after stress

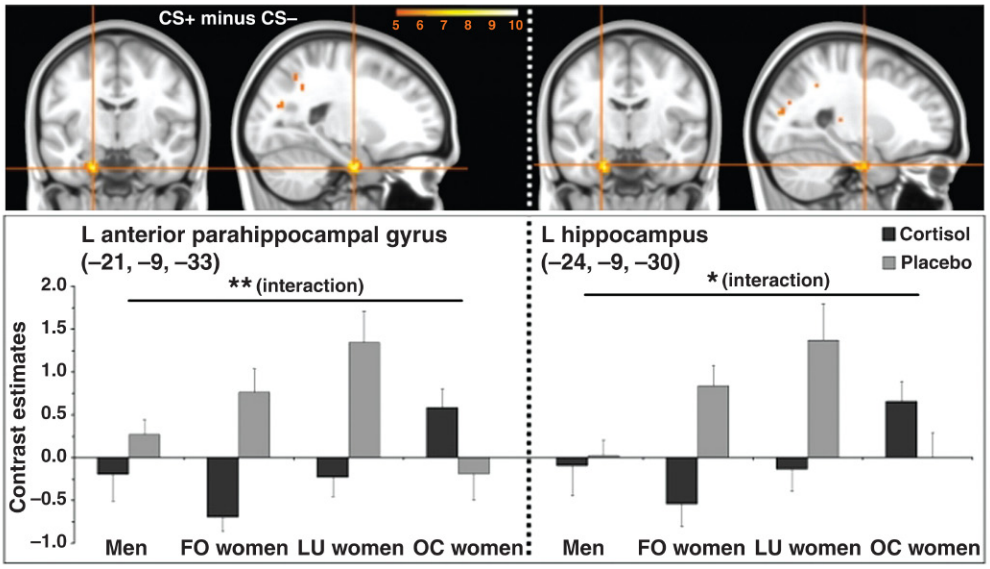

Figure 7.6 ***Sex hormone-dependent effect of the administration of 30 mg cortisol on fear memory formation (contrast CS+ minus CS−) in the left anterior parahippocampal gyrus and the left hippocampus.*** For illustration reasons, a threshold of $F \geq 5.0$ was applied to data (see color bar for exact F values), which were then displayed on the standard MNI brain template. In the bar graphs, mean contrast estimates to CS+ minus CS− are given for men, women in the follicular (FO) phase, in the luteal (LU) phase, and women taking oral contraceptives (OC) separately for the cortisol and the placebo group in the respective peak voxel. In both brain regions, cortisol reduced the CS+/CS− differentiation in men, FO, and LU women, but enhanced it in OC women. *$p < 0.05$; **$p < 0.005$ for the treatment × sex interaction. *(Reprinted from Merz et al. (2012). With permission from Elsevier.)*

induction is similar to the pattern obtained after GC administration (leading to comparable supraphysiological cortisol concentrations in all sex hormone status groups), an underlying difference in GC sensitivity in women taking oral contraceptives compared with men does not seem very likely. Oral contraceptives contain ethinylestradiol, which binds to estrogen receptors, and a gestagenic component, which binds to progestin receptors. A higher estradiol and/or progesterone binding after continuous oral contraceptive intake might lead to a subsequent downregulation and/or to a desensitization of these receptors in various brain structures such as the hippocampus. Stress or cortisol administration may abolish this reduced excitability enabling more pronounced learning processes compared with normal (stress-free) conditions. In men and free-cycling women, these receptors are not continuously affected by oral contraceptives, thus enabling learning and memory processes to function properly.

Furthermore, cortisol weakened fear contextualization and amplified fear generalization in women taking oral contraceptives, whereas the opposite pattern was observed in men (Van Ast et al., 2012). More precisely, in women taking oral contraceptives, cortisol increased fear toward cues signaling danger in both threatening and safe contexts, and toward safety signals in a threatening context. Such deficits in fear contextualization might be interpreted as a vulnerability factor in the development of anxiety disorders and PTSD.

In conclusion, activation of the SNS seems to enhance fear memory formation. When cortisol concentrations peak shortly before or during fear acquisition, they seem to inhibit the fear circuit surrounding the amygdala and the hippocampus. In contrast, fear-related brain activation in women taking oral contraceptives is enhanced by stress or cortisol administration. It remains to be tested how exactly gonadal and stress hormones interact in different brain areas, and, in particular, how fear memory consolidation is affected.

3.2 Fear extinction and retrieval

Statements on the effects of stress hormones on extinction and retrieval processes can only be made cautiously. Nevertheless, interesting preliminary findings have emerged in the past few years, pointing to potential influences of gonadal hormones on extinction learning, too. In a study investigating only women taking oral contraceptives, administration of cortisol before fear acquisition enhanced neuronal activation during fear learning, but reduced activation of the amygdala and the hippocampus during subsequent extinction learning (Tabbert et al., 2010). Similarly, cortisol administration directly after fear learning, 45 min before the fear extinction session (Merz et al., 2014a,b), reduced activation of the amygdala, the medial prefrontal cortex, and the nucleus accumbens in men, which was paralleled by an enhanced electrodermal fear response during extinction. Presumably, cortisol disrupted the interchange between these structures, which may have delayed fear extinction learning. Another experiment in healthy humans examined

how stress affects the extinction of a conditioned fear memory acquired the day before (Bentz et al., 2013). Exposure to stress attenuated fear retrieval (expressed as UCS expectancy) in men but not in women taking oral contraceptives.

Extinction learning is the experimental analogue to exposure therapy; we will now focus on clinical studies applying cortisol administration prior to exposure in men and women with spider phobia, height phobia, or social phobia (De Quervain et al., 2011; Soravia et al., 2006, 2014). Patients receiving cortisol reported less fear after these sessions as well as at a later point in time without medication. The explanation for these important findings was derived from the literature on episodic memory (see previous section; De Quervain and Margraf, 2008): while cortisol attenuated (fear) retrieval when patients encountered their feared stimulus, they could better consolidate the corrected information (less fear) at the same time. In addition to cortisol, pharmacologically increased noradrenergic activity before exposure therapy also reduced fear at a 1-week follow-up in male and female acrophobic patients (Powers et al., 2009). Unfortunately, all of these clinical studies did not differentiate between women in different phases of the menstrual cycle or according to the usage of oral contraceptives. It seems that these findings apply to both men and women; however, opposing or null effects in a distinct phase of the menstrual cycle or under the usage of contraceptives cannot be excluded.

A study extended these findings in female spider phobics taking oral contraceptives (Lass-Hennemann and Michael, 2014). The authors utilized the circadian cortisol rhythm, with high levels in the morning and low levels in the afternoon, when conducting the exposure session. Indeed, phobic fear was more reduced in the group in which the exposure session took place under high compared with low endogenous cortisol concentrations. The therapist thus might benefit from conducting exposure sessions in the morning (and not in the afternoon) in order to make them more effective.

A minor drawback of these studies is that the effects of stress or cortisol administration influence the retrieval of fear during the first encounter with the feared stimulus and also enhance consolidation at the same time; a clear distinction between these different memory phases cannot be made. This issue was addressed in the first study with humans to test the impact of stress on the consolidation of extinction in a renewal design, with fear learning toward discrete cues in context A, extinction in context B, and retrieval in both contexts realized on 3 consecutive days respectively (Hamacher-Dang et al., 2015). Stress was applied after the extinction session. In the retrieval test phase, the authors observed increased conditioned responses in the stress group in the acquisition, but not in the extinction context, leading to the assumption that exposure to stress augmented the integration of contextual cues into long-term memory. With the same design, the effects of stress on fear retrieval were tested using a slightly different timing (Merz et al., 2014a). Changing the timing of stress from postextinction to preretrieval led to a change in the results: stress attenuated fear retrieval in the acquisition context and also generally lowered skin conductance responses in the extinction context, in line

with the aforementioned reports from clinical samples undergoing exposure sessions (De Quervain et al., 2011; Lass-Hennemann and Michael, 2014; Soravia et al., 2006, 2014). However, male participants only were tested in both studies, therefore conclusions regarding sex differences or the impact of oral contraceptives cannot be drawn.

As the study of stress effects on fear conditioning is still in its early stages, modulating variables will need to be identified to deepen our understanding of the results obtained so far. At least, there exist clinical studies suggesting an anxiolytic effect of cortisol administration and of the utilization of the circadian rhythm on phobic fear. One promising avenue to follow in this context will undoubtedly be the investigation of sex differences and of circulating gonadal hormones in interaction with stress hormones.

3.3 Interim conclusion on fear conditioning

In summary, preliminary evidence exists for sex differences in fear learning after stress or cortisol administration. Neuroimaging studies have revealed that increases in cortisol attenuate the fear circuitry in men and free-cycling women, but increase conditioned fear in women taking oral contraceptives. Thus, these basic learning mechanisms seem to vary substantially in women depending on the individual status of gonadal hormones at the time of testing. From a clinical perspective, it would be desirable to investigate whether these altered fear-learning processes translate into vulnerability factors for the acquisition of an anxiety disorder or PTSD.

Regarding extinction and its application in exposure therapy, high cortisol levels, as observed after pharmacological administration or during the circadian rhythm, seem to exert beneficial effects: patients report less fear, and this effect transfers to follow-up sessions without medication. Moreover, stress hormones appear to inhibit fear retrieval and enhance the consolidation of fear extinction, similar to the impact of stress on episodic memory. Both effects are in play when the confrontation of phobic patients with their feared stimulus leads to reduced fear. However, the impact of gonadal hormones on fear extinction and retrieval processes needs to be addressed in future studies to better understand the underlying mechanisms and whether they work in all patients.

4 GENERAL CONCLUSIONS AND SUGGESTIONS FOR FUTURE WORK

Stress exerts manifold effects on learning and memory processes, both in the domain of episodic memory as well as in the domain of fear conditioning. Cortisol appears to reduce retrieval and enhance consolidation in episodic memory, particularly for emotionally arousing information. Similar effects have been reported for fear conditioning, which induces emotional arousal as well. In both domains, preliminary evidence suggests that the intake of hormonal contraceptives can either weaken the observed effects (such as in episodic memory) or even reverse them (such as in fear conditioning). However, the influence of sex and gonadal hormones has been largely ignored in this area, even

though initial studies have found important interactions between the HPA and the HPG axes. These experiments underline the importance of investigating women, and especially of examining the impact of circulating gonadal hormones on different learning and memory processes more closely. Sometimes, opposing effects in different groups of women have been observed, which need to be considered when trying to understand the basic mechanisms of stress-related clinical disorders as well as daily phenomena such as studying for an exam at school or university.

In some of the studies mentioned, it remains unclear whether the observed memory effects are due to differing cortisol responses in men and women or due to an altered central GC sensitivity. In the future, this issue clearly needs to be addressed. Furthermore, future studies examining the impact of stress hormones on episodic memory and conditioning processes should try to focus more on the investigation of women in different stages of the menstrual cycle and of women taking hormonal contraceptives. Crucially, free-cycling women should be tested several times to prove that both episodic memory consolidation and retrieval after stress or cortisol application change during different stages of the menstrual cycle. Accordingly, within-subject designs are highly desirable to explore women in their stress-related memory performance when they do not take oral contraceptives, and at a later point in time, when they have begun to take them (and later still, when they no longer take them). These suggested study designs are work-intense but undoubtedly important for a deeper insight into the modulation of episodic memory and fear conditioning processes by stress and gonadal hormones.

Fear conditioning processes in particular should be further explored to better understand critical factors facilitating extinction learning, such as fluctuating gonadal hormone concentrations over the course of the menstrual cycle. Future studies might derive neurobiological explanations for the different prevalence in men and women to acquire stress-associated disorders such as PTSD. These basic insights into fear learning and memory processes are also important for the amelioration of exposure therapy in the context of individualized treatment of patients with anxiety disorders or PTSD.

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