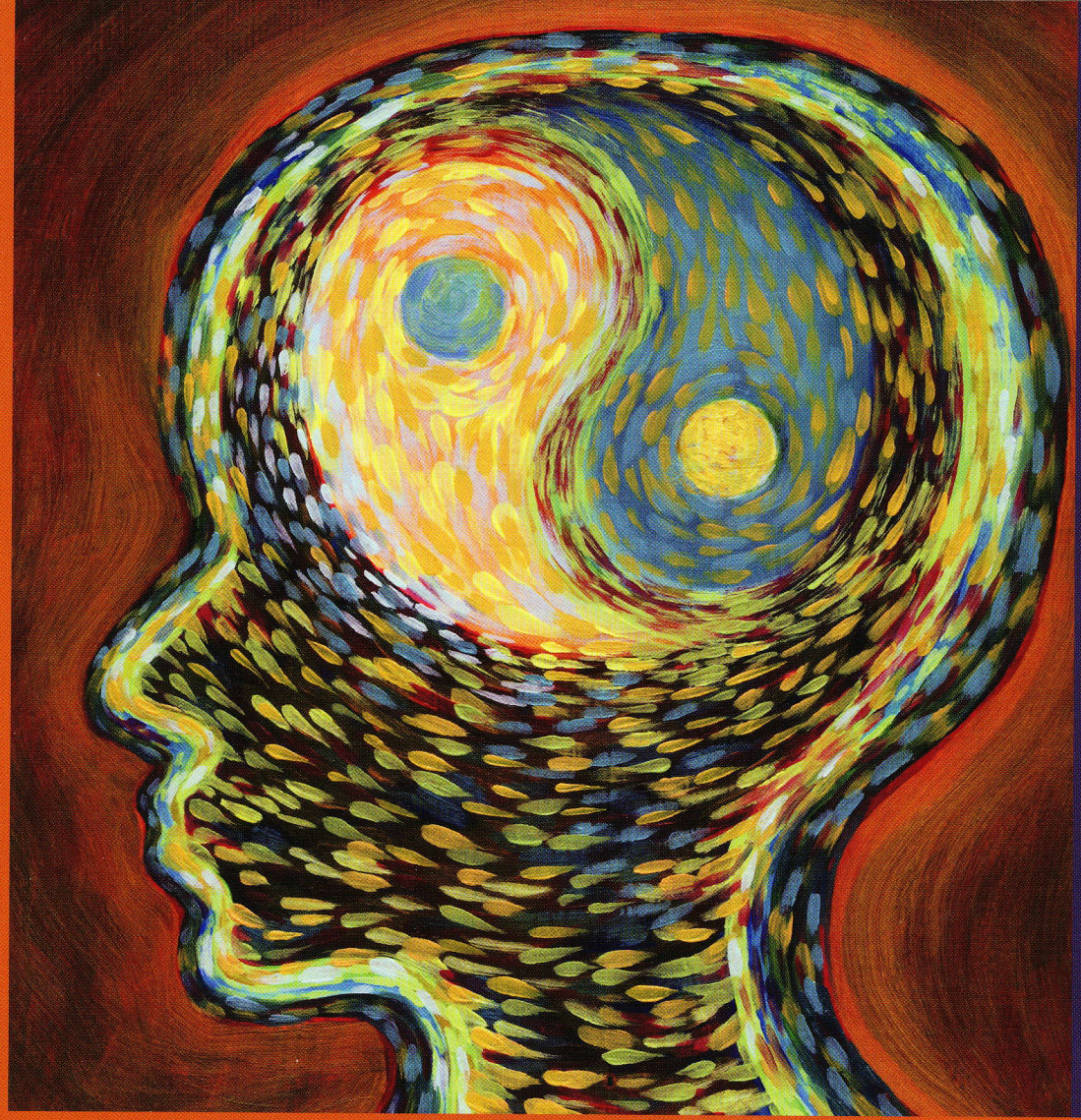

Wiley-Blackwell Handbooks of Behavioral Neuroscience

The Handbook of Stress

Neuropsychological Effects on the Brain

Edited by Cheryl D. Conrad

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Effects of Stress on Learning and Memory

Evidence for Sex Differences in Humans

Oliver T. Wolf

Introduction

There is good evidence 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 dissimilar stress-associated psychiatric disorders. Compared to men, women have, for example, a higher risk for major depression, posttraumatic stress disorder, and several anxiety disorders (Nemeroff et al., 2006; Yehuda, 2002), but lower prevalence in conduct disorders, psychopathy, substance abuse, and autism (Zahn-Waxler et al., 2008).

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 respond to stressors with the activation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to a rise in cortisol (the most prominent glucocorticoid in humans). The magnitude of the HPA axis response is modulated by gondal steroids (Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005; Taylor et al., 2000). Experimental studies in humans using psychosocial laboratory stressors often observed that men showed a stronger HPA axis response to a stressor than women (Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005). However, this might depend on the specific paradigm used (Stroud et al., 2002) and no strong overall influence of sex on the cortisol response to laboratory stressors

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was detected in a recent large meta-analysis, which however did not further investigate a possible influence of menstrual cycle (Dickerson and Kemeny, 2004). Moreover, in a real-life stress study (oral exam at the university), no sex differences in stress-induced cortisol elevations were detected (Schoofs et al., 2008a).

In women, fluctuations of gonadal steroids during the menstrual phase seem to further 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), which is characterized by elevated progesterone and estradiol levels. The situation in humans is further complicated by the fact that oral hormonal contraceptives appear to dampen the free (unbound; i.e., biologically active) cortisol stress response, possibly by increasing cortisol-binding globulin (Kirschbaum et al., 1999).

To conclude, sex and gonadal steroids impact HPA axis reactivity in humans, with the magnitude of this influence being moderate and the variance of the reported results large. Nevertheless, as a result of the complex interaction between the HPA axis and the hypothalamic–pituitary–gonadal axis, a lot of experimental human studies are conducted exclusively with men. Moreover, in studies with women, information about menstrual cycle phase and/or hormonal contraception are often not taken into account in the experimental design (e.g., Beckner et al., 2006; Smeets et al., 2008). Similarly, most rodent studies focus exclusively on males when conducting stress effects on memory (Diamond et al., 2007; Joels et al., 2006; Sandi and Pinelo-Nava, 2007).

For the current chapter, the focus is on possible differences in sensitivities of the brains of men and women for stress and stress hormones. I will review evidence for sex differences in the impact of acute experimentally induced stress on episodic long-term memory, working memory, and two forms of classical conditioning (eyeblink and fear conditioning).

Effects of Stress on Episodic Memory: Evidence for Sex Differences?

Episodic long-term memory refers to the conscious and voluntary storage of specific events that are connected to a spatial and temporal context. Together with semantic memory (the knowledge of facts and rules about the world) it is referred to as declarative or explicit memory. Episodic memory relies on the hippocampus, a brain structure within the medial temporal lobe (LaBar and Cabeza, 2006; Nadel and Moscovitch, 1997). Long-term memory processes can be further divided according to specific memory phases (encoding or acquisition), consolidation, and retrieval (see Roozendaal et al., 2006, Wolf, 2008, 2009).

Experiments in rodents and humans have established that stress influences episodic long-term memory (see Chapters 8, 9, 11, and 12 in this volume). It has been reported that stress within the learning context (i.e., when the learning condition is stressful) enhances memory consolidation (Joels et al., 2006; Roozendaal et al.,

2006). In contrast, memory retrieval of previously learned information is impaired when we are stressed (Roozendaal et al., 2006; Wolf, 2008, 2009). The beneficial effects on consolidation as well as the impairing effects on retrieval are more pronounced for emotionally arousing stimuli (e.g., emotional pictures or word; Wolf, 2009). Animal studies illustrate that these effects are mediated by an interactive effect of glucocorticoids with noradrenergic arousal (induced by a concurrent activation of the sympathetic nervous system). The basolateral nucleus of the amygdala influences the hippocampus, thereby creating a state where memory consolidation is enhanced, but memory retrieval is impaired (Roozendaal et al., 2006, 2009). Human behavioral, pharmacological, as well as neuroimaging studies demonstrate that similar results occur in humans (de Quervain et al., 2009; Wolf, 2008, 2009).

With respect to possible sex differences, studies in rodents report that acute (Conrad et al., 2004) as well as chronic (Bowman et al., 2001; Luine, 2002) stress impairs spatial (hippocampal-dependent) memory in male rats. In contrast to males, stress in females enhances memory, thus leading to truly opposing effects of stress on memory in the two sexes (Conrad et al., 2004; Bowman et al., 2001; Luine, 2002). However it has to be mentioned that not all studies observed strong sexual dimorphic response to stress (Park et al., 2008, see also Chapter 26 for more information on sex differences in rodents).

In a first study on the issue of sex differences in humans (Wolf et al., 2001b), it was investigated whether men and women differ in the association between the stress-induced cortisol response and its effect on episodic memory. A previous study from our laboratory (Kirschbaum et al., 1996) as well as findings from others (Takahashi et al., 2004) had reported that a more pronounced stress-induced cortisol rise was associated with impaired memory afterwards (encoding and immediate retrieval). Stress was induced prior to encoding with the use of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), a well-established human laboratory stressor combining a free-speech and a mental-arithmetic task in front of an audience, which leads to robust HPA axis activation. It is the combination of motivated performance, uncontrollability, and social-evaluative threat makes TSST so powerful (Dickerson and Kemeny, 2004). Overall no effects of stress on memory were found; however, the cortisol response within the stress group was strongly associated with poorer memory in men ($r = -.82$), while no such association was observed in women. In this study all women were tested in the luteal phase of their menstrual cycle to assure a similar HPA axis response to the stressor in both sexes (Kirschbaum et al., 1999). This suggests that women (at least in the luteal phase) are less sensitive to the memory-impairing effect of stress on immediate recall (Wolf et al., 2001b). The situation might be different for the beneficial effects of cortisol on memory consolidation. Here studies reported a significant positive correlation between cortisol and memory consolidation for women in the luteal phase (Andreano et al., 2008) or for women not stratified for menstrual cycle phase (Preuß and Wolf, 2009).

Additional studies on the topic of sex differences focused on stress or cortisol effects on memory retrieval. Using a pharmacological approach it had been shown

that cortisol administered prior to memory retrieval had impairing effects in men (Wolf et al., 2001a). This finding was extended later on to women (Kuhlmann et al., 2005a). In order to characterize the influence of gonadal steroids further, three groups of women were investigated: (1) women in the early follicular phase (low estradiol and progesterone), (2) women in the luteal phase (high estradiol and progesterone), and (3) women using oral contraceptives (low endogenous but high exogenous estrogens and progestins). Both groups of freely cycling women showed memory-retrieval impairment after cortisol treatment. In contrast, no effect was observed in the oral-contraceptive group (Kuhlmann and Wolf, 2005). This indicated that the exogenous synthetic sex steroids directly or indirectly reduced the sensitivity of the central nervous system to glucocorticoids.

Most recently, the effects of stress on memory retrieval in women in the luteal phase were tested using a psychosocial stress protocol (TSST). These women failed to show evidence for stress-induced retrieval impairment (Schoofs and Wolf, 2009), which was in contrast to results obtained in men (Kuhlmann et al., 2005b) and also in contrast to the results from the aforementioned pharmacological study (Kuhlmann and Wolf, 2005). Those data suggest that women in the luteal phase of the menstrual cycle are less susceptible to stress induced memory impairment (but not to pharmacological cortisol-induced memory impairments). There is good evidence to hypothesize that this effect is mediated by progesterone, since progesterone (among other ways of action) can bind to the glucocorticoid receptor (Schoofs and Wolf, 2009).

Taken together, research in humans provides evidence that the effects of stress on episodic long-term memory are sometimes less pronounced in women compared to men. This appears to be the case for encoding, consolidation, as well as retrieval. However, stress effects in women are by no means absent for this domain. Most importantly, an opposing pattern (as has been reported in rats; see Conrad et al., 2004, but see also Diamond et al., 2007) has so far not been reported. The conclusions to be drawn are so far limited by the fact that several studies tested only one sex and/or did not report possible sex differences. Finally specific menstrual-cycle phases have only be investigated in very few studies on this issue (Andreano et al., 2008; Kuhlmann and Wolf, 2005).

Effects of Stress on Working Memory: Evidence for Sex Differences?

Working memory refers to a short-term storage and manipulation system thought to be situated within the prefrontal cortex. Studies in rodents have reported that females are more susceptible to the acute effects of stress on working memory. This enhanced stress susceptibility was mediated by estradiol (Shansky et al., 2004, 2006; Shansky, 2009). In humans, the effects of stress (or cortisol treatment) on working memory have not been investigated very often. In addition, results are quite heterogeneous. Several recent studies, however, observed that stress impaired working

memory at least when difficult and challenging working memory tasks are used (Luethi et al., 2008; Oei et al., 2006; Schoofs et al., 2008b, 2009). However, those studies were all conducted in healthy young men, so that no information is available on the presence of sex differences. Along these lines, previous pharmacological studies investigating the effects of cortisol on working memory have also been conducted almost exclusively in men (Lupien et al., 1999; Wolf et al., 2001a). Thus additional studies are needed to test the hypothesis derived from studies with rodents that the female prefrontal cortex is more susceptible to stress.

Effects of Stress on Classical Conditioning: Evidence for Sex Differences?

Rodent studies on the topic of stress and learning have often used classical conditioning paradigms, with eyeblink conditioning and fear conditioning being used the most. In these studies the animal learns that a previously neutral stimulus (the conditioned stimulus, CS; e.g., a tone) predicts an aversive event (the unconditioned stimulus, US; e.g., an air puff to the eye, or a foot shock). Several conditioning paradigms need to be differentiated. Delay conditioning (CS coterminates with the US) has to be differentiated from trace conditioning (there is a short interval or *trace* between the CS and the US). Only the latter is thought to depend on hippocampal functioning (Christian and Thompson, 2003). In addition, simple conditioning paradigms (a single CS predicts the US) can be contrasted with discriminative tasks (a CS+ predicts the US, while in contrast a CS– predicts the absence of the US).

Eyeblink conditioning

The most impressive and consistent sex differences in rodents have been reported for the domain of eyeblink conditioning. Shors and colleagues observed that in the no-stress control condition female rats outperform their male counterparts in simple conditioning. This sex difference is reversed following acute stress, when males outperform females (Dalla and Shors, 2009; Shors, 2004). Several stressors produce this effect and it occurs in delay, as well as trace conditioning paradigms. Of note, the sex difference pattern differs (is a mirror image) from that observed with spatial tasks (Conrad et al., 2004). However, both describe scenarios whereby sex differences under nonstressed conditions are reversed following acute stress.

Surprisingly, few studies have investigated the effects of acute stress on eyeblink conditioning in humans. Of the few studies, one observed that a mild version of the Cold Pressor Test enhanced hippocampal-dependent trace conditioning in men, but females were not tested (Duncko et al., 2007). In addition, the stressor failed to activate the HPA axis, indicative of a failure to truly induce stress. This study suggests a beneficial effects of ardrenergic arousal on eyeblink conditioning while permitting a strong conclusion about HPA-mediated effects.

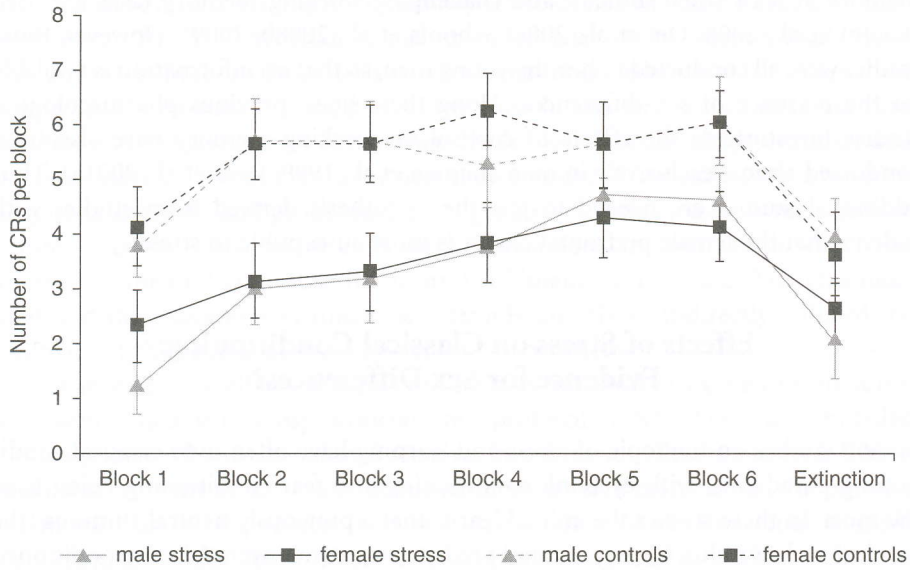

Figure 27.1 Effects of acute psychosocial stress on acquisition and extinction of delay eyeblink conditioning. Stress led to slower acquisition in men and women, but had no effect on extinction. CR, conditioned response. *Source:* Reprinted from Wolf et al. (2009). With permission from Elsevier.

Recently, the impact of a psychosocial stressor (TSST) on delay conditioning in healthy men and women was tested, representing the only study published, as of today, that tested acute stress effects on simple delay eyeblink conditioning (Wolf et al., 2009). In contrast to the observations made in rats, men and women performed similarly in their eyeblink conditioning in the control condition. In both sexes stress impaired eyeblink conditioning (Figure 27.1). Moreover, higher cortisol levels were associated with impaired conditioning (Wolf et al., 2009). Taken together this study indicates that stress induced cortisol elevations impair the acquisition of eyeblink conditioning in men and women.

The idea that stress-induced cortisol elevations cause impaired eyeblink conditioning in humans is supported by recent pharmacological studies (Vythilingam et al., 2006), as well as by studies in patients with endogenous hyppercortisolemia (Grillon et al., 2004). Why our study in humans failed to find the striking sex differences observed in rats (see Dalla and Shors, 2009; Shors, 2004) is perplexing. There are at least three possible explanations. First, Wolf et al. (2009) did not observe any a priori sex differences before acute stress was applied in the nonstressed controls, which contrasts with the work using rats (Dalla and Shors, 2009; Shors, 2004). Second, a psychosocial laboratory stressor was used in the human study, while Shors used physical stressors. Physical and psychological stressors differ with respect to

activated brain regions (Ulrich-Lai and Herman, 2009). Third, the conditioning procedure used is quite invasive in rats (the electrodes are implanted into the eyelid, whereas it is noninvasive in humans: we used special goggles for the assessment of the eyelid reflex). Rodent studies have repeatedly observed that task aversiveness is an important mediator in determining the effects of stress on memory (Conrad, 2005; Sandi and Pinelo-Nava, 2007). A fourth explanation would simply state that humans and rodents differ in how stress influences their eyelid-conditioning abilities. Additional studies in humans on this topic are needed, but this example illustrates that current extrapolation from animal studies to the human situation needs to be made with caution.

Fear conditioning

Surprisingly little information is available on possible sex differences in fear conditioning in rodents. The impressive sexual dimorphic acute stress effects observed with eyelid conditioning have not been reported for this amygdala-dependent form of emotional learning, making the evaluation of this topic difficult. Either it has not been tried or the results have been nonsignificant and therefore were not published. However, at least for chronic stress sexual dimorphic responses in rats have been studied and reported (Baran et al., 2009).

In human stress research, several studies report fear conditioning effects with sex differences consistently found. Stress or cortisol exerts sex-dependent effects on this form of emotional learning, which depends upon the amygdala and other brain regions (LaBar and Cabeza, 2006). Three previous studies related basal and/or stress-induced cortisol levels to fear conditioning performance in men and women. Stress exposure or elevated/rising cortisol levels were associated with enhanced fear conditioning in men, but not women (Jackson et al., 2006; Zorawski et al., 2005, 2006).

Recently an alternative approach was implemented to investigate the effect of stress hormones on fear conditioning. Cortisol levels were experimentally manipulated using a placebo-controlled design. In this neuroimaging study (functional magnetic resonance imaging, fMRI) fear conditioning was conducted inside the scanner using a discriminative fear-conditioning paradigm (CS+ compared to CS–) with neutral (geometric symbols) stimuli as the CS and a mild electric shock as the UC. In the first study on this topic, cortisol impaired peripheral as well as neural correlates of fear conditioning in men, yet enhanced them in women (Stark et al., 2006). Under placebo women showed poorer fear conditioning, while under cortisol the opposite pattern was observed (Stark et al., 2006). The same sex-dependent effects of cortisol administration were observed in three frontal regions; namely the anterior cingulate gyrus, the lateral orbitofrontal cortex, and the medial prefrontal cortex. In all three regions cortisol enhanced neuronal activity (the contrast CS+ minus CS–) in women, while reducing it in men.

In a second study (Plate 6) these opposing effects of cortisol on neural correlates of fear conditioning in men and women were replicated. This time an implicit (without contingency awareness) fear-conditioning paradigm was administered (Merz et al., 2010). Contingency awareness is known to influence the peripheral as well as neural correlates of classical conditioning. By interleaving the presentation of the CS stimuli with a second demanding task (an *n*-back working-memory task) participants can be successfully prevented from becoming aware of the contingencies between the CS+ and the US. Previous studies have established that a lack of contingency awareness causes an abolishment of some peripheral indices of fear conditioning (electrodermal response; Hamm and Weike, 2005). In contrast, clear evidence for fear conditioning can be detected at the neural levels using fMRI (Tabbert et al., 2006). Using the just-described paradigm the effects of cortisol on implicit fear conditioning were tested, focusing on possible sex differences (Merz et al., 2010). Again opposing effects of cortisol administration in men and women occurred. Due to the implicit nature of the fear-conditioning paradigm the location of the effects had shifted from prefrontal regions towards subcortical regions. It was observed that cortisol reduced activity in the thalamus, insula, and hippocampus in men. In contrast in women (who showed lower activity under placebo than men) cortisol enhanced activity in these regions (Merz et al., 2010). This second study again indicates that cortisol enhances the neuronal correlates of fear learning in women, while impairing them in men.

The direction of the observed effects in our pharmacological study (impairing effect of cortisol on fear conditioning in men) contrasts to those observed after psychosocial stress (Jackson et al., 2006; Zorawski et al., 2006). At least two explanations are plausible. Nonlinear dose–response relationships might underlie an enhancement of fear conditioning in men after stress, while a substantial increase in cortisol in response to pharmacological cortisol treatment might impair fear conditioning. A second explanation could focus on the timing and/or on the neuroendocrine mediators involved. An increase in cortisol levels due to stress is preceded by a rise in hypothalamic (and extrathalamic) corticotropin-releasing hormone, which could enhance fear conditioning directly (Croiset et al., 2000). In contrast, cortisol treatment reduces corticotropin-releasing hormone via its negative feedback on the HPA axis (Joels and Baram, 2009). In addition, other stress mediators (e.g., the sympathetic nervous system) might be responsible for the difference between experimental stress studies and cortisol-administration studies. Future studies are needed to test these hypotheses and to create a more detailed picture on the effects of stress on fear conditioning in humans.

Despite some of the unresolved issues discussed, one can conclude that our pharmacological studies (Merz et al., 2010; Stark et al., 2006) observed substantial and opposing effects of the stress hormone cortisol on neural correlates of fear conditioning. Together with the studies investigating the effects of stress-induced alterations on peripheral fear conditioning (see summary above; Jackson et al., 2006; Zorawski et al., 2005, 2006) they illustrate evidence that sex differences in the response to stressors or stress hormones in fear conditioning can be substantial.

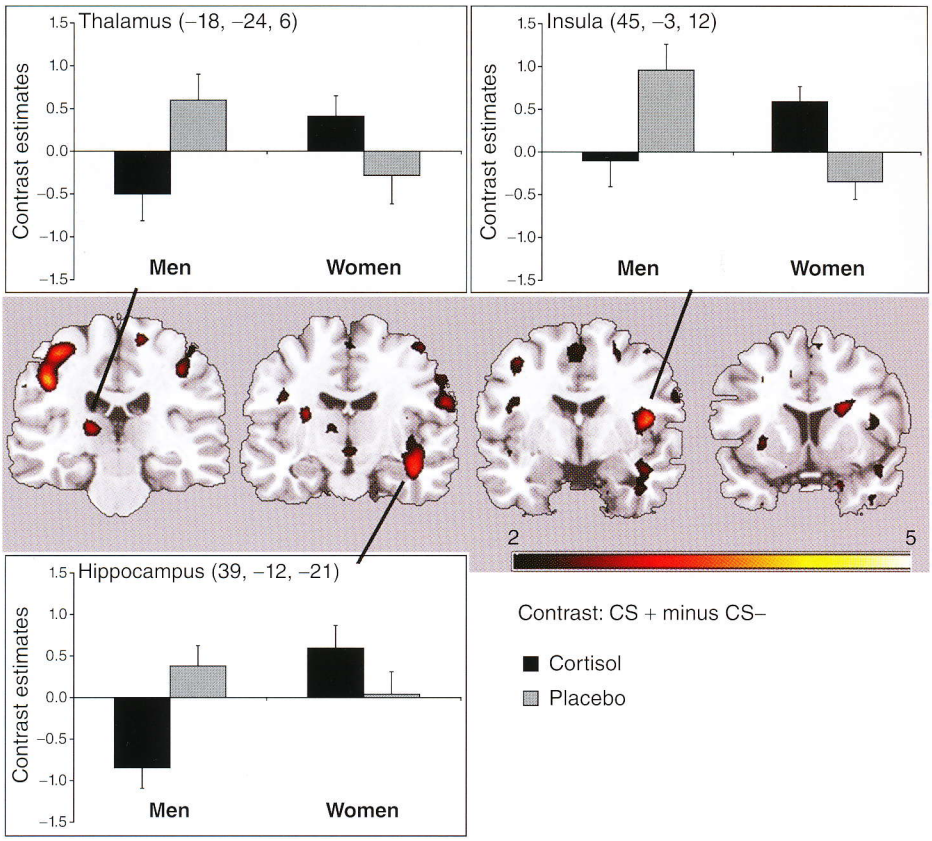

Plate 6 Neural activations for sex by cortisol interactions in the contrast CS+ minus CS– in a series of selected brain slices. This contrast is an index of emotional learning. Mean (and SEM) contrast estimates of the contrast CS+ minus CS– for women and men in the cortisol and placebo group in the insula, hippocampus, and thalamus in the respective peak voxels are illustrated in the bar graphs. All coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) space. *Source:* Reprinted from Merz et al. (2010). With permission from Elsevier.

Summary

In this chapter, evidence was reviewed for sex differences in the influence of stress and cortisol on learning and memory processes. For episodic memory, some evidence exists that women compared to men are sometimes less susceptible to stress or cortisol treatment (Kuhlmann and Wolf, 2005; Schoofs and Wolf, 2009; Wolf et al., 2001b). However, the empirical situation is quite heterogeneous. Truly opposing effects of stress on episodic memory in men and women have not been observed in humans as of today, as found in rodents (Conrad et al., 2004).

Possible sex differences have not been investigated sufficiently for the area of human working memory. Thus it awaits to be determined, whether the enhanced stress susceptibility observed in female rats (Shansky et al., 2004, 2006; Shansky, 2009) translates into a higher stress sensitivity in women (with respect to working memory).

For eyeblink conditioning stress impaired performance in men and women (Wolf et al., 2009). Thus, for this form of classical conditioning the strong and opposing sex differences observed in rodents (Dalla and Shors, 2009; Shors, 2004) could so far not be found in humans. Possible reasons for these discrepancies have been discussed above and additional empirical work is needed to decide which of the possible explanations are true.

In contrast sex differences have been repeatedly shown in the domain of fear conditioning. Studies observed that the effects of stress were more pronounced in men, while being blunted or absent in women (Jackson et al., 2006; Zorawski et al., 2005, 2006). Research using a pharmacological approach demonstrated that cortisol impaired the neuronal correlates of fear conditioning in men, while enhancing them in women (Merz et al., 2010; Stark et al., 2006). Thus, cortisol treatment during fear conditioning led to opposing results in men and women, similarly to those reported in rodents using spatial tasks (Conrad et al., 2004) or eyeblink conditioning (Dalla and Shors, 2009; Shors, 2004).

At the very least, the empirical evidence supports the notion that sex has to be taken into account when investigating the effects of stress on learning and memory (in all species). At the same time, the complex picture argues against any global conclusions that argue that "women are more (or less) susceptible to stress." The results appear to be mediated by numerous factors, among them type (and duration) of the stressor, and memory domain assessed. It is conceivable that the effects of psychological stressors might differ from those of more physical stressors so a systematic comparison would be of interest. In addition the memory phase investigated (acquisition, consolidation, and retrieval) needs to be taken into account. High estradiol levels in women might make them more stress-susceptible in some cognitive domains but not others. In addition, it is important to emphasize that activational effects of gonadal steroids might not be the source of sex differences, as organization, genetic or other events could be important.

The topic of human aging has not been addressed in this review. Due to the substantial changes in sex steroid levels after the menopause (and to a lesser degree

in aging men as well) the topic of sex steroids and memory after stress exposure is of substantial relevance for aging individuals (Wolf and Kudielka, 2008). The empirical evidence for antistress effects of sex steroid treatment in older women is so far sparse (Wolf and Kudielka, 2008). While basic science studies conducted in rodents are somewhat promising more research is needed before clinical trials can be initiated.

When Do We See Sex Differences? Some Hypotheses

Despite the somewhat unsatisfying empirical situation, it has become obvious that sex differences are not omnipresent in this field. Thus, the challenging theoretical question is to understand the conditions leading to sex differences (in the effects of stress on learning and memory). The fear-conditioning results could be interpreted in a way suggesting that sex differences occur most likely in tasks relying heavily on the amygdala. Studies on the topic of emotional memory have repeatedly observed sex differences (Andreano and Cahill, 2009; Cahill, 2006) and this has been in part attributed to a sexually dimorphic response of the amygdala. Thus, highly emotional learning and memory task might show sexually dimorphic stress effects.

Another broader and not mutually exclusive explanation focuses on baseline sex differences. Based on the human fear conditioning findings, as well as on some of the behavioral studies in rodents (Conrad et al., 2004; Dalla and Shors, 2009; Shors, 2004), one could hypothesize that sex differences under stress free control conditions predict a sexually dimorphic response after stress. Thus, stress might abolish or even reverse sex differences, which are present prior to stress and therefore might reflect sex differences in cerebral organization. Along these lines, there might be a sex-specific shift in neural processes underlying spatial memory after stress, which reflect in part sex differences prior to stress (Beck and Luine, 2010). This hypothesis focused on the observation that stress appears to induce a shift away from hippocampal (cognitive) forms of memory towards caudate-based (habit or stimulus response) forms of memory (Dias-Ferreira et al., 2009; Schwabe et al., 2010). While this hypothesis is quite attractive from a conceptual point of view, human studies on this topic have not observed strong sex differences (Schwabe et al., 2007; Schwabe and Wolf, 2009). The more global hypothesis that sex differences occurring in a stress-free control condition predict sex differences after stress could still be accurate and should be tested in future human studies using memory measures with known sex differences.

Outlook

The above summary indicates that there is some evidence for sex differences in how stress affects learning and memory, but clearly more research in this area is needed. Of course the inclusion of women into a psychoneuroendocrine study comes with

a whole package of additional issues. Should one differentiate menstrual cycle phases and if yes, then how many phases should be considered? What about hormonal contraceptives (which again come in hundreds of different varieties)? Depending on how detailed one would like to tease apart possible interactions between gonadal hormones and stress hormones, three or four groups need to be studied (Andreano et al., 2008; Kuhlmann and Wolf, 2005), which will substantially increase running costs and time for data collection. A feasible initial approach might be to first study women, without taking into account their current sex steroid status and depending on the initial findings, pay attention to the menstrual cycle issue in a follow-up study (e.g., Andreano and Cahill, 2006; Andreano et al., 2008). While the decision to study males only can be understood from a pragmatic point of view, it leads to an unsatisfactory empirical situation. It is clearly unacceptable when half of the population is ignored. Moreover, the inclusion of both sexes often leads to quite exciting results thus rewarding those scientists who take the extra effort to study both sexes in parallel.

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