

Stress Differentially Modulates Fear Conditioning in Healthy Men and Women

Eric D. Jackson, Jessica D. Payne, Lynn Nadel, and W. Jake Jacobs

Background: Stress and stress hormones modulate emotional learning in rats and might have similar effects in humans. Theoretic accounts of posttraumatic stress disorder (PTSD), for example, implicate the stress-induced modulation of fear conditioning in the development of intrusive emotional reactions. The present study examined the impact of acute stress and cortisol (CORT) on classically conditioned fear in men and women.

Methods: Ninety-four healthy undergraduates were exposed to a mild stressor (or control condition) while subjective anxiety and glucocorticoid stress responses (salivary CORT) were measured. One hour later, all participants participated in a differential fear conditioning procedure while conditioned skin conductance responses (SCR) were recorded.

Results: Exposure to the stressor increased subjective anxiety and elevated CORT levels. In men, stress exposure facilitated fear conditioning; whereas in women, stress appeared to inhibit fear conditioning. The impact of stress on differential conditioning in men was associated with increased CORT levels.

Conclusions: Consistent with animal models, these results demonstrate that stress exposure can modulate classical conditioning in humans, possibly via hormonal mechanisms. The enhancing effects of stress on the formation of conditioned fear might provide a useful model for the formation of pathological emotional reactions, such as those found in PTSD.

Key Words: Posttraumatic stress disorder, classical conditioning, psychological stress, glucocorticoids, gender differences, fear

Stressful experiences profoundly influence cognitive and emotional functioning, sometimes to a pathological degree. Animals exposed to uncontrollable stressors, for example, exhibit learning alterations that produce fear, anxiety, and helplessness (e.g., Maier 1993). In humans, stress might also modulate emotional learning and, as a consequence, contribute to the development of disorders such as posttraumatic stress disorder (PTSD). This compelling idea has been in the literature for at least 15 years (Pitman 1989); however, the ability of stress to produce alterations in human emotional learning remains unclear.

Fear conditioning is a form of associative learning that involves the acquisition of fear responses similar to those found in individuals with PTSD (Armony and LeDoux 1997; Rothbaum and Davis 2003). A number of studies with male rats indicate that exposure to uncontrollable stressors facilitates fear conditioning (Desiderato and Newman 1971; Maier 1990; Mineka et al 1984; Mowrer and Viek 1948). The glucocorticoid stress hormone corticosterone (CORT) might be partially responsible, because fear conditioning is also facilitated after acute and chronic doses of CORT in the absence of stress exposure (Conrad et al 2004; Thompson et al 2004). Some theoretic approaches to PTSD propose similar stress-induced modulations of human fear conditioning (e.g., Armony and LeDoux 1997; Bonne et al 2004; Charney et al 1993; Elzinga and Bremner 2002; Metcalfe and Jacobs 1998). Although such effects have not been examined in humans, stress exposure has been shown to enhance other forms of emotional learning, such as the formation of memories for emotionally arousing stimuli (Cahill et al 2003; Jelicic et al 2004; Payne et al 2004, in press).

The primary aim of this study was to investigate the impact of

acute stress on fear conditioning in men and women. To this end healthy undergraduates participated in a fear conditioning procedure 1 hour after being exposed or not exposed to a psychological stressor. The secondary aim was to assess potential mediators such as gender differences and individual differences in stress responsiveness that might identify individuals who are most vulnerable to the stress-induced alterations of emotional learning. Therefore, we also assessed individual differences in subjective anxiety and salivary CORT (cortisol in humans is functionally equivalent to corticosterone in rats; thus, both are abbreviated as CORT in this article).

The results from animal models suggest that fear conditioning will be enhanced in individuals exposed to acute stress, especially those with larger hormonal responses. These studies, however, have only been conducted with male rats. Studies with humans find significant gender differences in emotional memory (Cahill 2003; Payne et al, in press), hormonal stress responses (Kudielka and Kirschbaum 2005), risk of PTSD (Kessler et al 1995), and the impact of stress on eyeblink conditioning (Shors et al 2000). Therefore, gender differences were also expected in the current study.

Methods and Materials

Participants

Ninety-five (50 men, 45 women) undergraduates from the University of Arizona provided written consent for participation in the study. Forty-seven were randomly assigned to the stress group (22 women, 25 men) and forty-eight to the control group (23 women, 25 men). Data from one man in the stress group were removed from analyses owing to insufficient skin conductance responses. Written informed consent and study procedures were approved by the Human Participants Protection Program at the University of Arizona and conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983 and with HIPAA guidelines.

Procedure

Psychological Stressor. Participants assigned to the stress group were exposed to a psychological stressor, a 60 min recovery period, and then a fear conditioning procedure. Partic-

From the Department of Psychology, University of Arizona, Tucson, Arizona. Address reprint requests to W. Jake Jacobs, University of Arizona, Department of Psychology, Anxiety Research Group, 1503 E. University Blvd. Building 68, Tucson AZ 85721; E-mail: wjj@email.arizona.edu.

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ipants assigned to the control group began the study with the recovery period, and then proceeded with fear conditioning. Thus, the control group was exposed to neither the stress procedure nor a parallel control procedure.

The stress procedure was designed to elicit stress responses associated with anxious anticipation, public speaking, and mental arithmetic. Stressed participants were given 10 min to prepare a job speech to be delivered under intense lighting to three investigators behind a one-way mirror. Participants believed they would be video and audio recorded and that their performance would be evaluated. In actuality, when participants gave the 5-min extemporaneous speech, there were no investigators behind the mirror and participants' speeches were neither recorded nor evaluated (Lupien et al 1997). After the speech, participants were asked to remain in front of the cameras, lights, and mirror and to count backward from 1022 by 13's as quickly as possible for 5 min. If a mistake was made, the experimenter bluntly stated, "No. That is not correct. Start over with 1022." Therefore, the stress procedure was similar to the Trier Social Stress Test (TSST), but without a live audience (Kirschbaum et al 1993; Lupien et al 1997).

Recovery Period. A period was scheduled after stress exposure for the recovery of hormonal elevations that were not of primary interest, such as adrenocorticotropin hormone (ACTH), NE, and E (Kirschbaum et al 1993; Richter et al 1996). The CORT levels, which were of primary interest, typically remain elevated for at least an hour after exposure to a laboratory stressor (Dickerson and Kemeny 2004). The recovery period consisted of 30 min of listening to a relaxing CD and 30 min of personality questionnaires. The questionnaires included the Anxiety Sensitivity Inventory (ASI), a 16-item questionnaire designed to assess fear of anxiety-related symptoms (Reiss et al 1986), the trait portion of the State-Trait Personality Inventory (STPI Form Y), a subjective measure of trait anxiety, depression, anger, and curiosity (Spielberger 1995), and the NEO Five Factor Inventory (NEO-FFI) Form S, a self-report measure of the "big-five" personality traits: neuroticism, extraversion, openness, agreeableness, and conscientiousness (Costa and McCrae 1992).

Measures of Stress Response. There is considerable variation in individual responses to psychological stressors (Rohleder et al 2003). Hence, it was important to have objective and subjective measures of the stress response, including salivary CORT and self-reported anxiety (Spielberger State Anxiety Inventory; Spielberger 1983). For all participants, saliva samples and anxiety reports were collected before the recovery period, 30 min into the recovery period, and immediately before conditioning. An additional saliva sample and anxiety report was collected from the stress group immediately before exposure to the stressor. All saliva samples were assayed for cortisol content, in duplicate, with a commercially available enzyme immunoassay (Salimetrics, State College, Pennsylvania).

Fear Conditioning. Fear conditioning began 60 min after the stressor. Two conditioned stimuli (CS) were used in a differential (or discriminative) conditioning design; one was a picture of a man with a fearful facial expression, and the other was a picture of the same man with a neutral facial expression (Ekman and Friesen 1976). The CSs were presented serially on a computer monitor for 2 sec each, with a pseudo-random inter-trial interval ranging from 20 sec to 30 sec (mean = 25 sec). For each participant, order of CS presentation was randomized by DMDX presentation software (developed by K.I. Forster and J.C. Forster at the University of Arizona), resulting in a pseudo-random series with each CS repeated no more than two times in a row. The

unconditional stimulus (UCS) was a 2-sec female scream, generated from a WAV file, amplified to 105 db, and presented through headphones. When presented, the UCS immediately followed the termination of one of the pictures, labeled the CS+, and never followed the other picture, labeled the CS-. The fearful face served as the CS+ for 47% of control women, 53% of stressed women, 52% of control men, and 48% of stressed men.

To habituate participants to the novel stimuli, the fear conditioning procedure began with each CS being presented once without the UCS. Next, acquisition trials consisted of eight presentations of the CS+, each followed by the UCS (scream), and eight presentations of the CS- alone. Because the inter-stimulus interval (ISI) between the CS+ and the UCS was only 2 sec, there was not enough time to measure skin conductance responses (SCRs) to the CS+ before the presentation of the UCS. Therefore, after the fourth acquisition trial, an additional CS+ was presented with no UCS to allow for the measurement of conditioned SCRs without interference from unconditional SCRs. Extinction trials immediately followed the acquisition trials and consisted of eight presentations of each CS without UCS presentation. Because there is no consensus about which is the best method to measure the strength of fear conditioning, conditioned fear was evaluated both during acquisition and during extinction trials.

To measure skin conductance (SC), two Ag-AgCl reusable electrodes (TSD 103, BIOPAC Systems, Goleta, California) were first filled with .05 molar NaCl electrode gel (Discount Disposables, Saint Albans, Vermont) as suggested by Venables and Christie (1980). The electrodes were then attached by straps to the palmar sides of the distal phalanges of the first and second fingers on the left hand. An amplifier (GSR100, BIOPAC Systems) applied a constant voltage to the electrodes to detect changes in SC. The signal was amplified by 5 μ S/V, digitized at a rate of 200 Hz and acquired with AcqKnowledge acquisition software (BIOPAC). Skin conductance responses were scored offline as the maximal deflection in conductance 1–4 sec after stimulus onset (Prokasy and Kumpfer 1973). Trials in which SCRs initiated before or after this window were scored as having no SCR. According to recommendations, the resulting magnitudes were range-corrected (SCR/SCRmax), then log-transformed to better fit a normal distribution (Lykken and Venables 1971; Siddle and Packer 1987).

Statistical Analysis

T tests and Pearson chi-square tests were used to evaluate group differences in sample characteristics. Subjective anxiety and CORT at the three measurements before fear conditioning were analyzed with univariate ANOVAs with stress group (control vs. stress) as the between-participant factor (repeated measure ANOVAs were not used for this analysis because there were more measurements in the stress group than in the control group). To determine whether exposure to the stressor elevated subjective anxiety and CORT over baseline, an ANOVA was conducted with only the stress group, with measurement time as the within-participant repeated measure. For post hoc analyses, anxiety and CORT change scores were calculated by subtracting baseline measurements from the maximum measurement obtained after the stress procedure. Given the well-documented circadian rhythm of CORT release, start time (hours after midnight) of the experiment was used as a covariate in all analyses involving CORT (e.g., Van Cauter et al 1996).

The conditioning data was analyzed with ANOVAs with stress group (control vs. stress) and gender (men vs. women) as the

between-participant factors and with CS-type (CS+ vs. CS-) and blocks of trials (three levels) as the within-participant repeated measure factors. The first “block” included only the acquisition test trial; the second trial block included the first four extinction trials (“early extinction”); and the third trial block included the last four extinction trials (“late extinction”). To adjust for violations of the sphericity assumption in repeated measure ANOVAs, degrees of freedom and probability values were corrected with the Geenhouse-Geisser coefficient, when appropriate. For post hoc analyses and figures, conditioning difference scores were calculated as the mean CS+ response minus the mean CS- response. Post hoc analyses were conducted with *t* tests, Pearson correlations, or pairwise comparisons of estimated marginal means. All analyses used an α of .05.

Results

Sample Characteristics

Table 1 shows demographic variables separately for men and women in stress and control groups. There was a significant group difference in the time at which the study began, indicating that women in the stress group started the study significantly earlier than men in the stress group. Men in the control group also reported significantly less extraversion and conscientiousness than men in the stress group.

Fear Conditioning

The fear conditioning procedure successfully produced conditioned responding, and all conditional responses decreased over the extinction trials (main effects of trial blocks and CS-type: all *F* values > 4.9 and *p* values < .01). Stress had a significant gender-specific effect on the emotional responses elicited by the CS+ relative to the CS- [stress by gender by CS-type interaction: $F(1,90) = 4.3, p = .04$]. The interaction remained significant even after statistically controlling for the picture (fearful face vs. neutral face) that was assigned as the CS+ [$F(1,89) = 4.9, p = .03$]. Figures 1 and 2, respectively, illustrate the SCRs during the fear conditioning procedure for men and women.

For men, stress exposure significantly elevated emotional responses to the CS+ [$F(1,47) = 5.2, p = .03$] but not to the CS- [$F(1,47) = .93, p = .34$]. This enhancement of conditioned responding was detected during each trial block: acquisition test trial [$F(1,47) = 4.8, p = .03$], early extinction [$F(1,47) = 4.3, p = .04$], and late extinction [$F(1,47) = 4.2, p = .05$] (Figure 1). Post hoc analyses of the conditioning difference scores confirmed that differential conditioning, overall, was larger for men in the stress group than for those in the control group [$F(1,47) = 6.4, p = .02$]. This enhancement of differential conditioning was detected during the acquisition test trial [$F(1,47) = 5.0, p = .03$] and during late

Table 1. Comparison of Sample Characteristics and Stress Responses Among Men and Women in the Stress and Control Groups

	Men (<i>n</i> = 49)		Women (<i>n</i> = 45)		<i>p</i>
	Stress (<i>n</i> = 24)	Control (<i>n</i> = 25)	Stress (<i>n</i> = 22)	Control (<i>n</i> = 23)	
Oral Contraceptive use (%)			41	43	ns
Psychotropic Medication use (%)	8	16	9	9	ns
History of Trauma (%)	17	12	27	17	ns
Age (yrs)	19.4 ± .28	20.5 ± .72	19.2 ± .37	19.2 ± .53	ns
Start Time (hours after midnight)	13.0 ^a ± .35	12.5 ± .41	11.4 ^c ± .45	12.4 ± .45	a > c
Anxiety Sensitivity	33.3 ± 1.7	31.8 ± 1.7	34.1 ± 1.6	33.1 ± 1.6	ns
Trait Anxiety	18.0 ± 1.1	20.4 ± 1.0	19.2 ± 1.3	18.6 ± .87	ns
Trait Depression	16.2 ± .83	18.8 ± 1.1	16.4 ± 1.0	17.2 ± .93	ns
Trait Curiosity	28.3 ± .75	28.1 ± .93	29.5 ± .78	28.3 ± .69	ns
Trait Anger	19.4 ± 1.1	20.9 ± 1.3	20.6 ± 1.2	17.9 ± 1.0	ns
NEO: Neuroticism	22.5 ± 1.6	26.6 ± 1.7	25.7 ± 1.7	25.3 ± 1.7	ns
NEO: Extraversion	35.5 ^a ± .87	31.2 ^b ± 1.5	37.7 ± 1.4	37.1 ^d ± 1.4	a > b, b < d
NEO: Openness	28.2 ± 1.2	27.7 ± 1.2	28.0 ± 1.3	28.1 ± .97	ns
NEO: Agreeableness	25.9 ± .87	25.1 ± 1.4	28.2 ± 1.7	28.4 ± 1.4	ns
NEO: Conscientiousness	35.2 ^a ± 1.5	30.2 ^b ± 1.4	33.9 ± 1.3	33.2 ± 1.2	a > b
State Anxiety at T0	34.8 ± 1.7		37.6 ± 2.3		ns
State Anxiety at T1	45.9 ^a ± 2.3	35.4 ^b ± 1.7	45.5 ^c ± 2.7	38.4 ^d ± 2.3	a > b, c > d
State Anxiety at T2	32.1 ^a ± 1.8	26.7 ^b ± .90	33.0 ± 2.6	29.4 ± 1.5	a > b
State Anxiety at T3	32.7 ± 1.8	30.3 ± 1.3	31.5 ± 2.4	32.6 ± 2.3	ns
Salivary CORT at T0 (nmol/L)	6.4 ± 1.1		9.1 ± 1.4		ns
Salivary CORT at T1 (nmol/L)	9.3 ^a ± 1.3	6.0 ^b ± .72	9.7 ± 1.1	7.9 ± 1.3	a > b
Salivary CORT at T2 (nmol/L)	7.1 ^a ± .85	5.0 ^b ± .68	8.9 ^c ± .98	5.5 ^d ± .92	a > b, c > d
Salivary CORT at T3 (nmol/L)	4.6 ± .68	4.1 ± .64	6.5 ^c ± .71	3.7 ^d ± .67	c > d

Unless otherwise noted, data are presented as means ± SE. The following comparisons were tested with *t* tests: stress men versus control men, stress women versus control women, stress men versus stress women, and control men versus control women. Relationships between groups are listed for the significant ($p < .05$) comparisons. Salivary CORT and State Anxiety measurements were taken immediately before the stress procedure (T0), immediately after the stress or control procedure (T1), 30 min after the stress or control procedure (T2), and 60 min after the stress or control procedure (T3). NEO, NEO Five Factor Inventory; CORT, corticosterone.

^astress men.

^bcontrol men.

^cstress women.

^dcontrol women.

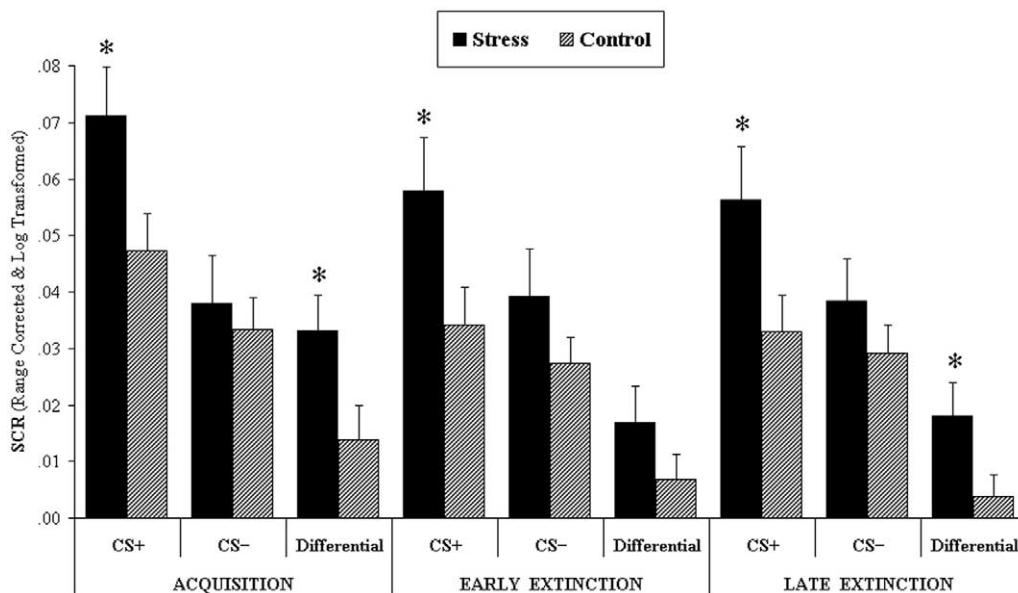


Figure 1. Magnitudes of skin conductance responses (SCR) to stimuli during the fear conditioning procedure for men. **Error bars** indicate the SEs. CS+, conditioned responses to the conditioned stimulus (CS) that was followed by the startling unconditional stimulus (UCS); CS-, responses to the stimulus that was never followed by the UCS; Differential, differential conditioned responses, calculated as the difference between CS+ and CS- responses. *Two-tailed *t* test indicated a significant group difference (stress vs. control; $p \leq .05$).

extinction [$F(1,47) = 4.2, p = .05$] but did not reach significance during early extinction [$F(1,47) = 1.7, p = .20$] (Figure 1). Exposure to the stressor, therefore, increased conditioned responding and differential conditioning in the male participants.

For women, there were no significant group differences in CS+ or CS- responses during any of the trial blocks (all *F* values < 2.0 and *p* values > .17) (Figure 2); however, post hoc analysis of the conditioning difference scores indicated that differential conditioning was smaller for women in the stress group, compared

with women in the control group, during early extinction [$F(1,43) = 4.0, p = .05$] but not during acquisition [$F(1,43) = .01, p = .92$] or late extinction [$F(1,43) = .95, p = .34$] (Figure 2). Thus, stress appeared to reduce differential conditioning in women, but only during the first block of extinction trials.

Unconditional Responses

Stress-related modulation of conditioning might arise from stress-induced changes in unconditional responding (see Jacobs

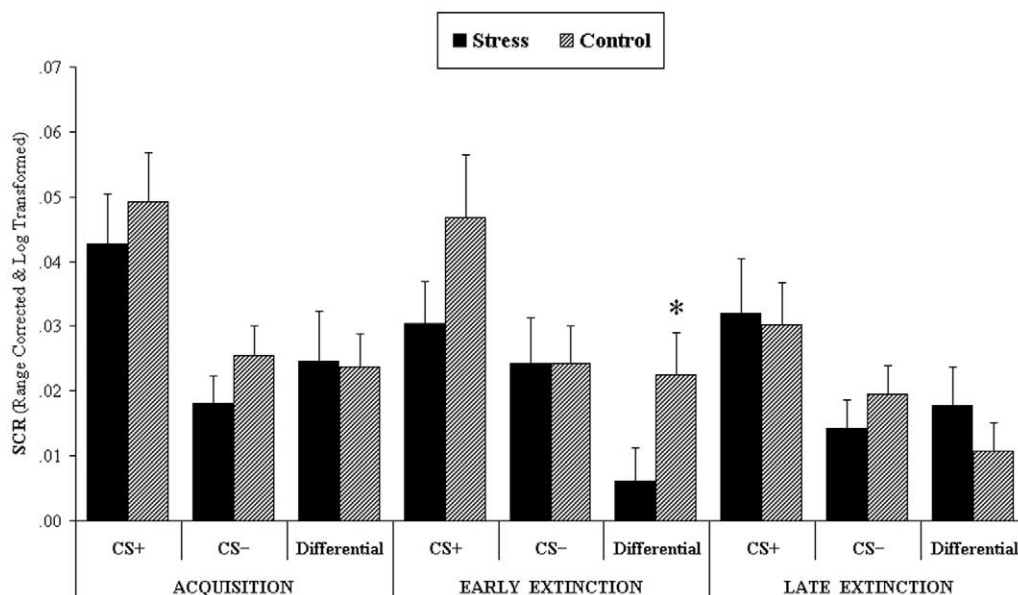


Figure 2. Magnitudes of skin conductance responses (SCR) to stimuli during the fear conditioning procedure for women. **Error bars** indicate the SEs. CS+, conditioned responses to the conditioned stimulus (CS) that was followed by the startling unconditional stimulus (UCS); CS-, responses to the stimulus that was never followed by the UCS; Differential, differential conditioned responses, calculated as the difference between CS+ and CS- responses. *Two-tailed *t* test indicated a significant group difference (stress vs. control; $p \leq .05$).

and Blackburn 1995 for a brief review). In our procedure, unconditional responses to the UCS were represented by SCRs in the CS+ trials during the acquisition phase, because each presentation of the CS+ was immediately followed by the UCS. The effects that reached significance were those indicating that participants exhibited the normal pattern of habituation to the CS+/UCS pair but not to the CS– (i.e., main effects of CS-type and interaction effects between CS-type and blocks, F values > 42.0 and p values $< .001$). Thus, unconditional responses were not influenced by stress exposure.

Anxiety Reports

At the beginning of the study, there were no group differences in anxiety reports (all t values < 1.0 and p values $> .30$). The participants in the stress group reported greater subjective anxiety than those in the control group immediately after the stressor [$F(1,90) = 12.78, p = .001$] and 30 min after the stressor [$F(1,90) = 6.84, p = .01$] but not 60 min after the stressor [$F(1,90) = .79, p = .37$]. Although the analyses detected no significant gender differences (all F values < 2.20 and p values $> .14$), post hoc analyses were conducted separately for men and women. The mean levels of subjective anxiety reported by men and women in the stress and control groups are included in Table 1. Men in the stress group reported greater subjective anxiety than those in the control group immediately and 30 min after the stressor [$t(47) = 3.7, p = .001$; $t(47) = 2.76, p = .01$] but not 60 min after the stressor [$t(47) = 1.1, p = .30$]. In women, the stress group reported greater anxiety than the control group only immediately after the stressor [$t(43) = 2.0, p = .05$; all other t values < 1.2 and p values $> .22$]. For both men and women in the stress group, subjective anxiety after the stressor was significantly elevated over baseline [men: $F(1,23) = 18.7, p < .001$; women: $F(1,21) = 28.5, p = .01$]. Subjective anxiety measures were not significantly correlated with differential conditioning in either gender (all r values $< .29$ and p values $> .10$).

Salivary CORT

At the beginning of the study, there were no group differences in CORT (all F values < 1.6 and p values $> .21$). The stress group had greater CORT levels than the control group at every measurement after stress exposure (all F values > 4.00 and p values $\leq .05$). Although the analyses detected no significant gender differences (all F values < 1.00 and p values $> .30$), post hoc analyses were conducted separately for men and women. The mean levels of salivary CORT collected from men and women in the stress and control groups are included in Table 1. Men in the stress group had higher CORT levels than those in the control group immediately and 30 min after the stressor [$F(1,45) = 6.0, p = .02$; $F(1,45) = 4.6, p = .04$] but not 60 min after the stressor [$F(1,45) = .60, p = .44$]. For men in the stress group, CORT levels after the stressor were significantly elevated over baseline [$F(1,23) = 10.6, p = .003$]. In stressed men, CORT change scores were positively correlated with differential conditioning during the acquisition test trial [$r(24) = .56, p = .01$] and during late extinction [$r(24) = .43, p = .04$] but not during early extinction [$r(24) = .15, p = .50$]. Thus, the stress-induced enhancement of differential conditioning found in our male participants was related to CORT responses to the stressor.

For women, CORT levels immediately after the stressor were not significantly higher than for the control group [$F(1,41) = .77, p = .39$] but became elevated 30 min and 60 min after the stressor [$F(1,41) = 4.9, p = .03$; $F(1,41) = 6.4, p = .02$]. Stressed women did not, however, exhibit elevated CORT levels after the stressor

relative to their own baseline [$F(1,21) = .86, p = .37$]. The CORT measures were not correlated with differential conditioning in stressed women (all r values $< .15$ and p values $> .49$).

Individual Differences

None of the personality measures were related to differential fear conditioning in stressed men or stressed women. Therefore, the measured individual differences did not mediate the stress-induced alterations in emotional learning. Significant correlations were found, however, in the control group. In control women, differential conditioning correlated positively with agreeableness and trait curiosity but correlated negatively with trait anger, trait anxiety, trait depression, and neuroticism (all r values $> .43$ and p values $< .05$). Interestingly, no significant correlations were detected in control men or stressed participants.

Discussion

This is the first study to investigate the impact of acute stress on classical conditioning in healthy human participants. Results indicated that exposure to a psychological stressor facilitated fear conditioning in men but not women. The men most vulnerable to stress-induced facilitation were those with elevated CORT levels. Furthermore, there was some evidence that exposure to the stressor suppressed conditioning in women. The results of the current study are consistent with animal models and are the first to provide support for the proposal that stress exposure, even if mild, modulates fear conditioning in humans.

Compared with men in the control group, men who were exposed to the psychological stressor evidenced greater conditioned fear during acquisition and extinction trials. Stress-induced facilitation of conditioning has also been found with a variety of procedures with male rats. For example, contextual fear conditioning is enhanced after exposure to acute and uncontrollable stressors (Cordero et al 2003; Maier 1990). Other forms of aversive conditioning, such as eyeblink conditioning, are also enhanced by stress exposure (Shors et al 1992).

Subjective and hormonal measures of stress response were used to identify individuals in the current study whose conditioning was most affected by stress exposure. Anxiety reports did not predict conditioning in either men or women. Thus, it is unlikely that generalized arousal was responsible for the enhanced fear conditioning in the stressed men. Enhanced conditioned responding was found, however, in men who had higher CORT responses to the stressor. The effects of stress on fear conditioning, therefore, might have been mediated by elevated CORT levels. Studies of fear conditioning in male rats, for example, show that CORT administration alone leads to enhanced conditioning (Conrad et al 2004; Thompson et al 2004). Furthermore, the acquisition of eyeblink conditioning is enhanced 30 min after male rats are injected with stress-levels of CORT (Beylin and Shors 2003). Humans with chronically high exogenous CORT levels, however, exhibit impaired eyeblink conditioning (Grillon et al 2004). Because CORT levels in the stressed men of the current study were no longer elevated at the time of conditioning, it is unclear if CORT was involved in the enhancement of fear conditioning.

Gender differences were found in the current study indicating that female participants did not exhibit a stress-induced enhancement of conditioning. In fact, during one trial block, women in the stress group exhibited significantly less differential conditioning compared with those in the control group.

The results of the current study add to an accumulating literature suggesting that there are significant gender differences in stress and emotional memory (Breslau et al 1997; Cahill 2003; Kessler et al 1995; Kudielka and Kirschbaum 2005; Payne et al, in press). For example, the current pattern of results resembles those obtained from rats, showing that stress enhances eyeblink conditioning in male rats but impairs conditioning in females (Wood and Shors 1998). In addition, CORT was not associated with conditioning in the female participants of the current study, a finding that is also similar to findings in female rats (Wood et al 2001).

There are a number of possible explanations for the gender differences in conditioning found in this study. First, the differences might have been related to the stimuli we used, male faces and a female scream. Future studies should use stimuli that are not gender-biased, such as geometric shapes and white noise. Second, the gender differences in conditioning might have been related to differences in responses to the stressor. In men, CORT responses to the stressor peaked sooner and recovered faster than those in women. In women, stress exposure did not significantly elevate CORT levels over baseline, even though levels were significantly larger than those in the control group at the time of fear conditioning. These results might indicate that women were not adequately affected by the stressor. Subjective anxiety reports in women, however, were significantly elevated and comparable with reports from men. In addition, CORT responses in women are often found to be smaller than those in men (Kudielka and Kirschbaum 2005). The apparent lack of CORT response to the stressor might also have been an artifact of elevated baseline CORT levels. Women in the stress group started the study significantly earlier than men in the stress group, suggesting that their CORT levels might have been inflated owing to the diurnal peak in CORT occurring in the morning (e.g., Van Cauter et al 1996). Menstrual cycle and smoking might have also modulated CORT responses to stress exposure (Kirschbaum et al 1992; Kudielka and Kirschbaum 2005). The lack of these data in the current study is a weakness that limits any conclusions drawn about CORT responses or the relationship between CORT and emotional learning.

Our measures of fear conditioning were taken mostly during extinction trials and, therefore, reflected both acquisition and extinction processes. Thus, it could be argued that the large conditioned responses found in stressed men reflected a resistance to fear extinction rather than a facilitation of fear conditioning. To better understand these effects, future studies will need to separate the processes by testing fear acquisition during one session and fear extinction during another.

It is tempting to generalize the current findings to the pathogenesis of PTSD, given the presumed involvement of fear conditioning in the development and maintenance of this disorder (e.g., Bonne et al 2004). There are a number of factors, however, that limit such a generalization. First, the theoretic accounts of PTSD that predict a stress-induced facilitation of fear conditioning do not predict gender differences in this effect. In addition, the pattern of gender differences found in the current study does not reflect the development of PTSD, which is twice as prevalent in women as in men (Breslau et al 1997; Kessler et al 1995). If this study accurately reflected the pattern of gender difference found in PTSD, then fear conditioning in the female participants should have been more facilitated by stress than conditioning in the

men. Second, the current study assessed fear conditioning 60 min after stress exposure, whereas, in PTSD, the stressor is concurrent with fear conditioning and typically acts as the UCS (Pitman et al 2000). Finally, compared with typical traumatic stressors, the stressor used in this study was more social in nature, relatively mild, and produced relatively small CORT elevations. By ethical necessity, however, any attempts to model PTSD in the laboratory will be limited in similar ways.

In sum, we have shown that exposure to a relatively mild psychological stressor, accompanied by elevations in CORT, modulates fear conditioning in healthy human participants. To our knowledge, this is the first study to demonstrate relations among stress, CORT, and conditioned fear in humans. The findings confirm the relevance of animal models and provide partial support for conditioning-based accounts of PTSD. To the extent that the symptomatology of PTSD is related to the conditioned associations formed during acute stress, the stress-induced modulation of fear conditioning might serve as a useful, yet limited, model for the pathological formation of emotional memories and phobic responses in individuals who develop PTSD.

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