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Memory

ISSN: 0965-8211 (Print) 1464-0686 (Online) Journal homepage: https://www.tandfonline.com/loi/pmem20

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To cite this article: Pauline Dibbets, Anne van den Broek & Elisabeth A. T. Evers (2015) Fear conditioning and extinction in anxiety- and depression-prone persons, Memory, 23:3, 350-364, DOI: 10.1080/09658211.2014.886704

To link to this article: https://doi.org/10.1080/09658211.2014.886704

Memory, 2015
Vol. 23, No. 3, 350–364, http://dx.doi.org/10.1080/09658211.2014.886704

Routledge
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Fear conditioning and extinction in anxiety- and depression-prone persons

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(*Received 1 March 2013; accepted 20 January 2014*)

Anxiety and depression frequently co-occur and may share similar deficits in the processing of emotional stimuli. High anxiety is associated with a failure in the acquisition and extinction of fear conditioning. Despite the supposed common deficits, no research has been conducted on fear acquisition and extinction in depression. The main aim of the present study was to investigate and compare fear acquisition and extinction in anxiety- and depression-prone participants. Non-clinical anxious, depressive, anxious-depressive and control participants performed a fear discrimination task. During acquisition, the CS+ predicted an aversive event (unconditioned stimulus, US) and the CS− safety (no US). During extinction, the CS+ was no longer followed by the US, rendering it (temporarily) into a safety signal. On each CS participants rated their US expectancy; skin conductance responses (SCRs) were measured throughout. The expectancy scores indicated that high anxiety resulted in less safety learning during acquisition and extinction; no effect of depression was observed. SCRs showed that high-anxiety persons displayed less discrimination learning (CS+ minus CS−) during acquisition than low-anxiety persons. During extinction, high-depression persons demonstrated more discriminative SCR than low-depression persons. The observed discrepancies in response patterns of high-anxiety and -depression persons seem to indicate distinctive information processing of emotional stimuli.

Keywords: Fear conditioning; Safety learning; Extinction; Depression; Anxiety.

Anxiety disorders and depression are highly prevalent with prospective lifetime estimates of 49.5% and 41.4%, respectively (Moffitt et al., 2010). Moreover, both disorders frequently co-occur, suggesting a possible common underlying factor. That is, both disorders are characterised by negative affect (Barlow & Campbell, 2000; Chorpita, 2002; see for an overview Lang & McTeague, 2009), disturbances in neurotransmitter systems and dysregulation of the hypothalamic–pituitary–adrenal axis (Boyer, 2000; Goddard et al., 2010). Some authors suggest a model of a continuum in anxiety and depression in which anxiety occurs first during the life course and major depressive episodes occur later (Boyer, 2000). This temporal relationship has been observed in some studies (Fava et al., 2000; Parker et al., 1999), but not in others (i.e., generalised anxiety disorder and major depressive disorder (MDD), Moffitt et al., 2007).

Studies of human Pavlovian fear conditioning have indicated that key components of the neural fear circuitry include, among other structures, the amygdala, dorsal and rostral anterior cingulate cortex, insular cortex and hippocampal areas (see for a review, Shin & Liberzon, 2009). Anxiety problems are linked to disturbances in these areas,

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We would like to thank Charlie Bonnemayer for his technical support and helpful comments.

with the most common observation increased amygdala activity in anxiety patients (Shin & Liberzon, 2009) and anxiety-prone persons (Stein, Simmons, Feinstein, & Paulus, 2007) during processing of disorder-related and facial emotional stimuli, respectively. Likewise, increased amygdala activation during expectation of negative stimuli (Abler, Erk, Herwig, & Walter, 2007) and sustained amygdala reactivity on emotional tasks (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007) have been observed in depressive persons. Amygdala activity is not only strongly associated with fear conditioning, but also linked to changes in skin conductance response (SCR) during fear conditioning (Shin & Liberzon, 2009). Indeed, next to increased amygdala activation, persons with anxiety problems also display elevated SCRs during fear conditioning (see for reviews, Lissek et al., 2005; Mineka & Oehlberg, 2008).

The most commonly observed associative-learning deficit in people with anxiety problems is impaired fear discrimination learning (Lissek et al., 2009; Sachs, Anderer, Doby, Saletu, & Dantendorfer, 2003; but see Lissek et al., 2005 and Orr et al., 2000). During fear discrimination, one stimulus (the CS+) predicts the occurrence of an aversive event (the unconditioned stimulus (US)), whereas another stimulus (the CS−) functions as safety signal, predicting the non-occurrence of the aversive event. Especially this inhibitory safety learning seems to be impaired in anxious persons (Davis, Falls, & Gewirtz, 2000; Hermann, Ziegler, Birbaumer, & Flor, 2002; Lissek et al., 2009). Anxiety patients show greater physiological reactions (e.g., SCR and startle response) and subjective anticipatory fear than controls during CS− presentations (Lissek et al., 2005; Mineka & Oehlberg, 2008). Such increased CS− responding automatically results in diminished discrimination between CS+ and CS− (but see for different results the meta-analysis of Lissek et al., 2005; and for a different approach, Orr et al., 2000).

Additionally, anxious persons have more difficulty in detecting a change in CS+ function during extinction, in which the CS+ is no longer followed by the US (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Hermann et al., 2002; Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007; Orr et al., 2000; but see Del-Ben et al., 2001; Lau et al., 2008). During extinction, the CS+ predicts the absence rather than the presence of the US, rendering it, at least temporarily, into a predictor of the non-occurrence of the US (Bouton, 2004). In summary, anxious persons show aberrant fear conditioning, mostly expressed in a lack of inhibitory/safety learning and a malleability to detect changes in reinforcement schedules.

Though anxiety and depression frequently co-occur, little research has been conducted on fear conditioning in depression. To our knowledge, only two fear conditioning studies have included depressive participants. Nissen et al. (2010) tested patients with MDD and healthy controls with a fear discrimination paradigm in which geometrical figures were either followed by a shock (US) or not. The results indicated that only depressed participants revealed a differential SCR to the CSs+ and CSs−, with stronger responding to the CS+ than CS−. The analysis of the US expectancies yielded no difference between the MDD and control group; both groups correctly predicted the occurrence of the US after the CS+, but not the CS−. Though this might indicate enhanced autonomic discriminative responding in the depressive group, this is not necessarily the case. To our knowledge, no control was exerted on the level of anxiety in the MDD patients. Given the high rate of co-morbidity, it is likely that some patients had increased anxiety levels, resulting in enhanced CS+ conditioning (Orr et al., 2000) and, thereby, increasing discrimination. Additionally, not observing any differential SCR to the CS+ and CS− in the healthy controls is unusual, questioning the validity of the paradigm used.

Jovanovic et al. (2010) examined the specificity of aberrant fear discrimination learning in persons with either post-traumatic stress disorder (PTSD), MDD, PTSD + MDD or trauma-exposed persons with no disorder. The startle results indicated that only the MDD and no disorder groups differentiated between the stimulus combination followed by an aversive air blast (AX+) and a non-reinforced combination (BX−) with increased responding to the former compared to the latter stimulus combination. Additionally, only these groups displayed transfer of inhibition to the novel combination (AB, with B transferring its inhibitory value to A). The PTSD and the PTSD + MDD failed to display differential startle responses and did not show transfer of inhibition. However, the latter can be explained by the lack of differential responding in the first place.

Both above-mentioned studies included patients with depressive problems, but with different results. Though both yielded autonomic discriminative responding in depressive persons, only Jovanovic et al. (2010) observed discriminative responding in

controls. However, none of the studies examined differences in the malleability of an acquired fear response during extinction, which thereby remains unstudied in relation to depressive problems.

The present study aims to examine fear conditioning and extinction in high-anxiety and/or high-depression persons. We hypothesised that high-anxiety persons, irrespective of depression, would display enhanced responding to a safety signal (CS−) during fear acquisition and delayed CS+ extinction. As depression was not linked to impaired fear expression and inhibition, we expected these impairments to be restricted to high anxiety.

METHODS

Participants

First- and second-year students (n = 391) completed the Dutch version of the State and Trait Anxiety Inventory (STAI-T; Van der Ploeg, 1982), the Beck Depression Inventory second edition (BDI-II-NL; Van der Does, 2002) and a 10-item version of the Marlowe-Crowne Social Desirability Scale (MCSDS; Crowne & Marlowe, 1960; Strahan & Gerbasi, 1972).

Selection of the participants was based on their level of anxiety (STAI-T scores) and depression (BDI scores). To ensure that high anxiety did not automatically coincided with high depression and vice versa, four groups were recruited: high anxiety and low depression (anxious persons: anx); high depression and low anxiety (depressive persons: dep); high anxiety and depression (anxious-depressive persons: anx-dep); and low anxiety and depression (control persons: cont).

Based on the scores the following students were invited to participate: STAI-T scores ≥ 45 and BDI scores ≤ 10 (anx); BDI scores ≥ 13 and STAI-T scores ≤ 42 (dep); STAI-T scores ≥ 45 and BDI scores ≥ 13(anx-dep); STAI-T scores ≤ 42 and BDI scores ≤ 10 (cont) and for all participants MCSDS scores ≤ 8, so that responses to the STAI-T and BDI were less likely to be affected by social desirability bias.

These cut-off scores were based on Dutch norm tables of a student population in which a STAI-T score of 45 (and higher) falls into the top 15% (Van der Ploeg, 1982). Likewise, in our screening sample, this score also fell in the top 15% (cumulative range: 83.7–86.1%). Similarly, the BDI persons with a score of 14 or higher were invited, indicating at least a mild depression (Van der Does, 2002). Additionally, we invited persons with a score of 13 (cumulative range 89.8–91.4%) as less than 10% of our persons scored over 14.

We acknowledge that the discrepancy between low (BDI ≤ 10; STAI-T ≤ 42) and high (BDI ≥ 13; STAI-T ≥ 45) cut-off scores is small. However, increasing the gap by lowering the low cut-off scores would have decreased the amount of suitable participants, resulting in a smaller sample size and less power.

A total of 42 students participated after invitation (dep: n = 8; anx-dep: n = 11; anx: n = 9; cont: n = 14, over 75% response rate). Combining the groups into the factors results in a total of 20 persons with high anxiety, 22 with low anxiety, 19 persons with high depression and 23 persons with low depression. For sake of clarity, the demographic information and questionnaire scores are presented per group (Table 1). Note that the

TABLE 1
Demographic variables and mean (SD) scores on the depression (BDI) and trait anxiety (STAI-T) scale of the four groups

Group	*Cont*	*Anx-dep*	*Anx*	*Dep*
Age	19.64 (1.01)	20.00 (1.67)	19.44 (1.59)	20.25 (2.49)
F/M	14/0	10/1	8/1	6/2
STAI-T1	30.29 (3.12)	56.91 (8.34)	45.44 (0.88)	39.88 (1.73)
BDI-1	2.43 (1.95)	21.00 (7.54)	7.11 (2.93)	15.13 (2.48)
MCSDS	5.71 (1.49)	3.91 (1.87)	4.78 (2.28)	4.13 (0.84)
STAI-T2	28.21 (5.19)	50.82 (7.72)	42.00 (2.78)	34.75 (4.13)
STAI-S	27.50 (6.41)	47.09 (10.40)	34.89 (6.49)	32.13 (4.70)
BDI-2	3.29 (4.80)	20.45 (7.23)	5.89 (3.79)	12.75 (1.67)

Notes: Cont: control group, Anx-dep: anxious and depressive group, Anx: anxious group, Dep: depressive group, STAI-T: State and Trait Anxiety Inventory subscale Trait, BDI: Beck Depression Inventory, MCSDS: Marlowe-Crowne Social Desirability Scale. Numbers 1 and 2 indicate the scores obtained from the screening and testing days, respectively.

gender distribution reflects the clinical distribution, with more females displaying internalising problems than males (Graaf, Have, Gool, & Dorsselaer, 2012). The study was approved by the ethical committee of Maastricht University (ECP-90) and carried out in line with the declaration of Helsinki (Seoul, 2008, see also Williams, 2008).

Materials

Questionnaires

The STAI-T consists of 20 short statements to which participants respond by indicating how they generally feel on four-point scales (1 almost never to 4 almost always, range 20–80). Items include worry, tension and psychological symptoms typical of generalised anxiety problems.

The BDI contains 21 statements related to depressive symptoms. Answer possibilities range from 0 to 3 with increasing depression severity (range total score: 0–63). Cronbach's alpha of the screenings sample for the STAI-T was .90 and for the BDI the score was .87, indicating good reliability.

Stimuli

Three coloured pictures of neutral faces (506 × 650 pixels) were selected: one Caucasian female and two Caucasian males, all presented against a white background (NimStim face set, Tottenham et al., 2009). The neutral male faces served as CS+ and CS− (counterbalanced), the female was only presented during the practice phase. The aversive event (US) was a loud, male scream of 95 dB (see for a similar stimulus, Hamm, Vaitl, & Lang, 1989), presented binaurally through headphones for 2 s accompanied by an angry facial expression of the CS+ male (Lau et al., 2008). Emotional facial expressions were used as they trigger amygdala responses (Sheline et al., 2001; Shin & Liberzon, 2009; Stein et al., 2007). The experiment was programmed with E-prime software (Version 2.08, Psychology Software Tools, http://www.pstnet.com/).

Dependent variables

US expectancy. The US expectancy was measured using an online visual analogue scale, VAS, which was presented against a grey band below each CS. The indicator, a vertical 1-cm line, could be set between the outer left ("certainly not") and right end ("certainly") by a left mouse click. The words "certainly not" and "certainly" referred to the expectance that the US would follow the CS. After the mouse click, the indicator was set and could not be changed.

CS ratings. Before and after the discrimination task, the CSs (neutral faces) were rated on a paper VAS (100 mm). For each picture the valence (negative–positive) and experienced amount safety (unsafe–safe) were measured.

Skin conductance response. Electrodermal activity was recorded with Ag/AgCl electrodes (1 cm diameter) attached to the volar surfaces of the medial phalanges of the first and second finger of the non-dominant hand. Prior to attachment, participants cleaned their hands with hand-warm tap water. A Brainvision professional Brainamp ExG Skin Conductor passed the signal to Brain Vision Analyzer 2.0 software. Data were sampled at 1000 Hz and no online filters were applied.

Procedure and discrimination task

Participants were seated in a comfortable armchair, read general information about the experimental procedure and then signed the informed consent. The STAI-T and BDI were filled out (STAI-T2 and BDI2). Next, the loud scream was presented; if requested by the participant, the volume was adjusted. The participant rated the CSs and the electrodes were attached.

The discrimination task started after a baseline resting period (5 min) and consisted of a practice, acquisition and extinction phase. The practice phase was included to familiarise participants with the task and the US expectancy rating on the VAS. After pressing the spacebar, three practice trials (neutral female face) without US were presented. This CS and accompanying VAS were presented simultaneously for 6000 ms. during which the marker could be set. The inter-trial interval varied between 7000 and 15,000 ms (mean: 11,000 ms). After trial 3, an instruction screen appeared telling participants to find the regularity between the pictures and loud scream and to adjust their ratings in case the regularities changed.

Acquisition was started by a spacebar press. The CS+ and CS− were each presented 10 times. On 8 out of 10 trials, the CS+ was followed by the US and the CS− was never succeeded by the US. The US was presented for 2000 ms immediately after CS+ offset. This intermittent schedule was

used to slow down acquisition and extinction (Dunsmoor, Bandettini, & Knight, 2007; Schurr & Runquist, 1973). Stimuli were pseudo-randomly presented: a specific CS was not presented more than two times in a row and the first CS+ was never followed by the US (to slow down learning). In case the US was presented, the inter-trial interval was at least 9000 ms. All other details were equal to the practice phase.

Transition to the extinction phase was not marked. CS+ and CS− were each presented 10 times; no US was presented.

After completion, participants rated the CSs again and received course credit or a voucher of 7.50 Euros for their contribution.

Response definition and statistical analyses

SCRs to the conditioned stimuli were analysed using Ledalab (V3.2.4; http://www.ledalab.de). Pre-processing included smoothing (8 Gauss, convolution with a Hanning window) and downsampling to 10 Hz. Artefacts were manually traced and corrected using a spline interpolation. Next, a continuous decomposition analysis was run, optimising the fit and reducing the error of the model (Benedek & Kaernbach, 2010). Baseline levels were set to zero by subtracting the average skin conductance level of the preceding and succeeding inter-stimulus intervals. Subsequently, event-related activation based on the event-locked markers was calculated by using the largest deflection in conductance between 900 and 4000 ms after the stimulus onset (first interval response) with a minimum response of .02 μs. The data were range corrected by dividing each participant's SCR by his/her maximum response (Lykken & Venables, 1971), in this experiment the highest US response (UR, largest deflection 900–4000 after US onset), and subjected to a square root transformation to normalise the distribution (Siddle & Packer, 1987). Note that the uncorrected US responses did not differ between high- and low-anxiety/depression persons, Fs(1, 38) < 2.06, ps > .16. The corrected SCRs were averaged across two trials resulting in five acquisition and five extinction blocks per stimulus.

Expectancy ratings were transformed to percentages: 0% indicating no US was expected and 100% that the US would certainly follow. Data were averaged across two trials resulting in five acquisition and extinction blocks per stimulus.

The CS ratings were transformed to percentages: 0% indicating a negative valence and highly unsafe and 100% indicating a positive valence and very safe.

Group differences regarding gender and group size were analysed nonparametrically using a Kruskal–Wallis test and chi-square, respectively. Age differences were analysed using an analysis of variance (ANOVA).

To analyse the STAI-T and BDI data, repeated-measures ANOVAs (rmANOVA) were run with time (screening day and testing day) as within-subjects factor and anxiety and depression as between-subjects factors. To analyse the acquisition and extinction expectancy ratings, and SCR acquisition and extinction, rmANOVAs with stimulus (CS+ and CS−) and trial block (1–5) as within-subjects and anxiety and depression as between-subject factors were used. The valence and safety ratings were analysed with stimulus and time (before and after the task) as within-subjects and anxiety and depression as between-subjects factors.

In case of violations of sphericity, Greenhouse–Geisser corrections were made. Bonferroni Holms corrections were used in case of multiple or pairwise comparisons. The standard rejection criterion was set at $p < .05$ throughout.

RESULTS

Demographic variables and questionnaire data

See Table 1 for demographic and questionnaire data. No group differences were observed regarding age, $F < 1$, gender distribution, $\chi^2 = 3.64$, $p = .30$, or group size, $\chi^2 = 2.00$, $p = .57$. For seven participants the US volume was adjusted to 92 dB (cont, $n = 1$; anx, $n = 3$; anx-dep, $n = 3$). This number did not differ between groups, $\chi^2(3) = 5.08$, $p = .17$.

The STAI-T analysis revealed a main effect of time, $F(1, 38) = 20.56$, $p < .001$, $\eta_p^2 = .35$, anxiety, $F(1, 38) = 138.35$, $p < .001$, $\eta_p^2 = .79$, and depression, $F(1, 38) = 47.64$, $p < .001$, $\eta_p^2 = .56$. No interactions were observed, Fs < 2.39, ps > .13, $\eta_p^2 < .060$. STAI-T scores declined over time and high-anxiety and -depression persons displayed higher scores compared to, respectively, low-anxiety and -depression persons. The observed decline was not considered to be problematic as the STAI-T scores strongly correlated, $r = .86$, $p < .001$,

indicating high test–retest reliability, and no interaction with anxiety or depression was observed (see also Spence, Blumenthal, & Brenes, 2012).

BDI analysis revealed a main effect of anxiety, $F(1, 38) = 15.39$, $p < .001$, $\eta_p^2 = .29$, and depression, $F(1, 38) = 90.54$, $p < .001$, $\eta_p^2 = .70$. No main effect of time and no interactions were observed, Fs < 2.17, ps > .14, $\eta_p^2 < .055$. Both high-anxiety and high-depression persons displayed higher BDI scores than low-anxiety and low-depression persons, respectively.

Expectancy ratings acquisition

The expectancy ratings analysis revealed a main effect of stimulus, block and anxiety (see Figure 1 and see Table 2 for statistics), and stimulus × anxiety, stimulus × block and stimulus × block × anxiety interactions. No other effects were observed.

The stimulus × block × anxiety interaction was examined using separate rmANOVAs for CS+ and CS− in which block functioned as within-subjects and anxiety as between-subjects factor. The CS+ analysis revealed a main effect of block, $F(4, 160) = 88.43$, $p < .001$, $\eta_p^2 = .69$ and anxiety, $F(1, 40) = 4.34$, $p = .044$, $\eta_p^2 = .098$. Furthermore, a block × anxiety interaction, $F(4, 160) = 10.54$, $p < .001$, $\eta_p^2 = .21$, was observed. This interaction was examined by comparing high- and low-anxiety persons on each block using independent t-tests. These indicated that on block 1, anxious persons displayed higher US expectancy ratings than non-anxious persons, $t(40) = 2.92$, $p = .017$, but that the reverse was true for blocks 3–5, ts(40) > 2.55, ps < .03.

The CS− analysis revealed a main effect of block, $F(4, 160) = 21.77$, $p < .001$, $\eta_p^2 = .35$, anxiety, $F(1, 40) = 27.51$, $p < .001$, $\eta_p^2 = .41$, and a block × anxiety interaction, $F(4, 160) = 4.86$, $p = .005$, $\eta_p^2 = .11$. Independent t-tests, to examine the interaction, revealed that high-anxiety persons displayed higher US expectancies on blocks 2–5 than low-anxiety persons, ts(40) > 3.36, ps < .004. No such difference was observed on block 1, $t(40) = 1.19$, $p = .24$.

Note that at the end of the acquisition phase both low- and high-anxiety persons were able to

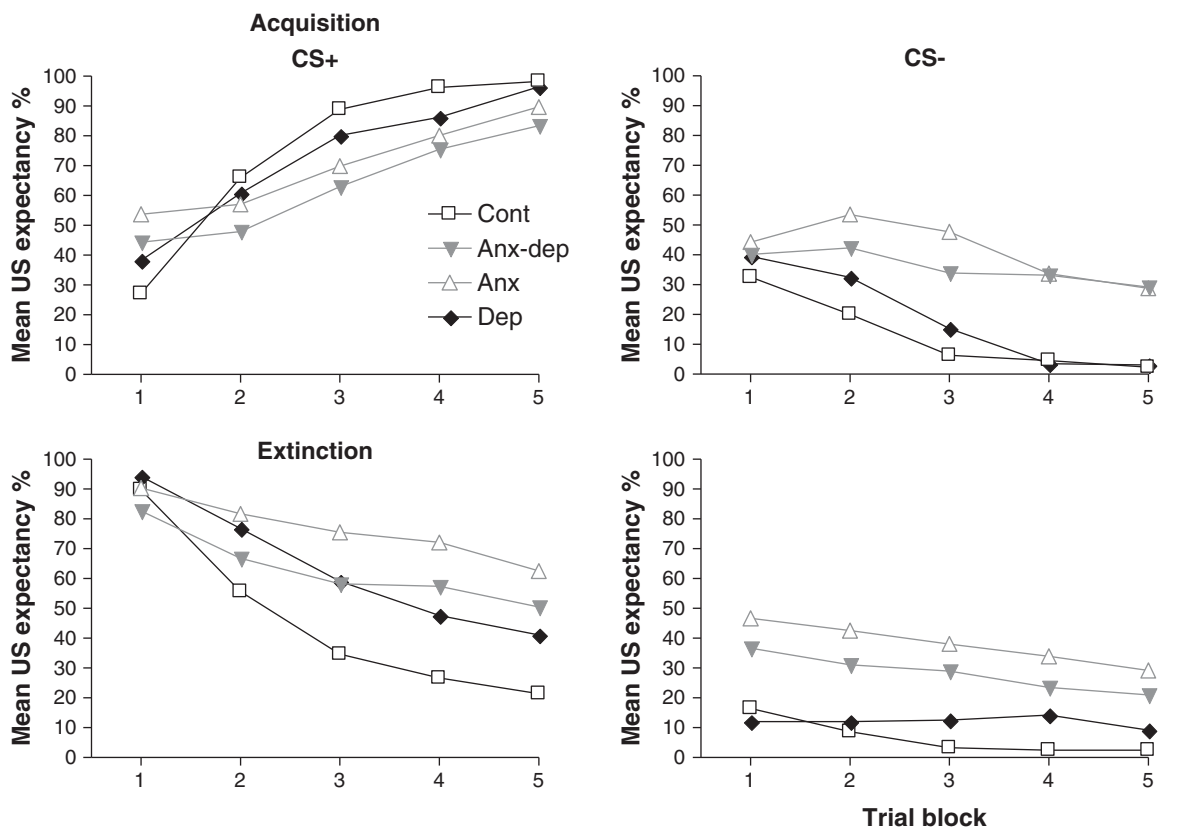

Figure 1. Mean US expectancy ratings in percent during the acquisition (upper panel) and extinction (bottom panel).

TABLE 2
rmANOVA US expectancy ratings

	Acquisition				*Extinction*			
Effect	*df*	*F*	$p_{corrected}$	$p\eta^2$	*df*	*F*	$p_{corrected}$	$p\eta^2$
Stim	1	177.95	<.001	.82	1	104.203	<.001	.73
Stim × Anx	1	21.98	<.001	.37	1	1.17	.29	.03
Stim × Dep	1	0.60	.44	.016	1	0.34	.57	.009
Stim × Anx × Dep	1	0.31	.58	.008	1	1.03	.32	.026
Block	4	9.57	<.001	.20	4	51.55	<.001	.58
Block × Anx	4	0.43	.66	.011	4	2.92	.061	.071
Block × Dep	4	0.49	.63	.013	4	0.73	.48	.019
Block × Anx × Dep	4	1.29	.28	.033	4	1.81	.17	.045
Stim × Block	4	115.60	<.001	.75	4	28.73	<.001	.43
Stim × Block × Anx	4	16.21	<.001	.30	4	11.90	<.001	.24
Stim × Block × Dep	4	0.23	.83	.006	4	0.14	.87	.004
Stim × Block × Anx × Dep	4	1.61	.20	.041	4	0.45	.65	.012
Anx	1	7.38	.01	.16	1	20.48	<.001	.35
Dep	1	0.85	.36	.022	1	0.00	.99	.00
Anx × Dep	1	1.93	.17	.048	1	7.34	.10	.16

Notes: The observed power (alpha = .05) for the observed significant effects was >.75. Stim: stimulus (CS+, CS−); Anx: anxiety (high or low); Dep: depression (high or low).

correctly discriminate between the CS+ and CS− (low anxiety: M_{cs+} = 97.65%, *SD* = 2.70% and M_{cs-} = 2.55%, *SD* = 2.94%; high anxiety: M_{cs+} = 86.28%, *SD* = 15.59% and M_{cs-} = 29.00%, *SD* = 22.57%), paired *t*-tests, *t*s > 8.33, *p*s < .001.

Expectancy ratings extinction

The analysis yielded a main effect of stimulus, block and anxiety, and a stimulus × block, a stimulus × block × anxiety and an anxiety × depression interaction. No other effects were observed (see Figure 1 and for statistics Table 2).

The stimulus × block × anxiety interaction was examined with separate rmANOVAs for CS+ and CS−, with block as within-subjects and anxiety as between-subjects factor. The CS+ analysis revealed a main effect of block, $F(4, 160) = 76.36$, $p < .001$, $\eta_p^2 = .66$, and anxiety, $F(1, 40) = 6.44$, $p = .015$, $\eta_p^2 = .14$, and a block × anxiety interaction, $F(4, 160) = 11.83$, $p < .001$, $\eta_p^2 = .23$. Independent *t*-tests per block indicated that high- compared to the low-anxiety groups gave higher US expectancy on blocks 3–5, *t*s(40) > 2.54, *p*s < .046, no group differences were observed on blocks 1 and 2, *t*s(40) < 1.48, *p*s > .21.

The CS− analysis revealed a main effect of block, $F(4, 160) = 8.09$, $p = .001$, $\eta_p^2 = .17$, and anxiety, $F(1, 40) = 22.08$, $p < .001$, $\eta_p^2 = .36$, with a general decline across trials and higher US expectancy ratings for high- than low-anxiety persons. No interaction effect was observed, $F < 1$.

The anxiety × depression interaction was examined by averaging all ratings across blocks and CSs, and running an ANOVA with group (cont, anx, anx-dep and dep) as factor. This analysis yielded a main effect of group, $F(3, 38) = 10.34$, $p < .001$, $\eta_p^2 = .45$. *Post hoc* tests indicated a lower overall mean ($M = 26.13$, $SD = 12.29$) for controls than for the anx-dep ($M = 45.67$, $SD = 12.74$) and anx ($M = 57.25$, $SD = 14.96$) group, *p*s < .006, but not from the dep group ($M = 37.86$, $SD = 15.48$), $p = .18$. Additionally, the anx group displayed a larger overall mean than the dep group, $p = .024$, no other differences were found, *p*s > .18.

SCR acquisition

The SCR analysis revealed a main effect of stimulus, with, in general, higher SCR on CS+ than CS−, and a main effect of block, indicating an overall decline for both stimuli across trial blocks (see Figure 2). This decline was not considered to be problematic as discrimination scores (CS+ minus CS− blocks) exceeded zero at the end of the acquisition, indicating differential responding to CS+ and CS− (Lipp, Siddle, & Dall, 1998; Neumann & Waters, 2006).

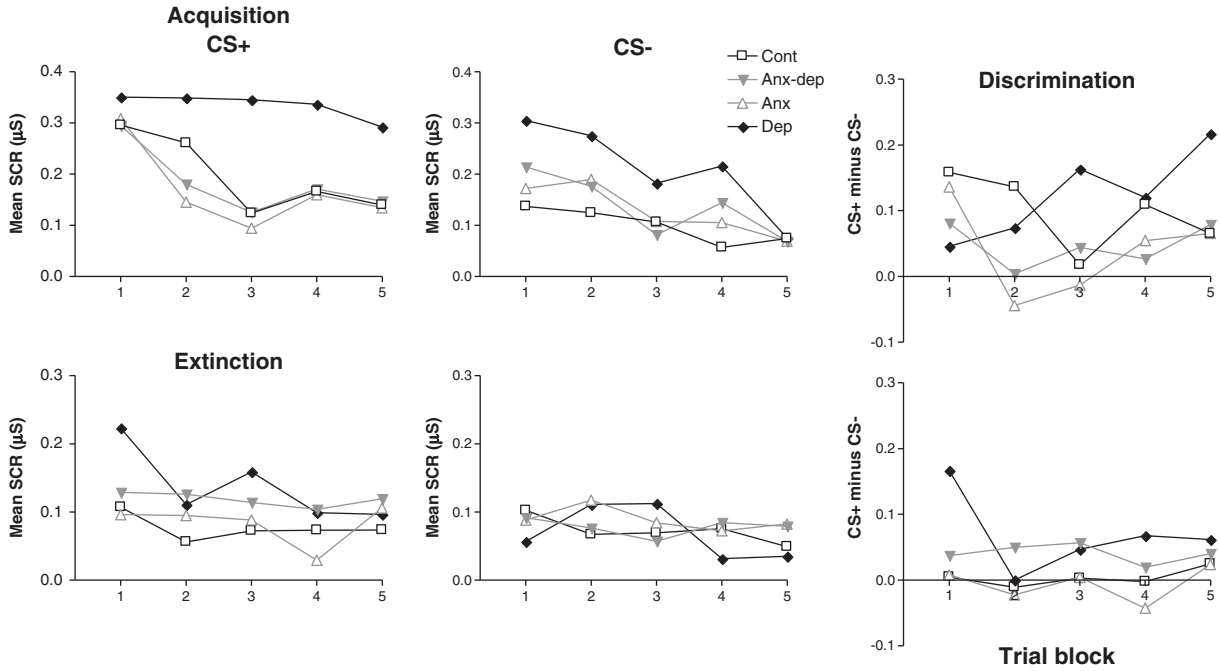

Figure 2. Mean SCR during the acquisition (upper panel) and extinction (bottom panel).

Additionally, a stimulus × anxiety interaction was observed. No other effects were found (see Table 3). To examine this interaction, separate *t*-tests were carried out on the overall means of CS+ and CS−, with anxiety as grouping variable. No effect of anxiety was found, $ts(40) < 1.38$, $ps > .17$. Separate rmANOVAs for the high- and low-anxiety persons were carried out, with stimulus and block as within-subjects factors. These analyses indicated for both groups a main effect of stimulus, $Fs(1, 19) > 5.24$, $ps < .034$, $\eta_p^2 > .21$, with higher CS+ than CS− responses, and a main effect of block, $Fs (4, 84) > 6.27$, $ps < .002$, $\eta_p^2 > .23$, with a general decrease in SCR across blocks. The interaction was analysed further using discriminations scores.

TABLE 3
rmANOVA skin conductance response

	Acquisition				*Extinction*			
Effect	*df*	*F*	$p_{corrected}$	$p\eta^2$	*df*	*F*	$p_{corrected}$	$p\eta^2$
Stim	1	34.94	<.001	.48	1	9.10	.005	.19
Stim × Anx	1	6.68	.014	.15	1	1.11	.30	.028
Stim × Dep	1	0.42	.52	.011	1	9.90	.003	.21
Stim × Anx × Dep	1	0.14	.71	.004	1	0.26	.62	.007
Block	4	14.26	<.001	.27	4	3.21	.024	.078
Block × Anx	4	0.85	.47	.022	4	1.74	.16	.044
Block × Dep	4	0.46	.70	.012	4	0.36	.80	.009
Block × Anx × Dep	4	0.30	.82	.008	4	1.84	.14	.046
Stim × Block	4	1.24	.30	.032	4	1.37	.26	.035
Stim × Block × Anx	4	0.80	.53	.021	4	0.98	.40	.025
Stim × Block × Dep	4	2.05	.091	.051	4	0.58	.61	.015
Stim × Block × Anx × Dep	4	0.94	.44	.024	4	1.06	.37	.027
Anx	1	1.57	.22	.040	1	0.008	.93	.00
Dep	1	2.31	.14	.057	1	0.404	.53	.011
Anx × Dep	1	1.58	.22	.040	1	0.067	.80	.002

Notes: The observed power (alpha = .05) for the significant effects was > .71. Stim: stimulus (CS+, CS−); Anx: anxiety (high or low); Dep: depression (high or low).

TABLE 4
rmANOVA US skin conductance response discrimination (SCR, CS+ minus CS−)

	Acquisition: discrimination				*Extinction: discrimination*			
Effect	*df*	*F*	$p_{corrected}$	$p\eta^2$	*df*	*F*	$p_{corrected}$	$p\eta^2$
Block	4	1.24	.30	.032	4	1.37	.26	.035
Block × Anx	4	0.80	.53	.021	4	0.98	.40	.025
Block × Dep	4	2.05	.091	.051	4	0.58	.61	.015
Block × Anx × Dep	4	0.94	.44	.024	4	1.06	.37	.027
Anx	1	6.68	.014	.15	1	1.11	.30	.028
Dep	1	0.42	.52	.011	1	9.90	.003	.21
Anx × Dep	1	0.14	.71	.004	1	0.26	.62	.007

Notes: The observed power (alpha = .05) for the significant effects was >.86. Stim: stimulus (CS+, CS−), Anx: anxiety (high or low), Dep: depression (high or low).

SCR discrimination score acquisition

The discrimination analysis revealed only a main effect of anxiety, with high anxiety resulting in less discriminative responding, explaining the previously observed interaction. No other effects were observed (see Figure 2 and Table 4).

SCR extinction

The analysis yielded a main effect of stimulus and block, with higher SCR for CS+ than CS− and a decrease of the responses across trial blocks. Additionally, a stimulus × depression interaction was observed. No other effects were observed (see Figure 2 and Table 3).

The observed stimulus × depression interaction was examined using separate *t*-tests on the overall means of CS+ and CS− in which depression was the grouping variable. No effect of depression was observed, *t*s(40) < 1.33, *p*s > .19. Separate rmANOVAs were carried out for the high- and low-depression persons. In these analyses, stimulus and block served as within-subjects factors. Only for the high-depression persons an effect of stimulus was observed, $F(1, 18) = 12.16$, $p = .003$, $\eta_p^2 = .40$, with CS+ exceeding CS− SCR; no other effects were observed, *F*s < 1.45, *p*s > .23, $\eta_p^2 < .062$. The interaction was additionally considered in a discrimination analysis (i.e., CS+ responses minus CS− responses).

SCR discrimination score extinction

The only effect observed in the discrimination analysis was a main effect of depression, with high depression corresponding with larger SCR discrimination explaining the previously observed interaction (see Table 4).

Ratings of the stimuli

Valence ratings

The analysis showed a main effect of time, a stimulus × time and stimulus × time × anxiety interaction. No other effects were observed (see Tables 5 and 6).

The stimulus × time × anxiety interaction was examined using separate rmANOVAs for CS+ and CS−, with time as within-subjects and anxiety as between-subjects factor. For both CS+ and CS− a main effect of time was observed, *F*s(1, 40) > 33.25, *p*s < .001, $\eta_p^2 > .45$, and time × anxiety interactions, *F*s(1, 40) > 5.19, *p*s < .029, $\eta_p^2 > .11$. For CS− a nearly significant effect of anxiety was observed, $p = .052$, $\eta_p^2 = .091$.

The CS− time × anxiety interaction was examined by comparing high- and low-anxiety persons on both measure moments using independent *t*-tests. These tests revealed that CS− received more negative ratings after the task in high-anxiety compared to low-anxiety persons, $t(40) = 2.79$, $p = .008$. Separate paired *t*-tests for the high- and low-anxiety group, to examine the CS+ interaction, indicated that in both groups the ratings declined, indicating a more negative valence, *t*s > 2.44, *p*s < .025, but with a sharper decline in the low-anxiety group, $t(40) = 2.28$, $p = .028$.

Safety ratings

The analysis of the safety ratings revealed a main effect of time, and a stimulus × time and a stimulus × time × anxiety interaction. No other effects were observed (see Tables 5 and 6).

TABLE 5
Mean (SD) stimulus ratings in percent of the four groups

Group	*Cont*	*Anx-dep*	*Anx*	*Dep*
Before discrimination task				
CS+ valence	43.96 (14.05)	38.33 (17.94)	35.28 (19.67)	43.58 (11.70)
CS− valence	42.71 (13.75)	35.33 (13.49)	44.22 (19.25)	37.89 (14.64)
CS+ safety	48.74 (18.53)	46.95 (21.42)	45.28 (19.46)	39.03 (18.74)
CS− safety	45.30 (16.56)	42.91 (18.93)	48.00 (20.93)	32.60 (12.22)
After discrimination task				
CS+ valence	26.21 (15.31)	33.07 (20.01)	23.60 (10.27)	22.95 (12.01)
CS− valence	68.37 (17.37)	46.30 (21.29)	52.70 (19.36)	61.09 (19.90)
CS+ safety	26.60 (12.40)	36.26 (15.50)	23.59 (10.98)	19.84 (15.99)
CS− safety	71.86 (16.43)	51.17 (22.63)	61.52 (19.23)	66.89 (16.71)

Notes: Cont: control group, Anx-dep: anxious and depressive group, Anx: anxious group, Dep: depressive group. The range of ratings varies between 0 and 100%, with 0% indicating highly negative (valence) or unsafe and 100% indicating highly positive or safe.

Separate rmANOVAs on CS+ and CS− to assess the observed three-way interaction revealed for both CS+ and CS− a main effect of time, Fs(1, 40) > .36.18, ps < .001, η_p^2 > .47, with a decrease in the experienced safety for CS+ and an increase in experienced safety for CS−. Additionally, for CS−, a time × anxiety interaction, $F(1, 40) = 11.73$, $p = .001$, $\eta_p^2 =$. 23, was observed. No other effects were observed, Fs < 1. Independent t-tests on the CS− data revealed that only after the discrimination task the high- and low-anxiety persons differed, $t(40) = 2.44$, $p = .019$, with high-anxiety persons displaying lower safety scores. No such effect was observed before task onset, t (40) = .82, $p = .42$.

DISCUSSION

This study evaluated fear discrimination and extinction learning in high-anxiety and -depression persons. The US expectancy results accord with previous studies that demonstrated diminished discrimination learning (see for a review, Lissek et al., 2009; Mineka & Oehlberg, 2008) and resistance to extinction in high-anxiety persons or patients (e.g., Blechert et al., 2007; Hermann et al., 2002; Michael et al., 2007; Orr et al., 2000). The results are also in line with the clinical startle data of Jovanovic and colleagues (2010), that is, during discrimination learning, less fear suppression to the safe CS− was associated with anxiety, but not

TABLE 6
rmANOVA valence and safety ratings of the CSs

	Valence				*Safety*			
Effect	*df*	*F*	*p*	$p\eta^2$	*df*	*F*	*p*	$p\eta^2$
Stim	1	0.89	.35	.023	1	0.25	.62	.006
Stim × Anx	1	0.33	.57	.009	1	2.83	.10	.069
Stim × Dep	1	0.068	.80	.002	1	0.84	.37	.022
Stim × Anx × Dep	1	1.06	.31	.027	1	0.076	.78	.002
Time	1	21.05	<.001	.36	1	23.79	<.001	.39
Time × Anx	1	0.90	.35	.023	1	1.27	.27	.032
Time × Dep	1	1.87	.18	.047	1	1.27	.27	.032
Time × Anx × Dep	1	0.53	.47	.014	1	1.08	.30	.028
Stim × Time	1	55.49	<.001	.59	1	99.09	<.001	.72
Stim × Time × Anx	1	9.39	.004	.20	1	9.35	.004	.20
Stim × Time × Dep	1	0.045	.83	.001	1	0.53	.47	.014
Stim × Time × Anx × Dep	1	0.068	.80	.002	1	1.79	.19	.045
Anx	1	2.48	.12	.061	1	0.036	.85	.001
Dep	1	0.59	.45	.015	1	1.92	.17	.048
Anx × Dep	1	0.29	.59	.008	1	1.69	.20	.043

Notes: The observed power (alpha = .05) for the significant effects was >.84. Stim: stimulus (CS+, CS−); Anx: anxiety (high or low); Dep: depression (high or low); Time (before and after experiment).

with depression. Likewise, anxious persons rated the CS− as more negative and less safe than did the low-anxiety persons. Additionally, we observed that high-anxiety persons showed a slower diminishment of the US expectancies on CS+ presentations during the extinction; no such effect was observed for depression.

The physiological data are in line with previous studies using anxiety patients (Grillon & Morgan, 1999; Lissek et al., 2009; Sachs et al., 2003), which demonstrated that high-anxiety persons showed less discriminative responding during fear acquisition than did non-anxious persons (but see, Orr et al., 2000). Furthermore, high depression resulted in more discriminative SCR during extinction compared to low depression. This increased discriminative physiological response concords with the fear acquisition findings of Nissen et al. (2010). In their study, though not corrected for levels of anxiety, the presence of depression also resulted in elevated skin conductance discrimination during fear acquisition.

The observed increased skin conductance discrimination during extinction in depression is indirectly in line with prior neuroimaging research. These studies support the notion that the amygdala is activated during the acquisition of a CS–US association and output is mediated (via the ventromedial prefrontal cortex) during extinction (Herry et al., 2010; Milad et al., 2007). Johnstone et al. (2007) demonstrated aberrant amygdala activity during reappraisal in depressive persons. Normally when individuals reappraise the affective meaning of a negative emotional stimulus, as is the case in learned extinction, amygdala activity decreases as a result of prefrontal top–down regulation. However, in the case of a depressive disorder, the down-regulation of amygdala activity was disturbed, visible as increased amygdala activity using functional magnetic resonance imaging (fMRI) and autonomic measures (pupil dilation). Additionally, Beauregard, Paquette, and Levesque (2006) showed that, while the experienced sadness was not significantly different between the control and depressed group, in depressed participants, the amygdala activation correlated positively with the difficulty they experienced during self-regulation of negative emotions. As amygdala activity and SCR are linked (Kim & Jung, 2006; Shin & Liberzon, 2009), these results indirectly correspond to our observations of more differential SCR in high-depressed compared to low-depressed participants during extinction and an absence of such an effect in non-autonomic measures. However, we cannot indicate whether this discrepancy in automatic and non-automatic responding during extinction is specific for depression as high-anxiety participants showed less discriminative autonomic responding between CS+ and CS−, which hinders interpretation of extinction-related responding (but see for trait anxiety and fMRI, Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011).

In Jovanovic et al. (2010), a lack of discriminative responding in the anxious patients was observed, which prohibited a valid test of safety transfer. In our experiment, one could use the same line of reasoning; less discrimination in the first place will result in less extinction. However, at the end of the acquisition, US expectancy ratings on CS+ were, respectively, 98% and 89% for the low- and high-anxiety groups, allowing a substantial decrease in ratings. Entering this CS+ rating as a covariate in the CS+ extinction analysis yielded similar results, indicating that resistance to extinction was not merely caused by lower CS+ ratings at extinction onset.

In contrast with our expectations and previous research (see for a review, Lissek et al., 2005), high-anxiety scores coincided with *lower* US expectancies on CS+ presentations during acquisition. This might be explained by stimulus generalisation, with CS+ transferring its excitatory strength to the CS− stimulus, and vice versa, CS− generalising part of its inhibitory value to the CS+ (see e.g., Pearce, 1987). Another explanation is that high-anxiety persons are less malleable to change their CS+ expectancies, which was tested by comparing the first CS+ trial (non-reinforced) to the second (safety learning) and the second (followed by the US) to the third (danger learning, see Appendix). The results indicate that during both safety and danger learning, high-anxiety persons more slowly adapted their response than low-anxiety persons (see also Derakshan & Eysenck, 2009).

A possible explanation for the diminished skin conductance discrimination in high-anxiety persons is their lack of contingency awareness. That is, previous studies have indicated that acquisition of a discriminatory SCR was only obtained for participants who were aware of the CS–US contingencies (Purkis & Lipp, 2001; Weike, Schupp, & Hamm, 2007). As the high-anxiety persons revealed decreased CS+ expectancy ratings and increased CS− ratings during acquisition, the lack of differential SCR might be the result of an absence of contingency awareness. Though this seems to be a plausible explanation, the US expectancy results indicated that both low- and

high-anxiety persons were well able to discriminate between the CS+ and CS−.

Though our results are indicative of diminished discriminative responding in high-anxiety persons, some studies have observed enhanced differential conditioning during acquisition and extinction in anxiety patients (e.g., Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 2000). According to Orr and colleagues many individuals who are prone for anxiety pathology display enhanced conditionability, resulting in increased fear to CS+, a larger discrepancy between CS+ and CS− (increased discrimination), and slower rates of extinction. Indeed in their studies, PTSD patients showed increased differential conditioning (Orr et al., 2000) and slower extinction (Orr et al., 2000; Peri et al., 2000) compared to trauma-exposed participants without PTSD. However, our results are more in line with inhibition account of Davis et al. (2000). That is, high-anxiety persons mainly displayed a failure to inhibit their fear response in the presence of the CS−; no increased CS+ or discrimination conditioning was observed. The discrepancy between our data and the data of Orr and colleagues can be explained by differences in research population and the paradigm employed. In the present study, non-clinical participants rather than PTSD patients were included. Additionally, we used meaningful CSs (faces) instead of coloured slides or circles, a partial instead of a continuous reinforcement schedule, and we incorporated a US expectancy measure next to the autonomic measure. Such differences can easily lead to different outcomes.

The results indicate that anxiety and depression have distinctive autonomic and behavioural response patterns. However, the following limitations need to be mentioned. First, it was difficult to find participants who fulfilled the depression criteria without co-morbid anxiety problems (see also Alloy, Kelly, Mineka, & Clements, 1990). Participants in the dep group displayed more anxiety symptoms than the cont group, but still lower anxiety scores than participants from the anx and dep-anx groups. As the factors anxiety and depression were not orthogonal, it was not possible to completely disentangle anxiety and depression effects.

Second, the research was carried out with a non-clinical sample, thereby limiting generalisability to clinical populations. Though we used a factorial design with enough power to detect main effects of anxiety (high, $n = 20$; low, $n = 22$) and depression (high, $n = 19$; low, $n = 23$), the sample size might have hindered the detection of interactions between anxiety and depression.

Additionally, the participants of the dep-anx group reported more depression than the dep group and more anxiety than the anx group ($ts > 2.1$, $ps \leq .05$). The observation that comorbidity rates tend to be higher in individuals with more severe conditions accords with clinical observations (Mineka, Watson, & Clark, 1998). However, as these persons were in the statistical analyses both part of the high-anxiety and -depression groups, this was not considered to be problematic.

Future studies should further disentangle differences in autonomic and explicit fear conditioning and extinction in anxious and depressive persons and add response measures such as the startle responses (see e.g., Grillon, 2002; Soeter & Kindt, 2010), which taps more directly on the valence of the stimulus, and add respiratory responses, as these responses might inflate error variance. Finally, using fMRI provides insight in brain regions that are involved in the acquisition, extinction and return of fear (e.g., lateral amygdala, ventromedial prefrontal cortex and hippocampus; see also Milad & Quirk, 2012) in anxious and depressive persons. Next to adding these physiological measures, we would recommend using a larger screening population to include more participants as the small sample size per group might have obscured possible interaction effects.

In conclusion, the present study seems to be indicative of differential effects of high anxiety and depression on autonomic and behavioural measures. Anxiety was mainly related to diminished safety learning and response adaptation during extinction at the behavioural level, whereas high depression was correlated with increased autonomic discriminative responding during extinction.

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APPENDIX

The first CS+ trial presented was non-reinforced, the second was followed by the US, and the third was non-reinforced. This trial order (interspaced by CS- presentations) allows us to examine the ability to (quickly) adapt responding to (non) reinforcement, especially as the US is presented after CS presentations and responses are collected prior to the US delivery. As an index of fast safety learning the response on the first CS+ trial can be compared to the second. As an index of danger learning, the responses on the second CS+ trial can be compared to responses on the third. For both the expectancy ratings and SCR two rmANOVAs were run with trial moment (first analysis: 1 vs. 2, and second analysis: 2 vs. 3) as within-subjects and anxiety and depression as between-subjects factors.

Expectancy ratings

See Figure A1. The safety learning analysis revealed a main effect of time and anxiety, and a time × anxiety interaction, Fs > 4.65, ps < .038, η_p^2 > .10. No other effects were observed, Fs < 2.88, ps > .098, η_p^2 < .071. In general, the ratings decreased, with overall higher ratings for the high-anxiety compared to the low-anxiety persons. The interaction was caused by the rapid decrease in ratings after non-reinforcement in the low-anxiety group, paired t-test $t(21) = 3.02$, $p = .006$, and an absence of response adjustment in the high-anxiety group, $t(19) = .088$, $p = .93$.

The danger-learning analysis revealed a main effect of time, and a time × anxiety interaction, Fs(1, 38) > 26.33, ps < .001, η_p^2 >. 40. No other effects were observed, Fs < 1.70, ps > .20, η_p^2 < .043. Overall, US expectancies strongly inclined; however, this effect was restricted to the non-anxious group, $t(22) = 7.53$, $p < .001$, as no increase was observed in the anxious group, $t(19) = .42$, $p = .68$.

Skin conductance response

See Figure A1. The safety-learning SCR analysis only revealed a general decline in SCR from CS+ trial 1 to trial 2, $F(1, 38) = 24.44$, $p < .001$, $\eta_p^2 = .39$, no other effects were observed, Fs < 1.06, ps > .31, η_p^2 < .027. For the danger-learning analysis, only a main effect of anxiety was observed, $F(1, 38) = 4.49$, $p = .041$, $\eta_p^2 = .11$, with high-anxiety persons displaying, overall, lower SCR than low-anxiety persons. No other effects were observed, Fs < 1.61, ps > .21, η_p^2 < .041.

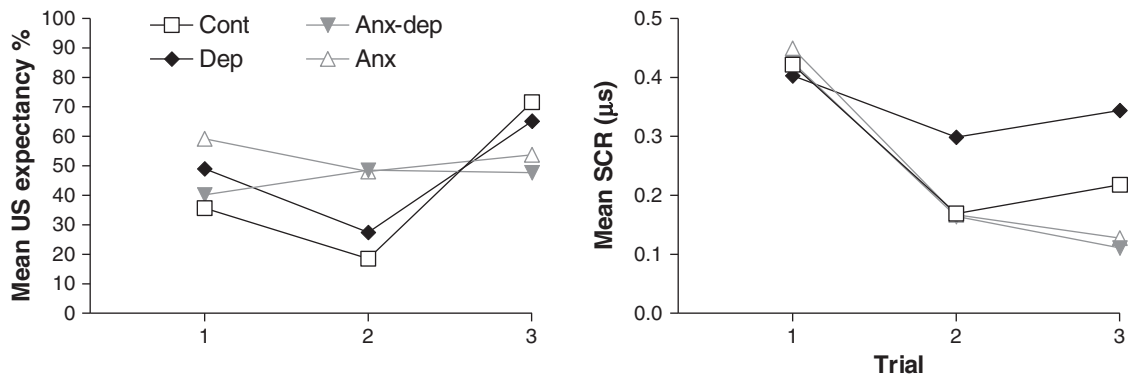

Figure A1. Mean US expectancy ratings in percent (left panel) and SCR (right panel) during the first three CS+ acquisition trials.