Journal of Psychiatric Research 135 (2021) 294–301

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Impaired fear learning and extinction, but not generalization, in anxious and non-anxious depression

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ARTICLE INFO

Keywords:
Major depressive disorder
Anxious depression
Fear learning
Psychotherapy

ABSTRACT

Fear conditioning and generalization are well-known mechanisms in the pathogenesis of anxiety disorders. Extinction of conditioned fear responses is crucial for the psychotherapeutic treatment of these diseases. Anxious depression as a subtype of major depression shares characteristics with anxiety disorders. We therefore aimed to compare fear learning mechanisms in patients with anxious versus non-anxious depression. Fear learning mechanisms in patients with major depression (n = 79; for subgroup analyses n = 41 patients with anxious depression and n = 38 patients with non-anxious depression) were compared to 48 healthy participants. We used a well-established differential fear conditioning paradigm investigating acquisition, generalization, and extinction. Ratings of valence, arousal and probability of expected threat were assessed as well as skin conductance response as an objective psychophysiological measure. Patients with major depression showed impaired acquisition of conditioned fear. In addition, depressed patients showed impaired extinction of conditioned fear responses after successful fear conditioning. Generalization was not affected. However, there was no difference between patients with anxious and non-anxious depression. Results differed between objective and subjective measures. Our findings show altered fear acquisition and extinction in major depression as compared to healthy controls, but they do not favor differential fear learning and extinction mechanisms in the pathogenesis of anxious versus non-anxious depression. The results of impaired extinction warrant future studies addressing extinction learning elements in the treatment of depression.

1. Introduction

Depression and anxiety disorders are among the most frequent mental illnesses with 12-month prevalence rates of 6.9% and 14%, respectively (Wittchen et al., 2011). Anxious depression has been classified as major depression with high levels of anxiety following a dimensional approach to describe the overlap between anxiety and depressive disorders (Fava et al., 2000). This subtype of major depressive disorder (MDD) is common with a reported prevalence between 45 and 55% (Fava et al., 2004, 2008) and associated with a worse prognosis (Schoevers et al., 2005), higher symptom severity (Kessler et al., 2003) and increased chronicity rates compared to non-anxious MDD (Van Valkenburg et al., 1984). Furthermore, depressed patients with high anxiety levels respond more slowly or not at all to treatment (Clayton

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https://doi.org/10.1016/j.jpsychires.2021.01.034
Received 1 October 2020; Received in revised form 15 January 2021; Accepted 18 January 2021
Available online 21 January 2021

et al., 1991; Davidson et al., 2002; Domschke et al., 2010b; Fava et al., 1997, 2008).

Enhanced fear conditioning and fear over-generalization are well-established factors in the pathogenesis of anxiety disorders. Fear conditioning delineates the learning process, by which a neutral conditioned stimulus (CS) comes to elicit fear through repeated pairing with an aversive unconditioned stimulus (UCS) (Lissek et al., 2005). Differential conditioning paradigms, in which one CS (CS+) but not another CS (CS-) is paired with the UCS (Britton et al., 2011; Lissek et al., 2005), allow to assess the ability to discriminate between reactions to danger cues versus safety cues (Shechner et al., 2015). Increased fear responses to conditioned safety cues (CS-) are present in anxiety patients compared to control probands during the acquisition of conditioned fear. This may indicate an impaired ability to inhibit fear in the presence of safety cues and/or an increased generalization of the fear response to safe stimuli comparable to the conditioned danger cue (Duits et al., 2015). Conditioned anxiety reactions can be alleviated by extinction. Presenting the CS + repeatedly in the absence of the UCS allows to learn a 'CS + -no threat-association' (Britton et al., 2011), which may ultimately dampens a previously learned 'CS + -threat' association (Hartley and Phelps, 2009). Results of a recent meta-analysis point at a delayed and/or reduced extinction of conditioned fear in anxiety patients (Duits et al., 2015).

Fear responses may generalize to non-threatening cues, leading to defensive reactions to stimuli not involved in the initial conditioning process, but similar to the conditioned stimuli (generalization stimuli; GS). Importantly, generalization represents an active process in which fear behavior is expressed despite the ability to discern perceptual differences (Dunsmoor and Paz, 2015). While generalization allows to respond adequately to new stimuli based on experience, over-generalization of fear to harmless stimuli results in maladaptive consequences as seen in clinically relevant fear (Dunsmoor et al., 2011). Over-generalization may therefore be a pathogenic marker of anxiety disorders (Lissek et al., 2014) and has been shown in specific phobia, panic disorder, generalized anxiety disorder and posttraumatic stress disorder (as reviewed by Dymond et al., 2015).

Only few studies analyzed fear conditioning in depression with inconclusive results. For instance, enhanced fear acquisition was observed in patients with MDD in a differential fear conditioning paradigm (Nissen et al., 2010), whereas no significant differences in fear acquisition were revealed in depressed patients as compared to healthy controls in a different setting (Kuhn et al., 2014). Moreover, to the best of our knowledge, generalization of conditioned fear has not yet been studied in MDD, and neither fear conditioning, generalization nor extinction have been studied in anxious versus non-anxious depression.

Here, we investigated these mechanisms in MDD for the first time with a particular focus on the potential influence of non-anxious and anxious depression. We expected impaired fear extinction in depressed patients as compared to healthy controls. For anxious depressed patients these impairments should be even more pronounced. Additionally, we hypothesized overgeneralization in anxious depressed patients.

2. Material and methods

2.1. Sample

We recruited 81 in-patients with a current depressive episode admitted to the Department of Psychiatry, Psychosomatics and Psychotherapy (University Hospital of Würzburg, Germany) and 48 healthy control subjects (HC). HCs were recruited via advertisements. Participants were 19–75 years, right-handed and of Caucasian ethnicity. Severe somatic or neurological medical conditions, pregnancy, drug abuse, and tinnitus lead to exclusion. Diagnosis of MDD was established by a structural clinical interview (SCID-I; Wittchen et al., 1997) and patients were excluded when a score < 14 on the 21-item Hamilton Depression Rating Scale (HAMD; Hamilton, 1960) was noted, representing a minor depression. In the control group, the absence of current and/or lifetime DSM-IV axis I disorder was confirmed using the German version of the M.I.N.I. International Psychiatric Interview (Ackenheil et al., 1999). All participants provided written informed consent. The study was approved by the ethical committee of the Medical Faculty of the University of Würzburg (No. 231/15) and conducted according to the ethical principles of the Declaration of Helsinki.

First analyses compared depressed patients and HCs, for subgroup analyses the sample of depressed patients was divided into groups with anxious vs. non-anxious depression using the anxiety-somatization index (Cleary and Guy, 1977) as applied in STAR*D (Fava et al., 2008). Patients with an index of ≥7 were classified as anxious depressed (aMDD); patients with a score < 7 were classified as non-anxious depressed (naMDD). All subjects completed the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001), Childhood Trauma Questionnaire (CTQ; Klinitzke et al., 2012), State-Trait-Anxiety-Inventory (STAI-T; Spielberger, 1989), List of Threatening Experiences (LTE; Brugha et al., 1985) and Anxiety Sensitivity Index (ASI; Alpers and Pauli, 2001) prior to the start of the experiment. Medication was categorized according to drug groups type/mechanism and compared between the two subgroups. Furthermore, a possible influence of anticholinergic medication on the Skin Conductance Response (SCR) was examined by including medication as covariate in all analyses of the SCR.

2.2. Sample characterization

Demographic information of the study subjects is presented in Table 1. Analyses were performed in a total sample of 48 HCs and 79 depressed patients (41 aMDD and 38 naMDD in subgroup analysis).

2.3. Stimuli and paradigm

Two pictures of females with neutral facial expression (NimStim Face Stimulus Set; Tottenham et al., 2009) served as either CS + or CS-. The US was a fearful female face (same actress as CS+) presented along with a 95 dB female scream (International Affective Digitized Sounds, IADS) for 1.5 s. Four generalization stimuli depicting gradual morphs from CS + to CS- in 20%-steps (GS1- GS4) were created using the graphics software Squirlz Morph Version 2.1 (Xiberpix, Solihull, UK). Stimulus presentation was performed using Presentation® software (version 16.5, Neurobehavioral Systems, Inc., Berkeley, CA). CSs and GSs were displayed for a duration of 6 s. Inter-trial intervals (ITI) varied from 9 to 12 s, during which a white fixation cross was displayed in the center of a black screen. The order of the presented stimuli was pseudo-randomized, i.e. in randomized order with a maximum of two identical consecutive stimuli.

The paradigm was based on Schiele et al. (2016), see Fig. 1.

Study participants rated each stimulus on valence, arousal and probability of UCS appearance following each experimental phase. Valence and arousal were rated on 9-point-Likert scales, ranging from 'very unpleasant' (1) to 'very pleasant' (9) and 'very calm' (1) to 'very arousing' (9), respectively. UCS expectancy was indicated as the probability of a scream following each stimulus in percent on a scale from 1 to 100 in 10% steps. Fatigue, nervousness and stress were examined on 9-point-Likert scales before and after the deployment of the paradigm.

2.4. Physiological data recording, data reduction

BrainVision Recorder software (Version 1.21.0303, Brain Products GmbH, Gilching, Germany) was used to record SCR continuously at a sampling rate of 1000 Hz. SCR was measured using two electrodes placed on the thenar and hypothenar eminences of the nondominant hand. The SCR signal was analyzed offline using Vision Analyzer 2 software (Brain Products, Gilching, Germany) and filtered at a notch filter of 50 Hz. SCR was defined as a difference between base-to-peak (in

Table 1
Descriptive characteristics of patients and controls.

	Controls (n = 48)	Anxious depression (n = 43)	Non-anxious depression (n = 38)	p-value
Female (N, %)	25 (52.1%)	27 (62.8%)	16 (42.1%)	.137
Age (M ± SD)	40.94 ± 13.44	44.88 ± 11.89	40.95 ± 14.33	.290
Number of depressive episodes (M ± SD)	–	8.24 ± 13.01	4.75 ± 5.08	.184
Bipolar disorder (N, %)	–	4 (9.76%)	6 (15.79%)	.420
Number of hospitalizations (M ± SD)	–	1.5 ± 1.52	1.97 ± 4.3	.518
Duration of illness in years (M ± SD)	–	14.34 ± 11.9	9.73 ± 7.78	.067
Suicide attempts (M ± SD)	–	0.38 ± 0.49	0.2 ± 0.41	.103
HAMD (M ± SD)	–	30.86 ± 5.07	22.47 ± 5.07	**< .001** **
anxiety-somatization index (M ± SD)	–	8.69 ± 1.35	4.55 ± 1.41	**< .001** **
HAMD score without anxiety-somatization index (M ± SD)	–	22.24 ± 4.81	19.92 ± 4.70	**< .001****
PHQ-9	3.02 ± 2.39	17.80 ± 4.61	17.44 ± 6.70	**< .001****
CTQ	45.48 ± 10.87	52.73 ± 12.51	47.87 ± 10.58	**.012** *
LTE	1.31 ± 1.24	1.85 ± 1.97	2.55 ± 2.11	**.007** *
STAI-T	34.76 ± 6.85	60.03 ± 10.66	56.69 ± 10.90	**< .001** **
ASI	10.06 ± 7.37	31.65 ± 12.65	25.45 ± 11.49	**< .001****
Medication				
SSRI (N, %)	–	10 (23.26)	11 (28.95)	.602
TCA (N, %)	–	14 (32.56)	10 (26.32)	.494
SNRI (N, %)	–	24 (55.81)	20 (52.63)	.685
NaSSA (N, %)	-	17 (39.53)	12 (31.58)	.408
Antipsychotic (N, %)	-	22 (51.16)	20 (52.63)	.982
Lithium (N, %)	-	3 (6.98)	7 (18.42)	.128
Benzodiazepine (N, %)	-	14 (32.56)	14 (36.84)	.742

M = mean; SD = standard deviation; HAMD Hamilton Rating Scale for Depression, PHQ-9 Patient Health Questionnaire, CTQ Childhood Trauma Questionnaire, LTE List of Threatening Experiences, STAI-T State-Trait-Anxiety-Inventory Trait, ASI Anxiety Sensitivity Index, SSRI Selective serotonin reuptake inhibitors, TCA Tricyclic antidepressant, SNRI Serotonin–norepinephrine reuptake inhibitors, NaSSA Noradrenergic and specific serotonergic antidepressants; * significant between-group differences at p-value < .05; ** significant between-group differences at p-value < .001.

μS) between response onset (900–4000 ms after stimulus onset) and peak (2000–6000 ms after stimulus onset). Automatic trough-to-peak analysis was corrected manually where necessary (e.g. after incorrect assignment of peaks). Responses under 0.02 μS were scored as zero responses and coded with '0'. SCR data was processed following an approach described by Dunsmoor et al. (2011). Accordingly, the base-to-peak differences were square root-transformed and gradients for each phase and each block were calculated as a function of the response to one stimulus type relative to the sum of responses to all stimuli. Thus, a comparison of response patterns between groups was possible.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 25 software (IBM Corp. Released, 2017. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). Ratings and SCR data were analyzed by repeated-measures ANOVAs with the between-subject factor group (main analysis: HC and depression, subgroups: HC, aMDD, naMDD) and the within-stimulus factors stimulus type (preacquisition and acquisition: CS+/CS-, generalization: CS+, GS1-GS4, CS-, extinction: CS+/CS-) and phase (2 levels for acquisition and generalization; 3 levels for extinction). ANOVAs were followed by t-tests where applicable necessary. Alpha was set at 0.05 and Bonferroni correction for multiple testing was applied where indicated. Greenhouse-Geisser corrections were performed for non-sphericity and adjusted values, as well as corrected values, were reported for violation of variance homogeneity assumption.

3. Results

All three investigated groups differed significantly regarding reported childhood traumata ($p = .012$) and trait anxiety ($p < .001$). Fatigue, nervousness and stress differed between all three groups ($p < .001$). The consideration as covariates had no influence on the results of the analyses performed. There was no significant difference between anxious and non-anxious depressed patients in medication, which was categorized according to drug groups type/mechanism (all $ps > .128$, see Table 1). Healthy control subjects were not taking any psychopharmacological medication according to the inclusion criteria.

3.1. Preacquisition

Prior to conditioning, there were no significant main effects or interactions for valence (all $Fs \leq 0.446$, $ps > .505$), probability ratings (all $Fs \leq 1.027$, $ps > .313$) as well as SCR (all $Fs \leq 3.317$, $ps > .071$). In contrast, a significant main effect of group was shown in arousal rating ($F(2, 125) = 4.367$, $p = .039$), driven by higher overall arousal ratings of depressed patients compared to HC ($t(125) = -2.090$, $p = .039$). To account for a potential influence of increased subjective arousal on the subsequent analyses, arousal recorded following preacquisition was added as a covariate in the model but showed no effect on the results. In the subgroup analysis, aMDD only showed higher arousal as compared to HC (1.01, 95%-CI[0.11, 1.91], $p = .024$). Again, no significant group effects emerged for valence, probability ratings, or SCR (all $ps > .088$). In total, stimuli were perceived as similar regarding dependent variables.

3.2. Acquisition

All participants showed successful conditioning as indicated by a significant main effect of stimulus type in all dependent variables (valence ($F(1, 125) = 97.02$, $p < .001$), arousal ($F(1, 125) = 168.768$, $p < .001$), probability ($F(1, 125) = 282.254$, $p < .001$) and SCR ($F(1, 121) = 9.590$, $p = .002$)), i.e., the CS + led to increased fear responses compared to the CS-. For valence ratings, an additional significant main

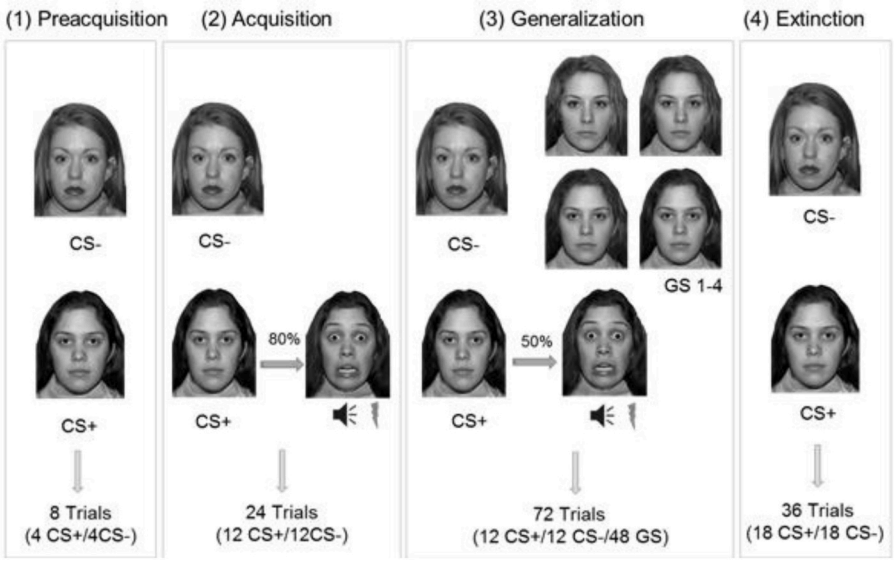

Fig. 1. Stimulus set and task design. The paradigm comprised four phases. Preacquisition consisted of four CS+ and four CS-; no US was presented. The acquisition phase consisted of 12 CS+ and 12 CS-. The CS + coterminated with the US in 80% of trials, whereas the CS- was never paired with the US. In the generalization phase, 12 CS+, 12 CS- and 12 of each generalization stimuli were presented. 50% of the CS + trials were followed by the US to maintain conditioning. CS- and all GSs were never paired with the US. The extinction phase consisted of 18 CS+ and 18 CS-, in which CS+ and CS- were never paired with US. Subjects were not informed about the CS-US contingencies. Both the acquisition and generalization trials were separated into two phases, each consisting of half the trials per phase (6 of each stimulus category). Extinction was separated into three phases, each containing one third of trials per phase (6 of each stimulus category respectively).

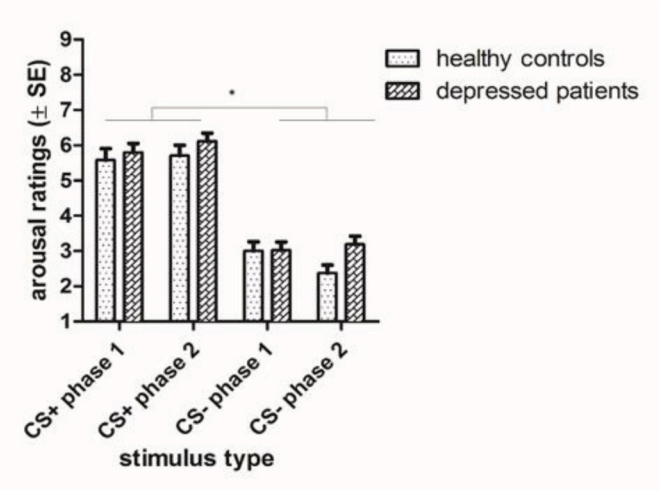

Fig. 2. Arousal ratings to the CS+ and CS- for phase one and two during acquisition. Significant interaction group × phase ($F(1, 125) = 4.237$, $p = .042$). *$p < .05$. The results indicate an impaired discriminatory learning in depressed patients. SE: Standard error of the mean.

effect of phase emerged ($F(1, 125) = 3.937$, $p = .049$). For arousal ratings, a significant phase × group interaction was revealed ($F(1, 125) = 4.237$, $p = .042$) indicating that arousal increased in MDD from phase 1 ($M = 4.41$) to phase 2 ($M = 4.65$) but decreased in HC (phase 1 $M = 4.29$; phase 2 $M = 4.04$) (see Fig. 2). For probability ratings, significant interactions emerged for stimulus × group ($F(1, 125) = 9.500$, $p = .003$), stimulus × phase ($F(1, 125) = 12.397$, $p = .001$) and stimulus × phase × group ($F(1, 125) = 4.673$, $p = .033$). The significant threefold interaction resulted from overall lower discrimination between the stimuli in depressed patients but increasing ratings for CS+ and decreasing ratings for CS- from first to the second phase. For SCR, in addition to the stimulus type main effect, a significant main effect of phase was shown ($F(1, 121) = 51.610$, $p < .001$). A possible influence of anticholinergic medication on the results of SCR was included. Here, a significant effect was shown for acquisition ($F(1, 118) = 8{,}136$, $p = .005$), generalization ($F(1, 98) = 5{,}462$, $p = .021$) and extinction ($F(1, 113) = 5{,}092$, $p = .026$), but not for preacquisition ($F(1, 118) = 2{,}814$, $p = .096$). The comparison of the results with and without anticholinergic medication showed no differences in content, so the effect seems to be rather independent.

In subgroup analyses, significant effects of group could be shown only in probability ratings ($F(2, 124) = 4.342$, $p = .015$) with Bonferroni-adjusted significant higher ratings of naMDD vs. HC (−0.74, 95%-CI[-1.40, −0.08, $p = .023$) and aMDD vs. naMDD (0.69, 95%-CI

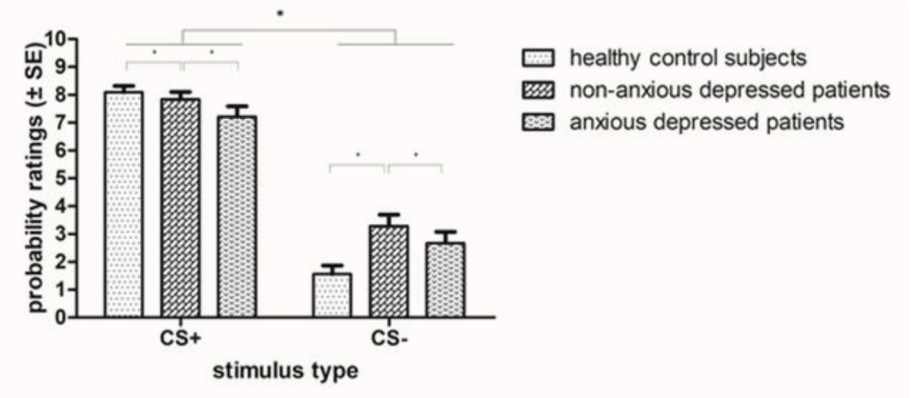

Fig. 3. Probability ratings to the CS+ and CS- during acquisition. Significant interaction stimulus type × group ($F(2, 124) = 4.718$, $p = .011$). *$p < .05$. The results show a stronger differentiation in the healthy control subjects as compared to both patient groups. SE: Standard error of the mean.

[0.00, 1.37], $p = .049$); aMDD and HC did not differ significantly. Furthermore, a significant stimulus type × group interaction was found ($F(2, 124) = 4.718$, $p = .011$; see Fig. 3). A further evaluation within groups revealed that all subgroups exhibited significantly higher probability rating for CS + vs. CS-, but this difference was stronger in HC versus aMDD and naMDD. In total, successful conditioning could be shown with deficits in safety learning in depressed patients. Interestingly, aMDD did not differ significantly from HC regarding their fear reaction to CS+.

3.3. Generalization

Valence and arousal ratings showed a significant main effect of stimulus type (valence: $F(5, 625) = 61.463$, $p < .001$; arousal: $F(5, 625) = 105.488$, $p < .001$), no other effects became significant (valence: all Fs ≤ 1.635, ps $> .192$; arousal: all Fs ≤ 2.669, ps $> .055$). For probability ratings, significant effects were shown for stimulus type ($F(5, 625) = 176.834$, $p < .001$), phase ($F(1, 125) = 21.062$, $p < .001$), group ($F(1, 125) = 1.371$, $p = .244$) and stimulus type × phase interaction ($F(5, 625) = 4.145$, $p = .001$). Depressed patients showed overall increased probability ratings as compared to HC. Ratings for all stimuli decreased from the first to the second generalization phase except ratings for CS+, which remained at the same level in all groups (see Fig. 4). For SCR only a significant effect of stimulus type was shown ($F(5, 505) = 10.215$, $p < .001$).

In subgroup analyses, a trend for between-group differences was revealed in probability ratings ($F(2, 124) = 2.879$, $p = .060$). No other main effect or interactions involving the factor group could be demonstrated (ps $> .062$). We could not perceive a stronger generalization, represented by a flatter generalization gradient, neither in depressed patients in general nor in the subgroup of anxious depressed patients.

3.4. Extinction

Valence ratings revealed significant effects for stimulus type ($F(1, 122) = 53.400$, $p < .001$), phase ($F(2, 244) = 3.994$, $p = .020$) and group ($F(1, 122) = 4.875$, $p = .029$). CS+ was rated more negative than CS-, even after the third extinction phase ($t(123) = -6.685$, $p < .001$). Similarly, for arousal ratings, significant effects were revealed for stimulus type ($F(1, 122) = 112.977$, $p < .001$) and group ($F(1, 122) = 11.880$, $p = .001$) with higher ratings for CS + than CS- and higher overall arousal ratings in depressed patients as compared to HCs (see Fig. 5). Additionally, a significant stimulus type × phase interaction ($F(2, 244) = 8.613$, $p < .001$) emerged, with a stronger decrease in CS + ratings relative to the CS-.

Probability ratings showed significant main effects for stimulus type

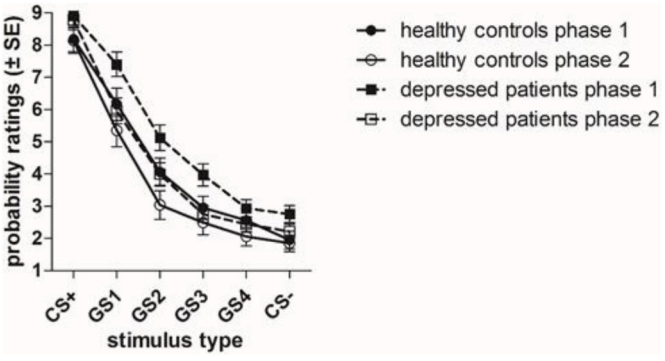

Fig. 4. Probability ratings to the CS+ and CS- during generalization. Significant stimulus type × phase interaction ($F(5, 625) = 4.145$, $p = .001$). The figure shows a sensitization effect in depressed patients as compared to healthy controls and a phase effect with decreasing ratings in second generalization phase for all stimuli except for the threat cue (CS+). SE: Standard error of the mean.

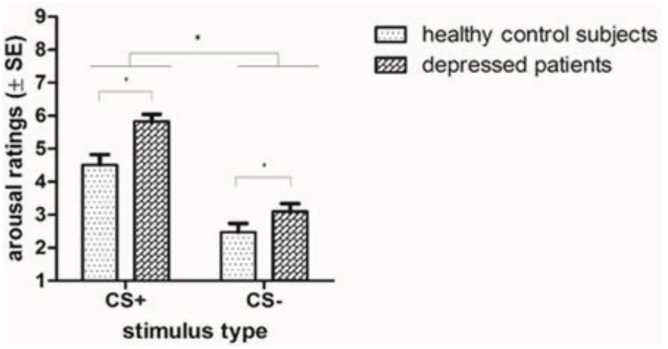

Fig. 5. Arousal ratings to the CS+ and CS- during extinction. *$p < .05$. In extinction, depressed patients rated both stimuli as more arousing as the healthy controls. Additionally, extinction took place only incompletely. SE: Standard error of the mean.

($F(1, 122) = 132.634$, $p < .001$), phase ($F(2, 244) = 36.887$, $p > .001$), and group ($F(1, 122) = 10.146$, $p = .002$). Additionally, the stimulus type × group ($F(1, 122) = 4.223$, $p = .042$) and stimulus type × phase interactions ($F(2, 244) = 9.507$, $p < .001$) were significant. CS+ was rated as more probable to occur with the UCS than the CS-, and the difference between patients and controls was higher for CS + vs. CS- ($M_{MDD} = 3.82$, $M_{HC} = 2.71$). The reduction in probability ratings over the extinction phases was stronger for the CS + as well. A significant main effect stimulus type ($F(1, 116) = 41.939$, $p < .001$) with higher responses to CS+ was observed for SCR with no other significant main effect or interaction (all Fs ≤ 0.889, ps $> .392$).

In subgroup analysis, group effects were shown in valence ratings ($F(2, 121) = 4.21$, $p = .017$) with more negative ratings in naMDD vs. HC (0.90, 95%-CI[0.14, 1.65], $p = .014$). For arousal ratings (after correction for the group differences in preacquisition, $F(2, 120) = 4.780$; $p = .010$) as well as for contingency ratings ($F(2, 121) = 5.091$, $p = .008$), a significant main effect of group could be demonstrated. For both, post-hoc tests revealed significant differences between naMDD vs. HC (arousal: −0.99, 95%-CI[−1.83, −0.15], $p = .016$; probability: −1.19, 95%-CI[−2.20, −0.17], $p = .016$), as well as aMDD vs. HC (arousal: −0.95, 95%-CI[−1.77, −0.14], $p = .017$; probability: −1.04, 95%-CI [−2.03, −0.06], $p = .035$), while patient groups did not differ significantly (arousal: 0.04, 95%-CI[−0.83, 0.92], $p = .993$; probability: −0.14, 95%-CI[−1.20, 0.91], $p = 1.000$). SCR analysis showed no significant group effects ($p = .376$). In total, extinction was impaired in depressed patients compared to healthy controls. However, no significant differences between aMDD and naMDD could be observed.

3.5. Influence of trait anxiety and childhood traumata

In addition, due to the group differences in trait anxiety reported above, analyses with the group factor high and low anxiety were performed using a STAI-T median split. There were no essential differences to the results of the preceding subgroup analyses using the anxiety-somatization factor. However, a medium effect was found in the correlation between STAI-T and HAMD ($r = .341$).

4. Discussion

To our knowledge, this is the first time that fear conditioning, generalization, and extinction were examined in one study in depressed patients.

Our applied paradigm lead to strong levels of differential conditioning as illustrated by higher responses to the threat cue compared to the safety cue across all participants. Arousal ratings revealed an impaired discriminatory learning in depressed patients. Group differences during acquisition emerged for probability ratings: depressed

patients differentiated less clearly and delayed between threat and safety cues. Only few studies have investigated fear conditioning in MDD so far. Results have been inconclusive, showing either no effect or increased fear acquisition in depression (Jovanovic et al., 2010; Kuehl et al., 2019; Nissen et al., 2010). Our results may be explained by methodological differences, e.g. different variables measured or social stimuli, thereby reducing the comparability to previous reports. Our study suggests generalization of fear responses as reflected in ratings and physiological measures. Increased probability ratings among depressed patients may represent a sensitization effect, rather than stronger generalization, as has been previously observed in generalization studies in anxiety patients (Lissek and van Meurs, 2015), but not been replicated in a clinically depressed sample until now. Importantly, no difference regarding the generalization gradients between depressed patients and controls was noted. One study on generalization in non-clinical depression (Park et al., 2018) observed also no correlation between depressive symptoms and fear generalization. Thus, our results showed successful conditioning, which was impaired in depressed patients. Furthermore, despite generalization was not stronger, a sensitization effect appeared in patients with MDD. Accordingly, our results suggest that acquisition is impaired in both depression and anxiety disorders, but generalization does not appear to be affected. This possibly suggests a differentiating factor between anxiety disorders and anxious depression.

In the extinction phase, probability ratings showed impaired extinction in depressed patients compared to controls. Only few studies have examined fear extinction in depression so far. Otto et al. (2014) also reported impaired extinction in depression, putatively due to cognitive deficits in depressed patients (Bora et al., 2012; Lee et al., 2012; McKinnon et al., 2009). Since cognitive deficits have been shown consistently in depression (Austin et al., 2001; Lee et al., 2012; Ravnkilde et al., 2002), future studies may assess and control for those. In addition, other mediating factors such as childhood traumata might be included, which are a well-known shared etiological factor of anxiety disorders and depression (Martins et al., 2014). Some studies showed that stratification for them might lead to different results (Dibbets et al., 2015; Kuehl et al., 2019; Kuhn et al., 2014).

In our study, anxious-depressed patients reported significant more traumata compared to the other groups. Given that fear learning patterns differed between patients and controls, but not between anxious and non-anxious depressed patients, additional moderating factors seem to be important. One such factor could be cognitive performance, as discussed above.

Contrary to our hypothesis, no differences between patients with anxious and non-anxious depression were observed. Anxious and non-anxious depressed patients showed impaired safety learning in probability ratings consistent with the results of a meta-analysis by Lissek et al. (2005), describing weaker inhibitory associations among anxiety patients in discrimination studies. Our findings may suggest that associative learning emerged in both MDD patients and controls, but patients were unable to inhibit the fear response in the presence of a safety cue (CS-) in terms of probability measures. This would be in line with a lack of specific patterns between anxious and non-anxious depression. Likewise, no differences between anxious and non-anxious depressed patients were noted for fear generalization, in contrast to several previous studies demonstrating overgeneralization of conditioned fear in anxiety disorders (as recently reviewed; Dunsmoor and Paz, 2015). Accordingly, overgeneralization seems to be characteristic of anxiety disorders and might therefore represent a risk factor in their pathogenesis. While our results showed that extinction in anxious and non-anxious depression was impaired, no differences between patients with anxious and non-anxious depression were noted. This is again in contrast to patients with anxiety disorders, showing elevated conditioned fear responses during extinction (Lissek et al., 2005). Importantly, anxious depressed patients showed high scores in anxiety questionnaires. Thus, a lack of anxiety is possibly not the underlying explanation for differences from the well-established findings in anxiety disorders. Therefore, it is tempting to speculate that our results may indicate that anxious depression results at least partly from other or additional etiological factors than anxiety disorders. This is also supported by the classification of anxious depression as a subtype of depression, which allows overlaps to anxiety disorders, but also takes differentiating factors into account.

According to classification of anxious depression as a subtype of MDD, we applied a categorical classification of anxious depression in this study, as this approach has produced a reliable classification in previous studies (Fava et al., 2008). However, there is a debate whether a dimensional classification could increase reliability by addressing the entire spectrum of anxiety. In addition, with regard to validity, an attention bias in depression and anxiety disorders must be considered (Garcia et al., 2019), which in the case of depression tends to refer to negative information, e.g. sad facial expressions (Bistricky et al., 2011; Peckham et al., 2010; Winer and Salem, 2016), and in the case of anxiety disorders tends to danger stimuli, e.g. angry facial expressions (Bantin et al., 2016; Bar-Haim et al., 2007). The reactions to the anxious facial expressions could thus be influenced to different extent by the presence of depression or anxiety. However, a strength of the paradigm certainly lies in the greater external validity with respect to other paradigms through the use of disorder-relevant social stimuli (Lissek et al., 2008b) and in the good comparability due to frequent use (Lau et al., 2008; Schiele et al., 2016).

Furthermore, on the methodological level, our results revealed discrepancies between SCR and ratings, and between valence/arousal ratings and probability ratings. SCR seems to depend on conscious discriminative fear learning. Some studies have suggested to implement startle instead of SCR, since a startle reaction seems to be independent from conscious discriminative fear learning (Sevenster et al., 2014). Importantly, our results showed a strong differential learning after acquisition and may therefore not be explained by this effect. However, probability ratings may represent a more cognitive expression of threat anticipation, reflecting declarative knowledge of stimulus contingencies (Sevenster et al., 2012; van Well et al., 2012). This is consistent with previous research providing evidence for a dissociation between cognitive expressions of fear (i.e. SCR and stimulus contingency awareness) and affective expressions of fear (i.e. self-reported anxiety and startle responses) (Soeter and Kindt, 2010, 2012).

The sample of the present study is comparable to other samples investigating anxious depression (Table 1; Fava et al., 2004; Fava et al., 2008). Anxious depressed patients had higher scores in HAMD than non-anxious depressed patients, indicating a more severe illness, even after subtracting the items of the anxiety/somatization index from the total HAMD score. Due to matching of the groups according to sex, detection of sex effects may be impaired. Importantly, there were no differences in the medication of anxious and non-anxious depressed patients. Furthermore, a strength of the paradigm lies in the use of social stimuli, which are described as more strongly associated with depression and anxiety than the geometrical shapes or natural scenes used in many of the above-mentioned studies (Lissek et al., 2008b).

Several limitations apply to our study. An explanation for missing group effects between anxious and non-anxious depressed patients could be the small sample size. A post-hoc power analysis was conducted using G*Power3.1 (Faul, 2007). Results indicated a 99% chance of detecting a medium effect size ($f = 0.25$) with an alpha $= .05$ between the three groups within the total sample of 129 participants. Additionally, controls did not receive medication, whereas depressed patients received medication according to doctor's choice within a naturalistic study design. Previous studies showed mixed results concerning the effect of drugs on fear generalization and extinction (Burghardt et al., 2013). To control for possible anticholinergic effects of medication on SCR, we conducted analyses for SCR with a covariate examining the influence of medications status on the results. The findings suggested a rather independent effect of anticholinergic medication. Moreover, our sample sizes were too small to perform further subgroup analyses. Further

studies in larger patient samples are needed to clarify these effects in the future. Larger sample sizes will allow analyses taking genetic markers into account, in systems known to modify fear conditioning and extinction as well as the anxious depression phenotype such as the neuropeptide Y system (Domschke et al., 2010a; Verma et al., 2012). Probability ratings were collected at the end of each experimental phase rather than continuously after presentation of each stimulus. Thereby, memory effects cannot be excluded but on the other hand, the suppression of fear responses through evaluative processes could be avoided (Lange et al., 2003; Taylor et al., 2003). Previous studies using on-line probability ratings showed qualitatively comparable results (Haddad et al., 2013; Lissek et al., 2008a). In general, a potentially confounding effect of motivational or other unspecific perceptual processes in relation to the stimuli cannot be excluded. Finally, individual differences in response to the kind of stimulus itself cannot be excluded given that we detected pre-conditioning group differences regarding overall arousal ratings. Despite the previously discussed limiting factors, this study offers some interesting results, which have not been examined so far and will be summarized in the following.

We observed delayed acquisition and impaired inhibitory learning in depressed patients as well as a sensitization effect in generalization, but no differences regarding the shape of the generalization gradient, i.e. no overgeneralization of conditioned fear compared to healthy controls. Additionally, impaired extinction in depressed patients was shown. In subsequent subgroup analyses, impaired extinction was observed in both patient groups compared to healthy controls in the context of similar patterns in acquisition and generalization of conditioned fear responses. These findings suggest that learning mechanisms are impaired in depression. Future studies are required to clarify if the observed alterations in learning mechanisms are specific for fear learning or rather general. In our study, anxious depressed patients do not differ substantially from non-anxious depressed patients and thereby our findings support the classification of anxious depression rather as a subtype of depression than as a form of an anxiety disorder (Nelson 2008). Due to the difficulties in safety learning as shown here, the use of cognitive techniques in addition to pharmacological antidepressant treatment seems to be relevant. In addition, the deficit or delay in extinction might suggest, that a sufficiently long therapy, as well as frequent repetitions of learned contents, should be provided in order to achieve a satisfying result. Furthermore, a strengthening of cognitive performance, e.g. by the use of specific psychological training, might be useful to support the learning process.

Author contributions

All authors were involved in the conception and design of the study and/or in analysis and interpretation of the reported data. The authors participated in drafting the work and/or added important intellectual content during the revision process.

Catherina Wurst: Investigation, Formal analysis, Writing - Original Draft, Visualization.

Miriam A. Schiele: Methodology, Writing - Review & Editing.

Saskia Stonawski: Investigation, Writing - Review & Editing.

Carolin Weiβ: Writing - Review & Editing.

Felix Nitschke: Writing - Review & Editing.

Leif Hommers: Writing - Review & Editing.

Katharina Domschke: Writing - Review & Editing.

Martin J. Herrmann: Writing - Review & Editing, Resources.

Paul Pauli: Conceptualization, Writing - Review & Editing.

Jürgen Deckert: Conceptualization, Writing - Review & Editing, Resources.

Andreas Menke: Conceptualization, Writing - Review & Editing, Resources.

Financial support

This work was supported by the Federal Ministry of Education and Research (BMBF) within the framework of the Comprehensive Heart Failure Center, Wuerzburg. It was also supported by the Interdisciplinary Center for Clinical Research, University of Wuerzburg (N-355 and N-258) as well as the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – project number 44541416 – TRR 58 "Fear, Anxiety, Anxiety Disorders" (project Z02 to KD, PP and JD, project C07 to MJH).

Declaration of competing interest

C. Wurst, M. A. Schiele, S. Stonawski, C. Weiβ, F. Nitschke, L. Hommers, M. J. Herrmann, P. Pauli: None. K. Domschke is a member of the Janssen Pharmaceuticals, Inc. Steering Committee Neurosciences. J. Deckert is the co-recipient of a grant of the Bavarian State Government to BioVariance and an investigator in a European grant to P1Vital. A. Menke has given educational lectures sponsored by the health insurance company AOK and the pharmaceutical companies Servier, Medice and Recordati.

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