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Fear extinction in anxiety patients

Comparing the different fear responses of anxiety patients and healthy controls and assessing the predictive value of fear extinction on exposure therapy treatment outcome.

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Abstract

Fear conditioning is often used in research to study which processes are involved in the extinction of fear. Comparing the fear extinction abilities of anxiety patients with healthy controls can enhance knowledge in how to treat anxiety disorders and comparing an anxiety patient's fear extinction before and after treatment can give valuable insight into the predictive value of fear extinction. A total of 135 participants, of which 70 were anxiety patients and 65 were healthy controls, participated in a fear conditioning experiment containing five phases; the habituation, uninstructed acquisition, instructed acquisition, uninstructed extinction and instructed extinction phase. Of those anxiety patients, 13 participated in the follow-up measurements. During each phase, pictures of two neutral faces served as either a danger cue (CS+) or a safety cue (CS-). During the acquisition phases of the conditioning task, an electric shock (US) was only administered after the CS+ was displayed. During the instructed phases, the participants were informed about the CS-US relationship. The subjective anxiety scores and the expectancy of a shock scores were measured using a VAS scale (0-100) and the objective anxiety was measured using startle responses that were provoked by aversive noises. Results demonstrate that anxiety patients show stronger fear responses to the CS+ and CS- than the control group in the extinction phases. There were no significant differences in how well both groups could discriminate the CS+ and the CS-. Finally, explorative studies demonstrated that anxiety patients had lower fear-responses at their post-treatment measurement in comparison with their pre-treatment measurements. Future research could focus on using fear-relevant stimuli, the use of verbal instructions or the use of D-cycloserine as an enhancer of fear extinction. It is important to further investigate the fear extinction process, because it is closely related to exposure therapy and could be of predictive value for treatment outcome.

Samenvatting

Angstconditionering is een vaak gebruikte methode in onderzoeken om te zien welke processen betrokken zijn bij het extinctie van een angst. Het vergelijken van de angst extinctie capaciteiten van angstpatiënten en een gezonde controlegroep kan meer inzicht geven in hoe angststoornissen behandeld dienen te worden. Het vergelijken van de angst extinctie van angstpatiënten voor en na een exposure behandeling kan inzicht geven in de voorspellende waarde van angst extinctie. In totaal hebben 135 participanten, waarvan 70 angstpatiënten en 65 controle groep personen waren, deelgenomen aan het angst conditioneringexperiment met 5 fasen; habituatie, ongeïnstrueerde acquisitie, geïnstrueerde acquisitie, ongeïnstrueerde extinctie, geïnstrueerde extinctie. Van de 70 angstpatiënten hebben 13 meegedaan aan het vervolgonderzoek. Gedurende iedere fase werden twee foto's van neutrale gezichten getoond die als teken van gevaar (CS+) of teken van veiligheid (CS-) fungeerden. Tijdens de acquisitiefasen werd een elektrische schok (US) alleen gegeven na de CS+. Tijdens de geïnstrueerde fasen werden de participanten geïnformeerd over de CS-US relatie. De subjectieve angstscore en de waarschijnlijkheid van een schok score werden gemeten met behulp van de VAS-schaal (0-100) en de objectieve angst werd gemeten aan de hand van startle reacties die werden opgewekt door aversieve geluiden. Het huidige onderzoek vergelijkt de angstreacties van de angstpatiënten en de gezonde controles in de extinctiefasen en vergelijkt de angstreacties van angstpatiënten voorafgaand aan hun exposure behandeling en naderhand. Uit de resultaten blijkt dat angstpatiënten hevigere angstreacties vertoonden tijdens de CS+ en CS- dan de controlegroep in de extinctiefasen. Er was geen verschil tussen de groepen in hoe goed ze konden discrimineren tussen de CS+ en de CS-. Ten slotte bleken angstpatiënten lagere angstreacties te hebben tijdens de nameting in vergelijking met de voormeting. Vervolgonderzoek zou zich kunnen richten op het gebruik van angstrelevante stimuli, het verder onderzoek van het nut van verbale instructies of het gebruik van D-cycloserine als verbeteraar van het extinctievermogen. Het is van belang om angst extinctie te bevorderen, omdat het nauw gerelateerd is aan exposure therapie en mogelijk van voorspellende waarde kan dienen.

Preface

During my master thesis I have worked together closely with An Nguyen Phuc at the Altrecht Academisch Angstcentrum in Utrecht. Although I had some previous knowledge about fear conditioning and fear extinction, this research took the information that I had learnt from textbooks to a whole new dimension. I am thankful for being able to conduct the research myself, allowing me to gain valuable insight into the procedures that are involved in research studies.

A special thanks to Puck Duits for all of the motivation, guidance and feedback she has given me during the research. Her patience and enthusiasm have made the experience very enjoyable and have really opened up my eyes to the research section of clinical psychology. I would also like to thank An Nguyen Phuc, my research colleague, for the great co-operation. Our brainstorm sessions and endless hours in the library have kept me focussed and optimistic throughout this process. Finally, I would like to thank Danielle Cath for her flexibility in lending us her room Altrecht Academisch Angstcentrum for the duration of this research. As I look back on this experience, I am truly proud of what I have accomplished.

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Introduction

Anxiety is an adaptive system in our body that helps us deal with danger or helps us to perform at the best of our abilities. Sometimes anxiety can become a pathological disorder when it is excessive and uncontrollable, requires no specific external stimulus, and manifests with a wide range of physical and affective symptoms as well as changes in behaviour and cognition. As outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), anxiety disorders include panic disorder with and without agoraphobia, social anxiety disorder, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder and posttraumatic stress disorder (American Psychiatric Association, 2007). Anxiety disorders have twelve-month prevalence estimates of 18.1%, making it the most prevalent class mental disorders (Kessler, Chiu, Demler, Merikangas & Walters, 2005).

Fears are developed through the principle of classical conditioning. The acquisition of a fear involves the pairing of a neutral stimulus (e.g. a light) with an aversive unconditioned stimulus (US; e.g. a shock). Reflexively, the US activates an unconditioned fear response (URs) (Rescorla, 1968; Watson & Rayner, 1920). The neutral stimulus is not automatically followed by an emotional reaction, but after repeated pairings with the US, the neutral stimulus becomes a conditioned stimulus (CS). The CS signals imminent US onset and induces a conditioned response (CR; e.g. anxiety) associated with the anticipation of the aversive US. This is the essence of fear conditioning. In the example of the light and a shock, after repeatedly administering a shock after presenting the light, a fear is developed for the light, because it is associated with the anticipated shock. Although fear conditioning is generally an adaptive and self-preserving form of learning, such conditioning may turn into an anxiety disorder when anxious reactivity to a CS persists without it being followed by a US (Lissek et al., 2005).

Lissek and colleagues (2005) determined two different types of paradigms that can be used during the fear acquisition; the simple paradigm and the discrimination paradigm. During the simple paradigm, one CS is repeatedly paired with an US. During the discrimination paradigm, there are generally two CSs. One stimulus (CS+) is paired with an US during the acquisition phase whilst another stimulus (CS-) is not. Participants will learn to fear the CS+ but not the CS-.

In the subsequent extinction phase, the CS+ and CS- will still be presented, but without the CS+ being reinforced by the US. The purpose of the extinction phase is to inhibit the retrieval of the previously learned, anxious response. This is known as extinction learning (Furini, Myskiw & Izquierdo, 2014). During the fear-conditioning task, the original CS-US association learned during acquisition is not erased during the extinction, but is left intact as a new secondary learning about the CS-US association (Bouton, 1993; Bouton & King, 1983). More explicitly, Bouton proposes that after extinction the CS possesses two meanings. The

first is the original excitatory meaning (CS-US) and the second is the inhibitory meaning (CS-noUS). Therefore, even though fear subsides with enough trials of the CS in the absence of the US, preservation of at least a part of the original association can still be uncovered, for example by a spontaneous recovery over time (Baum, 1988).

The most effective treatment for anxiety disorders is exposure therapy (Craske, Treanor, Conway, Zbozinek & Vervliet, 2014). 75-95% of patients show clinically significant improvement, when measured 1 year after their treatment (Öst, 1996). Exposure therapy is based on fear extinction and works in a similar way; by repeatedly and systematically confronting anxiety patients with a fearful stimulus (Moscovitch, Antony & Swinson, 2009). Although exposure therapy is relatively successful, about half of anxiety patients experience a relapse after having completed the therapy (Craske, Liao, Brown & Vervliet, 2012; Craske & Mystowski, 2006). For example, 23% to 27% of patients with panic disorders reportedly relapse following exposure-based therapies (Brown & Barlow, 1995; Fava et al., 2001). Because of the variable treatment outcomes, it is valuable to examine if extinction learning could predict the outcome of exposure therapy for a specific patient. This may help to improve exposure therapy and minimize the number and severity of relapses in the short and long run (Craske, Kircanski, Zelikowsky, Mystkowski, Chowdhury & Baker, 2008). Furthermore, as exposure therapy does not prove effective for all patients, enhancing the knowledge of the predictive features of fear extinction could be helpful in selecting which treatment would suit a specific anxiety patient. Especially since there are multiple different treatments that have been proven effective for anxiety disorders, such as cognitive restructuring therapy (Foa et al., 1999; Marks et al., 1998; Tarrier et al., 1999). Also, an early identification of the possible failure of exposure therapy helps the therapist adjust to a different treatment at an earlier stage, which may save a considerable amount of time and prevents dropouts during therapy.

The purpose of this study was to investigate the predictive value of fear extinction on treatment outcome in patients with anxiety disorders. Lissek et al. (2005) found that anxiety patients display stronger CRs during extinction of fear compared to healthy controls. Based on these findings, the first hypothesis was that anxiety patients, without yet having had exposure therapy, will have had a significantly stronger and more intense fear response to the CS+ in the extinction phase when compared to the control group. The second hypothesis was that anxiety patients, without yet having had exposure therapy, would have had a significantly stronger and more intense fear response to the CS- in the extinction phase, as compared to the control group. A third hypothesis was to examine if both groups can discriminate between the CS+ and the CS-, or if the groups will have generalized their fear response towards both stimuli. Grillon and Morgan (1999) found that within a study of PTSD patients and healthy controls, the patient group produces a generalized fear response to the CS+ and CS- and failed

to inhibit their fear response to the CS-. Thus, the third hypothesis was that the control group would be better able to discriminate between the CS+ and CS- than the patient group and would thus unlearn the fear response to the CS+ in the extinction phases more easily.

Furthermore, exploratory studies were conducted to examine if anxiety patients improve in their extinction learning after having had exposure therapy as opposed to before their therapy. Although exposure to a CS+ without presenting the US clearly reduces fear of the CS+, even prolonged exposure therapy typically leaves the CS+ with a fear-evoking power that can relapse under certain conditions (Bouton, 1988). Because extinction reduces the fear of the CS+, it was expected that anxiety patients would have a stronger fear response in the extinction phase prior to having exposure therapy than after having ended the therapy. The hypothesis is thus that patients will report a reduced fear response to the CS+ in the extinction phase at the post-treatment measurement as opposed to their initial fear response to the CS+ in the extinction phase before having received their exposure therapy.

Methods

Participants

The initial total number of participants was 137. Two data sets were excluded from the analysis due to two dropouts in the patient group. The final group of individuals participating in this study consisted 135 people, of which 70 were anxiety patients and 65 were healthy controls. Each patient met the DSM-IV criteria as diagnosed by the SCID-I (First, Spitzer, Gibbon & Williams, 2007) and via a structured interview for one or more of the following disorders: panic disorder, social anxiety disorder, obsessive compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder, or hypochondriasis. For the exploratory research, 13 patients participated a second time in the same experiment after having completed their exposure therapy.

Prior to their exposure therapy, the anxiety patients were asked if they would participate in a research study. The patients that had given consent to participate in future experimental trials during their initial participation were recalled for testing after having ended their exposure therapy. The control group was recruited by inviting people from the social networks of the researchers that matched the patient group or via flyers that were passed around at shopping malls, shops and lunchrooms. Prior to the experiment, the control subjects that had agreed to participate were interviewed by telephone using the Mini International Neuropsychiatric Interview (MINI; Overbeek, Schruers & Griez, 1998) via telephone. This was done to ensure that there were no anxiety patients or participants with other mental disorders in the control group.

All of the participants gave written informed consent. The research consisted of 135 participants. Table 1 shows the discriptives of all participants. The Medical Ethnical Testing committee of the UMC Utrecht approved of this study under the registration number 35780.041.11.

Table 1

Descriptive statistics of the participants

	Patient group		Control group	Total
	Pre-treatment	Post-treatment		
N	70	13	65	135
Age				
M in years	34.16	31.38	33.17	33.68
Range	(19-65)	(20-57)	(18-65)	(18-65)
Gender				
Male	41%	23%	24%	35%
Female	59%	77%	71%	65%
Level of education				
*M** (SD)	3.99 (1.59)	4.15 (1.68)	4.29 (1.37)	4.13 (1.49)

* Appendix A shows interpretations of highest completed level of education.

Apparatus and Physiological Recording

The fear-conditioning task was designed at the Altrecht Academic Anxiety Centre at Altrecht in Utrecht, the Netherlands. The Digitimer shocker was used to provide the electrical shocks, which served as the unconditioned stimulus (US). This stimulation consisted of 125 2 milliseconds pulses that were delivered consecutively with a 3 milliseconds interval in-between each pulse. The total duration of the shock was 625 milliseconds. The shock was delivered via the wrist of the participants' non-dominant hand. The intensity of the electrical shock was determined with help of the Shock Work Up, in which participants could rate on a 5-point Likert Scale how uncomfortable or painful their perception of the electrical shock was. The aim was to make the US comparably aversive for every participant by selecting the shock intensity that the participant rated at a score of 4, which was 'highly aversive, but not painful'.

The task contained two neutral faces from the NimStim Face set (Tottenham et al. 2002). The two faces with different colours served as the two conditioned stimuli, of which the CS+ was repeatedly paired with the US and the CS- was never paired with the US. For half of the participants stimulus 1 (blue neutral face) was used as the CS+ and for the other

half stimulus 2 (yellow neutral face) was used as the CS+ (figure 1). For the second measurement of the patient group, a different set of neutral faces and background colours were used to decrease the likelihood of the patients remembering the exact details of their previous participation. The duration of the presentation of the CS+ and CS- was 15 seconds. Between every stimulus were 15 seconds of time in-between trials (ITI), with a range from 14 seconds to 16 seconds. During the time in-between trials, a fixation cross was presented on the screen.

Figure 1. The two neutral faces from the NimStim Face set used for the first measurement of the anxiety group and the control group.

Physiological measurements of heart rate, skin conductivity and startle response were used in this study to measure the objective fear response. To measure the heart rate, one electrode was placed above the left ankle, one on the inner part of the right forearm and one on the right breast. To measure the skin conductance response (SCR), two electrodes were applied to the inner palm of the non-dominant hand. Two small eye-blink EMG electrodes were placed on the orbicularis orculi muscle and one electrode was placed on the fore head as an isolated ground electrode. The startle probes were 50 ms bursts of aversive noise (95 dB) given via headphones, to elicit the startle response. All the responses received from the electrodes were registered using the AcqKnowledge software program (AcqKnowledge III; Biopac Systems Inc.).

To measure subjective fear responses, six questions were displayed on the computer screen after each of the five phases (habituation, uninstructed acquisition, instructed acquisition, uninstructed extinction and instructed extinction). The first question was how fearful the participants felt when presented with the CS+ and CS-. Participants submitted their ratings using VAS scale, ranging from 1 = 'Not fearful' until 100 = 'Very fearful'. The second question was what the probability was that they would receive a shock after the faces were presented. Participants submitted their ratings using VAS scale, ranging from 1 = 'Not likely' until 100 = 'Very likely'. Additionally, participants were asked to rate how certain

they were of their answer, how good their concentration was in the previous phase, how uncomfortable they felt by the aversive noises and how uncomfortable they felt by the electrical shocks. These behavioural ratings were recorded with Presentation software.

Procedure

All instructions in this study between experimenter and subject were standardized in a written procedure. When the participants arrived, they were informed about the experiment that would be conducted and they were asked to sign the informed consent forms. After doing so, the control group had to complete the Dutch Adult Reading Test (NLV) (Schmand, Lindeboom & Van Harskamp, 1992) to measure the pre-morbid intelligence level and the Digit Span Task (Wechsler, 2008) to measure the working memory. Afterwards, the control group had to conduct an online test battery that contained a demographic questionnaire, the Outcome Questionnaire (OQ-45; Lambert et al., 1996), the Brief Symptom Inventory (BSI; Derogatis & Spencer, 1993), the Beck Depression Inventory-II (BDI-II; Beck & Steer, 1987), the Anxiety Sensitive Index (ASI; Peterson & Heilbronner, 1987), the Action Control Scale (ACS; Kuhl, 1994), the State Trait Anxiety Inventory Sampler Set (STAIS; Spielberger, 1983), the State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch & Lushene, 1970), the Beck Anxiety Inventory (BAI; Steer & Beck, 1997) and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; Gibbon & Spitzer, 1997). It should be noted that not all of these questionnaires were used in the current study. The patient group had to fill in two questionnaires; the BAI to measure the severity of anxiety in adolescents and adults and the STAI to measure two distinct anxiety concepts: state anxiety and trait anxiety. The patients also had to fill in personal questionnaires that matched their disorders to monitor in which degree their symptoms have reduced. After that, both the control group and patient group were asked to sit in front of the computer. The heart rate electrodes, SCR electrodes, EMG electrodes and the shock electrodes were attached and a shock workup procedure was completed. Next, the headphones were put on, the lights were turned off and the habituation phase took place. The following four phases were respectively the uninstructed acquisition, the instructed acquisition, the uninstructed extinction and finally the instructed extinction phase. After having completed the computer task, the control group was asked to fill in the STAI, BAI and a questionnaire for females about their menstrual cycle and use of the birth control pill. The patient group was asked to fill in a test battery containing the ACS, STAIS, BAI, SCID-II and STAI. Finally, blood or saliva samples were drawn from the participant and the participant was rewarded 10 Euros as compensation for their time and effort.

Design

The design included five phases: 1) *Habituation* – consisted of 4 CS+ stimuli, 4 CS- stimuli and 4 inter-trial-interval (ITI) stimuli. In each stimulus group, 75% was reinforced with the startle probe. No shocks were administered during habituation; 2) *Uninstructed acquisition* – consisted of 8 CS+ stimuli, 8 CS- stimuli and 8 ITI stimuli. In each stimulus group, 75% was reinforced with the startle probe. 6 electrical shocks were administered during this phase. Before starting this phase, the participant was not told when the shock would be administered; 3) *Instructed acquisition* – consisted of 6 CS+ stimuli, 6 CS- stimuli and 6 ITI stimuli. In each stimulus group, 75% was reinforced with the startle probe. 5 electrical shocks were administered after one of the two stimuli. Prior to starting this phase, the participant was told when the shock would be administered; 4) *Uninstructed extinction*– consisted of 8 CS+ stimuli, 8 CS- stimuli and 8 ITI stimuli. In each stimulus group, 75% was reinforced with the startle probe. No shocks were administered during this phase, but the participant did not receive any instructions about this information beforehand; 5) *Instructed extinction*– consisted of 6 CS+ stimuli, 6 CS- stimuli and 6 ITI stimuli. In each stimulus group, 75% was reinforced with the startle probe. During this last phase, the participant was told that no shocks would be administered.

2.8 Data Reduction and Data Analysis

All blinks occurring within a 20 to 100 milliseconds time interval after the startle probe onset were scored as a valid startle response trial. Any startles before 20 milliseconds or after 100 milliseconds were excluded, because they could be accidental blinks instead of an actual fear-potentiated startle response. Furthermore, all dropouts and all participants with more than 30% of the startle responses missing were excluded from the EMG analysis (Mezig, Michalowski, Holtz & Hamm, 2008). The missing startles either indicated that the electrodes were not placed correctly or that the participant virtually had no eye-blink reflex. In SPSS, these trials were defined as missing values. These participants were however included in the subjective data analysis, as their subjective responses were still valid.

For every individual startle response of every participant, the baseline and top startle amplitudes were subtracted from each other. To check if startle responses decreased during a certain phase, the responses were divided into two averages; the first average containing the first 3 startles and the second one containing the last 2 or 3 startles, depending on which phase was presented. Trials for the 5 phases of the study were arranged in quasi-random order so that no more than two stimuli of the same sort followed sequentially. The independent variables for this design were the CS+, CS- and the ITI. The dependent variable was the startle measurement.

To see if there were any significant differences in gender or highest completed level of education, the patient group and control group were analyzed with the Chi-Square Test of Contingencies. Independent Samples *t*-Tests were used to compare if there were any significant differences between the patient group and the control group on age, NLV, digit span forward, digit span backward, total digit span, BDI, BSI and BAI. Before conducting the analyses, the assumptions of normality and homogeneity were checked. No violations were found.

Next, three One-Way Repeated Measures ANOVA′s were used to compare the patient group and control group on startle responses, subjective anxiety scores and the probability of a shock scores. Before conducting the analyses, the assumptions of normality, homogeneity and sphericity were checked. The descriptive statistics revealed that most of the values had higher Skewness and Kurtosis values than desired. The Shapiro-Wilk statistics were significant in all cases. Because of this, the assumption of normality was analyzed visually and eventually accepted with the help of scatter plots and box plots. Furthermore, Maulchy′s test of Sphericity was significant, meaning that the assumption of sphericity was violated. The Huynh-Feldt correction was thus used in all repeated measures analyses. As independent variables, the two different groups were entered as between-subject factors (patient group and control group), the phases were entered as within-subject factors (uninstructed extinction and instructed extinction) and the types of stimuli were also entered as within-subjects factors (CS+ and CS-). In the analyses for the startle responses, the ITI was added as a third stimulus. The dependent variables in the different analyses were the startle data, the VAS score for subjective anxiety and the VAS score for probability of a shock.

To analyse if there are differences in discrimination learning between the patient group and control group, new variables were computed. The difference between the average subjective anxiety scores, likelihood of shock scores and startle responses in the uninstructed extinction and instructed extinction phases to the CS- were subtracted from the CS+ to see how big the differences were. Next, a One-Way Repeated measures ANOVA was used to analyse the data.

Finally, exploratory analyses were done to see if the patient group improved their fear extinction after having completed their treatment. The second measurement data was added to the participant first measurement data. After that, another One-Way Repeated measures ANOVA was conducted. No between-subjects factors were used, and the phases (uninstructed extinction and instructed extinction), the types of stimuli (CS+ and CS-) and the moment (pre-treatment and post-treatment) were entered as within-subject factors. The dependent variables in the different analyses were the startle data, the VAS score for subjective anxiety and the VAS score for probability of a shock.

Results

Participants

The total number of participants was 135, of which 70 were patients and 65 were healthy controls. For the startle data, participants with more than 30% of the startle responses missing were excluded from the EMG analysis. The total number of exclusions for the EMG startle analysis was 16 participants, of which 10 were patients and 6 controls. Together with the 2 dropouts this makes the resulting number of participants 117. The data for subjective anxiety and likelihood of shock scores of these 16 participants were still used in the analysis. The second data measurements of the 13 patients that participated in the follow-up measurements are not added to the analyses except for the exploratory analysis in the end.

Age, gender and highest completed education

The majority of the participants were female (64%) with a mean age of M=33.68 and had vocational school listed as highest completed education level (M=4.12). All results are displayed in table 2; the groups were significantly different on their highest completed level of education, χ^2 (1, N = 134) = 12.67, p =.049. However, the association was relatively low, Φ = .31.

Table 2

Descriptive statistics of the participants

	Patient group (N=70)		Control group (N=65)		Total (N=135)		p
	M	*SD*	*M*	*SD*	*M*	*SD*	
Age in years	34.16	(10.77)	33.17	(15.09)	33.68	(12.99)	.664
Gender							.139
Male	41%		29%		36%		
Female	59%		71%		64%		
Highest completed level of education*	3.96	(1.57)	4.29	(1.37)	4.12	(1.48)	.049

Note. p is tested at a α=.05 level of significance.

* Appendix A shows interpretations of highest completed level of education.

IQ scores and working memory scores

IQ scores were measured using the NLV. One patient was excluded from the IQ assessment, because his native language was Arabic and he had insufficient knowledge of the Dutch language. The groups had similar IQ scores. The working memory scores were measured using the Digit Span forward, backward and total. The control group scored significantly

higher on the digit span backward and total, which means the control group generally has a better working memory than the patient group (table 3).

Table 3
IQ scores and working memory scores participants

	Patient group		Control group		*p*
	M	*SD*	*M*	*SD*	
NLV	97.29	(12.57)	100.58	(11.61)	.118
Digit Span forward	9.03	(2.19)	9.65	(2.07)	.095
Digit Span backward	6.53	(2.24)	7.35	(2.14)	.031
Total Digit Span	15.56	(3.98)	17.00	(3.80)	.033

p = tested at a α=.05 level of significance

The BDI, BSI and BAI

The Shapiro-Wilk statistics revealed that the control group's scores were not normally distributed. This is in line with expectations, as the control group is healthy and should score reasonably low on the BDI, BSI and BAI. On all three tests, the patient group scores significantly higher than the control group, meaning that the patient group had more depressive and anxiety symptoms than the control group (table 4).

Table 4
BDI, BSI and BAI scores

	Patient group		Control group		*p*
	M	*SD*	*M*	*SD*	
BDI	23.55	(11.47)	4.89	(4.04)	.000
BSI	76.11	(36.96)	16.35	(12.95)	.000
BAI	26.35	(13.36)	4.32	(3.89)	.000

p = tested at a α=.05 level of significance

Subjective anxiety scores

The one-way repeated measures ANOVA showed three main effects for group, $F(1,194)=8.22$, $p<.01$, partial $\eta^2=.04$, phase, $F(1,194)=112.21$, $p<.001$, partial $\eta^2=.37$, and stimulus, $F(1,194)=91.07$, $p<.001$, partial $\eta^2=.32$. A significant interaction effect was found between phase and stimulus, $F(1,146)=44.08$, $p<.001$, partial $\eta^2=.19$. The three-way interaction between phase, stimulus and group was not significant $F(1,194)=3.14$, $p=.078$, partial $\eta^2=.02$.

The results in figure 2 show that anxiety patients generally report higher feelings of anxiety than the control group. Both groups had higher anxiety ratings in the uninstructed extinction phase than in the instructed extinction phase, but there was a difference in subjective anxiety scores per phase and depending on which stimulus was used.

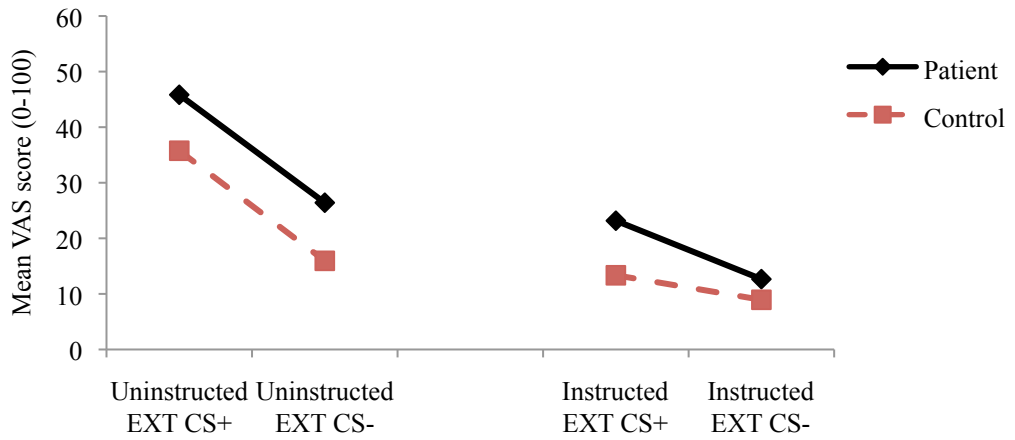

Figure 2. The subjective anxiety scores as rated by the patient and control group when either the CS+ or CS- stimuli were displayed on the screen in the uninstructed and instructed extinction.

Another repeated measures ANOVA was conducted to see how well the groups discriminated between the different stimuli. The groups were used as between-subjects factor and the discrimination variable per phase as within-subjects factor. There was a main effect for discrimination learning per phase, $F(1,194)=44.08$, $p<.001$, partial $\eta^2=.19$. However, there was no main effect found for the two groups, $F(1,194)=1.01$, $p=.316$, partial $\eta^2=.01$, and there was also no interaction effect found between the discrimination learning per phase and the groups $F(1,194)=3.14$, $p=.078$, partial $\eta^2=.02$. Pairwise comparisons revealed that both groups were better in discriminating between the stimuli in the uninstructed extinction phase ($M=19.62$) than in the instructed extinction phase ($M=7.46$), meaning that both groups have successfully learned to fear the CS+ but not the CS- and did not discriminate between the stimuli in the instructed extinction anymore, as they have then been told that the CS+ will not be followed by a shock anymore.

Likelihood of shock scores

The one-way repeated measures ANOVA showed three main effects for group, $F(1,194)=10.13$, $p<.01$, partial $\eta^2=.05$, for phase, $F(1,194)=128.49$, $p<.001$, partial $\eta^2=.40$, and stimulus, $F(1,194)=109.77$, $p<.001$, partial $\eta^2=.36$. There was also a significant interaction effect between phase and stimulus, $F(1,194)=68.95$, $p<.001$, partial $\eta^2=.26$. This means that the likelihood of shock scores differed during the two different phases and that the

scores on the CS+ were significantly different than the CS-. The three-way interaction between phase, stimulus and group was not significant $F(1,194)=.009$, $p=.926$, partial $\eta^2=.00$.

The results in figure 3 show that anxiety patients generally expected a shock more often than the control group. Both groups expected shocks more often in the uninstructed extinction phase than in the instructed extinction phase, but there was a difference in likelihood of shock scores per phase and depending on which stimulus was used.

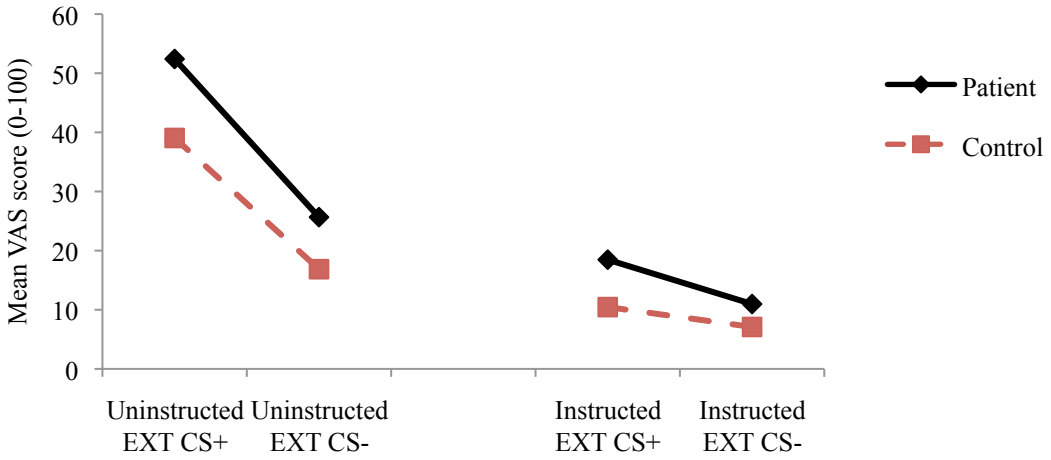

Figure 3. The likelihood of shock scores as rated by the patient and control group when either the CS+ or CS- stimuli were displayed on the screen in the uninstructed and instructed extinction.

To analyze discrimination learning, another repeated measures ANOVA was conducted for the likelihood of a shock with group as between-subjects factor and the discrimination variable per phase as within-subjects factor. There was no main effect found for the two groups, $F(1,194)=2.32$, $p=.129$, partial $\eta^2=.01$, and there was also no interaction effect found between the discrimination learning per phase and the groups $F(1,194)=.009$, $p=.926$, partial $\eta^2=.00$. There was, however a main effect for discrimination learning per phase $F(1,194)=68.95$, $p<.001$, partial $\eta^2=.26$. Pairwise comparisons revealed that both groups were better in discrimination learning in the uninstructed extinction phase ($M=24.47$) than in the instructed extinction phase ($M=5.43$), meaning that both groups have successfully learned to expect a shock when the CS+ is displayed but not when the CS- is displayed. It also shows that both groups don't discriminate between the two stimuli anymore in the instructed extinction, because they are told that the CS+ will not be followed by a shock anymore.

Startle responses

A one-way repeated measures ANOVA was used to compare the startle response following the CS+ or CS- for the patient and control group in the uninstructed and instructed extinction phases. The 5 or 6 startle trials per phase were divided into two averages; Average 1 contained the first three startle trials, and the Average 2 contained the last two or three startle trials. Box plots and scatter plot statistics indicated that the assumption of normality was supported; F_{max} was 17.311, which is a slight violation of homogeneity of variances. However, the outcomes of repeated measures ANOVA's are not sensitive to small-to-moderate violations of the homogeneity of variances.

The results showed four main effects. There were main effects found for group, $F(1,163)=7.834$, $p<.01$, partial $\eta^2=.05$, for phase, $F(1,163)=131.37$, $p<.001$, partial $\eta^2=.45$, for stimulus, $F(1.914,326)=38.858$, $p<.001$, partial $\eta^2=.19$, and for average, $F(1,163)=108.015$, $p<.001$, partial $\eta^2=.40$.

The interpretation of these results is that the patient group was more anxious than the control group during the whole two extinction phases. Both groups felt more anxious during the uninstructed phase, both groups were most anxious when the CS+ was presented, and less anxious during the CS- and ITI stimuli respectively. Both groups also had stronger fear responses at the start of a phase as opposed to the end of a phase (figure 4).

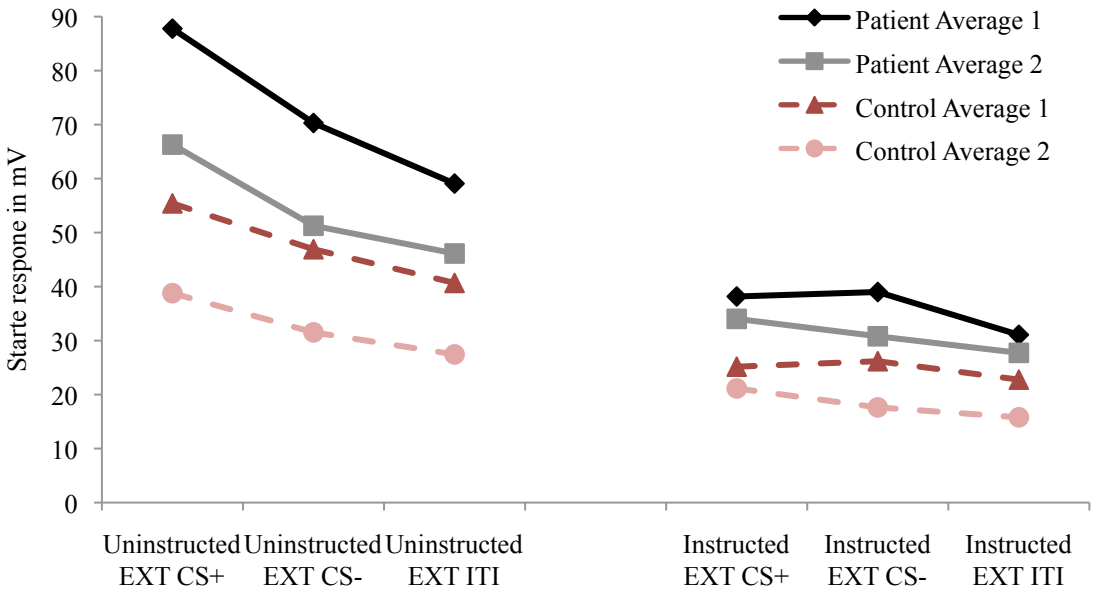

Figure 4. The first three trials (Average 1) and second two or three trials (Average 2) of startle responses of the patient and control group when either the CS+, CS- or ITI stimuli were displayed during the uninstructed and instructed extinction.

Results also showed four significant interaction effects. The first interaction effect was between phase and stimulus, $F(2,326)=16.968$, $p<.001$, partial $\eta^2=.09$, the second one was between phase and group, $F(1,163)=7.12$, $p<.01$, partial $\eta^2=.04$, the third one was between stimulus and group, $F(1.914,326)=3.42$, $p<.05$, partial $\eta^2=.02$, and the fourth one was between phase and average, $F(1,163)=24.264$, $p<.001$, partial $\eta^2=.13$.

Both groups had stronger startle responses in the uninstructed extinction phase than in the instructed extinction phase, but there was a difference in startle response per phase and depending on which stimulus was displayed. There was a difference in startle responses between the two groups during the different phases and when the three different stimuli were displayed. The interaction effect between phase and average show that averages differ more in the uninstructed extinction phase in comparison with the instructed extinction phase.
The three-way interaction between phase, stimulus and group was not significant, $F(2,326)=2.013$, $p=.135$, partial $\eta^2=.01$. The means and standard deviations of the subjective anxiety scores, likelihood of shock scores and startle responses during CS+, CS- and ITI are all displayed in table 6 in appendix B.
Finally, another repeated measures ANOVA was conducted to see how well the groups discriminated between the different stimuli. The groups were used as between-subjects factor and the discrimination variable per whole phase as within-subjects factor. There was one main effect for discrimination learning per phase, $F(1,167)=20.57$, $p<.001$, partial $\eta^2 =.11$. Pairwise comparisons revealed that both groups were better in discrimination learning in the uninstructed extinction phase (M=11.63) than in the instructed extinction phase (M=0.26), meaning that both groups have successfully learned to fear the CS+ but not the CS- and both groups don't discriminate between the two stimuli anymore in the instructed extinction, as they are then told that the CS+ won't be followed by a shock anymore.

Exploratory studies

Subjective anxiety measurements

To analyze if patients improve their extinction learning after having ended their exposure therapy, a repeated measures ANOVA was conducted. The results for the subjective measurement of anxiety showed three main effects. One for phase, $F(1,12)=24.45$, $p<.001$, partial $\eta^2=.67$, one for stimulus, $F(1,12)=11.09$, $p<.01$, partial $\eta^2=.48$, and one for moment, $F(1,12)=7.13$, $p<.05$, partial $\eta^2=.37$. Similar to previous results, the patients were significantly more anxious during the uninstructed extinction as opposed to the instructed extinction and scored significantly higher on the CS+ in comparison with the CS-. An interesting, new result is that the patients scored significantly higher at the pre-treatment moment (M=28.69) in comparison with post-treatment moment (M=18.92). Their subjective anxiety scores decreased after having had exposure therapy treatment.

There was an interaction effect between phase and moment, $F(1,12)=11.05$, $p<.01$, partial $\eta^2 = .48$. The patients rated their subjective anxiety significantly higher at the pre-treatment measurement in comparison with the post-treatment measurement and within those measurement moments they rated their subjective anxiety scores significantly higher during the uninstructed extinction phase in comparison with the instructed extinction phase (figure 5). Table 7 in appendix C displays the mean scores and standard deviations.

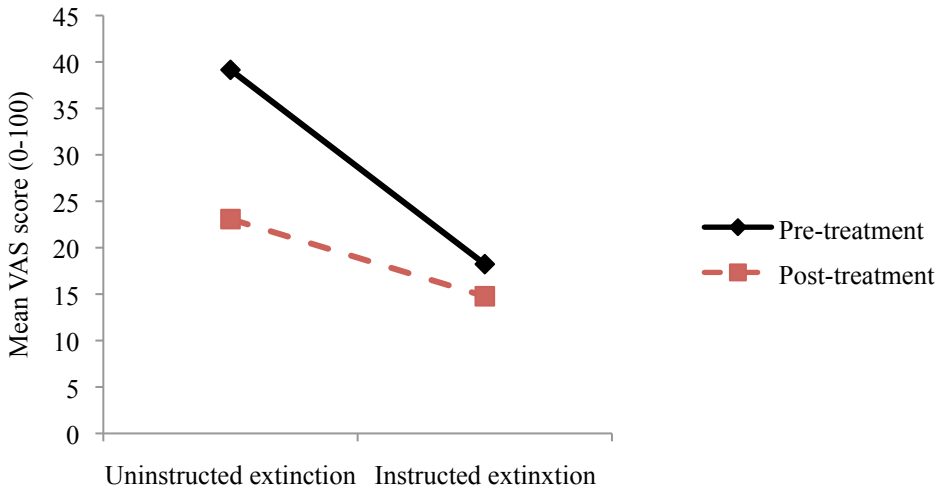

Figure 5. The subjective anxiety scores rated per phase during pre-treatment and post-treatment measurements

Likelihood of a shock

The repeated measures ANOVA results showed two main effects found for phase, $F(1,12)=20.03$, $p=.001$, partial $\eta^2=.63$, and for stimulus, $F(1,12)=14.28$, $p<.01$, partial $\eta^2=.54$. There was also a interaction effect between phase and stimulus, $F(1,12)=7.97$, $p<.05$, partial $\eta^2=.40$. Similar to the results when comparing the patient group with the control group, the patients found it more likely that a shock followed after a CS+ stimulus than after a CS- stimulus and that the likelihood was bigger in the uninstructed extinction phase and smaller in the instructed extinction phase.

However, no main effect was found for the differences in likelihood of shock scores between the pre- and post-measurements, $F(1,12)=0.402$, $p=.538$, partial $\eta^2=.03$. This means that patients do not have a lesser expectation of a shock less after having received treatment (figure 6). Table 8 in appendix D displays the mean scores and standard deviations.

Analyses for the startle responses were not included in this study. The cases had a lot of missing values, which made the participant sample too small to conduct any meaningful analyses.

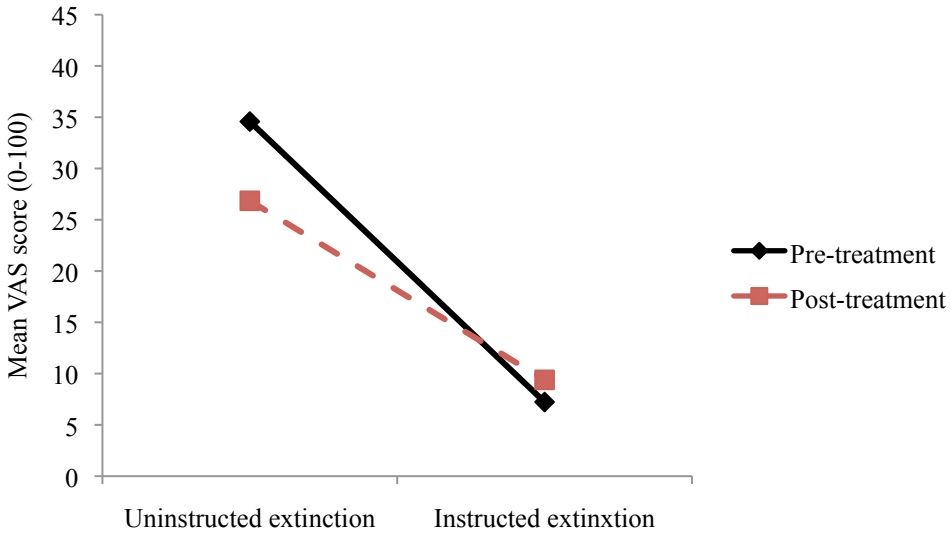

Figure 6. The likelihood of shock scores rated per phase during pre-treatment and post-treatment measurements

Discussion

Conclusions

This article described the differences in extinction learning between anxiety patients and healthy controls. The first two hypotheses were if the fear responses of anxiety patients to the CS+ and CS- were significantly larger than the fear responses that the healthy controls had to the stimuli in the uninstructed and instructed extinction phases. Anxiety patients displayed stronger fear responses to both the danger cue (CS+) and safety cue (CS-) in the extinction phases, which is in line with the research by Lissek and collegues (2005), in which anxiety patients displayed stronger conditioned responses during the extinction of fear learning. The first two hypotheses can thus be accepted.

The third hypothesis was that the control group would be better able to discriminate between the CS+ and CS- than the patient group and would thus unlearn the fear response to the CS+ in the extinction phases more easily. The results revealed that both groups could easily discriminate the CS+ from the CS- during the uninstructed extinction phase. It also revealed that both groups do not discriminate between the two stimuli when told that the CS+ will not be followed by a shock anymore. Therefore, both groups are able to successfully discriminate between the two stimuli and the third hypothesis can thus not be accepted. This finding stands in contrast to that of Grillon and Morgan (1999), whereby PTSD patients displayed a general fear response and failed to inhibit their fear response to the CS-. A possible explanation could be that that study only used EMG data for analysis.

Finally, a fourth, exploratory analysis was conducted to see if the patient would have reduced fear responses to the CS+ after having completed their treatment (post-treatment) as opposed to before having had their treatment (pre-treatment). The results showed that at both moments, the anxiety patients had higher subjective anxiety scores and US likelihood scores for the CS+ in comparison with the CS-. The post-treatment group had significantly lower subjective anxiety scores in the uninstructed and instructed extinction phases in comparison with the pre-treatment scores. However, the US likelihood scores were similar and the post-treatment scores during the instructed extinction were even slightly higher than at pre-treatment measurements. So even though the anxiety patients still expected the shock as often as before, subjective anxiety scores had decreased. It is unclear if these results can be attributed to the effects of exposure therapy, or if they should be attributed to a learning effect due to participating in the research for the second time. As the expectancy of a shock remained similar, the argument of a learning effect is questionable. Future research could control for possible remembrance of the task and/or aim of the study to find out if these results could be attributed to the improvement of extinction learning due to exposure therapy. At this time, these results are not sufficient to be able to accept the fourth hypothesis. The patients did have a significantly reduced fear response to the CS+, but the crucial interaction between stimulus and moment was not found. The patient group still expected a shock just as much at the post-treatment measurement as at the pre-treatment measurement, which means they still anticipated the shock as frequently as before, but were less fearful of it. Further research is needed to be able to conclude if exposure therapy enhances the speed with which a person unlearns the CS-US association.

Clinical implications

Davis et al. (2000) proposed that pathological anxiety might result from a failure to inhibit the fear response in the presence of safety signals. In the current study, the patient group has stronger fear responses to the safety cue (CS-) than the control group, suggesting that they indeed failed to inhibit their fear response. It seems that the anxiety patients have generalized their fear response to the CS- because it is similar to the CS+. Lissek et al. (2009) researched fear generalization in patients with panic disorder and found that interventions focussing on discriminative learning may facilitate the strength and speed of discriminative learning and reduce fear generalization. These conclusions could also be connected to the results from this study; focussing on discriminative learning during exposure therapy could reduce the fear generalization that anxiety patients have experienced.

Future research

The anxiety patients in the current study were not more fearful of the CS+ in the instructed extinction phase than the control group. This shows that there were no differences in how the groups interpreted the instructions and suggests that verbal and written instructions contribute to the inhibition of fear responses. A research by Lipp et al. (2010) found that verbal instructions effectively reduced the expectancy of a US during the extinction phase. As instructions show to be of a significant effect, future research could focus on checking if repeated instructions have an increased effect on fear responses and expectancy of a US.

Lipp & Edwards (2002) conducted a study in which fear-relevant and fear-irrelevant stimuli were used during a fear-conditioning task. Their results showed that fear-relevance of the stimulus affects extinction. Fear-relevant stimuli (e.g. pictures of spiders) significantly were not susceptible to verbal instructions during the process of extinction learning in comparison to fear-irrelevant stimuli (e.g. pictures of flowers). Future research could implement these findings and create a task with fear-relevant stimuli to see if this changes the outcomes of fear extinction.

A recent meta-analysis by Rodrigues et al. (2014) suggested that D-cycloserine enhances treatment outcomes for anxiety disorders when employed as an addition to exposure. D-cycloserine is a partial agonist of the NMDA-receptor, and it enhances the learning and memory processes underlying the extinction of fear. When administered correctly, D-cycloserine is a promising strategy to combine with treatment. It can reduce health care costs, drop-out rates and brings faster aid to patients. The meta-analysis states that more detailed evaluation should be done of the effects of D-cycloserine per exposure session. A possible recommendation for future research could be to add D-cycloserine and a placebo as variables to the present study, to explore the differences between D-cycloserine and a placebo during the multiple trials in the fear-conditioning task.

In the current study, the patient group still expected a shock just as much at the post-treatment measurement as at the pre-treatment measurement, but were less fearful of it. Further research with more participants is needed to be able to conclude if these results are substantial, or significant due to a small sample size. A bigger sample size could better analyze if fear extinction could have a predictive value for exposure therapy treatment outcomes. Having a predictive value that could show how efficient a treatment will be to a patient could again bring faster aid and reduce health care costs.

Restrictions

The results of the current study may be restricted due to unequal levels of intelligence. The control group had a significantly higher level of education and significantly better working memory scores than the control group. However, the effect size of the highest level of education was relatively weak and the IQ scores of both groups did not differ.

Another restriction is that medication was not used as a covariant. For example, benzodiazepines are often used as anti-anxiety medication because of their relaxing and calming effects. Previous research showed that benzodiazepines could lower the amplitude of the acoustic startle reflex in animals (Davis, 1979; Berg and Davis, 1984). This could possibly have also lowered the startle reflex amplitude that anxiety patients had.

As mentioned before, the limited sample size for the pre-treatment versus post-treatment analysis is a notable restriction. This increased the chance that these results may vary considerably in future research.

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Appendix

Appendix A (Table 5)

Legend of highest completed education

	Highest completed education
1	Elementary or Primary school (Lager of basisonderwijs)
2	High School or Middle school (MAVO/VMBO/LTS/LBO of gelijkwaardig)
3	Senior General Secondary Education (HAVO/VWO/Atheneum/HBS of gelijkwaardig)
4	Vocational Education (MBO/MEAO/MTS of gelijkwaardig)
5	University of Professional Education (HBO/HEAO/HTS of gelijkwaardig)
6	University of Science (Universiteit of gelijkwaardig)
7	Other (Andere opleiding, namelijk)

Appendix B (Table 6)

Subjective anxiety scores, likelihood of shock scores and startle responses differences between CS+, CS- and ITI

	Patient group		Control group	
Subjective anxiety score				
Uninstructed EXT	*CS+*	45.83 (32.48)	*CS+*	35.76 (30.02)
	CS-	26.41 (28.09)	*CS-*	15.95 (22.64)
Instructed EXT	*CS+*	23.17 (28.68)	*CS+*	13.35 (19.56)
	CS-	12.66 (20.18)	*CS-*	8.94 (16.73)
Uninstructed EXT	*CS+*	52.41 (31.24)	*CS+*	39.05 (28.78)
	CS-	25.66 (27,78)	*CS-*	16.86 (22.39)
Instructed EXT	*CS+*	18.47 (28.21)	*CS+*	10.45 (21.33)
	CS-	10.97 (23.06)	*CS-*	7.09 (18.40)
Startle responses – Average 1				
Uninstructed EXT	*CS+*	87.77 (79.44)	*CS+*	55.41 (43.57)
	CS-	70.30 (73.03)	*CS-*	46.92 (46.93)
	ITI	59.08 (62.57)	*ITI*	40.68 (37.71)
Instructed EXT	*CS+*	38.17 (41.91)	*CS+*	25.17 (29.50)
	CS-	39.00 (47.89)	*CS-*	26.18 (27.89)
	ITI	31.07 (40.44)	*ITI*	22.77 (25.88)
Startle responses – Average 2				
Uninstructed EXT	*CS+*	66.30 (75.87)	*CS+*	38.78 (36.42)
	CS-	51.27 (61.51)	*CS-*	31.52 (30.14)
	ITI	46.13 (50.21)	*ITI*	27.44 (29.50)
Instructed EXT	*CS+*	34.02 (43.29)	*CS+*	21.14 (23.67)
	CS-	30.80 (44.89)	*CS-*	17.63 (21.73)
	ITI	27.73 (38.12)	*ITI*	15.79 (19.09)

Appendix C (Table 7)

The subjective anxiety scores rated per phase during pre-treatment and post-treatment measurements

	Pre-treatment	Post-treatment
Uninstructed extinction (M, SD)	39.15 (5.48)	23.08 (4.69)
Instructed extinxtion (M, SD)	18.23 (3.95)	14.77 (4.52)

Appendix D (Table 8)

The likelihood of shock scores rated per phase during pre-treatment and post-treatment measurements

	Pre-treatment	Post-treatment
Uninstructed extinction (M, SD)	34.58 (6.08)	26.85 (6.86)
Instructed extinxtion (M, SD)	7.23 (3.17)	9.39 (5.52)