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Published in:
Journal of Anxiety Disorders

DOI:
10.1016/j.janxdis.2021.102361

Publication date:
2021

Journal of Anxiety Disorders 78 (2021) 102361

Contents lists available at ScienceDirect

Journal of Anxiety Disorders

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

Latent class growth analyses reveal overrepresentation of dysfunctional fear conditioning trajectories in patients with anxiety-related disorders compared to controls

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ARTICLE INFO

Keywords:
Fear conditioning
Fear extinction
Latent trajectories
Anxiety disorders
Cognitive Behavioral Therapy (CBT)
Latent class growth analyses (LCGA)
Treatment outcome

ABSTRACT

Recent meta-analyses indicated differences in fear acquisition and extinction between patients with anxiety-related disorders and comparison subjects. However, these effects are small and may hold for only a subsample of patients. To investigate individual trajectories in fear acquisition and extinction across patients with anxiety-related disorders ($N = 104$; before treatment) and comparison subjects ($N = 93$), data from a previous study (Duits et al., 2017) were re-analyzed using data-driven latent class growth analyses. In this explorative study, subjective fear ratings, shock expectancy ratings and startle responses were used as outcome measures. Fear and expectancy ratings, but not startle data, yielded distinct fear conditioning trajectories across participants. Patients were, compared to controls, overrepresented in two distinct dysfunctional fear conditioning trajectories: impaired safety learning and poor fear extinction to danger cues. The profiling of individual patterns allowed to determine that whereas a subset of patients showed trajectories of dysfunctional fear conditioning, a significant proportion of patients (≥50 %) did not. The strength of trajectory analyses as opposed to group analyses is that it allows the identification of individuals with dysfunctional fear conditioning. Results suggested that dysfunctional fear learning may also be associated with poor treatment outcome, but further research in larger samples is needed to address this question.

1. Introduction

A growing body of empirical evidence shows that fear conditioning is recognized as an important model to – at least partly - explain the development, maintenance and successful treatment of anxiety disorders (Berry, Rosenfields & Smits, 2009; Duits et al., 2015; Guthrie & Bryant, 2006; Kindt, 2014; Lommen et al., 2013a; Mineka & Zinbarg, 2006; Orr et al., 2012; Pittig et al., 2018; Sijbrandij et al., 2013). However, it is still largely unknown why some individuals develop pathological fear and anxiety and others do not, and what characteristics

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https://doi.org/10.1016/j.janxdis.2021.102361
Received 18 March 2020; Received in revised form 21 December 2020; Accepted 13 January 2021
Available online 18 January 2021

in anxiety-disordered patients predict therapy outcome (Lonsdorf & Merz, 2017). To study these questions, a shift in focus is required from the identification of general fear mechanisms to individual differences within these mechanisms. Innovative approaches are needed to develop individual prognostic markers and successful individualized therapy strategies (Craske et al., 2014; Dunsmoor et al., 2015; Pittig et al., 2016; Richter et al., 2017).

So far the field has focused mainly on comparing fear conditioning processes at group level between patients with anxiety disorders and healthy comparison subjects. Meta-analyses (Duits et al., 2015; Lissek et al., 2005) on case-control comparisons showed that during fear acquisition, patients with anxiety disorders compared to healthy comparison subjects demonstrate overall higher fear responses to safety stimuli (CS-) that are unpaired with a threatening event ($d = 0.296$; Duits et al., 2015). Elevated fear responses to the CS- can be defined as impaired safety learning. Impaired safety learning may indicate different underlying mechanisms such as impaired inhibition of fear, or increased fear generalization. Furthermore, patients show, on average, reduced fear extinction to the previous conditioned cue (CS+) relative to healthy comparison subjects ($d = 0.352$; Duits et al., 2015; Lissek et al., 2005).

Data-driven analyses to discern distinct patterns in fear responding across individuals have been proposed as a powerful next step to take patients' within-group variability in fear acquisition and extinction into account (Lonsdorf & Richter, 2017). In addition, these data-driven analyses are in line with recent dimensional approaches of studying anxiety (Ramaswamy, DeSarbo, Reibstein, & Robinson, 2019). A recent large scaled study using pooled data of both mice ($N = 122$) and humans (male patients suffering from PTSD; $N = 724$), applied latent class growth analysis (LCGA) to characterize individual differences in fear extinction (Galatzer-Levy et al., 2017). In this study three distinct individual trajectories of fear acquisition and extinction to the CS + were identified in both mice (based on freezing behavior in a simple conditioning paradigm) and men (based on fear-potentiated startle (FPS) in a differential fear conditioning paradigm), with outcome measures representing low level brain stem index of behavioral freezing (Löw, Weymar, & Hamm, 2015). The three distinct fear extinction trajectories in mice were: slow extinction (in 45 % of mice), rapid extinction (25 %), and no extinction, characterized by a complete failure to extinguish freezing behavior (30 %). In humans, three fear acquisition and extinction trajectories were distinguished: modal responding, in which FPS responses were moderate during acquisition and went back to zero during extinction (79 %), high FPS with rapid extinction (15 %) and high FPS with no extinction (6%). These findings suggest specific fear acquisition and extinction trajectories that are identified across species. In the current exploratory study 1, data from a past data set (see Duits et al., 2017) were re-analyzed to study latent fear conditioning trajectories in a sample including both patients with anxiety-related disorders and healthy comparison subjects (mixed gender). By using latent trajectory analyses, a data-driven, explorative method, various outcome measures of fear acquisition and extinction were studied over time.

In this previously conducted fear conditioning this study (Duits et al., 2017), a differential fear acquisition and extinction task was conducted in patients with various anxiety-related disorders at baseline prior to the start of treatment, and in a sample of healthy comparison subjects. Results of the previous traditional case-control analyses showed small but significant group differences between patients and healthy comparison subjects on overall levels of subjective fear, threat expectancy and startle responses during both the acquisition and extinction phases (ηp2 varying between 0.054 and .069; Duits et al., 2017). As a next step we aimed at extending the findings of these first analyses by re-analyzing the data to determine latent (not directly observable) trajectories of classical fear acquisition and extinction by means of a data-driven approach. With the aid of latent class growth analyses (LGCA) we aimed to investigate individual differences in fear learning in a heterogeneous anxiety disordered population. This data-driven, explorative method has the potential to yield latent trajectories of fear acquisition and fear extinction to gain further insights on how different profiles of fear learning are distributed across patients and comparison groups, based on their individual scores. In line with our previous meta-analysis (Duits et al., 2015), we expected that patterns of poor CS + extinction and impaired safety learning to the CS- would occur more often in patients as opposed to controls. Self-reported fearfulness and threat expectancy ratings as well as startle responses were used as different outcome measures. Due to the exploratory and data-driven approach used in the current study, no specific hypotheses regarding the latent trajectories were formulated.

In study 2 of this paper we investigated the relationship between latent fear conditioning trajectories and cognitive behavioral therapy (CBT) outcome in the patient group. Although fear extinction is considered to be a critical mechanism of change in exposure-based CBT (Craske et al., 2008; Hofmann, 2008; Kindt, 2014; Massad & Hulsey, 2006; Myers & Davis, 2008), this has been a sparsely studied topic to date, with -to the best of our knowledge- only four studies that have targeted this topic. Two studies included one session of CBT in individuals with specific phobias (Ball, Knopp, Paulus, & Stein, 2017; Forcadell et al., 2017) and two studies were performed in children (Geller, McGuire, Orr et al., 2019; Waters & Pine, 2016). All studies modelled extinction in a laboratory fear conditioning model and indicated that individuals who show reduced extinction of fear prior to therapy have reduced exposure therapy effects, which is in line with the idea that exposure therapy is supported by inhibitory learning (Craske et al., 2008). Even though these were very different studies, they all found a positive relation between parameters indicative of a fear extinction process and therapy outcome or a laboratory model for such a therapy. This evidence is somewhat compelling and limited to specific (sub)clinical populations including patients with a specific phobia (Ball, Knapp, Paulus, & Stein, 2017; Forcadell et al., 2017) and youth with anxiety disorders or obsessive compulsive disorder (Geller et al., 2019; Waters & Pine, 2016). Generalizability of these findings to clinical practice is limited because studies encompassed lab-based exposure settings instead of "real life" treatment protocols (Ball et al., 2017; Forcadell et al., 2017). In the current study, we hypothesized that trajectories characterized by a deficit in extinction learning would be associated with lower treatment response.

2. Study 1

2.1. Method

2.1.1. Participants

Patients with various anxiety-related disorders ($N = 104$) and healthy comparison subjects ($N = 93$) participated in the study from Duits et al. (2017). Patients with anxiety-related disorders and healthy comparison subjects did not differ significantly in age, gender and level of education. A detailed description of the study groups, inclusion criteria and recruitment has been reported elsewhere (Duits et al., 2017). Diagnoses were established according to the DSM-IV-TR criteria of anxiety disorders (American Psychiatric Association, 2000) The diagnostic categories mostly included were social anxiety disorder ($n = 27$), panic disorder and/or agoraphobia ($n = 24$), and obsessive compulsive disorder ($n = 17$), followed by post-traumatic stress disorder, generalized anxiety disorder (both $n = 12$), hypochondriasis[7] ($n = 7$), and specific phobia ($n = 5$). Latent fear conditioning trajectories were studied simultaneously in patients with various anxiety disorders, since dysfunctional fear conditioning has been demonstrated across

[7] Given the considerable overlap in cognitive and behavioral mechanisms between hypochondriasis and anxiety disorders (Olatunji, Deacon, & Abramowitz, 2009), we decided to include this group as well, even though, strictly speaking, hypochondriasis is not categorized as an anxiety disorder in the DSM-IV.

various anxiety-related disorders (Duits et al., 2015; Lissek et al., 2005). Furthermore, the idea of studying fear conditioning across anxiety disorders as a potential shared underlying mechanism of psychopathology, is in line with the NIMH Research Domain Criteria (RDoC) initiative (Insel et al., 2010; Lonsdorf & Richter, 2017; Morris & Cuthbert, 2012).

All patients had followed an intake procedure at our outpatient clinics with the aim to receive treatment for their anxiety complaints. Psychotropic medication was used in 53 % of all patients at baseline (anti-depressants, $n = 48$; benzodiazepines as sleep medication, $n = 7$). Patients participated in the fear conditioning procedure before starting outpatient treatment based on the principles of CBT. CBT encompassed on average 21 ($SD = 13$) 45- and 50-minute sessions in Utrecht and Greifswald respectively, applied by well-trained licensed cognitive behavioral therapists or by psychology trainees under strict weekly supervision of licensed CBT therapists. As prescribed in clinical guidelines (Keijsers, Minnen, Verbraak, Hoogduin, & Emmelkamp, 2017), all treatments consisted for a significant part of exposure therapy.

2.1.2. Fear conditioning procedure

All participants completed a fear conditioning task, with the patients completing the task before starting CBT. A detailed description of this task and associated apparatus is provided in the previous paper in the same study groups (Duits et al., 2017). Briefly summarized, the procedure consisted of 5 sequential phases: pre-acquisition, uninstructed acquisition, instructed acquisition, uninstructed extinction and instructed extinction. Two pictures of faces with neutral facial expression (following Klumpers et al., 2010a) with colored backgrounds (blue or yellow) served as conditioning stimuli. Assignment of these stimuli to conditions (CS + and CS-) was balanced across subjects. Stimulus presentation (8-s duration) was in a fixed random order with a fixation cross presented on a black screen during inter-trial intervals (ITI's, 6−8 s). Electric shock presented at CS + offset served as unconditioned stimulus (US). A schematic representation of a CS + trial is presented in Fig. 1. The preconditioning phase consisted of 4 presentations of the CS + and CS-. Uninstructed acquisition and extinction phases consisted of 8 CS + and CS- presentations, and instructed acquisition and extinction of 6 presentations of each. Prior to the uninstructed phases, no explicit information on CS—US contingencies was given. Preceding each instructed phase, participants received explicit written and verbal instructions about CS—US contingencies. The instructed phases were shorter (6 instead of 8 trials of each condition), because previous studies demonstrated that fear expression is stable after instructions (Heitland, Groenink, Bijlsma, Oosting, & Baas, 2013, 2016), in contrast to fear expression after the uninstructed phase. A standard shock work up procedure (Klumpers et al., 2010b) preceded the experimental task to ensure that all participants perceived the US as highly annoying but not painful.

During acquisition phases, the CS + was partially reinforced by the US to delay extinction of fear: 6 out of 8 CS + presentations were followed by a shock during uninstructed acquisition and 5 out of 6 during instructed acquisition. No US was delivered during pre-acquisition, uninstructed and instructed extinction phases.

Fearfulness and US expectancy were rated using visual analogue scales (VAS) presented on the computer screen together with the face belonging to the condition (CS+ / CS-). Fearfulness ratings regarding the CS + and CS- were obtained after pre-acquisition, (un)instructed acquisition and extinction phases with a scale ranging from not afraid/nervous at all (0) to very afraid/nervous (100). Ratings were not obtained online in order to prevent interference with implicit learning. US expectancy ratings to the CS + and CS- (occurrence of a shock very unlikely [0] up to very likely [100]) were assessed after acquisition and extinction phases, but not after the pre-acquisition phase.

Acoustic startle probes (95 dB, 50-ms white-noise bursts) were delivered during inter trial intervals (ITI) and 5.5 or 6.5 s after CS onset to elicit startle responses. Startle probes were presented 6 times per stimulus type (CS+, CS-, ITI) during uninstructed phases and 5 times during instructed phases. For measurement and apparatus details, see Duits et al. (2017). In contrast to the subjective ratings that range per definition between 0–100 for each individual, baseline startle amplitudes can vary greatly from ranging around 10 to ranging around 300 μV per individual. We controlled for individual differences in baseline startle magnitude by standardizing startle scores per subject using the mean and standard deviation of the ITI startles as norm: (raw startle value – mean of ITI startle trials) / standard deviation of ITI startle trials. Due to technical problems, startle data from 3 patients and 2 controls could not be included. On averaged, the percentage of data on startle trials missing is 10 %. Parallel to the analysis of subjective data, startle data for the CS + and CS- were averaged per phase. In Duits et al. (2017) skin conductance data were also reported. Because of the lack of significant group-related differences in this measure and a considerable percentage of null responses (in 29 % of all trials, an SCR response was not detectable) we decided not to include this measure in this paper.

2.1.3. Statistical analyses

LCGA is a data-driven, explorative statistical method used in the current study to identify latent (not directly visible) trajectory classes. LCGA's (Jung & Wickrama, 2008) were conducted in Mplus (version 6.1; Muthén & Muthén, 2007) and additional analyses comparing groups within different trajectories and associations with treatment effect were carried out with IBM SPSS Statistics (version 22).

The data points for the five phases of the conditioning experiment (pre-acquisition, uninstructed acquisition, instructed acquisition, uninstructed extinction, instructed extinction) were entered into the LCGA. Separate trajectory analyses were conducted for the stimulus types (CS + and CS-) and for each fear measure (subjective fear, US expectancy, and startle magnitude (corrected for ITI level)), since LCGA does not allow to combine multiple outcome measures within trajectory analyses.[8] The intercept and shape of the different trajectories were expected to vary both between and within latent classes. Because of this, the LCGA's were conducted in such a way that the algorithm could freely estimate the trajectories that fitted the data best, with no assumptions being made with regard to the intercept and slope parameters. A 'mixture type' of analyses was used within the LCGA and an 'overall model' in Mplus which allows free estimates across classes (Jung & Wickrama, 2008). In order to prevent the chance of local maxima and to optimize the reliability of the loglikelihood estimation, the number of random sets on starting values was set at 800 and the number of final optimizations was set at 200. Syntax and data files are available online via: https://osf.io/adxq2/.

Within LCGA, a final model is selected based on various statistical criteria and model considerations (Berlin, Parra, & Williams, 2014). In our study, model fit was compared between models with 1–6 trajectories, and model selection was based on three considerations. First, apparent drops in Bayesian Information Criterion (BIC) scores were used. The BIC is a widely used method in model selection, whereby a model associated with the largest decrease in BIC score between two models (N classes versus N + 1 classes) is preferred, because such a model is associated with good generalizability and corresponds to the highest Bayesian posterior probability (Neath & Cavanaugh, 2012). Second, entropy scores were used, in which a value close to 1 is associated with a very good fit of data within the given model (Richter, Pittig, Hollandt, & Lueken, 1993). In addition to these formal criteria, we subsequently considered whether the identified trajectories represent meaningful trajectories. A trajectory was considered meaningful in

[8] We considered the use of a composite outcome measure (CS+ minus CS-) in the trajectory analyses, but we decided not to do so, because a composite score would disable the possibility to distinguish between participants demonstrating generalized fear versus low fear, since composite scores will be low in both groups. Thus the added value of a composite score would be very limited, and therefore we decided to investigate responses to the CS+ and to CS- separately.

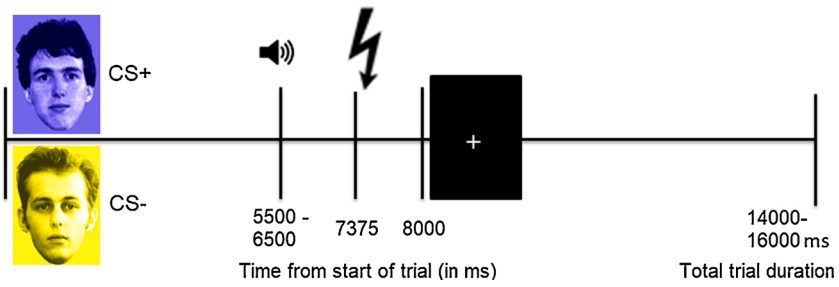

Fig. 1. Schematic representation of a CS + trial with US reinforcement.

case a reasonable number of participants had been allocated to the trajectory (≥ 5%, Nylund, Asparouhov, & Muthén, 2007) and in case the additional trajectory truly represented a pattern that is distinct from the previously included trajectories (instead of representing for example a few outliers). The identification of meaningful trajectories was assessed separately by four experienced researchers and a statistician who then exchanged their findings and reached consensus. The various models derived from LCGA are available online (https://osf.io/adxq2/) for those researchers who are interested.

In the model that provided the best fit, based on the combination of the three previously mentioned model considerations, participants received a probability score for each trajectory and were assigned to a specific trajectory based on their highest probability score[9] . Subsequently, using logistic regression analyses, the relative distribution of patients versus healthy comparison subjects across the various trajectories was studied to examine whether the distinct trajectories were associated with clinical status. In addition, characteristics of the subjects in distinct trajectories were examined (including age, sex, use of psychotropic medication, US valence, US intensity, and baseline symptom severity ratings on the BSI and BDI-II), using chi-square tests and ANOVAs. To account for overall patient-control differences in the analyses (specifically differences in clinical symptoms), clinical status (patient versus comparison) was included as a between-group factor in the ANOVAs. Results of these chi-square tests and ANOVA's are described in the supplemental material.

3. Results

3.1. Fearfulness ratings

3.1.1. Trajectories of fearfulness ratings to the CS+

Results of the LCGA on fearfulness ratings to the CS + led to the selection of a 3-class model (see also Table 1), as displayed in Fig. 2A.

The largest trajectory of the 3-class model contained 50 % of all participants, $n = 98$, of whom 52 (53 %) were patients. This trajectory contained 50 % of all patients, and 49 % of all controls. This trajectory represents normal fear acquisition and extinction (labeled as 'normal conditioning'), characterized by low subjective fearfulness to the CS + during pre-acquisition, a substantial increase in fearfulness during the acquisition phases and a substantial decrease during the extinction phases (see Fig. 2A). The second largest trajectory ('labeled as 'low fear conditioning') encompassed 32 % of all participants, $n = 63$, of which $n = 24$ (38 %) were patients; this trajectory contained 23 % of all patients and 42 % of all controls. Class members reported low subjective fear to the CS + during all phases, including pre-acquisition, acquisition and extinction phases. The third trajectory (labeled as 'poor extinction') entailed 18 % of all participants, $n = 36$, of which $n = 28$ (78 %) were patients; this trajectory contained 27 % of all patients and only 9% of all controls. This trajectory showed low subjective fearfulness ratings to the CS + during pre-acquisition, a strong increase in fear during acquisition, but *no* reduction of fear in the extinction phases, despite explicit instructions preceding the second phase of extinction that the aversive stimulus was no longer administered.

A multinomial logistic regression analysis was performed to predict latent trajectories membership by clinical status (patient versus healthy comparison), see Table 2. Results indicated that clinical status significantly predicted CS + subjective fearfulness trajectory membership: patients with anxiety-related disorders were more often associated with the trajectory of poor extinction, while comparison subjects were more frequently assigned to the normal conditioning trajectory. The specific distribution of various anxiety-related diagnoses over all the identified latent trajectories is shown in Table S6.

3.1.2. Trajectories based on fearfulness ratings to the CS-

A 2-class model was considered the best fit to the subjective fearfulness to the CS- data (see Fig. 2B and Table 1) based on the previously mentioned criteria.

The largest trajectory contained 70 % of all participants; $n = 138$, of whom 63 (46 %) were patients; this trajectory contained 61 % of all patients, and 81 % of all controls. This trajectory represented low subjective fearfulness to the CS- (labeled as 'normal safety learning') throughout the conditioning task (pre-acquisition, acquisition and extinction). The second trajectory entailed 30 % of all participants; $n = 59$, of whom 41 (69 %) were patients; this trajectory contained 39 % of all patients, and 19 % of all controls and represented higher fear to the CS- (labeled as 'impaired safety learning') throughout the task.

Results of the binary logistic regression (Table 2) indicated that clinical status was a significant predictor of CS- subjective fearfulness trajectory membership: patients with anxiety-related disorders were more often than comparison subjects characterized by increased fear responses to the CS-, while healthy comparison subjects more frequently reported low fear responses to the CS- during acquisition and extinction phases.

US expectancy ratings

3.1.3. Trajectories based on US expectancy ratings to the CS+

LCGA results favored a 2-class model with regard to US expectancy ratings to the CS+ (see Fig. 2C), based on the three model considerations (BIC, entropy, meaningful trajectories).

Within the 2-class model, the largest trajectory contained most of the participants (87 %, $n = 171$, of whom 86 (50 %) were patients; this trajectory contained 83 % of all patients, and 91 % of all controls), and was characterized as 'normal conditioning' (high US expectancy ratings to the CS + during acquisition phases and a strong decrease during extinction phases). The second trajectory entailed a small proportion of participants (13 %, $n = 26$, of whom 18 (69 %) were patients; this trajectory contained 17 % of all patients, and 8% of all controls), and was characterized by 'poor extinction' (high US expectancy ratings to CS + during acquisition, but no decrease during extinction). Binary logistic regression analyses demonstrated that clinical status (patients with anxiety-related disorders vs healthy comparison subjects) was no

[9] This approach was applied in all cases. Probability scores were generally very high (around 90%) and only in two cases were the probability scores substantially lower (at least 50% for one trajectory).

Table 1
Bayesian Information Criterion (BIC) and entropy scores presented per latent class growth model, shown separately for subjective fearfulness, US expectancy and startle outcome measures on the CS + and CS-.

BIC		1 class	2 classes	3 classes	4 classes	5 classes	6 classes
Subjective fear	CS+	9370	9107	**9021**	8953	8914	8896
	CS-	8934	**8682**	8591	8518	8476	8434
US expectancy	CS+	7185	**7017**	6936	6893	6866	6848
	CS-	7112	**6878**	6747	6705	6662	6622
Startle	CS+	**9318**	9212	9137	9054	9034	9012
	CS-	**8965**	8897	8861	8836	8821	8805
Entropy		1 class	2 classes	3 classes	4 classes	5 classes	6 classes
Subjective fear	CS+	NA	.877	**.877**	.927	.929	.924
	CS-	NA	**.905**	.946	.941	.943	.955
US Expectancy	CS+	NA	**.985**	.987	.974	.958	.948
	CS-	NA	**.981**	.991	.990	.981	.945
Startle	CS+	**NA**	.993	.909	.936	.940	.948
	CS-	**NA**	.998	.961	.970	.975	.974

BIC = Bayesian Information Criterion; NA = not applicable. Selected models are displayed in bold.

significant predictor of a trajectory based on US expectancy ratings to the CS+, see Table 2.

3.1.4. Trajectories based on US expectancy ratings to the CS-

A 2-class model was considered the best fit for US expectancy ratings to the CS- (see Fig. 2D and Table 1) based on the previously mentioned selection criteria.

Most participants were in the first trajectory (89 %, n = 176, of whom 90 (51 %) were patients; this trajectory contained 87 % of all patients, and 92 % of all controls). This trajectory was characterized by low US expectancy ratings to the CS- during acquisition and extinction phases, i.e. as a 'normal safety learning' trajectory. The second trajectory contained 11 % of all participants (10 %, n = 21, of whom 14 (67 %) were patients; this trajectory contained 13 % of all patients, and 8% of all controls). This trajectory was characterized by 'impaired safety learning' responses, demonstrating moderate US expectancy ratings to the CS- during acquisition, with an increase in ratings during extinction phases. Again, heightened fear responses to the CS- might also be interpreted as impaired fear inhibition. Clinical status (patients with anxiety-related disorders versus healthy comparison subjects) did not significantly predict assignment to a trajectory based on US expectancy ratings to the CS-. see Table 2.

In addition to the results described above, additional, exploratory logistic regression analyses were performed to examine the predictive value of symptom ratings (measured prior to treatment with the BSI and BDI) on the identified latent fear conditioning trajectories. Results indicated that symptom ratings were not significantly related to trajectory membership based on the identified latent fear conditioning trajectories (all p-values >.05), see also: https://osf.io/adxq2 and table S8.

3.1.5. Trajectories based on startle responses

LCGA on startle responses to the both the CS + and CS- (analyzed separately) demonstrated best fit indices for single class models (Table 1 and Fig. 2E). The decrease in BIC scores was mostly gradual, without an apparent drop. Furthermore, adding classes to the single class model showed very limited added value because the additional classes comprised only a few participants (n = 9 and n = 2 for the CS + and CS-, respectively) and trajectories of these additional classes were fairly similar to the largest class.

Since a single class model was selected, no additional analyses were performed regarding potential differences between participants from various classes based on startle data.

3.1.6. Overlap of individuals assigned to the different trajectories across models

We were interested in potential overlap in the individuals assigned to dysfunctional trajectories across the various selected models (based on different outcome measures, i.e. fearfulness and US expectancy ratings, and conditions, i.e., CS+/CS-). Probability ratings for combinations of trajectories based on different outcome measures are shown in Table S5. There was no complete overlap between the individuals assigned to various dysfunctional trajectories. As an example, based on CS + ratings, more participants were categorized in the poor extinction trajectory based on subjective fear ratings than based on US expectancy ratings.

4. Study 2

4.1. Method

4.1.1. Clinical measurements

Treatment outcome was calculated in 63 patients who completed the Brief Symptom Inventory (BSI; Derogatis & Spencer, 1993) and Beck Depression Inventory (BDI-II; Beck & Steer, 1987) pre and post treatment (not all patients completed post-treatment questionnaires). The BSI is a generic 53 item self-report scale with good psychometric properties (de Beurs & Zitman, 2006) that allows comparisons across diagnostic groups and has shown to be sufficiently responsive to change in anxiety symptom severity (de Beurs et al., 2019; Van der Mheen et al., 2018). The BDI-II measures symptom severity of depression and was included because of the high comorbidity between anxiety and depression.

Treatment outcome was defined as the percentage of change between baseline and post-treatment for each outcome measure: [(pre-treatment score – post-treatment score) / pre-treatment score] x 100. Positive values indicate improvement after treatment.

4.1.2. Statistical analyses

The predictive value of trajectories on treatment outcome (measured with BSI or BDI-II) was studied in patients using linear regression analyses. Site (Utrecht versus Greifswald) was added to the model as an independent variable to account for potential differences between sites in overall treatment success. Results on the regression analyses without factor 'Site' are described in the supplemental material on page 7. All regression analyses were conducted separately per trajectory model, measure of treatment outcome and stimulus type (CS+, CS-). Independent samples t-tests were conducted to study differences in the number of therapy sessions and use of psychotropic medication between patients of the distinguished fear conditioning trajectories.

5. Results

5.1. Associations between trajectories and treatment outcome

Results on the association between latent fear learning trajectories

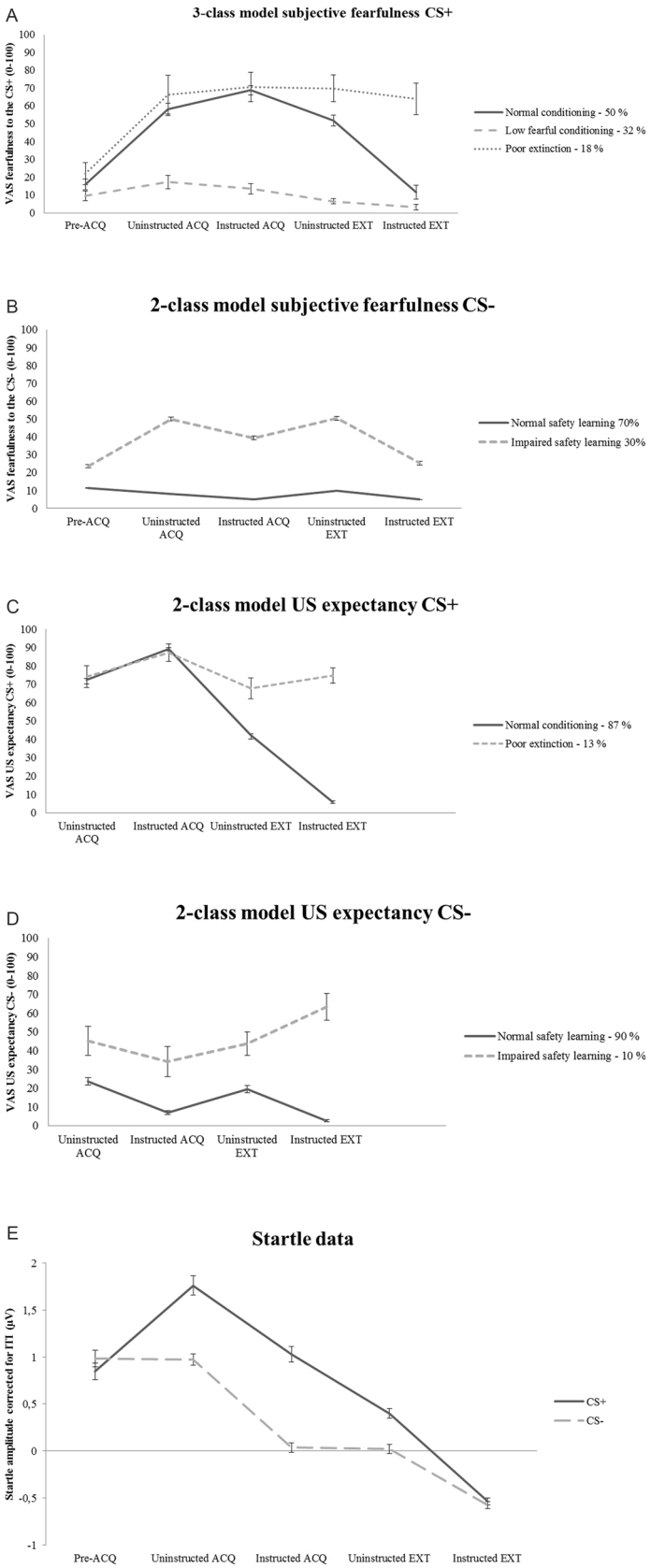

Fig. 2. Estimated means and standard errors of subjective fear responses (A, B), shock expectancy ratings (C, D) and startle data (E) for the selected models calculated based on the responses to the CS+ (A, C, E) and CS- (B, D, E). See text for further details. ACQ = acquisition; EXT = extinction.

Table 2
results on logistic regression analyses to examine the relationship between fear conditioning trajectories and clinical status (patient versus comparison subjects).

		B (SE)	Odds Ratio
CS + Subjective fear	Intercept	−.773 (.247)*	
	Low fearful	.608 (.329)	1.84
	Poor fear extinction	−1.130 (.449)*	0.32
CS- Subjective fear	Constant	−.430 (.201)*	.654
		−.998 (.330)*	.369
CS + US expectancy	Constant	−1.564 (.259)*	.209
		−.799 (.452)	.450
CS- US expectancy	Constant	−1.861 (.287)*	.156
		−.648 (.487)	.523

* $p < .05$.

and treatment outcome are displayed in Fig. 3 and Table S7, based on the mean percentage of improvement on the BSI in the patient group, displayed per outcome measure, condition (CS+/-) and trajectory. There were no differences in the number of therapy sessions between patients from different trajectories (all *p*-values > .05). Furthermore, there was no significant difference in treatment outcome between patients who used psychotropic medication during therapy versus patients who did not use medication (all *p*-values > .05). Visual inspection of the data of Fig. 3 suggests that the patients with a trajectory associated with maladaptive fear learning (poor extinction or impaired safety learning) showed on average lower improvement after treatment. However, statistical results on *fearfulness ratings* demonstrated no significant association between poor CS + extinguishers and poorer treatment outcome (CS+: $R^2 = .082$, $p = .077$), and no significant association between participants with impaired CS- safety learning and treatment outcome ($R^2 = .070$, $p = .115$). Trajectories based on *US expectancy* ratings showed no significant association between poor CS + extinguishers and poor treatment outcome ($R^2 = .091$, $p = .057$). However, there was a significant association between participants with impaired CS- safety learning (based on US expectancy ratings) and poorer treatment outcome ($R^2 = .105$, $p = .036$).

Fearfulness trajectories and US expectancy trajectories to CS + and CS- were not significantly associated with treatment outcome as measured with the BDI (all *p*-values > .05).

Figure S2 in the supplemental material shows mean improvement on the BSI, displayed for patients categorized in 0 up to 4 trajectories of poor extinction and/or impaired safety learning based on fearfulness and US expectancy data to the CS+ / CS-. Group sizes from 0 to 4 dysfunctional trajectories were small (21, 26, 9, 3, and 4 patients, respectively), which precludes a strong conclusion.

6. Discussion

In study 1, data-driven latent growth modeling was applied to identify distinct fear conditioning trajectories in patients with anxiety-related disorders and comparison subjects, by re-analyzing a previous data set (Duits et al., 2017). In study 2, the predictive value of these fear conditioning trajectories on treatment outcome was studied in a relatively small group of anxiety-related disordered patients in whom treatment outcome data were available.

In study 1, results on subjective outcome measures (fear and expectancy ratings) demonstrated maladaptive fear learning trajectories that correspond to the dysfunctional fear learning phenomena previously observed in patients with anxiety-related disorders (Duits et al., 2017; Lissek et al., 2005). Regarding the CS+, a trajectory characterized by poor fear extinction was identified. Thereby, it is rather remarkable to notice that those participants within the poor extinction trajectory continue to have difficulties with fear extinction even after receiving explicit instructions on CS—US contingencies during the instructed extinction phase. Regarding the CS-, a trajectory was identified characterized by impaired safety learning. Interestingly, corresponding to the conclusions of our previous meta-analysis (Duits et al., 2015) and in line with the study by Galatzer-Levy et al. (2017), these maladaptive trajectories of poor fear extinction and of impaired safety learning seem to be related to a specific deficit in safety learning. Moreover, the subjective outcome results indicated that patients were overrepresented in these dysfunctional fear conditioning trajectories. Strikingly, the 'normal' conditioning trajectories (representing adaptive extinction and safety learning) entailed almost equal numbers of patients and comparison subjects. Importantly, this observation underlines the variation between anxiety disordered subjects in safety learning, and indicate that dysfunctional safety learning may be part of the etiology of anxiety disorders for some, but not for all patients. In those patients who showed normal conditioning and normal safety learning trajectories, other important insufficiencies should be considered to explain their condition, such as information processing deficits (Beck & Clark, 1997; Beck, Emery, & Greenberg, 2005) or inefficient emotional reasoning (Lommen, Engelhard, van den Hout, & Arntz, 2013), and associated personality traits such as neuroticism (Engelhard, van den Hout, & Lommen, 2009; Lommen, Engelhard, & van den Hout, 2010). Taken together, these different individual characteristics may well explain why in many studies patient - control comparisons of fear conditioning parameters

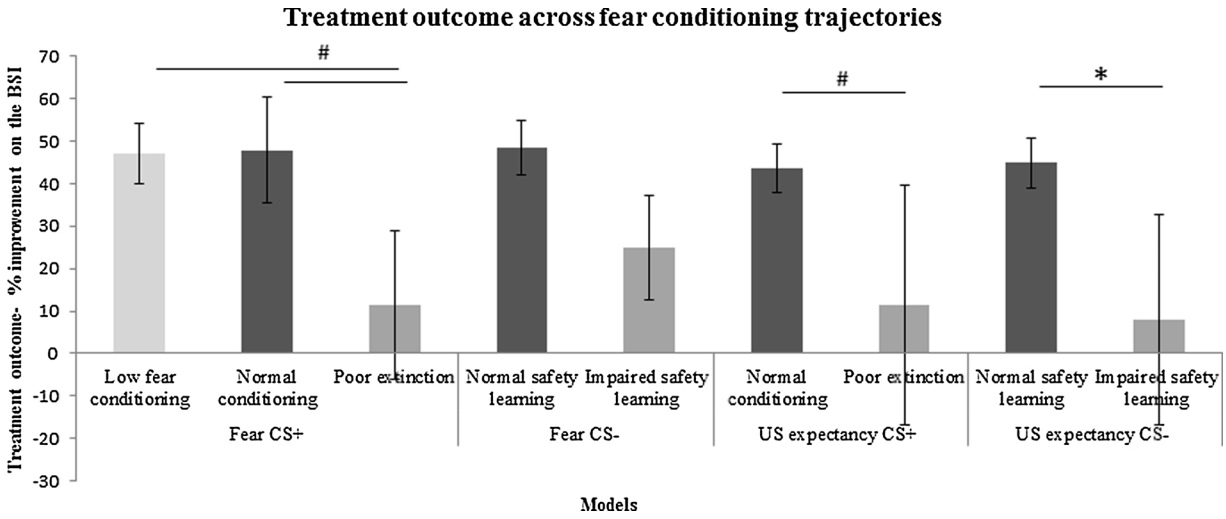

Fig. 3. Mean improvement on the BSI (Brief Symptom Inventory), displayed per model and trajectory. Error bars show the standard error. Error bars display the 95 % confidence interval. * $p < 0.05$, # $p < 0.10$.

yield on average only small to moderate group differences (Duits et al., 2015; Lissek et al., 2005). The strength of the LCGA method is that it allows to identify different fear conditioning trajectories at an individual level. In addition, these distinct fear conditioning patterns can be considered more or less functional, and the differences between the patterns observed in these analysis happen to closely follow the differences previously observed in cases-control analyses. Hence, this analysis allows to go beyond the case-control comparison at group level, and to identify individuals who display dysfunctional fear conditioning. We hypothesize that for those individuals, this could be a potential mechanism that contributes to anxiety pathology. In a recent follow-up study, the trajectories reported here are replicated in (Leen et al., 2021), giving even stronger support for the promise of this LCGA approach to differentiate individuals based on latent differences in fear acquisition and extinction.

Both subjective outcome measures on CS + yielded a poor extinction trajectory, but a low fear trajectory was only demonstrated in analyses based on subjective fear ratings and not in US expectancy ratings to the CS + . This may be explained by the more cognitively mediated relation between US expectancy and actual presentation of shocks in the acquisition phase of the experiment. A bias towards high US expectancy in patients with panic disorder has been shown in previous literature (Duits et al., 2016), but there is no reason to expect the opposite (indicating that no or fewer shocks are expected than are in fact being administered).

US expectancy ratings might be less sensitive to individual differences than subjective fear ratings. Overall, more subjects (both patients and comparison subjects) showed normal trajectories on US expectancy outcome data than with subjective fearfulness ratings. This may be explained by the more cognitively mediated process of risk assessment related to shock expectancy ratings, while fearfulness ratings represent a direct emotional response, which is thought to be largely independent from cognitive processing (Hermans & Baeyens, 2012).

In contrast to the fear conditioning trajectories identified based on subjective ratings, we were unable to identify distinct trajectories based on startle data using LCGA. Considering that the startle data were subject to group differences in the traditional patient-control comparison (Duits et al., 2017), this finding is against our expectations and is in contrast with the study by Galatzer-Levy et al. (2017) who demonstrated 3 different trajectories in fear-potentiated startle measures in human subjects. Discordance between findings from physiological data and subjective data has often been found within the fear conditioning literature (see for example, Heitland et al., 2012; Hermans, Craske, Mineka, & Lovibond, 2006; Lonsdorf et al., 2009). Due to a relatively limited sample size, we have not been able to study interaction effects in startle responding to the CS + versus CS- over time by using time-varying covariates within our analyses, and therefore, our previous findings (Duits et al., 2017) could not be replicated in the current study. Also, the disparity between our physiological outcomes and those described by Galatzer-Levy et al. in humans deserve additional comments. The paradigm used by us included uninstructed and instructed phases of fear acquisition and extinction to boost startle discrimination between CS + and CS- (see also Duits et al., 2017). This may have reduced within-group variance in startle responses as compared to the results of Galatzer-Levy et al. (2017). In addition, the sample size of the study by Galatzer-Levy and colleagues was substantially higher (N = 724), which increases the probability to detect small effects. For future work, an important challenge is to systematically investigate the optimal paradigm and the best way to analyze physiological data using LCGA. One important extension of our study to the study by Galatzer-Levy et al. (2017) was the investigation of responses to the CS- (safety learning), and studying the relationship between trajectory analyses and treatment outcome. Results on study 2 demonstrated that poorer treatment outcome was significantly related to a trajectory of impaired safety learning. Trajectories of high (compared to low) US expectancy to the CS- predicted poorer treatment outcome in patients with anxiety-related disorders. Treatment outcome was not significantly related to CS + trajectories based on US expectancy or subjective fear ratings. However, power issues seem to be a major limitation in interpreting the treatment outcome results, with only a proportion of patients on whom we were able to collect outcome data combined with small subgroups in the different trajectories. Moreover, we did not use a standardized treatment protocol, which might have led to increased variance in treatment outcome. Nevertheless, an advantage of this 'treatment as usual' approach is that the results are more generalizable to real world clinical practice. Furthermore, the overall pattern that maladaptive fear learning trajectories tend to be associated with poor treatment outcome holds the promise that future studies with larger sample sizes may clarify the extent to which fear conditioning response patterns can contribute to predicting treatment response. If so, assessment of patterns of fear learning may appear to be of added value in guiding individual treatment choices in the future.

Limitations and future directions: Conclusions of the current study are specific to the particular fear conditioning design used, which includes both uninstructed and instructed phases of fear acquisition and extinction. In addition, re-analyzing data from our previously published study (Duits et al., 2017) runs the risk of repeating sample-specific effects. The current results need replication and extension in larger study groups. Also, more detailed profiling of patients should be taking into account (such as comorbidity, chronicity, previous treatments, specific anxiety disorder diagnosis) to further study the association between patient characteristics and (dys)functional fear conditioning trajectories. Moreover, future studies in a larger sample might aim at exploring whether the fear conditioning trajectories identified are disorder specific. We also recommend to apply dimensional analyses in future studies, for example by investigating the relationship between anxiety specific symptom ratings (measured with various questionnaires) and latent fear conditioning trajectories. Furthermore, the use of latent growth mixture models (LGMM) or latent profile analysis (LPA) might be considered in future studies, because it is still under discussion what is considered the best methodology of studying latent fear conditioning trajectories (van de Schoot, Sijbrandij, Winter, Depaoli, & Vermunt, 2017). For future large-scale studies, studying differential fear responses in latent class analyses (CS + versus CS-) might be considered, for example by applying analyses with time-varying covariates in a sample of substantial size (Diallo, Morin, & Lu, 2017; van de Schoot et al., 2017). When conducting future studies in a larger sample, we recommend to further explore the relationship between latent fear conditioning and treatment response. By gaining more insight in this topic, we might eventually be able to predict who will respond to CBT, and for whom we need to design innovative augmentation strategies that include cognitive, pharmacological or neuromodulative techniques (Craske, 2015; Heinig et al., 2017; Karpova et al., 2011; Kindt, Soeter, & Vervliet, 2009; Thase, Weiller, Zhang, Weiss, & McIntyre, 2018).

Declaration of Competing Interest

None.

Acknowledgements

The authors thank Dr. Rens van de Schoot for his advice on LCGA, and Caroline Kwee for her help with statistical analyses.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.janxdis.2021.102361.

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